2026 ASCO® ANNUAL MEETING



MEETING ABSTRACTS

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2026 ASCO Annual Meeting Abstracts

Guide to Abstracts

Plenary Session 1s

Special Clinical Science Symposia 3s

Breast Cancer—Local/Regional/Adjuvant 6s

Breast Cancer—Metastatic 45s

Care Delivery/Models of Care 86s

Central Nervous System Tumors 132s

Developmental Therapeutics—Immunotherapy 158s

Developmental Therapeutics—Molecularly Targeted Agents and Tumor Biology 207s

Gastrointestinal Cancer—Colorectal and Anal 253s

Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary 299s

Genitourinary Cancer—Kidney and Bladder 364s

Genitourinary Cancer—Prostate, Testicular, and Penile 399s

Gynecologic Cancer 437s

Head and Neck Cancer 473s

Hematologic Malignancies—Leukemia, Myelodysplastic Syndromes, and Allotransplant 509s

Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia 536s

Hematologic Malignancies—Plasma Cell Dyscrasia 563s

Lung Cancer—Non–Small Cell Local-Regional/Small Cell/Other Thoracic Cancers 584s

Lung Cancer—Non–Small Cell Metastatic 619s

Medical Education and Professional Development 663s

Melanoma/Skin Cancers 675s

Pediatric Oncology 704s

Prevention, Risk Reduction, and Genetics 719s

Quality Care/Health Services Research 752s

Sarcoma 803s

Symptom Science and Palliative Care 828s

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LBA1 **Plenary Session**

Perioperative (neoadjuvant and adjuvant) apalutamide (APA) + androgen deprivation therapy (ADT) vs placebo (PBO) + ADT with radical prostatectomy (RP) in high-risk localized or locally advanced prostate cancer (HR LPC/LAPC): Final analysis of the PROTEUS phase 3 study. First Author: Mary-Ellen Taplin, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA2 **Plenary Session**

SARC041: A phase 3 randomized double-blind study of abemaciclib versus placebo in patients with advanced dedifferentiated liposarcoma. First Author: Mark A. Dickson, Memorial Sloan Kettering Cancer Center, New York, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA3 **Plenary Session**

Event-free survival with adjuvant selpercatinib in stage IB-IIIA *RET* fusion-positive NSCLC: Primary results of the phase 3 LIBRETTO-432 trial. First Author: Jonathan W. Goldman, University of California Los Angeles, Los Angeles, CA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA4 **Plenary Session**

Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy in previously untreated advanced squamous non–small cell lung cancer: Overall survival results of the phase 3 HARMONi-6 trial. First Author: Chen Zhiwei, Shanghai Chest Hospital, Shanghai, Jiao Tong University, School of Medicine, Shanghai, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA5 **Plenary Session**

Daraxonrasib, a RAS(ON) multi-selective inhibitor vs chemotherapy in previously treated metastatic pancreatic adenocarcinoma (mPDAC): Primary and final analysis from the phase 3 RASolute 302 study. First Author: Brian M. Wolpin, Dana-Farber Cancer Institute, Gastrointestinal Cancer Center, Boston, MA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA100 **Clinical Science Symposium**

NHS-Galleri: Primary results from a randomised controlled trial to assess the clinical utility of a multi-cancer early detection (MCED) test in population screening. First Author: Robert Charles Swanton, The Francis Crick Institute and University College London Cancer Institute, London, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA101 **Clinical Science Symposium**

Osimertinib with/without chemotherapy in patients with persistent ctDNA EGFR mutant (EGFRm) NSCLC at 3 weeks after 1L osimertinib: A randomized phase II study (FLAME study). First Author: Zhijie Wang, Cancer Hospital Chinese Academy of Medical Sciences (Langfang Section), Langfang, Hebei, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

102 **Clinical Science Symposium**

Benefit of adjuvant chemotherapy in resected stage I-IV CRC patients based on ctDNA dynamics across two timepoints: Results from GALAXY study. First Author: Mitsuru Yokota, Department of General Surgery, Kurashiki Central Hospital, Okayama, Japan

Background: In current clinical practice, ACT for stages IIB-III CRC is administered as soon as the patient is medically able, and within 8 weeks post-surgery. However, initiation >8 weeks may be appropriate in some patients. The interim analysis of the CIRCULATE-Japan GALAXY showed that patients with ctDNA-negativity during 2-10 weeks post-surgery do not derive benefit from ACT, although a small subset of these ctDNA-negative patients recurred. In this study, we analyzed early ctDNA dynamics to assess if turning ctDNA-positive at 12 weeks identifies the subgroup of initially (4-weeks post-surgery) ctDNA-negative patients who will benefit from ACT. **Methods:** This analysis included 1,034 patients with stage I-IV CRC undergoing curative-intent surgery from the GALAXY study who were ctDNA-negative at the first timepoint (TP#1; 4 $\pm$ 2 weeks post-surgery) and had subsequent ctDNA results available at the second TP (TP#2; 12 $\pm$ 2 weeks post-surgery). ctDNA was assessed using a personalized, tumor-informed assay (Signatera, Natera). DFS was assessed between TP#1-negative patients receiving ACT versus observation, stratified by ctDNA dynamics (turned positive at TP#2 or remained negative at both TPs). Analysis was landmarked at the TP#2 (12 weeks $\pm$ 2 weeks post-surgery) and Hazard ratios (HRs) were estimated using Cox proportional hazards models. **Results:** Of the 1,034 patients with ctDNA-negativity at TP#1 included in this analysis, 47.8% were females, and 73.8% had colon cancer, whereas 26.2% had rectal cancer. The pathologic stage distribution included: 11% Stage I / Low Risk Stage II, 72% High Risk Stage II / Stage III, and 17% Stage IV. The median patient age was 69 years (range 25-93) and the median follow-up was 33 months. Median time to ACT initiation was 6.7 weeks (range 3-12) post-surgery. Among patients who became positive at TP#2 (N=36), ACT was associated with significantly improved DFS compared with observation (HR 0.3; p=0.0165). Two-year DFS rates were 45.5% in the ACT group and 9.8% in the observation group, with a median DFS of 22 months and 2.5 months, respectively. In contrast, among patients who remained ctDNA-negative at both TPs (N=998), DFS outcomes were favorable regardless of ACT administration (HR 0.8, p=0.1744), with 2-year DFS rates of 87.1% and 84.1%, respectively, and median DFS was not reached in either group. **Conclusions:** A statistically significant and clinically meaningful benefit of ACT in resected stage I-IV CRC patients who were ctDNA-negative at 4 weeks but converted to positive at 12 weeks post-surgery was observed. These results underscore the critical role of both the 4- and 12-week post-surgery time points for risk stratification and indicate that early ctDNA dynamics can identify a subgroup of initially ctDNA-negative patients who may benefit from delayed ACT. Clinical trial information: UMIN000039205. Research Sponsor: Japan Agency for Medical Research and Development: 19ck0106447h0002, 21ck0106711h0001, 21ck0106710h0001, 22lk0201164h0001 and 22lk0201148h0002 National Cancer Center Research and Development Fund; no. 2021-A-6.

103 **Clinical Science Symposium**

Long-term outcomes of ^{18}F-fluoromisonidazole positron emission tomography (FMISO PET)–guided major radiation dose de-escalation in HPV-associated oropharyngeal cancer: The 30 ROC approach. First Author: Nancy Y. Lee, Memorial Sloan Kettering Cancer Center, New York, NY

Background: We previously demonstrated favorable short-term outcomes in patients with human papillomavirus–associated oropharyngeal carcinoma (HPV+ OPC) treated with biologically selected major radiation dose de-escalation, guided by functional hypoxia imaging. We now report mature long-term outcomes from a substantially larger prospective cohort to evaluate the durability and long-term safety of this approach. **Methods:** We conducted a pre-specified integrated analysis of a series of three consecutive phase II trials, each trial representing a progressive refinement with the same therapeutic strategy, enrolling patients with T0–3/N1–2c HPV+ OPC from 10/1/2015 to 11/30/2023. ^{18}F-fluoromisonidazole positron emission tomography (FMISO PET) assessed intratumoral hypoxia to stratify treatment: patients without hypoxia received de-escalated chemoradiotherapy (CRT) to 30Gy, while those with intra-treatment hypoxia received standard CRT to 70Gy. The primary endpoint was 5-year overall survival (OS); secondary endpoints included local, regional, and distant failure, progression-free survival (PFS), treatment-related toxicities, and patient-reported outcomes (PROs). Time-to-event outcomes were analyzed using Kaplan-Meier method and cumulative incidence function. **Results:** A total of 430 patients were enrolled and received treatment. T, N stages were: T0/TX(51), T1(198), T2(173), T3(8); N1 (62), N2a (48), N2b (252), and N2c (68). 96 patients (22.3%) had >10 pack-years of smoking history. There were 323 patients (75%) who had no hypoxia on FMISO PET and received 30Gy while 107 patients (25%) had evidence of intra-treatment tumor hypoxia and received 70Gy. With a median follow-up of 4.05 years (range 1.27–10.03 years), the 5-year OS was 97% in both the 30Gy and 70Gy cohorts. All oncologic endpoints were equivalent in the 30Gy vs 70Gy cohorts: 5-year local failure (2.2% vs 1.9%, p=0.7), regional failure (6.2% vs 3.9%, p=0.4), and PFS (91% vs 89%, p=0.5). Notably, patients with intra-treatment hypoxia, who received 70Gy had higher distant failure rates versus those without intra-treatment hypoxia and received 30Gy (7.5% vs 1.3%, p=0.004). Detailed acute/late toxicities and PROs will be presented at the meeting. **Conclusions:** FMISO PET–guided biological and personalized major radiation dose de-escalation results in durable long-term outcomes, benefiting ~75% of the patients. These findings establish a precision-based paradigm for definitive CRT in HPV+ OPC, currently being validated in an on-going randomized phase III trial (NCT06563479, >1/3 randomized). Patients with intra-treatment hypoxia had a higher rate of distant metastasis where additional therapy can be considered in future trials. Clinical trial information: NCT03323463, NCT05491512. Research Sponsor: U.S. National Institutes of Health.

104 Clinical Science Symposium

Phase 3, multicenter, randomized, controlled open-label study: Efficacy and safety of M701 (EpCAM×CD3 bispecific antibody) intraperitoneal infusion in advanced epithelial solid tumor with malignant ascites vs paracentesis. First Author: Jianming Xu, The First Medical Center, Chinese PLA General Hospital, Beijing, China

Background: Malignant ascites (MA) is a severe complication of advanced epithelial cancers, imposing a heavy symptom burden, compromising systemic therapy efficacy, and correlating with poor survival and impaired quality of life. While only one pharmacologic therapy is approved; guideline-recommended paracentesis provides merely transient symptomatic relief. Consequently, a significant unmet medical need persists for effective therapies that durably control MA. **Methods:** Patients with malignant ascites (MA) secondary to advanced gastric, colorectal, or ovarian cancer after failure of standard anticancer therapy were enrolled. Patients were randomized to Arm T, receiving therapeutic paracentesis plus intraperitoneal M701, or Arm C, receiving paracentesis alone. All patients continued background systemic treatment. The primary endpoint was puncture-free survival (PuFS), defined as the time from Day 18 to the subsequent paracentesis or death. Secondary endpoints included overall survival (OS), time to next paracentesis (TTNP), patient-reported outcomes (PROs) evaluated using the EORTC QLQ-C30 questionnaire and a Likert scale, and safety profiles between the two arms. **Results:** As of January 15, 2026, 312 pts were enrolled (Arm T, n = 206; Arm C, n = 106). Median PuFS was significantly longer in Arm T than in Arm C (87.59 vs 49.96 days; HR = 0.57, 95% CI: 0.42–0.78; p = 0.0003). TTNP was also markedly improved with M701 (186.7 vs 55.1 days; HR = 0.42, 95% CI: 0.29–0.60, p < 0.0001). Overall survival was comparable between arms (p = 0.8407, HR = 0.97, 95% CI: 0.74–1.28). Patient-reported outcomes showed a longer median time to global health status deterioration in Arm T (72.0 vs 39.0 days; HR = 0.73, p = 0.049). A statistically significant between-group difference was observed in the change from baseline in total Likert score at Day 116 (Visit 12) (mean difference −2.45; p = 0.0130), indicating sustained symptom relief with M701. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 70.39% of patients in Arm T and 51.89% in Arm C. Serious adverse events (SAEs) occurred in 48.54% and 33.02% of patients in the two arms, respectively. Only one grade 1 cytokine release syndrome (CRS) event was reported in Arm T, and the incidence of CRS-like symptoms (e.g., pyrexia and dyspnea) was very low. **Conclusions:** Intraperitoneal M701 was well tolerated when combined with systemic therapy. In patients with epithelial cancer-associated MA, M701 significantly prolonged puncture-free survival with comparable overall survival. These encouraging findings further support the clinical development of M701 and its potential therapeutic role in the management of malignant ascites. Clinical trial information: NCT06432296. Research Sponsor: Wuhan YZY Biopharma Co. Ltd.

105 Clinical Science Symposium

Patient reported outcomes (PRO) during and after multimodal treatment for resectable esophageal adenocarcinoma in the prospective, randomized, controlled, multicenter phase III ESOPEC trial. First Author: Jens Hoeppner, University of Bielefeld, University Medical Center OWL, Campus Hospital Lippe, Bielefeld, Germany

Background: The ESOPEC trial showed that perioperative chemotherapy improved survival compared with preoperative chemoradiotherapy in pts with esophageal adenocarcinoma (EAC). Here we report on PRO which was a key secondary endpoint. **Methods:** Pts with cT1 cN+ cM0 or cT2-4a cNany cM0 EAC were randomized between perioperative chemotherapy with FLOT (5-FU/leucovorin/oxaliplatin/docetaxel) or preoperative chemoradiotherapy with CROSS (41.4Gy/carboplatin/paclitaxel) both plus tumor resection. PRO was measured using the EORTC Quality of Life Questionnaire Core 30 (C30), Oesophageal Cancer Module (OES18) and Chemotherapy-Induced Peripheral Neuropathy Module (CIPN20) at baseline and during treatment and follow-up. The global health status / QOL (GH; C30), physical functioning (PF; C30), fatigue (FA; C30), dyspnoea (DY; C30), eating problems (EP; OES18), and sensory scale (SS; CIPN20) were chosen as primary outcomes. Predefined time points for comparison of PRO between treatment groups were directly before surgery, after discharge from surgery, and 6, 12, 24, and 36 months after start of treatment. Analyses were performed with mixed linear models for repeated measurements. **Results:** Of 438 randomized patients, 401 (197 FLOT, 204 CROSS) were included in the PRO analysis. Differences between The FLOT and CROSS groups are shown in the table. Before, surgery, GH and PF were higher in the FLOT group, while FA, DY, and EP were less pronounced in the FLOT as compared to CROSS group. At discharge from surgery and at follow-up, no significant differences in GH, PF, FA, DY, and EP were measured. Results in SS were worse in FLOT as compared to CROSS at all timepoints. **Conclusions:** Patients treated with FLOT as compared to CROSS reported better PRO results following neoadjuvant therapy and before surgery. In contrast, sensory problems were higher in FLOT versus CROSS over the whole treatment trajectory and follow-up. Clinical trial information: NCT02509286. Research Sponsor: Deutsche Forschungsgemeinschaft.

	Adjusted mean difference in points (FLOT minus CROSS) with 95%-CI and two-sided p-value			
	Preoperatively	Discharge	6 months	36 months
Global health status / QOL*	6.3 (1.1,11.5)p=0.019	0.6 (-4.9,6.1) p=0.83	-4.3 (-9.6,1.0)p=0.11	2.7 (-3.4,8.8) p=0.38
Physical functioning*	7.7 (3.1,12.4)p=0.001	5.3 (-0.6,11.1) p=0.076	-3.1 (-9.0,2.7)p=0.29	2.8 (-3.5,9.1) p=0.39
Fatigue**	-8.6 (-14.2,-3.0) p=0.003	-2.7 (-9.1,3.7) p=0.41	5.2 (-1.5,11.8)p=0.13	-4.8 (-12.3,2.6) p=0.20
Dyspnoea**	-10.9 (-17.1,-4.7) p<0.001	-1.8 (-10.5,6.8) p=0.68	1.5 (-7.5,10.4)p=0.75	0.7 (-8.9,10.2) p=0.89
Eating problems**	-12.7 (-18.9,-6.4) p<0.001	-2.9 (-10.1,4.3) p=0.43	-0.0 (-7.3,7.3)p=1.00	-5.3 (-13.5,3.0) p=0.21
Sensory scale**	14.8 (11.6,18.0) p<0.001	4.8 (1.7,8.0) p=0.003	14.6 (10.7,18.5) p<0.001	7.1 (1.1,13.0) p=0.020

*Higher scores indicate better QOL/function.
**Higher scores indicate more symptoms.

106 Clinical Science Symposium

An actionable machine learning–driven clinicogenomic model as a predictor of brain metastasis risk in breast cancer. First Author: Luke Roy George Pike, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Brain metastasis (BM) is a frequent site of disease progression for patients living with metastatic breast cancer (MBC). Guidelines do not recommend routine MRI brain surveillance in asymptomatic patients. Consequently, patients with MBC who develop BM often present with extensive disease, leading to lasting neurological damage or death. **Methods:** This study included MBC patients without known BM at presentation who underwent genomic sequencing of a non-BM specimen with MSK-IMPACT, a custom tumor-normal next-generation sequencing assay, within one year of M1 diagnosis. We developed an ensemble time-dependent LASSO machine learning (ML) model with BM-free survival (BMFS) as the primary endpoint, integrating baseline clinical, pathologic, and genomic features for risk stratification, using a cross-validation framework. Benchmarking was conducted using a time-dependent neural network designed to model competing risks (DeepHit), and further validation was performed using an independent clinical trial dataset. **Results:** 1594 MBC patients were divided into a training set (n=1118) and a test set (n=476), with 320 events over a median follow-up of 39.7 months. The ensemble ML model identified distinct clinicogenomic features associated with shorter BMFS, including receptor subtype, ER/PR percent positivity, menopausal status, metastatic burden, metastatic site distribution, disease-free interval, and alterations in *TP53*, *ERBB2*, and *RB1*. The model stratified patients into low-, intermediate-, and high-risk groups (training C-index: 0.690; test C-index: 0.696). In the test cohort, 24-month BMFS was 68%, 89%, and 98% in high, intermediate, and low risk groups (HR 19.2, p<0.001 high vs. low risk; HR 6.5, p<0.001 intermediate vs. low risk), with model predictions retaining robust predictive ability beyond 24 months (time-dependent AUC at 10 years of 0.79). These results were confirmed using DeepHit, a competing-risk-specific neural network (training C-index 0.71; test C-index 0.61). The model similarly identified high-risk patients within a single-arm phase II clinical trial dataset utilizing MRI screening in patients with MBC. **Conclusions:** We developed an actionable ML-driven clinicogenomic model that accurately identifies MBC patients at high risk of developing BM. Biologically plausible and readily available features defined a high-risk patient category with a >30% risk of developing BM within 2 years and would likely benefit from MRI screening. The results will be prospectively validated in BRAINSTORM (Breast Cancer Radiologic Assessment and Intervention for Neurological Surveillance, Tracking, and Optimized Risk Management), a phase II randomized clinical trial of intensified MRI surveillance versus standard symptom-based screening in high-risk MBC patients. Research Sponsor: National Cancer Institute; (P30-CA008748).

107 Clinical Science Symposium

External validation of a MMAI model for prognosis and chemotherapy benefit prediction in postmenopausal, node-positive, hormone receptor–positive breast cancer patients: Analysis of SWOG S8814. First Author: Corey Wayne Speers, Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL

Background: Despite effective endocrine therapy, the absolute benefit of adjuvant chemotherapy varies widely in node-positive HR+ disease, particularly among patients with 1-3 positive nodes. Prognostic tools for these patients often rely on genomic assays, which are costly, timely, or inaccessible in many clinical settings. We present a multimodal artificial intelligence (MMAI) model that integrates clinical and histopathological data to quickly stratify risk of distant metastasis and inform therapeutic decisions. Developed in six phase III randomized clinical and validated for chemotherapy benefit in N0 patients, MMAI offers an accessible alternative to genomic tools. Here, we validated MMAI for prognosis and prediction of chemotherapy benefit in SWOG S8814 – a randomized phase III trial of tamoxifen ± chemotherapy (CT) in postmenopausal women with node-positive (N+) HR+ breast cancer. **Methods:** Patients with digitized baseline H&E- stained diagnostic slides and clinical data (age, tumor size, nodal status) were analyzed (N = 413). The locked MMAI generated a continuous risk score and categorical risk groups (low, high). Associations with disease-free survival (DFS; 168 events) and overall survival (OS; 125 events) were assessed using univariable and multivariable Cox Proportional Hazard models. Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated. Differential CT benefit was evaluated by estimating relative risk reduction by MMAI risk groups. **Results:** MMAI was prognostic for DFS (HR per SD 1.73, 95% CI 1.48–2.03; p < 0.001) and OS (HR per SD 1.93, 95% CI 1.60–2.32; p < 0.001), remaining significant after adjustment for age, tumor size, and nodal burden. In the subset of patients with 1–3 positive nodes (n = 253), MMAI identified differential CT benefit: high-risk patients (56% of the patients) demonstrated a 26.3% relative reduction in 10-year DFS risk with CAF-T+TAM versus TAM alone, while low-risk patients (44% of the patients) derived minimal benefit (1.8% relative reduction in 10-year DFS risk). Additionally, the addition of CT resulted in DFS HRs of 1.21 (95% CI: 0.51-2.83) and 0.85 (95% CI: 0.55-1.23) in low- and high-risk patients, respectively. **Conclusions:** In SWOG S8814, a locked MMAI model using routinely available pathology and clinical data independently stratified prognosis and identified node-positive HR+ patients most likely to benefit from adjuvant CT, with minimal benefit among MMAI low-risk patients with 1–3 nodes. These findings support the use of MMAI as a fast (hours instead of weeks), scalable, cost-effective, and non-tissue consumptive alternative to genomic testing to inform adjuvant decisions in HR+ N+ EBC patients. Research Sponsor: None.

108 Clinical Science Symposium

An AI-based pathology classifier to predict benefit from enzalutamide in metastatic hormone-sensitive prostate cancer (mHSPC) from ENZAMET (ANZUP 1304). First Author: Sebastian R. Medina, Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University, Atlanta, GA

Background: The ENZAMET trial established that adding enzalutamide (ENZ) to androgen deprivation therapy (ADT) improves overall survival (OS) in mHSPC. However, heterogeneity in treatment response and toxicity complicate clinical decision-making. We evaluated a previously developed Artificial Intelligence Pathology Image Classifier (APIC) to determine whether it could identify ENZAMET participants (pts) more likely to benefit from adding ENZ rather than NSAA to ADT. **Methods:** This AI biomarker study analyzed digitized H&E tumor specimens from ENZAMET (ANZUP 1304, NCT02446405), a phase 3 trial randomizing pts with mHSPC to ADT plus ENZ or a non-steroidal antiandrogen (NSAA), with early docetaxel (EDx) permitted. APIC, a model quantifying nuclear morphology and tumor-immune architecture validated in CHAARTED (Medina et al, Clin Can Res 2025), was applied without modification. The primary multivariable analysis evaluated the treatment-APIC interaction for OS using Cox models adjusted for disease volume (CHAARTED criteria), EDx, and age. Sensitivity analyses excluded pts receiving EDx. APIC associations with 18 circulating immune markers were explored. All tests were two-sided with $p<0.05$ considered significant. **Results:** Among 393 evaluable pts (median follow-up 70 months), 248 (63%) were APIC-negative and 145 (37%) APIC-positive. APIC significantly modified ENZ benefit (interaction p=0.010). APIC-negative was associated with improved OS with ENZ versus NSAA (HR 0.42, $p<0.001$; 5-year OS 82% vs 59%), while APIC-positive showed no benefit (HR 0.98, p=0.92; 5-year OS 57% vs 57%). APIC-treatment interaction was significant (p=0.02) in the multivariable model adjusted for clinical covariates. In low-volume disease, ENZ improved OS in APIC-negative (HR 0.19, p=0.0001) but not APIC-positive (HR 1.12, p=0.8; interaction p=0.002). Excluding EDx use (n=227), APIC-negative was associated with ENZ benefit (HR 0.29, $p<0.001$; 5-year OS 88% vs 60%, interaction p=0.043), while no significant benefit was observed for APIC-positive (HR 0.75, p=0.39; 5-year OS 61% vs 54%) (Table). Analysis of circulating immune markers identified elevated plasma myeloid progenitor inhibitory factor 1 (MPIF1) in APIC-positive pts (1.32-fold, 95% CI 1.11–1.58, p=0.002). **Conclusions:** APIC status was associated with benefit of ENZ for pts with mHSPC. APIC might help guide treatment selection for pts with mHSPC considered for androgen receptor pathway inhibitors and/or docetaxel. Clinical trial information: NCT02446405. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; R01CA268287A1, R01CA26828703, U01CA269181, R01CA26820701A1, R01CA249992-01A1,R01CA202752-01A1,R01CA208236-01A1,R01CA216579-01A1,R01CA220581-01A1, R01CA257612- 01A1, 1U01CA239055-01, 1U01CA248226-01, 1U54CA254566-01; Astellas.

	APIC Status	HR (95% CI)	P Value	Interaction P
Biomarker cohort (n=393)	Negative	0.42 (0.27–0.64)	<0.001	0.01
	Positive	0.98 (0.61–1.56)	0.9	
Low-Volume Disease Subgroup (n=209)	Negative	0.19 (0.08–0.44)	0.0001	0.002
	Positive	1.12 (0.55–2.29)	0.8	
No docetaxel cohort (n=227)	Negative	0.29 (0.15–0.56)	<0.001	0.04
	Positive	0.75 (0.40–1.44)	0.4	

109 Clinical Science Symposium

Implementing a centralized navigator-led and AI-assisted platform to improve lung cancer screening rates and early detection: A 6-year health system analysis. First Author: Jun Zhang, OSF HealthCare Cancer Institute, Peoria, IL

Background: Despite the known mortality benefits of low-dose computed tomography (LDCT) for lung cancer screening (LCS), national uptake remains stagnant (~15-20%). Significant barriers include primary care burden and geographic disparities in rural areas. This study evaluates the impact of a centralized navigation model combined with AI-assisted electronic health record (EHR) alerts on LCS rates and stage distribution within a large integrated health system. **Methods:** We conducted a retrospective analysis of LCS performance across a 16-hospital system (OSF HealthCare) from 2019 to 2025. The intervention included: 1) centralization of LCS navigators to manage registries and scheduling, and 2) implementation of AI-assisted EHR alerts to identify eligible high-risk patients. Outcome measures included absolute LDCT volume, system-wide screening rates, and AJCC staging at diagnosis. Benchmarks were derived from American Lung Association (ALA) national and state (Illinois) data. **Results:** The system-wide LCS screening rate increased from 18.2% in 2020 to 42.8% in 2025, significantly outperforming the projected 2025 US national average (19.5%) and the Illinois state average (20.8%). Absolute screening volume nearly doubled, rising from 2,257 scans in 2019 to 4,108 in 2025. Notably, the program demonstrated high resilience during the 2020 COVID-19 pandemic, maintaining 98.5% of prior-year volume compared to a 5% national decline. Early-stage detection (Stage I) showed the greatest improvement in rural facilities, with some centers seeing a +21% increase in Stage I diagnoses over the study period. **Conclusions:** A centralized, technology-enabled navigation model effectively doubles the national benchmark for lung cancer screening uptake. By removing administrative burdens from primary care and utilizing AI-assisted EHR alert system to close the "eligibility gap", this model provides a scalable blueprint for improving early cancer detection and addressing rural health inequities. Research Sponsor: None.

OSF HealthCare lung cancer screening performance vs. national benchmarks (2020–2025).

Year	OSF Annual LDCT Volume	OSF Screening Rate (%)	National Screening Rate (%)*	Performance Gap (Percentage Points)
2020	2,223	18.2%	14.5%	+3.7%
2021	2,647	21.4%	14.8%	+6.6%
2022	3,280	27.8%	15.5%	+12.3%
2023	3,406	33.6%	16.0%	+17.6%
2024	3,522	38.2%	18.2%	+20.0%
2025	4,108	42.8%	19.5%	**+23.3%**

*National benchmarks based on American Lung Association "State of Lung Cancer" annual reports and CDC/ACS prevalence estimates.

500 Oral Abstract Session

First results from the OPTIMA phase III randomized non-inferiority trial of test-directed chemotherapy in patients with high clinical risk ER-positive HER2-negative early breast cancer. First Author: Robert C. Stein, National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, United Kingdom

Background: Tumor gene expression tests are widely used to assist adjuvant chemotherapy decisions for women with early breast cancer (EBC). OPTIMA (Optimal Personalised Treatment of early breast cancer using Multi-parameter Analysis) is an international RCT comparing chemotherapy decisions made with the Prosigna (PAM50) gene expression test with standard treatment in mostly node-positive patients. **Methods:** Women and men aged >40 recommended to receive chemotherapy for ER+ HER2- EBC with 0-9 involved axillary nodes and T size >30mm if node negative were eligible. Randomization was between standard chemotherapy followed by endocrine therapy (CET) or to a Prosigna test directed chemotherapy decision. Patients with Prosigna ROR score > 60 tumors were assigned CET whilst those with low ROR score (≤60) tumors received endocrine therapy (ET) alone. ET for premenopausal women included ovarian function suppression (OFS) in the absence of chemotherapy-induced ovarian insufficiency. ROR scores were not disclosed, and patients receiving CET were blinded to their randomization. OPTIMA was designed to demonstrate non-inferiority (NI) of 5-year invasive breast cancer free survival (IBCFS) in the test-directed arm with a 3% margin in the per protocol (PP) population using a 5% 1-sided alpha. Control arm testing allowed treatment comparison within the low ROR score population at a 3.5% NI margin. **Results:** From 16th Jan 2017 to 12th Dec 2025 4429 patients were randomized, 2215 to the control arm and 2214 to the test-directed arm of whom 2061 (93%) and 2097 (95%) were included in the respective PP group. Patient characteristics in the PP population were well-balanced; 62% were postmenopausal, 37% premenopausal and 0.8% male. 73% had pN1/pN1sn, 8% had pN0/pN1mi and 19% had pN2 tumors. 68% had low ROR score tumors. With a median follow-up of 3.9 years (interquartile range 2.0-5.9), 280 IBCFS events occurred (141 on control arm; 139 on test directed arm) of which 66% were distant recurrences. The 5-year IBCFS rate in the control arm was 91.5% [95% CI 89.7- 92.9%] and 90.4% [95% CI 88.6-92.0%] in the test-directed arm, Hazard Ratio (HR) 0.99 [90% CI 0.81- 1.20], NI p = 0.013, thereby meeting the pre-defined NI margin. The corresponding 5-year IBCFS rates for the low ROR score population were 94.9% [95% CI 92.9- 96.4%] and 93.7% [95% CI 91.8- 95.2%] for the two arms respectively, HR 1.06 [90% CI 0.78- 1.46] NI p = 0.0051 again demonstrating non-inferiority. There was no significant outcome heterogeneity between subgroups including for menopausal and nodal status. **Conclusions:** The OPTIMA trial demonstrates that women and men with ER+ HER2-EBC and ROR score ≤60 tumors can safely avoid chemotherapy. It provides evidence for the utility of test-directed chemotherapy in premenopausal women treated with OFS and patients with high levels of nodal involvement. Clinical trial information: ISRCTN42400492. Research Sponsor: UK National Institute for Health Research Health Technology Assessment Programme; 10/34/501; Norwegian Cancer Society; KLINBEFORSK (Norway); Pink Ribbon (Norwegian Breast Cancer Association); Breast Cancer Trials (Australia); Veracyte.

501 Oral Abstract Session

Prognostic and predictive impact of baseline gene expression (exp) in the NATALEE trial of adjuvant (adj) ribociclib (RIB) + nonsteroidal aromatase inhibitor (NSAI) in HR+/HER2− early breast cancer (EBC). First Author: Stephen K.L. Chia, BC Cancer Agency, Vancouver, BC, Canada

Background: In the NATALEE clinical trial, RIB + NSAI significantly improved invasive disease–free survival (iDFS) vs NSAI alone in patients (pts) with stage II/III HR+/HER2− EBC. We report on the prognostic and predictive value of baseline gene exp in NATALEE. **Methods:** Pts were randomized 1:1 to RIB + NSAI or NSAI alone. Men and premenopausal women received goserelin. Eligible pts had anatomical stage IIA (if N0 with additional risk factors [G3, or G2 with Ki67 ≥20% or high genomic risk] or N1 [1-3 axillary lymph nodes]), IIB, or III disease per AJCC (8th ed). Gene exp in surgical samples was profiled by NanoString BC360 panel. PAM50-based intrinsic subtype × treatment (tx) interaction was estimated by likelihood ratio test. Prognostic and predictive effects of PAM50 subtypes and genomic risk/proliferation signature scores created from gene exp data were assessed with Cox proportional hazards models. Differences in genomic risk and proliferation scores were analyzed by Wilcoxon test. Associations between gene exp and RIB benefit were estimated with Cox models. **Results:** In all, 3022 baseline surgical samples were analyzed. iDFS benefit with RIB + NSAI was consistent in the biomarker (hazard ratio [HR], 0.72) and intent-to-treat populations (HR, 0.71). PAM50 subtype distribution was comparable across tx arms and differed between N0 and N1-N3 in pts with luminal A (LumA; 50% vs 68%), luminal B (lumB; 41% vs 26%), and basal-like (BSL; 6.4% vs 2.5%) disease, with similar percentages for HER2-enriched (HER2E; 2.5% vs 3.0%). PAM50 subtypes were strongly prognostic (HRs vs LumA: LumB, 1.39; HER2E, 2.62; BSL, 3.92). RIB had benefit across all PAM50 subtypes (HRs: LumA, 0.77; LumB, 0.71; HER2E, 0.50; BSL, 0.42), with no significant subtype × tx interaction (P= .34). Higher genomic risk signature or proliferation signature scores showed a trend for increased RIB benefit, again with no significant interaction. Pts with N0 vs N1-N3 had significantly higher genomic risk scores and proliferation scores. Exploratory analysis of the predictive effect of gene exp on RIB benefit identified several genes for which higher (eg, *CEACAM6*, *NOD2*, and *GPX3)* or lower exp (eg, *GATA3*, *SLC39A6*, and *MAPT*) was associated with increased RIB benefit. **Conclusions:** In this analysis of NATALEE, which examined the largest dataset of surgical tumor samples from any adj CDK4/6i trial in HR+/HER2− EBC, RIB had benefit across all PAM50 subtypes, with a trend for increased benefit in pts with higher genomic risk signature or proliferation signature scores. Baseline exp levels of several genes were associated with differential RIB benefit in EBC, showing potential predictive and prognostic value. The findings reinforce the therapeutic benefit of RIB in combination with ET across HR+/HER2− EBC populations. Clinical trial information: NCT03701334. Research Sponsor: Novartis Pharmaceuticals Corporation.

502 Oral Abstract Session

Efficacy and safety of giredestrant (GIRE) in patients (pts) with estrogen receptor–positive, HER2-negative early breast cancer (ER+, HER2– eBC) in the phase III lidERA BC clinical trial: Results by menopausal status. First Author: Peter Schmid, Queen Mary University of London, London, United Kingdom

Background: The lidERA BC trial (NCT04961996) demonstrated a statistically significant, clinically meaningful improvement in invasive disease-free survival (IDFS) with GIRE (a next-generation oral SERD and full ER antagonist) vs standard-of-care endocrine therapy (SOC ET) in ER+, HER2–, Stage I–III eBC (Bardia SABCS 2025). We report efficacy and safety in pre-menopausal (PRE-M) vs post-menopausal (POST-M) pts. **Methods:** Pts with ER+, HER2– eBC who had BC surgery and (neo)adjuvant chemotherapy (if indicated) were randomized 1:1 to once-daily 30 mg GIRE or SOC ET (anastrozole/letrozole/exemestane [aromatase inhibitors; AIs] or tamoxifen [TAM]) for 5 years (y) of treatment (tx). PRE-M pts on GIRE and on AIs received an LHRH. **Results:** In the efficacy-evaluable population (n = 4170), 40.7% of pts were PRE-M and 59.3% POST-M. 58.0% of pts on TAM received LHRH. PRE-M pts generally had a slightly higher baseline risk of recurrence vs POST-M pts (high risk, 70.5% vs 66.4%; medium risk, 28.4% vs 32.5%; higher use of [neo]adjuvant chemotherapy, 91.2% vs 78.9%). GIRE showed IDFS benefit and higher 3-y rates in both PRE-M and POST-M subgroups; a similar trend was observed for distant recurrence-free interval (DRFI) (Table). Adverse events (AE) were comparable in both subgroups and across txs (Table). Fewer pts discontinued GIRE due to AEs compared with pts receiving an AI, regardless of menopausal status. Discontinuation due to musculoskeletal pain occurred in 1.6% vs 4.5% of pts receiving GIRE vs AI, respectively. More pts switched to alternative ET in the SOC ET arm vs GIRE (10.1% vs 5.7%), mainly due to AEs for both arms. **Conclusions:** Adjuvant GIRE improved IDFS and DRFI vs SOC ET; benefit was consistent irrespective of menopausal status. PRE-M pts experienced a 42% reduction in the risk of developing metastatic disease and POST-M pts a 24% reduction. Safety was comparable between menopausal groups and there were few discontinuations, regardless of menopausal status, although PRE-M and POST-M pts receiving GIRE had fewer tx discontinuations than those receiving an AI or TAM in the PRE-M and POST-M settings. Clinical trial information: NCT04961996. Research Sponsor: F. Hoffmann-La Roche Ltd.

	GIRE PRE-M n = 849	SOC ET PRE-M n = 838			GIRED POST-M n = 1220	SOC ET POST-M n = 1236		
IDFS hazard ratio (HR)	**0.65**				**0.74**			
3-yr rate, %	**94.0**	**91.5**			**91.3**	**88.3**		
DRFI HR	**0.58**				**0.76**			
3-yr rate, %	**95.5**	**92.6**			**93.6**	**91.6**		
	PRE-M n = 1672				**POST-M n = 2440**			
Pts, %	**GIRE n = 840**	**SOC ET n = 832**	**SOC ET (AI) n = 563**	**SOC ET (TAM) n = 269**	**GIRE n = 1209**	**SOC ET n = 1231**	**SOC ET (AI) n = 1183**	**SOC ET (TAM) n = 48**
All Grade/Grade 3–4 AE	**95.5/18.2**	95.3/ 17.3	96.3/16.9	93.3/18.2	**94.5/ 20.7**	93.7/ 18.4	94.1/18.6	85.4/14.6
AE leading to tx discontinuation	**4.9**	7.8	7.5	8.6	**5.7**	8.5	8.2	16.7
Musculoskeletal pain*	**58.1**	53.5	59.7	40.5	**50.8**	53.6	54.6	29.2

HRs are unstratified vs SOC ET.
*Includes other related terms.

LBA503 Oral Abstract Session

Omission of completion axillary dissection in patients with breast cancer and sentinel lymph node macrometastases: Overall survival and patient-reported arm morbidity from the randomized SENOMAC trial. First Author: Jana de Boniface, Department of Surgery, Capio St. Göran's Hospital and Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

504 **Oral Abstract Session**

Surgical de-escalation of implant-based breast reconstruction (IBBR) after mastectomy for breast cancer treatment or prevention: The international randomized phase III PREPEC trial (OPBC-02). First Author: Walter Weber, University Hospital Basel and Faculty of Medicine University of Basel, Basel, Switzerland

Background: The optimal positioning of implants following skin- (SSM) or nipple-sparing mastectomy (NSM) for breast cancer treatment or prevention is unclear. Pre-pectoral IBBR obviates the need to dissect the major pectoral muscle but provides less soft tissue coverage of the implant. The PREPEC trial hypothesized pre-pectoral IBBR would result in improved long-term quality of life (QoL) compared to sub-pectoral IBBR. **Methods:** OPBC-02/PREPEC (NCT04293146) was a pragmatic, international, randomized, phase III superiority trial. Women ≥18 years undergoing SSM or NSM for treatment or prevention of breast cancer were randomized (1:1) to pre-pectoral or sub-pectoral IBBR. Surgery otherwise followed standards of care. The primary endpoint was patient-reported physical well-being chest as assessed by BREAST-Q 24 mo after surgery (prespecified MID 4 points; SD 13). 372 pts provided 80% power (two-sided t-test α = 0.05). Multiple imputation was implemented for missing scores across all timepoints (day 10; 1, 6, 12, 18, 24 mo). The IBBR assignment difference at 24 mo was estimated by linear mixed modeling, adjusted for baseline score, stratification factors, pre-selected covariates, and random center effect. Loss or replacement of expander or implant for any reason within 24 mo was the primary safety endpoint. **Results:** From July 2020 to February 2023, 383 pts were randomized at 26 OPBC centers in 10 countries. The full analysis set comprised 380 pts (191 randomized to pre-pectoral, 189 to sub-pectoral IBBR). Surgery was unilateral in 72.9% of pts and NSM in 58.4%. The setting was therapeutic in 77.9% of pts, therapeutic and preventive in 15.5%, and preventive in 6.6%. BREAST-Q completion was 83-95% across 6 post-baseline timepoints. Pre-pectoral IBBR significantly improved physical well-being at 24 mo compared to sub-pectoral IBBR (least-square means 79.2 [95%CI 75.5-82.8] vs 74.3 [70.7-78.0], respectively). The mean difference of 4.8 (95%CI 1.0-8.7; p = 0.01) surpassed the predefined threshold for a clinically meaningful difference. The effect was robust in sensitivity analyses, and consistent in subgroup analyses. Loss or replacement of expander or implant for any reason within 24 mo occurred in 68 pts, 21.1% vs 14.5% after pre-pectoral and sub-pectoral IBBR, respectively. The covariate-adjusted model estimated 5.7% (95%CI -2.4% - 13.8%) more implant loss with pre-pectoral IBBR. At least one complication occurred in 54.1% vs 55.9% of pts, respectively. Early complications were more frequent after pre-pectoral IBBR (crude estimated increase range 3-5%); late complications were more frequent after sub-pectoral IBBR. **Conclusions:** Pre-pectoral IBBR significantly and relevantly improved long-term QoL at the cost of a higher risk of loss or replacement of expander or implant compared to sub-pectoral IBBR. Clinical trial information: NCT04293146. Research Sponsor: Swiss National Science Foundation; Krebsliga beider Basel; Swiss Cancer Research foundation.

505 **Oral Abstract Session**

Prediction of axillary response in 5,262 patients with node-positive breast cancer treated with neoadjuvant chemotherapy: Results from the prospective multicenter AXSANA/EUBREAST-03/AGO-B-053 study. First Author: Maggie Banys-Paluchowski, Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

Background: Axillary lymph node dissection (ALND) for node-positive breast cancer (BC) converting to clinical node-negativity after neoadjuvant chemotherapy (NACT) is increasingly being replaced by less invasive procedures, such as sentinel lymph node biopsy (SLNB) or targeted axillary dissection (TAD). Concerns remain regarding the use of de-escalated procedures in patients with high initial nodal burden. We aimed to determine factors associated with nodal response, with a focus on tumor biology and nodal burden, to enable less extensive surgery without compromising oncological outcomes. **Methods:** AXSANA is an ongoing study investigating oncological and patient-reported outcomes after different axillary procedures in cN+ BC treated with NACT. In the present analysis, the impact of nodal involvement and tumor biology on axillary response was analyzed. The entire dataset is continuously and systematically monitored for data quality assurance. **Results:** 7,071 patients from 288 sites in 26 countries were included between June 2020 and January 7th, 2026. Of these, 5,262 had completed surgery at the time of analysis. 2,341 patients (44.5%) had HR+ HER2- disease, followed by HR+ HER2+ (1,244; 23.6%), triple-negative (1,053; 20.1%) and HR- HER2+ (618; 11.7%). 91.3% of patients had an invasive ductal carcinoma of no special type (NST). 1,158 (22.1%) had ≥ 4 suspicious nodes at time of diagnosis. The highest nodal pCR rate (ypN0) was observed in patients with HR- HER2+ disease (86.1%), followed by HR+ HER2+ (70.7%), triple-negative (68.5%), and HR+ HER2- (30.5%; p < 0.001). Nodal pCR rate was higher in patients with NST tumors (55.6%), compared to those with invasive lobular (35.2%) and mixed histology (43.8%; p < 0.001). Patients with higher Ki67 (p < 0.001), higher grading (p < 0.001), multicentric tumors (p = 0.001), and without lymphangitis carcinomatosa (p = 0.046) were more likely to achieve nodal pCR in the univariate analysis. In contrast, the number of suspicious nodes at the time of diagnosis was not associated with axillary response (ypN0: 54.4% in pts. with 1-3 suspicious nodes vs. 53.6% in ≥ 4 suspicious nodes; p = 0.670). In the multivariable analysis, receptor status, Ki67, and grading, but not the number of suspicious lymph nodes at the time of diagnosis, were significantly associated with axillary response to treatment. **Conclusions:** This large prospective analysis shows that tumor biology, rather than the extent of nodal involvement is associated with axillary response to NACT. This challenges current guidelines and the common approach of restricting surgical de-escalation to patients with a low axillary tumor burden at presentation, and suggests that the selection of candidates for a potential de-escalation should be based on tumor biology rather than the extent of axillary disease at diagnosis. Clinical trial information: NCT04373655. Research Sponsor: AGO-B; AWOgyn; Claudia von Schilling Foundation for Breast Cancer Research; Ehmann Foundation Savognin; EndoMag; Merit Medical; Mammotome; Sirius Medical.

506 **Oral Abstract Session**

Updated overall survival results from a randomized phase III trial of non–cross-resistant adjuvant chemotherapy plus endocrine therapy versus endocrine therapy alone in HR+/HER2−/lymph node–positive breast cancer with residual disease following neoadjuvant chemotherapy (NCT01019616). First Author: Yang Yang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Breast Center, Peking University Cancer Hospital & Institute, Beijing, China

Background: Patients with HR+/HER2−, node-positive breast cancer and residual disease after neoadjuvant chemotherapy (NAC) represent a high-risk population yet substantial recurrence risk. Whether additional non-cross-resistant chemotherapy after surgery provides long-term survival benefit beyond endocrine therapy remains uncertain. Our previous analysis of this phase III trial (NCT01019616) with shorter follow-up (median, 72.4 months) did not show a statistically significant survival benefit. Here we report updated survival outcomes with extended follow-up. **Methods:** Women aged < 65 years with invasive HR+/HER2−, node-positive breast cancer who completed anthracycline-containing NAC and had residual disease (Miller–Payne grade 1–3 and/or residual nodal involvement) were randomized 1:1 to receive either 4 cycles of non-cross-resistant adjuvant chemotherapy plus endocrine therapy (CT+ET) or endocrine therapy alone (ET). The primary endpoint was distant disease-free survival (DDFS); overall survival (OS) was a secondary endpoint. Hazard ratios (HRs) were estimated using Cox proportional hazards models with multivariable adjustment. **Results:** A total of 379 patients were randomized (CT+ET, *n* = 187; ET, *n* = 192) with balanced baseline characteristics. At median follow-up of 135.0 months, 52 deaths occurred: 18 (9.6%) in CT+ET versus 34 (17.7%) in ET. OS was significantly improved with CT+ET (log-rank *P* = 0.023). Ten-year OS rates were 89.9% versus 82.9% (adjusted HR, 0.56; 95% CI, 0.32–0.99; *P* = 0.048). DDFS showed a favorable trend (*P* = 0.059) with 10-year rates of 85.5% versus 78.3% (adjusted HR, 0.67; 95% CI, 0.41–1.09). Greatest benefit was observed in patients with residual node-positive disease (OS HR, 0.47) and Miller–Payne grade 3 response (OS HR, 0.31). **Conclusions:** This randomized phase III trial demonstrates long-term overall survival benefit from the addition of non-cross-resistant chemotherapy to endocrine therapy for HR+/HER2−, node-positive patients with residual disease after NAC. Clinical trial information: NCT01019616. Research Sponsor: None.

507 **Oral Abstract Session**

Neoadjuvant pembrolizumab or placebo plus chemotherapy followed by adjuvant pembrolizumab or placebo for high-risk early-stage TNBC: Final analysis results from the phase 3 KEYNOTE-522 study. First Author: Peter Schmid, Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom

Background: KEYNOTE-522 (NCT03036488) showed statistically significant and clinically meaningful improvements in pCR, EFS, and OS with the addition of pembrolizumab (pembro) to chemotherapy (chemo) in participants (pts) with high-risk early-stage TNBC. Here, we present updated results from the final analysis. **Methods:** Eligible pts with previously untreated, non-metastatic, centrally confirmed TNBC (stage T1c N1-2 or T2-4 N0-2 per AJCC) were randomized 2:1 to neoadjuvant pembro 200 mg Q3W or placebo (pbo), both given with 4 cycles of paclitaxel + carboplatin, then 4 cycles of doxorubicin or epirubicin + cyclophosphamide. After definitive surgery, pts received adjuvant pembro or pbo for 9 cycles or until recurrence or unacceptable toxicity. Dual primary endpoints are pCR (ypT0/Tis ypN0) and EFS (time from randomization to disease progression that precluded definitive surgery, local/distant recurrence, second primary cancer, or death from any cause); OS is the key secondary endpoint. **Results:** 1174 pts were randomized to pembro (n = 784) or pbo (n = 390). At the data cutoff date (October 14, 2025), median follow-up (range) was 93.8 mo (84.7-102.8). The 7-yr EFS rate (95% CI) was 78.3% (75.3-81.1) in the pembro group vs 69.8% (65.0-74.2) in the pbo group; the HR was 0.68 (95% CI, 0.54-0.86). The 7-yr OS rate (95% CI) was 85.1% (82.5-87.5) in the pembro group vs 77.2% (72.7-81.1) in the pbo group; the HR was 0.64 (95% CI, 0.49-0.85). The benefit of pembro on EFS and OS was generally consistent across most prespecified subgroups, including those defined by PD-L1 expression, nodal status, and disease stage. Rates of grade ≥3 treatment-related AEs were 77.1% in the pembro group and 73.3% in the pbo group (death incidence, 0.5% vs 0.3%, respectively); rates of any grade immune-mediated AEs were 35.0% vs 13.1%, respectively. **Conclusions:** After a median follow-up of 7.8 years, neoadjuvant pembro + chemo followed by adjuvant pembro continues to show a clinically meaningful survival benefit compared with neoadjuvant chemo alone in pts with high-risk early-stage TNBC. Clinical trial information: NCT03036488. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

508 **Rapid Oral Abstract Session**

Adjuvant capecitabine and trastuzumab for stage IA HER2-positive breast cancer (IRIS-A): A phase II clinical trial. First Author: Ruoxi Wang, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Weekly paclitaxel and trastuzumab represents a standard option for most stage I human epidermal growth factor receptor type 2 (HER2)-positive breast cancer (BC)s based on results of the single arm phase II APT trial. However, the protocol-induced toxicity was not absent, prompting interest in better tolerated approaches that retain high clinical efficacy. The series of "IRIS" study including cohort A(2020, capecitabine and trastuzumab), B(2020, endocrine therapy and trastuzumab), C (2021, short-period capecitabine and trastuzumab) and D (2021, vinorelbine and trastuzumab) were designed as single arm trials regarding de-escaltion of adjuvant therapy without intravenous chemotherapy in early-stage HER2+ BCs. Herein we reported the results of IRIS-A, a single-group, phase II study to determine whether treatment with capecitabine and trastuzumab was well tolerated and yielded clinically acceptable outcome among stage IA HER2-positive breast cancer. **Methods:** Patients with stage IA (T1N0: hormonal receptor (HR) $<$ 10%, T$\leq$2cm or HR$\geq$10%, 1cm $<$ T$\leq$2cm) confirmed HER2+ BC were received oral capecitabine (1000 mg/m^2 twice daily for two weeks), and trastuzumab(8 mg/kg load$\rightarrow$6 mg/kg) every 3 weeks for 6 cycles, followed by 11 cycles of trastuzumab monotherapy (6 mg/kg once every 3 weeks). The primary end point was survival free from invasive disease (iDFS). **Results:** A total of 187 patients were enrolled in this study between May 20, 2020 and May 27, 2021 at Fudan University Shanghai Cancer Center in China. Among all these patients, 80.2% had tumors that measured 0.5 cm or less in the greatest dimension; a majority of tumors (87.2%) were hormone-receptor-negative. The median follow-up period was 62 months(ranges 56-68). The 5-year rate of survival free from invasive disease was 97.9% (95% confidence interval [CI], 94.4 to 99.2). Among the 4 relapses seen, 2 were due to contralateral primary invasive breast cancer (HER2-negative). Excluding these 2 patients and nonbreast cancers, 2 disease-specific events (1 with ipsilateral axilla and ipsilateral breast) were noted. There was no death in this trial. A total of 5 patients (2.7%) reported at least one episode of grade 3 adverse effect (AE)s, which did not influence the completion of treatment. The most common AE was hand-foot syndrome (46.5%), with 1.1% of patients experiencing a grade 3 event. **Conclusions:** Among patients with stage IA HER2+ BCs, treatment with adjuvant capecitabine plus trastuzumab was associated with an excellent 5-year iDFS of 97.9%. No adverse events that influence treatment continuity were observed. The regimen used in this trial would be an alternative in patients with small size HER2+ tumors with fewer toxic effects than the established regimens. A phase III study using the same protocol is being conducted currently. Clinical trial information: NCT04383275. Research Sponsor: None.

509 **Rapid Oral Abstract Session**

Neoadjuvant pyrotinib vs pertuzumab therapy for HER2-positive early breast cancer: The HELEN HER-013 randomized clinical trial. First Author: Jiujun Zhu, Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Background: Docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) is a standard neoadjuvant regimen for stage II–III human epidermal growth factor receptor 2 (HER2)–positive breast cancer; however, its use is associated with substantial treatment burden, particularly hematologic toxicity, highlighting the need for alternative strategies that maintain efficacy with different toxicity profiles.This study to determine whether a chemotherapy-de-escalated regimen of nanoparticle albumin–bound paclitaxel, trastuzumab, and the tyrosine kinase inhibitor pyrotinib (nab-PHPy) is noninferior to standard TCHP with respect to pathological complete response (pCR). **Methods:** The HELEN HER-013 trial was a multicenter, randomized, open-label, phase 3 noninferiority trial conducted at 15 centers in China. Women with previously untreated, operable stage II–III HER2-positive breast cancer were enrolled between May 2023 and May 2025.Participants were randomly assigned (1:1) to receive six 21-day cycles of either nab-paclitaxel, trastuzumab, and oral pyrotinib (nab-PHPy group) or TCHP group.The primary end point was pCR (ypT0/Tis ypN0), assessed in the modified intention-to-treat (mITT) population (patients who received $\geq$1 dose of study treatment). The prespecified noninferiority margin was $-$5.5%(ClinicalTrials.gov Identifier: NCT05918328). **Results:** Among 709 screened individuals, 610 were randomized, and 589 were included in the mITT population (295 in the nab-PHPy group and 294 in the TCHP group; all female). Median age was 51 years (interquartile range [IQR], 43–56) in the nab-PHPy group and 52 years (IQR, 45–57) in the TCHP group. The primary end point of pCR was achieved in 186 patients (63.1%; 95% CI, 57.4%–68.4%) in the nab-PHPy group and 174 patients (59.2%; 95% CI, 53.4%–64.8%) in the TCHP group. The between-group difference was 3.9% (95% CI, -4.2% to 11.9%), which met the prespecified criterion for noninferiority (noninferiority P = .01). Grade 3 or higher treatment-emergent adverse events occurred in 113 patients (38.3%) receiving nab-PHPy and 107 patients (36.4%) receiving TCHP. The most common grade 3 or higher adverse events were diarrhea (31.5% vs 17.0%), anemia (1.7% vs 10.2%), and nausea (0% vs 5.8%). No treatment-related deaths were reported. **Conclusions:** Among women with operable stage II–III HER2-positive breast cancer, neoadjuvant treatment with nab-PHPy was noninferior to TCHP with respect to pCR and was associated with a distinct toxicity profile, supporting its role as an alternative neoadjuvant strategy. Clinical trial information: NCT05918328. Research Sponsor: None.

LBA510 **Rapid Oral Abstract Session**

Primary results of the BETTER-CARE trial: Implementation of a needs-adapted and individualized follow-up care after primary breast cancer. First Author: Achim Woeckel, University Hospital Würzburg, Department of Obstetrics and Gynecology, Würzburg, Germany

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

511 **Rapid Oral Abstract Session**

The effects of Mediterranean diet, physical activity, and vitamin D on breast cancer recurrence and cardiometabolic health: A multicenter randomized trial. First Author: Livia Augustin, Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Napoli, Italy

Background: Low quality diets and physical inactivity are two modifiable lifestyle factors that together with vitamin D deficiency have been associated with unfavorable breast cancer (BC) outcomes and cardiometabolic health. We therefore tested the effect of a lifestyle program on BC recurrence and cardiometabolic risk factors on a background of vitamin D sufficiency. **Methods:** Women aged 30-74 years were enrolled in a phase III trial (NCT02786875) within 12 months of their primary BC diagnosis (stages I-III) in 7 oncologic centres in Italy. Consenting participants were randomized to one of two lifestyle treatments lasting 33 months: 1) positive control (n = 249), standard advice on a Mediterranean diet (MedDiet) and avoidance of sedentary behavior; 2) intervention (n = 243), high intensity advice on low-glycemic index MedDiet and 30-minute additional daily brisk walking. Oral vitamin D3 was administered throughout. Data were collected quarterly on health status, anthropometry, 7-day food records, daily steps, serum 25(OH)D concentrations and metabolic syndrome parameters. The primary outcome was BC recurrence (intention to treat analysis) at 33 months, with cardiometabolic risk factors as secondary outcomes. Hazard ratios (HR) and 95% confidence intervals (CI) for BC recurrence were computed using Cox proportional hazards models adjusted for recruitment center. One-year changes in treatment variables and cardiometabolic risk factors were tested by paired Student's t-test within each treatment arm and by analysis of covariance between treatment arms, adjusted for baseline values. **Results:** Approximately 58% of patients were aged $\geq$50 years, 94% were postmenopausal, 86% had stages I-IIB and 75% hormone-positive BC. A total of 37 recurrences were observed with no differences between arms (HR = 0.94, 95%CI: 0.49-1.79). Independently of randomization arm, women with hormone-positive BC who were more adherent to the intervention program (41%), showed 76% lower risk of BC recurrence (HR = 0.24, 95% CI: 0.06-0.95). Weight loss of 3 kg, representing a 4.2% drop of initial body weight, was significantly greater in the test arm compared to 1.7 kg or 2.4% in the control arm (p = 0.0034). This translated in reductions of body mass index from 27.5$\pm$5.7 to 26.3$\pm$5.4 kg/m^2 in the intervention arm and from 27.2$\pm$5.1 to 26.6$\pm$5.1 kg/m^2 in controls (p = 0.0032). The presence of metabolic syndrome dropped by 65% in the intervention arm and 34% in controls (p = 0.008). The probability of metabolic syndrome remission was 2.5-fold higher in the intervention arm. **Conclusions:** A safe and low-cost lifestyle program with low-glycemic index MedDiet, daily brisk walking and oral vitamin D supplementation resulted in weight loss, reduced metabolic syndrome prevalence and was significantly associated with lower recurrences in women with hormone-positive BC. Clinical trial information: NCT02786875. Research Sponsor: None.

512 **Rapid Oral Abstract Session**

Effect of elinzanetant on sleep disturbance and aspects of quality of life in women with breast cancer experiencing vasomotor symptoms: OASIS-4 subgroup analysis by type of endocrine therapy. First Author: Claudio Soares, Queen's University, Kingston, ON, Canada

Background: In the Phase III OASIS-4 trial, elinzanetant (EZN), a dual neurokinin (NK)-targeted therapy (NK-1 and NK-3 receptor antagonist), significantly improved vasomotor symptoms (VMS), sleep disturbance and menopause-related quality of life (QoL) in women taking endocrine therapy (ET) for breast cancer. This post hoc analysis evaluated the effect of EZN on sleep disturbance and menopause-related QoL by ET type. **Methods:** Women aged 18–70 years with ≥35 moderate-to-severe ET-associated VMS/week were randomized 2:1 to EZN 120 mg daily for 52 weeks or placebo (PBO) for 12 weeks then EZN 120 mg for 40 weeks. Mean change from baseline (BL) to week 12 in Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) 8b total T-score (range 28.9–76.5; < 55 normal, 55– < 60 mild, 60– < 70 moderate, ≥70 severe) and Menopause-specific QoL questionnaire (MENQOL) total/domain scores (range 1–8; higher score indicates greater bother) were analyzed descriptively by ET type (tamoxifen [TAM], aromatase inhibitor [AI], ovarian function suppression [OFS], no OFS). **Results:** Mean BL PROMIS SD SF 8b total T-scores and MENQOL total scores were numerically similar across ET subgroups (Table), with some variability in MENQOL domain scores (ranges: vasomotor 6.6–6.9; psychosocial 3.3–4.2; physical 4.1–4.6; sexual 3.7–5.5). Greater numerical reductions with EZN vs PBO from BL to week 12 were observed across all subgroups for PROMIS SD SF 8b total T-score and MENQOL total score (Table), as well as MENQOL domain scores (ranges: vasomotor -2.6 to -2.9 vs -1.2 to -1.5; psychosocial -0.8 to -1.0 vs -0.4 to -0.6; physical -0.7 to -0.9 vs -0.3; sexual -0.5 to -0.9 vs -0.3 to 0.0). **Conclusions:** In this post hoc analysis, EZN consistently improved sleep disturbance and menopause-related QoL, including vasomotor, psychosocial, physical and sexual aspects, across all ET subgroups. Taken with previous data, findings suggest to support the efficacy of EZN in reducing VMS, sleep disturbance and improving menopause-related QoL independently of ET type. Research Sponsor: Bayer.

	TAM		AI		OFS		No OFS	
	EZN (n=175)	PBO (n=90)	EZN (n=141)	PBO (n=68)	EZN (n=88)	PBO (n=48)	EZN (n=228)	PBO (n=110)
PROMIS SD SF 8b total T-score, mean (95% CI)								
BL	61.0 (60.1, 61.9)	60.5 (59.0, 62.0)	60.1 (59.0, 61.2)	61.1 (59.5, 62.7)	60.4 (59.0, 61.7)	61.6 (59.5, 63.7)	60.7 (59.9, 61.5)	60.4 (59.1, 61.7)
Change from BL to Week 12	-11.0 (-12.3, -9.7)	-4.3 (-5.9, -2.6)	-10.0 (-11.4, -8.7)	-3.8 (-5.5, -2.0)	-10.4 (-12.1, -8.7)	-6.5 (-8.7, -4.2)	-10.6 (-11.8, -9.5)	-3.1 (-4.5, -1.7)
MENQOL total score, mean (95% CI)								
BL	4.7 (4.5, 4.9)	4.5 (4.2, 4.7)	5.0 (4.8, 5.2)	5.2 (4.9, 5.5)	4.9 (4.6, 5.1)	4.9 (4.5, 5.3)	4.8 (4.7, 5.0)	4.7 (4.5, 5.0)
Change from BL to Week 12	-1.4 (-1.6, -1,2)	-0.5 (-0.7, -0.3)	-1.2 (-1.4, -1.0)	-0.6 (-1.0, -0.3)	-1.2 (-1.5, -1.0)	-0.6 (-1.0, -0.3)	-1.3 (-1.5, -1.2)	-0.5 (-0.7, -0.3)

513 **Rapid Oral Abstract Session**

Does resection of cavity shave margins impact survival in breast cancer patients? First Author: Anees B. Chagpar, Yale School of Medicine, New Haven, CT

Background: Randomized controlled trials have shown that resection of cavity shave margins (CSM) halves the margin positivity and re-excision rate in breast cancer (bc) patients (pts), but the impact on overall (OS) and disease-free survival (DFS) remains unclear. **Methods:** Between Oct 21, 2011 and Nov 25, 2013, the SHAVE trial enrolled 235 pts in a single center study. Between Jul 28, 2016 and Apr 13, 2018, SHAVE2 enrolled 396 pts across 9 other US sites. Both studies were similar in their study criteria and methods. Pts ≥ 18 years of age, with planned partial mastectomy (PM) for stage 0-3 bc were eligible. Surgeons performed their standard PM with excision of selective margins as needed based on gross evaluation and specimen radiograph. Pts were then randomized intraoperatively to either "shave" or "no shave" arms. In the former, surgeons were instructed to take additional CSM from ≥4 faces of the cavity; in the latter, to close. Pts were followed for a median of 60.4 months (mo). **Results:** Across both studies (n = 631), the median pt age was 64 (range; 29-94), and the median invasive tumor size was 1 cm (range; 0-8 cm). Forty pts had no further disease at the time of PM either due to all disease being removed in the core biopsy or due to neoadjuvant chemotherapy. Before randomization, margin positivity was similar between the "shave" and "no shave" arms (37.8% vs. 34.8%, p = 0.457). After randomization, the "shave" group had a significantly lower positive margin rate (14.0% vs. 34.8%, p < 0.001) and re-excision rate (9.2% vs. 24.1%, p < 0.001). In the "shave" arm, 13.3% of those with negative margins prior to randomization had cancer found in the CSM. Pts in the "shave" arm were less likely to have positive final margins (after re-excision where performed; 6.3% vs. 15.8%, p < 0.001). Both groups had similar rates of radiation therapy (XRT) (82.8% vs. 81.8%, p = 0.831). Local recurrence rates were nearly identical at a median follow-up of 60.4 mo (1.3% vs. 1.6%, p = 1.000). 5-year DFS (91.9% vs. 92.6%, p = 0.820) and OS were not significantly different between groups (93.5% vs. 93.5%, p = 0.841). On Cox proportional hazard modelling, including randomization arm, final margin (after re-excision), and use of XRT, only the use of XRT significantly improved DFS (5 yr DFS 86.3% vs. 94.4%, HR: 0.47; 95% CI: 0.256-0.865, p = 0.015). **Conclusions:** While CSM reduced margin positivity and re-excision rates, it does not have an impact on DFS or OS at a median of 60.4 mo of surveillance; only the use of XRT significantly improved DFS. Although resection of CSM removed additional disease in 13.3% of margin-negative pts and was associated with a lower final positive margin rate, this did not translate into lower local recurrence rates. These results suggest that XRT may effectively manage small-volume residual disease that remains after PM. Clinical trial information: NCT01452399; NCT02772731. Research Sponsor: Yale Cancer Center; David and Katie Burke Fund for Breast Cancer Research; Connecticut Breast Health Initiative; Troy Cancer Program; Cleveland Clinic Akron General Operations; Cleveland Clinic Akron General Foundation; Lineberger Comprehensive Cancer Center; Watson Clinic Center for Research Inc; LifeCycle.

LBA514 **Rapid Oral Abstract Session**

Neoadjuvant rilvegostomig (R) + trastuzumab deruxtecan (T-DXd) in high-risk HER2-negative breast cancer: Results from the I-SPY 2.2 trial. First Author: Ciara Catherine O'Sullivan, Mayo Clinic Rochester, Rochester, MN

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA515 **Rapid Oral Abstract Session**

Role of neoadjuvant versus adjuvant chemotherapy, dose density, and treatment schedule in biologically high-risk HR+/HER2- breast cancer: A pooled analysis of the WSG ADAPT-HR+/HER2- and PlanB trials. First Author: Oleg Gluz, West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and University Hospital Cologne, Cologne, Germany

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

516 Rapid Oral Abstract Session

Secondary safety analysis of trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in DESTINY-Breast05: Clinical and demographic risk factors of interstitial lung disease (ILD) and radiation pneumonitis (RP). First Author: Michael Untch, Breast Cancer Center, HELIOS Klinikum Berlin-Buch GmbH, Berlin, Germany

Background: In DESTINY-Breast05 (NCT04622319), T-DXd showed superior efficacy vs T-DM1 in patients (pts) with human epidermal growth factor receptor 2-postive (HER2+) early breast cancer (eBC) with residual invasive disease after neoadjuvant therapy (NAT) and high risk of recurrence—a population in which radiotherapy (RT) is broadly used. Safety was consistent with the established T-DXd profile; ILD remained an important risk, although most cases were low grade. Previous T-DXd pooled analyses suggested potential associations between ILD and clinical and demographic factors. We report additional safety outcomes stratified by these risk factors. **Methods:** Pts with residual invasive HER2+ eBC and at high risk of recurrence after NAT were randomized 1:1 to receive T-DXd 5.4 mg/kg (n = 818) or T-DM1 3.6 mg/kg (n = 817) once every 3 weeks for 14 cycles. All pts underwent low-dose non-contrast chest computed tomography (CT) at screening. Pts who received adjuvant RT (aRT; either concurrently with or sequentially before study therapy) underwent additional low-dose CT during and after treatment completion. CT scans showing ILD or RP underwent blinded central adjudication. **Results:** At data cutoff (July 2, 2025), 806 pts in the T-DXd arm and 801 pts in the T-DM1 arm received ≥1 dose of treatment; no pts were ongoing study treatment. In the T-DXd arm, 93.9% of pts received aRT vs 93.6% in the T-DM1 arm. Adjudicated drug-related (adj DR) ILD rates were generally consistent across global regions (Asia, Europe, North America [NA] + Australia, and Rest of World), though numerically lower in NA + Australia for T-DXd. In both arms, adj DR ILD rates were higher in pts from Japan (n = 147) vs outside Japan (n = 1460; T-DXd: 14.9% vs 8.9%; T-DM1: 6.7% vs 1.2%), Japan vs other Asian countries (T-DXd: 14.9% vs 9.6%; T-DM1: 6.7% vs 2.1%), and in pts with baseline moderate vs normal renal impairment (T-DXd: 14.3% vs 9.7%; T-DM1: 5.0% vs 1.0%). Adj DR ILD incidence was comparable across racial subgroups. In both arms, investigator-reported RP rates were higher in pts from Japan vs outside Japan (T-DXd: 47.1% vs 27.4%; T-DM1: 45.0% vs 27.3%). Most ILD/RP events recovered or were recovering with protocol-specific management. Recovery/resolution was observed in 64.5% vs 75.0% of adj DR ILD events and 38.2% vs 43.2% of RP events in the T-DXd and T-DM1 arms, respectively. **Conclusions:** Adj DR ILD and RP events were mostly low grade and reversible with protocol-specific management guidelines. Adj DR ILD rates were higher with T-DXd than T-DM1 and were influenced by country and baseline renal function, consistent with prior pooled analysis. These findings are consistent with, and further characterize, the safety profile of T-DXd in post-NAT HER2+ eBC. Clinical trial information: NCT04622319. Research Sponsor: This study is sponsored by Daiichi Sankyo, Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

517 Poster Session

International variation in diagnostic and treatment practices in patients with HER2+ EBC: The RWE PEARL-HER2 study. First Author: Soraia Lobo-Martins, Academic Trials Promoting Team (ATPT), Université Libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Brussels, Belgium

Background: Pts with HER2+ EBC achieving pCR post neoadjuvant chemotherapy (NACT) with trastuzumab (H) and pertuzumab (P) show favorable outcomes. Yet, management varies widely within healthcare systems, including access to continuation of adjuvant (adj) P. We compared diagnostic and treatment practices across countries. **Methods:** PEARL-HER2 is an international retrospective real-world cohort including pts with HER2+ EBC achieving pCR (ypT0/isN0) after NACT-HP (Jan 2014 to Dec 2023). This descriptive preliminary analysis (data cut-off Jan-2026) summarizes diagnostic and treatment data stratified by country. **Results:** 1345 pts with pCR were included. Significant heterogeneity in pts and disease characteristics was observed (Table 1). Diagnostic methods also varied: use of breast MRI ranged from 11-97% across countries (>85% in Spain/Portugal; Peru, 11%), while FDG-PET/CT ranged from 0-72% (overall 20%; Turkey, 72%; p<0.001). Anthracycline-based NACT varied from <20% in Argentina and Brazil to >85% in Portugal and Turkey (p<0.001). Adj P was administered to 33% of pts overall (0-97%; p<0.001), with high use in countries with public reimbursement and minimal in those without. Among ER+ pts, ET use was uniformly high (98%; p=0.590), but regimen selection varied substantially (p<0.001): tamoxifen (42%) and aromatase inhibitor (58%). Events occurred in 6% of pts (invasive/non-invasive relapses and death); median FU was 40 months (IQR 24–62). **Conclusions:** This analysis indicates marked cross-country variability in management of HER2+ EBC. Use of adj P closely aligned with national reimbursement policies, highlighting access as a major determinant of care beyond clinical risk and guideline recommendations. Research Sponsor: Association Jules Bordet.

Characteristics	Argentina (N=155)	Belgium (N=217)	Brazil (N=107)	Italy (N=52)	Peru (N=18)	Portugal (N=603)	Spain (N=110)	Turkey (N=83)	Total (N=1345)	P-value
Age, median (IQR)	47 (41–56)	54 (45–63)	46 (40–52)	53 (45–61)	45 (41–56)	52 (45–62)	53 (44–59)	51 (45–61)	51 (43–61)	<0.001
Pre-/perimenop., n (%)	96 (62)	91 (43)	72 (72)	26 (50)	13 (72)	286 (48)	52 (48)	38 (46)	674 (51)	<0.001
NST histology, n (%)	145 (95)	197 (91)	89 (83)	48 (94)	18 (100)	558 (93)	103 (95)	83 (100)	1241 (93)	<0.001
ER−, n (%)	77 (50)	95 (44)	61 (58)	16 (31)	5 (28)	277 (46)	57 (52)	44 (53)	632 (47)	<0.001
cN0, n (%)	58 (37)	28 (13)	43 (40)	24 (46)	2 (11)	267 (44)	50 (46)	21 (25)	493 (37)	<0.001
Breast MRI | PET-CT, n (%)	123 (80) | 14 (9)	126 (58) | 63 (29)	73 (71) | 27 (26)	13 (25) | 13 (25)	2 (11) | 0 (0)	521 (86) | 70 (12)	102 (97) | 21 (19)	35 (42) | 60 (72)	995 (75) | 268 (20)	<0.001 | <0.001
Anthracycline-based NACT, n (%)	19 (12)	137 (63)	19 (18)	44 (85)	2 (11)	532 (88)	84 (76)	79 (95)	916 (68)	<0.001
ET use in ER+, n (%)	79 (98)	112 (95)	46 (98)	35 (97)	13 (100)	339 (98)	58 (100)	43 (98)	725 (98)	0.590
Adj P, n (%)	89 (57)	210 (97)	63 (59)	20 (39)	0 (0)	49 (8)	9 (8)	0 (0)	440 (33)	<0.001
Public adj P reimbursement	Yes, high risk	Yes, N+ only	No	Yes, since 2023	No	No	No	No	–	–

Percentages exclude missing data.

518 Poster Session

Neoadjuvant atirmociclib plus letrozole versus letrozole alone in HR+/HER2− breast cancer: Results from FourLight-2, a randomized phase 2 window of opportunity study. First Author: Shom Goel, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: In the neoadjuvant setting, endocrine therapy is a standard of care option in patients (pts) with HR+ breast cancer (BC). Atirmociclib (ATI, PF-07220060) is a potent and selective CDK4 inhibitor and has shown favorable tolerability and promising early activity as a first-line treatment in pts with HR+/HER2− metastatic BC. CDK4 selectivity is hypothesized to limit hematologic and gastrointestinal toxicities that may be dose-limiting; therefore, ATI may improve efficacy and tolerability. Ki-67 is a biomarker used to assess the antiproliferative activity of therapies. Complete cell cycle arrest (CCCA, defined as Ki-67-positive tumor cells ≤2.7%) in the neoadjuvant setting is correlated with less BC tumor recurrence. This phase 2 randomized global study evaluated the effects of ATI + letrozole (LET) and LET alone on Ki-67 expression in HR+/HER2− BC tumors after 14 days of treatment in the neoadjuvant setting (FourLight-2; NCT06465368). **Methods:** Postmenopausal women with HR+/HER2− BC and Ki-67 score of ≥10% per local assessment, primary tumor ≥1.5 cm, no prior systemic therapy for BC, and ECOG PS ≤1 were enrolled. Eligible pts were randomly assigned to ATI (300 mg, orally BID) + LET (2.5 mg, orally QD) or LET alone (2.5 mg, orally QD), for 14 days. Baseline breast lesion biopsy and on-treatment biopsy on day 14 were obtained. The primary endpoint was centrally-assessed CCCA rate at day 14; secondary endpoints included Ki-67 expression change, safety, ctDNA assessments, and PK. **Results:** 121 pts were randomized to ATI + LET (n = 59) or LET alone (n = 62) arms; median age was 66 y and 63 y; 90% and 92% had Stage I/II disease, respectively. In Ki-67 evaluable pts (n = 51 and n = 56), 77% and 70% had Ki-67 ≥20% at baseline (centrally assessed) and 71% and 80% had grade 1/2 tumor, respectively. At day 14, the proportion of pts who achieved CCCA was 88.2% (95% CI, 76.6–94.5) for ATI + LET and 17.9% (95% CI, 10.0–29.8) for LET alone, with median relative change of Ki-67 from baseline of -97.3% (range -99.8%, 34.0%) and -72.4% (range -98.3%, 139.9%) in each arm, respectively. CCCA was achieved at a higher rate with ATI + LET than LET alone across baseline subgroups (Table). The most common TEAEs with ATI + LET and LET alone, respectively, were diarrhea (19% and 2%), fatigue (15% and 10%), and nausea (14% and 5%) (all grade 1/2); no grade 3/4 treatment-related TEAEs or treatment discontinuations due to TEAEs were reported. **Conclusions:** ATI + LET demonstrated substantially greater antiproliferative effects than LET alone, with a tolerable safety profile in pts with HR+/HER2− BC, suggesting that ATI + LET may have value in early BC. Clinical trial information: NCT06465368. Research Sponsor: Pfizer Inc.

Subgroup Analysis with CCCA, n (%)	ATI + LET n = 51	LET alone n = 56
Tumor grade		
1/2	32 (89)	9 (20)
3/X	13 (87)	1 (9)
Primary tumor stage		
T1c	12 (80)	2 (11)
T2	28 (93)	7 (22)
T3/T4	5 (83)	1 (20)
Baseline Ki-67 (central assessment)		
<20%	9 (90)	4 (27)
≥20%	35 (90)	6 (15)

519 Poster Session

Overall survival (OS) in premenopausal ER+/PR+, HER2− breast cancer (BC) treated with endocrine therapy (ET) ± chemotherapy (CT): A National Cancer Database (NCDB) analysis. First Author: Lan Lei, Winship Cancer Institute of Emory University, Atlanta, GA

Background: The comparative benefit of ET alone vs ET+CT in premenopausal women with stage I-III ER+/PR+, HER2- BC remains uncertain. Although Oncotype DX recurrence score (RS) guides CT use, management of premenopausal patients (pts) with low/intermediate RS remains challenging. The ongoing NRG-BR009 trial aims to clarify the relative benefit of CT but has faced accrual issues. To address this question, we evaluated OS difference by treatment among pts with N0 (n=0)/intermediate RS and N1 (n=1-3)/low-intermediate RS disease. **Methods:** NCDB data were analyzed for women <50 yrs with ER+/PR+, HER2−, stage I-III BC (2005-2022). Variables included tumor size, grade, nodal status (N0/N1), stage, lymphovascular invasion, Ki67, Charlson-Deyo comorbidity score (CCS), RS category (low=0-17, intermediate=18-30) and treatments (ET, CT, surgery, radiation [RT]). OS was compared between ET+CT vs ET only groups using the log-rank test. Multivariable Cox models (MVA) were conducted to identify predictors of OS. **Results:** Median age was 45 yrs (18-49) among 15591 enrolled pts. In N0/intermediate RS group, 3710 (42.5%) received ET+CT and 5022 (57.5%) received ET alone; 5-yr OS was 98.9% with ET+CT vs 98.7% with ET (p=0.40). In N1/low RS group, 1151 (26.2%) received ET+ CT and 3242 (73.8%) received only ET; 5-yr OS was 98.5% with ET+CT vs 98.6% with ET (p=0.85). In N1/intermediate RS, 1718 (69.7%) received ET+CT and 748 (30.3%) received only ET; 5-yr OS was 96.2% with ET+CT vs 95.0% with ET (p=0.28). On univariable analysis, ET+CT did not improve OS in the N0/intermediate RS, N1/low RS, or N1/intermediate RS groups (all p>0.05). MVA further confirmed ET+CT had no OS benefit compared to ET alone in all groups (all p>0.05, Table 1). Among N0/intermediate RS pts, grade 3 disease was associated with worse OS (p<0.05). In N1/low RS subjects, CCS=2 predicted worse OS (p<0.05). In N1/intermediate RS pts, stage III disease and lack of RT predicted worse OS (p<0.05). **Conclusions:** In premenopausal women with early-stage ER+/PR+, HER2- BC, ET+CT yielded similar OS to ET alone in low/intermediate RS pts. Limitations include inability to assess ovarian function suppression and invasive disease-free survival. Larger studies are needed to validate the above findings and to investigate whether CT could be safely omitted in low-intermediate risk pts. Research Sponsor: None.

MVA for OS by RS and nodal status (HR, 95%CI).

	N0, intermediate RS	N1, low RS	N1, intermediate RS
CCS (2 vs 0)	3.87 (0.52-29.00)	**23.62 (4.63-120.46)**	4.01 (0.43-37.77)
Grade (3 vs 1)	**7.39 (1.45-37.62)**	2.26 (0.26-19.57)	1.64 (0.26-10.35)
Stage (III vs I)	1.02 (0.21-4.99)	n/a	**11.77 (1.90-73.04)**
ET+CT vs ET	0.73 (0.33-1.62)	0.80 (0.25-2.51)	0.44 (0.14-1.35)
RT (yes vs no)	1.02 (0.48-2.19)	2.89 (0.65-12.82)	**0.22 (0.08-0.66)**

520 Poster Session

Socioeconomic and racial disparities in receipt of treatment among early-stage ER+/PR+ HER2- breast cancer: Insights from invasive breast cancer OncoDX recurrence score database. First Author: Lan Lei, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Oncotype DX Recurrence Score (RS) predicts recurrence risk and potential benefit from chemotherapy (CT) in early-stage ER+ and HER2- breast cancer (BC). However, real-world CT decision patterns remain poorly understood. This work evaluated how socioeconomic, racial and clinical factors influence CT decisions beyond RS-guided recommendations. **Methods:** We analyzed patients with early-stage ER+/PR+, HER2- BC in SEER OncoDX RS Database (2004-2019). Variables included age, rurality, poverty status, socioeconomic status (SES), RS, histology, tumor grade, nodal status, PR status, and CT receipt. Treatment disparities among patients with similar RS were evaluated using chi-square tests. Multivariable logistic regression model (MVA) identified independent predictors of CT utilization among patients with similar RS. **Results:** A total of 208,674 patients were included (median age 60). Median follow up was 4.9 years. Among postmenopausal (post-M, ≥50yrs) women with RS≥26 (CT indicated), lowest SES (60.6% vs 66.5% [highest], P<0.001) and Hispanic ethnicity (63.2% vs 63.3% [White], P=0.016) were associated with lower rate of CT. When CT was not indicated in post-M women (RS<26), Black patients were more likely to receive treatment (9.0% vs 7.9% [White], P<0.001). Among premenopausal (pre-M, <50yrs) women with N0 disease and RS>15, highest SES (41.0% vs 44.2% [lowest], P=0.032) and White race (41.2% vs 46.8 [Black], P<0.001) received less CT. Among pre-M women with N1-3 disease, rural residence (42.9% vs 47.1 [urban], P = 0.004) and White race (44.6% vs 50.1% [Black], P = 0.042) were associated with less CT. MVA showed that invasive ductal carcinoma, grade III tumor, PR-negative status and Black race increased the likelihood of CT irrespective of RS (Table 1). **Conclusions:** CT decisions were frequently influenced by socioeconomic, racial and clinicopathological factors beyond genomic guided recommendations. Our data highlights a gap between clinical guidelines and real-world practice. Future research should focus on understanding the underlying reasons for deviations in treatment selection and examining changes in practice patterns in the post-RxPONDER era. Research Sponsor: None.

MVA for CT decision by RS (OR, 95%CI).

	Pre-M, N0, ≤15	Pre-M, N0, >15	Pre-M, N1-3	Post-M, <26	Post-M, ≥26
SES (highest vs lowest)	-	0.88 (0.78-0.99)	-	-	1.34 (1.22-1.49)
Race (B vs W)	-	-	-	1.10 (1.01-1.19)	1.14 (1.03-1.26)
Histology (IDC vs ILC)	-	1.22 (1.11-1.33)	1.16 (1.01-1.32)	0.84 (0.80-0.88)	1.19 (1.09-1.28)
Grade (III vs I)	4.89 (3.72-6.42)	7.13 (6.42-7.93)	5.91 (4.96-7.04)	4.07 (3.80-4.36)	2.44 (2.21-2.71)
PR (pos vs neg)	-	0.49 (0.43-0.56)	0.44 (0.32-0.60)	0.53 (0.50-0.57)	0.82 (0.77-0.87)

Not statistically significant.

521 Poster Session

Associations between self-efficacy and symptom burden in young women with breast cancer initiating endocrine therapy (ET) on SWOG S2010. First Author: Norah Lynn Henry, University of Michigan Rogel Cancer Center, Ann Arbor, MI

Background: Self-efficacy (SE) is the belief in one's ability to succeed in specific situations or accomplish a task, influencing motivation, behavior, and resilience. Both symptom (sx) burden at the time of ET initiation and lower SE for sx management are associated with ET nonadherence. The SWOG S2010 clinical trial enrolled premenopausal women starting adjuvant ovarian function suppression (OFS) plus ET for breast cancer. We examined associations between sx burden and self-efficacy at the time of ET initiation. **Methods:** All participants completed the FACT GP5 question evaluating bother from side effects of treatment, individual symptom PROMIS measures, and the PROMIS SE for managing sx and for managing medication (meds)/treatment (tx). GP5 is measured on a 5 point scale ranging from "Not at all" to "Very much." T scores were calculated for PROMIS measures (Table), with a mean score of 50 and higher scores reflecting more of the item being assessed. We evaluated associations between baseline sx and SE using logistic regression. **Results:** Of 528 participants with data, mean age was 44.1 years (SD 5.8), 23.5% were Hispanic, 5.5% Black, 6.4% Asian, and 77.7% White. The majority (69.9%) had received chemotherapy. On the FACT GP5 (n=503), only 31.6% reported no treatment side effect burden. Patients reporting a higher side effect burden from tx immediately prior to ET initiation had lower SE for sx (odds ratio (OR) 0.93 (95% CI 0.91-0.96, p<.0001)) and lower SE for meds & tx (OR 0.97 (95% CI 0.95-1.00, p=.04). Increased baseline sx and worse physical function were also statistically significantly associated with worse SE for managing both sx and meds & tx (Table). For example, patients with greater than average fatigue had lower SE for sx (OR 0.32 (95% CI 0.23-0.46, p<.001)). **Conclusions:** Symptom burden at the time of ET initiation is high for premenopausal women starting OFS plus ET, which may partially explain high rates of early ET discontinuation in this patient population. Lower SE was strongly associated with worse individual symptoms. Interventions to improve SE for sx and med management starting at or before ET initiation may improve ET adherence, which could thereby improve disease outcomes and quality of life for young women with breast cancer. Funding: NIH/NCI/NCORP grant UG1CA189974. Clinical trial information: NCT05568472. Research Sponsor: National Cancer Institute; UG1CA189974; National Cancer Institute; R01CA266012.

Associations between self-efficacy and symptoms.

PROMIS domain		PROMIS <50	Self ≥50	Efficacy Sx OR (CI)	P value (Chi square)	PROMIS <50	Self ≥50	Efficacy Meds OR (CI)	& Tx P value (Chi square)
Fatigue	<50	97	144	0.32 (0.23,0.46)	<.001	82	158	0.52 (0.36,0.74)	<.001
	≥50	194	93			143	143		
Anxiety/Fear	<50	56	105	0.30 (0.20,0.44)	<.001	42	118	0.36 (0.24,0.54)	<.001
	≥50	235	132			183	183		
Sleep disturbance	<50	85	120	0.40 (0.28,0.58)	<.001	69	135	0.54 (0.38,0.78)	.001
	≥50	206	117			154	166		
Physical function	<50	195	82	3.84 (2.67,5.51)	<.001	146	131	2.40 (1.68,3.42)	<.001
	≥50	96	155			79	170		

CI: Confidence intervals; OR: Odds ratio.

522 Poster Session

Tumor-associated macrophage (TAM) score as an independent predictor of recurrence in residual disease after neoadjuvant chemotherapy and for identification of high-risk patients for adjuvant escalation. First Author: Aruna Korlimarla, Sri Shankara Cancer Foundation, Bangalore, India

Background: Tumor-associated macrophages (TAMs) drive immune evasion and chemotherapy resistance in breast cancer through tumor microenvironment reprogramming. We developed a composite TAM score integrating transcriptional programs with spatial IHC polarization markers to stratify recurrence risk and enrich macrophage-modulating trials, hypothesizing it would improve prognostic accuracy in treatment-naïve disease and predict neoadjuvant chemotherapy (NACT) response. **Methods:** TAM score was derived from scRNA-seq atlases (n=4), filtering survival-associated genes in METABRIC/TCGA (n=2,509), and weighting IHC markers CD163/CD206 normalized to CD68/CSF1R via Cox coefficients. Validation: treatment-naïve invasive carcinomas (n=83; follow-up 57 months; 24 events). Primary endpoint: recurrence-free survival (RFS); multivariable Cox adjusted for age, tumor size, nodal status, grade, subtype, treatment. Predictive utility assessed in matched primary/post-NACT residual tumors (n=45) correlating TAM dynamics with RCB. **Results:** High TAM score (≥median) independently predicted worse RFS (HR 3.8, 95% CI 1.6-9.1, p<0.05) and outperformed CD163/CD68 alone (HR 2.1, p<0.05); 5-year RFS was 68% vs 91% (TAM-high vs TAM-low). Prognostic value persisted in node-negative (HR 4.2, p=0.02) and luminal B (HR 3.5, p=0.01) subsets. In the NACT cohort, baseline TAM score inversely correlated with pCR (12% vs 38%, p=0.04). Among residual disease (RCB-II/III, n=34), persistent TAM-high post-NACT identified 3-year RFS 52% vs 85% in TAM-low/normalized cases (HR 4.1, p=0.01), independent of RCB; CD163+/CD206+ expansion occurred in 76% of RCB-III vs 29% of RCB-I (p=0.008). **Conclusions:** This TAM score predicts recurrence from pre-treatment tissue and identifies macrophage-driven resistance persisting post-NACT, nominating TAM-high residual disease for macrophage-modulating trials. Translational evidence supports this: CSF1R inhibition reduced immunosuppressive TAMs, increased M1-like programs, decreased PD-L1/PD-L2, and enhanced anti-PD-1 efficacy preclinically with ex vivo confirmation. Early-phase data (rebastinib plus chemotherapy in HER2-negative metastatic disease) demonstrate feasibility, supporting prioritization of TAM-high patients with residual disease for trials combining TAM modulation with checkpoint therapy. Research Sponsor: None.

TAM score performance in treatment-naïve and NACT cohorts.

Endpoint	TAM-High	TAM-Low	HR scores (95% CI)	p-value
Treatment Naïve cohort				
5 year RFS (Overall)	68%	91%	3.8 (1.6-9.1)	<0.05
RFS (node-negative)			4.0	0.02
RFS (luminal B)–			3.5	0.01
CD163/CD68 alone			2.1	<0.05
NACT Cohort (n=45)				
Baseline pCR rate	12%	38%-		0.04
3-year RFS(RCB-II/III n=34)	52%	85%	4.1	0.01
CD163+/CD206+ expansion	76% (RCB-III)	29%(RCB-I)-		0.008

523 Poster Session

Chemotherapy, endocrine therapy, and cognitive impairment in long-term breast cancer survivors. First Author: Armaan Jamal, Department of Public Health Sciences, The University of Chicago, Chicago, IL

Background: Chemotherapy and endocrine therapy have known neurobiological effects, yet evidence on their associations with long-term cognitive impairment remains limited. This study examined the relationship between prior chemotherapy, endocrine therapy, and cognitive impairment among long-term breast cancer survivors. **Methods:** Between July and September 2025, 1,338 participants from the Chicago Multiethnic Epidemiologic Breast Cancer Cohort were surveyed and completed the Functional Assessment of Cancer Therapy-Cognition (FACT-Cog), a validated self-report instrument assessing 4 specific domains: perceived cognitive impairment (PCI; scores 0–72), cognitive-related quality of life (QoL; scores 0–16), perceived cognitive abilities (PCA; scores 0–27), and comments-from-others (scores 0–16). Lower scores reflect worse cognitive function. Cognitive impairment was defined as a PCI score <54. Multivariable logistic regression was used to evaluate associations between chemotherapy and endocrine therapy with cognitive impairment. Multiple linear regression was used to assess associations with continuous FACT-Cog domain scores. All models were adjusted for age, race/ethnicity, radiotherapy, surgery history, and educational attainment. **Results:** The mean age at survey of the 1,338 study participants was 64.3 years (SD 11.7), and the median time from diagnosis to survey was 9.4 years (IQR 6.1–14.1). Overall, 299 (22.3%) met criteria for cognitive impairment. Additionally, 594 (44.4%) and 851 (63.6%) of the participants had prior chemotherapy and endocrine therapy, respectively. In adjusted analyses, chemotherapy (adjusted odds ratio [aOR] 1.39; 95% CI 1.03 to 1.89; p=0.033) and endocrine therapy (aOR 1.86; 95% CI 1.35 to 2.57; p<0.001) were significantly associated with cognitive impairment. Chemotherapy was associated with lower PCI (β −2.11; 95% CI −3.61 to −0.61; p=0.006), and lower QoL (β −0.60; 95% CI −1.01 to −0.19; p=0.04). Endocrine therapy was associated with lower scores in PCI (β −2.52; 95% CI −4.02 to −1.02; p=0.001), QoL (β −0.55; 95% CI −0.96 to −0.14; p=0.009), PCA (β −1.54; 95% CI −2.29 to −0.79; p<0.001), and comments-from-others (β −0.28; 95% CI −0.49 to −0.07; p=0.008). In joint models, those who received both chemotherapy and endocrine therapy (aOR 2.46; 95% CI 1.46 to 4.18; p=0.001) and those who received endocrine therapy alone (aOR 1.71; 95% CI 1.04 to 2.81; p=0.035) had significantly higher odds of cognitive impairment than participants who received neither therapy. **Conclusions:** In this multiethnic cohort of long-term breast cancer survivors, prior chemotherapy and endocrine therapy were independently associated with worse perceived cognitive functioning across multiple domains. These findings underscore the need for future studies to identify neuroprotective strategies and interventions to mitigate treatment-related cognitive sequelae. Research Sponsor: Breast Cancer Research Foundation; BCRF-20-071; National Cancer Institute; P20CA233307; Susan G. Komen; TREND21675016; National Institute on Aging; T32AG000243.

525 **Poster Session**

Adjuvant endocrine therapy omission in ER-positive breast cancer treated with neoadjuvant chemotherapy. First Author: Grace Mei Yee Choong, Mayo Clinic Rochester, Rochester, MN

Background: Adjuvant endocrine therapy (ET) decreases breast cancer (BC) recurrence and improves overall survival (OS) for patients (pts) with estrogen receptor positive (ER+) BC. Omission of adjuvant ET and nonadherence are major issues contributing to worse clinical outcomes. Recent data suggest that the number of pts who omit adjuvant ET may be increasing in Europe [1]. These data have yet to be evaluated in the U.S. We previously reported data from the National Cancer Database (NCDB) that ET omission was more likely in pts with ER+/HER2+ disease who achieved a pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) [2]. Herein we report an updated analysis with a larger cohort designed to examine trends in ET omission over time and the impact on OS in a group of pts at high risk of recurrence. **Methods:** The NCDB was queried from 2010-2022 for pts with stage I-III ER+BC treated with NAC and surgery. pCR was defined as ypT0, ypN0. Use of adjuvant ET and the impact of adjuvant ET omission on OS in pts with and without pCR were assessed separately based on HER2 status. Adjuvant ET initiation by 1 year was summarized using the cumulative incidence estimate to account for the competing risk of death. OS was analyzed with ET as a time-dependent covariate using multivariable Cox proportional hazards regression. **Results:** We identified 130,438 pts with ER+BC (78,778 ER+/HER2-, 51,660 ER+/HER2+) who received NAC. Median follow-up was 5 years. Overall, pCR was achieved in 10.0% of ER+/HER2- and 35.9% of ER+/HER2+. On multivariable analysis, ET omission was significantly associated with worse OS in pts with residual disease (RD) [ER+/HER2- (HR 1.80 $p<0.001$) ER+/HER2+ (HR 1.66 $p<0.001$] and in those with a pCR [ER+/HER2- (HR 1.38 p=0.002) ER+/HER2+ (HR 1.42 $p<0.001$)]. Between 2010-2017, adjuvant ET omission was stable, with approximately 10.0% of pts not having initiated ET by 1 year after surgery. The proportion of pts omitting ET overall increased thereafter to 12.9% in 2018, rising to 24.4% in 2022. A sharp increase in ET omission was observed 2021-2022 in ER+/HER2- BC who achieved pCR, with 42.4% omitting ET compared to 25.1% for 2018-2020 and 18.8% for 2010-2017 ($p<0.001$). Adjuvant ET omission showed more modest but significant increases for other subgroups ($p<0.001$): ER+/HER2- with RD (8.5% 2010-2017, 12.3% 2018-2020, 18.7% 2021-2022), ER+/HER2+ with pCR (15.1% 2010-2017, 14.0% 2018-2020, 24.4% 2021-2022), and ER+/HER2+ with RD (9.5% 2010-2017, 12.5% 2018-2020, 22.2% 2021-2022). **Conclusions:** In ER+BC treated with NAC, omission of ET is increasing over time and associated with a higher risk of death, regardless of HER2, RD, or pCR status. These findings have substantial public health implications as they may result in a reversal of the 4-decade improvements in breast cancer mortality. Additional intervention is critical to improve adherence to guidelines. [1] Verreck et al. Breast 2025 [2] Choong et al. SABCS 2022. Research Sponsor: None.

526 **Poster Session**

Impact of *BRCA* pathogenic variants and novel targeted agents on ovarian reserve measured by anti-Müllerian hormone levels in young women with early breast cancer: A biomarker analysis of the PREFER study. First Author: Luca Arecco, Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Bruxelles, Belgium

Background: The impact of germline *BRCA* (g*BRCA*) pathogenic variants (PVs) and of novel targeted agents (anti-HER2 therapy, CDK4/6 inhibitors, or immunotherapy) on ovarian reserve in young women treated with chemotherapy (CT) for early breast cancer (BC) remains limited. This biomarker analysis of the PREFER study prospectively evaluated ovarian reserve using anti-Müllerian hormone (AMH) according to main patient and treatment characteristics. **Methods:** We included premenopausal women enrolled in the prospective PREFER study (NCT02895165) and candidates to (neo)adjuvant CT at the coordinating centre, the IRCCS San Martino Policlinic Hospital, Genoa, Italy. Serial serum AMH measurements were performed at baseline (prior to any CT initiation), during, and after systemic treatment. Longitudinal changes in centrally measured AMH were analysed using mixed-effects models on log-transformed values. Analyses explored the impact of patient (including age and *gBRCA* status) and treatment (CT alone or with anti-HER2 therapy, CDK4/6 inhibitors, or immunotherapy) characteristics on AMH levels over time. **Results:** Between 2012 and 2025, 309 premenopausal patients were enrolled at the coordinating centre, of whom 194 were included in the present analysis. Median age at diagnosis was 37 (IQR 33-40) years, with 146 patients (75.3%) aged $\leq$40 years and 48 (24.7%) 41-45 years. Overall, 85 patients (43.8%) had hormone receptor-positive/HER2-negative, 62 (32.0%) HER2-positive, and 47 (24.2%) triple-negative BC. In the entire cohort, AMH levels showed a marked decline during CT, followed by partial recovery during follow-up ($p<0.001$), irrespective of patient and treatment characteristics. Younger women showed higher baseline values (2.31 vs 1.11 μg/L for $\leq$40 years and 41-45 years) and greater post-treatment recovery ($p<0.001$). Among patients with known *gBRCA* status (n=147), patients harbouring *gBRCA* PVs (n=29, 19.7%) showed lower baseline levels (1.60 vs 2.18 μg/L for *gBRCA* carriers vs non-carriers) and a lower post-treatment recovery compared to non-carriers (n=118, 80.3%) (p=0.01). Regarding treatment exposure, 106 patients (54.6%) received CT alone, 62 (32.0%) CT plus anti-HER2 agents, 10 (5.2%) CT plus immunotherapy, and 16 (8.2%) CT followed by CDK4/6 inhibitors. No significant differences over time were observed according to treatment exposure (p=0.41); however, numerically lower mean AMH values after end of CT were observed among patients treated with CDK4/6 inhibitors and immunotherapy. **Conclusions:** In this PREFER biomarker analysis, older age and *gBRCA* PVs were associated with reduced ovarian recovery after treatment. Limited sample size precludes definitive conclusions on the gonadal impact of immunotherapy or CDK4/6 inhibitors; further analyses are urgently needed in this field. Research Sponsor: Associazione Italiana Ricerca sul Cancro (AIRC).

527 **Poster Session**

Impact of the Breast Cancer Index on extended endocrine therapy recommendations in patients from the BCI Registry study. First Author: Tara B. Sanft, Yale University, New Haven, CT

Background: The Breast Cancer Index (BCI) test is an established genomic assay that provides individualized risks of overall and late distant recurrence and predicts the benefit from extended endocrine therapy (EET) in patients with early-stage, HR+ breast cancer. Previous findings from the large, prospective BCI Registry have shown that physicians changed their EET recommendation in over 40% of patients following BCI testing. This analysis investigates how physicians integrate prognostic and predictive BCI results in real care settings to decide whether or not to recommend extension of endocrine therapy. **Methods:** The BCI Registry study (NCT04875351) is evaluating the long-term clinical outcome, decision-impact and medication adherence in about 3000 patients. Pre- and post-BCI physician treatment recommendations were compared using McNemar's test. Clinicopathologic features of cases were correlated with BCI (H/I) predictive results and post BCI-EET recommendations using Fisher's exact test. Differences in mean BCI prognostic risk were assessed using analysis of variance (ANOVA). **Results:** Pre- and post-BCI testing physician questionnaires were completed for 2850 patients. The percentage of patients recommended for EET decreased from 54.6% before BCI testing to 41.2% after BCI testing, while those not recommended for EET increased from 44.9% to 58.0% ($p<.0001$). Among patients not recommended for EET pre-BCI, physicians cited low risk of recurrence (47.4%), osteoporosis risk (16.7%), side effects (8.6%), or multiple reasons (24.4%). Among BCI (H/I)-High patients (N=1063), recommendations for EET increased from 60.4% pre-BCI to 90.6% post-BCI, while EET non-recommendations decreased from 39.1% to 8.0%. Conversely, in BCI (H/I)-Low patients (N=1787), EET recommendations decreased from 51.1% to 11.8% and EET non-recommendations increased from 48.3% to 87.8%. Post-BCI, BCI (H/I)-High patients who were not recommended EET (8.0%) had more favorable clinicopathological features, including more T1 tumors (83.5% vs. 68.1%, p=.009), more G1 tumors (44.7% vs. 14.4%, $p<.0001$) and lower mean BCI prognostic risk compared to those for whom EET was recommended (4.4% vs 9.2%, $p<.0001$). Conversely, BCI (H/I)-Low patients who were recommended EET (11.8%) had a larger proportion of T2/T3 tumors (40.7% vs. 21.7%, $p<.0001$), more G2/G3 tumors (79.2% vs. 62.8%, $p<.0001$), more N+(1-3) cases (43.6% vs. 15.7%, $p<.0001$) and higher mean BCI prognostic risk (8.1% vs 4.7%, $p<.0001$). **Conclusions:** BCI results meaningfully inform physician recommendations for EET. Post-BCI, physician EET recommendations increased to 91% in BCI (H/I)-High patients and decreased to 12% in BCI (H/I)-Low patients, highlighting the important treatment guidance provided by BCI. Integration of both predictive and prognostic BCI results help further personalize patient care. Research Sponsor: None.

529 **Poster Session**

Platinum-based chemotherapy in early-stage, high-risk, triple-negative breast cancer: A systematic review and meta-analysis of randomized trials. First Author: Jesse Lopes da Silva, Division of Clinical Research and Technological Development, Brazilian National Cancer Institute (INCA), Rio De Janeiro, Brazil

Background: The clinical benefit of adding platinum agents to adjuvant chemotherapy for early-stage triple-negative breast cancer (TNBC) remains uncertain. A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to evaluate the impact of carboplatin-based adjuvant chemotherapy on survival outcomes in patients with early-stage, high-risk TNBC. **Methods:** RCTs comparing carboplatin plus standard adjuvant chemotherapy versus chemotherapy alone in early-stage, high-risk TNBC were identified through systematic searches of PubMed, Embase, Cochrane CENTRAL, and major oncology meeting proceedings. The primary endpoint was disease-free survival (DFS). Secondary endpoints included recurrence-free survival (RFS), distant disease–free survival (DDFS), and overall survival (OS). Hazard ratios (HRs) were pooled using random-effects models. Absolute survival differences at fixed timepoints were estimated using reconstructed individual patient–level data derived from published Kaplan–Meier curves. **Results:** Five randomized trials enrolling 3,153 patients were included; 1,576 (49.9%) received carboplatin-based chemotherapy. Median age ranged from 47 to 56 years, and most patients had grade 3 tumors and node-positive disease. Carboplatin-based chemotherapy significantly improved DFS compared with chemotherapy alone (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$). Consistent proportional benefits were observed for RFS (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$), DDFS (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$) and OS (HR 0.66, 95% CI 0.62–0.71; $p < 0.001$), with no substantial between-trial heterogeneity ($I^2 < 25\%$ for all endpoints). Reconstructed survival analyses demonstrated increasing absolute benefit over time. At 3 years, carboplatin-based chemotherapy was associated with absolute improvements of approximately 4–6% in DFS and 3–5% in OS. At 5 years, absolute differences favored carboplatin by approximately 7–9% for DFS, 6–9% for RFS, 6–8% for DDFS, and 6–8% for OS (log-rank $p < 0.001$ for all comparisons). DFS benefit was observed across clinically relevant subgroups, including node-negative (HR 0.69, 95% CI 0.53–0.90) and node-positive disease (HR 0.57, 95% CI 0.37–0.86), as well as among patients with and without germline *BRCA1/2* mutations. Greater proportional benefit was observed in patients with grade III tumors and pT2–T3 disease. **Conclusions:** Across RCTs, the addition of carboplatin to standard adjuvant chemotherapy was associated with significant and durable improvements in DFS and OS in patients with early-stage, high-risk TNBC. Absolute survival gains increased with longer follow-up, supporting the clinical relevance of platinum-based adjuvant strategies in selected high-risk populations. Research Sponsor: None.

530 **Poster Session**

Real-world treatment patterns and adherence to adjuvant abemaciclib among patients with early hormone receptor–positive (HR+) breast cancer (BC). First Author: Inimfon Jackson, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Adjuvant abemaciclib (2 years) is approved in combination with endocrine therapy (ET) for node-positive high-risk early HR+ BC. Although it improves invasive disease-free and overall survival, its long duration and toxicities increase treatment complexity. As adjuvant regimens become more intensive, long-term adherence is critical for real-world effectiveness. However, data outside clinical trials are limited. We examined treatment patterns and factors associated with adherence to abemaciclib in a younger population of patients with early BC. **Methods:** We conducted a retrospective cohort study using the Merative MarketScan Commercial Claims and Encounters database. Patients aged 18-64 years with early BC who received abemaciclib between 2017 and 2024 were identified. Index date was the date of the first abemaciclib claim. We included patients who underwent breast surgery within one year before the index date and had continuous enrollment for 6 months before and one year after index date. We excluded patients with metastatic disease prior to the index date. Medication adherence was assessed using the proportion of days covered (PDC), with adherence defined as PDC $\geq$80%. Multivariable logistic regression was used to examine factors associated with abemaciclib adherence at one and two years. **Results:** Among 640 patients (median age 51 years) treated with adjuvant abemaciclib (median follow up 1.5 years), 55% were adherent to therapy at one year. Adherence declined from 100% in month 1, to 66%, 57%, 55%, and 50% in months 2, 6, 12, and 24 ($p<0.001$). Overall, 84.5% of patients initiated abemaciclib at 150 mg, and 47.2% had no dose adjustments during treatment. On multivariable analysis of one-year adherence, patients prescribed lower abemaciclib doses (50 or 100mg) were less likely to be adherent compared to those prescribed 150 mg (aOR=0.52; 95%CI 0.31–0.90). Adherence to ET was also associated with higher abemaciclib adherence (aOR=3.63; 95%CI 2.55–5.18). Polypharmacy was associated with reduced abemaciclib adherence among patients taking two (aOR=0.56; 95%CI 0.37–0.85) or $\geq$3 drug classes (aOR=0.51; 95%CI 0.34–0.78) compared with 0–1 drug class. Patients with high-deductible health plans (HDHP) had higher odds of adherence compared to those with PPO insurance (aOR=2.10; 95%CI 1.23–3.59). At two years (n=213), younger age and adherence to ET were significantly associated with greater abemaciclib adherence. **Conclusions:** Abemaciclib adherence was low, 55% in year 1, and 50% in year 2. Although lower abemaciclib doses and polypharmacy were associated with lower odds of adherence, ET adherence was associated with higher odds. Adherence in HDHP patients may reflect demographics (White, young, higher income). These findings highlight the need for close patient monitoring and strategies to support long-term adherence to adjuvant treatment. Research Sponsor: Susan G. Komen Foundation; The Breast Cancer Research Foundation; National Cancer Institute.

531 **Poster Session**

Chemotherapy (CT) use by Oncotype DX (O-Dx) recurrence score (RS) in hormone receptor–positive, HER2-negative (HR+/HER2-) invasive lobular carcinoma (ILC): A contemporary National Cancer Database (NCDB) analysis. First Author: Marija Sullivan, Duke University School of Medicine, Durham, NC

Background: ILC has a distinct biology and is considered less chemosensitive than invasive ductal carcinoma (IDC). O-Dx RS can guide adjuvant CT decisions for patients with HR+/HER2- breast cancer (BC); however, pivotal trials largely included patients with IDC. Patients with high RS have been shown to benefit from CT. Whether this genomic risk threshold is applied to patients with ILC in real-world practice is not well understood. We evaluated contemporary CT use by O-Dx RS and its association with overall survival (OS) in patients with ILC. **Methods:** Patients $\geq$18 years with HR+/HER2- ILC diagnosed from 2018-2022 who underwent surgery, had pT1-T3, pN0-N1 disease, and known O-Dx RS were identified in the NCDB. Baseline characteristics were compared by RS groups: 0-10 (low), 11-25 (intermediate), and >25 (high). Multivariable logistic regression models identified factors associated with CT use in the overall cohort and stratified by RS. We evaluated the association between CT use and OS within each RS group, adjusting for covariates using propensity score matching (by year of diagnosis, age, pT, pN). **Results:** A total of 30,393 patients with early-stage HR+/HER2- ILC and O-Dx score were identified. Among them, 21% had low, 72% intermediate, and 7% high RS. Overall, 9.2% received CT, including 2.4% of those with low RS, 5.5% of intermediate RS, and 66% of high RS. CT use did not change over time (p=0.47). On multivariable analysis in all patients, higher RS was the key determinant of CT use (RS 11-25 vs 0-10: aOR=2.98, 95%CI 2.49-3.58; RS >25 vs 0-10: aOR=333.4, 95%CI 266.8-416.7), while older age was associated with lower CT use (aOR=0.91, 95%CI 0.91-0.92). In multivariable models stratified by RS, clinicopathologic features, including younger age, larger tumor size, higher nodal stage, and higher grade, were associated with CT use in low and intermediate RS groups (i.e., pN1 aOR=18.64 for RS 0–10; aOR=7.37 for RS 11–25; both $p<0.001$), whereas in high RS group, age had similar effect; however, tumor size and nodal status had significant but attenuated effects. In propensity-matched cohorts within RS groups, CT use was not associated with different OS in low RS (5-year OS 98% vs 100%, p=0.29) or intermediate RS (5-year OS 97% vs 97%, p=0.68) groups; however, in high RS group, CT use was associated with improved OS (5-year OS 96% vs 90%; p=0.01). **Conclusions:** In clinical practice, CT use in patients with ILC is guided by O-Dx RS but influenced by age and clinicopathologic risk. CT use conferred no OS benefit in patients with low or intermediate RS but was associated with OS benefit in high RS. Despite this, one-third of patients with ILC with high RS did not receive CT. These findings support RS-guided adjuvant CT decision-making in ILC and suggest that increasing CT use in patients with high RS may improve outcomes. Research Sponsor: Susan G. Komen Foundation; SAC150061, SAC220221; The Breast Cancer Research Foundation; BCRF-22-190, BCRF-23-190; The National Cancer Institute at the National Institutes of Health; P30 CA016672.

533 **Poster Session**

Pyrotinib plus nab-paclitaxel as adjuvant therapy for patients with N0/N1mi, HER2-positive early-stage breast cancer: 3-year iDFS results of the phase II PHAEDRA trial. First Author: Changjun Wang, Peking Union Medical College Hospital, Beijing, China

Background: While dual anti-HER2 therapy is standard in the adjuvant setting for HER2-positive early breast cancer, treatment de-escalation is an attractive strategy for patients with low-risk disease. Previous studies (e.g., APT, ATEMPT) of adjuvant trastuzumab plus chemotherapy or T-DM1 monotherapy in this population reported 3-year invasive disease-free survival (iDFS) rates of 93.4%-98.7%. Pyrotinib, an irreversible pan-HER2 tyrosine kinase inhibitor, is effective in HER2-positive breast cancer; however, data supporting its use in the adjuvant setting for low-risk disease are limited. This study evaluated the efficacy and safety of adjuvant pyrotinib plus nab-paclitaxel in this population. **Methods:** This multicenter, single-arm, phase II trial enrolled women aged 18-75 with primary tumor size $\leq$3 cm and node-negative (N0) or micrometastases (N1mi), histologically confirmed HER2-positive early breast cancer. Patients received nab-paclitaxel (260 mg/m² IV, q3w) plus pyrotinib (400 mg PO, qd) for 12 weeks (4 cycles), followed by pyrotinib monotherapy (400 mg, qd) for one year. The primary endpoint was iDFS. Secondary endpoint was adverse events (AEs) graded by CTCAE v5.0. **Results:** From January 8, 2021, to September 21, 2023, 263 patients were enrolled and received treatment. Median age was 51 years; 60.8% (160/263) were hormone receptor-positive, and 97.7% (257/263) were node-negative. At the data cutoff (December 30, 2025), with a median follow-up of 36.2 months, 9 iDFS events were observed. The estimated 3-year iDFS rate was 96.8% (95% CI 93.4-98.5). One death occurred and overall survival data were immature. The most common grade $\geq$3 treatment-related AEs were diarrhea (50.6%), neutropenia (14.4%), and decreased white blood cell count (14.4%). No serious AEs were reported. Treatment interruption, dose reduction, and discontinuation due to AEs occurred in 12.2%, 3.4%, and 1.5% of patients, respectively. **Conclusions:** Adjuvant pyrotinib combined with nab-paclitaxel showed promising 3-year iDFS and a manageable safety profile in patients with low-risk, HER2-positive early breast cancer. This regimen represents a potential oral de-escalation strategy for this population. Clinical trial information: NCT 04659499. Research Sponsor: General Project of the 2025 Annual Beijing Municipal Education Science; No. CDDB25233; National High Level Hospital Clinical Research Funding; 2025-PUMCH-A-148; Chronic Disease Management Research Project of National Health Commission Capacity Building and Continuing Education Center; No. GWJJMB202510041020.

Efficacy outcomes.

Efficacy outcomes	Pyrotinib + nab-Paclitaxel (n=263)		
Events, n(%)	9 (3.4)		
	24 months	36 months	48 months
iDFS rate, (95% CI)	98.77 (96.24, 99.60)	96.83 (93.42, 98.49)	93.17 (85.03, 96.96)
DDFS rate, (95% CI)	99.18 (96.76, 99.79)	98.77 (96.23, 99.60)	95.03 (86.00, 98.29)
LRFS rate, (95% CI)	99.18 (96.75, 99.79)	98.18 (95.18, 99.32)	94.47 (85.76, 97.92)

iDFS: invasive disease-free survival; DDFS: distant disease-free survival; LRFS: locoregional recurrence-free survival.

534 **Poster Session**

Real-world deployment of a multimodal artificial intelligence (AI) model for predicting response to neoadjuvant chemotherapy in early breast cancer. First Author: Bareket Daniel, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Multimodal AI models integrate morphological information from H&E-stained images with clinical information, identifying subtle disease signatures beyond the perceptual limits of human experts. However, the clinical utility of AI tools in real-world settings remains underexplored. Here, we evaluated Ataraxis Breast (ATX), a multimodal AI test predicting response to neoadjuvant chemotherapy, in a prospective silent trial. **Methods:** We previously assembled an international dataset of whole slide images of H&E-stained biopsy specimens and clinical information to develop ATX as a biomarker of neoadjuvant response. To evaluate real-world clinical translation, we conducted a prospective silent trial of ATX in patients with early breast cancer treated with neoadjuvant therapy at our center. None of these patients were included in the original training, validation, or test datasets. The primary outcome was pathologic complete response (pCR). Area under the receiver operating curve (AUROC) analyses were conducted. **Results:** The study cohort included 50 female patients treated during 2025, with a median age of 53.8 years. Tumor subtypes comprised 30% (n = 15) triple-negative breast cancer (TNBC), 24% (n = 12) HER2-positive disease, and 46% (n = 23) hormone receptor–positive (HR+), HER2-negative tumors. Overall, 66% (n = 33) of patients had node-positive disease, and 60% (n = 30) had grade 3 tumors. Notably, all patients with TNBC received pembrolizumab, whereas patients with HER2-positive tumors were treated with chemotherapy combined with HER2-directed therapies. The overall pathological complete response (pCR) rate in this external validation cohort was 34%. ATX scores were significantly higher among patients who achieved pCR (p = 0.005). Moreover, when evaluated as a predictive biomarker across the entire cohort, ATX achieved an AUROC of 0.745 (95% CI, 0.58–0.89) for pCR. These findings were consistent across predefined subgroup analyses, including patients with HR+/HER2− disease (AUROC = 0.73) and TNBC (AUROC = 0.77). **Conclusions:** In this prospective deployment study, among patients with early breast cancer treated with neoadjuvant chemotherapy, higher AI-derived predictions were independently associated with improved neoadjuvant therapy response. Given the accessibility of H&E-slides, ATX may serve as a scalable predictive biomarker in real-world settings. Research Sponsor: Israel Ministry of Health.

535 **Poster Session**

Adjuvant antibody-drug conjugate (ADC) eligibility and corresponding prognosis in HER2+ early breast cancer (eBC): A US-based real-world comparison of KATHERINE and DESTINY-Breast05 populations. First Author: Paolo Tarantino, Department of Medical Oncology, Dana-Farber Cancer Institute; Harvard Medical School, Boston, MA

Background: The KATHERINE trial established adjuvant T-DM1 as standard of care (SoC) treatment for patients with HER2+ eBC and residual invasive disease (RD) following neoadjuvant therapy. Recently, DESTINY-Breast05 (DB-05) demonstrated reduced recurrence risk with T-DXd vs. T-DM1 in a high-risk subset. While KATHERINE included any RD, DB-05 restricted eligibility to high-risk patients (inoperable at presentation or ypN+ at surgery). In this analysis, we aim to estimate the prevalence and associated outcomes of patients with HER2+ eBC and RD meeting eligibility for DB-05 vs. KATHERINE in a US real-world setting. **Methods:** This retrospective cohort study utilized the nationwide Flatiron Health electronic health record-derived de-identified database. We included patients diagnosed with stage I–III HER2+ eBC (Jan 1, 2011–Sept 30, 2025) who completed pertuzumab-based neoadjuvant therapy and surgery. RD status was determined via pathology reports. KATHERINE eligibility required any RD in breast/axillary nodes. DB-05 eligibility required high-risk RD: operable at presentation with node-positive disease at surgery (ypN1–3; "DB-05-operable") or inoperable at presentation (cT4 or cT1–3/cN2–3; "DB-05-inoperable"). Distant recurrence-free survival (DRFS) and overall survival (OS) were estimated at 3 years post-surgery. The analysis was conducted on complete cases only. **Results:** The cohort included 9561 patients with HER2+ eBC and RD after neoadjuvant therapy. Overall, 9447 (99%) met KATHERINE eligibility. Conversely, only 4567 (48%) met DB-05 high-risk criteria: 3241 (34%) DB-05-operable and 1326 (14%) DB-05-inoperable. DB-05-ineligible patients mostly presented with cT1–3/cN0–1 disease and had RD confined to the breast (ypN0). In the overall study population, with a median follow-up for DRFS of 44 months, 3-year DRFS and 3-year OS were 88% and 94%, respectively. Patients eligible only for KATHERINE (i.e. DB-05-ineligible) experienced relatively favorable outcomes, with a 3-year DRFS of 94% and 3-year OS of 97%; conversely, DB-05-eligible patients experienced a 3-year DRFS of 82% and 3-year OS of 91%. Within the DB-05-eligible population, the poorest outcomes were observed if patients had inoperable disease at baseline, with a 3-year DRFS of 73% and 3-year OS of 86%. **Conclusions:** Approximately half of the patients with RD did not meet DB-05 high-risk criteria yet would have been eligible for KATHERINE. While T-DXd may become a new option for high-risk patients, T-DM1 remains a SoC for those with operable disease at baseline and node-negative RD at surgery. As ADCs were not widely available for eBC during the study period, these outcomes do not reflect ADCs' treatment effect, and modern 3-year DRFS may possibly exceed 94% for this population. Research Sponsor: F. Hoffmann-La Roche Ltd.

536 **Poster Session**

A randomized phase II trial of folate receptor alpha peptide vaccine in early-stage triple-negative breast cancer. First Author: Keith L. Knutson, Department of Immunology, Mayo Clinic Florida, Jacksonville, FL

Background: Folate receptor alpha (FRα) is overexpressed in ~80% of triple-negative breast cancers (TNBC). We previously demonstrated that patients (pts) with breast cancer naturally mount immune responses to FRα. In prior Phase I and II studies, a GM-CSF-adjuvanted FRα peptide vaccine (FRPV) was safe and induced durable FRα-specific T-cell immunity in 83–90% of pts with breast and ovarian cancer. **Methods:** Eligible pts were women $\geq$18 years with TNBC (ER/PR $\leq$10%) with 1+ of the following: stage $\geq$T1c disease, node-positivity, or residual disease after neoadjuvant chemotherapy. Pts were randomized 2:1 to receive FRPV or placebo (GM-CSF alone) every 28 days for cycles 2-7 and then every six months for 7 booster doses, with cycle 1 consisting of cyclophosphamide 50mg orally twice daily for days 1-7 and 15-21 (in both arms). Randomization was stratified by chemotherapy setting (adjuvant only vs neoadjuvant) and stage (I/II vs III). FRα expression was evaluated by immunohistochemistry. The study was designed to detect (at 30 months after the last pt enrolled) a disease-free survival (DFS) difference of 14% assuming a 3.5-year DFS rate of 70% in the control group and with 78% power. **Results:** 280 pts were enrolled (median age 52). The majority had stage I or II tumors (n = 219, 78%). There were numerically more node-positive tumors in the vaccine arm, 78 (41%) vs 27 (32%), p = 0.15. Median follow-up was 3.5 years, and 33 (FRPV: 25, placebo: 8) DFS events were observed; 3.5-year DFS rate was 88% with FRPV and 90% with placebo (HR 1.42, 95% CI 0.64–3.15; p = 0.39). Overall survival (OS) also did not differ by arm (HR 2.48, 95% CI 0.55–11.20; p = 0.22). Among node-positive pts (n = 105), DFS did not differ between arms (HR 0.95, 95% CI 0.34–2.66; p = 0.92). However, a numerical DFS event rate improvement (14% for vaccine vs. 26% for placebo) was observed in 61 patients with stage III disease (HR 0.51, 95% CI 0.16–1.68; p = 0.26). DFS did not differ by chemotherapy setting or by receipt of anthracycline, capecitabine, and/or an immune checkpoint inhibitor. FRPV was well tolerated, with predominantly grade 1–2 adverse events (AEs) and no vaccine-related grade $\geq$4 AEs. FRα expression was available from tumor in 230 pts, with 72% expressing $>$ 0. Overall, DFS was not significantly associated with FRα expression (0 vs $>$ 0; HR 0.55, 95% CI 0.21–1.44; p = 0.21), and no significant differences in DFS by FRα expression were observed between treatment arms. **Conclusions:** FRPV following oral cyclophosphamide was safe, with no vaccine-related high-grade AEs. While no significant improvement in DFS or OS was observed overall, a numeric trend toward improved DFS was observed in pts with stage III TNBC. This finding is hypothesis-generating and supports further evaluation of FRα-targeted vaccination in higher-risk TNBC. Immune correlative analyses are ongoing to better define vaccine immunogenicity and its relationship to clinical outcomes. Clinical trial information: W81XWH-15-1-0293. Research Sponsor: U.S. Department of Defense; W81XWH-15-1-0293; U.S. Department of Defense; W81XWH-15-1-0292.

537 **Poster Session**

Disparities in utilization of genomic risk assays in early-stage hormone-positive breast cancer: A retrospective analysis using National Cancer Database (NCDB). First Author: Qi Jin Guo, Medical University of South Carolina, Charleston, SC

Background: Prognostic genomic assays (GA) have become crucial in the management of early-stage hormone receptor positive breast cancer, particularly in guiding adjuvant chemotherapy decisions. Despite this, GA remain underutilized. This study aimed to identify predictors of GA utilization and associated survival outcomes. **Methods:** The 2023 NCDB PUF dataset was used to identify patients aged $\geq$ 18 years with HR positive, HER2 negative breast cancer diagnosed between 2010-2023. Patients with T1-T4, N0-N1 disease who underwent surgical resection were included, while those with T1aN0 stage, M1 disease, unknown GA status, or receipt of BCI alone were excluded. Patients were stratified by the receipt of the GA. Descriptive and multivariable analyses were performed to identify factors associated with GA utilization, and survival was assessed using Kaplan-Meier (KM) analysis. **Results:** 594,872 patients were included in our study, of whom 63.12% (N=375,506) underwent GA testing. GA utilization increased over time from 52.7% in 2010-2015 period to 68.7% in 2021-2023 ($p<0.001$). Using multivariable analysis, higher odds of GA testing were seen among Whites vs Blacks (OR 1.13 (1.11-1.16)), those with T2 tumors vs T1 (OR 1.26 95% CI 1.24-1.27), Grade 2 (OR 1.49 (1.47-1.51) or Grade 3 (1.42 (1.39-1.45)) histology vs Grade 1, receiving regional lymph node surgery vs not (OR 2.47 (2.33-2.62)), hormonal therapy vs not (OR 2.39 (2.34-2.43)), radiation vs not (OR 1.32 (1.30-1.34)), and recent year of diagnosis, 2021+ vs 2010-2015 (OR 2.08 (1.99-2.18)). The odds of GA testing were lower for uninsured vs government insured patients (OR 0.86 (0.82-0.91)), those with higher T stages (T3: OR 0.63 (0.61-0.65) and T4: OR 0.26 (0.24-0.30)) vs T1, N1 disease vs N0 (OR 0.73 (0.72-0.74)) and increasing age with the lowest odds among patients aged$>$80 (OR 0.13 (0.13-0.14)) compared to 18-64 years old. KM analysis showed survival benefit favoring receipt of GA (HR= 0.4 (0.39-0.41), $p<0.001$). **Conclusions:** Our study portrays low utilization of GA despite increasing use over time reflecting the impact of the TAILORx and RxPONDER trials. Significant disparities persisted by age, insurance status, race, and tumor characteristics. Older, Black and uninsured patients were substantially less likely to receive testing, despite an associated survival benefit, underscoring the need for more equitable implementation of guideline-recommended GA. Research Sponsor: None.

LBA538 **Poster Session**

Preliminary injection site reaction immune response results from open-label arm of ongoing phase III study to evaluate the efficacy and safety of GLSI-100 (GP2 + GM-CSF) in patients with breast cancer with residual disease or high-risk PCR after both neo-adjuvant and postoperative adjuvant anti-HER2 therapy (Flamingo-01). First Author: Snehal Patel, Greenwich LifeSciences, Stafford, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

539 **Poster Session**

Real-world post-APT trial adoption of de-escalated systemic therapy and outcomes in small HER2-positive breast cancer: An NCDB analysis. First Author: Mengni Guo, Department of Oncology/Hematology, Loma Linda University Medical Center, Loma Linda, CA

Background: The APT trial shifted adjuvant management of small HER2-positive breast cancer towards paclitaxel-trastuzumab, yet real-world uptake and outcomes of de-escalated single-agent chemotherapy (SC) plus anti-HER2 therapy (H) vs multi-agent chemotherapy (MC) plus H remain uncertain. **Methods:** Using NCDB (2013-2022), we identified patients with invasive HER2-positive pT1a-pT1c, pN0/N1mi, M0 disease treated with surgery without neoadjuvant therapy. We compared treatment patterns pre-APT (2013-2014) vs post-APT (2016-2022), excluding 2015 as a washout. Regimens were grouped as local therapy only, H only, chemo only, SC + H, or MC + H. Predictors of SC + H were assessed with multivariable logistic regression in post-APT chemo + H recipients. OS was evaluated using time-varying Cox models (time zero surgery; treatment exposure starting at recorded systemic therapy initiation), adjusted for demographic, tumor, and facility factors. In the overall cohort, each regimen (H only, chemo only, SC+H, and MC+H) was compared with local therapy only. For pT1a tumors, comparisons were limited to H only, chemo only, and any chemo + H vs local therapy. To evaluate whether de-escalation was associated with similar OS, SC + H vs MC + H was compared in separate Cox models restricted to chemo + H recipients in pT1b and pT1c. **Results:** Among 56,455 patients, SC + H use increased from 12.5% pre-APT to 40.3% post-APT, while MC + H decreased from 46.6% to 24.8% ($p< 0.001$). In the post-APT era among chemo + H recipients (N = 24,867), SC + H use increased with age (per 10-year OR 1.32, 95% CI 1.27-1.36) and hormone receptor-positive (HR-positive) status (OR 1.37, 95% CI 1.27-1.49), and less common with pT1c (OR 0.47, 95% CI 0.43-0.51) and N1mi (OR 0.21, 95% CI 0.17-0.24) tumors. In OS analyses of the entire cohort with available systemic start dates (N = 51,078; deaths = 3,246), SC + H (HR 0.62, 95% CI 0.57-0.67) and MC + H (HR 0.63, 95% CI 0.58-0.68) were associated with improved OS vs local therapy only. Additional independent predictors of mortality included Black race, older age, and higher tumor burden (T1c and N1mi), while HR-positive was linked to better OS. In pT1a cohort (N = 10,212; deaths = 461), any chemo + H was associated with improved OS vs local therapy (HR 0.83, 95% CI 0.70-1.00, p= 0.049), while H only (HR 0.85, 95% CI 0.51-1.42) and chemo only (HR 1.14, 95% CI 0.74-1.74) were not. Among chemo + H recipients, OS was similar for SC + H vs MC + H in pT1b (HR 0.96, 95% CI 0.80-1.16) and pT1c (HR 1.09, 95% CI 0.97-1.24) cohorts. **Conclusions:** Since APT, real-world care has shifted towards de-escalated SC + H regimens. Among treated pT1b and pT1c patients, OS was similar with SC vs MC backbones, supporting the feasibility of de-escalation in selected patients. In pT1a disease, the OS association for chemo + H was marginal (p= 0.049) and should be interpreted cautiously given non-random treatment selection and low event rates. Research Sponsor: None.

540 **Poster Session**

Adjuvant chemotherapy (CT) benefit in invasive lobular carcinoma (ILC) by Oncotype DX Recurrence Score and menopausal status. First Author: Arya Mariam Roy, The Ohio State University - James Comprehensive Cancer Center, Columbus, OH

Background: The benefit of adjuvant CT in early-stage hormone receptor–positive (HR+) and HER2-negative (HER2–) ILC remains uncertain. The predictive utility of the Oncotype DX Recurrence Score (RS), widely used to guide CT decisions in HR+/HER2 BC, remains debated in ILC. To address these gaps, we analyzed the impact of adjuvant CT on overall survival (OS) across RS categories and by menopausal status. **Methods:** We queried the National Cancer Database for patients (pts) with early-stage HR+/HER2– ILC who had surgery between 2010 and 2021. Pts were grouped by receipt of adjuvant CT (CT+ vs CT–). Analyses were stratified by RS (low 0–15, intermediate 16–25, high ≥26) and menopausal status, using age (<50 vs ≥50 years) as a proxy. Overlap propensity score weighting (OPSW) balanced baseline covariates (race, ethnicity, comorbidities, clinical T and N stage, grade and radiation and hormone therapies), and OPSW Cox models assessed the association between time-varying adjuvant CT and OS. **Results:** Among 141,949 pts with ILC, 19.6% received adjuvant CT. The CT+ cohort was younger (median age 59 vs 67 years) and more often pre-menopausal (21.8 vs 9%), and had high grade tumors (8.7 vs 3.3%), advanced T stage (T2: 39.4 vs 21.8%; T3: 14.9 vs 3.4%), node-positive (N1-3: 22 vs 3.2%) disease and more frequently received radiation (74.6 vs 56.5%) and hormone therapy (93.3 vs 87.5%), all p<0.001. RS testing was available in 38% of pts; CT+ cohort more often had high (9.2 vs 1.2%) or unknown RS (75.4 vs 57.9%), p<0.001. In the high RS group, CT was associated with improved 5-year (93.3 vs 90.5%) and 10-year OS (79.4 vs 71.7%) and lower mortality (adjusted hazard ratio (aHR) 0.69, p <0.001) (Table 1). Among postmenopausal pts, the survival benefit with CT was greatest in pts with high RS (10-year OS: 78.6 vs 69.2%; aHR 0.65, 95% CI 0.52–0.82, p=0.0003). No OS benefit was observed in low (aHR= 1.16, p= 0.31) or intermediate (aHR= 1.07, p= 0.39) RS groups. Among pre-menopausal pts, CT benefit was limited to the intermediate RS group (10-year OS: 94.9 vs 91.3%; aHR 0.57, 95% CI 0.33–1.00, p=0.049); no benefit was observed in low (aHR= 1.11, p= 0.77) or high (aHR= 1.50, p= 0.55) RS. **Conclusions:** In early-stage HR+/HER2– ILC, RS has limited clinical utility. Adjuvant CT benefit was restricted to pts with high RS, predominantly in postmenopausal pts, while RS did not reliably predict benefit in premenopausal pts. No OS benefit was seen in low RS disease, supporting a selective, biology-driven approach to CT use in ILC. CT decisions in pts with unknown RS appear largely driven by clinicopathologic factors. Research Sponsor: None.

10-year survival analysis of ILC patients based on CT receipt and RS.

RS group	OS (%, 95% CI) CT +	OS (%, 95% CI) CT -	aHR (95% CI) Reference: CT-	p-value
Low	87.6 (84.6-90.6)	88.9 (88.0-89.9)	1.13 (0.87-1.47)	0.36
Intermediate	86.2 (84.4-88.1)	86.5 (85.3-87.7)	1.02 (0.87-1.20)	0.78
High	79.4 (76.4-82.5)	71.7 (66.9-76.8)	0.69 (0.55-0.87)	<0.01

541 **Poster Session**

Overall survival association of adjuvant endocrine therapy (ET) after pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC) in ER+/HER2+ early-stage breast cancer. First Author: Mengni Guo, Department of Oncology/Hematology, Loma Linda University Medical Center, Loma Linda, CA

Background: In ER+/HER2+ early breast cancer, adjuvant ET is standard; however, its survival benefit for patients achieving pCR after NAC remains uncertain. As pCR is associated with favorable prognosis and may inform postoperative decision-making, it is unknown if pCR identifies a subset in whom the ET survival benefit is reduced. We evaluated ET use patterns and its association with overall survival (OS) in ER+/HER2+ patients with pCR after NAC. **Methods:** Using NCDB, we identified women with ER+/HER2+ M0 breast cancer treated with NAC and definitive surgery (2018-2022) who achieved pCR (ypT0/ypTis and ypN0). The primary endpoint was OS. To reduce immortal time bias, we used a time-varying Cox model with ET initiation as a time-dependent exposure (time zero: surgery). A 6-month landmark analysis was performed as a sensitivity analysis. Multivariable models adjusted for demographic, clinicopathologic, treatment, and socioeconomic variables. Predictors of ET omission were assessed using multivariable logistic regression. Exploratory analyses evaluated ER-low (1-10%) and effect modification using an ET×ER-low interaction term. **Results:** Of 8,981 patients, 7,917 (88.2%) received ET and 1,064 (11.8%) did not. In the time-varying Cox model, ET receipt was associated with improved OS (HR 0.79, 95% CI 0.67-0.93). Worse OS was associated with older age (per 10 years: HR 1.17, 95% CI 1.10-1.24) and stage III disease (HR 1.39, 95% CI 1.16-1.67). In 6-month landmark analysis (n=8,756), ET benefit persisted (HR 0.58, 95% CI 0.39-0.86). There was no differential association by ER-low status (ET×ER-low interaction p=0.73), with similar ET associations in ER-high (HR 0.58) and ER-low (HR 0.63) groups. ET was omitted in 36.9% of ER-low patients compared to only 7.6% of ER-high patients. Logistic regression identified ER-low status as the strongest predictor of ET omission (OR 0.16, 95% CI 0.14-0.19). Omission was also more likely with older age (per 10-year increase: OR 0.92, 95% CI 0.85-0.99) and community facility treatment (OR 0.74, 95% CI 0.55-0.99), while ET receipt was more likely with PR-positivity (OR 1.54, 95% CI 1.32-1.79), radiation (OR 2.78, 95% CI 2.32-3.33) and HER2-targeted therapy (OR 2.62, 95% CI 2.03-3.38). **Conclusions:** In this NCDB cohort, adjuvant ET was associated with improved OS in ER+/HER2+ patients achieving pCR after NAC. The survival association did not differ by ER-low status, though event rates in this subgroup were limited. ER-low status was the strongest predictor of ET omission, highlighting a potential gap between real-world practice and outcomes. These findings support continued consideration of ET in post-pCR ER+/HER2+ patients, including the ER-low population. Research Sponsor: None.

Cohort	Total N	ET (%)	No ET (%)	Death (%)
Overall	8,981	7,917 (88.2%)	1,064 (11.8%)	152 (1.7%)
ER-low	1,316	831 (63.1%)	485 (36.9%)	32 (2.4%)

542 **Poster Session**

Three-monthly gonadotropin-releasing hormone agonist for ovarian function suppression in premenopausal breast cancer: A systematic review and meta-analysis. First Author: Pedro C.A. Reis, Universidade Federal do Rio de Janeiro, Rio De Janeiro, Brazil

Background: Ovarian function suppression (OFS) with gonadotropin-releasing hormone agonists (GnRHa) is a cornerstone of endocrine therapy (ET) for premenopausal women with hormone receptor–positive (HR+) breast cancer (BC), most commonly administered on a monthly (1M) schedule. Three-monthly (3M) formulations have been proposed to improve convenience and adherence, but comparative efficacy and safety versus 1M regimens remain uncertain. **Methods:** PubMed, Cochrane, and Embase libraries were systematically searched for randomized clinical trials (RCTs) and non-randomized interventional studies comparing 3M versus 1M GnRHa regimens in premenopausal women with HR+ BC receiving ET. Outcomes included the incidence of ovarian escape (OE), mean estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels, disease-free survival (DFS), progression-free survival (PFS), and adverse events, with a minimum follow-up of 12 weeks. Random-effects models were used to estimate pooled risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI). Subgroup analyses were performed by estradiol assay type, and a sensitivity analysis restricted to RCTs was conducted. **Results:** Fifteen studies comprising 4,324 patients were included; 2,098 (48%) received a 3M regimen. The overall incidence of OE was low (10%) and did not differ between 3M and 1M schedules (RR 0.86; 95% CI 0.60–1.22). Ultrasensitive assays revealed higher absolute OE rates (31%), without inter-regimen differences (RR 0.90; 95% CI 0.38–2.14). Mean E2 levels at 12 weeks were comparable across dosing strategies (MD 1.36 pg/mL; 95% CI −3.66 to 6.38), with no significant differences in mean FSH or LH levels; analyses restricted to RCTs yielded consistent findings (MD −1.77 pg/mL; 95% CI −5.71 to 2.17). DFS (RR 1.02; 95% CI 0.67–1.56) and PFS (RR 0.86; 95% CI 0.72–1.04) were similar between regimens. The most frequently reported adverse events were hot flashes, arthralgia, headache, and nausea, with no clinically relevant differences between dosing schedules. **Conclusions:** 3M GnRHa achieved OFS comparable to 1M dosing, with similar survival outcomes and safety profiles in premenopausal women with HR+ BC. Research Sponsor: None.

543 **Poster Session**

Real-world effectiveness and safety of adjuvant capecitabine in triple-negative breast cancer (TNBC) patients with residual disease following neoadjuvant chemotherapy. First Author: Anbarasan Sekar, The Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Homi Bhabha National Institute (HBNI), Kharghar, India

Background: The presence of residual disease in triple-negative breast cancer (TNBC) after neoadjuvant chemotherapy is associated with high recurrence risk and poor prognosis. The CREAT-X study demonstrated improved recurrence risk and survival outcomes with adjuvant capecitabine in this population [1]. We previously reported long-term outcomes in nonmetastatic TNBC, but the population is unselected, and the impact of adjuvant capecitabine is not assessed in the Indian scenario [2]. **Methods:** This single-center retrospective study included TNBC patients with residual disease after neoadjuvant chemotherapy treated between January 2020 and December 2024 with adjuvant capecitabine. Baseline clinicopathological characteristics were analyzed descriptively. Survival outcomes were assessed using the Kaplan–Meier method, and recurrence-free survival (RFS) and overall survival (OS) were estimated. Factors associated with survival outcomes were evaluated using univariate and multivariate Cox proportional hazards regression models. **Results:** Among 1548 patients diagnosed with Stage I-III TNBC, 1044 patients treated with neoadjuvant therapy underwent surgery; 671 patients had residual disease, out of which 315 patients who received adjuvant capecitabine were included in this retrospective analysis. The majority were premenopausal (66.3%), were older than 40 years (59.7%), and had stage III residual disease (71.4%). At a median follow-up of 25 months, the 2-year overall survival (OS) was 79.6%, with a median OS of 49.7 months. The 2-year recurrence-free survival (PFS) was 49.3%, with a median RFS of 23.9 months. On univariate analysis, higher nodal status ($P < 0.001$) and advanced stage ($P < 0.05$) were significantly associated with inferior RFS, while higher nodal status was also associated with inferior OS ($P < 0.05$). Multivariate analysis confirmed nodal status as an independent predictor of poor survival ($P < 0.01$). **Conclusions:** Adjuvant capecitabine demonstrated poor outcomes in our TNBC patients with residual disease compared to the randomized study; nodal status independently predicted poorer outcomes, emphasizing risk stratification and prospective validation. References: Toi M, Lee SJ, Lee ES, Ohtani S, Im YH, Im SA, Park BW, Kim SB, Yanagita Y, Takao S, Ohno S. Abstract S1-07: a phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X, JBCRG-04). Cancer Research. 2016 Feb 15; 76(4_Supplement): S1-07. Bajpai J, Kashyap L, Vallathol DH, Das A, Singh M, Pathak R, Rath S, Sekar A, Mohanta S, Reddy A, Joshi S. Outcomes of non-metastatic triple negative breast cancers: Real-world data from a large Indian cohort. The Breast. 2022 Jun 1;63:77-84. Clinical trial information: CTRI/2026/01/101798. Research Sponsor: None.

544 **Poster Session**

Chemotherapy use among women < 50 years with hormone receptor–positive breast cancer with low (≤15) Oncotype DX 21-gene recurrence score: A National Cancer Database (NCDB) analysis. First Author: Mitali Shah, The Ohio State University James Comprehensive Cancer Center, Columbus, OH

Background: RxPONDER demonstrated a benefit to chemotherapy (CT) in premenopausal women with hormone receptor-positive (HR+) breast cancer (BC) with 1-3 pathological positive lymph nodes (pN1) regardless of Oncotype DX RS. Whether the benefit is due to the cytotoxic effects of CT itself or potentially from the CT-induced ovarian suppression remains to be determined. In the absence of large prospective data evaluating the predictive ability of RS in this population, including pN1mi, we sought to examine adjuvant CT use patterns among premenopausal women and low RS. **Methods:** This retrospective analysis queries the NCDB from 2018-2022 for patients (pts) with BC <50 years old (surrogate for premenopausal status) and clinically node negative disease at the time of diagnosis. Pts with stage I-III HR+ HER2-negative BC who underwent upfront curative breast surgery and had pathologically confirmed lymph node status (pN) were included. Oncotype DX RS was categorized as low if RS ≤15. Multivariable binary logistic regression was used to examine associations between clinicopathological factors and the receipt of adjuvant CT. **Results:** 6040 pts with Oncotype DX RS ≤15 met inclusion criteria. Most pts, 5090 (84.3%), had invasive ductal carcinoma, and high (>51%) ER and PR expression (>93% of patients). Among all low RS, 5081 (84.4%) had pN0 and 939 (15.5%) had pN1 or higher disease, 704 pts (76.6%) having 1 LN involved, of which 317 pts were pN1mi; 148 (16.1%) had 2 LN and 67 (7.3%) had 3+ LN. Accounting for all pts, 265 (4.4%) received CT: 64 (24.2%) were pN0, while 201 (75.8%) were pN1+. Among pts with pN1 BC, older age was associated with lower odds of receiving adjuvant CT (aOR 0.96, 95%CI 0.93-1.00, p=0.03). Other factors including higher pathologic tumor stage (pT3/T4 vs pT1/T2; aOR 4.46, 95% CI 2.34–8.51), higher pN involvement, specifically 2 LN (aOR 2.45, 95% CI 1.60–3.75) and ≥3 LN (aOR 4.65, 95% CI 2.54–8.51) compared to 1 positive regional LN, and poorly (vs well) differentiated tumor (aOR 2.36, 95% CI 1.14–4.88) had higher odds of receiving CT. Similarly, pts with pN0 and low RS that had pT3/T4 tumors (aOR 3.99, 95% 1.16-13.72) and higher grade (moderately and poorly differentiated tumors) had higher odds of receiving CT (aOR 1.84 95% CI 1.03-3.27 and 6.11 95% CI 2.58-14.44, respectively). **Conclusions:** Among women <50 years with low RS (≤15), CT receipt was strongly associated with clinicopathologic risk factors, including higher tumor stage, poorly differentiated grade and higher regional nodal involvement. These findings indicate that despite a low RS, young age and node positivity are associated with adjuvant CT recommendation. These results highlight the importance of ongoing trials such as OFSET, which aims to better answer the appropriateness of CT among premenopausal women. Research Sponsor: None.

545 **Poster Session**

Comparative effectiveness of adjuvant chemotherapy on survival in node-positive (N2/N3), stage III ER+/HER2− invasive lobular breast cancer (ILC) versus invasive ductal cancer (IDC). First Author: Sumeet K. Yadav, Mayo Clinic Florida, Jacksonville, FL

Background: ILC is characterized by loss of E-cadherin expression, with distinct biological and clinical features, and is often perceived to be less sensitive to chemotherapy compared with IDC. Oncologists and pts may face a treatment dilemma regarding the benefits of adjuvant chemotherapy in pts with lower biologic risk but higher anatomic risk (N2/N3), stage III ILC. In this study, we sought to compare the benefit of adjuvant chemotherapy in pN2/N3 ILC compared with IDC. **Methods:** We used the National Cancer Database (NCDB) to identify adults with primary, non-metastatic, ER-positive/HER2-negative invasive breast cancer diagnosed between 2010 and 2022 who underwent upfront surgery. Patients receiving neoadjuvant systemic therapy were excluded. Analyses were limited to pathologic stage I–III disease with known nodal involvement (N2–N3) and tumor category (T1–4). Propensity score matching (1:3, caliper 0.2; using R 4.5.1) was performed to balance age, sex, race, insurance status, grade, pathologic stage, nodal category, tumor category, Charlson-Deyo comorbidity score, and year of diagnosis. Overall survival (OS) was assessed using Kaplan–Meier methods and Cox proportional hazards models used to estimate hazard ratios (SPSS v28). **Results:** After propensity matching, we analyzed 28,115 pts with pN2/N3 disease (ILC 9,603 and IDC 18,512). Upstaging from cN0 to pN2/3 was higher for ILC than IDC (20.3% vs 13.3%, $p<0.001$). ILC pts were more likely to undergo mastectomy compared to IDC (80.2% vs 71.2%, $p<0.001$). Receipt of adjuvant chemotherapy for pN2/N3 disease was similar between IDC and ILC (78.0% vs 78.4%, p=0.37), as was use of adjuvant radiation and endocrine therapy. Among patients receiving chemotherapy, treatment was associated with a 65% reduction in death in ILC (HR 0.35, 95% CI 0.32–0.38, $p<0.001$) and a 73% reduction in IDC (HR 0.27, 95% CI 0.26–0.29, $p<0.001$), compared with no chemotherapy. 5-year OS among chemotherapy-treated patients was lower for ILC compared with IDC (HR 1.4, 95% CI 1.33-1.49; $p<0.001$, Table 1). In contrast, no OS difference was observed between ILC and IDC among patients who did not receive chemotherapy (HR 1.03, 95% CI 0.96-1.11; p=0.38). Chemotherapy was associated with higher 5-year OS in both IDC (87.7% vs 58.9%) and ILC (84.3% vs 59.2%). **Conclusions:** Adjuvant chemotherapy was associated with a substantial improvement in 5-year OS among patients with pN2/N3 disease in both IDC and ILC. Pts with ILC and extensive nodal involvement benefit from adjuvant chemotherapy. Research Sponsor: None.

5-year survival of IDC and ILC.

	IDC (18,512)		ILC (9,603)	
	No Chemotherapy (4,078)	Adjuvant Chemotherapy (14,434)	No Chemotherapy (2,071)	Adjuvant Chemotherapy (7,532)
pN2 (18,669)	62.8%	90.1%	64.4%	87.6%
pN3 (9,446)	48.3%	82.2%	51.4%	79.4%
pN2/pN3 Combined (28,115)	58.9%	87.7%	59.2%	84.3%

$P < 0.001$, log rank.

546 **Poster Session**

AI-based pre-screening of *BRCA1/2* mutation likelihood from routine H&E histopathology in unselected breast cancer cases using peakPredictBRCA. First Author: Maher Sughayer, Department of Pathology, King Hussein Cancer Center, Amman, Jordan

Background: BRCA1/2 mutation status is essential for precision oncology in breast cancer, directly guiding therapy decisions such as eligibility for PARP inhibitors. However, not all patients globally have reimbursed access to genetic BRCA testing, due to cost and a lack of uniform global implementation, leading to actionable mutations being missed. We developed a scalable artificial intelligence pre-screening algorithm that estimates BRCA1/2 mutation likelihood from routine whole-slide H&E images, to enable systematic prioritization of patients for genetic testing. **Methods:** peakPredictBRCA, a deep learning-based algorithm, was developed to predict likelihood of BRCA1/2 mutations from H&E whole-slide images of primary and metastatic breast cancer cases, independent of hormone receptor or HER2 status. Breast cancer images were collected from 6 institutions across 5 countries using different whole-slide scanners (Argentina, Brazil, Germany, Jordan, and USA), with slide-level BRCA mutation labels derived from clinical sequencing (n=725 images, 60% mutated). Training data was augmented with open-access TCGA datasets for breast, prostate, and ovarian cancer (n = 1,633 images), resulting in 2,358 total images (21% mutated). Model performance was evaluated on the collected breast cancer images using five-fold cross-validation. The model was trained end-to-end without manual annotations using multiple-instance learning. **Results:** On the breast cancer cohort, peakPredictBRCA achieved a mean AUC of 0.81 ± 0.13. At a screening-oriented operating point, the model identified most BRCA1/2 mutated cases (mean sensitivity 0.82 ± 0.23) while excluding a substantial proportion of non-mutated cases (mean specificity 0.56 ± 0.38), without additional calibration on held-out images. Additional analyses during development demonstrated that robust generalization to unseen data depends on appropriate tumor tissue detection and model architecture selection. **Conclusions:** Our results demonstrate that BRCA1/2 mutation likelihood can be effectively triaged from routine H&E breast cancer histology with consistent performance across institutions, scanners, and slide preparations. Implementation of the peakPredictBRCA algorithm in routine pathology workflows could enable systematic prescreening of unselected breast cancer cases at diagnosis and prioritization for confirmatory genetic testing, particularly in resource-constrained settings. Ongoing work focuses on incorporating human-interpretable features and on prospective validation in real-world workflows. Research Sponsor: AstraZeneca International; Mindpeak GmbH.

547 **Poster Session**

Recurrence risk prediction using a large, multi-site observational dataset of patients with early breast cancer, including early-onset disease. First Author: Lilia Bouzit, Flatiron Health, New York, NY

Background: Accurate risk stratification in early breast cancer (eBC) is critical to guide adjuvant treatment intensity. In HR+/HER2- stage I-III disease, clinicians use clinical and genomic information to estimate recurrence risk, yet a comprehensive, real-world predictive model that synthesizes these inputs after curative-intent surgery is not established in routine practice. We developed a multimodal predictive survival model in a large, eBC cohort to predict recurrence-free survival (RFS) after surgery and derive risk groups to inform treatment escalation or de-escalation. **Methods:** This study used the US-based EHR-derived deidentified Flatiron Health Research Database (data cutoff: Sep 30, 2025). The cohort consisted of patients (pts) diagnosed with HR+/HER2- stage I-III eBC between Jan 1, 2016, and Jan 1, 2023, who received surgery and no neoadjuvant therapy. An Extreme Gradient Boosting (XGBoost) model was developed using 10-fold cross-validation, reserving 20% for testing, predicted time from surgery to recurrence or death. SHapley Additive exPlanations (SHAP) analysis was used to rank feature importance. Pts were classified into 3 risk groups by prediction percentile, and RFS by group was plotted in the test set using the Kaplan-Meier method. A second XGBoost model identified predictors specific to pts diagnosed with early onset (EO) eBC (age $\leq$ 45 yrs). **Results:** 158,111 pts qualified for the cohort, and the model C-index was 0.76. Top features that contributed to increased predicted hazard include age, higher tumor grade, higher stage, higher OncotypeDx score, longer time from diagnosis to surgery, ECOG score $\geq$2, and smoking history. Higher socioeconomic status (SES) decreased predicted hazard. Age had a non-linear association with predicted hazard; risk was elevated among pts $<$35 and $>$71, with lowest prediction occurring at ages 46-51. The median RFS in the high-risk group was 8.5 yrs (IQR, 8.2-8.8) and was not reached in the medium and low-risk groups. In the early onset subgroup of 12,196 pts, the C-index was 0.71. Top features in the EO model that contributed to increased hazard also included higher tumor grade and stage, and younger age. Importance of race and Ki67 percent staining (PS) superseded that of ECOG and SES in the EO model. Pts of Black or African American race and pts with Ki67 PS $\geq$20% had higher predicted hazard. **Conclusions:** This analysis elucidated key predictors of RFS following surgery in pts with eBC, specifically in non-neoadjuvant–treated pts at higher risk for recurrence, and illustrated predictors that vary in younger pts. Predictors from this large, representative dataset are aligned with known associations with recurrence risk. These findings suggest real-world data models may complement established tools guiding adjuvant treatment intensity, though external validation and prospective evaluation are needed. Research Sponsor: Flatiron Health, Inc.

548 **Poster Session**

AI-driven large language models for multimodal prediction of homologous recombination deficiency using clinical features and histopathological whole-slide images. First Author: Zhao Sun, School of Cyber Science and Engineering, Zhengzhou, China

Background: Homologous recombination deficiency (HRD) implies the dysfunction of homologous recombination repair at the cellular level. The assessment of HRD status benefits making treatment plans and fertility counseling of breast cancer patients. Standard diagnostic tests for detecting HRD are expensive and not universally available. **Methods:** We trained a deep learning framework to predict HRD status by integrating routinely collected clinical records and histopathological imaging data, including hematoxylin and eosin (H&E)–stained whole-slide images, from primary breast cancer patients (n = 397) across three independent regional medical centers. The patient cohort was split into a training set (80%) and a validation set (20%). Clinical text as well as whole-slide images were encoded using large language model. This model integrated multimodal representation learning and was applied to generate robust HRD predictions. **Results:** Across breast cancer cohorts from three independent regional medical centers, the proposed approach demonstrated robust and consistent performance in predicting HRD. The reported AUC of 0.82 (95% CI, 0.79–0.84) represents the mean value over ten independent experiments with different random seeds. Notably, the model achieved a precision of 0.84 and a specificity of 0.92, indicating strong discriminatory power with a tendency towards cautious decision-making. **Conclusions:** Our model showed promising HRD predictive performance in breast cancers directly from routine multimodal data integrating clinical characteristics, imaging description with pathological slides. The HRD-positive predictions generated by this model show promise for clinical translation. Research Sponsor: National Natural Science Fund of China; No.82472749.

549 **Poster Session**

Prediction of pathologic response using a taxane-based gene expression signature in RNA-sequencing data from breast cancer patients receiving neoadjuvant therapy. First Author: Jan Nart, Aida Oncology, Copenhagen, Denmark

Background: Taxanes are frequently used in both early and advanced breast cancer, but their use has not yet been guided by predictive biomarkers. We have previously validated a microarray-based 113-gene predictive signature for neoadjuvant taxane-based treatment across 6 independent cohorts, including I-SPY2. Here, we present our first validation of this signature in RNA-sequencing data. **Methods:** The study by Park et al. (2020; PMID: 33268821) enrolled 210 women with stage II–III invasive breast cancer, who received four cycles of neoadjuvant doxorubicin plus cyclophosphamide (AC) followed by four cycles of docetaxel (T) with trastuzumab (H) added for HER2-positive disease. We obtained pre-treatment TPM-normalized RNA-sequencing data from GEO (accession ID: GSE123845) for patients with available response data—pathologic complete response (pCR; n = 34) vs. residual disease (RD; n = 62)—following treatment completion (n = 96). To ensure compatibility between the RNA-sequencing data and microarray-based model, we performed frozen quantile normalization using the original training dataset for the model (GSE140494) as reference. We applied the signature on the normalized data to generate a response score for each patient in the range of 0-100 and evaluated the association between treatment response and patient score using logistic regression. **Results:** Increase in patient score was significantly associated with higher odds of pCR after adjusting for ER and HER2 status (one-sided P = 0.003), with a 50-point increase corresponding to an odds ratio of 3.44 (95% CI, 1.46-8.71), and an AUC of 0.74 for predicting pCR. Stratifying patients by median score revealed notable differences in pCR rates between low- and high-scoring patients. For ER+/HER2- patients (n = 28; median score = 26.6), the difference in pCR rates was 29% (0% vs. 29%) for patients below vs. above the median. Corresponding differences for triple-negative (n = 35; median score = 65.6) and HER2-positive patients (n = 33; median score = 51) were 13.8% (33.3% vs. 47.1%) and 39.4% (29.4% vs. 68.8%), respectively. **Conclusions:** We present the validation of a 113-gene predictive signature in RNA-sequencing data for achieving a pCR after taxane-based therapy. This is our first attempt at validating the signature in RNA-sequencing data, and the 7th successful validation overall across independent breast cancer cohorts. This result further highlights the signature's potential as a tool to support taxane-based treatment guidance. Research Sponsor: None.

550 **Poster Session**

Evaluating performance of an AI-based recurrence score in early breast cancer patients treated with chemoendocrine therapy: A secondary analysis of the UNIRAD trial. First Author: Thomas Bachelot, Medical Oncology Department, Centre Léon Bérard, Lyon, France

Background: Patients with node-positive HR+/HER2- early breast cancer are at high risk for relapse within 5 years of diagnosis, suggesting the potential need for treatment escalation. However, it is unclear which patients may experience worse recurrence-free outcomes and thus benefit from additional therapy. Ataraxis Breast (ATX) is an artificial intelligence (AI) test that integrates clinicopathologic variables with features extracted from whole-slide H&E images to estimate recurrence risk. Here, we perform a secondary analysis of the control arm of the UNIRAD trial, evaluating the ability of ATX to identify patients treated with standard-of-care therapy who may be candidates for treatment escalation. **Methods:** Clinical information and scanned H&E slides were sourced for 365 patients enrolled in the UNIRAD trial who were randomized to the control arm (standard-of-care therapy). ATX scores were generated using a locked model with pre-specified thresholds. No patients from UNIRAD were used in the training of ATX. Recurrence-free interval (RFI) was used as the primary endpoint. Kaplan-Meier estimators were used to predict the probability of meeting the RFI endpoint. To quantify relative differences in the hazard of experiencing an event contributing to the RFI endpoint associated with ATX scores, Cox proportional hazards models were fitted, from which hazard ratios (HRs) were estimated. The discriminative performance of ATX was evaluated using C-index. **Results:** Of the 365 patients randomized to the control arm of the UNIRAD trial with H&E slides available, 163 (45%) were classified as ATX low risk, and 202 (55%) as ATX high risk. Patients classified as ATX high risk had lower Kaplan-Meier-estimated probability of meeting the RFI endpoint (77%, 95% CI = 70-83%) than patients classified as ATX low risk (93%, 95% CI = 88-97%). Consistent with these findings, when modeled as a continuous variable, higher ATX scores were associated with a significantly higher hazard of an RFI-contributing event (HR = 1.57, 95% CI = 1.29-1.99, p-value $<$ 0.001) and demonstrated strong discriminatory performance (C-index = 0.66, 95% CI = 0.59-0.72). This association remained significant after controlling for receipt of neoadjuvant therapy, tumor, and nodal stage (HR = 1.53, 95% CI = 1.05-2.23, p = 0.027). **Conclusions:** In the clinically homogenous UNIRAD trial cohort of patients with node-positive HR+/HER2- early breast cancer, ATX high risk patients treated with standard-of-care therapy had a significantly increased hazard of an RFI-contributing event. These findings suggest that AI-based risk stratification identifies biologically high risk patients who may derive benefit from adjuvant treatment escalation. Clinical trial information: NCT01805271. Research Sponsor: Ataraxis AI.

551 **Poster Session**

Estimating individual benefit from adjuvant chemotherapy in hormone receptor–positive breast cancer using causal multimodal artificial intelligence. First Author: Frederick Howard, University of Chicago, Chicago, IL

Background: Adjuvant chemotherapy decisions in HR+/HER2– early breast cancer are often guided by prognostic gene expression assays. However, assessment of recurrence risk may not yield a predictive biomarker that accurately estimates treatment benefit. Here, we combine advances in deep learning and causality research to address this problem using routine histopathology and clinical data. We develop and validate a causal multimodal artificial intelligence (AI) model that predicts the patient-specific benefit of adding chemotherapy to endocrine therapy in HR+/HER2– early breast cancer. **Methods:** De-identified whole-slide histopathology images (WSIs) and clinical covariates from 9,269 patients across 12 observational cohorts were used to develop the Ataraxis Breast model (ATX). The locked model was then externally validated in a cohort from the University of Chicago (n = 435, stage I-III HR+/HER2– breast cancer, median age = 56, median follow-up = 7.2 years), grouped by adjuvant therapy received (endocrine therapy [ET] n = 322, chemoendocrine therapy [CET] n = 113). The primary endpoint was 5-year recurrence-free interval (RFI). WSIs were encoded via a pathology foundation model and integrated with clinical variables (including T/N stage, age, ductal vs lobular histology). ATX predicted counterfactual RFIs, assuming CET or ET, with the difference taken as the predicted treatment-benefit score. Discrimination was evaluated using Harrell's C-index. Multivariate Cox proportional hazards models were fitted, adjusting for clinicopathological factors (age and T/N stage), to estimate hazard ratios (HR). Subgroup differences were assessed using inverse-propensity-weighted Kaplan-Meier estimates and two-sided log-rank tests. **Results:** In the external validation cohort, ATX was significantly associated with the primary endpoint (adjusted HR = 1.65, 95% CI 1.05-2.6; p = 0.029), and demonstrated good discrimination at the patient-level (C-index = 0.704, 95% CI 0.588-0.821). Notably, ATX stratified patients into subgroups with differential chemotherapy effects: patients in the top tertile of predicted treatment benefit experienced improved RFI with CET (ET RFI = 0.744, CET RFI = 0.980; $p < 0.001$), with no difference observed in patients with low predicted treatment benefit (ET RFI = 0.975, CET RFI = 0.970; p = 0.85). The interaction between ATX and the magnitude of chemotherapy benefit, when adjusted for clinicopathological factors, was significant (p-interaction = 0.005). **Conclusions:** A causal multimodal AI model accurately estimates chemotherapy benefit for patients with HR+/HER2– early breast cancer, meeting the criteria for a predictive biomarker. The causal AI methodology presented here may provide a generalizable framework to optimize scalable, predictive biomarkers for other therapies and cancer types. Research Sponsor: Ataraxis AI.

552 **Poster Session**

Evaluating the prognostic performance of an AI-based model in clinically low-risk HR+/HER2− early breast cancer. First Author: Dhruva Biswas, Ataraxis AI, New York, NY

Background: Accurate prediction of recurrence risk in early HR+/HER2- breast cancer remains central to adjuvant treatment decision making. Clinically approved prognostic models largely rely on genomic features, yet their performance remains insufficient for optimal clinical stratification. To address these limitations, AI-based approaches have increasingly been developed to improve risk prediction. Ataraxis Breast (ATX) is a multimodal artificial intelligence test integrating clinical information with morphological information from H&E-stained whole slide images for HR+/HER2- patients. Here, we evaluate ATX's ability to prognosticate recurrence risk in an external cohort of clinically low risk early breast cancer patients from Dordrecht, the Netherlands. **Methods:** Clinical information and H&E images were accessed for 887 patients with HR+/HER2- breast cancer. ATX scores were generated using a locked model and a prespecified cut-off was applied to classify patients into ATX high vs low groups. The primary endpoint was recurrence-free interval (RFI); recurrence-free probabilities were estimated for the two groups using a Kaplan-Meier estimator. Additionally, performance of ATX was assessed using C-index and hazard ratio (HR per 0.1 increase in ATX score). No patients from this dataset were used in the training of ATX. **Results:** The cohort of 887 patients was characterized by low clinical risk, where 631tumors were classified as T1 and 239 as T2, and the majority of patients were node-negative (N0: n = 639). Tumors were predominantly low to intermediate grade (grade 1: n = 296; grade 2: n = 496), with relatively few high-grade cases (grade 3: n = 88). Histological analysis identified invasive lobular carcinoma in 131 patients. The median tumor size was 15 mm (interquartile range, 11-22 mm). Accordingly, most patients (n = 773, 87%) were classified as ATX low risk. Patients in the ATX high risk group had lower estimated 5-year probability of meeting the RFI endpoint (0.88, 95% CI = 0.80-0.93) than patients classified as ATX low risk (0.98, 95% CI = 0.96-0.98). When modeled as a continuous variable, ATX demonstrated strong discriminatory performance for recurrence risk (C-index = 0.740, 95% CI, 0.68-0.80) and was associated with a significantly increased hazard of an RFI-contributing event (HR = 2.68, 95% CI, 2.09-3.45; $p < 0.001$). To account for clinical confounding, we fitted a multivariate Cox proportional hazards model adjusting for T stage, N stage, grade, age at diagnosis, adjuvant endocrine therapy, adjuvant chemotherapy, and tumor size. We found that ATX score remained significant (HR = 1.99, 95% CI = 1.38-2.86, $p < 0.001$) and tumor size was the only other variable that was statistically significant ($p < 0.05$). **Conclusions:** ATX accurately prognosticates recurrence risk in a clinically low risk group of HR+/HER2- breast cancer patients from an external validation cohort. Research Sponsor: Ataraxis AI.

553 **Poster Session**

Standardized exam-style benchmarking of large language models in breast cancer clinical decision-making. First Author: Mariam Haji, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Large language models (LLMs) are increasingly used to support clinical reasoning in breast cancer (BC), yet reproducible benchmarking remains limited. In our prior work using complex breast cancer clinical scenarios (BCCS), OpenEvidence (OE) outperformed other LLMs; however, expert Likert-based grading may be influenced by subjective interpretation and human bias. Standardized, board-style multiple-choice questions—required even for expert clinicians—offer an objective framework to assess LLM accuracy and inform readiness for potential clinical decision support. We evaluated the accuracy of four LLMs on a standardized BC question set using binary grading and paired statistical testing. **Methods:** One hundred BC questions reflecting real-world clinical scenarios were submitted to four LLMs: ChatGPT-5.2 (GPT), Google Gemini 3 (Gemini), Claude Sonnet 4.5 (Claude), and OE. Questions were sourced from a hematology–oncology question bank and spanned major BC subtypes and treatment settings. Model responses were graded against bank-designated correct answers using binary scoring (1=correct, 0=incorrect). Overall accuracy with 95% confidence intervals (CI) was calculated. Pairwise comparisons were performed using McNemar's test. **Results:** One hundred clinical scenarios were evaluated spanning all major BC subtypes and treatment settings, including early-stage and metastatic disease, and neoadjuvant and adjuvant therapy. Overall accuracy was highest for Gemini at 94.0% (95% CI, 87.4–97.8), followed by GPT at 90.0% (95% CI, 82.4–95.1), OE at 90.0% (95% CI, 82.4–95.1), and Claude at 89.0% (95% CI, 81.2–94.4). McNemar's test showed no statistically significant differences between models. Compared with Gemini, GPT showed 4% lower accuracy (p=0.289), Claude 5% lower (p=0.267), and OE 4% lower (p=0.289). GPT and OE demonstrated equivalent accuracy (both 90.0%) with no significant difference (p=1.000). GPT vs Claude differed by 1% (p=1.000) and Claude vs OE differed by 1% (p=1.000). All models generated clinical reasoning, while OE was the only model providing citations. **Conclusions:** In standardized BC clinical scenarios, four widely used LLMs demonstrated high accuracy with no significant between-model differences. However, no model achieved 100% accuracy, reinforcing the need for ongoing refinement and clinician oversight prior to clinical use. Future studies should expand question volume, evaluate domain-specific error patterns, and incorporate question banks from multiple countries and geographic regions to improve generalizability before real-world clinical deployment. Research Sponsor: None.

554 **Poster Session**

Incremental prognostic value of an AI-derived histology signature beyond the 21-gene recurrence score: A prospective-retrospective validation in TAILORx. First Author: Magali Iacroix-Triki, Gustave Roussy, Department of Medical Biology and Pathology, IHU-National PRecISion Medicine Center in Oncology, Villejuif, France

Background: The 21-gene recurrence score (RS) is a foundational tool for risk-stratifying HR+/HER2- early breast cancer (EBC). However, clinical outcomes vary within RS categories. RlapsRisk BC (RR), an AI pathology-based test, integrates features from H&E-stained whole-slide images with clinical data (age, tumor size, nodal status) and was developed using 7 retrospective cohorts totaling 6,039 patients. We evaluated the clinical validity of RR and its histology-only component (RR-H) beyond RS and standard clinicopathologic factors. **Methods:** The clinical validity of RR was established through a validation program of 4 cohorts and over 8,521 patients across diverse geographic regions and laboratory settings. This included 3 international cohorts (n=933) and a prospective-retrospective analysis of the TAILORx trial, where RR-H was evaluable in 7,585 (97.5% of analyzable patients). The primary endpoint was distant recurrence-free interval (DRFI). In TAILORX, we assessed the additive value of the RR-H score to a base model (composed of age, tumor size, histological grade and RS) using Cox proportional hazards models and C-index comparison. **Results:** Across international validation cohorts (median follow-up 7.5 years, 9,8% DRFI events), RR successfully stratified patients (HR=4.91; 95% CI: 3.13-7.71; $p < 0.00001$), and identified a low-risk population with a 97.5% (95% CI: 95.8%-98.5%) 5-year DRFI rate. In the TAILORx population (n=7,584), the RR-H score was a highly significant independent predictor of DRFI. Incorporating RR-H as a continuous variable to the base model (including RS) significantly increased the C-index from 0.6730 to 0.7007 ($p < 0.0001$). The estimated HR for a 1-point difference in RR-H was 1.108 (95% CI: 1.078-1.138; $p < 0.0001$). When analyzed by quartiles, patients in the highest risk group (Q4) exhibited a significantly higher risk of distant recurrence compared to the lowest risk group (Q1) HR= 2.656 (95% CI: 2.003-3.522). Concordance analysis revealed that RR-H is independent of stromal TILs (R^2=0.01). While RR-H correlated with increasing histological grade, substantial distribution overlap confirms intra-grade prognostic granularity. Furthermore, RR-H distributions were consistent across ILC and non-NLC. **Conclusions:** RR demonstrated robust and reproducible prognostic value across 8520 patients from diverse populations and settings establishing its clinical validity. Additional findings on TAILORx demonstrate that RR-H provides significant, independent prognostic value that complements existing prognostic tools (including genomic assays and clinicopathological factors), suggesting that integrating AI-pathology can refine precision risk assessment, and thus optimize adjuvant treatment in HR+ HER2- EBC. Research Sponsor: National Cancer Institute; U10CA180820, U10CA180794, UG1CA233329, UG1CA233247; U.S. Postal Service Breast Cancer Stamp Fund; Breast Cancer Research Foundation (USA); CONS-23-007.

555 **Poster Session**

Prognostic validation of artificial intelligence (AI)–based Stratipath breast risk stratification in TAILORx. First Author: Johan Hartman, Department of Oncology-Pathology, Karolinska Institutet, and Stratipath, Stockholm, Sweden

Background: Stratipath Breast is an AI-based prognostic medical device for risk stratification of early-stage breast cancer using routine H&E-stained histopathology whole slide images (WSIs). AI-based analyses of histopathology slides offer an alternative to costly and logistically demanding genomic assays. In this study, the prognostic performance of Stratipath Breast was validated in the TAILORx trial (NCT00310180). **Methods:** WSIs from patients enrolled in TAILORx were analyzed by Stratipath Breast. After histopathology quality control and availability of clinical endpoints and WSIs, 5,519 patients were included. Stratipath Breast binary risk category, multi-level risk group, and continuous risk score were evaluated. The prognostic performance was analyzed by Kaplan-Meier statistic and log rank test, as well as concordance index (C-index). Multivariable Cox Proportional Hazard (PH) model adjusting for age, tumor size, histologic subtype and continuous Oncotype DX recurrence score (RS), both without and with histologic grade, was used to assess independent prognostic value. Recurrence-free interval (RFI) and distant recurrence-free interval (DRFI) were evaluated. **Results:** 53.9% (2,975/5,519) of patients were classified as Stratipath low risk and 46.1% (2,544/5,519) as high risk. A significant association of Stratipath risk category and group with RFI and DRFI was confirmed ($p < 0.05$). In multivariable Cox PH analyses, Stratipath high-risk category was an independent prognostic factor associated with worse outcomes (RFI HR = 1.54, 95%CI:1.29-1.84, $p < 0.05$; DRFI HR = 1.61, 95%CI: 1.30-1.99, $p < 0.05$). Stratipath risk category remained significant in multivariable analysis when histologic grade was included, whereas grade did not. RS remained prognostic significant in multivariable analyses together with Stratipath Breast, indicating potentially complementary prognostic information. C-index improved with inclusion of Stratipath Breast together with clinical variables and RS, exceeding that of grade. **Conclusions:** In the TAILORx trial Stratipath Breast was found to provide significant prognostic value. Stratipath Breast also provided independent prognostic value in multivariable analysis adjusting for standard clinicopathologic factors and RS. These findings support the clinical relevance of AI-driven morphology-based biomarkers for breast cancer risk stratification. Research Sponsor: the National Cancer Institute of the National Institutes of Health; Breast Cancer Research Foundation; The U.S. Postal Service Breast Cancer Stamp Fund.

556 **Poster Session**

Deep learning–based classification of benign and malignant breast lesions on ultrasound using knowledge distillation with external validation and global deployment. First Author: Jansi Rani Sethuraj, AIM DOCTOR, Thiruverkadu, India

Background: Breast cancer is the most common malignancy in women worldwide. Although breast ultrasonography is widely accessible, diagnostic accuracy remains limited by operator dependence and interobserver variability ($\kappa \approx 0.6–0.8$), contributing to delayed diagnosis and unnecessary biopsies. While deep learning has shown promise in ultrasound-based lesion classification, many models are computationally intensive and lack external validation, limiting clinical scalability. We developed a deployment-ready deep learning framework that balances diagnostic performance with computational efficiency using structured knowledge distillation. Objectives: To develop and externally validate a computationally efficient deep learning model for binary breast ultrasound lesion classification; to evaluate whether a distilled student model preserves clinically meaningful performance from a high-capacity teacher network; and to assess global clinical feasibility through independent radiologist evaluation. **Methods:** We analyzed 8,116 breast ultrasound images (4,074 benign; 4,042 malignant) independently annotated by two board-certified radiologists with consensus adjudication. A ResNet34 teacher network (21.8M parameters) was trained using ImageNet-pretrained weights. A lightweight ResNet18 student network (11.7M parameters; 46% reduction) was trained using structured knowledge distillation with confidence-aligned soft targets and KL-divergence regularization. External validation was performed on three independent ultrasound datasets not used during training. Performance metrics included accuracy, sensitivity, specificity, precision, F1 score, and AUROC. The model was deployed in a HIPAA-compliant cross-platform application and independently evaluated by physicians across six continents. **Results:** The student model achieved 91.9% accuracy on held-out test data with balanced performance (sensitivity 90.8%, specificity 93.0%, F1 score 0.918). External validation demonstrated stable generalization (accuracy 89–92%). In global clinical deployment, 94.2% of participating physicians rated the system clinically useful and suitable for integration into routine breast ultrasound workflows. **Conclusions:** Knowledge distillation enables substantial model compression while preserving diagnostic accuracy for breast lesion classification on ultrasound. This scalable, deployment-ready approach supports standardized interpretation across diverse clinical environments and warrants prospective evaluation for reducing unnecessary biopsies and improving diagnostic efficiency. Research Sponsor: None.

557 **Poster Session**

Prospective-retrospective HeCOG phase III trial validation of Polaris TME for the prediction of TILs from whole-slide images in high-risk early breast cancer. First Author: Elena Fountzilas, Hellenic Cooperative Oncology Group, Athens, Greece

Background: Tumor-infiltrating lymphocytes (TILs) are an established prognostic and predictive biomarker in early breast cancer. However, manual histopathologic scoring can introduce interobserver variability and limit throughput in analyzing at scale in routine practice. Recent advances in artificial intelligence (AI) offer the potential to standardize TILs quantification and enhance reproducibility. Our aim is to evaluate whether deep learning-based tumor microenvironment (TME) quantification from digitized hematoxylin- and eosin (H&E)-stained slides can accurately classify TILs and assess their prognostic role in patients with early breast cancer. **Methods:** We conducted a prospective-retrospective external validation of Polaris TME, a deep learning model for TME quantification. The analysis included patients with high-risk early breast cancer treated with adjuvant contemporary dose-dense chemotherapy, spanning all histological subtypes, enrolled in four HeCOG trials conducted between 1997 and 2008 (3 randomized and 1 observational). Manual TILs scoring had been centrally performed by pathologists according to International TILs Working Group guidelines, enabling direct comparison between manual and AI-derived scoring. The Polaris foundation model was used for feature extraction, while model performance was assessed using correlation for continuous TILs scores using the Spearman ρ and discrimination for clinically defined TILs categories (thresholds: 5% and 50% using the Area Under the Curve (AUC) with 95% CI. The prognostic value of the model was assessed using the log-rank test for invasive disease-free survival (iDFS). **Results:** Overall, 1,214 patients with whole slide images, TILs quantification and follow-up data were included; median age 53 [22-79]; 638 (63%) were hormone receptor-positive/HER2-negative, 394 (32%) HER2-positive, 176 (14%) triple-negative breast cancer (TNBC), and 6 patients of unknown subtype. Median follow-up was 116.59 (53.45 –157.06) months. When blindly deployed on the external cohorts, the model showed a significant correlation with the manual TILs scoring (ρ=0.60, $p<0.001$). The model yielded an AUC of 0.78 (0.75–0.81) for >5% TILs and AUC of 0.92 (0.88–0.95) for the >50% TILs. Predicted low-TILs tumors were associated with significantly lower 10-year iDFS in TNBC (55.1% versus 70.9%, p=0.034), with a similar pattern observed in HER2-positive (55.3% versus 64.8%, p=0.096), whereas there was no difference in 10-year iDFS between the predicted TILs groups for luminal cancers. **Conclusions:** These results indicate that Polaris TME accurately quantifies TILs derived from digitized H&E slides and provides prognostic measure for long-term iDFS in high-risk early breast cancer. Prospective validation and harmonization efforts to facilitate clinical implementation are warranted. Research Sponsor: None.

558 **Poster Session**

AI-driven risk stratification for distant recurrence in node-positive HR+/HER2− early breast cancer: Independent validation in the NSABP B-28 trial. First Author: Priya Rastogi, NSABP Foundation, and the UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Accurate prediction of risk of distant recurrence (DR) in HR+, HER2-negative early-stage breast cancer (EBC) is important for optimizing adjuvant therapy decisions, including treatment escalation with CDK4/6 inhibitors (CDK4/6i). Current guidelines recommend consideration of CDK4/6i for node-positive, clinically high-risk EBC, including N1 patients. However, it is not known which patients will benefit, and guideline recommendations suggest that the risks may outweigh benefits for patients with low risk of distant recurrence. Identification of these patients will help prevent over-treatment. RlapsRisk BC (RR) is an AI pathology-based test that integrates features from H&E-stained whole-slide images with clinicopathologic data (age, tumor size, nodal status) to assess risk of distant recurrence in HR+, HER2-negative EBC. The RR model was previously developed and validated using 7 retrospective cohorts totaling 6,039 patients. Here we report validation of RR in the NSABP B-28 cohort of HR+ HER2-negative N+ patients who received post-operative chemoendocrine therapy. **Methods:** This blinded independent validation study of the pre-specified RR included a subset of NSABP B-28 patients with HR+ and HER2-negative EBC (n=731) and digitized whole slide images from primary tumors. The primary endpoint was distant recurrence-free interval (DRFI). The objective was to validate the prognostic utility of RR score for DR. Univariable and multivariable Cox models were performed. **Results:** The evaluable cohort had a median follow-up of 11.1 years and included 504 (69%) patients with N1 disease, 87% grade 2/3 tumors, and a median tumor size of 21mm. Across the entire cohort, RR classified 58% of patients as low-risk and 42% as high-risk. RR (high vs low) was significantly associated with DRFI: HR=3.1 (95% CI: 2.3-4.3; $p < .001$). Estimated 10-year DR-free was 87.5% (95% CI: 83.9-90.4%) for low-risk vs. 65.0% (95% CI: 59.1-70.2%) for high-risk patients. In a multivariable Cox model, the histology-only score remained significant after adjusting for clinicopathologic data: HR=1.6 (95% CI: 1.4-1.9; $p < .001$). In the N1 subgroup, RR identified 65.7% of patients as low-risk with an estimated 10-year DR-free of 90.6% (95% CI: 86.9-93.4%), compared to 69.8% (95% CI: 62.2-76.2%) for high-risk. **Conclusions:** RR demonstrates robust prognostic performance in clinically high-risk N+, HR+, HER2-negative EBC patients from the NSABP-28 trial, in which the majority of patients had N1 disease. Our results demonstrate that approximately two-thirds of N1 patients, identified as low-risk by RR, exhibited favorable long-term outcomes with standard chemoendocrine therapies alone. As the clinical landscape shifts toward broader CDK4/6i use, RR could be used to identify N1 patients for whom the benefit of treatment intensification may be minimal. Research Sponsor: None.

559 **Poster Session**

Prognostic performance of a multimodal artificial intelligence histopathology-based tool versus the 21-gene recurrence score in early-stage breast cancer. First Author: Shayna L. Showalter, University of Virginia (UVA), Department of Surgery, Charlottesville, VA

Background: Genomic classifiers are widely used to assess risk of distant metastasis (DM) and inform chemotherapy (CT) benefit in patients with HR+/HER2- early breast cancer (EBC). While clinically validated, these assays are associated with high cost, long turnaround time, and tissue consumption. This study evaluates the performance of a histopathology based multimodal AI (MMAI) model in real-world institutional cohorts and compares its prognostic performance with the 21-gene recurrence score (RS). **Methods:** We conducted a retrospective analysis of 307 de-identified patients with node-negative HR+/HER2- EBC. Patients were treated at two institutions: Hoag Health System (n = 62) and the University of Virginia (n = 245). Median follow-up was 9.5 years. MMAI risk classifications (low vs. high) were compared to RS risk groups as defined in the TAILORx study (RS 0-10 (low), RS 11-25 (intermediate), RS≥26 (high)). The endpoint was time to DM and was analyzed using Kaplan-Meier (KM) methods and Cox proportional hazards models, including univariable (UVA) and multivariable analyses (MVA) adjusting for clinicopathologic factors. **Results:** In this study, 64% of patients were classified as MMAI low risk and 36% as MMAI high risk. The majority of patients received endocrine therapy alone (86% with low RS and 77% with intermediate RS), while 79% of patients in the high RS group were treated with CT. KM analyses demonstrated significantly lower 10-year DM rates for patients classified as MMAI low risk (1.6%, 95% CI: 0.4%-6.8%) compared with patients classified as MMAI high risk (10.8%, 95% CI: 5.5%-20.6%). Among patients with low RS, the MMAI model classified 84% as low risk, with no DM events observed in this group. In contrast, 16% of patients classified as MMAI high risk within the RS low group experienced a 10-year DM rate of 20% (95% CI: 5.4%-60.0%). MMAI further stratified intermediate RS patients into distinct risk groups: 66% were classified as MMAI low risk and 34% as MMAI high risk, with 10-year DM rates of 2.6% (95% CI: 0.6%-10.9%) and 11.4% (95% CI: 4.5%-27.2%) respectively. In UVA analysis of the intermediate RS group, MMAI high risk classification was associated with DM risk (hazard ratio (HR) of 4.2 (95% CI: 1.1-16.1, p = 0.03). In MVA, adjusting for RS groups, adjuvant systemic therapy, and age, MMAI remained independently associated with DM risk (HR = 5.8, 95% CI: 1.7-19.8, p = 0.005). **Conclusions:** MMAI demonstrated prognostic risk stratification within RS groups, particularly among intermediate RS. Concordance between MMAI low risk and favorable outcomes among patients with low RS suggests MMAI may identify patients with low risk of DM without requiring additional tissue consumption. Further studies are needed to evaluate outcomes among MMAI risk groups within high RS to define the optimal clinical integration of MMAI with existing genomic assays. Research Sponsor: ArteraAI.

560 **Poster Session**

Prognostic value of an MRI-derived recurrence assay in women with hormone receptor–positive, HER2-negative breast cancer: A retrospective, multi-center analysis. First Author: Matthew P. Goetz, Mayo Clinic Rochester, Rochester, MN

Background: Patients (pts) with early stage hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer (BC) remain at both short and long term risk of recurrence. While clinico-pathological and gene-based biomarkers provide insight into early and late recurrence risk, additional prognostic tools are needed. We previously developed (Saha et al. *Clin Cancer Res*, 2025) a new breast MRI image-based artificial intelligence prognostic tool (TumorSight Risk) composed of both radiographic and clinical information. Here we sought to validate this tool in an independent cohort. **Methods:** In this multi-center, blinded, prospective/retrospective validation study, we sought to validate the 5-year recurrence-free survival (RFS) according to pre-defined risk scores (0-100) and categories ("high" or "low") via pre-specified cutoff (≥47) for pts with HR+/HER2- BC. Kaplan-Meier and Cox regression analyses were then used to assess the unadjusted and adjusted association between risk category/score and the 5-year RFS. **Results:** 2,129 pts with HR+/HER2- BC diagnosed between January 1, 2010, and December 31, 2024, who underwent breast MRI prior to surgery (no neoadjuvant therapy) were included from four institutions. Median age was 57 years, 16% were Black, 15% had grade 3 disease, 93% were clinical T1 or T2, and 85%/15% were clinical N0/N1. At a median follow up of 6.24 years, the unadjusted hazard ratio (HR) for RFS comparing low (n=1808) and high risk (n=321) pts was 2.71 (95% CI = 1.95 – 3.76, p = $3x10^{-9}$). The estimated 5 year RFS rate according to risk score (low and high) was 95.5% (95% CI: 94.63 – 96.3%) and 89.6% (95% CI = 86.4 – 92.6%) while the 10 year RFS estimates were 88.9% (95% CI = 86.5 - 90.9%) and 69.6% (95% CI = 59.1 – 77.9%). Univariate subgroup analysis demonstrated that the risk score was prognostic by age (< 50 vs. ≥50 years), pathologic nodal status, grade, and surgery type, regardless of chemo-, endocrine, or radiation therapy administration. The observed continuous risk score was strongly associated with risk of recurrence, with a 22% increase in relative risk per 10-unit change in risk score (0-100), translating to a 2.4% (95% CI = 1.2 – 4.5%) and 25.5% (95% CI = 15.4 – 40.4%) risk of recurrence at 5-years for pts at the lowest (0-9) versus highest (90-100) risk score. The prognostic association between risk score and RFS remained after adjusting for pathologic T- and N-stage, grade, age, race, and treatment (p = 0.002). **Conclusions:** TumorSight Risk is a new image-based biomarker for HR+/HER2- BC that provides prognostic information independent of standard clinico-pathological parameters. Given the ready availability of breast MRI in most pts with BC, TumorSight Risk may be a convenient tool for estimating risk for recurrence. Research Sponsor: SimBioSys, Inc.

561 **Poster Session**

Association of the 70-gene assay and homologous recombination deficiency in patients with high risk 2 breast cancers. First Author: Steven J. Isakoff, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

Background: Homologous recombination deficiency (HRD) is a biomarker for impaired DNA repair proficiency and genomic instability, associated with sensitivity to DNA-damaging agents. MammaPrint (MP), a 70-gene assay, stratifies early breast cancer (EBC) by UltraLow, Low, High Risk 1 (H1) or High Risk 2 (H2) of recurrence. Compared to patients (pts) with H1 tumors, pts with H2 tumors derive greater benefit from anthracycline-based chemotherapy. Here we analyze HRD signatures to assess whether MP gene expression profiling may detect pathway activity in H2 tumors indicating DNA repair deficiency. **Methods:** We analyzed tumors from pts enrolled in the FLEX study who consented to full transcriptome and clinical data collection, with available MP and BluePrint (BP; Luminal or Basal) results (N=1298). HRD status assessed using a 228-gene signature was further refined into a 26-gene panel (Jacobson et al., 2023). The R-package Limma was used to preprocess gene expression data. For each gene, the median expression value of probes mapping to the gene was calculated. Differences in HRD scores were compared across MP and BP groups using a t-test. **Results:** Pts with HR+HER2- EBC HRD scores differed significantly by both MP and BP. Using the 228-gene HRD signature, H2 tumors were associated with higher HRD compared with H1 cancers ($p<0.001$). Luminal H2 tumors were also associated with higher HRD scores than Luminal H1 tumors ($p<0.001$). Basal tumors were associated with higher HRD compared with Luminal tumors within both H1 and H2 (Luminal H1 vs Basal H1 and Luminal H2 vs Basal H2; both $p<0.001$), and Basal H2 tumors had higher HRD scores than Basal H1 tumors ($p<0.001$). Similar patterns were observed within the 26-gene HRD panel. H2 tumors were associated with higher scores than MP H1 tumors ($p<0.001$), and Luminal H2 tumors were associated with higher scores than Luminal H1 tumors ($p<0.001$). Basal tumors were associated with higher HRD than Luminal tumors within both MP risk groups (Luminal H1 vs Basal H1, p=0.002; Luminal H2 vs Basal H2, $p<0.001$). Basal H2 tumors demonstrated numerically higher scores than Basal H1 tumors using the 26-gene panel, but did not reach statistical significance (p=0.062). **Conclusions:** In this real-world analysis, MP and BP identified differences in underlying HRD biology, with H2 tumors enriched for HRD and Luminal H1 tumors demonstrating relative homologous recombination proficiency. These findings may provide a biological rationale for the anthracycline chemotherapy and immunotherapy benefit observed in pts with H2 tumors and further evidence for MP as a tool for refined therapy selection. Additional research is warranted to examine MP as a biomarker for HRD-sensitive therapies such as PARP inhibitors and carboplatin. These results further highlight biological diversity within genomically high-risk tumors, uniquely detected by MP and BP. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

562 **Poster Session**

Predicting recurrence and survival in hormone receptor–positive (HR+)/HER2-negative (HER2–) early breast cancer (EBC) with machine learning models: Optimization of model complexity. First Author: Frederick Howard, University of Chicago, Chicago, IL

Background: A machine learning model was previously developed to predict distant recurrence (DR) in endocrine therapy–treated patients with HR+/HER2− EBC, with high accuracy achieved using 10 variables (Howard FM, et al. *Clin Cancer Res*. 2026). Here, optimal performance, based on the number and identity of variables, of recurrence models that include survival events (distant relapse–free survival [DRFS], overall survival [OS]) was determined. **Methods:** Retrospective data from patients with stage I-III HR+/HER2− EBC (diagnosed 1 January 2011 to 30 April 2024) were extracted from the Flatiron Health US electronic health record–derived database. Elastic net–penalized Cox proportional hazards–based machine learning models were developed with 2, 5, 10, 15, or 20 variables identified by gradient boosting to predict DR, DRFS, and OS; DRFS was defined according to STEEP criteria v2.0. Model performance was assessed using the C-index and Brier score (BS). **Results:** With modeling based on 7842 patients, DR prediction accuracy plateaued (C-index, 0.857; BS, 0.046) (Table) with 10 variables (N status, T status, tumor grade, Ki-67 score, age, time from diagnosis to surgery, percent estrogen receptor–positive cells, menopausal status [post-], Oncotype DX Recurrence Score, and percent progesterone receptor–positive cells). The DRFS (C-index, 0.740; BS, 0.089) and OS (C-index, 0.781; BS, 0.075) prediction models showed high accuracy with 5 to 10 variables, and accuracy continued to increase with up to 20 variables. In contrast to the DR prediction model, the DRFS and OS prediction models included functional status (ie, Eastern Cooperative Oncology Group performance status, Charlson Comorbidity Index) among the most impactful variables. **Conclusions:** DR model performance plateaued with 10 tumor-intrinsic variables. In contrast, optimal DRFS and OS prediction required expanding the model to 20 variables, including functional and comorbidity domains necessary to capture non-cancer competing risks critical for survival prediction in real-world populations, despite the modest statistical impact. The machine learning model for predicting DR, a reliable proxy for survival in HR+/HER2− EBC, is based on a lower number of risk factors that are commonly accessible in real-world clinics and has good accuracy. Research Sponsor: Novartis Pharmaceuticals Corporation.

Model performance by outcome and number of variables.

No. of variables	DR (C-index[a])	DR (BS[b])	DRFS (C-index[a])	DRFS (BS[b])	OS (C-index[a])	OS (BS[b])
2	0.812	0.044	0.667	0.093	0.611	0.081
5	0.849	0.046	0.718	0.092	0.770	0.075
10	0.857	0.046	0.736	0.089	0.774	0.075
15	0.858	0.046	0.737	0.089	0.776	0.076
20	0.851	0.047	0.740	0.089	0.781	0.075

[a]Concordance index; scores span from 0.5 to 1; 1 = perfect.
[b]Brier score; scores span from 0 to 0.25; 0 = perfect.

563 **Poster Session**

Gut microbiome characteristics in patients with hormone receptor–positive (HR+) HER2– breast cancer treated with adjuvant abemaciclib: Biomarker analysis of the TRADE trial. First Author: Ilana Schlam, Dana-Farber Cancer Institute, Boston, MA

Background: Adjuvant abemaciclib reduces recurrence risk and improves overall survival in patients with high-risk node-positive early HR+/HER2- breast cancer. However, treatment-emergent diarrhea may lead to dose modifications, treatment discontinuation, and impaired quality of life. The gut microbiome influences treatment response and toxicity across multiple cancer therapies; its role in abemaciclib-associated diarrhea remains undefined. We evaluated features of the gut microbiome during the initiation of adjuvant abemaciclib and any association with diarrhea. **Methods:** 90 patients with HR+/HER2– early breast cancer enrolled in the TRADE trial (NCT06001762) and were treated with dose-escalated adjuvant abemaciclib (50 mg BID x 14 days, then 100 mg BID x 14 days, then 150 mg BID onwards) plus endocrine therapy. Stool samples were collected at baseline, cycle 2 day 1 (C2D1), and end of treatment (EOT). Whole-genome shotgun metagenomic sequencing was performed, and species-level profiles were generated using MetaPhlAn4. Diarrhea was analyzed as a binary outcome (ever vs none). Associations between microbiome features and clinical variables were evaluated using linear mixed modeling with a random effect for repeated samples from the same individual (alpha diversity) or per-timepoint using PERMANOVA (beta diversity) and MaAsLin3 (species and genes, with false discovery rate correction). Models were adjusted for age, cancer stage, and type of endocrine therapy. **Results:** A total of 142 samples were analyzed (77 baseline, 58 C2D1, and 7 EOT; 77 total subjects, 28 with diarrhea, 49 without). Treatment was associated with a consistent microbiome shift from baseline to C2D1, characterized by a decline in alpha diversity (-0.26, 95% CI -0.39 to -0.14, $p < 0.001$) and a phylum-level shift with increased Bacteroidota and decreased Firmicutes abundance ($p < 0.002$ and $p = 0.001$, respectively, paired T-test). When assessing by timepoint, having any-grade diarrhea was not associated with differences in beta diversity or alpha diversity, nor with individual microbial species; pathway-level enrichment suggested diarrhea-associated functional trends that did not meet FDR significance. Limited EOT samples suggested partial recovery following treatment. **Conclusions:** Adjuvant abemaciclib induced consistent, treatment-related shifts in gut microbiome composition, characterized by reduced diversity and a phylum-level shift from Firmicutes to Bacteroidota, suggesting an early broad ecological treatment effect from exposure to a CDK4/6 inhibitor. This pattern has been reported in patients with inflammatory bowel disease. A species-specific diarrhea signature or predictive relationship between microbiome signature and the development of diarrhea was not observed. Further evaluation of the microbiome's evolution at EOT is ongoing. Clinical trial information: NCT06001762. Research Sponsor: Eli Lilly.

564 **Poster Session**

Distinct late recurrence patterns and immune landscape of HER2-positive invasive lobular carcinoma (ILC): Analysis of NCCTG N9831 (Alliance) trial and real-world cohort. First Author: Thiti Susiriwatananont, Jacoby Center for Breast Health, Mayo Clinic Florida, Jacksonville, FL

Background: HER2+ ILC is rare (~5% of ILC), with limited data on long-term adjuvant trastuzumab outcomes. We investigated late recurrence and immune landscapes of HER2+ ILC vs invasive ductal carcinoma (IDC) in the phase III NCCTG N9831 trial (NCT00005970) and a real-world cohort. **Methods:** We evaluated 3304 early-stage HER2+ breast cancer patients (pts) enrolled in N9831 (122 ILC, 3182 IDC). Recurrence-free survival (RFS) and overall survival (OS) were estimated (Kaplan-Meier) and compared using multivariable Cox regression adjusting for age, tumor size, grade, hormone receptor (HR), and nodal status. Findings were validated in a real-world cohort of HER2+ pts (Caris Life Sciences CODEai platform). Immune microenvironments were profiled by WTS deconvolution (Quantiseq). Real-world overall survival was calculated from trastuzumab start to last contact. **Results:** In N9831, ILC pts were older (median 54 vs 49 y), more ER+ (74.6% vs 51.4%), and had more N3 disease (25.4% vs 12.7%) compared to IDC. ILC pts derived a comparable magnitude of benefit from adjuvant trastuzumab compared to the overall population (HR 0.58 vs 0.67). However, long-term outcomes diverged: while the 5-year RFS was similar (77.1% vs 82.7%), ILC pts experienced a steep decline between years 5-15 (77.1% to 57.7%; ~20% decline) vs IDC (82.7% to 72.7%; ~10% decline) after multivariable Cox analysis (Table). In the real-world early/advanced cohort (n=1328; 26 ILC vs 1302 non-ILC [subset IDC n=595]) treated with trastuzumab-based therapy, ILC pts had worse mOS (33.7 vs 68.6 m, HR 2.01, 95%CI 1.00-4.07, p=0.04) compared to non-ILC. However, there was no statistically significant difference when compared specifically to IDC (HR 1.77, 95% CI 0.87-3.61, p=0.11). ILC had: i) numerically lower tumor mutation burden (TMB)-high (4.2% vs 9.5%, p=0.38); ii) higher infiltration of B cells, Tregs, and M2 macrophages ($p<0.05$); iii) upregulated MHC class II expression (HLA-DOA, $p<0.05$); and iv) downregulated proliferative and DNA repair pathways (E2F, G2M, MYC; FDR <0.25) compared to non-ILC. **Conclusions:** HER2+ ILC carries late recurrence risk despite initial trastuzumab benefit. The unique immune landscape (Treg/M2 macrophage enrichment and lower proliferative signatures) distinguishes HER2+ ILC from IDC, highlighting the need for tailored strategies. Research Sponsor: National Institutes of Health (NIH) / National Cancer Institute (NCI); U10CA180821, U10CA180882; Alliance for Clinical Trials in Oncology.

Long-term RFS and OS in HER2-positive ILC vs IDC (N9831 trial).

Population	N	5-year% (95% CI)	10-year% (95% CI)	15-year% (95% CI)
ILC	122	RFS 77.13% (69.9, 85.1) OS 84.04% (77.7, 90.9)	RFS 70.57% (62.7, 79.4) OS 76.0% (68.7, 84.2)	RFS 57.67% (44.2, 75.1) OS 65.22% (56.6, 75.2)
IDC	3182	RFS 82.71% (81.4, 84.1) OS 90.18% (89.1, 91.2)	RFS 77.45% (75.9, 78.9) OS 81.81% (80.4, 83.2)	RFS 72.68% (70.77, 74.6) OS 76.68% (75, 78.4)

565 **Poster Session**

Association of patient-reported stress and depression symptoms with ER-specific tumor transcriptional signatures in breast cancer (BC). First Author: Shipra Gandhi, Department of Medicine, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Psychological distress is common among women with BC, yet tumor-level biological correlates remain poorly defined. We used tumor transcriptomics to identify pathways associated with patient-reported stress and depression symptoms. **Methods:** RNA sequencing was conducted on FFPE tumor samples in 195 women with stage I-III BC (152 ER+, 43 ER–) from the Women's Health after Breast Cancer cohort. At diagnosis, participants completed Perceived Stress Scale (PSS-10) and Center for Epidemiologic Studies Depression (CES-D) Scale. High-low stress (PSS-10 >14 vs 0-14) and high-low somatic symptoms (CES-D somatic >3 vs ≤ 3) were defined. Differential expression and gene-set enrichment analyses compared high-stress/low-somatic-symptom (HS/LSS) and low-stress/high-somatic-symptom (LS/HSS) groups with low-stress/low-somatic-symptom controls, stratified by estrogen receptor (ER) status, adjusted for age and education. Caris Life Sciences CODEai evaluated overall survival (OS) from tissue collection to last contact. **Results:** In ER+BC, HS/LSS showed increased humoral-immune activity and checkpoint signatures, with reduced neuroendocrine activation. LS/HSS enriched for a neuroendocrine state, ribosome biogenesis, immune and cell-cycle pathways, with loss of epithelial regulatory programs. In ER– BC, HS/LSS showed growth-factor-driven proliferation with reduced epithelial differentiation and greater immune-checkpoint engagement. LS/HSS exhibited metabolic-stress features with loss of epithelial/immune programs and increased keratinization, consistent with impaired antigen presentation and altered differentiation. Table outlines key up- and down-regulated signatures. Using CODEai, in ER+ (n=11309), higher *PHOX2A* (41 m vs 38.4 m) and *TDGF1 (*42 m vs 37.4 m), and in ER– (n=6402), higher *SCL5A11* (24 m vs 20.7 m) and *KRT40* (23.5 m vs 21.1 m) were associated with better OS, all $p < 0.01$. **Conclusions:** Patient-reported stress and depressive somatic symptoms map to distinct ER-specific tumor transcriptional signatures involving immune regulation, proliferation, metabolism and differentiation. Concordant survival associations support potential clinical relevance and warrant validation to identify actionable targets. Research Sponsor: NIH/NCI and NIH/NCATS; R03TR004607.

			ER+	ER–
HS/LSS	Genes (log_2FC)	Up	*IGLV3-16* (3.3), *IGHV3-30* (2.5)	*IGF2* (4.2)
		Down	*CHGA* (–21.5)	KRT40 (–18.4), PADI3 (–24.1)
	Pathways (NES)		Fcγ-receptor (2.7), B-cell receptor (BCR) (2.7), PD-1 co-inhibition (2.1)	PD-1 co-inhibition (2.4), MHC-I (2.1), ribosome (–2.1)
LS/HSS	Genes (log_2FC)	Up	*PCSK1* (4.0)	*IGFBP1* (7.6), *HSD11B1* (4.6), *OSGIN2* (3.0)
		Down	*PHOX2A* (–6.0), *TDGF1* (–5.4)	*IGHV7-4-1* (–18.9), *MUC2* (–21.5), *SLC5A11* (–21.1), *PADI3* (–22.3)
	Pathways (NES)		Ribosome biogenesis (3.1), IFNα (2.7), G1/S (2.7), G2/M (2.6), BCR (2.6)	Keratinization (2.7), cornified envelope (2.3), antigen presentation (–1.8), G1/S (–1.7)

566 **Poster Session**

Shared and distinct molecular signatures of resistance to different endocrine therapies (Alliance A011106). First Author: Meenakshi Anurag, Baylor College of Medicine, Houston, TX

Background: Endocrine therapy (ET) resistance (ETR) remains a primary challenge in ER+ breast cancer. Analyzing pretreatment tumor transcriptomes across trials with early response endpoints can reveal shared and specific ETR signatures. This study utilizes baseline RNA data from the Phase III ALTERNATE trial (Alliance A011106, NCT01953588; Anastrozole [A], Fulvestrant [F], or AF) and the ACOSOG Z1031B trial (NCT00824941) to identify predictors of early Ki67 response in postmenopausal ER+/HER2– patients. **Methods:** ETR was defined as week-4 on-treatment Ki67 $>10\%$. Baseline gene expression from ALTERNATE was analyzed to identify differentially expressed (DE) genes (Wilcoxon test, $P<0.05$) and Hallmark pathways associated with ETR, both across and within individual treatment arms. Feature selection was performed using mixOmics. A Pan-Endocrine Therapy Signature (PETS) was developed by uniting DE genes identified across all three ALTERNATE arms and Z1031B. All statistical analyses were conducted in R ($P<0.05$). **Results:** Overall ETR rate in the ALTERNATE RNA-seq cohort (n=733) was 26%. ETR was associated with high Risk of Recurrence (ROR), Oncotype RS, and Mammaprint scores (calculated from RNA-seq data in research setting). In luminal tumors (n=649), ETR was linked to chr 3q13.33, 8q24.13, and 20q13.12 cytoband upregulation and 17q21, 18q23, 3p21.1, and 10q24.32 cytoband downregulation. ETR tumors showed T-cell, E2F target, and interferon-γ enrichment; sensitive tumors favored early estrogen response and muscle differentiation. At individual gene level, high *MYBL2*, *PIF1*, *TROAP* and with low HJURP predicted ETR across all samples (AUC>0.70). A deep learning model using all protein-coding genes achieved AUC 0.82 (training) and 0.79 (test) in predicting ETR. Cross-trial integration identified ETR-associated PETS, enriched for genomic instability. PETS performed comparably to established signatures and strongly correlated with *MYBL2* signature (r=0.93). Top ETR predictors were *MYBL2*, *AURKB*, and *EME1* for Arm A and *IL4I1*, *TNFAIP6*, and *ANLN* for Arm AF. AF-resistant tumors were enriched for systemic lupus and RIG-I–like receptor signaling; sensitive tumors favored PI3K–AKT, EGFR TKI resistance, AMPK, and insulin signaling. **Conclusions:** Baseline transcriptomics identify shared and therapy-specific ETR markers. The 15-gene PETS defines a convergent resistance signature, performing similar to established signatures in predicting ETR and correlating with MYBL2. Enrichment of cell-cycle and immune pathways in resistant tumors may suggest patient stratification approach for alternative or combinatorial strategies to overcome early ETR in ER+ breast cancer. Acknowledgement: https://acknowledgments.alliancefound.org. Support: U10CA180821, U10CA180882, U24CA1. Clinical trial information: NCT01953588. Research Sponsor: U.S. National Institutes of Health; U10CA180821, U10CA180882, U24CA196171; Susan G Komen; BCRF; AstraZeneca.

567 Poster Session

Spatial interactions between immune cells as a predictor of pCR to neoadjuvant chemotherapy (NACT) and nivolumab for ER+/HER2− breast cancer (BC): Analysis of the phase II GIADA trial. First Author: Valentina Guarneri, Department of Surgery, Oncology and Gastroenterology, University of Padua and Division of Oncology 2, Istituto Oncologico Veneto IRCCS, Padua, Italy

Background: Adding an immune checkpoint inhibitor (ICI) to NACT increases pathological complete response (pCR) rates in ER+/HER2− high-risk BC, at the cost of immune-related toxicity. Biomarkers are needed to improve patient (pts) selection. We here assess the association between immune cell spatial interactions and pCR in the GIADA trial (Dieci, CCR 2022). **Methods:** In the phase II GIADA trial, 43 premenopausal pts with stage II–IIIA ER+/HER2− Luminal B-like BC (Ki67 ≥ 20% and/or G3) received NACT with ECx3 followed by nivolumab (240mg q2w x8) and endocrine treatment. Tumor biopsies at baseline (T0) and after EC (T1) were assessed using multiplex immunofluorescence panels: (1) CD4, CD8, Granzyme B, FoxP3, CD20, pan-cytokeratin (CK), and DAPI; (2) CD3, CD68, CD163, PD-1, PD-L1, CK, and DAPI. Interactions were quantified using a count-within approach. The number of reference immune cells located in a ≤20 μm radius of cells with a different phenotype (high probability of cell-cell contact) was calculated and normalized to number of reference cells. Association with pCR was assessed by binomial generalized linear models. **Results:** At baseline (T0), spatial interaction of tumor cells (CK+) with multiple immune cells (CD4+, CD8+, FOXP3+, CD68+), including cytotoxic, immunosuppressive and macrophagic subpopulations, was associated with pCR. Moreover, interaction of cytotoxic CD8+GranzymeB+ T-cells with regulatory FOXP3+ cells was associated with pCR. Interactions between PD-1+ and PD-L1+ cells were associated with pCR, mainly CK+PD-L1+/CD3+PD-1+ in tumor area and CD3+PD-1+/CD68+PD-L1+ in stroma. After chemotherapy (T1), only spatial interactions between tumor cells and CD8+ and CD4+ T-cells were associated with pCR. The role of cytotoxic CD8+GranzymeB+ T-cells appeared stronger as interactions with multiple immune subpopulations (CD4+, CD8+, CD8+GranzymeB+, FOXP3+, CD20+) were associated with pCR, overall (OR 1.06-1.73) and in stroma (OR 1.06-1.40). Interaction of CK+ tumor cells with PD-1+ cells in the tumor area and with CD68+ PD-L1+ macrophages in the stromal area was associated with pCR. **Conclusions:** Spatial immune profiling identifies distinct tumor-immune interaction patterns associated with pCR in high-risk ER+/HER2− BC treated with NACT and ICI. Clinical trial information: NCT04659551. Research Sponsor: Bristol Myers Squibb; Fondazione AIRC; 22759; Veneto Institute of Oncology IOV-IRCCS; NA.

Selected spatial interactions significantly associated with pCR.

	T0 overall	T0 tumor	T0 stroma	T1 overall	T1 tumor	T1 stroma
CK+ / CD4+	OR 1.08, p=0.034	OR 1.13, p=0.017		OR 1.07, p=0.038		
CK+ / CD8+	OR 1.21, p=0.005	OR 1.34, p=0.005	OR 1.06, p=0.049	OR 1.12, p=0.008	OR 1.16, p=0.021	OR 1.08, p=0.011
CK+ / FOXP3+	OR 1.21, p=0.017	OR 1.28, p=0.024				
CK+ / CD68+	OR 1.07, p=0.016		OR 1.09, p=0.007			
CK+PD-L1+ / CD3+PD-1+		OR 1.22, p=0.025				
CD3+PD-1+ / CD68+PD-L1+			OR 1.08, p=0.047			
CK+ / PD-1+ cells			OR 1.13, p=0.027	OR 1.27, p=0.015	OR 1.29, p=0.027	
CK+ / CD68+PD-L1+			OR 1.21, p=0.036			OR 1.44, p=0.030

568 Poster Session

Characteristics of cancer patients undergoing molecular residual disease testing with a tumor-informed assay. First Author: Gargi D. Basu, Exact Sciences, Phoenix, AZ

Background: Detection of circulating tumor DNA (ctDNA) is strongly associated with recurrence across a variety of cancers. The use of ctDNA testing to measure molecular residual disease (MRD) is still in its infancy, and understanding sample characteristics may help set expectations for oncologists and their patients. **Methods:** For the first thousand patients with MRD testing in Exact Sciences' commercial laboratory, the tumor and first plasma sample were used to record tumor type, tumor sample type (biopsy/surgical), tumor stage, MRD assay panel size (up to 200 variants), cfDNA levels, and ctDNA status (qualitative and quantitative), and, when data were available, presence of targetable alterations (TAs) were recorded. **Results:** A total of 1088 samples with valid results were included. Patients were mostly female (N=703, 64.6%) with a median age of 64 (range 17–97) years, and most had either breast (N=380, 34.9%) or colorectal (N=335, 30.8%) cancer. Most (N=632, 58.1%) tumor samples were surgical, and average number of variants for MRD assays from 86 in ovarian cancer to 189 in melanoma. Plasma cfDNA yield ranged from 15 ng (the minimum required) to 10,709 ng and was significantly higher in 412 ctDNA+ (median 86.1 ng, mean 239.7 ng) compared to ctDNA− (median 73.5 ng, mean 114.6 ng) samples ($p<0.001$). In 13 cancers with at least 10 patient samples, only breast cancer showed a difference in the average number of identified variants between sample types (biopsy: 129.1 versus surgical: 101.5), stage IV cancers had more cfDNA than stage I, range of ctDNA+ samples was from 27% in melanoma to 65% in gastroesophageal cancers, and ctDNA+ proportion tended to increase with stage: 26 (14.2%) of 183 stage I, 84 (32.1%) of 262 stage II, 140 (38.9%) of 360 stage III, and 140 (65.1%) of 215 stage IV. ctDNA+ samples had levels between 2.6 and ≥352,000 parts per million (PPM), with 27 (6.6%) samples below 15 PPM, 40 (9.7%) between 15 and 50 PPM, and 345 (83.7%) above 50 PPM. Genomic profiling was performed on 158 samples, most from breast (N=50, 31.6%) and colorectal (N=17, 10.8%) cancer patients. The mean number of TAs per sample was 4.6, with little difference between the 114 ctDNA+ patients (mean = 4.4, range 0–24) and 44 ctDNA− patients (mean = 5.1, range 1–29). TAs were present in 83 (72.8%) and 36 (81.8%) tumors in ctDNA+ and ctDNA− patients, respectively. Of note, both high microsatellite instability and high tumor mutational burden tumors had numerically higher proportion in ctDNA− (15.9% and 9.1%, respectively) compared to ctDNA+ (5.3% in both) patients. **Conclusions:** ctDNA+ frequency varied by cancer type and cfDNA yields and ctDNA+ proportion increased numerically with stage, though where patients were in their treatment cycles was unknown. Of patients with profiling results, a large proportion of patients had TAs regardless of ctDNA status, indicating a potential for immediate consideration of matched therapies in ctDNA+ patients. Research Sponsor: Exact Sciences.

569 Poster Session

mTOR activation and racial disparity in early breast cancer survival. First Author: Ekaterina Proskuriakova, University of Illinois Chicago, Department of Hematology and Oncology, Chicago, IL

Background: Black women have lower survival rates following a diagnosis of estrogen receptor-positive (ER+) early breast cancer (EBC) compared with White women, with 80% higher mortality and more frequent genomically high-risk tumors (Hoskins et al, JAMA Oncol, 2021). A whole-transcriptome comparison of 412 luminal tumors from Black women with EBC and age-matched White women showed increased mTOR signaling in tumors from Black patients (Hoskins et al. J Clin Oncol 2021, 39:15_suppl, 1009-1009), suggesting a molecular driver of the survival disparity. This study aimed to confirm increased mTOR pathway activation at the protein level in Black patients with an independent cohort, and to explore factors responsible for racial differences in luminal tumor biology. **Methods:** A breast tumor tissue microarray (TMA) comprising primary tumor cores from diverse patients with EBC was analyzed with multiplex immunofluorescence staining to quantify protein markers of mTOR pathway activation (pS6K and pAkt). Image segmentation was performed with pan-cytokeratin staining to delineate tumor cells from stromal cells. Halo HighPlex image analysis software was used for automated digital image analysis to calculate an H-score for each tumor core. Ancestry admixture analysis was performed with ancestry informative markers that are located within coding regions of genes using RNAseq data generated from tumors represented on the TMA. Data on contextual factors was obtained by geocoding patients' residential address at the time of diagnosis and linking to a census tract-level measure of neighborhood disadvantage (Area Deprivation Index-ADI). mTOR pathway activation levels were compared by self-identified race, proportion of African ancestry, body mass index (BMI), insurance status, and ADI. One-sided t-tests evaluated mean H-scores for pS6K and pAkt in tumor cells for various comparisons. **Results:** Analysis of 70 ER+ primary tumors from Black patients and 43 tumors from White patients showed mean pS6K staining in pan-cytokeratin-positive cells was significantly higher in tumor cores from Black compared with White patients (p-value = .05). Ancestry admixture analysis (dichotomized by the proportion of African ancestry $>$ 0.4 vs. $<$ 0.4) showed significantly increased pS6K staining in patients with greater proportion of African ancestry (p-value = .04). There was no association with ADI (p-value = .30). Analyses of association with insurance status and BMI, multivariable analyses, and survival analyses are ongoing and results will be presented, along with data on pAkt staining. **Conclusions:** This study demonstrated increased mTOR pathway activation at the protein level in Black women with ER+ EBC, confirming the result of a prior gene expression analysis. The underlying cause of this racial difference is unknown, but findings support development of clinical trials targeting the mTOR signaling pathway to mitigate racial disparity in EBC survival. Research Sponsor: None.

570 Poster Session

Evaluation of whole-exome and whole-genome sequencing tumor-informed circulating tumor DNA MRD assays in patients with early triple-negative breast cancer (TNBC) receiving neoadjuvant chemotherapy (NAC) with or without olaparib: A prospective sub-study of the PARTNER trial. First Author: Andrew Dooley, Precision Breast Cancer Institute, Department of Oncology, University of Cambridge, Cambridge, United Kingdom

Background: Detection of molecular residual disease (MRD), using circulating tumor DNA (ctDNA), following treatment for early-stage TNBC is associated with a high risk of recurrence. ctDNA clearance in response to NAC has shown potential for predicting pathologic compete response (pCR) and improving the prognostic ability of pCR status. PARTNER is a prospective, phase II-III, randomized controlled clinical trial, which recruited early-stage basal TNBC BRCA1/2 wild-type patients (Nature April 2024). Control regimen was neoadjuvant carboplatin–paclitaxel followed by anthracycline-based NAC. Experimental arms added olaparib to the platinum-taxane backbone. A sub-study of serial blood samples for ctDNA analysis during NAC and post-op were analyzed with 2 tumor informed MRD assays using primary tumor and germline sequencing: 1) whole-exome sequencing (WES) to select ≤200 variants and 2) whole-genome sequencing (WGS) to select 400-5000 variants for the two bespoke MRD assays, respectively. Both assays were independently used to assess available plasma samples collected for the presence or absence of ctDNA. **Methods:** This prospective sub study included TNBC patients enrolled within PARTNER with serial blood collections at baseline (prior to NAC), mid-NAC, post-NAC, 2-4 weeks post-op, 3 months post-op and 12 months post-op. Germline and somatic DNA were provided via the Personalised Breast Cancer Program. The primary objective was to determine the association of ctDNA positivity post-op with distant recurrence-free interval (DRFI). The distribution of DRFI by ctDNA status was compared using the log-rank test. The Cox proportional hazards regression model was used to estimate the strength of the relationship between ctDNA positivity and DRFI. **Results:** Median WES MRD assay panel size was 159 variants (range 47 – 200). At baseline ctDNA was detected in 50 of 55 patients (91%). After NAC, 4 of 63 patients had detectable ctDNA. 24 of 28 non-pCR patients were ctDNA negative and 0 of 35 pCR patients were ctDNA positive. Of 61 post-op patients available to assess DRFI distant recurrences developed in 8 patients (13.1%) within a median follow up of 5 years. Post-op 5 patients were ctDNA positive and 3 developed distant recurrences (log-rank $p < 0.0001$, HR = 20.2, 95% CI = 4.3, 95.1). In addition, 56 were ctDNA negative and 51 (91%) were distant recurrence free. Median WGS MRD assay panel size was 2962 variants (range 552 - 5000). At baseline ctDNA was detected in 46 of 47 patients (98%). Additional WGS MRD results are being generated and will be presented at the meeting. **Conclusions:** Post-op detection of ctDNA using a WES MRD assay was highly prognostic for distant recurrence in TNBC patients following NAC. WGS MRD improved baseline detection. Research Sponsor: Exact Sciences.

571 **Poster Session**

Molecular profiling of male breast cancer in Brazil: Comprehensive genomic characterization of a Latin American cohort. First Author: Elizabeth Santos, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: Male breast cancer (MBC) is a rare disease, accounting for < 1% of all breast cancers. Current treatment recommendations are largely extrapolated from female breast cancer data, which may not reflect the distinct biological features of MBC. Notably, MBC is associated with higher mortality rates than female breast cancer. Molecular data from Latin America are scarce. This study aimed to characterize the clinicopathological and molecular features of MBC in a Brazilian cohort, addressing an important knowledge gap in an underrepresented population. **Methods:** Medical records of 106 men diagnosed with breast cancer at three Brazilian cancer centers between 2000 and 2022 were reviewed. Tumor samples from 48 patients were available for molecular analysis after centralized histopathological review. FFPE samples with ≥10% tumor cellularity were included. DNA and RNA were extracted using the AllPrep kit (Qiagen). Libraries were prepared using the Oncomine Focus Assay (Thermo Fisher Scientific) and sequenced on the Ion S5 platform. Bioinformatic analysis for single nucleotide variants (SNVs), insertions/deletions, copy number variations (CNVs), and gene fusions was performed using Ion Reporter software. **Results:** The median age at diagnosis was 58.5 years (range: 33–84). A family history of cancer was reported in 64% of patients, including female breast cancer in 32%. Most tumors were invasive ductal carcinomas (87.7%), high grade (grades 2–3; 90%), and hormone receptor–positive (93%). HER2+/HR– and triple-negative subtypes accounted for 0.9% and 3.9%, respectively. Most patients (88.5%) presented with localized or locally advanced disease. The most frequent pathogenic variants were PIK3CA (28%), followed by MAP2K1, BRAF, and AKT1 (6% each), and EGFR, JAK3, and MTOR (3% each). The most common CNV amplifications involved MYC (24%), FGFR1 (20%), CCND1 (16%), and ERBB2 (4%). No gene fusions were identified. Pathway analysis revealed alterations in PI3K/AKT/mTOR (37%), Cell Cycle (40%), FGF signaling (20%), and MAPK (12%) pathways. Overall, 46% of patients harbored potentially actionable SNVs, and 24% harbored potentially actionable CNVs. **Conclusions:** This is the first comprehensive molecular characterization of MBC in Brazil. Our findings confirm PIK3CA as the most frequent alteration, consistent with international cohorts, supporting the central role of the PI3K/AKT/mTOR pathway in MBC. Additional alterations in Cell Cycle and FGF signaling pathways highlight distinct oncogenic drivers. The high prevalence of potentially actionable genomic alterations suggests that molecular profiling may inform treatment selection for a substantial proportion of patients. These findings underscore the limitations of extrapolating treatment guidelines from female breast cancer and support biomarker-driven clinical trials for men with breast cancer in Latin America. Research Sponsor: None.

572 **Poster Session**

Functional domain disruption to define the molecular and clinical spectrum of germline *RAD51* family variants in hereditary breast cancer (BC). First Author: André Luiz Cicilini, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: RAD51 paralogs (RAD51C, RAD51D, XRCC2) and RAD50 are crucial in DNA repair. Germline pathogenic variants (PVs) increase hereditary breast/ovarian cancer risk, but domain-specific impacts remain unclear. **Methods:** Retrospective cohort study (2019-2025) of breast cancer patients undergoing multigene testing. PVs were mapped to functional domains. Tumor features included histology, stage, grade, TILs, and molecular subtype. Associations were assessed using Fisher's exact test. **Results:** Among 495 patients, 23 (4.6%) had RAD51 family PVs (RAD51C = 16, RAD51D = 4, RAD50 = 1, XRCC2 = 1). Median diagnosis age was 49. Synchronous malignancies were significantly more frequent in RAD51 carriers vs. BRCA1 carriers (34.8% vs.; OR 3.51, 95% CI 1.09–11.26). Most variants (22/23) were truncating (11 nonsense, 9 frameshift, 1 splice-site, 1 exon deletion). Domain mapping revealed disruption of critical regions: RAD51-like core domain truncations (RAD51D p.Arg186*; RAD51C p.Arg193*), RAD51C C-terminal truncations removing essential regions for complex integrity, and early RAD50 truncation predicted to abolish MRN complex function. Tumors were predominantly early-stage (65.2% stage I). Histology showed invasive carcinoma of no special type (69%) and invasive lobular carcinoma (25%), with strong enrichment of lobular histology in RAD51C carriers ($p < 0.001$). RAD51C tumors were basal-like or luminal A, while the RAD50 tumor was luminal B HER2-positive. RAD51C tumors often had high nuclear grade (77.3%) but low TILs (71%). **Conclusions:** RAD51 family PVs are primarily truncating, disrupting key HRR domains and supporting loss-of-function as the main mechanism. Domain location correlates with distinct clinicopathological features, refining genotype–phenotype correlations for improved risk assessment. Research Sponsor: None.

573 **Poster Session**

Multi-omic profiling to identify RNA-protein concordance and post-transcriptional dysregulation in HER2+ breast cancer. First Author: Pahini Pandya, Panakeia Technologies, Cambridge, United Kingdom

Background: Standard HER2 testing relies on single-modality assays, such as immunohistochemistry (IHC) for protein overexpression and in situ hybridization (ISH) for gene amplification. These tests may fail to capture the regulatory complexity underlying HER2 biology, including post-transcriptional modulation, which may result in RNA-protein discordance and potentially drive therapeutic resistance. We performed a multi-omic analysis to characterize functional HER2 biology and uncover regulatory mechanisms not captured by standard diagnostic testing. **Methods:** We utilized Panakeia's multi-omics platform to analyze a set of 475 breast cancer samples with a complete set of *ERBB2* RNA and protein expression values from the Cancer Genome Atlas (TCGA). HER2+ (n=79) and HER2− (n=396) cohorts were defined using clinical HER2 status assessed via IHC/ISH. Transcriptomic and proteomic over-expression states were binarized by thresholding RNA/protein expression values. RNA-protein concordance was assessed to define four molecular states of the tumor: coordinated activation (RNA+/Protein+), coordinated inactivation (RNA−/Protein−), translation blocks (RNA+/Protein−), or post-transcriptional upregulation (RNA−/Protein+). **Results:** A strong correlation was measured between RNA and protein over-expression (Pearson's correlation r=0.752, $p<0.001$) with 93.7% concordance (445/475). Molecular patterns with respect to HER2 clinical status were observed as follows: (1) coordinated activation (n=48, 10.1%) with 95.8% HER2+ concordance (46/48), validating HER2 over-expression; (2) coordinated inactivation (n=397, 83.6%) with 95.2% HER2− concordance (378/397), confirming HER2 inactivity; (3) RNA+/Protein− translation blocks (n=29, 6.1%) where *ERBB2* RNA was over-expressed but not translated; (4) RNA−/Protein+ (n=1, 0.2%). Among 79 HER2+ patients, only 46 (58.2%) showed functional translation (RNA+/Protein+), while 19 (24.1%) had complete molecular negativity (both inactive) and 14 (17.7%) exhibited translation blocks. Multi-omics profiling identified actionable changes in 35/475 cases (7.4%): 19 potential over-treatment candidates, 14 potential treatment resistance cases, and 2 potential under-treatment cases that are clinically HER2− but exhibit coordinated molecular activity. **Conclusions:** Integrative multi-omic analysis of the HER2 molecular landscape enabled assessment beyond standard-of-care assays, identifying non-responders to HER2-targeted therapy by capturing post-transcriptional dysregulation not detected by single-modality testing. Overall, multi-omic profiling can support precision stratification by confirming active HER2 signalling, identifying potential over-treatment, refining patient selection and guiding treatment decisions. Research Sponsor: None.

574 **Poster Session**

Exploring diversity and composition of sulfidogenic gut bacteria in breast cancer. First Author: Tazeena Khan, College of Medicine, University of Illinois at Chicago, Chicago, IL

Background: Sulfidogenic bacteria produce hydrogen sulfide, the excess of which is genotoxic and proinflammatory and is absorbed through the GI tract into the systemic circulation. The role of sulfidogenic bacteria in BC has not been explored. In this study, we aimed to evaluate sulfidogenic bacterial abundance and diversity in BC. We hypothesized that there will be lower alpha and beta diversity in BC groups. We also hypothesized that there will be a higher relative abundance of sulfidogenic bacteria in BC vs. controls. **Methods:** We used high throughput sequencing of the dsrA gene in stool samples of female participants with BC and controls without BC (n=283). Controls were further delineated into normal mammogram, abnormal mammogram with no evidence of BC (e.g. cysts, etc), and controls without BC but with a first degree relative who has BC. To process the sequences, QIIME2 bioinformatics pipelines were used with taxonomy assigned using the SILVA database. We performed alpha diversity analyses with nonparametric statistics, and beta diversity analyses using the Bray-Curtis and weighted/unweighted UniFrac metrics. Differential abundance of sulfidogenic bacteria at the genus level was calculated in R using the DESeq2 package. In the same samples, we used sequencing of the V3-V4 region of the 16s rDNA gene to compare relative abundance of total sulfidogenic bacteria between BC samples and controls in R using the DESeq2 package. **Results:** Using the Chao1 metric, we found higher sulfidogenic alpha diversity in BC vs. all controls ($p < 0.001$), BC vs. controls who have a first degree relative with BC ($p = 0.005$). as well as within controls with a normal mammogram vs. abnormal mammogram without BC ($p = 0.037$). We did not find significant differences in beta diversity between BC vs. controls. When analyzed visually using PCoA of unweighted UniFrac distances, there were two clusters within all patient groups, indicative of two enterotypes across all subjects. We did not find a significant difference in the relative abundance of overall sulfidogenic bacteria as identified by the 16S rDNA gene between BC and controls. However, *Desulfovibrio* was enriched in BC compared to normal mammogram samples with a log fold change of 1.69 ($p = 0.013$). **Conclusions:** These results suggest altered sulfidogenic gut bacterial community composition in individuals with BC, particularly in organisms with lower relative abundance. *Desulfovibrio* appears as a predominating organism in BC. This is supported by prior research, which suggests *Desulfovibrio* becomes less abundant in participants exposed to agents that inhibit BC cell proliferation. We propose that there are two enterotypes of sulfidogenic gut bacteria in women. Research Sponsor: NIH (National Institutes of Health); University of Illinois.

575 Poster Session

Beyond convolution: Attention-driven vision transformer modeling for breast cancer detection on mammography. First Author: Tanzeela Mariam Shuja, Northwestern McHenry Hospital, Mchenry, IL

Background: Breast cancer is the most commonly diagnosed malignancy among women worldwide, and screening mammography remains central to early detection and mortality reduction. Despite standardized reporting systems, mammographic interpretation is challenged by tissue overlap, subtle lesion morphology, and interobserver variability. Convolutional neural networks (CNNs) have demonstrated strong performance in automated mammography analysis but rely on localized receptive fields that may limit modeling of global spatial relationships critical for detecting architectural distortion and diffuse malignancy. Vision Transformers (ViTs) employ self-attention mechanisms that enable global contextual modeling across entire images. We evaluated the performance of a Vision Transformer for breast cancer classification on mammographic imaging. **Methods:** We analyzed over 8,000 anonymized mammography images obtained from publicly available Kaggle datasets curated and annotated by expert radiologists. Images included malignant and non-malignant breast findings and were preprocessed and resized to 224×224 pixels. Data were split into training and validation cohorts using stratified sampling at the patient level to prevent data leakage. A Vision Transformer B/16 model pretrained on ImageNet was fine-tuned for binary classification. Images were divided into non-overlapping 16×16 patches, embedded into token sequences with positional encodings and a learnable class token, and processed through 12 transformer blocks with multi-head self-attention. Model performance was evaluated using accuracy, sensitivity, specificity, F1 score, and area under the receiver operating characteristic curve (AUROC). **Results:** The ViT-B/16 model achieved high diagnostic performance, with validation accuracy approaching approximately 96% and AUROC exceeding 0.98. Sensitivity for malignant lesions remained robust across dense and non-dense breast tissue. Attention-based global processing reduced misclassification of lesions with diffuse margins, asymmetric density, and architectural distortion—patterns that are challenging for purely convolutional approaches. Performance was comparable to state-of-the-art CNN models, though achieved with higher parameter count and computational cost. **Conclusions:** Vision Transformer–based modeling enables accurate breast cancer detection on mammography by capturing global contextual relationships through self-attention. While computationally heavier than optimized CNNs, ViT offers complementary strengths in modeling complex spatial patterns and provides interpretable attention maps aligned with radiologic reasoning. These findings support further evaluation of transformer architectures in large-scale breast cancer screening and diagnostic workflows. Research Sponsor: None.

576 Poster Session

ILCness to stratify lobular-like breast cancer biology and as an outcome independent of *CDH1* mutation in early ER-positive/HER2-negative breast cancer. First Author: Masanori Oshi, Yokohama City University Hospital, Yokohama, Japan

Background: Invasive lobular carcinoma (ILC) represents a distinct histological subtype of breast cancer; however, its underlying molecular basis remains incompletely defined. Although loss-of-function mutations in CDH1 are considered a hallmark genetic event, substantial biological heterogeneity persists that cannot be fully explained by histology or mutation status alone. **Methods:** To address this limitation, we developed a continuous transcriptional framework, termed the ILCness score, to quantitatively capture lobular-like tumor biology. A tightly constrained principal component–based model was trained in the METABRIC cohort and fully fixed without retraining, enabling reproducible projection across independent datasets and expression platforms. **Results:** Unsupervised transcriptomic analyses demonstrated that invasive ductal carcinoma (IDC) and ILC did not form discrete expression clusters but instead distributed along a continuous molecular spectrum. The ILCness score robustly captured this continuum, with mixed-histology tumors occupying intermediate positions. Importantly, lobular-like transcriptional programs quantified by ILCness showed limited concordance with CDH1 mutation status. Across tumors, higher ILCness was consistently associated with reduced DNA repair and E2F target activity (Spearman $|\rho| > 0.4$, $P < 0.001$), whereas epithelial–mesenchymal transition displayed a context-dependent pattern. Tumor microenvironment analyses revealed that stromal and immune cell infiltration correlated more strongly with ILCness than with CDH1 mutation status. These associations were reproducibly validated in independent cohorts without model recalibration. Clinically, ILCness stratified prognostically distinct subgroups within histologically defined tumors, including IDC, independent of CDH1 mutation (disease-specific survival, $P < 0.01$). Across multiple neoadjuvant and systemic therapy datasets, higher ILCness showed consistent directional associations with reduced pathological complete response to chemotherapy and differential response patterns to immune checkpoint inhibition and endocrine therapy. **Conclusions:** These findings establish lobular breast cancer as a continuum of transcriptional states rather than a discrete entity defined by histology or single-gene alterations. The ILCness score provides a scalable RNA-based framework for integrating molecular heterogeneity with tumor biology and clinical behavior, with potential implications for biologically informed patient stratification. Research Sponsor: None.

577 Poster Session

Neighborhood disadvantage and correlation with differences in somatic mutations in a real-world breast cancer cohort. First Author: Jacquelyn Dillon, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Background: African compared to European genetic ancestry is associated with lower prevalence of clinically actionable alterations despite comparable overall prevalence of driver alterations by ancestry group. This likely contributes to breast cancer (BC) disparity. A limitation of prior ancestry studies is lack of neighborhood-level disadvantage (ND) data, a contributor to BC disparity. The objective of this study was to investigate associations between ND and somatic mutations in a real-world BC cohort. **Methods:** Somatic mutations from primary and metastatic BC samples and genetic ancestry data were identified from MSK IMPACT (FDA-authorized sequencing panel). Samples sequenced between 2015-2025 were annotated and linked with census-tract level socioeconomic status (Yost Index 1-100; higher reflects increasing ND). Multivariate logistic regression analyzed associations between ND and somatic mutations, adjusting for covariates (FDR $p<0.05$). **Results:** 6703 samples (62% primary, 38% metastatic) were analyzed. Mean age was 60 (SD 13). Mean Yost was 26 (SD 24). 67% had ER+/HER2- disease, 9.7% had ER+/HER2+, 5.1% had ER-/HER2+, and 19% had ER-/HER2-. Adjusting for age, BMI, ancestry, and subtype, patients from ND had lower odds of CDH1 (OR 0.99, 95% CI 0.98- 0.99, $p<0.001$), BRCA1 (OR 0.96, 95% CI 0.94-0.99, p=0.021), and AKT1 (OR 0.98, 95% CI 0.97- 0.99, p=0.006) somatic mutations in metastatic samples. **Conclusions:** We identify novel associations between ND and somatic mutations. Notably, patients with ND had lower odds of actionable BRCA1 and AKT1 mutations. This highlights the importance of ensuring patients of diverse ancestry and ND have equitable inclusion in clinical sequencing workflows to improve identification of actionable mutations in all populations. Research Sponsor: None.

Genetic ancestry (GA) and somatic mutational frequency by Yost.

	Total N=6703[1]	Yost 1-20 (Most Advantaged) N=3601[1]	Yost 21-40 N=1539[1]	Yost 41-60 N=826[1]	Yost 61-80 N=477[1]	Yost 81-100 (Most Disadvantaged) N=260[1]	p-value[2]
European GA*	0.75 (0.36)	0.83 (0.30)	0.72 (0.38)	0.64 (0.39)	0.58 (0.39)	0.42 (0.35)	<0.001
African GA*	0.12 (0.27)	0.04 (0.16)	0.15 (0.30)	0.21 (0.34)	0.25 (0.36)	0.44 (0.38)	<0.001
East Asian GA*	0.05 (0.21)	0.05 (0.21)	0.06 (0.22)	0.06 (0.21)	0.07 (0.23)	0.04 (0.17)	<0.001
South Asian GA*	0.06 (0.16)	0.06 (0.17)	0.05 (0.15)	0.06 (0.17)	0.04 (0.12)	0.03 (0.08)	<0.001
Native American GA*	0.03 (0.10)	0.01 (0.07)	0.03 (0.10)	0.04 (0.12)	0.06 (0.16)	0.08 (0.17)	<0.001
Mutational Frequency, metastases	N=2536[1]	N=1403[1]	N=584[1]	N=311[1]	N=165[1]	N=73[1]	p-value[2^A]
CDH1	341 (13%)	220 (16%)	66 (11%)	26 (8.4%)	18 (11%)	11 (15%)	<0.001
AKT1	127 (5.0%)	74 (5.3%)	34 (5.8%)	12 (3.9%)	4 (2.4%)	3 (4.1%)	0.006
BRCA1	21 (0.8%)	13 (0.9%)	7 (1.2%)	1 (0.3%)	0 (0%)	0 (0%)	0.021

*Calculated using >3,000 common SNP markers.
^MVA, control for age, BMI, ancestry, subtype.
[1]Mean (SD), n (%).
[2]Pearson's Chi^2 test; Kruskal-Wallis rank sum test; Fisher's exact test.

578 Poster Session

Does surgery improve breast cancer–specific survival in low-grade DCIS?: A 20-year population-based analysis by nuclear grade. First Author: Fatih Aydogan, ACIBADEM Health Group Breast Center, Istanbul, Turkey

Background: Active surveillance is increasingly discussed for low-risk ductal carcinoma in situ (DCIS), yet randomized trials report only short-term outcomes. Long-term survival data stratified by nuclear grade remain limited. We evaluated the association between cancer-directed surgery and long-term breast cancer–specific survival (BCSS) and overall survival (OS) in DCIS. **Methods:** We conducted a retrospective population-based cohort study using SEER 17 registries, including patients diagnosed with DCIS between 2000 and 2019 with follow-up exceeding 36 months. Exposure was cancer-directed surgery (yes vs no). Outcomes were BCSS, analyzed using cause-specific Cox models, and OS. Prespecified covariates included age, year of diagnosis, race, tumor size, nuclear grade, estrogen and progesterone receptor status, median household income, and residence type. Missing data were handled using multiple imputation. Confounding was addressed using inverse probability of treatment weighting with stabilized weights. Analyses were stratified by nuclear grade (Grades 1–3). **Results:** Among 51,637 patients, 50,346 (97.5%) underwent surgery and 1,291 (2.5%) did not. Median follow-up was 120 months. In the overall cohort, surgery was associated with improved BCSS (hazard ratio [HR] 0.13; 95% CI, 0.09–0.19) and OS (HR 0.65; 95% CI, 0.56–0.75). Outcomes differed substantially by nuclear grade. In Grade 1 DCIS, surgery was not associated with improved BCSS (HR 0.57; 95% CI, 0.05–6.16), with 20-year BCSS exceeding 99% regardless of treatment, although OS favored surgery. In Grade 2 DCIS, surgery reduced breast cancer–specific mortality (HR 0.22; 95% CI, 0.10–0.45) without an OS benefit. In Grade 3 DCIS, surgery conferred marked improvements in both BCSS (HR 0.10; 95% CI, 0.06–0.15) and OS (HR 0.49; 95% CI, 0.40–0.60). **Conclusions:** In this large population-based study with up to 20 years of follow-up, omission of surgery in low-grade DCIS was not associated with worse breast cancer–specific survival, whereas clear survival benefits were observed in intermediate- and high-grade disease. These findings support risk-adapted management strategies and provide long-term survival context for active surveillance approaches in DCIS. Research Sponsor: None.

579 **Poster Session**

Wire-guided versus radio-guided localization for non-palpable occult lesion in breast tissue: A systematic review and meta-analysis. First Author: Mobeen Farooqi, CMH Lahore Medical College, Lahore, Pakistan

Background: Accurate preoperative localization of non-palpable breast lesions is crucial for successful breast-conserving surgery. Wire-guided localization (WGL) has traditionally been the standard technique; radio-guided localization (ROLL) has emerged as an alternative approach with potential benefits in surgical precision and workflow. Current evidence comparing the efficacy and safety of these two techniques remains inconsistent. This systematic review and meta-analysis evaluates WGL versus ROLL for non-palpable breast lesions with respect to surgical and oncological outcomes. **Methods:** A systematic literature search was conducted on electronic databases from inception until January 2026. Outcomes included re-excision rates, margin involvement, specimen volume and weight, accurate localisation of lesions and operative time. We employed risk ratios (RRs) with 95% Confidence Intervals (CIs) for dichotomous outcomes. Mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs were computed for continuous outcomes using Review Manager V.5.4. Quality assessment and risk of bias were assessed using the Cochrane Risk of Bias Tool 2 on all included RCTs. **Results:** This systematic review and meta-analysis included 13 studies with a total of 5,318 patients. There was no statistically significant difference in the re-excision rates between the two interventions (OR = 1.44; 95% CI: [0.73, 2.83], p = 0.143). Localization time (SMD = 1.75; 95% CI: [-1.01, 4.51], p = $<$0.0001) and length of operation time was significantly shorter in the ROLL group (SMD = 0.22; 95% CI: [0.10, 0.34], p = 0.028). There was no statistically significant difference in the margin involvement between the two groups (OR = 0.61; 95% CI: [0.37, 0.99], p = 0.063). ROLL was associated with significantly smaller volume of specimen (SMD = 0.16; 95% CI: [-5.41, 5.73], p = $<$0.0001). **Conclusions:** ROLL and WGL demonstrate comparable oncological outcomes, with no significant differences in the re-excision rates or margin involvement. However, ROLL is associated with significantly shorter localization and operative times, suggesting procedural efficiency over WGL. Research Sponsor: None.

580 **Poster Session**

Intraoperative precision margin assessment in breast-conserving surgery using handheld fluorescence microscopy. First Author: Jing Wang, First Affiliated Hospital of USTC, Hefei, China

Background: Breast-conserving surgery (BCS) is the standard treatment for early-stage breast cancer and is increasingly preferred by younger patients. The key challenge in BCS is ensuring complete tumor removal while preserving healthy breast tissue. Surgical margin assessment plays a crucial role in reducing the risk of local recurrence. Traditional intraoperative frozen sections (FS) are time-consuming, limit sampling, and may cause tissue damage. This study evaluates the performance of EndoScell, a handheld fluorescence microscopy system, as a rapid and efficient alternative for intraoperative margin assessment. **Methods:** EndoScell provides real-time, high-resolution imaging of tissue margins during surgery. This system rapidly stains and scans tissue, allowing for micron-level visualization of cellular features. In this study, EndoScell was used to scan marked surfaces of breast tissue during surgery. The surgeon performed an initial assessment, while images/videos were recorded. Specimens were then sent for intraoperative FS analysis for comparison. If FS identified positive margins, the area was re-excised by 3–5 mm, and the process was repeated. Routine paraffin pathology served as the gold standard, with blinded side-by-side reading of ES images to evaluate consistency. **Results:** As of December 31, 2025, 300 patients undergoing BCS were included. EndoScell demonstrated high diagnostic accuracy with a sensitivity of 96.4%, specificity of 95.1%, and AUC of 0.953, showing strong agreement with paraffin pathology. Notably, the time required for EndoScell imaging was significantly shorter than FS, with an average of 3.14 $\pm$ 1.48 minutes compared to 37.50 $\pm$ 13.34 minutes for FS ($P<0.001$), leading to substantial improvements in surgical efficiency. **Conclusions:** This study confirms the feasibility and non-inferiority of EndoScell for intraoperative margin assessment in breast-conserving surgery. The system enables real-time decision-making, reducing secondary surgeries, improving outcomes, and enhancing surgical safety. Its significant clinical and social value supports further development and implementation. Research Sponsor: None.

Key metrics related to diagnostic accuracy and time efficiency between EndoScell and traditional frozen section methods.

Metric	EndoScell (ES)	Frozen Section (FS)
Positive Margin	54	56
Negative Margin	246	244
Sensitivity	0.964	1.000
Specificity	0.951	1.000
AUC	0.953 (95% CI: 0.912–1.003)	1.000
Imaging Time (min)	3.14 $\pm$ 1.48	37.50 $\pm$ 13.34
p-value	$<$0.001	N/A
Cohen's d	-3.64	N/A

581 **Poster Session**

Impact of time-to-surgery on survival outcomes in Korean breast cancer patients: A nationwide population-based cohort study. First Author: Je Hyun Chin, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

Background: The increasing incidence of breast cancer and the resulting surgical workload in South Korea have led to concerns regarding surgical delays. While the clinical impact of time-to-surgery (TTS) remains debated, defining an optimal threshold is crucial for health policy and patient outcomes. This study aimed to investigate the impact of TTS on overall survival (OS), disease-free survival (DFS), and breast cancer-specific survival (BCSS) using nationwide claims data. **Methods:** This study utilized a merged dataset from the National Health Insurance Service and Korean Statistical Information Service database. We identified 11,683 women newly diagnosed with Stage I-III primary breast cancer in 2016, excluding prior history or concurrent malignancies. TTS was defined as the interval from breast cancer diagnosis to the definitive surgical procedure. To determine the optimal clinical cutoff, the Contal and O'Quigley method was applied. Multivariable Cox proportional hazards models were used for OS. To account for competing risks, the Fine-Gray subdistribution hazard model was employed for DFS and BCSS, with non-breast cancer death treated as a competing event. Covariates included physical activity, type and region of institution, systemic treatments, income decile, and Charlson Comorbidity Index (CCI) score. **Results:** Initial analysis using 30-day and 60-day thresholds showed significant differences in survival outcomes. The Contal and O'Quigley method identified 68 days as the optimal cutoff for TTS. Patients with TTS $>$ 68 days exhibited significantly worse OS compared to those with TTS $\leq$ 68 days (adjusted Hazard Ratio [HR], 3.396; 95% CI, 2.402-4.802; $p<0.001$). In the competing risk regression, TTS $>$ 68 days was associated with inferior DFS (adjusted subdistribution HR [sHR], 1.496; p= 0.001) and BCSS (adjusted sHR, 5.868; $p<$ 0.001). The negative impact of delayed surgery remained consistent across various subgroups regardless of income level or comorbid status. **Conclusions:** Delays in surgery exceeding 68 days are significantly associated with poorer survival outcomes in Korean breast cancer patients. These findings suggest that every effort should be made to perform surgery within 68 days of diagnosis to optimize long-term prognosis. Clinicians should prioritize streamlining the diagnostic-to-treatment pathway to minimize surgical wait times. Research Sponsor: None.

582 **Poster Session**

Can robotic surgery better preserve sensory function?: The significance and strategy of nerve preservation in axillary lymph node dissection. First Author: Qiwen Liu, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Conventional axillary lymph node dissection (C-ALND) carries a high risk of damaging the intercostobrachial nerve (ICBN), which remains a critical clinical issue affecting both psychological recovery and quality of life in breast cancer patients. While advancements in minimally invasive surgery provide improved visualization and precision, evidence supporting its clinical benefit in preserving sensory function is lacking. **Methods:** A retrospective analysis was conducted on breast cancer patients who underwent robotic-assisted axillary lymph node dissection (R-ALND, n = 53) and endoscopic-assisted axillary lymph node dissection (E-ALND, n = 58) between 2021 and 2025 (total n = 111). The anatomical integrity of the ICBN (T1-3) was systematically identified and recorded during surgery. Additionally, a blinded evaluator performed standardized bedside sensory testing (BST) on four key ICBN areas (medial upper arm, axilla, upper chest, and lateral chest wall) three months postoperatively, using a scoring system adapted from the ISCIPS consensus group for the current study. A multivariate linear regression model was applied for analysis. **Results:** Compared with E-ALND, R-ALND demonstrated a significantly higher ICBN-trunk preservation rate (77.4% vs. 63.1%, p = 0.033) and a greater proportion of areas with normal sensation at three months postoperatively (89.2% vs. 74.6%, p = 0.025). Multivariate linear regression revealed that T2-ICBN trunk preservation was the strongest independent predictor of sensory recovery at three months (β = 0.571, 95% CI 0.477–0.664, P $<$ 0.001), with an effect size (standardized β = 0.720) far exceeding other factors. Patients with T2-ICBN preservation achieved a 77.4% rate of completely normal sensation across all four key ICBN areas at three months. After adjusting for variables including T2-ICBN preservation, tumor stage, age and so on, robotic surgery showed a tendency to be an independent protective factor for sensory recovery at 3 months postoperatively compared with endoscopic surgery. (β = 0.110, p = 0.016). **Conclusions:** Through three-dimensional visualization and tremor-filtering technology, R-ALND significantly reduces the risk of iatrogenic ICBN injury and outperforms E-ALND in preserving short-term postoperative sensory function recovery. In the early phase with a limited learning curve, preserving the ICBN trunk (particularly the T2-ICBN) is recommended to retain most of the patient's sensory function. Research Sponsor: None.

583 **Poster Session**

Synergistic efficiency of methylene blue and carbon nanoparticles for sentinel lymph node biopsy in early breast cancer: A large-scale real-world cohort study of 1,355 patients. First Author: Hongjin Liu, Peking University First Hospital, Beijing, China

Background: Sentinel lymph node biopsy (SLNB) using radioisotopes and fluorescence imaging is the gold standard but remains inaccessible in many resource-limited regions due to high costs and the lack of nuclear medicine infrastructure. Methylene blue (MB) is a globally available, low-cost tracer, but often lacks consistent nodal yield. This study evaluates a radiation-free, dual-tracer protocol combining MB with carbon nanoparticles (CN) to provide a highly accessible and reliable axillary staging method for diverse clinical settings. **Methods:** In this single-center retrospective cohort study, 1,355 female patients with cT1-2N0M0 breast cancer (May 2019 to December 2022) were stratified into the MB group (n=675) or the MB+CN group (n=680). Primary endpoints were the SLN detection rate and mean node retrieval (MNR). Sensitivity analyses adjusted for confounders, including Ki67 status, using multivariate regression. The goal was to determine if this dual-dye approach could match the reliability of high-cost methods without specialized equipment. **Results:** The MB+CN group achieved a comparable detection rate to MB alone (96.32% vs. 96.44%; P=0.905). Crucially, the dual-tracer protocol significantly increased the MNR (2.43±1.64 vs. 2.10±1.35; P<0.001). Adjusted linear regression confirmed a robust increase in node count (β=0.36, 95% CI: 0.19–0.52, P<0.001). Subgroup analysis demonstrated enhanced utility in aggressive molecular profiles, with significantly higher node retrieval in high-Ki67 (P=0.002), T2 stage (P=0.032), and ER-positive (P<0.001) cohorts. No significant differences in detection rates were observed across any clinicopathological subgroups. **Conclusions:** The MB+CN dual-tracer strategy significantly enhances nodal yield while maintaining high detection rates. By eliminating the need for radioactive tracers and expensive imaging hardware, this approach offers a precise, safe, and cost-effective SLNB solution. It is particularly suited for large-scale implementation in developing countries and rural healthcare systems, bridging the gap in breast cancer surgical standards globally. Research Sponsor: None.

Comparison of SLNB outcomes between MB and MB+CN groups.

Outcome	MB Group (n=675)	MB+CN Group (n=680)	Univariate *P*	Adjusted Estimate (95% CI)	Multivariate *P*
Detection Rate, % (n_1/n)	96.44% (651/675)	96.32% (655/680)	0.905	OR: 0.83 (0.64–1.09)	0.182
Mean Node Retrieval (SD)	2.10 (1.35)	2.43 (1.64)	<0.001	β: 0.36 (0.19–0.52)	<0.001

584 **Poster Session**

Oncological safety of oncoplastic breast conservation surgery: Experience of over a decade in early and locally advanced breast cancer from a tertiary care cancer center in India. First Author: Shalaka Prakash Joshi, Tata Memorial Hospital and Homi Bhabha National Institute, Mumbai, India

Background: Oncoplastic breast conservation surgery (O-BCS) is the norm. O-BCS improves cosmetic outcomes by restoring the shape, size, contour and symmetry of the breast and hence, quality of life. Carefully selected patients with locally advanced breast cancers (LABC) can be offered O-BCS after systemic therapy. We retrospectively evaluated our prospective dataset for oncological outcomes of patients who had O-BCS. **Methods:** Patients undergoing O-BCS between January 2013 and December 2023 were included. They received (neo)adjuvant chemotherapy, targeted and radiotherapy along with endocrine treatment as per standard institutional protocol and decision of Breast Cancer-Disease Management Group (BC-DMG). Clinico-pathological characteristics, type of oncoplastic procedure and follow-up details were updated from Electronic Medical Records. Data was collected and analyzed in SPSS-V29. **Results:** A total 1483 patients underwent O-BCS during the study period. The median age of the cohort was 45 (21- 86) years. Of 1483, 670 (45.2%) were operated upfront and 573 (38.6%) post-chemotherapy whereas 240 (16.2%) had had prior excision biopsy elsewhere. Clinically, 939 (63.3%) were early (EBC-T1/2, N0/1), 518 (34.9%) locally advanced (LABC-T3/4, N2/3) and 26 (1.8%) oligometastatic breast cancers. 1016 (68.5%) were HR+, 289 (19.5) TN and 396 (26.7%) HER2+. Median pT in upfront versus post-chemotherapy operated patients was 3 cm (0.1–8.5) and 2.7 cm (1-10) respectively. Upfront, 45.8% patients were node positive (median-2 {1-54}) and post-chemotherapy 38.3% (median-3 {1-38}). The median specimen volume was 432 cm^3(56.8–3528) in upfront and 270 cm^3(3–2875) in post-chemotherapy operated patients. The overall margin positive rate was 5.5% (81/1483). Of 1483, 573 (38.6%) patients had type-1 oncoplastic parenchymal closure, 377 (25.4%) had local dermo-glandular flaps, 344 (23.2%) a latissimus dorsi myo-cutaneous flap, and 189 (12.7%) bilateral reduction mammoplasty. At median follow-up of 47 months, there were 245 (16.5%) recurrences–77(5%) local and 211(14%) distant–and 153 (10.3%) deaths, and the disease-free survival (DFS) and overall survival (OS) were 84.1% and 89.5% respectively. The local recurrence rate in EBC was 4% and LABC 7.4%. The 5-year DFS was 82.1%(95%CI-79.75%-84.84%) and OS was 88.5%(95%CI-86.54%-90.46%) across the whole cohort. On Cox regression, high clinical nodal stage (HR-1.47, 95%CI-1.04-2.08, p=0.03) and histological grade 3 (HR-1.87, 95%CI-1-07-3.29, p=0.03) were predictors of poor DFS whereas type of O-BCS did not have impact on survival. **Conclusions:** The local recurrence rate in O-BCS was 5.3% in our setting which is reassuring considering that 1/3rd patients had locally advanced disease. A longer follow-up of this cohort of patients and future PROMs and QOL studies will be consolidatory. Research Sponsor: None.

585 **Poster Session**

Surgical outcomes and postoperative complications of robotic versus conventional nipple-sparing mastectomy in breast cancer: A meta-analysis. First Author: Fahad Amin, King Edward Medical University, Lahore, Pakistan

Background: Breast cancer is the most common type of cancer, affecting millions of women worldwide. Nipple-sparing mastectomy has emerged as a technique that leaves most of the healthy breast skin, areola, and nipple. This technique is widely used but there is little evidence comparing conventional and robotic nipple-sparing mastectomy. This meta-analysis aimed to compare the efficacy, safety, and postoperative complications of conventional and robotic nipple-sparing mastectomy. **Methods:** A systematic search of PubMed, Scopus, Web of Science, and the Cochrane Library was conducted to identify studies comparing robotic and conventional nipple-sparing mastectomy. The primary outcome was nipple and skin necrosis; secondary outcomes included operative time and Clavien-Dindo Grade III complications. Pooled estimates were calculated using a random-effects model, and heterogeneity was assessed using the I2 statistic. **Results:** A total of nine studies encompassing 1,220 participants (423 in the robotic group and 797 in the conventional group) were included in the final analysis. Robotic nipple-sparing mastectomy (RNSM) was associated with a significantly lower risk of nipple and skin necrosis compared to conventional nipple-sparing mastectomy (CNSM), with a pooled odds ratio of 0.47 (95% CI: 0.26–0.86; P = 0.01) and low heterogeneity (I2 = 20.5%). Conversely, RNSM was associated with a significantly longer operative time, with a weighted mean difference of 52.86 minutes (95% CI: 20.28–85.43; P = 0.001) and substantial heterogeneity (I2 = 96%). Regarding safety, there was no statistically significant difference in Clavien-Dindo Grade III complications between the two techniques (OR = 0.60; 95% CI: 0.35–1.05; P = 0.07; I2 = 0%), although the results showed a trend favoring the robotic approach. **Conclusions:** Robotic nipple-sparing mastectomy demonstrates a superior safety profile regarding ischemic complications, significantly reducing the risk of nipple and skin necrosis compared to the conventional approach. However, it is associated with longer operative times. The incidence of major complications (Grade III) is comparable between both techniques. Research Sponsor: None.

586 **Poster Session**

Evaluation of a novel diagnostic kit using the semi-dry dot-blot method with an automated reader for detecting breast cancer metastases in sentinel lymph nodes: A combined analysis of two multicenter prospective studies in Japan. First Author: Ryota Otsubo, Nagasaki University Hospital, Nagasaki, Japan

Background: The semi-dry dot-blot (SDB) method is a diagnostic procedure for detecting lymph node (LN) metastases using an anti-cytokeratin (CK) antibody, based on the premise that epithelial components such as CK protein are not present in normal LNs. Thus, the presence of CK protein in the lavage fluid of sectioned LNs indicates metastasis. Because this method does not involve loss of LN tissue, it can be used in parallel with conventional histopathological diagnosis. We developed a novel diagnostic kit utilizing the SDB method and a newly developed anti-CK19 antibody to detect macrometastases over 2.0 mm in diameter. Two multicenter prospective studies were conducted to evaluate the diagnostic performance of this kit, and we herein report a combined analysis of the two studies. **Methods:** A total of 825 sentinel LNs were dissected between January and December 2021, and 909 LNs between August 2023 and November 2024, at seven institutions in Japan from 880 patients with breast cancer. Patients who received neoadjuvant chemotherapy or endocrine therapy were excluded. LNs were sliced at 2-mm intervals and washed with phosphate-buffered saline. Cells in the lavage fluid were centrifuged and lysed, and the extracted proteins were applied to the SDB kit. Absorbance was measured using an automated reader to determine the presence of metastases. The washed LNs underwent blinded intraoperative and permanent histopathological examination. Diagnostic performance of the SDB kit was compared with permanent histology, with primary endpoints being sensitivity, specificity, and overall concordance for detecting macrometastases. **Results:** Of the 1,734 LNs analyzed, 199 were diagnosed as macrometastases and 1,535 as non-macrometastases, including 64 micrometastases measuring more than 0.2 mm and not up to 2.0 mm in diameter, based on permanent histopathology. Using a CK absorbance cutoff of 11.9, the SDB kit correctly identified 185 of the 199 macrometastatic LNs and 1,496 of the 1,535 non-macrometastatic LNs. This corresponded to a sensitivity of 93.0%, specificity of 97.5%, and overall concordance of 96.9%. Additionally, the kit enabled diagnosis within approximately 20 minutes, at a cost of under $30 per test and less than $3,000 for the reader device. **Conclusions:** The novel SDB kit with an automated reader demonstrated high accuracy, rapid turnaround, and cost-effectiveness in detecting breast cancer LN metastases, while preserving LN tissue. It proved particularly effective in identifying macrometastases. Commercial availability of the kit and reader is planned in the near future. Research Sponsor: None.

587 **Poster Session**

Distant recurrence–free survival in invasive lobular carcinoma (ILC) with isolated tumor cells: Does pN0(i+) behave like node-negative or node-positive disease? First Author: Jason A. Mouabbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ILC is a distinct breast cancer subtype with unique biology and clinical behavior compared with invasive ductal carcinoma. The prognostic significance of isolated tumor cells (ITCs; pN0(i+)) in ILC remains unclear, creating a management gap regarding whether patients with ITCs should be risk-stratified and treated similarly to node-negative (pN0) or node-positive (pN1) disease. **Methods:** We performed a retrospective analysis of patients with ILC treated at The University of Texas MD Anderson Cancer Center (Protocol PA20-0040). Distant recurrence-free survival (DRFS) was assessed using Kaplan-Meier methods and compared using log-rank testing. Univariate and multivariable Cox proportional hazards models evaluated associations between clinicopathologic and treatment variables and DRFS. The multivariable model included age, pathologic nodal stage, grade, HER2 status, histologic subtype (classical vs non-classical), and receipt of endocrine therapy, chemotherapy, radiation therapy, and definitive surgery. **Results:** The cohort included 4,217 patients (mean age 56.8 years). Most tumors were classical ILC (89.1%). ITCs were present in 169 patients; comparator groups included pN0 (n=1,799) and pN1 (n=1,040). In univariate analysis, there was no evidence that pN0(i+) were associated with worse DRFS versus pN0 (ITC negative) (HR 0.71, 95% CI 0.45-1.13; p=0.135), whereas pN1 was associated with inferior DRFS versus pN0 (HR 1.85, 95% CI 1.62-2.10; p$<$0.001). In multivariable analysis, there remained no evidence that pN0(i+) were associated with inferior DRFS versus pN0 (HR 0.661, 95% CI 0.404-1.081; p=0.099), while pN1 was independently associated with worse DRFS versus pN0 (HR 1.922, 95% CI 1.589-2.326; p$<$0.0001). **Conclusions:** In this large ILC cohort, pN0(i+) (ITCs) did not confer inferior DRFS compared with pN0, and outcomes were clearly distinct from pN1 disease. These findings support prospective validation and may inform nodal-status-driven risk stratification and treatment de-escalation strategies for pN0(i+) patients with ILC. Research Sponsor: None.

Key DRFS comparisons (reference = pN0).

Comparison	Univariate HR (95% CI)	Univariate p-value	Multivariable HR (95% CI)	Multivariable p-value
pN0(i+) vs pN0	0.71 (0.45-1.13)	0.135	0.661 (0.404-1.081)	0.099
pN1 vs pN0	1.85 (1.62-2.10)	$<$0.001	1.922 (1.589-2.326)	$<$0.0001

588 **Poster Session**

Can we omit surgical axillary staging in early-stage invasive lobular carcinoma?: Results from a large multicenter retrospective cohort study. First Author: Massimo Ferrucci, Breast Surgical Unit, Veneto Institute of Oncology IRCCS, Padova, Veneto, Italy

Background: The SOUND, INSEMA and BOOG 2013-08 randomized trials demonstrated that, in selected patients with clinically node-negative (cN0) early-stage breast cancer, omission of sentinel lymph node biopsy (SLNB) results in non-inferior disease-free and invasive disease-free survival. However, invasive lobular carcinoma (ILC) was underrepresented in these three studies, and the safety of this approach in ILC remains uncertain due to concerns about a potentially higher axillary nodal burden and risk of undertreatment. We evaluated the axillary nodal burden in ILC patients who met the trials eligibility criteria. **Methods:** This retrospective multicenter study included patients with cT1-2 cN0 ILC, undergoing upfront surgery between 2012 and 2025 across three high-volume Italian institutions. All patients underwent preoperative axillary ultrasound (US), with needle biopsy performed for US-suspicious lymph nodes. Uni- and multivariable logistic regression analyses identified factors associated with advanced nodal disease (pN2/3). **Results:** A total of 1886 patients (median age 65 years) were included. The median radiologic tumor size was 16 mm (IQR 11-23). Most patients underwent SLNB (84%), while the remaining were treated with axillary dissection. The overall rate of pN2/3 disease was 2.5% (48/1886). On univariable analyses, a palpable mass on physical exam (OR 3.59; p $<$ 0.001), the presence of US-suspicious axillary nodes (OR 8.19; p $<$ 0.001), tumor size $>$ 2 cm (OR 2.96; p = 0.002), multicentric disease (OR 4.5; p $<$ 0.0001), high tumor grade (OR 2.15; p = 0.03), the presence of lymphovascular invasion (LVI) (OR 3.25; p = 0.001) and HER2 positivity (OR 3.81; p = 0.022) were significantly associated with pN2/3 disease. On multivariable analysis, tumor size $>$ 3 cm (p = 0.003), the presence of US-suspicious axillary nodes (OR 6.29; p = 0.002), the presence of LVI (OR 3.65; p = 0.006), multicentric distribution (OR 5.19; p $<$ 0.0001), and HER2 positivity (OR 3.86; p = 0.041) were independently associated with pN2/3 disease. **Conclusions:** In this large real-world cohort of SOUND/INSEMA eligible patients with ILC, the rate of pN2/3 disease was 2.5%, higher than that reported in the aforementioned trials. Omission of axillary surgical staging in patients harboring high risk features may result in understaging, with potential implications for adjuvant treatment decisions and oncologic outcomes. Meticolous selection is critical to identify patients who are not at risk of potential undertreatment. Research Sponsor: None.

589 **Poster Session**

Changes in metastatic breast cancer (MBC) bone lesions and SREs/fractures via a single intratumoral injection for a first-of-its-kind drug: Preliminary phase 2a results. First Author: Manraj Heran, University of British Columbia, Vancouver, BC, Canada

Background: Lytic bone metastases develop in ~70% of breast cancer patients that lead to pain, functional decline, and skeletal-related events (SREs) that reduce quality of life (QoL) and survival. Prophylactic denosumab/bisphosphonate treatment offers limited protection, and current local palliative interventions, EBRT and surgery, don't reverse lytic destruction. Zeta-BC-003 is a first-in-class intratumoral (IT) injectable biomaterial infused with N-allyl noroxymorphone, a small molecule drug that acts through the p21 pathway to drive bone healing and local tumor control. Reports on two Compassionate Use patients (7 lesions, 2-yr follow-up; Palma et al, Pain Manag 2023) showed no SREs/fractures or tumor activity coupled with neo-trabecular bone regeneration and therapeutic spread to other lesions within treated bone, which align with these Phase 2a results. **Methods:** ZGMBC (NCT05280067), an open-label Phase 2a study, enrolled women (N=10; 8/23-3/25) with MBC lytic lesions and a Spinal Instability Numeric Score (SINS) $\geq$3 - $\leq$9. A single intratumoral (IT) Zeta-BC-003 injection was administered via fluoroscopic guidance. CT & MRI were obtained at Days 0, 84, and 180. Primary endpoints: SREs/fractures; defect volume; pain via the Numeric Rating Scale (NRS); post-op pain control via the Morphine Equivalent Dose (MED); and AE/SAEs. Secondary endpoints: QoL (SF-12v2); SINS; and tumor response. **Results:** Subjects (mean age 52) had the following MBC subtypes: HR+ (N=6), HR+/HER2+ (N=2), HER2+/HR- (N=1), and TNBC (N=1). Breakthrough lesions were seen in 5 subjects despite bisphosphonate therapy and 1 subject died from pleural edema prior to study end. Zeta-BC-003 was injected into 10 subjects with 11 lesions with additional therapeutic effect seen in 4 adjacent untreated lesions. A CR was shown for all lesions and there were no SREs/fractures. The bone defect volume decreased 65.4% ($\pm$20.5%; p=0.0003) and 84.1% ($\pm$13.1%; p$<$0.0001) at Days 84 and 180. NRS pain scores decreased 4.2% (p$<$0.05) and MED decreased $\geq$33% in opioid-treated subjects. SINS scores improved 18.5% (p$<$0.05), indicating increased stability. Increased PCS (24%) and MCS (12%) scores showed increased QoL. There were no treatment emergent SAE/AEs. **Conclusions:** Zeta-BC-003 prevented SREs/fractures in all lesions, reduced lytic defect volume, improved spinal stability, decreased pain/opioid use, improved QoL, ceased tumor activity, and demonstrated therapeutic spread to untreated lesions in the same vertebral body. These findings contrast with historical SRE rates of 53% in MBC and align with the durable CR seen in our Compassionate Use patients. Zeta-BC-003 may represent a first-of-its-kind intratumoral drug that ceases lytic activity, stimulates neo-trabecular bone growth, and improves QoL by eliminating SREs/fractures while also increasing overall survival. Clinical trial information: NCT05280067. Research Sponsor: Zetagen Therapeutics; National Institutes of Health, National Cancer Institute; R44 CA221553; National Institutes of Health, National Cancer Institute; R43CA221553; National Institutes of Health, National Cancer Institute; R44 CA221553; National Institutes of Health, National Cancer Institute; R43CA221553.

590 **Poster Session**

National real-world adoption of 5-fraction breast radiotherapy in the United States (2020–2023). First Author: Pragya Jain, Baptist Hospitals of Southeast Texas, Beaumont, TX

Background: The landmark FAST-Forward trial demonstrated that ultra-hypofractionated whole-breast irradiation with 26 Gy in 5 fractions over 1 week was non-inferior to 40 Gy in 15 fractions for local control (HR 0.67, 95% CI 0.38–1.16), with similar normal tissue effects at 5 years. In response, major international guidelines incorporated 26 Gy in 5 fractions as a standard approach or recommended option for selected patients. Despite robust randomized evidence and guideline endorsement, U.S. real-world adoption patterns and equity of uptake across patient populations remain incompletely characterized. This study evaluated national trends in 5-fraction breast radiotherapy and sociodemographic differences from 2020 to 2023. **Methods:** The National Cancer Database radiotherapy fractionation fields were used to identify radiotherapy (RT) courses with evaluable fraction counts, and a binary indicator for 5-fraction RT (yes/no) was created. Temporal trends by diagnosis year (2020–2023) were assessed, and associations between 5-fraction RT and sociodemographic factors (primary insurance, urban or rural status, neighborhood income quartile, and race) were examined using chi-square testing. **Results:** Among 536,783 RT courses with complete data from 2020 to 2023, use of 5-fraction RT increased substantially over time: 4.3% in 2020, 8.1% in 2021, 12.7% in 2022, and 17.4% in 2023, resulting in an overall adoption rate of 10.7% (p $<$ 0.001). In the subset eligible for fractionation (5, 15–16, 25–28 fractions; N = 31,448), 5-fraction RT accounted for 11.7% and differed significantly by insurance type (p $<$ 0.001): Medicare 17.4%, Private 7.6%, Medicaid 5.9%, and Uninsured 6.9%. Geographic variation was notable (p $<$ 0.001), ranging from 7.3% in mid-size metropolitan areas (250,000–1 million population) to 17.7%–18.1% in more remote or non-adjacent areas; large metropolitan areas ($\geq$1 million) had 12.8% uptake. Neighborhood income showed a gradient (p $<$ 0.001): 10.1% in the lowest quartile compared to 12.5% in the highest. Race was also associated with uptake (p $<$ 0.001), with lower use among Black patients compared to White patients (9.4% vs 12.2%). **Conclusions:** In routine U.S. practice, adoption of 5-fraction breast RT increased rapidly from 2020 to 2023, with the most pronounced growth after 2021, reflecting the swift translation of trial evidence into clinical practice. However, uptake varies by insurance, geography, income, and race, indicating that diffusion is not uniform. Given the potential benefits of ultra-hypofractionation in reducing treatment burden and supporting timely completion, targeted implementation strategies, such as provider education, reimbursement alignment, and facility-level operational support, may be necessary to ensure equitable access as 5-fraction regimens become more widely adopted and potentially become the standard of care. Research Sponsor: None.

591 **Poster Session**

A response-adapted and genomically informed strategy to optimize neoadjuvant chemotherapy versus endocrine therapy plus CDK4/6 inhibition in high-risk HR+/HER2− breast cancer. First Author: Zhengjun Yang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Premenopausal patients with locally advanced hormone receptor–positive, HER2-negative (HR+/HER2−) breast cancer are routinely recommended neoadjuvant chemotherapy (NAC) despite heterogeneous and often limited response. In advanced disease, endocrine therapy (ET) plus CDK4/6 inhibition has replaced chemotherapy as first-line treatment. Whether patients with poor early response to NAC may benefit from chemotherapy-sparing strategies remains unclear. We conducted a prospective response-adapted study integrating early chemosensitivity assessment with exploratory genomic profiling to guide neoadjuvant treatment selection. **Methods:** A total of 116 premenopausal patients with stage II-III HR+/HER2− breast cancer received two initial cycles of TAC chemotherapy (docetaxel, doxorubicin, and cyclophosphamide). Radiologic response was assessed after two cycles. Patients achieving partial response (PR) continued TAC. Patients with stable disease (SD) were randomized to either continue TAC (NAC) or switch to 16 weeks of ET consisting of dalpiciclib (CDK4/6 inhibitor), exemestane, and goserelin (NET). Whole-exome sequencing was performed in an exploratory subset. The primary endpoint was objective response rate (ORR). **Results:** After two cycles of TAC, 30 patients achieved PR, while 86 exhibited SD and were subsequently randomized. Among evaluable patients, the ORR was 68.3% in the NET group (41 evaluable patients) compared with 48.7% in the continued NAC group (39 evaluable patients), indicating a higher response rate with NET in tumors demonstrating poor early chemosensitivity. Exploratory genomic analyses further showed that NET-sensitive tumors were predominantly TP53 wild-type and lacked PIK3CA or AKT alterations, consistent with a highly endocrine-dependent biology. In contrast, nonresponders to NET frequently harbored TP53 mutations, often in combination with PIK3CA/AKT pathway alterations, whereas patients who responded to continued chemotherapy commonly exhibited TP53 or TTN mutations, suggesting a chemotherapy-responsive but endocrine-refractory phenotype. **Conclusions:** Taken together, our findings indicate that in premenopausal patients with stage II-III HR+/HER2− breast cancer who demonstrate suboptimal early response to intensive neoadjuvant chemotherapy, continued cytotoxic treatment may not be optimal for all patients. A response-adapted strategy integrating early functional assessment with genomic features, particularly TP53 and PI3K/AKT pathway status, distinguishes endocrine-sensitive from chemotherapy-sensitive disease. These results provide a biologically informed framework for neoadjuvant treatment selection and support biomarker-enriched randomized trials evaluating chemotherapy-sparing strategies in selected patients. Clinical trial information: NCT06009627. Research Sponsor: None.

592 **Poster Session**

Impact of age on breast cancer outcomes in the neoadjuvant I-SPY2 trial. First Author: Kelsey H. Natsuhara, University of California, San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: Historically, young women with early-stage breast cancer (EBC) have had worse outcomes than older women. This is based largely on population-based or adjuvant studies, with limited neoadjuvant data. **Methods:** Patients (pts) with Stage 2-3 EBC treated with neoadjuvant chemotherapy +/- immunotherapy (Cx-IT) on the I-SPY2 trial between 2010-2022 were included (data cutoff 07/2025). Pts were stratified by age at trial screening (<40 vs ≥ 40 yrs), and clinical/molecular subtypes, including ImPrint, an immune signature predictive of Cx-IT response. Pathologic complete response (pCR), residual cancer burden (RCB), and event-free survival (EFS) were evaluated by age and disease subtypes using Kaplan-Meier methods and Cox proportional hazard ratios (HR). **Results:** Among 2117 evaluable pts, 510 (24%) were <40 yrs and 1607 (76%) were ≥ 40 yrs. Overall, 43% of tumors were HR+/HER2-, 35% HR-/HER2- (TN), 22% HER2+. 34% / 66% were ImPrint +/- (27% / 73% for HR+; 44% / 56% for HR-), with similar rates of ImPrint+/- between age groups. Rates of pCR (31% vs 35 %) and RCB 0/1 (48% vs 51%) were similar between pts <40 and ≥ 40. Overall, pts < 40 had worse EFS ($p < 0.01$) vs pts ≥ 40; however, in pts who achieved pCR, there was no difference in EFS in all biologic subgroups (HR 0.90, p=0.77). In contrast, in pts with residual disease, those <40 had worse EFS than pts ≥ 40 (HR 0.72, $p<0.01$). The worse EFS in pts<40 with residual disease was limited to pts with ImPrint- disease, in both HR+/HER2- (HR 0.64, p=0.02) and TN (HR 0.62, p=0.04) subtypes, where response rates were lower. In ImPrint+ pts, no differences in EFS by age were observed (HR 1.01, p=0.98). Similar results were seen for pts with HR+/HER2- disease when stratifying by RCB (RCB 0/I vs 2/3). There was no difference in EFS by age for pts with RCB 0/1 disease in any subtype (HR 0.66, p=0.09). For ImPrint-, pts<40 with RCB 2/3 disease had worse EFS than pts ≥ 40 (HR 0.61, p=0.01). For HR+/HER2-, 64% of tumors were MammaPrint (MP) High 1 vs 36% MP High 2, and 74% were Luminal. When stratifying by pCR or RCB 0/1, similar age-related EFS differences were observed in HR+/HER2- Luminal or MP High 1 tumors, as in ImPrint- tumors. **Conclusions:** Overall, young pts <40 yrs with high-risk EBC in the I-SPY2 trial had worse 5-yr EFS than pts ≥ 40; however, when taking response into account, there were no age-related EFS differences for pts who had an excellent response to neoadjuvant Cx-IT (i.e. pCR or RCB 1). The EFS difference was driven by pts with residual disease, specifically in the subset with ImPrint- disease, which is associated with less response to Cx-IT. Whereas, for pts with ImPrint+ disease, there was no difference in EFS by age, regardless of pCR or RCB. This highlights the unmet need for more effective therapies for immune-negative tumors. Our results reinforce the importance and prognostic value of neoadjuvant therapy, particularly in our youngest pts, to better risk-stratify and optimize treatment based on tumor biology and response to therapy. Clinical trial information: NCT01042379. Research Sponsor: None.

593 **Poster Session**

Pathologic complete response in rare histologic subtypes of early-stage triple-negative breast cancer in the era of immunotherapy. First Author: Maeve Hennessy, Section of Hematology & Oncology, Department of Medicine, University of Chicago, Chicago, IL

Background: The addition of immunotherapy (IO) to chemotherapy has improved outcomes in early-stage triple-negative breast cancer (eTNBC). Rare histologic subtypes, like lobular and metaplastic, are managed using the same treatment algorithms as ductal TNBC but historically have been associated with worse outcomes. Whether the benefits of IO extend to these rare subtypes in real-world practice remains unclear. **Methods:** We used the National Cancer Database to retrospectively identify patients diagnosed with stage II-III TNBC who received neoadjuvant therapy from 2021 to 2022, after FDA approval of IO for eTNBC. TNBC was categorized as ductal, lobular, metaplastic or other. Logistic regression was used to assess pathologic complete response (pCR) stratified by IO use. All models were controlled for key demographic and clinicopathologic factors. **Results:** We identified 17,006 patients with stage II–III TNBC (mean age 55.0 years). Most patients had ductal histology (91.1%), with smaller proportions of metaplastic (2.5%), and lobular (1.9%). Overall, 11,132 (65.5%) patients received IO and achieved a higher pCR rate than those who did not receive IO (45.2% vs 33.1%). pCR rate differed significantly by histologic subtype treated with neoadjuvant chemotherapy, both with and without IO. Among patients who received IO, pCR rate was highest in ductal TNBC (47%) and was significantly lower in lobular (18.9%) and metaplastic (17.6%) tumors ($p<0.001$). Similarly, in patients who did not receive IO, ductal TNBC had the highest pCR rate (34.6%) with metaplastic and lobular subtypes having lower pCR rates (12.5% and 14.3%, respectively; $p<0.001$). After covariate adjustment, all non-ductal subtypes had significantly lower odds of pCR compared to ductal TNBC regardless of receipt of IO. This was most notable for metaplastic TNBC with an odds ratio [OR] of 0.19 (95% CI 0.10–0.33) with IO and OR 0.13 (95% CI 0.04–0.44) without IO. Lobular TNBC was also associated with significantly lower odds of pCR in IO-treated patients (OR 0.50, 95% CI 0.28–0.90) with similar trends observed in patients treated without IO. **Conclusions:** In this national real-world cohort, we demonstrate that despite the adoption of neoadjuvant IO for eTNBC and improved pCR rates overall, rare histologic subtypes continue to experience inferior treatment outcomes. Metaplastic and lobular TNBC had persistently low pCR rates, regardless of IO use. These results highlight the urgent need for novel therapeutic strategies and dedicated clinical trials for these rare histologic subtypes. Research Sponsor: National Institute on Aging; T32AG000243.

594 **Poster Session**

Association of immunotherapy infusion timing with outcomes in early-stage triple-negative breast cancer. First Author: Xianghui Zou, NYU Long Island School of Medicine Program, Perlmutter Cancer Center, Mineola, NY

Background: Circadian regulation of immune function has been shown to influence the efficacy of immune checkpoint inhibitors (IO) in several malignancies. However, the clinical relevance of IO infusion timing in breast cancer remains unclear. We evaluated the association between IO timing, baseline characteristics, pathologic complete response (pCR), and recurrence outcomes in patients with early-stage triple-negative breast cancer (TNBC). **Methods:** We conducted a retrospective cohort study of 139 patients with early-stage TNBC treated at Manhattan and Mineola campuses alongside with four sites in Queens, Brooklyn, and Long Island using a KEYNOTE-522-based neoadjuvant regimen including pembrolizumab, chemotherapy, and surgery between July 2021 and June 2025. IO infusion timing was dichotomized using the cohort median time (12:22 PM); patients receiving all first three IO infusions after this cutoff were classified as late. Baseline characteristics including age, body mass index (BMI), race, ECOG performance status, clinical T/N stage, and chemotherapy backbone were compared between groups. pCR was defined as absence of residual invasive disease. Recurrence outcomes included local recurrence, distant recurrence, or death. Multivariable analyses adjusting for baseline clinical factors were performed. **Results:** Amongst our 139 patients, 108 received early IO and 31 received late IO. Patients receiving early IO were younger (mean age 55.9 vs 63.5, p = 0.025) and had lower BMI (27.4 vs 30.6, p = 0.017), while ECOG performance status 0-1 (early: 98.1% vs late: 90.3% respectively, p = 0.075), non-white race (52.5% vs 56%, p = 0.825), clinical T/N stage ($T\geq 2$: 88.7% vs 90.3%, p = 0.999; $N\geq 1$: 37.4% vs 38.7%, p = 0.999), carboplatin/paclitaxel chemotherapy backbone distributions (93.5% vs 90.3%, p = 0.693) were similar between groups. pCR occurred in 63% of patients receiving early IO and 45.2% receiving late IO (p = 0.098). Recurrence outcomes occurred in 3.7% of the early IO group and 16.1% of the late IO group (p = 0.026), driven primarily by distant recurrence (0.9% vs 12.9%, p = 0.009). After adjusting for age, BMI, and clinical T/N stage, late IO remained associated with distant recurrence (adjusted odds ratio 16.1; 95% CI, 1.39–186.4; p = 0.026). **Conclusions:** In this retrospective analysis, early IO infusion timing was associated with significantly lower recurrence risk, particularly distant recurrence. While pCR rates were not statistically significant between early vs late IO, we observed a numerical difference favoring early IO. These findings may suggest that circadian timing of IO may influence long-term outcomes beyond pathologic response. Given the retrospective design and limited number of events, these results are hypothesis-generating and warrant prospective validation. Research Sponsor: The Betty Ajces grant (philanthropy fund), NYU Langone Long Island Grossman School of Medicine, Perlmutter Cancer Center.

595 **Poster Session**

Neoadjuvant chemotherapy combined with toripalimab for triple-negative breast cancer: A prospective, single-arm, multi-center study (NEOTORCH-BREAST02). First Author: Zhijun Dai, Department of Breast Surgery, College of Medicine, The First Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, China

Background: Neoadjuvant de-escalation chemo-immunotherapy with abbreviated cycles remains unclear. We aimed to assess the efficacy and safety of toripalimab, a novel PD-1 antibody, combined with an abbreviated course of epirubicin–cyclophosphamide (2 cycles) followed by nab-paclitaxel (2 cycles), as a neoadjuvant regimen for early-stage TNBC patients. **Methods:** This phase II trial, conducted from 2024 to 2025, involved stage II–III TNBC. The neoadjuvant regimen included epirubicin, cyclophosphamide, and toripalimab for 2 cycles, followed by nab-paclitaxel and toripalimab for another 2 cycles. Patients achieving a pathological complete response (pCR) received up to 13 cycles of adjuvant toripalimab, while those with residual disease received additional chemotherapy and toripalimab. Whole-exome sequencing (WES) and circulating tumor DNA (ctDNA) monitoring were also performed. The primary endpoint was the total pCR (tpCR) rate (ypT0/is ypN0). Secondary endpoints included breast pCR (bpCR; ypT0/is), residual cancer burden (RCB 0−1), objective response rate (ORR), and event-free survival. This trial was registered with ClinicalTrials.gov (NCT06682195). **Results:** As of January 20, 2026, 48 patients were enrolled, and 40 underwent surgery (median age: 48 years; 87.5% stage II). WES analysis in 37 patients identified BRCA1 mutations in 12 (32.4%). Baseline ctDNA was positive in 32 of 34 (94.1%) patients, and 24 (75%) achieved ctDNA negativity after neoadjuvant therapy. Among 40 surgical patients, tpCR, bpCR, RCB 0-I, and ORR rates were 55%, 60%, 70, and 92.5%, respectively. Subgroup analyses showed tpCR rates of 25% for CPS <1, 58.3% for CPS ≥1, 72.7% for CPS ≥10, and 80% for CPS ≥20. For TILs <10, tpCR was 25%, increasing to 66.6% for TILs ≥10, 82.3% for TILs ≥30, and 85.7% for TILs ≥50. Among BRCA1 mutation carriers, 75% achieved tpCR, and 62.5% of patients with ctDNA negativity also achieved tpCR. Grade ≥3 AEs occurred in 6 (15%) patients, most commonly vomiting (7.5%) and leukopenia (7.5%). Hypothyroidism was the most frequent immune-related AE (17.5%, all grade 1–2). **Conclusions:** Preliminary findings indicate that this 4 cycles de-escalation neoadjuvant strategy is effective and safe for early-stage TNBC, warranting further investigation in randomized trials. Clinical trial information: NCT06682195. Research Sponsor: None.

Response endpoints for the entire cohort (N = 40).

Efficacy endpoint	N (%)	95% CI(%)
tpCR(ypT0/is, ypN0)	22(55.0)	38.5–70.4
bpCR(ypT0/is)	24(60.0)	43.3–75.0
Miller–Payne (MP) grades		
MP score 1	2 (5.0)	0.6-23.2
MP score 2	3 (7.5)	1.6-27.3
MP score 3	7 (17.5)	7.3-34.7
MP score 4	4 (10.0)	2.8-23.7
MP score 5	24 (60.0)	43.3.-75.0
Residual cancer burden (RCB) class		
RCB class 0–I	28(70.0)	53.3–83.4
RCB class II	6 (15.0)	5.7-31.9
RCB class III	6 (15.0)	5.7-31.9

Abbreviations: tpCR, total pathological complete response; bpCR, breast pathological complete response; CI, confidence interval.

596 **Poster Session**

Application of a neoadjuvant 21-gene breast recurrence score assay to redirect surgical and systemic treatment pathways in early breast cancer: A multicenter prospective study. First Author: Natasha Caminsky, University of Montreal, Montréal, QC, Canada

Background: The 21-gene Oncotype DX Breast Recurrence Score assay is well established for determining use of adjuvant chemotherapy in hormone receptor (HR)-positive, HER2-negative breast cancer patients. However, the role of the 21-gene assay in the neoadjuvant setting has yet to be established. We previously reported the impact of the 21-gene assay in the neoadjuvant setting in node-negative breast cancer patients, which led to a reduction in the recommendation of chemotherapy in about one-third of patients. Here, we report the impact of the assay on neoadjuvant treatment pathways including surgery, endocrine therapy, and chemotherapy, in addition to overall costs. **Methods:** We performed a multicentre, prospective observational trial of HR-positive, HER2-negative breast cancer patients with T2-T3 disease and clinically negative axillary lymph nodes. Physicians completed questionnaires prior to and after Recurrence Score (RS) results, indicating their treatment choice for neoadjuvant endocrine or chemotherapy, or upfront surgery. Data was also collected at 6 months after initiation of therapy, to verify treatment received. The primary and secondary objectives were to evaluate impact of RS results on physician's treatment decisions and on drug (anti-emetics and pre-medication), and nursing (counselling and infusion time) costs, respectively. **Results:** A total of 70 patients were enrolled in the study as part of five hospital centers of the McPeak Sirois Group in the province of Quebec from 2018-2021. Feasibility of the 21-gene assay from core biopsy samples was 98.6%. At 6-month follow-up, the 21-gene assay led to a change in treatment decision in 52.2% of patients, including de-escalation from neoadjuvant chemotherapy to either upfront surgery in 21.7%, or to neoadjuvant endocrine therapy in a further 21.7%. The use of upfront surgery changed from 10.0% at baseline to 33.3% at 6-month follow-up (p = 0.0004). Use of neoadjuvant endocrine therapy also changed from 12.9% to 29.0% (p = 0.02). Among patients treated with upfront surgery or neoadjuvant endocrine therapy, 52.2% and 55.0% of patients, respectively, had a RS$\geq$16. At baseline, for all patients, total chemotherapy-associated drug costs were $190,656 CAD, and nursing-associated costs were $96,918 CAD. RS-guided treatment recommendation reduced chemotherapy-associated drug costs by 32.3% and nursing resource utilization by 44.1%. **Conclusions:** The use of the 21-gene assay reclassified treatment pathways in 52.2% of patients, including shifting patients from neoadjuvant chemotherapy toward upfront surgery or neoadjuvant endocrine therapy, while reducing chemotherapy-related resource utilisation. These data support the use of the 21-gene assay as a clinical decision-making tool in the neoadjuvant setting. Additional information: Coauthor André Robidoux, MD, died in July 2020. Research Sponsor: Exact Sciences; Scotiabank Chair in the Diagnosis and Treatment of Breast Cancer, University of Montreal.

597 **Poster Session**

Evaluation of a taxane mRNA-based profile in neoadjuvant therapy across I-SPY2 investigational arms. First Author: Jacob Niklassen, Aida Oncology, Copenhagen, Denmark

Background: Neoadjuvant chemotherapy is standard in early-stage breast cancer (eBC), enabling tumor downstaging and treatment tailoring. Taxanes are a core component of standard neoadjuvant regimens across breast cancer subtypes, and biomarkers of taxane response may inform treatment strategies. In I-SPY2, high-risk eBC patients (pts) were randomized to standard taxane-anthracycline-cyclophosphamide (T-AC) or investigational regimens (IRs). A 113-gene model has been validated in multiple cohorts and in the I-SPY2 T-AC arm. Here, we extend these analyses to nine I-SPY2 IRs, which all include a T-AC backbone. **Methods:** Agilent gene expression data from 987 high-risk eBC pre-treatment tumors (GSE194040) were analyzed from pts treated with T-AC $\pm$ nine IRs. Pts were scored on a scale from 0-100 and association of score (per 50-point increase) with pCR was assessed using logistic regression. For benchmarking, the raw score was Z-scaled, and OR was calculated per 1 standard deviation increase (OR/1SD) to enable comparison with published I-SPY2 biomarkers. **Results:** In a pooled multivariable logistic model including all treatment arms (N = 987), a 50-point increase in score was strongly associated with higher odds of pCR after adjusting for treatment arm, hormone receptor (HR) and HER2 (OR = 2.99, p = 7.93e-13). Allowing for treatment-specific score effects did not reveal statistically significant interactions. The score was benchmarked against 27 I-SPY2 qualifying biomarkers using OR/1SD increase. In the full cohort (N = 987), it ranked among biomarkers with the largest effect sizes for pCR. When analyses were stratified by treatment arm, the score was the top-ranked biomarker by effect size in the T-AC arm (N = 210) and trebananib arm (N = 134), while effect estimates in other arms were directionally consistent but not uniformly statistically significant. Furthermore, the score provided independent predictive information beyond I-SPY2 Response Predictive Subtypes (RPS). In multivariable models adjusting for RPS, the score remained significantly associated with pCR in the full cohort and the T-AC arm. As an illustrative example, using score quartiles defined in the full cohort, pCR rates among HR+/HER2− pts (N = 379) increased from 6.0% (8/134) in the lower quartile to 43.1% (28/65) in the upper quartile. Similarly, among TN pts (N = 363), pCR rates increased from 16.7% (5/30) in the lower quartile to 48.7% (77/158) in the upper quartile. **Conclusions:** A taxane-specific gene expression score was strongly associated with pCR across all taxane-containing I-SPY2 regimens and provided information beyond established response predictive subtypes. These findings suggest that taxane sensitivity contributes substantially to treatment response across I-SPY2 therapies and highlights the potential value of incorporating additional drug-specific biomarkers to further refine response prediction. Research Sponsor: None.

598 **Poster Session**

Efficacy and safety of neoadjuvant disitamab vedotin (DV) in combination with toripalimab (Tor) and concurrent/sequential chemotherapy (chemo) in patients with HR-negative, HER2-low breast cancer: A randomized multi-center phase 2 study. First Author: Zhi-Ming Shao, Fudan University Shanghai Cancer Center, Shanghai, China

Background: For patients (pts) with triple-negative early breast cancer (BC), recommended neoadjuvant regimens include chemo with or without immunotherapy, which achieve a modest rate of pathological complete response (pCR). Emerging data suggest that anti-HER2 antibody-drug conjugates (ADCs) have antitumor activity in HER2-low advanced BC. Notably, DV (anti-HER2 ADC) has shown encouraging efficacy both as monotherapy and in combination with Tor (PD-1 inhibitor) in pts with HER2-low advanced disease. We evaluated the efficacy and safety of neoadjuvant DV-containing regimens in pts with hormone receptor (HR)-negative HER2-low BC in a randomized phase 2 trial. Here, we report results from the pts receiving DV plus Tor combined with concurrent/sequential chemo. **Methods:** Eligible pts were aged $\geq$18 years with untreated histologically confirmed HR-negative and HER2-low (centrally confirmed as IHC 1+, or IHC 2+/ISH-) BC (T1cN1-2M0 or T2-3N0-2M0 as per AJCC 8th edition) who were planned to undergo curative-intent breast cancer surgery. Pts randomized to group A received DV (2.0 mg/kg Q2W) + Tor (3.0 mg/kg Q2W) + carboplatin (AUC 3 Q2W or AUC 1.5 QW) for 18 weeks. Pts randomized to group B received DV + Tor for 12 weeks followed by epirubicin (90 mg/m^2 Q3W) + cyclophosphamide (600 mg/m^2 Q3W) + Tor for additional 12 weeks. Stratification factors were PD-L1 status (positive or negative) and clinical staging (stage II or III). After neoadjuvant treatment, surgery was performed. Enrollment in group B was closed after 28 pts had been randomized to this group, while enrollment in group A continued. The primary endpoint was total pCR (tpCR, defined as ypT0/TisN0) rate; secondary endpoints included breast pCR (bpCR, defined as ypT0/Tis) rate, objective response rate (ORR), and safety. **Results:** 40 pts were enrolled in group A (median age: 46.0 years; clinical stage III: 37.5%; clinical N+: 82.5%; IHC 1+: 72.5%; PD-L1 CPS $<$ 10: 37.5%) and 28 in group B (54.0; 42.9%; 82.1%; 67.9%; 32.1%). The tpCR was achieved in 25 pts (62.5% [95% CI: 45.8-77.3]) in group A and 14 pts (50.0% [31.9-71.3]) in group B. The bpCR rate was 65.0% (95% CI: 48.3-79.4) and 53.6% (35.3-74.5) for groups A and B, respectively. The corresponding ORR was 92.5% (95% CI: 79.6-98.4) and 75.0% (55.1-89.3), respectively. Grade 3-4 treatment-related adverse events (TRAEs) occurred in 29 (72.5%) of pts in group A and 23 (82.1%) in group B. Serious TRAEs occurred in 6 (15.0%) and 7 (25.0%) of pts, respectively. Immune-related adverse events occurred in 3 (7.5%) of pts in group A and 7 (25.0%) in group B. No grade 5 TRAEs occurred. **Conclusions:** Both treatment regimens showed manageable safety profiles; DV + Tor + carboplatin showed numerically better efficacy in pts with previously untreated, HR-negative, HER2-low, early BC. Clinical trial information: NCT06227117. Research Sponsor: RemeGen Co., Ltd.

599 Poster Session

Efficacy and safety of a short-course (12-week) de-escalated neoadjuvant regimen (weekly paclitaxel/trastuzumab/pertuzumab) in early HER2-positive breast cancer: Interim analysis of a prospective study. First Author: Maxim Ruban, P. Hertsen Moscow Oncology Research Institute –Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow, Russian Federation

Background: Standard neoadjuvant regimens for HER2-positive early breast cancer (EBC), such as 6 cycles of TCHP, achieve high pathological complete response (pCR) rates but carry significant toxicity risks. De-escalation strategies aiming to reduce treatment intensity and duration without compromising efficacy are clinically relevant. We present the interim analysis of a prospective study evaluating a shortened (12-week), carboplatin-free and anthracycline-free regimen (THP). **Methods:** We enrolled patients (pts) with histologically confirmed HER2-positive (IHC 3+ or ISH+) EBC, clinical stages T0-1N1M0 or T2-3N0-1M0. Pts received a de-escalated regimen consisting of 12 weekly infusions of paclitaxel (80 mg/m²) combined with trastuzumab and pertuzumab administered every 3 weeks for 4 cycles (12 weeks total). The primary endpoint was pCR rate (ypT0/is ypN0). Secondary endpoints included safety and treatment adherence. This interim analysis reports data from the first 70 pts who completed surgery. **Results:** Median age was 50 years. The cohort included 69% stage IIA and 31% stage IIB pts; 57% were cN0. 60% had HR-positive and 40% had HR-negative disease. Treatment compliance was excellent: 100% of pts completed the full 12-week course. The overall pCR rate was 60.0% (42/70). Efficacy was strongly associated with hormonal status: the pCR rate reached 82.1% (23/28) in the HR-negative subgroup, compared to 45.2% (19/42) in the HR-positive subgroup. The safety profile was exceptionally favorable compared to historical TCHP data. Grade ≥3 neutropenia occurred in only 4% of pts. No cases of febrile neutropenia or symptomatic cardiotoxicity were observed. Grade ≥3 non-hematological toxicity (diarrhea/rash) was limited to 8%. Peripheral neuropathy was predominantly grade 1, with occasional grade 2 events; no grade ≥3 neuropathy occurred. **Conclusions:** The short-course (12-week) de-escalated THP regimen demonstrated high efficacy, particularly in HR-negative/HER2-positive pts (pCR 82.1%), comparable to longer, more toxic multi-agent regimens. With a 0% rate of febrile neutropenia and 100% completion rate, this regimen represents a promising "chemo-light" option for selected patients, potentially guiding future de-escalation strategies in personalized oncology. Research Sponsor: None.

Baseline characteristics and clinical outcomes (N=70).

Characteristic / Endpoint	N (%) or Median (Range)
Median Age, years	50 (29–75)
Node-positive disease (cN+)	30 (43%)
HR-negative / HER2-positive	28 (40%)
Completed full 12-week NACT	70 (100%)
Breast-conserving surgery	34 (49%)
Pathological Complete Response (Total)	42 (60.0%)
pCR in HR-negative subgroup	23/28 (82.1%)
pCR in HR-positive subgroup	19/42 (45.2%)
Grade 3-4 Neutropenia	3 (4%)
Febrile Neutropenia	0 (0%)

600 Poster Session

Neoadjuvant penpulimab combined with taxanes and carboplatin in triple-negative breast cancer: Updated efficacy and safety results from the phase II NeoTAPPL study. First Author: Guozhi Zhang, Department of Breast and Thyroid Surgery, Southwest Hospital, Army Medical University, Chongqing, China

Background: The KEYNOTE-522 and IMpassion031 trials established that adding immune checkpoint inhibitors to neoadjuvant chemotherapy significantly improves pathologic complete response (pCR) rates and survival outcomes in triple-negative breast cancer (TNBC). In our previously reported phase II NeoTAPPL trial, an anthracycline-free neoadjuvant regimen of penpulimab (anti-PD-1 antibody), carboplatin, and taxanes demonstrated promising efficacy and manageable safety. Here, we present updated efficacy and safety outcomes from the full trial cohort. **Methods:** In this open-label, multi-center phase II study, patients with untreated, histologically confirmed TNBC in stage II-III were enrolled. Patients received 6 cycles of neoadjuvant therapy with penpulimab (200 mg, d1, q3w) plus taxanes (docetaxel 75 mg/m2 or nab-paclitaxel 260 mg/m2, d1, q3w) and carboplatin (AUC=6, d1, q3w). Patients who either completed or discontinued the neoadjuvant treatment would undergo breast surgery. Adjuvant chemotherapy and immunotherapy were at the discretion of the treating physician, and radiation therapy was per standard of care. The primary endpoint was the rate of pCR based on the definition of ypT0/Tis ypN0. Secondary endpoints included residual cancer burden (RCB), event free survival (EFS), overall survival (OS), adverse events (AE), and immune response biomarkers. **Results:** 64 patients were enrolled, all of whom received neoadjuvant treatment and underwent surgery. The median age was 53 years (range, 32-73). At diagnosis, 54 patients (84.4%) had stage II disease. pCR was achieved in 41 of 64 patients (64.1%; 95% CI, 51.1%-75.7%), and 50 patients (78.1%; 95% CI, 66.0%-87.5%) achieved RCB 0-1. The objective response rate (ORR) and disease control rate (DCR) were 93.8% (95% CI, 84.8%-98.3%) and 98.4% (95% CI, 91.6%-100%), respectively. Subgroup analyses revealed pCR rates of 64.8% (35/54) in patients with stage II disease and 60.0% (6/10) in those with stage III disease. The pCR rate was 64.9% (24/37) in node-negative patients and 63.0% (17/27) in node-positive patients. Treatment-emergent adverse events (TEAEs) of any grade occurred in all 64 patients, with grade ≥3 TEAEs reported in 24 patients (37.5%). The most common grade ≥3 TEAEs were alopecia (20.3%), anemia (14.1%), neutropenia (10.9%), and leukopenia (10.9%). **Conclusions:** The NeoTAPPL trial demonstrates that an anthracycline-free neoadjuvant regimen is an effective and tolerable treatment strategy for patients with TNBC. The regimen achieved a high pCR rate, which remained consistent across key prognostic subgroups, including disease stage and nodal status. The safety profile was manageable, with no new safety signals identified. Clinical trial information: ChiCTR2300071925. Research Sponsor: National Science and Technology Major Project (2025ZD0543900); Development Center for Medical Science & Technology National Health Commission of the People's Republic of China WKZX2023CX010002.

601 Poster Session

Outcomes after recurrence on neoadjuvant chemo-immunotherapy (NCIT) in patients (pts) with high-risk early-stage triple-negative breast cancer (eTNBC). First Author: Chiara Corti, Dana-Farber Cancer Institute, Boston, MA

Background: NCIT improves survival in high-risk eTNBC; however, trial-based data show that most relapses after NCIT are early. Real-world data are lacking. **Methods:** This retrospective study included pts from the DFCI Multicenter TNBC registry with eTNBC or estrogen receptor (ER)-low (≤10%), HER2-negative breast cancer (BC) treated with NCIT who underwent surgery before 7/1/2025. Aims were to evaluate (1) patterns of relapse; (2) BC–specific event–free survival (BC-EFS) from the first NCIT dose to relapse, contralateral BC, or death; (3) first-line (1L) metastatic systemic treatment patterns, and (4) time to progression (TTP). **Results:** 220 pts were identified, with median age of 50.1 yrs (IQR: 40.5-60.8). Median follow-up (FU) was 32.7 months (mo) (IQR, 30.4–34.4). At last FU, 29 pts (13.2%) had relapsed (locoregional, n=2; distant, n=27). Among these, 86.2% had not experienced pathologic complete response. Among relapsed pts with PD-L1 assessment (n=16), 43.8% (n=7) had a Combined Positive Score (CPS) <10; 56.2% (n=9) had a CPS ≥10. BC-EFS is shown in the Table. 1L therapy consisted of antibody-drug conjugate (ADC) in 51.7% (n=15), Poly ADP-ribose Polymerase inhibitor (PARPi) in 13.8% (n=4), chemotherapy in 13.8% (n=4), ADC+PARPi in 3.4% (n=1), CIT in 3.4% (n=1), and HER2-directed in 3.4% (n=1); 10.3% (n=3) died before 1L therapy. Median (m)TTP in 1L (n=26) was 7.7 mo (95% CI, 6.0–13.0) and detailed in the Table. Among pts with disease-free interval (DFI) ≤6 mo (n=8), mTTP was 5.1 mos (2.7–NR), with TTP rates of 50.0% (25.0–100.0) at 6 mo and 16.7% (2.9–95.3) at 12 mo. In those with DFI 6–12 mo (n=9), mTTP was 9.7 mo (7.4–NR); TTP rates were 88.9% (70.6–100.0) at 6 mo and 25.4% (7.7–83.8) at 12 mo. For DFI >12 mo (n=9), mTTP was 8.6 mo (5.6–NR), with TTP rates of 71.4% (44.7–100.0) at 6 mo and 28.6% (8.9–92.2) at 12 mo. Among pts treated with 1L ADC (n=16), mTTP was 8.6 mo (7.4–NR); TTP rates were 77.9% (58.4–100.0) at 6 mo and 26.0% (9.9–68.3) at 12 mo. In non-ADC-treated pts (n=10), mTTP was 6.2 mo (3.78–NR), with TTP rates of 60.0% (36.2–99.5) at 6 mo and 20.0% (5.8–69.1) at 12 mo. Median overall survival (from diagnosis) among pts with relapse was 26.3 mo (95% CI, 25.0–NR). **Conclusions:** Relapse after NCIT was predominantly early with poor metastatic outcomes, underscoring an urgent need for new strategies in this population largely excluded from clinical trials. Research Sponsor: Dana-Farber/Harvard Cancer Center; 1P50CA168504; Susan G. Komen; Breast Cancer Alliance; Benderson Family Fund for TNBC Research.

	Any NCIT (n = 216)		KEYNOTE-522 (n = 176)			1L for metastatic TNBC (n = 26)	
Time from NCIT start (mo)	BC-EFS % (95% CI)	Event N	BC-EFS % (95% CI)	Event N	Time from 1L start (mo)	TTP survival % (95% CI)	Event N
6	100.0 (100.0, 100.0)	0	100.0 (100.0, 100.0)	0	6	70.8 (54.6, 91.7)	7
12	95.4 (92.5, 98.4)	9	95.0 (91.7, 98.4)	8	12	23.6 (11.0, 50.5)	17
18	89.4 (84.9, 94.0)	19	89.7 (84.9, 94.8)	15	18	14.2 (5.0, 40.3)	19
24	86.4 (81.3, 91.8)	23	86.0 (80.3, 92.2)	19	24	9.4 (2.5, 35.2)	20
36	79.9 (72.2, 88.3)	27	82.2 (74.8, 90.3)	21			

602 Poster Session

Predicting chemotherapy benefit in premenopausal women with intermediate genomic scores using deep learning. First Author: Arkadi Piven, Technion - Israel Institute of Technology, Haifa, Israel

Background: The TAILORx trial demonstrated that adjuvant chemotherapy can be safely omitted in postmenopausal women with node-negative HR+/HER2- breast cancer and a 21-gene Recurrence Score (RS) of 11–25. However, chemotherapy benefit could not be excluded for pre/peri-menopausal women with RS 16–25, creating a clinical dilemma that may lead to overtreatment. Using TAILORx data, we have shown that deep learning (DL) applied to hematoxylin and eosin (H&E) can accurately identify women with low or high RS (Shamai et al., Lancet Oncol, 2026). We hypothesized that DL applied to H&E could be used to predict chemotherapy benefit in pre/peri-menopausal women with RS 16–25, thereby facilitating precise treatment de-escalation. **Methods:** We trained a DL model using H&E slides of both post- and pre/peri-menopausal women from TAILORx, with low (RS<16) and high (RS>25) genomic scores (N=5811), to predict distant recurrence-free interval (DRFI), while excluding patients with RS 16–25 from the training process. The test cohort consisted of women from TAILORx with RS 16–25. Within TAILORx, this test group was originally randomized to either endocrine therapy alone or chemo-endocrine therapy, enabling a direct evaluation of the model's ability to predict chemotherapy benefit. For comparison, RSCLIN was also computed. **Results:** When testing on pre/peri-menopausal women with RS 16–25 (N=1234), the model classified 942 (76%) and 292 (24%) as low and high risk. For patients receiving no chemotherapy, the model demonstrated high prognostic performance for DRFI (C-index=0.75; 95% CI: 0.67–0.82), and strong risk stratification (HR=5.43; 95% CI: 2.87–10.29, p<0.001). In the low-risk group, no benefit from chemotherapy was observed (HR=1.07, 95% CI: 0.54–2.15, p=0.84). In the high-risk group, chemotherapy was associated with a significant improvement in DRFI (HR=3.57, 95% CI:1.54–8.30, p=0.003). A significant interaction between treatment and risk group was observed (p=0.024). The model outperformed RSCLIN (p-interaction=0.314). When testing on postmenopausal patients with RS 16–25 (N=2249), the model could not predict chemotherapy benefit (p-interaction=0.926). **Conclusions:** This digital pathology signature provides prognostic information for distant recurrence and predictive information for chemotherapy benefit in pre/peri-menopausal women with HR+/HER2-, node-negative early breast cancer with RS 16–25. These findings support the potential use of histopathology-based DL to guide chemotherapy de-escalation in this clinically challenging subgroup. The inability of the model to predict chemotherapy benefit in postmenopausal women suggests that the deep learning signature may be identifying tumors sensitive to chemotherapy-induced ovarian suppression, highlighting a subset who could benefit from OFS as an alternative to chemotherapy. Research Sponsor: Israel Innovation Authority; Zimin Institute for Artificial Intelligence Solutions in Healthcare; Israel Precision Medicine Partnership.

603 Poster Session

EA1181: Accuracy of pre-surgery MRI to predict pathologic complete response after taxane, trastuzumab, and pertuzumab (THP) in HER2-positive breast cancer. First Author: Nadine M. Tung, Dana-Farber Cancer Institute, Boston, MA

Background: Accurate prediction of pathologic complete response (pCR) after preoperative therapy for HER2-positive (HER2+) breast cancer can help triage patients to immediate surgery vs additional preoperative therapy. Pre-surgery (i.e., after neoadjuvant therapy) imaging studies may help estimate the likelihood of pCR. In EA1181, patients (pts) with stage II-IIIA HER2+ breast cancer received four cycles of preoperative taxane, trastuzumab, and pertuzumab (THP×4). Pre-surgery imaging was required, though the specific imaging modality was not mandated. Here, we report the accuracy of pre-surgery breast MRI to predict pCR (ypT0/Tis, ypN0). **Methods:** Among 2,141 pts treated with THPx4, 1,378 had pre-surgery breast MRI and were representative of the overall cohort, although T3 tumors were more common (16% vs 9%). MRI reports were available for 1,351 pts; all reports were centrally reviewed and classified as radiologic complete response (rCR; no residual tumor enhancement and normalization of lymph nodes, if applicable) or radiologic residual disease (rRD). Reports with indeterminate radiologic response were independently reviewed by two study radiologists blinded to pathology outcomes. Among pts with rCR who had pathologic residual disease (pRD), we also assessed the extent of residual disease by residual cancer burden (RCB) score. Among pts with rRD who had a pCR, we determined the proportion who only had residual ductal carcinoma in situ (DCIS). **Results:** See Table. **Conclusions:** After neoadjuvant therapy, preoperative MRI accurately predicted pCR in 86% of patients with HER2+/ER− disease and may help identify patients who can proceed directly to surgery. MRI is insufficient to predict pCR for pts with HER2+/ER+ disease, as only 55% with complete response on MRI had a pCR at surgery. A pre-surgery MRI that indicated residual disease was accurate in 80% of pts with HER2+/ER+ disease, but in only 45% of pts with HER2+/ER- cancer. Accurately predicting residual disease after THPx4 allows for consideration of additional therapy that may increase the chance of pCR. Combining imaging like MRI with other biomarkers, such as tissue-based markers or circulating tumor DNA, may improve prediction of pCR and facilitate personalization of treatment decisions in HER2+ breast cancer. Research Sponsor: National Cancer Institute; Breast Cancer Research Foundation; Susan G. Komen.

All pts with pre-surgery MRI (n=1351)
pCR rate overall in this cohort = 47%

MRI result	pCR	Pathology	pRD
rCR	**70.6%** (341/483)		29.4%(142/483) *78% had RCB1*
rRD	34%(295/868) *21% of 295 had DCIS only*		**66.01%** (573/868)

ER- (n=589)*
Overall pCR rate in ER- subset = 68%

MRI result	pCR	Pathology	pRD
rCR	**86.1%** (205/238)		13.9% (33/238) *85% had RCB1*
rRD	55.3% (194/351) *19% of 194 had only DCIS*		**44.7%** (157/351)

ER+ (n= 762)*
Overall pCR rate in ER+ subset = 31%

MRI result	pCR	Pathology	pRD
rCR	**55.5%** (136/245)		44.5% (109/245) *76% had RCB1*
rRD	19.5% (101/517) *26% of 101 had only DCIS*		**80.5%** (416/517)

604 Poster Session

Biological subtype discordance after neoadjuvant therapy in early breast cancer: Findings from a 1,500-patient cohort with residual disease. First Author: Katarzyna Pogoda, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Background: Although biomarker reassessment is standard in recurrent breast cancer, its role in early breast cancer with residual disease (RD) after neoadjuvant therapy (NAT) remains not well established, despite potential implications for adjuvant treatment decisions in the post-NAT setting. **Methods:** We retrospectively analyzed patients with early breast cancer who underwent surgery after NAT and had RD between January 2019 and May 2025. Only patients with estrogen receptor (ER), progesterone receptor (PR), and HER2 status assessed on both pretreatment biopsy and matched surgical specimens were included. Biological subtype discordance was analyzed across luminal, HER2-positive, and triple-negative breast cancer (TNBC). Multivariable logistic regression was used to identify clinicopathological factors associated with subtype change. **Results:** Among 1,504 eligible patients with residual disease, biomarker discordance involving ER, PR, and/or HER2 was observed in 502 cases (33.4%). A change in biological subtype occurred in 221 patients (14.7%). Subtype discordance was most frequent in tumors initially classified as HER2-positive (39.3%), compared with TNBC (10.6%) and luminal disease (6.2%) ($p<0.001$). Accordingly, patients with HER2-positive breast cancer at diagnosis were significantly more likely to experience subtype discordance after NAT compared with luminal tumors (absolute difference 33.1%, $p<0.001$) and TNBC (absolute difference 28.7%, $p<0.001$), with a smaller but statistically significant difference also observed between TNBC and luminal disease (absolute difference 4.4%, p=0.023). HER2-positive and TNBC tumors predominantly shifted toward a luminal phenotype, whereas luminal tumors more commonly converted to HER2-positive or TNBC subtypes, indicating substantial post-treatment biological heterogeneity. On multivariable analysis, baseline biological subtype remained the strongest independent predictor of subtype change, with higher odds for HER2-positive (OR = 9.14, $p<0.001$) and TNBC tumors (OR = 1.71, p=0.029) compared with luminal disease. Lobular histology was associated with a significantly lower likelihood of subtype discordance (OR = 0.50, p=0.040), whereas type of NAT, tumor grade, and Ki-67 were not associated with subtype change. **Conclusions:** In this large cohort of patients with residual disease after NAT, approximately one in seven experienced a change in biological subtype, with the highest discordance observed in initially HER2-positive tumors. These findings support routine biomarker reassessment in early breast cancer with residual disease to better inform adjuvant treatment decisions and to account for post-treatment biological heterogeneity. Research Sponsor: None.

605 Poster Session

Treatment patterns and oncologic outcomes in patients with triple-negative (TN) lobular breast cancer. First Author: Laura Burns Amin, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Triple-negative breast cancer (TNBC) with invasive lobular carcinoma (ILC) histology represents an exceedingly rare (<1% of breast cancers) and aggressive disease subtype with poorly described outcomes. In an effort to better understand treatment patterns and prognosis for these patients, we conducted an analysis using the National Cancer Database to assess treatments and outcomes in this high-risk, understudied population. **Methods:** We identified patients ≥18 years with stage I-III TNBC diagnosed between 2017-2022 who underwent mastectomy or lumpectomy with ILC or invasive ductal histology (IDC) (n=80,589). Of these patients, 69,940 were treated with chemo- or immunotherapy (CTx/IO). Subgroup analysis included patients treated with neoadjuvant chemotherapy (NACT) ± IO (n=47,822). Among this subgroup, trends in NACT±IO and pathologic complete response (pCR) rates by histology were assessed using the Cochran-Armitage test. Associations between histology and NACT use or pCR were evaluated with multivariable logistic regression. Impact of pCR on overall survival (OS) was examined via Kaplan-Meier estimates and multivariable Cox models with propensity score weighting and matching (1:1 by stage and NACT type). **Results:** Among 80,589 patients with TNBC (median age 58 years), 79,645 (98.8%) had IDC and 944 (1.2%) had ILC. Patients with ILC were older (66 vs 58 years) and less likely to receive CTx/IO compared to those with IDC (75.5% vs 86.9%). Among 69,940 patients treated with CTx/IO, those with ILC were older (median age 65 vs 56 years), had higher clinical tumor stage, and were less likely to receive NACT compared to those with IDC (61.9% vs 68.4%; $p<0.001$). Among 47,822 patients who received NACT ± IO, patients with ILC had significantly lower pCR rates (16.1% vs 40.2%; aOR=0.44, 95% CI 0.34-0.57). The addition of IO showed a trend toward improved pCR rates in ILC (aOR=1.69, 95%CI 0.95-3.01, p=0.07). In 29,330 matched patients, pCR was associated with improved 5-year OS (94% vs 78%, $p<0.001$). However, in 108 matched ILC patients, no survival difference was observed by pCR status (5-year OS: 66% with pCR vs 69% without pCR, p=0.54). In a multivariable Cox model with inverse probability weighting among patients who received NACT±IO, ILC was associated with increased mortality risk (aHR=1.34, 95%CI 1.05-1.70, p=0.02), after adjustment for pCR, IO, age, race, tumor size, and insurance status, among other factors. **Conclusions:** Patients with TN-ILC who received NACT had lower pCR rates and worse OS compared to those with TN-IDC. Although limited by small sample size, this is the largest analysis of its type in the current NACT and IO era. These data suggest that pCR in TN-ILC may lack the prognostic significance it has in TN-IDC. These findings highlight the need for larger studies and novel therapeutic approaches tailored to the distinct biology of this rare subtype. Research Sponsor: Breast Cancer Research Foundation; Susan G Komen Breast Cancer Foundation.

606 Poster Session

Early results of neoadjuvant therapy with pyrotinib, subcutaneous trastuzumab, and capecitabine for HER2-positive early breast cancer from a prospective, single-arm, multicenter trial. First Author: Lina Zhang, The Second Department of Breast Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin, China

Background: Neoadjuvant therapy has become a standard approach for HER2-positive early breast cancer, improving outcomes, pCR, and survival. Prior studies show pyrotinib combined with trastuzumab and chemo is effective and safe, but mainly via intravenous routes, impacting quality of life. This trial is the first to assess a fully oral regimen—pyrotinib, SC trastuzumab, and capecitabine—in low- to intermediate-risk patients, focusing on efficacy and safety. **Methods:** This single-arm, multicenter phase II trial (NCT06483386) will enroll 109 treatment-naïve adults with stage I-II, T1c-2N0-1 HER2-positive EBC (IHC 3+ or IHC 2+/FISH+). From May 2024 to June 2026, patients will receive 6 cycles of neoadjuvant pyrotinib (400mg daily), SC trastuzumab (600mg q3w), and capecitabine (1000mg/m² BID, days 1-14 followed by a 7-day break). The primary endpoint is pathological complete response (pCR) rate, as defined by RECIST 1.1. Secondary endpoints include event-free survival (EFS), objective response rate (ORR), breast-conserving rate (BCR) and safety. **Results:** A total of 47 patients were enrolled from May 2024 to December 2025, of whom 43 underwent surgery and 43 had pathologic assessment available. The median age was 51 years (range 33-65), and 97.9% had an ECOG PS of 0. The majority of patients had stage II disease (89.4%), with T2 tumors (91.5%); 57.4% were clinically node-positive. The pCR rate among pts with evaluable pathology was 48.8% (21/43), and ORR was over 90%. The BCR was 65.1% (25/48). In biomarker-defined subgroups, total pathological complete response (tpCR) was achieved in 53.6% (15/28) of ER negative, HER2 positive patients, and in 40.0% (6/15) of ER positive, HER2 positive patients. The most common AEs were diarrhea, nausea, anorexia, and gastrointestinal dysfunction. The incidence of grade 3 diarrhea is 19.1%, and all cases are controllable with medication, confirming good safety profile. **Conclusions:** The fully non-intravenous neoadjuvant regimen combining pyrotinib, SC trastuzumab, and capecitabine is an efficacious and safe regimen for patients with low- to intermediate-risk HER2-positive early breast cancer. This regimen offers a more convenient and less burdensome treatment for this patient population, potentially improving quality of life and treatment adherence. Clinical trial information: NCT06483386. Research Sponsor: None.

607 Poster Session

Health-related quality of life with low-dose pembrolizumab plus chemotherapy in early triple-negative breast cancer: Findings from the PLANeT trial. First Author: Adhip Arora, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Background: The PLANeT trial randomized stage II–III TNBC patients to neoadjuvant chemotherapy with or without low-dose pembrolizumab. Primary efficacy end point results were presented at ESMO Congress 2025. QoL was assessed at baseline, mid-treatment, and end-treatment using the EORTC QLQ-C30 across seven domains. Longitudinal changes were analyzed using mixed-effects models with LS-mean estimates and change from baseline at each timepoint. **Methods:** Stage II–III TNBC patients were randomized in a 1:1 ratio to receive standard NACT with or without pembrolizumab (50 mg Q6W ×3 cycles) prior to surgery. QoL was assessed at baseline, mid-NACT (after 4 cycles), and at the end of NACT (after 8 cycles) using the EORTC QLQ-C30 questionnaire. Seven key QoL domains were analyzed: global health status/QoL (GHS), physical, role, emotional, cognitive, social functioning, and pain. Longitudinal QoL changes were compared between arms using mixed-effects models (MMRM) adjusted for nodal status. Least-squares (LS) mean scores and changes from baseline were estimated for each timepoint. **Results:** Among 157 patients (median age 49), baseline QoL was high and comparable between arms. QoL declined during neoadjuvant therapy in both groups, with the greatest burden mid-treatment and partial recovery by cycle 8. LS-mean global QoL fell by 14 points in each arm, with no meaningful separation between treatments across any functioning domain. Pain increased in both groups, and financial difficulty peaked mid-treatment before improving by cycle 8. Overall, low-dose pembrolizumab did not compromise QoL compared with chemotherapy alone. **Conclusions:** Adding low-dose pembrolizumab to neoadjuvant chemotherapy in TNBC did not worsen patient quality of life. The trajectory of functioning and symptom scores was nearly identical to chemotherapy alone, indicating that incorporating reduced-dose immunotherapy does not add to the treatment burden from the patient's perspective. Clinical trial information: CTRI/2024/01/062088. Research Sponsor: Indian counsel of medical research; grant numbers Development; Research/Small/5411/2023-2024, EM/Dev/SG/170/1232/2023/JJC].

Least-squares mean (LS-mean) scores at cycle 8 and changes from baseline for all EORTC QLQ-C30 domains, comparing pembrolizumab + chemotherapy vs chemotherapy alone in the PLANeT trial.

Domain	Pembro + Chemo (C8 LS-mean)	Change	Chemo Alone (C8 LS-mean)	Change	Between-Arm Δ (Change)
Global QoL	39.61	−14.19	41.27	−13.61	−0.58
Physical Functioning	73.09	−19.92	74.49	−18.14	−1.78
Role Functioning	85.68	−10.90	85.65	−12.66	+1.76
Emotional Functioning	78.31	−11.11	77.00	−10.34	−0.77
Cognitive Functioning	88.03	−5.99	83.97	−8.44	+2.45
Social Functioning	83.33	−13.04	82.07	−12.87	−0.17
Pain	67.31	+20.73	52.11	+12.45	+8.28

608 Poster Session

Taxane and platinum combination as a predictor of pathologic complete response in I-SPY2 by gene expression breast cancer signatures. First Author: Jacob Niklassen, Aida Oncology, Copenhagen, Denmark

Background: Carboplatin is part of NCCN-preferred neoadjuvant chemotherapy (NAC) for stage II-III triple negative (TN) early-stage breast cancer (eBC) as addition to taxane-containing standard-of-care, and significantly improves pathologic complete response (pCR) rates in multiple trials. In hormone receptor (HR)+/HER2− disease, platinum addition has been explored in investigational settings but is not standard. In I-SPY2 (NCT01042379), high-risk eBC pts were randomized to standard taxane-anthracycline (T-AC) with or without investigational agents. One arm evaluated carboplatin plus the PARP inhibitor veliparib added to T-AC (VC arm; 32 HR+/HER2- and 39 TN pts, n = 71). Two gene signatures, a 205-gene Platin Drug Response Predictor (Platin-DRP) and a 113-gene taxane response predictor, have been validated for association with response to platinum agents and taxane-based regimens, respectively. This study evaluated their combined association with pCR in the I-SPY2 VC arm and their potential to inform platinum benefit in taxane-based NAC. **Methods:** Agilent gene expression data (GSE194040) from 987 high-risk eBC tumors were analyzed, focusing on 71 VC-arm pts and 179 HER2- T-AC pts. Samples were scored using each gene signature on a percentile scale (0–100). Associations between a 50-point increase in score and pCR were assessed using logistic regression with one-sided tests and 90% confidence interval (CI) lower bound (LB), unless otherwise specified. **Results:** The pCR rate in the VC arm was 38% (27/71), compared with 17.3% (31/179) in the control arm. In the VC arm, both the Platin-DRP (OR = 3.4, p = 0.016, 90% CI LB = 1.36) and the taxane predictor (OR = 3.88, p = 0.01, 90% CI LB = 1.54) were associated with pCR after adjustment for HR status and retained independent predictive value after adjustment for MammaPrint risk. The platinum and taxane scores were moderately correlated (r = 0.53). In a bivariable model, inclusion of the Platin-DRP trended toward improved fit beyond the taxane score alone (two-sided (2s) p = 0.082). Dichotomization at 50 showed highest pCR in double-high pts (55%, 16/29), intermediate rates in discordant pts (33%, 7/21), and lowest rates in double-low pts (19%, 4/21). Quartile stratification further separated outcomes, with 78% pCR (7/9) in the high-high quartile and 0% (0/8) in the low-low quartile.The taxane score showed no evidence of arm-specific effects (control vs VC; 2s p = 0.97), whereas the Platin-DRP showed directionally stronger associations in the VC arm (2s p = 0.12). **Conclusions:** Taxane and platinum gene expression signatures showed complementary associations with pCR in the I-SPY2 veliparib-carboplatin arm. Joint modeling and stratification identified subgroups with distinct responses, supporting the potential utility of combining drug-specific biomarkers to refine patient selection for platinum addition in taxane-based NAC. Research Sponsor: None.

609 Poster Session

Delayed serplulimab combined with nab-paclitaxel and epirubicin in high-risk, early HR+/HER2− breast cancer (HELEN-B 018): A multicenter, single-arm, phase 2 trial. First Author: Hao Dai, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China

Background: Novel treatment options are needed to improve long-term outcome of high-risk early HR+/HER2− breast cancer. Evidence shows a programmed death 1 inhibitor combined with chemotherapy increases pCR rates in this subtype. We aimed to evaluate the efficacy and safety of serplulimab combined with nab-paclitaxel and epirubicin in high-risk, early HR+/HER2− breast cancer. **Methods:** This multicentre, single-arm, phase 2 trial was conducted in China at 6 hospitals. Patients were eligible if they were 18 years or older, with previously untreated early HR+/HER2- breast cancer, and Ki-67 greater than or equal to 20%, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. Participants were allocated to intravenous nab-paclitaxel (260 mg/m^2) and intravenous epirubicin (75 mg/m^2) on the first day and intravenous serplulimab (4.5mg/kg) on the third day of the treatment cycle. 6 cycles of neoadjuvant treatment were administered. The primary outcome was pCR (defined as ypN0 or ypT0/is), assessed in the full analysis set, which included all patients who had started the trial treatment. We estimated that with enrollment of 109 participants, this trial would have 80% power to detect a true difference in the percentage of patients with a pCR of 10% at a one-sided alpha level of 0.025, with a dropout rate of 10%. This study is registered with ClinicalTrials.gov (NCT06394661). **Results:** Between Apr 28, 2024, and May 24, 2025, 136 patients were assessed for eligibility; 27 were ineligible and 109 participants were enrolled in this study, of whom 101 participants started trial treatment. Median age of the participants was 49 [range, 30 to 72] years at the time of enrolment, and 45 (44.6%) were PD-L1 positive (CPS ≥1). pCR was achieved in 23 patients (22.8%, 95%CI 15.3%-32.4%). PCR rate was numerically higher in patients with PD-L1 positive tumors (44.4%, 95%CI 30.0%-59.9%). During the neoadjuvant phase, 30 (29.7%) patients experienced grade 3 or higher treatment-related adverse events. The most common grade 3–4 adverse events were increased alanine aminotransferase (ALT; six [5.9%]), increased aspartate aminotransferase (AST; five [5.0%]), and diarrhea (four [4.0%]), There were no treatment-related deaths. **Conclusions:** Delayed serplulimab combined with nab-paclitaxel and epirubicin showed promising anti-tumour activity and manageable safety in patients with HR+/HER2− breast cancer; the pCR rate was higher in PD-L1 expression tumor. These findings support further evaluation of this regimen in randomized controlled trials. Clinical trial information: NCT06394661. Research Sponsor: None.

610 Poster Session

Impact of pembrolizumab infusion timing on outcomes in early-stage triple-negative breast cancer: A real-world exploratory analysis (Neo-Real). First Author: Natalia Nunes, Instituto Americas, Rio De Janeiro, Brazil

Background: Neoadjuvant pembrolizumab combined with chemotherapy is the standard of care for early-stage triple-negative breast cancer (TNBC) based on KEYNOTE-522, improving pathologic complete response (pCR) and event-free survival (EFS). Emerging data suggest that immunotherapy timing may influence oncologic outcomes; however, evidence in early-stage TNBC and in combination regimens is limited. We conducted an exploratory real-world analysis to evaluate the association between infusion timing and clinical outcomes. **Methods:** Neo-Real/GBECAM-0123 is a multicenter real-world cohort including patients with early-stage TNBC treated with neoadjuvant pembrolizumab-based chemotherapy in Brazil and Argentina. In this analysis, patients treated between 2019 and 2024 with available infusion timing data were included. Infusion timing was classified as Early (≤20% of pembrolizumab infusions initiated at or after 14:00) or Late (>20% initiated at or after 14:00). The primary endpoint was pCR (ypT0/Tis ypN0). Secondary endpoints included EFS, defined according to KEYNOTE-522 criteria. Sensitivity analyses using timing definitions were performed. **Results:** Among 419 patients with available infusion timing data (Early: n=265; Late: n=154); 385 underwent surgery and were evaluable for pCR. Baseline clinicopathologic characteristics were largely balanced between groups, although stage III disease was numerically more frequent in the Early group (30.9% vs 23.6%, p=0.134). Treatment features, including use of dose-dense chemotherapy and number of neoadjuvant pembrolizumab cycles (median 8 in both groups), were similar. pCR rates did not differ according to infusion timing (Early: 62.5% vs Late: 64.1%; p=0.827). Late infusion timing was associated with improved EFS, with a 2-year EFS of 90.7% versus 82.7% (p=0.013). In multivariable Cox regression adjusting for age, clinical stage, pathologic response, tumor grade, histology, and number of neoadjuvant pembrolizumab cycles, Late infusion timing remained associated with improved EFS (HR 0.34; 95% CI 0.15–0.80; p=0.013). Sensitivity and subgroup analyses, including evaluation of the timing of the first pembrolizumab infusion using an earlier cut-off (11:00), as well as analyses by histology, clinical stage, and pathologic response, yielded consistent results. **Conclusions:** In this exploratory real-world analysis of patients with early-stage TNBC treated with neoadjuvant pembrolizumab-based chemotherapy, infusion timing was not associated with pCR. However, later infusion timing was associated with improved EFS. These findings contrast with observations reported in other tumor types and underscore the need for further studies to clarify the impact of immune checkpoint inhibitor infusion timing on clinical outcomes in TNBC. Research Sponsor: None.

611 **Poster Session**

DCE-MRI for assessment of pathologic complete response after completion of neoadjuvant therapy in triple-negative breast cancer patients. First Author: Xiaofei Huo, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Triple-negative breast cancer (TNBC) is an aggressive molecular subtype that accounts for approximately 15%-20% of all breast cancer diagnoses. We aimed to investigate the utility of presurgical DCE breast MRI as a predictive marker for pathologic complete response (pCR) after neoadjuvant treatment (NAT) in TNBC patients and to compare the predictive value of early versus delayed enhancement for residual tumor detection. **Methods:** A total of 308 Stage I–III TNBC patients who underwent pre-operative DCE-MRI after completion of NAT followed by surgery were enrolled in an IRB-approved prospective clinical trial (NCT02276433). Tumor size was measured using three-dimensional measurements of the index lesion during both the early (1 min) and delayed (6 min) phases of DCE-MRI. Treatment response at surgery (pCR vs. non-pCR) and the pathologic size of residual disease were documented. Correlation between pCR and residual enhancement on DCE-MRI was assessed using McNamar's test. Spearman's rank correlation coefficient was used to assess concordance between the longest diameter on MRI and pathology. Differences between longest diameter on DCE-MRI and pathology were compared using the Wilcoxon signed-rank test. **Results:** Among the 308 TNBC patients, 47% (145/308) achieved pCR following treatment. Residual disease detection on the early phase of DCE-MRI demonstrated higher sensitivity for predicting pCR compared to the delayed phase (79% vs. 69%, $p < 0.001$); however, it had lower specificity (78% vs. 84%, p = 0.008). Absence of enhancement in both early and delayed phase DCE-MRI predicted pCR with positive predictive values (PPV) of 80% and 83%, respectively. Residual enhancement in both phases predicted non-pCR with negative predictive values (NPV) of 77% and 71%, respectively. Both early and delayed DCE-MRI phases demonstrated a similar moderate positive correlation with pathology (r = 0.64 vs. 0.62). There was no significant difference between the longest diameter measured on early phase DCE-MRI and pathology (p = 0.706), whereas a significant difference was observed for the delayed phase ($p < 0.001$), which over estimated residual disease. **Conclusions:** Presurgical DCE-MRI demonstrated strong performance in predicting pCR among TNBC patients following NAT. The early and delayed phases of DCE-MRI may each capture different aspects of tumor characteristics, potentially providing complementary information for prediction. Clinical trial information: NCT02276433. Research Sponsor: National Cancer Institute.

612 **Poster Session**

Development of a multivariable prognostic model for pathological response using anatomical and pathological variables in early triple-negative breast cancer treated with neoadjuvant chemo-immunotherapy: Initial results. First Author: Dana Narvaez, Alexander Fleming Institute, Ciudad De Buenos Aires, Argentina

Background: The combination of chemotherapy and immune checkpoint inhibitors is the standard of care for most patients with early triple negative breast cancer (eTNBC). Higher residual cancer burden (RCB) after receiving neoadjuvant chemo-immunotherapy (NCI) is associated with worse outcomes; however, reliable tools to predict pathological response remain limited. **Methods:** We conducted a multicenter prospective cohort study including patients with eTNBC treated with NCI. Anatomical and pathological variables were collected. Multivariable logistic regression was used to develop a prognostic model for pathological response. RCB 0–1 was the primary outcome. $p < 0.1$ was used for the selection of candidate parameters, and $p < 0.05$ for the final assessment of the multivariate model. ROC curves and the Hosmer-Lemmershow tests were applied to assess the model performance **Results:** A total of 109 patients with eTNBC with NCI from six centers in Argentina were included, with tumor samples centrally collected and reviewed for centralized pathological assessment. Regarding the immune microenvironment, qualitative tumor-infiltrating lymphocytes (TILs) were categorized according to the International Immuno-Oncology Biomarker Working Group classification as low (score 1) in 44.4% and intermediate-to-high (scores 2–3) in 55.6% of patients. Pathologic complete response (pCR) was achieved in 64.8% of patients. Histological grade (Grade 3 vs. 2: OR 3.2; 95% CI 0.95–11), TIL categories (TILs score 2: OR 3.4; 95% CI 0.84–14 and score 3: OR 6.3; 95% CI 1.1–37) and axillary node involvement (present vs. absent: OR 0.28; 95% CI 0.083–0.95) were selected for the final multivariate model. The final model showed good discrimination (AUC = 0.82) with adequate calibration, confirmed by a non-significant Hosmer–Lemeshow test ($\chi^2 = 3.28$, p = 0.35). **Conclusions:** The model enabled stratification of patients into distinct risk groups with significantly different probabilities of achieving RCB scores of 0 or 1. This approach may provide additional information for risk stratification and prognosis, improving our understanding of which patients are more likely to achieve pathological response. Further studies will assess the external validation of the model. Research Sponsor: Conquer Cancer, the ASCO Foundation.

613 **Poster Session**

Efficacy and safety of the pertuzumab biosimilar BCD-178 versus the originator pertuzumab in patients with HER2-positive locally advanced breast cancer: Results from the international, double-blind, randomized, phase III PREFER trial. First Author: Lyudmila Zhukova, Moscow Clinical Scientific Center Named After A.S. Loginov, Moscow, Russian Federation

Background: Pertuzumab, a HER2-targeting monoclonal antibody, significantly improves outcomes for patients with HER2-positive breast cancer (HER2+ BC) in different settings in combination with another HER2-agents with/without chemotherapy. BCD-178 is a biosimilar of the originator pertuzumab (OP). Preclinical and phase I clinical studies have demonstrated its equivalence to OP. The phase III PREFER trial compared the efficacy and safety of BCD-178 and OP as neoadjuvant and adjuvant therapy in HER2+ BC. **Methods:** The study hypothesized that neoadjuvant therapy containing BCD-178 would yield a pathological complete response (pCR) rate equivalent to that of therapy containing OP in women aged 18–75 years with stage II–III HER2+, hormone receptor-negative invasive BC and a primary tumor > 2 cm. Patients were randomized 1:1 to receive neoadjuvant therapy with either BCD-178 or OP, combined with trastuzumab and chemotherapy (TCHP regimen). The primary endpoint was the pCR rate (ypT0/is, ypN0) assessed by central independent review. Safety was monitored throughout, with adverse events (AEs) graded by CTCAE v5.0. Immunogenicity and pharmacokinetics were also evaluated (NCT05802225). **Results:** Of 398 randomized patients, 201 received BCD-178 and 197 received OP. The median age was 53 years; over one-third of patients in each group had stage IIIB/IIIC disease. pCR rates were 75.0% with BCD-178 and 72.2% with OP (risk ratio [RR] 2.7, 95% CI: -6.0 to 11.6). The 95% CI for the between-group difference in pCR rate fell within the predefined equivalence margins, confirming equivalent efficacy. The safety profiles were comparable. The most common AEs ($\geq$10%) were diarrhea and anemia. Immunogenicity was low and similar between groups: binding antibodies were detected in 1.6% (BCD-178) vs. 1.1% (OP) of patients, and neutralizing antibodies in 1.1% in both groups. The concentration-time profiles and pharmacokinetic profiles (Cmin, Ceoi) were also comparable. **Conclusions:** In patients with HER2+, hormone receptor-negative locally advanced breast cancer, the biosimilar BCD-178 demonstrated equivalent efficacy, safety, immunogenicity, and pharmacokinetics to the originator pertuzumab within a neoadjuvant TCHP regimen. Clinical trial information: NCT05802225. Research Sponsor: JSC BIOCAD.

614 **Poster Session**

Response to neoadjuvant chemotherapy in both the breast and lymph nodes in patients with inflammatory breast cancer. First Author: Megan McClanahan, Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Optimal outcomes in Inflammatory Breast Cancer (IBC) are achieved with trimodal therapy. We sought to evaluate how differences in response to neoadjuvant chemotherapy (NAC) in the breast and axilla impact locoregional recurrence-free, distant recurrence-free and overall survival in patients with IBC. **Methods:** A retrospective analysis was performed on patients with IBC enrolled in a prospective registry from 2007-2025. All patients underwent NAC followed by modified radical mastectomy. Comparisons between three pathologic response groups—(A) pCR, no residual disease in breast or lymph nodes, (B) complete response in breast but not axillary nodes, and (C) complete response in axillary nodes, but not breast—were performed using Kaplan-Meier and pairwise Cox proportional hazards models. **Results:** 545 patients were included; median age was 50 (IQR:41-58). pCR was identified in 150 (28%) patients, while 34 (6%) were in group B, and 55 (10%) were in group C. Of patients with pCR, 6 (4%) had locoregional recurrence (LRR), compared to 6 (17%) of patients in group B, 5 (9%) of patients in group C, and 79 (25%) in patients without pCR. There was decreased risk of LRR in patients with pCR compared to no pCR, or group B (HR:0.118 CI 0.05-0.27 $P<0.001$; HR:0.18 CI 0.06-0.55 P=0.017). A similar decreased risk of LRR was observed in patients with group C compared to no pCR (HR:0.297 CI 0.12-0.73 P=0.01). Of patients with pCR, 31 (20%) had distant recurrence, compared to 14 (41%) of patients in group B, 23 (41%) of patients in group C, and 183 (60%) in patients who did not have pCR. There was decreased risk of distant recurrence in patients with pCR compared to no pCR, or patients in group C (HR0.25 CI 0.17-0.37 $P<0.0001$; HR0.43 CI0.25-0.74 P=0.007). There was also a decreased risk of distant recurrence in patients with group C compared to no pCR (HR0.59 CI 0.38-0.91 P=0.027). Mean OS was longer in patients with pCR compared to partial response or no pCR (12.4 vs 7.95 years). The risk of death was lower in patients with pCR compared to partial or no pCR, as well as those with group C compared to no pCR. **Conclusions:** In patients with IBC, the lowest risk for recurrence was achieved with pCR. However, even with pCR, there was still a 20% chance of distant recurrence. Partial response through clearance of the lymph node disease provided some reduction in risk of recurrence compared to no pCR. Research Sponsor: None.

615 **Poster Session**

Preoperative combination radiotherapy (RT) and immune checkpoint inhibitor (ICI) in early-stage breast cancer: Influence of RT and ICI treatment sequencing (NCT04454528 post-hoc analysis). First Author: Julia C. Tchou, University of Pennsylvania, Philadelphia, PA

Background: The anti-tumor immune effects of combination radiotherapy (RT) and immune checkpoint inhibitors (ICI) are synergistic. Optimal treatment sequencing, i.e. RT before ICI vs. RT after ICI, remains unclear. Assuming clinical equipoise, we conducted a phase 1b/2 multi-arm adaptive window of opportunity study to evaluate feasibility and treatment response after preoperative (preop) RT before ICI vs. RT after ICI vs. ICI alone. **Methods:** Participants with early-stage breast cancer planning for upfront surgery were eligible to enroll to receive a single preop intravenous dose of pembrolizumab (pembro, an ICI), 200 mg, either alone (Arm 3) or in combination with RT (single fraction, 7 Gy) given before (Arm 1) or after pembro (Arm 2). Primary outcome measures included 1) feasibility of administration of combination RT + pembro in a 21-day preoperative window, and 2) tumor response as measured by % tumor size change post-treatment, including the proportion achieving $>$ 30% tumor reduction (TΔ30). Secondary endpoints included pathologic response as measured by residual cancer burden (RCB). Study sample size was powered for proportion of participants with TΔ30. Assuming 40% of treated participants would achieve TΔ30 compared to untreated participants, 15 subjects would yield 80% power at α = 0.05. Comparison of proportions was performed using Chi-squared test. **Results:** Between 1/6/2021 and 1/28/2025, 30 participants enrolled and completed the preop regimen assignment. Median follow-up was 634 days (IQR 256 –1120 days). All participants proceeded to surgery without delay. There were no adverse events (AEs) $\geq$ grade 3. There was one grade 2 immune-related AE (hypothyroidism). The proportion of participants achieving TΔ30 was 8 of 14 (57.1%), 6 of 11 (54.5%) and 0 of 5 (0%) in Arms 1, 2, and 3 respectively. For TNBC, TΔ30 rate was 6 of 7 (85.7%), 4 of 6 (66.7%) and 0 of 4 (0%) in Arms 1, 2, and 3 respectively. Compared with Arm 3, overall TΔ30 rate was significantly higher for those treated in Arm 1 or 2, p = 0.0307 and p = 0.0433; and for TNBC, p = 0.0088 and 0.0454, respectively. TΔ30 rate was similar in those treated with RT before (Arm 1) or RT after (Arm 2) ICI. The proportion of participants with major pathologic response (MPR) defined as RCB class 0 or 1 (RCB 0/1) treated in Arms 1, 2, and 3 were 7 of 14 (50%), 1 of 10 (10%), and 0 of 4 (0%) overall and 4 of 7 (57%), 0 of 5 (0%), and 0 of 3 (0%) for TNBC, respectively. The proportion of participants with RCB 0/1 in Arm 1 was numerically and statistically higher than Arm 2 overall and for TNBC, p = 0.0448 and p = 0.0479, respectively. **Conclusions:** RT given before ICI is more effective than RT given after ICI and resulted in MPR in 57% of participants with TNBC. This chemotherapy-free preop regimen may possibly facilitate chemotherapy omission decision in those achieving MPR in future studies. Clinical trial information: NCT04454528. Research Sponsor: None.

616 **Poster Session**

De-escalation of neoadjuvant chemotherapy for HER2-positive breast cancer: A systematic review and meta-analysis. First Author: Maria Clara Périco Perez, Faculdade de Ciências Médicas e da Saúde da Pontifícia Universidade Católica de São Paulo, Sorocaba, Brazil

Background: The addition of carboplatin to taxane-based dual HER2 blockade (TCbHP) is a standard neoadjuvant regimen for high-risk, HER2-positive breast cancer. However, this combination incurs significant hematological toxicities. Whether omitting carboplatin (THP) preserves efficacy while enabling de-escalation of toxicity remains a critical unanswered question. **Methods:** A comprehensive search of PubMed, Embase, Cochrane CENTRAL, and major oncology conference abstracts was conducted through June 15, 2025, for studies comparing THP with TCbHP. The primary endpoint was pathologic complete response (pCR). Secondary endpoints included grade $\geq$3 hematological toxicities. A non-inferiority margin for pCR was pre-specified at a risk ratio (RR) of 0.85. Data were pooled using a DerSimonian-Laird random-effects model. The study was registered on PROSPERO (CRD420251084035). **Results:** Seven studies (2 RCTs, 5 observational) comprising 2,061 patients (989 THP; 1,072 TCbHP) were included. The pooled pCR rate was 61.9% for THP versus 63.9% for TCbHP (RR 0.92, 95% CI 0.79–1.07). Statistical non-inferiority was not met, as the lower bound of the 95% CI crossed the pre-specified margin. The absolute pCR difference was a modest -2.0%. Although pCR showed substantial heterogeneity (I^2 = 69%), this was largely driven by study design differences (RCTs: RR 1.06 vs. observational: RR 0.80). In stark contrast, the THP regimen demonstrated a profound and remarkably consistent safety advantage, with an 82% reduction in grade $\geq$3 thrombocytopenia (RR 0.18, 95% CI 0.09–0.39), a 69% reduction in anemia (RR 0.31, 95% CI 0.17–0.57), and a 56% reduction in neutropenia (RR 0.44, 95% CI 0.33–0.58). Crucially, all three major hematological toxicity endpoints showed a complete absence of statistical heterogeneity (I^2 = 0% for all), indicating a robust and generalizable safety benefit. **Conclusions:** While the carboplatin-free THP regimen did not meet the strict criteria for statistical non-inferiority in pCR, the small absolute efficacy decrement is substantially offset by a large, clinically meaningful, and highly consistent reduction in severe hematological toxicities. These findings provide strong evidence to support THP as a reasonable and safer de-escalation strategy for selected patients with HER2-positive breast cancer, particularly those where toxicity is a major concern. Research Sponsor: None.

617 **Poster Session**

Structural determinants compared with genetic ancestry and self-reported race in triple-negative breast cancer disparities: A multilevel analysis in an admixed population. First Author: Patrick De Cerqueira, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: Triple-negative breast cancer (TNBC) exhibits marked racial disparities in outcomes. However, the contributions of genetic ancestry, self-reported race, and structural determinants remain unclear, particularly in admixed populations. We aimed to disentangle the independent and combined impact of these factors in a Brazilian cohort. **Methods:** We retrospectively studied 156 women with TNBC treated with neoadjuvant chemotherapy at a tertiary center in São Paulo, Brazil (2007-2022). Genetic ancestry was estimated using ancestry-informative markers (AIMs) from an unpublished dataset. Self-reported race followed national census categories. Healthcare system type (public/private) served as a proxy for socioeconomic status. Primary outcomes were pathologic complete response (pCR), overall survival (OS), and disease-free survival (DFS). Multivariable models were adjusted for age, stage, Ki-67, and year of diagnosis. Statistical techniques included multiple imputation, propensity score matching, LASSO regression, and causal mediation analysis. **Results:** The cohort was highly admixed: 27% had $\geq$20% African ancestry (AA). Discordance was observed between genetic and social classifications: 48% of self-identified Black patients had $<$20% AA, while 24% of non-Black patients had $\geq$20% AA. Patients with $\geq$20% AA had higher tumor proliferation (median Ki-67 90% vs 80%) and higher pCR (50.0% vs 41.2%, p=0.42) but higher mortality (35.7% vs 25.4%). Black patients more often to use public healthcare (48.4% vs 15.9%, p$<$0.001) present with stage III disease (45.2% vs 35.6%), and receive less dose-dense chemotherapy (41.9% vs 76.1%, p$<$0.001). In adjusted analyses, neither AA nor self-reported race independently predicted pCR, OS, or DFS. Public healthcare use was the strongest independent predictor of worse OS (HR 2.45, 95%CI 1.12-5.36, p=0.025) and DFS (HR 2.18, 95%CI 1.08-4.40, p=0.03). Clinical stage (OR 0.66, p=0.022) and carboplatin use (OR 2.8, p=0.018) were the only independent predictors of pCR. Causal mediation analysis showed that 60.1% of the detrimental effect of public healthcare on pCR was mediated by advanced stage at presentation. **Conclusions:** In this pre-immunotherapy Brazilian cohort, TNBC outcome disparities are primarily driven by structural determinants related to healthcare access rather than genetic ancestry or self-reported race. While ancestry and race capture relevant biological and social dimensions, delayed diagnosis and suboptimal treatment delivery were the main mechanisms underlying outcomes. These findings underscore the need to address structural inequities and ensuring equitable access to timely, evidence-based cancer care in admixed populations. Future prospective studies integrating genetic ancestry, socioeconomic factors, and tumor immune profiling are needed. Research Sponsor: National Program for Support of Oncological Care; PRONON - 2500.055.121/2015-12; São Paulo State Research Foundation; FAPESP: 2014/50943-1; 2013/23277-8; National Council for Scientific and Technological Development; CNPq: 465682/2014-6 ; 305464/2013-2.

618 **Poster Session**

Predicting treatment effect on distant recurrence free survival from functional tumor volume change during neoadjuvant therapy: A Bayesian hierarchical model of I-SPY 2 MRI and survival data. First Author: Keli Siqueiros Santos-Parker, Department of Surgery, University of California, San Francisco, San Francisco, CA

Background: In neoadjuvant cancer trials, early endpoints that predict treatment effect on survival identify promising agents early and support accelerated regulatory approval. However, binary endpoints like pathologic complete response inadequately characterize the full distribution of residual disease in breast cancer, while promising continuous biomarkers like MRI derived functional tumor volume (FTV) are associated with survival outcomes but not widely collected. Using a Bayesian hierarchical model, long-term treatment effects on distant recurrence free survival (DRFS) can be predicted from continuous MRI-derived functional tumor volume (FTV) in the I-SPY 2 platform trial. **Methods:** I-SPY 2 treated 2117 patients from 2010-2022 (12 weeks of paclitaxel $\pm$ experimental agent followed by 4 cycles of doxorubicin + cyclophosphamide), and 1,859 underwent dynamic contrast-enhanced MRI at baseline and after 12 weeks of neoadjuvant therapy. MRI-derived functional tumor volume provided volumetric quantification of dynamic tissue enhancement. ΔFTV was defined as the ratio of 12-week to baseline FTV. A Bayesian joint hierarchical model (brms) fit treatment effects on ΔFTV and DRFS for each treatment regimen by HR/HER2 subtype, controlling for clinical nodal status, clinical T stage, grade, and calendar year. Arms with $<$ 8 subjects are excluded. Performance was assessed using cross-validation, predicting DRFS treatment effects in one held out fold at a time from the learned ΔFTV-DRFS association in the remaining data, then comparing predicted to actual DRFS treatment effect. Sensitivity analyses on priors will be presented. **Results:** Across 1753 patients and 45 treatment–subtype combinations, the estimated treatment effects on ΔFTV and DRFS were highly correlated (posterior correlation -0.91; 95% CrI -1.00 to -0.23). Predicted DRFS treatment effect from ΔFTV demonstrated strong concordance with actual DRFS treatment effects (Pearson r = 0.94 in TNBC; 0.97 HER2+; 0.80 HR+HER2-). The top 5 treatment-subtype regimens ranked by predicted and actual DRFS were identical. 20 regimens predicted to have $>$ 70% probability of DRFS benefit over subtype specific controls showed DRFS improvement, yielding 100% specificity and 69% sensitivity at this decision threshold. **Conclusions:** We demonstrate internally validated prediction of neoadjuvant treatment effect on DRFS from MRI-derived change in functional tumor volume in the I-SPY 2 trial of high-risk early breast cancer. This suggests continuous imaging measures capture a range of response to therapy while Bayesian approaches can be effective for predicting treatment effects. This encourages collecting MRI biomarkers in trials to facilitate validation as early endpoints supporting decisions in screening platform trials as well as regulatory accelerated approval. Research Sponsor: None.

619 **Poster Session**

Systemic cytokine dynamics during neoadjuvant chemotherapy versus endocrine therapy and CDK4/6 inhibition in high-risk luminal breast cancer: Results from the GEICAM/2019-01-CARABELA trial. First Author: Angel Guerrero-Zotano, Instituto Valenciano de Oncología (IVO), Valencia, Spain; GEICAM Spanish Breast Cancer Group, Madrid, Spain

Background: Chemotherapy (CT) and CDK4/6 inhibitors modulate antitumor immunity primarily within the tumor microenvironment. Whether these effects are reflected systemically during neoadjuvant therapy, differ by treatment, or are associated with response remains unclear. **Methods:** CARABELA is a randomized neoadjuvant trial comparing letrozole (ET) + the CDK4/6 inhibitor abemaciclib vs standard CT in high-risk HR+/HER2− breast cancer. Plasma cytokines were measured at baseline (BL), 2 weeks (wks), 12 wks, and end of treatment (EOT) using multiplex proximity extension assay (Olink Target 96 Immuno-Oncology panel). Analyses included: (1) BL cytokine profiles by menopausal status, Oncotype DX Breast Recurrence Score test result (RS $\leq$25 vs $>$25), and Ki67 ($<$40% vs $\geq$40%); (2) longitudinal cytokine changes (BL to 2 and 12 wks, Δ) by residual cancer burden (RCB 0/I vs II/III), overall and by treatment; (3) EOT cytokine profiles by RCB. Group comparisons were adjusted by false discovery rate (FDR) threshold of 5% controlled by the q-value method. Multivariable logistic regression models were adjusted for menopausal status. Treatment–cytokine interactions were evaluated. **Results:** At BL, 40 cytokines were differentially expressed by menopausal status, with most showing higher levels in postmenopausal patients, including myeloid-associated inflammatory chemokines (CXCL9, CXCL10, MCP-1, MCP-4), angiogenic/matrix-remodeling factors (VEGFA, HGF, MMP7, MMP12), and TNF-related/immune regulatory molecules (TNFRSF12A, TNFRSF9, Galectin-9), indicating chronic systemic inflammation, without enrichment of cytotoxic immune effector programs. No BL cytokine differences met FDR threshold by RCB, RS or Ki67. Early cytokine changes (BL-2 wks) were not associated with RCB. In the ET + abemaciclib arm, no significant changes were observed between BL and 12 wks. In the CT arm, 25 cytokines had a significant increase (BL-12 wks) in patients with RCB II/III with respect to patients with RCB 0/I. These included inflammatory chemokines (IL8, CXCL1, CXCL5, CCL3, CCL4, MCP-3, MCP-4), angiogenic/growth factors (VEGFA, ANGPT1, EGF, PDGF-B), and stress-/TNF-related signaling molecules (CASP-8, TNFSF14, ADA). These cytokines were associated with RCB II/III in multivariable models adjusted for menopausal status. Cytokine–treatment interaction tests did not meet FDR threshold. **Conclusions:** Postmenopausal women display a distinct cytokine profile consistent with chronic systemic inflammation. Neoadjuvant CT induces pronounced systemic cytokine changes, while ET + CDK4/6 inhibition does not. Increased inflammatory and angiogenic cytokines during CT are associated with residual disease, supporting longitudinal systemic immune profiling as a marker of treatment resistance in high-risk luminal breast cancer. Clinical trial information: NCT04293393. Research Sponsor: GEICAM Spanish Breast Cancer Group.

620 **Poster Session**

Neoadjuvant mitomycin C plus carboplatin followed by paclitaxel vs. standard doxorubicin–cyclophosphamide followed by paclitaxel–carboplatin in BRCA1/2-associated breast cancer. First Author: Petr Krivorotko, "N.N. Petrov National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation, Saint Petersburg, Russian Federation

Background: Triple-negative breast cancer (TNBC) associated with BRCA1/2 mutations is an aggressive disease subtype characterized by high sensitivity to chemotherapy. Accumulating evidence suggests the efficacy of mitomycin C, both as monotherapy and in combination with platinum agents, in BRCA1/2-driven tumors. This clinical study aimed to compare mitomycin C–based chemotherapy regimens with standard neoadjuvant chemotherapy in patients with BRCA1/2-associated TNBC. **Methods:** A total of 52 patients with BRCA1/2 pathogenic variants and TNBC stage T1-3N0-3M0 were enrolled. Patients were randomized to an experimental arm (n=26) receiving mitomycin C (10 mg/m²) plus carboplatin (AUC 5) (MCbP) for four cycles followed by weekly paclitaxel (80 mg/m²) for 12 cycles (MCbP-T), or to a control arm (n=26) receiving doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) (AC) for four cycles followed by weekly paclitaxel (80 mg/m²) plus carboplatin (AUC2) for 12 cycles (AC-TCbP). Treatment efficacy was assessed according to RECIST criteria and the rate of pathological complete response (pCR) after surgery. **Results:** After four cycles of MCbP/AC, clinical complete response (cCR) was observed more frequently in the MCbP group compared with the AC group (58% vs 7.7%; p = 0.0002). Upon completion of neoadjuvant chemotherapy, cCR remained significantly higher in the experimental arm (65.4% vs 42%; p = 0.037). The pCR rate was 81% versus 62% (p = 0.12), while Miller–Payne grade V pathological response was achieved in 77% and 65% of patients, respectively (p = 0.084). During a 26-month follow-up, adverse events occurred in 3.8% of patients in the experimental group and 12% in the control group; one death was reported only in the AC-TCbP arm (p = 0.6). Grade III leukopenia and neutropenia were more frequent in the AC-TCbP group (42% and 46%) compared with MCbP-T (4% and 8%; p = 0.002 and p = 0.003, respectively). Thrombocytopenia of any grade occurred more frequently in the MCbP-T group (36% vs 0%; p $<$ 0.001). Grade II alopecia was observed in all patients in the control group and in none of the MCbP-T patients (p $<$ 0.001). **Conclusions:** In BRCA1/2-associated TNBC, the MCbP-T regimen demonstrates efficacy comparable to standard anthracycline-based chemotherapy with platinum agents, while providing a more favorable safety profile and a lower incidence of adverse events. Research Sponsor: Грант; 21-75-30015.

621 **Poster Session**

Integration of molecular subtyping and immune profiling to predict pathologic complete response in HER2+ breast cancer treated with neoadjuvant dual HER2 therapy. First Author: David B. Page, Providence Cancer Institute, Portland, OR

Background: Neoadjuvant outcomes are variable in human epidermal growth factor receptor 2-positive (HER2+) early breast cancer (EBC), highlighting the unmet need for predictive biomarkers. The BluePrint (BP) assay classifies tumors by molecular intrinsic subtype, whereas the ImPrint hormone receptor-positive (HR+) and ImPrint triple-negative genomic signatures predicted immune sensitivity in the ISPY2 trial. Because HER2+ EBCs are genomically heterogeneous, and because anti-HER2 has an immunologic mechanism of action, we hypothesized that BP and ImPrint could be used to predict outcomes (pathologic complete response, pCR) following neoadjuvant chemotherapy + anti-HER2 (trastuzumab + pertuzumab, HP). **Methods:** We evaluated n=252 HER2+ EBCs receiving neoadjuvant chemotherapy + HP in the prospective, observational FLEX study. Tumors were classified by BP subtype (HER2, Luminal A/B, or Basal) and ImPrint (+ or -). Fisher's exact test was used to compare pCR rates across BP/ImPrint results. Multivariable logistic regression was used to evaluate independent associations with pCR, adjusting for nodal status and tumor size. **Results:** 72% of HER2+ EBCs were HR+ and 28% were HR−. In HR+/HER2+ EBC, 52% were classified by BP as non-HER2 (Luminal A 6%, Luminal B 44%, Basal 2%), whereas in HR-/HER2+ EBC, 14% were classified genomically as non-HER2, all of which were Basal. In the HR+/HER2+ subgroup, pCR rates differed significantly by BP subtype and ImPrint, with the highest pCR observed in BP-HER2/ImPrint+ tumors (Table). Similar significant differences were observed in HR-/HER2+ EBC. In a multivariable model of the HR+/HER2+ subgroup, BP and ImPrint independently predicted pCR after controlling for node status and tumor size (BP-HER2 odds ratio/OR: 8.23 [95% CI: 3.47–21.44]; p$<$0.001; ImPrint+ OR: 4.48 [95% CI: 1.48–14.89]; p$<$0.05). **Conclusions:** An integrated genomic approach that combines BP and ImPrint maximizes prediction of pCR outcome in this dataset, particularly for the HR+/HER2+ subgroup. Further evaluation is warranted, as these data could be useful for guiding clinical decision-making, including selection of chemotherapy backbone and adjuvant therapy. Importantly, this approach may help identify patients who are overtreated or undertreated with current strategies, including those with exceptional treatment sensitivity who may be candidates for chemotherapy de-escalation. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

pCR rates by genomic subtypes within HR+/HER2− EBC (Fisher's exact test).

Biomarker	Subtype*	N	pCR rate (%)	p-value
BluePrint	HER2	87	55	$<$ 0.001
	Luminal B	80	20	
ImPrint	Positive	30	60	0.006
	Negative	151	32	
BluePrint + ImPrint	HER2, ImPrint+	14	79	$<$ 0.001
	HER2, ImPrint-	73	51	
	Luminal B, ImPrint+	14	43	
	Luminal B, ImPrint-	66	15	

*Excluded Luminal A and Basal due to small N.

623 **Poster Session**

Event-free survival from the randomized phase 2 neoHIP trial evaluating neoadjuvant taxane, HER2-targeted therapy, +/- pembrolizumab in early-stage HER2-positive breast cancer. First Author: Heather L. McArthur, UT Southwestern Medical Center, Dallas, TX

Background: In early-stage HER2–positive breast cancer, achieving a pathological complete response (pCR) after neoadjuvant therapy is strongly associated with improved event-free survival (EFS); however, a substantial proportion patients (pts) fail to achieve pCR, requiring subsequent adjuvant systemic therapy and remaining at higher risk for recurrence. Pembrolizumab (pembro) is well-tolerated, invigorates anti-tumor immunity, and may enhance response of chemotherapy and/or anti-HER2. We previously reported the positive primary outcome of the randomized phase 2 neoHIP trial, showing an improvement in pCR with the addition of pembro to neoadjuvant paclitaxel, trastuzumab, and pertuzumab (4 cycles, THP–pembro, pCR: 67% v. THP: 48%, p=.026). With long-term follow-up now mature, we now report EFS outcomes. **Methods:** Pts aged $\geq$ 18 years with stage II–III HER2–positive breast cancer were randomized, stratified by hormone receptor status and nodal status, to receive neoadjuvant THP or THP–pembro. EFS was defined as the time from randomization to progression of disease precluding surgery, local or distant recurrence, or death from any cause. EFS was estimated using the Kaplan–Meier (KM) method and compared between arms using a two-sided stratified log-rank test. Data were analyzed with a cutoff date of January 23, 2026. **Results:** Among 116 pts (58 per arm) randomized to THP +/- pembro, median follow-up was 37 months (range, 33–43). The 36-month EFS rate was 95% (95% CI, 89–100) for THP and 100% (95% CI, 100–100) for THP-pembro, with a trend towards significance (p=.099). Three EFS events were observed, all occurring in the THP arm, with one death related to recurrence and n=2/3 events occurring in patients with non-pCR. **Conclusions:** THP + pembro was associated with 100% EFS after a median follow-up of 37 months, whereas recurrences were observed in the THP arm, consistent with historical EFS expectations for neoadjuvant chemotherapy + dual HER2-targeted therapy. Although not powered for EFS, these findings support definitive evaluation of THP +/- pembro in a phase III trial. Clinical trial information: NCT03747120. Research Sponsor: Merch Sharp & Dohme; Breast Cancer Research Foundation.

625 **Poster Session**

Neoadjuvant DAN-222 plus niraparib in high-risk HER2-negative breast cancer: Results from the I-SPY 2 adaptive platform trial. First Author: Kay T. Yeung, UC San Diego Moores Cancer Center, La Jolla, CA

Background: I-SPY 2 is a multicenter phase II adaptive platform trial evaluating novel agents for stage II-III high-risk breast cancer using response-predictive subtypes (RPS) and a sequential neoadjuvant treatment design of up to three blocks (A/B/C). Investigational regimens are given in Block A, followed by response-guided escalation to standard-of-care (SOC) therapy (tx) in subsequent blocks or early surgery for responders. Topoisomerase I (TOPO1) inhibition plus PARP inhibition may enhance DNA damage and tumor response. DAN-222 is a tumor-targeted polymeric camptothecin conjugate designed to improve the therapeutic index of TOPO1 inhibition. Based on favorable phase 1 safety and preliminary activity in metastatic breast cancer, DAN-222 plus niraparib was evaluated as Block A tx in HER2− disease. Notably, the neoadjuvant regimen used a higher dose of niraparib (200 mg daily) than the prior phase 1 metastatic study. **Methods:** Patients (pts) with HER2− breast cancer were randomized to DAN-222 plus niraparib for up to 12 weeks in Block A. Response was assessed by serial MRI and biopsy. Inadequate responders escalated early to SOC tx in Blocks B/C. Primary endpoint was pathologic complete response (pCR). Secondary endpoints included residual cancer burden, safety, early discontinuation, and treatment-strategy performance versus subtype-specific SOC tx controls. Given established PARPi sensitivity in *BRCA*mut disease, the key objective was to assess clinically meaningful activity of DAN-222 plus niraparib in *BRCA*wt pts. Accordingly, a prespecified Bayesian interim futility analysis focused on *BRCA*wt and tested the probability of the true pCR rate after Block A alone exceeded 15% after 50 pts. **Results:** Fifty pts enrolled from Sep to Dec 2024. In *BRCA*wt (n=47), estimated Block A pCR was 3%, with posterior probability of 0.02 that that true pCR exceeded 15%, meeting futility criteria and prompting arm closure. Across all blocks, pCR rate was 57% (8/14) for HR-HER2−; 11% (4/36) for HR+ HER2−, largely after SOC tx. 2/3 BRCA*mut* pts achieved pCR. Treatment strategies initiating with DAN-222 plus niraparib underperformed subtype-specific controls. 68% discontinued Block A early, mainly due to toxicity. Grade ≥3 cytopenias were common: neutropenia (n=25; 50%), anemia (24%), and thrombocytopenia (18%). Cystitis occurred in 36% (1 grade ≥3). **Conclusions:** Neoadjuvant DAN-222 plus niraparib showed insufficient activity and no treatment-strategy benefit in *BRCA*wt HER2− breast cancer, underscoring challenges for TOPO1–PARP inhibitor combinations. Although not supported for further development in this setting, these results highlight the strength of I-SPY 2 in rapidly enrolling patients and quickly distinguishing ineffective from promising therapeutic strategies to accelerate progress toward improved outcomes for patients with curable breast cancer. Clinical trial information: NCT01042379. Research Sponsor: None.

626 **Poster Session**

Maternal and neonatal complications associated with breast cancer systemic treatments: A VigiBase disproportionality analysis study. First Author: Rayan Kabirian, Department of Medical Oncology, Institut Curie, Saint Cloud, France

Background: Pregnancy-associated breast cancer (PrBC) presents unique diagnostic and therapeutic challenges, with rising incidence due to delayed childbearing. Understanding maternal-fetal safety of systemic anticancer therapies during pregnancy is critical for informed treatment planning. **Methods:** We performed a case/non-case disproportionality analysis using VigiBase, the WHO global pharmacovigilance database up to January 2024, to evaluate maternal and fetal/neonatal outcomes associated with breast cancer (BC) systemic treatments. We included reports involving pregnancy, antineoplastic treatment during pregnancy, and cancer. The exposure group consisted of reports mentioning a BC treatment at any time during pregnancy. The primary outcome was the reporting odds ratio (ROR) of maternal-fetal complications in the BC treatment group involving at least one of the four main BC treatments: doxorubicin, epirubicin, docetaxel, paclitaxel, compared to other anticancer treatments. Secondary analyses assessed outcomes with all BC treatments and trimester-specific risks of the four main treatments. **Results:** Of 3,310 pregnancy-related reports, 1,789 involved BC treatments. Median maternal age was 27.4 years (standard deviation SD 13.8) in the BC treatment group versus 29.3 years (SD 11.7) in the other anticancer treatment group. Adverse pregnancy or neonatal outcomes were reported in 998 (55.8%) BC treatment reports versus 470 (30.9%) in other anticancer treatments. Anthracyclines were associated with neonatal immunodeficiency (ROR=11.0, 95%CI 3.2–40), hematologic disorders (ROR=1.7, 95%CI 1.1–2.5), infections (ROR=2.3, 95%CI 1.4–3.8), and pregnancy complications including IUGR (ROR=2.1, 95%CI 1.7–2.7) and hypertension/pre-eclampsia (ROR=1.9, 95%CI 1.2–2.9). Epirubicin was linked to craniofacial (ROR=7.6, 95%CI 2.5–23.5) and genitourinary malformations (ROR=6.3, 95%CI 2.1–18.9). Taxanes were associated with IUGR (paclitaxel ROR=2.8; docetaxel ROR=2.8), with paclitaxel linked to sensory defects (ROR=5.2, 95%CI 2.2–12.3) and hyperbilirubinemia (ROR=4.1, 95%CI 2.0–8.4), and docetaxel to neonatal neurologic disorders (ROR=3.6, 95%CI 1.4–9.3). First-trimester exposure (n=26) markedly increased risks of congenital malformations, i.e. face (ROR=13, 95%CI 2-79) and musculoskeletal malformation (ROR=8, 95%CI 1.1-60). **Conclusions:** BC treatments during pregnancy are associated with increased specific maternal and neonatal risks, with distinct drug- and trimester-specific variations. These findings highlight the need for individualized treatment planning and targeted fetal surveillance. Research Sponsor: "Contrats ED: Programme blanc Institut Curie PSL" during this study.; "SHS INCa", and is part of a research project on young women funded by Monoprix*; France 2030 Grant for the Women's Cancers Institute, referenced ANR-23-IAHU-0006.

627 **Poster Session**

Optimal timing of endocrine therapy interruption for pregnancy in young women with hormone receptor–positive early breast cancer. First Author: Floriane Jochum, Department of Gynecologic and Breast Surgery, INSERM U1109, Strasbourg University Hospital, Strasbourg, France

Background: The POSITIVE trial showed that temporary interruption of adjuvant endocrine therapy (ET) after 18–30 months to attempt pregnancy did not increase short-term recurrence risk in young women with hormone receptor–positive (HR+) breast cancer (BC). However, whether this effect varies by baseline recurrence risk and the timing of interruption remains uncertain. **Methods:** Using the French National Health Data System (SNDS), we emulated two target trials among women aged ≤42 years with early-stage HR+ BC diagnosed between 2011 and 2020. Trial 1 emulated the POSITIVE design, comparing ET interruption at 18–30 months with uninterrupted ET for ≥24 months. Trial 2 compared nine ET-interruption windows (6-month intervals) with uninterrupted ET for ≥24 or ≥60 months. The primary endpoint was the 5-year risk of BC events. Analyses used a clone–censor–weight approach with marginal structural models. **Results:** In Trial 1 (n = 10,835), ET interruption at 18–30 months was associated with a 5-year BC event risk of 17.2%, compared with 16.0% for uninterrupted ET ≥24 months (risk difference, 1.2 percentage points; 95% CI, −0.7 to 3.1). Risk varied by baseline recurrence risk: interruption had minimal impact in low- or intermediate-risk women (risk difference, −0.6 percentage points; 95% CI, −2.7 to 1.6) but increased risk in high-risk women (risk difference, 5.8 percentage points; 95% CI, 1.8 to 10.0). In Trial 2 (n = 22,916), earlier ET interruption was associated with higher 5-year BC risk, which decreased with longer prior ET duration. Compared with uninterrupted ET ≥24 months, interruption at 6–12 months increased risk by 8.3 percentage points, whereas interruption at 24–30 months increased risk by 2.7 percentage points. Low- or intermediate-risk women showed comparable risk when interruption occurred at 24–30 months, whereas high-risk women required ≥36–42 months of ET to achieve similar safety. Among pregnancy-seeking women, 64% conceived, and 47% resumed ET. **Conclusions:** The oncologic impact of temporary ET interruption depends on baseline recurrence risk and prior ET duration. Interruption after 24 months appears safe for low- or intermediate-risk women, whereas high-risk patients may benefit from delaying interruption to at least 36 months. These findings support a risk-adapted approach to fertility counseling. Research Sponsor: None.

628 **Poster Session**

GLP-1 RA for primary prevention of post-mastectomy lymphedema in breast cancer patients: A multicenter real-world analysis. First Author: Dawit Hailemariam Yesho, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: Post-mastectomy lymphedema (PML) remains a significant morbidity for breast cancer (BC) survivors, particularly following axillary lymph node dissection (ALND). Complications, including recurrent cellulitis, lymphangitis, and chronic pain, significantly impair quality of life. While weight optimization is a cornerstone of PML management, the specific role of Glucagon-like Peptide-1 Receptor Agonists for the primary prevention of PML is poorly characterized. Data is limited to single-center retrospective studies (1) and case reports. This is the first, large-scale, multi-center, real-world analysis to evaluate the efficacy of GLP-1 RA for the primary prevention of PML in BC patients. **Methods:** Utilizing the TriNetX Global Collaborative Network, a retrospective cohort study was conducted on a population of 150 million patients across 108 healthcare organizations (Jan 2000 – Jan 2025). We evaluated the impact of GLP-1 RAs on the incidence of PML in BC patients. Patients were stratified into two cohorts: those who underwent mastectomy and received GLP-1 RAs, and a control group of mastectomy patients without GLP-1 RA exposure. 1:1 Propensity Score Matching (PSM) was used to balance cohorts for demographics, BMI, comorbidities, concurrent medications, and laboratory values. Following a median 650-day follow-up, hazard ratios (HR) and 95% Confidence Intervals (CI) were calculated using Kaplan-Meier survival analysis and Cox proportional hazards models to assess PML risk. **Results:** After 1:1 propensity score matching, 61,630 patients were included (n = 30,815 per cohort). The GLP-1 RA cohort had a mean age of 62.1 ± 10.8 years and was mainly female (99.2%). Racial distribution was 71.0% White, 18.0% Black or African American, and 2.9% Asian. Standardized mean differences for all matched covariates were <0.1, indicating excellent balance within the cohort. Kaplan-Meier survival analysis demonstrated a 63% significant reduction in incident PML among GLP-1 RA users compared to the control group (HR 0.373; 95% CI, 0.324–0.429; $p < 0.0001$). The absolute incidence of PML was 0.88% (258/29,259) in the GLP-1 RA cohort vs 2.58% (779/30,237) in the control group, yielding an absolute risk reduction of 1.7% and a number needed to treat (NNT) of 59. **Conclusions:** In this large-scale, real-world analysis, GLP-1 RA use was associated with a profound 63% reduction in the risk of PML. These findings suggest that GLP-1 RAs may serve as a potent primary preventive role in BC survivorship, potentially through mechanisms beyond weight loss, including systemic anti-inflammatory effects and a disease-modifying role in the lymphatic microenvironment. With a NNT of 59, incorporating GLP-1 RAs into the supportive care of high-risk BC patients could significantly reduce the burden of chronic lymphedema. Prospective randomized controlled trials are warranted to validate these results. Research Sponsor: None.

629 **Poster Session**

Real-world treatment patterns and mortality associated with GLP1-RAs in breast cancer patients. First Author: Jasmine S. Sukumar, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: GLP1 Receptor Agonists (GLP1) are widely used for type 2 diabetes (DM2) and obesity in adults. However, data on modern utilization and associated health outcomes, including all-cause mortality, in breast cancer (BC) patients is limited. We evaluated these endpoints in a BC population from a large US national healthcare database. **Methods:** Using Truven MarketScan, a commercial insurance claims database which includes over 270 million patients, we extracted eligible invasive BC patients diagnosed between 2014 and 2023 who were ≥ 18 years old, completed definitive BC surgery (index date), received GLP1 for at least 3 continuous months, and had available mortality data. Overall survival (OS) was defined as the time from BC surgery to death from any cause; patients alive at the time of analysis or lost to follow-up were censored at last contact date. Propensity score matching (1:1 ratio) was used to match patients who received GLP1 with those who did not, based on clinical prognostic factors (age; sex; deyo comorbidity index (CI); receipt of immunotherapy, chemotherapy, adjuvant endocrine therapy; DM2; weight category; stroke; myocardial infarction (MI)/coronary artery disease (CAD); heart failure); Kaplan-Meier estimates and log-rank tests were used to compare OS between groups and hazard ratios (HR) were estimated using multivariable Cox proportional hazards models. **Results:** In 137,493 BC patients, 7,249 (5.3%) received a GLP1 and over half (n=4,019; 55.4%) initiated it after BC surgery. The median follow up time in GLP1 users was 32 (IQR 15-57) months. In GLP1 users the median age was 59 (IQR 53-64) years; 5,860 (80.8%) had DM2 and 1,825 (25.2%) had a CI ≥3; in those with weight data available (n=4,687), 4,609 (98.3%) were in the overweight or obese category. A total of 3,828 (52.8%) received GLP1 concurrent with anti-cancer systemic therapy (chemotherapy, immunotherapy, or adjuvant endocrine therapy). The median duration of GLP1 use was 2.1 (IQR 0.8-6.1) years. GLP1 use increased over time (3.2% in 2014, 5.2% in 2018, 7.2% in 2023). Semaglutide was the most common agent prescribed across all years (35.8%) and exhibited the greatest annual increase in use after 2018. In the propensity score matched cohort, OS was significantly higher in GLP1 users vs non-users (n=7,248 per group): 5 year OS 95.8% GLP1 vs. 89.5% non-users (adjusted HR 0.41, 95% CI: 0.34-0.49, p<0.001). **Conclusions:** We describe one of the largest observational studies on real-world GLP1 prescription patterns and associated mortality in a BC cohort. Use of these agents is increasing over time in BC patients. Our research supports other emerging epidemiologic data suggesting a potential all-cause mortality benefit with these incretin mimetics in this population. Prospective studies are warranted to clarify the biological mechanisms underlying this association, including metabolic health implications and effects on BC tumor biology. Research Sponsor: None.

630 **Poster Session**

Real-world cumulative exposure of various endocrine-disrupting chemicals and association with breast cancer risk via common carcinogenic pathway. First Author: Lijuan Tang, Department of Breast Surgery, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Background: Convergent evidence suggests carcinogenicity of endocrine disrupting chemicals (EDCs). But there is a lack of large-scale epidemiological evidence concerning real-world EDCs mixture exposure and breast cancer (BC). A dataset of emerging knowledge of toxic pathways provides a valuable toolkit to infer the carcinogenicity of chemicals, but current studies of this thus filed are rare. We test whether real-world EDCs exposure, independently or in mixture, increases BC risk in the population, through carcinogenic toxic pathways. **Methods:** A total of 234,273 women from the UK Biobank cohort were followed for a median of 13.85 years. The annual monitoring record from UK Water Quality Sampling Harmonised was used to estimate the exposure to 13 EDCs (e.g., lead and chlorpyrifos-methyl) for each woman by Kriging interpolation model. The association between EDCs and breast cancer was analyzed by Cox proportional hazard model (for single EDC) and weighted quantile sum (WQS) regression (for mixture). The EDCs were also added to the modified Gail model to test their additional contribution. Twenty-seven Olink proteins were selected via EDC-BC toxic pathway dataset and BC genetic propensity score model to examine their correlation with EDCs. Interaction between EDCs and these proteins and SNPs within their sequence were analyzed by multiplicative model. **Results:** During the follow-up period, 9,282 women developed BC, 984 of whom died. All the 13 EDCs showed association with increased BC risk. Each unit increase of the 13-EDC mixture was associated with 2.15 fold (95% CI, 2.01-2.31) of BC risk and 4.18 fold of BC-related mortality (95% CI, 3.39-5.17), and 34.38 % of total morbidity and 59.6% of BC-related mortality in the population were attributable to EDC mixture. The risk of hormone receptor-positive BC was higher than that of hormone receptor-negative BC (HR: 2.87 vs HR: 2.03, p = 0.002). The EDCs provided 2.1 % improvement to the modified Gail model of BC prediction. For the 27 Olink proteins referring to BC toxic pathway and genetic propensity score, 26 (96.3%) correlated with at least one EDC (average number ≥8), among which NACC1 protein mediated up to 98.8% (chlorpyrifos-methyl) of the individual EDC's effect on BC. The EDC mixture showed interaction with multiple proteins, including NACC1 and estrogen receptor 1, on BC-related mortality. **Conclusions:** Various EDCs in the real world may increase BC morbidity and mortality via common carcinogenic pathways. Future policies of novel EDC emission and safety evaluations must consider the cumulative EDC stressor in the environment because they may act as a whole. Research Sponsor: National Health Commission of China; Grant No. 2024ZD0525600.

631 **Poster Session**

Impact of fertility concerns on endocrine therapy. First Author: Kathryn Jean Ruddy, Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background: Adolescent and young adult (AYA) women with breast cancer who have not completed their desired childbearing pre-diagnosis may be more likely to decline adjuvant endocrine therapy (ET) and/or to temporarily or permanently stop ET to pursue pregnancy. Fertility counseling and use of fertility preservation strategies (e.g., oocyte/embryo cryopreservation) might impact these decisions. **Methods:** In the Valuing Opinions and Insights from Cancer Experiences (VOICE) Study, we investigated whether use of fertility preservation strategies were associated with ET initiation and early discontinuation amongst AYAs with fertility concerns. Eligible females were diagnosed with stage 1–3 estrogen-receptor positive breast cancer at age 15-39 during 2013-2022 and responded to a survey in 2023-2024. Those who reported that they had not completed their desired family size or had been unsure about having completed their desired family size at the time of their cancer diagnosis were categorized as having had fertility concerns. ET initiation was defined as 2+ ET prescription fills within 18 months after diagnosis. Among ET initiators, we assessed early discontinuation (defined as lack of ET prescription fill over any 180 day period until 5 years after their first ET fill date). Due to inadequate power, we did not model the relationship between oocyte/embryo cryopreservation and ET initiation. However, we did have power to assess the association between oocyte/embryo cryopreservation and ET discontinuation using multivariable Cox regression to calculate Hazard Ratios (HR) and 95% Confidence Intervals (CI). HRs for discontinuation were adjusted for age at diagnosis, stage, study site, diagnosis year, income, and children before diagnosis (yes/no). **Results:** Among 518 AYA breast cancer survivors, 56% (N = 290) had fertility concerns at diagnosis. Of these 290, 41% had 1+ child before diagnosis, 90% received fertility counseling, 27% froze eggs or embryos, and 10% had 1+ child after diagnosis. The majority (89%) initiated ET. Among the 32 who did not initiate ET, 7 (22%) reported that fertility concerns impacted that decision. Oocyte/embryo cryopreservation was used by 26% of ET initiators and 34% of ET non-initiators. Among the 258 ET initiators, 89 (35%) discontinued ET early. Compared to those who did not use fertility preservation strategies, patients who froze oocytes/embryos were more likely to discontinue ET (HR 1.89; 95% CI 1.18–3.05). Among those who discontinued ET, 19% had 1+ child after diagnosis (compared to 2% among those who did not discontinue ET). **Conclusions:** This study confirmed prior studies showing that many AYAs with breast cancer have fertility concerns, and these concerns may impact decisions about ET. In our analysis, those who cryopreserved oocytes/embryos were more likely to discontinue ET early, and a higher proportion who discontinued ET had 1+ live birth after breast cancer. Research Sponsor: National Cancer Institute; P01CA 233432.

632 **Poster Session**

Long-term safety outcomes of pregnancy among young breast cancer survivors: Results from a prospective, multicenter cohort study. First Author: Kimia Sorouri, Dana-Farber Cancer Institute, Boston, MA

Background: Prospective data on the risk of breast cancer (BC) recurrence among young BC survivors who have a subsequent pregnancy are limited. We sought to evaluate the long-term impact of pregnancy and live birth on BC outcomes in the Young Women's Breast Cancer Study (NCT01468246), a prospective multicenter study of women aged ≤40 years at BC diagnosis. **Methods:** Women with stage 0-III BC without prior hysterectomy were included. The primary endpoint was breast cancer-free interval (BCFI) between patients with and without a (a) pregnancy and (b) live birth after BC. Secondary endpoints were distant recurrence-free interval (DRFI) and overall survival (OS). A time-varying Cox proportional hazards model was performed by estrogen receptor (ER) status, controlling for age at diagnosis, tumor stage, HER2 status, tumor grade, parity at diagnosis, and germline pathogenic variant status. **Results:** Among 1,016 BC survivors at a median follow-up of 12 (range, 0.5-18.5) years, 198 reported ≥1 pregnancy and 165 reported ≥1 live birth post-diagnosis. Among survivors who reported a post-diagnosis pregnancy, median age at diagnosis was 32 (range, 17-40) years; most had stage I (35%) or II (40%) BC, with 72% hormone receptor (HR)-positive and 25% HER2+; 42% were nulligravid and 60% were nulliparous at diagnosis. Among BC survivors who did not become pregnant post-diagnosis, median age at diagnosis was 37 (range, 21-40) years; most had stage I (35%) or II (43%) BC, with 75% HR-positive and 28% HER2+; 25% were nulligravid and 29% were nulliparous at diagnosis. Among BC survivors with ER-positive tumors (n = 737), pregnancy after BC was not associated with a difference in BCFI (adjusted hazard ratio [HR] 0.60, 95% CI 0.31-1.16, *P*= 0.130), DRFI (HR 0.73, 95% CI 0.35-1.55, *P*= 0.416), or OS (HR 0.58, 95% CI 0.24-1.40, *P*= 0.227). Similarly, live birth after BC did not impact BCFI (HR 0.83, 95% CI 0.45-1.55, *P*= 0.560), DRFI (HR 1.04, 95% CI 0.52-2.06, *P*= 0.923), or OS (HR 0.77, 95% CI 0.34-1.76, *P*= 0.541). Outcomes among BC survivors with ER-negative tumors (n = 278) were also not affected by post-diagnosis pregnancy (BCFI [HR 1.48, 95% CI 0.70-3.14, *P*= 0.304], DRFI [HR 1.59, 95% CI 0.68-3.75, *P*= 0.287], OS [HR 0.99, 95% CI 0.39-2.49, *P*= 0.975]) or live birth (BCFI [HR 1.02, 95% CI 0.41-2.53, *P*= 0.974], DRFI [HR 0.80, 95% CI 0.24-2.69, *P*= 0.722], OS [HR 0.39, 95% CI 0.09-1.69, *P*= 0.208]). **Conclusions:** In this multicenter, prospective study with 12 years of median follow-up, pregnancy and live birth after BC did not impact BC events or overall survival, irrespective of ER status. These long-term data from a modern cohort provide reassurance for young BC patients interested in future fertility. Clinical trial information: NCT01468246. Research Sponsor: None.

633 Poster Session

Impact of an artificial intelligence–based management model on psychological and behavioral outcomes in breast cancer patients undergoing home CDK4/6 inhibitor therapy: A multicenter randomized controlled trial. First Author: Li Zhang, Department of Breast Internal Medical, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Patients receiving CDK4/6 inhibitors (CDK4/6i) often face significant psychological and physical challenges. This study evaluated the multi-dimensional impact of an AI-based management model (Group A), a customized active follow-up model (Group B), and conventional care (Group C) on the psychological status, quality of life (QoL), and biological indicators of patients with HR+/HER2- breast cancer and their primary caregivers. **Methods:** In this randomized controlled trial (2024–2025), 140 patient-caregiver dyads were enrolled and randomized into Group A (n=47), Group B (n=45), or Group C (n=48). Longitudinal assessments were conducted using the Self-Rating Anxiety/Depression Scales (SAS/SDS), EORTC QLQ-C30, and PRO-CTCAE. Statistical analyses included mixed-design ANOVA for longitudinal changes, multiple correspondence analysis (MCA) for caregiver coping patterns, and Pearson correlation for psychological and serological indicators. **Results:** Baseline characteristics were balanced across groups ($P > 0.05$). Mixed-design ANOVA revealed significant time-by-group interaction effects for anxiety ($F=5.961$, $P < 0.001$) and depression ($F=4.931$, $P < 0.001$). During follow-up, Groups A and B showed significantly better psychological stability and depression relief compared to Group C; Group C's psychological status deteriorated over treatment cycles, peaking at T3 (16 weeks), while Groups A and B remained stable or improved ($P < 0.001$). Regarding QoL, Groups A and B significantly outperformed Group C in cognitive, emotional, social functioning, and global health ($P < 0.05$), with Group A showing superior cognitive function scores. MCA identified a strong clustering between the AI-based model and "positive coping strategies" among caregivers, whereas Group C was associated with "severe psychological stress". Pearson analysis showed SAS/SDS scores positively correlated with ALT ($r=0.178$, $P < 0.05$) and glucose ($r=0.221$, $P < 0.05$). Furthermore, Group A achieved a higher capture rate of adverse events via AI monitoring, effectively mitigating high-grade toxicity risks. **Conclusions:** AI-based management and customized follow-up significantly improve psychological outcomes and QoL in breast cancer patients on CDK4/6i. The correlation between psychological stress and physiological markers (ALT, Glucose) highlights the necessity of a "bio-psycho-social" approach in oncology management. These findings support integrating AI models into precision survivorship care. Research Sponsor: None.

634 Poster Session

Temporal trends in adherence to adjuvant endocrine therapy across age groups in hormone receptor–positive breast cancer. First Author: Michael M. Caplan, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY

Background: Adjuvant endocrine therapy (ET) reduces recurrence and mortality in hormone receptor–positive breast cancer, yet adherence remains suboptimal. Adherence varies by age, with younger patients at higher risk for non-adherence. Whether increased awareness has improved adherence over time is unclear. We evaluated temporal trends in ET adherence. **Methods:** We conducted a retrospective cohort study using the MarketScan claims database. Eligible patients were 18–100 years old with non-metastatic breast cancer (2009–2022), treated with surgery within 6 months of diagnosis, and began adjuvant ET (aromatase inhibitor [AI] or tamoxifen) within 1 year of diagnosis. The analysis included patients insured 1 year prior to and 1 year following ET initiation. ET was assessed using proportion of days covered (PDC) and defined as adherent (PDC $\geq$0.80) vs non-adherent for the year after ET initiation. Trends in adherence were evaluated using the Cochran–Armitage trend test and logistic regression with an age–calendar year interaction. Age was categorized as $<$50 vs $\geq$50 years. Multivariable logistic regression was used to identify factors associated with ET adherence, reported as adjusted odds ratios (ORs). **Results:** Among 88,994 patients receiving ET (57,002 AI, 31,992 tamoxifen) from 2010–2022, the average adherence rate was 77.7% (79.3% AI, 74.9% tamoxifen). Adherence was lower in patients $<$50 vs $\geq$50 years (74.1% vs 78.8%; OR 0.85, 95% CI 0.81–0.89). In patients $<$50 on an AI, adherence increased over time from 66.6% in 2010 to 76.8% in 2022 (OR per year 1.07, 95% CI 1.05–1.09, $p < 0.001$), whereas no increase in adherence over time was seen in young patients on tamoxifen or in any patients aged $\geq$50 years. In a multivariable analysis of the entire cohort (Table), younger age and polypharmacy ($>$10 concurrent medications) were associated with lower odds of adherence, while receipt of 90-day prescription supplies, chemotherapy (neoadjuvant/adjuvant), and CDK4/6 inhibitors were associated with higher odds of adherence. **Conclusions:** Young women remain at high risk for ET non-adherence. While tamoxifen adherence did not improve over time, AI adherence increased over time in younger patients. This likely reflects heightened awareness, better supportive care, and clinician–patient discussions emphasizing AI adherence in young, high-risk populations. In contrast, despite similar increases in awareness, AI adherence has not improved in postmenopausal patients. These results highlight a persistent gap in ET adherence and the need for targeted interventions across age groups. Research Sponsor: None.

Factors associated with adherence to adjuvant endocrine therapy.

Covariate	Adjusted OR	95% CI
Age <50 vs ≥50 years	0.85	0.81–0.89
Polypharmacy	0.80	0.78–0.84
90-day prescription supply	2.80	2.71–2.89
Neoadjuvant chemotherapy	1.30	1.19–1.43
Adjuvant chemotherapy	1.29	1.23–1.34
CDK4/6 inhibitor use	1.55	1.15–2.08

635 Poster Session

Patient-reported outcomes from the adjuvant ado-trastuzumab emtansine (T-DM1) for older patients with HER2+ breast cancer (ATOP) trial. First Author: Kathryn Jean Ruddy, Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background: Prospective data on efficacy, quality of life, and treatment-related toxicities in older adults with breast cancer are limited. The ATOP trial (NCT03587740) evaluated T-DM1 in older adults and demonstrated favorable 5-year invasive disease-free survival. Here, we report patient-reported adverse events (AEs) and health-related quality of life (HRQOL) findings from ATOP. **Methods:** ATOP was a single-arm, phase II, multicenter study of adjuvant T-DM1 for those aged 60 with stage I-III HER2+ breast cancer. Protocol therapy included postoperative administration of T-DM1 (3.6 mg/kg) every 21 days for one year (17 cycles). PRO-CTCAE (assessing specific symptoms) and EQ-5D (a measure of HRQOL) surveys were administered electronically or on paper at baseline (pre-treatment), on Day 1 of each treatment cycle, and at a single 6–12-month post-treatment time point. Participants who responded to the baseline and at least one follow-up survey were included in the PRO analysis. EQ-5D changes from baseline were assessed using general linear mixed models. Summary statistics were used to assess PRO-CTCAE scores to evaluate which symptoms developed between baseline and 1 subsequent survey(s) and their severity. **Results:** Among the 111 patients enrolled on ATOP (median age=71, range 60-88 years), 98 responded to the baseline survey and 1 subsequent survey(s). 1435 surveys were returned that included at least one PRO-CTCAE response, and 1661 surveys were returned that included EQ-5D. The Table displays the % of participants who reported PRO-CTCAE symptoms that worsened from baseline to any severity level (scores $>$0) or to a severe level (scores $\geq$3). More than 60% of survey respondents reported new or increased dry mouth, fatigue, muscle aches, decreased appetite, nausea, pain, and/or numbness/tingling at some point during or after treatment, but these were usually not severe. EQ-5D scores did not change significantly from baseline at any time point. **Conclusions:** In this adjuvant trial for patients aged $>$60, participation rates for PRO data collection were high. Reassuringly, global HRQOL was not impacted by T-DM1, and though frequently reported, the vast majority of patient-reported symptoms were mild. Future analyses of this trial will focus on duration and predictors (clinical and biomarker-based) of severe AEs, agreement between patient-reported and clinician-reported AEs, and whether sharing PRO reports with clinicians impacted clinician-reported AE grades. Clinical trial information: NCT03587740. Research Sponsor: Genetech; Gateway for Cancer Research; Gloria Spivak Advancement Fund; Susan G Komen for the Cure; Bakes for Breast Cancer.

Most common new or worsening symptoms reported via PRO-CTCAE in ATOP (n=95).

Symptom	% with score >0	n (%) with score 3+
Dry mouth	79%	26%
Fatigue	71%	29%
Muscle aches	69%	20%
Decreased appetite	69%	12%
Nausea	67%	6%
Pain	66%	21%
Numbness/tingling	65%	9%
Blurry vision	60%	4%
Mouth or throat sores	60%	5%

636 Poster Session

Breast cancer–specific mortality in invasive lobular versus ductal carcinoma over 30 years. First Author: Jose Pablo Leone, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Invasive lobular carcinoma (ILC) differs biologically from invasive ductal carcinoma (IDC) and has been associated with delayed recurrence. However, long-term patterns of breast cancer-specific mortality (BCSM) following ILC remain incompletely described. We aimed to characterize temporal patterns of BCSM associated with ILC vs IDC over extended follow-up. **Methods:** We conducted a population-based study using the SEER program. Women diagnosed with stage I–III IDC or ILC from 1990 to 2012 were included. BCSM was the primary endpoint, with death from other causes treated as a competing event. Unadjusted cumulative incidence functions estimated BCSM by histology. Fine-Gray competing risks models were used to compare histologies overall and within hormone receptor (HR)-defined subgroups, with all models adjusted for age at diagnosis, year (y) of diagnosis, HR status (where applicable), tumor size, nodal status, tumor grade, surgery, radiation, and chemotherapy. Non-proportional effects were identified visually and modeled using time-varying coefficients. Landmark competing risks analyses assessed late BCSM among long-term survivors. **Results:** Among 423,479 women included, 41,027 (9.7%) had ILC and 382,452 (90.3%) had IDC; median follow-up was 16.7 y (range 0.1–33 y). During follow-up, 77,926 breast cancer deaths and 111,814 deaths from other causes occurred. In unadjusted analyses of the overall population, BCSM was lower for ILC than IDC at 5 and 10 years and higher for ILC at 20 and 30 years (Table). In adjusted Fine-Gray models, lobular histology demonstrated a significant time-varying association with BCSM ($p<0.001$). Associations between histology and BCSM differed by HR status (p for interaction=0.0029). In time-varying models restricted to HR+ disease, the adjusted subdistribution hazard ratio (sHR) for ILC versus IDC increased over time, reaching 1.19 (95% CI 1.15–1.23) at 10 y, 1.34 (1.28–1.41) at 20 y, and 1.44 (1.36–1.54) at 30 y. In landmark analyses among HR+ survivors, ILC remained associated with higher late BCSM beyond 10 y (sHR 1.36, 95% CI 1.29–1.43) and beyond 15 y (sHR 1.32, 95% CI 1.20–1.45). **Conclusions:** ILC is associated with a distinct temporal pattern of BCSM compared with IDC. Although unadjusted early BCSM is lower for ILC, adjusted risk increases over time and exceeds that of IDC in the late post-diagnosis period, particularly among HR+ disease. These findings highlight the importance of long-term risk assessment and survivorship strategies tailored to lobular histology. Research Sponsor: None.

Unadjusted cumulative incidence of BCSM by histology (%; 95% CI).

	Overall population		HR+	
Y since diagnosis	IDC	ILC	IDC	ILC
5	9.8 (9.7–9.9)	7.3 (7.0–7.5)	6.5 (6.4–6.6)	6.4 (6.1–6.6)
10	15.0 (14.9–15.2)	14.3 (13.9–14.6)	11.9 (11.8–12.0)	13.4 (13.1–13.8)
20	19.6 (19.5–19.8)	21.6 (21.2–22.1)	17.2 (17.0–17.4)	21.0 (20.5–21.4)
30	22.0 (21.8–22.2)	24.5 (23.9–25.2)	19.8 (19.5–20.0)	23.9 (23.1–24.6)

638 **Poster Session**

From treatment to survivorship: The CORE randomized study of a supervised exercise intervention in early-stage breast cancer. First Author: Maria Torrente, Universidad Francisco de Vitoria, Facultad de Ciencias de la Salud, Madrid, Spain

Background: Physical exercise is recommended by international guidelines to mitigate treatment-related toxicity and improve quality of life in patients with breast cancer (BC). However, adherence to physical activity recommendations remains low, and evidence from randomized studies conducted in real-world clinical settings is limited. The CORE study evaluated the impact of a structured, supervised exercise program on fatigue and health-related quality of life (HRQOL) in patients with early-stage BC. **Methods:** CORE is a single-center, randomized controlled trial enrolling patients with early-stage BC undergoing or recently completing curative treatment. Seventy patients were randomized 1:1 to usual care (control, n = 45) or a 3-month supervised exercise intervention (exercise, n = 45). Primary endpoints were physical fatigue (EORTC QLQ-BR45), cardiorespiratory fitness and muscle strength, and HRQOL (EORTC QLQ-C30 summary score). Secondary analyses explored changes in additional symptom and functional scales, as well as health status assessed by the EQ-5D questionnaire. Between-group differences in change from baseline to 3 months were analyzed with adjustment for multiple comparisons. **Results:** At 3 months, patients assigned to the exercise intervention experienced a statistically significant reduction in physical fatigue compared with usual care (mean difference −5.3; 95% CI −10.0 to −0.6; adjusted P = 0.027). HRQOL significantly improved in the exercise group (mean difference 4.8; 95% CI 2.2–7.4; adjusted P = 0.0003). In addition, within the exercise group, significant pre–post improvements were observed across several EORTC QLQ-C30 symptom and function scales, including fatigue, pain, dyspnea, nausea/vomiting, physical functioning, and role functioning, indicating a broad positive impact of the supervised strength training program on overall health status and daily functioning. Consistently, pre–post analyses in the exercise group using the EQ-5D demonstrated significant improvements in mobility, daily activities, and pain/discomfort dimensions. **Conclusions:** A 3-month supervised exercise program significantly reduced physical fatigue and improved HRQOL in patients with early-stage breast cancer. These findings reinforce the role of structured, supervised exercise as a key component of survivorship and supportive care, offering a scalable and effective strategy to reduce symptom burden, enhance functional capacity, and promote overall patient well-being. Research Sponsor: Spanish Society of Medical Oncology; AYUDAS A PROYECTOS DE INVESTIGACION.

639 **Poster Session**

Impact of GLP1 receptor agonists on survival of breast cancer patients. First Author: Tim Prior, Mayo Clinic Arizona, Phoenix, AZ

Background: Large cohort studies have shown a survival benefit with the use of GLP1 receptor agonists (GLP1 RA) in cancer patients. The impact of GLP1 RA usage in breast cancer (BC) and the different subtypes is unknown. To investigate the potential influence of GLP1 RA usage on BC survival, a study was conducted on a large institutional database. **Methods:** A de-identified institutional database identified newly diagnosed Stage I, II, and III BC patients from 2005 to present and use of GLP1 RA. The study compared survival rates for BC patients with and without GLP1 RA and further stratified by BC subtype [ER+HER2-, HER2+, ER-PR-HER2-(triple negative BC (TNBC))], BMI, and age. Kaplan-Meier survival curves were used to estimate overall survival. This study analyzed de-identified data accessed through Mayo Clinic Platform Discover. Per 45 CFR 46.102, this activity did not require IRB review. Data was extracted using an established privacy-preserving protocol and de-identified via expert determination under the HIPAA Privacy Rule. Raw EHR data and other unreported data cannot be shared due to de-identification parameters. **Results:** 88015 BC patients were identified, of which 3919 (4.5%) received GLP1 RA. The 5-year survival rate was 98.5% with vs 85.5% without GLP1 RA (p-value <0.0001). The survival benefit persisted for different BMI's and ages: BMI >30 (98.4% vs 85.1%), >25 (98.4% vs 85.4%), and age <50 (99.5% vs 89.3%) and >50 (98.1% vs 84.8%) [all $p<0.0001$]. 21770 patients with ER+ disease were identified, of which 1412 (6.5%) received GLP1 RA. The 5-year survival rate was 99.0% vs 87.7% (p-value <0.0001). The survival benefit persisted by BMI and age: BMI >30 (99.0% vs 86.2%), >25 (98.9% vs 87.1%) and age <50 (99.6% vs 90.5%) and >50 (98.7% vs 87.2%) [all $p<0.0001$]. 3599 patients with HER2+ disease were identified, of which 202 (5.6%) received GLP1 RA. The 5-year survival rate was 99.3% vs 80.1% (p-value <0.0001). The survival benefit persisted by stratification: BMI >30 (100.0% vs 80.0%, p-value <0.0004), and <25 (97.7% vs 76.2%, p-value <0.019), and age <50 (100% vs 87.0%, p-value <0.043) and >50 (99.0% vs 77.2%, p-value <0.0002). 8389 patients with TNBC disease were identified, of which 360 (4.3%) received GLP1 RA. The 5-year survival rate was 91.0% vs 71.9% (p-value <0.0001). The survival benefit persisted by stratification: BMI >30 (96.4% vs 72.9%, p-value <0.0001), >25 (93.2% vs 71.8%, p-value <0.0001), and age <50 (96.0% vs 73.0%, p-value <0.0028) and >50 (88.9% vs 71.8%, p-value <0.0001). For those TNBC patients who received GLP1 RA, having a BMI >30 conferred a protective effect with a 5-year survival rate was 97.9 vs 89.8% (p-value <0.0014). **Conclusions:** The study suggests that GLP1-RA improves 5-year survival rates of patients with BC and this applies to all subtypes of BC. These results suggest that further study of the impact of GLP1-RA on BC patients is warranted. Research Sponsor: None.

640 **Poster Session**

Lymphopenia in breast cancer and association with clinical outcomes: An analysis from over 30,000 patients. First Author: Alexis Ann LeVee, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Lymphopenia is an independent prognostic factor for overall survival in patients with solid tumors. Low circulating lymphocytes represents impaired adaptive immunity, which can compromise antitumor immune responses and increase the risk of treatment-related toxicity. Despite having an ICD-10 code (D72.810), lymphopenia as a diagnosis might be often underrecognized and overlooked. We aimed to analyze the prevalence and concordance of lab-defined lymphopenia with the clinical diagnosis and the association of lab-defined lymphopenia with clinical outcomes in a large cohort of patients with breast cancer. **Methods:** We identified patients with breast cancer between 1/1/2011-12/31/2024 in a single institution using ICD-10 codes. Stage and subtype was determined using ICD codes, with recurrence defined by any ICD code for metastatic disease at least 6 months after initial diagnosis. Lab-defined lymphopenia was defined by absolute lymphocyte count (ALC) <1000 cells/μL. Baseline and on-treatment lymphopenia using ICD codes was compared to lab-defined baseline and on-treatment lymphopenia using Cohen's κ concordance statistic (0-1). Univariate logistic regression was performed to evaluate the association of lab-defined lymphopenia with recurrence. Overall mortality was analyzed using Cox proportional hazards regression. **Results:** 36,496 patients with breast cancer were included in the analysis. Most (89.7%) patients had early-stage breast cancer and estrogen receptor (ER)-positive disease (50.5%). At breast cancer diagnosis, 2,368 (6.5%) patients had lab-defined lymphopenia and 56 (0.02%) had lymphopenia diagnoses, demonstrating significantly low concordance by ICD codes (κ = 0.0268). Similarly, on-treatment lymphopenia was also discordant by ICD codes, with lab-defined on-treatment lymphopenia occurring in 5,564 (15.2%) of patients and 257 (0.7%) by ICD codes (κ = 0.0459). In early-stage breast cancer, baseline lab-defined lymphopenia was associated with increased risk of recurrence (OR 1.74; 95% CI 1.42-2.06; $p<0.001$) and increased risk of mortality (HR 2.13; 95% CI 1.92-2.37; $p<0.001$). In the metastatic setting, baseline lab-defined lymphopenia was associated with increased risk of mortality (HR 1.50; 95% CI 1.32-1.69; $p<0.001$). Multivariable analysis demonstrated that lab-defined lymphopenia at diagnosis was associated with increased mortality (HR 2.47; 95% CI 2.01-3.02, $p<0.001$), after adjusting for ER status, stage, and type of treatment. **Conclusions:** Lymphopenia is significantly underdiagnosed during breast cancer treatment, and is independently associated with increased risk of recurrence and death. These findings highlight the need for improved recognition of lymphopenia as a prognostic factor and tailored strategies to augment systemic immunity and potentially improve long-term outcomes for patients. Research Sponsor: None.

641 **Poster Session**

Impact of social marginalization on stage at presentation and survival for invasive lobular versus ductal breast carcinoma. First Author: David Wai Lim, Women's College Hospital, Toronto, ON, Canada

Background: We aim to determine how indices of social marginalization impact stage at diagnosis, health services use, and overall survival comparing invasive ductal (IDC), pure (pILC) and mixed lobular (mILC) breast carcinoma (ILC) between 2005 and 2025 in the province of Ontario, Canada. **Methods:** Using population-based administrative healthcare datasets at Institute of Clinical Evaluative Sciences (ICES) Ontario, we identified all cases of IDC, pILC and mILC in Ontario, Canada between 2005 and 2025 using ICD-O-3 codes. We compared prior healthcare utilization between groups. We further compared clinical and healthcare utilization measures between four Ontario Marginalization (ON-MARG) indices: household and dwellings (includes % living alone, housing density), material resources (includes unemployment and education level), age and labour force (includes % seniors and not participating in the work force), and racialized and newcomer populations (includes % of recent immigrants). Using a multivariable Cox proportional hazards regression analysis incorporating sociodemographic, tumour and treatment factors, we assessed the impact of social marginalization indices on survival for the overall cohort and for ILC cases. Statistical analysis was performed using SAS and P values < 0.05 were significant. **Results:** We identified 16,122 (9%) pILC, 7,284 (4%) mILC and 156,870 (87%) IDC cases. At diagnosis, increasing marginalization for household and dwellings, material resources, and age and labour force correlated with less likelihood to having had a mammogram within 1 and 5 years prior to diagnosis ($P < .0001$). Increasing marginalization in these three quintiles correlated with worse clinical stage at diagnosis for both IDC and ILC ($P < .001$). Patients diagnosed with pure ILC breast cancer had 1.14 times (95%CI: 1.11 - 1.18) the likelihood of mortality in the follow-up relative to females diagnosed with IDC breast cancer. Increasing marginalization in the ON-MARG indices had a worse mortality for the overall cohort and for ILC cases, except for the racialized and newcomer populations quintile ($P < .0001$). **Conclusions:** In Ontario, Canada, the indices of social marginalization found to be associated with worse survival after a breast cancer diagnosis were household and dwellings, material resources, age and labour force but not racialized and newcomer populations. These findings highlight personalized risk factors for worse stage at presentation and survival for both IDC and ILC, independent of clinical and treatment factors. Research Sponsor: Conquer Cancer, the ASCO Foundation.

TPS642 **Poster Session**

HIGHLIGHT 1: A randomized, placebo-controlled, double-blind, phase 3 clinical study to investigate the efficacy and safety of fezolinetant for treatment of moderate to severe vasomotor symptoms (hot flashes) in women with stage 0 to 3 hormone receptor–positive breast cancer who are receiving adjuvant endocrine therapy. First Author: Céline Bouchard, Clinique RSF Inc, Québec, QC, Canada

Background: Breast cancer is the most common cause of death due to malignant neoplasms in women globally. Adjuvant endocrine therapy, e.g., tamoxifen and aromatase inhibitors, can lead to premature menopause and vasomotor symptoms (VMS). Fezolinetant is a non-hormonal neurokinin 3 receptor antagonist that is an approved treatment option for moderate to severe VMS due to menopause in multiple regions worldwide, including North America, Europe, Asia, and Australia, at a dose of 45 mg once daily. The pathophysiology of VMS in women undergoing cancer treatment is not fully elucidated but is hypothesized to have similar etiology to VMS associated with menopause, i.e., rapid decline of estrogen. **Methods:** This global, double-blind, placebo-controlled phase 3 study (HIGHLIGHT 1 [NCT06440967]) was designed to assess efficacy and safety of fezolinetant 45 mg once daily in moderate to severe VMS associated with tamoxifen or aromatase inhibitors for hormone receptor-positive breast cancer from stage 0 (cancer cells have not spread to nearby tissue) to stage 3+ (cancer has spread from breast to lymph nodes near the breast or the chest wall). HIGHLIGHT 1 comprises screening (28 days), treatment (52 weeks), follow-up (3 weeks after final treatment), and extension follow-up (until week 104). Eligible participants will be randomized 1:1 to fezolinetant 45 mg or placebo and stratified by adjuvant endocrine therapy and prior chemotherapy. Participants will record their VMS daily on an electronic diary. The study is currently recruiting. Participants are women (target enrollment n = 540; 382 enrolled as of 24 Nov) ≥18 years with ≥7 moderate to severe VMS episodes/day receiving hormone therapy for stage 0-3 hormone receptor-positive breast cancer. Key exclusions: history/current malignancy other than hormone receptor-positive breast cancer (stage 0 to 3) or basal cell carcinoma. Co-primary endpoints: mean change from baseline to week 4 and 12 in frequency and severity of moderate to severe VMS. Key secondary endpoints: mean change from baseline to week 12 in MENQOL VMS domain score and PROMIS Total Score Sleep Disturbance–Short Form 8b. Co-primary endpoints and key secondary endpoints will be analyzed using mixed models for repeated measures. Treatment-emergent adverse events (TEAEs) assess fezolinetant safety and tolerability. The DMC last reviewed the study in November 2025 and suggested that the study continue as planned. Clinical trial information: NCT06440967. Research Sponsor: Astellas Pharma Inc.

TPS643 **Poster Session**

Precision DC: Personalized neoantigen dendritic cell vaccine pilot trial for high-risk triple-negative breast cancer after neoadjuvant therapy. First Author: Hatem Hussein Soliman, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Treatment for stage II-III triple negative breast cancer (TNBC) uses neoadjuvant chemoimmunotherapy (NCT) with the goal of achieving pathologic complete responses. TNBC patients with significant residual cancer burdens (RCB II/III) after NCT have a high risk of early relapse/death despite use of adjuvant therapies like capecitabine. Moffitt Cancer Center's breast program uses a highly immunogenic dendritic cell vaccine platform (DC1) against HER2 overexpressing tumors in previous studies demonstrating antitumor efficacy (Han, JAMA Onc 2025). TNBC often has multiple somatic mutations leading to expression of altered immunogenic proteins known as neoantigens. We hypothesize that the residual primary TNBC after NCT can be sequenced to identify the most immunogenic neoantigens and include them as targets in an adjuvant DC1 vaccine to stimulate cytotoxic T cell responses that eliminate residual micrometastatic disease. The PRECISION DC trial was initiated to study the feasibility of adjuvant neoantigen DC1 vaccines for high risk TNBC. Correlatives include immune response to neoantigens using ELISPOT and immunopeptidomics to study processing of peptides by the dendritic cells (NCT06435351). **Methods:** PRECISION DC is a single-arm pilot study open at the Moffitt Cancer Center enrolling stage II-III TNBC patients with RCB II/III disease and who are within 18 months of their last dose of KEYNOTE-522 chemotherapy without known metastatic disease. Eligible patients will have their residual tumor tissue whole exome sequenced, and mutated 25 mer long peptides are analyzed using a modified NetMHCII pipeline to rank these mutations based on a combined score representing multiple factors including expression, predicted MHC binding, and agretopicity. The top ten scoring peptides that also pass a peptide synthesis screen for excessive hydrophobicity are selected for inclusion in each patient's personalized DC1 vaccine. The relevant peptides for each patient are used to stimulate pheresed autologous dendritic cells ex-vivo. Moffitt's GMP cell therapy facility creates cryopreserved aliquots of 50 million cells to create DC1 vaccine doses. Patients get three intranodal DC1 inguinal injections q2weeks under ultrasound guidance in the priming phase and then two booster shots at 6 and 12 months either before or after adjuvant capecitabine (if given) per treating physician guidance. PRECISION DC opened 10/2024 and accrual to date is 22/26 planned patients with 4 remaining patients already identified. Primary endpoint is feasibility (% pts with successful vaccine administration w/ goal > 60%); secondary endpoints include safety, immune responses, and 5-year disease-free outcomes. If successful, PRECISION DC will set the stage for a prospective randomized trial of personalized autologous DC1 neoantigen vaccines to prevent recurrence of residual TNBC following NCT. Clinical trial information: NCT06435351. Research Sponsor: None.

TPS644 **Poster Session**

ASPRIA: A single-arm phase 2 trial of atezolizumab with sacituzumab govitecan to prevent recurrence in triple-negative breast cancer. First Author: Payal Deepak Shah, Penn Medicine Abramson Cancer Center, Philadelphia, PA

Background: Despite marked improvements in neoadjuvant chemoimmunotherapy (NACT) and adjuvant treatment for patients with early-stage triple negative breast cancer (TNBC), over 30% of patients with residual disease after NACT experience disease recurrence or death within 36 months. Understanding which patients are at greatest risk of relapse and designing effective interventions to prevent disease recurrence are major unmet needs. Circulating tumor DNA (ctDNA) can detect molecular residual disease (MRD) in TNBC and has demonstrated prognostic and predictive ability in the neoadjuvant setting; ctDNA thus represents a promising biomarker to select at-risk patients. Sacituzumab govitecan is a Trop-2 targeted antibody-drug conjugate leveraging a topoisomerase 1 payload that is approved for metastatic HR+ breast cancer and TNBC. Atezolizumab is an immune checkpoint inhibitor that interferes with the binding of PD-L1 to PD-1. The ASPRIA trial hypothesizes that ctDNA can identify patients with TNBC and residual disease after NACT at greatest risk for relapse, and that the combination of sacituzumab govitecan and atezolizumab may effectively treat MRD through cytotoxicity and anti-tumor immunity, leading to ctDNA clearance and improved clinical outcomes. **Methods:** The ASPRIA trial is an open-label, single-arm phase II trial evaluating sacituzumab govitecan in combination with atezolizumab in patients with early-stage TNBC. Eligible patients have residual invasive disease in the breast and/or lymph nodes following curative-intent therapy and detectable ctDNA, as assessed by a personalized, tumor-informed assay (Signatera, Natera, Inc.). The study includes a screening phase, with ctDNA presence assessed for the first 60 individuals to ensure feasibility, with a minimum prevalence threshold of approximately 15%. Patients with detectable ctDNA will undergo restaging imaging, and those without evidence of metastatic disease proceed to treatment. Up to 32 ctDNA-positive patients will receive atezolizumab 1200 mg IV on day 1 plus sacituzumab govitecan 10 mg/kg IV on days 1 and 8 of a 21-day cycle for 6 cycles. On-treatment ctDNA assessments will occur at weeks 3, 9, and at end of therapy. Participants will be followed for recurrence and survival every 6 months for 3 years. The primary objective is to determine the rate of ctDNA clearance after 6 cycles of therapy. Secondary objectives include estimating the ctDNA prevalence, assessing clearance after 1 and 3 cycles, evaluating recurrence risk and survival outcomes (iDFS, RFI, DMFS), and characterizing safety (per CTCAE v5). Correlative studies will examine predictors of ctDNA positivity, associations between treatment response and Trop-2 or PD-L1 expression in primary and residual tumors, temporal ctDNA dynamics in relation to relapse, and patient perspectives on ctDNA testing. Clinical trial information: NCT04434040. Research Sponsor: Stand Up to Cancer (SU2C); Natera, Inc.

TPS645 **Poster Session**

NoLEEta: No chemotherapy in intermediate-risk HR+ HER2− early breast cancer treated with ribociclib in the adjuvant setting—A non-inferiority phase III trial. First Author: Francois Clement Bidard, Institut Curie, Paris, France

Background: Historically, the treatment paradigm for hormone receptor-positive, HER2-negative early breast cancer (HR+ HER2− eBC) has relied on endocrine therapy (ET) and adjuvant chemotherapy. However, the absolute benefit of adjuvant chemotherapy is closely tied to baseline risk, being notably modest in intermediate risk eBC, while associated with significant short- and long-term toxicities. The phase III NATALEE trial demonstrated the efficacy of an adjuvant three-year treatment with ribociclib and ET in prolonging invasive disease-free survival (iDFS) in patients with high-risk HR+ HER− eBC. Contrarily to similar studies of CDK4/6 inhibitors in this setting, NATALEE included a group of patients with intermediate clinical risk (pT1-2 pN1, pT3-4 pN0 or pT2 pN0 with histological grade 3 or grade 2 with Ki67≥ 20%). These patients are usually treated with adjuvant chemotherapy based on the tumor clinicopathological characteristics or the results of a genomic signature. Nevertheless, the absolute benefit of adjuvant chemotherapy in these patients is uncertain (and likely reduced) in the context of an adjuvant treatment strategy that includes a CDK4/6 inhibitor. The NoLEEta trial aims at demonstrating that patients with intermediate-risk HR+ HER2− eBC treated with ribociclib and ET could be spared chemotherapy side effects while ensuring similar survival outcomes. **Methods:** NoLEEta is an international, randomized, open-label, non-inferiority phase III trial. Main inclusion criteria are: HR+ HER2− eBC after curative surgery, at intermediate risk of relapse (pT0-2 pN1, pT3-4 pN0, pT2 pN0 G3 or pT2 pN0 G2 with Ki67≥20%), eligible for adjuvant chemotherapy (per investigator decision, based on clinicopathological parameters or using a genomic signature). Eligible patients are randomized (1:1) to either receive ribociclib and ET (investigational arm without chemotherapy) or chemotherapy followed by ribociclib and ET (control arm). Primary endpoint is invasive breast cancer-free survival (iBCFS), defined in accordance with the STEEP system as the interval between randomization and the earliest occurrence of ipsilateral invasive breast tumor recurrence, local–regional invasive recurrence, distant recurrence, invasive contralateral breast cancer, or death from any cause. Secondary endpoints include invasive disease-free survival, distant disease-free survival, overall survival, interval and type of iBCFS events, incidence and severity of adverse events, and health-related quality of life. Enrollment in NoLEEta started in December 2025, with a target objective of 3902 randomized patients across 8 countries. One interim analysis is planned. Clinical trial information: NCT07237256. Research Sponsor: Novartis; Menarini Silicon Biosystems; Women's Cancer Institute of Institut Curie.

TPS646 **Poster Session**

Interception of molecular relapse in breast cancer: The SURVIVE HERoes study (NCT06643585). First Author: Wolfgang Janni, University Hospital of Ulm, Ulm, Germany

Background: Current research on circulating tumor DNA (ctDNA) in the adjuvant setting of early breast cancer (eBC) demonstrates its strong prognostic significance. Patients who are ctDNA-positive in the absence of radiological evidence of disease recurrence (i.e., molecular relapse) have significantly reduced disease-free and overall survival. Secondary adjuvant intervention trials employing highly potent therapeutic agents represent an innovative and promising strategy to intercept disease recurrence at the molecular stage. **Methods:** SURVIVE HERoes is a phase III, randomized clinical trial comparing the antibody–drug conjugate trastuzumab deruxtecan (T-DXd) with standard of care (SoC) in patients with molecular residual or recurrent disease. Eligible patients must have a positive circulating tumor DNA (ctDNA) result detected using a tumor-informed assay (RaDaR), while staging examinations show no evidence of residual or recurrent disease. Participants must have HER2-positive, HER2-low, or—following an approved study amendment—HER2-ultralow early breast cancer (eBC), irrespective of hormone receptor (HR) status, and must have completed primary therapy, including surgery with R0 resection, with or without chemotherapy and/or radiotherapy. 180 participants are randomized in a 2:1 ratio to receive T-DXd (+ endocrine therapy for HR positive patients) or standard of care for 48 weeks, followed by a 48-week follow-up phase. Stratification factors include hormonal receptor status (positive versus negative) and HER2-status (positive versus low versus ultralow). Staging examinations and ctDNA assessments will be performed every 12 weeks during the 2-year study phase per patient. The study is accompanied by a comprehensive translational research program. The primary endpoint is the ctDNA clearance rate after 48 weeks, comparing participants in the experimental arm (receiving T-DXd) with those in the control arm (receiving standard of care), irrespective of ctDNA test results at other time points. Secondary endpoints include invasive disease-free survival, overall survival, ctDNA clearance at other time points, safety, and quality of life (QoL), as assessed by EORTC QLQ-C30 and PA-F12. Recruitment: Recruitment began in Q2/2025 and is anticipated to continue until 2030. Fifty sites across Germany are planned for participation. Discussion: Treating ctDNA-positive patients without radiographic evidence of recurrence is a novel therapeutic strategy. If SURVIVE HERoes and similar studies targeting molecular relapse yield positive results, they could pave the way for a new molecularly driven personalized surveillance and treatment approach. Clinical trial information: NCT06643585. Research Sponsor: Astra Zeenca; NeoGenomics; tosoh Bioscience; Menarini Silicon Biosystems.

TPS647 **Poster Session**

PREDICT-RD: Postoperative molecular residual disease by ctDNA surveillance in TNBC with residual disease (TBCRC-071). First Author: Yara Abdou, Division of Oncology, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Patients with residual triple-negative breast cancer (TNBC) post-neoadjuvant therapy, particularly those with higher residual cancer burden (RCB II/III), remain at high risk of recurrence despite standard adjuvant therapy. Current post-treatment surveillance relies primarily on clinical follow-up and imaging, which have limited sensitivity to detect disease at a subclinical stage and rarely enable early therapeutic intervention. Circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) assessment allows detection of tumor-derived DNA in the absence of radiographic disease and offers a framework to identify patients at high risk of recurrence, who may be candidates for early, biomarker-informed treatment escalation prior to overt metastatic recurrence. PREDICT-RD is designed to evaluate the clinical implications of post-surgical ctDNA surveillance in patients with high-risk, early-stage TNBC. We hypothesize that longitudinal monitoring with a tumor-informed, high sensitivity ctDNA assay will identify an MRD-only state in at least 10% of patients, defined by ctDNA positivity in the absence of clinical or radiographic recurrence. A secondary objective is to assess outcomes among patients with ctDNA-detected molecular relapse who undergo adjuvant treatment escalation with datopotamab deruxtecan (Dato-DXd). Dato-DXd is an antibody-drug conjugate composed of a monoclonal antibody targeting TROP2 linked to a topoisomerase I inhibitor payload. In TNBC, Dato-DXd has demonstrated a manageable safety profile and promising efficacy, including an improvement in median PFS of 5.3 months over SoC chemotherapy in the first line setting for patients who are not candidates to receive immunotherapy (TROPION-Breast02). **Methods:** PREDICT-RD (TBCRC-071) is a prospective phase II, interventional, open-label, single-arm, multi-center study. The trial will enroll 78 patients with Stage II or III TNBC with residual disease (RCB II/III) following neoadjuvant chemo-immunotherapy and surgery. Patients will undergo serial blood sampling for ctDNA assessments using a clinically available tumor-informed personalized assay (Signatera Genome, Natera, Inc.) at predefined intervals during adjuvant therapy and subsequent surveillance. ctDNA test results will be disclosed to both the treating provider and the patient. A positive ctDNA result will prompt consideration of imaging for distant disease. The primary endpoint is the prevalence of MRD-only relapse. Patients meeting these criteria will be considered for treatment escalation with Dato-DXd (up to eight cycles), with ctDNA clearance as a secondary endpoint. Patient-reported fear of recurrence and quality of life will be serially evaluated. Post-treatment surveillance will continue for up to three years following initial consent. Recruitment is anticipated to begin in early 2026 (NCT07069595). Clinical trial information: NCT07069595. Research Sponsor: Gateway for Cancer Research; G-24-800; Daiichi Sankyo; Conquer Cancer, the ASCO Foundation; Natera; Daiichi Sankyo.

TPS648 **Poster Session**

SIGNAL-ER-101: Signatera-guided CDK4/6 inhibitor therapy in breast cancer. First Author: Marla Lipsyc-Sharf, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: The monarchE and NATALEE trials showed that the addition of a CDK4/6 inhibitor (CDK4/6i; abemaciclib or ribociclib) to adjuvant endocrine therapy (ET) improves invasive disease-free survival (iDFS) in patients with ER+/HER2- high-risk and high-intermediate risk early breast cancer (eBC), including those with node-positive disease and select high-risk node negative tumors. However, the absolute benefit was modest (monarchE: 6.4% at 4 years; NATALEE: 3.3% at 3 years) suggesting that while a subset of patients derive benefit, many high-risk patients will not recur following ET alone. Improved strategies are needed to more precisely identify patients most likely to benefit from adjuvant CDK4/6i. Circulating tumor DNA (ctDNA) is an established biomarker of molecular residual disease (MRD) in eBC; its detection is associated with a significant risk of recurrence, and lack of detection with highly sensitive assays is associated with excellent prognosis. The SIGNAL-ER-101 trial evaluates whether tumor informed ctDNA detection during post-surgical adjuvant therapy can identify ER+/HER2- patients at highest risk of recurrence who are most likely to benefit from the addition of a CDK4/6i to standard-of-care (SOC) adjuvant ET and avoid overtreatment in patients who are likely to benefit with ET alone. **Methods:** SIGNAL-ER-101 is a Natera-sponsored prospective, open-label, single-arm, multicenter phase II treat-on-MRD study that aims to enroll 725 patients with intermediate-risk, stage II ER+/HER2- eBC who have undergone surgical resection and have no prior exposure to a CDK4/6i. Patients will be enrolled before receipt of any planned chemotherapy and/or radiation and within 6 months of initiating ET. Personalized, tumor-informed ctDNA testing will be performed using the Signatera Genome assay (Natera, Inc.), developed from archived tumor tissue and matched normal DNA to detect tumor-specific variants in plasma. Patients who are ctDNA-positive at baseline will be initiated on adjuvant CDK4/6i (ribociclib or abemaciclib) plus ET for a minimum of two years. Patients who are ctDNA-negative will receive ET alone and undergo MRD surveillance with ctDNA testing every three months. Upon detection of ctDNA during surveillance, patients will undergo staging scans to exclude distant metastatic disease prior to the addition of CDK4/6i therapy to ET. Selection of the specific CDK4/6i and ET will be at the discretion of the treating physician based on available SOC adjuvant therapy options. Patients will be followed for up to nine years to assess outcomes, including the study primary endpoint (iDFS) and key secondary endpoints (e.g., overall survival). The primary endpoint will be met if 4-year IDFS is non-inferior to that from NATALEE (3% non-inferiority margin: 93.9% vs 90.9%), aiming to evaluate whether ctDNA-guided treatment preserves efficacy while reducing over-treatment. Recruitment is expected to begin in March 2026. Clinical trial information: NCT07214532. Research Sponsor: Natera Inc.

TPS649 **Poster Session**

GEMINI-BREAST: Evaluating minimal residual disease (MRD) through longitudinal circulating tumor DNA (ctDNA) profiling in breast malignancies. First Author: Matthew E. Campbell, Tempus AI, Inc., Chicago, IL

Background: While advancements in early-stage breast cancer (ESBC) treatment have improved survival, disease recurrence and therapeutic resistance remain significant challenges. Current biomarkers guide initial treatment, yet novel diagnostics are required to improve risk stratification and recurrence prediction. Circulating tumor DNA (ctDNA) offers a non-invasive method for detecting minimal residual disease (MRD), potentially enabling the identification of molecular relapse before radiographic progression. However, deeper validation of ctDNA kinetics across the treatment continuum is needed to inform precision oncology strategies in ESBC. Additionally, the logistical complexity of tissue-dependent assays presents a barrier to scalability. In order to address these gaps, the purpose of the GEMINI-BREAST study is to evaluate a methylation-based, tissue-free ctDNA assay (Tempus xM) and integrate this with comprehensive clinical and multi-omic data to determine prognostic utility for invasive disease-free survival (iDFS) and long term outcomes in patients with ESBC. **Methods:** GEMINI-BREAST (NCT07211178) is a prospective, non-interventional, multi-center study enrolling up to 900 participants with ESBC treated with curative intent. Eligible patients enroll into one of three analytical cohorts (n ~ 300 each): Cohort 1 enrolls pre-neoadjuvant therapy (high-risk HR+/HER2- [Stage II-III], HER2+ [Stage II-III], or TNBC [Stage I-III]); Cohort 2 enrolls post-surgery/pre-adjuvant therapy (same subtypes, no evidence of disease); and Cohort 3 enrolls long-term survivors (high-risk HR+/HER2- [Stage II-III], $\geq$ 5 years since diagnosis). Longitudinal blood samples for ctDNA analysis and archival tissue for NGS are collected at standard-of-care intervals, including, as applicable: pre-neoadjuvant, neoadjuvant on-treatment (weeks 3, 6, 12) and post-treatment, post-surgical/pre-adjuvant, adjuvant on-treatment (every 3 months), end of definitive therapy, surveillance for up to 5 years (every 3-6 months for Cohorts 1/2; every 6-12 months for Cohort 3), and at progression/recurrence. The primary objective is to evaluate the association between ctDNA dynamics (Cohort 1) or MRD status (Cohort 2/3) and iDFS, with secondary endpoints assessing overall survival, lead time to recurrence, and the predictive value of ctDNA clearance for pathological complete response. Recruitment is currently ongoing at U.S. sites. Clinical trial information: NCT07211178. Research Sponsor: Tempus AI.

TPS650 **Poster Session**

A phase III trial evaluating addition of adjuvant chemotherapy to ovarian function suppression + endocrine therapy in premenopausal women with pN0-1, HR+/HER2− breast cancer and Oncotype recurrence score ≤ 25 (OFSET): NRG-BR009. First Author: Eleftherios P. Mamounas, AdventHealth Cancer Institute, Orlando, FL

Background: The TAILORx and RxPONDER trials showed that recurrence score (RS) identifies many postmenopausal pts who do not benefit from addition of ACT to endocrine therapy (ET); however, RS also identifies subsets who do benefit (node-neg/high clinical risk/RS 16-20, node-neg/RS 21-25, and node-pos/RS ≤25). Most premenopausal pts in these trials did not receive ovarian function suppression (OFS) as part of their ET regimen. Given the observed benefit from OFS in high-risk premenopausal pts with HR+/HER2− BC in SOFT/TEXT, we question whether the ACT benefit in TAILORx/RxPONDER was due to chemotherapy-induced OFS. To address this, we developed OFSET, a phase III clinical trial comparing OFS+ET to ACT+OFS+ET. **Methods:** We hypothesize that addition of ACT to OFS+ET is superior to OFS+ET in improving invasive breast cancer-free survival (IBCFS) among premenopausal pts with early-stage HR+/HER2− tumors, and a 21-gene RS between 16-25 (for pN0 pts) and 0-25 (for pN1 pts). Secondary objectives include invasive disease-free survival, overall survival, distant recurrence-free interval, breast cancer-free interval, and health-related quality of life (HRQOL). Pts must be node-neg with RS 16-20 (plus high clinical risk), RS 21-25, or have 1-3 positive nodes with RS ≤25. Stratification is by nodal status/RS status (pN0 RS 16-25; pN1 RS 0-15; pN1 RS 16-25), intent to receive CDK4/6 inhibitor (yes; no), and age (18-39; ≥40). Pts are randomized after surgery to either OFS+ET or ACT+OFS+ET. ET is an aromatase inhibitor (AI) per physician discretion; or tamoxifen if AI is not tolerated or if OFS is incomplete. Radiotherapy will be administered per protocol guidelines. An HRQOL sub-study will assess severe menopausal symptoms (measured by FACT ESS-19) and pain severity (PROMIS) between arms. Blood and tumor specimens will be collected for future research. We anticipate accrual of 3,960 pts in 7 yrs, 7 mos. Per NSABP B-28/RxPONDER data, 5-yr IBCFS of pN1 pts on the ACT+OFS+ET arm is estimated at 92.3%. Per TAILORx data, 5-yr IBCFS of pN0 pts on the ACT arm is ~95%. Assuming 56% of pts to be pN0 and 44% pN1, and a 0.5% annual loss-to-follow-up rate, the definitive analyses to detect a hazard ratio: 0.75 with ACT+OFS+ET *v* OFS+ET, with 1-sided α of 0.025 and 80% power, will require 380 IBCFS events, expected to occur ~11 yrs after study initiation. Accrual is 496/3,960 (from 8/2023 to 1/2026). NCT #: NCT05879926. Clinical trial information: NCT05879926. Research Sponsor: U.S. National Institutes of Health; U10 CA180868; U.S. National Institutes of Health; U10 CA180822; U.S. National Institutes of Health; UG1 CA189867; U.S. National Institutes of Health; U24 CA196067.

TPS651 **Poster Session**

A randomized trial of sentinel node biopsy omission after neoadjuvant systemic therapy in clinically node-negative or selected node-positive breast cancer. First Author: Ji-Jung Jung, Department of Surgery, Seoul National University College of Medicine, Seoul, South Korea

Background: Omission of axillary surgery has been established as a safe option in selected patients with early-stage breast cancer undergoing upfront surgery. In the neoadjuvant systemic therapy (NST) setting, however, axillary surgery remains standard practice. Ongoing trials, including EUBREAST-01, ASICS, and ASLAN, are evaluating the safety of omitting sentinel lymph node biopsy (SLNB) after NST, but these studies have largely been limited to single-arm designs and to patients with confirmed breast pathologic complete response (pCR). Retrospective studies suggest that axillary nodal clearance after NST may be predicted using tumor subtype, treatment response, and post-NST imaging, independent of breast pCR. The NeoNAUTILUS trial was designed to prospectively evaluate the safety of omitting SLNB after NST in patients predicted to have no residual axillary disease, using axillary response–based selection rather than breast pCR. **Methods:** NeoNAUTILUS is a prospective, multicenter, randomized, controlled, non-inferiority trial being conducted at 23 centers in Korea. Eligible participants are women aged ≥20 years with clinical T1–T3 invasive breast cancer who have completed NST and are candidates for breast-conserving surgery (BCS). Patients with clinical N0 disease of any subtype are eligible. Selected patients with clinical N1 disease are eligible if they have HER2-positive, triple-negative, or estrogen receptor–low-positive tumors and demonstrate a >30% reduction in primary tumor size on post-NST magnetic resonance imaging. All participants must have no suspicious lymph nodes on post-NST axillary ultrasound. Participants are randomized 1:1 to BCS with SLNB or BCS without axillary surgery, stratified by clinical nodal status (cN0 vs cN1) and tumor subtype. Patients remain blinded to treatment allocation until surgery. Whole-breast irradiation is planned for all patients, with protocol-defined axillary radiation fields in the no-SLNB group according to initial nodal status. The primary endpoint is 5-year invasive disease-free survival. Secondary endpoints include overall survival, distant metastasis-free survival, ipsilateral axillary recurrence, locoregional recurrence, and patient-reported quality of life. A total of 464 patients are planned for enrollment over 3 years with a minimum follow-up of 5 years. Enrollment began in May 2025 and is ongoing. Clinical trial registration: NCT06704945; KCT0010174. Clinical trial information: NCT06704945. Research Sponsor: None.

TPS652 **Poster Session**

MELODY: A prospective non-interventional multicenter cohort study to evaluate different imaging-guided methods for localization of malignant breast lesions (EUBREAST-4/iBRA-NET/AGO-B-062; NCT05559411). First Author: Maggie Banys-Paluchowski, Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

Background: In the last decades, the proportion of breast cancer patients receiving breast-conserving surgery has increased, reaching 70-80% in developed countries. In case of non-palpable lesions, surgical excision requires some form of breast localization. While wire-guided localization has long been considered gold standard, it carries several limitations, including logistical difficulties, the potential for displacement and patient discomfort, and re-excision rates reaching 21% (in DCIS up to 30%). Other techniques (radioactive seed or radio-occult lesion localization, intraoperative ultrasound, magnetic, radiofrequency, and radar localization) have been developed with the aim of overcoming these disadvantages. However, comparative data on the rates of successful lesion removal, negative margins, and re-operations are limited. In most studies, the patient perspective, addressing e.g. discomfort and pain, has not been evaluated. The aim of MELODY (MEthods for LOcalization of Different types of breast lesions) is to evaluate different imaging-guided localization methods with regard to oncological safety, patient-reported outcomes, surgeon and radiologist satisfaction and economic impact. **Methods:** The EUBREAST and the iBRA-NET have initiated the MELODY study to assess breast localization techniques and devices from several perspectives (NCT05559411, http://eubreast.org/melody). MELODY is a prospective intergroup cohort study which enrolls female and male patients planned for breast-conserving surgery with imaging-guided localization for invasive breast cancer or DCIS. Multiple or bilateral lesions and neoadjuvant chemotherapy are allowed. Primary outcomes are: 1) Intended target lesion and/or marker removal, independent of margin status on final histopathology, and 2) Negative resection margin rates at first surgery. Secondary outcomes are, among others: rates of second surgery and secondary mastectomy, Resection Ratio (defined as actual resection volume divided by the calculated optimum specimen volume), duration of surgery, marker dislocation rates, rates of marker placement or localization failure, patient-reported outcomes, rates of "lost markers", radiologist and surgeon satisfaction, and health economic evaluation of the different techniques. Enrollment started in January 2023. Up to 26 January 2025, 9727 patients from 27 countries were enrolled in the study. The study is expected to complete patient enrollment in year 2026. The study will be conducted in 30 countries and is supported by the Oncoplastic Breast Consortium (OPBC), AWOgyn, AGO-B, SENATURK, the American Society of Breast Surgeons (ASBS) and the Korean Breast Cancer Study Group (KBCSG). Clinical trial information: NCT05559411. Research Sponsor: None.

TPS653 **Poster Session**

A molecular subtype–guided, chemotherapy-free neoadjuvant strategy using SHR-A1811 plus pertuzumab for hormone receptor–positive/HER2-positive breast cancer: A phase II trial in progress. First Author: Zhengjun Yang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Hormone receptor–negative/HER2-positive breast cancer achieves high pathological complete response (pCR) rates with chemotherapy-based HER2-targeted therapy, whereas hormone receptor–positive (HR+)/HER2-positive disease consistently demonstrates lower pCR rates and substantial chemotherapy-related toxicity, representing an unmet clinical need. Antibody–drug conjugates (ADCs) may address this gap by enhancing HER2-directed cytotoxic delivery while potentially avoiding conventional chemotherapy. SHR-A1811 (ruikang-trastuzumab) is a next-generation HER2-directed ADC conjugated to a topoisomerase I inhibitor with a high drug-to-antibody ratio (≈6) and has demonstrated superior preclinical activity compared with trastuzumab emtansine. HER2-directed ADCs may be particularly advantageous in HR-positive/HER2-positive tumors, including those with HER2 immunohistochemistry (IHC) 2+ and in situ hybridization (ISH)–positive status, through bystander killing effects that may overcome heterogeneous or lower-level HER2 expression. Emerging evidence suggests that ADC activity is retained in HR-positive/HER2-positive breast cancer and may be enhanced when combined with pertuzumab, providing the rationale for evaluating neoadjuvant SHR-A1811 plus pertuzumab in this population. **Methods:** This prospective, open-label, single-arm phase II trial enrolls women aged > 18 and < 70 years with previously untreated stage II–III HR-positive/HER2-positive breast cancer. All patients receive neoadjuvant SHR-A1811 (4.8 mg/kg intravenously every 3 weeks) plus pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks) for four cycles. Baseline BluePrint profiling classifies tumors as luminal or non-luminal. Treatment is adaptively tailored based on molecular subtype and RECIST v1.1 response after four cycles. Patients with luminal subtype and stable disease switch to a chemotherapy-free regimen of trastuzumab, pyrotinib (a HER2-directed tyrosine kinase inhibitor), dalpiciclib (a CDK4/6 inhibitor), and an aromatase inhibitor, while patients with luminal subtype achieving partial or complete response and all non-luminal tumors continue SHR-A1811 plus pertuzumab for two to four additional cycles before surgery. Circulating tumor DNA (ctDNA) is assessed at baseline, after four cycles, and preoperatively. The primary endpoint is pCR (ypT0/is ypN0); secondary endpoints include event-free survival, objective response rate, and safety, with exploratory analyses evaluating associations among molecular subtype, ctDNA dynamics, and treatment response. Clinical trial information: NCT07307287. Research Sponsor: None.

TPS654 **Poster Session**

NOGA: Neoadjuvant treatment optimization via MRI-guided de-escalation in stage II–III TNBC—A phase 2 study. First Author: Tal Sella, Sheba Medical Center, Ramat Gan, Israel

Background: Pembrolizumab combined with neoadjuvant chemotherapy improves pathological complete response (pCR) rates and survival in stage II–III triple-negative breast cancer (TNBC), establishing the KEYNOTE-522 regimen as the standard of care. This regimen consists of two phases: four cycles of paclitaxel/carboplatin with pembrolizumab (TCa+P), followed by four cycles of adriamycin/cyclophosphamide with pembrolizumab (AC+P). However, anthracycline-containing chemotherapy contributes substantial short- and long-term toxicity. A subset of patients may achieve pCR after the initial TCa+P phase, raising the possibility that treatment intensity may be reduced in selected responders. Breast MRI demonstrates high concordance with pCR in hormone receptor–negative breast cancer and represents a promising, noninvasive biomarker to guide response-adapted de-escalation strategies. **Methods:** This is a prospective, investigator-initiated, multicenter, single-arm phase II trial evaluating MRI-guided de-escalation of neoadjuvant chemotherapy plus immunotherapy in patients with early TNBC. Eligible patients have Stage II-III (T2-T3N0 or T1-T3N1) TNBC and are candidates for the KEYNOTE-522 regimen. All patients receive four cycles (12 weeks) of TCa+P, followed by mid-treatment breast MRI. Patients achieving radiologic complete response (MRI-CR) proceed directly to surgery, omitting anthracycline-containing chemotherapy. Patients with radiologic residual disease (MRI-RD) complete the full neoadjuvant regimen including AC+P. The primary endpoint is pCR rate among patients with MRI-CR undergoing early surgery. Key secondary endpoints include recurrence-free survival, overall survival, toxicity, and patient-reported outcomes. Exploratory analyses include longitudinal circulating tumor DNA (ctDNA) dynamics to assess early molecular response, minimal residual disease, and correlates with MRI-CR, pCR, and long-term outcomes. The expected pCR rate among patients achieving MRI-CR is $\geq$87%, compared with a benchmark rate of 65%. The study uses a Simon's optimal two-stage design (one-sided α=0.05, 80% power). In stage 1, 10 MRI-CR patients proceeding directly to surgery will be evaluated, with early stopping for futility if the efficacy threshold is not met. If successful, stage 2 will enroll an additional 17 MRI-CR patients, for a total of 27 evaluable patients. Assuming an MRI-CR rate of ~50%, 54 patients will be enrolled overall. The study is open for recruitment at two tertiary academic hospitals in Israel, and 9 of the planned 54 patients have been enrolled. The NOGA trial represents a novel precision oncology approach in early TNBC, with the potential to minimize toxicity without compromising efficacy in selected responders. Clinical trial information: NCT07327021. Research Sponsor: None.

TPS655 **Poster Session**

A phase 2 clinical trial in progress of (Z)-endoxifen plus goserelin as neoadjuvant therapy in premenopausal women with ER+/HER2– breast cancer (EVANGELINE). First Author: Steven Quay, Atossa Therapeutics, Inc., Seattle, WA

Background: Early (14-28 day) on-treatment suppression of tumor proliferation during neoadjuvant endocrine therapy (NET) is strongly associated with favorable long-term outcomes in estrogen receptor–positive (ER+) HER2– breast cancer. In premenopausal women, tamoxifen with or without ovarian function suppression (OFS) results in suboptimal Ki-67 suppression compared with aromatase inhibitor + OFS. (Z)-endoxifen (ENDX), the active metabolite of tamoxifen, dually inhibits ER signaling and PKCβ1-mediated AKT activation, supporting its evaluation as an alternative NET strategy in this population. **Methods:** EVANGELINE (NCT05607004) is an ongoing, multicenter, open-label Phase 2 study evaluating daily 40 mg ENDX plus goserelin administered every 28 days as neoadjuvant therapy in premenopausal women with ER+/HER2–, cT2–3, cN0–1 breast cancer. The primary objective is to determine the proportion of patients with baseline Ki-67 $>$10% who achieve Ki-67 $\leq$10% after 4 weeks of therapy. A Simon two-stage design is used to test whether the Week 4 Ki-67 $\leq$10% rate is at least 65%, with 20 patients enrolled into the first stage and, if promising, another 25 patients enrolled into the second stage (cohort A). A parallel cohort of 20 patients with baseline Ki-67 $\leq$10% (cohort B) is enrolled to assess objective response rate (ORR) at 24 weeks per RECIST v1.1. Secondary objectives include examining safety and tolerability, residual cancer burden, and PEPI score. Correlative analyses include examining effect of treatment on select tumor and plasma biomarkers. Clinical trial information: NCT05607004. Research Sponsor: Atossa Therapeutics Inc.

TPS656 **Poster Session**

ETHAN: A phase II study comparing different endocrine therapies for male breast cancer. First Author: Jose Pablo Leone, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Male breast cancer is a rare disease, and most cases are hormone receptor-positive (HR+). Due to a lack of clinical trials, male breast cancer has historically been treated based on data extrapolated from women. However, there are substantial knowledge gaps in the comparative efficacy, safety, and patient-reported outcomes of endocrine therapies for men. While tamoxifen is the current standard of care, additional data are warranted for aromatase inhibitors (AI), gonadal suppression, and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. **Methods:** This is an open-label, multicenter, randomized, phase II trial designed to evaluate different endocrine therapies in men with HR+ and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. A total of 60 men will be enrolled across 9 sites within the Translational Breast Cancer Research Consortium (TBCRC). Key eligibility criteria include male sex and stage I, II, or III HR+/HER2- breast cancer before surgical resection of the primary tumor and axillary nodes. Key exclusion criteria include prior anti-cancer therapy within the past 12 months, and inflammatory breast cancer. The trial has two phases. The first phase is a window of opportunity in which newly diagnosed men are randomized 1:1:1 to either tamoxifen (Arm A), anastrozole (Arm B), or anastrozole plus degarelix (Arm C) given for 3 weeks. The primary endpoint for the window phase is Ki-67 reduction from the baseline diagnostic biopsy to the research biopsy at the end of the window phase. The second phase consists of neoadjuvant treatment, in which the tamoxifen group is randomized 1:1 to tamoxifen (Arm D) vs tamoxifen plus abemaciclib (Arm E), and the anastrozole alone (Arm B) and anastrozole plus degarelix (Arm C) groups are merged and then randomized 1:1 to anastrozole plus degarelix (Arm F) vs anastrozole plus degarelix plus abemaciclib (Arm G). The duration of the neoadjuvant phase is 4 months, and the primary endpoint of this phase is residual cancer burden (RCB) index at time of surgery. The trial is powered for the RCB endpoint in a 2 x 2 factorial design to detect a 0.6 unit decrease in RCB index with 80% power and alpha = 10%. For the Ki-67 endpoint, we assume an approximately 50% reduction in Arms A and B; Arm C will be of interest if it leads to $\geq$80% reduction in Ki-67. Secondary endpoints include: change in estradiol and testosterone levels from baseline, preoperative endocrine prognostic index (PEPI) score at surgery, adverse events, and patient-reported outcomes (including quality of life). Tumor tissue will be collected for correlative analyses. The study opened at Dana-Farber in October 2023, and is also open at Mayo Clinic, MD Anderson Cancer Center, Georgetown University, University of North Carolina, University of Pennsylvania, University of Pittsburgh, and Vanderbilt University. One more site will open in 2026. Clinical trial information: NCT05501704. Research Sponsor: TBCRC; BCRF; Eli Lilly; U.S. National Institutes of Health; Male Breast Cancer Global Alliance.

TPS657 **Poster Session**

Stereotactic body radiotherapy (SBRT) combined with PD-1 inhibitor and chemotherapy in early-stage treatment-naive triple-negative breast cancer patients: A multicenter phase III clinical study. First Author: Lei Liu, West China Hospital of Sichuan University, Chengdu, China

Background: Early-stage triple-negative breast cancer (TNBC) carries a high risk of locoregional recurrence and distant metastasis. The KEYNOTE-522 trial established that adding an immune checkpoint inhibitor to neoadjuvant chemotherapy in high-risk early-stage TNBC yields a pathologic complete response (pCR) rate of 64.8%. However, nearly 40% of patients still fail to achieve pCR. Radiotherapy not only directly eradicates tumor cells but also can induce systemic immunomodulatory effects, such as promoting tumor antigen release and enhancing T-cell infiltration. Therefore, combining radiotherapy with immune checkpoint inhibitors and chemotherapy represents a promising strategy to improve outcomes in early-stage TNBC. Preliminary data from small-sample, single-arm studies suggest that neoadjuvant stereotactic body radiotherapy (SBRT) combined with an anti-PD-L1 antibody and chemotherapy can increase pCR rate to 90%(Liu C., et al., *Elife*, 2023). However, this therapeutic modality lacks large-scale clinical data to further confirm the radiosensitizing effect of radiotherapy on immune checkpoint inhibitors. This phase III, randomized, controlled, multicenter study aims to evaluate the efficacy and safety of toripalimab (an anti-PD-1 monoclonal antibody) plus chemotherapy with or without SBRT in treatment-naïve TNBC patients. **Methods:** Eligible patients are treatment-naïve, non-metastatic TNBC with clinical stage cT1cN1-2M0 or cT2N0-2M0 (AJCC 8th edition). Patients are randomized 1:1 to receive toripalimab (240 mg, intravenously, every 3 weeks for 8 cycles) plus nab-paclitaxel (260 mg/m^2, intravenously, every 3 weeks for cycles 1-4) and carboplatin (AUC=5, intravenously every 3 weeks for cycles 1-4) and epirubicin (90-100 mg/m^2, intravenously, every 3 weeks for cycles 5-8) and cyclophosphamide (600 mg/m^2, intravenously every 3 weeks for cycles 5-8), with or without SBRT (8 Gy $\times$ 3 fractions). All patients undergo surgery 4-8 weeks after completing neoadjuvant therapy. The primary endpoint is investigator-assessed pCR. Secondary endpoints include breast conservation rate, ipsilateral breast recurrence or locoregional recurrence, overall survival (OS), and safety. Sample size was calculated assuming a pCR rate of 64.8% in the control arm (based on KEYNOTE-522) and 80% in the experimental (SBRT) arm. With a one-sided α of 0.025, 80% power, 1:1 allocation, and accounting for a 20% dropout rate, 159 patients per arm (total N=318) are enrolled. The study was initiated in November 2024. Clinical trial information: NCT06627712. Research Sponsor: National Major Science and Technology Projects.

TPS658 **Poster Session**

The SURVIVE study: Re-evaluating follow-up in early breast cancer. First Author: Sophia T. Huesmann, Department of Gynecology and Obstetrics, University Hospital Ulm, Ulm, Germany

Background: For decades, international guidelines unanimously recommended limiting routine follow-up in early breast cancer (EBC) to clinical exams and breast imaging, to detect potentially curable local relapse early. Additionally, guidelines explicitly advise against screening for distant recurrence in asymptomatic patients, as there remains no survival benefit in patients with earlier detected metastatic disease to date, at the cost of quality of life (1). However, as most of this data was published over 30 years ago, a re-evaluation of EBC follow-up strategies is urgently needed, considering numerous novel treatment options for both EBC and metastatic breast cancer patients. **Methods:** Study Design: The SURVIVE study is a prospective, multicenter, randomized controlled trial investigating a liquid-biopsy based follow-up in intermediate- to high-risk EBC patients. 3.500 EBC patients after completion of primary therapy (surgery, chemo- or radiotherapy) are randomized 1:1 to either standard or liquid-biopsy guided (intensified) follow-up. All patients receive guideline-based follow-up procedures. Additionally, blood samples are taken every 3 months (years 1–3), later every 6 months (years 4–5). While samples from patients in the standard-arm are biobanked, samples from the interventional arm are analyzed longitudinally for tumor markers (CA 27.29, CEA, CA 125, Tosoh Bioscience), CTCs (CellSearch, Menarini), and ctDNA (RaDaR, Neogenomics). The detection of abnormalities via liquid biopsy leads to staging examinations. For patients with confirmed recurrence, treatment hereafter follows national guidelines. The detection of true molecular relapse (positive liquid biopsy without clinical evidence of recurrence) leads to further monitoring within the SURVIVE protocol and creates the unique opportunity for treatment-intervention studies, such as SURVIVE HERoes (NCT06643585). Endpoints: The two co-primary endpoints are overall survival (OS) and the lead time, measured as the time from positive biomarker to positive imaging in the interventional arm. Secondary endpoints include breast cancer-specific survival, quality of life, and biomarker performance. Recruitment: As of January 2026, recruitment is active in 98 study centers in Germany. Currently, nearly 2,400 patients have been randomized since December 2022. **Conclusion:** The SURVIVE study is a long-anticipated study assessing whether intensified follow-up, guided by liquid biopsy, leads to earlier detection of recurrence and improved overall survival in EBC. NCT05658172. Funding: German Federal Ministry of Education and Research (BMBF), NeoGenomics, Menarini Silicon Biosystems, Tosoh Bioscience. Bibliography: Moschetti I, Cinquini M, Lambertini M, Levaggi A, Liberati A. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev. 2016;CD001768. Clinical trial information: NCT05658172. Research Sponsor: German Federal Ministry of Research, Technology and Space; NeoGenomics Inc.; Menarini Silicon Biosystems; Tosoh Biotech.

TPS659 **Poster Session**

Pre-operative chemotherapy versus surgery first with peri-operative interventions in early triple-negative and HER2-positive breast cancer: An open-label, phase 3, randomized controlled trial (PRaCTiSE). First Author: Shalaka Prakash Joshi, Tata Memorial Hospital and Homi Bhabha National Institute, Mumbai, India

Background: Surgery is a mainstay of treatment of breast cancer. Neoadjuvant chemotherapy (NACT) has not proven to be more effective in improving long-term outcomes when compared with adjuvant (EBCTCG, Lancet Oncol, 2018). Although pathological complete response (pCR) is surrogate at the individual patient level, it has not translated into improved outcomes across trials (BMJ, 2021).Triple-negative (TN) and HER2-positive breast cancer patients with non-pCR are treated with risk-adapted maintenance regimens (NEJM, 2025; NEJM, 2017). We previously proved efficacy of pre-operative progesterone and intra-operative peri-tumoural lignocaine in improving disease-free and overall survival (JCO, 2011; JCO, 2023). We are currently testing the effectiveness of a “Surgery first” versus “PRe-operative ChemoTherapy” approach in patients with early TN and HER2-positive tumours. **Methods:** This is a prospective, open-label randomized trial. Patients with cT1c/2,cN0/1, histologically proven, TN or HER2-positive breast cancer are screened. The study is approved by Institutional Ethics and has been registered on CTRI (CTRI/2024/02/063118). Eligible patients fit for surgery and NACT are randomized after consenting. Stratification criteria are menopausal status (pre-peri/post), cN stage (N0/N1), and TN/HER2+. “Surgery first” arm receives intramuscular progesterone injection 4-14 days before surgery and peri-tumoral 0.5% lignocaine infiltration intra-operatively. All patients are treated with standard adjuvant chemotherapy and targeted therapy and radiotherapy protocols. “PRe-operative ChemoTherapy” arm receives standard NACT. Chemotherapy backbone is anthracycline, cyclophosphamide, and paclitaxel in all patients, with addition of carboplatin and pembrolizumab in NACT for TN and anti-HER2 targeted therapy (dual if node positive) in HER2+ setting. Response assessment is done clinically after each cycle and with imaging after every 3-4 cycles. Maintenance pembrolizumab/capecitabine for TN and anti-HER2 targeted therapy/t-DM1 for HER2+ tumours as per response is offered for standard duration. Surgery in both arms is breast conservation surgery with or without oncoplasty or mastectomy with or without reconstruction, depending on imaging findings, response, and patient choice. All primary tumors are clipped in NACT arm. Axillary staging procedure is carried out and, if positive macro-metastatic nodes on frozen section, level I-III axillary dissection is done. A total sample size of 1350 (1500 accounting for loss-to-follow-up) split equally between two groups, or 257 events, achieves 80% power to detect hazard rate of 0.70173 when the proportions surviving in each group are 0.78 and 0.84 at a significance level (alpha) of 0.05 using a two-sided log rank test. An interim is planned at 50% DFS events. Clinical trial information: CTRI/2024/02/063118. Research Sponsor: None.

LBA660 **Oral Abstract Session**

Anbenitamab plus albumin-bound docetaxel (nab-docetaxel) ± carboplatin (Cb) versus trastuzumab and pertuzumab plus docetaxel (THP) ± Cb as neoadjuvant therapy for HER2-positive early or locally advanced breast cancer: A randomized, open-label, multicenter, phase 3 trial. First Author: Zhi-Ming Shao, Fudan University Shanghai Cancer Center, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA1000 **Oral Abstract Session**

Progression-free survival after next line of treatment (PFS2) and subsequent therapies (subs tx) in the ASCENT-04 study of participants (pts) with previously untreated PD-L1+ metastatic triple-negative breast cancer (mTNBC) treated with sacituzumab govitecan (SG) plus pembrolizumab (pembro) vs chemotherapy (chemo) plus pembro. First Author: Kevin Kalinsky, Winship Cancer Institute of Emory University, Atlanta, GA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

1001 **Oral Abstract Session**

Progression-free survival after next line of treatment (PFS2) and subsequent therapies (subs tx) in the ASCENT-03 study of participants (pts) with previously untreated metastatic triple-negative breast cancer (mTNBC) treated with sacituzumab govitecan (SG) vs chemotherapy (chemo). First Author: Sara A. Hurvitz, Department of Medicine, UW Medicine, Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA

Background: In ASCENT-03, first-line (1L) SG led to a clinically meaningful improvement in PFS vs chemo (median, 9.7 vs 6.9 months [mo]; hazard ratio [HR], 0.62; 95% CI, 0.50-0.77; $P < .0001$) in previously untreated pts with mTNBC who were not candidates for PD-(L)1 inhibitors. Since overall survival data are immature, PFS2 can be used to assess long-term benefit as it accounts for the impact of initial and subs tx, including trial crossovers. We report PFS2 and subs tx from ASCENT-03. **Methods:** Pts (N = 558) were randomized 1:1 to SG (10 mg/kg IV, days 1 & 8 in 21-day cycles) or chemo (paclitaxel, nab-paclitaxel, or gemcitabine + carboplatin); primary end point was PFS by blinded independent central review (BICR). Eligible pts in the chemo group could receive 2L SG provided on study via crossover following BICR-verified progressive disease or in any subs line commercially; other subs txs per local practice were also permitted. PFS2 was defined as the time from randomization to the first documented progression on next-line therapy per investigator assessment or death due to any cause, whichever occurred first. **Results:** Median follow-up for OS was 13.2 mo; 75 (27%) pts remained on study treatment in the SG group (n = 279) and 39 (14%) in the chemo group (n = 279). Of the 204 pts in the SG group who discontinued tx, 126 received any subs tx, the most frequent of which were platinum chemo (40%), taxanes (29%), and gemcitabine (19%). Of 240 pts in the chemo group who discontinued tx, 179 received any subs tx, the most frequent of which were SG (82%), capecitabine (16%), platinum chemo (9%), and trastuzumab deruxtecan (9%). Median (95% CI) PFS2 was 18.2 mo (15.9-not reached [NR]) in the SG group and 14.0 mo (12.5-17.4) in the chemo group (stratified HR, 0.70; 95% CI, 0.55-0.90). PFS2 rates are in the Table. Median (95% CI) time to first subs tx was 11.2 mo (10.0-13.0) and 7.9 mo (7.2-9.0) for SG and chemo, respectively; median (95% CI) time to second subs tx was 17.3 mo (15.2- NR) and 16.6 mo (13.6-18.5). **Conclusions:** PFS2 was improved in the SG group compared with the chemo group despite crossover tx, with most pts who initiated subs tx in the chemo group receiving SG. The benefit of first-line SG is clinically relevant and sustained until the next line of therapy, which further supports SG as a potential new standard of care in pts with previously untreated mTNBC who are not candidates for PD-(L)1 inhibitors. Clinical trial information: NCT05382299. Research Sponsor: Gilead Sciences, Inc.

	SG	Chemo
Pts with PFS2 events, n/N (%)	114/279 (41)	143/279 (51)
Median PFS2 (95% CI), mo	18.2 (15.9-NR)	14.0 (12.5-17.4)
Stratified HR[a] (95% CI)	0.70 (0.55-0.90)	
Stratified log-rank nominal *P*-value[a]	.0051	
PFS2 rate (95% CI), %		
12 mo	71 (65-76)	59 (53-65)
18 mo	52 (45-59)	41 (33-48)

[a]SG vs chemo.

1002 **Oral Abstract Session**

First-line datopotamab deruxtecan (Dato-DXd) vs chemotherapy in patients with locally recurrent inoperable or metastatic triple-negative breast cancer (TNBC) for whom immunotherapy was not an option: Additional efficacy endpoints from the TROPION-Breast02 study. First Author: David W. Cescon, Princess Margaret Cancer Centre/UHN, Toronto, ON, Canada

Background: In the primary analysis of the phase 3 TROPION-Breast02 study (NCT05374512), first-line Dato-DXd demonstrated statistically significant and clinically meaningful improvements in overall survival (OS; hazard ratio [HR]: 0.79 [95% confidence interval [CI]: 0.64–0.98]; p = 0.0291) and progression-free survival (PFS; HR: 0.57 [95% CI: 0.47–0.69]; p < 0.0001) compared with investigator's choice of chemotherapy (ICC) in patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy was not an option. Both median OS and PFS by blinded independent central review (BICR) were ≥5 months longer with Dato-DXd compared with ICC. Moreover, with Dato-DXd vs ICC, the confirmed objective response rate was more than double and median duration of response was > 5 months longer. The Dato-DXd safety profile was manageable and generally consistent with the known profile. Here we report additional efficacy endpoints. **Methods:** Adult patients with previously untreated locally recurrent inoperable or metastatic TNBC, for whom immunotherapy was not an option, were randomized 1:1 to Dato-DXd (6 mg/kg IV every 3 weeks) or ICC ([nab]-paclitaxel/capecitabine/eribulin mesylate/carboplatin). Dual primary endpoints were OS and PFS by BICR per RECIST 1.1; secondary endpoints included time to second progression or death (PFS2), time to first subsequent therapy or death (TFST), and time to second subsequent therapy or death (TSST). The planned sample size was approximately 600 randomized patients. A stratified log-rank test was used to analyze PFS2, TFST, and TSST. HRs and 95% CIs were estimated from a stratified Cox proportional hazards model. **Results:** A total of 644 patients were randomized (Dato-DXd: 323; ICC: 321). At data cutoff (25 Aug 2025), median study follow-up was 27.5 months and 53 (8.4%) patients remained on treatment (Dato-DXd: 45 [14.1%]; ICC: 8 [2.6%]). PFS2 was longer with Dato-DXd vs ICC: median 15.6 vs 11.8 months (HR: 0.61 [95% CI: 0.50–0.74]). Both TFST and TSST were prolonged in the Dato-DXd vs ICC arm: median TFST was 10.9 vs 5.6 months with Dato-DXd vs ICC (HR: 0.49 [95% CI: 0.41–0.59]) and median TSST was 16.7 vs 12.6 months (HR: 0.67 [95% CI: 0.55–0.81]). **Conclusions:** In TROPION-Breast02, improvements in the secondary endpoints of PFS2, TFST, and TSST were observed for patients receiving Dato-DXd compared with ICC, consistent with the dual primary endpoints of OS and PFS by BICR. Alongside the manageable safety profile for Dato-DXd, these data further support Dato-DXd as the new first-line standard of care in this setting. Clinical trial information: NCT05374512. Research Sponsor: This trial is sponsored by AstraZeneca. In July 2020, Daiichi Sankyo entered into a global development and commercialisation collaboration with AstraZeneca for datopotamab deruxtecan (Dato-DXd).

LBA1003 **Oral Abstract Session**

Izalontamab brengitecan (iza-bren) versus physician's choice of chemotherapy in patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC): A randomized phase III study. First Author: Jiong Wu, Fudan University Shanghai Cancer Center, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

1004 Oral Abstract Session

Prevalence of symptomatic skeletal events (SSE) with reduced denosumab (Dmab) dose density (every 12 weeks versus every 4 weeks): A randomized phase III non-inferiority trial SAKK 96/12 REDUSE. First Author: Roger Anton Fredy Von Moos, Kantonspital Graubünden, Chur, Switzerland

Background: Clinical guidelines recommend Dmab 120 mg every 4 weeks (Q4W) for patients (pts) with bone metastases. While dosing every 12 weeks (Q12W) is established for zoledronic acid based on phase III trials, prospective trials with Dmab evaluating the efficacy endpoint of skeletal-related events (SRE) for a Q12W schedule are missing. The results of an early dose-finding study of Dmab demonstrated a similar suppression of bone-turnover markers for 60 mg Q12W as for 120 mg Q4W at weeks 13 and 25, suggesting that Q12W dosing might be sufficient. The SAKK 96/12 REDUSE trial investigated whether a de-escalated Dmab schedule is non-inferior to the standard Q4W regimen in preventing symptomatic skeletal related events (SSEs; symptomatic pathological fracture, radiation or surgery to bone, or spinal cord compression). **Methods:** In this international, multicenter, randomized, phase III trial, pts with metastatic breast cancer (BC) or castration-resistant prostate cancer (CRPC) and at least three bone metastases were randomized 1:1. Arm A (standard) received Dmab 120 mg Q4W. Arm B (reduced) received 4 loading doses Q4W, followed by Q12W dosing. The primary endpoint was time to first on-trial SSE. The sample size of 1,380 pts was calculated to demonstrate non-inferiority using a log-rank test with a non-inferiority margin of 1.20 (80% power, 5% type I error). Secondary endpoints included time to first and subsequent on-trial SSE, and toxicity focusing on hypocalcemia and osteonecrosis of the jaw (ONJ). A health economic analysis is ongoing. **Results:** 1,380 pts were enrolled between 7/2014 and 3/2024 (784 and 596 with BC and CRPC, respectively). Median follow-up time was 37 months (mo) (42 mo for BC and 29 mo for CPRC). The trial met its primary endpoint, demonstrating that denosumab Q12W is non-inferior to Q4W. Median time to first on-trial SSE for arm A was 56.6 mo (95% CI (40.7, not reached [NR]) and for arm B 56.5 mo (95% CI 47.7, NR). The stratified HR and 90% CI calculated using a Cox regression model is 1.023 (0.874, 1.197) with the upper limit remaining below 1.20. Also, for time to first and subsequent on-trial SSE, non-inferiority was shown with a stratified HR 1.043 (90% CI 0.907, 1.198). Safety analysis showed less toxicity for the Q12W arm: Hypocalcemia occurred in 46% (Arm A) vs 30% (Arm B), and ONJ was reported in 8.5% vs 6.9% of pts, respectively. **Conclusions:** The SAKK 96/12 REDUSE trial demonstrates that a Dmab Q12W schedule, following a 3-month loading phase, is non-inferior to the Q4W regimen in pts with bone-metastatic BC or CRPC. The observed lower rates in ONJ and hypocalcemia indicate a more favorable safety profile for the Q12W schedule. These data indicate that Dmab Q12W represents the new standard of care in pts with bone metastasis from BC or CRPC, offering comparable efficacy while reducing toxicity, treatment burden, and costs. Clinical trial information: NCT02051218. Research Sponsor: Santesuisse; CSS and Helsana health insurance; Swiss Cancer Institute, Switzerland.

1005 Oral Abstract Session

Efficacy and safety of tucatinib (TUC) vs placebo (PBO) combined with trastuzumab and pertuzumab (HP) as maintenance therapy for HER2+ metastatic breast cancer by stratified subgroups. First Author: Erika P. Hamilton, Breast Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN

Background: In the phase 3 HER2CLIMB-05 study (NCT05132582), TUC + maintenance HP demonstrated a statistically significant improvement in progression-free survival (PFS) vs control treatment (Tx) (hazard ratio: 0.641, $P < 0.0001$) in patients (pts) with HER2+ locally advanced or metastatic breast cancer (MBC). Here we report additional efficacy and safety outcomes by stratified subgroups. **Methods:** Pts with centrally confirmed HER2+ MBC without evidence of progression following chemotherapy-based induction Tx (taxane + HP) were randomly assigned 1:1 to TUC (300 mg) or PBO BID + HP. Randomization was stratified by diagnosis (*de novo*/recurrent), hormone receptor (HR) status (positive/negative), and presence or history of brain metastases (BM; yes/no). Endocrine therapy (ET) is permitted for pts with HR+ disease. The primary endpoint is investigator-assessed PFS. Confirmed objective response rate (cORR), duration of response (DOR), and safety were evaluated in stratified subgroups. **Results:** Among pts assigned to TUC + HP (n = 326) or PBO + HP (n = 328), ~69% had *de novo* MBC, ~53% had HR+ status with ~45% having received concurrent ET, and ~12% had baseline BM. At data cutoff (Sep 5, 2025), median PFS was longer with TUC than PBO + HP in all stratified subgroups; TUC + HP consistently improved cORR vs PBO + HP (Table). Safety outcomes in subgroups aligned with the overall population. **Conclusions:** TUC + HP demonstrated clinically meaningful efficacy vs PBO + HP in pts with *de novo* or recurrent disease, HR+ or HR− disease, and baseline BM or not, with no new safety signals identified. Results were consistent with the overall population and support TUC + HP as a potential new maintenance therapy across pts with HER2+ MBC. Clinical trial information: NCT05132582. Research Sponsor: Pfizer Inc.

Efficacy outcomes.

	Overall		*De novo*		Recurrent		HR+ (± ET)†		HR−		BM (yes)		BM (no)	
	TUC+HP (n=326)	PBO+HP (n=328)	TUC+HP (n=227)	PBO+HP (n=226)	TUC+HP (n=99)	PBO+HP (n=102)	TUC+HP (n=168)	PBO+HP (n=176)	TUC+HP (n=158)	PBO+HP (n=152)	TUC+HP (n=41)	PBO+HP (n=40)	TUC+HP (n=285)	PBO+HP (n=288)
Median PFS, mos (95% CI)	24.9 (21.3–NE)	16.3 (12.6–18.7)	28.9 (22.7–NE)	16.8 (12.9–19.2)	21.3 (15.6–27.2)	12.7 (8.3–18.1)	25.0 (16.5–NE)	18.1 (13.0–20.8)	24.9 (19.4–NE)	12.6 (9.4–16.8)	8.5 (4.2–16.5)	4.2 (2.2–8.1)	27.2 (24.3–NE)	18.1 (14.8–20.7)
cORR*, % (95% CI)	22.6 (18.0–27.8)	15.2 (11.3–19.7)	26.1 (20.2–32.7)	18.5 (13.5–24.4)	15.1 (8.5–24.0)	7.0 (2.6–14.6)	20.1 (14.0–27.5)	12.9 (8.2–19.0)	25.2 (18.4–33.0)	17.9 (11.8–25.5)	15.0 (5.7–29.8)	8.3 (1.8–22.5)	23.8 (18.7–29.5)	16.1 (11.9–12.1)
Median DOR*, mos (95% CI)	20.9 (16.4–NE)	16.9 (12.3–NE)	NR (16.4–NE)	16.3 (10.4–NE)	17.9 (8.3–NE)	NR (7.2–NE)	20.9 (12.6–NE)	18.7 (7.8–NE)	NR (8.6–NE)	14.5 (10.4–NE)	12.6 (8.1–NE)	16.3 (12.5–NE)	20.9 (16.4–NE)	18.7 (10.4–NE)

*ORR and DOR were assessed in patients with target or non-target lesions at baseline.
†Data on HR+ w/ ET will be presented.

LBA1006 Oral Abstract Session

Giredestrant (GIRE) + palbociclib (PALBO) vs letrozole (LET) + PALBO as first-line (1L) therapy in patients (pts) with estrogen receptor–positive, HER2-negative locally advanced or metastatic breast cancer (ER+, HER2– LA/mBC): Primary analysis of the phase III persevERA BC trial. First Author: Nicholas C. Turner, Royal Marsden Hospital, Institute of Cancer Research, London, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA1007 Oral Abstract Session

First-line (1L) camizestrant (CAMI) for emergent *ESR1* mutations (*ESR1*m) in advanced breast cancer (ABC): Final progression-free survival 2 (PFS2) from the phase III SERENA-6 trial. First Author: Francois Clement Bidard, Institut Curie, Paris, France

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

1009 Clinical Science Symposium

Efficacy and safety of camrelizumab combined with docetaxel and carboplatin as neoadjuvant therapy for triple-negative breast cancer: The HELEN-Trio 011 randomized clinical trial. First Author: Zhenzhen Liu, The Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China

Background: The KEYNOTE-522 trial demonstrated that adding a PD-1 inhibitor to neoadjuvant chemotherapy significantly improves pathological complete response (pCR) rates, albeit with notable toxicity. The phase III Camrelief trial further confirmed that camrelizumab combined with sequential neoadjuvant chemotherapy significantly improved pCR compared with placebo in early-stage triple-negative breast cancer (TNBC). This study aimed to evaluate the efficacy and safety of camrelizumab plus neoadjuvant docetaxel and carboplatin in previously untreated stage II–III TNBC. **Methods:** This multicenter, randomized, open-label, phase III trial (ClinicalTrials.gov identifier: NCT05475678) enrolled eligible female patients aged 18-70 years with previously untreated stage II-III TNBC. Patients were randomized (2:1) to receive six 21-day cycles of docetaxel (75 mg/m²) and carboplatin (area under the curve=6) on day 1, with or without camrelizumab (200 mg intravenously on day 3). The primary endpoint was pCR (ypT0/Tis ypN0), assessed in the modified intention-to-treat (mITT) population, which included all patients who received at least one dose of the trial treatment. **Results:** Between December 2022 and June 2025, 369 patients from fourteen hospitals in China were enrolled and randomized to the camrelizumab-chemotherapy group (n=245) or the chemotherapy-alone group (n=124), of whom 352 comprised the mITT population. The pCR rate was 57.5% (134 of 233) in the camrelizumab-chemotherapy group versus 45.4% (54 of 119) in the chemotherapy-alone group (absolute difference, 12.2 percentage points; 95% CI, 1.4-22.9; one-sided P= 0.014). In the prespecified exploratory subgroup (CPS $\geq$1), pCR rates were 69.8% (97/139; 95% CI, 62.2%-77.4%) with camrelizumab-chemotherapy and 51.9% (41/79; 95% CI, 40.9%- 62.94%) with chemotherapy-alone (absolute difference, 17.9%; 95% CI, 5.3%-30.5%; one-sided P = 0.004). In the PD-L1-negative subgroup (CPS $<$1), pCR rates were 37.8% (31/82; 95% CI, 27.4%-48.2%) and 28.1% (9/32; 95% CI, 12.5%-43.7%), respectively (absolute difference, 9.7%; 95% CI, -10.5%-29.9%; one-sided P = 0.165). Grade 3 or higher treatment-related adverse events occurred in 24.8% (58/233) of patients in the camrelizumab-chemotherapy group, and 21.8% (26/119) in the chemotherapy-alone group. No treatment related deaths were reported. **Conclusions:** The addition of camrelizumab to neoadjuvant docetaxel and carboplatin significantly improved pCR rates in patients with stage II–III TNBC with a manageable safety profile. This anthracycline-free regimen represents a promising neoadjuvant treatment option for early TNBC. Clinical trial information: NCT05475678. Research Sponsor: None.

1010 Clinical Science Symposium

Time-of-day administration of immunotherapy in early-stage triple-negative breast cancer: Immune-dependent chronotherapy effects in the phase III A-BRAVE trial. First Author: Maria Vittoria Dieci, Department of Surgery, Oncology and Gastroenterology, University of Padova; Division of Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy

Background: Circadian rhythms regulate immune functions, and morning (AM) administration of immunotherapy (IO) is associated with survival in several solid tumors. However, whether time-of-day (ToDa) of IO delivery influences outcomes in early-stage triple-negative breast cancer (TNBC), and whether this effect depends on immune biomarkers, remains unknown. **Methods:** A-BRAVE randomized patients with high-risk early-stage TNBC to 1 year of adjuvant avelumab or observation. Infusion time of avelumab was retrieved from eCRF. AM-rate was calculated for each patient as the proportion of the first 4 infusions occurring before 12:30 PM (cohort median ToDa) and patients categorized as AM-dominant (AM-rate $\geq$50%) or PM-dominant. Tumor-infiltrating lymphocytes (TILs) and PD-L1 (Dako 73-10) were centrally assessed on treatment-naive tumor samples. We analyzed distant disease-free survival (DDFS) and overall survival (OS) by adjusted Cox models. **Results:** ToDa data were available for 221 avelumab-treated patients (94.0%); TILs and PD-L1 were evaluable in 188 (85%) and 195 (88%) of these, respectively. AM-rate was not associated with outcomes. However, ToDa effects were strongly immune-dependent. Increasing AM-rate was associated with improved DDFS and OS in immune-hot tumors (TILs [$\geq$20%] or PD-L1 [$\geq$21] high), but with worse outcomes in immune-cold tumors (TILs or PD-L1 low) (AM-rate*TILs interaction: DDFS p=0.008, OS p=0.001; AM-rate*PD-L1 interaction: DDFS p=0.030, OS p=0.039). These findings were concordant using AM-dominant vs. PM-dominant categorization (Table). Patients receiving immune-aligned treatment (immune-hot/AM-dominant OR immune-cold/PM-dominant) had superior survival compared with immune-misaligned (immune-hot/PM-dominant OR immune-cold/AM-dominant) and the observational arm (TILs-based: 3-year OS 95.7% vs 75.2% vs 78.0%; p$<$0.001; PD-L1-based: 3-year OS 93.4% vs 79.4% vs 76.1; p=0.035). **Conclusions:** In early-stage TNBC, time of IO administration may be a driver of efficacy, with opposing effects according to baseline immune milieu. Immune-informed circadian alignment may represent a previously unrecognized determinant of IO efficacy in TNBC. Clinical trial information: NCT02926196. Research Sponsor: Merck KGaA; CrossRef Funder ID: 10.13039/100009945.

	Outcome	AM-dominant 3-yr Rate % (95% CI)	PM-dominant 3-yr Rate % (95% CI)	Log-rank p	AM vs PM dominant HR (95% CI)
TILs High	DDFS	90.1 (81.3–99.8)	72.0 (56.4–91.9)	0.064	0.39 (0.13–1.21)
	OS	97.5 (92.8–100)	76.0 (61.0–94.7)	0.019	0.35 (0.10–1.20)
TILs Low	DDFS	63.1 (52.6–75.7)	84.7 (75.5–95.1)	0.003	2.61 (1.23–5.55)
	OS	74.9 (65.2–86.0)	94.3 (88.3–100)	0.003	3.84 (1.30–11.29)
PD-L1 high	DDFS	100 (100–100)	61.5 (40.0–94.6)	0.015	0.11 (0.01–0.94)
	OS	100 (100–100)	76.9 (57.1–100)	0.008	0.11 (0.01–1.03)
PD-L1 low	DDFS	66.4 (57.3–77.0)	83.0 (74.7–92.2)	0.026	1.82 (1.00–3.31)
	OS	79.8 (71.9–88.6)	91.5 (85.3–98.2)	0.025	2.05 (0.95–4.43)

1011 Clinical Science Symposium

Primary results from the triple-negative cohort of TBCRC-053 (P-RAD): A randomized trial of no, low, or high dose preoperative radiation with pembrolizumab and chemotherapy in node-positive breast cancer. First Author: Alice Yoosun Ho, Houston Methodist Academic Institute, Houston, TX

Background: Approximately one-quarter of patients with node-positive, triple-negative breast cancer (TNBC) did not experience a complete nodal response to neoadjuvant chemo-immunotherapy in KEYNOTE-522. We conducted a randomized trial to evaluate whether no-, low-, or high-dose preoperative radiotherapy (RT) to the breast primary tumor combined with pembrolizumab (pembro) enhances tumor T-cell infiltration (TCI) and pathologic response in non-irradiated lymph node (LN) metastases (NCT04443348). **Methods:** Between 2021-2025, 55 patients with cT1c-T4c, cN1-3, cM0, ER/PR $<$ 10%, HER2-negative breast cancer and biopsy-proven, clipped axillary LN metastasis were randomized to no RT (0 Gy), low-dose RT (9 Gy) or high-dose RT (24 Gy) to the primary tumor with concurrent pembro, followed by an on-treatment tumor biopsy at 2 wks. Stratification factors included cT stage (T1c vs. T2-4) and cN stage (N1 vs. N2-3). Patients subsequently received pembro (200 mg q3w or 400 mg q6w) with 12 wks of paclitaxel/carboplatin, followed by four cycles of doxorubicin-cyclophosphamide (q2w or q3w) with pembro, surgery and adjuvant therapy. Primary endpoints were 2-wk tumor TCI and nodal pathologic complete response (ypN0) at surgery. TCI was assessed by multiplexed immunofluorescence (panCK/CD3/CD8) using a rank-based Immunoscore. 2-wk TCI for each treatment arm was compared to a common reference cohort of pretreatment TCI measurements. The study was powered to detect an increase in upper-quartile TCI from 25% to 55%. Statistical comparisons used two-tailed Fisher's exact tests. ypN0 and secondary endpoints pCR (ypT0/TisN0) and Residual Cancer Burden (RCB) 0/1 were underpowered for a statistical test. **Results:** Among 55 enrolled patients, 48 were evaluable for TCI and 51 for ypN0. Median age was 50 years (range 28-77). 81.8% had cT2-4 disease, 20% had cN2-3, and 87.3% had grade 3 tumors. The proportion of tumors with upper-quartile TCI was significantly increased with RT plus pembro, but not pembro alone, when compared to the pretreatment cohort: 44% (0Gy; p = NS), 80% (9Gy, p $<$ 0.0001), and 82% (24Gy; p $<$ 0.0001). ypN0 rates were 73.3% (0Gy), 88.2% (9Gy) and 78.9% (24Gy). pCR/RCB 0-1 rates were 66.6%/66.6% (0Gy), 76.5%/82.4% (9Gy) and 68.4%/84.2% (24Gy). Tumors with upper-quartile TCI at the 2-wk timepoint had a significantly higher ypN0 rate relative to tumors without upper-quartile TCI (94% [31/33] vs. 46% [6/13]; p = 0.0009). **Conclusions:** The addition of preoperative RT to pembro significantly increased 2-wk TCI and yielded high rates of ypN0 and pCR after chemo-immunotherapy, with the numerically highest ypN0 rate observed in the 9Gy arm. 2-wk TCI correlated strongly with surgical ypN0 status. A larger study that tests whether preoperative RT and pembro increases pCR should be conducted in node-positive TNBC. Clinical trial information: NCT04443348. Research Sponsor: Breast Cancer Research Foundation; Translational Breast Cancer Research Consortium; U.S. National Institutes of Health; Merck, Inc.; Natera, Inc.

1012 Clinical Science Symposium

Trastuzumab deruxtecan (T-DXd) + durvalumab (D) in patients (pts) with previously untreated HER2+ unresectable/metastatic breast cancer (mBC): Final analysis from DESTINY-Breast07. First Author: Sherene Loi, Breast Unit, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: T-DXd is approved for adult pts with HER2+ mBC who received a prior anti-HER2–based regimen, or as 1L therapy when given in combination with pertuzumab (P). DESTINY-Breast07 (NCT04538742) is a Phase 1b/2, open-label, platform study exploring the safety, tolerability, and antitumor activity of T-DXd $\pm$ other anticancer agents in HER2+ mBC. 1L T-DXd $\pm$ P recently showed encouraging clinical activity and safety profiles consistent with previous reports. D, an anti-PD-L1 antibody, has shown efficacy in combination with T-DXd in HER2-low, hormone receptor (HR)–negative mBC. As part of the DESTINY-Breast07 final analysis, here we report the dose-expansion phase for T-DXd + D as a 1L treatment in HER2+ mBC. **Methods:** Pts had locally assessed HER2+ (IHC 3+ or IHC 2+/ISH+) mBC. A disease-free interval of $\geq$12 months (mo) from (neo)adjuvant therapy was required; no prior therapy for mBC was allowed. Pts were stratified by HR (positive vs negative), disease (recurrent vs de novo), and PD-L1 status (positive vs negative; positive defined as $\geq$1% IHC). Pts received T-DXd 5.4 mg/kg IV, in combination with D 1120 mg IV, every 3 weeks. Primary endpoints were safety and tolerability; secondary endpoints included confirmed ORR (cORR), duration of response (DOR) and progression-free survival (PFS) per RECIST 1.1 by investigator, time to progression on subsequent therapy or death (PFS2) by investigator, and overall survival (OS). **Results:** At data cutoff (DCO) (January 31, 2025), 64 pts were randomized to the T-DXd + D module, and 63 received treatment. Median follow up was 30.1 mo; median total treatment duration was 26.7 mo for T-DXd and 24.6 mo for D. Efficacy results are given in the Table. The most common adverse events (AEs) were nausea (79.4%), vomiting (46.0%), neutropenia (46.0% by grouped term [GT]), anemia (44.4% by GT), and fatigue (38.1%). Grade $\geq$3 AEs occurred in 58.7% (n=37/63) and serious AEs in 30.2% (n=19/63) of pts. There were two deaths due to AEs (3.2%): one pt with neutropenia and septic shock and one pt with sepsis. Adjudicated drug-related interstitial lung disease (ILD)/pneumonitis events occurred in 11 (17.5%; Grade 1, n=1; Grade 2, n=8; Grade 3, n=2) pts. Additional data by subgroups (stratification factors and biomarkers) will be presented. **Conclusions:** Encouraging clinical activity was seen for T-DXd + D as a 1L treatment for HER2+ mBC. Safety profiles were consistent with the known profiles for each therapy, with no fatal ILD events. These promising results provide a rationale for further investigation of this treatment combination. Clinical trial information: NCT04538742. Research Sponsor: AstraZeneca.

	T-DXd + D (n=64)
cORR (80% CI), %	82.8 (75.2, 88.8)
mDOR* (Q1–Q3), mo	36.1 (23.3, NE)
mPFS* (80% CI), mo	37.7 (35.1, NE)
PFS rate at 24 mo (80% CI), %	75.5 (67.2, 82.0)
mOS (80% CI), mo	NE (NE, NE)
mPFS2 (80% CI), mo	NE (NE, NE)

*Most pts were censored at DCO; m, median; NE, not evaluable; Q, quartile.

1013 Rapid Oral Abstract Session

ASCENT-04: Analysis of efficacy by biomarker subgroups with sacituzumab govitecan (SG) + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in participants (pts) with previously untreated PD-L1+ metastatic triple-negative breast cancer (mTNBC). First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: In the phase 3 ASCENT-04/KEYNOTE-D19 study (NCT05382286) SG + pembro showed significant and clinically meaningful progression-free survival (PFS) improvement vs chemo + pembro in pts with previously untreated PD-L1+ mTNBC. SG + pembro exhibited a manageable safety profile consistent with prior studies for each agent. We present preplanned exploratory efficacy analyses in ASCENT-04 by biomarker subgroups. **Methods:** 443 pts received (1:1 ratio) SG + pembro in 21-day cycles or chemo (gemcitabine + carboplatin; taxane) + pembro. From centrally tested fresh or archival tumor samples, Trop-2 expression was determined by immunohistochemistry (IHC), tumor BRCA (tBRCA) status by whole exome sequencing, and HER2 expression by in situ hybridization (ISH) + IHC. Pts were grouped by Trop-2 expression quartiles, tBRCA status (wild-type [WT] or mutant [mut] in *BRCA1/BRCA2*/both), and HER2 status (IHC 0 vs Low [IHC 1+ or IHC 2+/ISH−]). Biomarker subgroups were analyzed descriptively for association with PFS by blinded independent central review (BICR); other outcomes by biomarker status are forthcoming. **Results:** Median Trop-2 H-score was 280, ranges: quartile 1 (Q1) 0-224, Q2 225-279, Q3 280-298, Q4 299-300. SG + pembro demonstrated longer PFS by BICR in Q3/Q4 vs Q1/Q2, and benefit was observed for SG + pembro vs chemo + pembro in all quartiles (Table). Hazard ratios (HR; 95% confidence interval [CI]) were: Q1, 0.81 (0.48-1.36); Q2, 0.73 (0.44-1.22); Q3, 0.46 (0.27-0.80); Q4, 0.57 (0.33-0.99). Proportion of pts with tBRCA mutations (~20%) was similar between treatment groups. Longer PFS was observed with SG + pembro with HR (95% CI) of 0.67 (0.49-0.91) in the tBRCA WT and 0.88 (0.45-1.74) in the tBRCA mut subgroups. PFS was longer with SG + pembro vs chemo + pembro in the HER2 IHC 0 and HER2 low subgroups, HR (95% CI) 0.69 (0.46-1.04) and 0.67 (0.48-0.92), respectively. **Conclusions:** SG + pembro demonstrated longer PFS vs chemo + pembro across all Trop-2, tBRCA, and HER2 subgroups. These analyses strengthen support for the significant, clinically meaningful benefit of SG + pembro as first-line treatment for mTNBC across subgroups. Clinical trial information: NCT05382286. Research Sponsor: Gilead Sciences, Inc.

Efficacy, BICR Biomarker	Subgroup	N SG + pembro	N Chemo + pembro	Median PFS (95% CI), mo SG + pembro	Median PFS (95% CI), mo Chemo + pembro	HR (95% CI)
Trop-2 (n = 400)	Q1	48	47	9.3 (7.4-19.4)	9.0 (6.0-10.9)	0.81 (0.48-1.36)
	Q2	50	50	9.6 (7.3-16.7)	7.4 (6.9-9.7)	0.73 (0.44-1.22)
	Q3	55	50	13.5 (9.3-NR)	8.4 (5.6-10.8)	0.46 (0.27-0.80)
	Q4	51	49	16.6 (8.1-NR)	9.2 (5.5-11.3)	0.57 (0.33-0.99)
tBRCA (n = 332)	WT	130	131	9.6 (7.6-16.7)	7.4 (6.9-9.2)	0.67 (0.49-0.91)
	Mut	39	32	16.6 (7.5-NR)	12.9 (7.1-NR)	0.88 (0.45-1.74)
HER2 (n = 435)	IHC 0	84	82	16.6 (9.1-21.2)	9.0 (7.2-10.8)	0.69 (0.46-1.04)
	Low	133	136	11.2 (9.1-16.6)	7.7 (7.0-9.4)	0.67 (0.48-0.92)

1014 Rapid Oral Abstract Session

ASCENT-03: Efficacy by biomarker subgroup with sacituzumab govitecan (SG) vs chemotherapy (chemo) in participants (pts) with previously untreated advanced triple-negative breast cancer (TNBC) who are not candidates for PD-(L)1 inhibitors (PD-[L]1i). First Author: Carlos H. Barrios, Latin American Cooperative Oncology Group, LACOG, Porto Alegre, Brazil

Background: SG demonstrated significant and clinically meaningful progression-free survival (PFS) improvement vs chemo in pts with previously untreated, locally advanced unresectable or metastatic TNBC who were not candidates for PD-(L)1i in ASCENT-03 (NCT05382299). We report preplanned exploratory efficacy analyses in ASCENT-03 by Trop-2 expression, BRCA status, and HER2 expression. **Methods:** 588 pts randomized 1:1 to SG or chemo (taxane or gemcitabine + carboplatin). Trop-2 expression was measured by immunohistochemistry (IHC), tumor BRCA (tBRCA) status by whole exome sequencing, and HER2 expression by in situ hybridization (ISH) and IHC, all in centrally tested tumor samples (fresh or archival; 43% from metastatic sites). Pts were subgrouped by Trop-2 expression quartile, tBRCA wild-type (WT) or mutant (mut; mut in *BRCA1, BRCA2,* or both) status, and HER2 status (IHC 0 vs Low [IHC 1+ or IHC 2+/ISH-]). Biomarker status was analyzed to determine association with PFS by blinded independent central review (BICR). Other efficacy outcomes by biomarker status will be presented. **Results:** Median Trop-2 H-score: 240; H-scores by quartile (Q): Q1 0-184, Q2 185-239, Q3 240-283, Q4 284-300. Trop-2 expression was available in 499 pts. PFS by BICR was longer with SG vs chemo in all Trop-2 expression quartiles (Table). Hazard ratio (HR; 95% confidence interval [CI]) was 0.54 (0.35-0.84) in Q1, 0.62 (0.40-0.97) in Q2, 0.84 (0.54-1.31) in Q3, and 0.60 (0.38-0.95) in Q4. tBRCA status was available in 423 pts; proportion of pts with tBRCA mutations was comparable between treatment groups (~18%). PFS was longer with SG vs chemo in tBRCA WT and mut subgroups, with HR (95% CI) 0.70 (0.54-0.92) in tBRCA WT and 0.59 (0.32-1.09) in tBRCA mut. HER2 status was available in 551 pts; PFS was longer with SG vs chemo in both HER2 subgroups. HR was 0.63 (0.46-0.85) in the IHC 0 subgroup and 0.74 (0.55-1.01) in the HER2 Low subgroup. **Conclusions:** PFS was longer with SG vs chemo across all Trop-2 categories, tBRCA genotypes, and HER2 subgroups. These results reinforce the significant, clinically meaningful benefit of SG as first-line treatment for pts in this population across multiple biomarker subgroups. Clinical trial information: NCT05382299. Research Sponsor: Gilead Sciences, Inc.

Efficacy, BICR Biomarker	Subgroup	N SG	N Chemo	Median PFS (95% CI), months SG	Median PFS (95% CI), months Chemo	HR (95% CI)
Trop-2 (n = 499)	Q1	68	55	8.5 (5.6-12.7)	5.5 (4.2-8.1)	0.54 (0.35-0.84)
	Q2	60	62	8.3 (5.6-12.4)	6.8 (4.2-9.0)	0.62 (0.40-0.97)
	Q3	50	74	9.7 (7.6-11.3)	7.0 (5.3-8.5)	0.84 (0.54-1.31)
	Q4	74	56	9.9 (6.9-NR)	8.1 (4.4-8.5)	0.60 (0.38-0.95)
tBRCA (n = 423)	WT	177	169	8.8 (7.2-9.9)	6.9 (5.4-8.3)	0.70 (0.54-0.92)
	Mut	40	37	12.7 (7.2-18.7)	8.3 (5.6-11.2)	0.59 (0.32-1.09)
HER2 (n = 551)	IHC 0	115	138	8.3 (6.9-10.3)	5.6 (4.3-7.0)	0.63 (0.46-0.85)
	Low	159	139	9.8 (8.3-12.4)	8.3 (5.7-9.7)	0.74 (0.55-1.01)

1015 Rapid Oral Abstract Session

Impact of food access and poverty on somatic genomic profiles and clinical outcomes in metastatic breast cancer. First Author: Emily L. Podany, Washington University in St. Louis, St. Louis, MO

Background: Patients living in food deserts or experiencing food insecurity have higher cancer mortality rates. While neighborhood poverty correlates with more aggressive tumor biology, including higher OncotypeDX scores and rates of *TP53* mutations, the associations among food access, somatic genomic profiles, and clinical outcomes in metastatic breast cancer (MBC) remain understudied. **Methods:** This multi-institutional retrospective cohort study included patients with MBC and circulating tumor DNA (ctDNA) testing through the Guardant360 assay from Washington University in St. Louis (N = 651), Massachusetts General Hospital (N = 349), Weill Cornell Medicine (N = 187), and Northwestern University (N = 86). Patient census tracts were linked with the USDA Food Access Research Atlas, which provides data on census-level food access throughout the United States. Deidentified data were shared across sites. We categorized patients by: Food access: Low access (LA) if ≥33% of the census tract lived > 1 mile (urban) or > 10 miles (rural) from a food store Income and food access: Low-income and low access (LILA) if the census tract was both LA and poverty rate was ≥20% We assessed descriptive differences and determined associations between LA/LILA and ctDNA profiles using multivariate analysis adjusted for race, stage, and subtype. **Results:** Of the 851 patients with census tract data, 46.8% lived in LA and 8.0% lived in LILA areas. Although White patients were more likely to live farther from food stores than Black patients (48.9% vs 34.4%, p = 0.003), Black patients were significantly more likely to live in LILA areas (19.2% vs 6.1%, p = < 0.001). On multivariate analysis, patients in the overall cohort living in LA areas were more likely to have *RTK/RAS* pathway mutations (Odds ratio [OR] 2.05, 95% confidence interval [CI] 1.36-3.09, p = 0.001), confirmed in the hormone receptor positive, HER2 negative (HR+/HER2-) cohort (OR 2.18, 95% CI 1.34-3.55, p = 0.002). Patients in the overall cohort living in LILA areas were more likely to have *CCNE1* copy number variants [cnv] (OR 2.81, 95% CI 1.18-6.73, p = 0.02). Patients in LA areas had significantly shorter overall survival (OS) after first ctDNA test (24 months [mos] vs 31 mos, p = 0.01). In HR+/HER2- MBC, Black patients in LA areas had the shortest OS (11 mos) compared to those in high access areas (38 mos) and White patients in either setting (27-33 mos, p = 0.02). **Conclusions:** Patients with MBC living in food deserts appear to have distinct ctDNA profiles, including higher rates of *RTK/RAS* pathway mutations, which drive tumor growth, and *CCNE1* cnv, associated with poor prognosis. We also found a significant survival disadvantage associated with living in LA areas, particularly among Black patients. These findings demonstrate the necessity of considering the intersection of tumor biology and social determinants of health in understanding and treating MBC. Research Sponsor: None.

1016 Rapid Oral Abstract Session

Post-progression treatment (tx) analyses of evERA Breast Cancer (BC): A phase III trial of giredestrant (GIRE) + everolimus (E) in patients (pts) with estrogen receptor–positive, HER2-negative advanced BC (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor (i). First Author: Komal L. Jhaveri, Memorial Sloan-Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: evERA BC (NCT05306340) is the first Phase III trial to demonstrate a statistically significant and clinically meaningful improvement in investigator-assessed progression-free survival (INV-PFS) with an all-oral, selective ER degrader and full ER antagonist combination (GIRE + E) compared with standard-of-care endocrine therapy combinations (SOC ET + E) in pts with ER+, HER2– aBC post-CDK4/6i + ET (Mayer ESMO 2025). Improvement in INV-PFS was seen in all pts (hazard ratio [HR], 0.56) and in pts whose tumors had a detectable *ESR1* mutation (*ESR1*m; HR, 0.38), with no unexpected safety findings. We report exploratory post-progression tx analyses. **Methods:** Pts with ER+, HER2– aBC who had disease progression (PD) or relapse during/post-CDK4/6i + ET were randomized 1:1 to once-daily oral 30 mg GIRE + 10 mg E or SOC ET (exemestane/ fulvestrant/tamoxifen) + E until PD/unacceptable toxicity. Exploratory analyses included PFS2 (time from randomization to PD on next-line tx, or death), chemotherapy-free survival (CFS; time to first subsequent chemotherapy and/or antibody–drug conjugate [ADC], or death), and types of cancer tx following discontinuation from study tx. **Results:** Median PFS2 and CFS were longer with GIRE + E vs SOC ET + E in all pts (PFS2 HR, 0.69; CFS HR, 0.61), including in the *ESR1*m (PFS2, 0.61; CFS, 0.46) and *ESR1*m not detected populations (PFS2, 0.77; CFS, 0.80; Table). Of those receiving follow-up cancer therapy in all pts, and in the *ESR1*m and *ESR1*m not detected populations, 69.1%, 63.3%, and 73.8%, respectively, received chemotherapy in the GIRE + E arm vs 71.5%, 65.3%, and 79.0% in the SOC ET + E arm; 24.5%, 18.4%, and 29.5% received an ADC in the GIRE + E arm vs 31.4%, 25.3%, and 38.7% in the SOC ET + E arm. **Conclusions:** Delaying chemotherapy improves clinical and quality of life outcomes in ER+ aBC. These analyses further support the superior INV-PFS of GIRE + E over SOC ET + E observed in all pts and in the *ESR1*m population. Improvements in PFS2 and CFS, regardless of *ESR1*m status, suggest that the clinical benefit of GIRE + E is sustained beyond initial progression. Clinical trial information: NCT05306340. Research Sponsor: F. Hoffmann-La Roche Ltd.

	All pts GIRE + E (n = 183)	All pts SOC ET + E (n = 190)	*ESR1*m GIRE + E (n = 102)	*ESR1*m SOC ET + E (n = 105)	*ESR1*m not detected GIRE + E (n = 81)	*ESR1*m not detected SOC ET + E (n = 85)
PFS2						
Event, n (%)	81 (44.3)	108 (56.8)	39 (38.2)	57 (54.3)	42 (51.9)	51 (60.0)
Median, mo (95% CI)	19.0(15.5, not evaluable [NE])	13.2 (11.7, 15.9)	19.0 (15.5, NE)	12.9 (11.8, 17.6)	17.3(13.0, NE)	12.9 (9.8, 20.8)
Stratified HR (95% CI)	0.69 (0.51, 0.92)		0.61 (0.40, 0.93)		0.77 (0.51, 1.17)	
CFS						
Event, n (%)	111 (60.7)	146 (76.8)	51 (50.0)	78 (74.3)	60 (74.1)	68 (80.0)
Median, mo (95% CI)	11.1(9.6, 12.7)	7.9 (6.9, 9.5)	12.6 (10.9, 18.7)	8.5 (7.1, 10.0)	9.5 (7.4, 11.6)	7.2(6.1, 9.5)
Stratified HR (95% CI)	0.61 (0.47, 0.78)		0.46 (0.32, 0.66)		0.80 (0.57, 1.14)	

1017 Rapid Oral Abstract Session

Effectiveness of first-line ET+CDK4/6i continuation beyond disease progression in a large cohort of patients with HR+/HER2− advanced breast cancer: Results from the multicenter, real-world, Italian study PALMARES-2. First Author: Claudio Vernieri, Fondazione IRCCS Istituto Nazionale dei Tumori; IFOM ETS the AIRC Institute of Molecular Oncology; University of Milan, Milan, Italy

Background: Endocrine therapy (ET) plus Cyclin-Dependent Kinase 4/6 inhibitors (CDK4/6i) is the standard 1st line treatment for patients (pts) with Hormone Receptor-positive, Human Epidermal growth factor Receptor 2-negative, advanced Breast Cancer (HR+/HER2- aBC). ET+CDK4/6i continuation beyond progressive disease (PD) detection, plus/minus locoregional therapies, is often used in clinical practice for selected pts with oligoprogressive disease or minimal PD. However, the effectiveness of this approach has never been investigated in large studies. **Methods:** In this analysis of the multicenter, real-world study PALMARES-2 (NCT06805812), we evaluated clinical characteristics and outcomes in HR+/HER2- aBC pts who continued 1st line ET+CDK4/6i after detection of PD, as defined by physicians based on clinical-radiological assessment. The primary endpoint was real-world progression-free survival (rwPFS) beyond PD, defined as the time between the detection of the first PD event during 1st line ET+CDK4/6i and the occurrence of subsequent PD leading to definitive ET+CDK4/6i discontinuation, or patient death. We used multivariable Cox regression models to explore the association of 15 covariates with rwPFS beyond PD. We also assessed real-world overall survival (rwOS), as defined as the time between 1st line ET+CDK4/6i initiation and patient death. **Results:** Of 4,236 consecutive pts who initiated ET+CDK4/6i between January 2016 and September 2024 in 27 Italian Institutions, 2,434 pts experienced a PD event. Of these pts, 454 (18.7%) continued the same ET+CDK4/6i beyond PD and underwent radiotherapy (n = 306; 67%), surgery (n = 39; 9%), other locoregional treatments (n = 28; 6%) or no local therapies (n = 81; 18%). Pts continuing ET+CDK4/6i beyond PD were more likely to be younger and premenopausal, to have higher tumor estrogen receptor (ER) and/or progesterone receptor (PgR) expression, to have bone/lymph node metastases, and less likely to have liver metastases ($p < 0.05$ for all covariates). Median rwPFS beyond PD was 10.5 months (95% CI: 9.7-12). At multivariable analysis, higher tumor ER (p = 0.031)/PgR (p = 0.001) or lower Ki-67 ($p < 0.001$) expression, better ECOG Performance Status (p = 0.009) and the use of locoregional treatments ($p < 0.001$) were associated with longer rwPFS beyond PD. Pts continuing ET+CDK4/6i therapy beyond PD had better median rwOS than those discontinuing it after first PD detection (71.3 and 44.7 months, respectively; $p < 0.001$). **Conclusions:** This is the largest real-world study to show the effectiveness of 1st line ET+CDK4/6i continuation beyond PD in HR+/HER2- aBC pts. Our findings support the use of this well-tolerated and effective approach in selected pts, such as those with less biologically aggressive tumors and/or amenable to locoregional therapies. Clinical trial information: NCT06805812. Research Sponsor: Italina Ministry of Health; AIRC, the Italian Association of Cancer Research; Scientific Directorate of Fondazione IRCCS Istituto Nazionale dei Tumori.

LBA1018 Rapid Oral Abstract Session

Palbociclib plus tamoxifen ± goserelin in women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer (BC): PATHWAY, an Asian international double-blind randomized phase 3 trial—Final overall survival (OS) analysis. First Author: Yen-Shen Lu, National Taiwan University Hospital, Taipei, Taiwan

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

1019 Rapid Oral Abstract Session

Paclitaxel plus bevacizumab with or without atezolizumab for hormone receptor-positive/HER2-negative advanced breast cancer: JCOG1919E (AMBITION) phase III trial. First Author: Fumikata Hara, Aichi Cancer Center Hospital, Nagoya, Japan

Background: Hormone receptor-positive/HER2-negative (HR+/HER2-) advanced breast cancer (aBC) is immunologically "cold," with limited clinical benefit from immune checkpoint inhibitors. Since VEGF-mediated angiogenesis promotes an immunosuppressive tumor microenvironment, we hypothesize that inhibiting VEGF could reverse immunosuppressive state thereby augmenting response to immunotherapy. The JCOG1919E (AMBITION) phase III trial evaluates whether adding the anti-PD-L1 antibody: atezolizumab (ATZ) to paclitaxel (PTX) plus anti-VEGF antibody: bevacizumab (BEV) improves outcomes in patients (pts) with HR+/HER2- aBC. **Methods:** This multicenter, open-label, randomized phase III trial enrolled pts with HR+/HER2-aBC who had no prior chemotherapy for aBC and were endocrine-resistant or visceral crisis. Pts were randomized in a 1:1 ratio to PTX plus BEV (Arm A) or PTX plus BEV with ATZ (Arm B). Randomization was stratified by disease status (de novo stage IV vs. recurrent), liver metastasis (presence vs. absence), and PD-L1 expression (SP142 assay; negative [<1% on immune cells (ICs)] vs. positive [>=1%]). PTX was administered on days 1, 8, and 15 of a 28-day cycle, BEV on days 1 and 15, and ATZ on days 1 and 15 in Arm B. The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), PFS by blinded independent central review, and safety. Clinical trial information: NCT04732598. **Results:** From Sep 2021 to Sep 2023, 281 pts were randomized. At baseline, 33.1% were de novo stage IV, 68.0% had liver metastases, and 16.0% were PD-L1 positive. At a median follow-up of 30 months, median investigator-assessed PFS was 11.2 months in Arm A and 12.4 months in Arm B (hazard ratio [HR] 0.88; 95% CI, 0.67–1.15; p=0.17). Median OS was immature, but numerically longer in Arm B than in Arm A (39.1 vs. 31.2 months; HR 0.80, 95% CI, 0.58–1.11). The ORR was high and comparable between arms (71.9% vs. 73.0%). Grade ≥3 adverse events (AEs) were similar between arms. The most common immune related AEs (any grade) with ATZ were rash (17.3%), adrenal insufficiency (11.5%) and hypothyroidism (10.8%). No treatment-related deaths were observed, and no new safety signals emerged. **Conclusions:** PTX plus BEV with ATZ did not demonstrate a statistically significant improvement in PFS compared to PTX plus BEV as a frontline treatment for HR+/HER2- aBC, although a numerical extension in OS was observed. The safety profile of PTX plus BEV with ATZ was consistent with the known profiles. Clinical trial information: NCT04732598. Research Sponsor: None.

	ARM A PTX+BEV (n=140)	ARM B PTX+BEV+ATZ (n=141)
PFS events, n	117	109
Median PFS (95% CI), months	11.2 (9.6-13.5)	12.4 (10.3-15.2)
HR (95% CI)	0.876 (0.670-1.145)	
P-value	0.168	
OS events, n	81	71
Median OS (95% CI), months	31.2 (23.9-34.7)	39.1 (30.0-47.8)
HR (95% CI)	0.804 (0.584-1.108)	
ORR, %	71.9%	73.0%

1020 Rapid Oral Abstract Session

Impact of bevacizumab on the efficacy of antibody–drug conjugates as later-line treatment of basal-like immune-suppressed triple-negative breast cancer. First Author: Yin Liu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Basal-like immune-suppressed (BLIS) triple-negative breast cancer (TNBC) is associated with a poor prognosis; however, prior analyses from the FUTURE and FUTURE-SUPER clinical trials indicated clinical responsiveness to anti-angiogenic therapy. We conducted this study to evaluate the safety and efficacy of combining bevacizumab with antibody–drug conjugates (ADCs) in patients with the BLIS subtype. **Methods:** The FUTURE 2.0 study (NCT05749588) is an ongoing, open-label, multi-arm phase II platform trial evaluating novel molecularly targeted agents in patients with histologically confirmed TNBC who progressed after ≥1 line of systemic therapy for recurrent or metastatic disease. This report presents results from the BLIS arms: arm C (HER2-low) and arm D (HER2-zero). In arm C, patients received either SHR-A1811 (anti-HER2 ADC, 4.8 mg/kg IV q3w) alone (C1) or with bevacizumab (15 mg/kg IV q3w) (C2). In arm D, patients received either SHR-A1921 (Trop2-targeted ADC, 3.0 mg/kg IV q3w) alone (D1) or with bevacizumab (7.5 mg/kg IV q3w) (D2). The primary endpoint was confirmed objective response rate (ORR). Safety was assessed in all treated patients with available safety data. **Results:** From April 2022 to October 2025, 100 women were enrolled: 60 assigned to bevacizumab-combination arms (C2 and D2) and 40 to ADC monotherapy arms (C1 and D1). All 100 patients completed at least one post-baseline assessment. Confirmed ORR was 40.0% (8/20; 95% CI: 21.9–61.3%) in C1, 86.7% (26/30; 95% CI: 70.3–94.7%) in C2, 40.0% (8/20; 95% CI: 21.9–61.3%) in D1, and 83.3% (25/30; 95% CI: 66.4–92.7%) in D2. All four arms met the protocol-specified ORR success criterion with high posterior probability. Median PFS was 9.2 months in the combination group versus 4.6 months in the monotherapy group (HR = 0.47; 95% CI: 0.30–0.74), indicating a clinically meaningful improvement. Grade ≥3 treatment-related adverse events occurred in 27.5% (11/40) of monotherapy patients and 33.3% (20/60) of combination patients. No treatment-related deaths occurred. **Conclusions:** This study provides preliminary evidence of synergy between bevacizumab and ADCs, supporting a promising new strategy—especially for basal-like, immune-suppressed TNBC. Phase III trials are ongoing to confirm the efficacy and safety of this combination. Clinical trial information: NCT05749588. Research Sponsor: National Natural Science Foundation of China; 82403912.

The efficacy table.

	ADC monotherapy			ADC combined with bevacizumab		
	A1811 N=20	A1921 N=20	Total N=40	A1811+ Bev N=30	A1921+ Bev N=30	Total N=60
ORR, n (%, 95% CI)	8 (40.0) 21.9 – 61.3	8 (40.0) 21.9 – 61.3	16 (40.0) 26.4 – 55.4	26 (86.7) 70.3 – 94.7	25 (83.3) 66.4 – 92.7	51 (85.0) 73.9 – 91.0
mPFS (mo, 95% CI)	4.9 4.1 – 5.7	4.4 3.7 – 5.1	4.6 3.9 – 5.3	9.1 7.2 – 11.1	9.3 8.2 – 10.5	9.2 7.3 – 11.0
HR in PFS, 95% CI						0.47 0.30 – 0.74 (*P*=0.001)

1021 Rapid Oral Abstract Session

A DESTINY-Breast09 analysis of treatment duration and clinical outcomes by best response to trastuzumab deruxtecan (T-DXd) + pertuzumab (P). First Author: Yeon Hee Park, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: In DESTINY-Breast09 (NCT04784715), first-line (1L) T-DXd + P demonstrated durable responses, a near doubling of complete response (CR) rates, and significantly improved progression-free survival (PFS) vs taxane + trastuzumab + pertuzumab for patients (pts) with HER2+ advanced/metastatic breast cancer (a/mBC). Pts had a median treatment duration of 21.7 months (mo) with T-DXd + P. Safety was consistent with the known profiles of each treatment. These results led to US approval in Dec 2025. Here, we report an exploratory analysis of efficacy and safety outcomes by pts' best confirmed response to T-DXd + P. **Methods:** Pts had no prior systemic therapy for a/mBC (1 line of endocrine therapy was allowed). Endpoints included PFS and duration of response (DOR), both by blinded independent central review per RECIST 1.1, and safety. Best response subgroups included CR, partial response (PR), and stable disease / progressive disease (SD/PD). **Results:** Of 377 evaluable pts assigned to T-DXd + P, 58 (15.4%) had a CR, 268 (71.1%) had a PR, and 51 (13.5%) had SD/PD at interim data cutoff (Feb 26, 2025). Median time to PR was 1.5 mo (95% CI 1.4, 1.5), and median time to CR was 8.4 mo (95% CI 5.6, 11.1). Additionally, median time to achieve maximum tumor reduction (nadir) in the overall population (n=383) was ~11 mo (~16 cycles). Pts with a CR or PR had favorable PFS (see Table) and a longer median treatment duration (CR, 28.0 mo [range 4.8–44.5]; PR, 22.2 mo [range 2.8–42.7]) vs those with SD/PD (4.4 mo [range 0.3–37.2]). Exposure-adjusted incidence rates (EAIRs) of drug-related Grade ≥3 adverse events (AEs) were 0.30, 0.30, and 0.57 per pt-year, respectively. EAIRs of any AEs leading to discontinuation were 0.14, 0.11, and 0.16 per pt-year. Rates of adjudicated drug-related interstitial lung disease (ILD)/pneumonitis by CR, PR, or SD/PD were similar: 12.1% (n=7, all Grade 1/2), 11.9% (n=32, all Grade 1/2), and 12.2% (n=6, two Grade 5), respectively. Pts with a CR had a longer median time to first onset of ILD/pneumonitis (484 days [d] [range 84–967]) than those with a PR (227 d [17–1028]) or SD/PD (99 d [37–211]). **Conclusions:** In this exploratory analysis of DESTINY-Breast09, achieving a durable CR or PR was associated with favorable PFS outcomes and prolonged treatment duration. Complete response or maximum tumor reduction (nadir) was achieved with sustained T-DXd + P treatment. Safety findings were consistent with previously reported profiles of T-DXd and P. Clinical trial information: NCT04784715. Research Sponsor: AstraZeneca in collaboration with Daiichi Sankyo.

	CR (n=58)	PR (n=268)	SD/PD (n=51)
Median DOR, mo (95% CI)*	NC	39.2 (34.8, NC)	–
Median PFS, mo (95% CI)*	NC	40.7 (36.0, NC)	13.0 (4.0, 25.7)
6-mo PFS rate, % (95% CI)	100 (100, 100)	97.7 (95.0, 99.0)	57.2 (41.2, 70.4)
12-mo PFS rate, % (95% CI)	94.8 (84.8, 98.3)	89.8 (85.4, 92.9)	51.9 (35.9, 65.7)
24-mo PFS rate, % (95% CI)	85.1 (72.2, 92.3)	72.9 (66.6, 78.2)	35.5 (21.1, 50.2)

*Calculated by Kaplan-Meier technique. NC, not calculable.

1022 Poster Session

Identifying patients with human epidermal growth factor receptor 2 (HER2)–low and –ultralow breast cancer (BC): Use of digital, artificial intelligence (AI)–based computational algorithms to assist HER2 scoring by pathologists. First Author: Savitri Krishnamurthy, Department of Pathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Trastuzumab deruxtecan is approved in HER2-low (IHC 1+ or 2+/ISH negative) or -ultralow (IHC 0 with membrane staining in ≤10% of tumor cells) metastatic BC per DESTINY-Breast04 and -06 trials. Manual HER2 IHC scoring can be time-consuming and subjective. This retrospective, real-world study assessed manual scoring (ground truth) vs standalone AI-computational pathology-assisted (CPa) tools for scoring. **Methods:** Whole slide images (WSIs; N = 600, scanned with Aperio AT2) of BC samples stained with PATHWAY HER2 (4B5) assay, originally scored as HER2 IHC 0 (n = 400) or 1+ (n = 200), were rescored by 3 pathologists and using 4 CPa/AI tools in development as either IHC 0 absent membrane staining, 0 with membrane staining in ≤10% of cells, 1+, or 2+. Using 2023 ASCO/CAP guidelines, each pathologist performed 2 blinded readings per WSI; a reconciled score was used if the 2 readings differed. Manual consensus required ≥2/3 agreement. Concordance between pathologist manual consensus vs standalone CPa scoring was measured by positive and negative percentage agreement (PPA; NPA), overall percentage agreement (OPA), and Cohen κ, with review time recorded. **Results:** Of 600 WSIs, 586 (97.7%) had manual consensus. CPa tools were faster (Table) than manual scoring (manual median review time: 7.0 min; range, 3.0-11.5). PPA was high (≥92.5%) between manual consensus scoring and CPa tools; NPA across the tools was 79.1%, 68.9%, 67.4%, and 23.1%. Overall concordance varied across CPa tools; OPA ranged from 48.5% to 75.4% and Cohen κ from 0.26 to 0.61. **Conclusions:** Integrating CPa/AI tools as decision support aids for pathologists may reduce pathologist review time and augment pathologist inter-observer reproducibility, especially in HER2-ultralow identification. Refinement of CPa/AI algorithms in development may improve scoring to an even greater extent. Research Sponsor: This study was sponsored and led by AstraZeneca.

DP tool (N = 586[a])	Review time, median (range), min	PPA,[b,c] % (95% CI)	NPA,[b,d] % (95% CI)	OPA,[b,e] % (95% CI)	Cohen κ[e] (95% CI)
RV73X	2.7 (0.3-56.8)	94.9 (92.5-96.7)	79.1 (70.6-85.7)	75.4 (71.7-78.9)	0.61 (0.56-0.66)
MQ52G	0.7 (0.1-8.5)	93.4 (90.9-95.4)	68.9 (60.5-76.2)	73.0 (69.3-76.6)	0.57 (0.52-0.63)
KL84Q	3.1 (0.5-84.4)	92.5 (89.8-94.6)	67.4 (59.1-74.8)	69.5 (65.6-73.2)	0.54 (0.48-0.59)
ZX19P	2.5[f] (Not available)	99.1 (97.6-99.6)	23.1 (16.4-31.5)	48.5 (44.4-52.6)	0.26 (0.22-0.31)

[a]Primary and metastatic samples from biopsies, effusions, fine needle aspirations, and surgical resection; due to the inbuilt pre-QC module, a few WSI outputs were not processed by RV73X and ZX19P.
[b]Rounded to 1 decimal.
[c]Agreement for consensus-positive cases (IHC 0 with membrane staining, 1+, or 2+).
[d]Agreement for consensus-negative cases (IHC 0 absent membrane staining).
[e]Agreement across all IHC scores.
[f]Mean review time; median not available.

1023 Poster Session

Biology-informed predictive modeling and resistance monitoring in trastuzumab deruxtecan–treated metastatic breast cancer. First Author: Josh Wheeler, Genialis, Inc., Boston, MA

Background: The antibody-drug conjugate (ADC), trastuzumab deruxtecan (T-DXd), produces meaningful responses in metastatic breast cancer (mBC), yet current biomarkers inadequately identify likely responders or elucidate resistance mechanisms. We developed a biology-informed survival model to predict T-DXd benefit in real-world data, assess treatment specificity, and characterize resistance evolution at time of progression. **Methods:** We analyzed RNA-seq and clinical outcomes from 150 de-identified T-DXd–treated mBC patients in the Tempus real-world multimodal database. Baseline expression profiles were embedded into biology-structured biomodules using a large molecular foundation model trained on over 1-million transcriptomes, capturing processes relevant to ADC activity: DNA damage response (DDR), intracellular trafficking, cellular stress adaptation, and tumor microenvironment signaling. These biomodules informed a survival model trained to predict T-DXd–specific clinical benefit. Predictive specificity was evaluated in a matched cohort of T-DXd–eligible mBC patients treated with taxane-based chemotherapy and HER2-targeting therapy. Longitudinal tumor profiling from 15 patients with progressive disease were analyzed to monitor resistance evolution. **Results:** The survival model predicted and identified biologically distinct benefit groups within the T-DXd cohort, with minimal separation observed in a control standard-of-care cohort, confirming treatment-specific predictive value (HR 2.22 [95% CI 1.14–4.35], p = 0.017). Predicted-benefit patients had longer rwTTNT (median=345 vs 245 days), and no prognostic signal appeared in control cohorts (C-index = 0.51), suggesting predictive specificity. Longitudinal analysis of progressed patients revealed reproducible biological shifts at progression, including attenuation of programs associated with effective ADC engagement and upregulation of adaptive stress-response pathways. These molecular transitions correlated with clinical deterioration and earlier transition to subsequent therapy. **Conclusions:** This study delineates the biology associated with durable T-DXd benefit and captures resistance evolution at progression in real-world patients. These findings highlight opportunities to refine patient selection and identify therapeutically actionable biology driving acquired resistance to T-DXd in the mBC setting. Research Sponsor: None.

1024 Poster Session

Organ- and histology-specific molecular and immune landscape of metastatic breast cancer. First Author: Guilherme Nader Marta, Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Invasive lobular carcinoma (ILC) is a distinct breast cancer (BC) subtype with dissemination patterns differing from invasive breast carcinoma of no special type (IBC-NST). While genomic differences between ILC and IBC-NST have been described, the extent to which molecular and immune profiles vary by metastatic organ and histology is poorly characterized. **Methods:** We conducted a retrospective analysis to evaluate organ- and histology-specific molecular features of metastatic BC (mBC). Patients with metastatic IBC-NST or pure ILC underwent NGS (592, NextSeq; WES/WTS, NovaSeq; Caris Life Sciences). Tumor mutational burden (high ≥10 mut/Mb), PD-L1 expression (22C3), and immune cell fractions (RNAseq deconvolution, quanTIseq) were assessed. Analyses were restricted to sites with ≥10 biopsies per histology. Comparisons used chi-square or Mann–Whitney U tests with multiple testing correction ($q < 0.05$). **Results:** A total of 2645 mBC biopsies (605 ILC; 2040 IBC-NST) were analyzed (Table). In ILC, *ERBB2* mut frequency differed by metastatic site ($q<0.01$), with higher prevalence in liver (32.7%) and lower in gastrointestinal (GI) lesions (3.7%). In IBC-NST, *ESR1* and *GATA3* mut and *FGFR1* amplification were enriched in liver metastases, whereas PD-L1 expression was highest in skin (20.7%) and lowest in liver (5.0%). No organ-specific differences were observed for *PIK3CA, AKT, PTEN, BRCA1/2* or *RB1*. Across metastatic sites, both ILC and IBC-NST showed differences in B cells, macrophages (M1/M2), neutrophils, NK cells, dendritic cells, CD8+ T cells, and Tregs (all $q < 0.05$); CD4+ T-cell differences were observed only in IBC-NST (q = 0.002). In organ-specific ILC vs IBC-NST comparisons, *CDH1* mut were more frequent in ILC across sites, along with higher *PIK3CA* mut in skin (ILC 51.3% vs IBC-NST 34.4%) and higher *ERBB2* mut in liver (32.7% vs 3.3%), whereas a higher *TP53* mut frequency was observed in IBC-NST in skin (28.5% vs 52.3%) and lymph nodes (LND) (23.5% vs 55.5%) (all $q < 0.01$). **Conclusions:** mBC exhibits marked organ-specific molecular and immune heterogeneity that differs by histology. These findings support histology- and site-aware interpretation of metastatic biopsies and may inform biomarker assessment and treatment decisions in advanced disease. Research Sponsor: None.

	BC-NST Skin	LND	Bone	Breast	Liver	Perit.	CNS	q-value	ILC Skin	LND	Bone	Breast	GI	Liver	GYN	Perit.	CNS	q-value
N (specimens)	785	401	109	361	220	15	44	-	172	84	62	56	56	54	43	37	11	-
***ERBB2* mut (%)**	3.2	3.1	3.2	2.3	3.3	7.1	2.5	1.0	7.1	7.4	16.4	15.4	3.7	32.7	2.4	5.7	11.1	<0.01
***ESR1* mut (%)**	9.4	5.2	8.3	16.0	28.2	7.1	2.4	0.0	7.8	7.2	8.9	9.8	16.7	26.0	4.9	20.0	0.0	0.9
***FGFR1* amp (%)**	10.1	6.6	5.6	12.8	16.5	0.0	9.7	0.02	4.4	3.4	6.7	6.1	2.4	5.6	7.7	18.5	0.0	1.0
IHC-PD-L1 (%)	20.7	-	5.3	16.0	5.0	11.1	10.3	0.02	8.9	-	5.0	5.7	6.1	0.0	0.0	0.0	14.3	1.0
TMB-High (%)	10.7	10.1	8.8	8.8	8.5	14.3	21.4	0.8	27.6	11.0	19.6	28.0	11.3	19.6	9.8	32.4	22.2	0.8

Perit: peritoneum; CNS: central nervous system; GYN: genital tract.

1025 **Poster Session**

Using ML to predict rapid progression for patients (pts) with HR+/HER2- metastatic breast cancer (mBC) treated with frontline (1L) CDK 4/6 inhibitors (CDK 4/6i). First Author: Michael Peng, Gilead Sciences, Morris Plains, NJ

Background: CDK4/6i ± aromatase inhibitors is a preferred tx for pts with HR+/HER2- mBC in the 1L setting. While a subset of pts experience rapid progression on standard tx, addressing the unmet need remains challenging due to difficult pt identification. While multimodal data have predicted fast progressors in prior work, routinely collected electronic health record (EHR) variables may be more practical for clinical trial design and enrichment use cases. Thus, we performed a feasibility assessment to determine if EHR data can adequately predict fast progressors. **Methods:** Models were trained on pts in the Flatiron Health Research Database with 1L CDK4/6i start on February 3, 2015, or later and an event ≤12 months (mos) or follow-up ≥12 mos after tx start. Fast progression was defined as real-world progression or death ≤12 mos after tx start. Baseline demographics, clinical characteristics, and laboratory/vital signs were used to train a logistic regression (LR) and a full-feature XGBoost (XGB) model. A feature-reduced XGB model was also developed by sequentially removing least important features until area under the curve (AUC) declined. Hyperparameters were optimized by grid search. Performance was evaluated via AUC, with feature importance assessed via LR coefficients and SHapley Additive exPlanations. Test-set analyses included rwPFS comparisons between predicted fast progressor (pFPs) and predicted non-fast progressors (pNFPs) using Kaplan-Meier methods. **Results:** Among 10,811 included pts, 3,782 were identified as fast progressors, split 80/20 for train/test datasets. The 3 models had comparable performance for predicting fast progression and effectively stratified pts into risk groups (Table). LR and XGB models used 48 and 76 features, respectively, while a feature-selected XGB model retained 30 features with minimal performance loss. Top LR predictors included advanced age, BRCA/ESR1/AKT positivity, and de novo stage IV disease. Important XGB features were consistent across models and emphasized continuous measures, including shorter time to metastatic diagnosis, greater metastatic burden, elevated AST and alkaline phosphatase, and bone-only metastases. **Conclusions:** While these models are not optimized as point-of-care clinical risk scores, their ability to identify high- and low-risk groups using scalable, routinely captured variables highlights their potential utility for clinical trial design, enrichment strategies, and cohort stratification. These findings establish a real-world benchmark and support the feasibility of practical, EHR-only approaches to rapid progression prediction. Research Sponsor: None.

Model	AUC	pFP rwPFS, median (95% CI), mos	pNFP rwPFS, median (95% CI) mos
LR	0.67	10.8 (9.8–12.4)	25.6 (23.3–27.9)
XGB	0.67	10.8 (9.8–12.4)	25.4 (22.9–27.3)
XGB (feature selected)	0.66	11.3 (10.2–13.2)	25.6 (23.0–27.9)

1026 **Poster Session**

Development and evaluation of a novel digital pathology image analysis pipeline for prediction of clinical outcomes with the TROP2-directed antibody-drug conjugate (ADC) sacituzumab tirumotecan (sac-TMT) in triple-negative breast cancer (TNBC). First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Digital pathology (DP), including artificial intelligence (AI)-based image analysis methods, enables IHC biomarker assessment on a continuous scale, potentially improving precision and accuracy versus conventional IHC scoring. DP may also capture features relevant to ADC response that traditional methods miss. As proof of concept, we developed and evaluated an AI-assisted DP image analysis pipeline to explore the association between target antigen expression and clinical outcomes of sac-TMT, a TROP2-directed ADC with a unique bifunctional linker, in TNBC. **Methods:** We analyzed whole-slide images of IHC-stained tumor samples from participants with TNBC enrolled in the phase 1/2 MK-2870-001 study (NCT04152499) evaluating sac-TMT in pretreated advanced solid tumors. We established a set of prespecified human-interpretable features (HIFs), including IHC signal intensity, subcellular localization, and spatial patterns of cell and signal distribution. To mitigate overfitting, we prioritized a subset of 35 HIFs based on correlation structure and biological hypotheses, and in a blinded fashion, assessed their association with clinical outcomes (BOR; PFS) in a development cohort (DC) (n = 58). After unblinding clinical outcome data, additional HIFs and a multivariate model trained to predict clinical outcomes in the DC were prioritized for validation. Both sets of HIFs (identified from blinded and unblinded analyses) were assessed for their relationship to clinical outcomes in an independent validation cohort (IVC) from the same study (n = 34). In both cohorts, DP HIFs were compared with conventional TROP2 H-scores (on paired slides) for prediction of clinical outcome using the area under the receiver operating characteristic curve (AUROC) and Harrell C-index. **Results:** The blinded approach identified a HIF that was positively associated with BOR (multiplicity-adjusted $P = 0.023$), with an AUROC higher than TROP2 H-scores (0.76 vs 0.70). After unblinding, 5 additional HIFs and a multivariate model were selected for their associations with BOR (AUROC, 0.70-0.80). In the IVC, the 6 prioritized HIFs and 1 multivariate model were associated with response to sac-TMT (AUROC, 0.60-0.69); each outperformed TROP2 H-scores with respect to association with BOR (H-score AUROC, 0.57) and demonstrated incrementally better association with PFS than TROP2 H-scores (Harrell C-index, 0.64-0.66 vs 0.62). **Conclusions:** In this proof-of-concept study, DP-derived HIFs were associated with response to sac-TMT in TNBC and showed incrementally better nominal performance than conventional TROP2 H-scores. While the sample size was small, data from this study suggest that DP-based image analysis can identify novel biomarkers of response to sac-TMT in TNBC. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

1027 **Poster Session**

Antibody-drug conjugate (ADC) after ADC: Predicting survival in patients with HER2-low metastatic breast cancer with lung metastasis using artificial intelligence (AI) and radiomics. First Author: Rishi Dakarapu, Emory University School of Medicine, Atlanta, GA

Background: With the approval of multiple antibody drug conjugates (ADCs) for HER2-low metastatic breast cancer (MBC), defining which patients (pts) will benefit from an ADC after ADC approach is essential. No reliable biomarker exists to predict overall survival (OS) in the ADC after ADC setting. This study investigates whether AI informed radiomic texture features derived from CT scans prior to ADC therapy in pts with lung metastases who received both trastruzumab deruxtecan (T-DXd) and sacituzmab govitecan (SG) are associated with OS in HER2-low MBC. **Methods:** A single-institution retrospective study was conducted including pts with HER2-low MBC treated with both T-DXd and SG at Winship Cancer Institute of Emory University between 2020 and 2024. Among 44 pts reviewed (median age, 55 years), 21 pts with evaluable lung lesions were included. Radiomic texture features characterizing tumor heterogeneity were extracted from baseline pre-treatment CT scans of lung metastases before ADC initiation. A least absolute shrinkage and selection operator Cox regression model was applied within a 50-fold cross-validation framework to identify prognostic features associated with OS. OS was defined as the interval from initiation of first ADC therapy to death from any cause and was censored at the date of last follow-up for patients who were alive. A radiomic risk score (RRS) was calculated as a linear combination of the selected features weighted by their corresponding coefficients. Pts were stratified into high- and low-risk groups based on the median RRS. Cox proportional hazards regression was used to evaluate associations with OS. **Results:** Among the total 44 pts, the median duration of response was 6.1 months for the first ADC and 2.7 months for the subsequent ADC. 59.1% received SG as ADC1. For the 21 pts with lung metastasis, mOS was 20.8 months (95% CI: 14.33–30.8). In univariable analysis, the RRS was significantly associated with OS (HR = 2.5, 95% CI: 1.3–4.8; P = 0.006). In multivariable analysis adjusting for clinicopathologic factors including race, ER status, number of prior lines of therapy before ADC treatment, and relapsed vs de novo metastatic disease, RRS remained the only variable independently associated with OS (HR = 2.6, 95% CI: 1.2–5.5; P = 0.01). **Conclusions:** These preliminary findings suggest that CT-derived radiomic features may serve as a non-invasive biomarker to identify pts at higher risk of poor OS in the ADC after ADC setting for HER2-low MBC, for whom we need better, novel therapeutics after resistance develops to initial ADC therapy. This radiomics approach has the potential to inform treatment sequencing and risk stratification. Future work will include prospective validation in a larger cohort which includes other sites of metastatic disease. Research Sponsor: None.

1028 **Poster Session**

Cross-modality AI modeling of histopathology images to stratify outcomes among patients treated with hormonal or chemo-hormonal therapy in ER+/HER2− breast cancer. First Author: Hassan Muhammad, PATHOMIQ, Inc., Cupertino, CA

Background: Oncotype DX (ODX) is widely used to guide adjuvant treatment decisions in early-stage ER+/HER2− breast cancer. However, ODX provides limited stratification of residual metastatic risk within patients receiving hormonal therapy (HT) alone or hormonal therapy following chemotherapy (HT+CT). We developed a cross-modality AI approach that derives risk scores directly from routine H&E-stained whole-slide images (WSIs) to stratify metastatic outcomes among patients receiving standard adjuvant therapies. **Methods:** Using a cross-modality transfer learning framework, we first developed genomic biomarkers by mapping RNA-seq data to distant metastatic outcomes by integrating thousands of genes and signaling pathway activities in the publicly available ScanB dataset. Deep learning models were then trained to infer these biomarkers directly from WSI of breast tumors using the TCGA dataset. External validation was performed in an independent cohort of 287 early-stage ER+/HER2−, node-negative patients from MD Anderson Cancer Center. Among these, 147 patients with ODX<25 received HT alone, while 140 patients with ODX>25 were included, 121 of whom received HT+CT. Kaplan–Meier survival analysis, log-rank tests, and Cox proportional hazards models were used to evaluate outcome stratification within each treatment group. **Results:** Among patients treated with HT alone, AI score stratified metastatic outcomes (HR=2.75; $p < 0.01$), identifying patients who developed distant recurrence despite low ODX scores. Among patients treated with HT+CT, AI score also stratified outcomes (HR=3.94; $p < 0.03$), identifying patients who experienced metastasis despite combination therapy. Across treatment groups, AI score provided prognostic information beyond ODX and clinicopathologic variables. In multivariable analyses adjusting for ODX and clinical covariates, AI score remained independently associated with metastatic risk and demonstrated consistent stratification across clinically relevant subgroups. Validation of these findings in an expanded cohort is ongoing. **Conclusions:** This AI-based approach further stratifies outcomes among patients receiving HT or HT+CT as guided by ODX, directly from routine histopathology images in early-stage ER+/HER2− breast cancer. Thus, integration of AI-derived outcome stratification with ODX scores may improve individualized treatment decision-making and support consideration of alternative therapies. Research Sponsor: PATHOMIQ.

1029 **Poster Session**

Integrating artificial intelligence to evaluate outcomes and disparities in young-onset breast cancer: A SEER-based retrospective cohort study. First Author: Jahnavi Ethakota, Henry Ford Allegiance Health System, Jackson, MI

Background: Young-onset breast cancer (YOBC), defined as breast cancer diagnosed in women <40 years, is associated with aggressive tumor biology and affects patients differently depending on race, ethnicity, and socioeconomic status (SES). Traditional risk models may insufficiently predict disease severity and survival in this population. Artificial intelligence (AI) can integrate multidimensional clinical and demographic data to improve outcome prediction and identify high-risk subgroups. We evaluated AI-based prediction of advanced-stage disease and 5-year survival in a large U.S. cohort over two decades. **Methods:** We conducted a retrospective study using the SEER database, identifying women aged <40 years diagnosed with invasive breast cancer from 2000–2021. Variables included age, race, ethnicity, marital status, tumor stage, grade, receptor status, treatment, and county-level SES. A machine learning model was trained to predict advanced-stage disease (stage III–IV) and 5-year overall survival. Model performance was compared with multivariable logistic regression using area under the receiver operating characteristic curve (AUC). We also explored differences by race, ethnicity, and SES to understand disparities. **Results:** Our cohort included 97,462 women–38.9 percent non-Hispanic White, 26.7 percent non-Hispanic Black, 22.3 percent Hispanic, 11.1 percent Asian/Pacific Islander, and 1 percent American Indian/Alaska Native. Overall, 33 percent presented with advanced-stage disease, with higher rates among non-Hispanic Black (42 percent) and Hispanic (37 percent) patients compared with non-Hispanic White patients (26 percent, $p<0.001$). Women living in the lowest SES areas were 30 percent more likely to have advanced-stage disease than those in the highest SES areas. The AI model predicted advanced-stage disease (AUC 0.81) and 5-year survival (AUC 0.84) better than traditional regression (AUC 0.67 and 0.71, respectively). Importantly, 23 percent of high-risk patients identified by AI would have been missed by conventional criteria. Survival disparities persisted: 5-year survival was 77 percent for non-Hispanic Black women versus 89 percent for non-Hispanic White women, and 75 percent for women in the lowest SES areas versus 91 percent in the highest. The AI model's predictions were consistent across all subgroups. **Conclusions:** As per the study AI-based models improved prediction of advanced-stage disease and survival while highlighting persistent racial, ethnic and socioeconomic disparities. These findings suggest AI-driven risk assessment can help identify high-risk young women and support equity-focused interventions to improve outcomes in YOBC. Research Sponsor: None.

1030 **Poster Session**

Association between HER family expression and clinical outcomes with trastuzumab deruxtecan (T-DXd) in patients with hormone receptor–positive/HER2-negative (HR+/HER2-) metastatic breast cancer (mBC). First Author: Shivani K. Thaker, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: T-DXd improves outcomes in HR+/HER2- mBC, yet response remains heterogeneous. Treatment selection is based on HER2 IHC. Preclinical models suggest signaling from HER family dimerization partners like EGFR drive resistance; specifically, *EGFR* overexpression impairs T-DXd internalization by favoring EGFR/HER2 heterodimerization. Because clinical data linking HER dimerization partners to T-DXd outcomes are limited, investigation is warranted to understand how expression of these partners may serve as predictive biomarkers. **Methods:** The Tempus Lens Platform was used to identify and analyze a cohort of patients (pts) with HR+/HER2- mBC treated with T-DXd (n = 224) and sacituzumab govitecan (SG) (n = 81, comparator) who underwent RNA (Tempus xR) and DNA (Tempus xT) sequencing within one year of treatment initiation. HER family gene expression (*EGFR/ERBB1, ERBB2/3/4*) was quantified as transcripts per million (TPM) and reported as log2(TPM+1). High vs low groups were defined using median expression. Median real-world time to next treatment (rwTTNT) with T-DXd and real-world overall survival (rwOS) were calculated using Kaplan–Meier curves and compared using log-rank tests. Hazard ratios (HR) were calculated using Cox proportional hazards models. **Results:** The cohort (n = 305) had a median age of 60; 83% of pts' race was reported as White, 9.6% Black or African American, 2.7% Asian, 7.6% Hispanic or Latino, and 4.3% unknown. Median HER family gene expression values were: *ERBB1* (*EGFR*): 3.92; *ERBB2* 7.75; *ERBB3* 7.65; *ERBB4* 4.72. *EGFR* RNA expression was negatively correlated with *ERBB2/3/4* ($p < 0.0001$). *ERBB2/3/4* RNA expression was positively correlated with one another ($p < 0.0001$). Among pts treated with T-DXd, the *EGFR*-high group had shorter median rwTTNT (7.76 vs 13.25 months; HR = 2.17 95% CI 1.42-3.34, $p < 0.001$) and rwOS (13.71 vs 22.55 months, HR = 2.21; 95% CI 1.50-3.24, $p < 0.001$) compared to the *EGFR*-low group. In contrast, increased RNA expression of other HER family members was not associated with a significant difference in rwTTNT or rwOS. Among pts treated with SG, the *EGFR*-high group did not have significantly different rwTTNT (median 4.34 vs 5.56 months; HR = 1.30 95% CI 0.72-2.36, p = 0.4) or rwOS (median 14.47 vs 11.28 months; HR = 0.86, 95% CI 0.47-1.55, p = 0.6) compared with the *EGFR*-low group. **Conclusions:** Among pts with HR+/HER2- mBC treated with T-DXd, elevated *EGFR*, but not *ERBB2/3/4*, RNA expression was associated with worse outcomes. *EGFR* overexpression did not modulate outcomes in pts treated with SG, highlighting a potential differential impact based on antibody target rather than payload. Further research is needed to confirm the utility of pre-treatment *EGFR* expression as a predictive biomarker for T-DXd treatment. Research Sponsor: None.

1031 **Poster Session**

Concordance between circulating tumor DNA and tissue biopsy in patients with newly diagnosed recurrent breast cancer. First Author: Ana Elisa Lohmann, University of Western Ontario, London, ON, Canada

Background: Accurate determination of tumor origin and molecular subtype are recommended for patients with suspected recurrent breast cancer (BC). Circulating tumor DNA (ctDNA) provides a non-invasive alternative to tissue biopsy that offers identification of molecular tumor type (MTT) and molecular breast cancer subtype (MBS). This study aimed to assess the concordance between ctDNA and tissue biopsy in participants with suspected distant BC recurrence. **Methods:** This cross-sectional study evaluated patients with a previous history of primary BC who presented with suspected distant BC recurrence at least six months after initial BC diagnosis and underwent both tissue and liquid biopsy at enrollment. Blood samples were collected within 30 days before, or within 7-28 days after tissue biopsy and before any systemic or radiation treatment. Objectives were to assess concordance between tissue biopsy of the suspicious distant recurrent sites and liquid biopsy MTT and MBS (hormone receptor (HR)+/HER2−, HER2+ and triple negative BC (TNBC)). Patient blood samples were analyzed using the Guardant360 Liquid assay, reporting methylation-based prediction of MTT and MBS for samples predicted to be of BC origin. **Results:** A total of 120 patients (119 female, 1 male, median age 66 years) underwent biopsy a median 6.5 years after primary BC diagnosis. ctDNA was detected in 88% (105/120) subjects. Of these, 92% (97/105) yielded an evaluable MTT result with a high confidence score, with results as follows: Agreement between tissue pathology and ctDNA MTT was observed in 95 of 96 cases with diagnostic tissue pathology, including 99% agreement for breast cancer (88/89), and 100% agreement in lung adenocarcinoma (4/4), gynecological/ovarian (1/1), liver (1/1) and biliary (1/1). The non-diagnostic tissue biopsy was treated as BC by the oncologist. Among the 89 cases predicted BC by ctDNA, 88% (78/89) were evaluable for MBS while 2 did not have pathologic subtype available. In these 76 patients, positive predictive value for MBS predictions of HR+/HER2−, HER2+ and TNBC were 47/55 (85%), 6/11 (55%) and 8/10 (80%), respectively. Pathological tissue subtype of discordant HR+/HER2− cases were HER2+ (n = 7), TNBC (n = 1); of HER2+ cases were HR+/HER2− (n = 2), TNBC (n = 3) and of TNBC were HR+/HER2− (n = 2). **Conclusions:** Liquid biopsy demonstrated high agreement with tissue pathology for MTT classification, including identification of non-breast primary tumors. Differences in MBS classification between the two modalities warrant further investigation to assess potential contributing factors, including tumor heterogeneity. Research Sponsor: London Health Sciences Foundation; Academic Medical Organization of Southwestern Ontario (AMOSO); Medical Oncology Research Fund - London Health Sciences Centre; London Health Sciences Centre; Lawson Health Research Institute - Internal Research fund; Breast Cancer Canada; Epic Sciences (In kind); Guardant Health (In kind).

1032 **Poster Session**

***TP53* status and licensing complex/IFNγ transcriptional profiles to stratify endocrine-related outcomes with CDK4/6i exposure in 10,833 real-world ER+/HER2- breast cancers and a treatment-naïve subset.** First Author: Alekya Raghavan, Baylor College of Medicine, Houston, TX

Background: Endocrine therapy (ET) durability for ER+/HER2- breast cancer (BC) with CDK4/6 inhibitor (CDK4/6i) exposure is vastly heterogeneous. Aberrant activation of CDK4/6-Rb axis is mechanistically linked to DNA replication origin licensing programs, and IFNγ-mediated signaling has been observed at onset of CDK4/6i resistance (PMID 33536276). We previously reported licensing complex (LC) mRNA to be predictive of ET benefit in primary ER+/HER2- BC (SABCS24-P1-03-20). Here we assessed these findings in a large, real-world cohort of primary and metastatic ET±CDK4/6i-treated tumors. **Methods:** ER+/HER2- BC biopsies (N=10833 all-comers and a treatment-naïve subset of N=1960) with DNA- and RNA-seq profiling from Caris Life Sciences were reviewed. LC score was calculated as a mean z-score across 14 LC genes; IFNγ score of PMID 28650338 was used. Groupings of Q1 (low) and Q4 (high) LC and IFNγ score quartiles were compared (i.e., Q1/Q1, Q4/Q4, Q1/Q4, Q4/Q1). Endpoints inferred from claims data were time on 1st ET (To1) and cumulative time on ET (start of 1st ET to end of last ET; ToT). Logrank p-values and HRs were derived from Cox proportional hazard models. Immune microenvironment (TME) proportions were estimated via quanTIseq deconvolution. Corrected q-values were calculated for quanTIseq and genomic analyses. **Results:** For all-comers, LC score Q4 vs Q1 predicted shorter ToT for ET with or without CDK4/6i exposure (HR 1.27 [$p<0.0001$]; 1.13 [$p=0.0019$]). LC-Q1~IFNγ-Q1 tumors demonstrated longer ToT (ET HR 1.76 [$p=0.0015$]; ET+CDK4/6i HR 1.32 [$p=0.022$]) relative to Q4/Q4 when *TP53* was not mutated (^{mut}). In the treatment-naïve subset, the distribution of LC and IFNγ scores, PAM50 luminal subtype, and *TP53*^{mut} appeared similar to all-comers. IFNγ-Q4 vs Q1 predicted shorter To1 with CDK4/6i exposure (14.4 vs 19.9 months, HR 1.28 [$p=0.0074$]). LC/IFNγ profiles significantly stratified both To1 and ToT only with CDK4/6i exposure. Relative to Q1/Q1, all other quartile groups had shorter To1 (HR 1.53 [$p=0.071$], 1.88*, and 2.15* [*$p<0.01$]) and shorter ToT (HR 1.89, 2.33, and 1.98; all $p<0.05$). Relative to Q1/Q1, the Q4/Q4 cohort was enriched for *TP53*^{mut} (44.2% vs 12.5% [$q=0.002$]). In *TP53*^{WT} tumors, Q4~Q4 trended toward shorter ToT than Q1~Q1 (42.7 vs 26.5 months, HR 1.67 [$p=0.075$]). Finally, LC-Q4/IFNγ-Q4 vs Q1/Q1 tumors exhibited a more inflamed TME with higher M2 macrophages, myeloid DCs, and Tregs (all $q\leq0.01$). **Conclusions:** Real-world validation confirms the LC and IFNγ-stimulated transcriptional state jointly stratify outcomes in the CDK4/6i-treated setting, predicting shorter time on ET. Though enriched for *TP53*^{mut}, convergence of LC/IFNγ may hold potential predictive value in *TP53*^{WT} disease. The LC-Q1/IFNγ-Q1 CDK4/6i response predictor in the *TP53*^{WT} setting remains to be validated prospectively. Research Sponsor: None.

1033 Poster Session

Rapid digital patient-derived organoid testing for guiding therapy in patients with metastatic breast cancer receiving antibody drug conjugates (ADCs). First Author: Yuan Yuan, Cedars-Sinai Medical Center, Los Angeles, CA

Background: MBC remains incurable despite recent incorporation of ADCs. The optimal sequencing of FDA-approved ADCs such as trastuzumab deruxtecan (T-DXd) or sacituzumab govitecan (SG) are lacking and real-world data have shown cross resistance between the ADCs. The current study aims to develop a clinical diagnostic assay to guide optimal treatment for patients with MBC using digital patient organoid (DPO) in patients with MBC receiving or progressed on ADCs for a precision tool to guide therapy in post-ADC resistance setting. **Methods:** An institutional IRB was established for prospective collection of fresh tumor biopsies in patients with MBC undergoing ADC therapy. DPO drug sensitivity tests were conducted and analyzed for association with clinical outcome using progression free survival (PFS). DPO tests include ADCs (T-DXd, SG, Dato-DXd) or single agent chemo dosing experiments to determine drug sensitivities (AUC values calculated from CTG readouts) for downstream correlation analyses. **Results:** Between 09/2024–01/2026, 41 fresh tumor tissues were collected and processed. 22 samples had sufficient viable cells to pass QC for DPO establishment and were successfully assayed and 12 failed QC, giving a DPO establishment success rate of 64.71%. DPO success rates varies by breast cancer subtypes: 100% in HER2+, 73% in TNBC and 56% in HR+HER2- BC. and sites of metastasis. Sites of metastasis (met) also impacted DPO success rates: lymph node 0%, liver met 33%, skin met 60%, breast/ascites 100%. Organoids typically established and expanded within 7-14 days post-biopsy. The DPO drug assays were conducted for ADCs, payloads, and chemotherapy agents testing. Analysis revealed that prior clinical exposure and progression on an ADC correlated with reduced DPO sensitivity to the same agent, consistent with acquired resistance. The platform was capable of delineating between target- versus payload-based resistance. Notably, DPOs from heavily pretreated patients were often resistant to both ADCs but remained responsive to alternative agents, highlighting potential therapeutic opportunities. **Conclusions:** The DPO platform shows promise in predicting treatment responses and differentiating resistance mechanisms to ADCs in MBC. This approach provides a foundation for rational treatment selection in patients with MBC with prior ADC resistance. Research Sponsor: None.

1034 Poster Session

Real-world outcomes and tumor gene expression analysis of sacituzumab govitecan (SG)- and trastuzumab deruxtecan (T-DXd)-treated metastatic breast cancer (MBC). First Author: Greydon Arthur, BC Cancer Agency, Vancouver, BC, Canada

Background: While the antibody-drug conjugates (ADCs) SG and T-DXd have transformed MBC care, predictive biomarkers of ADC response are lacking. This retrospective study evaluates real-world outcomes of MBC patients treated with SG or T-DXd and explores potential genomic and transcriptomic correlates of response. **Methods:** MBC patients treated with SG or T-DXd at BC Cancer who underwent tumor whole genome and transcriptome sequencing (WGTS) between January 2020 - May 2025 were included. Biopsy for WGTS was obtained either before (ADC-naïve) or after ADC exposure (ADC-exposed). Progression free survival (PFS) was clinically evaluated and assessed using Kaplan-Meier analysis. Treatment response was classified into 2 groups using PFS benchmarks from ASCENT (Bardia et al 2021, SG: expected $\leq$6 months (mo), favorable $>$6 mo) and DESTINY-Breast04 (Modi et al 2022, T-DXd: expected $\leq$12 mo, favorable $>$12 mo). RNA-seq data were assessed with DESeq2 differential expression and gene pathway enrichment analyses. Immune cell deconvolution was performed using CIBERSORT, with group comparisons by Wilcoxon rank-sum tests. **Results:** Forty-three patients met eligibility for inclusion (17 SG, 24 T-DXd, 2 treated with both agents). Median PFS was 4.0 mo (95% CI 2.0-6.0) for those treated with SG and 7.4 mo (95% CI 4.6-10.7) for those treated with T-DXd. Among T-DXd-naïve patients, *ESR1* expression was higher in those with poor ADC response (69.8 vs 7.8 transcripts per million, p = 0.049). Oxidative phosphorylation gene cluster expression was reduced in T-DXd-exposed vs T-DXd-naïve patients (normalized enrichment score -1.9, p = 0.005). ADC target expression did not differ by response in either treatment cohort (*TACSTD2* p = 0.86, *ERBB2* p = 0.67). Whole genome sequencing identified 12 tumors with *FGFR1* amplifications, all with poor ADC response, and demonstrated homologous recombination deficiency in half of those with favorable SG response. While not statistically significant, the post-ADC tumor microenvironment of favorable responders trended toward enrichment with naïve B-cells and T-cell infiltrate in T-DXd-treated patients (p = 0.28, 0.33) and both monocytes and NK cells in SG-treated patients (p = 0.1, 0.27). **Conclusions:** This study highlights the heterogeneity of outcomes among SG- and T-DXd-treated MBC patients and identifies potential predictive and prognostic biomarkers warranting exploration in prospective trials of first-line ADC (NCT07299409) and ADC sequencing (NCT06665178). Research Sponsor: BC Cancer Foundation; Marathon of Hope Cancer Centres Network.

	SG-treated patients (n=19)	T-DXd-treated patients (n=26)
HR status:		
Positive	1	22
Negative	18	4
HER2 status:		
Negative/Ultralow	8	11
Low	10	11
Positive	1	4
Timing of biopsy for WGTS:		
Pre-ADC	12	15
Post-ADC	7	11
Favorable ADC response	4	3
Median lines of therapy for MBC pre-ADC (range)	2 (0-6)	4 (0-8)
Median lines of endocrine therapy for HR + MBC pre-ADC (range)	0 (N/A)	1 (0-5)

1035 Poster Session

Dominant chromosomal abnormalities in breast cancer metastasis to CNS as compared with systemic metastasis demonstrated by liquid biopsy. First Author: Maher Albitar, Genomic Testing Cooperative LCA, Lake Forest, CA

Background: Breast cancer (BrC) central nervous system (CNS) metastases are believed to be biologically and therapeutically distinct from systemic metastases. Detecting BrC metastasis to CNS using liquid biopsy (LBx) of the CSF is emerging as a reliable approach not only for confirming metastasis, but also for defining the molecular and biological characteristics of this metastasis. We compared the findings of LBx performed on CSF with those obtained by peripheral blood (PB) LBx. **Methods:** LBx was performed by next generation sequencing (NGS) of cell-free DNA and RNA (cfDNA/cfRNA) in PB plasma or CSF as well as RNA sequencing of CSF cell pellet. RNA sequencing was performed using a panel of almost 1600 genes and DNA sequencing using 302 genes. **Results:** Of the 339 tested CSF samples, 29 (8.5%) were negative for any mutation and 57 (16.8%) showed low level mutations characteristic of CHIP (clonal hematopoiesis of indeterminate potential). However, two samples showed only chromosomal gain or loss without mutations and 2 showed chromosomal abnormalities with CHIP but no cancer-related mutations. In contrast, 19 of 279 PB samples (6.8%) were negative for any abnormality and 33 (11.8%) had CHIP. One sample of the PB cases showed chromosomal abnormalities without cancer-related somatic mutations. Of the 253 positive CSF samples 207 (82.1%) showed chromosomal structural abnormalities while only 71 of the 227 positive PB samples (31.2%) showed chromosomal structural gain or loss ($P < 0.0001$). The most common chromosomal abnormality was 1q gain, detected in 42.8% of CSF and in 18.5% of PB samples. 17p (TP53) deletion was detected in 25.4% of CSF and in 6.6% of PB samples. 10q (PTEN) deletion was detected in 9.4% of CSF and 3.1% of PB samples. ERBB2 gene amplification was detected in 6.3% of CSF cases and in 1.3% of PB cases. In CSF positive samples, the most mutated genes were TP53, KMT2C, PIK3CA, DNMT3A, CDH1, NF1, PTEN and ESR1, detected in 37.3%, 29%, 27.8%, 10.3%, 8.7%, 8.3%, 7.9%, and 7.5%, respectively. These genes were detected in positive PB samples at 51%, 35.2%, 42.7%, 81.1%, 11.8%, 8.8%, 9.6%, and 20.2%, respectively. Variant allele frequency in all mutations was significantly higher in CSF (P=0.0001) than PB. Germline mutations in BRCA1/2 were detected in 5.1% of CSF and in 4.8% of PB. Ten patients had their PB and CSF tested concurrently. Two were positive by CSF and negative by PB and one was positive by PB but negative by CSF. The rest had concordant results. **Conclusions:** BrC with CNS involvement represents a distinct subgroup whose biological characteristics may best be defined using LBx to evaluate chromosomal abnormalities and gene gain/loss. As such, optimal characterization and qualification minimal residual disease in patients with BrC with CNS involvement warrants integration of CSF LBx-defined genetic abnormalities as it may permit earlier and targeted interventions. Research Sponsor: None.

1036 Poster Session

Prognostic impact of *PIK3CA* amplifications and co-occurring mutations detected through circulating tumor DNA (ctDNA) in metastatic breast cancer (MBC). First Author: Lorenzo Foffano, Weill Cornell Medicine, New York, NY

Background: Activating *PIK3CA* mutations are established oncogenic drivers and predictive biomarkers in MBC. In contrast, *PIK3CA* amplifications are rare, poorly characterized, and of unclear clinical significance. Tissue-based studies report a prevalence of 1–7%, but their detection and relevance in ctDNA are largely unexplored. Moreover, whether amplifications interact with co-occurring mutations to define a distinct high-risk subset is unknown. We therefore aimed to characterize the impact of *PIK3CA* amplifications detected in ctDNA through a multi-institutional cohort of patients (pts) with MBC. **Methods:** This retrospective study analyzed a multi-institutional cohort of 1579 pts with MBC and baseline ctDNA testing with the Guardant360 NGS panel within a large academic consortium (PMAC). Hormone Receptor positivity (HR+) and HER2 status were defined based on the most recent biopsy. Associations between SNVs, CNVs, and clinical characteristics were assessed using multivariable logistic regression. The impact of prognosis, adjusted for the number of prior treatment lines, was evaluated through Cox regression for overall survival (OS), defined from time of baseline ctDNA collection. **Results:** Among 1,579 pts, 1,121 (71%) were HR+/HER2−, 214 (13.5%) HER2+, and 244 (15.5%) had triple-negative breast cancer (TNBC). *PIK3CA* CNVs were detected in 7.7% of pts, and 44.7% harbored a concomitant *PIK3CA* SNVs. *PIK3CA* CNVs were significantly enriched in TNBC compared with other subtypes (Odds Ratio [OR] 2.02, p=0.011). In the overall population, *PIK3CA* CNVs were associated with significantly worse OS (HR 2.46, $p<0.001$), an effect observed across all subtypes, including HR+/HER2− (HR 2.21, $p<0.001$), HER2+ (HR 5.23, $p<0.001$), and TNBC (HR 1.81, p=0.018). In multivariable analysis, *PIK3CA* CNVs remained independently associated with inferior OS in the overall cohort (HR 1.61, p=0.015) and in HR+/HER2− disease (HR 1.38, p=0.048). Notably, the coexistence of a *PIK3CA* CNV and mutation identified a subset with particularly poor prognosis. Compared with patients harboring *PIK3CA* SNVs alone, those with concurrent SNVs and CNVs had significantly worse OS in the overall population (HR 1.80, p=0.002), in HR+/HER2− disease (HR 1.51, p=0.037), and in TNBC (HR 5.72, $p<0.001$). **Conclusions:** *PIK3CA* amplifications detected in ctDNA are relatively frequent in MBC and are associated with significantly worse survival across molecular subtypes. The coexistence of *PIK3CA* amplification and mutation identifies a distinct high-risk subset with particularly poor prognosis, beyond the effect of mutations alone. Further mechanistic understanding and real-world outcome analyses are needed to determine whether *PIK3CA* amplifications, alone or in combination with mutations, have predictive relevance for response or resistance to PI3K-pathway inhibitors. Research Sponsor: None.

1037 Poster Session

HRD-positive breast cancer genomics: Cross-application of ovarian cancer HRD scores. First Author: Xin Liu, Molecular Diagnosis Center, Yunnan Cancer Hospital, Third Affiliated Hospital of Kunming Medical University, Peking University Cancer Hospital Yunan, Kunming, China

Background: Homologous recombination deficiency (HRD) is a well-established biomarker for PARP inhibitor (PARPi) therapy in ovarian cancer and is increasingly being explored in breast cancer. However, current definitions of HRD positivity in breast cancer rely heavily on ovarian cancer–derived thresholds, raising questions about their biological relevance. Here, we characterize the genomic landscape of HRD-positive breast cancer and assess the applicability of ovarian cancer–based HRD scoring criteria. **Methods:** We performed next-generation sequencing on 1,159 breast cancer samples to evaluate HRD status, somatic alterations, and germline variants. HRD scores were calculated as the sum of loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST), using established ovarian cancer cutoffs. These results were compared with HRD scores from 617 ovarian cancer cases analyzed using the same methodology. **Results:** Pathogenic or likely pathogenic BRCA mutations were detected in 105 breast cancer patients (9.1%), including 33 somatic and 80 germline events, all of which occurred in HRD-positive tumors. Overall, 26.2% (304/1,159) of breast cancer cases were classified as HRD-positive, with a median HRD score of 21. HRD scores were significantly higher in triple-negative breast cancer (TNBC) than in non-TNBC subtypes ($P < 0.001$). HRD-positive tumors exhibited elevated genomic instability, marked by significantly higher copy number variation burden ($P < 0.001$) and tumor mutational burden (TMB) ($P < 0.001$), along with enriched TP53 alterations. Comparative analysis revealed that ovarian cancers had significantly higher HRD scores than breast cancers (median: 43 vs. 21, $P < 0.001$), suggesting that applying ovarian cancer–derived thresholds may underestimate HRD positivity in breast cancer. **Conclusions:** HRD-positive breast cancer displays distinct genomic features, including increased genomic instability and TP53 alterations. However, HRD scores in breast cancer are markedly lower than those in ovarian cancer, indicating that ovarian cancer–based cutoffs may not be optimal for breast cancer. Future studies should refine breast cancer–specific HRD thresholds to improve patient selection for PARPi therapy. Research Sponsor: YunnanInternational Joint Laboratory on Cancer MolecularImaging; 202503AP140032; Key Research and Development Program of Yunnan Provincefor Building a Science and Technology Innovation Center Facing South and Southeast Asia - The International Joint InnovationPlatform of Yunnan Province; Yunnan Science and Technology Talent and Platform Program (Academician Expert Workstation); 202505AF350067; Scientific Research Project of Yunnan Clinical Medicine Center; Startup Funds for Scientific Research of Yunnan Cancer Hospital; ZC0024.

1038 Poster Session

Characterization of genomic alterations between local breast cancers and cutaneous metastases. First Author: Francesca Thau, Yale Cancer Center, New Haven, CT

Background: Cutaneous metastases (CM) are a distinct manifestation of advanced breast cancer (BC), yet their genomic alterations (GA) relative to primary tumors are incompletely defined. In this study, we aimed to identify similarities and differences between GA in local BC and CM. **Methods:** Local BC and CM were profiled by comprehensive next-generation sequencing (FoundationOne CDx). Genomic biomarkers included tumor mutational burden (TMB), microsatellite instability (MSI), homologous recombination deficiency signature (HRDsig), reported as a laboratory professional service, and GA prevalence. Odds ratios (ORs) for enrichment in local BC versus CM were calculated using Fisher's Exact Test with false discovery rate (FDR) correction. **Results:** Across 14,769 BC and 1,731 CM cases, most had TMB-low (<10 mutations/Megabase; 94% vs 90%), were not MSI-high (99%), and were HRDsig-negative (83% vs 87%), respectively. Among BC cases, the most prevalent GA included *TP53* (54.1%), *PIK3CA* (34.5%), *MYC* (20.9%), *RAD21* (19.0%), *CCND1* (16.7%), and recurrent 11q13/8p12 amplicon–associated genes (*FGF19*, *FGF3*, *FGF4*, *NSD3*, *ZNF703*, and *FGFR1*; each 13–15%). Among CM cases, the most prevalent GA included *TP53* (48.4%), *PIK3CA* (37.6%), *MYC* (22.7%), and *RAD21* (20.0%), and also *CDH1* (18.8%) and *ESR1* (12.5%). Multiple genes differed significantly in prevalence between BC and CM, including enrichment of *ESR1*, *CDH1*, *NOTCH1*, *MAP3K1*, *CTNNA1*, *CBFB*, *NFE2L2*, *AKT1*, *BRAF*, and *GATA4* in CM, and higher frequencies of *TP53*, *MCL1* and *KDM5A* in BC biopsies (Table 1). In addition, several therapeutically relevant GA were observed at lower but clinically meaningful frequencies between BC and CM, such as alterations in the *PI3K/AKT* pathway beyond *PIK3CA*, including *AKT2* (1.8% vs 2.4%), *AKT3* (3.2% vs 3.6%), and *PTEN* (13.1% vs 13.0%); DNA damage repair genes, including *BRCA1* (3.9% vs 2.7%), *BRCA2* (4.1% vs 3.9%), *PALB2* (1.1% vs 0.8%), *RAD51* (*RAD51B/C/D* combined 1.3% vs 1.1%), *ATM* (2.6% vs 1.9%), *ATR* (0.9% vs 0.7%), *CHEK1* (0.1% vs 0%), and *CHEK2* (1.5% vs 2.2%); and additional potentially actionable GA, such as the *MTAP* (4.0% vs 3.8%), *SMARCA4* (1.0% vs 0.8%), *CCNE1* (4.2% vs 5.3%), and *ERBB2* (11.1% vs 11.3%) genes in local BC and CM biopsies, respectively. **Conclusions:** CM largely retain the GA profile of local BC, but may exhibit distinct enrichment of alterations in estrogen signaling, likely from selective pressure, cell adhesion, possibly due to more frequent lobular *CDH1*-mutated BC involving skin, and oncogenic pathways. A substantial proportion of both BC and CM samples harbor targetable GA, underscoring opportunities for precision therapy not only in advanced disease, but also in early stages. Research Sponsor: None.

Clinically significant genes with significant differences between local BC and CM.

Gene	BC (%)	CM (%)	Odds Ratio (CM vs BC)	p-value (FDR adjusted)
TP53	54.1	48.4	0.79	<0.001
CDH1	11.4	18.8	1.80	<0.001
ESR1	4.7	12.5	2.89	<0.001
AKT1	4.7	6.3	1.38	0.046

1039 Poster Session

Serum HER2 level as a predictor of treatment efficacy and prognosis in advanced breast cancer patients treated with trastuzumab deruxtecan (T-DXd). First Author: Yehui Shi, Department of Breast Internal Medical, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: No validated liquid biopsy biomarker currently exists to predict the efficacy of trastuzumab deruxtecan (T-DXd) in advanced breast cancer (aBC). Consequently, the role of serum HER2 (sHER2) in this setting remains unclear. This study aimed to determine whether baseline levels and early on-treatment dynamics of sHER2 are associated with progression-free survival (PFS) and objective response rate (ORR) in aBC patients receiving T-DXd. **Methods:** We analyzed 43 aBC patients treated with T-DXd who had baseline sHER2 data available. As the established 15 ng/mL cut-off was not associated with PFS in our preliminary analysis, the optimal baseline sHER2 cut-off for predicting PFS was determined using the maximally selected log-rank statistics method. Patients were stratified by this cut-off, and a multivariable Cox model adjusted for clinicopathological factors was used to evaluate the independent prognostic value of baseline serum HER2. In a subgroup of 20 patients, serum HER2 changes after two treatment cycles were assessed for association with efficacy outcomes. **Results:** Using the maximally selected log-rank statistics method, 10.94 ng/mL was identified as the optimal predictive cut-off, with PFS differing significantly between groups defined by this threshold (P=0.015). Multivariable Cox analysis confirmed that a baseline sHER2 level ≥10.94 ng/mL was an independent protective factor for longer PFS (Hazard Ratio [HR] = 0.129, 95% Confidence Interval [CI]: 0.019-0.875, P=0.038), corresponding to an approximately 87.1% reduction in disease progression risk. This predictive value was independent of primary tumor HER2 status, metastatic burden, and liver metastasis. Primary tumor HER2 status itself was not a significant prognostic factor in the model (P=0.530). Regarding ORR, no statistically significant difference was found between high and low sHER2 groups using the 10.94 ng/mL cut-off (P=0.392). In the 20-patient subgroup, early on-treatment sHER2 dynamics showed no significant association with PFS (P=0.455) or ORR (P=0.256). **Conclusions:** In aBC patients treated with T-DXd, a baseline serum HER2 level ≥10.94 ng/mL is a strong and independent predictive biomarker for PFS, with prognostic value potentially surpassing primary tumor HER2 status. This newly identified cut-off may help to better select patients who are most likely to benefit from T-DXd therapy using a convenient liquid biopsy approach. Clinical trial information: NCT06492447. Research Sponsor: None.

1040 Poster Session

PD-L1 upregulation as a reflection of distinct immune contexts in luminal and basal breast cancer. First Author: Lynne Chapman Cook, Department of Medicine, Section of Hematology and Oncology, Baylor College of Medicine, Houston, TX

Background: PD-L1 immunohistochemistry (IHC) is an approved biomarker to select patients with metastatic triple-negative breast cancer for immune checkpoint blockade (ICB). However, PD-L1 performs poorly in Luminal breast cancer, suggesting that PD-L1 upregulation may reflect distinct immune contexts across intrinsic subtypes. We hypothesized that PD-L1 expression can arise in either a canonical T-cell–inflamed state or a discordant PD-L1–high, T-cell–non-inflamed state. Discordance between PD-L1 expression and T-cell inflammation highlights the complexity of tumor–immune interactions, and accumulating evidence supports that malignancies can induce immune alterations systemically. To explore these broader immune features with a noninvasive approach, we examined plasma extracellular vesicles (EVs). **Methods:** We analyzed 1,084 primary invasive breast cancers from TCGA, focusing on Luminal (LumA/LumB) and Basal subtypes (n=867). PD-L1 status was defined using CD274 mRNA tertiles as a transcriptomic proxy for IHC, and a T-cell–inflamed signature (Ayers 18-gene TIS) classified tumors as inflamed (top 20th percentile), consistent with prior transcriptomic studies. Biomarker concordance was defined as the proportion of PD-L1-high tumors that were also TIS-high. Because CD274 is included in the TIS, analyses were interpreted conservatively with planned sensitivity analyses excluding CD274. For translational feasibility, EV profiling workflows were developed using plasma from the PyMT-N mouse model (immune-cold, myeloid-dominant TIME; method-development model, n=1). Plasma EVs from two patients with advanced breast cancer and one healthy control were profiled using proteomic and targeted EV RNA assays. **Results:** In Basal tumors, PD-L1 expression aligned with T-cell inflammation: 75.6% (65/86) of PD-L1-high tumors were TIS-high. In contrast, Luminal tumors showed reduced concordance, with only 39.4% (80/203) of PD-L1-high tumors classified as TIS-high. Basal PD-L1-high tumors were significantly more likely to be TIS-high than Luminal tumors (OR 4.76; 95% CI 2.70–8.39; $p=1.90\times10^{-8}$). These findings indicate frequent uncoupling of PD-L1 expression from T-cell inflammation in Luminal breast cancer. In PyMT-N plasma EVs, proteomic profiling detected myeloid-suppressive proteins with minimal T-cell–inflamed signals. In exploratory human plasma EVs, both proteomic and RNA assays captured immune-related signals, supporting EV profiling feasibility. **Conclusions:** PD-L1 upregulation occurs in distinct immune contexts that differ by intrinsic subtype, with reduced T-cell–inflamed concordance in Luminal breast cancer. This discordance may explain the limited utility of PD-L1 as a stand-alone biomarker in this subtype. Plasma EV profiling may capture systemic immune biology and provide orthogonal information to tumor-based assays, supporting further prospective evaluation. Research Sponsor: U.S. National Institutes of Health.

1041 Poster Session

A phase II study of trastuzumab emtansine (T-DM1) combined with ribociclib in patients with HER2-positive metastatic breast cancer (RibHER). First Author: Yuan Huang, Department of Breast Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Background: HER2-targeted therapy has significantly improved outcomes for patients with HER2-positive metastatic breast cancer (MBC). Cyclin D and cyclin-dependent kinases 4/6 (CDK4/6) act as downstream effectors of HER2 signaling, providing a rationale for combining CDK4/6 inhibitors with anti-HER2 therapies. However, combining CDK4/6 inhibitors with anti-HER2 antibody–drug conjugates (ADCs) raises the concerns of hematologic toxicities. This prospective, single-center, single-arm, phase II study evaluated the antitumor activity and safety of trastuzumab emtansine (T-DM1) plus ribociclib in patients with HER2-positive MBC previously treated with trastuzumab and a taxane, and with no prior ADC exposure. **Methods:** Patients received T-DM1 (3.6 mg/kg IV, day 1 of each 21-day cycle) and ribociclib (400 mg orally, days 8-21). Those with ER-positive disease could receive concomitant endocrine therapy (aromatase inhibitor or fulvestrant) per prior treatment; premenopausal patients also received ovarian function suppression. The primary endpoint was overall response rate (ORR). Secondary endpoints included clinical benefit rate (CBR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** From August 2020 to October 2024, 12 patients were enrolled. With the subsequent availability of trastuzumab deruxtecan (T-DXd), the study was terminated prematurely due to difficulties in patient enrollment. As of December 1, 2025, the median follow-up was 22.5 months (range: 8.7-25.2). The overall ORR was 41.7% and the CBR was 58.3%. Median PFS was 5.25 months (95%CI: 3.3-NA). In subgroup analyses, ORR (28.6% vs. 60.0%), CBR (57.1% vs. 60.0%), and median PFS (6.0 months, 95% CI: 3.5-NA vs. 4.5 months, 95% CI: 3.0-NA) differed between ER-positive and ER-negative subgroups, respectively. Median OS was not reached. All patients experienced treatment-related adverse events (TRAEs), most commonly thrombocytopenia (75.0%), neutropenia (66.7%), leukopenia (66.7%), anemia (50.0%), fatigue (50.0%), and elevated aspartate aminotransferase (50.0%). Grade ≥3 TRAEs included neutropenia (33.3%), leukopenia (25.0%), and thrombocytopenia (16.7%). Thrombocytopenia led to dose reduction in 5 patients and discontinuation in 2; one patient required platelet transfusion and another experienced grade 3 intracranial hemorrhage attributed to thrombocytopenia. No treatment-related deaths occurred. **Conclusions:** In this small preliminary study, T-DM1 plus ribociclib achieved an ORR of 41.7% in HER2-positive MBC. No clear PFS benefit was observed regardless of ER status. Overlapping hematologic toxicities, especially thrombocytopenia, were notable and warrant consideration in future combination strategies. Clinical trial information: NCT06481956. Research Sponsor: None.

1042 Poster Session

Tucatinib (TUC) combined with trastuzumab and pertuzumab (HP) as first-line (1L) maintenance therapy for HER2+ metastatic breast cancer (MBC): An in-depth safety analysis of HER2CLIMB-05. First Author: Veronique C. Dieras, Medical Oncology Department, Centre Eugène Marquis, Rennes, France

Background: The primary analysis of the phase 3 HER2CLIMB-05 study (NCT05132582) showed the addition of TUC to 1L maintenance HP yielded a statistically significant improvement in progression-free survival (per investigator) versus control treatment (hazard ratio: 0.641, $P < 0.0001$) in patients with HER2+ MBC. Here we report our findings from an in-depth safety analysis of HER2CLIMB-05. **Methods:** Patients with centrally confirmed HER2+ MBC without evidence of progression following chemotherapy-based induction treatment (taxane + HP) were randomly assigned 1:1 to TUC (300 mg) or placebo (PBO) BID, both in combination with HP. The safety analysis set included all randomly assigned patients who received ≥1 dose of any study treatment. Treatment-emergent adverse events (TEAEs), laboratory values, and TUC/PBO dose modifications and discontinuations were examined. **Results:** Among patients in the safety analysis set (TUC arm = 326; PBO arm = 324), median treatment durations of TUC and PBO were 17.1 months (range: 0.4–36.5) and 15.5 months (range: 0.5–41.3), respectively. Grade (G) ≥3 TEAEs occurred in 42.3% of patients in the TUC arm and 24.4% in the PBO arm; the most frequent G ≥3 TEAEs in the TUC arm were elevated alanine aminotransferase (ALT; 13.5%) and aspartate aminotransferase (AST; 7.1%). TUC was discontinued in 13.5% of patients due to a TEAE. Cardiac TEAEs were similar between TUC and PBO arms (4.3% vs 6.2%). TEAEs of hepatic events (43.6% vs 15.7%) and diarrhea (72.7% vs 51.2%) occurred at higher incidence in the TUC arm versus the PBO arm (Table). In the TUC arm, increased ALT (28.2%) and AST (25.8%) accounted for the majority of hepatic TEAEs. Most hepatic and diarrhea TEAEs were managed with TUC dose modifications and/or discontinuation; 7.7% of patients discontinued TUC due to hepatic TEAEs and 1.5% discontinued due to diarrhea (Table). Among the patients with a TEAE of diarrhea, 57.7% and 29.9%, respectively, in the TUC and PBO arms used antidiarrheals; the most used medication was loperamide. Further details of the in-depth safety analysis will be presented. **Conclusions:** TUC addition to 1L HP maintenance therapy may be an effective option for HER2+ MBC with a clinically manageable safety profile. Clinical trial information: NCT05132582. Research Sponsor: Pfizer Inc.

TEAEs*	Any		Any hepatic		Increased ALT/AST		Diarrhea	
Arm	TUC	PBO	TUC	PBO	TUC	PBO	TUC	PBO
Any G, %	99.1	96.6	43.6	15.7	28.2/25.8	7.1/9.0	72.7	51.2
G ≥3	42.3	24.4	18.1	1.2	13.5/7.1	0.6/0.6	6.1	4.0
Any G: Median time to onset (days)			34.5	85.0			11.0	32.0
Median time to resolution (days)			25.0	22.0			2.0	5.0
Any G: TUC/PBO dose hold, %	49.4	25.3	19.3	2.5	12.6/4.0	0.6/0.6	8.6	3.4
TUC/PBO dose reduction, %	29.1	11.1	16.3	0.9	11.7/2.8	0.3/0.6	6.4	3.1
TUC/PBO discontinuation, %	13.5	2.2	7.7	0	4.0/0.3	0/0	1.5	0.9

*As of data cutoff, Sep 5, 2025.

1043 Poster Session

Risk factors and long-term prognostic impact of trastuzumab deruxtecan-related interstitial lung disease in metastatic breast cancer. First Author: Takayuki Kobayashi, Breast Oncology Center, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Trastuzumab deruxtecan (T-DXd) has demonstrated substantial efficacy in HER2-positive and HER2-low metastatic breast cancer (MBC). Interstitial lung disease (ILD), however, remains a clinically significant safety concern. While ILD incidence has been reported, its long-term prognostic impact and associated risk factors are not well established. **Methods:** This retrospective, single-center study evaluated patients with MBC treated with T-DXd. ILD was defined as clinically and radiologically confirmed ILD, which led to T-DXd discontinuation per institutional protocol. Time to treatment failure (TTF) and overall survival (OS) were analyzed according to ILD occurrence. Potential clinical and treatment-related risk factors for ILD were assessed using univariable and penalized multivariable Cox regression models. **Results:** At a median follow-up of 12.7 months, 15 of 132 patients (11.4%) developed ILD leading to treatment discontinuation. Among these 15 patients, 9 (60%) had grade 1 disease, 3 (20%) had grade 2, and 3 (20%) had grade 3 disease; no grade 4 or fatal events were observed. There were no significant differences in TTF (P = 0.59) or OS (P = 0.21) between patients with and without ILD. Among patients who developed ILD, onset occurred significantly earlier in those with HER2-low disease compared with HER2-positive disease (median 6.0 vs. 14.6 months, P = 0.029). In univariable analyses, age ≥65 years (HR 3.39, 95% CI 1.18-9.68; P = 0.023), prior immune checkpoint inhibitor (ICI) therapy (HR 4.74, 95% CI 1.01-22.34; P = 0.049), and prior abemaciclib exposure (HR 4.11, 95% CI 1.19-14.14; P = 0.025) were significantly associated with ILD. In the penalized multivariable model, prior abemaciclib exposure remained the only independent risk factor (HR 10.38, 95% CI 1.07-NA; P = 0.042). **Conclusions:** Although ILD onset tended to occur earlier in HER2-low MBC, its development did not significantly affect long-term TTF or OS. Prior exposure to abemaciclib is a significant independent risk factor for T-DXd-related ILD, warranting careful monitoring in this population. Research Sponsor: None.

1044 Poster Session

Zongertinib combination therapy in HER2-positive metastatic breast cancer (mBC): First results from a phase Ib/II trial. First Author: Shigehisa Kitano, Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Zongertinib, an irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Beamion BCGC-1 (NCT06324357) is an ongoing Ph Ib/II multicohort trial investigating zongertinib as monotherapy or in combination with other agents in HER2-positive mBC, metastatic colorectal cancer, and metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. Here, we report the first data from 4 Ph Ib cohorts evaluating zongertinib plus antibody-drug conjugates (ADCs) or trastuzumab-based therapy in patients (pts) with HER2-positive mBC, focusing on ADC combinations, as well as supporting preclinical data. **Methods:** Preclinical activity of zongertinib combinations was assessed in xenograft mouse models. Beamion BCGC-1 includes pts with confirmed, unresectable HER2-positive mBC who progressed following HER2-directed therapy. Pts received escalating doses of zongertinib plus fixed doses of T-DM1 (Cohort A; 3.6 mg/kg), T-DXd (Cohort B; 5.4 mg/kg), trastuzumab (Cohort K; 8 mg/kg loading dose followed by 6 mg/kg) or capecitabine (1000 mg/m^2) plus trastuzumab (Cohort G; 8 mg/kg loading dose followed by 6 mg/kg). The primary endpoint is the occurrence of DLTs during the MTD evaluation period. Secondary endpoints included further safety assessments and objective response (investigator-assessed; RECIST v1.1). **Results:** In xenograft mouse models, the addition of zongertinib to T-DM1 or T-DXd led to increased antitumor activity. As of November 4, 2025, 12 pts had been enrolled to Cohort A (median age: 58 years), 16 to Cohort B (median age: 58 years), 4 to Cohort G (median age: 48 years) and 7 to Cohort K (median age: 58 years). Most pts were heavily pretreated, with prior exposure to T-DXd, T-DM1 and/or TKIs. In Cohort A, treatment emergent adverse events (TEAEs) and zongertinib-related AEs (any grade [G]/G3) were reported in 12/5 (100%/42%) and 11/5 (92%/42%) pts, respectively. Three (25%) pts had AEs leading to zongertinib dose reduction. No pts had an AE leading to zongertinib discontinuation. The most common TEAEs (any G/G3) were increased AST (7/1 [58%/8%] pts), decreased platelet count (5/2 [42%/17%] pts) and increased ALT (5/1 [42%/8%] pts). In Cohort B, TEAEs and zongertinib-related AEs (any G/G3) were reported in 14/7 (88%/44%) and 14/5 (88%/31%) pts, respectively. Three (19%) pts had AEs leading to zongertinib dose reduction and 3 (19%) had AEs leading to zongertinib discontinuation. The most common TEAEs (any G/G3) were anemia (8/2 [50%/13%] pts), diarrhea (8/2 [50%/13%] pts) and nausea (8/1 [50%/6%] pts). No grade 4 or 5 TEAEs occurred in Cohorts A and B. Efficacy analyses are ongoing and will be presented. **Conclusions:** No new safety signals were observed with zongertinib plus T-DXd or T-DM1. Dose escalation was ongoing in Cohorts A and B at data cutoff. Clinical trial information: NCT06324357. Research Sponsor: Boehringer Ingelheim.

1045 **Poster Session**

Overall survival by genomic profile in HER2-positive (HER2+) metastatic breast cancer (mBC): A large US clinico-genomic database study. First Author: Paolo Tarantino, Department of Medical Oncology, Dana-Farber Cancer Institute; Harvard Medical School, Boston, MA

Background: Over the past few years, the landscape of treatment for HER2+ breast cancer has evolved significantly. Multiple active 1L treatment options have emerged, including T-DXd plus pertuzumab, maintenance palbociclib or tucatinib, providing an opportunity to tailor treatment according to the disease profile. This study aims to describe real-world treatment patterns and evaluate overall survival (OS) in a modern cohort of patients with HER2+ mBC, with sub-analysis by genetic profile of the disease. **Methods:** This retrospective study used the Flatiron Clinico-Genomic database (CGDB), where each patient received at least one Foundation Medicine next generation sequencing (NGS) test along the course of disease. Adults (≥18 years) diagnosed with HER2+ mBC between 1 January 2018 and 31 March 2024 (one year prior to the data cutoff) were included. OS was examined using the Kaplan-Meier method, with descriptive analyses by genetic alteration. **Results:** Among 7,933 mBC patients who underwent NGS profiling, 732 (9.2%) patients with HER2+ mBC were included. The median age at diagnosis was 59 years (range: 23-85); 68.3% had hormone receptor positive disease, and 37% had de novo mBC. Patients received a median of 3 lines of therapy (range: 1–14). The use of anti-HER2 antibodies ranged from 59.4% to 33.6% across 1L through 5L. Trastuzumab deruxtecan was prescribed more often in later lines (23.9% for 3L, 19.6% for 4L, and 23.0% for 5L) compared to 2L and 1L (11.3% and 4.2%). Similarly, the use of anti-HER2 tyrosine kinase inhibitors increased in later lines. The median (95% CI) OS for the entire population was 48 (41.6-53.1) months, with notable differences based on the detection of key genetic alterations. Patients with mutations in DNMT3A (14.2%), ARID1A (11.9%), MLL2 (10.9%), and CHEK2 (9%) had numerically longer mOS (64 [49.5-NE], 51.4 [35.8-69.4], 51.4 [36.1-68.9], 51.4 [40.1-NE] months, respectively) while patients with mutations in BRCA1 (6.6%), CDH1 (10.9%), BRCA2 (10.9%), PIK3CA (37.4%), TP53 (59.6%), ERBB2 (11.5%), and ATM (12.7%) experienced numerically shorter mOS (36 [25.0-56.3], 40.1 [28.0-70.1], 40.1 [34.1-62.5], 40.1 [35.2-46.9], 40.6 [35.9-48.7], 43.3 [36.2-58.9], 44.3 [36.5-62.8] months, respectively). **Conclusions:** The present study provides key insights into clinico-genomic characteristics, modern treatment patterns and OS for HER2+ mBC patients in the US. Although survival was 4 years in the overall cohort, patients with mutations in key DNA repair genes (BRCA1, BRCA2, ATM, TP53), in CDH1, PIK3CA or ERBB2 experienced a numerically worse prognosis, representing key unmet needs for drug development. Research Sponsor: Boehringer Ingelheim.

1046 **Poster Session**

A phase Ib/IIa study of BAT8010+BAT1006, an anti-HER2 monoclonal antibody-exatecan conjugate combined with an ADCC-enhanced HER2 mAb in patients with advanced solid tumors: Results from the 1L HER2-positive breast cancer cohort. First Author: Wen Xia, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: BAT8010 is an ADC targeting HER2, while BAT1006 is a humanized monoclonal antibody targeting another epitope of HER2, with ADCC enhancement activity via completely devoid of fucose. Expansion cohort of 1st-line HER2-positive breast cancer (BC) patients enrolled, treated with BAT8010 + BAT1006. **Methods:** Patients in this open-label, multicenter clinical trial received BAT8010 + BAT1006 on day 1 of a 21-day cycle until intolerable or disease progression occurred. The study objectives included assessing tolerability, safety, pharmacokinetic characteristics, immunogenicity, and preliminary efficacy. **Results:** As of January 9, 2026, 46 HER2-positive BC patients were enrolled, and received BAT8010 2.4 mg/kg in combination with BAT1006 15 mg/kg. Favorable efficacy was observed with a manageable and predictable safety profile; dose optimization is ongoing in the BAT8010 2.1 mg/kg in combination with BAT1006 15 mg/kg dose cohort. Safety: Among the 46 patients who received at least one dose of BAT8010 in combination with BAT1006, at least one treatment-emergent adverse event (TEAE) was reported in 41/46 (89.1%) patients. The most common TEAEs (≥30%) were neutropenia, leukopenia, anemia, infusion-related reaction (IRR), thrombocytopenia, elevated alanine aminotransferase and diarrhea. Most TEAEs were Grade 1/2; however, Grade 3 or higher AEs were reported in 67.4% of patients, including neutropenia (27/46, 58.3%), leukopenia (16/46, 34.8%), and anemia (7/46, 15.2%). No cases of interstitial lung disease (ILD)/pneumonitis were reported. Efficacy: Among 46 patients with at least one tumor assessment, 1 patient achieved CR, 34 PR, and 11 SD, yielding an ORR of 76% (35/46) and a DCR of 100% (46/46); mPFS: not yet mature. **Conclusions:** BAT8010 in combination with BAT1006 is well-tolerated with manageable toxicity, and demonstrates promising preliminary antitumor activity in HER2-positive BC. Dose expansion studies in this patient population are ongoing, and further confirmatory clinical trials are planned to initiate for the additional validation of its safety and efficacy. Clinical trial information: NCT06376136. Research Sponsor: None.

1047 **Poster Session**

Efficacy, safety, and immunogenicity of pertuzumab biosimilar versus reference pertuzumab in combination with trastuzumab and docetaxel in HER2-positive metastatic breast cancer: A randomized, double-blind, multicenter, parallel group, phase III clinical trial. First Author: P. K. Chaithanya, MNJ Institute of Oncology & Regional Cancer Centre, Hyderabad, India

Background: Pertuzumab plus trastuzumab and docetaxel is a standard first-line treatment regimen for HER2-positive metastatic breast cancer (MBC). This phase III trial evaluated the therapeutic equivalence of pertuzumab biosimilar (manufactured by Intas Pharmaceuticals Ltd., Ahmedabad, India) versus Perjeta when combined with trastuzumab and docetaxel. **Methods:** This was a randomized (1:1), double-blind, multicenter, parallel-group, phase III equivalence study. Adults with HER2-positive MBC were enrolled and received pertuzumab I.V. (biosimilar or reference product) 840 mg loading dose in cycle 1, then 420 mg every 3 weeks for 24 weeks, in combination with trastuzumab and docetaxel as first-line therapy. Primary endpoint was independently assessed objective response rate (ORR) at week 24 per RECIST v1.1. Secondary endpoints included PFS, OS, duration of response, time-to-event outcomes, pharmacokinetics (T_{max}, C_{max}, AUC_{0-t}), safety, and immunogenicity (anti-drug antibodies, ADA). **Results:** A total of 213 patients were randomized (pertuzumab biosimilar n=106; reference product n=107). ORR at week 24 was comparable between the biosimilar and reference pertuzumab arms: in the mITT set, ORR was 71.3% (72/101) versus 65.0% (67/103), respectively. 6-months PFS rate was 90.1% vs 89.3% in biosimilar and reference pertuzumab arms respectively. Pharmacokinetic parameters (T_{max}, C_{max}, AUC_{0-t}) and immunogenecity were comparable between both the arms. Treatment-emergent adverse events (AEs) occurred in 65.1% (pertuzumab biosimilar) and 72.9% (reference product) of patients; most common AEs observed in ≥5% patients in pertuzumab biosimilar vs reference product arm were the following: diarrhea (32.1% vs 30.8%), alopecia (17.0% vs 12.1%), anaemia (8.5% vs 18.7%), vomiting (10.4% vs 11.2%), pyrexia (8.5% vs 10.3%), fatigue (8.5% vs 7.5%), neutropenia (6.6% vs 8.4%), leukopenia (6.6% vs 8.4%), nausea (4.7% vs 7.5%), cough (4.7% vs 5.6%) and headache (3.8% vs 5.6%). **Conclusions:** Pertuzumab biosimilar demonstrated therapeutic equivalence to reference product in combination with trastuzumab and docetaxel for first-line HER2-positive MBC. Efficacy, safety, pharmacokinetic similarity, and comparable immunogenicity support biosimilarity and its potential as an effective treatment option. Clinical trial information: CTRI/2022/12/048133. Research Sponsor: Intas Pharmaceuticals Limited, Ahmedabad, India.

Summary statistics for objective response rate (ORR) at week 24 (mITT set, N=204).

Parameter	Pertuzumab biosimilar (N=101), n (%)	Reference product (N=103), n (%)
Complete response	4 (4%)	1 (1%)
Partial response	68 (67.3%)	66 (64.1%)
Overall response rate	72 (71.3%)	67 (65.0%)
Difference in ORR (95% CIs)	-7.50, 19.97	

1048 **Poster Session**

Phase Ia study of VRN101099, a brain-penetrant, highly selective covalent HER2 inhibitor, in HER2-positive or HER2-mutant advanced solid tumors. First Author: Jee Hung Kim, Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: Despite advances in HER2-targeted therapies, including trastuzumab deruxtecan (T-DXd), unmet needs remain in patients with HER2-driven solid tumors who develop treatment resistance, particularly those with central nervous system (CNS) metastases. VRN101099 is an orally bioavailable, brain-penetrant covalent HER2 inhibitor that irreversibly inhibits HER2 and induces receptor internalization and degradation. Preclinical studies demonstrated antitumor activity in subcutaneous and intracranial xenograft models of HER2-positive breast and gastric cancers. **Methods:** This open-label phase Ia study assesses the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activity of VRN101099 in patients with HER2 IHC 1+/2+/3+ or HER2-activating mutant advanced solid tumors. A standard 3+3 dose-escalation design determines the maximum tolerated dose and recommended phase 2 dose (RP2D), with dose-limiting toxicities assessed during the first 21-day cycle. VRN101099 is given orally once daily in continuous 21-day cycles. Optional backfill cohorts may enroll up to 12 patients at tolerated dose levels to characterize safety, PK, and PD further. Data are descriptive as of the 18 January 2026 cutoff and inform ongoing dose escalation, backfill enrollment, and RP2D selection; early reporting reflects emerging safety and activity. Safety is overseen by a Safety Review Committee defined by protocol. **Results:** As of January 2026, 17 patients received VRN101099 (80–320 mg). Median age was 63 years; 65% were female, and 35% had breast cancer. HER2 IHC 3+ expression was seen in 29% of patients; 35% were ISH-positive, and 24% had HER2-activating mutations. Patients had received a median of 3 prior systemic therapies (range 0–10); 58% had prior anti-HER2 therapy, including T-DXd (47%). No Grade ≥3 treatment-related adverse events occurred. The most common treatment-related adverse event was Grade 1–2 diarrhea. Among eleven patients with at least one post-baseline tumor assessment at data cutoff, five with HER2 IHC 3+ expression or HER2-activating mutations experienced tumor size reduction after two cycles. Confirmed partial responses were observed in two patients previously treated with T-DXd: one with HER2 IHC 3+ breast cancer and one with HER2 S310Y-mutant NSCLC. PK analyses showed dose-dependent exposure, with trough concentrations at 240 mg exceeding preclinically defined HER2 inhibitory thresholds. **Conclusions:** VRN101099 was well tolerated across evaluated dose levels and demonstrated encouraging antitumor activity in heavily pretreated HER2-driven solid tumors, including patients previously treated with T-DXd. These findings support continued dose escalation and expansion to define the RP2D and further characterize the therapeutic potential of VRN101099. Clinical trial information: NCT06806982. Research Sponsor: Voronoi Inc.

1049 **Poster Session**

Phase II study of T-Bren (BL-M07D1) monotherapy or in combination with pertuzumab in patients with treatment-naïve HER2-positive unresectable locally advanced or metastatic (LA/M) breast cancer. First Author: He-Rui Yao, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: T-Bren is a HER2-directed antibody-drug conjugate (ADC) consisting of an anti-HER2 monoclonal antibody linked to a potent topoisomerase I inhibitor (Ed-04). In phase I study, T-Bren demonstrated encouraging antitumor activity with a manageable safety profile in patients (pts) with HER2-positive unresectable LA/M breast cancer (BC) who had failed standard treatments. Results of safety and efficacy from a phase II study assessing T-Bren monotherapy or in combination with pertuzumab in treatment-naïve HER2-positive unresectable LA/M BC are presented. **Methods:** Treatment-naïve pts with HER2-positive (IHC3+, or IHC2+/ISH+) unresectable LA/M BC were treated with T-Bren monotherapy at 4.4mg/kg Q3W (cohort A) or T-Bren 4.4mg/kg Q3W in combination with pertuzumab (cohort B). Primary endpoints were ORR and RP2D for combination treatment. **Results:** As of Nov 30, 2025, a total of 83 pts were enrolled and treated in cohort A (n = 43) and cohort B (n = 40). All pts were included in the analysis (see table below). The median follow-up was 10.6 months. In cohort A, ORR was 93.0%, confirmed ORR (cORR) was 86.0%. In cohort B, ORR and cORR were 87.5%. Median PFS have not reached in either cohort. The landmark PFS rate at 12-months was 79.1% in cohort A and 90.8% in cohort B. The most common grade 3 and above hematologic TRAEs in both cohorts were neutropenia (51.8%), anemia (37.3%), leukopenia (36.1%), and thrombocytopenia (26.5%); the most frequent grade 3 and above non-hematologic TRAEs were weight decreased (7.2%), hypokalemia (6.0%), and nausea (6.0%). Grade 3 and above TRAEs were able to be effectively managed with standard supportive measure including dose reductions, as demonstrated by the TRAE leading to discontinuation rate of 4.8%. No treatment related death or ILD was reported. **Conclusions:** T-Bren as monotherapy or in combination with pertuzumab has demonstrated a promising antitumor activity and a manageable safety profile in pts with treatment-naïve HER2-positive unresectable LA/M BC. Phase III study assessing T-Bren in treatment-naïve HER2-positive unresectable LA/M BC is in preparation. Clinical trial information: NCT06445400. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	Cohort A: T-Bren 4.4 mg/kg D1Q3W (N=43)	Cohort B: T-Bren 4.4 mg/kg D1Q3W+ pertuzumab D1Q3W (N=40)	Total (N=83)
ORR, % (95% CI)	93.0 (80.9, 98.5)	87.5 (73.2, 95.8)	90.4 (81.9, 95.7)
cORR, % (95% CI)	86.0 (72.1, 94.7)	87.5 (73.2, 95.8)	86.7 (77.5, 93.2)
DCR, % (95% CI)	100 (91.8, 100)	97.5 (86.8, 99.9)	98.8 (93.5, 100)
12-mo PFS rate, % (95% CI)	79.1 (32.9, 95.2)	90.8 (74.1, 97.0)	89.9 (77.8, 95.6)
12-mo OS rate, % (95% CI)	100 (100, 100)	95.0 (81.5, 98.7)	97.4 (89.9, 99.3)

1050 **Poster Session**

Efficacy and safety results of a prospective phase II study (IPUtrial) of inetetamab and pyrotinib in combination with utidelone for first- or second-line treatment of HER2-positive metastatic breast cancer. First Author: Hui Cao, Department of Oncology, Cancer Hospital of Dalian University of Technology, Cancer Hospital of China Medical University, Liaoning Cancer Hospital and Institute, Shenyang, China

Background: Despite standard anti-HER2 regimens with chemotherapy, therapeutic challenges persist in HER2-positive metastatic breast cancer (MBC). Inetetamab (anti-HER2 monoclonal antibody) and pyrotinib (tyrosine kinase inhibitor) demonstrate established efficacy in advanced disease. Utidelone, a novel epothilone analog, exhibits antitumor activity with a differentiated safety profile. This phase II study assessed the triplet combination in first- or second-line HER2-positive MBC. **Methods:** This multicenter single-arm phase II trial enrolled HER2-positive MBC patients for first- or second-line therapy. Patients who have previously used trastuzumab must meet the followings: for first-line treatment, neoadjuvant therapy was effective, and relapse occurred over 1 year after the end of adjuvant therapy; for second-line treatment, progressed in previous adjuvant/neoadjuvant therapy or progressed within 1 year of completion of trastuzumab therapy; disease progression occurred after 6 months of treatment with trastuzumab in advanced setting. Patients with stable brain metastases were enrolled with or without prior local treatment. ECOG PS 0-1, and measurable disease (RECIST v1.1). Eligible patients received inetetamab (8 mg/kg cycle 1, then 6 mg/kg, IV, day 1), pyrotinib (400 mg, PO, daily), and utidelone (30 mg/m², IV, days 1-5) every 21 days until progression or intolerance. Primary endpoint was investigator-assessed ORR. Secondary endpoints included PFS, OS, and safety. **Results:** By data cutoff (December 31, 2025), the recruitment has been completed. 94 patients were enrolled. Median treatment cycles were 11 (range 4-57). 56 (65.9%) and 29 (34.1%) patients were in first- and second-line settings, respectively. 85 patients were evaluable for response with 6 CR, 64 PR and 7 SD. The ORR was 82.4% (95% CI, 72.6%-89.8%). Median PFS was 13.1 months (95% CI, 10.420-15.780). Median OS was not reached. The OS rate of 12-month, 26-month and 35-month was 94.6% (95% CI, 89.5%-99.7%), 85.2% (95% CI, 76.6%-93.8%) and 78.5% (95% CI, 67.7%-89.3%), respectively. Predominant Grade ≥3 TRAEs were diarrhea (28.2%) and peripheral neuropathy (4.7%). Other Grade ≥3 TRAEs included nausea (3.5%), transaminitis (2.4%) and neutropenia (1.2%). Treatment discontinuations due to TRAEs occurred in 6 patients (6.6%). No treatment-related deaths occurred. **Conclusions:** The regimen demonstrated clinically meaningful activity of this triplet regimen for the first/second-line treatment of HER2-positive MBC, evidenced by high ORR (82.4%), durable median PFS (13.1 months), with encouraging 35-month OS rate (78.5%). Predominant toxicities (diarrhea, neuropathy) were controllable through supportive measures and dose adjustments. These data support phase III evaluation of this combination strategy. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

1051 **Poster Session**

Real-world brain metastasis outcomes with T-DXd versus tucatinib-based therapy in second-line HER2-positive metastatic breast cancer. First Author: Zunairah Shah, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Brain metastases (BM) remain a major cause of morbidity and mortality in HER2+ metastatic breast cancer (MBC). HER2CLIMB established tucatinib/trastuzumab/capecitabine (TTC) as a standard regimen with CNS activity, including improved outcomes in patients (pts) with active BM. DESTINY-Breast12 further demonstrated clinically meaningful intracranial outcomes with trastuzumab deruxtecan (T-DXd) in pts with stable and active BM. However, real-world (RW) comparative estimates of incident BM risk and timing between these two regimens among pts without baseline BM are limited, particularly in the second-line (2L) setting. **Methods:** We conducted a retrospective cohort study using TriNetX, a federated electronic health record network. Eligible pts had HER2+ MBC previously treated with first-line THP (taxane + trastuzumab + pertuzumab) and were BM-free at index. To approximate a 2L comparison, index was the first dose of T-DXd or TTC; cohorts were mutually exclusive and prior T-DM1 exposure was excluded. Pts with documented BM prior to index were excluded. To reduce misclassification from occult baseline BM, a landmark sensitivity analysis excluded BM events within 60 days post-index. Cohorts were balanced using 1:1 propensity score matching (PSM) for age, comorbidity burden, and lines of treatment. Incident BM was compared using risk-based measures (risk difference, risk ratio [RR]) and time-to-event analyses (Kaplan–Meier [KM]; Cox [HR]; log-rank). OS was assessed from index to death using KM and Cox regression. **Results:** In the PSM cohorts (n=540 per arm; mean age 57.8±12.4 vs 59.2±12.3 years), median follow-up was 13.4 months. Incident BM occurred in 12.6% (68/540) with T-DXd vs 20.9% (113/540) with TTC, corresponding to an absolute risk difference of −8.3% (95% CI −13.34% to −2.90%; p=0.0015) and RR 0.62 (95% CI 0.46–0.83). 1-year BM-free survival probability was 72.65% with T-DXd vs 67.89% with TTC (log-rank p=0.03), with an HR of 0.72 (95% CI 0.54–0.97). Among pts who developed BM, TTC was associated with higher BM-associated healthcare encounter burden compared with T-DXd (mean 9.64 vs 5.20; p=0.03). CNS morbidity events were less frequent with T-DXd vs TTC, including seizures (4.77% vs 13.06%; OR 0.33, 95% CI 0.23–0.49; p<0.0001) and cerebral edema (5.47% vs 14.22%; OR 0.35, 95% CI 0.24–0.51; p<0.0001). OS did not differ significantly between T-DXd and TTC (HR 0.89, 95% CI 0.76–1.04; p=0.16). **Conclusions:** In HER2+ MBC pts without baseline BM following first-line THP, T-DXd was associated with significantly lower incident BM, delayed onset, and reduced CNS morbidity compared with TTC. These findings warrant validation using standardized CNS surveillance and may help inform treatment selection in pts at high risk for BM. Research Sponsor: None.

BM outcomes in HER2+ MBC.

	T-DXd	TTC	
Incident BM	12.6%	20.9%	RR 0.62 (0.46–0.83)
1-year BM-free	72.65%	67.89%	HR 0.72 (0.54–0.97)

1052 **Poster Session**

Molecular imaging as a tool to predict patient outcomes in advanced HER2-low breast cancer on trastuzumab deruxtecan (T-DXd): The FHERAD trial. First Author: Xiaoyi xiaoyi Guo, NMPA Key Laboratory for Research and Evaluation of Radiopharmaceuticals, Department of Nuclear Medicine, Peking University Cancer Hospital & Institute, Beijing, Beijing, China

Background: The DESTINY-Breast04 trial demonstrated for the first time that trastuzumab deruxtecan (T-DXd), a HER2-targeting antibody-drug conjugate (ADC), benefits patients with HER2-low metastatic breast cancer (mBC). This efficacy in HER2-low disease (45–65% of cases) has spurred research into optimal methods for identifying eligible patients. We propose molecular imaging to explore intra-/interpatient heterogeneity in HER2 mapping of metastatic disease and to identify patients unlikely to benefit from T-DXd. **Methods:** HER2-low mBC patients with IHC1+ or IHC 2+/FISH ≤ 2.2 scheduled for T-DXd underwent paired HER2-targeted [^{18}F]AlF-HER2-BCH PET/CT (HER2−PET) and [^{18}F]FDG−PET/CT (FDG−PET) at baseline and 2 cycle follow-up. High-uptake was defined as having >50% of tumors with a baseline SUVmax >6.0 on HER2−PET; otherwise, it was low uptake. HER2-PET was defined as nonresponding showed no significant reduction of HER2 uptake (10%) at 2 cycle follow-up. Negative (NPV) and positive predictive values (PPV) of HER2−PET, FDG−PET, early HER2/FDG response, and their combination were assessed to predict morphological response (RECIST 1.1) after two T-DXd cycles and time-to-treatment failure (TTF). **Results:** In the 32 HER2-low mBC patients analyzed, 24 (75%) had high baseline HER2-PET uptake (SUVmax >6.0), while 8 (25%) had low uptake. Of 24 high-uptake patients, 14 (58.3%) achieved a complete response (CR), 7 (29.2%) initially reached a partial response (PR) after two T-DXd cycles but later developed progressive disease (PD) between cycles 5–10, and 3 (12.5%) experienced PD as early as cycle 2. In the low-uptake group (n=8), one patient (12.5%) with isolated pulmonary metastases maintained stable disease (SD) through 14 cycles, whereas 7 (87.5%) patients with multiple metastases developed rapid PD. Compared with RECIST1.1, respective NPV/PPV for baseline HER2−PET were 87.5%/87.5% for predicting treatment response at 2 cycles. When combining baseline HER2-PET uptake with early 2 cycles, patients with high baseline uptake and a ΔSUVmax >40% had a median TTF of 15.3 months [n = 14, 95% confidence interval (CI) 7.7−−not calculable], those with high baseline uptake and a 10% < ΔSUVmax <40% a median TTF of 4.8 months [n = 7, 95% CI: 3.8−9.8]; and patients with a ΔSUVmax <10% a median TTF of only 1.3 months [n = 10, 95% CI: 1.3, 3.9]. Baseline FDG uptake was not associated with lesion response status, and while trends in ΔSUVmax aligned with those observed in HER2-PET, no clear cutoff value was established in this study. **Conclusions:** Baseline HER2-PET uptake, especially when combined with early on-treatment ΔSUVmax, not only improves the understanding of tumor heterogeneity but also offers an imaging-guided strategy to personalize management and select patients most likely to benefit from T-DXd in HER2-low mBC. Clinical trial information: NCT06909604; NCT04547309. Research Sponsor: None.

1053 **Poster Session**

Intracranial efficacy and safety of trastuzumab deruxtecan in HER2-positive and HER2-low metastatic breast cancer with central nervous system involvement: A systematic review and proportional meta-analysis. First Author: Dua Azim, Department of Medicine, Rochester General Hospital, Rochester, NY

Background: Central nervous system (CNS) metastases and leptomeningeal disease (LMD) are major drivers of morbidity and mortality in metastatic breast cancer (MBC). Trastuzumab deruxtecan (T-DXd) has demonstrated intracranial activity across multiple studies; however, evidence remains fragmented across heterogeneous CNS subgroups. We conducted a systematic review and meta-analysis to assess intracranial efficacy and survival outcomes, along with interstitial lung disease (ILD) risk with T-DXd monotherapy in CNS-involved HER2-positive and HER2-low MBC. **Methods:** Following PRISMA guidelines, prospective trials and retrospective cohorts reporting CNS outcomes with T-DXd monotherapy were included. Fifteen unique cohorts met eligibility criteria. The primary endpoint was intracranial objective response rate (iORR). Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Safety analysis included ILD incidence. Random-effects proportional meta-analyses and prespecified subgroup and sensitivity analyses were performed (RevMan 5.4.1). **Results:** In patients with active brain metastases (11 cohorts), pooled iORR was 0.61 (95% CI 0.55–0.66; I^2=0%). Similarly, in stable brain metastases (6 cohorts), pooled iORR was 0.61 (95% CI 0.50–0.71; I^2=75%); exclusion of an influential cohort increased pooled iORR to 0.65 (95% CI 0.55–0.75) and reduced heterogeneity. In LMD (3 cohorts), pooled CNS response was 0.53 (95% CI 0.35–0.70; I^2=0%). HER2-low cohorts demonstrated a pooled iORR of 0.51 (95% CI 0.33–0.69), which did not differ significantly from HER2-positive CNS subgroups (p=0.75). Where comparative data were available, treatment with T-DXd was associated with improved PFS (HR 0.33, 95% CI 0.19–0.58) and overall survival (log HR −0.32, 95% CI −0.55 to −0.09; ≈HR 0.73). Safety analyses showed a pooled incidence of ILD (any grade) of 0.12 (95% CI 0.09–0.15), with higher rates observed in high-risk (0.16) and intermediate-risk (0.13) cohorts compared with low-risk cohorts (0.04). **Conclusions:** Across 15 cohorts, T-DXd demonstrates consistent and clinically meaningful intracranial activity in active and stable brain metastases, substantial activity in LMD, and a survival signal where comparative data exist, with quantifiable ILD risk. These findings support T-DXd as a key systemic therapy for CNS-involved HER2-positive and HER2-low MBC and underscore the need for standardized CNS endpoints and ILD mitigation strategies in future studies. Research Sponsor: None.

1054 **Poster Session**

Neoadjuvant dalpiciclib combined with letrozole and dual HER2 blockade in HR+/HER2+ breast cancer: First-stage results of the HELEN HER2 017 trial. First Author: Jiujun Zhu, Department of Breast Disease, Henan Breast Cancer Center, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Background: Triple-positive breast cancer (TPBC; HR+/HER2+) represents a distinct subtype with suboptimal responses to conventional neoadjuvant chemotherapy combined with anti-HER2 therapy, with reported pCR rates of only 26%–43.8%, and is associated with significant treatment-related toxicities[1-3]. This highlights an urgent need for more effective and less toxic therapeutic strategies. We hypothesize that simultaneously targeting ER, HER2, and CDK4/6 pathways may enhance antitumor efficacy while enabling chemotherapy de-escalation. This phase II study investigates a response-guided, chemotherapy-free neoadjuvant regimen using dalpiciclib (a CDK4/6 inhibitor), aromatase inhibitor (AI), and dual HER2 blockade. **Methods:** This prospective, single-arm, two-stage Simon optimal design study planned to enroll 71 patients. In stage one, 20 patients were enrolled; proceeding to stage two required ≥6 pCRs. The final success threshold is ≥24 pCRs in 71 patients (α=0.05, power=80%, H0: pCR≤25% vs. H1: pCR≥40%). Eligible patients had stage II–IIIa HR+/HER2+ invasive breast cancer. Treatment included oral dalpiciclib (150 mg/day, 3 weeks on/1 week off), oral letrozole (2.5 mg/day; with ovarian suppression if premenopausal), and IV trastuzumab (loading 8 mg/kg, then 6 mg/kg) plus pertuzumab (loading 840 mg, then 420 mg) every 3 weeks. This was a response-adaptive design: after 2 cycles, MRI assessed tumor response. Patients achieving PR (≥30% reduction per RECIST 1.1) continued the same regimen for 6 cycles; non-responders switched to TCHP chemotherapy (docetaxel, carboplatin, trastuzumab, pertuzumab). The primary endpoint was pCR (ypT0/is ypN0) in the all-treated population. Secondary endpoints included ORR, RCB 0-1, EFS, and safety. **Results:** In the first stage, 20 patients were enrolled. Median age was 48 years (range 34–59). All were ER+ and HER2+ by central review. After 2 cycles, 15 of 20 patients (75%) achieved PR and continued on the dalpiciclib, letrozole, and dual HER2 blockade regimen. Of the 20 patients, 8 achieved pCR, with a rate of 40%. Among the MRI responders who continued the experimental arm, the pCR rate was 40% (6/15). Treatment was generally well-tolerated; the most common adverse events were neutropenia, leukopenia, anemia, and thrombocytopenia. No treatment-related discontinuations or cardiac toxicity of grade 3 or higher were observed. **Conclusions:** The first stage of this response-guided study met its predefined efficacy threshold (≥6 pCR in 20 patients). The neoadjuvant regimen combining dalpiciclib, an AI, and dual HER2 blockade shows promising pCR rates and a favorable safety profile in TPBC, supporting continued evaluation in the second stage of the trial. Clinical trial information: NCT06276868. Research Sponsor: None.

1055 **Poster Session**

Safety and efficacy of ZN-A-1041, a highly blood-brain barrier (BBB)–permeable HER2 tyrosine kinase inhibitor (TKI), + trastuzumab deruxtecan (T-DXd) or pertuzumab-trastuzumab (PH) in HER2-positive metastatic breast cancer (HER2+ mBC): Phase Ic expansion results from the ZN-A-1041-101-US trial. First Author: Nancy U. Lin, Dana-Farber Cancer Institute, Boston, MA

Background: Brain metastases (BMs) are a common site of progression in HER2+ mBC due to limited BBB penetration of systemic therapies. ZN-A-1041 is an oral, selective HER2 TKI designed for high intact BBB permeability. We report ZN-A-1041-101-US (NCT05593094) Phase Ic expansion results of ZN-A-1041 + T-DXd in patients (pts) with HER2+ mBC refractory to prior treatments (txs), or + PH as maintenance therapy after first-line taxane + H ± P induction. Phase Ia and Ib (dose-escalation as single agent or in combination therapies) results have been reported (Anders ASCO 2023). **Methods:** The study enrolled pts with HER2+ mBC, with or without BMs (including leptomeningeal disease). Pts in Phase Ic received ZN-A-1041 800 mg twice daily (BID) + PH (Arm C), or were randomized to ZN-A-1041 800 mg or 600 mg BID, + T-DXd 5.4 mg/kg every 3 weeks (Arms A and B, respectively). Primary objectives: safety and tolerability. Secondary objectives included systemic objective response rate (ORR) and disease control rate (DCR) per Response Evaluation Criteria in Solid Tumours version 1.1. **Results:** As of July 31, 2025 (last pt in), enrollment in Arms A, B, and C was 24, 23, and 20 pts, respectively; median age was 57, 54, and 46 years; 50, 36, and 70% had *de novo* stage IV disease. Baseline central nervous system (CNS) metastases were present in 58, 59, and 16% of pts. Median prior lines of therapy for metastatic disease was 1, 1, and 0. Median ZN-A-1041 tx duration was 23.0, 24.6, and 42.9 weeks. The most frequent all-grade tx-emergent adverse events (TEAEs) across Arms A, B, and C, respectively, were nausea (83, 96, and 47%), diarrhea (62, 77, and 68%), and vomiting (46, 64, and 47%); diarrhea (17, 9, and 5%) was the most frequent Grade ≥3 TEAE. Preliminary systemic efficacy is summarized in the Table. Intracranial lesion shrinkage was observed in pts with BMs across all tx arms. **Conclusions:** ZN-A-1041 showed manageable safety profiles and promising clinical activity when combined with standard anti-HER2 therapies in pts with HER2+ mBC, both with or without CNS metastases. High disease control in pts pretreated with T-DXd and notable continued responses in the PH maintenance setting support further clinical evaluation of these combinations. Clinical trial information: NCT05593094. Research Sponsor: F. Hoffmann-La Roche Ltd.

Arm	n	ORR, % (95% CI)	Complete response, % of pts	DCR, % (95% CI)
A: ZN-A-1041 800mg + T-DXd	20	**65.0** (40.8, 84.6)	**10.0**	**95.0** (75.1, 99.9)
B: ZN-A-1041 600mg + T-DXd	21	**76.2** (52.8, 91.8)	**9.5**	**90.5** (69.6, 98.8)
C: ZN-A-1041 800mg + PH	13*	**30.8** (9.1, 61.4)	**5.6**	**100** (75.3, 100.0)

*Efficacy reported for 13 pts with measurable disease receiving maintenance therapy with ZN-A-1041 + PH after taxane + H ± P induction.
CI, confidence interval.

1056 **Poster Session**

TBCRC 050: A phase 1b/2 trial of niraparib and trastuzumab in HER2-positive metastatic breast cancer (MBC): Efficacy and correlative analyses. First Author: Erica Michelle Stringer-Reasor, O'Neal Comprehensive Cancer Center at The University of Alabama at Birmingham, Birmingham, AL

Background: Resistance to HER2-directed therapies remains a major challenge in HER2-positiveMBC. In preclinical models, HER2+ tumors overexpress poly (ADP-ribose) polymerase (PARP), and PARP inhibition induces apoptosis through NF-κB suppression even in the absence of pathogenic mutations in *BRCA 1/2*. We evaluated the safety, efficacy, and translational correlates of niraparib combined with trastuzumab in patients (pts) with refractory HER2+ MBC. **Methods:** This open-label Phase 1b/2 trial (NCT03368729) enrolled pts with HER2+ MBC (IHC 3+ and/or FISH amplified), measurable disease, LVEF ≥50%, and progression on ≥1 prior HER2-targeted therapy; stable CNS disease was allowed. Pts with germline BRCA1/2 mutations or prior PARP inhibitor exposure were excluded. Niraparib 300 mg orally was administered on Days 1–21 of a 21-day cycle with trastuzumab 6 mg/kg IV every 3 weeks (loading dose 8 mg/kg on cycle 1). The Phase 2 portion used a Gehan/Simon two-stage design with early stopping for futility (P0=24%); ≥1 response among the first 20 patients triggered expansion to 40 patients. ORR was assessed by RECIST v1.1, meeting the primary endpoint and allowing response rate estimation with <7% standard error and a two-sided 95% exact CI width of 0.28. Gene expression profiling of paired tumor tissue and peripheral blood mononuclear cells (PBMCs) was performed using the NanoString nCounter Tumor Signaling 360 panel at pretreatment compared to cycle 2. **Results:** Forty-six pts were enrolled (9/2019–2/2025); 41 were evaluable for response. Pts were heavily pretreated (median 3 prior regimens), including trastuzumab deruxtecan in 22 pts; 33% had brain metastases. Treatment-related adverse events were predominantly grade 1–2 and manageable. Clinical benefit rate (CBR) was 44% (18/41) including 1 complete response, 2 partial responses, and 15 stable disease. Eleven patients achieved disease control ≥ 6 months; 1 patient remained on treatment at data cutoff. Tumor profiling revealed enrichment of a B-cell–driven tertiary lymphoid structure signature with reduced hypoxia signaling in responders. Matched PBMC analyses demonstrated coordinated downregulation of interferon signaling, DNA damage response, metabolic activation, angiogenesis, and resistance pathways in clinical responders, whereas non-responders retained signatures of chronic stress and immune exhaustion. **Conclusions:** Niraparib plus trastuzumab demonstrated a favorable safety profile and durable clinical benefit in heavily pretreated HER2+ MBC. Integrated tumor and blood-based analyses identify immune-organized tumor microenvironments and systemic immune normalization as key correlates of prolonged response, supporting further investigation of PARP inhibition strategies. Clinical trial information: NCT03368729. Research Sponsor: GlaxoSmithKlin (GSK); V Foundation for Cancer Research; T20180005; Susan G. Komen; CCR17483582; National Cancer Institute; U54 CA118623; TBCRC by its foundation partners.; TESARO.

1057 Poster Session

Real-world cardiotoxicity with HER2 antibody–drug conjugates and survival after treatment continuation. First Author: Sumbal Aziz, AdventHealth Sebring, Sebring, FL

Background: HER2 antibody–drug conjugates (ADCs) are central to HER2-positive breast cancer (BC) treatment, yet cardiotoxicity remains a clinically relevant complication that may prompt treatment interruption. While HER2-related cardiac dysfunction is frequently reversible, uncertainty persists regarding the safety and survival impact of treatment continuation, particularly with newer ADCs. We assessed real-world cardiotoxicity and the association between treatment continuation and overall survival (OS), focusing on trastuzumab deruxtecan (T-DXd) and trastuzumab emtansine (T-DM1). **Methods:** Using the TriNetX Research Network (2010–2025), adults with BC treated with HER2-targeted therapy and no prior diagnosis of heart failure or cardiomyopathy were identified. Incident cardiotoxicity (heart failure or cardiomyopathy) within one year of therapy initiation was captured. OS from cardiotoxicity diagnosis was compared between patients (Pts) who resumed versus discontinued HER2-targeted therapy. Kaplan–Meier methods were used to estimate survival, and Cox proportional hazards models generated hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** Among 31,656 HER2-treated Pts, 4,593 (14.5%) developed cardiotoxicity within one year; 629 (11.1%) occurred with HER2 ADCs. Incidence was lower with ADCs than non-ADC therapy (T-DM1 11.6%, T-DXd 9.9%). After cardiotoxicity, 3,374 Pts (73.5%) resumed HER2 therapy, including 48.5% with T-DM1 and 47.7% with T-DXd. 5-year OS was significantly higher with HER2-targeted treatment resumption versus discontinuation (79.5% vs 66.9%; absolute difference 12.6%; $p<0.0001$), with a 55% mortality risk reduction (HR 0.45, 95% CI 0.39–0.51). ADC-specific analyses showed benefit, greatest for T-DXd (HR 0.25, 95% CI 0.14–0.43; absolute 5-year OS difference 19.3%) and T-DM1 (HR 0.34, 95% CI 0.23–0.50; absolute difference 21.0%). Pts who resumed therapy were younger than those who discontinued (58.0±13.1 vs 61.8±13.5 years). After multivariable adjustment, treatment resumption remained independently associated with improved OS (adjusted HR 0.45, 95% CI 0.39–0.51), though residual confounding cannot be excluded. **Conclusions:** In this large real-world cohort, continuation of HER2 ADCs after cardiotoxicity was associated with substantially improved OS. These findings support a multidisciplinary cardio-oncology approach and suggest that, when feasible, resuming HER2 ADCs—particularly T-DXd and T-DM1—may confer meaningful survival benefit. Research Sponsor: None.

Cardiotoxicity and survival outcomes with HER2/ADCs.

Agent	Total Treated (N)	Cardiotoxicity (%)	Therapy Resumed (%)	5-year OS % (Resumed vs Not)	Absolute OS Difference	HR (95% CI)
All HER2	31,656	14.5	73.5	79.5 vs 66.9	+12.6%	0.44 (0.39-0.51)
T-DM1	4,085	11.6	48.5	74.9 vs 53.9	+21.0%	0.34 (0.23-0.50)
T-DXd	1,558	9.9	47.7	48.0 vs 28.7	+19.3%	0.25 (0.14–0.43)

1058 Poster Session

HER2-targeted tyrosine kinase inhibitors in breast cancer: Real-world analysis of gastrointestinal and musculoskeletal toxicities using the FAERS database. First Author: Sneha Singh, Sunrise Hospital and Medical Center, Las Vegas, NV

Background: Human Epidermal Growth Factor Receptor 2 (HER2)-targeted tyrosine kinase inhibitors (TKIs) lapatinib, neratinib, and tucatinib are approved for HER2-positive breast cancer but have distinct adverse event (AE) profiles. We analyzed the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database to characterize gastrointestinal (GI) and musculoskeletal (MSK) toxicities associated with these agents. **Methods:** We conducted a retrospective FAERS data review to assess GI and MSK AEs associated with the three TKIs from 2020-2025. The chi-square test was used to compare categorical variables across drugs and age groups (<65 vs ≥65 years). **Results:** Among 9,045 total cases (lapatinib n=1,897; neratinib n=1,113; tucatinib n=6,035), neratinib demonstrated the highest GI toxicity rate at 64.2%, compared to 40.4% for tucatinib and 31.3% for lapatinib (χ^2=319.3, $p<0.001$). Diarrhea was the predominant GI AE across all agents, affecting 82.1% of neratinib-treated patients, 64.8% of tucatinib-treated patients, and 55.6% of lapatinib-treated patients. Other common GI AEs included nausea (33.2 neratinib, 34.6 tucatinib, 23.1 lapatinib) and vomiting (21.1% neratinib, 19.5% tucatinib, 23.9 lapatinib). MSK AE rates were comparable across all three agents (lapatinib 10.5%, neratinib 11.3%, tucatinib 10.5%; χ^2=0.72, p=0.70). The most frequent MSK AEs were pain in extremities (23% overall), arthralgia (18% overall), back pain (17.8% overall), and muscle spasms (17.6% overall). Age-stratified analysis revealed significant differences in GI toxicity. In patients <65 years, neratinib showed the highest GI AE rate at 63.1%, versus 34.8% for tucatinib and 28.1% for lapatinib (χ^2=74.0, $p<0.001$). In patients ≥65 years, this pattern persisted with neratinib at 73.7%, tucatinib at 36.9%, and lapatinib at 40.1% (χ^2=49.4, $p<0.001$). Moreover, older patients (≥65 years) experienced significantly higher rates of both GI and MSK AEs with lapatinib (GI: 40.1% vs 28.1%, $p<0.001$; MSK: 19.3% vs 9.6%, $p<0.001$) and neratinib (MSK: 25.3% vs 6.3%, $p<0.001$). Tucatinib showed no significant age-related differences in AE rates. **Conclusions:** The findings in this study highlight trends for selected AEs with various TKIs in order to help guide shared decision-making and tailored management strategies for patients with HER2-positive breast cancer. Research Sponsor: None.

1059 Poster Session

Dual HER2 blockade with or without taxane induction in HR+/HER2+ metastatic breast cancer: A comparative analysis of clinical outcomes. First Author: Mariah Black, Texas Tech University Health Sciences Center El Paso, El Paso, TX

Background: In the era of modern dual HER2 blockade, the necessity of taxane induction for ER+/HER2+ metastatic breast cancer (MBC) remains debated. While CLEOPATRA established pertuzumab/trastuzumab plus taxane as a standard backbone, emerging de-escalation strategies suggest that endocrine therapy (ET) combined with HER2 blockade may provide durable disease control in this favorable-prognosis subgroup (SYSUCC002, PERTAIN). Robust real-world comparative data addressing the survival–toxicity trade-off between chemotherapy-free versus taxane-induction approaches are limited. **Methods:** The TriNetX Global Collaborative Network (168 healthcare organizations; data updated Dec 2025) was queried for adults (≥18 years) with incident HR+/HER2+ MBC treated with dual HER2 blockade (trastuzumab + pertuzumab) plus ET. Patients receiving induction taxane (paclitaxel or docetaxel) comprised the induction cohort (IND); those treated with dual blockade + ET without induction comprised the chemotherapy-free cohort (Chemo-Free). 1:1 propensity-score matching (greedy nearest-neighbor; caliper 0.10) on demographics and comorbidities yielded 137 well-balanced pairs (N=274) with all post-match standardized mean differences <0.10. The primary endpoint was 3-year overall survival (OS; 1095-day window). Secondary outcomes included neutropenia, sepsis, heart failure, emergency department (ED) visits, and ICU admission. **Results:** Among 957 eligible patients, 153 received Chemo-Free and 804 received IND; 137 matched pairs were analyzed. Three-year OS was similar between cohorts with no statistically significant separation of survival curves (3-year OS 89.1% Chemo-Free vs 82.0% IND; HR 0.65 [0.32–1.31]; p=0.219). Deaths within 3 years were 13/137 (9.5%) in Chemo-Free versus 19/137 (13.9%) in IND, corresponding to an absolute death risk difference of −4.4% (95% CI −12.0% to +3.2%). Omitting induction was associated with reduced neutropenia (12.4% vs 21.9%; absolute risk reduction 9.5%; OR 0.51 [0.26–0.97] and a lower time-to-neutropenia hazard (HR 0.50 [0.28–0.91]; p=0.020). Serious adverse events and acute care utilization were not increased with Chemo-Free: heart failure 16.1% vs 16.1%; sepsis 10.9% vs 13.1%; ICU admission 11.7% vs 13.9%; ED visits 40.9% vs 45.3%. **Conclusions:** In a propensity-matched real-world cohort receiving contemporary dual HER2 blockade plus ET, a chemotherapy-free strategy demonstrated similar 3-year OS compared with taxane induction, with a clinically meaningful reduction in neutropenia (number needed to treat ≈11 to prevent one event) and no signal for higher sepsis, heart failure, or acute care utilization. These data support the feasibility of chemotherapy de-escalation in selected HR+/HER2+ MBC patients and motivate prospective validation to refine patient selection and minimize treatment-related toxicity. Research Sponsor: None.

1060 Poster Session

Nanochemo-immunotherapy of ER-positive metastatic breast cancer (MBC) with PEG-liposomal doxorubicin (PLD) and pembrolizumab (PEM). First Author: Alberto A. Gabizon, Shaare Zedek Medical Center - Oncology Institute, Jerusalem, Israel

Background: PLD is a nanomedicine containing doxorubicin, a potent immunogenic cell death inducer. Based on the pharmacological profile of PLD, we hypothesized that PLD-based chemotherapy should allow for improved immune recognition of tumor cells and activation of T cells by PD1 blockade. We report here the results of a phase 1B study with a combination of PLD and PEM in ER+/Her2 negative MBC. **Methods:** Patients with MBC, whose disease progressed on hormonal, CDK 4/6 inhibitors and up to 3 lines of chemotherapy, were eligible for enrollment. Primary objectives were evaluation of safety and tumor response, and secondary objectives were overall survival and pharmacokinetic analysis of PLD and PEM. In a first cohort of 15 patients, PLD 30 mg/m^2 was infused along with PEM 200 mg on day 1 every 3 weeks. In a second cohort of 20 patients, PLD 40 mg/m^2 was infused on day 1 every 4 weeks without change of PEM dose-schedule. Responding and stable patients continued treatment until disease progression or treatment intolerance. All patients were followed up on for survival. **Results:** 35 patients were enrolled. A total of 201 PLD and 257 PEM treatments were administered until data lock. Treatment was well tolerated with no grade 3-4 neutropenia, no cardiac events, and no grade 2 hair loss. In one patient, a severe infusion reaction to PLD was observed forcing discontinuation of PLD in the 2nd cycle. There were 2 cases of grade 4 hepatitis, 1 case of grade 4 hemolytic anemia, and 5 cases of grades 1-2 hypothyroidism, possibly or probably related to PEM. PLD-related skin toxicity (palmar-plantar erythema, grades 1-2) was observed after 3 or more cycles, forcing treatment delays. Among evaluable patients receiving ≥3 cycles of PEM (n=30), we observed 8 partial and 2 complete responses with a long median duration of response (11 mo) and survival (28 mo). In 5 patients, near complete responses of large liver metastases were observed. Median survival was 25 mo for all patients and 26 mo for evaluable patients. Eight patients, including 1 patient still under treatment, remain alive at data lock with survival in the range of 10+ to 51+ mo. The plasma clearance of PLD was mono-exponential with high Cmax, long $T^1/_2$ (~3 days), slow clearance, and small Vcc. There was a significant increase of ~20% in the average AUC of PLD between the 1st and 3rd cycle indicating delayed clearance upon PLD retreatment. Analysis of PEM plasma levels revealed a mean $T^1/_2$ of ~11 days with high trough concentration by end of the cycle implying saturation of all accessible PD1 receptors. **Conclusions:** The combination of both dose levels of PLD with PEM is well tolerated, active, and feasible for extended treatment with durable responses. The favorable response and survival data in this heavily pretreated patient group suggest that PEM has significant contribution to the anti-tumor effect. A randomized study in ER+ MBC patients based on this regimen is warranted. Clinical trial information: NCT03591276. Research Sponsor: Merck USA; MK-3475 733.

1061 **Poster Session**

Effectiveness outcomes by treatment-free interval among patients receiving palbociclib plus endocrine therapy in HR+/HER2− advanced breast cancer in the real-world setting: Results from the PERFORM study. First Author: Rupert Bartsch, Medical University of Vienna, Department of Medicine 1, Division of Oncology, Vienna, Austria

Background: Combination of CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET) is first-line (1L) standard of care for patients (pts) with HR+/HER2- advanced breast cancer (ABC). Treatment-free interval (TFI) is an established prognostic factor in ABC. Shorter TFI is associated with more aggressive disease biology, inferior treatment outcomes, and reduced overall survival (OS). Real-world (RW) evidence complements clinical trials by providing insights into pts underrepresented in clinical trials. We present interim analysis 5 (IA5) of the PERFORM study, evaluating outcomes by TFI in pts receiving 1L palbociclib + ET. **Methods:** The prospective, non-interventional study PERFORM (NCT04767594) enrolled pts across Germany and Austria receiving 1L palbociclib + ET. Primary endpoint is progression-free survival (PFS). Secondary endpoints include second line (2L) PFS, PFS2 (time from 1L start to progression on 2L or death) and OS. Tumor assessments followed local medical standards. Quality of life (QoL) was assessed using FACT-B questionnaires. Pts were stratified by TFI, defined as time from last (neo) adjuvant treatment to recurrence: >12 months, ≤12 months, and de novo advanced disease. Time-to-event endpoints were estimated using the Kaplan-Meier method. **Results:** At database cutoff (Sep 30th, 2025), 1268 pts were included in IA5 and 1010 pts had available TFI data for subgroup analysis (TFI >12 months: 373 pts; ≤12 months: 133 pts; de novo: 504 pts). Median age was 69.5, 64.4, and 68.8 years, respectively. Pts with TFI ≤12 months showed a more aggressive disease profile such as higher rates of G3 tumors, N2-3 nodal status and liver metastasis compared to other TFI subgroups. Overall median PFS was 25.5 months (95% CI: 23.0-28.6), while median PFS was 29.2 months (95% CI: 23.3-33.1) for TFI >12 months, 14.6 months (95% CI: 9.3-19.4) for TFI ≤12 months, and 31.5 months (95% CI: 26.5-36.7) for pts with de novo disease. Median PFS2 was 39.0 (95% CI:33.7-51.4), 21.2 (95% CI: 17.4-37.0), and 40.9 months (95% CI: 37.0-46.9) for TFI >12, ≤12, and de novo, respectively. Median OS was not reached for TFI>12 months and was 37.4 and 52.8 months for TFI ≤12 and de novo, respectively. QOL with 1L therapy was maintained in all subgroups. **Conclusions:** The PERFORM IA5 supports TFI as a relevant prognostic factor for pts treated with palbociclib + ET in the 1L RW setting. QOL was maintained in TFI subgroups. Longest clinical benefit was observed in pts with TFI > 12 months and those with de novo disease. Treatment was associated with shorter clinical outcome in pts with TFI≤12 months compared to those in other TFI subgroups. These results complement those in the RCT setting. Research Sponsor: Pfizer Pharma GmbH, Germany.

1062 **Poster Session**

Clinical efficacy of a novel oral SERD TFX06 in prior fulvestrant-treated ER+/HER2− advanced breast cancer patients in a dose expansion study. First Author: Wenxing Qin, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Patients with ER+/HER2- advanced breast cancer who have progressed on prior endocrine therapies, including fulvestrant, represent an area of unmet medical need, particularly those harboring ESR1 mutations. As far as we know, there was limited reports on efficacy of oral SERD in prior fulvestrant treatment progressed patients. TFX06 is an investigational next-generation oral SERD. Here, we report results from a Phase I/II study of TFX06 in patients with ER+/HER2- advanced breast cancer who had progressed from prior fulvestrant treatment (NCT05927779). **Methods:** Eligible patients regardless of their menopausal status, who had received ≥1 lines of endocrine therapy (ET), prior fulvestrant (fulv) treated with or without CDK4/6i, and ≤2 line of chemotherapy in metastatic disease, were allowed to enroll. TFX06 tablets were orally administered at 150mg once daily (QD) in 28-day cycles until disease progression or intolerable toxicity. This analysis focuses on the subgroup with prior fulvestrant exposure. As of cut-off date December 22, 2025, 42 patients received TFX06 monotherapy at 150mg. Median age was 60.5 years (range, 34-73), 76.2% had an ECOG performance status of 1. 88.1% had visceral metastasis, and 16.7% had brain metastasis. The median number of prior endocrine therapies in the advanced or metastatic setting was 2 (range, 1-3), including fulvestrant (100%), CDK4/6i (85.7%) with combination (76.2%). Tumor assessments by investigators according to RECIST v1.1 were performed every eight weeks. **Results:** Of the 42 enrolled patients, 40 were evaluable for efficacy. In the full analysis set (n=40), median progression-free survival (PFS) was 5.5 months (95% CI, 3.2−7.8). The objective response rate (ORR) was 7.5% (3/40), disease control rate (DCR) was 60.0% (24/40), and clinical benefit rate (CBR) was 44.1% (15/34). In the ESR1-mutant subgroup (n=23), median PFS was 5.7 months (95% CI, 2.5−8.8), ORR was 8.7% (2/23), DCR was 65.2% (15/23), and CBR was 47.1% (8/17). Treatment emergent adverse events (TEAEs) occurred in 95.2% of patients (40/42), with grade ≥3 events in 26.2% (11/42). Most common TEAEs (≥20%) are laboratory abnormalities; they included hypertriglyceridemia (47.6%), increased AST (31.0%), anemia (31.0%), decreased lymphocyte count (23.8%), and decreased white blood cell count (21.4%). No TEAEs led to treatment termination. **Conclusions:** TFX06 showed promising clinical activity and a manageable safety profile in patients who progressed from prior fulvestrant-treatments including combination with CDK4/6i in ER+/HER2- advanced breast cancer, including those with ESR1 mutations. These findings support further development of TFX06 as a potential therapeutic option in this population. Clinical trial information: NCT05927779. Research Sponsor: None.

1063 **Poster Session**

Impact of adherence to interstitial lung disease (ILD)/pneumonitis toxicity management guidelines (TMGs) on ILD/pneumonitis outcomes: A retrospective analysis of patients (pts) treated with trastuzumab deruxtecan (T-DXd) in DESTINY-Breast06 (DB-06). First Author: Carla Mateo, Chief Medical Office, Patient Safety, Oncology R&D, AstraZeneca, Barcelona, Spain

Background: DB-06 (NCT04494425) showed a progression-free survival benefit with T-DXd vs physician's choice of chemotherapy for pts with hormone receptor–positive, HER2-low/-ultralow metastatic breast cancer, with no new safety signals. We report adherence rates to ILD/pneumonitis TMGs and their impact on ILD/pneumonitis outcomes. **Methods:** We retrospectively analyzed pts who received ≥1 dose of 5.4 mg/kg T-DXd and had adjudicated drug-related ILD/pneumonitis by the Mar 18, 2024 data cutoff. Adherence criteria were defined by ILD/pneumonitis severity at diagnosis (per investigator assessment) and associated TMGs (Table); adherence was classified as complete (CA), partial (PA), or non-adherence (NA) by TMG criteria met (all, ≥1 but not all, or none, respectively). Investigator-reported ILD/pneumonitis outcomes were 'recovered' (± sequelae), 'recovering', 'not recovered', and 'fatal'. **Results:** Of 49 pts with adjudicated drug-related ILD/pneumonitis, respective rates of CA, PA, and NA were 73.5% (n=36), 14.3% (n=7), and 12.2% (n=6). By Mar 24, 2025, 66.7% (n=24) of pts with CA and 71.4% (n=5) with PA had an outcome of recovered ± sequelae, with no fatalities. Of pts with NA, 50% (n=3) did not recover, including one fatality. At diagnosis, 31 (63.3%), 15 (30.6%), and 3 (6.1%) pts had Grade (Gr) 1, 2, and 3 ILD/pneumonitis, respectively. Across all cases, 38.8% (n=19) progressed to a worse grade after diagnosis; progression from Gr 1 to Gr 2 represented 84.2% of progressions. Of 25 pts with Gr 1 ILD/pneumonitis and CA (optional steroid use), 16 received steroids and 9 did not; recovery rates were comparable (68.8% with steroids vs 66.7% without). For pts with Gr ≥2 ILD/pneumonitis and CA or PA (n=18), steroid use as recommended was associated with improved recovery rates (66.7% with steroids vs 33.3% without). Two pts with Gr 1 ILD/pneumonitis at diagnosis were rechallenged with 4.4 mg/kg T-DXd; both had recurrent Gr 1 ILD/pneumonitis but recovered. **Conclusions:** Adherence to ILD/pneumonitis TMGs was associated with improved ILD/pneumonitis outcomes in this small subset of pts. Steroid use as recommended for Gr ≥2 cases was associated with improved recovery. While further investigation of patient-level determinants of recovery is needed, these data demonstrate that adhering to ILD/pneumonitis TMGs may optimize ILD/pneumonitis outcomes. Clinical trial information: NCT04494425. Research Sponsor: AstraZeneca in collaboration with Daiichi Sankyo.

Adherence criteria by ILD/pneumonitis grade at diagnosis.

	Gr 1	Gr 2	Gr ≥3
T-DXd interrupted after AE onset	Yes	–	–
T-DXd discontinued after AE onset	–	Yes	Yes
500–1000 mg/day methylprednisolone for 3 days	–	–	Yes
≥1 mg/kg/day prednisone*	–	Yes	Yes
Steroid duration ≥14 days	–	Yes	Yes
≥4-week taper	–	Yes	Yes
If no improvement 5 days from AE onset, switched to 2 mg/kg/day IV prednisone*	–	Yes	Yes

*Or equivalent; AE, adverse event.

1064 **Poster Session**

CAPTURE: A phase II trial evaluating alpelisib + fulvestrant vs capecitabine in advanced breast cancer patients with *PIK3CA*-mutant circulating DNA following CDK4/6 inhibition. First Author: Eileen Geoghegan, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: *PIK3CA* mutations are a key therapeutic target in ER+ advanced breast cancer (ABC) readily detectable through circulating tumor DNA (ctDNA). The PI3Kα inhibitor alpelisib is approved in ER+ HER2- ABC but it remains unclear when to incorporate it into the current treatment algorithm. To address this, we conducted a phase II study assessing superiority of alpelisib + fulvestrant vs capecitabine in ABC pts with detectable *PIK3CA* mutant ctDNA following CDK4/6i plus aromatase inhibition (AI). **Methods:** Eligible pts had ER+ HER2- ABC, prior progression on CDK4/6i+AI and *PIK3CA* mutations detected via ctDNA ddPCR. Pts were randomized 1:1 to receive alpelisib (300mg daily) + fulvestrant (Arm A), or capecitabine (1000-1250mg/m^2 BD D1-14 q21d) (Arm B); strata were prior chemo for ABC and visceral disease. Primary endpoint was progression free survival (PFS) defined from randomization until progressive disease per RECIST 1.1 or death. Secondary endpoints included objective response rate (ORR), clinical benefit rate (CBR) and adverse events (AE). Imaging was q8 weeks. Exploratory objectives included efficacy according to baseline ctDNA levels. Sample size was reduced from 140 to 66 pts randomized for 53 PFS events to detect median PFS of 9 vs 5 mo (HR=0.56;1-sided α=0.1,80% power). Interim inefficacy analysis (60% events) estimated HR>1.0 and IDMC recommended early termination. Follow-up continued until all pts completed alpelisib. Reported are stratified Cox model HR (2-sided 80% CI) and 2-sided log rank test. **Results:** From July 2020-Oct 2024, 396 pts were screened, 113 (29%) had PIK3CA mutant ctDNA, 58 were randomized and 55 initiated treatment (Arm A: 29/30; Arm B: 26/28). Median age was 56 (32-82 yrs), 75% had visceral disease; 87% had no prior chemo for ABC. At final analysis, 43 PFS events occurred. Median PFS was 7.4 mo for alpelisib + fulvestrant vs 9.4 mo for capecitabine (HR 1.28, 80% CI: 0.84-1.96, p=0.45). For pts with visceral disease, median PFS was 5.4 mo (80% CI:3.7-5.1) for alpelisib + fulvestrant and 12.1 mo (80% CI:5.4-15) for capecitabine. ORR was 24.1% vs 50.0% and CBR 55.2% vs 61.5% for alpelisib + fulvestrant vs capecitabine. Overall, 79.3% pts on alpelisib + fulvestrant had grade 3/4 AEs with 24% grade 3 hyperglycemia vs 46.2% on capecitabine with 12% grade 3 palmar-plantar erythrodysesthesia. Six of 30 pts discontinued alpelisib due to AEs; 5 of the 6 continued fulvestrant. There was no evidence of association between baseline ctDNA levels (PIK3CA mutant copies/ml; median 90; range 2-13678) and PFS (HR 1.03; 90%CI:0.90-1.19). **Conclusions:** In our trial of pts with *PIK3CA* mutant ABC after progression on CDK4/6i plus AI, targeted therapy with alpelisib + fulvestrant was not superior to standard chemotherapy with capecitabine. Compared with the targeted therapy, capecitabine was better tolerated and resulted in longer PFS. Clinical trial information: ACTRN12619001117101. Research Sponsor: National Health and Medical Research Council (NHMRC); #1143025.

1065 Poster Session

Subgroup analysis of participants (pts) with HER2 IHC0 in the ASCENT-07 study of sacituzumab govitecan (SG) vs chemotherapy in HR+/ HER2− metastatic breast cancer (mBC). First Author: Yeon Hee Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: SG was evaluated in the phase 3 ASCENT-07 study (NCT05840211) of pts with HR+/ HER2−, locally advanced unresectable or mBC who had received prior endocrine therapy (ET) and were eligible for first chemotherapy; the primary end point (PFS by blinded independent central review [BICR] vs chemotherapy treatment of physician's choice [TPC]) was not met (HR 0.85; 95% CI, 0.69-1.05; P = .130). We report exploratory outcomes in pts with HER2 IHC0 expression status. **Methods:** Pts were randomized 2:1 to receive SG 10 mg/kg IV or TPC (capecitabine, nab-paclitaxel, or paclitaxel). Descriptive analyses of pts with HER2 IHC0 were performed for the primary end point of PFS by BICR, secondary end points of PFS by investigator (INV), overall survival (OS), objective response rate (ORR) and duration of response (DOR) by BICR, and safety. HER2 status was tested locally. **Results:** Of 690 pts enrolled, 292 (42%) had HER2 IHC0 (SG: 192; TPC: 100). Baseline demographics and pt characteristics were similar to the overall population. Median age was 58 yrs; 176 (92%) and 91 (91%) pts in SG and TPC groups, respectively, received prior ET + CDK4/6i in the metastatic setting; 88% and 86% had visceral disease. At 15.4-mo median f/u, SG showed numerical improvement in PFS vs TPC by BICR (HR 0.75; 95% CI 0.55-1.02; nominal P = .0601) and by INV (HR 0.66; 95% CI 0.50-0.86; nominal P = .0024). Although OS data were not mature (maturity rate for IHC0 subgroup, 28%), an early improvement trend favoring SG was observed. ORR by BICR was similar for SG and TPC, and median DOR by BICR was longer for SG vs TPC. Despite a higher proportion of pts experiencing grade ≥ 3 treatment-emergent adverse events (TEAEs) with SG vs TPC, the rate of treatment discontinuation was lower with SG (Table). The most common grade ≥ 3 TEAEs were neutropenia (SG: 54%; TPC: 21%), leukopenia (12%; 7%), and anemia (11%; 5%). Safety profile was consistent with overall population and prior reports. **Conclusions:** In this exploratory analysis from ASCENT-07, numerical trends of improved efficacy vs TPC and the overall population as well as a manageable safety profile support further investigation into the potential benefit of SG in patients with HR+/HER2− mBC and HER2 IHC0 status who are candidates for first chemotherapy. Clinical trial information: NCT05840211. Research Sponsor: Gilead Sciences, Inc.

	SG (n = 192)	TPC (n = 100)
Median PFS by BICR (95% CI), mo	9.2 (8.2-10.4)	8.1 (6.3-10.4)
HR (95% CI)	0.75 (0.55-1.02); P = .0601[a]	
Median PFS by INV (95% CI), mo	8.5 (8.2-10.4)	6.1 (4.5-8.1)
HR (95% CI)	0.66 (0.50-0.86); P = .0024[a]	
Median OS (95% CI), mo	Not reached (NR-NR)	20.2 (19.5-NR)
HR (95% CI)	0.68 (0.44-1.05); P = .0820[a]	
ORR by BICR (95% CI), %	41 (34-48)	40 (30-50)
Median DOR by BICR (95% CI), mo	**n = 78**	**n = 40**
	10.8 (6.4-12.6)	8.3 (5.5-11.2)
TEAEs, n (%)	**n = 190**	**n = 100**
Any grade	189 (99)	97 (97)
Grade ≥ 3	139 (73)	46 (46)
Led to dose reduction	83 (44)	35 (35)
Led to treatment discontinuation	4 (2)	7 (7)

[a]Nominal P value; unstratified log rank.

1066 Poster Session

First disclosure of frontline treatment (1L tx) with the selective CDK4 inhibitor BGB-43395 in combination with letrozole for metastatic HR+/ HER2− breast cancer (BC): A phase 1 safety expansion. First Author: Shom Goel, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: BGB-43395, a highly selective CDK4i, showed preclinical antitumor activity characterized by improved CDK4 target coverage and selectivity over CDK6. This enhanced selectivity may reduce off-target toxicity and the need for tx modifications. BGB-43395 is being evaluated as monotherapy or with endocrine therapy in patients (pts) with HR+/HER2− BC and other advanced solid tumors in an ongoing phase 1a/1b open-label, international study (NCT06120283). We report on the safety, preliminary anti-tumor activity, and pharmacodynamics (PD) of BGB-43395 + letrozole as 1L tx for BC. **Methods:** In safety expansion cohort 2, CDK4/6i-naive pts with advanced/metastatic HR+/HER2− BC were randomized to receive BGB-43395 240, 400, or 600 mg PO BID + letrozole to determine the recommended dose for further development. The objectives were to assess safety, preliminary anti-tumor activity, and PD. **Results:** As of Nov 11, 2025, 58 pts received study tx (240 mg n = 19; 400 mg n = 19; 600 mg n = 20). Treatment emergent adverse events (TEAEs) occurred in 98% of pts; grade (G)≥3 TEAEs in 32%, 37%, and 65% of pts on 240 mg, 400 mg, and 600 mg, respectively. The most common TEAEs (mostly G1/2) were (240 mg / 400 mg / 600 mg): diarrhea (79% / 95% / 90% [G3 5% / 11% / 30%]), nausea (53% / 68% / 85% [G3 0% / 5% / 0%]), and vomiting (26% / 47% / 60% [G3 0% / 0% / 0%]). Rates of TEAE hematologic toxicities (mostly G1/2) were low; neutrophil count decreased/ neutropenia (240 mg 26% [G3 0%]; 400 mg 21% [G3 0%]; 600 mg 20% [G3 10%]); anemia (240 mg 5% [G3 0%]; 400 mg 21% [G3 0%]; 600 mg 20% [G3 5%]); platelet count decreased/thrombocytopenia ([all G1 or 2] 240 mg 5%; 400 mg 0%; 600 mg 5%). TEAEs led to dose modification in 53% of pts (median relative dose intensity: 240 mg 100%; 400 mg 97%; 600 mg 69%), tx discontinuation in 3% (240 mg, 1 pt; 600 mg, 1 pt), and 0 deaths. BGB-43395 + letrozole demonstrated early efficacy (Table) and strong PD effects, indicated by TK1 reduction and ctDNA decrease. Median study follow-up was 6.8 (range 3.2-9.7) mo, median time-to-response was 3.6 (range 1.6-8.4) mo, and median PFS was not reached. **Conclusions:** The CDK4-selective inhibitor BGB-43395, in combination with letrozole, demonstrated a favorable safety profile, with low hematologic and manageable gastrointestinal toxicity. Antitumor activity in 1L tx of pts with advanced HR+/HER2− BC was promising. Doses of 400 mg and 240 mg BID demonstrated efficacy and safety that support further development in combination with letrozole. Clinical trial information: NCT06120283. Research Sponsor: BeOne Medicines, Ltd.

BGB-43395 BID dose + letrozole	240 mg (n=19)	400 mg (n=19)	600 mg (n=20)
Median tx follow-up, mo	7.0	7.1	5.2
Best overall response, %			
PR[a]	58	68	40
SD	37	32	55
PD	5	0	0
NE	0	0	5
Objective response rate (CR + PR), %(95% CI)	58(33-80)	68(43-87)	40(19-64)
Disease control rate (CR + PR + SD), %(95% CI)	95(74-100)	100(82-100)	95(75-100)

RECIST v1.1 (investigator).
[a]Unconfirmed.

1067 Poster Session

Vepdegestrant, a proteolysis targeting chimera (PROTAC) estrogen receptor (ER) degrader, plus abemaciclib (ABE) in ER+/human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): TACTIVE-U phase 1b/2 results. First Author: Rachel M. Layman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Substudy A of the open-label, phase 1b/2 TACTIVE-U umbrella study is evaluating vepdegestrant, an oral PROTAC ER degrader, in combination with ABE for treatment of ER+/HER2− ABC (NCT05548127). Here, we report results for all patients (pts) in phases 1b and 2 treated with vepdegestrant (200 mg orally once daily) plus ABE (150 mg orally twice daily). **Methods:** Eligible pts were adults (age ≥18 years) with ER+/HER2− ABC who had received 1–2 prior lines of therapy in the ABC setting; 1 prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)-based regimen (in any setting) was required. The primary endpoint of phase 1b was dose-limiting toxicities during the first cycle. The primary endpoint of phase 2 was objective response rate (ORR); secondary endpoints included clinical benefit rate (CBR), progression-free survival (PFS), safety, and pharmacokinetics (PK). **Results:** As of October 10, 2025, 37 female pts (median age, 59 years [range, 38–84]; 20 pts [54.1%] had *ESR1*-mutated [*ESR1*m] tumors) received vepdegestrant plus ABE in phases 1b and 2, with 26 pts treated for ≥5 28-day cycles; 10 remain on treatment. All pts received prior CDK4/6i (ribociclib, 48.6%; palbociclib, 43.2%; ABE, 8.1%) in any setting; prior treatments in the metastatic setting included aromatase inhibitors (64.9%), fulvestrant (35.1%), and chemotherapy (21.6%). Among pts with measurable disease at baseline, the ORR was 30.6% (95% CI, 18.0–46.9) in all pts and 45.0% (95% CI, 25.8–65.8) in pts with *ESR1*m tumors. The CBR was 59.5% (95% CI, 43.5–73.7) in all pts and 65.0% (95% CI, 43.3–81.9) in pts with *ESR1*m tumors. Median PFS was 7.2 months (95% CI, 5.5–16.5) in all pts and 10.9 months (95% CI, 5.5–not estimable) in pts with *ESR1*m tumors. Five pts (13.5%) discontinued treatment due to treatment-emergent adverse events (TEAEs). TEAEs led to dose reduction of vepdegestrant in 6 pts (16.2%) and dose reduction of ABE in 19 pts (51.4%). Treatment-related adverse events of any grade that occurred in ≥20% of pts were diarrhea (73.0% [grade 1/2, 70.3%; grade 3/4, 2.7%]), fatigue (54.1% [grade 1/2, 40.5%; grade 3/4, 13.5%]), neutropenia (54.1% [grade 1/2, 21.6%; grade 3/4, 32.4%]), nausea (35.1% [grade 1/2, 32.4%; grade 3/4, 2.7%]), anemia (32.4% [grade 1/2, 29.7%; grade 3/4, 2.7%]), vomiting (24.3% [grade 1/2, 21.6%; grade 3/4, 2.7%]), and decreased appetite (21.6% [grade 1/2, 18.9%; grade 3/4, 2.7%]). There were no grade 5 TEAEs. PK data showed that vepdegestrant was associated with a modest 22% increase in exposure of ABE and its active metabolites, indicating no significant drug-drug interaction. **Conclusions:** In this phase 1b/2 study of pts with ER+/HER2− ABC, vepdegestrant plus ABE demonstrated antitumor activity and a safety profile that was generally consistent with the known profiles of each agent. Clinical trial information: NCT05548127. Research Sponsor: Pfizer Inc.

1068 Poster Session

Long-term safety results and adverse event (AE) management recommendations in patients with ER+/HER2− metastatic breast cancer (mBC) receiving prifetrastat, a first-in-class KAT6 inhibitor, at the recommended phase 3 dose (RP3D) of 5 mg once-daily (QD). First Author: Rachel M. Layman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Prifetrastat (PF-07248144) is a first-in-class, potent, and selective inhibitor of the epigenetic modifiers KAT6A and KAT6B. In an ongoing phase 1/2a study (NCT04606446), prifetrastat has demonstrated encouraging antitumor activity and manageable safety when combined with fulvestrant (FUL) in patients with heavily pretreated ER+/HER2− mBC (Mukohara T, et al. *Nat Med.* 2024;30:2242-50). Here, we report comprehensive and long-term safety results and AE management recommendations after extended follow-up of patients receiving prifetrastat (± FUL) in this phase 1/2a study. **Methods:** This dose escalation (part 1)/expansion (part 2) study included patients with ER+/HER2− mBC whose disease progressed after prior treatment with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) and endocrine therapy. In part 1, patients received prifetrastat at varying doses as monotherapy or in combination with 500 mg FUL. In part 2, patients received prifetrastat (± FUL) at the recommended dose for expansion (RDE; 5 mg QD) identified in part 1. Primary objectives were safety/tolerability assessment and RDE selection. **Results:** 5 mg QD prifetrastat was previously identified as the RDE and RP3D in combination with FUL based on safety, PK/PD, and antitumor activity. As of Oct 13, 2025, a total of 92 patients were treated at the 5 mg QD dose (43 as monotherapy and 49 in combination with FUL). The most common treatment-related AEs (TRAEs) were dysgeusia (84.8%; all grade [G] 1 [66.3%] or 2 [18.5%]), neutropenia (68.5%), and anemia (50.0%). Weight loss was reported infrequently as a TRAE (5.4%). The most common G3/4 TRAEs were neutropenia (G3, 34.8%; G4, 6.5%), anemia (G3, 15.2%; no G4), and leukopenia (G3, 12.0%; no G4); no G5 TRAEs were reported. TRAEs led to dose reductions in 45 (48.9%) patients, 75.6% (n = 34/45) of whom reduced their dose due to reversible neutropenia. TRAEs led to discontinuation in 2 patients (G2 neutropenia [n = 1]; G3 myocardial injury/troponin increased [n = 1]). G3/4 neutropenia was reversible and well-managed with dose modifications and supportive care. No febrile neutropenia was reported. Dysgeusia was managed with supportive care, including patient education, weight monitoring, and nutrition consultation, as clinically indicated. Dysgeusia did not lead to any treatment discontinuations or dose reductions. **Conclusions:** After extended follow-up of the phase 1/2a study, the RP3D of prifetrastat (5 mg QD) maintained a manageable safety profile when dose modifications and supportive care measures were implemented for AEs such as neutropenia and dysgeusia. These AE management strategies have been incorporated into the ongoing phase 3 study (KATSIS-1; NCT07062965) in patients with HR+/ HER2− mBC after progression on CDK4/6i-based therapy. Clinical trial information: NCT04606446. Research Sponsor: Pfizer Inc.

1069 Poster Session

HRS-8080, an oral selective estrogen receptor degrader (SERD), in ER+/HER2− advanced breast cancer (aBC) with *ESR1* mutations (*ESR1*m): Results from a first-in-human phase 1 trial. First Author: Zefei Jiang, Department of Breast Oncology, Fifth Medical Center of PLA General Hospital, Beijing, China

Background: HRS-8080 is a novel, potent oral SERD that binds ER with high affinity. We conducted a multi-part, first-in-human phase 1 trial of HRS-8080 in ER+/HER2- aBC, and here report findings in the *ESR1*m subset from the dose-escalation/expansion parts for HRS-8080 monotherapy. **Methods:** This multicenter, open-label, single-arm phase 1 study enrolled patients (pts) with locally advanced/metastatic ER+/HER2- BC previously treated with ≥1 line of endocrine therapy (ET) and ≤2 lines of chemotherapy for aBC; *ESR1*m status was centrally assessed by ctDNA. In Part A (i3+3 design), pts received HRS-8080 QD (50, 150, 300, 600, or 900 mg) or BID (300 mg); in Part B, 300 mg BID/600 mg QD were selected for expansion. Safety was a primary objective. **Results:** 40 pts with *ESR1*m were treated (≥2 prior lines of therapy, 70.0%; ≥2 prior lines of ET for aBC, 42.5%; chemotherapy for aBC, 57.5%), including 32 at expansion doses. Overall, grade ≥3 treatment-related adverse events (TRAEs) occurred in 8 (20.0%) of 40 pts; the most common were decreased lymphocyte count and decreased neutrophil count (2 [5.0%] pts each). TRAEs led to dose reduction in 1 (2.5%) pt. There were no treatment-related deaths. Efficacy in the *ESR1*m subset is shown in Table 1. At expansion doses of 300 mg BID/600 mg QD, the confirmed objective response rate was 34.4% (11/32; 95% CI 18.6–53.2) and the disease control rate was 75.0% (24/32; 95% CI 56.6–88.5). Median duration of response was 11.1 mo (95% CI 6.5–not reached), with over half of responses remained ongoing. As of data cutoff, 21 (65.6%) pts had disease progression or died; median progression-free survival was 7.2 mo (95% CI 3.6–11.1). **Conclusions:** HRS-8080 demonstrated a favorable safety and tolerability profile and encouraging antitumor activity in ESR1m ER+/HER2− aBC, supporting ongoing clinical development both as monotherapy and in combination regimens. Clinical trial information: NCT05189717. Research Sponsor: None.

Key baseline characteristics and efficacy in *ESR1*m subset.*

	50mg QD~300mg QD (n=6)	300mg BID+600mg QD (n=32)	900mg QD (n=2)	All patients (n=40)
≥2 prior lines of therapy, n (%)	5 (83.3)	21 (65.6)	2 (100.0)	28 (70.0)
≥2 prior lines of ET for aBC, n (%)	3 (50.0)	13 (40.6)	1 (50.0)	17 (42.5)
Chemotherapy for aBC, n (%)	5 (83.3)	16 (50.0)	2 (100.0)	23 (57.5)
Confirmed ORR, % (n/N; 95% CI)	0	34.4 (11/32; 18.6–53.2)	0	27.5 (11/40; 14.6–43.9)
Median DoR, mo (95% CI)	–	11.1 (6.5–NR)	–	11.1 (6.5–NR)
Median PFS, mo (95% CI)	2.2 (1.7–5.5)	7.2 (3.6–11.1)	NR (9.2–NR)	7.2 (3.6–10.9)
Median follow-up, mo (range)	3.0 (0.3–24.6)	6.7 (1.5–34.3)	21.3 (10.4–32.2)	6.6 (0.3–34.3)

Data cutoff, Dec. 18, 2025.
*Patients relapsed after 24 months if receiving adjuvant ET, and had disease progression ≥6 months of the first-line ET in the advanced setting. aBC, advanced breast cancer; DoR, duration of response; ET, endocrine therapy; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

1070 Poster Session

Real-world survival benefit of glucagon-like peptide-1 receptor agonists (GLP-1 Ras) concomitant with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) and endocrine therapy in hormone receptor-positive (HR+)/HER2− metastatic breast cancer: A large propensity-matched analysis. First Author: Michela Palleschi, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Background: Obesity increases hormone receptor-positive (HR+) breast cancer risk through adipose-derived estrogens and inflammation. In metastatic HR+/HER2- disease, endocrine therapy (ET) combined with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) is standard first-line therapy, improving survival. The widespread use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for diabetes and obesity management induces meaningful weight loss and may enhance ET efficacy by reducing body fat mass, which modulates estrogen levels and cancer-related inflammation, albeit their impact on mBC survival in patients receiving ET plus CDK4/6i remains unclear. **Methods:** Using the TriNetX Global Collaborative Network, we retrospectively identified two cohorts of patients with mBC receiving endocrine therapy (ET) plus a CDK4/6i: 26,689 patients treated with ET+CDK4/6i alone and 604 patients who also received a GLP-1 RA initiated within 3 months of CDK4/6i start. Propensity score matching (PSM) was applied to balance cohorts for age, race, body mass index, heart failure, hypertension, diabetes mellitus, fulvestrant use, and type of CDK4/6i. Overall survival (OS) was estimated using the Kaplan–Meier method, and hazard ratios (HRs) were calculated to compare OS between cohorts. **Results:** After PSM, 604 matched pairs of patients were identified in the ET plus CDK4/6i and GLP-1 RA groups, respectively (mean age +/- standard deviation:61.4 ±11.3 and 61.8 ±11.8 years), with well-balanced baseline characteristics. After a median follow-up of 18.8 months (interquartile range, IQR 27.9) in the non-exposed cohort and 15.8 months (IQR 24.5) in the non-exposure and in the exposure cohorts, median OS was 67,9 months among patients receiving GLP-1 RA compared with 49 months in those not receiving GLP-1 RA (HR 0.70; 95% CI,0.56–0.89; P=0.003), corresponding to a 30% reduction in the risk of death mortality risk. **Conclusions:** This is the largest real-world, propensity-matched analysis demonstrating a significant OS benefit with GLP-1 RAs added to ET+CDK4/6i in HR+/HER2− mBC. These provocative findings warrant prospective validation to elucidate underlying mechanisms—such as metabolic reprogramming or immune modulation—and explore GLP-1 RAs as a novel therapeutic strategy in this setting. Research Sponsor: None.

1071 Poster Session

Beyond *ESR1*: Multi-pathway genomic drivers of endocrine resistance in HR$^+$/HER2$^-$ breast cancer. First Author: Humaid Obaid Al-Shamsi, Burjeel Cancer Institute, Abu Dhabi, United Arab Emirates

Background: Endocrine resistance in HR$^+$/HER2$^-$ breast cancer is often associated with acquisition of *ESR1* point mutations, but many patients at progression remain *ESR1* wild type. Identifying *ESR1*-independent, multi-pathway acquired resistance mechanisms is critical for guiding subsequent therapy. **Methods:** We analyzed 1,429 HR$^+$/HER2$^-$ breast cancer samples (468 tissue, 1,171 cfDNA), including 210 paired cases, from patients with metastatic breast cancer undergoing molecular testing for treatment guidance or disease monitoring. Next-generation sequencing performed at Datar Cancer Genetics assessed SNVs, CNAs, and gene fusions. Alterations implicated in endocrine resistance were analysed for incidence, specimen type, and co-alteration patterns. **Results:** *ESR1*-wild-type tumors frequently harbored clinically relevant endocrine resistance mechanisms, most commonly involving the *PI3K/AKT, FGFR, ERBB2, MAPK*, and cell-cycle pathways. At least one resistance-associated alteration was identified in 40.4% (473/1172) of evaluable *ESR1*-wild-type cases, while 14.8% (173/1172) harbored alterations across multiple resistance pathways, highlighting substantial *ESR1*-independent resistance biology. Among *ESR1*-driven mechanisms, *ESR1* SNVs were detected slightly more frequently in cfDNA than tissue (13.7% vs 12.8%), despite inclusion of cfDNA samples obtained during clinical surveillance, supporting the sensitivity of liquid biopsy for detecting emergent resistance. *ESR1* fusions represented a distinct, non-overlapping resistance mechanism, identified in 7.4% (28/379) of tissue samples, most commonly *ESR1–CCDC170* (71%) and *ESR1–AKAP12* (14%); 21 fusion-positive cases lacked *ESR1* SNVs, underscoring the need for fusion assessment to fully capture *ESR1*-driven resistance. Dynamic pathway activation was further supported by acquired *PI3K* pathway mutations, detected in cfDNA in 3.3% (4/122) of cases initially *PIK3CA*-wild-type in paired tissue samples. **Conclusions:** Endocrine resistance in HR$^+$/HER2$^-$ breast cancer is mediated by multiple actionable genomic pathways beyond *ESR1*, including *PI3K/AKT, FGFR, ERBB2, MAPK*, and cell-cycle alterations. These findings expand opportunities to personalize therapy and guide clinical trial selection by targeting non-*ESR1* resistance mechanisms. Research Sponsor: None.

Incidence of endocrine resistance-associated genomic alterations beyond *ESR1* point mutations in tissue and liquid biopsy for HR$^+$/HER2$^-$ breast cancer.

Endocrine Resistance Biomarker	*ESR1*-Mutant Cases (%)	*ESR1* Wild-Type Cases (%)
***ESR1* fusions**	11.1	6.7
***FGFR1* alterations**	13.2	7.0
***CCND1* amplification**	15.2	7.0
***FGFR2/3* alterations**	3.7	2.0
***HER2*-mutant, non-amplified**	2.5	2.6
***PIK3CA* mutation**	43.7	25.1
***PTEN* mutation**	2.0	1.6
***AKT1* mutation**	5.6	3.6
***MAPK* Pathway (*RAS/RAF/MEK*)**	4.6	4.0

1072 Poster Session

A phase 1/2 trial of tersolisib (LY4064809/STX-478), a pan-mutant-selective PI3Kα inhibitor (PI3Kαi), in *PIK3CA*-mutant advanced solid tumors: Updated results from PIKALO-1. First Author: Komal L. Jhaveri, Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine, New York, NY

Background: PI3Kαi have demonstrated clinical benefit in ~40% of patients (pts) with HR+, HER2- advanced breast cancer (ABC) with *PIK3CA* mutations (*PIK3CA*m). However, broad use is often constrained by toxicities mediated through wild-type PI3Kα inhibition, and exclusion of pts with diabetes (DM) or prediabetes (pDM). Here we report updated results from PIKALO-1 evaluating tersolisib (terso), an oral, allosteric CNS-penetrant, pan-mutant-selective PI3Kαi in pts with *PIK3CA*m HR+ HER2- ABC. **Methods:** PIKALO-1 enrolled pts to receive terso (≥1 prior treatment [tx]), terso + fulvestrant (fulv, 1-2 prior txs), or terso + fulv/imlunestrant (imlu) and CDK4/6i (≤2 prior txs). Pts with pDM/DM (HbA1c <8% /FBG <140mg/dL) were eligible. **Results:** As of 6 Jan 2026, 193 pts with *PIK3CA*m HR+ HER2- ABC were treated: terso (n=52; 20-160 mg QD); terso (60 mg or 100 mg QD) + fulv (n=45) and terso (20-100 mg QD) + fulv + CDK4/6i (palbociclib, n=70; ribociclib, n=21; abemaciclib, n=5) (n=96). Median age was 62 yrs (Range: 27-84), 54% had pDM/DM. Median prior txs was 2 (0-7) including: CDK4/6i (81%) and SERD (47%). Hyperglycemia (HG) rates (any Grade [G]/G≥3) were 16%/0% in pts without pDM+DM and 37%/1% in pts with pDM+DM. TEAEs (any G/G≥3) ≥25% of all pts; neutropenia (39%/27%), fatigue (35%/4%), diarrhea (34%/<1%), and nausea (31%/1%). Incidence of PI3Ki-class toxicities (rash; 4%/0% and stomatitis; 12%/<1%) were relatively low. TEAEs led to terso dose reduction/discontinuation in 11%/<1%. T. no significant drug-drug interactions. *PIK3CA*m ctDNA was reduced at all dose levels. Updated data, including dose escalation data with terso + imlu+ abemaciclib, will be presented. **Conclusions:** Terso, alone or combined with fulv ± CDK4/6i, continues to be well-tolerated, with lower incidence of PI3Ki-class toxicities and no 3 HG in pts with normal baseline glycemic control. Target engagement was robust and clinical benefit continues to mature favorably in heavily pretreated pts with *PIK3CAm* HR+ HER2- ABC, supporting further study in the Phase 3 PIKALO-2 trial (NCT07174336). Clinical trial information: NCT05768139. Research Sponsor: Eli Lilly and Company.

Efficacy summary.

	Terso	Terso + fulv	Terso + fulv + CDK4/6i[c]
Efficacy Evaluable Population[a], n	48	31	48
Prior Therapies[b], n (Range)	3 (1-7)	1 (0-5)	1 (0-6)
ORR, n (%)	9[d] (19)	11[e] (35)	13[f] (27)
DCR, n (%)	32[d] (67)	27[e] (87)	38[f] (79)

[a]Pts who had measurable disease and ≥1 post baseline response assessment or discontinued prior to first post baseline response assessment.
[b]Locally Advanced/Metastatic Setting, summary based on safety population; all enrolled pts who received ≥1 tx dose.
ORR incl. PR, uPR; DCR incl. PR, uPR, SD.
[c]Incl. palbociclib, ribociclib, abemaciclib.
Incl. [d]1, [e]4, [f]6 uPR (ongoing, pending confirmation).

1073 **Poster Session**

(RW) post-progression outcomes following first-line (1L) ribociclib (RIB) + aromatase inhibitor (AI) versus AI alone in African American and low socioeconomic status (SES) patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) metastatic breast cancer (MBC) in US. First Author: VK Gadi, University of Illinois Cancer Center, Chicago, IL

Background: RIB + endocrine therapy (ET) demonstrated significant overall survival over ET alone in all three phase III MONALEESA trials for HR+/HER2− MBC. RW studies can provide insight into pt subgroups who may be under-represented in clinical trials. This is particularly important for African American pts and those with low SES, groups who often face disparities in access and outcomes. This study assessed RW post-progression outcomes among these under-represented populations in the US, to guide treatment (tx) for those affected by social determinants of health. **Methods:** This retrospective study used deidentified data from the Flatiron Health Research Database, including 5,649 US women with HR+/HER2− MBC who began 1L RIB + AI or AI monotherapy between Jan 1, 2020 and Jan 31, 2025, with follow-up through Jul 31, 2025. Analyses of RW progression-free survival 2 (rwPFS2; time from start of 1L to first disease progression during 2L, or death during 1L or 2L, whichever occurred first) and RW chemotherapy-free survival (rwCFS) used unadjusted and adjusted time-to-event methods (Kaplan-Meier and Cox regression), with baseline differences addressed using inverse probability tx weighting with stabilized weights (sIPTW). Key pt demographics and characteristics were used for adjustment; details to be provided in the full presentation. **Results:** A total of 520 African American pts were included in the analysis; 243 received RIB + AI and 277 received AI monotherapy. After sIPTW, median rwPFS2 was 19.4 months longer for the RIB + AI group vs AI monotherapy (median 36.8 vs 17.4 months; HR, 0.44; 95% CI, 0.29–0.67). Median rwCFS was also extended by 14.3 months with RIB + AI (median 39.5 vs 25.2 months; HR, 0.49; 95% CI, 0.33–0.72). Among 1805 pts with low SES index (pts area-level SES categorized in the lowest two quintiles to represent the lowest 40% of block groups in terms of SES), 810 received RIB + AI and 995 received AI monotherapy. The median rwPFS2 was 14.2 months longer for those receiving RIB + AI vs AI monotherapy (median 37.2 vs 23.0 months; HR, 0.54; 95% CI, 0.44–0.67) after sIPTW adjustment. Similarly, median rwCFS was prolonged by 22.0 months for the RIB + AI group vs AI monotherapy (median 51.4 vs 29.4 months; HR, 0.58; 95% CI, 0.47–0.71). **Conclusions:** This study demonstrates that treating African American pts and individuals with low SES using 1L RIB + AI, compared with AI alone, leads to longer rwPFS2 and rwCFS. These results support 1L RIB + AI as an effective tx choice for these pt groups and underscores the importance of ensuring access to optimal tx for better outcomes. Research Sponsor: Novartis Pharmaceuticals Corporation.

1075 **Poster Session**

Vepdegestrant, a proteolysis-targeting chimera (PROTAC) estrogen receptor (ER) degrader, plus atirmociclib (ATI) in ER+/HER2− advanced breast cancer (ABC): TACTIVE-K phase 1b/2 results. First Author: Melinda L. Telli, Department of Medicine, Stanford University School of Medicine, Stanford, CA

Background: There is unmet need for therapies that improve clinical outcomes in patients (pts) with ER+/HER2− ABC and disease progression on existing endocrine therapies (ETs). Both vepdegestrant, and ATI, a selective cyclin-dependent kinase (CDK) 4 inhibitor (CDK4i), have shown antitumor activity in pts with ER+/HER2− ABC previously treated with CDK4/6i plus ET. This study evaluated the efficacy and safety of vepdegestrant plus ATI in pts with ER+/HER2− ABC. **Methods:** This open-label, multicenter, phase 1b/2 study (NCT06206837) enrolled pts with ER+/HER2− ABC who received >1 (phase 1) or 1–2 (phase 2) prior lines of therapy in the ABC setting; 1 prior CDK4/6i-based regimen in any setting was required in phase 2. The study included a dose escalation/de-escalation phase 1b to select recommended doses, and a randomized phase 2 to further assess efficacy, safety, and PK. Baseline *ESR1* mutation status (via ctDNA) and its association with efficacy outcomes were also assessed in phase 2. **Results:** As of Sep 5, 2025, 70 pts (median age, 60 y) received vepdegestrant 200 mg daily plus ATI 100 mg BID (ATI100; n = 36), or 300 mg BID (ATI300; n = 34). Pts received a median of 1.0 prior regimens in the ABC setting. Most pts previously received an aromatase inhibitor (ATI100, n = 33, 91.7%; ATI300, n = 26, 76.5%) and/or a CDK4/6i (ATI100, n = 36, 100%; ATI300, n = 32, 94.1%). Confirmed objective response rate (ORR), clinical benefit rate (CBR; complete response, partial response, or stable disease for ≥ 24 wks), and median progression-free survival (mPFS) are shown in the Table. Efficacy outcomes for pts with baseline *ESR1* mutations (n = 27) were consistent with the total population (Table). Two dose-limiting toxicities were reported in phase 1b: a grade (G) 3 platelet count decreased (ATI100) and a G3 neutrophil count decreased (ATI300). Most treatment-related adverse events (TRAEs) were G1/2; G3/4 TRAEs were mainly neutropenia (ATI100, 16.7%; ATI300, 35.3%). PK parameters including AUC_{tau} and C_{max} for vepdegestrant and ATI100/300 at steady state were consistent with previous reports, indicating no clinically impactful drug-drug interactions. **Conclusions:** In previously treated pts with ER+/HER2− ABC, vepdegestrant plus ATI showed clinical activity in the full pt population and in pts with *ESR1* mutations. The safety profile of the combination was consistent with each agent. Clinical trial information: NCT06206837. Research Sponsor: Pfizer Inc.

	Vepdegestrant + ATI 100 mg	Vepdegestrant + ATI 300 mg
Pts with measurable disease at baseline	n = 31	n = 33
Confirmed ORR, % (95% CI)	16.1 (7.1–32.6)	24.2 (12.8-41.0)
All pts	n = 36	n = 34
CBR, % (95% CI)	44.4 (29.5–60.4)	52.9 (36.7–68.5)
mPFS, mo (95% CI)	9.3 (5.4–NE)	11.5 (7.2–NE)
Pts with *ESR1* mutation	n = 13	n = 14
Confirmed ORR, % (95% CI)	15.4 (4.3–42.2)	21.4 (7.6-47.6)
CBR, % (95% CI)	46.2 (23.2–70.9)	64.3 (38.8–83.7)
mPFS, mo (95% CI)	NR (3.0–NE)	NR (3.7–NE)

NE, not estimable; NR, not reached.

1076 **Poster Session**

Efficacy and safety of SPH4336 plus endocrine therapy in HR-positive/HER2-negative metastatic breast cancer with brain metastases: A multicenter, single-arm, phase II study. First Author: Kuikui Jiang, Department of Internal Medicine, Sun Yat-Sen University Cancer Center, Guangzhou, China

Background: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors plus endocrine therapy are standard first-line treatment for HR-positive/HER2-negative ($HR^+/HER2^-$) metastatic breast cancer (MBC). However, patients with brain metastases have poor prognosis and limited treatment options due to inadequate blood-brain barrier penetration of most agents and limited evidence for intracranial efficacy. SPH4336, a novel oral CDK4/6 inhibitor, exhibits potent CDK4/6 inhibition in preclinical models with favorable blood-brain barrier penetration. It has shown acceptable safety profiles and preliminary antitumor activities in advanced solid tumors, including $HR^+/HER2^-$ MBC. This study assessed the efficacy and safety of SPH4336 plus endocrine therapy in $HR^+/HER2^-$ MBC with brain metastases. **Methods:** This open-label, single-arm, phase II study enrolled patients aged 18-75 years with histologically confirmed $HR^+/HER2^-$ and radiologically confirmed brain metastases at 25 centers in China. Prior CDK4/6 inhibitor exposure before brain metastases was limited to <2 agents. Patients received SPH4336 (400 mg orally once daily) plus physician's choice of endocrine therapy (letrozole, fulvestrant, or exemestane) in 28-day cycles until disease progression or unacceptable toxicity. Primary endpoint was intracranial objective response rate (ORR) per RANO-BM criteria. **Results:** Between September 19, 2023, and August 22, 2025, 30 patients were enrolled. Two patients (6.7%) had a history of palliative radiotherapy for brain metastases. As of December 10, 2025, the median follow-up was 11.7 months (range: 1.6-26.7). Per RANO-BM criteria in 29 evaluable subjects, the intracranial ORR, disease control rate (DCR), and clinical benefit rate were 37.9% (95% CI: 20.7-57.7), 72.4% (95% CI: 52.8-87.3), and 44.8% (95% CI: 26.4-64.3), respectively. Based on RECIST 1.1, the extracranial ORR and DCR were 33.3% (95% CI:17.3-52.8) and 66.7% (95% CI: 47.2-82.7), respectively. The overall ORR was 33.3% (95% CI: 17.3-52.8), and the overall DCR was 60.0% (95% CI: 40.6-77.3). The median intracranial, extracranial, and overall progression-free survival were 8.4 months (95% CI: 1.9-not reached [NR]), 11.0 months (95% CI: 1.9-NR), and 8.1 months (95% CI: 1.9-11.0), respectively. Grade ≥3 treatment-related adverse events occurred in 70.0% of patients, most commonly γ-glutamyltransferase elevation (43.3%), aspartate aminotransferase elevation (20.0%), and neutrophil count decrease (20.0%). No treatment-related death occurred. **Conclusions:** SPH4336 plus endocrine therapy demonstrated clinically meaningful intracranial antitumor activity with a manageable safety profile in $HR^+/HER2^-$ MBC with brain metastases. These findings warrant further investigation in randomized studies for this patient population with high unmet medical need. Clinical trial information: NCT05872347. Research Sponsor: Shanghai Pharmaceuticals Holding Co., Ltd.

1077 **Poster Session**

[^{18}F] Fluoroestradiol PET/CT to guide second-line treatment decision-making in patients with estrogen receptor–positive, HER2-negative advanced breast cancer after progression on first-line aromatase inhibitor and CDK4/6 inhibitor: Primary results of ESTROTIMP. First Author: Francois Clement Bidard, Institut Curie, Paris, France

Background: Despite availability of novel endocrine treatment (ET) options for patients with ER+ HER2- ABC, many patients experience early disease progression under 2nd line ET-based regimen after AI+CDK4/6i, underscoring a significant rate of endocrine resistance. Timely identification of endocrine-refractory disease at progression under 1st line is critical to optimize treatment selection and consider non-ET strategies, such as antibody-drug conjugates or chemotherapy. FES PET/CT enables a non-invasive, whole-body assessment of ER expression; absent or heterogeneous FES uptake may indicate ER loss or downregulation, key mechanisms of resistance. Our objective was to evaluate the impact of FES PET/CT on 2nd line treatment decisions. **Methods:** In this non-randomized prospective multicenter trial (NCT05486182), patients with ER+ HER2- ABC progressing on 1st line AI+CDK4/6i underwent standard-of-care FDG PET/CT followed by FES PET/CT. Oncologists prospectively documented therapeutic management plans, before and after FES PET/CT. Patients rated pain and apprehension for FES PET/CT vs. biopsy on a Visual Analogue Scale. Primary endpoint was the proportion of patients with a therapeutic management change after FES PET/CT, and primary objective was to demonstrate that at least 10% of patients had their therapeutic management changed after FES PET/CT (Wald test). **Results:** Of 153 patients enrolled, 129 were evaluable for the primary endpoint. When compared with FDG PET/CT, FES uptake was classified as "all lesions ER+" in 65 (50%), "mixed ER+/- lesions" in 38 (30%), and "all lesions ER-" in 25 (19%) patients. Therapeutic management was changed based on incorporation of FES PET/CT results in 46/129 patients (35.7%; 96% CI [27.0-44.3], p<0.0001), including treatment type (n=38), diagnostic modalities (n=8), and planned follow-up (n=12). Treatment changes mostly consisted of using chemotherapy instead of ET (n=16), ET instead of chemotherapy (n=3), adding targeted therapy to single agent ET (n=2), changing the targeted therapy paired with ET (n=8), adding radiation therapy to disease sites (n=4), and performing surgery (n=2). Oncologist confidence in FES PET/CT was on average 7.8/10 (Q1-Q3: 7-9). Patients reported significantly lower pain and apprehension for FES PET/CT vs. biopsy (Pain: Mean 0.8 vs 4.5; Apprehension: Mean 1.8 vs 5.2; both p<0.0001). **Conclusions:** ESTROTIMP shows that, at progression under AI+CDK4/6i, ER expression is completely or partially lost in about half of patients with ER+ HER2- ABC. The trial reached its primary endpoint, demonstrating a clinically meaningful impact on therapeutic management, and supporting the use of FES PET/CT as a standard workup at time of progression under 1st line AI+CDK4/6i. Clinical trial information: NCT05486182. Research Sponsor: GE HealthCare.

1078 Poster Session

BL0175, a novel nano-mediated polypeptide conjugate of protein degrader, in patients (pts) with locally advanced/metastatic HR+/HER2− breast cancer (HR+, HER2- LA/mBC): Initial results from a phase 1 study. First Author: Nanya Wang, The First Hospital of Jilin University, Jilin, China

Background: BL0175 is a novel nano-conjugate (~10 nm) composed of PEG-modified poly (amino acid), enzyme-responsive peptide linkers, and the protein-degrader payload fulvestrant. It accumulates in the tumor microenvironment (TME), where enzymatic cleavage releases fulvestrant continuously. The released fulvestrant penetrates tumor cells, effectively inducing cell death. Nonclinical studies demonstrated that BL0175 provides superior tumor distribution of fulvestrant, enhanced tumor growth inhibition, and greater progesterone receptor suppression compared with conventional fulvestrant injection at equivalent doses. This first-in-human Phase I study reports preliminary safety, efficacy, and pharmacokinetic (PK) data for BL0175. **Methods:** Postmenopausal pts with HR+, HER2- LA/mBC received intramuscular BL0175 (Cycle 1: Days 1, 15; thereafter every 4 weeks) at doses ranging from 50 mg to 500 mg. Data are summarized across all cohorts unless otherwise specified. **Results:** As of January 14, 2026, 22 pts were treated (50 mg: n=1; 100, 200, 300, 400, 500 mg: n=3 each; 250 mg: n=6). The median number of prior lines of therapy was 3 (range: 1–7). Safety: Adverse events (AEs) and treatment-related AEs (TRAEs) occurred in 64% of pts (14/22). All AEs were Grade 1–2, with no dose-dependent trends or unexpected safety signals. Efficacy: Eleven pts had post-baseline tumor assessments (50 mg & 300 mg: n=1 each; 100, 200, 400 mg: n=3 each). Disease control rate (DCR) was 100% in cohorts receiving $\geq$200 mg. Three partial responses (PR) were observed in cohorts $\geq$200 mg, yielding an objective response rate (ORR) of 42.9% (3/7). The pts who achieved PR comprised individuals with prior progression on standard CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (aromatase inhibitor or fulvestrant injection), as well as those presenting with brain metastases at baseline. These data suggest that 200 mg may be an effective therapeutic dose. Pharmacokinetics: PK exposure (C_{max} and AUC_{0-336h}) of both released and total fulvestrant increased dose-proportionally. BL0175 was stable in systemic circulation (release rate $\leq$0.03% across doses). Notably, in two pts (50 mg and 100 mg cohorts), released fulvestrant concentrations in tumor tissue were 9-fold and 18-fold higher, respectively, than in plasma, confirming tumor-specific enrichment. **Conclusions:** BL0175 demonstrated promising efficacy in pts with HR+, HER2- LA/mBC, including those with prior progression on fulvestrant injection and CDK4/6i-based therapy and in brain metastases. The preliminary results validate BL0175's design rationale, supporting its tumor-targeted delivery and potential for enhanced efficacy at lower doses. These findings warrant further investigation of BL0175 in this patient population. Clinical trial information: NCT06738966. Research Sponsor: None.

1079 Poster Session

Outcomes by lobular (lob) histology status at initial diagnosis in patients (pts) in the INAVO120 phase 3 trial with *PIK3CA*-mutated (mut), hormone receptor-positive (HR+), HER2-negative (HER2−), endocrine-resistant advanced breast cancer (aBC) treated with inavolisib (INAVO)/placebo (PBO) + palbociclib (PALBO) + fulvestrant (FULV). First Author: Nicholas C. Turner, Royal Marsden Hospital, Institute of Cancer Research, London, United Kingdom

Background: INAVO (a highly potent and selective PI3Kα inhibitor that also promotes mut p110α degradation) + PALBO + FULV is approved for *PIK3CA*mut, HR+, HER2−, endocrine-resistant aBC based on statistically significant and clinically meaningful investigator-assessed progression-free survival (PFS) benefit over PBO + PALBO + FULV in INAVO120 (NCT04191499). We report exploratory analyses of treatment (tx) outcomes by lob histology status documented at initial diagnosis. **Methods:** Baseline characteristics, PFS, overall survival (OS), objective response rate (ORR), and duration of response (DoR) were evaluated for 53 pts with reported lob only and 64 with reported lob only or mixed lob (lob + $\geq$1 other selected subtype) histology at initial diagnosis. *PIK3CA*mut distribution, and association of histology and PFS with *CDH1* alteration (alt) status, were also assessed. **Results:** At the clinical data cut-off for the updated PFS and final OS analyses (Nov 15, 2024), 24 and 29 pts with lob only histology, and 29 and 35 pts with mixed lob histology, were randomized to the INAVO and PBO arms, respectively. Baseline characteristics were balanced across tx arms. Median follow-up was 34.2 and 32.3 months (m) in the INAVO and PBO arms, respectively. Pathogenic *CDH1*alts were more frequent in the lob only (65.2%) and mixed lob (58.9%) subgroups compared with no lob histology (6.3%). Efficacy by lob status is shown in the Table. *PIK3CA*mut distribution was similar across histologies. PFS benefit of INAVO over PBO was observed regardless of baseline *CDH1*alt status (hazard ratio 0.3 for *CDH1*alt and 0.5 for no alt detected). **Conclusions:** In this INAVO120 exploratory analysis, efficacy was improved with INAVO vs PBO, regardless of lob histology status at initial diagnosis and *CDH1*alt status. This further supports the benefit of INAVO + PALBO + FULV in *PIK3CA*mut, HR+, HER2−, endocrine-resistant aBC. Clinical trial information: NCT04191499. Research Sponsor: F. Hoffmann-La Roche Ltd.

	Lob only: INAVO n = 24	Non-lob: INAVO n = 137	Lob only: PBO n = 29	Non-lob: PBO n = 135	Mixed lob: INAVO n = 29	Non-mixed lob: INAVO n = 132	Mixed lob: PBO n = 35	Non-mixed lob: PBO n = 129
PFS, m (95% CI)	21.7 (9.3–25.8)	17.2 (11.6–24.3)	7.2 (3.7–9.4)	7.4 (5.8–9.7)	21.7 (11.3–27.9)	16.6 (11.2–24.2)	7.2 (3.8–9.4)	7.4 (5.8–9.7)
OS, m (95% CI)	NR (18.1–NR)	33.0 (27.1–44.8)	24.1 (11.1–NR)	27.0 (22.8–40.7)	NR (28.4–NR)	33.0 (27.0–38.0)	24.1 (11.1–NR)	28.0 (22.8–40.7)
ORR, n (%; 95% CI)	15 (62.5; 40.6–81.2)	86 (62.8; 54.1–70.9)	6 (20.7; 8.0–39.7)	40 (29.6; 22.1–38.1)	19 (65.5; 45.7–82.1)	82 (62.1; 53.3–70.4)	7 (20.0; 8.4–36.9)	39 (30.2; 22.5–38.9)
DoR, m (95% CI)	21.2 (9.3–NR)	18.7 (12.2–28.3)	11.1 (8.5–NR)	10.7 (7.5–20.2)	20.3 (9.6–NR)	18.8 (11.1–28.7)	11.1 (3.1–NR)	11.1 (7.5–20.2)

CI, confidence interval; NR, not reached.

1080 Poster Session

Impact of FES-PET imaging in the management of estrogen receptor–positive breast cancer: Real-world experience. First Author: Joanne E. Mortimer, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: F18 labeled estradiol PET imaging (FES-PET) is endorsed by NCCN guidelines to identify advanced/recurrent estrogen receptor positive (ER+) breast cancer, especially invasive lobular disease. As an adjunct to conventional imaging, FES-PET may provide information about estrogen dependence in lesions that are not readily biopsied. We reviewed the use of FES-PET imaging at City of Hope, Southern California and how it impacted treatment. **Methods:** This is a retrospective chart review study of pts undergoing FES-PET imaging in the management of ER+ breast cancer. Demographic data, indications for FES-PET imaging, and impact on subsequent care were extracted from the electronic medical record. **Results:** Between 1/21/22 and 12/31/25, 191 patients with a median age of 52 (Range 32-89) underwent an initial FES-PET scan at City of Hope and its Southern California Network. All had a diagnosis of estrogen receptor + (ER+) breast cancer; 124 were Invasive Ductal Carcinoma (IDC), 59 Invasive Lobular Carcinoma (ILC), 7 mixed IDC with ILC features, and 1 adenocarcinoma. FES-PET was used to stage "high-risk" local disease in 85, 76 continued their initial treatment plan, 8 were found to have metastatic disease, and 1 underwent additional surgical resection for residual disease in the breast. Of 102 pts. with metastatic disease, 58 were FES positive; 44/50 responded to endocrine therapy, 7 received chemotherapy and 1 refused treatment; 44 were FES negative and 23 received chemotherapy, 10 had no response to endocrine therapy, and 11 received no further treatment. Four patients had synchronous primary tumors and FES was used to distinguish lesions that were attributable to breast cancer. Of the patients with metastatic FES+ disease, 33 underwent serial FES-PET imaging; 3 were part of a clinical trial assessing radiation therapy in oligometastatic disease, 3 had been on prolonged treatment with chemotherapy and FES-PET was obtained to assess potential for reintroduction of endocrine therapy, 27 had response evaluation to aromatase inhibitor therapy where conventional staging did not adequately assess the measurable/evaluable disease as well as FES-PET. **Conclusions:** Our data support the use of FES-PET which altered treatment in 11% of patients with high-risk localized and identified patients for whom chemotherapy was the appropriate choice of systemic therapy. In select pts, serial FES-PET imaging was more helpful in monitoring disease response to AI-based therapy than conventional imaging and should be considered in future guideline recommendations. Research Sponsor: National Cancer Institute; P30CA033572.

1081 Poster Session

Oral selective estrogen receptor degraders in HR+/HER2- advanced breast cancer and impact of ESR1 mutation status: A systematic review and meta-analysis. First Author: Amal AlJuhani, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Oral selective estrogen receptor degraders (SERDs) are a promising therapeutic class for hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. Several randomized controlled trials (RCTs) have evaluated oral SERDs, but results have varied across agents and populations. **Methods:** We searched MEDLINE, EMBASE, CENTRAL, and conference proceedings until December 31st 2025 and identified RCTs comparing oral SERDs with standard endocrine therapy in adults with HR+/HER2- advanced breast cancer. Two reviewers independently screened studies, extracted data, and assessed risk of bias using Cochrane RoB 2. Random effects meta-analysis was performed using generic inverse variance for hazard ratios for progression-free survival (PFS). Odds ratios for safety outcomes were pooled using Mantel-Haenszel (fixed effect). **Results:** A total of 9 trials comprising 4,258 participants were included. Overall, oral SERDs demonstrated a statistically significant improvement in PFS compared with standard endocrine therapy (HR 0.76, 95% CI 0.60 to 0.97; p=0.03). In the estrogen receptor 1 gene mutated (ESR1m) subgroup (7 trials, n=1,273), oral SERDs showed a more pronounced PFS benefit (HR 0.53, 95% CI 0.39 to 0.70; I^2=53.4%; p=0.002). In contrast, patients with ESR1 wild-type tumors (6 trials, n=1,212) derived no significant benefit (HR 0.95, 95% CI 0.81 to 1.12; I^2=0%). The interaction between ESR1m and treatment was statistically significant ($p<0.001$). Grade $\geq$3 adverse events were similar between groups (RR 1.09, 95% CI 0.87 to 1.38). Treatment discontinuation due to adverse events was significantly higher with oral SERDs (RR 1.65, 95% CI 1.02 to 2.65). **Conclusions:** Oral SERDs lead to a statistically significant improvement in PFS over standard endocrine treatments albeit with the effect seemingly limited to patients with ESR1m. These results support the use of biomarkers to determine which patients are most likely to receive clinical benefits from oral SERD therapy and underscore the importance of ESR1 testing in order to tailor treatment optimally. Research Sponsor: None.

ESR1 mutation status subgroup analysis.

Subgroup	Trials	Participants	HR	95% CI	P-value
ESR1 Mutant	7	1,273	0.53	0.39 – 0.70	0.0015
ESR1 Wild-Type	6	1,212	0.95	0.81 – 1.12	0.4684

1082 **Poster Session**

Culmerciclib (CDK2/4/6 inhibitor) plus fulvestrant in HR+/HER2− advanced breast cancer after progression on CDK4/6i: Preliminary results from a phase II trial. First Author: Tao Sun, Liaoning Cancer Hospital & Institute, Shenyang, China

Background: CDK4/6 inhibitors (CDK4/6i) in combination with endocrine therapy (ET) have been the standard first line treatment for HR+/HER2- advanced breast cancer (ABC). However, there is currently no established standard treatment after progression on a CDK4/6i–based regimen. Culmerciclib (Culm), a novel potent CDK2/4/6 inhibitor, has shown significant PFS benefits when combined with Fulvestrant (Ful) in both first-line and later-line settings for HR+/HER2− ABC (ESMO 2025; CSCO 2024). Here we evaluated the combination in HR+/HER2- ABC following disease progression on prior CDK4/6i + ET. **Methods:** In this prospective, multicenter, single-arm phase II trial (TQB3616-II-04), eligible patients (pts) who had progressive disease on a CDK4/6i + ET as initial therapy for ABC or relapse on/after a CDK4/6i + ET as adjuvant therapy for early BC, previous up to 2 lines of ET and 1 line of chemotherapy for ABC, received Culm (180mg, qd) + Ful. The primary endpoint was ORR, and secondary endpoints included DCR, PFS, DOR, CBR and safety. Assuming a power of 0.9 to test the hypothesis that ORR would be 30.0% against the null hypothesis that it would be 8.0% or lower, with 0.025 as one-sided significance level; considering the dropout rate of 20%, a total of 33 pts was required. **Results:** 35 female pts were enrolled and treated, 31.4% were pre- or perimenopausal (received a concomitant GnRH agonist), 71.4% had visceral metastases (including 45.7% with liver metastases and 5.7% with brain metastases). All pts had received prior CDK4/6i +ET (AI and/or SERM) therapies, prior CDK4/6i was 68.6% palbociclib, 28.6% dalpiciclib, and 8.6% ribociclib (2 pts with dual CDK4/6i); 28.6% had received prior two lines endocrine therapy, also 37.1% had received prior chemotherapy for metastatic disease. As of data cutoff on Jan 17, 2026, median follow-up time was 7.3 months. Among 34 evaluable pts, the overall ORR was 29.4% (95% CI: 15.1, 47.5, $p < 0.0001$), meeting the predefined primary endpoint, which significantly rejected the null hypothesis of ORR. The overall DCR was 88.2% (95% CI: 72.6, 96.7), and the CBR was 82.4% (95% CI: 65.5, 93.2). Median TTR was 3.7 months, mPFS and mDOR were not yet reached, while 6-month PFS rate was 72.5% (95% CI: 52.7, 84.7). Grade≥3 TRAEs and serious TRAEs were reported in 14 (40.0%), 3 (8.6%) pts, respectively. The most common TRAEs included diarrhea, neutropenia, vomiting etc. No new safety signals were observed, with findings consistent with the known safety profile of Culm. Dose reductions due to TRAEs occurred in 14.3% of pts, and no deaths or discontinuations related to TRAEs were reported. **Conclusions:** Culm combined with Ful demonstrated promising antitumor activity in HR+/HER2- ABC after progression on previous CDK4/6i + ET, offering a potential targeted therapeutic strategy for this population (NCT06702618). Clinical trial information: NCT06702618. Research Sponsor: None.

1083 **Poster Session**

Genomic markers of resistance to first-line (1L) therapy with a CDK4/6 inhibitor (CDKi) and endocrine therapy (ET) in patients (pts) with hormone receptor−positive (HR+) metastatic breast cancer (MBC). First Author: Albert Grinshpun, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Pts with HR+ MBC exhibit variable responses to 1L ET + CDKi therapy. We analyzed clinicopathologic features and genomic landscapes of biopsies obtained at the time of the diagnosis of MBC to identify determinants of sensitivity/resistance to 1L CDKi, with a focus on distinguishing endocrine-sensitive from endocrine-resistant (ETR) disease. **Methods:** A single center cohort included pts with biopsies obtained within 3 months of diagnosis of HR+, HER2-negative MBC (distant recurrent and de-novo [DNIV]), diagnosed between 2013 - 2020. Tumors underwent targeted DNA sequencing (OncoPanel). Clinical data were obtained from the EMBRACE database. **Results:** The entire cohort included 666 pts, of them 321 (48%) treated with 1L ET + CDKi. Among pts who received adjuvant ET (n = 347), 54 (15.6%) had primary ETR, 140 (40.3%) secondary ETR, and 153 (44.1%) were endocrine-sensitive. Of these pts, 56% (n = 191) received 1L CDKi therapy. The median time to next treatment (TTNT) in pts treated with 1L CDKi differed significantly by disease presentation, with a median of 1.3 years (95% CI, 0.9–1.5) for recurrent MBC and 2.3 years (95% CI, 1.7–3.6) for DNIV (log-rank p = 0.0005). TTNT also varied significantly according to endocrine sensitivity, with median TTNT of 0.6, 0.9, and 1.8 years for primary ETR, secondary ETR, and endocrine-sensitive disease, respectively (p = 0.0005). In the entire cohort, SNVs/indels were most frequent in *PIK3CA*, *TP53*, and *CDH1*. *CCND1*, *FGFR1*, and *MYC* amplifications were most frequent amplifications. *TP53* and *ESR1* mutations were enriched in ETR tumors, compared with ET sensitive cancers ($q < 0.2$). *ESR1* mutations were detected in 15% of ETR tumors, versus 8% in endocrine-sensitive cancers and 3% in DNIV. Prior adjuvant aromatase inhibitor exposure occurred in 39%, 61%, and 44% of patients with primary ETR, secondary ETR, and ET-sensitive tumors, respectively. When comparing poor and exceptional responders to 1L CDKi, TTNT <6 months versus >36 months, mutations in *TP53* and *NF*1 were significantly enriched in the poor responders ($q < 0.2$). We also evaluated the association between specific genomic alterations and TTNT on 1L CDKi; mutations in *TP53*, *NF1*, and *ERBB2*, as well as amplifications of *RAD21*, *FGFR1* and deletions of *RB1*, *CDKN2A* were associated with shorter TTNT on 1L ET plus CDKi ($q < 0.2$). **Conclusions:** In our cohort, distinct genomic alterations were associated with ETR and shorter TTNT on 1L CDKi. These findings underscore the biology of ETR and support the clinical relevance of early genomic profiling to refine risk stratification and guide therapeutic decision-making. Notably, the high prevalence of *ESR1* alterations in ETR tumors carries important implications for adjuvant and 1L treatment strategies, particularly the potential role of oral selective estrogen receptor degraders in this setting. Research Sponsor: None.

1084 **Poster Session**

Impact of oral SERDs, including giredestrant, on survival in HR+ HER2− metastatic breast cancer: A meta-analysis. First Author: Changtai Tian, Stony Brook University Hospital, Stony Brook, NY

Background: Oral selective estrogen receptor degraders (SERDs) are designed to overcome endocrine resistance in HR+ HER2- breast cancer due to ESR1 mutations. Several SERDs have been evaluated in recent trials. We performed a meta-analysis evaluating oral SERDs in previously treated patients with HR+ HER2- metastatic breast cancer (MBC). **Methods:** Randomized controlled trials comparing oral SERDs to standard endocrine therapy in previously treated HR+, HER2- MBC, reporting progression-free survival (PFS) or overall survival (OS) and adverse events (AEs), were identified via a systematic PubMed search. To incorporate the latest SERDs data, results from the recently presented giradestrant trial were included. Meta-analysis was performed for the overall intention-to-treat (ITT) population and the ESR1-mutant (ESR1m) subgroups. Leave-one-out analyses excluding giradestrant were conducted to highlight its specific impact. Rates of serious adverse events (grade ≥3) and treatment discontinuation were also analyzed. **Results:** A total of 2324 patients from six phase III trials were included in this analysis. Oral SERDs improved PFS compared with standard endocrine therapy in the ITT population (HR 0.734, CI 0.620-0.869, p<0.001) with greater benefit observed in the ESR1m subgroup (HR 0.538, CI 0.430-0.673, p<0.001). Excluding giradestrant data from the evERA trial led to modest reduction in PFS benefit in both the ITT (HR 0.755, CI 0.661-0.908, p<0.05) and the ESR1m (HR 0.582, CI 0.471-0.718, p<0.05) subsets, though overall PFS benefit remained. Additionally, SERDs were associated with an OS advantage in pooled analyses for the ITT population (HR 0.743, CI 0.621-0.889, p<0.05) and ESR1m population (HR 0.584, CI 0.433-0.768, p<0.001). Excluding giradestrant did not result in significant changes in OS estimates. Grade ≥3 AEs were more frequent with SERDs (OR 1.53, CI 1.20-1.95, p<0.001) while discontinuation rates were similar between groups (OR 1.53, CI 0.99-2.37, p=0.06). **Conclusions:** Oral SERDs significantly improve PFS in previously treated HR+ HER2- MBC with the greatest benefit in patients with ESR1 mutations. Pooled analysis suggests an OS advantage favoring SERDs. Giradestrant contributes to the observed PFS class effect without altering OS outcomes. SERDs are associated with increased toxicity. Although a trend towards higher discontinuation rates was noted, it did not reach statistical significance, and discontinuation rates remain comparable to standard endocrine therapy. These findings support the use of oral SERDs in the second- and third-line treatment of HR+ HER2- MBC, particularly in ESR1-mutant disease. Research Sponsor: None.

1085 **Poster Session**

Ethnicity-based comparative analysis of treatment endpoints of 30,000 HR+/HER2− metastatic breast cancer patients on CDK4/6 inhibitors (palbociclib/ribociclib/abemaciclib). First Author: Olivia Benny, School of Medicine, Keele University, Staffordshire, UK, United Kingdom

Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), in combination with endocrine therapy, are the mainstay for HR+/HER- metastatic breast cancer (MBC). However, ethnically diverse populations remain underrepresented in randomised clinical trials, limiting the ability to stratify by ethnicity. This meta-analysis utilises real-world evidence to compare treatment endpoints i.e., overall survival (OS), progression-free survival (PFS), objective response rate (ORR) and adverse effects (AE) across ethnic groups. **Methods:** 116 studies from MEDLINE and Embase were included (Palbociclib: 67, Abemaciclib: 29, Ribociclib: 20). 31580 HR+/HER- MBC patients (Asian [AS]:22067; White [WH]: 8993; Black [BL]: 510) were included. Median survival and response rates were calculated using a random effects model to account for between-study variability. Parentheses represent 95% confidence intervals (CI). **Results:** Pooled analysis shows disparities in efficacy and significant variation in haematological toxicity. Maximum mOS benefit for AS was on palbociclib (61.8mo) whereas for WH was ribociclib (63.9mo), primarily driven by long-term follow-up in MONALEESA. mPFS benefit was longest in BL patients on abemaciclib (17mo), WH patients on palbociclib (27.7mo), AS patients on ribociclib (25.2mo). ORR was highest for ribociclib across all ethnic groups (Table). Meta-regression indicated ethnicity was not a significant independent moderator of AE risk (p > 0.05). AS cohorts demonstrated the highest incidence of Grade 3+ neutropenia across all agents: Palbociclib (72.0%; 49.5–87.1), Abemaciclib (52.8%; 46.1-59.4), and Ribociclib (45.8%; 39.1-52.5; p < 0.0001). In contrast, WH and BL patients exhibited significantly lower G3+ neutropenia rates, ranging from 12.0% to 33.8% (p < 0.0001). AS patients also showed the highest rates of leukopenia and anaemia across all CDK4/6i. **Conclusions:** Our large-scale meta-analysis findings establish a novel, evidence-based ethnicity-informed CDK4/6i selection framework to optimize treatment endpoints in HR+/HER2- MBC patients. This highlights the urgent need for prospective trials focused on underrepresented populations to close the survival gap. Research Sponsor: None.

Metric	Subgroup	Palbociclib	Abemaciclib	Ribociclib
ORR (%)	AS	34.0 (27-42)	28.7 (16.1-41.3)	52.4 (46.4-58.5)
	WH	34.0 (28-65)	41.9 (14.9-68.9)	44.9 (32.1-57.7)
	BL	25.0 (17-23)	N/A	34.6
mPFS (mo)	AS	21.0	13.0	25.2
	WH	27.7	21.8	24.1
	BL	14.1	17.0	10.8
mOS (mo)	AS	61.8	25.2	58.7
	WH	60.5	37.6	63.9

1086 **Poster Session**

An early resistance genomic state (ERGS) as an identifier of primary CDK4/6 inhibitor failure in HR+/HER2− metastatic breast cancer. First Author: Mobina Shrestha, Sentara Albemarle Medical Center, USACS, Elizabeth City, NC

Background: CDK4/6 inhibitors combined with endocrine therapy are the standard first-line treatment for patients with hormone receptor-positive (HR+), HER2-negative metastatic breast cancer (mBC). However, a substantial subset of patients experience early disease progression, and there are currently no clinically practical tools available at treatment initiation to identify patients unlikely to derive lasting benefit. In this study, we attempt to define a clinically actionable genomic resistance phenotype using routine tumor sequencing. **Methods:** We conducted a retrospective real-world analysis using the MSK CHORD 2024 cohort, including 1,690 patients with HR+/HER2− mBC treated with first-line CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib). An Early Resistance Genomic State (ERGS) was pre-specified based on alterations in five genes with established roles in endocrine and cell-cycle resistance: TP53, ESR1, RB1, PTEN, and NF1. The primary endpoint was time to first documented progression following CDK4/6 initiation, with early progression defined as progression within 6 months. Multivariable Cox proportional hazards models were adjusted for age, visceral disease, and central nervous system (CNS) involvement. Model performance was assessed using internal validation with resampling. **Results:** ERGS alterations were present in 41% of patients. ERGS demonstrated a graded, dose-dependent association with progression risk. Compared with ERGS-negative patients, those with one ERGS alteration had a 29% higher risk of progression (Hazard Ratio (HR) = 1.29, 95% CI: 1.15-1.45), those with two alterations had a 58% higher risk (HR = 1.58, 95% CI: 1.30-1.91), and those with three or more alterations had more than double the risk (HR = 2.19, 95% CI: 1.24-3.87; global log-rank $p<0.0001$). Twelve-month progression rates were 48%, 62%, 71%, and 85% across ERGS 0, 1, 2, and $\geq$3 groups, respectively. The prognostic impact of ERGS remained consistent across endocrine partner (aromatase inhibitor vs fulvestrant) and metastatic pattern subgroups. Incorporation of ERGS significantly improved model discrimination beyond clinical covariates alone, increasing the concordance index from 0.61 to 0.85 in internal validation analysis. **Conclusions:** ERGS defines a systems-level intrinsic CDK4/6 resistance phenotype identifiable using routine tumor sequencing at treatment initiation. This parsimonious genomic state provides clinically meaningful risk stratification beyond standard clinicopathologic features and identifies patients unlikely to derive lasting benefit from CDK4/6-based therapy. Therefore, ERGS may serve as a practical biomarker to prioritize enrollment on escalated first-line trials or alternative therapeutic strategies in HR+/HER2− metastatic breast cancer. Research Sponsor: None.

1087 **Poster Session**

Oral estrogen receptor (ER) degraders compared to standard endocrine therapy (ET) in ER-positive, human epidermal growth factor receptor 2 (HER2)−negative metastatic breast cancer (MBC): A systematic review and meta-analysis. First Author: Hadar Goldvaser, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Treatment with ER-positive HER2-negative (ER+HER2-) MBC has evolved during the past decade. Several novel oral ER degraders have shown to modestly improve progression free survival (PFS) compared to standard ET, with significant results specifically in patients carrying activating *ESR1* mutations. However, whether overall survival (OS) is also improved is unknown. **Methods:** This was a PRISMA guided meta-analysis. We identified all randomized controlled trials (RCTs) comparing ER degraders to standard ET in patients with ER+HER2- MBC. Efficacy outcomes included PFS and OS for the intention to treat (ITT) population, as well as for patients with *ESR1* mutation, and for patients with wildtype *ESR1*. Hazard ratios (HRs) and 95% confidence intervals (CI) for PFS and OS were extracted, and pooled into meta-analysis using RevMan Version 9.18.0. Statistical tests were two-sided, and statistical significance was defined as $p<0.05$. Subgroup analyses comparing outcomes based on *ESR1* mutation were also performed. In trials with multiple investigational arms, the monotherapy ER degrader arm (EMBER-3) and the dose selected for further development (SERENA-2) were include. **Results:** Seven RCTs comprising 3926 patients were analyzed. Compared to standard ET, ER degraders were associated with statistically significant improvement in OS in the ITT population, HR 0.74, 95% CI 0.62-0.89, p=0.001. Analysis by *ESR1* status demonstrated that ER degraders were associated with significant improvement in OS for patients with *ESR1* mutation (HR 0.60, 95% CI 0.47-0.77, $p<0.001$), but not for patients with *ESR1* wild type (HR 0.87, 95% CI 0.66-1.15, p=0.33), p=0.05 for the subgroup difference. ER degraders were associated with significant improvement in PFS in the ITT population, HR 0.80, 95% CI 0.66-0.98, p=0.03. Analysis based on *ESR1* status demonstrated significant improvement is PFS for patients with *ESR1* mutation (HR 0.54, 95% CI 0.43-0.68, $p<0.0001$), but not for patients with *ESR1* wild type (HR 0.95, 95% CI 0.82-1.09, p=0.46), p=0.001 for the subgroup difference. **Conclusions:** Compared to standard ET, ER degraders were associated with statistically significant improvement of OS and PFS. While this impact was notable in the ITT population, subgroups analyses confirmed the statistically significant benefit is limited to patients with *ESR1* mutations. Research Sponsor: None.

1088 **Poster Session**

Capivasertib plus fulvestrant in Chinese patients with HR+/HER2− advanced breast cancer: Interim analysis of CAPItrue. First Author: Peng Yuan, Department of VIP Medical Services, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: After disease progression on cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET), patients (pts) with HR+/HER2- advanced breast cancer (ABC) face limited treatment options and poor prognosis, particularly those with PI3K/AKT pathway tumor alterations, which are major drivers of disease progression and treatment resistance mediated centrally by AKT. Targeting the PI3K/AKT pathway represents a mechanism-driven precision strategy to overcome CDK4/6i/ET resistance, with potential to maximize ET benefit and delay subsequent chemotherapy. In the phase III CAPItello-291 trial, capivasertib (CAPI) plus fulvestrant (FUL) improved progression free survival (7.3 vs 3.1 months, HR 0.50) versus placebo plus FUL in pts with *PIK3CA/AKT1/PTEN*-altered tumors. CAPItrue (NCT06635447) is an ongoing phase IIIb study of CAPI plus FUL in Chinese pts with HR+/HER2- ABC progressing on ET, with a focus on *PIK3CA/AKT1/PTEN-altered* disease, aiming to inform precision 2nd line treatment following CDK4/6i progression. **Methods:** CAPItrue enrolled Chinese pts with HR+/HER2- ABC progressing on ET$\pm$CDK4/6i. All pts received oral CAPI (400 mg BID, 4 days on, 3 days off) and intramuscular FUL. This pre-specified interim analysis was performed in the cohort (C1) without prior FUL (conducted after the last C1 pt received $\geq$1 dose of study treatment). Baseline characteristics, biomarker profiles, preliminary efficacy (interim objective response rate [ORR] was evaluated in pts with $\geq$4 months of follow-up) and safety were summarized. **Results:** By Aug 20, 2025, 195 pts were enrolled in C1 and received study treatment. *PIK3CA/AKT1/PTEN* alterations were detected in 115 (59.0%) pts (altered group). The median age was 55.0 yrs; 64.1% were post-menopausal. Prior therapy for ABC included: 75.4%/8.7% 1/2 prior lines of ET; 65.1% CDK4/6i, 17.9% chemotherapy. The altered group showed similar characteristics. In patients with $\geq$4 months of follow-up, ORR was 35.6% overall (37/104, 1 complete and 36 partial responses [PR]) and 43.1% in the altered group (25/58, 25 PR). Overall, at a median follow-up of 4.1 months,92.8% had $\geq$1 adverse event (AE); 88.7% had AEs possibly related to CAPI; and 34.9%/11.8% had grade $\geq$3/serious AEs (SAE). A similar safety profile was seen in the altered group (any AE: 92.2%, grade $\geq$3 AE: 30.4%, SAE: 11.3%). No new safety signal was observed. **Conclusions:** In Chinese pts with *PIK3CA/AKT1/PTEN*-altered HR+/HER2- ABC previously treated with ET$\pm$CDK4/6i, CAPI plus FUL showed encouraging preliminary efficacy and safety. Follow-up is ongoing. Clinical trial information: NCT06635447. Research Sponsor: AstraZeneca AB.

1089 **Poster Session**

***CBFB* mutations as a predictive biomarker of endocrine therapy benefit in hormone receptor−positive (HR+) breast cancer: Discovery and validation in 3,799 patients.** First Author: Adar Yaacov, Helmsley Cancer Center, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Endocrine therapy (ET) is the mainstay approach for treating HR+ breast cancer, yet resistance frequently limits efficacy. Identifying reliable genomic biomarkers to predict superior treatment response remains an unmet clinical need. **Methods:** We performed unbiased genomic analysis of HR+ patients from the MSK-CHORD cohort (n=2,058), stratified by disease stage (metastatic vs. non-metastatic). Outcomes included progression-free survival (PFS), recurrence-free survival (RFS), and overall survival (OS). FDR-corrected Cox models were used for gene-level discovery. A chemotherapy-treated subset of the MSK-CHORD cohort served as a control to assess treatment specificity. Findings were externally validated in the independent METABRIC cohort (n=1,741). **Results:** Beyond known resistance biomarkers (ESR1, TP53, RB1), loss-of-function mutations in CBFB emerged as a significant predictor of ET benefit. CBFB mutations were present in 6.7% of metastatic breast cancer (MBC; n=80) and 6.3% of non-MBC (n=54). In MBC patients, CBFB mutations were associated with significantly longer PFS (HR=0.44; p=0.0002); in the adjuvant setting, RFS was similarly improved (HR=0.48; p=0.009). OS was prolonged in both settings (HR=0.49 and 0.50; $p<0.05$ for both). CBFB mutations were enriched in lobular histology (OR=2.3; $p<0.0001$); however, multivariable Cox regression confirmed CBFB as an independent predictor after adjusting for histology (HR=0.46; p=0.0003). To provide biological validation, we analyzed RUNX1, the obligate functional partner of CBFB in the CBF transcription complex. Combined CBFB/RUNX1 mutations (n=122, 10.2% in MBC; n=82, 9.5% in non-MBC) demonstrated consistent predictive benefit (HR=0.48 and 0.56; $p<0.0001$ and p=0.007, respectively). Notably, the survival benefit associated with CBFB or CBF-complex mutations was absent in chemotherapy-treated controls, confirming treatment-specific predictive value rather than general prognostic effect. In the METABRIC validation cohort, CBFB mutations (5.9%; 103/1,741) independently predicted longer relapse-free survival (HR=0.59; p=0.005) and OS (HR=0.52; $p<0.0001$). Gene expression analysis revealed that CBFB mutations were associated with significantly lower APOBEC gene family expression ($p<0.001$), suggesting a mechanistic link between CBF-complex loss and reduced APOBEC-mediated mutagenesis, an established driver of endocrine resistance. **Conclusions:** We identify CBF-complex (CBFB/RUNX1) mutations as a novel genomic biomarker of ET benefit in HR+ breast cancer, independent of disease stage and histology, and validated across two large cohorts. These findings highlight a subset of patients with exceptional outcomes and provide a potential mechanistic link between CBF alterations and APOBEC-mediated resistance. Research Sponsor: None.

1090 **Poster Session**

First-line fovinaciclib versus placebo combined with aromatase inhibitor for advanced breast cancer: A randomized, double-blind phase 3 study. First Author: Peng Yuan, Chinese Academy of Medical Sciences Cancer Hospital, Beijing, China

Background: Endocrine therapy combined with a cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor is the standard first-line therapy for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. Fovinaciclib is a novel CDK4/6 inhibitor that showed survival benefit when added to fulvestrant in the later-line setting. This randomized, double-blind, placebo-controlled phase 3 trial evaluated the efficacy and safety of fovinaciclib plus an aromatase inhibitor (AI) as initial therapy. **Methods:** Adult women with HR-positive, HER2-negative advanced breast cancer who had no prior systemic therapy in the advanced setting were enrolled across 63 centers. Eligible patients were randomized in a 1:1 ratio to receive oral fovinaciclib (200 mg, once daily, days 1–21) or placebo plus an AI (letrozole 2.5 mg or anastrozole 1 mg, orally, once daily, days 1–28) in 28-day cycles. Pre- or perimenopausal patients also received goserelin (3.6 mg, subcutaneous, day 1). The primary endpoint was progression-free survival (PFS) assessed by blinded independent central review (BICR). Secondary endpoints included other efficacy endpoints and safety. **Results:** A total of 417 patients were assigned to the fovinaciclib (n = 208) or placebo arm (n = 209) with balanced baseline characteristics. At the protocol-specified interim analysis (median follow-up 16.6 months, data cutoff date June 25, 2024), adding fovinaciclib significantly improved PFS (hazard ratio 0.55, 95% CI 0.38–0.77; p = 0.0003): median PFS was not reached in the fovinaciclib arm and 20.2 months (95% CI 16.4 months–not evaluable) in the placebo arm. The 2-year PFS rates were 65.5% (95% CI 55.3%–73.9%) and 38.9% (95% CI 27.5%–50.2%), respectively. Consistent PFS benefit was observed in investigator assessments (hazard ratio 0.49 [95% CI 0.36–0.68], p $<$ 0.0001) and across most subgroups. Fovinaciclib also showed favorable results across secondary efficacy endpoints. OS data remain immature. Treatment-emergent adverse events (TEAEs) occurred in 207 (99.5%) and 199 (95.2%) patients in the fovinaciclib and placebo arms, respectively, with serious adverse events (SAEs) reported in 30 (14.4%) and 24 (11.5%). Discontinuation due to TEAEs was only 1.4% in both arms. The most common TEAEs were hematologic toxicities, which did not lead to SAEs or study drug discontinuation. Grade ≥3 gastrointestinal toxicities (2.4% versus 0) or renal toxicities (0 versus 0.5%) were rare. **Conclusions:** Adding fovinaciclib to first-line AI therapy provided a significant and clinically meaningful PFS benefit, along with consistent improvements in other survival outcomes and a manageable safety profile. These findings support fovinaciclib as a first-line treatment option for patients with HR-positive, HER2-negative advanced breast cancer. Clinical trial information: NCT05439499. Research Sponsor: Avanc Pharmaceutical Co., Ltd.

1091 **Poster Session**

Effects of SGLT2 inhibitor dapagliflozin on anticancer resistance and alpelisib- and fulvestrant-induced cardiomyocyte injury under hyperglycemic conditions. First Author: Vincenzo Quagliariello, Division of Cardiology, Istituto Nazionale Tumori-IRCSS-Fondazione G. Pascale, Naples, Italy

Background: Activating PIK3CA mutations occur in approximately 40% of hormone receptor–positive (HR+)/HER2-negative breast cancers and drive resistance to endocrine therapy. The PI3Kα-selective inhibitor alpelisib combined with fulvestrant significantly improves progression-free survival, as demonstrated in the SOLAR-1 trial, but its clinical benefit is limited by frequent treatment-induced hyperglycemia. Beyond metabolic toxicity, hyperglycemia promotes oxidative stress, inflammation, and mitochondrial dysfunction, thereby increasing cardiovascular vulnerability and potentially reactivating oncogenic PI3K/AKT signaling through compensatory hyperinsulinemia. Retrospective clinical evidence suggests that sodium–glucose cotransporter-2 (SGLT2) inhibitors may mitigate these effects. We investigated the direct redox-dependent cardiotoxic effects of alpelisib and fulvestrant under hyperglycemic conditions and evaluated whether dapagliflozin confers cardioprotection in human cardiomyocytes. **Methods:** Human iPSC-derived cardiomyocytes were exposed to alpelisib and fulvestrant under hyperglycemic conditions (25 mM glucose) in the absence or presence of dapagliflozin. Cell viability (MTS), mitochondrial membrane potential, reactive oxygen species generation, lipid peroxidation (MDA and 4-HNE), intracellular antioxidant defenses (GSH/GSSG, SOD, catalase/GPx), inflammatory and inflammasome-related mediators (IL-1β, IL-18, IL-6, TNF-α, NLRP3, MyD88), and apoptotic signaling (caspase-3/7 activity) were quantified. Cardiac injury was assessed by high-sensitivity cardiac troponin I and T release. Transcriptomic profiling was performed to interrogate cardiometabolic and redox signaling pathways. **Results:** Alpelisib and fulvestrant synergistically induced a pro-oxidative and pro-inflammatory injury phenotype characterized by mitochondrial depolarization, increased ROS and lipid peroxidation, depletion of antioxidant defenses, activation of the NLRP3/IL-1 axis, and caspase-dependent apoptosis. Dapagliflozin markedly restored redox homeostasis, preserved mitochondrial integrity, suppressed inflammasome and cytokine signaling, and reduced troponin release, indicating robust cardioprotection. Transcriptomic analysis confirmed coordinated downregulation of oxidative stress, inflammatory, and insulin-stress pathways. **Conclusions:** Dapagliflozin directly protects human cardiomyocytes from hyperglycemia-driven, PI3Kα inhibitor–associated oxidative injury by restoring redox and mitochondrial homeostasis. These findings provide a strong mechanistic rationale for repurposing SGLT2 inhibitors as dual cardio-metabolic protectants in precision oncology. Research Sponsor: Ministero della Salute, 5x1000 project 5XMILLE_2022_17.

1092 **Poster Session**

Prognostic impact of tumor recurrence dynamics in patients with HR+/HER2- advanced breast cancer treated with ET+CDK4/6i: Results from the multicenter, Italian study PALMARES-2. First Author: Claudio Vernieri, Fondazione IRCCS Istituto Nazionale dei Tumori; IFOM ETS the AIRC Institute of Molecular Oncology; University of Milan, Milan, Italy

Background: Endocrine sensitivity/resistance (ES/ER) is a key prognostic and predictive factor in patients (pts) with Hormone Receptor-positive, Human Epidermal growth factor Receptor 2-negative advanced Breast Cancer (HR+/HER2- aBC). Cyclin Dependent Kinase 4/6 inhibitors (CDK4/6i)+Endocrine Therapy (ET) are standard 1st line therapy for HR+/HER2- aBC pts regardless of tumor ES/ER status at diagnosis. However, the prognostic value of tumor recurrence dynamics within ES/ER groups has never been investigated. **Methods:** We conducted a pre-planned analysis of the multicenter, real-world, Italian study PALMARES-2 (NCT06805812) to evaluate the prognostic role of tumor recurrence dynamics, de novo aBC presentation and distant recurrence-free interval (DFRI) in pts with HR+/HER2- aBC treated with 1st line ET+CDK4/6i between January 2016 and September 2024. DRFI was defined as the time from surgery to the detection of aBC. The primary endpoint was real-world progression-free survival (rwPFS), defined as the time between ET+CDK4/6i initiation and disease progression (PD) or patient death. Results were adjusted through Multivariable Cox regression for 16 relevant covariates. **Results:** Of 4,234 pts enrolled, 2,858 (67.5%) had ES and 1,376 (32.5%) had ER disease at aBC diagnosis. Median follow-up was 38.6 and 42.7 months, respectively. After adjustment, ER was associated with poorer rwPFS compared to ES (adjusted hazard ratio [aHR] 1.78, 95% CI 1.60-1.96). In the ER cohort, secondary tumor resistance with recurrence during years (y) 3-5 of adjuvant (adj) ET or $<$1 y from its end, and recurrence during extended adj ET or $<$1 y from its end, were associated with increasingly better rwPFS when compared to primary resistance (Table). In the ES cohort, pts with tumor recurrence $>$10 y from adj ET end had significantly longer rwPFS when compared to pts recurring $<$10 y from adj ET end, or pts with no prior adj ET or de novo aBC (Table). Among pts with recurrent disease (N=2,792), any additional y of DRFI resulted in 3% reduction in the risk of disease progression (aHR:0.97, 95% CI: 0.96-0.99). **Conclusions:** The current ES/ER classification fails to capture the whole spectrum of prognostic heterogeneity in HR+/HER2- aBC pts treated with 1st line ET+CDK4/6i. Recurrence dynamics, including DRFI, improve prognostic classification and may inform treatment selection and personalised patient management in this clinical context. Clinical trial information: NCT06805812. Research Sponsor: Associazione Italiana per la Ricerca sul Cancro; Italian Health Ministry.

Recurrence dynamic	N	rwPFS (mo)	aHR (95% CI)
Primary resistant	334	13.4	Ref
Secondary resistant-during 5 y adj ET	668	15.7	0.85 (0.72-0.99)
Secondary resistant-during extended adj ET	375	19.4	0.73 (0.61-0.89)
No adjuvant ET	288	30.0	0.46 (0.36-0.59)
1-5 y from adj ET end	453	29.3	0.54 (0.45-0.65)
5-10 y from adj ET end	377	32.6	0.50 (0.40-0.61)
>10 y from adj ET end	275	45.2	0.30 (0.23-0.40)
De novo aBC	1422	31.3	0.50 (0.42-0.59)

1093 **Poster Session**

Association of *ESR1* amplification with survival and benefit from CDK4/6 inhibition in breast cancer. First Author: George W. Sledge Jr., Caris Life Sciences, Phoenix, AZ

Background: While ESR1 mutations are established mediators of endocrine resistance in breast cancer (BC), the significance of ESR1 amplification (amp) remains poorly understood with reported amp rates vary widely due to platform-specific differences. We leveraged a large clinico-genomic real-world database and applied a stringent NextGen sequencing (NGS) approach to test ESR1 amp. We identify ESR1 amp as a molecular entity distinct from canonical estrogen-driven resistance mechanisms. **Methods:** Breast tumors underwent NGS of DNA and RNA (WES/WTS; NextSeq and NovaSeq; Caris Life Sciences, Phoenix, AZ). Gene copy number was determined by CNVKit with $>$=6.0 copies defined as amp to identify focal, high-level copy number events, minimizing misclassification of chromosome 6 copy gains. Real-world clinical data were obtained from insurance claims. Time on treatment (TOT) was defined treatment start to end; overall survival (OS) from tissue collection to last contact. Cox proportional hazards model and log-rank tests were used for survival analysis. Molecular comparisons used χ^2 or Mann-Whitney U with multiple-testing adjustment (q$<$0.05). Gene set enrichment analysis was performed, with significance defined as FDR$<$0.05. **Results:** Among 27,979 BC tumors, 165 were ESR1 amp (0.6%), a prevalence much lower than prior reports. ESR1 amp was significantly enriched in the Luminal B (LumB) subtype (1.4%, 81/5,915) versus other subtypes (0.1–0.4%, p$<$0.0001). ESR1 amp tumors exhibited features of genomic instability, including higher genomic loss of heterozygosity (61% vs 24%), TP53 mutations (59% vs 27%), and amplifications on chromosomes 6, 8, and 11 (q$<$0.05). Transcriptomically, ESR1 amp tumors had significant enrichment of G2M checkpoint and MYC target gene sets by GSEA in the overall cohort (G2M NES 2.61, MYC NES 2.41,) and in LumB (G2M NES 3.18; MYC NES 3.04, all FDR$<$0.001), consistent with CDK4/6-independent cell-cycle progression. Unlike ESR1 mutations, ESR1 amplification was not associated with increased GREB1 expression (4.4 vs 4.2 TPM, p$>$0.05), consistent with the absence of estrogen-response pathway enrichment. Clinically, ESR1 amp was associated with reduced OS in the overall cohort (HR 1.296, p=0.016) and LumB subset (HR 1.43, p=0.009). Palbociclib TOT was significantly shorter in ESR1 amp vs. non-amp tumors (all BC: 7.0 vs 11.0 months, HR 1.39 [95% CI 1.045–1.85], p=0.023; LumB: 4.9 vs 11.4 m, HR 1.57 [1.1–2.2], p=0.01). This effect was significant after adjusting for TP53, gLOH, and CDH1 alterations (adjusted HR 1.47 [1.04–2.06], p=0.027). No TOT difference was observed with aromatase inhibitors. **Conclusions:** In this large real-world analysis, ESR1 amplification defines a rare, genomically unstable breast cancer subset with proliferative signaling and reduced clinical benefit from CDK4/6 inhibition, supporting its potential role as a negative predictive biomarker. Research Sponsor: None.

1094 Poster Session

A phase 1/2, first-in-human study of AVZO-021, a selective cyclin-dependent kinase 2 inhibitor (CDK2i), as monotherapy and in combination for patients with advanced solid tumors, including hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) breast cancer (BC) and cyclin E1 (CCNE1)–amplified solid tumors: Updated safety and efficacy results. First Author: Manish R. Patel, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL

Background: AVZO-021 is a potent, once-daily, oral CDK2i with high selectivity against CDK1, thus minimizing off-target toxicity. Initial Phase 1 data from the ongoing first-in-human Phase 1/2 study of AVZO-021 (NCT05867251) showed clinical responses and a favorable tolerability profile. **Methods:** The ongoing Phase 1 portion of the study is evaluating the safety, pharmacokinetics (PK), and preliminary efficacy of AVZO-021 alone and in combination with fulvestrant. As of January 20, 2026, the safety population included all patients treated with AVZO-021 monotherapy (n=50) or in combination with fulvestrant (n=13). Efficacy evaluable population included patients treated at ≥150 mg once daily (QD) with HR+/HER2- breast cancer or CCNE1-amplified solid tumors with at least 1 post-baseline scan (n=23 in monotherapy and n=12 in combination with fulvestrant). **Results:** The median age was 63 years for monotherapy patients and 60 years for combination with fulvestrant. Overall, 95% of patients were female, 78% had BC, 10% had ovarian/fallopian tube cancer, and 5% had endometrial/uterine cancer. AVZO-021 monotherapy patients had a median of 3 prior lines of systemic therapy and those in combination therapy had a median of 4 prior lines, in the metastatic setting. All patients with HR+/HER2- BC received prior CDK4/6i and hormonal therapy. Most common (>25%) all-grade treatment-emergent adverse events (TEAEs) were nausea (51%), fatigue (43%), anemia (33%), and vomiting (32%); 13 patients required dose reductions due to TEAEs and 2 patients discontinued due to TEAEs (1 unrelated Grade 3 intestinal obstruction, 1 related Grade 4 neutropenia). Four patients with HR+/HER2- BC and CCNE1-amplified solid tumors had confirmed partial responses and remain ongoing, demonstrating prolonged clinical benefit. Additionally, 23 patients had stable disease for a disease control rate of 77%. Continuous CDK2 target coverage and significant decreases in ctDNA were observed at ≥90 mg QD monotherapy and in combination with fulvestrant. **Conclusions:** With longer follow-up, AVZO-021 as monotherapy and in combination with fulvestrant continues to show an encouraging tolerability profile and clinically meaningful efficacy. Gastrointestinal and hematologic adverse events continue to be of low incidence and severity allowing for prolonged treatment and potential safe combination with AVZO-023, a highly potent and selective CDK4i currently enrolling patients with HR+/HER2- BC in combination with fulvestrant. Clinical trial information: NCT05867251. Research Sponsor: Avenzo Therapeutics.

1095 Poster Session

Liquid-based methylation profiling of molecular breast cancer subtypes (MBS) in hormone receptor positive (HR+) metastatic breast cancer (MBC) treated with CDK4/6 inhibitor (CDK4/6i). First Author: Daniel L. Abravanel, Dana-Farber Cancer Institute, Boston, MA

Background: MBC remains incurable due to the invariable development of resistance, with most deaths resulting from HR+ MBC that acquires resistance to endocrine therapy (ET) combinations. HR and HER2 remain the most important biomarkers in MBC but, while it is known that receptor status and expression based molecular subtypes (e.g. PAM50) can vary over an individual patient's (pts) disease course, serial evaluation is currently limited in routine clinical care by tissue requirements. **Methods:** The EMBRACE cohort study collects biospecimens with matched clinical annotations from pts with MBC at Dana-Farber Cancer Institute. A subset of 510 plasma samples collected around CDK4/6i treatment (tx; pre-tx: -90 to +30 days from start; on-tx; post-tx: -30 to +90 days from end) from 323 pts with HR+ MBC were assessed with Guardant360 Liquid. MBS calls were generated using a previously described cell-free DNA methylation-based deconvolution model that classifies HR and HER2 status in cases with tumor fraction (TF) ≥0.5% with accuracy >85%, and compared with tissue-based HR and HER2 status by immunohistochemistry (IHC). **Results:** Of 510 samples profiled, 308 (60.4%) were evaluable for MBS with TF ≥0.5%. The evaluable rate was lowest in on-tx samples at 48.7%, in line with lower median TF in this set. Of evaluable samples, 285 (92.5%) aligned with sufficient confidence to report a subtype: 273 (88.6%) of evaluable samples were classified as HR+, 23 (7.5%) undetermined, and only 12 (4.9%) HR-, all of which were either from on- or post-tx timepoints. MBS calls on pre-tx samples showed high concordance with clinical IHC, with higher concordance at metastatic diagnosis (91%) than primary diagnosis (86%). Notably, all discordances were cases abstracted as HR+/HER2- at metastatic diagnosis by IHC where MBS yielded HR+/HER2+. Overall, samples from 28 pts were assigned a HER2+ MBS and, in 9 (32%) of these, a concordant genomic alteration in *ERBB2* (copy number gain, gain-of-function mutation and/or fusion) was detected on Guardant360 Liquid. Out of 48 pts with multiple classifiable samples, 11 (22.9%) showed differences in MBS across serial samples including 9 with changes in HER2 (5 gaining and 4 losing HER2 MBS), and 2 with changes in HR (both with an on-tx sample classified as HR- but the subsequent post-tx sample HR+). **Conclusions:** A methylation-based liquid biopsy assay can classify MBS with high correlation to clinical pathology in pre-tx samples and facilitate identification of discordant, or perhaps heterogenous, subtype while capturing the dynamics of MBS over disease course and treatment. Future studies are indicated to investigate the clinical utility of this assay as a biomarker for therapy selection. Research Sponsor: None.

1096 Poster Session

Time on treatment for systemic therapies for patients with hormone receptor-positive breast cancer and *BRCA1*, *BRCA2*, or *PALB2* pathogenic variants. First Author: Gerneiva Parkinson, Stanford Cancer Institute, Stanford, CA

Background: For patients with hormone receptor-positive/HER2- (HR+) metastatic breast cancer and pathogenic variants (PVs) in *BRCA1*, *BRCA2* or *PALB2* (mBRCA), data suggests longer cancer-specific survival compared to patients without PVs (wtBRCA). One hypothesis is that their innate DNA repair deficiency improves response to cytotoxic therapy, as seen in poly (ADP-ribose) polymerase inhibitors (PARPi), which results in longer progression free survival (PFS). However, it remains unclear whether mBRCA is associated with a longer PFS with other therapies such as endocrine therapies (ET), including aromatase inhibitors (AI) and Selective Estrogen Receptor Degraders (SERDs). Some data suggests a shorter PFS with CDK 4/6-inhibitors (CDK4/6i) for mBRCA. Therefore, we compared time-on-treatment (TOT), a real-world surrogate for PFS, for mBRCA vs wtBRCA treated with ET, CDK4/6i, or PARPi. **Methods:** DNA and RNA somatic sequencing were performed on tumors submitted to Caris Life Sciences. HR+ was defined by IHC per ASCO/CAP. TOT was calculated from first to last of treatment time based on insurance claims. Univariable Cox-proportional hazard analyses were utilized to assess TOT between mBRCA vs wtBRCA for each therapy (ET, PARPi and CDK4/6i). Protocol was approved prior by Caris research committee. **Results:** From 8263 HR+ breast cancer patients, 628 were mBRCA+ (median age: 57 years; range 23-90; 96% Female, 4% Male), and 7635 were wtBRCA (median age: 63 years; range 22-89; 98% Female, 2% Male). PVs were *BRCA2*: 66%, *BRCA1*: 19% and *PALB2*: 15%. As shown in Table 1, there was a shorter TOT for AI, SERDs and CDK4/6i, but a longer TOT with PARPi among mBRCA. Patients with mBRCA and high tumor mutational burden (TMB-Hi ≥10 mutations/Mb) had shorter TOT across all analyzed treatments vs low TMB (27.9 vs 35.8 mos, HR=1.47 95%CI 1.14-1.89; p = 0.003), except AI where TMB-Hi had longer TOT (23.5 vs 16.9 mos; HR=0.79, 95% CI 0.62-1.021; p = 0.07). **Conclusions:** This real-world data analysis demonstrates distinct TOT patterns among ET, CDK4/6i and PARPi for mBRCA patients when compared to wtBRCA. This calls for further studies in this specific patient population to understand the various treatment responses, associated tumor biology and immunologic landscape of mBRCA. Research Sponsor: None.

TOT comparisons by therapy between mBRCA and wtBRCA patients.

	Therapy	TOT (months) mBRCA	TOT (months) wtBRCA	Hazard Ratio (HR), Confidence Interval (CI) at 95%
Samples collected at all sites (including breast)	AI	21.7	25.8	HR=1.16 (CI 1.04-1.29 p=0.009
	SERDs	7.6	11.1	HR=1.40 (CI 1.21-1.62) p<0.00001
	CDK4/6i	10.3	13.6	HR=1.39 (CI 1.22-1.59) p<0.001
	PARPi	5.8	2.1	HR=0.51 (CI 0.36-0.73) p<0.001
Samples collected at metastatic sites	AI	25.2	28.3	HR=1.14 (CI 0.994-1.30; p=0.06
	SERDs	6.4	11.5	HR=1.40 (CI 1.20-1.68; p<0.0001
	CDK4/6i	10.3	13.6	HR=1.31 (CI 1.12-1.54; p<0.001
	PARPi	5.8	1.8	HR=0.46 (CI 0.31-0.70; p<0.001

1097 Poster Session

Influence of *TONSL* on tumor suppressor function of *RAD51* and resistance to CDK4/6 inhibitors in ER+ breast cancer. First Author: Harikrishna Nakshatri, Indiana University School of Medicine, Indianapolis, IN

Background: Homologous Recombination (HR) and Replication Stress (RS) resolution mechanisms help to maintain genomic stability. TONSL, MMS22L, RAD51, BRCA1/2 are the few proteins that cooperatively coordinate HR and RS resolution. Therefore, genes in these pathways are expected to function as tumor suppressors. However, only *BRCA*1/2 function as tumor suppressors as their germline mutations increase cancer susceptibility. *TONSL* and *RAD51* are frequently overexpressed in tumors. Here, we investigated the relationship between *TONSL-RAD51* axis in breast cancer (BC) outcome and response to CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET). **Methods:** 10,980 ER+ BC samples tested by NGS (592, NextSeq; WES/WTS, NovaSeq, Caris Life Sciences). Dual expression group *TONSL/RAD51*-high (H), *TONSL*-H/*RAD51*-low (L), *TONSL*-L/*RAD51*-H, and *TONSL/RAD51*-L were classified by RNA expression above or below median. HRD score and *TONSL*/HRD-H/L survival was analyzed using METABRIC (ER+ BC, n = 1904) dataset. *TONSL-RAD51* role in sensitivity to CDK4/6i was determined using *TONSL*-amplified ER+ MCF-7 cells. Real-world median overall survival (mOS) of *TONSL/RAD51* groups was derived from insurance claims and calculated from biopsy, start of ET or CDK4/6i to last contact using Kaplan-Meier. Statistical significance was assessed using chi-square and Mann-Whitney U with multiple comparison adjustments (q<0.05). **Results:** *TONSL*-H had higher HRD score (33.7 vs 21.1, p<0.01) compared to *TONSL*-L (n=952 each). *TONSL*/HRD-H (n=573) had worse mOS (109 m vs 138 m, p<0.05) compared to *TONSL*/HRD-L (n=630). *TONSL*-H had higher frequency of LOH (31.6% vs 19.8%), *BRCA2* (5.1% vs 2.9%) and *BRCA1* (1.5% vs 0.8%) mutation, all q<0.05. *TONSL/RAD51*-H had worse mOS compared to *TONSL*-H/*RAD51*-L, *TONSL*-L/*RAD51*-H or *TONSL/RAD51*-L (Table). *TONSL*-H/*RAD51*-L had worse survival with ET compared to other groups. With ET+CDK4/6i, *TONSL/RAD51*-H and *TONSL*-H/*RAD51*-L had similar but worse mOS compared to *TONSL*-L/*RAD51*-H and *TONSL/RAD51*-L (Table). *TONSL* knockdown in CDK4/6i resistant MCF-7 cells created *TONSL*-L/*RAD51*-H phenotype and cells regained the sensitivity to CDK4/6i. **Conclusions:** These findings suggest that *TONSL*-H independent of *RAD51* expression is associated with poor response to ET or ET+CDK4/6i. Therapeutic targeting of TONSL to create TONSL-L/RAD51-H status may improve response to ET+CDK4/6i. Moreover, as the activity of TONSL is regulated by various protein complexes, destabilizers of TONSL-protein complexes could potentially help in sensitizing ER+ BC to ET or CDK4/6i. Research Sponsor: Susan G Komen for the Cure; SAC232147.

	TONSL/RAD51-H OS in months	*TONSL*-H/*RAD51*-L OS in months	*TONSL*-L/*RAD51*-H OS in months	*TONSL/RAD51*-L OS in months	p-value
Overall	35 m (n=4176)	41.4 m (n=1473)	37.9 m (n=1476)	44.3 m (n=4173)	<0.01
ET	63.4 m (n=1361)	58 m (n=461)	65.2 m (n=508)	76.1 m (n=1430)	<0.01
ET+CDK4/6i	73.8 m (n=2261)	73.8 m (n=866)	84.6 m (n=799)	80.7 m (n=2291)	<0.01

1098 **Poster Session**

Elacestrant in combination with capivasertib in patients with ER+/HER2− advanced breast cancer: Update from ELEVATE, a phase 1b/2, open-label, umbrella study. First Author: Wassim McHayleh, AdventHealth Cancer Institute, Orlando, FL

Background: Disease progression in patients (pts) with ER+/HER2- ABC on 1L ET+CDK4/6i is associated with several mechanisms of resistance, including intrinsic alterations in the PI3K/AKT/mTOR or cell cycle pathways, and/or *ESR1* mutations, a type of acquired resistance that emerges in up to 50% of pts. Elacestrant is the only single-agent oral SERD to significantly improve PFS vs SOC ET in all pts (HR 0.70; 95% CI 0.55-0.88; P=0.0018) and in those with *ESR1m* tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) with manageable safety in EMERALD, a trial that required prior ET+CDK4/6i [Bidard 2022]. In CAPItello-291, capivasertib + fulvestrant showed a mPFS of 7.3 mo (AKT-pathway altered) and 5.5 mo (prior CDK4/6i exposure) [Turner 2023]. In ER+ BC MCF7 CDX and CTG-2308 PDX models (*ESR1*wt/*PIK3CAm*), elacestrant + capivasertib showed superior antitumor activity compared with single-agent treatment, including an improvement in activity vs fulvestrant + capivasertib, further supporting the rationale to combine elacestrant with an AKT inhibitor in ER+ BC [Data on file]. This analysis reports updated Ph 1b safety and preliminary efficacy for elacestrant + capivasertib. **Methods:** ELEVATE is evaluating elacestrant in combination with everolimus, alpelisib, capivasertib, abemaciclib, ribociclib, or palbociclib to address different resistance mechanisms. Pts with ER+/HER2- ABC and 1-2L of prior ET±CDK4/6i are eligible regardless of *ESR1m* status; no prior chemo allowed in the ABC setting. Objectives are to identify the RP2D (Ph 1b) and evaluate PFS (Ph 2). **Results:** As of Dec 2025, 31 pts have been enrolled in the Ph 1b elacestrant (258-345 mg) + capivasertib (320-400 mg) cohorts. Key baseline characteristics include pts with visceral mets (90%), primary endocrine resistance (23%), *ESR1m* (45%), prior CDK4/6i (94%), and prior fulvestrant (45%). The most common (≥35%) TEAEs were diarrhea (81%; 6% Gr 3), nausea (74%; 0% Gr 3), rash (61%; 13% Gr 3), fatigue (58%; 3% Gr 3), vomiting (42%; 0% Gr 3); observed hyperglycemia was 29% (10% Gr 3). Elacestrant 345 mg QD + capivasertib 320 BID [4 days on/3 days off] was determined as the RP2D based on the safety profile and PK analysis; no DLTs were observed. In RP2D response-evaluable pts (n=9), preliminary efficacy showed an ORR of 22%, CBR24 wk at 67% (1 CR, 1 PR, and 6 SD), and a mPFS of 11.3 mo. Median follow-up is 10.2 mo [1.8-12.0]. Updated results and additional data will be reported. **Conclusions:** Elacestrant + capivasertib shows a manageable safety profile, consistent with known capivasertib + fulvestrant Gr 3 AEs, and clinically important efficacy in pts with AKT-pathway altered ER+/HER2- ABC with progressive disease. Enrollment in Ph 2 is ongoing. Elacestrant + capivasertib combination therapy offers pts the benefit of receiving both drugs with manageable safety and potential extended clinical benefit as an all-oral treatment option. Clinical trial information: NCT05563220. Research Sponsor: Menarini Group.

1099 **Poster Session**

Real-world comparative safety and outcomes of ribociclib versus palbociclib in hormone receptor-positive, HER2-negative metastatic breast cancer: A propensity score–matched sensitivity analysis. First Author: Noura Abbas, American University of Beirut Medical Center, Beirut, Lebanon

Background: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors are widely used in hormone receptor-positive (HR+) / HER2-negative (HER2-) metastatic breast cancer, yet real-world differences in survival and clinically relevant toxicities across agents remain unclear. We performed a propensity score-matched (PSM) sensitivity analysis comparing ribociclib and palbociclib, focusing on mortality and selected safety endpoints. **Methods:** Using the TrinetX database, a federated real-world data network, adult patients with HR+/HER2- metastatic breast cancer treated with ribociclib (cohort 1) or palbociclib (cohort 2) were identified. 1:1 propensity score matching was performed on more than 20 baseline characteristics. Outcomes were evaluated using (1) risk analyses excluding patients with the outcome prior to the time window and (2) Kaplan-Meier time-to-event analyses with hazard ratios (HRs). Endpoints included all-cause mortality, prolonged QT, cardiac arrest, liver injury, hospital admission, and emergency department (ED) visits. **Results:** Patient counts were 2,819 vs 11,871 before matching and 2,696 vs 2,696 after matching. In the matched cohorts, ribociclib was associated with significantly lower all-cause mortality compared with palbociclib (HR 0.65, 95% CI 0.552-0.758, $p<0.0001$). No statistically significant differences were observed in major cardiovascular safety outcomes. Specifically, rates of cardiac arrest were comparable between groups (HR 0.76, 95% CI 0.384-1.505, $p=0.43$), as were rates of long QT syndrome (HR 0.837, 95% CI 0.425-1.648, $p=0.61$). With respect to hepatic and healthcare utilization outcomes, liver injury occurred numerically more often in the ribociclib group, but this difference did not reach statistical significance (HR 1.209, 95% CI 0.896-1.632, $p=0.21$). Ribociclib was associated with numerically lower rates of hospitalization (HR 0.845, 95% CI 0.700-1.021, $p=0.08$) and ED visits (HR 0.82, 95% CI 0.659-1.02, $p=0.07$), though neither outcome met conventional thresholds for statistical significance. **Conclusions:** In this PSM analysis of HR+/HER2- metastatic breast cancer, ribociclib was associated with significantly lower all-cause mortality compared with palbociclib. Rates of hospitalization, ED visits, prolonged QT, and cardiac arrest were not significantly different. These real-world findings support clinically meaningful heterogeneity across CDK4/6 inhibitors and highlight the importance of individualized agent selection, balancing survival, hepatic toxicity, and healthcare utilization. Research Sponsor: None.

1100 **Poster Session**

Impact of GLP-1 receptor agonists in hormone receptor–positive breast cancer patients receiving CDK4/6 inhibitors. First Author: Kiara Patino, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for type 2 diabetes and obesity due to their efficacy in weight reduction and glycemic control. Beyond their metabolic benefits, GLP-1 RAs delay gastric emptying, which may affect the absorption of oral medications like cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i). Additionally, CDK4/6i and GLP-1 RAs share overlapping gastrointestinal (GI) toxicities such as diarrhea and nausea, which could impact medication tolerability and clinical outcomes. This investigation aimed to characterize the safety of concomitant GLP-1 RA and CDK4/6i use in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer. **Methods:** We performed a single-center, retrospective chart review evaluating adult patients prescribed a CDK4/6i for HR+ breast cancer at Winship Cancer Institute between October 2022 and May 2025. Patients receiving concomitant GLP-1 RA and CDK4/6i (Group 1) were matched 1:1 to patients receiving a CDK4/6i without GLP1-RA (Group 2). Matching criteria included prescribed CDK4/6i, treatment indication (adjuvant or metastatic), age (≥65 years, 45-64 years, and <45 years), and race. The primary outcome was safety, assessed by adverse drug reactions, dose reductions, and discontinuations. **Results:** 82 patients were reviewed, median age 54 years old. Half (41 patients, 50%) were prescribed abemaciclib, 21 (25.61%) palbociclib, and 20 (24.39%) ribociclib. 41 patients receiving concomitant GLP-1 RA and CDK4/6i (Group 1) were matched to 41 patients receiving a CDK4/6i without GLP1-RA (Group 2). Of those in Group 1, 20 were prescribed a GLP-1 RA for diabetes and 18 for obesity. Median BMI was 32.76 kg/m2 (range, 28.44-36.28 kg/m2) in Group 1 compared to 26.32 kg/m2 (range, 23.74-28.05 kg/m2) in Group 2. Semaglutide and tirzepatide were the most prescribed GLP-1 RAs. 38 patients (51.35%) in Group 2 experienced an ADR associated with CDK4/6i compared to 36 patients (48.65%) in Group 1 (p-value, 0.457). Median time to first documented ADR was 14 days (range, 8-21 days) in Group 2 compared to 18 days (range, 11-36 days) in Group 1 (p-value, 0.086). 24 patients (55.81%) in Group 1 experienced a GI ADR compared to 19 patients (44.19%) in Group 2 (p-value, 0.269). **Conclusions:** Patients receiving CDK4/6i without GLP-1 RA experienced earlier onset and a numerically higher incidence of ADRs compared with those receiving concomitant GLP-1 RA and CDK4/6i therapy, though differences did not reach statistical significance. Ongoing analyses of treatment adherence and progression-free survival will be reported out at a later date. Larger, multi-center studies are warranted to further characterize safety and potential pharmacologic interactions between GLP-1 RAs and CDK4/6i. Research Sponsor: None.

1101 **Poster Session**

Fovinaciclib versus placebo combined with fulvestrant for advanced breast cancer after endocrine therapy: A randomized, double-blind phase 3 trial. First Author: Xichun Hu, Fudan University Shanghai Cancer Center, Shanghai Medical College, Fudan University, Shanghai, China

Background: Approximately 70% breast cancer (BC) patients have hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative disease. Fovinaciclib is a novel, potent, oral selective cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. A multicenter, randomized, double-blind, placebo-controlled phase 3 trial was conducted to compare fovinaciclib versus placebo plus fulvestrant in patients with advanced BC that relapsed or progressed on previous endocrine therapy. **Methods:** Eligible patients were randomly assigned (1:1) to receive 200 mg fovinaciclib (fovinaciclib arm) or placebo (placebo arm) orally once daily on days 1–21 in 28-day cycles. All patients also received intramuscular fulvestrant 500 mg (cycle 1: days 1 and 15; subsequent cycles: day 1). Premenopausal or perimenopausal patients also received subcutaneous goserelin 3.6 mg (day 1). The primary endpoint was blinded independent central review (BICR)-assessed progression-free survival (PFS). Secondary endpoints included other efficacy endpoints and safety. Exploratory endpoints included patient-reported outcomes. **Results:** A total of 319 patients were randomized to the fovinaciclib (n = 160) or placebo arm (n = 159). Baseline characteristics were balanced. Interim analysis at 9-month median follow-up (data cutoff date May 11, 2023) showed significant PFS benefit from adding fovinaciclib (p = 0.0001). Sustained PFS benefit of greater extent (median 14.0 months versus 5.6 months, hazard ratio 0.48, 95% confidence interval 0.36–0.65) was observed at updated analysis at 23-month follow-up (data cutoff date August 30, 2024). Trends of the PFS benefit were observed in all subgroups. Consistent improvements were observed in investigator-assessed PFS and objective response rate, disease control rate, clinical benefit rate, duration of response, and time to progression according to BICR or investigator's assessments. At updated analysis, all patients in the fovinaciclib arm and 148 (93.7%) in the placebo arm reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs were hematological toxicities. TEAEs leading to study drug discontinuation were reported in 9 (5.6%) and 2 (1.3%) patients in the respective arms. No grade ≥3 venous thromboembolism or interstitial lung disease was reported. The two arms showed similar overall longitudinal profiles of global health status, function domains and symptom domains assessed with the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire. **Conclusions:** Adding fovinaciclib to fulvestrant conferred statistically significant and clinically meaningful PFS benefit and consistent improvements in other survival outcomes, along with manageable safety. These findings support fovinaciclib as a later-line option. Clinical trial information: NCT05438810. Research Sponsor: Avanc Pharmaceutical Co., Ltd.

1102 Poster Session

Should CDK4/6 inhibitor plus endocrine therapy be standard of care for ER-low (1–10%) HR+/HER2− metastatic breast cancer? A multicenter registry cohort. First Author: Kelvin K.H. Bao, Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong, Hong Kong

Background: ER-low (1–10%) HR+/HER2− metastatic breast cancer (MBC) is increasingly recognized as a distinct clinical subgroup with limited endocrine sensitivity, yet ER-low–specific evidence to guide optimal first-line treatment is sparse. We assessed real-world effectiveness of CDK4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) in ER-low MBC and benchmarked outcomes against contemporaneous ER-high disease treated with the same approach. **Methods:** We performed a multicenter cohort study using a prospective institutional registry of women with HR+/HER2− MBC who initiated CDK4/6i (palbociclib/ribociclib/abemaciclib) plus an aromatase inhibitor or fulvestrant between January 2018 and October 2024, with follow-up through December 2024. ER expression by immunohistochemistry was categorized as low (1–10% or Allred 3–4), intermediate (10–66% or Allred 5–6), or high (>66% or Allred 7–8). Primary endpoints were progression-free survival (PFS) and overall survival (OS), analyzed by Kaplan–Meier/log-rank methods and multivariable Cox regression adjusting for age, ECOG performance status, progesterone receptor status, disease extent, CDK4/6i choice, and other clinicopathologic factors. **Results:** Among the 540 women with advanced HR+ HER2- breast cancer, 75% received CDK4/6i+ET in the first-line setting; ER-low tumors comprised 4.8% (n=26). ER-low disease had poor outcomes on CDK4/6i+ET with median PFS 2.9 months (95% CI 1.2–4.7) and median OS 12.6 months (95% CI 7.24–18.0), versus ER-high median PFS 23.3 months (95% CI 18.8–27.8) and median OS 49.7 months (95% CI 40.6–54.9) (log-rank $p<0.001$). ER-low status remained independently associated with inferior PFS (HR 10.6, 95% CI 5.02–22.4; $p<0.001$) and OS (HR 4.66, 95% CI 3.03–7.95; $p<0.001$) compared with ER-high after adjustment. Within the ER-low patients, the poor outcome was universally observed regardless of ET partner (AI vs fulvestrant), disease extent (visceral vs bone only), ECOG and HER2 status (low vs 0). **Conclusions:** ER-low HR+/HER2− MBC demonstrated very poor outcomes with CDK4/6i+ET, suggesting CDK4/6i plus AI/ET should not be assumed to be an effective default "standard HR+" approach for this subgroup. Given reported clinicopathologic and molecular similarities between ER-low/HER2− tumors and triple-negative breast cancer, ER-low–dedicated prospective trials and evaluation of TNBC-oriented strategies (including prioritization of chemotherapy-based regimens and TNBC clinical trial enrollment) are urgently needed. Research Sponsor: None.

1103 Poster Session

Optimizing denosumab treatment strategies to balance skeletal-related events for prevention and osteonecrosis of the jaw risk in metastatic breast cancer patients: A Korean nationwide target trial emulation. First Author: Ji Eun Lee, Division of Medical Oncology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Background: Administration of bone-modifying agents (BMAs) is essential for reducing the incidence of skeletal-related events (SREs) in breast cancer bone metastases patients. As denosumab showed superior effect for prevention of SREs compared to zoledronic acid, denosumab is commonly used BMA in this setting; however, the optimal administration interval and treatment duration of denosumab remain unclear. **Methods:** This study utilized the Health Insurance Review and Assessment Service (HIRA) database and emulated a target trial using the clone–censor–weight approach. Among the overall breast cancer population, 2,023 metastatic breast cancer patients who received regular denosumab administration were identified during Jan 2009 to Aug 2023. We examined the administration patterns and duration of denosumab therapy and evaluated their associations with the incidence of skeletal-related events (SREs) and osteonecrosis of the jaw (ONJ). **Results:** During follow-up, approximately 23% of patients continued regular denosumab administration at intervals of less than 8 weeks. Patients who received denosumab for ≥25 months exhibited a low risk of skeletal-related events (SREs) (3.42–6.15%, according to treatment compliance); however, the cumulative risk of osteonecrosis of the jaw (ONJ) increased to 19.47% (95% confidence interval [CI], 13.79–26.75) at 4 years of follow-up. Among patients treated with denosumab for 13–24 months, the risk of SREs was comparable to that observed in those treated for ≥25 months (5.15–6.77% vs. 6.15%), while the risk of ONJ remained relatively low (10.02–10.19%, depending on compliance). In contrast, patients who received denosumab for less than 12 months demonstrated a substantially higher risk of SREs, reaching 19.44% (95% CI, 6.47–45.69). Shorter administration intervals were associated with increased ONJ risk but did not significantly affect SRE prevention. **Conclusions:** This nationwide real-world study is the largest to date to evaluate the optimal duration and administration interval of denosumab in metastatic breast cancer patients with bone metastases. To effectively prevent SREs while minimizing the risk of ONJ, a denosumab treatment duration of 13–24 months appears to offer the most favorable benefit-risk balance and may be considered an optimal treatment strategy in clinical practice. Research Sponsor: None.

1104 Poster Session

Real-world insights into bone marrow carcinomatosis in metastatic breast cancer: A retrospective analysis from two large university breast cancer centers. First Author: Nikolas Tauber, Department of Gynecology and Obstetrics, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

Background: Bone marrow carcinomatosis (BMC) is a rare but severe manifestation of metastatic breast cancer (mBC) characterized by diffuse bone marrow infiltration and hematologic dysfunction. Data on incidence, clinical presentation, and treatment outcomes remain limited. **Methods:** This bicentric retrospective real-world study included breast cancer patients diagnosed with BMC between 2010 and 2023 at two German university centers. BMC was diagnosed using bone marrow biopsy and/or leukoerythroblastic blood smear in the presence of cytopenia. Clinical characteristics, systemic treatments, and overall survival (OS) were analyzed descriptively. Survival was estimated using Kaplan–Meier method. **Results:** During the study period, 1,399 patients presented with mBC at one of two participating centers. Among these, 37 were diagnosed with BMC, corresponding to an incidence of 2.6% (0.5% of all breast cancer cases). Median age was 58 years (range 30 – 76). Most patients had hormone receptor (HR)–positive HER2-negative disease (89%). At BMC diagnosis, anemia occurred in 84%, thrombocytopenia in 76%, and pancytopenia in 57% of patients. Median OS after BMC diagnosis was 12.0 months (95% CI: 6.0, 38.0). Patients with bone-only metastases showed longer survival compared with those with additional visceral involvement (median OS not reached vs. 9 months). In HR-positive HER2-negative disease, patients receiving endocrine-based therapy including CDK4/6 inhibitors demonstrated numerically longer survival compared with chemotherapy-based approaches; however, subgroup sizes were small and analyses exploratory. **Conclusions:** BMC is an uncommon but clinically relevant manifestation of mBC associated with substantial morbidity and limited prognosis. This largest European real-world cohort highlights heterogeneous treatment approaches and outcomes. Endocrine-based strategies combined with targeted agents appear feasible in selected patients. Multicenter registries and prospective studies are needed to optimize diagnostic and therapeutic strategies in this patient group. Research Sponsor: None.

Real-world data of the analyzed cohort of patients with BMC.

No of patients	IHC subtype n (%)	Metastatic status at initial BC presentation n (%)	Metastatic site at BMC diagnosis n (%)	Diagnostic method n (%)	Median time to BMC in months (range)	Initial treatment for BMC n (%)
	a) HR pos/HER2neg b) HER2 pos c) TNBC	a) M0 b) M1	a) visceral b) brain c) bone +/- other d) bone only	a) BM biopsy / smear b) blood smear	a) after mBC diagnosis b) after initial BC diagnosis	a) combined CT b) mono CT c) ET+CDK4/6i d) ET only e) Anti HER2 f) BSC
37	a) 33 (89) b) 4 (11) c) 0 (0)	a) 16 (43) b) 21 (57)	a) 22 (60) b) 1 (3) c) 37 (100) d) 11 (30)	a) 26 (70) b) 11 (30)	a) 28 (0-107) b) 58 (0-249)	a) 3 (8) b) 20 (54) c) 6 (16) d) 1 (3) e) 1 (3) f) 1 (3) Other: 5 (14)

1105 Poster Session

Final results of a phase II study of utidelone capsule, the first solid oral microtubule stabilizer, in metastatic breast cancer patients. First Author: Binghe Xu, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: Attempts to develop oral microtubule inhibitors have not made significant progress in decades. Utidelone is a novel microtubule inhibitor insusceptible to P-glycoprotein, enabling higher oral bioavailability and response against multidrug-resistant tumors. Utidelone injection (UTD1) has been approved for metastatic breast cancer (mBC) in China in 2021; utidelone capsule (UTD2) is the first solid oral formulation of microtubule stabilizer in clinical stage globally. Our previous phase I study of UTD2 showed promising activity with no DLTs being observed in late line metastatic solid tumors, and 75 mg/m^2/d*5 was recommended as monotherapy dose (ASCO 2025). PopPK analysis indicated that AUC of UTD2 of 75 mg/m^2/d reached 80%-125% of the AUC of UTD1. The absolute bioavailability of UTD2 vs. UTD1 was 35.1%. Here we report the final results of a phase II study of UTD2 in combination with capecitabine (CAP) in mBC. **Methods:** This is a single-arm, multi-center phase II trial. The key inclusion criteria included patients with metastatic breast cancer, refractory to anthracycline or taxane treatment, ≤ 4 lines of prior chemotherapy, ECOG score of 0-1 and an expected survival of ≥ 12 weeks. Eligible patients received UTD2 at 60mg/m^2/d*5 in combination with CAP at 1000mg/m^2 bid*14 in a 21-day cycle. The primary endpoint was ORR; the secondary endpoints included PFS and safety. **Results:** By data cutoff on October 8, 2025, the recruitment had been completed. 50 mBC pts were enrolled with 72% of HR+/HER2-, 24% of TNBC, and 2% of HR+/HER2+. Twenty-one (21) pts (42%) had received ≥3 lines of treatment. 100% of the patients had received taxane or anthracycline and 86% had visceral metastases. Forty-four (44) pts were evaluated for efficacy with the best responses of 27 PR and 12 SD. The confirmed ORR was 52.3% (95%CI 36.7, 67.5) and DCR was 88.6% (95%CI 75.4, 96.2). Median PFS was 8.25 (95%CI 5.36, 10.58) months and median DoR was 7.62 months (95%CI 4.17, NE) (median treatment cycles was 9.0), demonstrating better efficacy than UTD1 +CAP (ORR 40.4%, CBR 53.9%, PFS 7.72 months, Lancet Oncol 2017) in mBC pts. The most prominent ≥ Grade 3 TEAEs was diarrhea (28%). However, the incidence of peripheral neuropathy (PN) was significantly decreased compared with UTD1+CAP (Grade 3 PN only 2% vs 25.1%) while maintaining the characteristic of low hematological toxicity (only 10% for both ≥ Grade 3 Neutropenia and Leukopenia). Treatment related discontinuations occurred in only 2 pts (4%). **Conclusions:** This study demonstrated excellent efficacy of UTD2+CAP in mBC pts. The safety profile with significantly decreased PN and low hematological toxicity highlighted another advantage of this regimen. Utidelone capsule is anticipated to dramatically improve medication convenience and enhance patient compliance. Clinical trial information: NCT05700084. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

1106 **Poster Session**

ADAPT-T-DXd: Multi-institutional real-world study of dose-adapted trastuzumab deruxtecan in HER2-positive and HER2-low metastatic breast cancer. First Author: Minakshi Roy, NH RN Tagore Hospital, Kolkata, India

Background: Trastuzumab deruxtecan (T-DXd) has demonstrated substantial efficacy in HER2-positive and HER2-low metastatic breast cancer (MBC) at a standard dose of 5.4 mg/kg in the DESTINY trials. But high treatment cost remains a major barrier to access in low/middle-income countries. We evaluated the clinical activity and safety of dose-adapted T-DXd in a multi-institutional real-world Indian cohort, where dose modification was primarily driven by financial constraints. **Methods:** This retrospective analysis included 63 patients with HER2+ or HER2-low MBC treated with dose-adapted T-DXd across multiple Indian centers. Dose-adapted T-DXd refers to the administration of T-DXd at doses lower than the standard 5.4 mg/kg dose in DESTINY trials. Dose selection was based on affordability. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints were progression-free survival (PFS), duration of response (DoR), and safety. An evaluable cohort (n = 53) was defined as patients receiving ≥2 cycles of therapy. DoR measured from treatment initiation to radiologic progression or last drug exposure. **Results:** The median age was 57 years; 42.9% had hormone receptor–positive disease. HER2 subtypes included HER2 3+ (63.5%), HER2 2+/ISH+ (11.1%), and HER2-low (22.2%). Patients had received a median of three prior lines of therapy. The median administered dose of trastuzumab deruxtecan was 3.7 mg/kg, corresponding to 68% of the standard dose. At a median follow-up of 8.3 months, the objective response rate (ORR) was 58.7% (95% CI, 46–71%) in the full cohort and 66.0% (95% CI, 53–79%) in the evaluable cohort. The highest ORR was observed in HER2 3+ disease (76.5%). Median progression-free survival was 5.3 months (95% CI, 4.2–6.4) in the full cohort and 7.1 months (95% CI, 5.8–8.4) in the evaluable cohort. Median duration of response was 8.3 months, with 40–45% of responses ongoing at data cutoff. Grade ≥3 neutropenia occurred in 9.0% of patients, and interstitial lung disease occurred in 7.0%; no grade 5 pulmonary events were observed. Dose reductions due to toxicity were uncommon. **Conclusions:** Dose-adapted trastuzumab deruxtecan demonstrated clinically meaningful activity with a manageable safety profile in patients with HER2-positive and HER2-low metastatic breast cancer in a real-world setting. The shorter median PFS likely reflects reduced dose intensity, limited follow-up and real-world heterogeneity, rather than loss of intrinsic drug activity. These findings support further prospective evaluation of dose-adapted strategies to improve treatment accessibility in resource-limited settings. Research Sponsor: None.

1107 **Poster Session**

Quality of life and treatment tolerability of Bria-IMT + CPI in metastatic breast cancer. First Author: Saranya Chumsri, Jacoby Center for Breast Health, Mayo Clinic Florida, Jacksonville, FL

Background: Bria-IMT is an allogeneic whole cell immunotherapy expressing tumor associated antigens and GM-CSF to stimulate adaptive and innate immunity. The phase 3 Bria-ABC trial (NCT06072612) evaluates Bria-IMT + retifanlimab vs physician's choice in MBC w/ no meaningful therapeutic options. Characterization of on-trial pt experience, including quality of life (QOL) and tolerability, remains clinically relevant yet underreported. We evaluated QoL and toxicity to assess feasibility of home self administration. **Methods:** EORTC QLQ-C30 at baseline (BL) and subsequent visits. Raw item responses were aggregated into domain scores. Changes quantified as absolute point differences; domain scores defined as medians of constituent items. Lower functional/symptom and higher global scores indicate better outcomes. Wilcoxon matched pairs test assessed change from BL. Missing QoL data handled by observed cases approach. QoL evaluated at BL, V3, V6, and V9. TWiST and TOX summarized descriptively. TOX defined as cumulative time w/ grade ≥3 TEAEs w/o progression; TWiST as time w/o grade ≥3 toxicity or progression. TOX and TWiST constitute component health states for planned QTWiST analysis pending mature OS. **Results:** At submission, 251 pts screened, 173 randomized, 147 treated. 75% Caucasian, 20% other, 5% not reported; median 6 prior lines (2-15); ECOG 2 -6%; intracranial mets 9%; 42% HR+, 37% TNBC, 12% HER2+. Median 5 QoL assessments/pt completed. 127 pts completed ≥2 assessments. Paired data available at V3 52%, V6 17%, V9 6%. Global health medians BL 5.0, V3 5.0, V6 5.0, V9 4.5. Score maintenance/improvement: @V3 63% (p=0.7), V6 62%, V9 71%. Functional domains: role (BL 1.5, V3 2.0, V6 2.0, V9 2.0; maintenance 62.7% [p=0.02], 52.4%, 71.4%). Physical (BL 1.0, V3 2.0, V6 2.0, V9 2.0; maintenance 68.7% (p=0.002), 47.6% (p=0.03), 71.4%), cognitive (BL 1.5, V3 1.5, V6 1.5, V9 1.5; maintenance 63.6%, 61.9%, 85.7%). Emotional (BL 1.5, V3 1.5, V6 1.5, V9 1.5; maintenance 75.8% (p=0.9), 81.0%, 85.7%). Social (BL 1.5, V3 1.5, V6 2.0, V9 2.5; maintenance 58.5%, 75.0%, 57.1%). Symptoms: nausea/vomiting (1.0 throughout; maintenance V3 73%, V6 86%, V9 86%), fatigue median 2.0 all timepoints; maintenance 61%, 67%, 71%), pain (BL/V3 1.5, V6/V9 2.0; maintenance V3 57% [p=0.03], V6 62% [p=0.9], V9 86%). TWiST and TOX restricted mean 3.12 mo and 0.63 mo, respectively; 83.2% and 16.8% of observed follow-up. Pts w global health maintenance demonstrated longer median TWiST v deterioration (4.3 v 2.7 mo). ECOG stable in 78% (n=99). **Conclusions:** Heavily pretreated MBC pts in Bria-ABC demonstrated stable global health and key functional domains. Findings support sustained QoL in advanced disease. TWiST demonstrates meaningful benefit w/o significant toxicity. Ongoing follow up will further characterize durability of pt-reported outcomes and clinical correlation. Results support decentralized care and potential home self administration. Clinical trial information: NCT06072612. Research Sponsor: None.

1108 **Poster Session**

Survival with Bria-IMT + CPI in advanced metastatic breast cancer at 12 and 24 months. First Author: Chaitali Nangia, Hoag Memorial Hospital Presbyterian, Newport Beach, CA

Background: Metastatic breast cancer (MBC) remains limited by resistance and cumulative toxicity in heavily pretreated patients. Bria-IMT combines a whole-cell vaccine (SV-BR-1-GM) with anti-PD-1 (CPI) to enhance tumor antigen presentation and overcome immune exhaustion. SV-BR-1-GM is an irradiated breast cancer cell line engineered to secrete GM-CSF, promoting HLA class I and II antigen presentation and T-cell activation. We identified a subset with durable clinical benefit and biologic correlates. **Methods:** Phase I/II evaluating the Bria-IMT regimen (SV-BR-1-GM with CPI (pembrolizumab or retifanlimab). In the phase II portion, pts were randomized 1:1 to CPI initiation at cycle 1 (C1) or delayed start at cycle 2 (C2). Two SV-BR-1-GM formulations were administered: IFNγ-stimulated (IFγ) or unstimulated (≠IFγ). Baseline circulating tumor cells (CTCs) and delayed-type hypersensitivity (DTH) responses to SV-BR-1-GM were assessed as biomarkers. Progression free survival (PFS) and overall survival (OS) were analyzed using Kaplan Meier (KM). Subgroup comparisons (CPI sequencing, IP formulation, DTH status, and baseline CTC status) are exploratory. **Results:** 32 phase 2 pts were randomized: median age 61 (range 41-80); median prior lines 6 (range 2-13); PFS 3.5 mo (95% CI 3.0 - 4.2); OS 9.5 mo (95% CI 7.0 - 17.4). Among CPI C1 vs C2 starts: median OS 13.3 v 7.4mo (HR 0.8; 95% CI 0.4-1.9, p = 0.6); OS KM probability at 12 mo 47% v 58%. Median OS w ≠IFγ v IFNγ IP =16.6 v 9.1 mo (HR 0.58; 95% CI 0.2-1.4, p = 0.23); OS KM at 12 mo 52.4% v 27.3%. DTH+ v DTH- median OS 11.9 v 4.7 mo (HR 0.0009; p = <0.001), OS KM @12 mo 48% v 0%. CTCs <5 v > 5 at baseline had median OS 16.6 v 5.5 mo (HR 0.005; 95% CI 0.0003-0.09, p < 0.001), OS at 12 mo 49% vs 33%. Among long term survivors @12mo, OS probability 44.0% (95% CI 26.2-59.7%) and @24 mo 26% (95% CI 12.1-42.4%). Median follow up 25.8 with PFS 5.4 mo. 5 received ≠IFγ formulation v 1 w IFNγ. All 6 (3 with CPI @C1, 3@C2) experienced delayed type hypersensitivity reaction to inoculation. 67% of long responders matched HLA at >1 allele, 33% no match. Grade ≥3 AEs in 47% of pts, most common injection site rxn, nausea, fatigue; no tx related D/C; no unexpected safety signals. **Conclusions:** In heavily pretreated MBC, Bria-IMT demonstrated a tolerable safety profile and the emergence of a long-term survivor cohort. Durable survival was observed beyond 12 and 24 months. Differential survival favoring Ph3 formulation, DTH positivity, lower baseline CTC burden, and early CPI sequencing was observed. These findings support prospective validation of DTH and CTC as predictive biomarkers and the continued use of the Ph3 IP formulation in the ongoing phase 3 study Bria-ABC (NCT06072612). Clinical trial information: NCT06072612. Research Sponsor: None.

1109 **Poster Session**

Health-related quality of life. First Author: Erinne Wasalski, Rutgers University, School of Health Professions, Newark, NJ

Background: Trials typically pool patient-reported outcomes across demographics, assuming baseline differences reflect normal variation. When adequate enrollment permits disaggregation, nuanced patterns emerge across quality-of-life domains. **Methods:** Individual participant data meta-analysis of 15 breast cancer trials (N=12,656). HRQoL domains (Physical, Emotional, Social, Role, Cognitive) and breast symptoms assessed via EORTC QLQ-C30/FACT-B at baseline, treatment, and post-treatment. Comparisons: Hispanic vs Not-Hispanic; White vs Asian vs Black vs Other. Dual approach: 1) direct between-group comparisons, 2) pooled within-group trajectories revealing between-group mean differences and absolute changes. **Results:** Population: 2.3% Black, 9.6% Hispanic, 19.9% Asian. Baseline disparities were substantial and domain-specific. Hispanic demonstrated higher cognitive functioning (MD 2.72, $p<0.05$). Black had superior role functioning versus White (84.11 vs 67.19, MD -7.80, $p<0.001$); all minority groups scored lower on emotional functioning (Black MD -4.76, Asian MD -3.34, Other MD -1.88, all $p<0.001$). During treatment, Hispanic maintained physical (MD 1.99, $p<0.05$) and role functioning (MD 3.67, $p<0.05$); Asian showed less role decline (MD 2.61, $p<0.01$). All groups experienced similar symptom improvement and cognitive decline. Post-treatment divergence: Black patients' breast symptoms worsened (change +1.27) while Asian showed highest improvement (change -2.09, $p<0.05$). Hispanic cognitive advantage eroded (MD -1.77, $p<0.05$), and treatment resilience disappeared. Uniform 60% attrition across all groups. **Conclusions:** Equal treatment response does not equal equity when groups enter with disparate baselines and experience differential post-treatment trajectories. Post-treatment divergence was striking: Black patients' symptoms worsened while Asian improved most—invisible in binary White vs Not-White comparisons. Hispanic treatment resilience disappeared in survivorship and cognitive advantages eroded. Uniform 60% attrition demonstrates recruitment, not retention, is the barrier requiring redirection of diversity initiatives. Even pooling 15 trials, Black and Hispanic representation remained inadequate. Equal treatment perpetuates existing disparities from unequal starting points or creates new disparities through differential recovery. Trial equity requires adequate diverse enrollment and interventions addressing pre-enrollment disparities and post-treatment survivorship needs. Research Sponsor: None.

1110 Poster Session

Potential BMI-dependent overall survival differences in postmenopausal breast cancer patients treated with CDK4/6 inhibitors: A Mayo Clinic platform study. First Author: Chenyu Sun, Mayo Clinic Rochester, Rochester, MN

Background: CDK4/6 inhibitors with endocrine therapy are widely used for HR+/HER2− metastatic breast cancer (BC). While studies have shown similar progression-free outcomes across agents, overall survival (OS) data are limited. Since OS is a definitive endpoint and BMI may influence outcomes, this study examines BMI-dependent OS differences among CDK4/6 inhibitors. **Methods:** A retrospective cohort study was conducted using the Mayo Clinic Platform full AMC1 dataset. Postmenopausal women with BC receiving palbociclib/ribociclib/abemaciclib plus aromatase inhibitor (AI) were included. Patients with prior use of fulvestrant, anthracyclines, radiation therapy, GnRH agonists, or history of MACE, heart failure, myocardial infarction, or stroke before BC diagnosis were excluded. Patients were stratified by BMI and CDK4/6 inhibitor. The primary outcome was 5-year OS. **Results:** Among 1,989 patients (palbociclib: 868; ribociclib: 465; abemaciclib: 656), palbociclib was associated with significantly worse OS compared to ribociclib in BMI <25 (HR 2.91; 95% CI: 1.76–4.79; $P < 0.01$) and BMI ≥ 30 (HR 1.91; 95% CI: 1.21–3.01; $P < 0.01$). Compared to abemaciclib, palbociclib showed worse OS: BMI <25 (HR 1.73; $P < 0.01$), BMI 25–30 (HR 1.56; $P < 0.01$), and BMI ≥ 30 (HR 1.82; $P < 0.01$). No significant OS differences were observed between ribociclib and abemaciclib. Palbociclib patients were older, particularly in BMI <25 (Cohen's D = 0.39 vs. ribociclib; 0.27 vs. abemaciclib) and BMI ≥ 30 (0.28 vs. ribociclib; 0.23 vs. abemaciclib). In the BMI 25–30 group, palbociclib group was also older than ribociclib group (Cohen's D = 0.26). **Conclusions:** In postmenopausal BC patients on AIs and CDK4/6 inhibitors, palbociclib was associated with worse OS in BMI < 25 and BMI ≥ 30 groups, while ribociclib and abemaciclib showed similar outcomes across BMI groups. Palbociclib patients were older than those on other drugs, which may partially confound results; however, in the BMI 25–30 group, despite similar age differences, no survival difference was observed between palbociclib and ribociclib, suggesting age alone may have limited impact. These findings indicate a potential interaction between BMI and drug choice, and highlight the need for prospective studies to confirm and adjust for these variables. Limitations include the observational design and inability to perform multivariable regression analyses to adjust for confounders. Research Sponsor: None.

Overall survival comparisons by CDK4/6 inhibitor and BMI subgroup.

Comparison	BMI Group	Hazard Ratio (95% CI)	P-value
Palbociclib vs Ribociclib	<25	2.91 (1.76 – 4.79)	< 0.01
	25 – 30	1.34 (0.87 – 2.071)	0.17
	≥30	1.91 (1.21 – 3.01)	< 0.01
Palbociclib vs Abemaciclib	<25	1.73 (1.29 – 2.32)	< 0.01
	25 – 30	1.56 (1.09 – 2.23)	< 0.01
	≥30	1.82 (1.15 – 2.88)	< 0.01
Ribociclib vs Abemaciclib	<25	1.27 (0.81 – 1.99)	0.29
	25 – 30	0.87 (0.54 – 1.43)	0.59
	≥30	1.05 (0.63 – 1.75)	0.85

1111 Poster Session

Baseline circulating tumor cells and association with early resistance in patients with metastatic breast cancer undergoing palbociclib therapy. First Author: Qiang Zhang, Department of Medicine, Division of Hematology and Oncology, CTC Core Facility, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

Background: Palbociclib has significantly improved outcomes in metastatic breast cancer (MBC); however, a substantial proportion of patients experience early treatment resistance. Reliable biomarkers to identify high-risk patients prior to therapy initiation remain limited. Our previous work has demonstrated that circulating tumor cell (CTC) and ctDNA monitoring is associated with poor prognosis in MBC (ASCO 2025 #1042; AACR 2025 #3613). Here, we report new findings of the association between baseline CTC level and timing of resistance in patients receiving palbociclib. **Methods:** This study included 178 patients with ER+/HER2− MBC treated with palbociclib at the Robert H. Lurie Cancer Center between 2016 and 2025 (IRB: NU16B06), all of whom developed treatment resistance. Time to resistance was defined as the interval from treatment initiation to first documented resistance; the median follow-up period was 8.0 months. Patients were stratified a priori into early resistance ($\leq$6 months; n = 71) and later resistance ($>$ 6 months; n = 107). Baseline CTCs were enumerated prior to treatment using FDA-approved CELLTRACKS system (Menarini). Associations between baseline CTC levels and time to resistance were assessed using Spearman rank correlation, treating CTC as a continuous variable and analyzing early and later resistance groups separately. **Results:** Among patients with early resistance, the median time to resistance was 3.25 months (range, 0.16–6.0), compared with 16.0 months (range, 6.5–57) among those with later resistance. Patients with early resistance exhibited higher baseline CTC levels on average than those with later resistance (mean CTC: 36.7 vs 25.8), although CTC distributions were highly right-skewed with substantial overlap between groups. Within the early resistance group, 29 of 71 patients had baseline CTC $\geq$5, with markedly higher mean CTC levels compared with patients with CTC $<$ 5 (88.6 vs 0.8). In contrast, baseline CTC $\geq$5 was not associated with timing of resistance among patients with later resistance. Using Spearman rank correlation, higher baseline CTC levels were significantly associated with earlier resistance among patients with early resistance ($\rho = -0.24$, P = 0.043), whereas no association was observed in patients with resistance occurring beyond 6 months ($\rho = 0.04$, P = 0.71). **Conclusions:** Baseline CTC levels were associated with the timing of treatment resistance in patients with metastatic breast cancer receiving palbociclib, with a significant inverse correlation observed exclusively among patients experiencing early resistance within 6 months. These new findings suggest that elevated baseline CTC burden reflects aggressive disease biology underlying rapid treatment failure. Time-dependent assessment of CTC may provide clinically relevant insights into early resistance risk and inform clinical decision-making. Research Sponsor: None.

1112 Poster Session

Prognostic impact of digitally quantified tumor-infiltrating lymphocytes in HR+/HER2- metastatic breast cancer treated with CDK4/6 inhibitors. First Author: Yeon Gil Jeong, Division of Medical Oncology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors plus endocrine therapy are the first-line treatment for hormone receptor (HR)-positive/HER2-negative metastatic breast cancer(MBC). Prognostic biomarkers are needed to guide treatment decisions. Although Tumor-infiltrating lymphocytes (TILs) have been studied in breast cancer, their prognostic value in HR+/HER2- MBC remains unclear. Therefore, we aimed to assess the prognostic value of TILs in this patient population. **Methods:** We retrospectively analyzed patients with HR+/HER2- MBC receiving CDK4/6 inhibitors (palbociclib, ribociclib, or abemaciclib) plus endocrine therapy at Gangnam Severance Hospital, Seoul, Republic of Korea, from 2017 to 2025. We included 180 of 326 treated patients who met prespecified criteria. TILs were assessed according to the International Immuno-Oncology Biomarker Working Group guidelines using the digital pathology software QuPath (v0.6.0). Stromal TILs were quantified in two representative regions of interest (ROIs; each approximately 1,000 μm wide) using the formula TIL (%) = [immune cell area / (annotation area − tumor cell area)] $\times$ 100, and the values were averaged across ROIs. Patients were classified into high- and low-TIL groups using the median TIL as the cutoff. Progression-free survival (PFS) and overall survival (OS) were compared using Kaplan-Meier analyses and log-rank tests. Hazard ratios (HRs) were estimated using Cox proportional hazards models. **Results:** Among 180 patients, the median age was 53.9 years (range, 28.0–87.5) and the median follow-up was 32.4 months (range, 4.6–104.4). Median PFS was 23.2 months (98 progression events) and median OS was 32.4 months (28 death events). Using a median TIL cutoff of 7.31%, 90 patients were classified into each group. The high-TIL group showed numerically longer PFS than the low-TIL group (median 35.2 vs. 28.1 months, 95% confidence interval [CI] 25.6–not reached[NR] vs. 22.7–42.0; log-rank p=0.15; HR 0.75, 95% CI 0.50–1.12; Cox p=0.154). For OS, the high-TIL group had significantly longer survival (median NR in both groups; log-rank p=0.028; HR 0.41, 95% CI 0.18–0.93; Cox p=0.033). In the primary breast tumor subset (n=111), similar trends were observed for PFS (median 42.2 vs 27.6 months; 95% CI 24.8–NR vs 19.3–61.4; log-rank p=0.072; HR 0.62, 95% CI 0.36–1.05; Cox p=0.075) and OS (median NR in both groups; log-rank p=0.073; HR 0.41, 95% CI 0.15–1.13; Cox p=0.083). **Conclusions:** Higher TIL levels may be associated with more favorable outcomes in patients with HR+/HER2- MBC treated with CDK4/6 inhibitor-based therapy. In contrast, patients with low TILs, who may derive less benefit, could be considered for alternative targeted therapies or chemotherapy. These findings suggest TILs may have prognostic value in this setting and warrant confirmation in further prospective, multicenter studies. Research Sponsor: None.

1113 Poster Session

Analysis of information received and perceived by patients with metastatic breast cancer: Results of the Croyances et Réalités 3 French survey. First Author: Claudia Plesse Lefeuvre, Centre Eugène Marquis, Rennes, France

Background: Despite therapeutic advances, metastatic breast cancer (mBC) and its treatments substantially impact quality of life. This impact, as well as prognosis and treatment strategies, varies by histological subtype. The Croyances et Réalités 3 (R3) survey, building on the 2015 and 2020 editions (R1 and R2), provides a longitudinal perspective on how French mBC patients perceive information and the support they receive. **Methods:** R3 was a multicenter, cross-sectional mirror survey involving patients with recurrent or *de novo* mBC (HR+/HER2−, HER2+, Triple-negative (TN)), and oncologists who completed paired questionnaires. Subgroup analyses were prespecified by histological subtype. **Results:** The survey was completed by 331 patients with mBC and 56 oncologists, enabling robust patient–physician comparisons with 80% mirroring. Mean patient age was 64 and 37% lived alone. Only 10% were still in the workforce while 58% were retired. The mean medical consultation duration was 40 minutes and in 26% of cases, was followed by a consultation with a nurse. Patients showed good understanding of their histological subtype, with 62% able to report it correctly (vs 37% in R2). Communication metrics also improved: 86% of patients felt their physician took time to explain, 79% felt listened to, and 69% reported good comprehension, closely matching physicians' perceptions ($>$80%). For 28% of patients, the treatment decision was shared, while 35% would like to be more involved. Supportive care and disease information brochures were the most common resources handed out (60% and 47% respectively). Uptake of supportive care increased to 65% overall (53% in R2). Psychologist (48% vs 36% in R2), dietitian (44% vs 26%), oncology aesthetician (35% vs 26%), and adapted physical activity (28% vs 18%) use increased. Among patients who did not seek supportive care, 37% stated that it was not offered to them, while 38% stated that they did not wish to receive it. Regarding impact of the disease on daily life, patients with HER2+ and TN mBC reported greater physical burden, including general fatigue and pain with significant impact (HER2+: 52%, TN: 50% vs HR+/HER2−: 33%), and reported greater use of supportive care (HER2+: 67%+, TN: 72% vs HR+/HER2−: 49%). The use of patient associations remained limited, at 11%. **Conclusions:** This current study R3 documents meaningful progress—patients' knowledge of their disease has improved, and oncologists have enhanced communication and supportive care delivery. However, despite recent improvements, supportive care remains underutilized, while the burden of the disease and its treatments remain substantial, underscoring the need to formalize care pathways that systematically integrate supportive care. Further progress is needed to improve shared decision-making, a recognized patient priority. Research Sponsor: PFIZER SAS.

1114 Poster Session

Data-driven precision prognostic stratification in breast cancer leptomeningeal metastasis: The BC-LGPA model and treatment refinement. First Author: Jian Zhang, Department of Medical Oncology/Phase I Clinical Trial Center, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Breast cancer leptomeningeal metastasis (BCLM) lacks data-driven prognostic models integrating diagnostic certainty with molecular features, resulting in empirical treatment limitations. **Methods:** We analyzed 403 BCLM patients (Nov 2013-Nov 2025) from four centers, constructing the Breast Cancer Leptomeningeal Graded Prognostic Assessment (BC-LGPA) based on diagnostic criteria (CSF cytology, symptoms, MRI patterns) and molecular subtype, validated externally. **Results:** The median overall survival (OS) was 7.5 months. As the first data-driven prognostic classification for BCLM, the BC-LGPA integrates diagnostic certainty scores (0–2) and molecular scores (0–1). ECOG performance status and extracranial metastases were excluded owing to collinearity with neurological symptoms and because leptomeningeal metastasis itself constitutes the primary survival-limiting factor. The model stratifies patients into high-risk (0 points, 4.7 months), intermediate-risk (1–2 points, 8.0 months), and low-risk (3 points, 16.6 months) groups (training p=0.001; validation: 4.1 vs. 7.9 vs. 16.0 months, p=0.003). Key innovations include: (1) Granular diagnostic stratification into Class A (cytology-proven), B (clinical-radiological), and C (incidental-radiological), with subclasses A1/A2/A3, B1/B2, and C1/C2/C-special; (2) Ultra-indolent entity identification: Class C-special (localized calvarial-meningeal disease without diffuse LM) shows exceptional median OS of 68.0 months, representing a distinct clinical entity unsuitable for conventional prognostic models; (3) Treatment refinement: Intrathecal therapy improved survival in Class A and Class B-Linear subgroups, whereas focal radiotherapy demonstrated no independent benefit, including in Class C2 (31 patients, p=0.794), challenging empirical RT practices. **Conclusions:** BC-LGPA establishes the first data-driven BCLM prognostic framework, correcting treatment recommendations through subgroup efficacy analyses to guide precision management and clinical trial design. Research Sponsor: None.

The scoring criteria of the BC-LGPA.

Prognostic Factor	Score		Criteria Definition		
Diagnostic Certainty			CSF cytology	Neurological symptoms	MRI
	Class A (Cytology-proven)	0	+	+ / -	+ / -
	Class B (Clinico-radiological)	1	- / NA	+	+
	Class C* (Incidental radiological)	2	- / NA	-	+
Molecular Subtype	TNBC	0	ER -	PR - ER/PR + and/or HER2 +	HER2 -
	non-TNBC	1			

Total score = *Diagnostic Certainty* score + *Molecular Subtype score*

NA: Not Available; * Localized calvarial-meningeal disease were excluded.

1115 Poster Session

Clinicopathologic features, treatment patterns, and outcomes in young women with metastatic breast cancer: A National Cancer Database analysis. First Author: Cher Ying Foo, Rochester General Hospital, Rochester, NY

Background: Young women with metastatic breast cancer (MBC) represent a distinct and understudied population and often present with aggressive disease features. However, population-level studies characterizing clinicopathologic features, treatment patterns, and outcomes in this group remain limited. **Methods:** The National Cancer Database (NCDB) was queried to identify women diagnosed with MBC. Patients were stratified by age ($<$40 vs $\geq$40 years). Baseline characteristics were compared using chi-square tests. Overall survival (OS) was assessed using Kaplan–Meier analysis and compared using log-rank tests. Multivariable Cox regression was performed to evaluate independent associations with OS. **Results:** Among 59,213 women with MBC, 4,406 (7.4%) were aged $<$40 years. Median follow-up was 25.3 months (IQR 9.3–42.1). Compared with women $\geq$40, young women had more grade III tumors (61.0% vs 50.4%), lymphovascular invasion (44.2% vs 31.7%), and liver metastases (35.3% vs 23.5%). Young women were also more likely to receive chemotherapy (44.6% vs 21.7%), immunotherapy (44.2% vs 27.2%), radiation (39.3% vs 29.8%), and surgery of the primary tumor (26.7% vs 13.3%), whereas receipt of hormonal therapy was lower compared to their older counterparts (56.9% vs 54.8%). Receptor subtypes in young women were distributed as follows: HR+/HER2+ (22.6%), HR+/HER2- (50.8%), HR-/HER2+ (11.0%) and TNBC (15.5%). Young women demonstrated longer median OS compared with those $\geq$40 (68.7 months [95% CI 65.2–74.6] vs 37.1 months [95% CI 36.4–37.7]). TNBC had the worst OS among receptor subtypes ($p<0.0001$), with more than three-fold mortality risk compared with HR+/HER2- (HR 3.65, 95% CI 3.22–4.15). Metaplastic histology was associated with inferior OS compared to IDC (HR 3.11, 95% CI 1.72–5.64), and Black race was associated with worse OS compared to White race (HR 1.65, 95% CI 1.47–1.87). Receipt of radiation (HR 0.75, 95% CI 0.67–0.84), immunotherapy (HR 0.59, 95% CI 0.53–0.66), hormonal therapy (HR 0.42, 95% CI 0.38–0.47), and surgery to the primary site (HR 0.42, 95% CI 0.37–0.49) were associated with improved OS, whereas chemotherapy was not associated with OS. Most patients had a single metastatic site (55.5%), among which bone was the most common site (59.8%), followed by liver (18.4%), lung (7.7%), and brain (1.6%). Compared to bone-only metastases, brain (HR 2.04, 95% CI 1.17–3.56), lung (HR 2.08, 95% CI 1.58-2.74), and distant lymph node involvement (HR 1.54, 95% CI 1.18–2.00) were associated with worse OS. **Conclusions:** In this largest population-level study to date, young women with MBC presented with more aggressive disease features, yet demonstrated better OS compared with older patients. Survival outcomes were associated with receptor subtype, histology, and metastatic site. These findings provide valuable insights to guide clinical management of young women with MBC. Research Sponsor: None.

1116 Poster Session

Temporal changes in mortality among adults with breast cancer and diabetes mellitus in the United States. First Author: Sufia Ahmed, Dow International Dental College, Dow University of Health Sciences, Karachi, Pakistan

Background: Breast cancer and diabetes mellitus represent major and intersecting public health challenges in the United States. Although breast cancer mortality has declined over recent decades, the growing prevalence of metabolic comorbidities, particularly diabetes, may offset these gains. National patterns of mortality among individuals with both conditions remain incompletely defined. We evaluated long-term trends and demographic disparities in breast cancer–and diabetes-associated mortality from 1999 to 2023. **Methods:** We conducted a retrospective population-based analysis using the CDC Wide-Ranging Online Data for Epidemiologic Research (WONDER) Multiple Cause of Death database (1999–2023). Decedents aged 45–85+ years with breast cancer (ICD-10: C50) and diabetes mellitus (ICD-10: E10–E14) listed as underlying or contributing causes of death were included. Age-adjusted mortality rates (AAMRs) were calculated using the 2000 U.S. standard population. Trends were evaluated using Joinpoint regression to estimate annual percent change (APC) with 95% confidence intervals (CI). Analyses were stratified by age, sex, race/ethnicity, census region, and urbanization. **Results:** Between 1999 and 2023, 78,253 deaths occurred among adults aged 45–85+ years with breast cancer and diabetes mellitus (1.6% male, 98.4% female). Overall AAMRs increased modestly from 2.64 to 2.84. Females consistently exhibited higher mortality than males (5.00 vs 0.13 in 2023). Non-Hispanic Black individuals had the highest AAMRs (5.61), whereas non-Hispanic American Indian/Alaska Native, Asian, and Native Hawaiian/Pacific Islander populations had the lowest (2.05). Mortality counts were greatest in the Southern region and lowest in the Northeast. Nationally, AAMRs declined from 2004 to 2018 (APC -1.82%; 95% CI, -2.12 to -1.51; $P<0.001$), followed by a sharp increase from 2018 to 2021 (APC 12.30%; 95% CI, 6.64 to 18.25; $P<0.001$), with subsequent stabilization. In contrast, males demonstrated a steady increase throughout the study period. **Conclusions:** Breast cancer– and diabetes-associated mortality declined for more than a decade but reversed sharply after 2018, highlighting the vulnerability of patients with metabolic comorbidity. Persistently higher mortality among women and non-Hispanic Black individuals and the disproportionate burden in the Southern United States underscore important disparities. These findings emphasize the need for integrated oncologic and metabolic risk management strategies and renewed attention to chronic disease control in breast cancer survivorship. Research Sponsor: None.

1117 Poster Session

Real-world analysis of the association between new-onset depression and outcomes in metastatic breast cancer. First Author: Tornike Zabakhidze, Boston Medical Center - Brighton, Boston, MA

Background: Depression is prevalent in patients with advanced cancers and it may influence the disease course and treatment. While depression is associated with worse survival in solid tumors, real-world data quantifying its impact on mortality and healthcare utilization patterns in metastatic breast cancer (MBC) are limited. We utilized a global de-identified database to evaluate the association of new-onset depression with overall survival (OS) and care utilization. **Methods:** We conducted a retrospective cohort study using the TriNetX global network. We identified adult women with MBC and survival greater than 6 months from diagnosis. Two cohorts were defined: (1) patients with first instance of depression 1-month to 3-years after MBC diagnosis, and (2) patients without depression before or during this period. Propensity score matching was performed (1:1) to balance baseline demographics, comorbidities, tumor receptor status, and previous cancer therapies. Outcomes included OS, palliative care utilization, ED visits, and Inpatient Hospitalizations over follow-up of 5 years. **Results:** We matched 2,753 patients per cohort with well-balanced baseline characteristics (mean age 60.1 $\pm$ 13.2 years). Depression was associated with shorter median OS (1,703 days vs not reached; HR 1.28, 95% CI 1.17–1.40, $p<0.001$) and 6.7% absolute increase in mortality risk (38.1% vs 31.4%). Patients with depression demonstrated significantly higher care utilization: with increased hospitalization (HR 1.52, CI 1.39–1.67), increased ED Visits (HR 1.41, 95% CI 1.30–1.52), and increased use of palliative care visits (HR 1.65, 95% CI 1.49–1.83). Subgroup analysis showed that those treated with common anti-depressants had lower median OS and higher care utilization, with a larger effect size and more statistical significance for SSRIs than SNRIs. **Conclusions:** In this large real-world cohort, new-onset depression in women with MBC was associated with significantly worse survival and increased emergency department, inpatient, and palliative care utilization. This finding may suggest a higher symptom burden or earlier recognition of complex needs. Exposure to common antidepressants was associated with lower OS and higher healthcare utilization, which may suggest residual confounding in the form of depression severity or MBC disease burden. Prospective studies are needed to further understand this relationship. These findings underscore the critical need for integrated psychosocial oncology screening. Research Sponsor: None.

1118 Poster Session

Breast cancer incidence and mortality in LGBTQ+ populations compared with cisgender heterosexual individuals: A comparative epidemiologic synthesis. First Author: Manas Pustake, Texas Tech University Health Sciences Center, El Paso, TX

Background: Breast cancer incidence and mortality by sexual orientation and gender identity remain poorly characterized. We aimed to systematically review comparative studies in LGBTQ+ populations versus cisgender heterosexual comparators. **Methods:** We conducted a PRISMA 2020–guided systematic review evaluated breast cancer incidence and mortality in LGBTQ+ populations versus cisgender heterosexual comparators. PubMed, Embase, and Scopus were searched from inception to January 2026. Population-based cohort, registry, and health system studies reporting comparative incidence or mortality were eligible. Two reviewers independently screened records. Of 189 records, 105 were excluded at title/abstract, 84 underwent full-text review, and 8 studies were included. Due to heterogeneity in SOGI ascertainment, comparators, and effect measures, results were synthesized qualitatively. **Results:** Among transgender populations, breast cancer incidence varied by reference group. In a nationwide cohort, trans women had higher incidence vs cis men (SIR 46.7) but lower vs cis women (SIR 0.3), while trans men showed the inverse pattern (vs cis women SIR 0.2; vs cis men SIR 58.9). In a U.S. health system cohort, incidence was similar for FTM vs cis women (0.4% vs 0.5%) but higher for MTF vs cis men (0.2% vs 0.004%). Among sexual minority women, incidence did not differ from heterosexual women in UK Biobank (HR 0.63–0.93) or Nurses' Health Study (aIRR 1.19; 95% CI, 0.92–1.53). Mortality data were sparse; one national linkage found higher breast cancer–specific mortality in same-sex partnered women (HR 3.24; 95% CI, 1.01–10.37). **Conclusions:** Breast cancer incidence in transgender populations is comparator-dependent: trans women have higher incidence vs cis men but lower vs cis women, with the inverse pattern in trans men; incidence among sexual minority women is similar to heterosexual women. Research Sponsor: None.

Comparative studies.

Study (Year)	Data Source / Country	SGM Population	Comparator	Outcome	Key Estimate (95% CI)
Yang 2025	UF Health IDR, USA	FTM	Cisgender women	Incidence	RR ≈ 0.72 (0.4% vs 0.5%)
de Blok 2019	Nationwide registry, Netherlands	Trans women	Cisgender women	Incidence	SIR 0.30 (0.20–0.40)
de Blok 2019	Nationwide registry, Netherlands	Trans men	Cisgender women	Incidence	SIR 0.20 (0.10–0.50)
Brown 2014	VHA cohort, USA	Transgender veterans	Expected population	Incidence	SIR ~1 vs cis women; >1 vs cis men
Underwood 2023	UK Biobank	WSWM	WSEM	Incidence	HR 0.93 (0.79–1.10)
Underwood 2023	UK Biobank	WSEW	WSEM	Incidence	HR 0.63 (0.37–1.07)
Huang 2024	Nurses' Health Study, USA	Lesbian women	Heterosexual women	Incidence	aIRR 1.19 (0.92–1.53)
Cochran 2012	NHIS mortality linkage, USA	Same-sex partnered women	Different-sex partnered	Mortality	HR 3.24 (1.01–10.37)
Chan 2025	NCDB, USA	TGD breast cancer cases	Cisgender cases	Overall survival	5-yr OS: 84.6% vs 91.7% (P=0.04)

1119 Poster Session

The role of FOXM1 in regulating immune memory in triple-negative breast cancer and targeting FOXM1 to develop a therapeutic vaccine. First Author: Jian Huang, UTHSA-Long School of Medicine, San Antonio, TX

Background: Triple-negative breast cancer (TNBC) is an aggressive malignancy with limited therapeutic options and poor long-term outcomes. Although immune checkpoint blockade has improved survival for a subset of patients, durable responses remain uncommon, underscoring the need for strategies that enhance tumor immunogenicity and immune memory. We recently identified a novel function of the transcription factor FOXM1 in promoting an immune-suppressive tumor microenvironment (TME) in TNBC by regulating stress ligands and the STING pathway. This study investigates the role of FOXM1 in shaping antitumor immune memory and leverages FOXM1 targeting to identify tumor antigens for therapeutic peptide vaccine development. **Methods:** FOXM1 was knocked out in TNBC cell lines using CRISPR/Cas9, and syngeneic mouse models were utilized to evaluate tumor-immune interactions. Single-cell RNA sequencing (scRNA-seq) evaluated immune landscape remodeling following FOXM1 loss. Immunopeptidomics was performed to identify tumor-associated antigens enriched following FOXM1 loss. Candidate peptides were functionally validated using dendritic cell–based antigen presentation assays and patient-derived peripheral blood mononuclear cells (PBMCs). Clinical relevance was evaluated using TNBC patient datasets and immunotherapy response cohorts. **Results:** scRNA-seq of syngeneic tumors revealed that FOXM1 deletion reshaped the immune microenvironment, with increased CD8+ T cell and NK cell infiltration and expansion of memory T cell populations. Tumor-intrinsic FOXM1 suppressed antitumor immunity by downregulating MHC-I and the stress ligand ULBP1, disrupting signaling pathways required for NK and CD8+ T cell–mediated cytotoxicity. FOXM1-deficient tumors conferred durable protection upon tumor rechallenge, consistent with long-term immune memory. Analysis of patient datasets demonstrated that elevated FOXM1 and DNMT1 expression, coupled with reduced STING and ULBP1 levels, correlated with poorer survival and reduced responsiveness to immunotherapy. Leveraging enhanced antigen presentation in FOXM1-depleted cells, immunopeptidomics identified 275 differentially presented tumor antigens. Dendritic cell pulsing of the top 15 enriched peptides induced robust T cell responses in patient-derived PBMCs, supporting their immunogenicity and its potential to serve as bona fide candidates for a therapeutic vaccine tailored for TNBC patients. **Conclusions:** These findings establish FOXM1 as a clinically relevant regulator of immune evasion and immune memory in TNBC. Importantly, the identification of immunogenic peptides provides a strong rationale for the development of a peptide-based therapeutic vaccine, either as a monotherapy or in combination with immune checkpoint blockade, to improve long-term disease control in patients with TNBC. Research Sponsor: None.

1120 Poster Session

Rare histologic subtypes of triple-negative breast cancer: The impact of immunotherapy on outcomes for metastatic disease. First Author: Jincong Q. Freeman, Cancer Prevention and Control Research Program, UChicago Medicine Comprehensive Cancer Center, Chicago, IL

Background: The addition of immunotherapy (IO) to chemotherapy (chemo) has significantly improved survival for patients with PD-L1-positive, metastatic triple-negative breast cancer (mTNBC), establishing chemo+IO as the standard first-line treatment in this population. However, the impact of IO on real-world outcomes of rare histologic subtypes of TNBC, such as metaplastic and lobular, as well as inflammatory presentation, are unknown. **Methods:** We conducted a retrospective study analyzing data from the US National Cancer Database (NCDB). Patients diagnosed with *de novo* stage IV TNBC who received chemo alone or chemo+IO between 2019 and 2022 (after FDA approval of IO for mTNBC) were included. mTNBC was classified as ductal, lobular, inflammatory, metaplastic, or other by the NCDB. Overall survival (OS) was assessed using the Kaplan-Meier method and multivariable Cox regression models controlled for sociodemographic and clinicopathologic factors. **Results:** A total of 6,711 patients with *de novo* mTNBC were identified (mean age 59.2 years), with a median follow-up of 19.8 months. Ductal histology was the most common (74.2%), followed by inflammatory (8.7%), metaplastic (4.5%), and lobular (3.6%) cases. Overall, 40.0% of the patients received chemo+IO. Immunotherapy use was the highest in mTNBC with inflammatory presentation (46.8%), followed by ductal (40.0%), lobular (37.5%), and metaplastic (37.2%) subtypes (P = 0.002). Among patients who received chemo+IO, the median OS time was the longest in ductal mTNBC (30.3 months) compared to the lobular (23.5 months) and metaplastic (22.9 months) subtypes and inflammatory presentation (16.5 months) (log-rank test $P < 0.001$). In the adjusted models, inflammatory mTNBC had a significantly higher risk of mortality than ductal cases treated with chemo+IO (adjusted hazard ratio [aHR], 1.96; 95% CI, 1.31–2.92); lobular (aHR, 1.59; 95% CI, 0.84–3.00) and metaplastic (aHR, 1.10; 95% CI, 0.44–2.71) subtypes also had a higher mortality risk, though the differences were not statistically significant due to small group sample sizes. Among patients who received chemo alone, inflammatory presentation (aHR, 2.10; 95% CI, 1.58–2.80) and lobular subtype (aHR, 1.67; 95% CI, 1.03–2.70) also had a higher risk of mortality than the ductal subtype. **Conclusions:** In this real-world analysis, patients with inflammatory, lobular, and metaplastic *de novo* mTNBC continued to experience inferior survival outcomes despite the use of chemo+IO. Our findings highlight persistent disparities in mortality outcomes and support the need for biomarker-driven strategies and dedicated clinical trials for these rare subtypes and inflammatory mTNBC. Research Sponsor: National Institute on Aging; T32AG000243.

1121 Poster Session

Homologous recombination deficiency signature (HRDsig+) in older women with advanced breast cancer (ABC). First Author: Tamar Kaminski, Department of Medicine (Medical Oncology), Yale University School of Medicine, New Haven, CT

Background: The identification of homologous recombination deficiency (HRD) may expand targeted therapy options in the management of advanced breast cancer (ABC). However, the frequency of positive HRD signature (HRDsig+) status in older women with ABC is not widely known. We explored the prevalence of HRDsig+ status, and its co-occurrence with other genomic alterations (GAs). **Methods:** Comprehensive genomic profiling (CGP) was performed on 6,221 cases of patients ≥ 65 years old with ABC to assess GA including base substitutions, short insertions and deletions, copy number changes and rearrangements and fusions. Microsatellite instability (MSI) status, tumor mutation burden (TMB), genomic ancestry, and trinucleotide signature were determined from the sequencing data. HRDsig status, provided as a clinical service, was determined by measuring large scale copy number changes and DNA repair errors. **Results:** Of the 6,221 cases, 662 (10.6%) were HRDsig+. Compared to the HRDsig- cases, HRDsig+ cases more frequently had genomic alterations (GA) associated with DNA repair, including *BRCA1* (13.7% vs 1.2%; p<.0001), *BRCA2* (22.8% vs 1.1%; p<.0001) and *RAD21* (25.1% vs 14.6%; p<.0001). When compared to HRDsig- cases, HRDsig+ cases had more frequent *PTEN* GA (16.3% vs 9.9%; p<.0001) *MTAP* loss (5.6% vs 2.7%; p<.0001), and TMB >10 mutations/Mb (12.7% vs 9.3%; p=.015). HRDsig- ABC cases had more frequent *PIK3CA* GA (47.6% vs 20.4%; p<.0001), *ERBB2* (10.9% vs 6.0%; p<.0001), *ESR1* (11.0% vs 5.3%; p<.0001) and *CDH1* (24.6% vs 6.5%; p<.0001). MSI-H status (0.3% vs 0.8%) and PD-L1 low 1-49% (36.1% vs 30.1%) were similar in both groups (NS). **Conclusions:** Among older adults with ABC, HRDsig+ status was identified in over 10% of patients undergoing CGP. Those with HRDSig+ more frequently had GAs in tumor suppressor genes involved in HRD, including *TP53, BRCA1, BRCA2*, and *RAD21*. The association of HRDSig+ with high TMB could provide the rationale for future trials with combination of PARP inhibitors with immunotherapy. Research Sponsor: None.

HRD signature status and associated genomic alterations in older women with advanced breast cancer.

	HRDsig positive (N=662)	HRDsig negative (N=5559)	P-value
MSI-H	0.3%	0.8%	NS
TMB>10 mut/Mb	12.7%	9.3%	0.015
PD-L1 low positive (1-49%)	36.1%	30.1%	NS
BRCA1	13.7%	1.2%	<.0001
BRCA2	22.8%	1.1%	<.0001
ERBB2	6.0%	10.9%	<.0001
ESR1	5.3%	11.0%	<.0001
PIK3CA	20.4%	47.6%	<.0001
TP53	73.1%	40.4%	<.0001

1122 Poster Session

AI-driven H&E plasma cell to predict pathological complete response in IO-treated triple-negative breast cancer (Yale; NCT02489448). First Author: Amritpal Singh, Department of Biomedical Engineering, Emory University, Atlanta, GA

Background: Pathological complete response (pCR) remains difficult to predict in triple-negative breast cancer (TNBC) patients treated with immune checkpoint inhibitors due to limited validated biomarkers. While tumor-infiltrating lymphocytes (TILs) are prognostic in TNBC, they are commonly treated as a composite population. Plasma cells are central to humoral immunity and can influence antitumor response through antibody production, antigen presentation, and T-cell modulation. However, the independent and cooperative prognostic role of plasma cells, either alone or in spatial interaction with other immune cells has not been systematically evaluated, particularly in TNBC. Here, we evaluated the value of plasma cells to predict pathological complete response using AI-based analysis of routine H&E slides. **Methods:** We analyzed 239 stage I–III TNBC patients across four cohorts. Models were trained on KEYNOTE-522 regimen treated patients (D1, N=130) and validated in both the Yale TNBC immunotherapy trial cohort (D2, N=65; NCT02489448) treated with durvalumab (anti-PD-L1 antibody) and University Hospital cohort (D3, N=25) treated with pembrolizumab. Plasma cells and lymphocytes were automatically detected on whole-slide H&E images using deep learning–based nuclear segmentation and tumor region classification. Quantified metrics included immune cell density, tumor-infiltrating plasma cell (TIP) ratios, and spatial features capturing plasma cell clustering and interaction with lymphocytes. Density-based classifiers were trained on D1 and evaluated for pCR prediction. **Results:** Plasma cell density alone predicted pCR with higher accuracy than lymphocyte density across both validation cohorts. In D2), plasma cell density achieved an AUC of 73.2 compared with 62.9 for lymphocyte density. Similarly, in the external institutional cohort (D3), plasma cell density outperformed lymphocyte density (AUC 69.2 vs 60.8, respectively; Table 1). These findings demonstrate the superior predictive value of plasma cell density over conventional lymphocyte-based measures for pCR in immunotherapy-treated TNBC. **Conclusions:** Plasma cells demonstrate independent and cooperative predictive value in immunotherapy-treated TNBC. AI-derived plasma cell density and spatial interaction features improve pCR prediction and survival stratification beyond conventional lymphocyte-based metrics. Research Sponsor: None.

Comparison of plasma cell performance compared to lymphocytes on holdout set D2 (Yale TNBC clinical trial NCT02489448) and D3.

	Holdout 1	Holdout 2
	Yale NCT02489448 (N=64), D2	UH Hospital (N=25), D3
M_{plasma}	73.2	69.2
M_{lymph}	62.9	60.8

1123 Poster Session

JSKN016, a first-in-class anti-TROP2/HER3 bispecific antibody-drug conjugate (ADC), in patients (pts) with HER2-negative locally advanced or metastatic breast cancer: Results from a phase I study. First Author: Herui Yao, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: TROP2 and HER3 are frequently overexpressed in most of solid tumors. JSKN016 is a first-in-class bispecific ADC targeting TROP2/HER3, site specifically conjugated to topoisomerase I inhibitor via a cleavable linker (DAR4). Glycan conjugation provides high stability and minimizes off-target toxicity. **Methods:** JSKN016-101 (NCT06592417) is a first-in-human, dose-escalation and expansion study in China, enrolling patients with advanced solid tumors to receive JSKN016 monotherapy. This analysis focused on the HER2-negative BC cohort. **Results:** As of December 22, 2025, JSKN016 was escalated to 8 mg/kg IV Q3W without reaching the maximum tolerated dose. A total of 82 HER2- BC pts were enrolled: 50 TNBC and 32 HR+/HER2- BC, treated at 4 mg/kg (n=14), 6 mg/kg (recommended phase II dose [RP2D]; n=65), and 8 mg/kg (n=3). Overall, 98.8% (81/82) had stage IV disease including 13.4% (11/82) with brain metastases. Median age was 50 (TNBC) and 52y (HR+/HER2- BC); ECOG PS 1 was reported in 78.7% and 76.7%, respectively. All TNBC pts had prior taxane-based chemotherapy, 28.0% had received ≥3 prior systemic regimens. All HR+/HER2- BC pts had progressed after ≥1 endocrine therapy with CDK4/6 inhibition and ≥1 chemotherapy. Among 47 efficacy-evaluable TNBC pts, objective response rate (ORR) was 61.7% (by INV and IRC). At RP2D (n=31), ORR was 64.5% (INV) and 61.3% (IRC), with disease control rates (DCR) of 83.9% and 90.3%. The median PFS was 7.9 months (95%CI: 5.5, NE) by IRC and 7.6 months (95%CI: 4.1, NE) by INV. Among 30 efficacy-evaluable HR+/HER2- BC pts, ORR was 50.0% (INV) and 53.3% (IRC); at RP2D (n=29), ORR was 51.7% (INV) and 55.2% (IRC), with DCR of both 100%. The median PFS was 11.1 months (8.3, NE) by IRC and was not yet mature by INV. With a median follow-up of 8 months, grade 3 or above TRAEs occurred in 25.6% (21/82) pts, with no G4 or 5 events reported. The most common G3 TRAEs were neutrophil count decreased (6.1%), amylase increased (4.9%), white blood cell count decreased (4.9%), stomatitis (3.7%), asthenia (2.4%), lymphopenia (2.4%). The incidence of TRAEs was 9.8%. Only one TRAE (G3 conjunctivitis) led to treatment discontinuation. No interstitial lung disease (ILD) was reported. **Conclusions:** JSKN016 demonstrated robust antitumor activity with good safety profile in pts with HER2-negative BC. The results support further development of JSKN016 as monotherapy or in combination. Clinical trial information: NCT06592417. Research Sponsor: None.

Efficacy of JSKN016 in HER2-BC at 6 mg/kg Q3W.

	TNBC (N=31)		HR+/HER2- BC (N=29)	
Assessed by	INV	IRC	INV	IRC
uORR, % (95% CI)	64.5 (45.4, 80.8)	61.3 (42.2, 78.2)	51.7 (32.5, 70.6)	55.2 (35.7, 73.6)
DCR, % (95% CI)	83.9 (66.3, 94.5)	90.3 (74.2, 98.0)	100 (88.1, 100)	100 (88.1, 100)
mPFS, mos (95% CI)	7.6 (4.1, NE)	7.9 (5.5, NE)	NR	11.1 (8.3, NE)
6-months PFS rate, %	57.7 (38.5, 72.9)	68.4 (47.9, 82.2)	74.0 (53.0, 86.7)	84.5 (63.8, 93.9)

1124 Poster Session

Real-world effectiveness and safety of first-line pembrolizumab plus chemotherapy in patients aged ≥65 years with metastatic triple-negative breast cancer. First Author: Aleksandra Konieczna, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Background: Patients aged ≥65 years constitute a substantial proportion of individuals with metastatic triple-negative breast cancer (mTNBC), but remain underrepresented in clinical trials due to comorbidities and concerns regarding treatment tolerability. While pembrolizumab combined with chemotherapy (P+C) has been established as a standard first-line treatment for mTNBC with a combined positive score ≥10, real-world evidence on its safety and effectiveness in older patients remains limited. **Methods:** This multicenter observational real-world study (RWS), CEBCC-101, retrospectively analyzed clinical data from 178 female patients with mTNBC treated with P+C in routine clinical practice. Patients were stratified according to age at treatment initiation (<65 vs. ≥65 years). Baseline characteristics, treatment modifications (including dose reductions and treatment delays), adverse events (AEs; graded according to CTCAE v5.0) and clinical outcomes were assessed. Clinical endpoints included progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) evaluated according to RECIST 1.1. Survival outcomes were estimated using the Kaplan–Meier method and compared between age groups using the log-rank test. **Results:** Among 178 patients, 57 (32.0%) were aged ≥65 years. Median age in the older cohort was 72.4 years (mean 72.3 ± 4.7). Patients ≥65 years had a significantly higher prevalence of relevant comorbidities compared with younger patients (71.9% vs. 39.7%; p<0.001) and more frequently presented with visceral metastases (78.9% vs. 61.2%; p=0.029), driven primarily by a higher incidence of lung metastases (59.7% vs. 42.2%; p=0.043). Rates of chemotherapy dose reductions at treatment initiation or during therapy, treatment delays due to AEs and treatment discontinuation due to toxicity were comparable between age groups. ORR did not differ significantly between patients ≥65 and <65 years (52.6% vs. 55.4%; p=0.767). Median PFS was 9.1 months (mo) in patients ≥65 years versus 8.3 mo in younger patients (p=0.594). Median OS was 22.1 mo and 19.5 mo, respectively (p=0.985). The incidence of grade ≥2 AEs, including pulmonary, neurological, dermatological events and fatigue was similar across age groups. **Conclusions:** In this RWS, patients aged ≥65 years with mTNBC treated with first-line P+C achieved clinical outcomes and safety profiles comparable to those of younger patients, despite a higher burden of comorbidities and more frequent visceral disease. These findings suggest that chronological age alone should not be a limiting factor for immunochemotherapy and underscore the importance of treatment decisions based on clinical fitness. Broader incorporation of geriatric assessment into routine oncology practice may further optimize patient selection and outcomes. Research Sponsor: None.

1125 Poster Session

Real-world evaluation of CXCL9/10 with PD-L1 and TMB as predictors of pembrolizumab benefit in triple-negative breast cancer (TNBC). First Author: Shipra Gandhi, Department of Medicine, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Pembrolizumab is approved for TNBC; however, current biomarkers PD-L1 and tumor mutational burden (TMB) have limited predictive accuracy and show weak correlation with clinical benefit. We evaluated whether chemokines (CXCL9 and CXCL10) that recruit cytotoxic T cells into the tumor microenvironment (TME) may improve prediction of pembrolizumab benefit beyond PD-L1 and TMB. **Methods:** TNBC tumors (n=3662) were profiled by next-generation sequencing (592 NextSeq; WES/WTS NovaSeq; Caris Life Sciences, Phoenix, AZ). Chemokine expression was classified as high vs low based on 50th percentile. Immune cells were estimated using WTS deconvolution (Quantiseq). PD-L1 was assessed by immunohistochemistry (22C3 ≥10%), and TMB by nonsynonymous mutations/Mb (high ≥10). Real-world median overall survival (mOS) was derived from insurance claims and calculated from pembrolizumab initiation to last contact. Associations were tested using chi-square and Mann-Whitney U with multiple comparison adjustment ($q<0.05$). **Results:** *CXCL9/10*-high expression showed increased fraction of CD8$^+$ T, dendritic cells and higher IFN-γ signatures (*CXCL9-high vs low*: 1.3% vs 0%, 3.1% vs 2.8%, −0.09 vs −0.47; *CXCL10*-high vs low: 1.1% vs 0%, 3.1% vs 2.7%, −0.1 vs −0.46), respectively all $q<0.05$. Among patients treated with pembrolizumab (n=750), *CXCL9/10*-high expression was associated with improved mOS (*CXCL9-high*: 24.5 months (m) vs 15.8 m; *CXCL10-high*: 23.4 m vs 17 m; all $p<0.05$) compared to *CXCL9/10*-low; PD-L1+ tumors had improved mOS (24.3 m vs 18.6 m, $p=0.007$) compared with PD-L1-negative; and TMB-low tumors had numerically improved mOS (21.7 m vs 17.5, $p=0.08$) compared with TMB-high. Combining *CXCL9/10* with PD-L1 or TMB identified subgroups of tumors with PD-L1-negative and TMB-high expression that showed better OS with pembrolizumab (Table). In multivariable cox analysis, adjusting for TMB and PD-L1, *CXCL9* [HR 0.67 (95% CI 0.54-0.83)] and *CXCL10* [HR 0.79 (95% CI 0.64-0.97)] remained independent predictors of pembrolizumab benefit, all $p<0.05$. **Conclusions:** In this large real-world study, PD-L1 but not TMB predicted pembrolizumab benefit in TNBC. *CXCL9/10-high* define an immune-active TME and are independent predictors of pembrolizumab response. When integrated with PD-L1 and TMB, these chemokines help identify additional patients with TNBC who may derive benefit from pembrolizumab, supporting their inclusion as biomarkers in prospective studies. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

PD-L1	Chemokine	*CXCL9* mOS (in months) (95% CI)	p	*CXCL10* mOS (in months) (95% CI)	p
+	High	25.7 (22.1 - 32.1)	<0.01	25.7 (22.2 - 34.1)	<0.01
–	High	26.9 (17.8 - 39.2)		21.7 (17.5 - 28.2)	
+	Low	18.5 (11.9 - NR)		20.7 (13.3 - 30.1)	
–	Low	15.8 (12.2 - 19.2)		16.7 (13.1 - 21.5)	
TMB					
Low	High	25.0 (22.1 - 30.1)	<0.01	23.7 (20.9 - 28.2)	<0.01
High	High	20.6 (17.5 -37.1)		19.5 (16.3 - NR)	
Low	Low	18.3 (14.1 - 21.3)		18.6 (15.7 - 22.2)	
High	Low	6.6 (3.6 - 13.7)		7.6 (5.1 - 16.2)	

1126 **Poster Session**

Single cell spatial profiling for identification of organ-specific immune features in the peritumoral microenvironment of triple-negative breast cancer with liver metastases. First Author: Jin Sun Bitar, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Breast cancer liver metastasis (BCLM) is associated with poor prognosis. Prior studies have described liver metastases as immune-cold, yet the mechanisms underlying this phenotype remain incompletely understood. We hypothesized that the peritumoral microenvironment, in addition to the tumor itself, contributes to the distinct immunobiology of BCLM. **Methods:** We performed imaging mass cytometry (IMC) with a 42-antibody panel on TNBC tissues from primary breasts (PB) (n = 22) and liver metastases (LM) (n = 26). For each case, one region of interest (ROI) from tumor bed and one from peritumoral tissue were profiled. Cell segmentation was performed using DeepCell. Single-cell phenotyping and clustering were conducted using Scanpy with lineage markers. Functional marker expression was analyzed and differences between PB and LM were assessed using non-parametric tests with Benjamini–Hochberg false discovery rate (FDR) correction. Spatial analysis was performed using Squidpy with Wilcoxon testing and FDR correction across all tested interaction pairs. **Results:** IMC analysis resolved 407,160 cells into distinct immune, stromal, and tumor cell clusters across compartments. Within tumor beds, PB and LM exhibited largely similar functional marker expression and spatial organization, indicating minimal tumor-intrinsic divergence. In contrast, peritumoral tissues diverged substantially between PB and LM. Peritumoral tissues in PB demonstrated M2 macrophage dominance while LM exhibited M1 macrophage dominance. The comparative analysis of peritumoral tissues revealed that cancer cells in LM demonstrated significantly increased spatial proximity to CD8 T cells compared to PB with concurrent upregulation of PD-L1 on macrophages and NK cells, alongside elevated PD-1 expression on multiple immune cell types, indicating that CD8 T cells are potentially exhausted despite their physical presence. Additionally, CCR7, CD6, and CXCL13 were significantly elevated across all cell types in LM, while PB demonstrated higher expression of CD44, CXCR3 and CXCL12, indicating broad immunophenotypic differences in peritumoral tissues. Spatial analysis further revealed that CD4 T cells maintained closer proximity to cancer cells, M1 macrophage, and stromal populations in PB, indicating distinct spatial organization between sites. **Conclusions:** Single-cell spatial profiling reveals that organ-specific tumor and immune biology in TNBC BCLM is encoded primarily within the peritumoral tissue rather than the tumor bed itself. Our findings reveal a paradoxical phenotype in BCLM where CD8 T cells successfully infiltrate and localize near cancer cells but show features consistent with functional impairment. These findings support further investigation of immunotherapy in TNBC BCLM and biomarker validation. Research Sponsor: 2024 Cedars-Sinai Cancer Center Developmental Funds.

1127 **Poster Session**

Trends in immunotherapy use and survival outcomes by metastatic pattern in metastatic triple-negative breast cancer. First Author: Michael Schwartz, Department of Medicine, Winship Cancer Institute of Emory University, Atlanta, GA

Background: KEYNOTE-355 demonstrated that adding pembrolizumab to chemotherapy improved progression-free and overall survival (OS) vs chemotherapy alone in patients with metastatic TNBC (mTNBC) and PD-L1 CPS ≥10. Approved in 2020, this regimen transformed advanced TNBC management. However, the benefit of immunotherapy (IO) according to metastatic site remains underexplored given the varied immune environments between organs, with the liver being particularly immune-suppressed. **Methods:** We conducted a retrospective analysis of 2022 NCDB data for female patients diagnosed 2016–2021 with de novo mTNBC. OS was defined as months from diagnosis to death/last contact. Patients were stratified by first-line therapy (chemotherapy alone vs chemotherapy + IO) and metastatic pattern (isolated liver/lung/bone/brain; multiple sites). IO type was not specified. P-values were calculated by chi-squared/Fisher's exact tests as appropriate. Hazard ratios (HR) were estimated by a univariate Cox model. **Results:** 2329 patients with de novo mTNBC were included in our study. Median age was 59 years, median follow-up time was 42 months. 1723 (74%) received chemotherapy alone and 606 (26%) received chemotherapy + IO. The proportion of patients receiving IO increased each year between 2016 and 2021 (3.3% - 34.3%). Overall, patients treated with chemotherapy + IO had better OS compared to chemotherapy alone (HR = 0.58, 95% CI, 0.51-0.65, P<0.001). Isolated lung metastasis was the most common pattern (n=402, 20.9%), followed by bone (n=374, 19.4%), liver (n=246, 12.8%), and brain metastasis (n=14 , 0.7%). 892 (46.3%) patients had multiple metastatic sites. Patients with isolated lung, liver or bone metastases had better OS vs those with multiple metastatic sites (lung, HR 0.54, [95% CI 0.47–0.62]; liver, HR 0.62, [95% CI 0.53-0.73]; bone, HR 0.69, [95% CI 0.60–0.79]). Kaplan–Meier analysis showed superior OS with chemotherapy + IO vs chemotherapy alone across lung, liver, bone, and multiple metastases subgroups (log-rank P<0.0001, P=0.0003, P=0.0017, P<0.0001, respectively); brain metastasis analysis limited by small sample size (Table 1). **Conclusions:** In this large real-world mTNBC cohort, IO adoption increased post-KEYNOTE-355 approval and associated with an overall 42% lower mortality risk vs chemotherapy alone. Additionally, increased IO adoption correlated with increased survival over time. The survival benefit of IO was preserved across different metastatic sites of disease. Research Sponsor: None.

Overall survival in mTNBC patients by metastatic site and treatment modality.

Met site	Treatment	N	Median survival, months	24-mo survival, %	36-mo survival, %
Lung	Chemo + IO	57	32.1	60.6	49.4
	Chemo	220	15.9	38	24.8
Liver	Chemo + IO	47	27.7	52.4	37.7
	Chemo	141	15.5	33.4	18.7
Bone	Chemo + IO	67	23.5	49.2	26.3
	Chemo	221	13.2	29.7	19.8
Multiple	Chemo + IO	155	16.4	36.3	26.4
	Chemo	593	8.7	18.1	10.3

1129 **Poster Session**

Long-term responders to sacituzumab govitecan in metastatic triple-negative breast cancer: Real-world outcomes and predictors from a multicenter Italian cohort. First Author: Roberta Caputo, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy

Background: Sacituzumab govitecan (SG) has reshaped the treatment landscape of metastatic triple-negative breast cancer (mTNBC), demonstrating superior survival outcomes compared with standard chemotherapy in the ASCENT trial. Despite the overall poor prognosis of mTNBC, a subset of patients experiences remarkably durable responses and prolonged survival, far exceeding the median progression-free survival (PFS) observed in pivotal trial. However, the clinical characteristics and prognostic determinants of these "long-term responders" (LTRs) remain poorly defined, and real-world evidence specifically addressing this population is currently lacking. This multicenter study aims to characterize outcomes and identify potential predictors of long-term benefit from SG in a real-world setting. **Methods:** This multicenter observational analysis included 271 patients with mTNBC treated with SG across 18 Italian cancer centers, within a study incorporating both retrospective and prospective cohorts (NCT02284581). LTRs were defined as patients achieving a real-world PFS (rwPFS) ≥ 9 months. The primary endpoint was rwPFS, while secondary endpoints included real-world overall survival (rwOS) and objective response rate (ORR). Survival outcomes were estimated using the Kaplan-Meier method, and independent prognostic factors were identified using Cox proportional hazards models. **Results:** Seventy-four of 271 patients (27.3%) were identified as LTRs. Within this cohort, median rwPFS was 14 months (95% CI: 13.3–16.3) and median rwOS was 25.6 months (95% CI: 21.0–NR). The ORR was 68.9% (all partial responses; n=51), while 29.7% of patients (n=22) achieved stable disease. On multivariable analysis, previous therapy with immune checkpoint inhibitors (ICI) was independently associated with a reduced risk of progression (HR 0.47; 95% CI: 0.22–0.98; p=0.04). De novo metastatic disease also showed a trend towards a lower risk of progression (HR 0.44; 95% CI: 0.16–1.17; p=0.10). Conversely, treatment with SG in the third line compared with the second line was associated with a higher risk of progression (HR 2.04; 95% CI: 1.02–4.07; p=0.04). No significant association were observed for brain metastases (p=0.37), BRCA mutation status (p=0.33), or visceral involvement (p=0.27). **Conclusions:** In real-world setting, more than 25% of mTNBC patients experience a durable benefit from SG. Prior exposure to immunotherapy and earlier use of SG in the second-line setting were associated with a higher likelihood of LTR, while de novo disease showed a favourable trend. Notably, the presence of brain or visceral metastases did not preclude prolonged benefit. These findings suggest that a subset of patients with mTNBC may derive sustained clinical benefit from SG and support its use earlier in the treatment sequence. Clinical trial information: NCT02284581. Research Sponsor: Gilead Sciences.

1131 **Poster Session**

Progression-free survival as a surrogate endpoint for overall survival in metastatic triple-negative breast cancer: A systematic review and meta-analysis. First Author: Yashasvi Srivastava, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

Background: Overall survival (OS) remains the gold standard endpoint in metastatic triple negative breast cancer (mTNBC), but its assessment is confounded by post progression therapies and prolonged follow up. Progression-free survival (PFS) is frequently used as a primary endpoint; however, its validity as a surrogate for OS in mTNBC remains uncertain. We conducted an updated systematic review and meta analysis to evaluate the strength and reliability of PFS as a surrogate endpoint for OS across contemporary RCTs. **Methods:** We searched PubMed, Embase, Cochrane Library, and major oncology conference proceedings through January 2026 for randomized controlled trials evaluating systemic therapies in metastatic or unresectable TNBC. Eligible trials reported hazard ratios (HRs) for both PFS and OS. Trial level correlations between log(HR_PFS) and log(HR_OS) were assessed using weighted Spearman correlation and weighted linear regression, with sample size based weights. Certainty of evidence was assessed using a modified GRADE framework. **Results:** Twenty-seven treatment comparisons from 29 trials (8,527 patients) met inclusion criteria. Across all comparisons, PFS demonstrated a strong correlation with OS (weighted Spearman ρ = 0.80; 95% CI, 0.55-0.91), with a moderate surrogate relationship (R^2 = 0.64). The regression slope (0.66; 95% CI, 0.46-0.87) indicated attenuation of OS benefit relative to PFS. The surrogate threshold effect corresponded to an HR PFS of 0.96. Eight trials (30%) showed concordant PFS and OS benefit, while 44% demonstrated PFS improvement without significant OS gain. Surrogacy was strongest in phase III trials (R^2 = 0.71). Treatment class analyses revealed strong surrogacy for immune checkpoint inhibitors (R^2 = 0.95) and platinum based chemotherapy (R^2 = 0.87), but weak correlation for AKT pathway inhibitors (R^2 = 0.31). Overall certainty of evidence was moderate. Risk of bias assessment using the Cochrane RoB 2.0 tool showed 30% of comparisons at low risk, 56% with some concerns (primarily due to open label design), and 15% at high risk, mainly related to crossover and outcome assessment. **Conclusions:** PFS is a moderate and clinically acceptable surrogate for OS in metastatic TNBC, particularly for immune checkpoint inhibitors and platinum based regimens. However, surrogate validity varies substantially by treatment class, underscoring the need for confirmatory OS data especially for targeted therapies with novel mechanisms. Research Sponsor: None.

1132 Poster Session

Measuring KEYNOTE-522 response from TNBC patient biopsies ex vivo using the E-slice assay. First Author: Kyuson Yun, Houston Methodist Cancer Center, Houston, TX

Background: The KEYNOTE-522 regimen demonstrated a significant survival advantage of adding neoadjuvant pembrolizumab (pembro) to standard-of-care (SOC) chemotherapy (chemo) in TNBC patients. However, most patients will not benefit from this costly and potentially toxic therapy. A diagnostic test that can stratify responders and non-responders in advance will reduce overtreatment in this population. The E-slice assay is a proprietary 3D human tumor tissue culture platform that enables rapid, personalized drug sensitivity testing. E-slices preserve immune cells in their native state ex vivo, enabling immunotherapy response measurement from tissue resident immune cells. **Methods:** In this prospective clinical study, newly diagnosed triple-negative breast cancer (TNBC) patients scheduled to receive KEYNOTE-522 treatment at MD Anderson Cancer Center were enrolled. E-slices were generated from 14-gauge core biopsies and treated with IgG control, pembrolizumab, or a combination of pembrolizumab with paclitaxel + carboplatin followed by doxorubicin + cyclophosphamide. Diagnostic performance of the E-slice assay was evaluated using sensitivity, specificity, and ROC analysis, with the optimal cutoff determined by the Liu method. Concordance between assay-based predictions and clinical treatment response was assessed using Cohen's kappa, and paired classification differences were tested with McNemar's test. Patient tumor responders were defined solely by pathological complete response (pCR) or not, at the time of surgery, after standard-of-care neoadjuvant chemoimmunotherapy treatment. **Results:** A blinded interim analysis was scheduled after the first 10 patients evaluated in the clinic for pCR. The mean and SD of age were 52.10±12.52. The mean and SD for E-slice combo response, relative to DMSO @ day12 were 0.68±0.18. The optimal cutoff point for E-slice combo response was 0.78. The proportion of responders in patients was 0.8 (8/10). The proportion of responders from E-slice combo response was 0.7 (7/10). There was no significant difference based on McNemar's test (p=1.0). The concordance rate is 75% (95% CI: 42.81%-94.51%). The sensitivity, specificity, positive predictive value, negative predictive value, and area under ROC curve at cutoff point for E-slice were: 87.5% (95% CI: 47.3%-99.7%), 100% (15.8%-100%), 100% (59%-100%), 66.7% (9.43%-99.2%), and 0.94 (0.82-1.0), respectively. **Conclusions:** E-slice assay predicts TNBC patient responses to pembrolizumab alone or pembrolizumab + chemo by providing drug sensitivity data in a clinically actionable time frame. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Confusion matrices E-slice combo response.

		E slice Response		
		Non-Responders	Responders	Total
Patient Response	Non-responders	2	0	2
	Responders	1	7	8
	Total	3	7	10

E-slice Responder was defined as E-slice combo response relative to DMSO @ day12 <0.7816. Non-responder was defined as ≥0.7816.

1133 Poster Session

Determinants of triple-negative breast cancer among African patients: Early results from The African Cancer Atlas. First Author: Emmanuella Amoako, Yemaachi Biotech, Accra, Ghana

Background: Triple-negative breast cancer (TNBC) is disproportionately common among women of African ancestry and is associated with aggressive clinical behavior and limited therapeutic options. Understanding demographic and contextual determinants of TNBC across African countries is essential to improving prevention, early detection, and precision oncology strategies. Using harmonized data from The African Cancer Atlas (TACA)—an initiative of Yemaachi Biotech, we examined factors associated with TNBC across Côte d'Ivoire, Ghana, Kenya, Nigeria, and Seychelles. **Methods:** We analyzed 236 participants with complete immunohistochemistry data enrolled in TACA. Associations between TNBC and demographic variables were assessed using Wilcoxon rank-sum tests, Fisher's exact tests, and multivariable logistic regression. **Results:** TNBC accounted for 38.1% of breast cancers in the cohort. TNBC had prevalence rates ranging from 21.1% in Kenya to 68.1% in Nigeria ($p<0.001$). Seychelles exhibited no TNBC cases (0/23). TNBC prevalence among females was 38.5% (89/231), compared with 20.0% (1/5) among the few male participants. Women in Nigeria had markedly higher odds of TNBC compared with Kenya (OR 10.4, 95% CI 3.72–31.4, $p<0.001$). Women in Ghana also demonstrated increased odds (OR 2.55, 95% CI 1.10–6.12, p=0.032). Age showed no significant association with TNBC (mean age 51.6 years for TNBC vs. 50.2 years for non-TNBC, p=0.6), though the 60–69 age group showed a modestly increased proportion of TNBC (38.1%, OR 0.26, 95% CI 0.07–0.93, p=0.042, relative to 50–59). Education level was significantly associated with TNBC (p=0.004). Women with no formal education had a 59.2% TNBC prevalence (29/49), compared with 26.9% among those with primary education (18/67, OR 0.69, 95% CI 0.26–1.85) and 33.3% among those with higher education (17/51, OR 0.77, 95% CI 0.28–2.14). Family history of cancer was also associated with TNBC (p=0.006). Among women reporting a positive family history, 23.8% had TNBC (15/63), compared with 76.2% with non-TNBC (48/63). **Conclusions:** TNBC prevalence in this multi-country African cohort was high and characterized by substantial geographic variation, with Nigeria demonstrating the highest burden. Lower educational attainment and family history of cancer were also associated with TNBC, independent of country. These findings highlight the importance of considering sociodemographic and contextual factors when designing TNBC-focused screening and treatment strategies and underscore the need for country-specific precision oncology approaches in African settings. Research Sponsor: None.

1134 Poster Session

Immune infiltration features relative to cancer cell clumps as predictors of survival in triple-negative breast cancer. First Author: Himangi Srivastava, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Triple-negative breast cancer (TNBC) is an aggressive subtype with poor prognosis. While immune infiltration and abundance have been established as prognostic indicators, we examine how immune spatial organization and tumor geometry jointly influence survival. **Methods:** Whole-slide H&E images from 125 TNBC TCGA cases were analyzed using pathology instance learning models to generate tile-based predictions, which were reconstructed into polygon annotations for tumor epithelium, tumor-infiltrating lymphocytes (TILs), and tertiary lymphoid structures (TLS). From these annotations, we extracted novel spatial features describing abundance, fragmentation, dispersion, shape, and boundary properties of immune and tumor regions, as well as immune–tumor distances, overlap gradients, and boundary engagement. Associations with disease-specific survival (DSS) were assessed using univariate Cox models, and significant features were incorporated into a multivariate Cox model. Kaplan–Meier and correlation analyses were performed for dichotomized features. **Results:** Among all spatial features analyzed, global immune dispersion emerged as a strong indicator of survival. This metric, quantified by the radius of gyration of immune islands, was significantly associated with worse disease-specific survival (DSS) (HR per SD = 1.90; p = 0.03) and demonstrated clear Kaplan–Meier separation (log-rank p = 0.028). Increased tumor boundary complexity, measured by edge density normalized to tissue area, was also associated with poorer DSS (HR per SD = 1.77; p = 0.007). Kaplan–Meier analysis for edge density showed only modest separation (log-rank p = 0.071), consistent with a gradual, continuous risk effect rather than a discrete threshold. Similarly, greater intratumoral immune area correlated with adverse DSS (HR per SD = 1.26; p = 0.020), supporting the interpretation of intratumoral immune accumulation as a marker of ineffective or dysfunctional immune infiltration rather than protective immunity. In a multivariable Cox model, immune dispersion, tumor boundary complexity, and intratumoral immune area retained concordant effect directions and jointly achieved strong discrimination (C-index ≈ 0.74). Correlation analysis confirmed that the dominant spatial features were non-redundant, with minimal multicollinearity (all variance inflation factors < 1.2). **Conclusions:** In TNBC, survival is not solely dependent on immune abundance and proximity to the tumor region, but on the immune spatial dispersion, aggressive tumor boundaries, and ineffective immune accumulation in the intratumoral space. Novel spatial biomarkers examined here may refine risk stratification beyond conventional metrics. Research Sponsor: MSK Cancer Center Support grant; P30 CA008748; Simons Foundation, and a Breast Cancer Research Foundation; BCRF-17-193.

1135 Poster Session

Impact of protein–energy malnutrition on outcomes of metastatic triple-negative breast cancer patients receiving chemotherapy: A real-world analysis. First Author: Vaishali Deenadayalan, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Protein–energy malnutrition (PEM) is common in patients with advanced cancer and is associated with increased toxicity, decreased treatment tolerance, and worse survival across malignancies. Data specific to metastatic triple-negative breast cancer (mTNBC), a biologically aggressive subtype, remain scarce. We evaluated the impact of PEM on outcomes in mTNBC patients receiving chemotherapy. **Methods:** We conducted a retrospective cohort study using de-identified data from TriNetX, a global federated health research network. Females with mTNBC on chemotherapy (paclitaxel, doxorubicin, capecitabine, eribulin, vinolrebine) were identified. PEM was defined using ICD-10 codes along with secondary definitions like BMI (<20). The primary endpoint was overall survival (OS), estimated using the Kaplan-Meier method. Propensity matching was used to adjust for age, race and comorbidities. Two sided p≤0.05 was used to determine statistical significance. **Results:** A total of 1,644 patients with mTNBC were identified, of whom 761(46.3%) patients had PEM. The mean age was higher in the PEM group compared to the non-PEM group (64.5 vs 63 years, $p<0.05$). African American patients were more likely to have PEM (37.0% vs 31.4%, $p=0.02$). After propensity score matching, 595 patients were included in each cohort for analysis. Patients with PEM had significantly worse 1-year OS compared to non-PEM group (65.7% vs 70.8%; HR 0.76, 95% CI 0.62–0.94, $p<0.05$). At 2 years, survival remained numerically lower in the PEM group (56.2% vs 57.8%; HR 0.92, 95% CI 0.76–1.12), but the difference was not statistically significant. **Conclusions:** In this large real-world cohort of mTNBC, PEM was independently associated with worse 1-year overall survival. These findings underscore the prognostic significance of nutritional status in mTNBC and support routine nutritional assessment and early supportive interventions to improve outcomes in this high-risk population. Research Sponsor: None.

Overall survival (OS) outcomes in matched mTNBC cohorts.

Overall Survival	PEM Group (n=595)	Non-PEM Group (n=595)	Hazard Ratio (95% CI)	P-value
1-Year OS	65.7%	70.8%	0.76 (0.62–0.94)	<0.05
2-Year OS	56.2%	57.8%	0.92 (0.76–1.12)	0.41

1136 **Poster Session**

Leveraging single-cell trajectory analysis and machine learning to build a robust prognostic classifier for triple-negative breast cancer to pinpoint CCDC171 as a master regulator. First Author: Jialiang Feng, Zhongnan Hospital of Wuhan University, Wuhan, China

Background: Triple-negative breast cancer (TNBC) is limited by high heterogeneity and a lack of robust biomarkers for risk-stratified management. While chemotherapy is standard, traditional bulk signatures fail to capture high-resolution cellular transitions driving recurrence. This study integrates scRNA-seq with multi-algorithmic machine learning to identify key regulatory programs. We developed a trajectory-informed prognostic classifier to improve individual risk assessment and uncover potential therapeutic targets in the TNBC tumor microenvironment (TME). **Methods:** We performed single-cell RNA sequencing (scRNA-seq) on 24 TNBC samples to map the cellular landscape and applied pseudotime trajectory analysis to identify dynamic gene programs associated with cell-fate decisions. Prognostic genes derived from trajectory-informed differential expression were integrated with bulk RNA-seq data from TCGA-TNBC and validated in two independent cohorts (GSE58812, GSE135565). A robust prognostic model was constructed using an extensive machine-learning framework combining forward stepwise Cox regression and gradient boosting (StepCox[forward] + GBM). Model performance was evaluated using Harrell's C-index and Kaplan–Meier analysis, and predictive utility was assessed in neoadjuvant treatment cohorts. Virtual gene knockout experiments were used to analyze the function of CCDC171. **Results:** We developed an 18-gene prognostic signature that robustly stratified TNBC patients into high- and low-risk groups across multiple cohorts (TCGA: HR = 55.12, $p = 2.9\times10^{-12}$; GSE58812: HR = 3.96, $p = 6.3\times10^{-4}$; GSE135565: HR = 7.73, $p = 4.0\times10^{-3}$). The model outperformed existing prognostic signatures and generalized to non-TNBC breast cancer subtypes. Four genes (CRISP3, PDZK1IP1, CCDC171, IGFL1) were consistently retained across top-performing algorithms. CCDC171 emerged as a central regulator whose expression correlated with poor survival and coordinated a network involving complement activation (C1QB), metabolic reprogramming (CA8), and mitochondrial stress response (MTRNR2L8). In silico knockout of CCDC171 downregulated these effectors and suppressed oncogenic pathways including PI3K–Akt signaling, ECM interaction, and platinum resistance. **Conclusions:** Our study presents a TNBC prognostic model grounded in TME cellular dynamics and machine learning, with superior predictive accuracy and cross-subtype applicability. CCDC171 is identified as a novel master regulator of a multi-effector network driving tumor aggressiveness, offering a potential therapeutic target. This integrative framework supports risk-stratified management and personalized therapy in breast cancer. Research Sponsor: None.

1137 **Poster Session**

VISTA: Targeted combination immunotherapy for suppression of breast cancer metastasis and recurrence. First Author: James Stuart Garner, Percheron, Melbourne, VIC, Australia

Background: Triple-negative breast cancer (TNBC) has limited treatment options and poor outcomes, with ~12% 5-year overall survival in stage IV. In early-stage TNBC (II/III), recurrence remains substantial among patients without pathological complete response after chemo-immunotherapy. Current PD-1/PD-L1 inhibitors show limited efficacy in metastatic TNBC (median OS ~23 months) and infrequent durable responses. Novel immune targets are urgently needed to overcome resistance and prevent metastasis. V-domain Ig suppressor of T-cell activation (VISTA) is a next-generation checkpoint with distinct biology, enriched in tumor-infiltrating immune cells in TNBC. **Methods:** Comprehensive bioinformatic analyses of VSIR (VISTA) and ligands were performed across multi-cohort TNBC datasets spanning early and advanced stages, including pre-treatment, post-treatment, and progression samples. Spatial single-cell profiling of stage III TNBC tumors with recurrence versus non-recurrence was conducted using NanoString CosMx. VISTA expression in tumor tissue and circulating tumor cells (CTCs) was assessed by optimized immunofluorescence and digital pathology. Clinically relevant TNBC mouse models evaluated VISTA-mediated immune modulation alone and combined with chemo- or immunotherapy. **Results:** Single-cell bioinformatic analyses revealed enrichment of VSIR and ligands SELPLG/LGALS9 in post-treatment and progression-stage TNBC versus pre-treatment, observed in tumors and liquid biopsies. VSIR/SELPLG were enriched in progenitor and terminally exhausted immune subsets, whereas early-stage TNBC showed broader immune distribution. Digital pathology identified VISTA in metastasis-initiating tumor cells and dysfunctional immune cells, with induction following anti–PD-1 therapy in TNBC mouse models. Spatial profiling of recurrence-associated tumors showed co-enrichment of VSIR/SELPLG with inhibitory receptors TIM3, LAG3, and TIGIT across immune niches in recurrence-associated tumors. VISTA targeting with a novel antibody, HMBD-002, enhanced anti-tumor immunity, synergized with chemo- and immunotherapy, and suppressed recurrence and metastatic burden in preclinical models. **Conclusions:** VISTA is a treatment-emergent checkpoint associated with T-cell exhaustion, recurrence, and metastasis in TNBC. Its enrichment in exhausted T-cell niches, metastasis-initiating tumor cells, and CTCs post–chemo-immunotherapy supports its role in adaptive resistance. VISTA expression in tissue and liquid biopsy CTCs represents a clinically actionable biomarker for patient selection and response monitoring. These data provide strong rationale for early-phase clinical trials of combination VISTA blockade with ICIs in high-risk early-stage TNBC with residual disease and metastatic TNBC after prior ICI exposure. Research Sponsor: None.

1138 **Poster Session**

Clinical and translational analysis of a phase Ib/II combination of atezolizumab, cobimetinib, and eribulin (ACE) to demonstrate inflammatory and metabolic programs define divergent response states. First Author: Elyse R. Lopez, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Inflammatory breast cancer (IBC) is a rare, aggressive subtype with poor outcomes and limited immunotherapy data. Preclinical studies suggest MAPK inhibition enhances antitumor immunity and synergizes with checkpoint blockade. We report results from a phase Ib/II trial of atezolizumab (A), cobimetinib (C), and eribulin (E) in metastatic IBC with integrated molecular profiling. **Methods:** Patients (pts) with metastatic/recurrent IBC received ACE (cohort 1, n=17). Following cobimetinib supply discontinuation, an exploratory cohort received AE (cohort 2, n=10). Primary endpoint: objective response rate (ORR) per RECIST v1.1. Secondary endpoints: safety, progression-free survival (PFS), overall survival (OS), and correlative genomic, transcriptomic, spatial immune, and circulating tumor DNA (ctDNA) analyses. **Results:** ACE achieved ORR 50% (7/14; 3 patients were unevaluable for response), disease control rate (DCR) 71% (10/14), median PFS 3.7 months (mo), and median OS 10.6 mo, with 2 exceptional responders achieving >5-year survival. AE showed limited activity (ORR 10%, median OS 7.8 mo). No grade 4/5 toxicities occurred. Molecular profiling revealed distinct response states: responders demonstrated immune-activated, epithelial-like transcriptional programs with CD8+ T-cell infiltration; non-responders exhibited metabolically hyperactive, immune-excluded phenotypes with KRAS pathway activation, T-reg enrichment, CD8+ T-cell exclusion, VEGFA/GSDMB upregulation, and elevated ctDNA. **Conclusions:** ACE demonstrated encouraging activity in metastatic IBC with durable benefit in two pts. Resistance was associated with metabolic reprogramming and stromal immune exclusion, supporting rational development of metabolism-targeting, stroma-modifying, or T-reg/macrophage-directed combinations in this high-risk population. Clinical trial information: NCT03202316. Research Sponsor: None.

1140 **Poster Session**

Sequence of similar-payload ADCs: Does it make sense in real-world HER2-low advanced breast cancer?—The Portuguese national study. First Author: Gonçalo Fernandes, Hospital da Luz Lisboa, Lisboa, Portugal

Background: New-generation Antibody-Drug Conjugates (ADC) have expanded treatment options for HER2-low advanced breast cancer (ABC), regardless of hormone receptor (HR) status. Sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd) are used sequentially in clinical practice, but real-world data on efficacy, sequencing and potential cross-resistance are limited. We aimed to evaluate efficacy, sequencing patterns and predictors of outcome in a national real-world cohort of HER2-low ABC. **Methods:** We conducted a multicenter, retrospective real-world cohort study including patients with HER2-low ABC treated sequentially with SG and T-DXd, regardless of sequence, across 14 Portuguese centers. Eligible patients initiated the first ADC between 2023 and 2025 and received ≥1 cycle of both ADCs. The primary endpoint was progression-free survival (PFS), evaluated for the first (PFS1) and second ADC (PFS2). Secondary endpoints included objective response rate (ORR), primary resistance to the second ADC (PFS2 ≤3 months) and safety. PFS was analyzed using time-to-event methods. For exploratory analyses, PFS1 and PFS2 were dichotomized at the median and associations with longer PFS were assessed using chi-square tests. Predictors of PFS2 were explored in an exploratory multivariable Cox regression model. **Results:** Sixty-four patients were included; 36 (56%) had HR-positive disease and 28 (44%) were HR-negative. Median age at ADC1 initiation was 51 years (27–79). T-DXd was used as the first ADC (ADC1) in 34 (53%) patients and was more frequently administered as ADC1 in HR-positive disease. A total of 22 (34%) patients received ≥1 intermediate line, mainly chemotherapy (91%). Median PFS1 was 8.9 months (95% CI 5.8–9.7) and median PFS2 was 2.7 months (95% CI 2.1–3.2). PFS2 was consistently shorter than PFS1 across subgroups, independent of treatment line, with 43 (70%) patients presenting primary resistance to the second ADC. ORR to ADC2 was 3%. No significant differences in PFS1 or PFS2 were observed by ADC sequencing. Longer PFS1 was not associated with improved PFS2 (p=0.44). In the multivariable model, none of the evaluated variables, including the use of ≥1 intermediate line between ADCs, were significantly associated with longer PFS2 (all $p>0.05$). No new safety signals were observed; rates of dose reductions and interruptions were consistent with known safety profiles of SG and T-DXd. **Conclusions:** In this national real-world cohort of HER2-low ABC, clinical benefit from a second ADC was limited, with shorter PFS and frequent early progression, irrespective of sequencing order. Importantly, no baseline clinical factors predicted PFS2. These findings may suggest clinically relevant cross-resistance between ADCs with similar payloads and highlight shared resistance mechanisms as a key challenge in optimizing ADC sequencing. Research Sponsor: None.

1141 **Poster Session**

Clinical impact and temporal evolution of mutational signatures in metastatic lobular breast cancer. First Author: Sherry Shen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Invasive lobular carcinoma (ILC) has distinct genomic features, including frequent *CDH1* alterations, yet the mutational processes shaping metastatic ILC and their prognostic significance remain poorly defined. We evaluated mutational signatures inferred from targeted sequencing in a large single-center cohort of metastatic ILC and their association with outcomes. **Methods:** Patients were included if they had ILC histology on early-stage breast biopsy/surgical pathology, and/or *CDH1* mutation on metastatic site biopsy and MSK-IMPACT sequencing from a metastatic site. For survival analyses, only biopsies performed within 2 months of metastatic diagnosis were included. Clinicopathologic data were abstracted from electronic medical records. Single base substitution (SBS) signatures were inferred using SigMA; cases with $\leq$5 SBS were excluded. Overall survival (OS) was estimated using Kaplan–Meier and compared by dominant signature using the log-rank test. **Results:** 654 patients were included. 467 (71%) had hormone receptor-positive (HR+)/HER2-, 56 (8.6%) had HER2+, and 65 (9.9%) had triple negative disease at metastatic diagnosis. Among 307 (47%) with ILC variant data available, 139 (45%) had classic type, 65 (21%) had pleomorphic, 45 (15%) had mixed, and 58 (19%) had other ILC variants. 385 patients (59%) had MSK-IMPACT testing on a tissue biopsy performed within 2 months of metastatic diagnosis. Among them, the most prevalent mutations included *CDH1* (85%), *PIK3CA* (47%), *TP53* (21%), *TBX3* (16%), *PTEN/AKT1* (14.5%), *FOXA1* (12%), *ERBB2* (12%), *KMT2C* (9.9%), *CBFB* (9.9%), *ARID1A* (9.6%), *MAP3K1* (8.8%), and *NF1* (7.5%). 320/385 (83%) MSK-IMPACT tests had $\geq$5 SBS and were analyzable for mutational signature. The dominant mutational signature was APOBEC in 44%, clock-like (aging) in 38%, Signature 3 (homologous recombination deficiency) in 12%, Signature 17 in 5.6%, and Signature 8 in 1%. Median OS in the total cohort was 4.4 years (95%CI 4.1-4.8) and differed significantly by dominant mutational signature (log-rank p=0.001). Median OS for those with APOBEC-dominant disease was 3.1 years (95%CI 2.5-3.7) and for those with clock-like (aging) signature was 4.4 years (95%CI 3.8-6.5). Among 61 patients who had paired samples analyzable for mutational signature within 2 months of metastatic diagnosis and at another timepoint following metastatic diagnosis, the prevalence of APOBEC as the dominant mutational signature increased (29/61 [48%] to 36/61 [59%]), whereas clock-like (aging) decreased (25/61 [41%] to 17/61 [28%]). **Conclusions:** Dominant APOBEC mutational signature at metastatic ILC diagnosis was associated with shorter OS, with differences observed between APOBEC- and aging-dominant tumors. Serial testing demonstrating increasing APOBEC dominance over time supports mutational signatures as dynamic, clinically relevant features of metastatic ILC. Research Sponsor: Lisa Bonchek Adams Memorial Fund.

1142 **Poster Session**

Phase II study of olaparib plus ATR inhibitor ceralasertib in patients with metastatic breast cancer and germline BRCA1/2 pathogenic variants who progressed on prior PARP inhibitor therapy. First Author: Banu Arun, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: PARP inhibitors (PARPi) olparib and talazoparib improve objective response rate (ORR) and disease-free survival (DFS) compared with chemotherapy in patients with metastatic breast cancer and germline BRCA 1/2 pathogenic variants (gBRCA 1/2 PVs). Although the ORR is approximately 60%, about 40% of patients do not respond, and nearly all responders eventually develop progressive disease. Therefore, new strategies to overcome PARPi resistance are needed. Preclinical studies suggest that ATR inhibition combined with olaparib may restore PARPi sensitivity. Phase I studies have shown that olaparib (Ola) plus the ATR inhibitor ceralasertib (Cerala) is safe and have established the recommended phase II dose. This prospective phase II study evaluated the ORR of Ola plus Cerala in patients with metastatic breast cancer with gBRCA 1/2 PVs who previously progressed on PARPi therapy. **Methods:** Eligible patients had metastatic breast cancer (HER2- negative), prior PARPi exposure, and no more than two prior lines of chemotherapy. After informed consent, all patients underwent the baseline research biopsy of a metastatic lesion and provided blood samples for exploratory analysis aimed at identifying mechanisms of PARPi resistance. Treatment consisted of olaparib 150 mg orally twice daily on days 1-28 plus ceralasertib 80 mg orally twice daily on days 1-14 of each 28-day cycle. The primary endpoint was ORR per RECIST 1.1. Secondary endpoints included safety, DFS, and duration of response. Exploratory endpoints focused on biomarker analysis of PARPi resistance. This abstract reports the primary end point. **Results:** Fifteen patients were enrolled. The median age was 39 years. Eight patients had hormone receptor-positive disease; 6 of these had received endocrine therapy before first-line PARPi. Two patients achieved a partial response (PR) and two had stable disease (SD), resulting and an ORR of 13.3% and a clinical benefit rate of 26.7%. No grade 4 toxicities were observed. Grade 3 adverse events included anemia (N=5), neutropenia (N=1), decreased white blood cell count (N=1), lymphopenia (N=1), and thrombocytopenia (N=1). **Conclusions:** The combination of olaparib plus ceralasertib is well tolerated and demonstrates clinical activity in patients with metastatic breast cancer with gBRCA 1/2 PVs who have progressed on prior PARPi therapy. A study of this combination in the first-line setting may help determine whether ATR inhibition can overcome or delay PARPi resistance. Biomarker analysis to identify mechanisms of resistance are ongoing and will be reported separately. Clinical trial information: NCT04090567. Research Sponsor: CPRIT; Astra Zeneca.

TPS1143 **Poster Session**

A phase II study evaluating treatment discontinuation of dual anti-HER2 therapy in metastatic HER2-positive breast cancer after five years of sustained complete response (FREEDOME-trial). First Author: Albert Grinshpun, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Dual anti-HER2 therapy with trastuzumab (T) and pertuzumab (P) has transformed outcomes in HER2-positive metastatic breast cancer (mBC), with approximately 20% of patients maintaining response beyond 8 years based on CLEOPATRA trial data. Current practice continues anti-HER2 therapy indefinitely in responding patients, despite lack of evidence supporting necessity of lifelong treatment in long-term responders. This approach is associated with cumulative financial burden, and quality of life impact from indefinite therapy requirements. No prospective data exist regarding optimal duration of anti-HER2 therapy in long-term responders, nor are there validated biomarkers to guide treatment discontinuation decisions. Minimal residual disease (MRD) assessment has shown promise in other malignancies for identifying patients at low risk of recurrence. This study addresses an unmet need for evidence on safety of treatment discontinuation in long-term responders. **Methods:** This prospective, multicenter, single-arm phase II trial enrolls patients with HER2-positive mBC who have maintained CR for $\geq$5 years on dual anti-HER2 therapy (T plus P). Target enrollment is 40 patients based on Fleming's single-stage design to detect median progression-free survival (mPFS) $>$12 months with 80% power (α=0.05). Key eligibility criteria include: confirmed HER2-positive mBC, sustained CR by RECIST 1.1 for $\geq$5 years, normal tumor markers (CA125, CEA, CA15-3), and no evidence of progression on baseline PET-CT. Patients with concurrent malignancies requiring systemic therapy are excluded. Following enrollment, participants discontinue T+P therapy but should continue endocrine therapy (if given). Surveillance includes PET-CT at baseline, 3, 6, 12 months, then annually; annual mammography/ultrasound per institutional standards; and blood collection for tumor markers at baseline, 3, 6, 12 months, then annually. Patients resuming anti-HER2 therapy upon progression remain on study for survival assessment. Primary endpoint is mPFS post-discontinuation. Secondary endpoints include 6-month PFS, 12-month PFS, and median overall survival. Exploratory analyses examine tumor markers as predictive biomarkers. Kaplan-Meier methodology will estimate survival probabilities with 95% confidence intervals. As of January 2026, one site is open for recruitment. Minimal residual disease analysis is planned and will be submitted to the IRB committee for approval. Study completion is anticipated by 2031 with interim analysis planned after 2 years. Clinical trial information: MOH_2025-12-27_015564. Research Sponsor: None.

TPS1144 **Poster Session**

A phase 1b/2 study of QLS1304, a novel, highly potent, and selective dual inhibitor of KAT6A/6B, plus endocrine therapy (ET) in patients (pts) with estrogen receptor–positive (ER+), human epidermal growth factor receptor 2–negative (HER2–) breast cancer (BC). First Author: Jiong Wu, Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: QLS1304 is a novel, highly-potent, and selective dual inhibitor of KAT6A/6B. KAT6A acetylates histone H3 at the 23rd lysine residue, thereby modulating gene transcription, and implicated in ER+/HER2- BC. QLS1304 showed potent efficacy in standard of care resistant, KAT6A-high and *ESR1*-mutant ER+/HER2- BC patient-derived xenograft model, whether administered as a monotherapy or combination therapy (*Cancer Res (2025) 85 (8_Supplement_1): 457*). In the ongoing phase 1 trial, QLS1304 monotherapy showed an acceptable safety profile and potential anti-tumor activity in pts with BC. This study aimed to evaluate the safety and preliminary efficacy of QLS1304 + ET combination (fulvestrant or QLC1401, a novel oral selective ER degrader) $\pm$ CDK4/6 inhibitor (CDK4/6i) in pts with ER+/HER2- locally advanced or metastatic (LA/M) BC. **Methods:** This multicenter, open-label, phase 1b/2 trial consists of phase 1b combination dose-escalation and phase 2 dose-expansion. The phase Ib study will enroll pts with LA/M ER+/HER2- BC, who have received prior ET plus CDK4/6i, utilizing the Rolling-Six design. There are 2 cohorts: Cohort 1A QLS1304 + fulvestrant and Cohort 1B QLS1304 + QLC1401. Three dose levels of QLS1304 are planned, which are 4 mg/d, 8 mg/d, and 12 mg/d. The dose of QLC1401 is 150 mg, which is the recommended phase 2 dose (RP2D) of monotherapy. Both QLS1304 and QLC1401 are orally administered in a 28-day cycle. A total of 12~18 pts per cohort are planned to be enrolled, which might be adjusted based on the occurrence of dose-limiting toxicities (DLTs) during the first cycle. The primary endpoints are safety, tolerability, and RP2D of QLS1304 combined with fulvestrant/QLC1401. In phase 2, 1~2 dose levels of QLS1304 will be explored in 5 cohorts. In Cohort 2A (QLS1304 + fulvestrant) and Cohort 2B (QLS1304 + QLC1401), pts with LA/M ER+/HER2- BC who received prior ET plus CDK4/6i will be enrolled. In Cohort 2C (QLS1304 + CDK4/6i + letrozole), pts with LA/M ER+/HER2- BC with no prior therapy will be enrolled. In Cohort 2D (QLS1304 + CDK4/6i + fulvestrant), adjuvant ET-resistant or ET+CDK4/6i pretreated LA/M ER+/HER2- BC pts will be enrolled in 2 subgroups. In Cohort 2E (QLS1304 + CDK4/6i + QLC1401), adjuvant ET-resistant, treatment naïve, or ET+CDK4/6i pretreated LA/M ER+/HER2- BC pts will be enrolled in 3 subgroups. Doublet combination will be firstly explored, which will support the dose selection of triplet combination. In triplet cohorts 2C–2E, 6 pts will be enrolled in a safety run-in to assess the preliminary safety profile in each cohort. Expansion will be started after safety confirmation. A total of 316~366 pts will be enrolled. The primary endpoint of phase 2 is ORR per RECIST v1.1. Patient enrollment is currently ongoing. Clinical trial information: NCT07235176. Research Sponsor: QIlu Pharmaceutical Co. Ltd.

TPS1145 **Poster Session**

TUC-TOC phase II trial (NCT05955170): Tucatinib in combination with oral etoposide (VP16) and trastuzumab in patients with metastatic HER2-positive breast cancer (HER2+ mBC). First Author: Diana Bello Roufai, Medical Oncology Department, Institut Curie, Saint-Cloud, France

Background: Patients with HER2-positive metastatic breast cancer (HER2+ MBC) have limited therapeutic options after progression on tucatinib–trastuzumab–capecitabine. There is a need for later-line regimens combining chemotherapy with dual HER2 targeting. TUC-TOC was designed to evaluate the efficacy and safety of tucatinib combined with oral etoposide (VP16) and trastuzumab in this setting. Oral VP16 was selected because (i) topoisomerase II inhibitors are rarely used in HER2+ MBC, (ii) TOP2A and ERBB2 are frequently co-amplified, and (iii) it enables an almost all-oral regimen. A prior retrospective analysis suggested favorable activity and tolerability of VP16 plus trastuzumab in heavily pretreated HER2+ MBC (PMID: 35565244). **Methods:** TUC-TOC (NCT05955170) is an open-label, multicenter, academic phase II trial. Eligible patients have histologically-confirmed HER2+ MBC with disease progression on tucatinib-trastuzumab-capecitabine or a contraindication to capecitabine, measurable disease per RECIST v1.1, and adequate cardiac function. Patients with brain metastases are eligible unless urgent local treatment is required. The study includes a safety run-in followed by an expansion phase. In the safety run-in, six patients received oral VP16 50 mg/d on days 1–14 of a 3w cycle, tucatinib 300 mg PO BID, and trastuzumab 600 mg SC q3w. The primary endpoint of this phase was the rate of dose-limiting toxicities (DLTs). The primary endpoint of the expansion phase is the objective response rate (ORR), defined as the best overall response within 24 weeks according to RECIST v1.1. Secondary endpoints include PFS, OS and safety. A total of 55 evaluable patients is planned. As of 01.2026, the safety run-in phase has been completed and enrollment into the expansion phase is ongoing. Clinical trial information: NCT05955170. Research Sponsor: pfizer; Women's Cancer Institute of Institut Curie.

TPS1146 **Poster Session**

HER2-positive central nervous system (CNS) surveillance: A study of the feasibility of randomizing women and men with HER2-positive metastatic breast cancer to CNS surveillance versus no surveillance. First Author: Talvinder Bhogal, Institute of Systems, Molecular and Integrative Biology, Liverpool, United Kingdom

Background: Breast cancer (BC) is the second most common primary tumour to metastasise to the brain (Aragon-Ching, 2017). Clinical data have demonstrated that BC brain metastases (BCBM) are an increasing clinical problem (Akshara, 2024). Improved systemic treatment of extracranial disease has prolonged survival (DESTINY-Breast9, 2025); coupled with more CNS imaging, this likely contributes to rising BCBM incidence (Frisk, 2012; Pedrosa, 2018). HER2+ BC has a predilection for the CNS (Sun, 2022), and real-world data from the ESMÉ programme report BCBM incidence in metastatic BC (MBC) (Darlix, 2019). Cumulative incidence at 12 months after MBC diagnosis in a cohort of 16,703 MBC pts was 16.8% and 32.4% for HER2+ /HR+ and HER2+ /HR- respectively; at 24 months, 29.2% and 49.0%, respectively. Given the high risk of CNS disease in HER2+ MBC, associated morbidity/mortality (Riecke, 2023) and the evidence that there may be a survival and quality of life advantage for early asymptomatic detection (Hurvitz, 2019; Laakmann, 2020), surveillance strategies for early detection need evaluation. **Methods:** This is a multi-centre, randomised study in pts with HER2+ MBC without prior CNS disease. The study is testing the feasibility of randomising pts to CNS screening vs none. The study is recruiting male/female pts, aged ≥16 years with HER2+ BC with visceral metastases who are currently on HER2 directed therapies. It excludes pts with a history/clinical symptoms of CNS disease, unable to undergo MRI, or with bone only MBC. Pts following a baseline MRI brain, to exclude occult disease, are randomised 1:1 to 6 monthly MRI brain with contrast for a year or no CNS imaging. Primary endpoint: feasibility of randomising HER2+ MBC pts with no CNS disease to surveillance vs no surveillance. Secondary endpoints: proportion of pts with occult CNS disease at baseline, proportion developing occult CNS disease during surveillance and proportion developing symptomatic CNS disease during the study. The management of detected CNS disease on study will be documented. Further qualitative research through a series of interviews/focus group discussions will explore reasons why pts either agree/refuse randomization, to identify challenges with study implementation and delivery. Statistics: A maximum of 193 pts are to be approached; with 69 pts agreeing to be consented to the study for a larger study to be deemed feasible (based on alpha=5% and power 90%). Recruitment will halt at 69 consented/193 approached, whichever is reached first. REC/IRAS project ID: 341272. Research Sponsor: Make 2nd Count; Pfizer; Breast Cancer Ireland; NIHR-BRC research fellowship (for T.B); Clatterbridge Cancer Centre Charity (for T.B); The Grace Trust (for T.B).

TPS1147 **Poster Session**

A single-arm, phase II study of sequential therapy with curative intent in de novo HER2+ metastatic breast cancer: The SAPPHO study. First Author: Stefania Morganti, Dana-Farber Cancer Institute, Boston, MA

Background: Due to dramatic improvements in neoadjuvant and adjuvant HER2-directed therapy (tx), most patients (pts) with early HER2+ breast cancer are cured. As a result, over half of pts newly diagnosed with HER2+ metastatic breast cancer (MBC) now present with *de novo* stage IV disease. Anti-HER2 tx has also significantly extended survival for pts with HER2+ MBC, with a subgroup of exceptional responders alive many years (yrs) after diagnosis. However, the paradigm for HER2+ MBC remains non-curative, and pts receive tx indefinitely with significant toxicities and costs. The SAPPHO study is investigating whether an intensification approach of sequential, non-cross resistant anti-HER2 tx followed by tx discontinuation is associated with long-term disease control in pts with HER2+ MBC. **Methods:** SAPPHO is an open-label, phase II, single-arm trial testing a sequential regimen of non-cross resistant, HER2-targeted tx with curative intent in pts with *de novo* HER2+ MBC. Eligible pts must have biopsy-proven, *de novo* MBC with high HER2 expression (3+ by immunohistochemistry). Pts with brain metastases are eligible upon receipt of local tx. Treatment consists of an induction regimen (trastuzumab-pertuzumab-taxane [THP] x 4 cycles, followed by trastuzumab deruxtecan [TDXd] x 6 cycles, followed by trastuzumab emtansine [TDM1]-tucatinib x 4 cycles), followed by a maintenance regimen (HP-tucatinib for 1 yr). Given results from DESTINY-Breast09, the sequence of TDXd-P x 6 cycles followed by THP x 4 followed by TDM1-tucatinib x 4 can be chosen as alternative induction tx per investigator and patient choice. Pts who remain progression-free after completing maintenance will stop all anti-HER2 tx. Endocrine tx will be continued for pts with hormone receptor+/HER2+ tumors. Tumor specimens from breast and a metastatic site are collected at baseline and the end of induction. Serial plasma samples for ctDNA analysis are collected at baseline, during treatment, and during follow-up. The primary endpoint is the probability of being progression-free and off anti-HER2 tx 4 yrs from the start of induction. With a sample size of 72 pts, the study is designed to have 91% power to reject the null hypothesis that the probability of being off anti-HER2 tx and progression-free is less than 24%, with an alternative hypothesis of 40%. Key secondary endpoints are overall survival, overall response rate by modified RECIST 1.1 after induction, and safety. Correlative endpoints include the relationship between ctDNA dynamics and outcomes. Patient-reported outcomes will be analyzed, including quality of life, illness intrusiveness, financial toxicity, anxiety, distress about cancer progression, perception of benefit and risk of progression. SAPPHO began enrollment in Q3 2024, and the study is open at 4 US sites within the Translational Breast Cancer Research Consortium (NCT05721248). Clinical trial information: NCT05721248. Research Sponsor: Pfizer.

TPS1148 **Poster Session**

ReDiscover-2, a phase 3 study of zovegalisib (zovega, RLY-2608) + fulvestrant (fulv) versus capivasertib (capi) + fulv as treatment for locally advanced or metastatic *PIK3CA*-mutant HR+/ HER2- breast cancer following recurrence or progression on or after treatment with a CDK4/6 inhibitor. First Author: Hope S. Rugo, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: *PIK3CA* mutations constitutively activate PI3Kα and drive ~40% of HR+/ HER2- breast cancer (BC). The PI3K inhibitors alpelisib and inavolisib and the AKT inhibitor capi are approved therapeutic options; however, they are limited by significant toxicity, notably hyperglycemia, rash, and diarrhea, due to non-selective targeting of the pathway. Zovega is a pan-mutant-selective allosteric PI3Kα inhibitor designed to optimize dose intensity and target inhibition with reduced toxicity and improved tolerability. The first-in-human ReDiscover study of zovega demonstrated encouraging antitumor activity with a median progression-free survival (PFS) of 10.3 mo (95% CI: 7.2, 18.4) across a range of *PIK3CA* genotypes and a favorable safety profile when combined with fulv in patients with *PIK3CA*-mutated HR+/HER2- advanced BC previously treated with a CDK4/6 inhibitor. Based on these findings, zovega in combination with fulv is being studied in this phase 3 study, ReDiscover-2 (NCT06982521), in *PIK3CA*-mutated HR+/ HER2- advanced BC following recurrence or progression on or after a CDK4/6 inhibitor. **Methods:** ReDiscover-2 is a global, multicenter, open-label, randomized phase 3 study comparing the efficacy and safety of zovega + fulv to capi + fulv in patients with *PIK3CA*-mutated HR+/HER2- advanced BC. Approximately 540 patients will be randomized 1:1 to receive zovega (400 mg BID with food) + standard-dose fulv or capi (400 mg BID, 4 days on and 3 days off, with or without food) + fulv. Randomization will be stratified by *PIK3CA* mutation type, visceral disease, and geographic region. The primary endpoint is PFS assessed by blinded independent central review in patients having tumors with *PIK3CA* kinase domain mutations and in all patients. Overall survival is a key secondary endpoint within the same populations. Key eligibility criteria: ≥18 years of age with ECOG performance status of 0-1; confirmed diagnosis of HR+/HER2- locally advanced or metastatic BC with radiological or objective evidence of recurrence or progression; presence of one or more oncogenic *PIK3CA* mutations without evidence of *AKT* or *PTEN* alterations; measurable disease per RECIST v1.1 or evaluable bone-only disease; previous treatment for HR+/HER2- advanced BC with at least 1 and no more than 2 lines of endocrine therapy (ET) (prior fulv is allowed) or 1 prior line of CDK4/6 inhibitor therapy; HbA1c <7.0% (<53 mmol/mol) and fasting plasma glucose <140 mg/dL (Type 1 diabetes or Type 2 diabetes requiring antihyperglycemic medication are excluded); no prior PI3K, AKT, or mTOR inhibitors. ReDiscover-2 (NCT06982521) is open for enrollment. For information: clinicaltrials@relaytx.com. Clinical trial information: NCT06982521. Research Sponsor: Relay Therapeutics.

TPS1149 **Poster Session**

HERTHENA-Breast04: A phase 3, randomized, open-label study evaluating the efficacy and safety of patritumab deruxtecan (HER3-DXd) versus treatment of physician's choice in hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) unresectable locally advanced or metastatic breast cancer. First Author: Barbara Pistilli, Department of Medical Oncology, Gustave Roussy, Villejuif, France, and IHU PRISM National PRecISion Medecine Center in Oncology, Gustave Roussy, Villejuif, France

Background: There is an unmet therapeutic need for patients with HR+/HER2− metastatic breast cancer who experience disease progression and recurrence after first-line standard of care treatment with a CDK4/6 inhibitor (CDK4/6i) and endocrine therapy (ET). The main therapy options, for those patients who are not considered suitable for additional ET-based therapy, are chemotherapy and antibody-drug conjugates (ADCs). Human epidermal growth factor receptor 3 (HER3) is overexpressed in HR+/HER2− breast cancer and is associated with poor prognosis and drug resistance. Patritumab deruxtecan (HER3-DXd) is a novel ADC composed of a fully human anti-HER3 IgG1 antibody linked to a cytotoxic topoisomerase I inhibitor via a stable tetrapeptide-based linker that is selectively cleaved within tumor cells. In the phase 2 ICARUS-Breast01 study, HER3-DXd showed clinically meaningful antitumor activity and manageable safety in patients with HR+/HER2− advanced breast cancer who progressed on CDK4/6i treatment and 1 line of chemotherapy. The phase 3, multicenter, open-label, HERTHENA-Breast04 study (NCT07060807) evaluates efficacy and safety of HER3-DXd monotherapy vs treatment of physician's choice (TPC) in participants with HR+/HER2− advanced breast cancer after progression on 1 line of CDK 4/6i treatment. **Methods:** Participants must be aged ≥18 y and have centrally confirmed HR+/HER2− (per most recent ASCO/CAP guidelines: HER2 IHC 0 or 1+ or IHC 2+/in situ hybridization negative) unresectable locally advanced or metastatic breast cancer. Participants must have experienced disease progression or recurrence following prior treatment with a CDK4/6i and ET and must be eligible for at least 1 TPC option, as determined by the investigator. Participants must have measurable disease per RECIST v1.1 and ECOG PS of 0 or 1. Participants who have received prior chemotherapy or are candidates for an additional line of ET-based therapy in the advanced setting are ineligible for the study. Participants are randomized 1:1 to Arm 1 or 2, with ~500 participants assigned to each arm. Participants in Arm 1 will receive HER3-DXd 5.6 mg/kg IV on day 1 Q3W, and participants in Arm 2 will receive TPC consisting of 1 of the following options: paclitaxel, nab-paclitaxel, capecitabine, liposomal doxorubicin, or trastuzumab deruxtecan. Treatment will continue until disease progression, unacceptable toxicity, or participant withdrawal. The dual primary endpoints are PFS per RECIST v1.1 by BICR and OS. Secondary endpoints are ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes. Imaging assessments occur Q6W from randomization through week 60 and Q12W thereafter. Enrollment began in 2025. Clinical trial information: NCT07060807. Research Sponsor: Daiichi Sankyo Company, Limited and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS1150 **Poster Session**

Camizestrant plus ribociclib in hormone receptor–positive/HER2-negative advanced breast cancer: The phase II CADILLAC trial. First Author: Javier Cortes, International Breast Cancer Center (IBCC), Quironsalud Group, Barcelona, Spain, Scientific Department, Medica Scientia Innovation Research, Valencia, Spain, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain and Universidad Europea de Madrid, Madrid, Spain

Background: CDK4/6 inhibitors combined with endocrine therapy (ET) are the standard first-line treatment for hormone receptor–positive (HR+)/HER2–negative (HER2–) advanced breast cancer (ABC). Secondary endocrine resistance includes patients (pts) relapsing after ≥2 years of adjuvant ET during treatment or within 12 months of discontinuation but does not distinguish according to adjuvant ET duration; thus, whether HR+ tumors progressing after prolonged adjuvant ET (≥5 years) constitute a biologically and prognostically distinct entity remains unclear. Next-generation oral selective estrogen receptor degraders (SERDs) provide more potent estrogen receptor (ER) degradation and have demonstrated superiority over standard ET in pts with previously treated endocrine-resistant ABC. We hypothesized that camizestrant plus ribociclib as first-line therapy may improve outcomes versus historical ribociclib plus aromatase inhibitor (AI) or fulvestrant in HR+/HER2– ABC relapsing after long-term adjuvant ET. **Methods:** CADILLAC (NCT07195227) is an international, multicenter, open-label, single-arm, external historical-controlled phase II trial. A total of 150 pts with HR+/HER2– ABC who have not received systemic treatment for advanced disease will be enrolled from Spain, Germany, and China. Key eligibility criteria include: (a) ≥18 years; (b) histologically confirmed unresectable locally recurrent or metastatic breast cancer; (c) evaluable disease as per RECIST v.1.1; (d) prior adjuvant ET duration ≥5 years, including ≥2 of AI (with a cap of 30% pts with an ET-free interval ≥12 months); and (e) ECOG performance status 0-1. Pts will receive camizestrant 75 mg orally once daily continuously in 28-day cycles, combined with ribociclib 600 mg orally once daily on days 1-21 of each 28-day cycle, until unacceptable toxicity, disease progression, death, or discontinuation for other reasons, whichever occurs first. The primary endpoint is progression-free survival (PFS). Key secondary endpoints include overall response rate (ORR), clinical benefit rate (CBR), quality of life assessed by EORTC QLQ-C30 and QLQ-BR42 questionnaires, and safety according to NCI-CTCAE v5.0. PFS, ORR, and CBR will be locally assessed by investigators per RECIST v1.1. and compared with outcomes from a historical control cohort of at least 150 pts treated with ribociclib plus AI or fulvestrant. The null hypothesis is defined as a median PFS ≤20.3 months, whereas the alternative hypothesis corresponds to a median PFS ≥28.7 (target hazard ratio 0.707). The primary hypothesis will be tested using a stratified log-rank test at one-sided 5% significance level with 70% power. An effective total of 157 PFS events across arms is required. Interim efficacy and safety analyses are planned once the first 50 pts have completed ≥6 months of treatment. Enrollment will not be paused during this interim analysis. Clinical trial information: NCT07195227. Research Sponsor: AstraZeneca; Novartis.

TPS1151 **Poster Session**

A phase 1/2 study of EP0062 (vosilasarm), a first-in-class oral selective androgen receptor modulator (SARM), in combination with standard-of-care endocrine therapy +/- targeted therapies in patients with advanced or metastatic AR+/ER+/HER2− breast cancer. First Author: Rafael Grochot, Sarah Cannon Research Institute, London, United Kingdom

Background: EP0062 (vosilasarm), a first-in-class, oral, non-steroidal, Selective Androgen Receptor Modulator (SARM) acts as a potent tissue-selective AR agonist, suppressing growth and proliferation of multiple endocrine-sensitive or -resistant AR+/ER+/HER2- breast cancer (BC) cell lines and patient-derived xenograft (PDX) models. Pre-clinically, AR activation–rather than AR suppression–exerts potent antitumor activity in AR+/ER+ breast malignancies, including those resistant to endocrine therapy and CDK4/6 inhibitors. EP0062 has been shown to inhibit the growth of AR+/ER+ BC PDX models as a single agent, and in combination with palbociclib, everolimus or elacestrant. Phase 1 of this study reported promising safety and evidence of clinical benefit with EP0062 monotherapy in advanced AR+/ER+/HER2- BC. The ongoing Phase 2 cohorts described here are the first clinical evaluation of a SARM in combination with various standard of care therapies in patients that have previously received a CDK4/6 inhibitor. **Methods:** The Phase 2 cohorts will include up to 75 post-menopausal women, ≥ 18 years, ECOG ≤ 1, with locally advanced/metastatic, endocrine-sensitive (> 2 y adjuvant or >6 mo treatment prior to recurrence), AR+/ER+/HER2- BC, that is measurable per RECIST v1.1, or non-measurable with an evaluable bone component. AR positivity is defined as ≥ 10% AR nuclei staining by IHC. Patients may have previously received ≤ 2 lines of endocrine therapy (including CDK4/6 inhibitor), and ≤ 1 line of chemotherapy in the advanced/metastatic setting. Treatment arms are as follows: Arm 1: EP0062 + elacestrant (mandatory ESR1 mutation); Arm 2: EP0062 + exemestane + everolimus; Arm 3: EP0062 + fulvestrant + abemaciclib. A 3+3 safety run-in will confirm the combination dose for each cohort before expansion. Starting EP0062 dose was 10 mg BID. The primary objective is to evaluate safety and tolerability. Secondary objectives are to characterise the PK profile and preliminary efficacy. Biomarkers, including CA15-3, PSA, and molecular genetics are also being evaluated. Exploratory objectives are to evaluate potential biomarkers of efficacy, safety and/or PD activity. The study is currently recruiting across the three treatment arms in USA, UK, and Spain. Clinical trial information: NCT05573126. Research Sponsor: None.

TPS1152 **Poster Session**

OPERA-02: A phase 3 study of palazestrant plus ribociclib as first-line treatment of ER+, HER2- advanced breast cancer. First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Estrogen receptor-positive, human epidermal growth factor 2-negative advanced breast cancer (ER+, HER2- ABC) accounts for nearly 70% of all ABC. The standard first-line treatment for ER+, HER2- ABC is the combination of an aromatase inhibitor (AI) with cyclin–dependent kinase 4/6 inhibitor (CDK4/6i). When combined with AI, the CDK4/6i ribociclib has demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) in this setting. Despite these advances, resistance to AI + CDK4/6i develops in a substantial proportion of patients (pts), most commonly driven by acquired mutations in the ligand-binding domain of ERα, resulting in constitutive ligand-independent ER activation. Early and sustained suppression of both wild-type and mutated ERs in the first line treatment of ER+, HER2- ABC may enhance endocrine sensitivity, delay resistance to endocrine therapy and improve clinical outcomes. Palazestrant (OP-1250) is an investigational oral, complete estrogen receptor antagonist (CERAN) and selective estrogen receptor degrader (SERD). In early phase studies, palazestrant has shown favorable safety and encouraging antitumor activity as monotherapy (Hamilton et al, 2025) and in combination with ribociclib (Lin et al, 2025), regardless of ESR1 mutation status, including in those previously treated with CDK4/6i. Palazestrant showed no clinically meaningful drug-drug interactions with ribociclib, and the combination safety profile was consistent with the known profiles of each drug. **Methods:** OPERA-02 (NCT07085767) is a phase 3, international, multicenter, randomized, double-blind, study designed to evaluate the efficacy and safety of palazestrant plus ribociclib versus letrozole plus ribociclib in the first line treatment of pts with ER+, HER2- ABC. Approximately 1,000 pts will be randomized 1:1 to either palazestrant plus ribociclib or letrozole plus ribociclib, with matching placebos. The primary endpoint is investigator-assessed PFS; secondary endpoints are OS, PFS by a blinded-independent review committee, overall response rate, duration of response, clinical benefit rate, safety, pharmacokinetics, pt-reported outcomes and PFS2. Eligible pts are adult women, regardless of menopausal status, and men, with de novo or recurrent disease (≥ 12 months after completion of adjuvant endocrine therapy) who have not received prior systemic therapy for ER+, HER2- ABC. Pts must have measurable disease per RECIST 1.1 or evaluable bone disease, ECOG performance score of 0-1, and adequate organ function. Pts with a contraindication to ribociclib are excluded. Pre- or perimenopausal women and men must receive gonadotropin-releasing hormone (GnRH) agonists for gonadal function suppression. The study has been recruiting globally since November 2025. Clinical trial information: NCT07085767. Research Sponsor: None.

TPS1153 **Poster Session**

ELEGANT: Elacestrant versus standard endocrine therapy (ET) in women and men with node-positive, estrogen receptor–positive (ER+), HER2-negative (HER2−), early breast cancer (eBC) with high risk of recurrence in a global, multicenter, randomized, open-label phase 3 study. First Author: Aditya Bardia, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Adjuvant ET is the standard of care (SOC) for treating ER+/HER2- eBC. Despite advances to optimize adjuvant treatment in high-risk ER+/HER2- eBC, there continues to be risk of local and metastatic recurrence that persists, new therapies with desirable safety profiles are warranted. Elacestrant is a next-generation oral SERD that provides a novel mechanism of action that has shown both SERD (degradative) and SERM (partial agonist) activity that differs from currently available adjuvant ET (Wardell, ERC 2015). In the EMERALD trial, elacestrant significantly prolonged PFS vs SOC ET in the overall population (HR 0.70; 95% CI 0.55-0.88; P=0.0018) and in patients with *ESR1m* tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) (Bidard, JCO 2022). In patients with *ESR1m* tumors who received prior ET+CDK4/6i ≥12 mo, mPFS with elacestrant was 8.6 vs 1.9 mo with SOC ET (Bardia, CCR 2024). In patients with ER+/HER2− eBC, the SOLTI-1905-ELIPSE and SOLTI-2104-PremiERe trials showed that preoperative elacestrant was associated with a statistically significant mean change of complete cell cycle arrest rate and led to a shift in tumor biology towards a more endocrine-sensitive and less proliferative tumor phenotype in both pre- and postmenopausal women (Vidal, CCR 2025; Bellet, SABCS 2025). Given that elacestrant demonstrated efficacy in mBC regardless of *ESR1m* status relative to SOC ET and has shown biologic activity in eBC, it is hypothesized that elacestrant can prolong invasive breast cancer-free survival (IBCFS) in patients with high-risk eBC who received prior adjuvant ET±CDK4/6i. **Methods:** ELEGANT (NCT06492616) is a global, multicenter, open-label Ph3 study designed to evaluate elacestrant vs SOC ET (AI or tamoxifen) in patients with eBC and high risk of recurrence. Patients will be randomized 1:1 to continue SOC ET or to elacestrant for a duration of 5 years. Eligible patients are women/men with ER+/HER2− node-positive eBC who received between 2-5 years of SOC ET±CDK4/6i and have ECOG PS ≤1. Patients who received a prior CDK4/6i or PARP inhibitor must have completed or discontinued these treatments. Pre/perimenopausal women and men will be administered a LHRH agonist. Exclusion criteria include stage IV mBC, inflammatory BC, history of prior invasive BC, history of malignancy within 3 years of randomization date, >6 mo continuous interruption of prior SOC adjuvant ET or discontinuation of adjuvant ET >6 mo prior to randomization, and received prior treatment with SERDs. The primary objective is IBCFS. Key secondary objectives are distant relapse-free survival, overall survival, invasive disease-free survival, safety, PROs-QoL, and PK. Planned enrollment is 4,220 patients; recruitment is ongoing. Clinical trial information: NCT06492616. Research Sponsor: Menarini Group.

TPS1154 **Poster Session**

ADELA: A double-blind, placebo-controlled, randomized phase 3 trial of elacestrant (Ela) + everolimus (EVE) versus elacestrant + placebo in ER+/HER2− advanced breast cancer (aBC) patients with *ESR1*-mutated tumors progressing on endocrine therapy (ET) + CDK4/6i. First Author: Antonio Llombart-Cussac, Medica Scientia Innovation Research (MEDSIR); Hospital Arnau de Vilanova, FISABIO; Traslational Oncology Group, Department of Medicine, Facultad de Ciencias de la Salud, Universidad Cardenal Herrera-CEU, Valencia, Spain

Background: ET+CDK4/6i is the standard-of-care (SOC) in 1L ER+/HER2- aBC; however, tumors eventually develop resistance. Constitutive activation of the PI3K/AKT/mTOR pathway can contribute to endocrine resistance in breast cancer. *ESR1* mutations (*ESR1m*) are a common type of acquired resistance that emerges in 40-50% of patients (pts) in the metastatic setting after prolonged aromatase inhibitor exposure. There is an unmet need for novel therapeutic approaches to overcome resistance mechanisms and improve outcomes in pts with ER+/HER2- aBC with *ESR1m* tumors progressing after ET+CDK4/6i. Ela is a next-generation oral SERD that binds and degrades ERα. In the Ph3 EMERALD trial, single-agent Ela improved mPFS vs SOC ET in pts with *ESR1m* tumors (HR 0.55; 95% CI 0.39-0.77; P=0.0005) [Bidard 2022]. Among pts who received prior ET+CDK4/6i ≥12 months, mPFS with Ela was 8.6 vs 1.9 months with SOC ET (HR 0.41; 95% CI 0.26-0.63) [Bardia 2024]. The crosstalk between the ER and PI3K/AKT/mTOR pathways provides a rationale for evaluating Ela+EVE (a mTORC1 inhibitor). In the ELEVATE Ph2 trial (NCT05563220), the combination of Ela 345 mg + EVE 7.5 mg showed a clinically meaningful mPFS of 8.3 months (95% CI, 4.0-10.2) in all pts (N=50) with ER+/HER2- aBC who progressed after ET+CDK4/6i, regardless of *ESR1*m status (Rugo, SABCS 2025). Safety was consistent with the known profile of EVE+SOC ET. **Methods:** ADELA (NCT06382948) is an international, multicenter, double-blind, placebo-controlled, randomized Ph3 trial that compares Ela+EVE vs Ela+placebo in pts who have ER+/HER2- aBC with *ESR1m* tumors progressing on ET+CDK4/6i. Eligible pts are adults (≥18 years) with ER+/HER2- aBC and centrally confirmed *ESR1m* who received 1-2 prior lines of ET for aBC and progressed on ET+CDK4/6i for aBC after ≥6 months. Pts receiving CDK4/6i-based adjuvant therapy are eligible if progression occurred after ≥12 months of treatment but <12 months following CDK4/6i completion. Exclusion criteria include prior chemotherapy for aBC and active uncontrolled/symptomatic brain metastases and/or leptomeningeal disease. Pts will be randomized 1:1 to 28-day cycles of Ela 345 mg + EVE 7.5 mg QD or Ela 345 mg + placebo QD until disease progression or unacceptable toxicity. Pts will receive dexamethasone mouthwash during the first 8 weeks. Stratification factors are visceral metastases (yes vs no) and duration of prior CDK4/6i therapy (≥12 vs <12 months). Primary objective is PFS assessed by BICR. Secondary objectives are investigator-assessed OS, PFS, ORR, CBR, DoR, TTR, best percentage change in tumor burden, safety, HRQoL. Planned enrollment is 240 pts. Recruitment is ongoing across Spain, France, Greece, Italy, Germany, Austria, Czech Republic, United Kingdom, and Brazil. Clinical trial information: NCT06382948. Research Sponsor: Menarini Group; MEDSIR.

TPS1155 **Poster Session**

ELECTRA: An open-label, multicenter, phase 1b/2 study of elacestrant in combination with abemaciclib in patients with brain metastasis from ER+/HER2− breast cancer. First Author: Nuhad K. Ibrahim, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Endocrine therapy (ET) + cyclin dependent kinase 4/6 inhibitor (CDK4/6i) is the mainstay for the management of ER+/HER2- mBC as 1st-line therapy. However, tumors eventually develop resistance to ET, leading to disease progression. In the EMERALD phase 3 trial, single-agent elacestrant demonstrated a significantly prolonged progression-free survival (PFS) vs SOC ET (*ESR1*m tumors HR 0.55; 95% CI 0.39-0.77; all pts HR 0.70; 95% CI 0.55-0.88) with a manageable safety profile (Bidard 2022), leading to the first oral SERD approved. In a subgroup analysis in patients with *ESR1m* tumors who had received prior ET+CDK4/6i ≥12 months, the median PFS for elacestrant was of 8.6 months vs 1.9 months with SOC ET (HR=0.41; 95% CI, 0.26-0.63) [Bardia CCR 2024]. Currently, there are no approved systemic treatments for patients with ER+/HER2- breast cancer who have brain metastasis. ELECTRA (NCT05386108) is an open-label phase 1b/2, multicenter study evaluating elacestrant in combination with abemaciclib. The phase 1b portion of ELECTRA evaluated the combination of elacestrant with abemaciclib in patients with ER+/HER2- mBC regardless of metastatic site and *ESR1* status. The recommended phase 2 dose (RP2D) of the combination was determined to be elacestrant 345 mg QD with abemaciclib 150 mg BID (Ibrahim ASCO 2024). The phase 2 portion of ELECTRA is ongoing to further characterize efficacy and safety of this combination in patients with brain metastases from ER+/HER2- breast cancer, as both compounds cross the blood-brain barrier (Conlan, 2020; Tolaney, 2020). **Methods:** Phase 2 eligibility includes patients with ER+/HER2- locally advanced or metastatic breast cancer and measurable brain metastasis (≥ 1 active and measurable brain metastasis per RECIST v1.1). Patients must have received prior therapy in the metastatic setting, including ≥ 1 endocrine therapy, ≤ 2 chemotherapy regimens, and 0-2 prior CDK4/6i (excluding abemaciclib). The phase 2 primary objective is ORR per RECIST v1.1; secondary objectives include intracranial response rate, DoR, CBR, PFS, OS, PK, and quality of life. The phase 2 portion of ELECTRA is actively recruiting patients worldwide. Clinical trial information: NCT05386108. Research Sponsor: Menarini Group.

TPS1156 **Poster Session**

CAPELA: A phase II multicenter open-label randomized study of capecitabine in combination with elacestrant versus capecitabine alone in advanced estrogen receptor (ER)–positive breast cancer (TBCRC 070). First Author: Kristina Fanucci, Dana-Farber Cancer Institute, Boston, MA

Background: Endocrine therapy (ET) in combination with targeted treatments can effectively treat metastatic ER-positive (ER+) breast cancer (BC); however, nearly all patients ultimately progress on these therapies, eventually requiring treatment with chemotherapy. Current standard of care, based on older data, is to discontinue ET when starting chemotherapy. Many of these studies used tamoxifen, which has partial agonist activity, in combination with chemotherapy. Newer estrogen-targeting agents, e.g. oral selective ER degraders (SERDs), function as ER antagonists. Preclinical work investigating the combination of SERD and chemotherapy has demonstrated an additive effect of the agents in ER wildtype tumors and a synergistic effect in tumors with *ESR1* mutation (*ESR1m*); this synergy was attenuated with P53 silencing. **Methods:** CAPELA, an investigator-initiated, multicenter, open-label randomized phase II study, is designed to assess the safety and efficacy of capecitabine monotherapy vs. capecitabine + elacestrant in patients with advanced/unresectable ER+ HER2- BC. Eligible patients will have progressed on a CDK4/6 inhibitor and had no prior treatment with chemotherapy for metastatic disease. At least 50% of enrolled patients are required to have *ESR1m* tumors. Patients will be randomized 1:1 to receive capecitabine 1000mg/m^2 PO BID days 1-14 of a 21-day cycle +/- the oral SERD elacestrant 345 mg PO daily. Randomization will be stratified by prior lines of ET in the metastatic setting (1 vs. >1), visceral disease (yes/no), *TP53* mutation status, and *ESR1m* status. Patients with tumors with an *ESR1m* who are randomized to the monotherapy arm will have the option to crossover to elacestrant monotherapy at the time of progression to evaluate benefit of concurrent vs. sequential use of these agents. The primary endpoint is hierarchical assessment of median progression free survival (mPFS) in 1) the *ESR1m* population and if positive 2) the intention to treat (ITT) population. Secondary endpoints include safety/tolerability, median overall survival (OS), objective response rate, median time to second progression, clinical benefit rate, and patient reported outcomes in the *ESR1m* and ITT populations. PFS and OS in the *ESR1m* not detected population will also be evaluated. Exploratory correlative studies on collected plasma, serum, and archival tissue will also be conducted. The study will enroll 297 patients over an estimated 3 years. The trial will open at 10 sites through the Translational Breast Cancer Research Consortium (TBCRC). Clinical trial information: NCT07222215. Research Sponsor: Menarini-Stemline; Gateway for Cancer Research.

TPS1157 **Poster Session**

AVATAR: Efficacy of personalized tumorogram-based therapy in breast cancer established from patient-derived organoids. First Author: Luc Cabel, Institut Curie, Paris and Saint-Cloud, France

Background: Despite therapeutic advances in advanced breast cancer (ABC), predicting drug efficacy for individual patients remains difficult. Patient-derived tumor organoids (PDTOs) could enable drug efficacy testing within a timeframe compatible with clinical decision-making. We hypothesize that personalized treatment based on PDTO-guided tumorograms can improve outcomes for patients with HER2-negative ABC. **Methods:** AVATAR (NCT06459791) is a single-arm multicenter phase II trial assessing tumor response rate within 6 months as the primary endpoint in patients with HER2-negative ABC treated with tumorogram-guided chemotherapy. A biopsy of a tumor lesion is performed and transferred to the laboratory for PDTO establishment. While waiting for the result of the tumorogram, the patient receives standard-of-care treatment. A drug screening of standard-of-care drugs is performed on the PDTO (~5-10 drugs per patient), with selection adapted to the clinical setting. A multidisciplinary team makes therapeutic recommendations based on the tumorogram. A tumorogram is considered informative if it identifies at least one chemotherapy drug that is considered effective in the PDTO model. When possible, patients with an informative tumorogram receive one of the recommended treatments as their next line of therapy. Otherwise, they receive standard treatment. Eligible patients include those with HER2-negative ABC who are treated with chemotherapy (endocrine-resistant for HR+/HER2-), have a performance status of 0-1, and have a tumor lesion that can be biopsied. Patients who have received more than three lines of chemotherapy in the metastatic setting or who have progressive brain or leptomeningeal metastases are excluded. We hypothesize that the prescription of chemotherapy based on an informative tumorogram will be clinically meaningful if the tumor response rate is at least 25% (p0). With a one-sided α of 9%, a power of 90%, and an alternative hypothesis of 45% (p1), 39 patients should be treated according to an informative tumorogram, and 110 patients need to be included (assuming a minimum of 40% informative tumorograms and accounting for dropouts). Enrollment began in December 2024 and is ongoing. Clinical trial information: NCT06459791. Research Sponsor: PHRC-I.

TPS1158 **Poster Session**

Exploratory analysis of prognostic value of ctDNA monitoring among advanced breast cancer with oligometastatic disease: An ancillary biomarker study of JCOG 2110 (JCOG2110A1). First Author: Takahiro Kogawa, Department of Advanced Medical Development, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan

Background: Oligometastatic advanced breast cancer represents a biologically heterogeneous disease state in which a subset of patients may achieve prolonged disease control or potential cure through the addition of definitive local therapy to systemic treatment. However, conventional imaging has limited sensitivity for detecting minimal residual disease (MRD), and reliable biomarkers to identify patients most likely to benefit from local therapy remain lacking. Circulating tumor DNA (ctDNA) has emerged as a sensitive, minimally invasive marker of tumor burden and treatment response and may provide complementary information beyond radiographic assessment. JCOG2110 is a phase III randomized trial evaluating whether the addition of definitive local therapy (surgery or radiotherapy to all detectable lesions) to systemic therapy improves survival in patients with advanced breast cancer with three or fewer oligometastatic lesions. JCOG2110A1 is an ancillary biomarker study designed to characterize ctDNA dynamics in this clinical setting and to explore the clinical significance of ctDNA-based MRD assessment. **Methods:** Eligible patients are those enrolled in JCOG2110 who provide written informed consent prior to initiation of protocol-defined systemic therapy. Plasma ctDNA will be analyzed using Guardant Reveal, a next-generation sequencing–based assay integrating genomic alterations and methylation signatures, and reported as ctDNA positive or negative with quantitative estimates of tumor fraction. Blood samples will be collected longitudinally at predefined timepoints: before systemic therapy, prior to completion of the initial 12-week systemic treatment, and during protocol-specified follow-up aligned with imaging assessments after second registration. In cases of disease progression, ctDNA will be collected at progression and subsequent sampling will be discontinued. The primary endpoint is the proportion of ctDNA clearance and ctDNA level reduction after initial systemic therapy among patients who are ctDNA-positive at baseline. Secondary endpoints include ctDNA positivity at each timepoint, associations between ctDNA kinetics and radiographic tumor prognosis, and correlations with clinical characteristics such as tumor subtype, number of metastatic lesions, and treatment allocation. This study aims to define the detectability and early kinetics of ctDNA in oligometastatic advanced breast cancer and to generate prospective evidence regarding the prognostic and potential predictive value of ctDNA for treatment outcomes and benefit from local therapy. Clinical trial information: jRCTs031230439. Research Sponsor: Guardant Health contracted research fund.

TPS1159 **Poster Session**

Phase II single-arm trial of low-dose capecitabine in patients with advanced breast cancer. First Author: Humaira Sarfraz, University of Alabama Birmingham, Birmingham, AL

Background: Capecitabine is approved for use in both the adjuvant and metastatic settings of breast cancer. The clinical activity of capecitabine was established at the maximum tolerated dose of 1000–1250 mg/m² given on days 1–14 of a 21-day cycle. As seen with other cytotoxic agents, dose escalation may lead to increased toxicity without clear efficacy benefit, while lower, fixed-dose capecitabine maintains antitumor activity with fewer adverse effects, including diarrhea, hand–foot syndrome, mucositis, and neutropenia. This approach is especially important for older and frail patients, who are more vulnerable to toxicity and underrepresented in trials. **Methods:** This single-arm, open-label phase 2 study aims to evaluate the anti-tumor effect of continuous daily oral low-dose capecitabine at 1500mg in 40 patients aged 60 years or older, and/ or considered frail at any age (ECOG 0-2). Frailty is defined by the investigator as an individual at greater risk of complications and poorer outcomes with systemic therapy, secondary to a lower physiologic reserve and higher comorbidities and functional deficits. Eligible patients include those with HER2-negative unresectable or metastatic breast cancer (hormone positive or triple negative) with measurable disease, who have progressed on at least 1 prior line of therapy. Major exclusion criteria include HER2-positive breast cancer, severe hepatic or renal failure, inability to swallow pills, and uncontrolled CNS/ leptomeningeal disease. Patients will be evaluated for toxicity every 4 weeks and for response every three cycles using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Therapy will be continued until evidence of disease progression or unacceptable toxicity. The primary objective is the clinical activity of daily low dose capecitabine by overall response rates (ORR) per RECIST. The secondary objectives include progression-free survival (PFS), overall survival (OS), and determining the safety and tolerability of daily low dose capecitabine using the Common Terminology Criteria for Adverse Events (CTCAE) v.6.0. Exploratory analyses include evaluating quality of life, measurement of sarcopenia, geriatric assessment using the CARE (Cancer and Aging Resilience Evaluation) tool before registration and at the end of treatment, and evaluating adherence to capecitabine. Simon's two-stage minimax design will be used with a type I error rate of 0.05 and power of 80%. The null hypothesis response rate of 10% will be tested against a one-sided alternative response rate of 25%. In the first stage, 22 patients will be accrued. If there are 2 or fewer responses in the first 22 patients enrolled, the study will be discontinued. The trial was approved by the Institutional Review Board at the University of Alabama at Birmingham (UAB) and has been accruing since February 2025. 8 of the planned 40 patients have been enrolled. Clinical trial information: NCT06105684. Research Sponsor: Dr. Francisco Robert Award O'Neal Comprehensive Cancer Center (OCCC) University of Alabama at Birmingham.

TPS1160 **Poster Session**

Phase III trial of brain MRI surveillance in stage IV breast cancer. First Author: Kamran A. Ahmed, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: The incidence and prevalence of breast cancer patients who develop brain metastasis is increasing. Intracranial surveillance of asymptomatic stage IV breast cancer patients with brain MRIs is not currently recommended by the National Comprehensive Cancer Network (NCCN) Guidelines. In a previously conducted phase II brain MRI surveillance trial, approximately 25% of patients with stage IV breast cancer, independent of tumor subtype, were found to have newly detected brain metastases on the 6-month follow-up MRI from study entry. **Methods:** The study is designed as a randomized phase III, multi-institutional prospective trial evaluating the role of surveillance brain MRIs in neurologically asymptomatic patients with metastatic breast cancer, based on subtypes (triple negative (TN), HER2+, and hormone receptor (HR)+ breast cancer). Following study enrollment, patients will be randomized in a 1:1 fashion to surveillance brain MRIs at baseline and q6 months for 24 months compared to a baseline MRI followed by standard-of-care brain MRI surveillance for symptomatic presentation. Newly diagnosed stage IV patients (within $\leq$ 60 days of starting systemic therapy for HER2+ or TN or within $\leq$ 60 days of initiating 1st or 2nd line therapy for HR+/HER2- disease) with an ECOG $\leq$ 2 and life expectancy $\geq$ 6 months are eligible. The primary objective is to evaluate the treatment characteristics of brain metastases diagnosed via brain MRI surveillance or standard of care imaging. Secondary objectives include the frequency of asymptomatic brain metastases and leptomeningeal disease, the number and size of brain metastases at diagnosis, quality of life, and overall and brain metastases specific survival following brain metastasis diagnosis in patients randomized to brain MRI surveillance compared to standard of care imaging. A total of 156 patients will be enrolled with an equal distribution of TN, HER2+, and HR+/HER2- subtypes, respectively. Funding: Florida Department of Health. Clinical trial information: NCT07357298. Research Sponsor: Florida Department of Health; 25B01.

TPS1161 **Poster Session**

Evaluation of the safety and efficacy of TRC003 in metastatic triple-negative breast cancer: A prospective, open-label, multicenter, single-arm exploratory clinical trial. First Author: Xiaorong Sun, Shandong Cancer Hospital and Institute, Jinan, Shandong, China

Background: TRC003 (also named ^{225}Ac-TR2205) is a novel molecule of targeted alpha therapy (TAT) designed to deliver alpha-particle radiation to cancer cells expressing prostate-specific membrane antigen (PSMA). Compared to beta-particles, alpha-particles have a shorter path length and higher linear energy transfer, resulting in more frequent double-strand DNA breaks and potentially superior antitumor efficacy. In an ongoing pilot study, TRC003 has demonstrated a favorable safety profile and promising activity in patients with prostate cancer. Notably, PSMA expression has been reported in up to 60% of breast cancer neovasculature, with the highest rates observed in triple-negative breast cancer (TNBC). A head-to-head study found valuable insights into the expression of PSMA in TNBC and underscore the potential clinical significance of PSMA PET/CT in enhancing both diagnostic and therapeutic approaches for TNBC. This study aims to investigate the preliminary safety and efficacy of ^{225}Ac-TRC003 in patients with metastatic TNBC (mTNBC). **Methods:** This is a prospective, open-label, multicenter, single-arm study in accordance with ICH GCP guidelines at two centers. The primary objective is to evaluate the safety and tolerability of TRC003. Secondary endpoints include Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DoR), Time to Progression (TTP), progression-free survival (PFS) and overall survival (OS). Key eligibility criteria include: 1) age $\geq$18 years; 2) histologically confirmed mTNBC with documented progression after $\geq$2 prior lines of systemic therapy (including at least 1 line for metastatic disease); 3) presence of PSMA-positive lesions on imaging, without FDG-positive & PSMA-negative target lesions; 4) at least one measurable lesion per Response Evaluation Criteria in Solid Tumors version (RECIST) 1.1; 5) Eastern Cooperative Oncology Group performance status of $\leq$ 1; and 6) adequate bone marrow, renal, and hepatic function. Fifteen eligible participants will be enrolled to receive 7.40 MBq (200 μCi) ($\pm$10%) of TRC003 by intravenous infusion every 8 weeks ($\pm$1 week), for up to 8 cycles if clinical benefit is observed. Treatment will continue until disease progression, unacceptable toxicity, or consent withdrawal, meeting any study withdrawal criterion, whichever occurs first. Tumor assessments (contrast-enhanced CT/MRI and bone scan) will be performed every 8 weeks until disease progression is confirmed per RECIST 1.1. Clinical trial information: MR-37-25-039070. Research Sponsor: C Ray Therapeutics (Chengdu) Co., Ltd.

TPS1162 **Poster Session**

TBCRC 058: A randomized phase II study of enzalutamide, enzalutamide with mifepristone, and treatment of physician's choice in patients with androgen receptor-positive metastatic triple-negative or estrogen receptor-low breast cancer (NCT06099769). First Author: Tiffany A. Traina, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Triple-negative breast cancer (TNBC) refers to a heterogenous group of breast cancers that lack expression of ER, PR, and HER2. Despite recent advances with immunotherapy (IO) and antibody-drug conjugates (ADCs), TNBC remains the most aggressive subtype, with short overall survival in the metastatic setting. Breast tumors with low levels of ER and PR expression (1-10%) clinically behave like TNBC, and clinical management follows the TNBC treatment (tx) paradigm. We and others have identified a subset of ER/PR/HER2-negative breast cancers (BCs) that express the androgen receptor (AR). Enzalutamide (enza), an AR-antagonist, has demonstrated activity in AR-positive metastatic TNBC (Traina et al, JCO 2018). Activation of the glucocorticoid receptor (GR) has been implicated as a mechanism of resistance to AR inhibition in prostate and BCs (Kach et al, Sci Transl Med 2015). Effective therapies for advanced TNBC remain an unmet need, particularly in patients who are ineligible for or progress following a checkpoint inhibitor. This randomized study evaluates the efficacy of enzalutamide or enzalutamide plus the GR antagonist mifepristone (mif) as compared to physician's choice chemotherapy (TPC). **Methods:** This is a randomized phase II trial; 201 patients (pts) will be randomized in a 1:1:1 fashion to enza, enza with mif, or TPC (carboplatin, paclitaxel, eribulin, or capecitabine). The primary endpoint (endpt) is progression-free survival (PFS), and the trial is designed to test the hypothesis that PFS in the pooled enza arms is superior to TPC; there is 80% power to detect a hazard ratio (HR) of 0.70, corresponding to an increase in median PFS from 3.5 months (mos) with TPC to 5.0 mos with enza-based tx. Secondary endpts include comparisons of PFS among the 3 arms and evaluation of response rate, clinical benefit rate, duration of response, overall survival, safety, and patient-reported outcomes by arm. Exploratory endpts include correlation of tumor and circulating markers (constitutively active AR variants in circulating tumor cells and cfDNA) with tx response. Eligible pts must have: ECOG 0-2, metastatic measurable or evaluable disease (dz), normal organ function, no history of brain mets, $<$ prior lines of chemotx, any # of prior endocrine txs, no prior anti-AR tx, no prior mif, no concurrent CYP17 inhibitor use. Tumors must test ER/PR low or negative, HER2 negative, AR $>$10%. Pts with PD-L1+ BC must have received prior IO if not contraindicated. As of December 28, 2025, 32 of 201 pts have been enrolled on study. Clinical trial information: NCT06099769. Research Sponsor: Breast Cancer Research Foundation; TBCRC; Astellas; Corcept; The TaTa Sisterhood Foundation; Pfizer.

TPS1163 **Poster Session**

A randomized phase II study of pembrolizumab plus paclitaxel with or without bevacizumab in PD-L1–positive recurrent triple-negative breast cancer previously treated with perioperative immune checkpoint inhibitors: WJOG16522B (PRELUDE) trial. First Author: Kazuki Nozawa, Department of Advanced Clinical Research and Development, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan

Background: Perioperative pembrolizumab combined with chemotherapy has become a standard of care for patients with early-stage triple-negative breast cancer (TNBC). However, a substantial proportion of patients experience disease recurrence after perioperative immune checkpoint inhibitor (ICI)–based therapy, and the optimal systemic treatment for this population remains undefined. Angiogenesis has been implicated as a potential mechanism of resistance to immunotherapy. Bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), may enhance antitumor immunity through vascular normalization and modulation of the tumor microenvironment. The PRELUDE trial was designed to evaluate whether the addition of bevacizumab to pembrolizumab plus paclitaxel improves clinical outcomes in patients with PD-L1–positive recurrent TNBC previously treated with perioperative ICIs. **Methods:** PRELUDE is a multicenter, open-label, randomized phase II trial conducted in Japan. Eligible patients have recurrent TNBC with PD-L1 expression (combined positive score $\geq$10 using 22C3) and prior exposure to perioperative ICI-containing chemotherapy. Patients are randomized 1:1 to receive pembrolizumab plus paclitaxel with or without bevacizumab. Pembrolizumab is administered at 400 mg every 6 weeks, paclitaxel at 90 mg/m² on days 1, 8, and 15 every 4 weeks, and bevacizumab at 10 mg/kg on days 1 and 15 every 4 weeks in the experimental arm. Treatment is continued until disease progression or unacceptable toxicity. Tumor assessments are performed according to RECIST v1.1. Exploratory biomarker analyses using tumor tissue and peripheral blood samples are planned. The primary endpoint is progression-free survival. Secondary endpoints include overall response rate, disease control rate, overall survival, and safety. Exploratory endpoints include translational biomarker analyses to investigate mechanisms of response and resistance. Enrollment is currently ongoing. ClinicalTrials.gov: NCT06976944, jRCT2031250076. Research Sponsor: MSD.

TPS1164 **Poster Session**

Phase Ib randomized open-label trial of sacituzumab govitecan plus nivolumab or sacituzumab govitecan plus nivolumab and relatlimab as second-line therapy metastatic triple negative breast cancer: SIMONE trial. First Author: Adriana Matutino Kahn, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: The use of immunotherapy beyond first-line setting is not yet routine in the treatment arsenal of patients with metastatic triple-negative breast cancer (TNBC), and this opens an opportunity for clinical trials examining whether adding novel immunotherapy agents to standard of care therapies would benefit patients. Prior studies have combined immunotherapy with standard chemotherapy (Cortes J, NEJM 2022), but combining immunotherapies with antibody-drug conjugates (ADCs) is a strategy worth pursuing given improvement of outcomes of ADCs when compared to standard chemotherapy (Bardia A et al, NEJM 2021). Sacituzumab govitecan (SG), a TROP2-ADC, is currently the standard second-line therapy for patients with metastatic TNBC, and in this study it is being combined with either nivolumab (programmed cell death [PD-1] inhibitor) or nivolumab plus relatlimab (lymphocyte activation gene-3 [LAG3]-inhibitor) due to preliminary data showing that simultaneous PD-1 and LAG3 inhibition enhances the anti-tumor immune response and restores the effector function of exhausted T-cells (Woo S-R et al, Cancer Res 2012; Tawbi HA et al, NEJM 2022). **Methods:** This is an ongoing investigator-initiated randomized, open-label, phase Ib study to assess safety and efficacy of SG plus nivolumab (n= 30 patients) or SG plus a fixed dose combination (FDC) of nivolumab and relatlimab (n = 30 patients) in patients with metastatic TNBC; NCT06963905. The study is accruing patients whose tumors are PD-L1 positive (combined positive score $>$10) and an amendment in under review to also include patients whose tumors are PD-L1 negative on routine testing, with 1 prior line of cytotoxic chemotherapy with or without prior immunotherapy use in the metastatic setting or within 6 months from completion of curative intent treatment. Study treatment will be continued until progression of disease, unacceptable toxicity, death, or withdrawal of consent. Safety will be monitored, and tumor response will be regularly evaluated by RECIST 1.1 criteria every 9 weeks. The primary endpoint includes safety as the incidence of dose-limiting toxicities (DLT) in 3 weeks after C1D1. Secondary endpoints include objective response rate (defined as either complete response or partial response), duration of response, clinical benefit rate (objective response plus stable disease), progression-free survival, and safety with SG plus nivolumab or SG plus nivolumab + relatlimab FDC. Exploratory endpoints include overall survival, and biomarkers of prediction of response and resistance. There will be a follow-up visit after the last study treatment administration or before starting a new anticancer treatment, whichever occurs first, followed by long-term/survival chart review follow-up every three months for 2 years. Clinical trial information: NCT06963905. Research Sponsor: None.

TPS1165 **Poster Session**

Phase IIa, open-label, multi-center study of the DNA polymerase theta inhibitor ART6043 administered orally in combination with olaparib to patients with HER2-negative breast cancer with a germline BRCA1/2 mutation (randomized expansion of study NCT05898399). First Author: Mark Robson, Breast Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Microhomology-mediated end joining (MMEJ) repair of DNA double-strand breaks is reliant on DNA polymerase theta (Polθ). ART6043 inhibits Polθ and hence MMEJ without affecting other forms of DNA double-strand break repair (DSBR) such as homologous recombination (HR) and non-homologous end joining (NHEJ). MMEJ becomes essential for tumor survival in patients with germline BRCA1/2 mutations being treated with poly adenosine diphosphate ribose polymerase (PARP) inhibitors. Polθ inhibition is therefore a powerful strategy to target HR-deficient cancers by potentiating the DNA damage induced by PARP inhibition. Combination of Polθ inhibition with PARP inhibition may also delay or prevent emergence of PARP inhibitor resistance through circumvention of MMEJ-mediated BRCA1/2 gene reversions that restore HR activity. The restricted expression profile of the *POLQ* gene in normal tissues compared with tumor tissues predicts a high therapeutic index for combining Polθ inhibition with DNA damaging agents without synergistic toxicity. Data from 61 pts dosed in the ART6043 dose escalation as monotherapy and in combination with the PARP inhibitor, olaparib, in a tumor agnostic population were presented at ESMO 2025 (Yap et al 2025). These data showed that ART6043 was well-tolerated alone and with the approved dose of olaparib; good ART6043 exposure with no evidence of drug-drug interaction with olaparib; pharmacodynamic engagement as monotherapy and enhanced with olaparib and promising signals of anti-tumor activity for the combination of ART6043 + olaparib. These data support a randomized expansion of ART6043 + olaparib compared to olaparib alone to demonstrate the first proof of concept for Polθ inhibition in HR-deficient cancers. **Methods:** In this expansion to study NCT05898399, approximately 80 pts with locally advanced or metastatic HER2 negative breast cancer with a germline BRCA1/2 mutation will be randomized to ART6043 + olaparib vs olaparib (stratified by use of prior platinum). Patients must have received prior chemotherapy and no or ≤1 month of prior PARP inhibitor. Patients with hormone receptor positive breast cancer should have been treated with prior endocrine therapy. Patients in the investigational arm will receive ART6043 600 mg once daily with olaparib 300 mg twice daily. Patients on the olaparib-alone arm may cross over to receive ART6043 + olaparib on progression. Key objectives include preliminary efficacy (progression-free survival, objective response rate etc), safety and tolerability. Cell free DNA samples will be collected to assess stratification biomarkers, response and compare the occurrence of resistance mechanisms (eg BRCA reversion) between the two arms. Enrollment will continue until Q4-2027. Clinical trial information: NCT05898399. Research Sponsor: Artios Pharma Ltd.

TPS1166 **Poster Session**

IvoLoC: A phase II trial of ivonescimab (IVO) in endocrine-refractory hormone receptor (HR)−positive or triple-negative (TN) metastatic invasive lobular carcinoma (mILC). First Author: Jason A. Mouabbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ILC accounts for approximately 10–15% of breast cancers and is predominantly hormone receptor−positive (HR+)/HER2−. Patients with endocrine-refractory mILC have poor outcomes, with median progression-free survival (PFS) of less than three months following standard therapies. ILC is biologically distinct from invasive ductal carcinoma, with unique tumor microenvironmental features. Molecular profiling of primary untreated ILC has demonstrated marked heterogeneity, including immune-enriched (IE) and highly vascularized (HV) molecular functional portraits associated with PD-1/PD-L1 signaling and VEGF pathway activation. IVO is a novel bispecific antibody targeting PD-1 and VEGF, designed to enhance antitumor immunity while inhibiting angiogenesis. We hypothesize that dual immune and vascular targeting will improve clinical outcomes in patients with endocrine-refractory HR+/HER2− or TN mILC. **Methods:** Trial Design: IvoLoC (NCT07229417) is a single-center, open-label, phase II study conducted at The University of Texas MD Anderson Cancer Center. Eligible patients include those with HR+/HER2− mILC with progression on prior endocrine therapy, including combinations with CDK4/6, PI3K, AKT, and/or mTOR inhibitors, as well as patients with TN mILC. Patients may have received any number of prior endocrine-based regimens but no more than two prior cytotoxic therapies, including antibody−drug conjugates, in the metastatic setting. IVO is administered intravenously at 20 mg/kg every three weeks until disease progression or unacceptable toxicity. Radiographic assessments are performed every 9 weeks and evaluated per RECIST v1.1. Endpoints: The primary endpoint is 6-month PFS. Secondary endpoints include 12-month PFS, median PFS, objective response rate, disease control rate, duration of response, overall survival, and safety. Exploratory objectives include correlation of outcomes with molecular functional portraits, longitudinal circulating tumor DNA analyses, and integrated genomic and transcriptomic biomarker discovery. Enrollment: The study plans to enroll 29 patients. Accrual is ongoing in the United States. Clinical trial information: NCT07229417. Research Sponsor: Summit Pharmaceuticals.

1500 Oral Abstract Session

Impact of access to effective post-progression therapies on survival outcomes in first-line randomized oncology trials. First Author: João Pedro Apolinário, Hospital Madre Teresa, Belo Horizonte, Minas Gerais, Brazil

Background: Effective anticancer systemic therapies are expected to improve overall survival (OS) or quality of life in randomized controlled trials (RCTs) for patients with cancer. However, access to effective post-progression therapies in control arms is inconsistent and may confound the observed OS benefits, especially for agents with known survival benefit in later lines. Here, we investigated whether control-arm post-progression access to effective therapies is associated with improved OS. **Methods:** This cross-sectional analysis included 52 phase II–III RCTs published between 2010 - 2025 in selected high impact journals. Eligible trials evaluated first line targeted therapies (TT), immune checkpoint blockers (ICB), or hormone therapy (HT) in the experimental arm for advanced lung, breast, or prostate cancer, where the investigational agent had proven OS benefit in later lines. Post-progression access to effective therapies was quantified as the proportion of patients in the control arm receiving the investigational agent (or similar class) relative to all pts randomized to control arm (Ratio_Effective/Control), and relative to patients receiving any subsequent treatment (Ratio_Effective/Therapy). Correlations between the ratio of post-progression access and OS HRs were assessed, with prespecified subgroup analyses by treatment class and tumor type. Geographic distribution was evaluated in trials reporting enrollment by region. **Results:** Across all trials, the mean proportion of patients in the control-arm receiving any post-progression therapy was 66% (SD 14%), of which 42% (SD 22%) received an effective therapy (or, 62.5%, considering relative numbers). Post-progression access differed significantly by tumor type ($p < 0.001$), with the lowest rate in breast cancer, followed by prostate and lung cancer. The median proportion of pts enrolled outside the United States and Europe (US/EU) was 36%. The overall median HR for OS was 0.78. No correlation was observed between rate of post-progression access to effective therapies and the HR for OS across studies. However, in TT trials, higher post-progression access to effective treatments was moderately associated with a less pronounced OS benefit ($r = 0.44$, $p = 0.056$, Ratio_Effective/Control and $r = 0.46$, $p = 0.046$, Ratio_Effective/Therapy). No association was observed in RCTs evaluating ICB. The difference in the correlation between the TT and ICB trials was statistically significant ($p = 0.032$). No correlation was observed between ratio of effective therapies and tumor type, and enrollment outside of US/EU. **Conclusions:** Post-progression access to effective therapies in control arms influenced OS benefits in TT trials but not ICB trials in this study. These results warrant caution interpreting TT survival benefits and underscore the need for RCTs to report and standardize post-progression therapy access. Research Sponsor: None.

1501 Oral Abstract Session

Expert validation of an artificial intelligence–enabled trial matching solution using real-world data from patients with cancer. First Author: Jai Narendra Patel, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Wake Forest, NC

Background: Under-enrollment in cancer trials remains a major barrier for advancing cancer research in part because few patients are offered clinical trials and pre-screening is manual and laborious. One solution involves artificial intelligence (AI)-enabled centralized screening of patients, but this requires robust validation to facilitate trust and adoption. **Methods:** This is a retrospective study from a large community-academic hybrid cancer center comparing the performance of an AI system - Trial Recommendations using Intelligent Assessment to Guide Eligibility and Enrollment (TRIAGE) - to real-world enrollment using longitudinal electronic health records (EHRs), full versioned trial protocols, and expert clinical research coordinator (CRC) adjudication at the trial- and criterion-levels. The train set was composed of 629 patients and 4,094 patient-trial pairs. A large language model (LLM)-only solution was used to predict successful patient enrollment based only on answers to individual eligibility criteria. Next, a machine learning-based approach was used to train the model on top of LLM responses to yield robust, consistent decision rules across patients, with priorities set by the real-world behavior of CRCs. The test set was comprised of 198 patients with breast, lung, and pancreatic cancers and 793 patient-trial pairs. A stratified random sample of 100 patient-trial pairs (83 patients, 21 trials) underwent manual CRC adjudication. The primary outcomes were sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's κ for trial-level eligibility using a predefined trial match threshold of 0.40, and accuracy for criterion-level decisions. Performance evaluations were based on a binary classification: eligible or potentially eligible vs. ineligible. **Results:** In the training set, TRIAGE demonstrated 72% sensitivity and 90% specificity for trial enrollment. The table summarizes performance metrics in the test set for trial-level eligibility across 3 trial match thresholds. Criterion-level evaluation across 1,770 adjudications showed 93.1% raw agreement, improving to 94.2% after structured re-adjudication; 10/25 (40%) initial CRC discordances were overturned in favor of the AI decision. **Conclusions:** TRIAGE accurately determined trial-level eligibility from real-world EHR data with high performance and strong criterion-level agreement for oncology protocols. The system surfaced potential missed enrollment opportunities and supports adjustable trial-level decision thresholds. Prospective studies of TRIAGE implementation into research workflows are ongoing. Research Sponsor: None.

Trial Match Threshold	Sensitivity	Specificity	PPV	NPV	Cohen's κ
0.13 (max Sensitivity)	98.7%	97.6%	91.2%	99.7%	0.84
0.40 (study threshold)	78.3%	98.5%	92.6%	94.8%	0.68
0.62 (max Specificity)	39.3%	100%	100%	87.0%	0.45

1502 Oral Abstract Session

Development and external validation of a computational approach for accelerated read out of randomized clinical trials in metastatic prostate cancer. First Author: Ali Sabbagh, Memorial Sloan Kettering Cancer Center, New York, NY

Background: While overall survival (OS) is the gold standard endpoint for clinical trials in metastatic prostate cancer (mPC), it requires years of follow-up. We sought to develop and externally validate a computational model for accelerated OS readout based on short term (4 months) PSA kinetic data. **Methods:** Longitudinal PSA data were obtained from 8 completed phase 3 mPC trials. Using data from the first 4 months on trial, 18 different PSA kinetic variables were developed, including 50% and 90% decline in PSA, PSA=0.1, and PSA=0.2 at 1, 2, 3, and 4 months, and slope and base of the exponential fit of PSA. TITAN, COU-AA-301, and ACIS comprised the training cohort. Data from those trials was used to model OS using a relaxed LASSO approach. The resulting model was applied to 5 validation trials (see Table 1) to simulate 1,000 potential outcomes for each trial (after Harden and Kropko). For the CHAARTED trial, a model using only PSA-kinetic data was used as most baseline variables were missing. The distribution of 1,000 simulated Hazard Ratios (HR) for each trial was compared against the reported HR. **Results:** Overall, $>$ 100,000 PSA values were used with a total $>$ 7,500 eligible study pts, with ~ 70,000 PSA values and ~5,000 patients comprised the validation cohort. The model identified baseline PSA at treatment, PSA50 at 4 months, and the PSA slope as the most informative PSA predictors of OS. Table 1 below compares the median predicted HR and 95%-interpercentile range from the 1,000 simulations with the reported HR for each validation trial. The model correctly predicted the OS point estimate and 95%-confidence interval using the first 4 months of PSA data in every validation trial. **Conclusions:** A computational simulation approach to predict the OS outcome of phase 3 mPC trials based on PSA kinetics from the first 4 months on trial was developed. This model correctly predicted OS outcomes in 5 completed validation phase 3 trials. This included phase 3 trials with both positive and negative outcomes for OS as well as in both hormone sensitive and resistant mPC, and involving AR signaling inhibitors, chemotherapy and a PARP inhibitor. This model is being further validated with additional completed phase 3 trials, and once prospectively validated, has the potential to significantly shorten the follow up required for OS readout from phase 3 trials in mPC. Research Sponsor: Prostate Cancer Foundation; 22CHAS02.

Predicted vs. reported HR of each trial.

Validation Trial	Predicted HR (median [95th interpercentile range])	Actual HR [95%-CI]
LATITUDE	0.64 [0.54 – 0.74]	0.66 [0.56 – 0.78]
COU-AA-302	0.69 [0.60 – 0.80]	0.81 [0.70 – 0.93]
MAGNITUDE	1.06 [0.88 – 1.26]	0.97 [0.79 –1.19]*
CALGB 90401	0.89 [0.78 – 1.01]	0.91 [0.78 – 1.05]
CHAARTED (Unselected)	0.79 [0.61 – 0.98]	0.72 [0.59 – 0.89]
CHAARTED (High Volume)	0.72 [0.53 – 0.92]	0.63 [0.50 – 0.79]
CHAARTED (Low Volume)	0.95 [0.61 – 1.52]	1.04 [0.70 – 1.55]

*Observed HR used as overall OS HR not reported in manuscript.

1503 Oral Abstract Session

Impact of outpatient CAR T-cell therapy administration on healthcare utilization in patients with hematologic malignancies. First Author: Susanna Goggans Bowen, Mayo Clinic Rochester, Rochester, MN

Background: CAR T-cell therapy has revolutionized treatment outcomes in hematological malignancies, but has traditionally required inpatient post-infusion monitoring, which is associated with significant cost and time toxicity. Outpatient CAR T infusion and monitoring has been the standard approach at Mayo Clinic site in Rochester, MN, with demonstrated feasibility and safety (Bansal et al., ASCO 2023). We present data comparing healthcare utilization between CAR T recipients who underwent outpatient remote monitoring and those with traditional inpatient monitoring. **Methods:** Electronic medical records were retrospectively analyzed for 293 patients who received CAR T-cell therapy for a hematological malignancy at any of the 3 Mayo Clinic sites (MN, AZ, FL) between 2020 and 2024 . Healthcare utilization was compared between patients who received outpatient CAR T with remote patient monitoring in Rochester, MN (N = 125) and those who received inpatient CAR T in the Arizona (n = 90) and Florida (n = 78) sites. Per protocol, patients in the inpatient group underwent mandatory inpatient monitoring for 7 days, with extension per provider discretion. Data was analyzed through Chi-Square and Wilcoxon tests. P values $<$ 0.05 were considered statistically significant. **Results:** There was no significant difference in baseline sex, age, ethnicity, LDH, platelets, or neutrophils among the 293 patients. Diagnoses included lymphoma (n = 175), multiple myeloma (n = 106), and B-ALL (n = 12). The most common CAR T-cell products used were axicabtagene ciloleucel (n = 138) idecabtagene vicleucel (n = 56), and ciltacabtagene autoleucel (n = 50). Median hospital days were lower in the outpatient group vs the inpatient group at 30 days (4.4 vs 13.3, $P < 0.001$) and 90 days (4.6 vs 13.6, $P < 0.001$). ICU admission occurred in 1 outpatient patient ($< 1\%$) vs 18 inpatient patients (11%) in the first 30 days ($P < 0.001$). In the first 30 days, 22% of patients in the outpatient group did not require hospitalization, while 56%, 15%, and 6% required 1, 2, and 3 hospitalizations, respectively. Similarly, only 11 (8.8%) patients in the outpatient group had $\geq$1 ED visit in the first 30 days compared with 32 (20%) pts in the inpatient group (P = 0.009). At 30 days, there was no difference in patient portal use, with 58% of patients using the portal at least once and a median of 1 message in both groups. Within the first 30 days, 53% and 2% of patients in the outpatient group required 1 and 2 outpatient visits, respectively, vs 29% and 2% in the inpatient group ($P < 0.001$). There was no difference in 30-day mortality (1.6% outpatient vs 2.4% in inpatient) between the 2 groups (P = 1.00). **Conclusions:** Outpatient CAR T-cell therapy monitoring was associated with significantly fewer hospital days without increased ED visits, ICU stays, portal use, or 30-day mortality. This demonstrates lower healthcare utilization for outpatient CAR-T therapy. Research Sponsor: None.

1504 **Oral Abstract Session**

Outcomes of patients with cancer admitted to a dedicated oncology service within a multisite home hospital program. First Author: Thomas J. Roberts, Mass General Brigham Cancer Institute, Boston, MA

Background: Home hospital programs deliver acute, inpatient-level care in patients' homes, and many health systems have adopted these programs after CMS granted a waiver for acute hospital care at home in November 2020. These programs may offer advantages for patients with cancer, including reduced exposure to hospital-associated complications and increased time at home. However, evidence describing outcomes for patients with cancer admitted to home hospital programs remains limited. In March 2025, Mass General Brigham (MGB) launched an oncology service within the system's multisite home hospital program. Here we describe outcomes among patients with cancer admitted to this service and compared them with outcomes of patients admitted to a brick and mortar (B&M) oncology service. **Methods:** We conducted a retrospective cohort study of patients with cancer admitted to MGB's home hospital program between March 1, 2025 and December 31, 2025. Patient demographics, admission diagnosis, length of stay (LOS), the rate of escalations (patients requiring transfer back to a B&M hospital for increased acuity of care), and 30-day readmission rates were collected. Propensity score matching was used to construct a cohort of patients discharged from a B&M oncology service during the year prior to the launch of the home hospital oncology service. Total LOS and 30-day readmission rates were compared between the cohorts using multivariable regression models. **Results:** There were 137 patients admitted to the home hospital oncology service during the period of analysis. The mean age was 69.7, 53.3% of patients were male, 70.8% were non-Hispanic White, and 87.6% spoke English. The most common admission diagnoses were sepsis (16.1%), skin/soft tissue infections (13.9%), urinary tract infections (10.2%), and renal and electrolyte disorders (10.2%). Twenty patients (14.6%) were admitted directly from an Emergency Department and 85.4% of patients were transferred from inpatient services. The average LOS was 8.9 days, 4.5 days on a B&M service and 4.4 days admitted to home hospital, and the escalation rate was 10.2%. The 30-day readmission rate was 15.8%. When compared to a propensity score matched cohort of patients discharged from a B&M oncology service, the average LOS was not significantly different while the 30-day readmission rate was significantly lower among patients discharged from home hospital. **Conclusions:** These data show that patients with cancer can be successfully managed in a multisite home hospital program. This dedicated oncology service was able to care for patients with cancer with broad array of admission diagnoses, and the 30-day readmission rate was lower when compared to a cohort of matched patients discharged from a B&M oncology service. Home hospital is a promising model to provide acute care at home for patients with cancer and warrants further study. Research Sponsor: None.

1505 **Oral Abstract Session**

Impact of remote symptom monitoring on acute care utilization in phase I cancer patients: Secondary analysis of a randomized clinical trial. First Author: Jack Stover, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with advanced cancer undergoing Phase I therapies often experience high symptom burden and complications, which may result in acute care encounters (i.e., emergency department [ED] visits and hospitalizations). Few studies have characterized these acute care encounters in Phase I patients. Furthermore, it is unclear if these encounters were avoidable and whether remote symptom monitoring (RSM) could reduce acute care utilization. We performed a secondary analysis of a randomized clinical trial to assess the impact of RSM on ED visits and hospitalizations in Phase I patients. **Methods:** This is a secondary analysis of a randomized clinical trial comparing specialist palliative care (SPC) alone and SPC+RSM in patients with advanced cancer enrolled in Phase I trials at MD Anderson Cancer Center. The key outcomes were the frequency of ED visits and hospitalizations over 6 months following enrollment. We documented the main presenting symptoms and reasons for acute care encounters. Additionally, two independent reviewers assessed whether these encounters were potentially avoidable, defined as whether timely outpatient involvement (e.g., nursing telephone call, clinic visit) could have prevented the encounter. We compared the outcomes between the two study groups using Fisher's exact test. **Results:** Among 100 enrolled patients (mean age 64, 63% female, 33% gastrointestinal cancers, median survival 221 [95% CI 171, 271] days), 43 were in the SPC group and 57 were in the SPC+RSM group. 22/43 (51%) SPC patients and 30/57 (53%) SPC+RSM patients had at least one ED visit over 6 m (P=0.61, Table). 15/43 (35%) SPC patients and 21/57 (37%) had at least one hospitalization over 6 m (P=0.63, Table). Only 4/84 (5%) ED visits and 0/100 (0%) of the admissions were deemed avoidable. The most common presenting symptoms were pain (ED 27%, hospitalizations 30%) and respiratory distress (ED 23%, hospitalization 23%). The main reasons for acute care encounters were disease progression (ED 49%, hospitalizations 58%), acute complications (ED 26%, hospitalizations 28%) and treatment-related complications (ED 13%, admissions 11%). **Conclusions:** Phase I patients had high rates of ED visits and hospitalizations even when they were followed by SPC. The addition of RSM did not reduce the rates of these encounters. A vast majority of these visits were deemed unavoidable, attributed to disease progression and acute complications. These findings underscore the need for novel interventions to support Phase I patients as they navigate the acute care system near the end of life. Clinical trial information: NCT04989556. Research Sponsor: American Cancer Society; CSDG-19-153-01.

Frequency of acute care utilization over 6 months in phase I patients.

	ED Visits	ED Visits	Hospitalizations	Hospitalizations
# of visits	SPC n=43 (%)	SPC+RSM n=57 (%)	SPC n=43 (%)	SPC+RSM n=57 (%)
0	21 (49)	27 (47)	25 (58)	36 (63)
1	16 (37)	16 (28)	14 (33)	12 (21)
2	4 (9)	8 (14)	3 (7)	7 (12)
3	1 (2)	5 (9)	1 (2)	1 (2)
4	0	0	0	0
5	1 (2)	1 (2)	0	1 (2)

1506 **Oral Abstract Session**

Analysis of an oral anticancer repository program and the impact on access to care. First Author: Allyson Waller, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Patients with cancer face many barriers to timely access of oral anticancer agents, including financial toxicity and delays in insurance and patient assistance program (PAP) approval. The Ohio State University Comprehensive Cancer Center (OSUCCC) launched a pharmacist-led Oral Oncology Drug Donation Repository (OODDR) program in 2020 to allow patients to donate unused oral anticancer medications with the intent to re-dispense to other patients in need. The goal of this study was to describe our OODDR experience and its impact on access to anticancer care. **Methods:** A retrospective chart review was conducted for OSUCCC patients who received at least one dispense of oral anticancer medication from the start of the program in February 2020 through August 2025. Data were collected on patient characteristics, anticancer therapy, barriers to access, and long-term medication access outcomes. **Results:** A total of 392 medication access encounters were identified for 376 patients through OODDRR dispense reports. Four encounters were excluded for missing data or not starting treatment, leaving 388 encounters for analysis. The median age of patients was 65 years, majority were female (51%), white (83%), and had commercial insurance (38%), Medicare (39%), or were uninsured (18%). The most common treatment indications included breast (23%), leukemia (17%), lymphoma (15%), and gastrointestinal (13%) malignancies. The OODDR dispensed 53 unique medications, mostly for on-label indications (76%), with 91% of encounters dispensing one treatment cycle/month or less (median 14 days [IQR 10-28]). Patients accessed long-term drug supply primarily via manufacturer PAP (42%) or insurance approval (31%), while 28 patients (7%) received the full course of treatment with OODDR supply. Reasons that repository supply was utilized included (multiple may apply): delay in prior authorization or appeal process (25%), delay in drug delivery from pharmacy (22%), delay in PAP approval and/or supply delivery (30%), and loss or change of insurance/assistance (19%). The OODDR notably improved the time from treatment decision to initiation with a median start of 6 days (IQR 1-13 days) compared to 14.5 days (IQR 6-30 days) to non-repository drug access. The average retail cost of drug dispensed per encounter was $10,789.28. Utilizing repository supply when patients required inpatient treatment (19%) resulted in hospital savings of $207,654.78. In total, the OODDR provided more than $4.1 million worth of anticancer treatment at no charge. **Conclusions:** The OSUCCC OODDR is an instrumental resource for patients and care teams to remove barriers and improve access to anticancer medications. Patients were able to initiate therapy sooner using the OODDR than would have otherwise been possible using routine insurance and assistance programs. Future efforts to improve medication access and awareness of medication assistance platforms are vital. Research Sponsor: None.

1507 **Oral Abstract Session**

Follow-up of outpatients taking oral anticancer drugs in the multidisciplinary community hospital ONCORAL care plan. First Author: Anissa Guillemin, Lyon I University, EA 3738 - CICLY, Lyon Sud University, Lyon, France

Background: The increasing use of oral anticancer drugs (OADs) has shifted cancer care toward outpatient and home-based management, raising major challenges related to treatment adherence, drug-related problems (DRPs), and coordination between hospital and community healthcare professionals. ONCORAL is a structured multidisciplinary community-hospital care plan designed to secure OAD use through coordinated personalised pharmacist-nurse-oncologist follow-up, by face-to-face consultations and phone-calls. The present study aims to assess the impact of ONCORAL over the course of treatment. **Methods:** This prospective real-life cohort study included adult outpatients treated by OADs and followed within ONCORAL between October 2021 and April 2024 in a tertiary referral hospital within the Hospices Civils de Lyon (Lyon, France). The 6-months follow-up was structured in two sequential phases from initiation, with hospital-led consultations, to community monitoring. The primary outcome was the number and nature of nurse and pharmacist interventions (NPIs), classified between DRPs and coordination issues. The secondary outcome was relative dose intensity (RDI), defined as the ratio of prescribed to theoretically approved dose, assessed at months 1 (M1), 3 (M3), and 6 (M6). Based on the literature, a RDI target range of 80-85% is associated with OAD efficacy. Descriptive analyses were performed at both patient and treatment follow-up levels. **Results:** Five hundred and thirty-six patients were included: mean age 69 $\pm$ 13 years; M/F ratio 0.8; 52.4% women; 55.8% with solid tumours. Targeted therapies accounted for 55.2% of treatments. Overall, 71.3% of patients received OADs for $\geq$ 6 months. Mean RDI was above 80% throughout follow-up for 86.1% at M1, 84.3% at M3, 83.5% at M6. Four hundred and eighty-one patients (90.0%) had at least 1 NPI during follow-up, for a mean of 4.8 NPIs per patient. DRPs (88.5%) were identified in 426 patients (79.5%): patient-reported symptoms and adverse effects (37.5%), drug-drug interactions (DDIs) (30.1%), and adherence issues (20.4%). Clinically relevant DDIs were identified in almost more than 1 in 3 patients (n = 145; 27%), with respectively 26.2% and 43.4% of DDIs potentially reducing OAD efficacy or increasing toxicity. Most NPIs concerned information relay to community healthcare professionals (64.2% of patients), and pharmaceutical counselling on side-effects management and treatment schedules (58.4%). **Conclusions:** This longitudinal evaluation demonstrates that the ONCORAL multidisciplinary community-hospital program enables safe outpatient management of OADs, with sustained dose intensity and early detection of DRPs. Pharmacist-nurse collaboration plays a crucial role in securing treatment pathways and optimising the use of anticancer therapies in a real-world setting. Research Sponsor: None.

1508 Oral Abstract Session

Essential but unaffordable: Real-world costs of WHO essential cancer medicines in a low-income setting. First Author: Vivek Ghosh, CancerCare Manitoba, Winnipeg, MB, Canada

Background: The World Health Organization (WHO) Essential Medicines List (EML) defines priority anticancer medicines. In many low-and-middle-income countries (LMICs), EML inclusion may not translate into financial accessibility. Using Nepal as a case study, we mapped availability pathways and real-world prices to quantify affordability of WHO EML regimens. **Methods:** We conducted a cross-sectional audit of WHO EML anticancer medicines in Nepal. Regimens were selected for high-incidence and high-curability cancers and to reflect commonly used standard-of-care regimens. Patient prices were abstracted from Nepal distributor and manufacturer price lists (2024–2026), using the lowest listed patient price when multiple listings existed. Regimen costs were estimated using standard dosing and typical cycle numbers. Metastatic regimens were excluded because treatment duration is open-ended. Fixed-duration curative-intent regimens were analyzed. The primary outcome was affordability, expressed as regimen cost divided by annual GDP per capita (Y), used as a proxy for yearly income. **Results:** WHO EML drugs were broadly identifiable, but free access to high-cost agents via NGO programs was confined to three city hospitals, creating a geographic lottery. Using Y = US$1,447/year, estimated total costs for standard regimens were substantial: dd AC-T for breast cancer US$552 (0.38Y); FOLFOX for colon cancer US$1,226 (0.85Y); CAPOX US$1,090 (0.75Y); FLOT for gastric cancer US$1,063 (0.73Y); and R-CHOP for lymphoma US$1,144 (0.79Y). Add-on biologics were far higher: trastuzumab for HER2-positive therapy (17 cycles) was US$3,998 (2.76Y). Pembrolizumab (9 cycles) was US$27,246 (18.83Y). One year of oral targeted therapy was osimertinib US$4,448 (3.07Y) and olaparib US$10,716 (7.41Y). **Conclusions:** In this LMIC case study, most WHO EML curative regimens approached/exceeded one year of average income, while add-on components approached two decades. EML prioritization alone was insufficient to ensure financial access at the point of care. The findings support targeted national procurement with financial-risk protection for a small set of high-impact medicines, complemented by high income countries (HIC)–LMIC access partnerships, like said NGO-programs, to extend reach beyond a geographically advantaged catchment. Research Sponsor: this work was carried out with the aid of a grant from Royal College Canada International, a charity affiliated with the Royal College of Physicians and Surgeons of Canada.

Nepal oncology regimen costs.

Regimen	Cost/cycle (USD)	Total treatment cost (USD)	Cycles/duration
Breast			
dd AC-T	68	551	8
dd AC-TH	235	3,998	17
TNBC-pembro	3,027	27,246.	9
Colon			
FOLFOX	102	1,226	12
CAPOX	136	1,089	8
NSCLC			
Paclitaxel + carboplatin	119	715	6
Pemetrexed + carboplatin	78	470	6
SCLC			
Carboplatin + etoposide	40	245	6
EGFR TKI in NSCLC			
Osimertinib		4,393	1
BRCA+ breast/ovarian			
Olaparib (300 mg BID assumption)		10,716	1
Gall bladder			
Gemcitabine + carboplatin	108	653	6
Gemcitabine + capecitabine	145	874	6
Stomach			
FLOT	177	1,062	6
NHL			
CHOP	13	81	6
R-CHOP	190	1,144	6
HL			
ABVD	27	108	4

1509 Clinical Science Symposium

Implementation science insights from a community-embedded cervical cancer screening program integrating high-risk human papillomavirus DNA testing with non-communicable disease screening in rural South India. First Author: Shailendra Dandge, Society for Health Allied Research Education India (SHARE INDIA), Hyderabad, India

Background: The WHO Cervical Cancer Elimination Initiative recommends screening ≥70% of eligible women and linking ≥90% of those with identified disease to treatment. However, in most low- and middle-income countries (LMICs), screening rate remains around 30–40%, and only 40–60% of high-risk human papillomavirus (HR-HPV)–positive women complete colposcopy thereby precluding identification of disease and linking to treatment. To address this gap across the screening–diagnosis–treatment pathway, we implemented a multi-pronged community-based program integrating community participation, self-swab HR-HPV DNA screening at doorsteps, with non-communicable disease (NCD) screening and patient centric treatment linkage. **Methods:** This longitudinal implementation study was conducted within the Rural Effective Affordable Comprehensive Health (REACH) cohort in Medchal district, Telangana, India. Trained non-physician health workers conducted door-to-door outreach among women aged 25–65 years. Community engagement was supported by a local Community Advisory Board and village influencers, who guided outreach strategies and timing. Counseling and self-collection of vaginal samples were carried out at participants' homes. Educational content was developed based on prior formative research using the Health Belief Model to address fears, stigma, and misconceptions. Screening for HR-HPV DNA was offered as part of a bundled women's health package that included blood pressure and diabetes testing. Appointments for both swab collection and colposcopy/biopsy were coordinated and scheduled at the convenience of the community. HR-HPV testing was done using a chip-based PCR platform. Women who tested positive were referred for colposcopy, biopsy, and treatment at an affiliated teaching hospital. **Results:** Of 1,869 women approached, 1,747 (93.5%) completed HR-HPV self-sampling, surpassing the WHO's 70% screening target. HR-HPV was detected in 89 women (5.1%). Of these, 64 (71.9%) underwent colposcopy, higher than LMIC averages. All with abnormal findings had biopsies. Four women were diagnosed with high-grade lesions or early invasive cancer, all successfully linked to definitive care or referral, meeting the WHO ≥90% treatment linkage benchmark. **Conclusions:** Integrating HR-HPV screening with NCD services, enabled by community leadership, doorstep access, and logistical support, achieved high coverage, improved follow-up, and complete linkage to care. This model offers practical, scalable insights for cervical cancer screening programs in rural, resource-limited settings. Research Sponsor: None.

LBA1510 Clinical Science Symposium

Low-dose pembrolizumab with chemotherapy in advanced NSCLC: A phase 3 randomized trial. First Author: Nandini Sharrel Menon, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

1511 Clinical Science Symposium

Immunotherapy access disruptions in Mexico: Real-world delivery irregularities at a public cancer referral center. First Author: Brenda Jimenez, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Ciudad De México, DF, Mexico

Background: Immunotherapy improves outcomes in selected cancers, but access in middle-income countries may be limited by cost and supply instability. We quantified eligibility, initiation, and delivery disruptions attributable to drug unavailability at a public cancer referral center in Mexico. **Methods:** Retrospective cohort of adults with a first oncology consultation at Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Mexico City) between January 2023 and March 2025. Records were reviewed to identify standard indications for immunotherapy per NCCN/ESMO/ASCO guidelines current at evaluation. Among eligible patients, we assessed initiation and delivery fidelity. Deviations were defined as delay to initiation >30 days, regimen modification, or temporary/permanent suspension due to drug shortages. **Results:** Among 1,201 first-time consultations, 228 (18.9%) had an immunotherapy indication; 114/228 (50.0%) initiated immunotherapy. Among eligible patients who did not initiate (n=114), medication unavailability was the most frequent reason (48, 42.1%). Among treated patients (n=114), delivery disruptions were common: 42 (36.8%) had treatment suspensions due to shortages, 9 (7.9%) received regimens deviating from approved protocols, and 8 (7.0%) started with >30-day delay. Overall, only 55/228 (24.1%) immunotherapy-eligible patients received treatment as recommended by international guidelines. **Conclusions:** In this public Mexican referral center, only half of immunotherapy-eligible patients initiated treatment, and over half of treated patients experienced delivery disruptions linked to drug unavailability. These findings support urgent procurement and supply-chain strategies to ensure timely, uninterrupted access to high-impact cancer therapies in publicly funded systems. Research Sponsor: None.

Extent of immunotherapy eligibility, initiation, and delivery disruptions attributable to drug unavailability.

Measure	Value
First-time oncology consultations	1201
Immunotherapy indication	228 (18.9%)
Initiated immunotherapy	114/228 (50.0%)
Non-initiation due to medication unavailability	48/114 (42.1%)
Any delivery irregularity among treated patients	59/114 (51.8%)
Suspension due to drug shortages	42/114 (36.8%)
Regimen deviation due to unavailability	9/114 (7.9%)
Initiation delay >30 days	8/114 (7.0%)
Guideline-concordant immunotherapy among eligible patients	55/228 (24.1%)

Values are n (%) unless otherwise indicated. Delivery irregularities include initiation delay >30 days, regimen modification, or temporary/permanent treatment suspension due to drug shortages. Percentages are calculated using the denominators specified in each row.

1512 Clinical Science Symposium

Sustaining oncology clinical trials under wartime conditions: Strategic lessons from Ukraine. First Author: Igor Bondarenko, Dnipro State Medical University, Dnipro, Ukraine

Background: On February 24, 2022, when Russia launched its full-scale invasion of Ukraine, our center had already treated more than 5,000 patients across 410 oncology clinical trials (CTs) since 2002. At the onset of the war, 125 active CT contracts across 18 cancer types (64 sponsors) were ongoing, with 413 patients enrolled or under follow-up, including 210 in active treatment (57 CTs), 203 in follow-up (53 CTs), and 15 CTs pending initiation. The sudden transition to wartime conditions posed unprecedented challenges to patient safety, continuity of care, trial operations, regulatory compliance, and data integrity, requiring rapid adaptation of clinical, logistical, and digital infrastructures. **Methods:** We conducted statistical analyses to evaluate the feasibility of sustaining CTs over 35 consecutive months of martial law. Key domains included personnel retention, trial activity, protocol adherence, supply chain continuity for a research center located 80 miles from the frontline, and digital infrastructure performance, including utilization of the Medical Control Records (MCR) management system. Our goal was to identify factors applicable to clinical research in armed conflict, natural disasters, and other protracted crises. **Results:** Despite ongoing air raids, missile attacks, power outages, and mass displacement, 99% of scheduled patient visits and data transfers were completed. Of the 413 patients at the start of the war, 150 (36.3%) remain in active treatment (n = 42) or follow-up (n = 108) across 55 trials, representing 44% of the pre-war portfolio. Since February 2022, 7,891 patient visits, 16,155 blood tests, 1,762 tumor response assessments, 3,525 intravenous infusions, and 3,272 oral drug distributions have been completed, with 176 deaths recorded as protocol endpoints. Rapid restoration of supply chains, communications, patient logistics, and secure data management enabled uninterrupted trial activity. A key facilitator was the adaptive MCR digital platform, developed during the COVID-19 pandemic, enabling real-time monitoring, centralized, high-quality electronic medical records, timely e-CRF entry, and remote oversight of CT processes under extreme conditions. The system's AI-assisted planning and multilingual tools are now being tested as a new paradigm for global CT continuity and effective performance. **Conclusions:** Armed conflict disrupts clinical research at every level, threatening patient safety, data integrity, and national research infrastructure. Our experience shows that rapid digital adaptation, operational flexibility, and collaborative governance can sustain oncology trials under extreme geopolitical conditions. These lessons offer a scalable framework for research continuity, regulatory alignment, and patient protection in conflict zones and disaster settings, reinforcing global oncology's role in health system resilience and recovery. Research Sponsor: None.

1513 Rapid Oral Abstract Session

Randomized controlled trial of a psychosocial digital application (THRIVE-MM) for patients living with multiple myeloma. First Author: Areej El-Jawahri, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Patients living with multiple myeloma (MM) struggle with considerable quality of life (QOL) impairments, fatigue, and psychological distress throughout their illness course. However, few accessible and scalable interventions address the supportive care needs of these patients. We assessed the efficacy of a self-guided psychosocial digital application, THRIVE-MM, for improving QOL, fatigue, and psychological distress in patients living with MM. **Methods:** We conducted a single-center randomized controlled trial of THRIVE-MM vs. usual care for adults living with MM. Eligibility criteria included patients newly diagnosed with MM receiving first line therapy, those with relapsed MM receiving second- or third-line therapy, or those with MM on maintenance therapy. Participants were randomly assigned 1:1 to THRIVE-MM or usual care, stratified by line of therapy (first line vs. second/third line vs. maintenance) and were given access to the THRIVE-MM digital app up to 8 weeks after enrollment. THRIVE-MM comprises five modules designed to improve patients' physical and psychological symptoms via psychoeducation and evidenced-based self-management skills training for behavioral change and coping, delivered through interactive activities, educational games, and videos. Participants completed self-report measures at baseline and at week-8 after enrollment. The primary endpoint was QOL at week-8 assessed by the Functional Assessment of Cancer Therapy (FACT)-MM. Secondary outcomes were fatigue (FACT-Fatigue), depression and anxiety symptoms (Hospital Anxiety and Depression Scale), and symptoms of posttraumatic stress disorder (PTSD Checklist). We used analysis of covariance controlling for baseline criterion value to assess the effect of THRIVE-MM on outcomes. **Results:** From 12/2023-6/2025, we enrolled 59.1% (120/203) of eligible patients (mean (SD) age = 68.2 (10.0) years; 49.2% women). Mean (SD) use time for THRIVE-MM in the intervention group was 221.9 (197.1) minutes. At week-8, QOL did not differ significantly between the two groups (THRIVE-MM; 125.2 vs. usual care; 125.1, p = 0.977]). THRIVE-MM participants reported lower fatigue (40.6 v. 37.6, p = 0.012) and lower depression symptoms (2.5 vs. 3.4, p = 0.044) at week-8. Anxiety or PTSD symptoms did not differ significantly between the two groups at week-8. **Conclusions:** THRIVE-MM, a psychosocial digital health intervention, decreased fatigue and depression symptoms but not QOL among patients living with MM. Clinical trial information: NCT06073353. Research Sponsor: None.

1514 Rapid Oral Abstract Session

Use of a patient-facing digital tool for glioblastoma outside scheduled clinic visits. First Author: Jason Binder, Ember Health Inc, Summerfield, NC

Background: Care for patients with glioblastoma is largely organized around scheduled clinic encounters, yet symptom management, decision-making, and caregiver responsibility extend beyond office visits. While patient portals, phone triage, and after-hours call coverage exist, these pathways are often resource-intensive, variably available, and insufficient to meet ongoing informational and emotional needs. Scalable, low-cost tools that extend access to vetted support outside clinic hours without increasing clinician workload may help address gaps in care delivery. We evaluated real-world use of a freely accessible, patient- and caregiver-facing digital support tool in glioblastoma. **Methods:** A freely accessible AI chatbot supporting informational, emotional, and care-navigation needs was deployed online without registration or recruitment. The tool excluded medical decision-making and clinical recommendations. De-identified conversation logs generated during routine use were retrospectively analyzed over a 4-month period (Sep 15, 2025 – Jan 14, 2026). Analyses included descriptive characterization of conversation volume, geographic distribution, timing of use, engagement depth, user-reported feedback, and primary topics addressed. All analyses used aggregate, de-identified data with no interaction or intervention involving human subjects. The protocol is IRB exempt per 45 CFR 46.104(d)(4) (WCG IRB 20260304). **Results:** During the study period, the chatbot supported 1,661 conversation threads comprising 15,197 messages across 54 countries. Most conversations originated from the United States (59.9%), followed by the United Kingdom (7.3%), Australia (5.2%), Canada (4.1%), and Greece (3.8%). Conversations were predominantly multi-turn and included use outside clinic hours. The tool was used primarily in English; however, ~12% of messages occurred in other languages, most commonly Spanish and French with additional use of Arabic, German, Italian, Portuguese, Hebrew, Hindi, and several Central and Eastern European languages. Conversations most frequently addressed imaging interpretation and scan-related uncertainty, treatment decision-making, symptom management and treatment-related side effects, and caregiver concerns. Additional topics included clinical trial exploration and prognosis clarification. When clinical trial–related questions arose, users were directed to a brain tumor trial finder. Across the study period, 374 users engaged in trial searches across 22 countries; among respondents to a trial-interest query (n = 251), 92% expressed interest. Voluntary user feedback (n = 97) demonstrated high perceived usefulness and trust (net promoter score, 80). **Conclusions:** A freely accessible AI chatbot demonstrated feasibility as a scalable approach to extending access to care for patients with glioblastoma and their caregivers outside office hours. Research Sponsor: None.

1515 Rapid Oral Abstract Session

Telehealth visits to support extended dosing of pembrolizumab and reduce health care visits: A pragmatic trial. First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Single agent pembrolizumab is standardly administered every 3 weeks (q3wk). Although extended interval dosing every 6 weeks (q6wk) was approved during the pandemic, most oncologists (65%) prefer q3-week dosing to monitor and mitigate immune-related adverse events (irAEs). We hypothesized that telehealth (TH)-enabled safety monitoring may facilitate broader adoption of q6 week dosing with reduced in-person health care visits while maintaining safety and patient experience. **Methods:** MAking Telehealth Delivery of Cancer Care at Home Effective and Safe for Immunotherapy (MATCHES-IO) is a single-arm pragmatic trial among patients with solid tumors receiving single-agent pembrolizumab. The intervention consisted of q6-week in-person pembrolizumab infusions with interim (eg. weeks 3,9,15) telehealth toxicity assessments during the first 6 months of therapy. Intervention components included a TH clinician visit, home phlebotomy, and biometric monitoring. The primary outcome was the number of days with an in-person health care facility visit, ascertained from the electronic health record. Participants were compared to a contemporaneous matched cohort receiving standard q3-week pembrolizumab, matched 1:1 on cancer type, stage (I–III vs IV), and age (15-year bands). Safety was evaluated by comparing irAEs requiring steroid use. Patient experience was assessed using a survey that included likelihood to recommend the intervention. **Results:** Between May 2023 and February 2025, 60 patients were enrolled (median age 69.5 [range: 25-85], 38% female, 78% white). Cancer diagnoses included thoracic (52%), genitourinary (30%), and melanoma (18%) in cases and controls. In matched analyses, there was a 3.5-day difference in total healthcare facility contact days between cases and controls (median 8.5 vs. 12.0, p = 0.14) that did not achieve statistical significance. Rates of irAEs requiring steroids were similar between groups (25.0% vs. 27.1%, p = 0.84). Fifty-two patients (87%) in the intervention group completed a patient experience survey. The median likelihood to recommend score was 10 (Q1,Q3: 8.0, 10.0). Most respondents (96%) perceived a benefit from the telehealth platform, including saved time (85%), increased convenience for patients (75%) and caregivers (44%), and cost savings (52%). **Conclusions:** Extended interval pembrolizumab supported by TH-enabled toxicity monitoring with remote phlebotomy and biometric assessments was associated with reduced in-person health care facility days but did not achieve the significance threshold. The intervention was associated with high patient satisfaction and no increase in irAEs. These results may address clinicians' concerns about the safety of q6 week immunotherapy dosing and inform future care-delivery strategies integrating telehealth with immunotherapy treatment. Research Sponsor: National Cancer Institute; P50 CA271357; National Institutes of Health and National Cancer Institute; P30 CA008748.

1516 Rapid Oral Abstract Session

Addressing geographic disparities in cancer care: An examination of the contributions of international medical graduates (IMGs). First Author: Nazli Dizman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: IMGs comprise 38% of the US hematology and medical oncology workforce according to the Association of American Medical Colleges. We examined the geographic distribution of oncologists by IMG status to quantify and contextualize the role of IMGs in providing cancer care across the United States, particularly in rural and underserved areas. **Methods:** We used Medicare Care Compare to identify and locate physicians practicing in the U.S. as hematology and medical oncology specialists. IMG status, defined as graduation from a medical school outside of the US, Puerto Rico, and Canada, was assigned from Care Compare where information was available (51%), then from AMA Masterfile data (43%). For the 6% missing IMG data, Google Gemini was used for imputation. We cross-tabulated oncologist IMG status with whether they practiced in a rural county, a county with high cancer incidence (in top 25% of counties for age-adjusted cancer incidence from the National Cancer Institute), and a primary care Health Provider Shortage Area (HPSA). Across counties, we assessed the distribution of new cancer cases by oncologist availability according to IMG status. Proportions and odds ratios with 95% confidence intervals are reported to demonstrate associations. **Results:** There were 14,946 oncologists practicing in the US as of March 2025, of which 5,840 (39%) were IMGs. IMG status was associated with locations that are rural, have high cancer incidence, and have provider shortages (Table). In county-level analysis, among 1,395 counties with oncologists, 1,105 (80%) had IMG oncologist presence. In 662 (47%), IMGs comprised ≥50% of the oncology workforce, corresponding to areas where 32% of patients with newly diagnosed cancer live (549K/1.72M). In 250 counties (18%), only IMG oncologists provided care; 191 (76%) of those were rural and/or had high cancer incidence. **Conclusions:** IMG oncologists play a pivotal role in the geographic availability of cancer care in the United States. They are more likely to practice in rural areas and in areas with increased cancer burden and provider shortages. Any reductions in the IMG oncologist workforce could impede patient access to cancer care on a broad scale and further aggravate shortages in rural and underserved areas. Research Sponsor: None.

Oncologist practice site characteristics by IMG status.

Site Characteristic	All Oncologists, N (%)	IMG Oncologists, n (%)	Non-IMG Oncologists, n (%)	Odds Ratio for IMG vs. Non-IMG (95% CI)
Overall	14,946	5,840	9,106	
Rural				1.34 (1.20, 1.50)
Yes	1,488 (10)	677 (12)	811 (9)	
No	13,458 (90)	5,163 (88)	8,295 (91)	
High Cancer Incidence*				1.54 (1.41, 1.68)
Yes	2,346 (16)	1,116 (20)	1230 (14)	
No	12,264 (82)	4,554 (80)	7710 (86)	
HPSA				1.38 (1.29, 1.49)
Yes	3,923 (26)	1,760 (30)	2,163 (24)	
No	11,023 (74)	4,080 (70)	6,943 (76)	

*County incidence data unavailable for 336 (2%) oncologists.

1517 Rapid Oral Abstract Session

Evaluation and appraisal of quality indicators for end-of-life cancer care in an African context. First Author: Vivens Nsabimana, Partners in Health, Kigali, Rwanda

Background: Population-based quality indicators (QIs) for end-of-life (EoL) cancer care are used to monitor and improve care delivery. Most QIs measure overuse of anticancer therapy or acute care near death and underuse of palliative care. This enables optimization of patient-centered care and healthcare resource utilization, which is especially critical in low-resource settings. Yet, QIs developed in U.S. may not be directly transferable in Africa. We evaluated EoL cancer care in Rwanda using existing QIs and appraised their relevance and feasibility in Rwanda. **Methods:** We conducted a retrospective chart review of all patients who died or were referred for EoL care (i.e., hospice) in 2022 in a Rwandan cancer center. Missing death dates were sought from family and community health workers. Relevance and feasibility of established QIs were appraised by the study team. QI performance was compared with published U.S. benchmarks. **Results:** Of 297 patients (median age 43; 16% pediatric; 61% female), the most common cancers were breast (19%), cervical (9%), acute lymphoid leukemia (9%), gastric (8%), lymphoma (7%), rectal (5%). Nearly half (46%) were stage IV at diagnosis. Most (72%) received treatment; 61% had chemotherapy. After outreach, death dates were available for 95%. Of 18 QIs validated in U.S., 5 were retained or adapted for Rwanda and 13 excluded due to contextual irrelevance or inadequate documentation. Length of stay in EoL care achieved its benchmark, while performance on other QIs was suboptimal (see Table). **Conclusions:** This study is among the first to evaluate and appraise established EoL cancer care QIs in Africa and highlights opportunities to reduce overuse of non-beneficial chemotherapy near death, increase use of palliative care and hospice, and adapt or develop novel EoL QIs to best fit African contexts. Research Sponsor: UCSF Society of Hellman Fellows award; National Cancer Institute; K08CA279874.

Comparison of EoL Care in Rwanda with published benchmarks.

	Rwanda	Benchmark
% referred for EoL care before death (n=297)	45%	>55%
% with length of stay in EoL care 3 days (n=114)	5%	<8%
% who died in a hospital (n=281)	48%	<17%
% starting new chemo within 30 days of death (n=297)	12%	<2%
% receiving chemo within 14 days of death (n=297)	17%	<10%
% receiving chemo within 30 days of death (n=297)	24%	N/A*

*Not a published benchmark; 45% in a published report from Uganda.

1518 Rapid Oral Abstract Session

Timing of telepalliative care and end-of-life outcomes in advanced cancer: A multicenter retrospective cohort study. First Author: Alexandra Mendes Barreto Arantes, Oncoclinicas & Co - Medica Scientia Innovation Research (MEDSIR), Sao Paulo, SP, Brazil

Background: Telemedicine has become an integral component of palliative care delivery; however, its impact on end-of-life outcomes in oncology remains insufficiently explored, particularly in low- and middle-income countries (LMICs). Place of death is a key quality indicator in palliative oncology and reflects goal-concordant care. This study evaluated whether the timing of palliative care teleconsultations was associated with a higher likelihood of home death among patients with advanced cancer receiving care in a Brazilian multicenter setting. **Methods:** We conducted a multicenter retrospective cohort study in Brazil including adults with advanced cancer who received interdisciplinary palliative care and died due to disease progression between January 1, 2024, and December 31, 2025. Exposure to telepalliative care was defined according to the timing of teleconsultations relative to death (any teleconsultation, ≤7 days, ≤30 days, or exclusively in-person care). The primary outcome was place of death (home vs other). Secondary outcomes included intensive care unit (ICU) admission and receipt of disease-modifying therapy in the last 30 days of life. Given the sample size, associations were evaluated using univariate logistic regression. **Results:** Among 116 patients (median age 65 years; 55% female), 63 (54.3%) received telepalliative care. Exposure to telepalliative care overall, irrespective of timing, was not associated with home death. In contrast, telepalliative care delivered closer to death was significantly associated with a higher likelihood of home death, particularly when performed within the last 7 days of life (OR 5.93; 95% CI 1.75–20.15; p = 0.004) and within the last 30 days (OR 3.08; 95% CI 1.04–9.10; p = 0.042). Telepalliative care was also associated with lower odds of ICU admission in the last 30 days of life (OR 0.34; 95% CI 0.16–0.73; p = 0.006) and reduced odds of receiving disease-modifying therapy in the final month of life (OR 0.35; 95% CI 0.15–0.79; p = 0.012). **Conclusions:** In this Brazilian multicenter retrospective cohort, the timing of telepalliative care, rather than teleconsultation exposure alone, was a key determinant of end-of-life outcomes. Telepalliative care delivered closer to death was associated with a higher likelihood of home death and reduced use of high-intensity end-of-life care. These findings highlight the importance of timely integration of telepalliative care to maintain continuity of interdisciplinary care and support goal-concordant end-of-life care, particularly in resource-constrained and geographically diverse settings. Research Sponsor: None.

1519 Rapid Oral Abstract Session

LLM-generated serious illness conversation summaries to improve care for hospitalized patients: A pilot clinical trial. First Author: Christopher Manz, Dana-Farber Cancer Institute, Boston, MA

Background: Patients with cancer often receive intensive care near the end of life that does not align with their goals and preferences. Hospitalization is a critical opportunity to engage in serious illness conversations (SICs) that can align care with preferences, but SICs rarely occur. Large language model (LLM)-generated SIC summaries may help busy inpatient clinicians by identifying patient preferences in fragmented SIC documentation in voluminous electronic health record (EHR) notes. **Methods:** This randomized pilot clinical trial enrolled adults with solid tumors admitted to an academic hospital with a 90-day predicted mortality > 40%. Patients were randomized 3:1 (intervention:control) to usual care or to an intervention consisting of an LLM-generated summary of SIC documentation in EHR notes from the last 6 months emailed to their inpatient and outpatient oncology and palliative care teams within 16 hours of admission. Summaries included 8 SIC topics and up to 18 bullet points, and emails included a message encouraging SICs and incorporation of patients' preferences into care plans. The primary outcome was SIC summary accuracy: manual review determined whether each summary bullet point accurately reflected the source note, and the proportion of accurate bullet points were calculated. Other outcomes included user perspectives from day 3 patient interviews and day 7 clinician surveys and 90-day care delivery outcomes (days in the hospital, number of hospitalizations, hospital re-admission). **Results:** 58 enrolled patients were 55% female, 76% White, 91% non-Hispanic and had a mean 90-day predicted mortality of 57.7%. 902 of 936 (96.4%) summary bullet points accurately reflected underlying documentation. Inaccuracies were typically not clinically significant and related to overstating the strength of preferences (e.g., documentation stating a plan to start treatment to improve symptoms might be summarized to state the patient is "focused on improving symptoms") and misattribution of clinician concerns to the patient. 32 patients participated in interviews. They were generally supportive of the intervention and felt it would improve patient-clinician understanding and communication around preferences. 31 clinicians completed surveys and evaluated SIC summaries as "moderately" to "extremely accurate." 90-day outcomes were mature for 24 patients. In 90 days after enrollment, preliminary mean hospital days (20.9 vs 13.2), mean number of hospitalizations including index admission (2.3 vs 1.5) and re-admission (42.9% vs 23.5%) were all lower in the intervention arm. Full trial data will be available in March. **Conclusions:** LLM-generated SIC summaries can be accurately generated, delivered within 16 hours of hospital admission, are received favorably by patients and clinicians, and may reduce care utilization. An effectiveness clinical trial starts May 2026. Clinical trial information: NCT07147023. Research Sponsor: The Fund for Innovation in Cancer Informatics.

1520 **Rapid Oral Abstract Session**

Effect of a financial navigation intervention on financial toxicity among patients with breast cancer: A randomized controlled trial in China. First Author: Weijie Xing, Fudan University School of Nursing, Shanghai, China

Background: Financial toxicity (FT) is a common and burdensome consequence of breast cancer treatment, adversely affecting patients' psychological well-being, treatment adherence, and quality of life. Financial navigation (FN) has been proposed as an effective strategy to mitigate FT; however, high-quality randomized evidence evaluating its impact on patient-centered outcomes remains limited. **Methods:** This assessor-blinded, parallel-group randomized controlled trial enrolled adult female patients with breast cancer who had undergone surgery and were receiving or scheduled for adjuvant therapy. Participants were randomized to an FN intervention or usual care (n = 41 per group). The FN intervention included individualized needs assessment, cost-related health education, referral to financial and social resources, and personalized counseling. Outcomes were assessed at baseline (T0), 1 month (T1), and 3 months (T2) post-discharge. Primary outcome was FT, with secondary outcomes including cost-related health literacy (CRHL), shared decision-making (SDM) ability, and perceived stress. Intention-to-treat analysis using generalized estimating equations was applied. **Results:** Of 311 patients screened, 82 were enrolled. Compared with controls, the FN group demonstrated significantly lower subjective FT at T1 (mean difference = 4.76, 95% CI 0.75–8.76, P= 0.020) and T2 (mean difference = 4.66, 95% CI 0.94–8.37, P= 0.014). CRHL significantly improved at T1 (mean difference = 3.15, 95% CI 0.91–5.38, P= 0.006) and further increased at T2 (mean difference = 5.56, 95% CI 3.53–7.59, $P<$ 0.001). SDM ability was also higher in the FN group at T2 (mean difference = 3.24, 95% CI 0.47–6.00, P= 0.022). No significant effects were observed in material or behavioral FT domains. Perceived stress was higher in the FN group at T2 (P= 0.032). **Conclusions:** This randomized controlled trial demonstrates that financial navigation is an effective intervention for alleviating subjective financial toxicity and improving cost-related health literacy and shared decision-making among patients with breast cancer. By providing rigorous randomized evidence, this study advances the field beyond descriptive and observational research and offers high-level evidence supporting financial navigation as a clinically actionable strategy to address cancer-related financial toxicity. These findings contribute to the global effort to mitigate financial toxicity and support the integration of structured financial navigation programs into survivorship care models across diverse healthcare settings. Clinical trial information: NCT06484140. Research Sponsor: National Natural Science Foundation of China.

1521 **Rapid Oral Abstract Session**

Effect of group community health worker–led advance care planning education on advance care planning documentation, satisfaction, palliative care, and hospice: Results from a randomized clinical trial. First Author: Olivia Viruet Quintero, Stanford University School of Medicine, Staford, CA

Background: Advance Care Planning (ACP) is recommended for all patients with cancer yet engagement remains low due to multilevel barriers including limited clinician time, lack of adequate reimbursement, and workforce shortages. Our team demonstrated that one-on-one community health worker (CHW)-led education interventions can improve ACP documentation, satisfaction, and hospice use. Group CHW-led interventions may improve scale and spread, however, the effectiveness of such approaches compared to usual cancer care remains unknown. **Methods:** This prospective randomized clinical trial compared a 1-month CHW-led group ACP education intervention plus usual cancer care (intervention group) with usual cancer care alone (control group). Veterans newly diagnosed with solid tumor malignancies, 18 years of age or older, and planned to receive cancer care at one VA facility were eligible. All who verbally consented were randomized 1:1 to the intervention group or the control group. The intervention consisted of two 90-minute group sessions over 1-month post-randomization with 8-10 participants per group led by trained CHWs. The sessions included tailored education regarding ACP, surrogate decision-maker designation, and communication strategies with cancer clinical teams. Usual care included access to nurse navigators, social workers, palliative care and hospice teams, and ancillary support services. The primary outcome was ACP documentation (comprised of the VA Life Sustaining Treatment, VA Advance Directive, and Goals of Care documentation by the oncology clinician) in the electronic health record within 6-months after randomization. Secondary outcomes included satisfaction with care decision, palliative care use, and hospice use. **Results:** 65 patients were screened with 60 (92.3%) eligible of whom all 60 (100%) participated with 30 in each group. There were no withdrawals or participants lost to followup; 55 (91%) were male; 5 (8.3%) were female; median age was 79 years (IQR 67-86); 53 (88.3%) had stage 3 or 4 cancer; 9 (15%) reported ethnicity as Hispanic or Latino; 39 (65%) reported race as White; 12 (20%) Black; 3 (5%) American Indian; and 6 (10%) multiple races. At 6-months followup, intervention group participants had greater ACP documentation (30 (100%) versus 12 (40%)), strongly agreed that they were satisfied that care matched their preferences (27 (90%) versus 18 (66.7%)); no differences in palliative care use (3 (10%) versus 3 (10%)) and greater hospice use (15 (55.6%) versus 3 (10.0%)) than control group participants. **Conclusions:** This group CHW-led ACP education intervention improved ACP documentation, satisfaction, and hospice use at one VA. Group CHW-led ACP approaches may be a potentially scalable approach to address workforce shortages and effectively improve ACP. Clinical trial information: NCT06646614. Research Sponsor: VA Health Services Research & Development.

1522 **Poster Session**

Association of socioeconomic and clinical factors with overall survival in immunotherapy-eligible stage III non-small cell lung cancer following definitive chemoradiation. First Author: Chaewon Hwang, Department of Radiation Oncology, Tufts Medical Center | Department of Radiation Oncology, Beth Israel Deaconess Medical Center, Boston, MA

Background: Use of consolidative immunotherapy (IO) for stage III non-small cell lung cancer (NSCLC) has increased since FDA approval in 2018, yet disparities in access persist. Few studies have examined survival in the IO era accounting for both socioeconomic and clinical factors. We evaluated determinants of overall survival (OS) in IO-eligible patients (pts) after definitive chemoradiation (CRT). **Methods:** Retrospective National Cancer Database analysis was performed, of adults ≥18 years with stage III NSCLC (2018-2020) receiving ≥60 Gray in ≥30 fractions of RT with known IO status, defined as receipt 50-150 days from CRT start. Surgical cases were excluded. Variables included race/ethnicity (R/E), insurance, facility type, Charlson-Deyo comorbidity index (CCI), high school graduation rate (HSGR), household income, sex, age, NSCLC primary site, and histology. OS was assessed using the Kaplan-Meier method, followed by multivariable Cox regression models adjusting for aforementioned variables, including IO receipt. **Results:** Among 19,418 pts, 54.4% received IO. Median age was 68 years; 44% were female; 85% White, 12.5% Black, 2% Asian, and 2% Hispanic. Median OS was higher with IO (42.1 vs 22.3 months [mo], $P<$.001) and in females (38.8 vs 28.1 mo, $P<$.001). OS differed by R/E: Asian (52 mo), Black (40.3 mo), Hispanic (37.2 mo), American Indian/Alaska Native (24 mo) vs White pts (31.1 mo), $P<$.001. Privately insured pts (41.7 mo) and those treated at academic/research (A/R) centers (36.5 mo) had higher OS ($P<$.001). On multivariable analysis, IO receipt was associated with lower all-cause mortality (HR 0.53; 95% CI, 0.51-0.56). Reduced mortality was seen in Asian (HR 0.82; 95% CI, 0.68-0.99) and Black pts (HR 0.83; 95% CI, 0.77-0.89) vs White pts. Higher mortality was associated with male sex (HR 1.28; 95% CI, 1.22-1.34), urban (non-metropolitan) vs metropolitan residence (HR 1.14; 95% CI, 1.07-1.22), Medicare (HR 1.10; 95% CI, 1.03-1.18) or no insurance (HR 1.36; 95% CI, 1.14-1.63) vs private insurance, nonacademic facilities (comprehensive: HR 1.09; 95% CI, 1.03-1.16; integrated network: HR 1.15; 95% CI, 1.07-1.23), and CCI of 2 (HR 1.13; 95% CI, 1.04-1.21) or ≥3 (HR 1.29; 95% CI, 1.19-1.40). Income and HSGR showed marginal association with OS. Upper-lobe vs main bronchus sites were associated with better OS ($P<$.02), while squamous histology was associated with worse OS ($P<$.001). **Conclusions:** Approximately half of IO-eligible stage III NSCLC pts received IO, which was independently associated with improved OS, adjusting for socioeconomic and clinical factors. Asian and Black race, and treatment at A/R centers, were associated with lower mortality. Insurance and facility type significantly influenced OS, highlighting persistent access-related disparities and the need for targeted interventions to promote equitable care. Research Sponsor: National Institute on Aging; T32AG000243.

1523 **Poster Session**

Intersecting rural, racial, and Medicaid disparities in cervical cancer outcomes across North Carolina, 2019–2023. First Author: Vaidehi Mujumdar, Atrium Health Levine Cancer, Charlotte, NC

Background: Although national cervical cancer incidence has declined, mortality disparities persist, particularly among rural and racially diverse populations. North Carolina—marked by heterogeneous access to care and recent Medicaid expansion—offers a unique setting to examine geographic and socioeconomic inequities in cervical cancer outcomes. **Methods:** County-level *Cervix Uteri* incidence and mortality data (2019–2023) were obtained from the North Carolina Central Cancer Registry via State Cancer Profiles. Counties were categorized by USDA Rural–Urban Continuum Codes (2023) (urban = 1–3; rural = 4–9). Rates per 100,000 women were calculated using 2020 county populations; 95 % CIs were derived by Poisson approximation. Race-specific rates were determined from State Cancer Profiles (2017–2021 incidence; 2018–2022 mortality). Medicaid enrollment was derived from NC DHHS (SFY 2024) and merged by county rurality. **Results:** Between 2019–2023, 1,624 new cervical cancer cases and 541 deaths occurred. Rural counties comprised 36 % of the female population but 42% of deaths. Incidence was similar between rural and urban counties (18.1 vs 18.9 per 100 000; 95 % CI 14.9–21.2 vs 17.4–20.6), whereas mortality remained higher in rural areas (7.0 vs 5.9; 95 % CI 5.0–8.9 vs 5.1–6.8). Medicaid enrollment was 33.7 % in rural vs 27.1 % in urban counties. High-mortality counties (Robeson, Halifax, Bladen) also had > 45 % Medicaid coverage and higher proportions of Black and Native American residents. Race-specific analyses showed Black women had the highest burden (incidence 8.0; mortality 2.6 per 100 000) compared with White (6.2; 2.0) and Hispanic (7.1; 1.9) women, highlighting overlapping racial and geographic disadvantage. **Conclusions:** In North Carolina, 1) rural residence, 2) race, and 3) Medicaid dependence intersect to drive cervical cancer mortality disparities. Despite comparable incidence, rural and racially diverse counties experience 20–30% higher mortality. Elevated Medicaid enrollment in these regions suggests that insurance expansion alone cannot offset structural barriers in access to gynecologic oncology care. Sustained Medicaid funding, equitable provider reimbursement, and targeted investments in rural cancer infrastructure are essential to improve survival and equity. Research Sponsor: None.

1524 **Poster Session**

Lost in translation? Evaluating associations between English proficiency and next generation sequencing completion, and comparing understandability across different translation modalities among Spanish speakers with metastatic breast cancer. First Author: Daniela Tovar, UT Southwestern, Dallas, TX

Background: Disparities in next-generation sequencing (NGS) utilization persist among patients with metastatic breast cancer (MBC), disproportionately affecting Hispanic/Latino populations. We hypothesized that the challenges in explaining NGS, particularly when mediated through translation, could be contributing to this observed discrepancy in NGS testing rates within the Hispanic/Latino populations. We evaluated the associations between limited English proficiency and NGS testing by comparing the understandability between English, certified Spanish translations, and artificial intelligence (AI)-generated Spanish translations of provider explanations of NGS testing. **Methods:** We analyzed 191 patients with recurrent MBC from the Dallas Metastatic Breast Cancer Study. Ethnicity was categorized as Hispanic vs non-Hispanic. NGS completion between 2014–2022 was assessed. Three versions of NGS explanations (original English, certified Spanish translation, and AI-generated Spanish translation) were evaluated using the Flesch-Kincaid Readability Score (English) and the Fernández-Huerta Index (Spanish) using 10 provider-patient interactions. Scores range from 0–100, with higher scores indicating greater understandability; CDC/NIH-recommended patient materials target scores of 60–70. Readability discordance $<$ 10 points was considered acceptable. **Results:** 81.7% (156) of patients were proficient in English and were 3.2 times more likely to complete NGS testing than Spanish speakers (95% CI 1.35-7.73, p $<$ 0.01). Mean readability score between the English, certified Spanish, and AI Spanish were 47.9, 51.4, and 54.1, respectively. The mean discordance was 6.1 points between English and certified Spanish, 5.9 points between certified Spanish and AI Spanish, and 8.6 points between English and AI Spanish. All ten original English explanations fell below CDC/NIH readability targets, and only 4 of 10 certified Spanish translations met the recommended standards. When refining the prompts to maximize patient understanding, AI-generated text generated perfect understandability scores. **Conclusions:** Although translation fidelity was preserved, most provider-generated explanations failed to meet recommended readability standards, suggesting that communication quality, not translation alone, may limit patient understanding. AI-generated explanations may serve as a tool to mitigate language-related barriers when certified interpreters or optimized explanations are unavailable and enhance informed decision-making across varied clinical discussions, not limited to NGS testing. Research Sponsor: None.

1525 **Poster Session**

Mapping access to retinoblastoma care: Geographic disparities and service availability across Africa, and West and Central Asia. First Author: Rima Torosyan, Yerevan State Medical University, Yerevan, Armenia

Background: Retinoblastoma, the most common childhood eye cancer, is highly manageable with prompt diagnosis and appropriate care. Access to specialist services is, however, unequal in low- and middle-income countries (LMICs), leading to unnecessary morbidity and death. This study assesses the geographic reach of retinoblastoma treatment centers, estimates the burden of cases relative to available services, and analyzes referral barriers—in terms of distance and cost of travel—across Africa, West and Central Asia. **Methods:** We used the One Retinoblastoma World Map to categorize African, West and Central Asian (excluding India, China, and Mongolia eastern countries) specialized treatment centers. The centers were classified as Tier 1 (comprehensive care with focal therapy and radiotherapy) or Tier 2 (lacking at least one essential treatment modality). The availability of genetic testing was also recorded. Country-specific incidence of retinoblastoma was estimated at 1 case per 18,000 live births, using UN population and birth rate data. For countries without Tier 1 or Tier 2 centers, we calculated minimum travel distances and estimated one-way costs for a child and guardian to reach the nearest facility. **Results:** Among 71 countries analyzed, there were just 28 (39%) countries with Tier 1 or Tier 2 retinoblastoma centers and 43 (61%) countries without such centers. Tier 1 centers were available in just 16 countries (22.5%), predominantly middle- and high-income countries: only 2 of 25 low-income countries (Uganda, Mali) had access to Tier 1 versus 11 of 39 middle-income and 3 of 7 high-income countries (Saudi Arabia, Israel, Russia). Notably, 64% of low-income and 59% of middle-income countries did not have any retinoblastoma center. Twenty-two high-burden nations ($\geq$10 cases/year) had no Tier 1 or Tier 2 center, including the Democratic Republic of Congo (242 cases/year), Mozambique (65), and Yemen (63). Average one-way travel distance in these environments exceeded 1,000 km at a cost of nearly $1,000 per referral trip. While some nations (e.g., Nigeria, Egypt, Pakistan) had acceptable case-to-center ratios (50–80 cases/center), others (e.g., Uganda, Tanzania) had possible overcapacity with single-center systems. Genetic testing was accessible in just 24% of nations. **Conclusions:** Despite potential underreporting of more recently established centers, this study reveals profound inequalities in the availability of retinoblastoma care, with most LMICs lacking sufficient essential services. Excessive case volumes within underserved regions overwhelm existing infrastructure and necessitate prompt interventions: (1) focused expansion of Tier 1 hubs within regions of greatest need, (2) streamlining of regional referral chains, and (3) integration of genetic and focal treatments to reduce disparities in survival. Research Sponsor: None.

1526 **Poster Session**

Financial toxicity in early-phase cancer clinical trials: A review of sponsor-supplied information at a large trials unit. First Author: Akul Purohit, The Christie NHS Foundation Trust, Manchester, United Kingdom

Background: Financial toxicity (FT), the objective financial burden and resulting subjective distress experienced by oncology patients, adversely impacts clinical outcomes and access to care. Reimbursement practices between studies vary, possibly exacerbating the lack of representation of people from socioeconomically deprived areas and marginalized groups in early phase cancer clinical trials (EPCCTs). An ASCO roundtable in 2018 emphasized the need for clear details on out-of-pocket costs for trials. Studies in EPCCTs show FT is a recognized problem; however, management of this remains inconsistent. **Methods:** A retrospective portfolio review of open EPCCTs at a large UK cancer centre (Jan-Dec 2025) was conducted to assess reimbursement practices. Sources included informed consent forms (ICFs), contract trial agreements (CTAs) and sponsor provided patient materials. Reimbursement details (including amounts and timelines) were also assessed. **Results:** 64 studies were reviewed, encompassing 41 sponsors (38 industry and 3 academic). Reimbursement was mentioned in ICFs for 62 studies (96.8%) and by 39 sponsors (95.1%). The 2 studies lacking information were academic studies. Specific reimbursable activities were described in 15 studies (23.4%) across 11 sponsors (26.8%). No sponsor included a defined reimbursement timeline in any provided materials. Only 1 sponsor (2.4%) provided additional reimbursement information for patients. Third party vendors for reimbursement were used for 18.8% of studies, with 8 different vendors across 10 sponsors. Reimbursement processes were often detailed in CTAs, with 55 studies (85.9%) outlining specific reimbursable activities. Of 8 academic studies reviewed, 75% listed a maximum budget for each patient to cover the whole study duration (median £350; range £300-£500). Among studies reporting mileage repayment (53; 82.8%), the median rate was £0.45/mile (range £0-£0.45). Median patient travel expense entitlement per visit, where mentioned (55; 85.9%), was £150 (range £40–£700), while refreshment reimbursement was noted in 26 studies (40.6%) with a median value of £15/visit (range £5–£80). The total reimbursement offered per patient per visit was reported in 55 studies (85.9%), with a median of £152.50 (range £40–£1,145). Additional costs covered included reimbursement for carers (9 studies; 14.1%) and unforeseen/inconvenience payments (2 studies; 3.1%). **Conclusions:** Reimbursement terms are regularly specified in CTAs but there is limited inclusion in patient-facing trial documents and lack of flexibility for additional costs. Academic studies restrict reimbursement. Patients may decline clinical studies due to fear of financial toxicity, compounding health inequity. We are partnering with patients to co-develop clearer communication about reimbursement, supporting informed decision-making prior to study enrollment. Research Sponsor: NIHR Manchester Biomedical Research Centre; Roche.

1527 **Poster Session**

Geographic migration patterns of practicing medical oncologists in the United States, 2020-2025. First Author: Jag S. Lally, University of Rochester Medical Center, Rochester, NY

Background: The regional provision of cancer care in the United States (US) remains plagued by disparities along the continuum of screening, diagnosis, and treatment. The geospatial accessibility and migration patterns of medical oncologists may contribute to these disparities. We aimed to assess urban-rural and state-level migration patterns of practicing medical oncologists in the US using national datasets. **Methods:** The Doctors and Clinicians national downloadable file was used as the primary dataset for these analyses. Physician data from August 2020 and August 2025 was used to identify changes in geographic location. The specialties "Hematology/Oncology" and "Medical Oncology" were used to identify oncologists. We utilized Rural-Urban Continuum Codes (RUCC) to classify counties as urban (RUCC 1-3) or rural (RUCC 4-9). If oncologists practiced in multiple states, they were included in all relevant states for these analyses. For categorical variables, the chi-squared test was used for statistical significance. For continuous variables, the two-sample t-test was used for statistical significance. **Results:** There were 12,222 oncologists in 2020 and 13,420 oncologists in 2025. Our final cohort for analysis comprised 10,172 oncologists present in both datasets. 1,233 oncologists (12.1%) began practicing in a new state during this time period. The five states with the largest percentage of oncologists gained from net migration were: Hawaii (10.8%), Montana (6.7%), Vermont (5.5%), Idaho (5.0%), and Nebraska (4.1%). The five states with the largest percentage of oncologists lost from net migration were: Wyoming (-8.7%), West Virginia (-6.2%), Delaware (-6.2%), Alaska (-4.2%), and Arkansas (-4.1%). Female oncologists were more likely to migrate to a new state (12.6%) than male oncologists (11.8%); however, the difference was not statistically significant (p-value = 0.25). The mean number of years since medical school graduation was 25.1 years for oncologists who began practicing in a new state and 28.4 years for oncologists who did not (p-value $<$0.001). Oncologists in rural areas were more likely to migrate to urban areas (N = 492; 48.7%) than oncologists in urban areas were to migrate to rural areas (N = 380; 4.1%; p-value $<$0.001). **Conclusions:** Oncologists in the US exhibit distinct regional and urban-rural migration patterns. Targeted interventions to ensure adequate geospatial supply of physicians should focus on rural areas and states such as Wyoming and West Virginia. Improving understanding of the underlying factors driving oncologist migration patterns is crucial to ensuring a distributed oncology workforce. Research Sponsor: None.

1528 **Poster Session**

Scaling digital patient navigation to improve access to multidisciplinary melanoma care. First Author: Govind Warrier, Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Multidisciplinary (multiD) melanoma care is associated with improved patient (pt) outcomes, yet access is variable due to geographic, informational, and system-level barriers. We previously reported preliminary single-center feasibility of engaging pts using a digital patient navigation platform (DPNP) that provides information about melanoma, cutaneous oncology subspecialists, and clinical trials. We now report results from a multi-site expansion evaluating engagement across academic (Johns Hopkins; JH) and regional health systems (RHS). **Methods:** In this IRB-approved study, adult pts recently diagnosed with melanoma at JH or at a participating RHS were identified monthly using ICD-10 codes. Pts who were not already receiving multiD melanoma care at JH were sent DPNP invitations via their electronic medical record (EMR)-based pt portal. The primary endpoint was clickthrough rate (CTR; % of eligible pts who clicked the link in the invitation), benchmarked against web-based healthcare messaging standards (7%); invitation of $\geq$183 pts per setting was targeted (one-sided 90% CI exceeding benchmark if CTR $\geq$7.5%). Secondary endpoints included conversion rate (registration after clickthrough; benchmark 10%) and subsequent pursuit of multiD melanoma care. **Results:** From Nov 2023 - Dec 2025, 194 eligible pts were identified at JH; from Dec 2024 - Dec 2025, 356 at RHS; all were sent DPNP invitations. CTR: 41% at JH (80/194, 95% CI 34.2%-48.5%), 30% at RHS (106/356, 95% CI 25.1%-34.8%). Conversion rates were 23% (18/80, 95% CI 13.9%-33.2%) and 25% (27/106, 95% CI 17.5%-34.9%), respectively. Of 45 total registrants, 42 (93%) provided demographic data: mean age 59.7 yrs (range 25-83), 55% female, melanoma stage 0-IV. Among 16 JH and 26 RHS registrants, 2 (13%) and 6 (23%), respectively, had high-risk (stage $\geq$II) melanoma warranting a multiD consultation. After registering, 2/2 (100%) and 0/6 (0%) high-risk pts sought multiD care. Median distance to JH was 45 miles and 100 miles for JH and RHS registrants, respectively. **Conclusions:** In this multi-site study, melanoma pt engagement with a DPNP significantly exceeded established benchmarks across academic and RHS, demonstrating scalability of EMR-integrated outreach. However, among pts with high-risk melanoma, transition to multiD care occurred more frequently at the academic center than in RHS, revealing setting-specific barriers to converting engagement into subspecialty care. These findings indicate that while digital navigation can effectively identify unmet need across care environments, patient-initiated pathways alone may be insufficient to close access gaps. In response, we are developing a clinician-facing platform designed to overcome informational and geographic barriers by enabling collaboration between community clinicians and multiD oncology teams, thereby facilitating delivery of subspecialty cancer care closer to home. Research Sponsor: Blackbird Laboratories; 1104Health; Maryland Cigarette Restitution Fund.

1529 **Poster Session**

Trends in biosimilar bevacizumab adoption and Medicare spending by socioeconomic deprivation and rurality, 2019-2023. First Author: Taemin Kim, The Warren Alpert Medical School of Brown University, Providence, RI

Background: Biosimilar bevacizumab has the potential to reduce oncology drug spending, but the equity of its real-world adoption across socioeconomic and geographic contexts remains uncertain. **Methods:** We analyzed Medicare Part B provider-year claims from 2019-2023 for bevacizumab administrations. Biosimilar adoption was defined as the proportion of total bevacizumab services delivered as biosimilars. Neighborhood socioeconomic deprivation was measured using Area Deprivation Index (ADI) quintiles (Q1=least deprived; Q5=most deprived). Rurality was classified using provider-level Rural-Urban Commuting Area (RUCA) codes available in Medicare Part B, with urban defined as RUCA 1-3 and non-urban as RUCA $\geq$4. Adoption patterns were compared using chi-square tests for categorical outcomes and independent t-tests for spending measures. Temporal trends in adoption by ADI quintile were compared using logistic regression with Year $\times$ ADI interaction terms to test whether adoption trajectories diverged over time. Statistical significance was defined as $p<0.05$. **Results:** The study included 11,803 provider-year observations. Biosimilar market share increased from 0.5% of services in 2019 to 61.3% in 2023. In 2023, biosimilar adoption differed significantly by ADI quintile (p=0.0004), ranging from 55.7% in ADI Q4 to 81.3% in the most deprived quintile (Q5), patterns that may reflect institutional purchasing or practice-level factors rather than patient-level access alone. Adoption was higher in urban compared with non-urban areas (62.0% vs 33.6%, p=0.002), despite no baseline differences in 2019. Biosimilars were less expensive than originator bevacizumab in all years (all $p<0.001$). Mean per-administration savings increased from $8.03 (10.3%) in 2019 to $36.4 (52.2%) in 2023 (p=0.001). Originator prices did not differ by ADI in 2023 (p=0.58). **Conclusions:** Biosimilar bevacizumab adoption expanded rapidly and generated increasing Medicare savings, but uptake varied by socioeconomic deprivation and rurality. Differences in adoption, rather than pricing, appear to drive inequities in realized savings. Targeted policy strategies may be needed to promote equitable biosimilar diffusion in oncology care. Research Sponsor: None.

Biosimilar bevacizumab adoption in 2023 by socioeconomic deprivation and rurality.

Category	Biosimilar share of services (%)
ADI Q1 (least deprived)	58.1
ADI Q2	61.1
ADI Q3	61.7
ADI Q4	55.7
ADI Q5 (most deprived)	81.3
Urban	62.0
Non-urban	33.6

1530 **Poster Session**

Patient characteristics, treatment patterns, social determinants of health, and safety in patients prescribed nivolumab and hyaluronidase-nvhy by early adopters. First Author: Lucio N. Gordan, Florida Cancer Specialists & Research Institute, Tampa, FL

Background: Subcutaneous (SC) nivolumab and hyaluronidase-nvhy (nivo + hyal) is approved for administration across most adult solid tumor indications previously treated with intravenous (IV) nivolumab (nivo) and offers substantially shorter administration time (3-5 minutes). While clinical trial data demonstrate comparable efficacy and safety, real-world evidence on early adoption, patient selection, access-to-care considerations, and safety in community oncology settings remains limited. This study provides early real-world insight into the use of SC nivo + hyal in routine clinical practice. **Methods:** This non-interventional, retrospective medical chart review collected routine-care data from Florida Cancer Specialists & Research Institute LLC. Adults receiving $\geq$ 1 dose of nivo + hyal SC or nivo IV in 2025 were included. Follow-up extended from index (first receipt of SC or IV) through last available record, disenrollment, death, or database cutoff. Patient demographics, disease characteristics, treatment patterns, social determinants of health (SDOH; including proximity-to-care measures), and safety outcomes were summarized descriptively. **Results:** Ninety-eight patients were included (SC n=49; IV n=49). Baseline demographic and disease characteristics were comparable between cohorts, include age, sex, performance status, and metastatic disease prevalence. A greater proportion of SC-treated patients resided in suburban settings (45% SC, 37% IV). Mean travel distance to care was greater among SC recipients, with similar median distances and overlapping interquartile ranges; the longest observed travel distance occurred in a patient receiving SC therapy (110 miles vs 33 miles for IV). Treatment patterns were similar between groups; all patients receiving concurrent therapy were treated with oral anti-cancer agents. SC administration was primarily abdominal (90%). Among SC-treated patients, 54% initiated therapy in the first line setting, while remaining use reflected conversion from IV therapy, most commonly following nivo IV + ipilimumab induction, where SC administration is not currently indicated. No new or unexpected safety signals were observed with SC administration compared with IV nivo. **Conclusions:** In this early real-world community oncology analysis, nivo + hyal SC use demonstrated patient characteristics, treatment patterns, and safety comparable to nivo IV. Difference in proximity-to-care measures, including greater variability and longer travel distances among SC recipients, suggest SC administration may support treatment delivery for patients with higher geographic burden. Findings should be interpreted cautiously given the limited sample size but offer early insight into real-world adoption and access considerations for subcutaneous immunotherapy. Research Sponsor: Bristol Myers Squibb.

1531 **Poster Session**

Impact of advanced practice provider–led new consults in community oncology: Expanding access and volume in benign hematology. First Author: Eileen Vella, McKesson Corporation, The Woodlands, TX

Background: Community oncology practices face rising patient volumes and workforce shortages, leading to delays in access to care. Although Advanced Practice Providers (APPs) are increasingly utilized to expand capacity, the structure and impact of APP-led new consult models, particularly in benign hematology, remains unclear. This analysis evaluated the operational and clinical impact of APP-led benign hematology consult programs to determine whether this model improves timely access and supports high-quality, patient-centered care. **Methods:** A retrospective, multi-site analysis was conducted in four community oncology practices within The US Oncology Network that implemented APP-led new consult models in benign hematology. Key performance indicators included total new consult volume, time to first appointment (T2F), percentage of APP visits, and APP engagement. Data were obtained from internal scheduling platforms, productivity dashboards, and operational reports. Pre- and post- implementation comparisons assess changes in access and throughput. **Results:** Across all sites, APP-led consults significantly enhanced access and capacity. In a four-year period at Practice A, median T2F decreased by 50% (24 to 14 days; 36 to 18 days across two regions). During the same timeframe, monthly new consults increased from 208 to 1,045, and total new patient volume rose 403% (2,495 to 12,544). APP participation expanded from 93 to 162 clinicians. In Practice B, APP-led consults increased from 55 (2024) to 406 (2025; 638% YOY growth), with daily new visits rising from 0 to 3 per day and APP share of total practice visits increasing from 0% to 23%. The model generated 295 physician hours saved and reduced T2F for new cancer patients from 8 to 4 days. Physicians and patients expressed confidence and satisfaction with APP new visit care. Practice C grew APP-led consults from 171 (2024) to 235 (2025; 37% YOY growth), increasing APP share of total practice visits from 5% to 23%. Practice D expanded from 2 to 7 visits/day (September 2024 to Oct 2025) with consults rising from 81 to 1,221 (1,407% YOY). APP visit share grew from 6% to 59%, and T2F decreased from 15 days to 7 days. **Conclusions:** APP-led new consult models in benign hematology improved access, operational efficiency, and growth within community oncology settings. By optimizing APP utilization, the model addressed workforce shortages, accelerated time to care, and enabled early triage of patients. Broad APP engagement and sustained growth across diverse settings demonstrates its scalability and impact. Together, these findings support the integration of APP-led new consults as a practical and transformative approach to addressing critical gaps in oncologic care delivery. Ongoing prospective evaluation will further define the model's impact and inform broader adoption of this approach and best practices across the oncology landscape. Research Sponsor: None.

1532 Poster Session

Transportation insecurity and RBC transfusion burden in multiple myeloma and related plasma cell disorders in New Mexico: A CRIIS statewide analysis (2013-2019). First Author: Altamash Jawadi, The University of New Mexico School of Medicine Department of Internal Medicine, Albuquerque, NM

Background: Multiple myeloma (MM) and related plasma cell disorders are commonly complicated by anemia requiring red blood cell (RBC) transfusion. In geographically large and predominantly rural states such as New Mexico, transportation insecurity may contribute to fragmented outpatient access and downstream supportive care burden. Using statewide oncology informatics data, we characterized RBC transfusion utilization patterns and their association with county-level vehicle access. **Methods:** Using the Cancer Research Integrated Informatics System (CRIIS), a novel statewide oncology informatics platform, we identified patients with MM and related plasma cell disorders (including Waldenström macroglobulinemia and plasma cell leukemia) receiving care from 2013-2019. We performed a repeated cross-sectional county-level analysis, using county-year as the analytic unit. Transportation insecurity was defined as the percent of households without vehicle access and summarized using the median county value across 2013-2019 due to minimal year-to-year variability. Counties were categorized as higher versus lower transportation insecurity using a median split. The primary outcome was receipt of ≥1 RBC transfusion within a calendar year, summarized at the county level. **Results:** Among 2,436 patients statewide, 614 (25.2%) received ≥1 RBC transfusion. Annual transfusion utilization increased from 15.0% in 2013 and stabilized at ~25-30% thereafter. Median county transportation insecurity ranged from 0% to 12.8%. Across multiple years, counties with higher transportation insecurity accounted for a disproportionate share of statewide transfusion burden relative to patient volume (~1.3-1.5-fold higher absolute transfusion burden). Transfusion burden was concentrated in a subset of counties, with Bernalillo contributing the largest share, while several smaller counties demonstrated high transfusion rates despite low total patient volume. Transfusion delivery remained concentrated in access-rich counties, consistent with regional centralization of oncology supportive care. **Conclusions:** In this statewide real-world analysis, RBC transfusion burden in MM and related plasma cell disorders clustered disproportionately among residents of transportation-insecure counties. Transportation insecurity may serve as a pragmatic structural marker to identify regions bearing elevated supportive care burden and supports collaborative evaluation of transportation-focused care delivery strategies to improve equity across rural and underserved communities. Research Sponsor: None.

Statewide cohort size and RBC transfusion utilization by year.

Year	Total Patients	Transfused Patients	Transfusion Rate (%)
2013	240	36	15.0
2014	238	49	20.6
2015	301	67	22.3
2016	373	109	29.2
2017	411	118	28.7
2018	427	107	25.1
2019	446	128	28.7
Total	2,436	614	25.2

1533 Poster Session

Neighborhood social vulnerability and clinical trial enrollment in colon cancer: Does age matter? First Author: Shannon S. Yoo, Rutgers Robert Wood Johnson, New Brunswick, NJ

Background: Colorectal cancer is now the leading cause of cancer-related death in people under 50, and young adults living in poverty have increased mortality. Despite younger age being associated with higher clinical trial enrollment, young adults face distinct social and structural barriers that may impede participation. This study examines how neighborhood social vulnerability is associated with clinical trial participation for colon cancer in young and older adults. **Methods:** Patients diagnosed with colon cancer were identified in the nationally representative Vizient Clinical Database from January 2022 – June 2025 and stratified into young adult (age 18-49) and older adult (50 and above) cohorts. The outcome of interest was clinical trial enrollment, identified by billing codes. Social vulnerability was defined by the Vizient Vulnerability Index in quartiles at the census tract level. Multivariable analyses were performed in both cohorts. An interaction analysis was performed between age and social vulnerability. **Results:** Of 234,047 patients, 15% were young adults, of which 5.1% enrolled in a clinical trial. Eighty-five percent were older adults, of which 3.0% enrolled in clinical trials. Most young adults had private insurance (73.1%) while most (56.6%) of the older patients were enrolled in Medicare. Non-Hispanic (NH) Black patients were less likely to enroll than NH White patients in both the young adult (OR 0.72, p=0.0001) and older adult cohorts (OR 0.79, p<.0001), as were young and older patients with Medicaid vs. private insurance (OR 0.75, p=0.0001 and OR 0.71, p<.0001, respectively). Diagnosis at an academic medical center vs. community hospital increased the odds of enrollment for both groups: young (OR 2.79, p<.0001) and older (OR 2.04, p<.0001), as did being married vs. single: OR 2.31, p=0.0016 for younger and OR 1.85, p<.0001 for older adults. Among older adults only, Hispanic patients (OR 0.87, p=0.0056; ref NH White) and female patients (OR 0.91, p=0.0002; ref male) were less likely to enroll. Living in the most vs. least socially vulnerable neighborhoods impacted trial enrollment more for young adults (OR 0.75, p<.001) than for older adults (OR 0.91, p<.0001), p= 0.0042 for interaction. **Conclusions:** Many factors that influence trial enrollment, including insurance, social support, diagnosis at an academic center, and race/ethnicity, are similar among young and older adults with colon cancer. However, the negative impact of neighborhood disadvantage on trial enrollment is more pronounced among young adults, highlighting the need for practical trial design, targeted navigation, and strategic recruitment of young adults living in socially vulnerable areas. Research Sponsor: None.

1534 Poster Session

Accessibility of study contact information in ClinicalTrials.gov: A comprehensive analysis. First Author: Fangdi Sun, Stanford University, Stanford, CA

Background: While the official purpose of ClinicalTrials.gov is to satisfy regulatory requirements from the U.S. Food and Drug Administration meant to safeguard human subjects, the database also serves as the most comprehensive record of ongoing clinical trials for patient and provider use. Previous studies have focused on compliance with results reporting and completeness of information within restricted subsets of the database. Taking the perspective of a potential participant or their provider, the purpose of this study was to assess the accessibility of ClinicalTrials.gov contact information across actively recruiting oncology and non-oncology studies. **Methods:** This study included all actively recruiting interventional studies listed in the ClinicalTrials.gov database as of June 11, 2025. We assessed the completeness of location and contact information by multiple factors including oncology versus non-oncology study, sponsor type, trial phase, study start date, and date of last posted update. Within oncology studies, we further analyzed information availability by disease subsite. **Results:** We identified 47,703 actively recruiting interventional trials, among which 12,400 (26.0%) pertained to oncology. Within these oncology studies, 3178 (25.6%) had an industry sponsor, 9729 (78.5%) had a study phase listed (among which 59.4% were Phase 2 studies), and 4311 (34.8%) involved an FDA-regulated drug. Across both oncology and non-oncology studies, 2678 (5.6%) were missing any central contact information. While all trials had at least one study location listed, 3492 (7.3%) did not include a location-specific contact name and 9994 (21.0%) had neither a location-specific contact phone nor email address (24.1% for oncology, 19.8% for non-oncology). Within oncology trials, 50.9% of studies with an industry sponsor lacked any location-specific contact phone or email, compared to 11.3% for NIH sponsors and 14.9% for other (including academic) sponsors. Completeness of location-specific contact information was similar across trial phases. By oncology disease subsite, thoracic trials (29.8%) or those including multiple disease subsites (33.8%) most often lacked location-specific contact phone and email, whereas head and neck (15.4%) and neuro-oncology (16.3%) trials were least likely to do so. **Conclusions:** Location remains a primary means by which many potential trial participants filter clinical trial opportunities. Missing location-specific contact information, particularly among trials with industry sponsors, is an area of potential improvement that could be addressed by increased attention or more stringent registration requirements. While emerging strategies to improve clinical trial accessibility include artificial intelligence-powered platforms, these are only as good as the primary data on which they are built. Research Sponsor: None.

1535 Poster Session

Hospital designation and survival disparities in young-onset gastrointestinal cancer. First Author: Mrinalini Ramesh, University at Buffalo, Buffalo, NY

Background: Early-onset gastrointestinal (GI) cancers (<50 years) are increasing in incidence. We examined the impact of National Cancer Institute (NCI) designation and academic affiliation on mortality and care delivery for young-onset GI cancer patients in New York State. **Methods:** We performed a retrospective analysis using the Statewide Planning and Research Cooperative System (SPARCS) database from 2009 to 2024. Patients were stratified by admission type (emergency vs elective) and hospital site (NCI vs non-NCI; academic vs community). GI cancers included anal, biliary, colorectal, esophageal, gallbladder, liver, pancreatic, peritoneal, small intestine, and gastric cancers. Clinical characteristics were defined using the All Patient Refined grading system. Academic hospitals were classified via the Association of American Medical Colleges Database. Wilcoxon rank-sum tests compared continuous variables; Chi-squared or Fisher's exact tests for categorical variables. Linear regression was performed for continuous outcomes, and multinomial logistic regression for categorical outcomes, with significance at $P \leq 0.05$. **Results:** A total of 29,753 young-onset GI cancer patients were included, of which 48.7% were emergency admissions. For emergency admissions, NCI sites treated patients with higher illness severity, and most had private insurance (P<0.001). There was no significant difference in length of stay (LOS) between NCI and non-NCI sites. Cost of treatment was significantly higher at NCI sites (P<0.001), which also performed more procedures (P = 0.002). NCI sites were associated with 36% lower odds of in-hospital mortality (OR=0.64 [0.55-0.75], P<0.001) despite higher illness severity. For elective admissions, in-hospital mortality was 0.5% at NCI sites vs 7.3% at non-NCI sites (OR=0.04 [0.03-0.05], P<0.001). For emergency admissions, academic sites treated patients with higher illness severity, and most patients had private insurance (P<0.001). Admission to an academic site was associated with increased LOS (β=0.03 [0.02-0.05], P<0.001). Cost of treatment was significantly higher at academic sites (P < 0.001), which performed more procedures (P <0.001). No significant difference in mortality was seen between academic and community sites. For elective admissions, in-hospital mortality was 0.5% at academic sites vs 5.8% at community sites (OR=0.08 [0.06-0.11], P<0.001). Across all hospitals and admission types, private insurance was independently associated with shorter length of stay (P<0.001). **Conclusions:** Treatment at NCI-designated centers for both emergent and elective admissions was associated with significantly lower in-hospital mortality among young-onset GI cancer patients despite higher illness severity. Insurance-based disparities highlight the need for interventions to ensure equitable access to high-quality cancer care for this vulnerable population. Research Sponsor: Roswell Park Cancer Institute; National Cancer Institute (NCI) grant; P30CA016056.

1536 **Poster Session**

Transportation access as a structural determinant of quality of life and symptom burden among cancer patients. First Author: Hailey Ivanson, Keck School of Medicine of University of Southern California, Los Angeles, CA

Background: Growing evidence links the built environment to cancer outcomes, with NCCN recommendations emphasizing the importance of transit access in cancer care. Cancer patients, especially at advanced ages, are vulnerable to inadequate transit access due to frequent medical appointments and treatment-related physical and financial toxicity. This study examined the relationship between public transit access, quality of life (QoL), pain, and fatigue among adults with cancer. **Methods:** We analyzed data from 31,126 adults with cancer enrolled in the NIH All of Us cohort, which is designed to include populations historically underrepresented in biomedical research. Cancer cases were identified using ICD and SNOMED codes. Multivariable ordinal logistic regression was used to assess associations between distance to public transit and self-reported QoL, pain, and fatigue adjusted for age, sex, race/ethnicity, income, education, and insurance. Similar models examined sociodemographic predictors of transportation-related healthcare delays. **Results:** Decreased public transit access was associated with worse QoL, pain, and fatigue (Table 1). Transportation-related delays in care were more likely among older adults aged 65+ (aOR=0.30, p=0.02) compared to 18-25 year olds; women (aOR=1.13, p=0.03); unemployed individuals (aOR=1.13, $p<0.001$); and those with lower income (aOR=7.60, $p<0.001$). Participants identifying as Black (aOR=1.65, $p<0.01$), Hispanic (aOR=1.27, $p<0.01$), or multiracial (aOR=1.73, $p<0.01$) also reported higher odds of transportation-related delays. **Conclusions:** Reduced public transit access is associated with worse quality of life, symptom burden, and care delays among adults with cancer. Providers can utilize transportation coordination as a tool for improving patient outcomes, particularly in the functional domains of pain and fatigue and among underserved populations. Further, policymakers should identify and address gaps in public transit access, yielding downstream benefits for population health, quality of life, and survivorship among cancer patients. Consideration for transportation should be integrated into treatment plans for all cancer patients to reduce financial toxicity and treatment costs while improving outcomes. Research Sponsor: National Institutes of Health, Office of the Director.

Adjusted odds of worse health outcomes by decreased transit access: Adjusted association between public transit access and pain, fatigue, and quality of life among adults with cancer.[a]

Outcome	aOR (95% CI)[b]	P-value
Low Quality of Life	1.09 (1.00, 1.19)	0.04*
Moderate/High Pain	1.12 (1.06, 1.18)	<0.001****
Moderate/High Fatigue	1.14 (1.08, 1.20)	<0.001****

[a]Adjusted for age group, sex, race/ethnicity, employment, income, insurance.
[b]Public transit stop >15 minutes away.
*$p < 0.05$, ****$p \leq 0.001$.

1537 **Poster Session**

Travel time to cancer care as it relates to care access, transportation distress, and financial toxicity: Findings from the Cancer Experience Registry. First Author: Erica Fortune, Cancer Support Community, Washington, DC

Background: Longer travel time to cancer care has been linked to worse prognosis and quality of life for patients. This study aims to examine how travel time to cancer care is associated with access to care, transportation-related distress, and financial toxicity. **Methods:** Participants in Cancer Support Community's Cancer Experience Registry (CER) from Oct 2021-Dec 2025 reported sociodemographic and clinical information, financial toxicity (11-item FACIT-COST), travel time to cancer care (min/hr), transportation-related distress (1=*not at all* to 5=*very seriously concerned*), and delays/barriers to accessing cancer care (yes/no). Descriptive findings and between-groups analyses (Chi-square) are presented. **Results:** 3,590 U.S. adults (75% women; 82% non-Hispanic (NH) White, 7% NH Black, 5% Hispanic/Latino, 5% multiple or other races; 18-95 years old [Mean=62.2, SD=13.1]) reported various cancer diagnoses (34% breast, 25% blood, 10% colorectal, 7% gynecologic, 25% other), with 54% in remission/NED, 18% localized, and 15% metastatic (time since diagnosis Median=3yrs). FACIT-COST indicates 52% with no financial toxicity, 26% mild, 20% moderate, and 2% severe financial toxicity (M=24.9, SD=12.0). For travel time, 67% of participants reported < 1hr, 23% 1–2hrs, 7% 3–4hrs, and 4% 5+hrs. 79% reported no transportation distress, while 10% were slightly concerned and 12% moderately to very seriously concerned. Over one-quarter (29%) reported ever experiencing a delay in cancer care. Among patients traveling <1hr to their care center, 24% reported experiencing delays/barriers, compared with 46% of those traveling 5+hrs (χ^2=84.3, $p<.001$). Similarly, transportation-related distress increased with travel time: 84% of patients traveling <1hr reported no concern, whereas only 60% of those traveling 5+hrs reported no concern, with 29% reporting moderate to very serious concern (χ^2=167.9, $p<.001$). Lastly, financial toxicity increased with travel burden: 43% of patients traveling <1hr reported mild-to-severe financial toxicity versus 64% of those traveling 5+hrs (χ^2=63.7, $p<0.001$), and 85% of those reporting moderate to severe transportation distress also reported at least mild financial toxicity (χ^2=388.4, $p<0.001$). **Conclusions:** Most patients surveyed reported living within 1hr of their care site and experienced little transportation distress; however, those who travel longer distances for care report higher rates of delays/barriers, greater transportation-related distress, and more financial toxicity. Collectively, these findings underscore that longer travel times are linked to both objective barriers and subjective distress, highlighting that travel burden may limit timely cancer care and worsen patient outcomes. Policy solutions that bring quality care closer to patients are essential to reduce travel burdens and distress. Research Sponsor: Genentech; Bristol Myers Squibb.

1538 **Poster Session**

Exploring transportation insecurity among cancer patients in urban cancer clinics in Ontario, Canada. First Author: Clarissa Skorupski, University of Toronto, Toronto, ON, Canada

Background: Advancements in cancer therapeutics have led to increasing care complexity, higher visit frequency, and increased economic burdens for many patients undergoing cancer treatment. Emerging data suggests that transportation challenges may have an important, and uneven impact on the delivery of cancer care. We completed a cross-sectional survey to better understand the prevalence and impact of transportation insecurity in cancer clinics serving a diverse urban and inner-city patient population in a public-payor system. Objectives: The Care for All Health Equity Pilot aims to explore the barriers that patients experience when engaging with cancer treatment. In a pilot exploratory analysis we identified transportation insecurity as associated with missed oncology appointments. The objectives of this study were to explore factors associated with higher level of transportation insecurity amongst our patient population. **Methods:** A cross-sectional survey on patient demographics, financial toxicity (COST tool), transportation challenges, housing and food insecurity was delivered to all adult patients attending cancer clinics at two major urban centres in Toronto, Ontario from July – August 2025. We conducted an exploratory, descriptive, and bivariate analysis of factors correlated with higher levels of transportation insecurity amongst survey respondents. **Results:** 576 patients completed the survey, 48.6% of whom identified as female. 44.8% and 25.0% of respondents had solid tumour or malignant hematologic diagnoses respectively. The most common diagnoses were breast cancer (18.8%), and lymphoma (10.8). Nearly a third (28.8%) of survey respondents endorsed stress related to accessing and paying for transportation to and from their medical appointments. The most common transportation-related stressors preventing patients from attending appointments were parking/travel expenses (26.7%), and the ability to locate accessible parking (13.9%). In an exploratory bivariate analysis patient age, non-English preferred language, access to a personal vehicle, self-identifying with a disability, and living alone emerged as correlates for transportation insecurity. **Conclusions:** Health-related transportation insecurity is common, impacting nearly a third of adult cancer patients receiving care at major urban cancer clinics in a public-payor system. Transportation related costs, and lack of accessible parking, are key contributors to transportation related stress. A multivariate analysis exploring the impact of transportation insecurity on missed oncology appointments, and healthcare utilization, is underway and further information will be available at the meeting. Research Sponsor: Academic Health Sciences Center (AHSC) Alternate Funding Plan (AFP) Innovation Fund.

1539 **Poster Session**

Access to trastuzumab deruxtecan for HER2-low metastatic breast cancer in Brazil's Unified Public Health System: A population-impact model. First Author: Angela Theresa Zuffo Yabrude, Universidade Regional de Blumenau, Blumenau, Santa Catarina, Brazil

Background: HER2-low disease has recently emerged as a distinct, targetable category in metastatic breast cancer (MBC), with trastuzumab deruxtecan (T-DXd) demonstrating a clinically meaningful overall survival (OS) benefit. In Brazil, however, access to innovative oncology therapies within the Unified Health System (SUS) is frequently delayed. We quantified the population-level consequences of delayed access to T-DXd for patients with HER2-low MBC. **Methods:** We conducted a nationwide population-impact analysis from the public-payer perspective, combining Brazilian epidemiologic data with survival benefit estimates derived from randomized clinical trials, using an exponential approximation to model long-term outcomes under delayed-access scenarios. An annual eligible cohort was constructed stepwise from incident MBC (21,133/year), applying: SUS dependence (proxy: 1 - private coverage, p=0.759), HER2-low prevalence (p=0.320), HR+ proportion among HER2-low (proxy using luminal status, p=0.747), and probability of reaching the eligible line of therapy (p line=0.50). Treatment effect inputs were taken from the DESTINY-Breast04 HR+ subgroup (median OS 23.9 vs 17.5 months. OS HR=0.64 [95% CI 0.48–0.86]). Primary outcome was preventable deaths/year, computed as treated/year $\times$ (1 $-$ HR), where treated/year equals the annual eligible cohort multiplied by uptake (95%, 75%, 50%). A sensitivity range for preventable deaths was generated by varying HR across its trial-reported 95% CI. Life-years gained over 10 years were estimated as treated/year $\times$ 10 $\times$ Δmedian OS (years). One-way sensitivity varied p (HER2-low) from 0.25 - 0.46 (uptake fixed at 95%). **Results:** The modeled annual eligible cohort was 1,917 patients/year, treated/year was 1,821 (95% uptake), 1,438 (75%), and 959 (50%). Estimated preventable deaths/year were 656 (range 255-947), 518 (201-748), and 345 (134-498), corresponding to 6,560, 5,180, and 3,450 deaths avoided over 10 years, respectively. Life-years gained over 10 years were 9,713, 7,668, and 5,112 across the three uptake scenarios. Varying p(HER2-low) from 0.25-0.46 yielded 513-943 preventable deaths/year and 7,588-13,962 life-years gained (10 years) at 95% uptake. **Conclusions:** Delayed access to T-DXd within Brazil's public health system may result in substantial, avoidable mortality among patients with HER2-low MBC. These findings highlight the urgent need for accelerated incorporation pathways, consistent HER2-low testing, and operational readiness to translate proven survival gains into real-world benefit. Research Sponsor: None.

Scenario	Uptake	Treated/ year	Preventable deaths/year	Range (HR 95% CI)	Life-years gained (10 years)
Base-case (95%)	95.0%	1,821	656	255 – 947	9,713
Moderate (75%)	75.0%	1,438	518	201 – 748	7,668
Conservative (50%)	50.0%	959	345	134 – 498	5,112

1540 Poster Session

Geographic accessibility of recruiting clinical trials for rare and common gastrointestinal malignancies in the United States. First Author: Rahul Kumar Thakur, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Gastrointestinal (GI) cancers account for substantial cancer mortality, with rare GI malignancies experiencing particularly poor outcomes and limited therapeutic options. Clinical trials are essential for treatment development; however, the geographic accessibility of disease-specific trials for rare GI cancers remains insufficiently characterized. **Methods:** We queried ClinicalTrials.gov to identify actively recruiting interventional disease-specific trials for GI cancers in the United States (accessed Jan 2026). Trials were classified as common (colorectal, pancreatic, hepatocellular, gastroesophageal) or rare (anal, appendiceal, small bowel adenocarcinoma, biliary tract) GI cancers. Trial sites were geocoded by ZIP code. Geographic accessibility was defined as the proportion of the U.S. population residing within 30 miles of a recruiting trial site; areas without a site within 30 miles were defined as clinical trial deserts. Urban–rural status and income quartiles were derived from census-based classifications. A 60-mile access definition was evaluated as a sensitivity analysis. **Results:** A total of 283 disease-specific GI cancer trials encompassing 1,322 unique U.S. trial site ZIP codes were included. More than 80% trials were early-phase (Phase I–II). Using a 30-mile access definition, overall population coverage was 83.6%, with lower coverage in rural versus urban populations (47.5% vs 90.9%) and in the lowest vs highest income quartiles (65.8% vs 98.0%). Common GI cancers had broad access, including colorectal cancer (80.2% population coverage) and pancreatic cancer (75.3%). In contrast, more than half of the population resided in a clinical trial desert for rare GI cancers (biliary tract = 55.2%, small bowel = 56.4, anal cancer= 80.8%, appendiceal 99.5%). Over 75% of rural residents resided in trial deserts for any rare GI cancer. Findings were consistent using a 60-mile access definition. **Conclusions:** Geographic accessibility remains a major barrier for disease-specific clinical trials of rare GI malignancies. This results in extensive clinical trial deserts and perpetuates existing disparities for rural and lower-income populations. These findings highlight structural gaps in trial availability and support the need for more geographically inclusive trial designs. Research Sponsor: None.

Geographic access to disease-specific gastrointestinal cancer clinical trials.

Cancer type	Trials(N)	Trial site ZIP (N)	% Pop ≤30 mi	%Pop in trial desert	%Rural Pop in trial desert	%Lowest income quartile in trial desert
Common						
Colorectal	82	1,026	80.2	19.8	59.2	38.5
Pancreas	75	730	75.3	24.7	67.1	45.1
Gastroesophageal	46	684	71.9	28.1	69.1	49.8
Hepatocellular cancer	45	210	54.7	45.3	93.2	64.5
Rare						
Biliary tract cancer	28	109	44.8	55.2	95.1	70.3
Small bowel adenocarcinoma	2	419	43.6	56.4	77.5	67.2
Anal	5	19	19.2	80.8	99.1	86.6
Appendicular	1	1	0.5	99.5	99.9	99.7

1541 Poster Session

Validation of prognostic scores in Hispanic patients with advanced solid tumors enrolled in a single-center phase I clinical trial program. First Author: Darin Poei, University of Southern California/Los Angeles General Medical Center Hematology and Medical Oncology Fellowship Program, Los Angeles, CA

Background: Prognostic scores are commonly used to guide enrollment in early-phase oncology trials. Despite their widespread use, these models have not been specifically evaluated in Hispanic patients, to the best of our knowledge — a population historically underrepresented in clinical trials. We evaluated the predictive performance of the Royal Marsden Hospital (RMH) score, the Princess Margaret Hospital Index (PMHI), and the MD Anderson Cancer Center (MDACC) score in a cohort of Hispanic patients with advanced solid tumors enrolled in phase I clinical trials. **Methods:** We performed a retrospective chart review of Hispanic patients with advanced solid tumors enrolled in phase I clinical trials at USC Norris Comprehensive Cancer Center and its affiliated safety-net institution, Los Angeles General Medical Center, between 2015 and 2022. Prognostic scores were calculated using the established criteria: RMH score (albumin <3.5 g/dL, LDH $>$ ULN, >2 metastatic sites), PMHI (albumin <3.5 g/dL, ECOG >0, >2 metastatic sites), and MDACC score (albumin <3.5 g/dL, LDH $>$ ULN, ECOG >0, >2 metastatic sites, gastrointestinal tumor type). RMH and PMHI risk groups were categorized as low (0–1 points) or high (2–3 points), while MDACC risk groups were defined as low (0–1 points), intermediate (2–3 points), or high (4–5 points). Overall survival (OS) was analyzed using Kaplan–Meier methods. **Results:** A total of 191 Hispanic patients were included (109 gastrointestinal, 36 lung/head and neck, 20 other, 16 gynecologic, 6 genitourinary, 4 breast). Median age was 59 years (25–86). The median OS for this cohort was 13.1 months (95% CI, 8.8-18.3). Significant differences in OS were observed across prognostic risk groups for all three prognostic scores. Median OS for RMH high- versus low-risk patients was 5.1 versus 18.3 months (p=0.004); for PMHI high- versus low-risk patients, 6.5 versus 20.0 months (p=0.002); and for MDACC high-, intermediate-, and low-risk patients, 4.1, 15.7, and 32.7 months, respectively (p=0.007). **Conclusions:** In this Hispanic solid tumor phase I trial population, higher RMH, PMHI, and MDACC scores were associated with poorer overall survival. These findings support the use of established prognostic scores in Hispanic patients for identifying candidates with poor prognosis and informing early-phase trial enrollment. Prospective studies are warranted to further validate prognostic scores in the Hispanic population. Research Sponsor: None.

RMH	Median OS (Months)	PMH	Median OS (Months)	MDACC	Median OS (Months)
Low (0-1)	5.1	Low (0-1)	6.5	Low (0-1)	4.1
High (2-3)	18.3	High (2-3)	20.0	Intermediate (2-3)	15.7
				High (4-5)	32.7
	p=0.004		p=0.002		p=0.007

1542 Poster Session

Breaking barriers: Evaluation of a low-threshold community-based HPV vaccination model for gender minorities and sex workers in Milan. First Author: Nicla Maria La Verde, Department on Oncology, Luigi Sacco Hospital, ASST Fatebenefratelli Sacco, Milano, Italy

Background: Human Papillomavirus (HPV) is the primary etiological factor for anogenital and oropharyngeal cancers. Sexual and gender minorities (SGM) and sex workers (SW) face an increased risk of HPV-related diseases but encounter significant barriers to vaccination, including stigma, discrimination in healthcare settings, and low risk perception. "VaccinaMILAN*" is a community-based initiative designed to enhance vaccine accessibility by offering the first dose of the 9-valent vaccine in safe and inclusive environments, such as Milan's "rainbow" districts during weekend evening hours. This study assessed the demographic characteristics, risk factors, and barriers within this hard-to-reach population. **Methods:** An anonymous paper-based questionnaire was administered to participants vaccinated during the May and October 2024 editions of VaccinaMILAN*. The survey evaluated demographics, gender identity, sexual behaviors, HPV knowledge, vaccination barriers, and satisfaction with the community approach. Categorical variables were described using frequencies and percentages; data were analyzed using Chi-square tests (two-tailed p-value < 0.05). **Results:** 320 questionnaires were collected (response rate: 76.2%). Most respondents were under 35 years old (68.7%) and held a university degree (65.9%). The sample primarily consisted of cisgender MSM (76.9%), followed by cisgender female SWs (13.4%) and gender minorities (9.8%). Despite a high prevalence of receptive anal intercourse (61.7%), 95.4% had never undergone anal cancer screening. HPV knowledge was significantly higher among younger participants (p = 0.0063) and university graduates (p = 0.0169). Reported barriers included: 45.7% did not know how to access vaccination; 25.4% did not perceive themselves at risk; approximately 20% had previously experienced vaccination refusal in traditional healthcare settings. Overall, 99.7% expressed satisfaction with the initiative. **Conclusions:** The VaccinaMILAN* project demonstrates the effectiveness of a multidisciplinary community-based approach in improving vaccine equity for marginalized populations. The findings highlight the urgent need for targeted awareness campaigns and specific training for healthcare providers regarding HPV vaccination and anal cancer screening recommendations for these populations. Research Sponsor: None.

1543 Poster Session

Participation of older adults (aged ≥65 years) in SWOG cancer clinical trials. First Author: Jyotsana Parajuli, The University of North Carolina at Charlotte, Charlotte, NC

Background: Cancer disproportionately affects older adults. Approximately 60% of cancer diagnoses occur in adults aged 65 and older in the United States. However, disparities persist in participation of older adults in cancer clinical trials. **Methods:** Using 38 years of data from phase III trials of the SWOG Cancer Research Network between 1985 to 2022, this study examined clinical, socio-demographic, and trial factors associated with participation of older adults (≥65 Years) in cancer clinical trials. Summary statistics were used to describe patient and trial characteristics. To examine factors associated with enrollment of older adults, mixed-effects multivariate logistic regression was performed with the odds of being an older adult (≥65 years) as the dependent variable. **Results:** A total of 45,670 patients accrued to 64 SWOG phase III trials were included in the analysis. Across all trials, 30.6% participants were aged 65 and older, and 57.8% were female. Participants were predominantly non-Hispanic (96.2%) White (87.4%) and most resided in urban areas (82.4%). Regression analysis results showed that adjusted odds of enrollment as an older adult did not differ statistically significantly by cancer stage or intervention type (targeted therapy, immunotherapy, hormonal therapy, chemotherapy, radiation, or surgery). Compared with breast cancer trials (reference group with the lowest proportion of older adult enrollment), the odds of enrolled participants being older adults were higher in gastrointestinal cancer trials (OR=3.39), lung/thoracic cancer trials (OR=3.24), and genitourinary/prostate cancer trials (OR=6.77). Compared with White participants, Black participants (OR=0.64) and Asian/Pacific Islander (OR=0.64) had lower adjusted odds of being older adults. The odds of being aged ≥65 years were nearly twice as high among non-Hispanic participants compared with Hispanic participants (OR=1.85). Participants from rural areas had higher adjusted odds of being aged ≥65 years than those from urban areas (OR=1.10). No statistically significant differences were observed across Area Deprivation Index (ADI) quartiles. **Conclusions:** Although some progress has been made in the participation of older adults in cancer clinical trials in the past decades, more work needs to be done to enhance their participation (especially those belonging to underrepresented groups) in cancer clinical trials. Tailored and targeted recruitment efforts are needed to improve participation of diverse older adults in cancer clinical trials. Research Sponsor: Hope Foundation for Cancer Research.

1544 **Poster Session**

Time to treatment initiation for triple-negative breast cancer in Brazil: A call for public health action. First Author: Fernanda Madasi Pinheiro, Instituto Nacional de Câncer, Rio De Janeiro, Brazil

Background: Timely initiation of treatment is a critical determinant of outcomes in breast cancer. In Brazil, national legislation mandates treatment beginning within 60 days of histopathological diagnosis. Adherence to this interval may be particularly relevant in triple-negative breast cancer (TNBC), an aggressive subtype associated with rapid disease progression and poor prognosis. **Methods:** Data were collected from patients (pts) diagnosed with primary TNBC, stages I-III, treated at two large public cancer centers in Brazil between 2010-2016 and in 2022 and one private oncology network in Brazil between 2020-2023. Treatment delay was defined as an interval ≥60 days. Data were compared between public and private settings. Logistic regression models were used to identify factors associated with treatment delay. **Results:** A total of 1,644 pts were included, 1,347 (82%) in the public and 297 (18%) in the private setting. Pts aged <50 years accounted for 40.3% of those in the public healthcare system and 67.7% of those in the private sector. Patients in the private setting presented with earlier-stage disease (49.5% diagnosed at stage I-IIA vs. 28.1% in the public setting), whereas a higher proportion of stage IIB-III disease was observed in the public setting (71.9% vs. 50.5%; P < 0.001). Treatment initiation beyond 60 days occurred in 75.4% of pts in the public setting, compared with 14.1% in the private setting (P < 0.001). In multivariable logistic regression analysis, factors independently associated with treatment delay included public healthcare service (OR 19.26, 95% CI 13.3–27.9; P < 0.001), older age compared to ≤30 ys, ranging from OR = 2.06 among patients aged 31–39 years (95% CI 1.02–4.16; p = 0.045) to OR = 5.48 among those aged ≥70 years (95% CI: 2.55–11.81; p < 0.001) and earlier stage (I–IIA vs. IIB-III OR = 1.45, 95% CI 1.10–1.91; p = 0.008). **Conclusions:** Rates of treatment initiation beyond 60 days after diagnosis are alarmingly high in the Brazilian public health system, indicating that the 60-day law implementation remains suboptimal. Lower odds of treatment delay among younger patients and those with more advanced disease likely reflect clinical prioritization of individuals with more aggressive or symptomatic presentations. These findings underscore the urgent need for health policy interventions aimed at reducing delays in cancer care, particularly for high-risk subtypes such as TNBC. Research Sponsor: None.

1545 **Poster Session**

Impact of neighborhood socioeconomic deprivation and diet quality on immune checkpoint blockade outcomes. First Author: Anushri Kulkarni, UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Immune checkpoint blockade (ICB) has significantly improved survival across multiple advanced malignancies; however, outcomes remain heterogeneous. While socioeconomic disadvantage (SED) is known to adversely affect cancer outcomes through delayed diagnosis and access to care, impact of SEDupon ICB efficacy remains incompletely characterized. The Area Deprivation Index (ADI) is a validated, neighborhood-level measure of SED. We evaluated the association between ADI and clinical outcomes to ICB across a large, multi-state integrated cancer network. **Methods:** We identified 1,699 adult patients with advanced cutaneous melanoma (CM), renal cell carcinoma (RCC), or urothelial carcinoma (UC) treated with first-line ICB (monotherapy or combination) between 2013–2025 within the UPMC Hillman Cancer Center network (>70 sites across four states). ADI scores were derived from 9-digit ZIP codes at ICB initiation using the Neighborhood Atlas and categorized into quartiles, with higher quartiles indicating greater SED. Primary endpoints were time-to-next therapy (TTNT) and overall survival (OS), measured from ICB initiation to initiation of subsequent systemic therapy or death, respectively. Outcomes were analyzed by ADI quartile using Kaplan–Meier methods and Cox proportional hazards models adjusted for relevant clinical covariates. Analyses were limited to first ICB exposure. **Results:** Across 2,156.3 person-years follow-up, patients in highest ADI quartile experienced a significantly higher incidence of TTNT events compared with lowest quartile (31.1% vs 22.8%; χ^2 p=0.008), without a corresponding increase in deaths (39.2% vs 38.4%; χ^2 p=0.86). Highest ADI status was independently associated with inferior TTNT after first-line ICB in CM (HR 1.51; 95% CI 1.01–2.27; p=0.04), RCC (HR 1.58; 95% CI 1.02–2.45; p=0.04), and UC (HR 2.02; 95% CI 1.11–3.68; p=0.01). Association between ADI status and OS were not statistically significant after adjustment for confounding variables. Univariate and multivariate analyses were performed to control for confounding variables, and confirmed independent prognostic impact of highest ADI quartile upon inferior TTNT. Within a subset of ICB-treated CM patients with available dietary intake data, highest ADI quartile had lowest Healthy Eating Index (HEI) scores (Wilcoxon p=0.01). **Conclusions:** Neighborhood-level SED is associated with inferior durability of response to first-line ICB across multiple solid tumors. These findings suggest that SED may influence ICB effectiveness beyond treatment access alone and underscore the need to identify biologic and care-delivery mechanisms—potentially including diet, comorbidities, and the gut microbiome—through which deprivation impacts ICB outcomes. Prospective, pan-cancer studies integrating social, clinical, and biological variables are warranted. Research Sponsor: None.

1546 **Poster Session**

CancerTrialsBR: An open-access, collaborative platform to improve visibility and access to cancer clinical trials in Brazil. First Author: Felippe Lazar Neto, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

Background: Lack of timely and understandable information is a major barrier for cancer trials recruitment, particularly outside high-income countries. ClinicalTrials.gov (CTGov) has been widely used to address this need, but language barriers and inconsistent identification of research facilities limit its use. Large language models (LLMs) now offer opportunities to address these limitations. We describe CancerTrialsBR, a pilot platform that integrates CTGov, Google Maps (GMaps), and LLMs to provide Portuguese-language geographically contextualized cancer trial information in Brazil. **Methods:** Clinical trials data and listed research sites are retrieved from CTGov on a daily basis with condition as "cancer", location as "Brazil", and status as "recruiting". Using prompt engineering techniques (CoT and few-shot), trial information is processed by LLM to generate a Portuguese brief summary, ideal patient profile, and trial descriptors according to primary site (N=39), treatment settings (N=8, i.e. first-line), and biomarkers (N=18, i.e. PDL1). For each site, its address components (i.e. name, city) are queried through the GMaps API for standardized facility identification. A LLM performs facility-matching validation, and invalid cases are manually reviewed. This enriched database is made available as an open-access clinical research platform of the Brazilian Society of Clinical Oncology since November 4th, 2025 (https://pesquisaclinica.sboc.org.br), where users can suggest real-time status updates. We report facility identification metrics, database statistics, and site interactions since launch. **Results:** Of 2,873 unique CTGov addresses, 654 (22.76%) retrieved zero results from GMaps, of which 612 (93.57%) were subsequently identified by zip code. For the 2,219 GMaps retrieved locations, LLM validation demonstrated an accuracy of 85.78%, with positive and negative predictive values of 96.9% and 59.0%. Overall, only 93 (3.2%) addresses remained unidentifiable after human review. As of January 19th, 2026, the database comprised 272 trials conducted across 191 research facilities, encompassing 22 of 27 Brazilian states and 76 cities. The median (IQR) of clinical trials per facility was 2 (1-9) with 8 facilities hosting 40 trials or more. São Paulo (260/272, 95.6%), Rio Grande do Sul (195/272, 71.6%), and Rio de Janeiro (108/272, 39.7%) had the largest availability of trials. The platform had 2,320 visits from 220 cities within 76 days, and the leading searched cancer was breast. Users feedback resulted in 34 of 57 (59.6%) suggested status updates incorporated in the database. **Conclusions:** CancerTrialsBR demonstrates the feasibility of integrating LLMs and GMaps to deliver accessible, real-time cancer trial information in Brazil, with early adoption highlighting unmet need and offering insights into the country's cancer research infrastructure. Research Sponsor: None.

1547 **Poster Session**

Breast cancer patient navigation to identify individual needs and offer medical and supportive care referrals. First Author: Fernanda Mesa-Chavez, Tecnologico de Monterrey, School of Medicine and Health Sciences, Monterrey, Mexico

Background: Despite evidence that patient navigation (PN) improves access to comprehensive care for patients with breast cancer (BC), its adoption in Mexico remains limited, likely due to multifactorial barriers. To address this gap, our center implemented one of the country's first PN programs to systematically identify and document patients' medical and support needs and provide referrals to appropriate services. This study describes patient needs and referral attendance up to 6 months (m) post-diagnosis. **Methods:** Patients newly diagnosed with BC are identified after their first medical oncology consultation at Hospital Zambrano Hellion TecSalud and are consecutively invited to the PN program, which consists of assessments at baseline, 3m, and 6m. At each timepoint, patients answer validated surveys and target questions to explore their needs. The navigator then shares the results with each patient and refers them to the required specialty or support services. Attendance to baseline and 3m referrals is assessed at 3m and 6m, respectively. This analysis includes patients navigated from 2020-2025. **Results:** 421 patients had reached 6m of follow-up: 357 (85%) and 261 (62%) completed their 3m and 6m navigation, respectively. Median age at diagnosis was 48 years (IQR 41-58). Most were married (76%), and had ≥1 child (84%), higher education (75%), and private healthcare (76%). The most common baseline referrals were to nutrition (86%), psychology (68%), support groups (47%), and wig providers (42%). At follow-up, patients mainly required referral to sexology counseling (3m: 82%, 6m: 79%), nutrition (3m: 78%, 6m: 77%), psychology (3m: 51%, 6m: 39%), and lymphedema counseling/therapy (3m: 40%, 6m: 66%). Attendance was highest to support groups (90-95%), wig providers (64-87%), and geriatric assessment (67-80%). Despite high need, attendance was notably lower for nutrition (47-52%), psychology (58%), and sexology counseling (0%). Main reasons for nonattendance were lack of interest (48%), time constraints (38%), and financial issues (10%). **Conclusions:** In this PN program, referrals were mostly needed for nutrition, sexology, and psychology. While attendance was high for some services, rates were suboptimal for the most common referrals, especially sexology counseling. Efforts to better convey referral rationale and importance may increase uptake and access to comprehensive quality-of-life focused care. Research Sponsor: None.

Patient needs and attendance to referrals.

	Baseline referrals N=421 (%)	Baseline - 3m attendance %	3m referrals N=357 (%)	3m - 6m attendance %	6m N=261 (%)
Nutrition	361 (86)	47	278 (78)	52	202 (77)
Sexology	-	-	291 (82)	0	206 (79)
Psychology	287 (68)	58	181 (51)	58	102 (39)
Support group	197 (47)	90	90 (25)	95	47 (18)
Wigs	175 (42)	87	22 (6)	64	8 (3)
Lymphedema	134 (32)	28	144 (40)	23	171 (66)
Geneticist	126 (30)	69	42 (12)	43	25 (10)
Fertility preservation	78 (19)	52	19 (5)	100	3 (1)
Geriatrics	7 (2)	67	5 (1)	80	5 (2)

1548 Poster Session

Impact of broadening trial eligibility criteria on the inclusion of patients infected with HIV in cancer clinical trials. First Author: Hong Xiao, Fred Hutch Cancer Center, Seattle, WA

Background: In October 2017, an ASCO, Friends of Cancer Research (FoCR), and US FDA (ASCO/FoCR/FDA) task force recommended that common eligibility criteria be modified to make trials more inclusive. We examined whether patterns of HIV-related eligibility criteria changed over time in relation to these recommendations. **Methods:** Trial eligibility criteria were abstracted from ClinicalTrials.gov for any phase, US-based clinical treatment trials for patients with cancer from 2010-2024. Trials were classified as not excluding, conditionally excluding (ie, excluding under specific circumstances such as unstable or untreated cases), or completely excluding patients with HIV. Eligibility criteria were classified using OpenAI language models with prompt refinement and independent validation. Interrupted time series analyses were used to determine whether the recommendations in 2017 were associated with changes in HIV criteria. We also examined whether eligibility-criteria changes varied by phase and lead sponsor (federal vs. industry). **Results:** We evaluated 20,751 trials, mostly phase I-II (80.3%), with 7.8% federally and 40.6% industry funded, including breast (19.1%), lung (11.0%), prostate (16.2%), and colorectal (14.1%) cancers. The AI classification achieved 97% accuracy on the development sample and 94% on an independent validation sample. Overall, patients with HIV were wholly excluded in 28.9%, conditionally excluded in 26.1%, and not excluded in 45.0% of trials. The guidance was associated with an increase in conditional exclusion (13.1% to 29.1%; p<.001) and no exclusion (24.1% to 28.9%; p=.002), and a decrease in wholly exclusion (62.8% to 42.0%; p<.001). Similar shift patterns were observed across trials with different main funding sources (federal vs industry) and phases (I–II vs III) (Table). **Conclusions:** Following the ASCO/FoCR/FDA task force recommendations, HIV exclusion criteria shifted predominantly from complete exclusion to conditional exclusion, indicating progress toward more inclusive clinical trial designs. Acknowledgement: We thank Dr. Roy Burstein, PhD, at the Institute for Disease Modeling, Gates Foundation, for his invaluable advice. Research Sponsor: None.

HIV exclusion criteria before and after the guidance.

	Jan 2010-Oct 2017, No. (%)	Nov 2017- Dec 2025 Without guidance (%)	With guidance (%)	p
All				
C	4175 (48.1)	62.8	42.0	<.001
Cond	1905 (22.0)	13.1	29.1	<.001
N	2597 (30.0)	24.1	28.9	<.001
Federal led				
C	342 (41.5)	41.4	22.3	<.001
Cond	299 (36.2)	36.2	57.2	<.001
N	184 (22.3)	22.3	20.5	0.40
Industry led				
C	1589 (48.7)	61.1	40.2	<.001
Cond	532 (16.3)	12.6	25.5	<.001
N	1141 (34.9)	26.3	32.6	<.001
Phase 1-2				
C	3742 (53.8)	69.3	46.6	<.001
Cond	1622 (23.4)	13.4	30.1	<.001
N	1581 (22.8)	17.3	22.5	<.001
Phase 3				
C	958 (46.3)	52.0	29.1	<.001
Cond	442 (21.4)	10.2	26.2	<.001
N	666 (32.2)	37.8	44.7	0.10

C/Cond/N: completely/conditionally/not excluded.

1549 Poster Session

Impact of a centralized APP-led peer-to-peer program on patient access, provider burden, and institutional revenue. First Author: Sarah J. Bottomley, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Prior authorization (PA) and peer-to-peer (P2P) requirements impose a significant administrative burden on oncology clinicians, contributing to burnout and care delays. At our Comprehensive Cancer Center, internal data showed frontline Advanced Practice Providers (APPs) and oncologists spent unsustainable hours on insurance denials. To mitigate clinical fatigue and optimize workflows, we launched a centralized initiative transitioning P2P responsibilities from frontline clinicians to a specialized APP team. **Methods:** Following a successful pilot project, a centralized P2P program was established for outpatient diagnostic imaging denials. Based on early success, the program expanded to include outpatient medication-related denials. A dedicated APP team utilized standardized workflows, documentation, and formal escalation pathways to manage all outpatient P2P referrals. Program performance was evaluated on these metrics: 1) Access to Care: Measured by completion rate, authorization turnaround time (TAT) and pre-authorized status at arrival. 2) Provider Burden: Assessed by administrative hours reclaimed from frontline staff and qualitatively via a provider satisfaction survey. 3) Institutional ROI: Evaluated via denial overturn rates and net reclaimed revenue from authorized billable services. **Results:** Centralization markedly improved operational efficiency. The program achieved a clear increase in P2P completion rate from 80% provider-led baseline to 99% by centralized team. This coupled with a reduction in TAT for both imaging and medication authorizations, increased the percentage of patients arriving with pre-authorized status by 12% in the first two years. Overturn rates and positive disposition for initial denials rose to 85% or greater compared to the provider-led baseline of 78%. Frontline clinicians reported a substantial decrease in daily administrative tasks, facilitating increased patient-facing hours and improved work-life integration. Financially, the program demonstrated a robust ROI by securing authorization for high-cost services previously denied and providing payer trend data to inform broader managed care strategies. **Conclusions:** Centralizing P2P responsibilities within a dedicated APP team is a multidimensional solution that extends beyond revenue recovery. This model effectively mitigates provider burnout, optimizes patient flow, and protects clinical capacity. As oncology practices face increasing complexity in 2026, this scalable model offers a vital roadmap for balancing financial health with workforce sustainability. Research Sponsor: None.

1550 Poster Session

Operational and clinical drivers of subcutaneous PD-1/PD-L1 inhibitor adoption: A mixed-methods analysis of U.S. oncology practice patterns. First Author: Kimberly Peihsi Ku, Illinois CancerCare, P.C., Bloomington, IL

Background: Subcutaneous (SC) formulations of PD-1/PD-L1 inhibitors have recently been approved across multiple solid tumors. While these agents offer operational and patient-centric advantages, their perceived clinical value relative to established intravenous (IV) formulations remains unclear. Understanding real-world oncologist perceptions may inform future adoption patterns and practice impact. **Methods:** A national mixed-methods study surveyed 102 U.S. hematologist-oncologists from academic (44%, n=45) and community (56%, n =57) practices across all U.S. regions (Nov-Dec 2025). A structured online questionnaire assessed brand utilization, regimen sequencing, physician satisfaction, switching behavior, and perceived comparative benefit between pembrolizumab- and nivolumab-based therapies using Likert-type scales and utilization metrics. All participants met predefined patient volume and clinical practice criteria. Eight qualitative interviews explored drivers of brand choice, sequencing, and switching decisions. **Results:** Across tumor types, oncologists reported modest current use of SC PD-1/PD-L1 inhibitors, with incremental uptake expected over the next six months. SC formulations were viewed as convenience-enhancing rather than clinically transformative, with reduced chair time (75% reporting significant benefit), improved infusion center efficiency (68%), and better patient experience (70%) cited as key benefits. Approximately half of PD-1/PD-L1–eligible patients across NSCLC, melanoma, and RCC were considered suitable for SC administration. Perceived benefit was largely limited to monotherapy and maintenance settings, with limited added value in curative-intent or combination regimens where infusion time is driven by other agents. In NSCLC, projected near-term uptake of SC PD-1/PD-L1 therapy was highest among PD-L1–high patients receiving monotherapy, while in melanoma and RCC, SC was more often positioned later in the treatment sequence, particularly after treatment stability. Insurance coverage (39% reporting a significant barrier) and cost (58%) were the primary barriers to broader adoption, outweighing concerns about safety (22%) or efficacy (27%). Overall uptake was expected to primarily substitute for IV monotherapy rather than expand total PD-1/PD-L1 use. **Conclusions:** U.S. oncologists view SC PD-1/PD-L1 inhibitors as operational alternatives to IV therapy, with adoption driven by efficiency and patient convenience and constrained by payer dynamics. SC administration is best positioned to enhance care delivery in monotherapy and maintenance settings, with limited incremental value in curative-intent or combination regimens. Addressing real-world access barriers will be key to broader integration across solid tumors. Research Sponsor: None.

1551 Poster Session

Patient-reported barriers to treatment access and home delivery in rare cancers across five European countries. First Author: Raymond A. Huml, Sciensus, London, United Kingdom

Background: Patients with rare diseases, including rare cancers, frequently experience barriers to timely treatment access. Sciensus, an end-to-end pan-European service partner, and Rare Patient Voice, a patient-led advocacy organisation, conducted a multicounty, European survey to characterise treatment logistics, delivery models and patient burden, with a focus on implications for oncology populations. **Methods:** A cross-sectional survey was conducted in December 2025 among adult patients with rare diseases, including cancer diagnosis, and caregivers across Italy, the United Kingdom, France, Spain, and Germany. Quantitative and qualitative data were collected on treatment access, medication collection or home delivery, financial and emotional burden, reliability of services, and participation in Early Access Programs (EAPs). Descriptive analyses were performed. **Results:** Among 860 respondents, approximately 120 (14% of total; 28% of validated rare disease responses) reported a cancer diagnosis spanning ~34 cancer types. While most respondents reported infrequent treatment delays, a notable minority experienced frequent disruptions. Over half reported no access to, or lack of awareness of, home delivery services. However, more than 40% indicated that home delivery would significantly or fundamentally improve quality of life. Ratings of homecare reliability varied widely, ranging from very poor to excellent, indicating substantial inconsistency across delivery models and regions. **Conclusions:** Patients with rare cancers in Europe experience fragmentation and heterogeneity across treatment access pathways. Limited awareness, variable availability, and inconsistent reliability of homebased delivery services likely contribute to ongoing burden. Additional longitudinal study of burden should be conducted to confirm the findings of the experiences in this study. Expanding, standardising and systematising patient-centred delivery models represents a key opportunity to improve continuity of care and quality of life for oncology patients with complex needs. Research Sponsor: Sciensus.

1552 **Poster Session**

Advancing health equity in oncology: Virtual collaborative behavioral health engagement and outcomes among Medicaid-insured and BIPOC patients. First Author: Nina Balanchivadze, Sarah Cannon Research Institute, Norfolk, VA

Background: Depression and anxiety are common among patients with cancer, yet access to behavioral health care remains limited, particularly for Medicaid-insured and racially minoritized populations. We evaluated reach, baseline symptom burden, and longitudinal outcomes of a virtual collaborative behavioral health program embedded within community oncology. **Methods:** We conducted a retrospective cohort study of patients referred to a virtual collaborative behavioral health program (Cerula Care) across community oncology practices from 2024–2026. Outcomes included representation of Medicaid-insured and BIPOC patients among those initiating care, baseline symptom burden assessed by PHQ-9, GAD-7, and FACT-G7 stratified by insurance (Medicaid vs commercial+Medicare) and race/ethnicity (BIPOC vs White), and longitudinal symptom change during program participation. Independent t-tests were used for between-group comparisons, and paired t-tests were used for within-patient comparisons. **Results:** Between program launch and data cutoff, 1,400 patients were referred by oncology providers; 850 consented and scheduled an intake, and 631 completed intake and initiated behavioral health care. Among 631 patients initiating behavioral health care, 43.5% identified as BIPOC (36.5% Black) and 18.7% were Medicaid-insured, indicating a strong reach into populations historically underserved by behavioral health services. Baseline symptom severity was significantly higher among Medicaid-insured compared with commercial+Medicare patients across all measures, indicating clinically meaningful greater symptom burden. Baseline severity did not differ by race/ethnicity. Improvements in depression, anxiety, and quality of life were observed over time. Between-group differences in symptom improvement by insurance or race were not statistically significant, though Medicaid-insured and BIPOC patients showed directionally greater PHQ-9 and FACT-G7 improvement, and Medicaid-insured greater GAD-7 improvement. Patient-reported experience indicated high acceptability (Net Promoter Score 88); 60% reported improved oncology visit adherence and 61% improved adherence to non chemotherapy medications. **Conclusions:** Embedding virtual collaborative behavioral health in community oncology was associated with high reach among Medicaid-insured and BIPOC patients. Medicaid-insured patients entered care with greater symptom burden yet experienced symptom improvements comparable to commercially ensured and Medicare patients, with similar outcomes across racial/ethnic groups. These findings support collaborative care as a scalable strategy to expand access to behavioral health services and promote equitable supportive oncology care. Research Sponsor: None.

1553 **Poster Session**

FALCON-Lung: Evolving global real-world treatment choices and outcomes for metastatic NSCLC in different patient populations. First Author: Annelies Verbiest, Antwerp University Hospital UZA, Edegem, Belgium

Background: Despite rapid global adoption of immune checkpoint inhibitors (ICI) for metastatic non–small cell lung cancer (mNSCLC), real-world treatment access, selection, time on treatment and transitions between regimens remain poorly characterized across health systems and patient populations. Whether observed outcomes are consistent across regions, data sources, and age groups is largely unknown. Addressing these gaps at scale requires a federated analytic approach with standardized analyses across sites, enabling reliable and comparable results while preserving patient privacy. **Methods:** We launched FALCON (Federated Alliance for Large-scale Cancer Observational Network), the largest federated, most diverse oncology network supporting observational cancer research, and its subnetwork FALCON-Lung. FALCON-Lung includes 23 sites (hospitals, registries, public-private) providing longitudinal cancer data from 2015 onwards standardized to OMOP common data model, from 11 countries in Europe, US and Australia. All sites completed data quality assessments and targeted improvements to improve completeness and overall cancer data quality. Analyses were executed locally using shared analytic code without sharing patient-level data. **Results:** Among 111,574 NSCLC pts included, 62% developed metastatic disease, of whom 59% initiated antineoplastic drugs within three months; 88% received a guideline-recommended 1st line regimen. ICI uptake rose sharply between 2017 - 2019; by 2022 59% received ICI (± platinum) in 1st line. ICI monotherapy showed a tendency toward longer overall survival (OS) compared with platinum (±ICI), although no single regimen demonstrated a consistent advantage across all databases. OS decreased with age across sites. Patients aged ≥81 years were less likely to receive systemic therapy and, when treated, more often received ICI monotherapy. No clear or consistent differences in OS were observed between different treatment regimens in this age group. **Conclusions:** In this global federated study, ICI uptake showed consistent patterns across sites and regions. OS varied across sites and no consistent survival advantage was observed for ICI regimens, either as monotherapy or in combination, although higher OS with ICI monotherapy was observed in some settings. Older patients (aged ≥81 years) were more frequently treated with ICI monotherapy without a corresponding survival advantage, possibly reflecting real-world treatment selection driven by tolerability rather than biomarkers. Research Sponsor: iCAN.

	Total	18-64y	65-81y	≥81y
NSCLC	111,574	36,239	62,328	13,007
Metastatic NSCLC	68,678	24,059	36,397	8,222
1st line systemic therapy	40,619	15,226	21,397	3,980
1st line guideline-approved systemic therapy	35,560	13,458	18,725	3,361
1st line in 2022 (%)				
ICI monotherapy	17	12	18	32
ICI + platinum doublet	42	43	45	26
Other guideline-approved regimen	41	45	37	43

1554 **Poster Session**

Coverage of subcutaneous versus intravenous oncology therapies by US commercial health plans. First Author: Sophie E. Knox, Center for the Evaluation of Value and Risk in Health at Tufts Medical Center, Boston, MA

Background: Several widely used intravenous (IV) oncology therapies have recently been reformulated for subcutaneous (SC) administration. Compared with IV infusions, SC formulations reduce administration time and chair use, improve patient convenience, and enable more flexible sites of care. At the same time, SC formulations may alter established reimbursement and contracting arrangements, including shifts away from buy-and-bill payment, changes in site-of-care management, and differences in how net costs are realized by payers. We examined how US commercial health plans prioritize SC formulations relative to IV formulations in their drug coverage policies. **Methods:** We used the Tufts Medical Center Specialty Drug Evidence and Coverage (SPEC) Database to identify US commercial health plans with coverage policies for both SC and IV formulations of oncology therapies. SPEC includes detailed treatment access criteria from 17 large US commercial health plans. Coverage policies were current as of December 2025. The unit of analysis was a plan-drug combination, e.g., UnitedHealthcare's policies for trastuzumab. Coverage was classified as *IV preferred*, *on par*, or *SC preferred*, depending on if one formulation is required before another. **Results:** We identified 86 coverage policies across 6 oncology therapies. One payer excluded the SC formulation from coverage in two instances, thereby denying enrollees access to the therapy. Among the remaining 84 policies, 8 (9.5%) were classified as *IV preferred* and 76 (90.5%) as *on par*; no policies classified the SC formulation as preferred (Table 1). Coverage varied across therapies, with the frequency of IV-preferred coverage among payers covering both formulations ranging from 0% to 21%. Among the 76 on-par policies, 55 (72.4%) allowed patients to initiate treatment with either the IV or SC formulation without prior treatment requirements. In contrast, 21 (27.6%) required patients to first try and fail an alternative therapy before coverage for either formulation was granted. These step-therapy requirements were more common for older therapies with available biosimilars, and the required prior therapy was most often a biosimilar of the reference product. **Conclusions:** Across six oncology therapies, most US commercial plans covered SC and IV formulations on par, with a minority preferring IV and none preferring SC. Preferences varied by product, and access restrictions mainly reflected step-therapy requirements for older therapies with available biosimilars. Research Sponsor: National Pharmaceutical Council.

Overview of coverage for intravenous (IV) and subcutaneous (SC) formulations.

Drug	# Payers Covering IV & SC Formulations	SC Only Preferred	Coverage Parity (SC vs IV)	IV Only Preferred
Drug A	16	0	14 (87.5%)	2 (12.5%)
Drug B	15	0	14 (93%)	1 (7%)
Drug C	15	0	14 (93%)	1 (7%)
Drug D	15	0	15 (100%)	0 (0%)
Drug E	14	0	11 (79%)	3 (21%)
Drug F	9	0	8 (89%)	1 (11%)
Total	**84**	**0**	**76 (90.5%)**	**8 (9.5%)**

1555 **Poster Session**

Inpatient financial toxicity among women hospitalized with breast cancer in the United States, 2013–2022. First Author: Fathima Shehnaz Ayoobkhan, Trinity Health Oakland Hospital/Wayne State University, Pontiac, MI

Background: Financial toxicity is an increasingly recognized consequence of cancer care. While the outpatient costs of breast cancer are well described, national trends and drivers of inpatient financial toxicity are not well understood. We evaluated temporal trends in hospitalization volume, inflation-adjusted inpatient charges, and factors associated with high financial toxicity among women hospitalized with breast cancer in the United States. **Methods:** We performed a retrospective analysis of the National Inpatient Sample (2013–2022), including women aged ≥18 years with a breast cancer diagnosis. Survey weights, strata, and clusters were applied. Charges were inflation-adjusted to 2022 USD. High financial toxicity was defined as inpatient charges ≥75th percentile. Temporal trends were assessed using weighted regression, and multivariable survey-weighted logistic regression identified predictors of high financial toxicity. **Results:** An estimated 1.70 million weighted hospitalizations were identified. Annual hospitalizations declined significantly (P for trend <0.001), from 178,660 in 2013 to 168,630 in 2022, with a nadir in 2020. In contrast, mean inflation-adjusted inpatient charges increased by 35.5%, from $58,869 to $79,797 (P for trend <0.001), totaling more than $119.3 billion in cumulative charges. Most hospitalizations occurred at urban teaching hospitals (71.2%). On multivariable analysis, urban teaching (OR 3.84, 95% CI 3.58–4.12) and urban non-teaching hospitals (OR 3.53, 95% CI 3.28–3.79) had nearly four-fold higher odds of high financial toxicity compared with rural hospitals. Compared with White patients, Hispanic (OR 1.53), Asian/Pacific Islander (OR 1.44), and Black patients (OR 1.10) had higher odds. Private insurance (OR 1.14) and residence in the highest income quartile (OR 1.35) were associated with increased odds, while older age was associated with lower odds. Odds of high financial toxicity increased steadily over time, peaking in 2020 (OR 1.58) (P for trend <0.001). **Conclusions:** Despite declining hospitalization rates, inpatient financial toxicity among women with breast cancer has worsened substantially, driven primarily by hospital setting and structural factors. Racial and ethnic disparities were also evident, with minority groups experiencing higher odds of high inpatient charges. These findings underscore the need for value-based strategies and policy interventions to mitigate inpatient financial burden in oncology care. Research Sponsor: None.

1556 Poster Session

Geographic distribution of cancer treatment trials and population-level cancer outcomes in the U.S. First Author: Hong Xiao, Fred Hutch Cancer Center, Seattle, WA

Background: Access to cancer clinical trials varies geographically in the U.S., yet the relationship between trial availability and population-level cancer outcomes is poorly characterized. Understanding this relationship is critical for policymakers and trial sponsors seeking to reduce disparities in cancer outcomes. **Methods:** We conducted an ecological analysis of U.S.-based cancer treatment trials (1990–2025). Trial availability was measured using population-adjusted cumulative trial density (trials/10,000 population) and classified as none, low, medium, or high. County-level cancer mortality-to-incidence ratios (MIRs) were used to indicate post-diagnosis outcomes (lower MIR is better). Associations with trial density were assessed using logistic regression, with and without adjustment for the structural factors, including area deprivation index (ADI), health system performance, and area type (metro, micro, non-metro/non-core). Analyses were stratified by area type and ADI to stabilize estimates and assess associations across strata. **Results:** Between 1990 and 2025, 32,332 U.S.-based trials were conducted. The majority of counties (1,680, 52%; 10% of the U.S. population) had no trials. In counties with trials, counts ranged from 1 to 6,840 and density from 0.05 to 1,992 per 10,000 population. Compared to counties without trials, low-, medium-, and high-density counties were more likely to have lower MIR (OR = 1.9, 3.6, and 3.3, respectively; all $p < .001$). After adjustment for structural factors, associations persisted in medium- and high-density counties (OR = 1.7, 1.9; $p < .001$), but not in low-density counties (OR = 1.2; p = .30). Associations were strongest in metro counties (Table), with ORs of 1.91, 2.61, and 2.61 in high-ADI areas (all $p<0.0001$). In low-ADI areas, medium and high density were associated with lower MIR (OR=2.58 and 2.00; $p<.001$), but low density was not (OR=1.33; p=0.70). **Conclusions:** Cancer clinical trial availability in the U.S. is highly concentrated and strongly associated with improved population-level cancer outcomes. The co-occurrence of low trial density, structural deprivation, and higher cancer MIRs highlights opportunities to improve cancer outcomes by expanding the geographic reach of trial infrastructure. Research Sponsor: None.

Associations between trial density and MIR.

Areas	Trial Density	OR*	p	Adjusted OR*	p
All counties	None	**Ref**			
	Low	1.90	<.001	1.16	.30
	Medium	3.64	<.001	1.72	<.001
	High	3.34	<.001	1.86	<.001
Metro	None	**Ref**			
	Low	2.10	.005	1.37	.30
	Medium	3.70	<.001	2.31	.005
	High	4.13	<.001	2.83	.001
Micro	None	**Ref**			
	Low	1.35	.05	1.10	.60
	Medium	2.00	.001	1.33	.20
	High	2.35	<.001	1.46	.04
Non-metro/non-core	None	**Ref**			
	Low	0.97	.90	0.88	.80
	Medium	3.72	.01	3.74	.02
	High	2.37	.01	1.86	.10
Low ADI	None	**Ref**			
	Low	1.33	.07	1.25	.20
	Medium	2.58	<.001	2.38	<.001
	High	2.00	<.001	1.91	<.001
Higher ADI	None	**Ref**			
	Low	1.91	<.001	1.36	.05
	Medium	2.61	<.001	1.59	.02
	High	2.61	<.001	1.99	<.001

*Odds of lower MIR.

1557 Poster Session

Access to immunotherapy and molecular diagnostics for lung adenocarcinoma in Syria: A mixed-methods study from the country's main cancer center. First Author: Ayla Kouli, Damascus University- Faculty of Medicine, Damascus, Syrian Arab Republic

Background: Immunotherapy is now a standard-of-care treatment for lung cancer across most stages. Access to immunotherapy and molecular diagnostic tests in conflict-affected countries such as Syria remains poorly described. As the principal cancer center in Syria, Al-Bairouni University Hospital (ABUH) provides care for nearly three-quarters of all cancer cases nationally. We conducted this study to evaluate access to immunotherapy and molecular diagnostic services at ABUH. **Methods:** A mixed-methods study was performed between 2022 and 2024 at ABUH. This study included a retrospective cohort of all patients diagnosed with lung adenocarcinoma. Quantitative data included disease stage at diagnosis, molecular testing rates, and immunotherapy utilization. In addition, a qualitative patient survey was thematically analyzed to explore barriers to treatment access in a separate cohort of patients with mixed tumor types. **Results:** Among 2,920 patients diagnosed with lung cancer, 1,393 (47.7%) had lung adenocarcinoma. The median age at diagnosis was 61 years; 79.7% of patients were male. Smoking history was as follows: Current 792 (56.9%), Former 268 (19.2%), never smoked 318 (22.8%) At presentation, 3 patients (0.2%) had stage I disease, 40 (2.9%) stage II, 174 (12.5%) stage III, and 778 (55.8%) stage IV disease, staging was unknown for the rest of the patients. EGFR mutation testing was performed by ABUH for 226/1393 patients (16.2%) only, with positive results identified in 124 cases (8.9%). PD-L1 testing was conducted by ABUH in only 32/1393 patients (2.3%) and was positive in 23 (1.65%). Of all patients with lung adenocarcinoma, only 5 patients (0.6%) with stage IV disease received immunotherapy. All were treated with nivolumab. Thematic analysis of qualitative data (35 patients) revealed that high treatment costs and limited drug availability are the primary barriers to accessing immunotherapy. **Conclusions:** This study represents the first evaluation of access to immunotherapy for patients with lung cancer in Syria. Even at ABUH, the country's main cancer center, access to immunotherapy and molecular testing remains markedly limited. International collaboration is necessary to expand diagnostic infrastructure, standardize data reporting, and enhance financial protection mechanisms. These are critical steps toward achieving better cancer care in Syria. Research Sponsor: None.

1558 Poster Session

Assessment of CAR-T clinical trial availability and accessibility in the United States. First Author: Rahul Kumar Thakur, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has transformed outcomes in hematologic malignancies and is increasingly evaluated in solid tumors. CAR-T trials requires specialized infrastructure, potentially limiting access by geography and institutional concentration. We assessed the national distribution of CAR-T clinical trials, population distant from trial sites, and institutional clustering. **Methods:** All active U.S. interventional Phase I-III CAR-T trials (adult/pediatric) were identified via ClinicalTrials.gov (accessed January 2026). Trial locations were geocoded by ZIP code and linked to 2020 Census ZIP Code Tabulation Areas. Population access was defined as residence within 30 or 60 miles of a trial site using Haversine distance. Rurality (RUCA codes), income quartiles, and race/ethnicity (ACS 2023) were evaluated to assess disparities. Institutional concentration was assessed by the proportion of trial sites contributed by individual institutions. **Results:** Out of 264 identified trials, 189 were selected, conducted across 356 unique institutions. More than 85% of trials were early phase(Phase I–II), spanning lymphoma, myeloma, leukemia, and solid tumor indications. Access was limited. At a 30-mile radius, 43.3% of the U.S. population (~145 million individuals) lacked proximity to an active CAR-T trial site; 27.1% (~91 million) remained without access at 60 miles. Within 30 miles, lack of access affected 94.1% of rural residents, compared with substantially lower coverage in urban areas, and 63.2% of individuals in the lowest income quartile. By race and ethnicity, 37.4% of Hispanic and 32.0% of Black populations lacked access within 30 miles. These patterns were consistent when access was defined at 60 miles. Trial availability was highly centralized. The top 10 of institutions accounted for over 60% of all CAR-T trials, led by large academic centers such as City of Hope, Memorial Sloan Kettering, MD Anderson, Texas Children's Hospital, and Stanford University. These centers are located in major metropolitan regions, resulting in dense trial availability for populations living nearby while leaving large geographic regions without access. In contrast, approximately 60% of participating institutions hosted only a single CAR-T trial, indicating limited diffusion of trial infrastructure beyond major academic hubs. **Conclusions:** CAR-T clinical trial access in the United States is restricted by both geographic exclusion and marked institutional concentration. As CAR-T indications expand, addressing these structural bottlenecks will be critical to improving equitable access and ensuring broader participation in cellular therapy development. Research Sponsor: None.

Access to CAR-T clinical trials.

Population Group	30 mi	60 mi
Overall US Pop	43.3%	27.1%
Rural Pop	94.1%	65.6%
Lowest income quartile	63.2%	45.8%
Hispanic	37.4%	25.9%
Black	32.0%	20.1%

1559 Poster Session

20-year trends in socioeconomic disparities in breast cancer care for patients aged < 65 years old. First Author: Olivia Frances Lynch, National Clinician Scholars Program, Yale School of Medicine, New Haven, CT

Background: Socioeconomic disparities (SES) in cancer care have been well described, especially for younger patients with limited financial reserve and insurance vulnerability. It remains unclear, however, whether innovations in breast oncology have mitigated or exacerbated these gaps over time. We evaluated nearly 20-year trends across key breast cancer treatment and diagnostic modalities and sought to determine whether advances in care promote, or further undermine, health equity. **Methods:** Using the National Cancer Database, we identified working-aged individuals (18-64 yo) diagnosed with breast cancer from 2004–2022. As surrogates for improvements in breast cancer care, we examined: (i) Oncotype DX testing for stage I–II ER/PR-positive, HER2-negative disease; (ii) immediate breast reconstruction (IBR) after mastectomy; (iii) receipt of neoadjuvant chemotherapy (NACT) for stage II HER2-positive (HER2+) and triple-negative breast cancer (TNBC); and, (iv) immunotherapy by subtype and stage (2018–2022). We used multivariable logistic regression to generate adjusted predicted probabilities by median income quartile (MIQ) and year (or year group). Median Income Disparities (MID) were measured as the difference between the highest and lowest MIQ. **Results:** The final sample included 1,349,691 patients with mean age 51.8 (SD 8.64). Patient population included 7.7% Hispanic, 72.3% Non-Hispanic White, 13.2% Black, 5.9% Asian, and 0.9% unknown race/ethnicity. 76.7% of patients were privately insured, 10.8% Medicaid-covered, 6.2% Medicare-covered, 1.5% other, 1.8% unknown, and 3.1% uninsured. During the study period, overall adoption of treatment increased substantially over time, with SES disparities differing across modality. Oncotype DX testing demonstrated persistent income-related disparities across the study period (MID: 4.2–5.5%, $p<0.05$ for all). The largest and most durable inequities were seen in post-mastectomy IBR (17.60% in 2004-2008, narrowing to 11.70% in 2018-2022, $p<0.05$ for all). Receipt of NACT was associated with modest income-based differences that were greatest during years of rapid uptake for stage II HER2+ (4.9% in 2014–2017, $p<0.05$) and TNBC (4.8% in 2018–2022, $p<0.05$) breast cancer. Adoption of immunotherapy rose sharply from 2018–2022 across all incomes, with modest but narrowing gaps for stage III–IV disease (MID: 4.9% in 2019, $p<0.05$ to 1.1% in 2022,NS). Adjustment for insurance status did not significantly change socioeconomic gradients. **Conclusions:** Socioeconomic disparities in breast cancer care for women <65 years old vary markedly by treatment modality and adoption phase. Advancing equitable access to best-practice breast cancer care will require interventions at the health system, societal guidelines, and policy levels. Research Sponsor: None.

1560 **Poster Session**

Clinical trial participation among adolescents and young adults diagnosed with cancer in the United States (2004-2021). First Author: Vianessa Andion Camargo, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Adolescents and young adults (AYAs, 15-39 years) have low historical participation in cancer clinical trials (CTs) than pediatric patients, which limits access to novel therapies and slows progress in outcomes. Although cooperative-group networks and AYA-focused initiatives have improved accrual, enrollment remains uneven across care settings and patient subgroups, highlighting the need for contemporary population-level estimates of participation and its predictors. **Methods:** The National Cancer Database was utilized to identify AYAs diagnosed between 2004 and 2021 with one of the 20 cancer types associated with the highest mortality. Patients with confirmed malignant neoplasms, known vital status, and ≥6 months of follow-up were included. The final analytic cohort comprised 865,923 patients. The primary endpoint was documented CT participation (yes/no). Multivariable logistic regression was used to estimate adjusted odds ratio (aOR) of enrollment by diagnosis epoch, age group, sex, race/ethnicity, insurance status, area-level education and median income, residence, Charlson-Deyo comorbidity score, and receipt of surgery, radiation, and systemic therapy. **Results:** Overall, 2,621 patients (0.3%) were enrolled in a CT. Enrollment increased from 0.1% (2004–2009) to 0.2% (2010–2013), 0.3% (2014–2017), and 0.5% (2018–2021); compared with 2004–2009, enrollment was higher in 2018–2021 (aOR: 4.92, 95% CI: 4.34–5.60). Compared to those aged <24 years, the odds of enrollment were lower for ages 25–29 (aOR: 0.52, 95% CI 0.46–0.58), 30–34 (aOR: 0.45, 95% CI 0.41–0.51), and 35–39 (aOR: 0.46, 95% CI 0.41–0.50). Enrollment was lower among non-Hispanic Black (aOR: 0.84, 95% CI 0.74–0.96) and Hispanic patients (aOR: 0.79, 95% CI: 0.69–0.90) compared to non-Hispanic White patients. Compared with uninsured patients, enrollment was higher among those with private (aOR: 1.74, 95% CI 1.38–2.21) or government insurance (aOR: 1.60, 95% CI: 1.26–2.05), and was also higher in areas with greater education attainment (aOR: 1.14, 95% CI: 1.03–1.25) and individuals in the high median income group (aOR: 1.13, 95% CI: 1.02–1.25). Patients who had received radiation (aOR 1.56, 95% CI 1.44–1.70) or systemic therapy (aOR 3.59, 95% CI 3.23–4.01) were more likely to enroll. **Conclusions:** CT participation among AYAs was exceedingly low but has increased over time. Differences in enrollment by age, race/ethnicity, insurance, and area-level socioeconomic measures suggest persistent barriers to CT access and participation. These findings support expanding trial availability beyond high-resource settings, strengthening AYA-focused referral pathways and infrastructure, and implementing equity-centered strategies such as navigation, reduced trial burden, and financial/insurance support to improve representation and access to investigational therapies. Research Sponsor: None.

1561 **Poster Session**

Financial vulnerability among U.S. cancer survivors: Differences by veteran status and VA health care utilization in the National Health Interview Survey, 2020–2024. First Author: Aimee Pehrson, Titan Alpha, Chantilly, VA

Background: Current national comparisons of financial factors affecting cancer care among Veterans and non-Veteran adults with a self-reported history of cancer are limited. Moreover, little is known about how financial vulnerability influences Veterans receiving care primarily through the VA system versus in community settings. We hypothesize that Veteran status and primary care setting (VA vs. community) are associated with differences in financial vulnerability and related barriers to medical care among U.S. adult survivors of cancer. **Methods:** We pooled 2020–2024 National Health Interview Survey data (n=19,410) to examine associations between Veteran status, VA care use, and financial vulnerability among adult survivors from cancer (including non-melanoma skin cancer). Missing data were addressed using multiple imputation leading to an analytic sample size n=18,846. Survey-weighted logistic regression models accounted for complex sampling and adjusted for age, sex, cancer site, number of cancers, years since diagnosis, poverty ratio, and survey year. Analyses were limited to years when outcomes were collected. Two comparisons were conducted to understand the unique social factors Veterans face compared to non-Veteran patients and differences between primary setting of Veteran care: Model(A) Veterans vs. non-Veterans and (B) VA primary users vs. non-primary VA users. Binary outcomes included delayed care due to cost, delayed care due to transportation barriers, inability to afford care, unpaid medical bills, insurance gaps, medication cost-skipping, and inability to pay expenses. Sensitivity analyses compared weighted and unweighted models. **Results:** The analytic sample of adult survivors from cancer was n=18,846 from 2020–2024 (mean age 68 years; 43% male) and included 2,511 (13%) who self-reported as Veterans (mean age 74 years; 94% male). Adjusted models showed Veteran status was associated with higher odds in care delay due to transportation barriers (OR 1.57; 95% CI, 1.13-2.19) and lower odds of worry regarding unpaid medical bills (OR 0.79; 95% CI, 0.68-0.91) and difficulty obtaining medical care due to cost OR 0.78(0.63-0.98). All other compared variables were not significant. Among Veterans, those who primarily used the VA had lower odds of delaying care due to cost (OR 0.34; 95% CI, 0.17-0.69), not obtaining medical care due to cost (OR 0.50; 95% CI, 0.35-0.72), and skipping medication due to cost (OR 0.25; 95% CI (0.12-0.49). Sensitivity analyses supported these patterns. **Conclusions:** Veterans who are primarily VA users have cost-related vulnerability without a difference in delaying care to non-Veteran counterparts. Such systems that remove financial hardship may be an approach to improve care for survivors from cancer in the U.S. Research Sponsor: None.

1562 **Poster Session**

Recovery with residual disparities: Real-world patterns of platinum chemotherapy use after the 2023 drug shortage. First Author: Omer Sayed Ashruf, Indiana University School of Medicine, Indianapolis, IN

Background: The 2023 national shortages of cisplatin and carboplatin disrupted standard cancer treatment across multiple malignancies. Although the acute effects have been described, patient-level evidence of recovery in platinum chemotherapy access after supply stabilization is limited. We evaluated real-world recovery in platinum initiation across platinum-dependent cancers. **Methods:** We conducted a retrospective cohort study using the TriNetX U.S. Collaborative Network. Adults with platinum-sensitive malignancies, including lung, ovarian, bladder, uterine, testicular, and head and neck cancers, were identified using ICD-10-CM and ICD-O codes and assigned according to the national platinum chemotherapy shortage timeline: shortage (February 10, 2023-January 31, 2024) and post-shortage (July 1, 2024-June 30, 2025) eras. The primary endpoint was time from cancer diagnosis to first receipt of any platinum chemotherapy (cisplatin or carboplatin), analyzed using Kaplan–Meier methods and multivariable Cox proportional hazards models, adjusted for demographic characteristics, NCI Comorbidity Index, risk factors, BMI, and cancer type. Secondary analyses evaluated agent-specific initiation (cisplatin vs carboplatin) and heterogeneity of recovery across cancer sites. Prespecified subgroup analyses assessed differences in recovery by sex and race/ethnicity within matched cohorts. **Results:** The analysis included 33,856 patients diagnosed during the shortage and 30,256 diagnosed post-shortage. Platinum initiation improved post-shortage compared with the shortage period (adjusted hazard ratio [aHR], 1.11; 95% CI, 1.09–1.14; p<.001), with median time to initiation decreasing from 206 to 128 days. This improvement was driven primarily by increased carboplatin initiation, while cisplatin initiation continues to stall. Recovery patterns varied by cancer type, with greater improvement observed in ovarian and head/neck cancers and incomplete recovery in bladder cancer. Across eras, slower platinum initiation was observed among older patients (aHR per year increase, 0.99), male patients (aHR 0.92), and racial/ethnic minority groups, including Black (aHR 0.92) and Hispanic patients (aHR 0.90). Comorbidities associated with platinum toxicity, such as CKD (aHR, 0.79), neuropathy (aHR, 0.63), heart failure (aHR, 0.93), and liver disease (aHR, 0.84), were also associated with delayed initiation. **Conclusions:** After resolution of the 2023 platinum shortage, platinum chemotherapy initiation improved across multiple cancers, providing patient-level evidence of recovery in access. However, recovery was heterogeneous, driven largely by carboplatin, and modified by patient clinical and demographic factors, suggesting that restoration of drug supply does not uniformly translate into timely or equitable recovery of standard-of-care treatment. Research Sponsor: None.

1563 **Poster Session**

Trends in incidence, survival, and cause of death in Kaposi sarcoma in the antiretroviral therapy era. First Author: Joseph Antony Elengickal, University of South Carolina School of Medicine - Prisma Health, Columbia, SC

Background: Kaposi sarcoma (KS) is a malignancy driven by human herpesvirus-8 infection and is most commonly associated with HIV. Although often considered indolent, KS can cause significant morbidity and mortality, particularly if HIV is uncontrolled. This study aimed to characterize current incidence and survival trends in KS using the Surveillance, Epidemiology, and End Results (SEER) Database. **Methods:** Cases of KS were identified using ICD-O-3 codes 9140-9143 in the SEER Research Plus Data (17 Registries, 2000-2022). SEER registry incidence rates were calculated over time. Overall survival (OS) across diagnostic eras was estimated using Kaplan-Meier methods. Multivariable Cox models were used to assess associations between race/ethnicity, neighborhood income, rural-urban status, and mortality, adjusting for age, sex, and year of diagnosis. Cause-of-death analyses were performed using SEER cause-specific recodes. **Results:** 9,931 patients with KS were identified, 91% male and 9% female. Racial and ethnic distribution was 45% non-Hispanic White (NHW), 24% Hispanic, 24% Black, 3.7% Asian/Pacific Islander (A/PI), and 0.7% American Indian/Alaska Native (AI/AN). Registry incidence of KS declined from 0.33 per 100,000 in 2000-2004 to 0.22 in 2015-2019 and 0.20 in 2020-2022. One-year OS in 2000-2004 was 77.3% (95% CI 75.7-78.9), in 2015-2019 was 82.2% (95% CI 80.4-83.9), and in 2020-2022 was 80.9% (95% CI 78.3-83.5). In multivariable analyses, Black patients had higher mortality compared with NHW patients (HR 1.55, 95% CI 1.43-1.67), while mortality did not differ significantly among Hispanic, A/PI patients, or AI/AN patients. Residence in the highest neighborhood income quartile was associated with improved overall survival compared with the lowest quartile (HR 0.81, 95% CI 0.73-0.89). Across 2000-2022, HIV/infectious causes accounted for 55.6% of deaths (95% CI, 53.9-57.2), followed by cardiovascular disease (15.1%) and cancer-related causes (13.3%). In cause-specific analysis, later year of diagnosis was strongly associated with lower HIV/infectious mortality (HR 0.96 per year, 95% CI 0.96-0.97), whereas mortality from cancer did not improve over time. **Conclusions:** In the modern antiretroviral therapy era, KS incidence and HIV-related mortality have declined. Despite these advances, inequities persist, with higher mortality observed among Black patients and persons residing in poorer neighborhoods. These findings highlight the need for focused efforts to address disparities in KS outcomes. Research Sponsor: None.

Adjusted hazard ratios for overall survival in Kaposi sarcoma.

Variable	Adjusted HR	95% CI	P value
Race/Ethnicity			
Non-Hispanic White	Reference	-	-
Black	1.55	1.43-1.67	<0.001
Hispanic	1.02	0.95-1.11	0.54
Asian/Pacific Islander	1.02	0.86-1.20	0.82
American Indian/Alaska Native	1.26	0.89-1.80	0.20
Neighborhood Income			
Highest vs Lowest Quartile	0.81	0.73-0.89	<0.001

1564 Poster Session

Fertility concerns, counseling, and preservation in AYA females with early-stage breast cancer: Chemotherapy receipt and timing. First Author: Bolun Liu, Department of Hospital Internal Medicine, Mayo Clinic Health System, Mankato, MN

Background: Adolescent and young adult (AYA) females with early-stage ER-negative and/or HER2-positive breast cancer commonly receive chemotherapy to reduce risk of recurrence. Fertility concerns, counseling, and preservation may influence chemotherapy decisions and time to chemotherapy (TTC) initiation. **Methods:** We surveyed AYA survivors of stage I–III premenopausal ER-negative and/or HER2-positive breast cancer treated at Kaiser Permanente Northern and Southern California (2013-2022). Fertility concerns were defined as not having completed desired family size or being unsure about having completed desired family size at diagnosis. We summarized receipt of fertility counseling, receipt of chemotherapy, and use of oocyte/embryo cryopreservation for fertility preservation (FP). Among fertility-concerned patients who received chemotherapy, TTC (days from diagnosis) was assessed separately for neoadjuvant chemotherapy (NAC) vs for adjuvant chemotherapy (AdjC). Time to NAC was natural log–transformed and modeled with multivariable log-linear regression to estimate relative differences in TTC, adjusting for stage, study site, ER, HER2, age, and diagnosis year. **Results:** Of 363 respondents, 197 (54%) had fertility concerns at diagnosis; 183/197 (93%) received chemotherapy, similar to 153/166 (92%) among those without concerns (p=0.7). Of the concerned chemotherapy recipients, 45 (25%) saw a fertility specialist but did not pursue FP while 55 (30%) underwent FP. For the 112 fertility-concerned NAC recipients, FP was associated with longer TTC than no fertility specialist counseling (mean=41 vs. 30 days; adjusted ratio=1.39; 95% CI 1.15–1.69), whereas fertility specialist counseling without FP was not (mean= 31 vs. 30 days, adjusted ratio=1.04; 95% CI 0.86–1.25). For the 71 fertility-concerned AdjC recipients, TTC was similar for patients who did not see a fertility specialist (mean=63 days), those who froze oocytes/embryos (mean=65 days), and those who saw a fertility specialist but did not pursue FP (mean=69 days). **Conclusions:** In this AYA breast cancer cohort, there was no evidence that fertility concerns led patients to decline chemotherapy. FP was associated with a modest delay in NAC initiation (<2 weeks on average). Research Sponsor: National Cancer Institute; P01CA233432.

Time to chemotherapy (TTC) among 183 AYA patients with ER− and/or HER2+ breast cancer and fertility concerns.

Fertility-focused care	N (n=183)	Neoadjuvant chemotherapy (n=112)	Mean TTC, days	Relative difference in TTC, adjusted ratio (95%CI)	Adjuvant chemotherapy (n=71)	Mean TTC, days
No fertility counseling from a specialist	83 (45%)	55 (49%)	29.6	Reference	28 (39%)	62.6
Received fertility counseling from a specialist						
No fertility preservation	45 (25%)	28 (25%)	30.7	1.04 (0.86,1.25)	17 (24%)	68.6
Fertility preservation	55 (30%)	29 (26%)	41.2	1.39 (1.15,1.69)	26 (37%)	64.6

1565 Poster Session

Impact of the Taylor Cancer Research Center (TCRC) and Tempus AI TIME Partnership on clinical trial start-up and accrual. First Author: John Nemunaitis, Taylor Family Research Foundation, Maumee, OH

Background: TCRC is a nonprofit oncology community practice serving patients in Northwestern Ohio. TCRC's partnership with the Tempus AI TIME program leverages proprietary software and nursing teams to support patient matching across a portfolio of industry-sponsored clinical trials. Trials may be rapidly opened "prospectively" before an eligible patient is identified, or "just-in-time" (JIT) once a patient is identified and ready to consent, allowing studies to be activated in response to patient need. The goal of this partnership is to utilize AI-enabled technology and clinical workforce support to alleviate site burden associated with activating and enrolling patients to oncology clinical trials, thereby increasing patient access to novel therapies and optimizing resource utilization. **Methods:** Tempus' AI-enabled platform analyzes trial eligibility criteria and compares this against patient-level information from a combination of structured EMR data, natural language processing, and large language models. All patients are evaluated against the full TIME trial portfolio nightly, with potential matches reviewed by Tempus nurses. Patients likely to be eligible for a trial are communicated to TCRC for final confirmation. Trials are rapidly activated through a standardized operational model including a pre-negotiated clinical trial agreement, rate card, and central IRB. Program metrics include number of patients pre-screened, trial activation timelines, and trial consents. **Results:** From June 2024 to August 2025, Tempus nurses spent approximately 219 hours pre-screening 1,195 patients from TCRC, yielding 278 potential matches across 92 TIME trials. TCRC activated 16 TIME trials, leading to a total of 66 consents. Within the same time, TCRC activated 9 non-TIME trials resulting in 30 consents. TIME trials averaged 4.1 consents per trial, compared to 3.3 consents for non-TIME trials. TIME activations averaged 10.5 business days for JIT and 15.9 days for prospective trials, versus 55.4 days for non-TIME trials. **Conclusions:** TCRC's partnership with the Tempus AI TIME program, including enhanced patient pre-screening resources and rapid trial activation model, reduced trial start-up time with an increase in total consents and consents per trial compared with traditional trials. TCRC activated TIME trials 4x faster with a 2x increase in interventional consents and 120% increase in overall consents compared with non-TIME studies. This demonstrates how AI-enabled trial matching, combined with a streamlined operational model, can improve resource utilization and patient access to precision oncology trials in a community setting. Research Sponsor: None.

	Average activation time (days)	Interventional trials	Consents per trial (interventional)	Observational trials	Consents per trial (observational)	Total consents	Consents Per Trial
TIME	13.7	12	2.3	4	9.8	66	4.1
Non-TIME	55.4	6	1.1	3	7.6	30	3.3

1566 Poster Session

User-centered design of a COPD care pathway embedded in oncology care for patients receiving immune checkpoint inhibitors. First Author: Thomas William Lycan Jr., Wake Forest University School of Medicine, Winston-Salem, NC

Background: Chronic obstructive pulmonary disease (COPD) is one of the most common comorbidities among patients treated with an immune checkpoint inhibitor (ICI) for cancer, and it is often underdiagnosed and undertreated. We aimed to assess COPD treatment burden among patients with cancer and design a scalable intervention. **Methods:** This mixed-methods study enrolled (1) patients with confirmed/suspected COPD and ICI-treated cancer, and (2) clinicians providing ambulatory cancer or COPD care. Semi-structured surveys assessed treatment burden, self-confidence in COPD care, and barriers. Interviews, guided tours, and focus groups informed the user-centered design of a novel COPD care pathway, and the primary endpoint was participant-perceived feasibility. Qualitative analysis used a matrix approach informed by interview-guide constructs and emergent concepts, with quotations synthesized iteratively. **Results:** Between Feb-Dec 2025, the study team screened 478 individuals to enroll the planned cohort of 100 participants, including 20 patients and 80 clinicians. Nearly all participants completed a survey (n = 96), and 36 completed either an interview, tour, or focus group. Most patients reported their diagnosis of COPD had been confirmed (90%), and all were ≥50 years old. Clinicians were nurses (47%), physicians (44%), or APPs (6%); 41% practiced at a community oncology clinic. Most patients would use COPD-related services if integrated into oncology visits (75%) and 65% felt they had effective treatment options for both cancer and COPD. Nearly all clinicians (97%) agreed that COPD increased the risk of complications during cancer treatments, and 59% agreed that COPD care should be addressed within oncology clinics. Although most reported feeling confident in managing COPD in patients with cancer (80%), many reported a lack of skills to do so (e.g., teaching inhaler technique, 34%). Commonly cited barriers were insufficient time (63%), limited availability of COPD providers (65%), and COPD medication costs (50%). Qualitative analysis identified key themes: limited awareness of COPD guidance in oncology; resource constraints in community clinics; reliance on specialist referrals; conditional willingness to implement a COPD pathway if it did not detract from cancer care; and needs for educational materials and interoperable electronic medical records. These integrated datasets informed the design of a COPD care pathway to be embedded within oncology infusion visits using flowchart-based decision support to stratify COPD control (green/yellow/red) and support self-management and targeted clinician education at the point of care. **Conclusions:** COPD imposes a substantial treatment burden on patients with cancer, but there are actionable opportunities for care delivery. A user-centered COPD care pathway was designed for feasibility in community oncology settings. Research Sponsor: National Center for Advancing Translational Sciences; 5K12TR004931-02; National Cancer Institute; P30CA012197.

1567 Poster Session

Greening a chemotherapy day ward. First Author: Alannah Kelly, School of Medicine, University College Cork, Cork, Ireland

Background: Cancer care is climate toxic and contributes to the triple planetary crisis which threatens human health and cancer care delivery. Despite this toxicity, sustainability guidelines in oncology are lacking. Our objectives are based on the sustainability touchpoints identified in previous research in our department. Study aims were to understand prescribing patterns, quantify plastic waste, and assess patients' and healthcare professionals' views on acceptability of proposed "green" strategies with the aim to develop a green prescribing checklist. **Methods:** A prospective review of systemic anticancer therapy (SACT) delivery at a tertiary oncology outpatient unit was performed. Variables collected included SACT regimen details, dosing interval extensions, supportive medication details and treatment value as rated by the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS). Daily plastic waste output was measured. Anonymous surveys of patients and healthcare professionals were developed using previously validated questionnaires and circulated among adult patients attending cancer services locally and cancer care professionals nationally. Survey domains included sustainability knowledge, perceived barriers/facilitators, and willingness to adopt sustainability measures such as oral therapy. Findings were reported using descriptive statistics. Institutional and ethical approval was received prior to study commencement. **Results:** Selected findings show 23% (n=200/864) of supportive medications were given intravenously (IV). There was widespread adoption of subcutaneous formulations and extended dosing intervals. Most regimens with ESMO-MCBS scores showed substantial clinical benefit. Each patient attendance generated a mean of 46 grams of plastic waste. Seventy-two healthcare professionals responded to the survey; 97% (n=70/72) agreed that climate change adversely impacted human health and 82% (n=59/72) agreed that sustainable practices can decrease the effects of climate change yet only 15% (n=11/72) reported routinely considering environmental impacts when prescribing. Barriers to sustainable practices included time 65% (n=47/72), inadequate training 61% (n=44/72) and lack of institutional support 63% (n=45/72). A total of 211 patients submitted responses; 91% (n=190/208) agreed that reducing environmental impact should be a priority for hospitals, and 82% (n=159/194) were in favour of oral medications over IV where appropriate. **Conclusions:** This study, integrating provider and patient perspectives, demonstrates support for sustainable practices in oncology, but ad-hoc current implementation of same. The findings will guide development of a green checklist informed by patients and prescribers, followed by implementation and re-audit. Patient-centred strategies can align high value cancer care with planetary health and fill the current gap in sustainable oncology practice. Research Sponsor: Health Service Executive.

1568 **Poster Session**

Accelerated diagnostic pathway for undifferentiated malignancy via interventional radiology triage: A comparative effectiveness study. First Author: Suken Shah, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Efficiently triaging patients presenting with imaging findings suggestive of malignancy but lacking a definitive tissue diagnosis poses a considerable challenge for large cancer centers. Without a tissue diagnosis in the setting of metastatic disease it is unclear which specialized medical oncologist would be the optimal physician to see the patient. Traditional referral patterns may lead to significant diagnostic delays until the patient reaches the appropriate oncologist. We evaluated the efficacy of a dedicated "Rapid Biopsy" (RB) pathway, which directs such patients immediately to the Interventional Radiology (IR) Outpatient Clinic for streamlined, image guided diagnosis and compared this new pathway to the traditional, standard institutional referral approach. **Methods:** This retrospective cohort study included 1157 patients at Memorial Sloan Kettering Cancer Center (MSKCC) who underwent a first diagnostic biopsy between 2020 and 2023. The cohort comprised 532 patients from the prospectively enrolled RB program and 625 patients in a rigorously matched comparison cohort (CC), derived from standard referrals who presented with an "unknown primary" malignancy, excluding any patient with a history of prior tissue sampling or recurrence. The primary endpoints were the mean time from initial consultation to biopsy and the mean time from initial consultation to treatment initiation. Independent t-tests were used for cohort comparison. Patients exhibiting outlier time-to-treatment intervals exceeding 90 days were excluded from the treatment analysis. **Results:** The RB and CC cohorts were well-matched demographically (mean age RB: 65.75 years; CC:66.05 years). Malignancy was confirmed in 90.4% and 92.3% of the respective cohorts. The RB pathway demonstrated a 71% reduction in time from initial consult to biopsy than the CC (4.59 vs 15.66 days, $p<0.001$), representing an 11.07 reduction. Furthermore, this operational efficiency translated into a 63% reduction in time from initial consult to treatment compared to the CC (14.57 vs 39.88 days, $p<0.001$), achieving an 11.88 day reduction in time to start. **Conclusions:** The dedicated Interventional Radiology first Rapid Biopsy pathway provided a clinically significant meaningful acceleration in the cancer diagnostic and treatment process, saving 11 days from consult to biopsy and nearly 12 days to definitive treatment initiation. This model effectively streamlines care by eliminating multi-specialty diagnostic detours prevalent in traditional triage, establishing a crucial operational standard for comprehensive cancer centers managing new suspected malignancies. Research Sponsor: None.

1569 **Poster Session**

Patient-reported performance status as a predictive tool for mortality and supportive care needs in patients with advanced cancer. First Author: Manan P. Shah, Division of Hematology-Oncology, University of California, Los Angeles, Los Angeles, CA

Background: Performance status is a key prognostic factor among patients with advanced cancer and can inform the need for supportive care services. However, assessment and documentation of performance status is inconsistently integrated into standard oncology care. Patient-reported performance status (PRPS) is a surrogate for clinician-assessed performance status and has the potential to address this challenge. We piloted a decision support tool in our electronic health record (EHR) that uses PRPS to prompt clinician assessment of performance status and suggest referrals to supportive care services. **Methods:** We identified patients with advanced cancer using a pre-built and validated registry driven by ICD codes in our EHR (EPIC). For patients with advanced cancer seen at one of our clinics, a multiple-choice question with options derived from the Eastern Cooperative Oncology Group (ECOG) scale in patient-friendly language was added to the pre-visit questionnaire sent electronically prior to oncology visits. For patients with a poor PRPS (2 or greater), a clinical decision support tool alerted providers of the patient's self-reported performance status, encouraged input of the clinician's ECOG assessment, and suggested referral orders to supportive care services such as palliative care, nutrition, and social work. We assessed the relationship between PRPS and ECOG with mortality using logistic regression and by calculating median time to death stratified by patients' highest (poorest) score. **Results:** Between 3/11/24 and 3/11/25, 3,376 PRPS surveys were completed by 1,343 oncology patients. Seventeen percent of patients reported poor PRPS ($\geq$2). Worsening PRPS was strongly associated with mortality (3% for PRPS 0 vs. 44% for PRPS 4) and with shorter median time-to-death (163 days for PRPS 0 vs. 19 days for PRPS 4). PRPS correlated with clinician-assessed ECOG (ρ=0.3, $p<0.001$) and predicted mortality (ρ=0.8) comparably with ECOG (ρ=0.7). By contrast, ECOG documentation by clinicians was incomplete in 39% of patients. **Conclusions:** Results suggest feasibility of a PRPS-driven decision support tool to flag patients with advanced cancer and declining function at greatest risk of mortality. PRPS can help allocate limited supportive care resources and prompt advance care planning discussions for patients with greatest need. Research Sponsor: None.

1570 **Poster Session**

Impact of a patient-facing app to address surgical oncology patients' social determinants of health: Preliminary results of a phase II clinical trial. First Author: Ying Sun, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: Unmet Social Determinants of Health (SDH) needs, including housing, transportation, food insecurity, utilities, and social support, are associated with adverse outcomes in cancer care, including delays in treatment, missed appointments, and hospital readmissions. Few interventions have been rigorously evaluated to address these SDH needs in surgical oncology populations. We conducted a Phase II randomized controlled trial to evaluate whether a patient-facing mobile application (Carealth), integrated with a follow-up resource referral platform (findhelp.org), could improve clinical and process outcomes compared to a "sham" app that included an attention-control (static CDC site). **Methods:** We enrolled adult patients with cancer (or suspected cancer) scheduled for surgery at three large U.S. centers. Participants were randomized to Carealth (intervention) or sham (control). We assessed 30-day readmission after surgery, distribution of where resources were sought among interventions clients (among those with baseline needs), time from consultation to surgery, and missed/rescheduled visits within 90 days. Analyses used descriptive statistics, Fisher's exact tests and crude odds ratios for readmission, Kaplan–Meier/log-rank methods for time to surgery, and proportional odds models for missed visits, under an intention-to-treat framework. **Results:** Of 585 patients screened, 161 were randomized (81 intervention, 80 control). Baseline characteristics were well balanced, with 17% reporting at least one SDH need at baseline. App uptake was 80% overall. Thirty-day readmissions were rare and similar between groups, occurring in 5 of 80 patientsOR 1.64, p = 0.72). Median time to surgery was 45 days in the intervention group vs 49 days in controls (log-rank p = 0.42). Missed/rescheduled visits within 90 days did not differ (proportional OR 1.28, p = 0.79). Among participants with SDH needs, multiple resource pathways were used, including counselor or patient navigator services, community or online resources, and the Carealth app; a subset reported partial or complete resolution of needs through the app. **Conclusions:** In this Phase II trial, an SDH-focused patient-facing app achieved outcomes comparable to standard-of-care navigation with respect to readmissions, time to surgery, and appointment adherence. While underpowered for rare clinical events, the intervention demonstrated high uptake and sustained patient engagement, supporting its potential role as a scalable, low-resource adjunct to existing support and navigation services. Larger trials enriched for patients with unmet SDH needs are warranted to assess clinical and health-system impact. Clinical trial information: NCT06688513. Research Sponsor: The National Institutes of Health (NIH); 75N91023C00056.

1571 **Poster Session**

National implementation of electronic patient-reported outcomes (ePROs) for remote symptom monitoring in oncology: The OncoPRO initiative. First Author: Ethan Basch, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Remote symptom monitoring with electronic patient-reported outcomes (PROs) during cancer care improves quality of life, reduces acute care events, lengthens time on treatment, and can improve survival. US oncology practices are increasingly implementing PROs, but barriers to implementation remain. To facilitate uptake of PROs, the OncoPRO Initiative was established as a national PRO learning collaborative with funding from PCORI, in partnership with ASCO, the American Cancer Society, the PROTEUS Consortium, federal agencies, practice networks, and the major EHR and PRO software vendors. Oncology practices/health systems may join OncoPRO at no cost if they are committed to implementing PROs and can submit implementation metrics for monitoring progress. Practices are sorted into "affinity groups" by EHR and PRO software systems. Affinity groups meet monthly, led by coaches from the ASCO, PRO experts, and representatives of respective technology companies. Affinity groups follow a curriculum of key topics in PRO implementation, exchange training materials and information about facilitators and experiences, and provide feedback to software vendors. Little is known on how such learning collaboratives can support PRO growth. **Methods:** Implementation measures and characteristics were identified to quantify progress including the total number of practices joining, the phase of these practices (early implementation, scale-up, maintenance), topic areas for support requested by practices, number of personnel trained for PRO at practices, number of patients enrolled in PRO at practices, and proportion of enrolled patients completing PRO surveys. Data were collected via direct EHR data transfers and surveys. **Results:** Since 3/1/2024, 23 community and academic oncology practices/health systems have joined OncoPRO, across 23 different states, among which 13 practices were in early implementation, 7 in scale-up, and 5 in maintenance. These practices were sorted into four monthly affinity groups, in which the most commonly requested topics were: personnel roles/responsibilities; workflow; patient/clinician engagement; key performance metrics; technology customization; integration with quality programs; symptom management pathways; and billing/coding. Practice participation in monthly meetings has been 100%. Data are available from 12 initial practices, which collectively enrolled 47,052 patients over their initial 15 months of the program, with 24,566 patients (52%) completing at least one PRO survey. **Conclusions:** The OncoPRO learning collaborative is successfully supporting practices across the US to implement PROs, with strong practice engagement and high patient participation. Research Sponsor: Patient-Centered Outcomes Research Institute; DI-2023CI-31283.

1572 **Poster Session**

Achieving epidemiologically representative enrollment and social determinants of health in the phase III evERA Breast Cancer study (NCT05306340). First Author: Gregory A. Vidal, West Cancer Center and Research Institute and University of Tennessee Health Sciences Center, Germantown, TN

Background: Clinical trials have historically under-enrolled patients (pts) from racial and ethnic minority groups, resulting in study populations that do not reflect the epidemiology of cancer in the United States (US), limiting generalizability of the findings. In parallel, social determinants of health (SDOH) are increasingly recognized as key drivers of cancer outcomes, yet are infrequently collected in oncology trials due to operational, ethical, and privacy concerns. The Phase III evERA breast cancer (BC) study (Mayer et al ESMO 2025) was intentionally designed to address both challenges through proactive enrollment strategies and prospective SDOH data collection. **Methods:** evERA BC is a global study in pts with ER+, HER2− advanced BC. In the US, a multi-pronged operational strategy was implemented to achieve epidemiologically representative enrollment, including expanded and pragmatic eligibility criteria, prioritization of community-based sites, real-time enrollment monitoring, patient navigation and financial support, and advocacy partnerships. A tailored survey assessing 5 key social determinants of health (education, income, employment status, marital status, insurance type) was offered to US pts to support a protocol-specified exploratory SDOH efficacy objective. **Results:** The multifaceted operational enrollment strategy used in the evERA BC study resulted in a US cohort (n=144 of total accrual 373) whose racial and ethnic composition exceeded SEER epidemiologic distributions for ER+, HER2− advanced BC for African American (AA) (12.5% vs 11.1%), Asian (9% vs 5.7%), and Hispanic (H) pts of any race (16% vs 8.9%). Enrollment for the aggregate White race (71.5%) and non-Hispanic (NH) ethnicity (83.3%) categories were slightly lower than SEER estimates for White race (82.9%) and NH ethnicity (91.1%). These enrollment patterns contrast with historic Phase III BC trials, in which AA pts typically comprise $<$5% and H pts $<$9% of enrolled populations. Of the 144 U.S. evERA BC pts, 128 (89%) completed the optional SDOH survey, demonstrating feasibility of SDOH data collection in a clinical trial setting and informing evaluation of potential trends and associations with outcomes. **Conclusions:** The evERA study demonstrates that key operational strategies can achieve epidemiologically representative enrollment while enabling robust and compliant SDOH data collection in oncology clinical trials. These findings provide a practical roadmap for industry sponsors seeking to improve recruitment of underrepresented populations and to generate more clinically meaningful and generalizable evidence by integrating social context into trial design and data interpretation. Clinical trial information: NCT05306340. Research Sponsor: F. Hoffmann-La Roche Ltd.

1573 **Poster Session**

Implementation of an expedited cancer workup clinic for uninsured patients at a metropolitan safety net hospital. First Author: Dominick Zheng, Harbor-UCLA Medical Center, Torrance, CA

Background: Timely evaluation of patients with suspected cancer is essential; yet delays in diagnosis and treatment remain common in safety-net health systems, particularly for uninsured or underinsured patients. Such delays are associated with advanced stages of disease at the time of diagnosis and increased mortality. While inpatient evaluation can facilitate multidisciplinary coordination, it is associated with higher costs. Outpatient delivery models designed to expedite cancer workups have been demonstrated to reduce time to diagnosis and number of hospitalizations. We describe outcomes from an Expedited Workup Clinic (EWC) in a large Los Angeles County safety-net hospital. **Methods:** The EWC was designed to coordinate outpatient imaging, biopsy, and oncology specialty referrals for vulnerable patients with suspected malignancy. All patients were uninsured and lacked a primary care provider. Referrals originated from the Emergency Department (ED), Urgent Care, or inpatient admissions. We retrospectively analyzed outcomes from 2022 to 2025 using real-world data extracted from the Electronic Health Record. **Results:** 255 patients were referred to the EWC encompassing 153 men (60%) and 102 women (40%). 155 patients (60%) were Hispanic/Latino, with other represented ethnicities including 28 (10.9%) Asian/Pacific Islander, 22 (8.6%) Black/African American, and 14 (5.5%) White/Caucasian. Spanish was the preferred language of 150 patients (58.8%). The majority of patients (87.9%) were referred from the ED with a median time to first EWC appointment of 11 days (IQR 7-14). From the first EWC appointment, the median time to imaging was 6 days (IQR 1-14), to biopsy was 21 days (IQR 12-54), and to initiation of oncologic treatment was 51 days (IQR 34-83). 92 patients (36.1%) ultimately had a negative malignancy workup, and 38 patients (14.9%) were lost to follow-up. Among patients with confirmed malignancy, the most commonly identified primary sites were colorectal (19.2%), lung (10.6%), hematologic (9.6%), pancreatobiliary (9.6%), prostate (6.7%), head and neck (6.7%), hepatic (6.7%), renal (4.8%), gynecological (3.8%), melanoma (3.8%) and breast (3.8%). **Conclusions:** The EWC demonstrates the feasibility of providing timely malignancy evaluation for high-risk, uninsured patients within a resource-limited setting. These findings support the use of an outpatient rapid evaluation clinic, while surfacing opportunities for improvement including reducing the number of patients lost to follow-up. Further evaluation of cost-effectiveness and access barriers may continue to strengthen the design of rapid workup clinics meant to serve our most vulnerable patients. Research Sponsor: None.

1574 **Poster Session**

PRiMAL (precision randomized clinical trial comparing MTB assisted care to usual care): Quality of life analysis in patients with newly diagnosed non-small cell lung cancer (NSCLC). First Author: Jill M. Kolesar, University of Iowa, Iowa City, IA

Background: Precision medicine—tailoring cancer treatment to a tumor's genomic profile—is more effective and less toxic than traditional chemotherapy. However, its use in community oncology remains limited. Molecular Tumor Boards (MTBs), interdisciplinary teams that interpret genomic data and guide treatment, have improved precision medicine adoption and clinical outcomes, especially in academic centers. However, MTBs are less accessible in community practices, where most cancer care is delivered. **Methods:** The PRiMAL trial is a prospective, parallel-group, cluster randomized trial, comparing MTB assisted care (MTB-AC) to usual care in 10 community medical oncology practices aligned with the Markey Cancer Network. MTB-AC included nurse navigator assistance with next generation sequencing (NGS) ordering, MTB referral, and communication with treating oncologists. Usual care allowed access to the MTB at the discretion of treating oncologist. Eligible patients had untreated stage IIb-IV NSCLC. The co-primary endpoints were 1-year overall survival and health related quality of life (QOL) as measured by the Functional Assessment of Cancer Therapy (FACT) Trial Outcome Index-Lung Cancer (FACT-L TOI), FACT-G, and FACT-L Cancer (FACT-L) administered at baseline, 8 weeks and 12 weeks after treatment initiation. A multilevel linear mixed-effects model was used to estimate the intervention effects for the QOL outcomes while controlling for demographic, clinical, and socioeconomic covariates. **Results:** At the data cut-off of 1/12/26, 405 pts were included for assessment of QOL at baseline (MTB, n=250; usual, n=155). Baseline demographics and disease characteristics were similar for sex, age, race, ethnicity, histology, stage and performance status. QOL assessments were completed by 292 patients at 8 weeks and 245 patients at 12 weeks; MTB-AC patients experienced numerically greater declines at 8 weeks compared to usual care (FACT-L TOI: -2.7 vs -0.5; FACT-G: -1.9 vs 0.50; FACT-L: -1.4 vs 1.1), but these differences were not significant. Between weeks 8 and 12, QOL was estimated to have declined in usual care patients while MTB-assisted care patients improved, FACT-L TOI (3.28, 95% CI: 0.10 to 6.46); FACT-G (between-group difference: 3.97, 95% CI: 0.56 to 7.38); and FACT-L (4.70, 95% CI: 0.58 to 8.81). Survival is immature. **Conclusions:** The preliminary analysis showed that MTB-AC demonstrated significant, and in some cases clinically meaningful, improvement in QOL between weeks 8 and 12 after treatment across all three FACT measures compared to usual care, suggesting a delayed but meaningful benefit of MTB-AC. Clinical trial information: NCT05254795. Research Sponsor: Eli Lilly.

1575 **Poster Session**

Addressing health-related social needs for cancer patients: An implementation assessment. First Author: Samuel Woo, Albert Einstein College of Medicine, Bronx, NY

Background: Health-related social needs (HRSNs) are associated with delayed diagnosis and treatment, worsened quality of life, and higher recurrence and mortality rates for cancer patients. Health systems are beginning to recognize the tremendous impact of HRSNs by recommending standardized HRSNs screening and referral in cancer care. Further research is needed to effectively design and implement HRSNs interventions for cancer patients. We evaluated the implementation of a novel community health worker (CHW) referral and navigation intervention to address unmet HRSNs in a National Cancer Institute (NCI)-designated comprehensive cancer center serving a highly disadvantaged community of patients in Bronx County, NY. **Methods:** We conducted a retrospective study of cancer patients utilizing data from HRSNs screenings, clinician CHW referral orders, and CHW navigation services between October 2023 and March 2025. Patients were identified as eligible for CHW assistance if they were screened for and self-reported at least one unmet HRSN. We organized process and outcome measures using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) implementation framework and evaluated measures through descriptive statistics. **Results:** There were 30 cancer center clinical practices who adopted the HRSNs screening tool. A total of 8,591 patients were screened for unmet HRSNs, with 20.5% self-reporting at least one unmet HRSN. Of those with at least one unmet HRSN (n=1,758), 43.4% were referred to CHWs by clinicians. Referral rates to CHWs ranged from 26-55% by clinical practice. Of patients referred to CHWs, 794 (64.5%) were assisted with HRSNs navigation by CHWs, with the most common HRSNs identified as financial (50.3%), housing (48.7%), and food insecurities (45.5%). CHWs were successful in outreaching referred patients (95.5%) in a timely manner (Median: 3 days from referral order, IQR: 1-6 days), connecting patients to at least one social service (98.9%), and resolving or improving at least one social need (97.6%). The median annual cost to implement and maintain the CHW referral and navigation intervention to address unmet HRSNs was $345.58 per patient. **Conclusions:** Implementation of CHW referral and navigation services within an NCI-designated comprehensive cancer center was feasible and effective in addressing unmet HRSNs within a safety-net cancer population. CHWs were successful in reaching patients and connecting them with essential social services that helped to resolve their HRSNs. Further research is needed to improve clinician screening and referral and understand the impact of CHW navigation on oncologic care delivery and clinical outcomes. Research Sponsor: None.

1576 **Poster Session**

Identifying patients at risk for non-receipt of guideline-concordant treatment in pancreatic cancer using electronic health record data and machine learning. First Author: Annabelle Fonseca, University of Alabama at Birmingham, Birmingham, AL

Background: Non-receipt of guideline-concordant treatment (GCT) for pancreatic cancer is associated with worse outcomes and occurs disproportionately in safety-net settings. Timely identification of patients at risk using traditional approaches remains challenging. We developed machine learning (ML) risk prediction models using electronic health record (EHR) data available at presentation to predict non-receipt of GCT and support targeted navigation. **Methods:** We conducted a retrospective analysis of patients with pancreatic cancer treated at two safety-net hospitals in Alabama from 2018-2022. GCT was defined based on NCCN guidelines. Candidate predictors included demographic, clinical, laboratory, access-to-care and healthcare utilization variables available at presentation. Primary outcome was non-receipt of GCT. Data were split into stratified 80/20 training and test sets given class imbalance (2/3rd received GCT). Feature engineering was applied to reduce overfitting from high-cardinality variables. Classification and Regression Tree (CART) analysis was used to explore feature interactions and rank predictors. Multiple ML models were trained using PyCaret with default hyperparameters. Model performance was evaluated on the test set, with recall prioritized to reflect a screening use case in which false positives were acceptable. **Results:** Of 902 patients, 67.5% (n=609) received GCT. CART identified 30 candidate features. Highly ranked features included Area Deprivation Index, age, albumin, time from symptom onset to start of workup, employment status, presence of primary care physician, BMI and ECOG performance status. Performance metrics of the top 5 models are summarized in Table 1. Across models, test-set accuracy ranged from 72.9% to 86.2%, and recall for non-GCT ranged from 35.6% to 61.0%. Light Gradient Boosting model demonstrated the strongest overall screening performance, achieving the highest recall (61.0%), precision (94.7%), F1 score (0.74), and AUC (0.94). **Conclusions:** ML models using EHR data readily available at presentation can identify patients at high risk for non-receipt of GCT, driven in part by modifiable access-to-care and social vulnerability factors. Integration of these models into EHR workflows could enable automated risk flagging at diagnosis and trigger early referral to navigation and supportive services, with the potential to improve treatment delivery and outcomes. Research Sponsor: U.S. Department of Defense.

Test-set performance of machine learning models.

Model	Accuracy	AUC	Recall	Precision	F1 score
Decision Tree Classifier	0.79	0.77	0.51	0.77	0.61
Logistic Regression	0.73	0.79	0.36	0.66	0.46
Light Gradient Boosting Machine (LGBM) Classifier	0.86	0.94	0.61	0.95	0.74
Extreme Gradient Boosting (XGB) Classifier	0.81	0.87	0.54	0.80	0.65
Ada Boost Classifier	0.77	0.85	0.46	0.73	0.56

1577 **Poster Session**

Real-world implementation of an integrated exercise medicine model within routine oncology care. First Author: Lauren Whiting, Lift Cancer Care Services, Kurralta Park, SA, Australia

Background: Exercise is an evidence-based intervention for people with cancer, with demonstrated benefits for physical function, symptom burden, and treatment tolerance. Despite international guideline recommendations, exercise remains inconsistently implemented as a prescribed medical treatment in routine oncology care. This study describes the real-world implementation of an integrated Exercise Medicine model embedded within a supportive oncology service. **Methods:** This descriptive implementation study reports on the Lift Model of Care, a clinician-led supportive cancer care service established in Australia in 2018. Exercise Medicine is delivered as a core, medically prescribed intervention and integrated with Physiotherapy, Psychology, Dietetics, and subspecialty services across the cancer continuum. Exercise prescriptions are individually tailored and dosed by qualified clinicians in accordance with Clinical Oncology Society of Australia exercise guidelines and delivered in a medically supervised environment. Routinely collected service data were analysed descriptively. The primary outcome was annual service reach and treatment volume from 2018 to 2025. Secondary outcomes included patient-reported experience measures related to Exercise Medicine. **Results:** Annual service reach increased from 607 individuals in 2018 to 1,353 individuals in 2025. Delivery of Exercise Medicine increased from 2,077 to 12,255 treatments annually, reflecting sustained growth in access and longitudinal engagement. Concurrent increases in Physiotherapy, Psychology, Dietetics, and Lymphoedema services were observed, supporting coordinated multidisciplinary care delivery. Patient-reported experience data demonstrated high acceptability, with over 90% of respondents reporting high satisfaction and perceived improvements in fatigue, strength, functional capacity, and ability to tolerate cancer treatment. **Conclusions:** This real-world implementation study demonstrates the feasibility of embedding Exercise Medicine as a prescribed treatment within routine oncology care at scale. The model provides a pragmatic framework for integrating guideline-recommended exercise into standard cancer pathways and may inform broader adoption across health systems. Research Sponsor: None.

1578 **Poster Session**

Therapeutic strategies and reduced drug spending as a signal of early impact of the Enhancing Oncology Model. First Author: Rachel Mosher Henke, Lewin Group, Falls Church, VA

Background: Building on lessons learned from the predecessor Oncology Care Model, the Centers for Medicare & Medicaid Services designed the Enhancing Oncology Model (EOM), a voluntary, two-sided risk, episode-based payment model, to incentivize participating practices to provide high-quality, patient-centered oncology care while targeting Medicare spending reductions. At the start of the model, 44 oncology practices voluntarily joined EOM. Practices are held financially accountable for 6-month episodes of care for Medicare Fee-for-Service beneficiaries with 7 high-risk cancers. The objective of this study is to evaluate how practices implemented EOM and whether they were able to reduce Medicare spending during its first six months of implementation. **Methods:** To identify strategies practices used to meet model goals, we interviewed 93 key informants during site visits at 6 EOM practices from November 2024 through February 2025. We analyzed claims-based impacts on spending using a difference-in-differences approach using a sample of episodes of care from EOM practices and propensity score matched comparison practices during a baseline period (July 1, 2018 – June 30, 2022) and the first performance period of the model (July 1–December 31, 2023). **Results:** EOM practices reported focusing on reducing drug expenditure. Strategies included (1) substitution to value-based treatment alternatives, such as biosimilars, while mitigating the impact of drug shortages; (2) dose rounding and weight-based dosing to minimize waste and improve efficiency; and (3) avoiding drugs with limited clinical benefit, such as white blood cell growth factors for metastatic tumors. While not statistically significant, we found the model reduced total Medicare spending by $646 per episode (1.1%; 90% confidence interval [CI]: −$1,724, $433), likely driven by reductions in Part B systemic cancer therapy payments of $645 per episode (90% CI: −$1,622, $332). This is consistent with practice reports of implementing value-based prescribing strategies. **Conclusions:** Early EOM implementation results show emerging evidence of systemic cancer therapy payment reductions. These findings may reflect expanded biosimilar availability and practices' strategic focus on value-based drug substitution and dosing. Research Sponsor: Centers for Medicare and Medicaid Services.

1579 **Poster Session**

Association of routine electronic symptom monitoring with reduced opioid use in patients with head and neck cancers. First Author: Laila A. Gharzai, Northwestern University, Chicago, IL

Background: Patient reported outcomes (PROs) have become increasingly important in modern healthcare. Head/neck cancer (HNC) is associated with numerous side effects that significantly impact patients quality of life short and long term. We developed FACT-HN-RAD, a brief cancer and treatment specific PRO aiming to efficiently capture side effect burden for patients with HNC undergoing radiotherapy (RT). Here we report the clinical implementation of this measure through the electronic medical record (EMR) at two institutions. **Methods:** The PRO was prospectively integrated into routine clinical care for patients with HNC through deployment in the EMR weekly during RT (up to 7 weeks) and at 1-, 3-, 6-, 9-, and 12-month post RT. We compared a historic cohort of patients (treated July 2021-July 2023) to those treated after PRO deployment (Aug 2023-Aug 2025), assessing PRO adherence, opioid use, emergency room (ER) encounters and inpatient admissions. Baseline demographic characteristics were summarized using descriptive statistics. Clinical outcomes were compared using parametric and nonparametric statistical tests. **Results:** OF the 2,288 patients, 1,304 were in the PRO cohort and 984 were in the historic cohort. Patients had a median age of 65 (IQR 56-73) and were mostly White (81.9%), non-Hispanic (91.3%), and current/former smokers (57.5%) with a median of 20 smoking pack years (IQR 3.8-46.5). In the PRO cohort, 51.9% (n=677) submitted at least one response to the assigned PRO. Within each individual patient for the total assigned series, within patient adherence was 50.9% (ie each patient filled out approximately half of the assigned PROs over a one year timeframe). Patients in the PRO cohort required less opioids with 49.1% (n= 640) receiving any opioid prescription in the PRO cohort as compared to 60.9% (n=577) historically ($p<0.001$). The average daily strength of opioids decreased 28% in the PRO cohort (mean MME 150.1mg, SD 458.7) versus historically (mean MME 207.9mg, SD 574.8) ($p<0.001$), and the total opioids prescribed to patients decreased 44% in the PRO cohort (mean MME 3,565mg, SD 12,105) versus historically (mean MME 6,363mg, SD 18,387) ($p<0.001$). Patients in the PRO cohort overall had fewer ER visits during and within the first year after finishing RT, with 13.3% (n=173) visiting the ER as compared to 29.4% (n=289) historically ($p<0.001$). Patients in the PRO cohort had fewer inpatient admissions within the first year after finishing RT, 28.8% (n=375) as compared to 48.8% (n=480) historically ($p<0.001$). **Conclusions:** We demonstrate that the integration of routine electronic PROs into the care of patients undergoing HNC RT is associated with clinical benefits when compared to a historic cohort including reduced opioid use, reduced ER visits, and reduced inpatient admissions. This promising approach in the definitive RT setting warrants further study in a randomized clinical trial. Research Sponsor: PROTEUS Consortium.

1580 **Poster Session**

Rethinking cancer attribution in oncology VBC models: E&M vs treatment-based approach. First Author: Haibei Liu, McKesson, Irving, TX

Background: Patients with multiple cancers are uncommon. In value-based care models such as EOM (Enhancing Oncology Model),episode attribution and financial accountability rely on assigning a cancer type based on the plurality of predefined E&M visits. However, this administrative approach may not accurately represent the cancer for which a patient is receiving active treatment, especially in the presence of concurrent malignancies. Despite this, little is known about how often the E&M based cancer type differs from the treatment-based cancer type. **Methods:** We analyzed EOM performance period data (July 2023–June 2025) from practices in The US Oncology Network. Injected based initiating episodes were identified using EOM Part B claims that occurred at practices' sites, then matched to the Electronic Health Record by patient, drug, and initiating date. For oral agents, additional to patient, drug and prescribing provider, order dates within 60 days of the fill date in Part D Claims was used as a proxy in matching process. Cancer type associated with the initiating treatment was extracted from the EHR and then compared with EOM-attributed cancer types. **Results:** Episodes were predominantly triggered by injection-based chemotherapy with 13,803 initiated in physician office setting, and 5,441 were initiated by oral chemotherapy. Matching rates to an initiating event in EHR differed substantially by route:~ 90% for injection-initiated episodes vs. about 40% for oral-initiated episodes. Among injection-based episodes, 5% of episodes did not have a treatment-based cancer diagnosis in EHR and 4.5% had discordant cancer diagnoses, while oral-based episodes showed markedly higher rates of missing cancer diagnosis at 32%, with 24% mismatched diagnoses. Chronic leukemia and prostate had a higher proportion of oral initiations and correspondingly lower matching rates. Oral-initiated episodes demonstrated particularly low EHR matching in breast, lung, prostate, and small intestine/colorectal cancers. **Conclusions:** Cancer attribution in VBC models remains challenging, particularly for episodes initiated with oral therapies. As the use of oral agents continues to expand and patients increasingly present with concurrent cancers, attribution difficulties are likely to grow, resulting in greater discordance over time. Incorporating treatment-based cancer type into attribution could improve accuracy and better align assigned cancer types with actual care in value-based oncology models. Research Sponsor: None.

EHR matching by route of chemotherapy initiation.

Cancer Type	Injection Episodes (n)	Injection Concordance (%)	Oral Episodes (n)	Oral Concordance (%)
Breast Cancer	3836	91.8%	727	23.9%
Chronic Leukemia	171	83.6%	1370	50.1%
Lung Cancer	3539	93.1%	323	31.3%
Lymphoma	1724	84.6%	512	47.9%
Multiple Myeloma	1976	93.2%	1211	73.6%
Prostate Cancer	558	83.2%	1210	21.4%
Small Intestine/Colorectal Cancer	1999	89.1%	88	21.6%

1581 **Poster Session**

Modernizing injectable cancer care delivery: A telemedicine-supported home injection model for breast cancer care. First Author: Erin Mary Bange, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Among the growing population of premenopausal patients with breast cancer, years-long endocrine therapy often requires repeated clinic-administered injections, creating substantial time burden and adherence challenges. This pilot evaluated the feasibility of a telemedicine-supported home injections program designed to improve access, convenience, and patient experience. **Methods:** Patients were recruited from 4 outpatient medical oncology practices at a comprehensive cancer center between October 2024 and January 2025. Eligibility criteria included a breast cancer diagnosis, an active treatment plan including leuprolide and/or denosumab, and use of the patient portal. Patients proceeded to pilot participation after insurance approval for outpatient administration of medications and (if applicable) acceptability of copay cost. Patients and/or caregivers received in-clinic training by nursing staff on injection preparation and administration, were provided both written and video-based educational material and were followed for up to 2 home injections over a 6-month period, with telemedicine support. The primary outcome was feasibility, assessed by home injection completion rates. Patient and clinician satisfaction were assessed using the Net Promotor Score (NPS) and rates of continued at home injection administration post pilot completion. Patients were also invited to participate in 60-minute semi-structured exit interviews. **Results:** Of 105 eligible patients, 54 agreed to participate in the pilot and 24 obtained insurance approval for the medication with an acceptable copay. All 24 patients were trained in injection administration of intramuscular leuprolide, of whom 50% had no prior injection experience. Overall, 96% successfully completed one home injection, 79% of patients completed two home injections, and 75% continued home administration after follow-up. Notably, only 1 patient discontinued home injection administration due to telemedicine scheduling related issues. Patients reported high satisfaction, citing time savings and convenience as key benefits. Both patients and providers strongly endorsed the model with highly compelling net promoter scores of 69 and 61, respectively. **Conclusions:** This pilot demonstrated the feasibility of a telemedicine supported home injection care delivery model for breast cancer patients in the oncology setting, evidenced by high completion rates and patient preference to continue home administration. Educational materials and optional telemedicine visits for initial injections were leveraged to support adherence without increased healthcare utilization. Further evaluation across broader geographic, demographic, and payor mix is warranted to inform scale up. An ongoing pragmatic trial (NCT06954337) is testing this approach as part of an innovative model of care: Enhanced Telehealth. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P50 CA271357; National Cancer Institute/U.S. National Institutes of Health; P30 CA008748.

1582 **Poster Session**

Feasibility and implementation of remote geriatric assessment–guided supportive care (GAIN-S) in public oncology settings. First Author: Cristiane Decat Bergerot, Oncoclinicas&Co - Medica Scientia Innovation Research (MEDSIR), Sao Paulo, Brazil

Background: The ASCO Global Guideline recommends routine geriatric assessment (GA) for adults aged ≥65 years with cancer to identify vulnerabilities beyond standard oncology evaluation and guide tailored management. However, real-world implementation of GA-guided interventions in low-resource settings remains limited. Building on prior feasibility work in private (PRI) oncology settings, we evaluated the feasibility and implementation of a remote, multidisciplinary GA-guided intervention in public (PUB) oncology settings in Brazil. **Methods:** We conducted a prospective feasibility and implementation study in PUB settings, with contextual reference to prior PRI experience. Patients aged ≥65 years initiating chemotherapy underwent baseline GA assessing functional status, depressive symptoms (GDS), cognitive screening (Mini-Cog), chemotherapy toxicity risk (CARG), nutritional status, and quality of life (FACT-G), with repeat assessment at 12 weeks. Identified impairments prompted referral to telehealth interventions (geriatrics, nutrition, psychology/psychiatry, exercise). Feasibility outcomes included recruitment, GA completion, referral recommendations, and follow-up retention. Implementation barriers in PUB settings were prospectively documented. **Results:** A total of 109 patients were included (PRI n=61; PUB n=48). The PUB cohort was younger (mean age 72 vs 76), included a higher proportion of Black participants (58% vs 44%), had lower education (no/limited 19% and elementary school 50% vs college degree 47%), and more advanced disease (92% stage III-IV vs 54% stage IV). Baseline geriatric vulnerability was similar (median CARG 6 vs 7, GDS 2); weight loss was more frequent in PUB (54% vs 36%). Quality of life was lower in PUB (FACT-G -5 points). GA identified actionable vulnerabilities, with 21% referred to ≥1 specialist (vs 33% in PRI) and 44% to ≥2 specialists (vs 28% in PRI). Key challenges included delayed recruitment, limited digital literacy (63%), restricted videoconferencing (73%), delays in nutritional supplements (38%), and exercise adaptation (50%), prompting ongoing, context-specific adaptations. **Conclusions:** Remote GA delivery and identification of actionable vulnerabilities were feasible in PUB settings in Brazil. Similar geriatric vulnerability profiles and characterization of implementation barriers support the scalability of GA-guided care in low-resource settings. Clinical trial information: NCT07084454. Research Sponsor: Rising Tide Foundation for Clinical Cancer Research; CCR-24-200; Conquer Cancer The ASCO Foundation; Conquer Cancer The ASCO Foundation; Conquer Cancer The ASCO Foundation.

1583 **Poster Session**

From plenary to practice: A large language model (LLM)–based thematic analysis of landmark clinical trial discussions and factors influencing their real-world adoption. First Author: Aaron B. Cohen, Flatiron Health, New York, NY

Background: Landmark trials define standard-of-care (SOC), yet the translation of trial evidence into routine practice remains poorly characterized. LLMs enable the systematic extraction of nuanced clinical discourse from unstructured EHR data previously infeasible at scale. We performed an LLM-based thematic analysis of past ASCO Plenary Session (PS) trial discussions to better understand the nature of shared decision-making in routine care and characterize themes influencing SOC adoption. **Methods:** We designed a retrospective study of clinician-documented discussions with patients about PS trials presented at ASCO Annual Meetings 2021-2025. 2 trials (negative study; non-therapeutic trial) were excluded. Patient records from the Flatiron Health Database with mention of a relevant trial/NCT number within 2 years of presentation were selected. We prompted an LLM (Claude 4.5 Sonnet) to summarize documentation of clinician-patient trial discussions and extract: 1) context of discussion, 2) clinician sentiment toward trial (positive, neutral, negative) and 3) documented receipt of trial therapy (yes/no; if no, reason why not). To characterize the gap in SOC adoption, a thematic analysis was performed using a multi-model consensus approach (Gemini 2.5pro, GPT-4o, Claude 4.5 Sonnet) to identify EHR-documented discussion themes associated with trial treatment omission. LLMs provided supporting evidence for all answers; a human-in-the-loop approach was used to verify concordance between LLM-extracted themes and expert clinical interpretation. LLMs were hosted on Flatiron Health private servers and HIPAA compliant. **Results:** The study included 8650 patients and 21 trials discussed across 15 cancer types. Common discussion topics were: efficacy (78%), eligibility (78%), patient education (63%), and toxicity (28%). Clinician sentiment across studies was favorable (47%-93% positive), yet real-world trial therapy initiation occurred in only 64% of cases. Main themes associated with trial treatment omission were: clinical factors (biomarker ineligibility, comorbidities), systemic barriers (insurance, transportation, incarceration), and patient preferences (prioritizing quality of life, preserving life roles). **Conclusions:** This is the largest thematic analysis of clinician-patient trial discussions to date. We uncovered rich qualitative insights into how clinicians engage in shared decision-making with their patients, balancing positive evidence and sentiment with practical and patient-centered factors that define individualized care. Novel LLM methods can transform clinician-patient narratives into actionable evidence to mitigate disparities and optimize real-world SOC adoption. Future work will examine thematic differences by cancer type and prevalence and correlate findings with outcomes. Research Sponsor: Flatiron Health, Inc.

1584 **Poster Session**

Unmet rehabilitation needs in cancer survivors: A population-level analysis. First Author: Subha Hanif, Mayo Clinic Rochester, Rochester, MN

Background: Decades of evidence demonstrate that patients across the cancer continuum may benefit from validated rehabilitation services, yet delivery remains inconsistent. Prior reports of underuse have largely relied on small, single-site cohorts and have lacked population-level estimates of service need, referral, and visit completion, contributing to the assumption that provider reluctance to refer is a primary driver. Using post hoc exploratory analyses of population-level trial data, we evaluated patient- and system-level factors associated with non-use of rehabilitation services. **Methods:** This secondary analysis used data from the Enhanced Electronic Health Record–Facilitated Cancer Symptom Control (E2C2) pragmatic trial, an unblinded, stepped-wedge, cluster-randomized cohort study comparing an EHR-embedded symptom surveillance and management system with usual care. All patients receiving care in Mayo Clinic Midwest medical oncology practices were enrolled regardless of cancer stage or phase. Symptoms and physical function were assessed using 11-point numerical rating scales linked to oncology encounters. Sociodemographic and clinical characteristics and all outpatient rehabilitation encounters across the Mayo Clinic Enterprise were extracted from the EHR. Rates and types of completed, canceled, and no-show rehabilitation encounters were examined. **Results:** Between March 28, 2019, and January 31, 2023, 50,207 patients were enrolled; 34% reported moderate or severe physical function impairment during follow-up. Despite this, only 8,818 patients (17.6%) completed at least one rehabilitation encounter. Of 91,220 encounters scheduled, 57,669 (63.3%) were completed (mean 6.5; median 3 per participant), leaving a substantial proportion canceled or no-showed (n=33,523, 36.7%). Completed encounters were predominantly physical therapy (68.3%), with fewer occupational therapy (16.4%), physician (9.4%), and speech therapy (4.2%) visits. Encounters were concentrated among patients with breast, hematologic, gastrointestinal, and genitourinary cancers. Completion was more likely among patients who were older, female, partnered, retired, and federally insured, whereas cancellations and no-shows were more common among younger, racial or ethnic minority, urban, unpartnered, employed, college-educated, and commercially insured patients (all $P<0.001$). Virtual visits and encounters in community (vs academic) settings were more likely to be completed (all $P<0.001$). **Conclusions:** A substantial gap persists between cancer survivors' rehabilitation needs and service receipt, varying by cancer type and sociodemographic factors. High cancellation and no-show rates suggest that underuse extends beyond referral and underscore the need for redesigned, more accessible rehabilitation delivery models. Research Sponsor: None.

1585 **Poster Session**

Implementing a clinical research coordinator–led care delivery model (CRC model) in an early-phase oncology program: A pilot to streamline workflow, improve collaboration, and enhance patient-centered trial conduct. First Author: Christina Chukri, Cleveland Clinic Taussig Cancer Center, Cleveland, OH

Background: Early-phase oncology trials involve medically complex patients with narrow enrollment windows. Traditionally, CRC roles focused on data management and scheduling, with limited integration into visit-based workflows, creating gaps in protocol execution and prescreening. This pilot embedded CRCs into patient-facing workflows to improve visit preparedness, protocol reliability, and enrollment readiness in biomarker-driven Phase I trials. **Methods:** CRCs were embedded alongside investigators and research nurses during patient visits to support coordination of protocol requirements. This included standardized patient schedule education; CRC-led week-ahead planning; proactive symptom monitoring with escalation pathways; multidisciplinary supportive care coordination; and prescreening/enrollment support for biomarker-driven trials, including tissue tracking and coordination of enrollment-sensitive testing timelines. A pre- and post-evaluation was conducted. Active patients during matched 8-month pre- and post-implementation periods were identified through a CRC-maintained prescreening tracker and electronic health record review. Protocol deviations were categorized by primary attribution. Visit preparedness, timeliness of symptom escalation, supportive care coordination, and prescreening workflow adoption were assessed. Statistical significance was evaluated using the Wilcoxon signed-rank test. **Results:** Scheduling protocol deviations decreased from 42 pre- to 20 post-implementation (52% reduction), driven by fewer missed or delayed assessments and communication gaps. CRC-led week-ahead reviews improved visit preparedness, with assessment-related deviations decreasing from 37 to 4 over matched 8-month periods (~89% reduction). CRC presence centralized protocol and logistical oversight, supporting timely trial readiness in Phase I. CRC-led prescreening improved visibility into tissue availability, biomarker testing status, and cohort eligibility. Mean time to tissue submission decreased from 9 business days pre-implementation (range, 2–25; n = 20) to 2.2 business days post-implementation (range, 1–4; n = 20; $p = 3.54 \times 10^{-5}$). Across three tissue-dependent interventional trials, identification of patients meeting protocol-specified eligibility criteria increased from 39 to 59 over matched 8-month periods (51.3% increase). **Conclusions:** Adopting a CRC model improved operational reliability and prescreening efficiency, enabling faster tissue submission, quicker identification of biomarker-eligible patients, and top of scope team function. Programs facing trial complexity or staffing constraints may benefit from CRCs in visit support and prescreening roles to improve efficiency and trial access. Research Sponsor: None.

1586 **Poster Session**

Spatial heterogeneity of structural inequities in diagnostic delay and survival in early-onset colorectal cancer in a large urban catchment area. First Author: Rohan K. Patel, Department of Radiation Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Disparities in early-onset colorectal cancer (EO-CRC) stage at diagnosis and survival persist despite expanding specialty care, suggesting that structural and neighborhood-level factors, beyond traditional access measures, influence timeliness of cancer detection and treatment. We applied geospatial modeling integrating clinical data with census-based Social Vulnerability Index (SVI) and historical redlining to characterize geographic variation in diagnostic delay and median overall survival (mOS). **Methods:** We retrospectively analyzed 214 patients diagnosed with EO-CRC (<50 years) treated an urban tertiary center (2018-2025), identified via ICD-10 codes. Geocoded addresses were linked to census-tract level SVI and Home Owners' Loan Corporation redlining grades (A/B vs C/D). Access was quantified using network drive-time and Euclidean distance to colorectal surgery and gastroenterology. Spatial analyses in ArcGISPro included hotspot mapping, tract-level aggregation, and Geographically Weighted Regression (GWR) to model spatially varying associations between race, stage, access, and OS. GWR residuals $>\pm 2$ standard deviations (SD) identified clusters of excess risk. **Results:** Among 214 patients: 32% were non-White; 62% were stage III/IV; 49% lived in redlined neighborhoods. Time from symptom onset to diagnosis was non-linear with access: patients living <5 miles (89 days) and >20 miles (101 days) from specialty care experienced longer delays than those 5-10 miles (67 days) or 10-20 miles (72 days) away ($p<0.01$), consistent across drive-time and Euclidean measures. GWR demonstrated that the effects of race and stage on diagnostic delay (median local R^2=0.52, range 0.28–0.67) and OS (median local R^2=0.46, range 0.23–0.60) varied by location. High-residual clusters (>2 SD above predicted delay) localized to the Southeast and East neighborhoods of the catchment area, where non-White patients experienced 48-82 excess days of diagnostic delay after adjustment for stage, access, and SVI. High-residual areas had higher emergency or inpatient index presentation than in low-residual areas (42% vs 21%, p=0.01). The mOS was significantly lower in high-SVI vs low-SVI tracts (22 vs 38 mo; HR 1.9, $p<0.01$), in redlined versus non-redlined neighborhoods (24 vs 50 mo; HR 2.1, $p<0.002$). Within low-SVI areas, non-White patients had inferior mOS compared to White patients (28 vs 37 mo, HR 1.5, p=0.001). **Conclusions:** Spatial modeling suggests that EO-CRC disparities reflect place-based structural factors beyond clinical stage or proximity to care. Clustering of excess diagnostic delay and inferior survival in historically redlined and high-SVI neighborhoods identifies priority geographies for future studies integrating clinical and population data to design targeted, place-based navigation and early-detection interventions. Research Sponsor: None.

1587 **Poster Session**

Effect of an EHR-facilitated symptom surveillance intervention on rehabilitation utilization in cancer patients. First Author: Toure Barksdale, Department of Physical Medicine and Rehabilitation, Mayo Clinic Rochester, Rochester, MN

Background: Rehabilitation services (physical medicine and rehabilitation [PM&R], physical therapy [PT], occupational therapy [OT], and speech-language pathology [SLP]) improve physical function, symptom burden, and quality of life for cancer survivors, yet utilization remains low due to persistent barriers. The collaborative care model–based Enhanced Electronic Health Record–Facilitated Cancer Symptom Control (E2C2) pragmatic trial improved symptom burden and palliative care utilization. Using post hoc exploratory analyses of population-level trial data, we evaluated whether this EHR-facilitated approach also increased rehabilitation service use. **Methods:** E2C2 was conducted across Mayo Clinic Midwest medical oncology practices using an unblinded, stepped-wedge, cluster-randomized cohort design. The EHR-embedded intervention targeted SPPADE symptoms (sleep interference, pain, impaired physical function, anxiety, depression, and fatigue). Symptoms and physical function were assessed using 11-point numerical rating scales linked to oncology encounters. Patients received self-management materials for moderate symptoms (4–6/10) and care manager support for severe symptoms (7–10/10). All outpatient rehabilitation encounters across the Mayo Clinic Enterprise were abstracted. Mixed-effects Poisson models estimated intervention effects on rehabilitation visits during the first 365 days of exposure. **Results:** Between March 28, 2019, and January 31, 2023, 50,207 patients were enrolled. Intervention and control conditions included 31,719 and 28,938 patients, respectively, with 10,450 contributing data to both periods. Cross-sectionally, 25% of participants reported moderate and 9% severe physical function impairment. Of 91,220 rehabilitation encounters scheduled, 57,669 (63.3%) were completed. Completed encounters were predominantly PT (68.3%), followed by OT (16.4%), physician visits (9.4%), and SLP (4.2%). The intervention was associated with a more than fourfold increase in completed rehabilitation encounters during the six weeks following index symptom assessment (adjusted mean 2.22 [95% CI, 0.14–4.29] vs 0.54 [0.40–0.68]; incidence rate ratio 4.11 [1.43–11.82]; P=0.009). Scheduled encounters also favored the intervention but did not reach statistical significance. **Conclusions:** An EHR-embedded symptom surveillance intervention increased short-term rehabilitation service completion, but overall utilization remained low relative to the prevalence of physical function impairment, highlighting the need for system-level strategies to translate symptom identification into sustained rehabilitation engagement. Research Sponsor: None.

1588 **Poster Session**

Impact of the Navya Earthshot–enabled clinical decision support system on treatment turnaround time in oncology care: A real-world study from a tertiary cancer center in India. First Author: Umesh Mahantshetty, Homi Bhabha Cancer Hospital and Research Centre, Visakhapatnam, India

Background: Delays in Oncology care often result from systemic inefficiencies and patient-related barriers, leading to delayed treatment decision. Navya Earthshot is a validated Artificial Intelligence (AI) enabled clinical decision support system that matches patient records to standard-of-care oncology guidelines to generate evidence-based treatment recommendations. This study evaluated the real-world impact of Navya Earthshot implementation at a Tertiary Cancer Centre in India on turnaround time (TAT) for cancer directed treatment decision. **Methods:** This was a prospective, pre–post observational study conducted in two phases at a tertiary cancer centre in India. Baseline data collected prior to Navya Earthshot integration (December 2023–February 2024; n = 148) were compared with data from the post-implementation phase (February 2025–May 2025; n = 488). Navya Earthshot was embedded into routine clinical workflows, matching patient-specific clinical information to National Cancer Grid (NCG) guidelines to generate treatment options. These recommendations were reviewed by treating oncologists and discussed in daily multidisciplinary tumour boards. Patients were tracked from registration through diagnostic completion to treatment decision. The primary outcome was the turnaround time (TAT) for treatment decision, defined as the number of days from patient registration to treatment decision. Statistical comparisons were performed using the Mann–Whitney U test, with significance set at $p < 0.05$. **Results:** A total of 636 patients were included in the analysis, with 148 (pre-implementation phase) and 488 (post-implementation phase). Median TAT decreased from 21.4 Interquartile Range (IQR) days pre-implementation to 16.73 days (IQR) post-implementation, representing a 21.8% reduction ($p < 0.05$). The use of the Navya Earthshot decision support system was associated with a statistically significant reduction in overall TAT. This reduction reflects faster progression from patient registration through diagnostic completion to treatment decision in the post-implementation cohort. **Conclusions:** Integration of Navya Earthshot-enabled decision support system significantly improved treatment decision timelines in a high-volume public oncology setting. These findings demonstrate that scalable, guideline-aligned, patient-centric AI solutions can enhance workflow efficiency and strengthen end-to-end cancer care delivery in resource-constrained environments. Research Sponsor: None.

Impact of Navya Earthshot implementation on turnaround time for treatment decision.

Metric	Pre-Implementation Phase	Post- Implementation Phase	% Change	p-value
Turnaround Time (TAT)	21.4 days	16.73 days	↓ 21.8%	<0.05

1589 **Poster Session**

Trial characteristics and results reporting among oncology clinical trials involving African countries. First Author: Oyepeju Folashade Abioye, Allegheny Health Network, Pittsburgh, PA

Background: Sub-Saharan Africa (SSA) faced ~801,000 new cancer cases and ~520,000 cancer deaths in 2020, with deaths projected to reach 1 million annually by 2030. African trial activity remains scarce (<1% of global trials), with sparse reporting. We measured results reporting for oncology trials involving African sites and identified trial characteristics associated with results disclosure. **Methods:** Using ClinicalTrials.gov, we identified 1,140 completed oncology trials (1992-2023) involving ≥1 African site. We classified trials by country, institution, region, and funder, reporting proportions, ORs (95% CI), and multivariable logistic regression. **Results:** Among 1,140 trials across 38 countries, most were single-country (93.7%), single-institution (76.7%), and North Africa only (58.2%). Most were non-industry-sponsored (68.8%), interventional (79.5%) and randomized (61.1%). Enrollment was ≤100 participants in 666 trials (58.4%). Overall, 25.2% posted results. Multi-country trials reported more than single-country (59.7% vs 22.8%); multi-institution exceeded single-institution (60.5% vs 14.4%). SSA-only (48.0%) and both-region trials (72.1%) exceeded North-Africa-only (7.2%). Industry-funded reported more than non-industry (70.5% vs 4.6%). Phase III exceeded other phases (64.0% vs 10.6%). In multivariable analysis, industry sponsorship, multi-institution and multi-country configuration, SSA region, and phase 3 status were independently associated with results posting (Table 1). **Conclusions:** Nearly three-quarters of completed oncology trials conducted in Africa have not publicly reported results, highlighting substantial research waste and a critical ethical failure to translate participant contributions into accessible evidence. This analysis identifies independent, actionable determinants of reporting transparency. Strengthening African clinical trial infrastructure and coupling reporting requirements with systematic monitoring and accountability are essential to improve evidence generation and promote equity as the continent's cancer burden continues to rise. Research Sponsor: None.

Multivariable predictors of results reporting.

Predictor	Adjusted OR (95% CI)	p-value
Industry funding (ref: non-industry)	28.40 (19.1-42.2)	0.001
Multi-institution (ref: single)	5.81 (4.08-8.26)	0.001
Multi-country (ref: single)	2.12 (1.18-3.81)	0.012
Sub-Saharan only (ref: North Africa)	6.82 (4.68-9.94)	0.001
Both regions (ref: North Africa)	8.46 (3.45-20.7)	0.001
Phase 3 (ref: other/NA)	3.24 (2.26-4.64)	0.001
Interventional (ref: observational)	4.12 (1.48-11.5)	0.007
Enrollment >100 (ref: ≤100)	1.89 (1.32-2.71)	0.001

1590 **Poster Session**

Cancer stigma in low- and middle-income countries: A scoping review of frameworks, measurement approaches, and interventions. First Author: Emma Pearson Seevak, Harvard Medical School, Boston, MA

Background: The incidence and mortality rates of cancer are rising fastest in low- and middle-income countries (LMICs). While cancer early detection and treatment are increasingly available in LMICs, several care barriers contribute to persistent disparities in survival outcomes. One identified barrier is stigma regarding cancer and its treatment approaches. However, there is limited literature on validated measurement tools for cancer stigma and interventions to address this stigma in LMICs. **Methods:** A systematic search of six electronic databases (OVID Medline, Embase, Web of Science, EBSCO: Africa-Wide Information, EBSCO: Global Health, and WHO Global Index Medicus/African Index) was performed on August 17, 2023, and updated on November 20, 2025. Two reviewers independently screened 3174 titles/abstracts and 425 full-text articles. Three researchers extracted data from 129 eligible articles following sufficient agreement on pilot testing. The findings were synthesized using descriptive statistics and content analysis based on the Health Stigma and Discrimination framework. **Results:** Of the 129 articles, the study types included: cross-sectional surveys (109, 84%), randomized controlled trials (9, 7%), prospective cohorts with an intervention (9, 7%), one prospective cohort with no intervention, and one retrospective study. The studies were from 30 LMICs, with the plurality from China (59, 46%), followed by Turkey (12, 9%) and Kenya (10, 8%). Many studies focused on general cancer stigma (rather than a particular type of cancer) (34, 26%) and involved patients with cancer (90, 70%) or the general community (22, 17%). The studies commonly assessed stigma at the individual (113, 88%) and interpersonal (97, 75%) socio-ecological levels. 126 (98%) studies included a quantitative cancer stigma measurement tool, with the most common established tools being the Social Impact Scale (SIS, 33, 26%) and the Cancer Stigma Scale (CASS, 13, 10%). However, many used other adapted cancer stigma or HIV stigma scales. 41 (33%) studies were validation studies of a tool in the local context, 58 (46%) used previously validated tools, and 27 (21%) did not mention local validation. There were 18 studies with interventions, most of which focused on educational approaches, and 15 (83%) were published since 2021. **Conclusions:** This review demonstrates a wide variation in tools and validation practices in studies measuring cancer stigma in LMICs. Effective comprehensive interventions remain lacking and should be the focus of future studies. Research Sponsor: Harvard Catalyst CMerit/KL2; TR002542-05; Breast Cancer Research Foundation-AACR Career Development Awards to Promote Diversity and Inclusion; AGR-25-0533; Center of Global Cancer Medicine, Dana-Farber Cancer Center.

1591 **Poster Session**

Validation of pathology-based triage for the 21-gene recurrence score: A meta-analysis and qualitative synthesis of the Magee equations. First Author: Thiti Susiriwatananont, Jacoby Center for Breast Health, Mayo Clinic Florida, Jacksonville, FL

Background: The 21-gene OncotypeDX (ODX) recurrence score (RS) is the standard for chemotherapy decision-making in HR+/HER2- early breast cancer (EBC), but cost limits accessibility in resource-constrained settings. The Magee equations (MEs) use routine pathology features (Nottingham grade and IHC; ER/PR/HER2/Ki-67) to estimate RS. We performed a meta-analysis to validate MEs performance as a triage tool for ODX testing and a qualitative synthesis to identify sources of discordance, highlighting the transition toward objective digital pathology AI models. **Methods:** A systematic review identified validation studies comparing MEs with RS in HR+ EBC. Studies with sufficient data to construct a 2X2 contingency table were included; neoadjuvant trials were excluded. Primary outcomes were Negative Predictive Value (NPV) for identifying low-risk cases (RS <26 for the current TAILORx cutoff and RS<31 for the historical cutoff) and ODX test sparing rate (TSR). Data were pooled using random-effects models. Qualitative themes regarding interpretation variability were extracted from study results and discussion sections. **Results:** Thirteen studies met the inclusion criteria, representing 5396 patients in global cohorts from the USA, Mexico, Colombia, Jordan, France, Belgium, and Canada. For RS >26, Magee <18 achieved pooled NPV of 0.96 (95% CI: 0.94-0.97) and TSR 61% (95% CI:51%-69%). For RS >31, NPV increased to 0.99 (95% CI: 0.97-1.00) and TSR 52% (95% CI: 44%-59%). Pooled diagnostic performance for Magee <18 predicting RS <26 demonstrated 83% sensitivity and 71% specificity (AUC 0.81, LR+:2.53, LR-:0.28). Qualitative analysis of discordance identified: (1) Inter-observer variability: Nottingham mitotic counts and Ki-67 scoring were the primary drivers of score fluctuations. (2) IHC quantification: Variations in H-score calculation and Allred-to-H-score conversion introduced heterogeneity (3) Pre-analytical and biological factors: Inflammation and stromal proliferation occasionally inflated genomic RS; selection of non-representative blocks and intratumor heterogeneity further contributed to discordance (4) Technological solutions: Digital pathology and AI models emerge as solutions to standardize these variables. **Conclusions:** Magee-based triage provides a safe and cost-effective strategy for HR+ EBC risk stratification, with NPV up to 99% for excluding high-risk disease and sparing up to 61% of ODX testing. These results confirm a robust histopathological signal. Transitioning to objective digital pathomics provides a pathway to reduce manual subjectivity and democratize precision oncology globally. Research Sponsor: None.

Pooled diagnostic accuracy of Magee equations by cutoff.

Magee score and RS cutoff	Number of studies	Total patients	Pooled NPV (95% CI)	ODX test sparing rate (95% CI)
Magee <18/ RS>26	8	4153	0.96 (0.94-0.97)	61% (51%-69%)
Magee <18/ RS>31	5	1243	0.99 (0.97-1.00)	52% (44%-59%)

1592 **Poster Session**

Representing people's experience of cancer and its treatment (ResPECT) pilot study: A global collaborative study to improve cancer care and outcomes as part of the Lancet Commission on Cancer and Health Systems. First Author: André Pfob, Department of Obstetrics & Gynecology, Heidelberg University Hospital, Heidelberg, Germany

Background: Measurement of cancer burden increasingly informs survivorship research, health system design, and policy. Existing approaches rely on structured patient-reported outcome measures, which are costly to administer, culturally constrained, and difficult to scale globally. Advances in artificial intelligence (AI), particularly large language models (LLMs), offer the opportunity to systematically analyze unstructured patient narratives at scale. The ResPECT pilot study evaluates whether an LLM-driven framework can assess multidimensional cancer burden from patient-reported free text. **Methods:** Adult cancer patients and survivors provided structured burden ratings (Likert scale, 1–10) and open-text narratives describing physical, psychological, social, financial, and other impacts of cancer and its treatment. Unstructured text was analyzed using a retrieval augmented generation (RAG) architecture combining dense semantic embeddings (Nomic Embed), an open-weight LLM (Mistral 7B), and an ensemble retriever integrating vector similarity search and BM25 retrieval. Performance was evaluated across three predefined domains: (1) analytical concordance with quantitative analyses across 23 hypotheses as well as (2) contextual correctness and (3) hallucination rate over 50 questions, assessed by two independent reviewers. **Results:** A total of 1,642 participants from 23 countries were analyzed; 66.9% identified as female and 22.0% identified themselves to be part of an underrepresented group. Overall, impact on psychological well-being was ranked significantly higher compared to physical, social, or financial well-being (all $p \leq 0.001$). Younger participants and individuals identifying with underrepresented groups reported significantly higher overall and domain-specific burden, while U.S. participants reported greater financial burden than UK participants ($p \leq 0.001$). The LLM-based analyses reproduced quantitative findings in 21 of 23 hypotheses (91.3% concordance). Contextual correctness was 90% (90 of 100), and hallucinations occurred in 3% (3 of 100) of generated responses, predominantly involving minor paraphrasing of patient quotations. The LLM consistently identified key themes, particularly related to psychological well-being, including emotional stress, depression, relationship strain, isolation, guilt, and hope. **Conclusions:** The ResPECT initiative demonstrates that an LLM-driven framework can reliably provide and effectively scale qualitative insights into cancer burden from a patient perspective. While we acknowledge that the current pilot is not representative of cancer patients worldwide, the ResPECT approach may be scalable to derive comparable and actionable insights to inform investment in cancer services around the world. Research Sponsor: None.

1593 **Poster Session**

Understanding barriers to the clinical breast exam in Telangana, India: A survey study of participants and non-participants in underserved rural and urban areas. First Author: Nina Tamirisa, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In low-resource settings where mammography is not feasible, Clinical Breast Examination (CBE) performed by trained healthcare workers is an effective alternative for breast cancer early detection. Despite prior success of large-scale CBE programs in India, national uptake remains extremely low. This study evaluated knowledge, attitudes, beliefs, and structural barriers associated with participation in CBE screening among women in rural and urban Telangana, India and assessed factors influencing participation. **Methods:** We conducted a prospective, nested case-control study in October 2025, in which CBE participants and non-participants were drawn from the same source population. Women aged >35 years who were non-pregnant and able to consent were approached during home visits or at primary health centers (PHCs) to complete standardized surveys; participation in CBE was voluntary. Surveys captured sociodemographic factors, breast cancer knowledge, attitudes toward CBE, stigma, and treatment beliefs. Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with CBE participation, adjusting for relevant sociodemographic and belief-based covariates. **Results:** A total of 669 women were included (urban n=426; rural n=243), of whom 421 participated in CBE (participants) and 248 declined(non-participants). Among 403 CBE participants, 81.1% (n=327) reported never having had a prior breast examination. Belief that CBE is necessary even in the absence of symptoms was strongly associated with participation (81.1% vs 51.6%, $p<0.001$) as was belief that breast cancer is curable (80.6% vs 56.9%, $p<0.001$). There was no difference in fear of stigma between participants and non-participants (62.2% vs 65.3%, p=0.61). Fear of losing the breast was highly prevalent among non-participants (72%) and independently associated with lower participation (OR 0.49, 95% CI 0.28–0.87). After adjustment, urban residence was associated with lower odds of participation compared with rural residence (adjusted OR 0.28, 95% CI 0.14–0.56) as was higher household income (>☐100,000 vs ≤☐15,000; adjusted OR 0.24, 95% CI 0.12–0.46). Among non-participants, the most cited facilitators for future participation were examination by a doctor (33.5%), clinic-based exams (28.2%), and convenient timing (28.2%). **Conclusions:** Participation in CBE is influenced by modifiable belief-based and structural barriers that vary by setting. Addressing fears related to diagnosis and treatment of breast cancer and tailoring CBE delivery strategies may improve uptake and enhance early detection of breast cancer in low-resource settings. Research Sponsor: Charles M. Balch, M.D. Endowed International Fellowship in Surgical Oncology.

1594 **Poster Session**

Interpretable machine learning to identify health system levers for survival outcomes of patients with breast cancer. First Author: Erin Feliciano, NYC Health + Hospitals/Elmhurst, New York, NY

Background: Breast cancer is the most commonly diagnosed cancer and a leading cause of cancer death among women worldwide. Despite advances in screening and treatment, global disparities in breast cancer outcomes remain stark. The mortality-to-incidence ratio (MIR) is an ecological measure of cancer control performance. We applied interpretable machine learning to quantify country-level determinants of the breast cancer MIR within the health system, facilitating examination of interrelated factors for each individual country. **Methods:** We developed a CatBoost gradient-boosting model with SHAP (SHapley Additive exPlanations) analysis to predict female breast cancer MIR across 185 countries using GLOBOCAN 2022 data. Health system indicators were compiled from WHO, World Bank, and DIRAC databases, including GDP per capita, UHC index, radiotherapy centers per 1000 population, health spending metrics, workforce densities (physicians, nurses, surgical workforce per 1000), pathology services, gender inequality index, and breast screening program status. The model was trained with repeated leave-one-country-out cross-validation (10 repeats; 1850 total predictions) and nested hyperparameter optimization. SHAP values quantified country-specific feature attributions. **Results:** The model demonstrated robust predictive performance, with $R^2 = 0.793$ (95% CI: 0.726-0.844), RMSE = 0.068 (95% CI: 0.060-0.076), and correlation r = 0.891 ($p<0.001$). Global SHAP analysis identified GDP per capita as the most influential predictor (mean |SHAP| = 0.0245), followed by the UHC index (0.0217), physicians per 1000 population (0.0196), the gender inequality index (0.0151), radiotherapy centers per 1M population (0.0150), and nurses/midwives per 1000 (0.0143). The binary breast screening program indicator showed low importance (0.0066), reflecting collinearity with other health system measures. Country-specific SHAP decompositions revealed substantial heterogeneity in dominant drivers, with workforce density and deficits in radiotherapy infrastructure emerging as major barriers in lower-resource settings. **Conclusions:** Strategic investments in healthcare workforce development, radiotherapy infrastructure, and UHC expansion are associated with improved national breast cancer survival, alongside complex health system strengthening factors. These findings enable evidence-based, context-specific prioritization of health system strengthening interventions for global breast cancer control, though prospective validation is needed. Research Sponsor: Prostate Cancer Foundation; National Cancer Institute.

1595 **Poster Session**

Interpretable machine learning to identify health system levers for survival outcomes of patients with prostate cancer. First Author: Edward Christopher Dee, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Global disparities in prostate cancer outcomes are among the most pronounced across all cancer types. While incidence continues to rise globally, mortality reductions are more pronounced in countries with advanced healthcare systems. Understanding how health system factors relate to prostate cancer outcomes is critical for targeted policy interventions, particularly as the cancer burden is projected to rise substantially. We used explainable machine learning models to examine how these factors are associated with prostate cancer outcomes across countries. **Methods:** We compiled national mortality-to-incidence ratios (MIRs) for prostate cancer from GLOBOCAN 2022 and integrated them with system-level indicators from the WHO, the World Bank, UN agencies, and the Directory of Radiotherapy Centres (DIRAC). Variables included GDP per capita, the Universal Health Coverage (UHC) index, radiotherapy center density, physician and nursing workforce capacity, pathology services, and health expenditure composition. We implemented a CatBoost ensemble with repeated cross-validation and integrated SHAP (SHapley Additive exPlanations) for feature attribution to quantify country-level determinants of prostate cancer MIR while accounting for nonlinear, context-dependent relationships. **Results:** The model demonstrated strong predictive performance ($R^2 = 0.796$, RMSE = 0.078, correlation = 0.892). SHAP analysis identified radiotherapy center density, UHC index, and GDP per capita as the leading system drivers of MIR. Countries with robust radiotherapy capacity and comprehensive UHC consistently achieved lower MIR, whereas higher generic health spending alone showed a weaker correlation with outcomes. Yemen exhibited the highest MIR (0.720), driven by deficits in GDP, gender inequality, radiotherapy infrastructure, and UHC. The United States achieved the lowest MIR (0.107), driven by extensive radiotherapy density, high health expenditure, and robust coverage systems. Country-specific SHAP decompositions revealed heterogeneity: in higher-income settings, radiotherapy and health workforce predominantly lowered MIR, whereas in lower-SDI countries, lack of insurance and infrastructure remained major barriers. **Conclusions:** SHAP-empowered machine learning accurately predicts country-level prostate cancer MIR and provides actionable policy guidance. Investments in radiotherapy infrastructure and universal health coverage are likely to yield greater reductions in mortality than undifferentiated budget increases. This reproducible framework enables data-driven resource allocation and supports a precision-aligned approach to global cancer control, emphasizing equity, access, and the optimization of system-specific interventions. Research Sponsor: Prostate Cancer Foundation; National Cancer Institute; P30 CA008748.

1596 **Poster Session**

Machine learning approach to identify country-specific drivers of global cancer outcomes. First Author: Erin Feliciano, NYC Health + Hospitals/Elmhurst, New York, NY

Background: Global disparities in access to cancer diagnostics and care drive substantial variation in cancer outcomes worldwide. Identifying actionable health system factors at the country level is critical to improving survival and closing global equity gaps. We applied explainable machine learning methods to explore the interrelations among these interrelated factors. **Methods:** We developed and validated a machine learning model using data from 185 countries, obtained from GLOBOCAN 2022, WHO, and the World Bank. Mortality-to-incidence ratios (MIRs) were predicted using repeated leave-one-country-out cross-validation. SHapley Additive exPlanations (SHAP) analysis decomposed each prediction into country-specific health system-feature attributions, revealing the principal drivers of cancer outcomes. **Results:** The model achieved robust performance (R^2=0.852; RMSE=0.057; Pearson r=0.923, $p<0.001$). Globally, GDP per capita, radiotherapy center density, and the universal health coverage (UHC) index were the top contributors to MIRs. SHAP analysis revealed significant heterogeneity, identifying distinct priority drivers for each country. For example, radiotherapy infrastructure was most impactful in Turkey, UHC in Brazil and Ghana, and GDP per capita in Malaysia and China. Higher health spending as a percent of GDP was often paradoxically associated with higher MIR, underscoring the need not only for sufficient funding but also for strategic allocation. We developed a web tool that provides policymakers with country-specific SHAP estimates. **Conclusions:** Explainable machine learning translates global associations into actionable, country-specific insights. Access to radiotherapy, workforce development, and UHC expansion are consistently associated with improved cancer survival. These findings support resource prioritization in national cancer control planning and inform hypothesis generation for future causal studies. National-level analyses guide targeted investment in infrastructure and health coverage, potentially accelerating progress toward reducing global disparities in cancer mortality. Research Sponsor: Prostate Cancer Foundation; National Cancer Institute; P30 CA008748.

1597 **Poster Session**

Leukemia mortality in Latin America and the United States: A population-based analysis. First Author: Leticia Campoverde, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Leukemia outcomes depend on timely diagnosis, specialized care, and access to effective therapies. Despite improvements in high-income settings, population-level leukemia mortality in Latin America remains incompletely characterized. Comparisons across regions are further complicated by differences in diagnostic capacity and mortality reporting. We compared leukemia mortality across Latin American countries and the United States (US), using U.S. Hispanic individuals as the reference population, to characterize regional disparities, age-specific patterns, and temporal trends. **Methods:** We conducted a population-based analysis of leukemia mortality using the WHO Mortality Database for 15 countries and U.S. National Vital Statistics/SEER data. The burden of leukemia mortality was assessed from 2008 to 2019. Mortality rate ratios (MRRs) were estimated using Poisson regression. Trends were assessed using Joinpoint regression, and associations with the Human Development Index (HDI) were evaluated using linear regression. **Results:** Among children (0-19 years), most Latin American countries had significantly higher leukemia mortality than U.S. Hispanic children (MRRs 1.23-3.18), with the highest rates observed in Mexico (2.58/100,000; MRR = 3.18) and Ecuador (2.49/100,000; MRR = 3.06). In contrast, U.S. non-Hispanic White, African American, Asian/Pacific Islander, and American Indian/Alaska Native children had lower mortality than U.S. Hispanic children. Among adults (≥20 years), leukemia mortality patterns were heterogeneous. U.S. non-Hispanic White adults had higher mortality than U.S. Hispanic adults (9.6/100,000; MRR = 1.74), as did higher-HDI Latin American countries, including Uruguay and Costa Rica, whereas most countries demonstrated comparable or lower mortality. Childhood leukemia deaths were dominated by ALL, while adult mortality showed greater subtype heterogeneity, with a predominance of AML, chronic leukemias and a high proportion of deaths coded as leukemia not otherwise specified (NOS). Higher HDI was associated with lower mortality among young adults, but higher reported mortality among elderly adults. **Conclusions:** Leukemia mortality across Latin America and the US remains highly heterogeneous, with substantial excess mortality among children and older adults in several countries. Age associations with HDI and the high burden of leukemia NOS coding suggest disparities and limitations in diagnostic capacity and registry. Research Sponsor: None.

Leukemia mortality* and subtype distribution.

Population	Children Mortality Rate	Children MRR	Adult Mortality Rate	Adults MRR
U.S. non-Hispanic White	0.5	0.65	9.6	1.74
Mexico	2.58	3.18	5.76	0.92
Ecuador	2.49	3.06	5.47	0.88
Colombia	2.22	2.5	6.05	0.85
Uruguay	1.31	1.1	7.15	1.35
Costa Rica	1.28	1.05	7.09	1.13
Leukemia subtype	Children (%)		Adults (%)	
ALL	50–70		10–20	
AML	15–25		25–40	
Chronic leukemias	<5		20–35	
Leukemia NOS	8–40		17–50	

*Reference group: U.S. Hispanics.

1598 **Poster Session**

Machine learning–based decision support for ICU admission in febrile oncology patients: Optimizing care delivery and resource allocation. First Author: Aditya Venkat Iyer, Green Hope High School, Cary, NC

Background: In febrile oncology patients, distinguishing self-limiting illness from life-threatening sepsis is a critical challenge for care delivery, particularly in resource-constrained settings. Over-triage strains limited critical care capacity, while under-triage compromises patient safety. We aimed to develop and validate a machine learning–based decision support tool to assist clinical judgment in identifying patients requiring intensive care. **Methods:** In a retrospective cohort of 149 febrile oncology patients, we extracted routinely available clinical features (including MASCC score, qSOFA, hypotension status, tumor characteristics, and comorbidities). We developed an XGBoost classifier to predict ICU admission and compared its performance against logistic regression and standard clinical risk scores (MASCC, qSOFA). Model performance was rigorously evaluated using 10×5-fold cross-validation with bootstrap confidence intervals, with specific attention to its utility as a supportive screening tool. **Results:** Of 149 patients, 81 (54.4%) required ICU admission. The XGBoost model demonstrated superior discrimination with an AUROC of 0.934 (95% CI: 0.863-1.000), significantly outperforming logistic regression (0.917), MASCC (0.656), and qSOFA (0.838). The model showed excellent calibration (Brier score: 0.092). Crucially, in a sensitivity analysis excluding hypotension—a clinically obvious trigger for ICU transfer—the model retained high discriminative ability (AUROC 0.887), indicating its value in identifying high-risk patients before hemodynamic collapse. **Conclusions:** This machine learning model effectively identifies febrile oncology patients requiring ICU admission, significantly outperforming traditional scores. By functioning as a high-fidelity decision support tool, it holds the potential to improve care delivery outcomes: ensuring timely escalation for high-risk patients while preventing unnecessary resource utilization for stable patients. Ultimately, this tool is designed to augment, rather than supersede, expert clinical judgment in complex acute care settings. Research Sponsor: None.

1599 **Poster Session**

Oncology drug shortages and disruptions to cancer treatment delivery in Mexico: A national oncologist survey. First Author: Francisco Guadarrama-Conzuelo, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, DF, Mexico

Background: Oncology drug shortages increasingly disrupt cancer care delivery worldwide, yet quantitative data describing their impact on treatment decisions in middle-income countries are limited. This study evaluates how drug and supply shortages affected cancer treatment delivery in Mexico during 2024–2025. **Methods:** Between September and December 2025, we conducted a national, cross-sectional, anonymous online survey of practicing oncologists in Mexico. The survey, promoted by the Mexican Society of Oncology (SMEO), consisted of structured multiple-choice questions assessing whether oncology drug or supply shortages required treatment modifications during routine clinical practice within the preceding 12 months. Respondents could select multiple types of treatment adaptations. Descriptive statistics were used to summarize responses. **Results:** A total of 196 oncologists and hematologists completed the survey. Overall, 191 respondents (97.4%) reported performing at least one therapeutic modification due to drug or supply shortages. The most frequently reported modifications were changes in treatment regimen (79.6%), omission of one or more planned treatment cycles (71.9%), and delayed or non-timely administration (62.8%). Additional adaptations included substitution with alternative drugs within the same pharmacologic class (57.7%), non–clinically indicated dose reductions (37.8%), and use of non–guideline-approved regimens (25.5%). Referral of patients to other institutions because of treatment unavailability wasreported by 12.8% of respondents. Only 2.6% reported no treatment modifications. **Conclusions:** In this national survey of oncologists and hematologists, drug and supply shortages in Mexico were highly prevalent and associated with frequent, clinically meaningful disruptions to cancer treatment delivery, including regimen changes, treatment omissions, and delays. These findings highlight a substantial challenge for cancer care delivery in a middle-income setting and underscore the need for health-system strategies aimed at preserving treatment continuity. Research Sponsor: None.

Shortage-related therapeutic modifications reported by oncologists (n = 196).

Therapeutic modification due to shortage	n (%)
Any modification performed	191 (97.4)
Change of treatment regimen	156 (79.6)
Omission of ≥1 planned treatment cycle	141 (71.9)
Delayed / non-timely administration	123 (62.8)
Drug substitution within same class	113 (57.7)
Non-indicated dose reduction	74 (37.8)
Non–guideline-approved regimen	50 (25.5)
Referral to another institution	25 (12.8)
No modifications performed	5 (2.6)

1600 **Poster Session**

Expanding access to tyrosine kinase inhibitors for treatment of Philadelphia chromosome–positive acute lymphoblastic leukemia in low- and middle-income countries. First Author: Lauren Herzog, The Max Foundation, Seattle, WA

Background: Acute lymphoblastic leukemia (ALL) is a hematological malignancy affecting 300,000 people worldwide, with an estimated incidence of 100,000 new cases annually. An important cytogenetic abnormality, the Philadelphia chromosome, causes an aggressive form of disease that affects 3-4% of pediatric and 20-30% of adult patients. Since the early 2000s, tyrosine kinase inhibitors (TKIs) have dramatically transformed the treatment of Philadelphia chromosome positive ALL (Ph+ALL). In high-income countries, different TKI regimens in combination with chemotherapy achieve remission rates >90%, but survival rates in low- and middle-income countries (LMICs) are persistently worse, largely due to access barriers, including high costs of innovative therapies. **Methods:** The Max Foundation provides TKIs at no cost to eligible patients with Ph+ALL and other diseases in resource-limited settings worldwide. We conducted a retrospective review of all patients with a diagnosis of PH+ALL initiating treatment with TKIs between January 1, 2007 and July 31, 2025 through the Glivec International Patient Assistance Program (2007-2017) or Max Access Solutions (since 2017). Data on age at diagnosis, treatments, sex, country of origin, program status, and reason for closure were analyzed using descriptive statistics, with correlations between available variables and length of treatment explored. **Results:** Of 1,671 patients enrolled, 342 (20.5%) remained active at the time of analysis. Males accounted for 967 patients (57.9%). Patients enrolled from 47 LMICs in the Americas (542, 32.4%), Asia excluding India (414, 24.8%), Eastern Europe (365, 21.8%), Africa (219, 13.1%), and India (131, 7.8%). Median age at diagnosis was 29, with 485 (29.0%) 18 years old or younger. Most patients (1594, 95.4%) initiated treatment with imatinib as first-line treatment; of these, 110 (6.9%) moved to a second-line treatment and 18 (1.1%) to a third-line. Among 1,329 closed cases, reasons for closure included death (526, 39.8%), lost to follow-up (291, 21.9%), and clinical reasons (260, 19.6%). Median treatment length was 17 months (range 0-197 months). Patients who died were older at diagnosis (median 34 vs 28 years old) and had a shorter median treatment duration (13 vs 19 months) compared with other patients. Treatment duration tended to decrease with age; with a significant negative correlation between age at diagnosis and total months of treatment (r=-0.171, $p<0.001$). Since 2024, 25 patients received additional supportive services through The Max Foundation, including transportation assistance. **Conclusions:** This program demonstrates the feasibility of providing TKIs for the treatment of PH+ALL in diverse resource-limited geographies. Increasing access to TKIs is a critical step in eliminating global disparities in the burden of Ph+ALL. Research Sponsor: None.

1601 **Poster Session**

"Who even talks to her anymore?" Misalignment between cervical cancer care landscape and community awareness in Rwanda. First Author: Eulade Rugengamanzi, Butaro Level 2 Teaching Hospital, Butaro, Rwanda

Background: Cervical cancer remains the most common female cancer in Rwanda. Despite the significant advancement in early detection and treatment of cervical cancer in the country, many patients do not seek care or experience significant delays in seeking and getting care. Historically, elements of stigma have contributed to care non-engagement and patient delays. With ongoing growth and expansion of care services over the past decade, we sought to explore the current state of Rwandan patients' perspectives on and experience with cervical cancer stigma. **Methods:** We conducted an exploratory qualitative study using semi-structured interviews of a purposeful sample of 25 patients with cervical cancer, including 12 living with HIV, who were treated at a tertiary cancer facility in Northern Rwanda. Interviews were conducted in Kinyarwanda, audio-recorded, transcribed verbatim, and translated into English. Guided by the Health Stigma and Discrimination Framework, the team conducted thematic analysis supported by NVivo (LUMIVERO). **Results:** Our analysis revealed that cancer stigma remains prevalent in participants' communities, and this stigma has multifaceted impacts on their cancer care journey. Despite the national expansion in the availability of screening, early detection, and curative cervical cancer care services, patients continue to report limited community awareness of cervical cancer, with prevailing beliefs of fatalism and care scarcity. Knowledge gaps in cervical cancer diagnosis, treatment, and side effects contribute to stigmatizing behaviors by family members and neighbors, including rumors and social isolation. Participants also described perceptions of cancer incurability as contributing factors to social isolation. However, illness acceptance and religious engagement were identified as helpful coping mechanisms to mitigate stigma and promote care-seeking. Finally, participants' lived experiences with cervical cancer and survivorship motivated them to encourage others in their community to participate in screening and seek medical care. **Conclusions:** Our findings highlight the influence of community beliefs about cervical cancer on medical care-seeking behavior and community reception of patients. Some beliefs were misaligned with patients' current lived experiences with recent advances in the national cancer care environment. For Rwanda to achieve its cervical cancer elimination goals, these findings reinforce the need for continued community awareness of cervical cancer symptoms and treatment as well as sensitization to the available community assets for early detection and treatment. Research Sponsor: 2025 Breast Cancer Research Foundation; AGR-25-0533; Harvard Catalyst; TR002542-05; Center of Global Cancer Medicine, Dana-Farber Cancer Center.

1602 **Poster Session**

National analysis of cancer care for refugees in Moldova during the war in Ukraine (2022–2025). First Author: Horia Vulpe, Southern Ohio Medical Center, Portsmouth, OH

Background: Following Russia's invasion of Ukraine in February 2022, Moldova, a non-EU country of 2.3 million, had one of Europe's highest refugee-to-population ratios (6.4%). To meet refugee cancer care needs, the Institute of Oncology and Moldova's Ministry of Health (MOH) established a multi-sectoral financing model with the International Organization for Migration (IOM) and the Blue Heron Foundation (BHF), an American NGO. Refugee patients received a free MOH-funded consultation and access to screening and early detection. Diagnostic tests were then funded by IOM and treatment costs covered by BHF for the initial 15 months of the war, after which all services were reimbursed by IOM-led projects. **Methods:** We conducted a retrospective review of Ukrainian refugee cancer patients at Moldova's main oncology centers from May 1 2022 to July 30, 2025, with near complete national data. We analyzed demographics, diagnoses, diagnostic tests and treatments, and per-patient costs adjusted for PPP. **Results:** Of 1,398 Ukrainian refugees evaluated with suspicion of cancer, 681 (48.7%) were diagnosed with malignancy. 412 unique patients (60.5%) remained to receive medical services in Moldova. Among these, 391 were seen at the Institute of Oncology, 25 at Medpark International Hospital (including 7 seen at both institutions), and 3 at Republican Clinical Hospital. The cohort included 221 women (53.6%) and 191 men (46.4%) with an average age at presentation of 58.8 (range 5 – 88 years-old). The most common malignancies were breast (n=71, 17.2%), urological (n=62, 15%), colorectal (n=51, 12.4%), head and neck (n=40, 9.7%), and gynecological cancers (n=38, 9.2%). 292 patients (70.9%) had locoregional disease, 82 (19.9%) were metastatic, and 38 (9.2%) were unstaged. Diagnostic tests over 39 months included 400 CT scans, 70 bone scans, 69 MRIs, 5 PET-CTs, 83 mammograms, 129 endoscopies, and 20,265 lab tests. 326 (79.1%) received treatment, including 203 surgeries, 695 chemotherapy administrations, and 46 radiotherapy courses. Total costs for diagnostics and treatments covered by IOM and BHF at the Institute of Oncology were available for 305 patients, amounting to 9,943,111 MDL, equivalent to $552,782 USD at an average exchange rate of 18.02 MDL/USD. This corresponds to a mean cost of $1,812 per patient, or $4,502 per patient in purchasing-power-adjusted (PPP) international dollars, using a Moldova PPP conversion factor of 7.24. **Conclusions:** This analysis shows that comprehensive cancer care for refugees in resource-limited settings is possible via rapid partnerships among different sectors. Moldova's model offers replicable lessons for other nations facing similar humanitarian challenges. However, to this day, refugees continue to depend on humanitarian donors such as IOM for cancer services, highlighting the need to develop sustainable financing mechanisms that move beyond emergency response. Research Sponsor: None.

1603 **Poster Session**

Closing the gap in germline testing in patients with cancer through a clinic-based awareness initiative: From booth to patient's agenda. First Author: Luisina Ines Bruno, Instituto Alexander Fleming, Ciudad Autónoma De Buenos Aires, Argentina

Background: Germline genetic testing (GT) is a standard of care for a broad range of patients (pts) diagnosed with cancer due to expanded guidelines and targeted treatments options. The consequent identification of hereditary cancer susceptibility syndromes (HCS) enables optimal surveillance measures, prophylactic interventions and the identification of at-risk family members. Unfortunately, GT rates in oncology are still low worldwide. Barriers are complex but commonly related to deferred appointments and overwhelmed pts. In Argentina, GT and genetic counseling (GC) have not been endorsed as a public health need, insurance coverage relies on a case-by-case basis and mainstreaming has not been fully implemented, therefore, integrating GT into oncology workflows remains a challenge. **Methods:** Our aim was to describe the impact on GT intake of an information campaign coupled with an appointment help desk in a cancer center. We conducted a high-risk, one-month awareness social media campaign, following a one-week, in-person, information booth (during 06/26/2024 -07/03/2024), strategically placed near the waiting room of a cancer center in Argentina. Both offered informative material and the possibility to attend a free, hybrid- mode, interactive, "meet the expert" session on 07/11/2024. For those who visited the booth, in-person orientation by health providers and scheduling for a personalized GC session (in person or by telemedicine) in the following 3 months was offered. After informed consent, information from social media, landing page interaction and medical records was extracted for analysis. Descriptive statistics with Stata program was performed. **Results:** On social media: ≥600 likes, ≥20 comments, ≥350 landing page visits, ≥278 interactions and 976 new e-mail contacts were registered in the landing page. A peak of 119 visits was recorded on 07/09/2024. Media engagement rate: 5,14 %. 814 individuals registered to the hybrid session with an attendance rate of 30% (245/814), with no differences related to format option (in-person 21/73: 29% and virtual 224/741: 30%, p-value 0.794954). At the booth: 165 pts requested in-person information, 160 were scheduled for a visit: first assessments (1As): 114/160 (71%). Compliance with appointment was 64% between 1As (73/114), GT was suggested to 92% of 1As (67/73) with GT intake of 49/73 (67%) by multi-gene germline panel. Overall, 10/160 HCS were identified (diagnostic yield in intention-to-treat): 6,5%: 3 gATM, 2 gBRCA1-2, 2 gHOXB13, 1 gCHEK2, 1 heterozygous MUTYH, 1 heterozygous FANCA. Risk-reducing surgeries were performed in 4/10 carriers. **Conclusions:** Social media engagement combined with lowering appointments barriers can achieve a high compliance to 1As genetic consultations, GT and consequently identification of HCS among high-risk pts with cancer in resource-limited scenarios. Research Sponsor: None.

1604 Poster Session

Validation of a generative AI-based clinical decision support system for surgical extent in thyroid cancer in Brazil: Potential aid to de-escalating treatment to preserve function. First Author: Sergio Ferreira Juacaba, Wayne University, Detroit, MI

Background: The decision between thyroid lobectomy (TL) and total thyroidectomy (TT) for differentiated thyroid carcinoma involves balancing oncological control with morbidity. While NCCN guidelines support TL for low-risk cases, clinical practice often favors TT due to risk aversion, exposing patients to lifelong levothyroxine dependence. We validated "Korina," a clinical decision support system based on the Gemini Large Language Model developed at Instituto do Câncer do Ceará (ICC), Brazil, to assess its ability to optimize surgical decision-making and identify candidates suitable for organ-preserving surgery. **Methods:** We validated the AI model using a retrospective thyroid cohort (N = 100). The median age was 47 years (IQR 38–55), 87% were female, and histology was predominantly papillary thyroid carcinoma (99%) with 1% follicular. The median reported nodule size was approximately 1.7 cm (IQR 1.2–2.4). We (three independent medical evaluators, one head neck specialist, blinded) compared the surgical recommendations of the AI and a senior head and neck surgeon against NCCN guidelines (ground truth). The primary outcome was the accuracy of the indicated surgical extent (TL vs. TT). Performance metrics included AUC, Accuracy, Precision, and Recall (Sensitivity) for identifying TL candidates. **Results:** In the validation analysis, the AI model demonstrated superior concordance with guidelines compared to standard clinical assessment. The AI achieved an Accuracy of 0.894 and an AUC of 0.895, significantly outperforming the clinician (Accuracy 0.532; AUC 0.542). Critical analysis revealed that the clinician had a high rate of unnecessary TT recommendations, with a Recall of only 0.083 (8.3%) for the TL class. In contrast, the AI model achieved a Recall of 0.833 (83.3%) for TL. **Conclusions:** The Gemini-based system (the first in Brazil to the best of our knowledge) outperformed standard clinical judgment in adhering to NCCN guidelines. The clinician demonstrated a bias toward aggressive surgery, missing over 90% of eligible lobectomy cases. Implementing this AI tool potentially could safely increase the rate of partial thyroidectomies, directly benefiting patients by preserving thyroid function and eliminating the lifelong burden of hormone replacement therapy for a significant proportion of cases. Research Sponsor: None.

Performance metrics of AI vs. clinician (reference: NCCN).

Model	Precision	Recall (Sensitivity)	F1-Score	Accuracy	AUC
AI (Gemini)	0.952	0.833	0.889	0.894	0.895
Clinician	1.000	0.083	0.154	0.532	0.542

1605 Poster Session

Validation of an AI-based clinical decision support system for guideline-concordant prostate cancer treatment at a Brazilian cancer center. First Author: Sergio Ferreira Juacaba, Instituto do Cancer do Ceara, Fortaleza, Brazil

Background: Clinical decision support systems (CDSS) based on large language models may improve adherence to evidence-based guidelines in prostate cancer. We developed a Gemini-based CDSS for localized and locally advanced prostate cancer treatment at Instituto do Câncer do Ceará (ICC), Fortaleza, Brazil, and conducted a validation study comparing its recommendations with National Comprehensive Cancer Network (NCCN) guidelines and real-world physician decisions. **Methods:** We retrospectively included 198 consecutive patients prostate cancer treated at ICC. For each case, the CDSS generated a recommended primary treatment. Independent clinician reviewers assigned reference NCCN-concordant treatment categories. We calculated per-treatment precision, recall, F1-score, and one-vs-rest AUC comparing CDSS and physicians, with particular focus on active surveillance (AS) and radical prostatectomy (RP). **Results:** Overall NCCN concordance was 87.9% for the CDSS and 82.3% for physicians. Treatment-level analysis showed that the CDSS more often and more accurately identified candidates for active surveillance. For AS, the CDSS achieved precision 1.00, recall 1.00, F1-score 1.00, and AUC 1.00, while physicians had precision 1.00 but substantially lower recall (0.24), F1-score 0.39, and AUC 0.62. In contrast, physicians more frequently recommended RP beyond NCCN indications: for prostatectomy, the CDSS showed precision 1.00, recall 1.00, F1-score 1.00, and AUC 1.00, whereas physicians had lower precision (0.40) with recall 1.00, F1-score 0.58, and AUC 0.90. **Conclusions:** In this single-center validation study, a Gemini-based CDSS for prostate cancer treatment achieved higher overall NCCN concordance than treating physicians and improved alignment with guidelines for the appropriate use of AS. These findings suggest that integration of large language model–based CDSS into clinical workflows at cancer centers in low- and middle-income settings may reduce overtreatment and support more value-based prostate cancer care. Although we did not include data on social impossibility of AS, the finding leads to reflections on the possibility of greater use of AS, even in a region with limited resources. Research Sponsor: None.

Performance of a Gemini-based clinical decision support system vs physicians for active surveillance and radical prostatectomy (NCCN-concordant treatment metrics).

Treatment modality	Metric	CDSS (Gemini-based)	Physicians
Active surveillance (VA)	Precision	1.00	1.00
Active surveillance (VA)	Recall	1.00	0.24
Active surveillance (VA)	F1-score	1.00	0.39
Active surveillance (VA)	AUC	1.00	0.62
Radical prostatectomy (P)	Precision	1.00	0.40
Radical prostatectomy (P)	Recall	1.00	1.00
Radical prostatectomy (P)	F1-score	1.00	0.58
Radical prostatectomy (P)	AUC	1.00	0.90

1606 Poster Session

A clinical prediction score to identify symptomatic patients at high risk for colorectal cancer in South Africa. First Author: Yoanna S. Pumpalova, Columbia University Medical Center, New York, NY

Background: Colorectal cancer (CRC) is the third most diagnosed cancer globally with a rising incidence across sub-Saharan Africa. In South Africa (SA), advanced stage at diagnosis drives poor outcomes and limited endoscopic capacity makes early CRC diagnosis guidelines difficult to implement. We developed a clinical prediction score to identify patients with lower gastrointestinal (GI) symptoms at high risk for CRC in SA. **Methods:** Adults (≥18 years old) with ≥1 "red flag" lower GI symptom (weight loss, change in bowel habits, rectal bleeding, anemia, abdominal mass) referred for colonoscopy at two public hospitals in Durban were eligible for this prospective study (Sept 23, 2022 – Dec 9, 2025). Demographic and clinical data, results from a pre- or intra-colonoscopy POC-FIT, and colonoscopy results were recorded. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of POC-FIT for CRC were calculated. A clinical prediction score was derived using this cohort. The optimal number of prognostic factors for a predictive multivariate logistic regression model were determined using LASSO and model validation was done using bootstrapping technique. Overall performance was assessed using the scaled Brier score, Hosmer-Lemeshow test, and AUC. Analysis was performed using R (v 4.4.1). **Results:** Of 393 enrolled patients (median age 52 years, 54.5% female), 306 (77.9%) had a valid FIT result, with 194 (63.4%) positives. In this symptomatic cohort, the adenoma detection rate was 19.6%, with 15 low-risk (3.8%), 14 high-risk (3.6%) adenomas, and 31 (7.9%) CRCs. POC-FIT had 75% sensitivity, 38% specificity, 9% PPV and 95% NPV for CRC. If patients with a negative POC-FIT had not immediately proceeded to colonoscopy, 102 (33.3%) urgent colonoscopies could have been avoided, but diagnosis would have been delayed for 4 patients with high-risk adenomas and 6 with CRC. The LASSO model, utilizing λ=0.017, selected 3 variables associated with CRC: age greater/less than 50, weight loss (yes/no), symptom duration >3 months (yes/no) (risk score 0-3), with AUC 78.6% for predicting CRC (Table 1). Adding negative FIT result to the clinical prediction score (risk score 0-4) improved performance (AUC 79.2%). Setting a symptom score of ³2 as positive, the specificity for diagnosing CRC was 47.9%, and sensitivity 95.8%. **Conclusions:** Among South African patients referred for diagnostic colonoscopy, FIT has a strong NPV but weak PPV for CRC. A clinical prediction score for CRC among symptomatic South African patients was derived with good performance for ruling out CRC. Future studies will validate this model in the primary care setting. Research Sponsor: ASCO/Conquer Cancer; 2023CDA-8960359887.

Clinical prediction score derived from cohort of symptomatic patients undergoing colonoscopy in Durban, South Africa.

Clinical Score	No CRC	%	CRC	%	Total
0	30	100	0	0	30
1	105	99	1	1	106
2	112	91	11	9	123
3	32	74	11	26	43
4	3	75	1	25	4
Total	**282**	**92**	**24**	**8**	**306**

1607 Poster Session

Delivering oncology care in Syria: Implementation lessons from conflict-affected and resource-limited settings. First Author: Maria Hafez, St Luke's University Health Network, Bethlehem, PA

Background: Oncology services are often excluded from humanitarian health response packages despite the rising cancer burden in conflict-affected populations. In northwest Syria, protracted conflict disrupted referral pathways, depleted the specialist workforce, and constrained diagnostic infrastructure. The Syrian American Medical Society (SAMS) implemented a conflict-adapted oncology model that evolved from remote specialty support (2017) to decentralized service delivery with phased diagnostic strengthening and workforce development. We report multi-year program outputs as indicators of implementation feasibility and scale. **Methods:** We conducted a retrospective program evaluation using routinely collected, aggregate operational indicators from SAMS-supported oncology services in northwest Syria (fixed sites with referral/outreach pathways). Annual indicators (2022–2025) included: total patients served, new patients, new malignant diagnoses, total oncology diagnoses (benign + malignant), and chemotherapy administrations. Longitudinal patient-level outcomes were not consistently captured due to displacement, insecurity, and lack of a unified electronic medical record during early scale-up. **Results:** Total patients served increased from 20,779 (2022) to 28,392 (2025) (+36.6%). New patients increased from 4,648 to 12,467 (+168.2%). New malignant diagnoses increased from 1,373 to 2,000 (+45.7%), and total oncology diagnoses increased from 15,102 to 21,918 (+45.1%). Chemotherapy administrations increased from 7,177 to 15,008 (+109.1%). Key implementation milestones included the establishment of the Idlib Cancer Center (2018), phased immunohistochemistry enabled through cross-border workflows and remote expert interpretation, and the institutionalization of local diagnostic capacity through a pathology residency launched around mid-2023, supported by hybrid local/remote mentorship and digital pathology infrastructure (slide scanning for remote review). A persistent system gap was the lack of local radiotherapy, requiring cross-border referral pathways that were vulnerable to administrative and access disruptions. **Conclusions:** A phased "minimum oncology service package" integrating decentralized delivery, tele-enabled expertise, and staged diagnostic/workforce strengthening can be implemented and scaled in protracted conflict settings. In the SAMS model, structured fellowship teaching, e-consultations, and a virtual breast tumor board supported timely decision making, while missions and workshops reinforced local capacity. This transferable framework supports integrating oncology into humanitarian responses, alongside investment in radiotherapy access and continuity-of-care data systems. Research Sponsor: None.

1608 **Poster Session**

Optimization of immunotherapy duration for advanced melanoma: The prospective OTIMAS trial. First Author: Milena Perez Mak, Instituto do Cancer do Estado de São Paulo - Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil

Background: Anti-PD1 monotherapy is a common option for first-line treatment for advanced melanoma in resource-constrained settings. A shorter duration of therapy and associated biomarkers of response can reduce financial burden for healthcare systems. **Methods:** In this phase 2 single-arm trial, pts with unresectable stage III-IV melanoma received pembrolizumab (Pem) 200mg intravenously every 3 weeks for a maximum of 12m. Primary endpoint was 24m progression-free survival (PFS); secondary endpoints included overall response rate per RECIST 1.1 and overall survival (OS) and safety. An additional course of therapy was allowed if progression was observed after 6m of treatment interruption. Exploratory analysis included miRNA cargo of small extracellular vesicles (sEVs) and cost-effectiveness analysis of 12m vs. 24m in the context of the universal Brazilian health system. **Results:** 29 pts were enrolled from Jan 2022 to Jan 2025. As of Sep 2025, all had completed treatment, with a median follow-up of 19.1m (0.6-45.3). Median age was 59 years (28-85), 55.2% were male, 72.4% had metastatic disease and 20.7% had ECOG-PS $>$1. 41.4% presented with high baseline LDH. 2 pts had acral melanoma. 20.6% had received previous chemotherapy. Median PFS was 5.7m (IC95% 3.1-8.4) and 24m-PFS, 23.8%. 2-y OS was 42.8% (IC 95% 24.2-61.4). ORR was 34.5% (10/29), with 51.7% DCR. Among 24.1% who completed 12m of Pem, only one pt experienced PD less than 6m after completion of Pem. One death due to immune related pneumonitis was observed. The percentage of variable expressed regions in sEVs differed according to immunotherapy (IO) response profile. Cost analysis showed that the medication cost was reduced by 53.75% when compared to the 2-year strategy. **Conclusions:** This trial demonstrated that one year treatment with IO is feasible and provides comparable outcomes to a standard 24m treatment (mPFS 5.6 range 3.4–8.2; 2-year OS 55% IC 95% 49-61%), regardless of response. This strategy can be cost effective and provide broader access to immunotherapy and improve resource allocation in public health systems. Specific miRNAs were identified for a potential response signature to select patients with long-term benefit. Clinical trial information: NCT07376317. Research Sponsor: Medical Oncology Department - Instituto do Cancer do Estado de Sao Paulo.

1609 **Poster Session**

Optimization of geospatial oncologist placement: A maximum coverage problem approach. First Author: Ryan James Crowley, NYU Grossman School of Medicine, New York City, NY

Background: Rural communities in the United States (US) experience persistent shortfalls accessing oncology care due to an uneven workforce distribution. Non-specific county-level metrics fail to pinpoint precisely where new oncologists can maximize impact. By adapting a maximal coverage algorithm to the ZIP code level, our study aims to provide a data-driven solution to physician placement by identifying high demand areas with significant unserved populations. **Methods:** We developed a model to simulate capacity-constrained maximal coverage expansion of oncology care with up to 500 oncologist placements per state, 40 kilometer catchment radii, and an assumption that one oncologist could cover up to 6,667 individuals over 55 years old (based on baseline US prevalence of 15 oncologists per 100,000 individuals over 55). We used physician data from the Doctors and Clinicians national downloadable file, geographical data from the US Census, and Rural-Urban Continuum Codes (RUCCs) to measure rurality. Outcomes measured included baseline state-level coverage, number of placements needed to achieve 90% state-level population coverage, and urban-rural placement differences. For continuous variables, the two-sample t-test was used for statistical significance. **Results:** Nationally, approximately 26 million additional individuals would gain coverage with 5,578 additional placements. 2,912 (52.2%) of the optimal ZIP codes were in rural counties. Placements provided a mean coverage of 4,684 people per physician. Median baseline state coverage was 67.8% (IQR 59.9%-77.1%), with 3 states having $>$90% coverage at baseline (Rhode Island, Connecticut, and New Jersey). To achieve 90% coverage, states required a median of 40 placements (IQR 18.25-63.25). Coverage gains per state were front-loaded with the first 25 oncologists in a state capturing on average 46.7% of all achievable gains. The states that required the greatest number of additional oncologists to achieve 90% coverage were: California (N=209), Florida (N=174), and Texas (N=163). The top five rural placements per state covered an average of 6,505 individuals while the top five urban placements per state covered an average of 6,220 individuals (p-value = 0.009). **Conclusions:** Our approach precisely identified underserved ZIP codes where oncologist placement would maximize access to care. Strategic placement of oncologists can lead to increased access to care, particularly for rural residents. These policies should initially be directed toward states and ZIP codes with the largest baseline gaps to maximize coverage and advance equitable healthcare access. Research Sponsor: None.

1610 **Poster Session**

Scaling prior authorization for philanthropic funding with artificial intelligence (AI): Five-year outcomes from Indian Cancer Society Cancer Cure Fund (ICS-CCF) NavyaAI implementation. First Author: Nehal Rishi Khanna, Indian Cancer Society, Mumbai, India

Background: Indian Cancer Society - Cancer Cure Fund (ICS-CCF) is one of the largest charitable program for directly reimbursable treatment expenses to needy cancer patients. The prior authorization process at ICS-CCF requires the Due Diligence Team (DDT) and the Governing Advisory Council (GAC) to review every application for compliance with standardized treatment guidelines, expected cure rates, and approved costs. To augment and enhance this process, ICS-CCF evaluated and implemented the use of Artificial Intelligence (AI) to support application review and recommendations over a five-year study period. This study is a five year report on operational outcomes to reduce dependence on expert oncologists in the prior authorization setting using AI for care delivery. **Methods:** The NavyaAI platform is a clinically validated AI model that matches clinical data from beneficiary applications (input) with available clinical evidence and National Cancer Grid (NCG) guidelines, adapted to ICS-CCF approval criteria (output). Applications in which the AI output matched the input were classified as "recommended" and forwarded directly to the GAC for approval. All remaining cases were referred to the DDT, comprising a minimum of two expert oncologists, who reviewed the applications and forwarded recommendations to the GAC as appropriate. Concordance between NavyaAI and GAC decisions was assessed. The time spent by the DDT reviewing referred applications was recorded. DDT reviews were conducted weekly, and GAC reviews were conducted bi-monthly. **Results:** From April 2020 to November 2025, a total of 12001 (malignant solid tumors 63.77% (7653/12001) and hematolymphoid malignancies 36.23% (4348/12001) applications were reviewed by NavyaAI. Of these, 82.58% (9,910/12001) were recommended, 1.71% (205/12001) were rejected, and 15.72% (1,886/12001) were referred to the DDT. Concordance between NavyaAI and GAC decisions was 99.57% (9,867/9,910) for authorizations and 92.68% (190/205) for rejections. The DDT spent an average of 3 minutes reviewing each application referred by NavyaAI. On average, NavyaAI forwarded 35 applications directly to the GAC per week, saving a minimum of 210 minutes of oncologist review time weekly. **Conclusions:** NavyaAI can independently review and assess the majority (~84%) of beneficiary applications for recommendation or rejection with high concordance to expert decision-making. Further implementation of AI-assisted authorization models is warranted to scale their long-term impact on quality, efficiency, and scalability of philanthropic funding decisions within governmental and non-governmental healthcare schemes. Research Sponsor: None.

1611 **Poster Session**

Predicting immune-related adverse events (irAEs) with large language model (LLM) embeddings. First Author: Tiffany Tian, Georgetown University School of Medicine, Washington, DC

Background: irAEs are a common side effect of immune checkpoint inhibitor (ICI) therapy. Predicting irAEs from clinical records relies on traditional machine learning methods, which require time-consuming and extensive feature engineering such as removing features with many missing values or imputing values. Using LLM vector embeddings to train classifier models may require less feature engineering and leverage LLM understanding of semantic information. We assessed whether this LLM method could predict development of irAEs 12 weeks after initiating an ICI. **Methods:** We used patient (pt) data from the Immuno-Oncology Registry, a database of cancer pts from 10 DC-Baltimore-based MedStar Health network hospitals and Hackensack Meridian Health system in New Jersey. The data were divided into training (80%) and testing (20%) datasets. The training dataset was oversampled to balance the irAE class distribution. Tabular data was serialized into natural language, then passed into a LLM with original text, 0-shot, 1-shot, or few-shot prompting. Due to LLM context length limits, pt information was separated into 9 components, and each component embedding was max-pooled before concatenation. The embeddings were used to train 4 classifier models with hyperparameter tuning: XGBoost, support vector machine (SVM), logistic regression (LR), and multilayer perceptron (MLP). Five different sentence transformer or text embedding LLMs were tested. Model classification performance was evaluated by Area Under the Receiver Operating Characteristic curve (AUROC). **Results:** Of the 1459 pts, 585 (40%) experienced irAE(s). The most common cancers were lung cancer (34.5%) and melanoma (27.7%). ICIs included anti-CTLA-4 (11.0%), anti-PD-1 (58.9%), anti-PD-L1 (4.6%), anti-PD-1 + anti-CTLA-4 (14.0%), anti-PD-1 + chemotherapy (3.1%), anti-PD-1 + tyrosine kinase inhibitor (0.07%), and others (8.4%). The most common irAEs were skin rash (14.5%) and colitis (8.9%). Median AUROC was highest for XGBoost (0.654), followed by LR (0.641), MLP (0.627), and finally SVM (0.596). Median AUROC was highest for 0-shot (0.641), followed by original (0.636), 1-shot (0.619), and few-shot (0.516). Of the LLMs tested, intfloat/e5-base combined with XGBoost and the original prompt demonstrated the strongest performance (AUROC = 0.712, see Table), although for 0-shot and 1-shot LR was a stronger classifier. **Conclusions:** Using LLM embeddings to train classifier models is feasible for making predictions with tabular medical data, works best with XGBoost, and does not need prompt engineering. This method requires less feature engineering and data processing compared to standard approaches and leverages the extensive pre-training and semantic understanding of LLMs to achieve predictive power. Research Sponsor: Georgetown Lombardi Comprehensive Cancer Center; CCSG P30CA051008; National Institutes of Health (NIH) Memorial Sloan Kettering Cancer Center (MSKCC); P30 CA008748; Georgetown Lombardi Comprehensive Cancer Center.

e5-base	original	0-shot	1-shot	few-shot
XGBoost	0.71	0.62	0.67	0.62
SVM	0.56	0.61	0.67	0.65
LR	0.64	0.66	0.69	0.64
MLP	0.63	0.65	0.65	0.59

1612 Poster Session

The use of generative AI tools by cancer patients and caregivers: A cross-sectional survey of awareness, attitudes, and experiences. First Author: Rashad Ismayilov, Baskent University, Ankara, Turkey

Background: Generative artificial intelligence (AI) tools offer novel avenues for patient support, yet data on their adoption in oncology remain limited. This study evaluated the awareness, attitudes, and usage patterns of these tools among cancer patients and caregivers to inform clinical integration. **Methods:** A descriptive, cross-sectional survey was conducted at a tertiary oncology center. Adult cancer patients and caregivers completed an anonymous, structured questionnaire assessing sociodemographics, digital literacy, AI usage patterns, and perceptions. Multivariate logistic regression identified independent predictors of AI use. **Results:** A total of 400 participants (68% patients, 32% caregivers; mean age 59 years) were included. While 75% were aware of AI chatbots, only 24% used them for cancer-related information. Multivariate analysis revealed that university-level education (adjusted odds ratio [aOR] = 4.47, $p < 0.001$), younger age ($\leq$55 years; aOR = 2.64, $p < 0.001$), and recent diagnosis ($<$1 year; aOR = 2.16, p = 0.003) were independent predictors of AI use (Table 1). Notably, 69.1% of users did not disclose their AI use to their physician. Despite this, no user reported decreased trust in their physician; in fact, 26.8% reported an increase. A substantial 73.3% of all participants expressed a willingness to use a physician-verified AI tool. Subgroup analysis revealed divergent usage patterns: caregivers used AI more regularly (weekly/daily: 54.3% vs. 30.6%; p = 0.022) and focused on researching medical terminology (62.9% vs. 38.7%; p = 0.022) and alternative medicine (34.3% vs. 16.1%; p = 0.040), whereas patients were significantly more likely to seek emotional support (22.6% vs. 5.7%; p = 0.032). **Conclusions:** Generative AI use among cancer patients and caregivers remains moderate and reflects a marked digital divide driven by age and education. The prevalence of "silent" AI use raises significant patient safety concerns related to the risks of unverified information. Nevertheless, the strong demand for physician-endorsed tools highlights a clear opportunity for clinical integration. Oncologists should proactively address AI usage to mitigate misinformation risks and ensure safe integration into clinical practice. Research Sponsor: None.

Independent predictors of generative AI use for cancer information (n=400).

Parameter	aOR	95% CI	*p* value
Age (≤55 years vs. >55 years)	2.64	1.594 - 4.381	<0.001
Education level (University or higher vs. lower)	4.47	2.195 - 9.109	<0.001
Time since diagnosis (<1 year vs. ≥1 year)	2.16	1.289 - 3.625	0.003

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

1613 Poster Session

Identifying cancer cachexia using clinical reasoning artificial intelligence (AI). First Author: Vibhor Gupta, Pangaea Data, London, United Kingdom

Background: Cancer cachexia, a severe wasting syndrome, affects up to 87% of cancer patients[1] and contributes to $\geq$20% of cancer deaths[2]. Despite this burden, ~85% of healthcare providers are unfamiliar with diagnostic criteria[3], leaving patients often undiagnosed. This study evaluated whether a Clinical Reasoning AI model configured on four cachexia guidelines (Fearon[4], Evans[5], GLIM[6] and mGPS[7] criteria) and designed to emulate clinician chart review, could accurately identify cancer cachexia. **Methods:** Using structured (vitals, labs) and unstructured (clinical notes) electronic health record data the Clinical Reasoning AI employed retrieval-augmented generation[8] and agentic techniques with large language models (LLMs) to: (1) retrieve clinically relevant information based on the clinical guidelines via natural language processing (NLP) and embedding, and (2) apply guideline-based reasoning to classify patients into Group 1 (no cachexia features), Group 2 (meets $\geq$1 guideline regardless of documented diagnosis), or Group 3 (documented cancer cachexia). Accuracy was assessed against a gold standard of 50 patients classified by two independent clinicians, with conflicts resolved by a third. Performance was compared against baseline methods: ICD coding (ICD-9 799.4; ICD-10 C80.9), NLP using keywords like cancer or cachexia, and LLMs (Vanilla OpenAI GPT-o4-mini) prompted without explicit instruction to use guidelines. **Results:** The Clinical Reasoning AI demonstrated high precision, sensitivity, and specificity, outperforming baselines, particularly for Group 2 patients. ICD and NLP methods could not detect Group 2, due to code- and keyword-based constraints. Performance of LLMs without guidelines worsened with structured and unstructured data, indicating sensitivity to data overload and inability to prioritise clinically relevant information. **Conclusions:** These results show that embedding clinical guidelines within a structured retrieval-and-reasoning architecture enabled accurate identification of cancer cachexia, addressing a critical gap where standard coding and keyword methods fail. The guideline-driven approach maintained accurate clinical reasoning while processing complex EHR data. The Clinical Reasoning AI model is currently being deployed at the point of care to assess real-world implementation and impact on patient outcomes. Research Sponsor: Pangaea Data.

	Group 2				Group 3			
AI Model	**Precision**	**Sensitivity**	**F1**	**Specificity**	**Precision**	**Sensitivity**	**F1**	**Specificity**
ICD	N/A	N/A	N/A	N/A	0.759	0.815	0.786	0.696
Simple NLP	N/A	N/A	N/A	N/A	0.727	0.593	0.653	0.739
Vanilla OpenAI GPT-o4-mini (unstructured data only)	0.500	0.500	0.500	0.765	0.594	0.704	0.644	0.438
Vanilla OpenAI GPT-o4-mini (structured and unstructured data)	0.500	0.062	0.111	0.971	0.385	0.185	0.250	0.652
Clinical Reasoning AI with GPT-o4-mini	0.762	1.00	0.865	0.853	0.964	1.00	0.982	0.957

1614 Poster Session

Prospective evaluation of AI-assisted documentation and summarization in virtual multidisciplinary cancer conferences. First Author: Luxiga Thanabalachandran, Queen's University School of Medicine, Kingston, ON, Canada

Background: Multidisciplinary cancer conferences (MCCs) are central to high-quality oncologic decision-making but are frequently constrained by time-intensive and variable documentation processes. Artificial intelligence (AI) can enhance multidisciplinary collaboration by improving the accuracy, timeliness, and consistency of documentation. However, prospective evaluations of AI tools embedded within MCC workflows remain limited. **Methods:** We conducted a prospective pilot study at the Cancer Centre of Southeastern Ontario, a regional academic cancer center in Ontario, Canada. In October 2025, a hospital-approved AI system, Microsoft Copilot, was integrated into all virtual lung and gastrointestinal (GI) MCCs conducted via Microsoft Teams. All conferences were recorded and transcribed. Structured prompts for AI-generated summaries were co-developed with MCC stakeholders and refined through iterative Plan-Do-Study-Act (PDSA) cycles. AI-generated summaries were validated against clinician-prepared electronic health record (EHR) documentation. Two independent reviewers assessed case identification accuracy and concordance of key clinical content. Following validation, AI summaries were distributed to MCC participants after case discussions to support EHR documentation, with mandatory clinician verification prior to finalization. **Results:** A total of 125 patient cases from lung and GI MCCs were analyzed, of which 108 had corresponding clinician-prepared EHR documentation available for comparison. Inter-rater agreement between reviewers assessing concordance of AI-generated and clinician-prepared summaries demonstrated high agreement (Cohen's κ = 0.87). Case identification accuracy was high, with agreement rates of 97% for case number, 93% for medical record number, 96% for patient initials, 98% for presenter, 99% for diagnosis, and 99% for cancer stage; most identification discrepancies were minor and improved over time. Clinical content concordance was high, including discussion summaries at 99%, radiology at 99%, pathology at 98%, and treatment plans and next steps at 96%. Major discrepancies involving key clinical decisions were identified in 0.9% of cases. All AI-generated summaries were distributed within 24 hours following MCC completion, with a median clerical preparation time of 14 minutes per case. **Conclusions:** In this prospective, real-world evaluation, AI-assisted summaries integrated into virtual MCC workflows demonstrated high accuracy, strong safety performance, and meaningful efficiency gains. With mandatory clinician oversight, AI-supported summarization was feasible and timely, supporting its role as a scalable model for MCC documentation across oncology programs. Further multicenter studies are warranted to evaluate generalizability, clinician workload impact, and downstream effects on care delivery. Research Sponsor: None.

1615 Poster Session

Assessing the true burden of immune-related colitis in lung cancer through large language model–enabled clinical phenotyping. First Author: Himil Mahadevia, Mayo Clinic Florida, Jacksonville, FL

Background: Immune checkpoint inhibitors (ICIs) have revolutionized lung cancer treatment but cause adverse events, including immune-related colitis (ir-colitis). Accurate identification of ir-colitis is critical for improving patient outcomes and clinical research. However, current methods relying on ICD codes have substantial limitations: non-specific categories that fail to capture the cases or distinguish cases from infectious or ischemic etiologies, as well as incomplete coding that leads to missed cases. Large language models (LLMs), with advanced natural language understanding capabilities, offer a scalable approach for automated phenotyping using unstructured clinical notes. We aimed to develop and evaluate an LLM-based approach for identifying ir-colitis in patients with lung cancer receiving ICIs and compare it with ICD code based method. **Methods:** We identified 5,278 lung cancer patients with ICI administration at Mayo Clinic (2012-2025). To investigate ir-colitis occurrence within two years after ICI initiation, patients were stratified into three ICD-based cohorts: (1) IR-Colitis, with clinician-assigned ir-colitis-specific diagnosis codes; (2) Non-IR Colitis, with colitis diagnosis codes excluding ir-colitis; and (3) No-Colitis, absent of any colitis-related codes. We used three open-source LLMs to process clinical notes : Llama4, MedGemma, and Qwen. Prompts were designed to extract both gold standard evidence (explicit ir-colitis terminology, such as "immune-mediated colitis" and "checkpoint inhibitor colitis") and supportive evidence (such as pathology and lab results). **Results:** Llama4 demonstrated superior accuracy among three LLMs in manual evaluation and was thus selected for all cohort analyses. Among ICD-based IR-Colitis patients (n = 339), 82.0% had confirmatory evidence while 18% lacked evidence, suggesting potential false-positive coding. In the Non-IR Colitis cohort (n = 297), LLM-based extraction identified 43.8% patients in fact had ir-colitis, demonstrating substantial misclassification. In the No-colitis cohort (n = 4,642, random sample of 996 for analysis), the LLM identified 10.7% with documented ir-colitis, revealing substantial missing by administrative coding. **Conclusions:** LLM-based phenotyping demonstrates superior sensitivity for identifying ir-colitis compared to ICD codes alone, successfully uncovering cases missed by administrative coding. This scalable approach enables more comprehensive case identification for immunotherapy safety research and clinical surveillance. Research Sponsor: None.

	LLM-Identified ir-Colitis		
ICD-Based Cohorts	**Gold Standard Evidence**	**Supportive Evidence**	**Any Evidence**
ir-Colitis (n = 339)	277/339 (81.7%)	275/339 (81.1%)	278/339 (82.0%)
Non-ir-Colitis (n = 297)	129/297 (43.4%)	126/297 (42.4%)	130/297 (43.8%)
No Colitis (n = 996)	106/996 (10.6%)	104/996 (10.4%)	107/996 (10.7%)

1616 Poster Session

Correlation of tumor-naive methylation-based preoperative ctDNA testing with pathologic upstaging and occult metastasis in early-stage solid tumors. First Author: Xiangnan Li, Department of Thoracic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background: The TNM staging system serves as the cornerstone for most solid tumor treatment strategies. However, preoperative evaluation of early-stage cancers is not always reliable, with a particular propensity to overlook occult lymph node metastasis (OLNM) or even distant metastases. In turn, incorrect staging may lead to suboptimal perioperative decisions, including inappropriate surgical strategies, unjustified neoadjuvant therapy, and inadequate lymph node dissection. This study evaluated whether preoperative circulating tumor DNA (ctDNA) detected by methylation-based assay is associated with pathologic upstaging and the presence of OLNM or distant metastasis across multiple types of solid tumor. **Methods:** This study analyzed preoperative blood samples from a validation cohort within a multi-cancer early detection (MCED) study, encompassing 16 high-burden cancer types in China. Lymphomas, liver cancer, and nasopharyngeal carcinoma were excluded, due to limited use of TNM staging and/or non-routine radical surgery. Patients who had received neoadjuvant therapy were also excluded. ctDNA was detected using a targeted methylation-based MCED assay. Associations between ctDNA positivity and discrepancies between clinical (cTNM) and pathologic (pTNM) staging-including upstaging due to OLNM or distant metastasis-were examined statistically. **Results:** A total of 681 cases of clinical stage I–II cancers were analyzed, including lung cancer (n=124), breast cancer (n=113), colorectal cancer (n=88), gastric cancer (n=79), pancreatic cancer (n=55), cervical cancer (n=54), ovarian cancer (n=36), prostate cancer (n=34), esophageal cancer (n=32), endometrial cancer (n=31), bladder cancer (n=17), renal cancer (n=17), and gallbladder cancer (n=1). Preoperative ctDNA was detectable in 46.8% (184/393) of stage I and 71.5% (206/288) of stage II patients. ctDNA-positive patients were more likely to undergo pathologic upstaging than ctDNA-negative patients (16.9% vs. 6.9%; p=0.0002). For patients with clinical N0 (cN0), OLNM (defined as preoperative cN0 with postoperative confirmation of pN1–3) was more common in ctDNA-positive patients (12.6% vs. 4.7%; p=0.0012) . Among clinically M0 patients, three were confirmed as pathologic M1, all ctDNA-positive. **Conclusions:** Methylation-based preoperative ctDNA testing correlates with pathologic upstaging and OLNM, and may also be associated with occult distant metastasis. This finding supports the potential of ctDNA testing to refine preoperative staging and inform perioperative decision-making. Further validation with an expanded sample size will be conducted in an additional blinded cohort to confirm these findings. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co. Ltd.

1617 Poster Session

Sources matter: Learning to evaluate large language models for oncology treatment plans and changes observed by anchoring models to an oncology-specific database. First Author: Connor Yost, Creighton University School of Medicine-Phoenix, Phoenix, AZ

Background: Large language models (LLMs) are increasingly evaluated for oncology decision support, yet guideline concordance and hallucinations remain variable across cancer types and tasks. Retrieval-augmented generation (RAG) may improve safety by constraining the evidence base used during generation. Prior oncology LLM studies report discordance with guideline-based care, but few describe a reproducible health-system "vetting mechanism" that couples guideline-only retrieval with clinician-scored safety rubrics across multiple oncology domains. **Methods:** We assembled 316 de-identified oncology cases in a tumor-board template: medical oncology (breast, GI, GU, leukemia; n=216), gynecologic oncology (n=50), and neuro-oncology/CNS metastatic cancer (n=50). Each case was run on three systems: baseline GPT-4 (O1), NCCN-guideline anchored RAG (O2; guideline-constrained retrieval), and a literature-anchored system (OpenEvidence; O3). Oncologists independently scored outputs using a modified Generative Performance Score (mGPS; −1 to +1) combining guideline concordance with hallucination penalties; readability/rationality was scored on a 1–5 Likert scale. Inter-rater reliability was assessed (κ =.63). This workflow was designed as a pre-deployment model credentialing step for health-system governance (source policy → case bank → clinician-scored acceptance criteria). **Results:** Across all 316 cases (case-averaged), O2 achieved the highest mean total mGPS (0.75) compared with O1 (0.43) and O3 (0.59). In the medical oncology cohort (n=216), O2 outperformed O1 and O3 (mean mGPS 0.72 vs 0.35 and 0.54), with higher guideline concordance (0.85 vs 0.68 and 0.75) and lower hallucination penalties (−0.09 vs −0.25 and −0.19); readability was also highest for O2 (4.17 vs 3.22 and 3.86). In gynecologic oncology (n=50), O2 again performed best (mGPS 0.827) relative to O3 (0.697) and O1 (0.647). In the CNS cohort (n=50), mean composite mGPS favored O2 (0.82) over O3 (0.68) and O1 (0.55), while readability remained stable across models (3.55–3.73). Severe hallucination/unsafe recommendation rate: O1 [26%], O2 [5%], O3 [17%] (pre-specified definition; e.g., major fabricated citation or guideline-discordant harmful recommendation). **Conclusions:** In a 316-case, multi-domain clinician-scored evaluation, limiting retrieval to oncology guideline sources improved safety-aligned performance relative to unconstrained generation or literature-only anchoring. A guideline-constrained RAG configuration paired with clinician-scored rubrics and tail-risk reporting can serve as a practical health-system vetting mechanism for governance, re-validation, and change control of LLM decision support, including in resource-limited settings where reliable guideline-consistent recommendations are essential. Research Sponsor: None.

1618 Poster Session

Impact of AI-augmented histopathology review on next-generation sequencing (NGS) success. First Author: Boleslaw Leszek Osinski, Tempus AI, Inc., Chicago, IL

Background: Insufficient nucleic acid quantity (QNS) can compromise NGS success (QNS rates can be >20%), necessitating re-biopsies and delaying therapy. While interventions like extended de-crosslinking (EXT) can rescue samples with low total nucleic acid (TNA) yield tissues, they prolong processing times, demanding a precise method to identify samples requiring such processing. We developed an AI system, Paige Predict (PP), that analyzes digitized H&E slides to predict NGS QNS and recommend tissue input quantity. This study evaluates PP in two contexts: (1) optimizing internal lab workflows by selectively routing high-risk samples to EXT, and (2) exploring its utility in an external setting, Cedars-Sinai (CS), to triage samples for comprehensive Tempus genomic profiling (CGP), requiring >50ng input, vs targeted low-input assays (>5ng) performed at CS. **Methods:** We conducted a validation study in the Tempus lab comparing a baseline period prior to introduction of EXT (July 2024 - Sept 2024 n=17,026) against an intervention period (Oct 2025 - Nov 2025, n=12,975) where PP automatically routed at-risk samples to EXT. To evaluate external utility, we also performed a retrospective analysis on a cohort of CS pts. We assessed PP's ability to predict CGP QNS, and compared it against pathologist assessment for inter-institutional sample referral. **Results:** In the validation study, PP-guided EXT routing reduced joint DNA+RNA QNS rates by 19.6%, with a number needed to test (NNT; 1/Absolute Rate Reduction) indicating that for every 40.2 pts, one received a result that would otherwise not have. RNA QNS rates reduced by 15.9% (NNT 63.7) relative to the baseline period. This reduction was achieved while decreasing net tissue input by 16.7% and increasing TNA yields in the optimal range (100–1500ng) by 19.0% (NNT 10.1). Similar benefits were observed in the NSCLC subset. In the external CS cohort, PP could have triaged 74% of samples that failed Tempus CGP to low input sequencing at CS. Conversely, PP indicated that over 70% of samples sequenced at CS could have succeeded with Tempus CGP. **Conclusions:** PP significantly reduces NGS failure rates and improves tissue stewardship by deploying rescue workflows only when necessary. These analyses lay the groundwork for a future multi-institution prospective trial and establish PP as a scalable AI tool to amplify access to precision oncology. Research Sponsor: None.

(Tempus) EXT routing validation metrics (N=12,975 all / 3,530 NSCLC)	PP % change vs. baseline (p-value) / NSCLC subset	NNT vs. baseline / NSCLC subset	(Cedars-Sinai) retrospective analysis metrics (N=1,082)	PP % flagged for QNS (50ng)
DNA+RNA QNS rate	-19.6% (2.0e-9) / -30.4% (8.6e-9)	40.2 / 24.4	DNA QNS	74%
DNA pass & RNA QNS rate	-15.9% (1.1e-4) / -3.1% (7.0 e-1)	63.7 / 384.6	DNA Pass	16.4%
Optimal TNA range	+19.0% (2.0e-12) / +21.0% (5.3e-11)	10.1 / 9.0	Not referred	28.6%
Median N input slides	-16.7% (3.0e-11) / -14.3% (6.4e-7)	N/A		

1619 Poster Session

Validation of electronic phenotyping algorithms for prostate cancer in All of Us and their impact on genetic association studies. First Author: Zachary Creech, Department of Medicine, Duke University School of Medicine, Durham, NC

Background: The *All of Us* Research Program enables large scale population-based genetic association studies of cancer. *All of Us* does not contain cancer registry data, risking misclassification of cancer diagnosis. Thus, validated electronic phenotyping algorithms for cancer diagnoses are needed. We sought to develop and validate prostate cancer (PCa) phenotyping algorithms in *All of Us*, and assess the impact of different algorithms on gene-cancer associations. **Methods:** We conducted a cross-sectional analysis of *All of Us* male participants aged ≥50 years with structured electronic health record (EHR), personal health history survey, and whole genome sequencing (WGS) data (Duke IRB Pro00119057). Using self-report of PCa history as the gold standard, we developed and evaluated two electronic phenotyping algorithms: (1) two PCa diagnosis codes; or (2) two PCa diagnosis codes plus evidence of PCa treatment with radical prostatectomy, radiotherapy, or androgen deprivation. For each algorithm, we computed positive predictive value (PPV), and negative predictive value (NPV) with 95% confidence intervals (CI). Using each algorithm, we conducted genetic association studies between PCa and rare pathogenic variants (RPVs) in PCa predisposition genes (*ATM, BRCA1, BRCA2, HOXB13* G84E) among male participants with structured EHR and WGS data. Included RPVs had pathogenic/likely pathogenic designation in ClinVar with at least two stars. Gene-based odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression, adjusting for age and top 5 principal components. **Results:** We included 21,883 males in the validation study of PCa phenotyping algorithms, 3,961 (18.1%) of whom reported a personal history of prostate cancer. Algorithm 1 demonstrated a PPV of 0.897 (95% CI 0.885 – 0.907) and NPV of 0.927 (95% CI 0.923 – 0.931). Algorithm 2 demonstrated a PPV of 0.927 (95% CI 0.910 – 0.942) and NPV of 0.864 (95% CI 0.860 – 0.869). In the study of gene-PCa associations, 94,446 male participants were included, except for *HOXB13* G84E (n = 59,915), which was limited to those of European ancestry. Associations between RPVs in PCa predisposition genes and PCa diagnoses using the two algorithms are shown in the Table. **Conclusions:** The inclusion of PCa treatment improves the PPV of PCa electronic phenotyping algorithms. PCa phenotyping definitions influence the results of downstream genetic association studies, and highlight the need for accurate and validated electronic phenotyping algorithms when using *All of Us*. Research Sponsor: None.

Gene	OR[a] (Algorithm 1[b])	95% CI[c] (Algorithm 1)	OR (Algorithm 2[d])	95% CI (Algorithm 2)
ATM	2.10	1.47 - 2.92	2.68	1.67 - 4.08
BRCA1	1.11	0.73 - 1.61	1.16	0.61 - 1.98
BRCA2	2.14	1.53 - 2.92	3.11	2.04 - 4.56
***HOXB13* G84E**	3.88	2.75 - 5.39	3.31	1.98 - 5.22

[a]OR = odds ratio.
[b]Two prostate cancer diagnosis codes.
[c]CI = confidence interval.
[d]Two prostate cancer diagnosis codes plus treatment.

1620 Poster Session

A context-constrained oncology agent for automated, guideline-concordant treatment decision support in precision oncology. First Author: Deva Datta Reddy Jyothi, Cancer Moonshot, Bengaluru, India

Background: Precision oncology requires biologically plausible, clinically executable decisions aligned with regulatory approvals. General-purpose Large Language Models (LLMs) often produce recommendations rejected by molecular tumor boards due to semantic drift, inappropriate agent extrapolation, and ignored clinical constraints, raising significant safety concerns for point-of-care adoption. **Methods:** GenOnco is a constrained oncology agent integrating NCCN, ASCO, and ESMO clinical practice guidelines; FDA/EMA regulatory approvals; NEJM seminal articles and high-impact publications; curated clinicogenomic resources (e.g., Molecular Oncology Almanac); comprehensive clinical trials knowledge (ClinicalTrials.gov, landmark phase III results); and practice-changing trial evidence. The system utilizes a dual-layer architecture: a reasoning LLM paired with a deterministic, non-LLM clinical decision layer that enforces line-of-therapy requirements and actionability filters independent of generative output. We evaluated GenOnco on 102 multi-institutional oncologist-derived real-world solid tumor queries, independently scored by two blinded oncologists (κ = 0.87). Performance was benchmarked against published datasets: MEREDITH (200 cases) and Google DeepMind AMIE (100 cases). Primary endpoints were guideline concordance and clinical executability, analyzed via McNemar's test (N = 162). **Results:** GenOnco achieved 95.1% accuracy (95% CI: 91.2%–98.4%) on synthetic benchmarks and 93.1% (95% CI: 89.1%–96.5%) on real-world queries, eliminating 100% of expert-rejected outputs from comparators. GenOnco significantly outperformed GPT-4o (48.1%), Claude 3.7 (49.4%), Gemini 2.5 (50%), ASCO Guidelines Assistant (67.3%), OpenEvidence, MEREDITH, and Google DeepMind AMIE (all $P < .001$; N = 162), with gains of 15-47 percentage points. **Conclusions:** Constrained reasoning prioritizing executable pathways outperforms unconstrained LLMs for precision oncology support. Limitations include solid tumor focus and query diversity; diverse population validation planned. GenOnco demonstrates potential for point-of-care integration. Research Sponsor: None.

1621 Poster Session

Comparing oncologists, a GPT-based model, and a SEER-based survival calculator for cancer prognostication. First Author: Lyndon Huang, Dell Medical School, The University of Texas at Austin, Austin, TX

Background: Prognostic estimates guide cancer treatment planning and goals-of-care discussions. Clinicians often rely on population-based survival statistics (e.g., SEER), which may not reflect individualized risk. Large language models (LLMs) such as ChatGPT may offer more personalized estimates, but their performance relative to oncologists and population-based tools remains unclear. **Methods:** We conducted a retrospective comparative study of 205 adult cancer patients treated in a safety net cancer clinic. For each patient, one deidentified clinical note from the time of diagnosis was provided to a HIPPAA compliant instance of ChatGPT (GPT-4.1) and an oncologist unfamiliar with the patient. Both generated binary (alive/deceased) and probabilistic (0–100%) predictions of survival at 6 months, 1, 2, and 5 years. The primary endpoint was per-patient binary accuracy (0–4 correct timepoints) comparison between ChatGPT and the oncologist. Secondary outcomes (n=189) included Brier scores, and calibration metrics compared with oncologists and a publicly available SEER-based cancer-specific survival calculator (CancerSurvivalRates.com), and subgroup analyses by cancer stage. Significance testing used exact binomial methods for per-patient win–loss comparisons and paired nonparametric tests to compare probabilistic performance across methods. **Results:** Of the 205 patients, 25, 53, 53, and 74 were stages I, II, III, and IV, respectively. Gender was balanced (53% male). All surviving patients had at least 5 years of follow-up. Notes varied in final staging and treatment plans, as some patients were in their initial evaluation. In the primary analysis (N = 205), ChatGPT was numerically, not statistically, superior to the oncologist (52 vs. 41, p=0.299). In secondary analyses (n = 189), ChatGPT had superior overall accuracy with lower Brier scores at 1 year ($p < 0.001$) and 2 years ($p = 0.030$). Calibration analyses showed that at 5 years, ChatGPT achieved near-ideal reliability (calibration slope 1.018), whereas oncologists demonstrated overconfidence (slope 0.535). As expected, cancer specific survival by CSR was significantly higher than OS estimates from oncologists or ChatGPT. Stage-stratified analyses revealed oncologist superiority in Stage I disease ($p = 0.036$), while ChatGPT significantly outperformed oncologists in Stage IV disease at 2- and 5-year horizons (both $p < 0.001$). **Conclusions:** For a safety-net cancer clinic, using one unstructured note, ChatGPT demonstrated comparable or superior prognostic estimates for clinically relevant time points as compared to oncologists, particularly in long-term outcomes for advanced disease. Future studies should evaluate cancer specific survival and prognosis after or during treatment. Research Sponsor: None.

1622 Poster Session

Machine learning modeling for predicting 60-day prognosis in newly diagnosed advanced solid tumors. First Author: Yakir Malyanker, Sheba Medical Center, Ramat Gan, Israel

Background: Accurate mid-term prognosis estimation in patients newly diagnosed with advanced, non-operable or metastatic cancer is critical for evaluation and treatment prioritization and palliative care planning. A 60-day time horizon is clinically meaningful, as major oncologic assessments typically occur at 2–3-month intervals. Existing prognostic tools have shown limited clinical adoption. **Methods:** We conducted a retrospective analysis of patients evaluated at the Sheba Medical Center Oncology Rapid Diagnosis Clinic between 2017 and 2025. Eligible patients had metastatic or locally advanced, non-operable solid tumors. A raw dataset was generated using the MDClone platform (overall 60-day mortality ~18%). A case-enriched training cohort (n=524; 39.3% 60-day mortality) and an independent test cohort (n=343; 19% 60-day mortality) were randomly selected. Seventy-four features were included, encompassing demographics, laboratory values, ECOG performance status, and clinical variables extracted from physician notes using a large language model (LLM). LLM extraction accuracy was validated against expert manual review in 32 randomly selected cases (accuracy 0.91–1.0). Logistic Regression, Random Forest, and XGBoost models were trained with grid-search hyperparameter optimization to predict 60-day survival (y=1) versus death (y=0). Performance was evaluated on the independent test set. Wilson score intervals were used for proportion confidence intervals, and Hanley–McNeil method for AUC confidence intervals. Feature importance for the top-performing model was assessed using SHAP. **Results:** Performance of different ML models is summarized in table 1. Random Forest demonstrated the best overall performance. All models showed high positive predictive value for survival but limited ability to predict short-term mortality. The most influential Random Forest features included INR, CRP, albumin, ECOG status, total protein, LDH, emergency-related hospitalizations, age, neutrophil count, and history of cardiovascular disease. **Conclusions:** A Random Forest–based model accurately identifies patients likely to survive 60 days, supporting timely evaluation and initiation of oncologic treatment. Prediction of short-term mortality remains limited, suggesting intrinsic unpredictability of mid-term outcomes or the need for additional clinical or biological features. Research Sponsor: None.

Metric (95%CI)	Random Forest	Logistic Regression	XGBoost
ROC AUC	0.84 (0.79-0.88)	0.81 (0.76-0.86)	0.80 (0.75-0.85)
Sensitivity	0.89 (0.85-0.92)	0.82 (0.77-0.86)	0.80 (0.75-0.84)
Specificity	0.62 (0.49-0.72)	0.62 (0.49-0.72)	0.63 (0.51-0.74)
PPV	0.91 (0.87-0.94)	0.90 (0.86-0.93)	0.90 (0.86-0.93)
NPV	0.57 (0.45-0.68)	0.45 (0.35-0.55)	0.43 (0.33-0.53)
Accuracy	0.84 (0.80-0.87)	0.78 (0.74-0.82)	0.77 (0.72-0.81)

1623 Poster Session

Evaluation of AI-guided questioning versus standard information delivery in a simulated newly diagnosed breast cancer population. First Author: Emma Singel, Aspiring Scholars Directed Research Program, Fremont, CA

Background: Patients newly diagnosed with breast cancer frequently experience information overload and anxiety, which can impair understanding and participation in shared decision-making. Artificial intelligence (AI)–guided educational approaches may support individualized information delivery; however, their impact on patient understanding and emotional response remains incompletely characterized. **Methods:** We conducted a prospective, randomized vignette-based survey study among adults (≥18 years) asked to imagine receiving a new diagnosis of early-stage breast cancer. Participants were randomized 1:1 to receive either standard written information or AI-guided questioning that adapted presentation of identical content based on stated preferences and level of detail. Outcomes included a composite breast cancer knowledge score (range 0-20) (primary endpoint), perceived information overload, anxiety, decision confidence, and clarity (all Likert-scale measures, range 1-5). Group comparisons were performed using Welch's two-sample t-test. Exploratory subgroup analyses included educational level and health-related background. **Results:** 102 participants completed the survey (51 per group). Mean knowledge scores were higher in the AI-guided group compared with standard information (17.6 vs 13.2, p=0.00022). Participants receiving AI-guided questioning reported lower information overload (2.31 vs 3.35, p=0.00012), lower anxiety (3.67 vs 4.16, p=0.031), greater decision confidence (4.06 vs 2.84, $p=1.2\times10^{-6}$), and higher perceived clarity (4.20 vs 3.18, $p=2.9\times10^{-5}$). Exploratory analyses showed greater benefits among participants without graduate education or health-related background (both $p<0.001$), with smaller, non-significant differences in those with higher education or healthcare experience. **Conclusions:** In a simulated newly diagnosed breast cancer population, AI-guided questioning was associated with improved understanding, reduced information overload and anxiety, and greater decision confidence compared with standard information delivery. Exploratory analyses suggested that benefits were more pronounced among participants without graduate-level education or medical background, supporting a potential role for human-centered AI in equitable patient education. Given exploratory nature and unequal subgroup distributions, confirmation in prospectively stratified studies is needed. Research Sponsor: None.

Outcomes by information delivery approach.

Outcome (range)	Standard information (n=51)	AI-guided questioning (n=51)	p value
Knowledge score (0-20)	13.2	17.6	0.00022
Information overload (1-5)†	3.35	2.31	0.00012
Anxiety (1-5)†	4.16	3.67	0.031
Decision confidence (1-5)‡	2.84	4.06	1.2×10^{-6}
Clarity (1-5)‡	3.18	4.20	2.9×10^{-5}

†Lower scores indicate better outcome.
‡Higher scores indicate better outcome.

1624 Poster Session

Age-dependent pathogenic variant risk in female breast cancer. First Author: Lina Sulieman, Vanderbilt University Medical Center, Nashville, TN

Background: Germline pathogenic and likely pathogenic variants (GPVs) in *BRCA1*, *BRCA2*, and *PALB2* raise female breast cancer risk. Genetic counseling and screening guidelines rely on fixed age estimates. Using two large biobanks, All of Us Research Program (AoURP) and BioVU biobank, we aim to characterize age-dependent breast cancer risk trajectories and associations with family history (FH). **Methods:** In AoURP, we extracted data on female participants with genetic data to identify those with *BRCA1*, *BRCA2*, and *PALB2* GPVs, FH surveys to identify those with first degree breast cancer FH (BCFH), and electronic health records (EHR) to determine presence of breast cancer diagnosis and diagnosis age. Age served as the time scale, with left truncation at first EHR entry and censoring at last EHR event. Gene-specific breast cancer risk was estimated using Cox models with age-dependent genetic effects, adjusted for genetic ancestry (first five principal components) and FH. Analyses in AoURP were stratified by self-reported race and BCFH. We validated results in BioVU using the same methodology excluding FH which was unavailable as discrete data. **Results:** In AoURP, 100,916 women with genetic, FH, and EHR data were available. The majority (67%) were White, based on self-reported race, and 5208 had breast cancer. The sample included 291 *BRCA1* GPVs, 505 *BRCA2* GPVs, and 139 *PALB2* GPVs, with breast cancer diagnosed in 36%, 23%, and 19% respectively. BioVU included 127,147 women, of whom 85.5% were White and 5,664 had breast cancer. The sample had 262 BRCA1 GPVs, 515 BRCA2 GPVs, and 210 PALB2 GPVs, with breast cancer diagnosed in 29%, 22%, and 16% respectively. Across the genes, we observed a bimodal distinct age-dependent breast cancer risk pattern. Bimodal peaks for *BRCA1* in AoURP were at 26 and 36 years, while in BioVU were at 35 and 62 years. The bimodal peaks for *BRCA2* in AoUPR were at 32 and 51 years, while in BioVU were at 32 and 55 years. Finally, bimodal peaks for PALB2 in AoUPR were 35 and 51 years, while in BioVU were at 41 and 64 years. Age-specific risk trajectories also varied by FH where risk peaks for participants with BCFH were earlier by 2-7 years compared to those without BCFH. **Conclusions:** We presented population based study providing unbiased estimates of breast cancer risk associated with GPVs in BRCA1, BRCA2, and PALB2 in two enrollment-based cohorts. Leveraging these large datasets, we identified novel bimodal age-dependent patterns of breast cancer risk across genes, with consistent peak ages for BRCA2 and PALB2 and cohort specific differences for BRCA1, highlighting the importance of population context. Replication in BioVU confirmed similar bimodal trends with later peak ages, supporting our finding robustness. Our results show that breast cancer risk in GPVs genes is more dynamic than previously recognized. Integrating age and FH risk estimates into genetic counseling and screening may improve personalized risk assessment and clinical decision making. Research Sponsor: U.S. National Institutes of Health; 5R21MD019103.

1625 Poster Session

Clinical utility analysis of a computational reasoning system on large-scale tumor genomic data. First Author: Dora Lakatos, Genomate Health Inc, Cambridge, MA

Background: Comprehensive tumor molecular testing has become routine in clinical oncology. However, interpretation of complex molecular profiles in clinical practice can be challenging and subjective. The Digital Drug Assignment (DDA) system is a knowledge-graph-based computational method that automates reasoning at the patient level and scores molecularly targeted agents (MTAs) based on the full tumor genome. This approach was predictive of relative benefit of the agents as used in the SHIVA01 trial (NPJ Precis Oncol. 2021 5:59) and in real-world setting (NPJ Precis Oncol. 2025 9:159). Here, we assessed the potential clinical utility of DDA by analyzing large-scale tumor genomic data. **Methods:** Tumor molecular profiles of 20,923 patients of the MSK-CHORD real-world clinicogenomic dataset (Nature. 2024 636:728-36) were processed by DDA. DDA classified all alterations and scored all associated MTAs based on a functional and pharmacological evidence network. Previous research evidenced that high-score MTAs (1000 $\leqq$ DDA score) predict increased clinical benefit. Utility of DDA was assessed by the proportion of patients with at least one high-score MTA option associated with their molecular profiles. **Results:** Tumor molecular complexity is evidenced by the number of driver alterations, with an average of 4.6 (range: 1 – 45) drivers per tumor (Table). 75% of all tumors were associated with high-score MTAs, 55% had on-label options. Availability of high-score options was high in all tumor types, with the exception of prostate tumors (24%). Only 3% of pancreatic cancer patients were associated with on-label high-score MTA options. Of the patients with known MTA treatments (n = 14,168), only 37% were administered a high-score MTA during their treatment course (Table). **Conclusions:** Our analysis recapitulates the presence of multiple driver alterations, highlighting the need for methods like DDA that consider the totality of molecular profiles for assigning MTAs, rather than relying on identifying single 'actionable biomarkers'. The substantial gap between the proportion of patients who did receive and those whose tumor genomes were associated with high-score MTAs indicates a strong potential for improving outcomes in precision oncology. Moreover, the proportion of high-score off-label (i.e., approved in other oncological indications) MTAs highlights the potential of DDA in drug repurposing. Research Sponsor: National Research Development and Innovation Fund, Hungary; 2022-1.1.1-KK-2022-00005.

Tumor site	Mean no. of alterations (±SD)	Mean no. of drivers (±SD)	HS MTAs associated*	HS MTA administered*	HS developmental MTAs associated*	HS off-label MTAs associated*	HS on-label MTAs associated*
All (20,923)	9.9 (11.8)	4.6 (3.9)	75	37	74	71	55
Breast (5,164)	8.1 (8.1)	4.3 (3.4)	90	57	90	89	86
Colorectal (4,565)	13.2 (18.0)	6.0 (5.5)	69	18	67	60	46
Lung (5,932)	11.6 (10.2)	4.6 (3.2)	85	57	83	84	79
Pancreas (2,619)	6.2 (6.0)	3.6 (2.3)	86	2.5	86	86	3
Prostate (2,643)	7.4 (9.5)	3.6 (3.3)	24	6.6	21	11	7

HS: high-score.
*% of patients.

1626 Poster Session

Resolving the ambiguity between genomic rearrangements and gene fusions: An AI-augmented structural framework to define therapeutic eligibility in kinase-driven cancers. First Author: Kai Wang, OrigiMed, Shanghai, MA, China

Background: A critical disconnect exists in precision oncology: clinical guidelines frequently conflate genomic "rearrangements" with functional gene "fusions", utilizing inconsistent terminology that obscures biological reality. While confirmatory RNA sequencing is recommended, it is often clinically infeasible due to tissue exhaustion or poor sample quality. Consequently, clinicians are forced to prescribe targeted therapies based on DNA-level proxies without knowing if a druggable protein actually exists. We addressed this unmet need with VeraFusionDx, an AI-augmented decision support system that moves beyond simple classification to determine therapeutic eligibility. **Methods:** We developed a universal framework integrating AI-driven report parsing with generative molecular modeling, trained on a massive real-world dataset ($>$10,000 gene fusions and $>$50,000 rearrangements) from a CAP/CLIA-certified lab. An AI normalization module standardizes heterogeneous inputs (unstructured NGS reports, gene+exon number pairs, or coordinates) into a unified format. Distinct from static database lookups, the core engine performs *de novo* characterization of each patient variant. It computationally reconstructs chimeric sequences and models 3D protein architecture to verify critical druggability criteria, including reading frame alignment and kinase domain integrity. Finally, an AI-literature agent cross-references validated targets with clinical evidence to define definitive therapeutic eligibility (https://verafusiondx.origimed.com). **Results:** Analysis using this generative engine revealed a heterogeneous landscape where genomic rearrangement proved a poor proxy for druggability, highlighting the necessity of structural validation. For *NTRK* genes, approximately two-thirds of detected variants were rearrangements rather than actionable fusions, with striking discordance by gene and tumor type. Notably, *NTRK2* rearrangements were 4-fold more common than fusions, and *FGFR1* were 90% rearrangements. Even among canonical partners (*EML4-ALK, KIF5B-RET, CD74-ROS1*), the analysis identified a persistent 1-2% rate of non-functional mimics. To resolve this complexity, the system generated definitive outputs for each case, including *de novo* chimeric DNA and protein sequences, predicted 3D structural models, therapeutic actionability assessments, and an AI-curated summary of comparable literature evidence. **Conclusions:** Functioning as a comprehensive computational firewall, this framework integrates *de novo* sequence generation, structural modeling, and therapeutic intelligence to definitively filter out inert genomic noise, ensuring that life-altering TKI prescriptions are grounded in verified functional reality rather than ambiguous terminology. Research Sponsor: None.

1627 Poster Session

SMS message sentiment as a predictive indicator of quality of life and program adherence in oncology nutrition. First Author: Mélanie Guirette, Savor Health, New York, NY

Background: A text-message based artificial intelligence nutrition platform called "Ina" was previously developed and shown to be equivalent to human dietitians in providing nutritional recommendations to patients with cancer. Once registered on the platform, patient users exchange conversational texts with and receive tailored dietary recommendations and recipes from Ina. We investigated whether the emotional sentiment of SMS messages can act as a proactive predictor of program-related Quality of Life (QoL) and program adherence. **Methods:** QoL was captured via a 1-5 Likert scale ("Has using Ina improved your quality of life?") survey, and program adherence was captured by a binary response to a question ("Have you used any of Ina's suggested tips?"). We extracted SMS messages within a 60-day window prior to each survey and question. Sentiment was measured using the Jockers-Rinker lexicon via the validated sentimentr package; scores were calculated as a weighted average ranging from -1 (negative sentiment) to +1 (positive sentiment). Linear mixed-effects models (LMM) were used to quantify the relationship between pre-survey message sentiment and program QoL/adherence outcomes, adjusting for total number of surveys completed and user's unique baseline sentiment. **Results:** Between October 2019 and January 2026, 14,700 unique text messages were analyzed from 540 unique patient users of the platform (mean age: 51$\pm$ 20 years; 91% female). Cancer types included breast (40%), ovarian (24%), bladder (16%), lung (13%), and colon (7%); metastases were present among 34%. For every one-point improvement in digital sentiment, users experienced a 14% improvement in subsequent program-related QoL (?= 0.72, p $<$ 0.001). Furthermore, there was a trend toward an association between higher positive digital sentiment and subsequent reported adherence to nutritional recommendations (? = 0.12, p = 0.097). **Conclusions:** Sentiment analysis of unstructured SMS messages successfully identified subtle shifts in digital tone that precede structured assessments. This 'leading indicator' of sentiment could enable proactive supportive care and provider escalation for timely triage and intervention. Given rapid symptomatic deterioration in oncology that often leads to non-adherence, text-based sentiment analysis could enable early detection of declining engagement to support improved quality of life and long-term outcomes. Research Sponsor: None.

1628 **Poster Session**

Toxicity risk calculator for personalised prediction of irAEs in patients with solid tumours receiving ICIs, developed based on a clinical dataset and machine learning approaches. First Author: Marina Lyadova, Moscow State Budgetary Healthcare Institution "Moscow City Hospital Named After S.S. Yudin, Moscow Healthcare Department", Moscow, Russian Federation

Background: Immune checkpoint inhibitors (ICIs) can cause severe (grade 3-4) immune-related adverse events (irAEs), which complicate treatment and require immunosuppressive therapy. To address this, we developed a machine learning (ML)-based tool to predict individual risk. Aim: To identify predictors and develop an ML calculator for assessing the risk of grade 3–4 irAEs in patients receiving ICIs for solid tumours. **Methods:** This retrospective study included 1,001 patients (585 men, 415 women; mean age 62.4) treated with ICIs for melanoma, kidney, lung, GI, or cervical cancers. The workflow was implemented in Python using pandas, scikit-learn, and SHAP. The cohort was split 70/30 for training and testing. Only pre-treatment variables were used. Data preprocessing included imputation (median for numeric, most frequent for categorical), one-hot encoding, and standardization. Two classifiers were trained: elastic-net logistic regression and gradient boosting. Hyperparameters were tuned via 5-fold CV. Class imbalance (~7-8% positives) was addressed with class_weight="balanced" and SMOTE. Probabilities were calibrated. Performance was assessed by PR-AUC (primary), ROC-AUC, F1, and Brier score. Predictors were selected in a two-stage process: 1) Retention of pre-IO variables, removal of low-variance/high-missingness ($>$30%) features, and collinearity pruning (|correlation| $>$ 0.85). 2) Model-agnostic ranking using three normalized signals: elastic-net coefficients, permutation importance, and mean absolute SHAP values, combined into a consensus score (weights: 0.5, 0.3, 0.2). Stability was verified by bootstrap resampling. **Results:** The final 10 features maximized cross-validated PR-AUC while maintaining calibration and interpretability. Selected predictors: ICI type/combination; age; haemoglobin; creatinine; treatment regimen (mono/combo); K-RAS/N-RAS mutation status; skeletal muscle index; lymphocyte-to-monocyte ratio; immunotherapy line; T4 level.The model identifies patients at increased risk with calibrated probabilities. Results are presented as probabilities (95% CI) categorized as low ($<$0.10), moderate (0.10–0.25), and high ($\geq$0.25). The colored pictogram visualizes risk distribution for a sample of 100 patients (based on the database; median, quartiles). **Conclusions:** We developed the 'Toxicity Risk Calculator' using 10 clinical factors to assess the probability of severe irAEs. This calculator enables routine assessment of the low, moderate, or high probability of grade 3–4 irAEs, facilitating more effective personalization of cancer immunotherapy in everyday practice. Further prospective studies in real-world clinical settings are needed. Research Sponsor: None.

1629 **Poster Session**

Fitbit-derived activity and heart-rate patterns for predicting 12-month hospitalization in an NIH All of Us cancer cohort. First Author: Kenan Najjar, Carle Illinois College of Medicine, Champaign, IL

Background: Hospitalizations in oncology are common and diverse, and are often limited in their predictive accuracy with routine variables. Wearable devices capture functional and physiological patterns that may indicate vulnerability. We examined whether Fitbit-derived activity and heart rate features enhance the prediction of all-cause hospitalization beyond demographic and clinical factors like frailty. **Methods:** Using data from the NIH All of Us Research Program, we conducted a retrospective analysis of participants aged $\geq$50 years with a history of cancer, linked electronic health records, and short-term Fitbit data (with imputed missing days). Baseline predictors included demographic variables, clinical factors such as the All of Us frailty index, and indicators of cancer subtype. The outcome was any hospitalization within 12 months of the index date, relative to the last Fitbit data day. Features included step count, step variability, activity distribution, rhythmicity, heart rate, and heart rate variability. Missing data were imputed using predictive mean matching. Models were optimized via nested stratified cross-validation and evaluated with out-of-fold predictions. Discrimination was measured by AUC and average precision with bootstrap confidence intervals. Predictive value for the top 10% at-risk group was also assessed. **Results:** The study cohort consisted of 278 participants (average age 64.6). Twelve percent (35) experienced hospitalization within a year. Time to hospitalization ranged up to 342 days. Hospitalization diagnoses were heterogeneous. Models using demographic and clinical data alone had limited discrimination (AUC 0.41–0.50). Incorporating Fitbit activity features improved logistic performance: average steps yielded an AUC of 0.522, step-pattern quartiles yielded 0.559, and distributional rhythmic features yielded 0.628 (CI 0.520–0.733; average precision 0.283). Heart rate and variability did not materially enhance logistic prediction. Gradient-boosted trees combining activity and heart rate data achieved the highest discrimination (AUC 0.704; CI 0.621–0.786; average precision 0.286). Using the best-performing model, the top 10% predicted-risk group had a hospitalization rate of 28.6% (8/28), compared with the overall cohort hospitalization rate of 12.6%, capturing 8 of 35 events. **Conclusions:** Fitbit-derived activity patterns and heart rate patterns, when modeled using machine learning, improved near-term hospitalization prediction in an NIH cancer cohort beyond demographic and clinical models, supporting their potential for practical risk assessment. Ongoing analyses will address missingness, calibration, and subgroup robustness to inform prospective validation. Research Sponsor: National Institutes of Health (NIH) – All of Us Research Program; Jensen Research Scholars Fund.

1630 **Poster Session**

Evaluating AI decision support in a rapidly evolving therapeutic landscape: *EGFR*-mutant metastatic NSCLC. First Author: Chinmay Jani, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Large language models (LLM) are increasingly used in oncology, yet may deviate from evidence-based care due to outdated knowledge, hallucinations, and inconsistent confidence calibration. EGFR-mutant metastatic Non small Cell Lung Cancer (NSCLC) treatment sequencing is rapidly evolving following 1L OS benefits from MARIPOSA and FLAURA2 and an expanding 2L landscape. In this study, we evaluate concordance, variability, and expert alignment across artificial intelligence (AI) systems. **Methods:** Twelve expert-curated EGFR-mutant metastatic NSCLC vignettes (6 per 1L and 2L) were evaluated across 4 general-purpose LLMs (ChatGPT, Gemini, Claude, Grok) with deep-research enabled and 2 evidence-based platforms [ASCO AI, OpenEvidence (OpenE)]. Each system simulated percentage-based treatment selections simulating how 100 U.S. med-oncologists might distribute choices across predefined therapies. 5 thoracic oncologists from 3 academic centers established a human reference standard, with unanimous agreement in all but 1 vignette where probability-weighting was applied. Inter-system and expert concordance was assessed using Kendall's τ, while divergence was quantified using Jensen–Shannon (JS) divergence. **Results:** Guideline-based platforms showed strong agreement (ASCO AI–OpenE τ=0.73). Among LLMs, ChatGPT aligned the most with ASCO AI (τ=0.72), while Claude showed the highest divergence (JS=0.30); the highest inter-LLM concordance was observed between ChatGPT and Gemini (τ=0.64). Although ASCO AI is built on Gemini, agreement was only moderate (τ=0.55), suggesting added guideline constraints enhance consistency. In 1L, all systems demonstrated moderate-to-strong concordance with experts ($\tau>$0.50), with ChatGPT and ASCO AI the highest (τ=0.80). ASCO AI appropriately emphasized guideline-endorsed options, including Osimertinib monotherapy and combination strategies, without preferential commitment. In 2L, concordance declined substantially with ChatGPT demonstrating inverse correlation with experts ($\tau=-0.06$). **Conclusions:** AI systems align with expert decision-making in 1L EGFR-mutant metastatic NSCLC but diverge substantially in 2L, where evidence is evolving. Guideline-constrained platforms show greater consistency than general-purpose LLMs; despite ASCO AI using Gemini as its base model, agreement was only moderate, highlighting the value of guideline constraints. These findings highlight the need for rigorous validation and clinical safeguards when integrating AI into oncology decision-making. Research Sponsor: None.

AI–expert concordance.

System	1L - Experts (τ, JS)	2L – Experts (τ, JS)	Max Inter-System (τ)
ASCO AI	0.80, 0.14	0.25, 0.39	OpenE (0.73)
ChatGPT	0.80, 0.15	-0.06, 0.36	ASCO AI (0.72)
OpenE	0.67, 0.25	0.27, 0.24	ASCO AI (0.73)
Gemini	0.61, 0.21	0.49, 0.19	ChatGPT (0.64)
Claude	0.59, 0.32	0.27, 0.22	ChatGPT (0.60)
Grok	0.54, 0.26	0.27, 0.25	OpenE (0.64)

1631 **Poster Session**

Wearable-derived physical activity monitoring with AI-based detection of treatment-related adverse events during neoadjuvant chemotherapy for early breast cancer: TRACK-BC. First Author: Nobuhiro Shibata, Department of Clinical Oncology, Kansai Medical University Hospital, Hirakata, Japan

Background: Neoadjuvant chemotherapy (NAC) for early breast cancer (EBC) is commonly delivered in the outpatient setting, yet within-cycle changes in adverse events reduce physical activity (PA). Wearable devices may capture these short-term changes. However, prospective data describing activity patterns during modern regimens, including pembrolizumab (PEMB)-based therapy, are limited. This study evaluated changes in PA using Fitbit-derived digital biomarkers (dBM) and explored associations with patient-reported outcomes (PROs). **Methods:** We conducted a multicenter, prospective observational study in patients (pts) with stage I–IIIA EBC initiating NAC. Eligible pts were $\geq$18 years old, smartphone users, and able to wear a Fitbit daily. Chemotherapy regimens were grouped into weekly, q2w, or q3w cohorts. Fitbits were worn from $\geq$7 days before treatment initiation through four cycles. Total PA (TPA), moderate-to-vigorous PA (MVPA), heart rate, sleep, and other metrics were collected. PRO-CTCAE and HADS were completed weekly electronically (ePROs). The primary outcome was change in TPA and MVPA from baseline to the week following cycle 2. As a secondary endpoint, machine learning approaches extending conventional multivariable regression incorporated multiple wearable-derived parameters to individually predict the worst change in ePRO scores from baseline. Model performance was evaluated by cross-validation, and feature contributions were examined using SHapley Additive exPlanations (SHAP) to enhance clinical interpretability. **Results:** A total of 101 pts were enrolled across the three predefined chemotherapy cohorts. Fitbit use was feasible with high adherence. The primary outcome indicated a consistent decline in PA during NAC. From baseline to the week following cycle 2, mean TPA decreased by 141.4 METS-min/day and MVPA by 33.7 min/day. ePROs revealed worsening symptoms including fatigue, insomnia, appetite loss, and neuropathy. Symptoms varied according to the chemotherapy schedule and generally aligned with changes in PA levels and dBM. The secondary outcomes identified multiple vital signals showing absolute correlations $>$0.3 with all PRO and HADS metrics. For fatigue, the best model (ridge regression) yielded mean R^2 0.33$\pm$0.20 and RMSE 1.86$\pm$0.26; SHAP analysis highlighted contributions from nocturnal heart-rate-variability minima and overall variability. **Conclusions:** Continuous wearable monitoring during NAC for EBC was feasible. Objective declines in PA occurred early and paralleled symptom worsening captured by ePROs. AI-based models explained a modest but clinically meaningful proportion of symptom deterioration with acceptable error. These findings support the potential utility of wearable-derived dBM for real-time surveillance of treatment-related toxicities during NAC. Clinical trial information: UMIN000053991. Research Sponsor: Daiichi Sankyo Co., Ltd.

1632 **Poster Session**

Impact of remote symptom monitoring program on payor-specific healthcare costs. First Author: Gabrielle Betty Rocque, Division of Hematology and Oncology, University of Alabama at Birmingham, Birmingham, AL

Background: Remote symptom monitoring (RSM) programs are currently being implemented across oncology practices nationwide; however, the impact of RSM on costs by payor has been understudied. **Methods:** This is a secondary analysis of a hybrid implementation-effectiveness trial of electronic, patient reported outcome-based RSM for patients with cancer initiating systemic therapy (May 2021-May 2024). Differences in costs for healthcare services for RSM-enrolled patients were compared to historical controls. Outcomes included overall, monthly, payor-, and service-specific costs of care received at 3 and 6 months after RSM-enrollment date or initiation of systemic therapy for controls. Adjusted generalized linear models estimated predicted mean costs, mean cost ratios (MR) and 95% confidence intervals (CIs) for RSM-enrolled patients versus controls. **Results:** Patients receiving RSM (n=968) were 25% Black, 44% privately insured, and 27% living in a highly disadvantaged neighborhood. Historical controls (n=3,488) were demographically similar. Though non-statistically significant, RSM enrolled patients had 5% lower mean costs 3 months post-index date compared to historical controls (MR 0.95, 95% CI 0.78-1.16), translating to an estimated cost savings of $1,347 per patient (95% CI -$3,596, $6,290). Medicare Fee-for-Service (FFS) beneficiaries showed the greatest, though non-statistically significant, cost reductions, with RSM FFS beneficiaries having 10% lower costs than FFS controls (MR 0.90, 95% CI 0.67-1.19) at 3 months post-index date. Though non-statically significant, RSM-enrolled patients had 23% lower costs for radiation, 14% lower inpatient costs, 9% lower costs for labs, scans, or tests, and 2% lower outpatient costs compared to controls at 3 months post-index date. At one-month post-index date, RSM enrolled patients had statistically significantly lower payor costs compared to controls ($11,849 [95% CI $9,364-$14,335] vs. $15,706 [$14,291-$17,121]; p=.004). Costs for RSM enrolled patients and controls were similar two to six-months post-index date. **Conclusions:** We observed payor cost savings of $1,347 in the 3 months of RSM enrollment compared to controls. As the largest payor cost differences were seen for Medicare FFS beneficiaries, our results suggest RSM may address a gap in the provision of care coordination to patients not offered these services through their insurer. Cost savings were most prominent within the first month of treatment initiation; thus, RSM may aid in reducing acute care needs and optimizing resource utilization for patients with cancer. Our results support future research in potential risk-stratification methods to improve RSM engagement and delivery to reduce costs and improve outcomes for patients with cancer. Research Sponsor: None.

1633 **Poster Session**

Earlier CRS identification with continuous wearable monitoring in outpatient CAR T-cell therapy. First Author: Jonas Paludo, Mayo Clinic Rochester, Rochester, MN

Background: CAR-T cell therapy has transformed outcomes of hematologic malignancies and is poised to expand into solid malignancies. However, broader use of CAR-T remains constrained by the need for timely cytokine release syndrome (CRS) detection. Current episodic monitoring may miss early physiologic changes. Wearable digital health technologies (DHTs), offering continuous monitoring and real-time alerts, could enable earlier CRS detection, further support outpatient delivery, and expand access to CAR-T and potentially other immunotherapies associated with CRS. **Methods:** This single-center observational study (NCT05018208) enrolled patients receiving FDA-approved CAR-T products in the outpatient setting at Mayo Clinic, Rochester MN. Management of post-CAR-T complications (e.g. CRS) followed the institution's standard of care. Patients were monitored from day -5 to day +30 post infusion with intermittent remote patient monitoring (SoC) and an arm-worn wearable device for continuous monitoring (DHT). Patients were included in this analysis if DHT data were available for $\geq$ 5h of data/day or $\geq$ 2h of data/night on $\geq$2 days or nights for baseline and $\geq$1 day or night within 72h prior to CRS, or at least 2h within 4h of CRS onset, or if DHT was available for $\geq$7 days/nights post infusion with no CRS event. CRS detection time by DHT was defined as the onset of pyrexia or threshold-based deviation from an individual's baseline pulse distributions. **Results:** 32 patients were included in this report (median age 64 years, gender 12 F/20 M, diagnoses 18 MM/14 NHL). 25 patients experienced a CRS event, with maximum CRS grades ranging from 1-3 (16 G1, 8 G2, 1 G3). 24/25 patients with CRS required tocilizumab/steroid. Median CRS onset time was 3.4 days (range 0.4-18.4). 12/32 patients had sufficient DHT data (7 CRS, 5 no CRS) for analysis. 5 patients with CRS had a DHT detection time in advance of the SoC by a median of 13h (range 2.8 - 69.2). The DHT prediction of CRS by baseline HR change was earlier than the first episodic fever by a median of 14.5h (range 13-77.5). The remaining 2/7 patients who did not have CRS detected by the DHT had missing DHT data for more than 45h before a treated CRS event. DHT detected CRS in 2/5 patients without CRS according to SoC. One patient had fever caught with intermittent monitoring. The other was treated for neutropenia fever with suspicion of CRS and/or infection. **Conclusions:** These results offer evidence that continuous DHT can identify CRS events earlier than intermittent monitoring (SoC). Despite limitations related to compliance with wearable device use and data missingness, and variability in clinical management of CRS, we highlight the usability of DHT and its potential for future studies with optimized strategies to address these limitations. Clinical trial information: NCT05018208. Research Sponsor: Biofourmis.

1634 **Poster Session**

Validating a single-item screener for low digital health literacy among surgical oncology patients. First Author: Thomas S. Gunning, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: Digital health literacy (DHL; the ability to find and understand health information using electronic media) may affect surgical oncology patients' ability to navigate patient education and discharge coordination activities that rely on technology. Screening for low DHL can identify patients who may benefit from alternate modalities or additional support. In our prior work, a single item from the validated electronic Health Literacy Scale (eHEALS) had strong sensitivity and specificity for identifying low DHL in the outpatient setting. In this cross sectional, secondary analysis, we explored which sociodemographic and clinical factors were related to low DHL and tested whether the single-item screener could identify patients with low DHL in the surgical oncology setting. **Methods:** Surgical oncology patients were recruited during their post-operative hospitalization for a parent study on health literacy and clinical outcomes. The 8-item eHEALS assessed DHL; total scores $\leq$20 indicate low DHL. Chi-squared, Fisher's exact, or Mann-Whitney tests were used to examine whether DHL varied by patients' sociodemographic (age, sex, race/ethnicity, education, marital status, general health literacy) or clinical characteristics (cancer type, ECOG performance status, comorbidities). Receiver operating characteristic (ROC) curve analysis assessed sensitivity, specificity, and accuracy of eHEALs item 4 ("I know where to find helpful health resources on the Internet") to identify low DHL. **Results:** Participants (N=224) were primarily non-Hispanic White (87%), older (median=68, IQR 61-75 yrs), married (69%), men (59%) with gastrointestinal cancer (60%) who completed at least some college education (76%). On the 8-item eHEALS, 23 patients (10.3%) reported low DHL. Patients with lower general health literacy ($p<0.001$), lower education level (p=0.007), and unpartnered marital status (X^2 = 4.359, p=0.039) were more likely to have low DHL. Other factors were not associated with DHL (p-values$>$0.299). Older patients were marginally more likely to report low DHL than younger patients (U=2847, p=0.069). In ROC curve analysis, eHEALS item 4 strongly distinguished low DHL vs. high DHL (AUC=0.989; 95% CI 0.977-0.997). At the optimal threshold (item scores $<$3, on a 1-5 Likert scale), item 4 predicted low DHL with an accuracy of 96.9%, sensitivity of 97.0%, and specificity of 95.7%. **Conclusions:** These data suggest a single-item screener (eHEALS item 4) can accurately identify patients with low DHL in the surgical oncology setting, adding support for its ability to detect low DHL in patients with cancer. Among surgical oncology patients, those with lower education, lower general health literacy, and older age may be more likely to experience lower DHL. Future prospective studies with larger samples are warranted to assess utility, acceptability, and feasibility of the screener in clinical practice. Research Sponsor: None.

1636 **Poster Session**

Conversational AI-assisted exploratory data analysis (CA-EDA): A comparative evaluation of commercial large language models for clinical trial analysis. First Author: Yaacov Lawrence, Chaim Sheba Medical Center, Ramat Gan, Israel

Background: Conventional analysis of clinical trial data requires statistical expertise, time and effort. Previous AI approaches have used structured, pre-processed datasets on specialized platforms. We hypothesized that widely available commercial large language models (LLMs) would perform rapid analysis of raw data. We evaluated three commercial LLM platforms fed identical data, and subsequently validated the outcomes with a formal statistical analysis. We name this approach "Conversational AI-assisted Exploratory Data Analysis" (CA-EDA). **Methods:** We used data from a completed phase 2 trial (NCT03323489; Lancet Oncol 2024; 25:1070-9); n=125; 2165 variables) that evaluated the efficacy of celiac plexus radiosurgery in controlling retroperitoneal pain syndrome amongst pancreatic cancer patients. Raw individual patient data was uploaded to three commercial LLMs: Claude Opus 4.1 (Anthropic), ChatGPT 5.2 (OpenAI) in deep research mode, and Gemini 3 Pro (Google). Each LLM received identical inputs: the raw Excel dataset, the codebook, the protocol, and the published manuscript. The prompt requested identification of baseline predictors of pain response and development of a clinical score. Outputs were compared for statistical analyses performed, predictors identified, visualizations generated, and clinical utility. Findings were formally verified using Stata IC/16.1. **Results:** Analysis completion time ranged from 10 to 30 minutes across all three platforms. Claude performed a comprehensive statistical analysis, generated a 9-panel visualization dashboard, identified prior exposure to neurotoxic chemotherapy as a novel predictor of response (OR 0.20, $p<0.001$), and created a 4-variable clinical score predictive of response (AUC 0.71). ChatGPT performed a statistical analysis but missed neurotoxic chemotherapy, creating a 3-variable score. Gemini produced an 8-page narrative with biological insights, but did not perform any statistical analysis. Analysis using Stata confirmed the association between prior exposure to neurotoxic chemotherapy and response (35% with prior exposure vs 75% without, $p<0.001$). **Conclusions:** Claude Opus 4.1 identified a clinically significant predictor that had not previously been recognized, and developed a helpful clinical score. CA-EDA always requires formal biostatistical verification due to concerns about LLMs' tendency to hallucinate, may analyse only sampled data and potentially implement incorrect Python code. Despite these concerns, here we found CA-EDA of clinical trial data to be rapid, accurate and cost-effective. Financial support for clinical trial: Gateway for Cancer Research, The Israel Cancer Association. Research Sponsor: Gateway for Cancer Research; Israel Cancer Association.

1637 **Poster Session**

Evaluating the organizational benefits of remote symptom monitoring during injectable outpatient cancer treatment: The final analysis of the randomized OPTIMACURE trial. First Author: Audrey Faveyrial, Centre François Baclesse, Medical Oncology Department, Caen, France

Background: Remote monitoring (RM) to assess whether patients are apt for cancer treatment is already used during standard of care (SOC) in several French centers. Optima RM includes structured phone calls by a nurse, 2-3 days before the planned administration, with the transfer of biological results 48 h before the administration, with a physician's validation the day before administration. Cureety RM, in addition to preparing visit, also monitors symptoms between cures. We aimed to evaluate the organizational benefit of Cureety RM compared to Optima-like RM in patients initiating outpatient injectable cancer treatments. **Methods:** OPTIMACURE was designed as a multicentric, randomized, open-label trial to compare Cureety RM versus Optima-like RM. Patients aged ³18 years, starting an injectable cancer treatment, and capable of using a RM tool were eligible. Patients with dysphonia/difficulties with oral communication were not eligible. Enrolled patients were randomly allocated (2:1) to either Cureety RM or to SOC (with Optima-like RM). Randomization was stratified by type of cancer treatment, ECOG PS, frequency of treatment, and center. Only centers using Optima-like RM participated in the trial. The primary objective was to assess the effectiveness of adding Cureety RM to usual care, in terms of the number of outgoing calls, overall and by reason (preparing visits or for toxicity), within the first 2 months. Secondary outcomes included safety, toxicity-free survival (TFS), and hospitalizations. **Results:** Between April and August 2024, 192 patients were allocated: 127 (66%) to Cureety RM and 65 (34%) to SOC (with Optima-like RM). The trial population was mainly female (73%) and with an ECOG PS 0-1 (96%). Most were being treated with chemotherapy (98%) and less frequently than every 2 weeks (61%). The demographic and disease characteristics were similar in the groups. The mean number of outgoing calls were fewer with Cureety RM, 2.53 (SD: 2.21) versus 3.77 (SD: 2.45). The difference of least-squares means was significantly different in the groups: -1.25 (95% CI: -1.91 to -0.59), $p<0.0001$. The number of outgoing calls for preparing visit were significantly fewer with Cureety RM, 0.43 (SD: 0.82) versus 3.09 (SD: 2.18), $p<0.001$. While there were significantly more outgoing calls for toxicity with Cureety RM, 1.68 (SD: 1.89) versus 0.20 (SD: 0.71), $p<0.001$. No adverse events (AEs) related to RM were reported. The median TFS was significantly shorter with Cureety RM, 10 days versus not reached: driven by early detection of grade ≤4 AEs. The number of hospitalizations was similar in the groups. **Conclusions:** Implementing Cureety RM during injectable cancer treatment had an organizational benefit by reducing the number of outgoing calls. More precisely, reducing the outcalls for preparing visit while increasing those for AEs. Clinical trial information: NCT06371911. Research Sponsor: None.

1638 **Poster Session**

Feasibility and preliminary efficacy of a 12-week remotely delivered exercise program in patients receiving immunotherapy: A phase II randomized controlled trial. First Author: Paulo Gustavo Bergerot, Oncoclinicas&Co - Medica Scientia Innovation Research (MEDSIR), Sao Paulo, Brazil

Background: Patients with advanced cancer receiving immunotherapy experience reduced physical function, increased symptom burden, and poorer health-related quality of life (HRQOL). Limited access to structured exercise programs makes technology-supported interventions a potentially scalable alternative. We assessed the feasibility and preliminary efficacy of a 12-week remote exercise program on HRQOL, symptom burden, and fear of cancer recurrence (FCR), with an exploratory economic evaluation. **Methods:** In this Phase II trial, adult receiving immunotherapy alone or in combination were randomized 1:1 to a remote exercise intervention or usual care (UC). The study was powered to detect a 10-point difference in Functional Assessment of Cancer Therapy-General (FACT-G) scores (80% power, α=0.05). The intervention included weekly virtual sessions with an exercise physiologist, individualized Borg-guided exercise prescriptions, video support, and telehealth monitoring 12 weeks (30-45 minutes/day). Outcomes assessed at baseline and 12 weeks included HRQOL (FACT-G), symptom burden (Edmonton Symptom Assessment Scale; ESAS), and FCR (FCR-7). Between-group differences were analyzed using ANCOVA adjusted for baseline values, with effect sizes estimated using Cohen's d. A preliminary provider-perspective cost-consequence analysis estimated cost per one-point FACT-G improvement. **Results:** Seventy patients were randomized (35 per arm); five died before 12 weeks (3 control, 2 intervention). Baseline characteristics were balanced. At 12 weeks, the intervention group had significantly higher FACT-G scores compared than UC (mean difference = 11.1; $p<0.001$; Cohen's d=1.30). Symptom burden was lower in the intervention arm ($p<0.001$; Cohen's d=1.68), and FCR was reduced (p=0.014; Cohen's d=0.85). Group assignment remained a significant predictor in adjusted ANCOVA models (all $p<0.01$). Estimated intervention cost was R$7,023 per participant, or R$634 per FACT-G point gained. **Conclusions:** A 12-week remote exercise intervention produced a clinically meaningful 11-point improvement in HRQOL at an estimated cost of R$ 634 per FACT-G point, supporting its economic feasibility and scalability. The program reduced symptom burden and FCR. These findings justify larger trials to confirm effectiveness and further evaluate cost-effectiveness. Research Sponsor: None.

Changes in patient-reported outcomes at 12 weeks.

Outcome (scale)	Group	Baseline Mean ± SD	12-week Mean ± SD	Mean Change	P-value	Cohen's *d*
FACT-G	Control (n=32)	87.3 ± 9.7	85.9 ± 10.2	-1.4	**0.001**	**1.30**
	Intervention (n=33)	85.2 ± 9.1	**96.9 ± 6.7**	**+11.8**		
ESAS	Control (n=32)	17.3 ± 12.1	19.0 ± 12.8	+1.7	**0.001**	**1.68**
	Intervention (n=33)	20.6 ± 9.6	**5.5 ± 3.7**	**-15.1**		
FCR-7	Control (n=32)	15.0 ± 6.0	15.4 ± 6.5	+0.4	**0.014**	**0.85**
	Intervention (n=33)	16.2 ± 6.3	**11.3 ± 3.8**	**-4.9**		

1639 **Poster Session**

Disparities in receipt of guideline-concordant adjuvant chemotherapy and survival outcomes among immigrant patients with colon cancer: Real-world evidence from Ontario. First Author: Bishal Gyawali, Queen's University, Kingston, ON, Canada

Background: Immigrants comprise a growing proportion of the Canadian population and may face unique barriers to accessing timely and guideline-concordant cancer care. While the "healthy immigrant effect" suggests that immigrants initially experience better health outcomes, it remains unclear whether this advantage extends to cancer treatment and survival. We studied whether disparities exist in the receipt of adjuvant chemotherapy and survival outcomes among recent immigrant patients with stage III colon cancer in Ontario compared with long-standing Ontario residents. **Methods:** A population-based real-world retrospective cohort study was conducted using linked administrative health databases housed at the ICES. Adults diagnosed with stage III colon cancer between 2007 and 2020 who underwent surgery within six months of diagnosis were included. Recent immigrants were defined as individuals with a landing date as a resident within ten years before diagnosis, identified using the Immigration, Refugees and Citizenship Canada database; long-standing residents had no recorded immigration date. The primary outcome was receipt of adjuvant chemotherapy within four months of surgery for their cancer. Secondary outcome was all-cause mortality. **Results:** The cohort included 16,724 patients, of whom 304 were recent immigrants (including 47 refugees). Compared to long-standing residents, recent immigrants were younger, had fewer comorbidities, and were more likely to reside in urban areas. In unadjusted analyses, recent immigrants were more likely to receive adjuvant chemotherapy (RR 1.37; 95% CI 1.23–1.53); however, this association was attenuated in the multivariate analysis (RR 1.08; 95% CI 0.99–1.19). Recent immigrants had significantly lower all-cause mortality, with an adjusted hazard ratio (HR) of 0.70 (95% CI 0.58–0.84). **Conclusions:** In this large population-based study, recent immigrants with stage III colon cancer in Ontario received comparable guideline-concordant adjuvant chemotherapy and had significantly better overall survival than long-standing residents. These findings suggest that, within a universal healthcare system, recent immigrants may not be disadvantaged in colon cancer treatment and perhaps have better outcomes once engaged in care. Further research is needed to assess whether these findings extend to other cancer types and to non-permanent resident populations. Research Sponsor: Department of Medicine, Queen's University and ICES.

1640 **Poster Session**

Sociodemographic variation in live birth incidence and access to assisted reproductive services among female cancer patients in the United States. First Author: Isabel Beshar, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Sociodemographic variation in fertility outcomes after cancer is not well described. We constructed a novel longitudinal dataset to capture sociodemographic variation in 1) live births and 2) use of assisted reproductive technology (ART) among female cancer patients across the US from 2004-2022. **Methods:** We linked population-based cancer registry data (2004–2018 in 12 states; 2004–2011 in California) with live birth certificates (2004–2022) and the Society for Assisted Reproductive Technology (2004-2022) database, which captures ~90% of ART cycles nationally, to create a dataset integrating oncologic characteristics, obstetric outcomes, and ART use. Patients aged 15-45 at diagnosis of cancer were included. The primary outcome was 5-year cumulative live birth incidence (CLBI) using the Fine and Gray method to account for all-cause death as a competing event and log-rank tests to compare by age, race/ethnicity, insurance, cancer site, cancer stage, and receipt of systemic therapy. Secondary outcome was use of ART after cancer diagnosis, defined as >1 autologous oocyte/embryo cryopreservation or embryo transfer cycles. Patients were categorized by expected fertility detriment, defined as pelvic malignancy and/or receipt of chemotherapy, hormone therapy, or abdominal or pelvic radiation, and covariates compared descriptively. Person-years were accrued from diagnosis date to first post-diagnosis birth/use of ART, death, age 51 (oldest age a post-cancer birth was observed), or December 31, 2022, whichever occurred first. The study was approved by the institutional review board. **Results:** 286,198 female cancer patients were included with 15 live births per 1,000 person-years. 5-year CLBI was 6.14% [6.05, 6.24]. Lower CLBI was observed in Hispanic (4.5% [4.31, 4.76]) and non-Hispanic Black (NHB) (5.23% [4.98, 5.50]) populations compared to non-Hispanic white (NHW) populations (6.75% [6.62, 6.88]) ($p<0.001$). Patients with public insurance also had significantly decreased CLBI (4.68% [4.47, 4.90]) than those with private insurance (6.08% [5.95, 6.20], $p<0.001$). NHB, Hispanic, and patients with public insurance comprise higher proportions of patients with expected fertility detriment versus those without detriment (12.6 vs 8.6%, 18.2 vs 13.1%, and 18.7 vs 13.3%, $p<0.001$) but lower proportion of patients that use ART versus those that do not (5.9 vs 11.4%, 7.6 vs 16.6%, and 4.1 vs 17.1%, $p<0.001$). **Conclusions:** National vital statistics data demonstrates high fertility rates among Hispanic and NHB populations; among cancer patients, however, these trends are flipped, with lower cumulative incidence of live births in these groups. Despite a higher burden of anticipated fertility detriment, NHB, Hispanic, and publicly insured patients were less likely to access fertility care, revealing stark inequities in survivorship care. Research Sponsor: National Institutes for Health; MD017999.

1641 **Poster Session**

Comorbidity-related medical expenditures and health outcomes in cancer patients. First Author: Panpan Xiao, School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China

Background: Comorbidities are common among adults with cancer and necessitate effective medical management. However, research is scarce on how cancer affects healthcare utilization and expenditures for comorbid conditions. This study used a U.S. database to compare medical expenditures and health outcomes between adults with comorbidities who have cancer and those without. **Methods:** This longitudinal analysis utilized the data from the 2008-2014 Medical Expenditure Panel Survey (Household Component). Participants with one or more of 19 chronic health conditions (ICD-9 coded) relevant to primary care were classified based on self-reported cancer history. Outcomes from the second year of each panel (2009-2015) included comorbidity-specific healthcare utilization, medical expenditures, functional status, HRQoL, and health utility. Cost differences conditional on positive expenditures were analyzed using generalized linear models (gamma regression and log-link), while differences in healthcare utilization were examined using negative binomial regression. All models were adjusted for demographic, socioeconomic, and lifestyle covariates. **Results:** A weighted total of 24,057,137 adults with at least one comorbidity (mean age 58.3±15.8 years; 59% female) were included, of whom 10% (n=2,393,300) reported a history of cancer. Compared with non-cancer patients, cancer patients received more comorbidity-specific home health visits (IRR 2.01, 95% CI 1.13-3.57) but had lower total comorbidity-specific expenditures (OR 0.81, 95% CI 0.71-0.92). Cancer patients also incurred lower comorbidity-specific hospitalization costs and out-of-pocket costs for emergency department (ED) visits ($p<0.05$). Specifically, they had reduced total expenditures for arthritis (OR 0.60, 95% CI 0.39-0.93) and stomach problems (OR 0.42, 95% CI 0.22-0.81) and reduced out-of-pocket costs for thyroid problems (OR 0.55, 95% CI 0.36-0.86) and osteoporosis (OR 0.41, 95% CI 0.18-0.92). Among multimorbid patients (≥2 conditions; 55.4%), cancer patients incurred lower out-of-pocket costs for ED visits (OR 0.42, 95% CI 0.26-0.68). For health outcomes, cancer patients reported more functional limitations than non-cancer patients in instrumental activities of daily living (10.8% vs 8.5%), role functioning (26.2% vs 20.5%), and cognitive function (13.6% vs 11.2%), all $p<0.05$. Moreover, multimorbid patients with cancer had lower HRQoL and health utilities ($p<0.05$). Similar trends were observed for cancer patients with depression, hypertension, chronic lung disease, osteoporosis, and thyroid problems. **Conclusions:** Cancer patients with comorbidities had greater functional limitations but lower medical expenditures for comorbidity care than non-cancer patients, suggesting inequities in primary care. Healthcare resources should be prioritized for cancer patients with comorbidities and poor functional status. Research Sponsor: None.

1642 **Poster Session**

Retrospective assessment of Duffy-Null associated neutrophil counts (DANC) status and impact on treatment among patients with and without cancer in an urban academic medical center. First Author: Bhawneet Chadha, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: Duffy-Null Associated Neutrophil Count (DANC) is a non-pathologic state characterized by a low absolute neutrophil count (ANC) without increased risk of infections. Despite this, cancer patients (pts) with DANC have often been excluded from clinical trials due to low ANC and may receive inappropriate dose delays or reductions of standard anticancer therapy. Testing for Duffy-null phenotype is readily available, but no standard of care exists for management of chemotherapy dosing in cancer pts with DANC. In preparation for a prospective study evaluating chemotherapy dose modifications in cancer pts with DANC, we examined characteristics of pts, both with and without cancer, who underwent Duffy antigen testing at our institution, as well as whether results of testing in cancer pts impacted cancer management. **Methods:** Pts who received Duffy antigen testing from 05/02/2024-05/01/2025 were identified from the Montefiore Health System pt registry. Baseline characteristics including white blood cell count (WBC), ANC, demographics, and cancer status were obtained and correlated with Duffy status. Reviewed documentation for Duffy-status impact on chemotherapeutic management. **Results:** 523 pts [283 (54.1%) Non-Hispanic Black (NHB), 168 (32.1%) Hispanic (H), 18 (3.4%) Non-Hispanic White (NHW), and 54 (10.3%) Other] were identified. Median age was 56 yrs. Indication for testing was neutropenia in 518 pts (99.0%). 407 (77.8%) pts were found to have DANC and 116 (22.2%) were Duffy-antigen positive. Duffy-null phenotype was seen in 265 (93.6%) pts; 103 (61.3%) H pts, and 4 (22.2%) NHW pts. Race/ethnicity was strongly correlated with Duffy-status ($p < 0.001$). Median baseline WBC and ANC were lower in pts with DANC than in pts without [WBC 3.4 vs 4,4 ($p < 0.001$); ANC 1.1 vs 1.8 ($p < 0.001$)]. 32 (6.4%) pts of the total cohort had cancer [23 (71.9%) NHB, 7 (21.9) H, 2 (6.3%) other], of which 26 pts (22 NHB, 4 H) had DANC. 13 (40.6%) ordering providers were adult solid tumor oncologists [8 Breast, 4 GYN, 1 GU], 5 (15.4%) pediatric hematologist-oncologists, 6 (18.8%) classical hematologists, 6 (18.8%) hematology/oncology providers, and 2 (6.3%) family medicine providers. Knowledge of Duffy antigen status impacted management in 26 (81.3%) pts with cancer, leading to fewer dose delays and reductions in cancer pts with DANC, while in 6 (18.8%) pts testing did not ($p = 0.31$). **Conclusions:** In our diverse cohort of pts undergoing Duffy antigen testing, predominantly as part of evaluation for neutropenia, almost all NHB pts were found to have Duffy-null phenotype. DANC was also seen in over half of H pts, and in 22% of NHW pts. Among cancer pts, testing for DANC is underutilized, but frequently impacts chemotherapy management, emphasizing the need for prospective evaluation of the utility of Duffy antigen testing in cancer pts receiving chemotherapy. Research Sponsor: None.

1643 **Poster Session**

Emergency department visits and hospitalizations in cancer survivors with disabilities: A national analysis. First Author: Mariana Lilani Henry, Weill Cornell Medicine, New York, NY

Background: One in four Americans has a disability. Adults with disabilities are known to have a higher cancer burden than the general U.S. population, but the healthcare utilization patterns and needs of this population remain understudied. We examined factors associated with emergency department (ED) visits and hospitalizations among cancer survivors, with a focus on disability status. **Methods:** We used National Health Interview Survey (NHIS) data from 2022-2024. Adults aged 18+ years who self-reported a diagnosis of breast, prostate, or colon cancer were included. Our key explanatory variable was disability status, defined by receipt of Supplemental Security Income or Social Security Disability Insurance, or a positive designation using the Washington Group Short Set Composite Disability Indicator. The primary outcomes were ED visits and hospitalization in the past 12 months. Logistic regression models adjusted for demographics and health status (e.g., body mass index, self-rated health, and smoking status). All analyses incorporate NHIS survey weights to account for the complex survey design. **Results:** Our sample included 4,179 NHIS respondents with breast, prostate, or colorectal cancer; 999 (23.9%) had a disability. Cancer survivors with disabilities were more likely to have less than a high school education (19.7% vs 9.2%), be enrolled in Medicaid (6.0 vs 2.7%) or Medicare (49% vs 44.8%), and report poor health status (22.3% vs 3.6%) compared to those without disabilities. Compared to cancer survivors without disability, those with disability had higher odds of ED visits (aOR 1.59 [95% CI 1.27-1.99], $p<0.001$) and hospitalizations (aOR 1.70 [95% CI 1.30-2.22], $p<0.001$). Other factors associated with increased odds of ED visits in cancer survivors were region (Ref=Northeast, South: aOR 1.33 [95% CI 1.01-1.77], p=0.046; West: aOR 1.46 [95% CI 1.09-1.98], p=0.01), Medicaid insurance (Ref=no insurance, aOR 1.93 [95% CI 1.01-3.69], p=0.046), and poor self-rated health (Ref=excellent, aOR 6.69 [95% CI 4.05-11.07], $p<0.001$). Factors associated with increased odds of hospitalizations in cancer survivors were Medicare (Ref=no insurance, aOR 2.18 [95% CI 1.21-3.92], p=0.01), private insurance (Ref=no insurance, aOR 1.83 [95% CI 1.02-3.26], p=0.04), multiple insurance (Ref=no insurance, aOR 2.07 [95% CI 1.15-3.74], p=0.02), and poor self-rated health (Ref=excellent, aOR 6.96 [95% CI 3.82-12.70], $p<0.001$). **Conclusions:** We observed an independent association between disability and ED visits and hospitalizations among cancer survivors in a national, population-based dataset. Geographic region, insurance, and poor health perception were additional risk factors for acute care utilization in cancer survivors. Our findings highlight the need for targeted interventions to improve ambulatory care access and reduce preventable acute care utilization in this vulnerable population. Research Sponsor: National Cancer Institute; 5R37CA288492.

1644 **Poster Session**

Healthcare resource use (HCRU) intensity prior to cancer diagnosis and real-world outcomes in early-stage cancers. First Author: Syed Irteza Abbas Shamsi, University of Calgary, Calgary, AB, Canada

Background: *Choosing Wisely* initiatives aim to reduce futile care by emphasizing the role of clinicians in healthcare decision-making. However, HCRU is strongly shaped by patient preferences with some inherently favoring high-intensity ("maximalist") care and others preferring low-intensity ("minimalist") approaches. We hypothesized that HCRU in the years before an early-stage cancer diagnosis may, in part, represent the healthcare seeking preferences of patients rather than strictly reflecting their clinical needs. **Methods:** We conducted a population-based retrospective cohort study of adults diagnosed with stage I-II breast, lung or colon cancer from 2015 to 2020 in Alberta, Canada with follow-up to 2025. Pre-diagnosis HCRU was quantified using ambulatory, emergency, and inpatient encounters. Patients were categorized as high (≥75th percentile) or low (≤25th percentile) users; intermediate users were excluded. Cohorts of high vs. low users were matched based on age, sex, rurality, stage and Charlson Comorbidity Index (CCI) and stratified by tumor site. Outcomes included cancer-specific survival (CSS), overall survival (OS) and post-diagnosis HCRU. **Results:** The matched cohort included 7,384 patients (64% breast, 21% lung, 15% colon) with balance across all covariates. Median age was 67 years, 68% had stage I disease and 95% had CCI<2. For all cancer sites, CSS did not differ between high and low users (see Table). High pre-diagnosis HCRU was associated with worse OS in breast (HR 1.34, $p<0.001$) and colon cancer (HR 1.36, p=0.003), but not in lung cancer (HR 1.02, p=0.76). Importantly, HCRU patterns pre-diagnosis strongly persisted post-diagnosis, with high users continuing to consume significantly more healthcare resources than low users for 4 years after cancer diagnosis ($p<0.001$). **Conclusions:** In this relatively healthy cohort of early-stage, highly curable cancers, greater pre-diagnosis HCRU was associated with sustained post-diagnosis HCRU intensity without any significant differences in cancer-specific outcomes. Our findings suggest that utilization patterns may reflect patient-level behaviors as much as clinical necessity, thus contributing to volume-driven care that may have limited clinical value. Advancing future *Choosing Wisely* initiatives in oncology must extend beyond clinician stewardship to address patient expectations about their healthcare interactions. This strategy would better align with value-based care and promote health system sustainability. Research Sponsor: None.

CSS based on pre-diagnosis HCRU.

Cancer site	Pre-diagnosis HCRU	10-year CSS (95% CI)	HR for CSS (95% CI)	P value
Breast	Low	89% (87%, 92%)	Reference	0.55
Breast	High	91% (90%, 93%)	0.93 (0.74,1.18)	
Lung	Low	63% (58%, 69%)	Reference	0.72
Lung	High	68% (64%, 72%)	1.04 (0.85,1.26)	
Colon	Low	90% (87%, 93%)	Reference	0.39
Colon	High	92% (89%, 95%)	0.82 (0.52,1.29)	

1645 **Poster Session**

Reframing access to innovative oncology medicines: The impact of policy and governance reform in a Bismarck-type system in Bosnia and Herzegovina. First Author: Timur Ceric, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Background: Access to innovative oncology medicines is often assumed to depend primarily on available financial resources. In health systems organized under the Bismarck model, however, access is frequently constrained by structural and policy-related factors, including fragmented governance, rigid reimbursement pathways, and infrequent updating of positive drug lists. These limitations may result in delayed access, restricted indications, and misalignment with contemporary clinical standards, even in the absence of absolute budget shortages. In Bosnia and Herzegovina, such constraints are compounded by complex administrative arrangements, leading to pronounced regional disparities in cancer care. In Sarajevo Canton prolonged waiting times and loss of treatment eligibility underscored that the key barrier was not lack of money, but lack of timely policy action. In October 2024, Sarajevo Canton launched a program shifting financing responsibility locally to improve timely access. **Methods:** We analyzed drug access before and after program initiation in 641 patients, assessing waiting times from indication to treatment approval and the proportion of patients losing indication prior to therapy availability. **Results:** Patients whose indication was established before the program were significantly more likely to remain without therapy compared to those after initiation (23.8% vs. 10.3%, $p < 0.001$). Among 547 patients with available waiting time data, mean waiting time decreased from 251.6 days (SD ≈ 190; range 21–910) to 40.4 days (SD ≈ 21; range 6–199), representing a >6-fold reduction. Variability also decreased, making access more predictable and equitable. Levene's test indicated unequal variances ($F = 517.3$, $p < 0.001$), and Welch's t-test confirmed the difference ($t(157.5) = 13.91$, $p < 0.001$; 95% CI 181–241 days), with a very large effect size (Cohen's $d \approx 2.0$). **Conclusions:** This policy intervention dramatically reduced waiting times and improved equity in therapy access. This demonstrates that substantial improvements in oncology drug access can be achieved without increasing overall healthcare spending. The observed gains were the result of a deliberate policy and governance shift—redefining responsibility, prioritization, and accountability—rather than additional financial input. This intervention highlights that, within Bismarck-type systems, access gaps are often policy failures rather than funding failures, and that targeted policy change can serve as a powerful lever to rapidly improve equity and quality of cancer care. Research Sponsor: None.

1646 **Poster Session**

Association between physician characteristics and likelihood of caring for underserved patients with cancer. First Author: William Roberts, National Clinician Scholars Program, Yale School of Medicine, New Haven, CT

Background: Despite evidence that a diverse workforce may improve access to care for underserved patients, emerging policies threaten to limit diversity in the physician workforce. We assessed whether nonwhite and foreign-born physicians were more likely than White and US-born physicians to care for underserved (minority race, low-income, rural) Medicare beneficiaries with cancer. **Methods:** Using SEER-Medicare, we analyzed Medicare beneficiaries aged 18+ newly diagnosed with breast, colorectal, lung, or prostate cancer from 2015-2019. We linked patients to cancer physicians (medical, radiation, and surgical oncology) using claims in the 6 months after diagnosis. We assessed physician race/ethnicity (data from Association of American Medical Colleges) and country of birth (American Medical Association). For each physician race and foreign-born status, we calculated the standardized treatment ratio (STR) as the percent of that group's dyads with a given patient characteristic divided by the percent of all dyads with that patient characteristic. Thus, STR > 1 indicates physicians in that group are more likely than the average physician to treat patients with the given characteristic. **Results:** We linked 434,923 patients (30% breast, 16% colorectal, 29% lung, 25% prostate) to 35,257 physicians. The patient population (mean age 74.7) was 79% White, 8% Black, 7% Hispanic, 3% Asian, 17% Medicaid dual-eligible, and 16% rural. Black physicians were more likely than expected to care for Black patients (STR 2.55; 95% CI 2.48–2.63; Table) and dual-eligible patients (STR 1.26; 1.22–1.29). Hispanic physicians were more likely to care for Hispanic (1.97; 1.91–2.03) and dual-eligible (1.11; 1.08–1.14) patients. Asian physicians were more likely to care for Asian (1.93; 1.89–1.96) and Hispanic (1.18; 1.16–1.20) patients and less likely to care for rural (0.73; 0.72-0.74) patients. Foreign-born physicians (20.7% of physicians) were more likely to care for Asian (1.36; 1.33–1.39), Hispanic (1.25; 1.23–1.27), and dual-eligible (1.20; 1.18–1.21) patients and less likely to care for rural patients (0.90, 0.89-0.91). **Conclusions:** Nonwhite and foreign-born cancer physicians disproportionately care for nonwhite and low-income patients. Policies restricting entry of minority and foreign-born physicians into the oncology workforce may hinder access to care for underserved cancer patients. Research Sponsor: None.

Standardized treatment ratios (STRs) by physician race, ethnicity and country of birth.

Physician characteristic	Patient Characteristic Asian	Black	Hispanic	White	Dual eligible	Rural
Race & ethnicity						
Asian	1.93	1.00*	1.17	0.95	1.09	0.73
Black	0.60	2.55	1.08	0.85	1.26	1.04
Hispanic	0.79	0.97*	1.97	0.94	1.11	1.01*
White	0.68	0.92	0.81	1.04	0.88	1.09
Foreign born						
No	0.86	0.96	0.89	1.02	0.88	1.04
Yes	1.36	1.05	1.25	0.96	1.20	0.90

*Denotes STRs NOT significantly different from 1.0; all other values are significant ($P<0.05$).

1647 **Poster Session**

Racial disparities and nonconcordance with endocrine and HER2 therapy for breast cancer: A sequential mediation analysis of neighborhood deprivation and insurance status. First Author: Jay Patel, University of Central Florida College of Medicine, Orlando, FL

Background: Racial disparities in breast cancer treatment persist, but the mechanisms driving inequities may differ by therapy type. We evaluated whether neighborhood racialized economic segregation (mediator 1, M1) and insurance status (M2) sequentially mediate racial disparities in receipt of guideline-concordant endocrine and anti-HER2 therapy. **Methods:** We conducted a retrospective cohort analysis of women diagnosed with breast cancer using the Florida Cancer Data System (2013–2021). Eligible women included those with invasive, nonmetastatic disease with hormone or HER2-receptor-positive tumors. Treatment nonconcordance was defined as failure to receive recommended systemic therapy based on tumor receptor status. M1 was measured by the racial-income version of the Index of Concentration at the Extremes (ICE) at the census tract level and divided into quintiles from the most to least deprived. Insurance status was categorized as insured versus Medicaid/uninsured/unknown (MUU). Simple frequencies were obtained to assess the relationships between race, the mediators, and therapy nonconcordance. Causal mediation analyses using the parametric g-formula quantified natural course risks and the proportion of the racial disparity mediated by ICE and insurance status, while adjusting for confounders (disease stage, molecular subtype [endocrine only], tumor grade, age, region of the state, and marital status). **Results:** There were 71,077 and 3,021 women available for the analysis of endocrine and HER2 therapy, respectively. For nonconcordance with endocrine therapy, disparities were present by race (37.2% vs. 29.0%, Black vs. White), the ICE (37.2% vs. 26.2%, most vs. least deprived), and insurance status (36.1% vs. 29.4%, MUU vs. other). Smaller disparities were present for nonconcordance with HER2 therapy by race (18.1% vs. 12.9%, Black vs. White), the ICE (16.2% vs. 14.2%, most vs. least deprived), and insurance status (18.5% vs. 13.4%, MUU vs. other). In causal mediation analysis for nonconcordance with endocrine therapy, the natural course counterfactual risks showed a 5% absolute disparity by race (34.3% vs. 29.3%); 59% of this disparity was mediated by the ICE and insurance status. For nonconcordance with HER2 therapy, the natural course counterfactual risks showed a 4% absolute disparity by race (17.1% vs. 13.1%); none of this disparity was mediated by the ICE and insurance status. **Conclusions:** Racial disparities in receipt of endocrine therapy are largely mediated by neighborhood deprivation and access to care, whereas these factors played no role in explaining disparities in anti-HER2 therapy. These findings suggest that treatment disparities are therapy-specific and that analyses of aggregate treatment outcomes may obscure distinct mechanisms of inequity. Research Sponsor: University of Central Florida College of Medicine.

1648 **Poster Session**

Survival outcomes with immune checkpoint inhibitors among patients with cancer from minoritized racial and ethnic groups: A systematic review and meta-analysis. First Author: Alfredo Viray Chua Jr., Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Immune checkpoint inhibitors (ICIs) have transformed the treatment landscape across multiple malignancies; however, minoritized racial/ethnic groups remain underrepresented in pivotal trials, limiting the generalizability of efficacy estimates. Whether treatment outcomes with ICIs differ across these groups remains incompletely characterized. Thus, we conducted a systematic review and meta-analysis of published randomized controlled trials (RCTs) to evaluate differences in overall survival (OS) and progression-free survival (PFS) among these groups treated with ICIs. **Methods:** We systematically searched MEDLINE, Embase, Cochrane CENTRAL, and ClinicalTrials.gov for RCTs published through December 31, 2024, that evaluated ICIs in adult patients with cancer and reported OS or PFS by race/ethnicity. Risk of bias was independently assessed using the Cochrane Risk of Bias tool for randomized trials (RoB 2). Hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted. Between-study heterogeneity was quantified using I^2. Random-effects meta-analyses were performed using Review Manager (RevMan) and stratified by: non-White and White patients; Asian, Black, and White patients; Asian and non-Asian patients; and Hispanic and non-Hispanic patients. Publication bias was evaluated using funnel plots. This review followed Cochrane methodology and PRISMA guidelines and was registered in PROSPERO (CRD42025027941). **Results:** A total of 97 trials comprising 59,949 patients were included. For OS, ICIs were associated with significant benefit in both non-White (HR 0.70, 95% CI 0.63–0.77; $p<0.001$) and White patients (HR 0.75, 95% CI 0.67–0.84; $p<0.001$). Significant OS benefit was also observed in analyses stratified by Asian (HR 0.81, 95% CI 0.76–0.86; $p<0.001$) and White patients (HR 0.86, 95% CI 0.82–0.91; $p<0.001$), and by Asian (HR 0.83, 95% CI 0.76–0.91; $p<0.001$) and non-Asian patients (HR 0.79, 95% CI 0.73–0.86; $p<0.001$). Similar patterns were observed for PFS. Estimates for Black and Hispanic patients were not statistically significant, reflecting limited sample sizes. Heterogeneity ranged from low to substantial (I^2 0–87%), with higher heterogeneity observed in PFS analyses. Only one trial reported race-specific survival outcomes for American Indian/Alaska Native (AI/AN) patients, and none reported outcomes for Native Hawaiian/Pacific Islander (NH/PI) patients, precluding analyses for these groups. **Conclusions:** ICIs were associated with improved OS and PFS across racial/ethnic groups, with no consistent evidence of differential treatment effects. However, the persistent underrepresentation of minoritized populations, particularly AI/AN, Black, Hispanic, and NH/PI patients, limits definitive conclusions and highlights the need for more equitable representation in oncology trials. Research Sponsor: National Institutes of Health, National Cancer Institute; UG3/UH3 CA262602; National Institutes of Health, National Cancer Institute; R01 CA247281; Breast Cancer Research Foundation.

1649 Poster Session

ZIP-code–level distress as a predictor for advanced stage and mortality in female breast cancer across a multiethnic cohort in Hawai'i. First Author: Chalothorn Wannaphut, Department of Internal Medicine, University of Hawai'i John A. Burns School of Medicine, Honolulu, HI

Background: Native Hawaiian and Pacific Islander (NHPI) patients experience worse breast cancer outcomes; however, the role of neighborhood-level structural disadvantage remains underexplored. We evaluated whether the Distressed Communities Index (DCI), a ZIP-code–level socioeconomic measure, is associated with stage at diagnosis and survival in a multiethnic breast cancer cohort. **Methods:** We conducted a retrospective cohort study of 10,421 female patients with breast cancer treated at a major tertiary cancer center in Honolulu, Hawai'i (2000-2024). DCI was assigned by residential ZIP code using the Economic Innovation Group DCI (American Community Survey 5-year estimates, 2019–2023) and dichotomized as low (DCI 1–3) versus high (DCI 4–5). Patients missing ZIP code or stage at diagnosis were excluded. Associations with advanced stage (III/IV) were assessed using logistic regression. Overall survival (OS), defined as time from diagnosis to death from any cause or last follow-up, was evaluated using multivariable Cox regression, adjusting for age, race/ethnicity, insurance, tumor characteristics, and stage. **Results:** The cohort included 1,982 White, 6,206 Asian, 2,067 NHPI, and 166 patients of other races/ethnicities. Baseline DCI distribution differed by race/ethnicity and insurance: NHPI patients were more likely to reside in high-distress communities than non-NHPI patients (38.9% vs 29.3% OR 1.54, $p<0.001$), as were Medicaid/uninsured patients compared with privately insured patients (51.4% vs 27.8%; OR 2.76, $p<0.001$). Advanced stage at diagnosis was more frequent in high-DCI neighborhoods than low-DCI neighborhoods (10.0% vs 6.7%; $p<0.001$) and remained independently associated with high DCI after adjustment (aOR 1.29; p=0.021). Higher DCI was also associated with worse survival (aHR 1.16, 95% CI 1.07–1.27; $p<0.001$), demonstrating a dose-response pattern across DCI categories (p for trend <0.001). No significant interaction was observed between DCI and NHPI status (p=0.493). Median OS was 247 (234-260) months for White patients, 247 (241-253) months for Asian patients, 227 (215-239) months for NHPI patients (log-rank $p<0.001$). In multivariable analysis, NHPI patients had higher mortality than White patients (HR 1.27, 95% CI 1.12–1.43; $p<0.001$), while Asian patients had improved survival (HR 0.78, 95% CI 0.71–0.87; $p<0.001$). Medicaid/uninsured remained independently associated with higher mortality (HR 2.18, 95% CI 1.85–2.57; $p<0.001$). **Conclusions:** ZIP-code–level socioeconomic distress is independently associated with advanced stage at diagnosis and mortality in breast cancer and disproportionately affects NHPI and Medicaid/uninsured patients. DCI identifies communities at higher risk and provides a scalable, policy-relevant tool to support geographically targeted navigation, screening access, and resource allocation strategies. Research Sponsor: None.

1650 Poster Session

Racial variation in pain medication prescriptions among breast, prostate, and pancreatic cancer patients treated in a large community oncology setting. First Author: Ila Sruti, Ontada, Boston, MA

Background: Patients (pts) from racially and ethnically minoritized populations are less likely to receive opioid analgesics for cancer-related pain, raising concern for inequitable symptom management. Although guidelines support opioid therapy within a multimodal approach, large scale evidence on racial differences in pain medication use across cancer types remains limited. This study uses real-world data from a large community oncology network to evaluate prescribing patterns of pain medication among high prevalence and high pain burden cancers by race and cancer type. **Methods:** Electronic medical record data from The US Oncology Network identified pts diagnosed with breast, prostate, or pancreatic cancer between January 2021 and June 2025, followed through December 2025. Pain medication (acetaminophen, NSAID, opioid) prescriptions and median time from cancer diagnosis to pain medication prescription were described. Strong opioids were defined as fentanyl, hydromorphone, morphine, or oxycodone, while general opioid use included hydrocodone and tramadol. **Results:** Among breast cancer patients overall (58,308 White; 7,705 Black; 3,652 Asian), pain treatment was received by 19% of White pts and by 24% of both Black and Asian pts, with median time to first pain medication shortest for White patients (65 d) and longest for Black patients (80 d). Prescriptions for strong opioids for breast cancer were lowest among Asian patients (28%), compared to 32% in Black patients and 35% in White patients. Among prostate cancer overall (19,268 White; 3,385 Black; 469 Asian), where receipt of pain medication was 17%, 20%, and 15%, respectively, Asian pts experienced the longest time to pain medication (86 d) versus the shortest among White patients (50 d). Asian patients had the fewest prescriptions for strong opioids (28%) compared with Black (54%) and White patients (50%). In pancreatic cancer (7,972 White; 1,035 Black; 330 Asian), pain medication prescriptions overall (52%, 55%, 50%, respectively) and for strong opioids (71%, 68%, 73%, respectively) were comparable across racial groups, and median time to pain medication showed minimal variation (18–22 d). **Conclusions:** In this large, nationally representative community oncology population, clinically meaningful racial differences in time to pain medication initiation and strong opioid prescribing were observed for breast and prostate cancer but not pancreatic cancer. Minoritized populations experienced delays in pain management, and Asian patients consistently received fewer strong opioid prescriptions. These results highlight that inequities in pain management vary across malignancies, and categories of pain medication. These findings underscore the need for culturally informed, cancer specific interventions to promote equitable symptom management. Research Sponsor: None.

1651 Poster Session

Racial representation in clinical trials supporting NCCN breast cancer guidelines: A retrospective analysis. First Author: Shreya Motkur, Michigan State University, Lansing, MI

Background: Racial disparities in breast cancer are well established, with Black women having disproportionately higher mortality rates. The NCCN guidelines are valuable in the management of breast cancer, highlighting the importance of evaluating racial representation and its trends over time within the studies cited in these guidelines. **Methods:** We conducted a retrospective analysis of 735 references cited in NCCN Breast Cancer Guidelines Version 4.2025. All clinical trials were included, while reviews, case reports, and non-clinical references were excluded. The primary outcome of interest was the reporting of racial demographics within each reference. Fisher's exact test was used to assess statistically significant differences in racial representation across time periods. **Results:** Of 735 references screened, 384 met the inclusion criteria, and 89 (23%) reported racial demographics. Studies reported a total of 87.9% White, 4.5% Black, 4.1% Asian, 0.5% Hispanic, 0.1% American Indian/Alaska Native, 0.0% Native Hawaiian/Pacific Islander, and 0.1% reporting more than one race. Time block 5 had significantly more reported races than blocks 2, 3, and 4 (p-value < 0.05). A statistically significant decrease in percentage reported as White was seen when comparing time blocks 1 to 5 (p = 0.0495), 2 to 5 (p = 0.0336), and 2 to 6 (p = 0.028). Changes in representation among other racial groups were primarily driven by Black and Asian groups, with Asians comprising the largest proportion in time blocks 4 (6.1%) and 6 (17.9%), while the Black race was the largest group in all other time blocks. All other racial groups remained consistently low across time blocks. **Conclusions:** Only 23% of references reported racial data. While the proportion of the White race decreased over time and an increased representation of other racial groups was observed, the overall reporting of these groups remained low across all time periods. This emphasizes the need for standardized reporting of race in clinical trials to ensure that NCCN guidelines accurately reflect the diversity of patients in breast cancer care. Research Sponsor: None.

Race demographics from clinical trials cited in the NCCN breast cancer guidelines.

Time block	Time Bracket	Percentage of White	Percentage of Non-White	Percentage of Black	Percentage of Asian	Percentage of Hispanic	Percentage of AI/AN	Percentage of NI/PI	Percentage of More than one race
1	1980-1999	95.6%	1.6%	2.8%	0.0%	0.0%	0.0%	0.0%	0.0%
2	2000-2004	92.4%	1.4%	4.6%	0.1%	1.3%	0.0%	0.0%	0.2%
3	2005-2009	86.9%	5.4%	5.2%	1.6%	0.9%	0.0%	0.0%	0.0%
4	2010-2014	88.7%	1.8%	2.8%	6.1%	0.1%	0.0%	0.0%	0.5%
5	2015-2019	87.1%	1.8%	5.7%	4.7%	0.3%	0.3%	0.1%	0.1%
6	2020-2025	78.3%	0.2%	3.1%	17.9%	0.3%	0.1%	0.0%	0.1%
	Total	87.9%	2.7%	4.5%	4.1%	0.5%	0.1%	0.0%	0.1%

AI/AN = American Indian/Alaska Native; NH/PI = Native Hawaiian/Pacific Islander.

1652 Poster Session

Are socio-economic status indicators barriers for enrollment in phase 1 clinical trials? First Author: Reema Mody, Hackensack University Medical Center, Hackensack, NJ

Background: Socio-economic Status (SES) indicators create barriers to access Phase 1 clinical trial (Ph1) enrollment, particularly for underrepresented minorities (URM). However, it remains unclear whether they directly affect enrollment after screening, or represent upstream barriers. We evaluated whether SES indicators impacted the enrollment rate in Ph1. **Methods:** All patients were screened for Ph1 at Hackensack University Medical Center (2014-2025). Patient ZIP codes were linked to the U.S. Census data (ACS 2018-2022) to derive neighborhood-level SES indicators: median household income (MHI), educational attainment (Bachelor), poverty rate (PR), unemployment rate (UR), and median home value (MHV). SES indicators were compared to national and state census benchmarks. The primary outcome was enrollment rate by SES indicators. We performed univariate analyses (Mann-Whitney U tests, chi-square), stratified analyses by race/ethnicity and gender, temporal trend analysis, and multivariable logistic regression. **Results:** A total of 1,316 patients were screened for 140 Ph1. Demographics were non-Hispanic White (NHW) 66.2%, Hispanic 19.0%, African American/Black (AA) 7.8%, Asian 6.5%. No SES variable predicted enrollment: median income (enrolled $62,646 vs not-enrolled $61,820, p=0.450), education (38.3% vs 37.9%, p=0.598), poverty (12.9% vs 12.3%, p=0.416), unemployment (6.1% vs 6.0%, p=0.422), home value ($277,461 vs $275,697, p=0.605). SES quartile analysis showed no enrollment gradient (Q1=61.7%, Q2=58.1%, Q3=60.5%, Q4=63.8%; p=0.491). Findings were consistent across all racial/ethnic groups (all $p>0.05$), see Table 1, gender (all $p>0.05$), age groups <65 and ≥ 65 years (all $p>0.05$), and time periods 2014-2019 vs 2020-2025. When compared to their respective racial/ethnic groups U.S. Census averages, it demonstrated atypical SES profiles: Hispanic patients had higher education (36.6% vs 20.6%), AA showed higher SES across all indicators, and Asians showed lower SES, suggesting regional selection bias in who reaches Ph1 screening. **Conclusions:** When patients reach Ph1 screening, SES indicators do not predict enrollment, demonstrating that equitable enrollment practices can be achieved at screening. Although there were no visible SES-related barriers at the enrollment point, disparities exist among groups likely suggesting referral patterns prior to screening. Future research should examine how to improve access to Ph1 in URM and upstream inequities. Research Sponsor: None.

SES analysis stratified by race/ethnicity.

Race	SES Variable	p-value
NHW	MHI	0.4476
NHW	Education	0.4585
NHW	PR	0.7483
NHW	UR	0.6957
NHW	MHV	0.4982
Hispanic	MHI	0.8270
Hispanic	Education	0.4104
Hispanic	PR	0.0646
Hispanic	UR	0.2401
Hispanic	MHV	0.9677
AA	MHI	0.9569
AA	Education	0.7355
AA	PR	0.9112
AA	UR	0.3962
AA	MHV	0.3076
Asian	MHI	0.2037
Asian	Education	0.3200
Asian	PR	0.2067
Asian	UR	0.0867
Asian	MHV	0.1677

1653 Poster Session

Early-onset gastrointestinal cancers: Racial disparities in stage and survival from large-scale community oncology data. First Author: Saamir Pasha, Ontada, Boston, MA

Background: Research on early-onset (EO) gastrointestinal (GI) cancers has focused predominantly on colorectal cancer, leaving knowledge gaps regarding racial variations across other GI malignancies. We used real-world data from a large, nationally representative community oncology network to assess age-of-onset differences in clinical characteristics and survival for colorectal, gastric, and esophageal cancers across key social determinants. **Methods:** This was a retrospective cohort of patients with colorectal, gastric and esophageal cancers treated within the U.S. Oncology Network and non-Network practices from 2000–2025. Patients were categorized as EO (<50 years) or average-onset (AO) (≥50 years) at diagnosis. Characteristics including demographics, stage at diagnosis (I–II, III–IV, or unknown), and distress level (NCCN Distress Thermometer) were sourced from iKnowMed. Overall survival (OS) was assessed from diagnosis using Kaplan–Meier methods, stratified by race/ethnicity and stage. **Results:** Among 195,624 patients with GI cancers, 23,244 (11.9%) had EO disease. In the EO cohort, 20,203 (87%) had colorectal, 1,693 (7%) gastric, and 1,348 (6%) esophageal cancers. EO disease occurred in a more racially and ethnically diverse population, with higher representation of Hispanic/Latino (10.3% vs 6.7%), Black (8.2% vs 6.6%), and Indigenous/Native (1.3% vs 0.8%) patients, and higher female representation (46.4% vs 43.9%), versus AO disease. Advanced-stage (III–IV) disease at diagnosis was more common in EO vs AO disease across colorectal (41% vs 32%), esophageal (41% vs 31%), and gastric (37% vs 29%) cancers. Among EO patients, stage III/IV disease at diagnosis was higher in Black (75.3%) and Asian (73.1%) versus White patients (64.9%), whereas among AO patients advanced stage was more balanced across racial groups (66.2%, 64.9%, 62.9%, respectively). Within EO advanced-stage disease, median OS was 8.1 m shorter in Black vs White patients (51.0 vs 59.1 m), compared with only a 1.6 m difference in AO disease (35.0 vs 36.6 m). Among patients with available distress data (N=3,426), distress was higher in EO versus AO patients (median 4 vs 3) but did not differ by race, sex or ethnicity. **Conclusions:** This study represents one of the largest real-world characterizations of EO GI cancers, revealing that EO patients more often present with advanced-stage and higher distress than AO counterparts. While racial disparities in stage were relatively balanced in AO disease, they were exacerbated in EO disease, with Black and Asian patients presenting with substantially higher rates of advanced disease. The resulting survival gap between Black and White EO patients underscores a widening disparity less pronounced in older patients. A precision–public health approach is needed to address biological and socioeconomic drivers of outcomes in young, diverse GI cancer populations. Research Sponsor: None.

1654 Poster Session

Global sex-based disparities in pancreatic cancer clinical trial enrollment: A systematic review and meta-analysis. First Author: Amir H. Sohail, The Christie NHS Foundation Trust, Manchester, United Kingdom

Background: Sex-based disparities in oncology trial enrollment are well recognized, yet their magnitude and consistency in pancreatic cancer clinical trials remain poorly-defined. We conducted a global systematic review and meta-analysis to quantify women's representation in pancreatic cancer trials relative to disease incidence. **Methods:** We identified phase I–III randomized and prospective interventional pancreatic cancer trials published through November 2025 in the top 25 general medicine, oncology, and gastroenterology journals. Women's enrollment was compared with sex-specific pancreatic cancer incidence from Global Burden of Disease estimates. Enrollment disparity difference (EDD) was calculated as the proportion of women enrolled minus the proportion of women in the underlying disease population. Random-effects meta-analyses, subgroup analyses, and temporal meta-regression were performed. **Results:** Among 191 eligible trials including 37,688 participants, 16,393 (43.5%) were women. Overall, women were significantly under-enrolled, with a pooled EDD of −0.050 (95% CI, −0.058 to −0.042). Under-enrollment was observed across all geographic regions, with the largest disparity in European trials (EDD −0.069; 95% CI, −0.080 to −0.058). Significant disparities were present across all trial phases except combined phase I/II studies and were most pronounced in trials enrolling fewer than 50 participants (EDD −0.081; 95% CI, −0.105 to −0.057). Women remained under-enrolled across chemotherapy, immunotherapy/biologic, vaccine, and multimodal trials, while no significant disparity was observed in radiotherapy studies. Trials with women in leadership roles demonstrated slightly attenuated but persistent under-enrollment (EDD −0.046 vs −0.052). Temporal analyses showed narrowing of disparities between 2016 and 2020, followed by worsening under-enrollment from 2021 to 2025 (EDD −0.033). Sensitivity analyses limited to chemotherapy, immunotherapy/biologic, and phase III trials confirmed consistent patterns of under-representation. **Conclusions:** Women are persistently under-enrolled in pancreatic cancer clinical trials worldwide, with disparities evident across regions, trial phases, and treatment modalities. Recent reversals in progress highlight the need for durable, equity-focused trial design and enrollment strategies. Research Sponsor: None.

1655 Poster Session

Who gets access? National discrepancies in clinical trial enrollment among patients with brain metastases. First Author: Manuela Jaramillo, Duke University, Durham, NC

Background: Patients with brain metastases (BM) have historically been underrepresented in clinical trials. Contemporary national data describing clinical trial enrollment (CTE) patterns and sociodemographic predictors in this population remain limited. **Methods:** Using the National Cancer Database, adults (≥18 years) diagnosed with BM (2010-2021) from the five most common primary sites (lung, breast, melanoma, colorectal, and renal cell carcinoma) were included. The key outcome was CTE (yes/no). Multivariable logistic regression was used to evaluate associations between enrollment and primary tumor site, age, sex, race/ethnicity, facility type, geographic region, residence, insurance status, area-level education and income, comorbidity burden (Charlson-Deyo score), and time epoch (2010-2013, 2014-2017, 2018-2021). **Results:** The analytic cohort included 238,129 patients with BM (lung n=206,813; melanoma n=10,394; breast n=9,915; renal n=7,409; colorectal n=3,598). Overall, <1% of patients (n=385) had CTE. In adjusted analyses, compared with patients aged 18-39 years, those aged 40-64 years (aOR: 0.15) and ≥65 years (aOR: 0.12) had significantly lower odds of enrollment (P<0.001). Female sex was associated with higher enrollment (aOR: 1.30, P=0.013), while Hispanic ethnicity was associated with lower enrollment compared with non-Hispanic White patients (aOR: 0.39, P=0.014). Higher comorbidity burden (Charlson–Deyo score: 2-3) was associated with lower enrollment (aOR: 0.68, P=0.04). Treatment at an academic/research facility had the highest odds of CTE compared with community facilities (aOR: 4.83, P<0.001), as well as care within an integrated network (aOR: 1.87, P=0.001). CTE increased over time (2014-2017, aOR 1.58, P=0.002; 2018-2021, aOR 1.63, P=0.001, vs 2010-2013). **Conclusions:** CTE among patients with BM was low across primary tumor sites. Enrollment was higher at academic facilities and among younger patients, while Hispanic patients had lower odds of enrollment. These findings indicate persistent disparities in clinical trial access and support more inclusive enrollment strategies for patients with BM. Research Sponsor: None.

Key predictors of CTE.

Variable	Strata	aOR (95% CI)	P
Sex	Male (Ref)	-	-
	Female	1.30 (1.06–1.60)	0.013*
Race/ethnicity	NH-White (Ref)	-	-
	NH-Black	0.83 (0.57–1.16)	0.292
	Hispanic	0.39 (0.16–0.77)	0.014*
	Asian/Other	0.87 (0.54–1.32)	0.526
Facility type	Community (Ref)	-	-
	Academic/Research	4.83 (3.69–6.39)	<0.001*
	Integrated Network	1.87 (1.31–2.67)	0.001*

*Geographic region, residence, and insurance status were insignificant.

1656 Poster Session

Validation of a 10-item frailty index based on a comprehensive geriatric assessment (FI-CGA-10) for predicting survival in older adults with cancer. First Author: Tomohiro F. Nishijima, Geriatric Oncology Service, NHO Kyushu Cancer Center, Fukuoka, Japan

Background: The FI-CGA-10 is a content- and construct-validated measure for quantifying frailty from a CGA [Oncologist, 26, e1751 (2021)]. For criterion validation, we evaluated the predictive validity of the FI-CGA-10 for survival in older adults with cancer. **Methods:** This prospective cohort study included 1,630 consecutive older adults with cancer who underwent CGA prior to their cancer treatment decision at a geriatric oncology service in Japan from September 2018 through September 2024. Fitness and frailty were evaluated using the FI-CGA-10, which comprises ten domains: cognition, mood, communication, mobility, balance, nutrition, basic and instrumental activities of daily living (ADLs/IADLs), social support, and comorbidity. Deficits in each domain were scored 0 (no problem), 0.5 (minor problem), or 1.0 (major problem). FI-CGA-10 scores were calculated as the sum of domain scores divided by 10 and categorized as fit (<0.20), pre-frail (0.20–0.35), and frail (>0.35). The primary outcome was overall survival (OS) at 1 year from the date of CGA. Two Cox proportional hazards models were fitted to predict 1-year overall survival (OS): a base model (age, sex, cancer type, and stage) and the base model plus the FI-CGA-10 as a categorical variable. Model performance was compared using the likelihood ratio test and Harrell's c-index. We also examined associations between each FI-CGA-10 domain and 1-year OS, adjusting for the same covariates. **Results:** Median age was 80 years (range, 51–99); 61% were male, 46% had gastrointestinal cancer, and 41% had distant-stage disease. Overall, 22% were fit, 38% pre-frail, and 40% frail; 29% died within one year. By the likelihood ratio test, adding the FI-CGA-10 significantly improved model fit compared with the base model (LR χ^2 = 140.7; P < .001). Adding the FI-CGA-10 also significantly improved discrimination (c-index 0.70 vs 0.76; P < .001). Kaplan–Meier curves for the three groups showed clear separation, demonstrating the FI-CGA-10's discriminatory ability (log-rank P < .001). After adjustment for covariates, pre-frail (HR 2.26; 95% CI 1.61–3.19) and frail (HR 5.06; 95% CI 3.64–7.04) patients had higher hazards of death versus fit patients. Estimated 1-year OS probabilities were 90% (fit), 78% (pre-frail), and 58% (frail). In multivariable analyses adjusted for age, sex, cancer type, and stage, major problems in all domains—and minor problems in cognition, mobility, balance, nutrition, IADL, and comorbidity—were significantly associated with worse survival compared with no problems. **Conclusions:** These findings support the predictive validity of the FI-CGA-10 for 1-year OS in older adults with cancer. Together with prior work demonstrating its content and construct validity, the FI-CGA-10 satisfies core components of measurement validation that can help clinicians care for older cancer patients. Research Sponsor: JSPS KAKENHI; 20K16540 (T.F.N.) and 25K20897 (T.F.N.).

1657 Poster Session

Use of parsimonious Fitbit step metrics to improve frailty classification in adults ≥50 with cancer in NIH All of Us. First Author: Kenan Najjar, Carle Illinois College of Medicine, Champaign, IL

Background: Frailty predicts treatment intolerance and adverse outcomes in older adults with cancer, yet scalable screening remains limited. Scalable frailty screening is particularly relevant for treatment selection and risk stratification in routine oncology care. We tested whether routine Fitbit step metrics improve frailty classification beyond basic variables and whether high-dimensional step-pattern features add benefit. **Methods:** Retrospective cross-sectional study in the NIH All of Us Research Program including adults ≥50 years with cancer history and Fitbit step data (N=378). Frailty was defined by a 33-item All of Us deficit frailty index (fit <0.15, vulnerable 0.15–0.25, frail >0.25); primary endpoint was frail vs not frail (fit+vulnerable). Valid wear day required ≥10 hours with activity or heart-rate evidence. Missing days were imputed for daily totals and minute-level profiles reconstructed using within-person donor days or weekday/weekend templates. Prespecified feature tiers were: basic (9), basic+average steps (10), and high-dimensional step-pattern features (108; minute-level intensity, variability, and frequency-domain summaries). Class-weighted elastic-net logistic regression, random forest, and gradient-boosted trees were tuned and evaluated with nested 5×5 cross-validation. Discrimination was pooled out-of-fold area under the receiver operating characteristic curve (AUC) with stratified bootstrap 95% confidence intervals (CI); incremental value used paired bootstrap ΔAUC. **Results:** Participants were 64.8±8.6 years; 67.7% were female. Frailty categories were fit 43.7%, vulnerable 40.7%, and frail 15.6% (59/378). Mean daily steps were lower in frail vs not frail participants (5505 vs 7648 steps/day). Elastic-net logistic regression with step features achieved the highest AUC (0.713, 95% CI 0.636–0.783) vs the basic model (0.644, 95% CI 0.567–0.720; ΔAUC 0.068, paired bootstrap 95% CI 0.002–0.133). At ≥90% specificity, sensitivity increased from 25.4% (15/59) to 39.0% (23/59). In secondary analyses predicting not-fit status (vulnerable/frail vs fit), adding step features improved AUC from 0.551 (95% CI 0.493–0.609) to 0.635 (95% CI 0.580–0.694). High-dimensional step features did not improve AUC. **Conclusions:** In adults ≥50 with cancer, a parsimonious step-based metric improved frailty classification and increased sensitivity at high specificity, while complex feature sets and models did not add benefit. These findings support low-burden step metrics as scalable adjuncts to frailty screening in oncology; external validation is needed. Research Sponsor: National Institutes of Health (NIH) All of Us Research Program.

1658 Poster Session

GRACE: A conversational AI platform for geriatric oncology risk and capability evaluation. First Author: Arash Naeim, UCLA Medical Center, Los Angeles, CA

Background: Comprehensive geriatric assessment (CGA) is a multidimensional evaluation of health in older adults and endorsed by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) for improved outcomes in geriatric cancer patients. However, CGA is underutilized due to time constraints and staffing shortages. Artificial intelligence (AI) can provide autonomous geriatric assessments (GA) but require validation. **Methods:** GRACE, an AI platform for GA via natural language interaction, was tested against manual GA. 70 adults aged ≥65 were enrolled from UCLA using the portal MyChart and at affiliated active senior living centers. 15 clinicians contributed qualitative perspectives. Concordance was evaluated using sensitivity, specificity, predictive values, and agreement (Cohen's κ, Gwet's AC1). Usability was measured with the System Usability Scale (SUS), and patient and provider interviews were thematically analyzed. **Results:** GRACE showed high diagnostic performance (sensitivity 0.73, specificity 0.94, κ=0.63, AC1=0.82) with highest agreement in polypharmacy (κ≈0.97; AC1≈0.98). Usability was high (SUS >80th percentile) and 84% of participants reported confidence using GRACE. Clinicians endorsed GRACE as a practical pre-visit intake tool that integrates with electronic health records and facilitates timely referrals. **Conclusions:** GRACE demonstrates that conversational AI can replicate key elements of clinician-administered GA while reducing burden on oncology teams. Larger multi-site studies are warranted to evaluate clinical impact and integration into routine oncology practice. Research Sponsor: None.

Performance of GRACE versus manual geriatric assessment.

Domain	Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)	Cohen's Kappa (CI)	Gwet's AC1 (CI)
General Health	0.872 (0.748, 0.940)	0.931 (0.891, 0.957)	0.719 (0.592, 0.819)	0.973 (0.943, 0.988)	0.741 (0.637, 0.845)	0.887 (0.839, 0.935)
Physical	0.859 (0.760, 0.922)	0.971 (0.956, 0.981)	0.753 (0.649, 0.834)	0.985 (0.973, 0.992)	0.781 (0.704, 0.858)	0.953 (0.935, 0.970)
Functional	0.563 (0.332, 0.769)	0.985 (0.971, 0.993)	0.529 (0.310, 0.738)	0.987 (0.974, 0.994)	0.532 (0.298, 0.765)	0.972 (0.957, 0.986)
Social Support	0.629 (0.530, 0.718)	0.873 (0.839, 0.900)	0.508 (0.420, 0.596)	0.918 (0.889, 0.940)	0.458 (0.359, 0.558)	0.753 (0.702, 0.805)
Psychological	0.570 (0.460, 0.673)	0.920 (0.894, 0.940)	0.506 (0.404, 0.607)	0.937 (0.913, 0.955)	0.465 (0.353, 0.576)	0.839 (0.802, 0.876)
Comorbidity	0.641 (0.484, 0.773)	0.996 (0.989, 0.998)	0.862 (0.694, 0.945)	0.985 (0.975, 0.991)	0.726 (0.601, 0.851)	0.980 (0.971, 0.989)
Polypharmacy	0.974 (0.865, 0.995)	1.000 (0.893, 1.000)	1.000 (0.906, 1.000)	0.970 (0.847, 0.995)	0.971 (0.915, 1.027)	0.972 (0.916, 1.027)
Overall	0.721 (0.674, 0.763)	0.956 (0.949, 0.963)	0.649 (0.603, 0.692)	0.968 (0.962, 0.974)	0.645 (0.604, 0.687)	0.917 (0.907, 0.927)

1659 Poster Session

Development of a composite risk score for chemotherapy toxicity and unplanned hospitalization in older adults with cancer: A prospective cohort study. First Author: Lirong Yang, Shanghai Clinical Research and Trial Center, Shanghai, China

Background: Older adults receiving chemotherapy are at high risk for severe treatment-related toxicities, which may compromise treatment completion and lead to unplanned hospitalizations. We developed a composite risk score integrating the components of Cancer and Aging Research Group (CARG) chemotherapy toxicity score and proved clinical predictors to enhance prediction of grade 3–5 (G3–5) chemotherapy-related toxicities, treatment tolerance, and unplanned hospitalization. **Methods:** Patients aged ≥70 years with solid tumors initiating chemotherapy were enrolled between December 2024 and August 2025 at a tertiary hospital in Shanghai, China. The primary endpoint was the occurrence of any G3–5 chemotherapy-related toxicity; secondary endpoints included chemotherapy incompletion and unplanned hospitalization. Baseline characteristics included the CARG score, tumor- and treatment-related characteristics, and laboratory parameters. Toxicities (graded using CTCAE v5.0), treatment completion, and unplanned hospitalizations were assessed at each cycle for up to 6 months or until completion of the planned treatment course. Predictors of G3–5 toxicities were screened by LASSO-penalized multivariable logistic regression, and model discrimination was evaluated by receiver operating characteristic curve. **Results:** Among 242 patients (median age 74 years; range 70–88), 71.9% were male, 64.5% had gastrointestinal malignancies, and 73.1% had stage IV disease. Overall, 164 patients (67.8%) experienced G3–5 toxicities, and 63 (26.0%) had unplanned hospitalizations. The score system included cancer type, hemoglobin, estimated glomerular filtration rate, falls within 6 months, medication management ability, C-reactive protein/albumin, MAX2 index, walking ability, and social activity level. The median score was 10 (range 6–14). Each one-point increase in score was associated with higher risk of any G3–5 toxicity (OR 1.21, 95% CI 1.14–1.30; AUC 0.75) and non-hematologic G3–5 toxicity (OR 1.19, 95% CI 1.12–1.27; AUC 0.73).The score was also positively associated with unplanned hospitalization (OR 1.07, 95% CI 1.01–1.13; AUC 0.62), but was inversely associated with chemotherapy incompletion (OR 0.93, p=0.019), suggesting more proactive treatment modifications in high-risk patients. In this cohort, the new score showed superior discrimination for any G3–5 toxicity, with a higher AUC than the CARG score (0.75 vs. 0.63). The optimal cutoff point of any G3–5 toxicity was 7.5 with relatively good specificity (72%) and sensitivity (65%). **Conclusions:** The composite score may help predict G3–5 toxicity, non-hematologic G3-5 toxicities, and unplanned hospitalization, potentially outperforming the CARG score. External validation and evaluation of clinical utility are warranted. Research Sponsor: None.

1660 Poster Session

Practice patterns and outcomes by genomic risk in octogenarians with high-risk localized prostate cancer: A national real-world data analysis. First Author: James Robert Janopaul-Naylor, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Chronologic age and traditional clinical-pathologic prostate cancer (PCa) risk factors (e.g. PSA, Gleason Score) are useful but incomplete predictors of prognosis. While some octogenarians may benefit from watchful waiting for clinically high risk (HR) and very high risk (VHR) PCa due to competing risks, others may survive more than a decade with curative prostate-directed treatment. We examined real-world data (RWD) on practice patterns and outcomes for octogenarians with HR PCa stratified by genomic classifier (GC) scores. **Methods:** A retrospective cohort study was conducted using a national database of clinical–genomic linkage of Decipher GC with longitudinal RWD (Veracyte, South San Francisco, CA). The cohort included 1,519 patients, ≥80-years-old with HR/VHR PCa who underwent GC testing with >1 year of follow-up. Patients were stratified by low (GC-Low) compared to intermediate or high (GC-High/Int) GC scores. Observational management was determined by absence of treatment with evidence of prostate cancer–related services (e.g. GC-High/Int-Obs). Freedom from distant metastases (FFDM), metastasis-free survival (MFS), and overall survival (OS) were modeled using Kaplan-Meier analysis and log-rank tests. **Results:** Most patients (88%, n=1,341) had GC-High/Int. The rate of observational management was significantly lower in the GC-High/Int compared to GC-Low cohorts (26% vs 38%, p=0.001). Among treated patients, there were similar rates of ADT only use (52% GC-Low vs 54% GC-High/Int) but amongst those who were treated with radiotherapy, concurrent ADT use was lower in GC-Low compared to GC-High/Int (55% vs 69%, OR 0.83, 95% CI 0.73-0.95, p=0.007). There were significant differences between groups for FFDM (p=0.003), MFS (p<0.001), and OS (p<0.001) (Table). Among observed patients, GC-Low had significantly better FFDM than GC-High/Int (HR 0.11, 95% CI 0.02–0.80; p=0.03). **Conclusions:** Geriatric patients with aggressive, localized PCa decide between potentially morbid, curative treatments and heterogeneous risk of distant metastases in the setting of limited life expectancy. We present RWD that patients ≥80 years old with NCCN HR/VHR PCa with low GC scores have <5% rate of metastatic disease within 5 years with observation alone. This hypothesis generating data suggests GC score may be a useful prognostic tool in addition to standard clinical-pathologic factors for elderly patients. Patient-specific risk calculators for cancer and non-cancer specific mortality may help this underserved but growing population. Research Sponsor: Veracyte Inc.

	NCCN HR (%)	NCCN VHR (%)	FFDM Hazard Ratio (95% CI)	5-yr FFDM	5-yr MFS	5-yr OS
GC-Low-Obs	58 (85%)	10 (15%)	0.11 (0.02-0.80)	98%	70%	71%
GC-Low-Treat	90 (82%)	20 (18%)	0.76 (0.36-1.59)	82%	75%	91%
GC-High/Int-Obs	250 (71%)	104 (29%)	Reference	83%	37%	43%
GC-High/Int-Treat	633 (64%)	354 (36%)	1.35 (0.93-1.98)	81%	59%	64%

1661 Poster Session

Evaluation of a co-designed nurse-led geriatric oncology multidisciplinary model in treatment-naive older adults with solid cancers. First Author: Surein Arulananda, Monash Health, Clayton, VIC, Australia

Background: Integration of geriatric assessment into cancer care improves outcomes for older adults but remains limited by resource intensity and reliance on physician time, hence restricting scalability. We evaluated the implementation of a co-created multidisciplinary (MDT) nurse-led geriatric oncology (GO) model developed to address these barriers. **Methods:** Implementation evaluation was conducted across two tertiary cancer centers. Older adults (≥65 years) with solid cancers underwent nurse-led structured geriatric assessment and MDT review involving medical oncology and geriatric medicine prior to oncology consultation. MDT recommendations addressed identified vulnerabilities, with referral for geriatrician-led CGA reserved for complex cases. Outcomes included G8 screening, referral for CGA, SACT delivery, treatment modification due to frailty, treatment discontinuation, delays, dose modification due to toxicity, and health service utilization (ED, SURC and unplanned hospital admissions within 12 weeks). Demographic and clinical characteristics were summarized using descriptive statistics. Associations with health service use were determined using logistic regression analyses. **Results:** Of 431 eligible pts, 204 (47.3%) participated in the GO assessment. Median age was 76 years. Most pts had lung cancer (73.1%), followed by GU (14.8%) and upper GI cancers (8.6%). Disease stage did not differ between groups; GO pts were more likely to have ECOG PS 1–2 and 81.4% scored ≤14 on the G8 screening tool. Half (50.7%) were referred for CGA and 67.1% of this cohort received SACT while 32.4% of the cohort not referred for a CGA received SACT. Upfront treatment modification due to frailty was numerically higher in GO pts compared to non-participants (21.1% vs 13.1%, p=0.076). GO participation was associated with higher receipt of SACT (70.6% vs 59.7%, p=0.019), increased use of monotherapy (22.5% vs 13.7%, p=0.016), and lower rates of BSC alone (41.0% vs 59.0%, p=0.033). There were no differences between groups in treatment discontinuation (p=0.64), delays (p=0.074), or dose modifications due to toxicity (p=0.42). GO pts were more likely to be admitted to hospital within 12 weeks of initial oncology consultation. **Conclusions:** GO assessment supported detailed evaluation of older pts with borderline ECOG PS and increased access to SACT, particularly monotherapy, without increasing treatment-related toxicity. Higher hospitalization rates likely reflect appropriate escalation of care following identification of frailty-related needs. Research Sponsor: None.

GO vs no GO.

	GO (n=204)	No GO (n=227)	p-value
Age median (range)	76.0 (72.0, 81.0)	76.0 (71.0, 81.0)	0.77
Monotherapy	46 (22.5%)	31 (13.7%)	0.016
Doublet, or more therapy	98 (48%)	101 (44.5%)	0.46
ED presentation	93 (45.6%)	86 (37.9%)	0.11
SURC use	43 (21.1%)	49 (21.6%)	0.90
Inpatient admission	74 (36.3%)	62 (27.3%)	0.046

1662 Poster Session

Outcomes of mortality and health care utilization in frail older patients with cancer receiving target therapies and/or immunotherapy. First Author: Amit Arora, Kaiser Permanente, Fremont, CA

Background: ASCO & NCCN guidelines recommend geriatric assessment for cancer patients aged 65+ to identify vulnerabilities missed on standard evaluations. Patients with G8 ≤14 (High risk) are potentially frail and at risk for chemotherapy toxicity, early mortality and ED visits/hospitalizations. However, there is currently limited evidence regarding the impact of a high-risk G8 score on outcomes among older frail patients receiving immunotherapy or targeted therapies. **Methods:** G8 screening was done at initial oncology consultation. Data was analyzed for individuals aged 65 and above referred between January 2021 and December 2024. Outcomes were measured 180 days after referral. A chi-square test assessed the relationship between demographic or outcome variables and G8 score. Multivariate regression and survival models predicted outcomes using age, sex, ethnicity, cancer type, and risk score. **Results:** This study included 1,671 patients receiving targeted therapy and/or immunotherapy. Participants ranged in age from 65 to 102 (median 75). Higher risk scores were linked to lower BMI (underweight: 92%, healthy: 74%, overweight/obese: 57%, $p < .0001$), older age ($p < .0001$), and female sex (73% vs 62%, $p < .0001$). Ethnicity was not related to risk scores. High risk patients receiving target and/or immunotherapy had over 3x higher mortality rates at 180 days than low risk ones ($p < 0.0001$). They were also 1.4x as likely to have an ED Visit or hospitalization, 2x as likely to be referred to palliative care, and 5x as likely to be referred to hospice ($p < 0.0001$). Multivariate analysis showed patients with upper GI and thoracic cancers were 1.4x more likely to be admitted and had over 2.7x mortality rate compared to those with breast cancer ($p < .0001$ - 0.0188). A total of 515 patients underwent only immunotherapy. Outcome trends and the association between risk score and demographics were similar to the combined target therapy and/or immunotherapy study. **Conclusions:** A high-risk G8 score (≤14) is linked to higher mortality and more emergency visits or hospitalizations in older cancer patients receiving immunotherapy or targeted therapies. It is recommended that oncologists integrate geriatric assessment results into treatment decisions involving immunotherapy and targeted therapies. Research Sponsor: None.

Outcomes of patients by risk score and treatment type 180 days after referral.

Risk Score/Treatment Type	Mortality	ED Visits or Hospitalizations	Palliative Care Referral	Hospice Referral
High risk G8-Combined target/Immunotherapy	15.3%	51.1%	33.0%	12.1%
Low risk G8 - Combined Target/Immunotherapy	3.7%	29.2%	14.8%	2.3%
p-value	<0.0001	<0.0001	<0.0001	<0.0001
High risk G8 - Immunotherapy alone	26.5%	61.5%	40.1%	22.3%
Low risk G8 - Immunotherapy alone	8.7%	43.5%	19.6%	5.1%
p-value	<0.0001	0.001	<0.0001	<0.0001

1663 Poster Session

G8 screening-defined geriatric vulnerability as a predictor of survival and quality of life in older patients with advanced cancer treated with novel therapies. First Author: Andrea De Giglio, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Background: Older patients with advanced cancer are a highly heterogeneous population, in whom geriatric vulnerability may significantly influence survival, treatment tolerance, and patient-reported outcomes. The G8 screening tool is a validated instrument designed to identify geriatric vulnerability and select patients for comprehensive geriatric assessment; however, its prognostic and longitudinal impact on quality of life in patients receiving novel anticancer therapies remains poorly explored. **Methods:** The ONC-OLD study prospectively enrolled patients aged ≥70 years with advanced cancer treated with novel therapies across six referral centers. The primary objective was to assess the prognostic impact of baseline G8-defined geriatric vulnerability on overall survival (OS). Geriatric vulnerability was assessed at baseline using the G8 screening tool (≤14 vs >14). Health-related quality of life (HRQoL) was assessed using the EORTC QLQ-C30 and QLQ-ELD14 at baseline, after 3 months, and at disease progression. Baseline associations were analyzed using multivariable regression models, while longitudinal HRQoL changes were assessed using ANCOVA adjusted for baseline scores and relevant clinical covariates. **Results:** A total of 143 patients were included (median age 78 years, IQR 75-82); 78% had ECOG performance status (PS) 0-1, and 73% had G8 ≤14. Treatments consisted mainly of immunotherapy, either as monotherapy (31%) or in combination (36%), and targeted therapy (30%). At baseline, patients with G8 ≤14 were older (≥80 years: 46% vs 20%, p=0.019), more frequently female (42% vs 16%, p=0.016), and had worse ECOG PS (PS ≥2: 25% vs 0%, p=0.005) compared with those with G8 >14, with a different distribution of primary tumor types (lung cancer: 67% vs 29%, p=0.001). Median OS was 16.1 months (95% CI, 13.4-not reached) and was significantly shorter in patients with G8 ≤14 compared with those with G8 >14 (14.2 vs not reached; p=0.019). G8 ≤14 was independently associated with an increased risk of death (HR 2.71, 95% CI 1.01-7.24; p=0.047), after adjustment for ECOG PS, number of metastatic sites, treatment line and type. G8 ≤14 was associated with a trend toward a higher risk of grade ≥3 adverse events (OR 2.00, 95% CI 0.69-7.25; p=0.23), without specific treatment-related safety signals. At baseline, patients with impaired G8 reported worse global health, physical and role functioning, fatigue, pain, and mobility (all p≤0.01). In longitudinal analyses adjusted for baseline HRQoL and clinical covariates (ECOG PS, age, treatment), G8 remained significantly associated with higher fatigue (+12.6 points; p=0.039). **Conclusions:** Baseline G8 impairment is associated with poorer survival, worse baseline HRQoL, and a higher risk of severe toxicity, supporting the clinical value of G8 screening in older patients treated with novel therapies. Research Sponsor: PNRR - M4C2-I1.3 Project PE_00000019 "HEAL ITALIA"; CUP J33C22002920006.

1664 Poster Session

Age-related efficacy of antibody-drug conjugates in solid tumors: A meta-analysis. First Author: Mariana Macambira Noronha, Department of Clinical Medicine, Federal University of Ceara, Fortaleza, Brazil

Background: Antibody–drug conjugates (ADC) have revolutionized cancer therapeutics, with various ADC improving clinical outcomes across solid tumors and several now approved as standard of care. Older adults with cancer are historically underrepresented in trials. As therapies with ADC are shifting to earlier lines of therapy, investigating whether clinical outcomes differ from those of younger patients with cancer is of interest. **Methods:** We searched PubMed, Embase, and the CENTRAL databases from inception through Dec 2025 for phase III randomized controlled trials (RCTs) that included adult patients with metastatic solid tumors treated with ADC and reported survival outcomes stratified by age group: elderly (>65 years) and younger (<65 years). The co-primary endpoints were progression-free survival (PFS) and overall survival (OS) across these age subgroups. Pre-specified subgroup analyses were performed according to ADC drug, target, and cancer types. Time-to-event outcomes were pooled as hazard ratios (HR) using the inverse-variance method with random-effects models. Heterogeneity was assessed using the I^2. PROSPERO: CRD4202612924710. **Results:** Of 2194 records, 17 RCTs (phase 3) met eligibility, including 9,929 patients, spanning breast (n=12), lung (n=2), urothelial (n=1), ovarian (n=1), and gastric cancer(n=1). ADCs were stratified by payloads: topoisomerase I inhibitors (TOPO1i; 65%), microtubule inhibitors (MMAE; 29%), alkylating agents (6%); and targets: TROP-2 (53%), HER2 (41%), and FRα (6%). Elderly pts treated with ADC exhibited significant improvement in PFS with a HR of 0.57 (95% CI 0.46-0.71; $p < 0.01$; $I^2 = 62\%$). Similarly, younger pts exhibited longer PFS, with a HR of 0.55 (95% CI 0.45-0.67; $p < 0.01$; $I^2 = 86\%$). Likewise, elderly patients exhibited significantly greater OS with a HR of 0.78 (95% CI 0.66-0.91; $p < 0.01$; $I^2 = 41\%$), comparable to that observed in younger pts (HR 0.74; 95% CI 0.65-0.85; $p < 0.01$; $I^2 = 63\%$). Specifically, in elderly patients with breast cancer treated with ADC (n=7,213), significant improvements were seen with an HR of 0.49 (95% CI 0.36-0.67; $p < 0.01$) and 0.65 (95% CI 0.48-0.87; $p < 0.01$; I^2= 39%) for PFS and OS, respectively. Similar improvements in survival outcomes were seen in younger pts (HR of 0.53; 95% CI 0.42-0.67 and HR of 0.66; 95% CI 0.57-0.77, for PFS and OS, respectively. Pre-specified subgroup analyses according to ADC payloads showed no differences in pts treated with ADC plus TOPO1i (HR 0.76 and 0.70, $p < 0.01$). Notably, ADCs with MMAE payloads were associated with benefit only in the elderly (HR 0.77, $p < 0.01$), with no significant benefit in younger patients (HR 0.82, p =0.11). **Conclusions:** In this pooled analysis, including 5,111 pts treated with ADC under phase III RCTs, survival outcomes with ADC therapies were similar regardless of age. As the number of ADCs approved for the standard of care setting is expected to increase, age should not be an exclusion criteria. Research Sponsor: None.

1665 **Poster Session**

Integrating objective sarcopenia assessment into geriatric screening as a predictor of treatment tolerance. First Author: Hojung An, St. Vincent's Hospital, The Catholic University of Korea, Suwon, South Korea

Background: Geriatric assessment (GA)–based screening tools, including the G8 screening tool, the Korean Cancer Study Group Geriatric Score (KG-7), and the Cancer and Aging Research Group (CARG) toxicity score, are widely used to guide treatment decisions in older patients with cancer. However, these tools incompletely capture biological reserve and show limited accuracy in predicting treatment tolerance, particularly in patients with indeterminate risk. We evaluated whether incorporating objective sarcopenia assessment could improve risk stratification. **Methods:** We retrospectively analyzed 97 elderly patients with cancer (age ≥70 years) who underwent GA screening prior to treatment decision-making at a single tertiary center between May 2024 and December 2025. In addition to standard GA tools (G8, KG-7, and CARG toxicity score), skeletal muscle index (SMI) and functional frailty were assessed. SMI was measured using the DYPHI body water analysis (BWA) system, which estimates appendicular lean mass through multi-frequency bioelectrical impedance analysis. Functional frailty was evaluated using the Short Physical Performance Battery (SPPB). Treatment intolerance was defined as grade 3–5 toxicity, unplanned hospitalization, emergency room visit, or treatment discontinuation. Multivariable logistic regression and subgroup analyses were performed. **Results:** The median age was 76 years (range, 61–87), and 77 patients (79.4%) were male. Most patients had advanced-stage disease (72.2%), and 55.7% received palliative treatment. Initial dose reduction (<100%) occurred in 63.9%. GA tools, sarcopenia, and frailty showed modest concordance. Among GA tools, G8 demonstrated the strongest association with treatment intolerance (odds ratio [OR] per point increase 0.86, 95% confidence interval [CI] 0.74–0.99; p=0.03; area under the curve [AUC] 0.64). Sarcopenia was independently associated with treatment intolerance (OR 2.45, 95% CI 1.02–5.87; p=0.045) and improved discrimination across G8, KG-7, and CARG tools (ΔAUC up to +0.12). The benefit of sarcopenia was greatest in borderline or intermediate GA risk groups (ΔAUC approximately +0.10–0.12), with minimal improvement in low- or high-risk groups (ΔAUC ≤0.02). A minimal model incorporating G8, sarcopenia, and Eastern Cooperative Oncology Group (ECOG) performance status achieved the best performance (cross-validated AUC 0.68). **Conclusions:** Incorporation of objective sarcopenia assessment using the DYPHI BWA system significantly improves prediction of treatment tolerance beyond established GA tools, particularly in intermediate-risk subgroups. A pragmatic model combining G8, sarcopenia, and ECOG performance status may refine risk stratification and personalize treatment decisions in geriatric oncology. Research Sponsor: None.

1668 **Poster Session**

Online peer support for breast cancer survivors: A decentralized multicenter non-blinded parallel-group pilot randomized controlled trial (HOPE-BC study). First Author: Yoshie Hasegawa, Department of Breast Surgery, Hachinohe City Hospital, Hachinohe, Aomori, Japan

Background: Peer support effectiveness for breast cancer survivors has reportedly varied, and no study has examined patient–supporter matching. This decentralized, multicenter, non-blinded pilot randomized controlled trial aimed to assess online peer support effectiveness and explore factors for a matching algorithm. **Methods:** Breast cancer survivors within three years of completing initial treatment were recruited and provided electronic informed consent. Based on the sample size estimation, the target sample size was set at 50. Participants were randomly assigned either to the peer support group, which scheduled an online peer support session immediately after registration, or to the waitlist group, which scheduled their session two weeks later. Participants could choose their preferred time and date through a web-based scheduling system. Peer support sessions were conducted online by two trained peer supporters. The primary outcome was the UCLA Loneliness Scale score, assessed one week after the session in the peer support group and at the end of the 2-week waiting period in the waitlist group. Secondary outcomes included satisfaction with peer support and other psychosocial measures, all collected through an electronic patient-reported outcome system. Effect sizes for outcomes were calculated to inform sample size estimation for future trials. Analyses were performed to explore factors associated with satisfaction. The study protocol was registered in the UMIN Clinical Trials Registry (UMIN000056741). **Results:** From February to July 2025, 54 participants enrolled and 52 individuals completed the study (27 peer support group, 25 waitlist group). At the primary endpoint, the mean (standard deviation) UCLA Loneliness Scale scores were 38.4 (11.2) in the peer support group and 41.3 (13.3) in the waitlist group (Cohen's d = 0.24; t-test, P = 0.40). The change from baseline corresponded to a Cohen's d = 0.32. Among the secondary outcomes, the changes in Generalized Anxiety Disorder-7 scores differed between groups (mean difference [MD] = -1.3; 95% CI = -2.5 to -0.1), and the changes in Patient Health Questionnaire-9 scores tended to be greater in the peer support group (MD = -1.2; 95% CI = -2.5 to 0.1). The global health status on EORTC QLQ-C30 did not differ between groups (MD = 1.0; 95% CI = -6.6 to 8.7). The median (IQR) satisfaction score was 46 (41.5, 50) on a 50-point scale. A linear mixed-effects model indicated that sharing ≥1 topic and age proximity between the participant and peer supporter were significantly associated with higher satisfaction. **Conclusions:** Results demonstrate the feasibility of future decentralized randomized trials on online peer support and provide effect size estimates to guide sample size planning. Shared topics and age proximity between participants and peer supporters may be considered when scheduling sessions. Research Sponsor: None.

1669 **Poster Session**

Evaluation of a remote electronic assessment of survivors with tailored follow-up recommendations and survivorship messaging (REASSURE) to improve the delivery of follow-up for low-risk breast cancer survivors. First Author: Heather B. Neuman, University of Wisconsin School of Medicine and Public Health, Madison, WI

Background: Current follow-up care for the 2 million+ low-risk breast cancer survivors fails to adequately address survivors' needs and burdens survivors and oncology teams. We evaluated a novel approach to follow-up that comprehensively assesses survivors' symptoms and concerns and uses that information to tailor follow-up frequency. **Methods:** We conducted a randomized trial at an academic and community breast clinic. Eligible survivors had a history of stage I breast cancer that was ER or PR +/Her2-, were 6-36 months from diagnosis, and did not receive chemotherapy. Survivors were randomized 1:1 to REASSURE versus usual care and followed for 18-months. REASSURE was developed through stakeholder engagement and comprises three components integrated around follow-up visits: 1) Online patient-reported symptoms and concerns (PRO), 2) Tailored follow-up visit recommendations based on the PRO, and 3) Survivorship messaging. The primary outcome was survivors' preparedness for survivorship and confidence about follow-up, measured at 18-months by the Preparing for Life as a (New) Survivor (PLANS) scale. Secondary outcomes included number of oncology follow-up visits, proportion of reported symptoms that were discussed, and acceptability of REASSURE. Continuous variables were analyzed using t-tests or Wilcoxon tests. The proportion of symptoms discussed was analyzed using a generalized linear mixed model for binomial data. **Results:** Of the 104 consented patients, 3 did not complete any study activities and 1 withdrew (n=100). The median age was 63 (range 36-86), most were White (98%), and 19% resided in a rural locale. Preparedness for survivorship and confidence did not differ between REASSURE and usual care (Table). Symptoms or concerns were reported on 50.4% of PRO assessments. In the REASSURE arm, 80% of survivors accepted the recommendation to forgo a visit. Fewer follow-up visits were observed with REASSURE (M=2.1, SD 1.0) than usual care (M=2.6, SD 1.0), p=0.007. There was no difference in likelihood of discussing symptoms. REASSURE was acceptable to survivors, with 78% saying they would recommend REASSURE to others. **Conclusions:** In this implementation of a novel tailored approach to follow-up for low-risk breast cancer survivors, we did not find improvement in preparedness for survivorship. However, we demonstrated a decrease in number of follow-up visits with strong survivor support for this approach. Further research will focus on implementing REASSURE in more diverse clinical settings. Clinical trial information: NCT05609435. Research Sponsor: Wisconsin Partnership Program.

	REASSURE M (SD) or %	Usual Care M (SD) or %	P value
PRIMARY OUTCOMES			
Preparedness	29.3 (1.7)	28.9 (2.1)	0.36
Confidence	24.0 (14.4)	18.7 (13.6)	0.08
SECONDARY OUTCOMES			
# of follow-up visits	2.1 (1.0)	2.6 (1.0)	0.007
% of symptoms discussed	89.3%	83.0%	0.29
% of survivors who would recommend REASSURE	78%	NA	

1670 **Poster Session**

The Engage program for childhood cancer survivors: Results from a multidisciplinary, distance-delivered intervention. First Author: Christina Signorelli, University of New South Wales and Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia

Background: As the growing number of childhood cancer survivors exceeds follow-up care capacity, scalable models to improve access and support self-management are needed. We evaluated the effectiveness of the 'Engage' survivorship program (primary outcomes: self-efficacy and health-related quality of life; HRQoL). **Methods:** Engage is a multidisciplinary program comprising a treatment summary; online health/lifestyle assessment; telehealth nurse consultations; multidisciplinary review; tailored survivorship recommendations for survivors and their nominated primary-care physician. Survivors treated at two Australian hospitals were eligible if diagnosed <18years, >5 years post-diagnosis, and completed treatment. Mixed-effects models examined change over time (baseline, 1-, 6-, 12-month) and differences by diagnosis (brain cancer vs other), adjusting for sex and age at diagnosis. **Results:** Of 138 consenting survivors 92% completed the health assessment and 89.1% completed the whole program (n=123). Median age was 24 years; median time since diagnosis was 15 years; 28% lived in rural/remote/regional areas; and 53% were brain cancer survivors. Program acceptability was high, with >80% of survivorsreporting Engage was helpful, improved knowledge and confidence, and was easy to access. Health-related self-efficacy improved over 12 months ($\chi^2(3)=146.52$, $p<.001$), with no evidence of differences in change between diagnostic groups (time × group; $p=.97$). HRQoL (EQ-5D index) improved modestly by 12 months (0.77 to 0.82; $p=.011$); brain cancer survivors reported lower baseline scores, with similar patterns of change over time. Satisfaction with care improved over time ($\chi^2=35.59$, $p<.001$), with higher satisfaction among non-brain cancer survivors ($\chi^2=4.03$, $p=.045$) but not over time (time×group $p=.75$). Among health behaviours, alcohol consumption decreased over time ($\chi^2=16.20$, p=001) and was higher overall among non-brain survivors ($\chi^2=5.97$, p=.015), with no time×group interaction ($p=.94$). Adherence to personalised healthcare recommendations >50%, with greater adherence if discussed briefly during a follow-up nurse consult. **Conclusions:** Engage was associated with sustained improvements in survivors' self-efficacy and satisfaction with care and modest improvements in HRQoL at 12-months follow-up. Similar trajectories across diagnosis groups suggest telehealth survivorship models can also support survivors with higher risk profiles (e.g., brain cancer survivors). Clinical trial information: ACTRN12621000590864. Research Sponsor: None.

1671 **Poster Session**

Survivorship-focused content at the American Society of Clinical Oncology (ASCO) 2022-2024 annual meetings. First Author: Lauren Rynar, Rush University Medical Center, Chicago, IL

Background: Survivorship is a core component of comprehensive cancer care yet its representation in major oncology scientific meetings remains unclear. This study systematically evaluated survivorship-focused content presented over three years at the ASCO Annual Meetings for prevalence, characteristics, and thematic patterns. **Methods:** All abstracts presented at the ASCO Annual Meeting from 2022-2024 were obtained (N=8,928). Abstracts containing the root word "survivor" (e.g., survivor, survivors, survivorship) in the title, text, or submission category "Symptoms and Survivorship" were identified using an automated data-extraction tool. Each extracted abstract underwent structured review to determine relevance to survivorship and then mapped to domains of the Quality of Cancer Survivorship Framework. Two independent reviewers evaluated each abstract, with discrepancies resolved by consensus. Descriptive statistics were used to summarize abstract content. **Results:** A total of 568 abstracts from 2022-2024 contained the root word "survivor" in the title, text or the submission category, representing 6.4% of all presented abstracts. Prevalence of survivorship-focused abstracts increased modestly from 2.2% in 2022 to 4.1% in 2024. Reviewers identified 63.8% of the extracted abstracts as relevant to the survivorship care framework and abstracts most frequently addressed the survivorship domains of physical effects (28.3%) and contextual factors (14.6%). Additional analyses examined cancer type and stage studied (36.6% mixed, 19.5% breast; 55.2% cancer stage not specified), survivorship stage (45% not specified, 19.3% in curative treatment), study design (65.9% observational), and healthcare setting (58.2%). **Conclusions:** Despite a rapidly growing population of cancer survivors, survivorship-focused content at the ASCO Annual Meeting remained largely static between 2022 and 2024, highlighting a gap between emerging survivorship needs and representation within oncology research programming. Further, abstracts frequently failed to specify the study population or context, or reference specific implications to survivorship domains. This study establishes a reproducible benchmark for monitoring survivorship content and provides a scalable methodology for ongoing surveillance of future meeting abstracts. The abstraction method may have excluded relevant survivorship-focused content. These findings could guide ASCO educational planning committees as they refine strategies to strengthen and advance survivorship-focused content in future meetings, ensuring alignment with the evolving needs of the survivor community. Research Sponsor: Rush University Medical Center.

1672 **Poster Session**

Impact of medically tailored meals plus nutrition counseling on treatment adherence in vulnerable lung cancer patients: Results from NutriCare randomized controlled trial. First Author: Zhongyao Li, Tufts University, Newton, MA

Background: This study aims to evaluate the impact of a Food is Medicine intervention on reducing treatment interruptions among vulnerable patients with lung cancer in a multi-site randomized controlled trial (RCT). **Methods:** Newly diagnosed stage I-IV lung cancer patients (n=249) enrolled from four cancer centers (MD Anderson Cancer Center, The Ohio State University Comprehensive Cancer Center, Fox Chase Cancer Center, and Tufts Medical Center) were randomized to the NutriCare (intervention; n=134) or NutriTool (control; n=115) arm in a 1:1 ratio. Patients on NutriTool received a nutrition toolkit for cancer survivors and monthly nutrition information and recipes. Patients on NutriCare additionally received 6-8 months (mo) of tapered home-delivered medically tailored meals (initially 21 meals/week) plus remote nutrition counseling provided by registered dietitians. Treatment interruptions, including overall interruptions and those due to treatment toxicities, were assessed using the relative dose intensity (RDI) and number of treatment cycles with dose delay or reduction among patients receiving curative or first-line palliative treatment. The primary analysis was intention-to-treat, comparing treatment interruptions between arms using Poisson regression models. **Results:** The mean (SD) of RDI was 0.84 (0.26) and 0.81 (0.26) for patients on NutriCare and NutriTool, respectively (p=0.24), with approximately 31% of the NutriCare patients having RDI reduction of 15% or more compared to 38% of the NutriTool patients (p=0.36). After restricting the analyses to treatment interruptions due to toxicities, 14.4% of NutriCare versus 25.4% of NutriTool patients experienced RDI reduction of 15% or more (p=0.08). After multivariable adjustments, NutriCare patients had 16% lower risk of having RDI reduction of 15% or more (relative risk [RR]=0.84, 95% confidence interval [CI]: 0.47-1.47) and 41% lower risk of having toxicity-related RDI reduction of 15% or more (RR=0.59, 95% CI: 0.28-1.24) than NutriTool patients. For dose delays, NutriCare patients had 35% lower risk of having any dose delay (RR = 0.65, 95% CI: 0.28-1.49) and 44% lower risk of having toxicity-related dose delay (RR=0.56, 95% CI: 0.16-1.97) compared to NutriTool patients. For dose reduction, NutriCare patients had 19% lower risk of having any dose reduction (RR=0.81, 95% CI: 0.49-1.34) and 35% lower risk of having toxicity-related dose reduction (RR=0.65, 95% CI: 0.35-1.22) compared to NutriTool patients. None of the differences reached statistical significance. **Conclusions:** Findings suggest that a Food is Medicine intervention comprising medically tailored meals and nutrition counseling may reduce treatment interruptions among vulnerable patients with lung cancer undergoing treatment. Clinical trial information: NCT04986670. Research Sponsor: Bristol Myers Squibb Foundation.

1673 **Poster Session**

Performance of ChatGPT in generating patient-facing cancer survivorship care plans. First Author: Kaili Du, Cayuga Medical Center at Ithaca, Ithaca, NY

Background: Survivorship care plans (SCPs) summarize cancer treatments and provide evidence-based recommendations for surveillance, screening, and management of treatment-related complications. Despite the availability of guidelines and templates, SCPs remain underutilized in routine practice due to the time-intensive and error-prone nature of manual creation. Empowering cancer survivors to use publicly available large language models (LLM)–based chatbots, such as ChatGPT, may offer a feasible solution to this problem. **Methods:** Standardized patient profiles were developed for six common cancers: breast, colorectal, non–small cell lung, small cell lung, prostate cancer, and diffuse large B-cell lymphoma. Profiles were reviewed by a primary care physician and an oncologist to ensure clinical accuracy and representativeness of common survivorship scenarios. Using lay language to simulate real-world patient input, ChatGPT (version 5.2, publicly available at the time of the study) was prompted with each profile using the question, "What follow-up care do I need?" Common survivorship symptoms for each cancer were also tested. Responses were evaluated across five domains: medical accuracy (concordance with current ASCO or NCCN guidelines), thoroughness, patient safety and risk framing, clarity and patient comprehension, and actionability. Five-point Likert scales were used (1 = not at all; 5 = very much). Scores were averaged across two independent physician raters. Readability was assessed using the Flesch Reading Ease Score. **Results:** ChatGPT-generated SCPs demonstrated high medical accuracy (mean score 4.25/5), with no factual errors or hallucinations identified on manual review. Patient safety and risk framing scored 3.75/5; symptom red flags and care escalation guidance were appropriately stated in most scenarios. Thoroughness was moderate (3.50/5), with key survivorship elements, such as smoking cessation counseling or genetic risk considerations; sometimes omitted unless explicitly prompted. Readability was limited, with a mean Flesch Reading Ease Score of 40.5, corresponding to a college reading level and exceeding recommended readability standards for patient education materials. Clarity (3.38/5) and actionability (3.38/5) were similarly constrained due to dense medical language. **Conclusions:** ChatGPT demonstrated high medical accuracy in generating survivorship care plans across six common cancers, supporting the feasibility of using publicly available LLMs to guide survivorship care. However, improvements in comprehensiveness, readability, and patient-centered actionability are necessary before such tools can be safely integrated into clinical survivorship workflows. Research Sponsor: None.

1674 **Poster Session**

Temporal trends and sociodemographic differences in influenza vaccination among U.S. cancer survivors, 2005-2024. First Author: Kerry Conlin, Yale School of Public Health, New Haven, CT

Background: Given the increased risk of complications and adverse outcomes associated with influenza infection among individuals with cancer, even in the post-treatment setting, clinical oncology guidelines support annual vaccination in cancer survivors. Few studies have investigated long-term trends and potential disparities in the prevalence of influenza vaccination among individuals with a history of cancer. Therefore, we examined temporal trends in and factors associated with influenza vaccination in a nationally representative sample of cancer survivors in the United States. **Methods:** Using data from 20 survey years (2005-2024) of the National Health Interview Survey, we included adults aged ≥18 years with a self-reported history of cancer and complete data on influenza vaccination. The primary outcome was self-reported influenza vaccination in the past 12 months. Crude annual prevalence estimates were calculated overall and by select sociodemographic characteristics using survey-weighted logistic regression models. Temporal trends were quantified using annual percent change (APC) estimates. **Results:** Among 43,932 adults with a history of cancer (median age: 65.7 years), representing approximately 15.0 million U.S. cancer survivors annually, crude influenza vaccination prevalence increased from 45.5% (95% CI: 43.0-48.1) in 2005 to 63.3% (95% CI: 61.2-65.4) in 2024, corresponding to an absolute change of 17.8 percentage points (pp; 95% CI: 14.5-21.1) and an APC of +0.79 pp/year (95% CI: 0.52-1.06). Younger survivors aged 18-44 years experienced a particularly large absolute change over the 20-year study period (+32.4 pp; APC: +1.32 pp/year), yet fewer than half were vaccinated in 2024 (46.4%), compared to 77.4% of those aged ≥75 years. Cancer survivors without insurance (change: +24.7 pp; APC: +0.83 pp/year) had a 2024 vaccination prevalence of 32.0%, compared to insured survivors (63.8%). Survivors without a usual source of care (change: +31.0 pp; APC: +1.63 pp/year) had a 2024 vaccination prevalence of 39.9%, compared to those with a usual source of care (63.8%). Hispanic survivors (change: +25.3 pp; APC: +1.30 pp/year) had a 2024 vaccination prevalence of 51.9%, compared to non-Hispanic White survivors (64.9%). **Conclusions:** Influenza vaccination prevalence among U.S. cancer survivors increased substantially over the past two decades; however, more than one-third were unvaccinated in 2024. Despite overall gains, vaccination coverage remained particularly low among younger survivors, uninsured individuals, and those without a usual source of care, with persistent differences across racial and ethnic groups. Targeted clinical and public health strategies are needed to address these gaps and improve guideline-endorsed uptake of seasonal influenza vaccination among cancer survivors. Research Sponsor: None.

1675 **Poster Session**

Rethinking MRI surveillance after breast cancer in the context of persistent racial disparities in mortality. First Author: Elizabeth Susan McDonald, University of Pennsylvania, Philadelphia, PA

Background: Detection of asymptomatic breast cancer recurrence by imaging is associated with improved survival compared to detection after symptoms develop. Currently, both the American Cancer Society and ASCO recommend against routine MRI for patients with a history of breast cancer and no clinical findings, unless they meet specific high-risk criteria. The American College of Radiology Appropriateness Criteria similarly characterizes surveillance MRI as conditionally appropriate, supporting its use only when additional risk factors are present. Since randomized trials to address surveillance strategies in diverse populations are unlikely to be feasible, we performed an observational study comparing MRI performance in intermediate and high-risk screening populations, and women with a history of breast cancer, stratified by race. **Methods:** We retrospectively analyzed 41,041 breast MRI exams performed in an urban health system from 1/2/2014 to 10/29/2025. In Pennsylvania, insurance covers supplemental MRI for women with dense breasts, and in our network, screening MRI is generally performed in asymptomatic patients current with mammography. Exams were categorized as high-risk screening (n=15,682, 38%), supplemental (n=10,905, 27%), or surveillance for a personal history of breast cancer (n=11,476, 28%). Logistic regression was used to estimate odds ratio for true and false positives by indication adjusted for age and race. **Results:** Cancer detection rates were higher in the surveillance group compared with high risk screening (true positive [TP] rate 21.0, n=241 vs 12.4, n=194), a 53% difference after adjusting for age and race (OR 1.53 [1.26–1.86], $p<0.001$), with similar false-positive rates (7.5%, n=857 vs 8.7%, n=1,359; OR 1.02 [0.93–1.11], p=0.7). MRI cancer detection rate was higher for supplemental than high-risk screening (OR 1.35 [1.24–1.46], $p<0.001$). Notably, in a subset comparison of screening MRI in Black vs. white women (n=37,383), TP rates were higher among Black women than white women across all MRI indications. The highest TP rate was observed in Black women undergoing surveillance MRI (31.9 vs. 20.5; OR 1.62 [1.11, 2.31], p=0.010), followed by supplemental (25.6 vs. 14,5; OR 1.84 [1.17, 2.77], p=0.005), and high-risk (21.6 vs. 11.4; OR 1.97 [1.22, 3.03], p=0.003). The TP rate remained higher for Black compared with white women for first MRI as well as subsequent MRI for surveillance, high-risk, and supplemental screening. **Conclusions:** Black women in the U.S. have 40% higher breast cancer mortality compared to non-Hispanic white women, and early detection offers the best chance for optimal survival. Our findings suggest surveillance MRI identifies a higher burden of clinically occult cancer than high-risk screening MRI, especially among Black women. Expanding access to surveillance MRI may help address persistent racial disparities in breast cancer outcomes. Research Sponsor: Pennsylvania Breast Cancer Coalition; American Cancer Society; PASD-22-1003156-01 & RSG-23-1038098-01-HOPS.

TPS1676 **Poster Session**

CTNow pilot study: A multilevel clinical trial education and clinical trial referral coordination intervention for rural oncology providers and patients with cancer. First Author: Izumi Okado, University of Hawai'i Cancer Center, Honolulu, HI

Background: Enhancing patient access to cancer clinical trials is an ASCO and NCI priority. Major barriers to clinical trial access in rural areas include limited awareness and knowledge of available cancer clinical trials among both rural oncology providers and patients with cancer. Our preliminary research found that only 9% of rural cancer patients have knowledge of clinical trials, and many providers lack the time or resources to discuss them in clinical settings. Hawai'i's geographic isolation presents persistent barriers to clinical trial access, particularly for residents of the five rural neighbor islands of Hawai'i. Expanding clinical trial access requires not only increasing infrastructure and trial availability; enhancing provider and patient awareness and knowledge is a critical step toward improving access to trials in rural communities. A coordinated, culturally informed, and statewide approach is urgently needed to build trust, increase literacy on clinical research participation, and ensure that clinical trials become an equitable part of standard cancer care for all communities in Hawai'i. This pilot trial evaluates the preliminary efficacy of *CTNow*, a novel multilevel, multicomponent clinical trial education and clinical trial referral coordination intervention designed for rural oncology providers and patients with cancer. **Methods:** This multi-site pilot trial is currently open in three rural counties in Hawai'i. The multilevel *CTNow* intervention includes: 1) two interactive webinar sessions for rural oncology providers; 2) a tablet-based multimedia education program for patients; and 3) referral resources for providers and an optional video chat feature for patients to connect with clinical trials staff for questions and/or referrals to trials. The study team developed intervention components that provide rural-specific provider clinical trial information, along with evidence-based patient education materials adapted for varying levels of health literacy. Key patient inclusion criteria include patient self-report of cancer diagnosis, current/past/planned treatment, and residency in rural areas. Provider participants include rural-based oncologists and advanced practice providers not currently involved in clinical trials. Planned enrollment includes 30 patients with any cancer type and 5 oncology providers practicing in rural Hawaii. The primary endpoint is within-patient and within-provider changes in knowledge of cancer clinical trials from baseline. Secondary endpoints include changes in attitudes toward clinical trials and self-efficacy related to trial participation, and utilization of video chat sessions. Enrollment began in March 2025. To date, 80% of patients and 100% of planned providers have been enrolled. Clinical trial information: NCT06237816. Research Sponsor: Agency for Healthcare Research and Quality.

TPS1677 **Poster Session**

Genetic testing uptake through an enhanced oncology nurse–led intervention in patients with solid tumors (GENESIS): A pilot study. First Author: Ranjan Pathak, Enloe Health, Chico, CA

Background: Identification of pathogenic germline variants (PGV) in patients with solid tumors is critical for directing targeted therapies, surveillance, and cascade testing for family members. Despite established National Comprehensive Cancer Network (NCCN) guidelines, uptake of genetic counseling and testing (GCT) remains suboptimal, with recent data suggesting <7% utilization in some cancer populations. Barriers are pronounced in community oncology settings due to limited access to genetic counselors and reliance on physician-initiated referrals. Oncology nurses routinely provide education during systemic therapy initiation, presenting a unique, underutilized touchpoint to bridge this gap. The GENESIS study (NCT06436157) evaluates the feasibility and impact of a novel, nurse-led "enhanced education" intervention on GCT uptake. **Methods:** This is a single-center, prospective, randomized (1:1) pilot trial conducted at a community cancer center. Eligible participants are adults (≥18 years) with solid tumors (breast, ovarian, prostate, pancreatic, colorectal, and others per NCCN guidelines) who are starting or switching systemic therapy, meet NCCN criteria for GCT, and have no prior germline testing. The study plans to accrue 60 patients. Participants are randomized to the Usual Care arm (standard therapy education; clinician-initiated referral) or the Enhanced Education Intervention arm. In the intervention arm, trained oncology nurses integrate a specific GCT educational module into the standard chemotherapy teaching session. For eligible/agreeable patients, the nurse directly places the GCT referral order and executes a follow-up "nudge" to referral coordinators within one week. The primary endpoint is the percentage of patients proceeding to GCT consultation. Secondary endpoints include GCT referral rates, time from order to consultation, time to testing completion, and implementation feasibility assessed via the Acceptability of Intervention Measure (AIM) and retention rates. Clinical trial information: NCT06436157. Research Sponsor: Robert A. Winn Excellence in Clinical Trials Awards Program (Winn Awards).

TPS1678 **Poster Session**

Patient preference for subcutaneous vs. intravenous immune therapy (PSI-Immune). First Author: Vincent Edgar Reyes, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA

Background: Immune checkpoint blockade (ICB) has improved outcomes for patients (pts) with advanced solid tumors. Conventional intravenous (IV) route of administration (RoA) requires repeated, time-intensive infusions involving cannulation, monitoring, pharmacy preparation, and chair time, increasing treatment burden and constraining infusion center capacity, staffing, and scalability as ICB use expands. Subcutaneous (SC) formulations of pembrolizumab and nivolumab—two widely used PD-1 inhibitors—have recently been approved across multiple indications. PD-1 ICB SC formulations contain the same active drug as IV formulations and have demonstrated comparable PK exposure, efficacy and safety profiles (CheckMate 8KX; 3475A-D77). Beyond pt convenience, SC RoA may enable more scalable delivery by reducing infusion chair utilization, nursing time, and workflow bottlenecks, supporting access across high-volume cancer networks. Real-world pt preference and perceived health-system impact of SC versus IV PD-1 ICB remain incompletely characterized. We therefore designed a distributed, real-world clinical trial to evaluate patient preference and health-system implications of PD-1 ICB RoA across a large integrated cancer network (>70 sites across 4 states). **Methods:** PSI-Immune is a randomized, phase II, open-label, crossover study evaluating pt preference for SC versus IV RoA of PD-1 ICB in pts with locally advanced (LA) or advanced/metastatic (A/M) solid tumors pending initiation PD-1–based therapy, either as monotherapy or in combination. The primary endpoint is pt preference for ICB RoA, assessed using a validated pt preference questionnaire (PPQ). Key secondary endpoints include pt-reported treatment satisfaction (TASQ), HCP-reported time and resource utilization, pt-reported health-related quality of life (HRQoL), and time to next therapy (TTNT). A subcohort permits enrollment of pts who are already on IV PD-1 ICB. Eligible pts must have an FDA-approved indication for SC pembrolizumab or nivolumab singly or in combination with other FDA-approved agents and a planned duration of PD-1–based therapy exceeding six months. Patients are randomized 1:1 to receive either SC therapy for three cycles followed by IV therapy for three cycles, or the reverse sequence (crossover phase). Subsequently, pts select their preferred route of administration (continuation phase). Treatment regimen is identical across cohorts and differs only by ICB RoA. Randomization is stratified by disease setting (LA vs A/M) and ICB regimen (monotherapy vs combination). The planned sample size is 280 patients. Assuming equal allocation and up to 10% attrition, the exact 95% confidence interval for the proportion of patients preferring SC administration will exclude 50% if the observed preference rate is at least 60%. This study is open and enrolling across the entire UPMC Hillman Cancer Center Network (NCT07223424). Clinical trial information: NCT07223424. Research Sponsor: None.

TPS1679 **Poster Session**

Cancer CARE (Connected Access and Remote Expertise) beyond walls: Pilot, phase 2 clinical trial to evaluate administration of cancer-directed therapy in the patient's homes versus in clinic in the Florida Panhandle and surrounding areas. First Author: Dina Elantably, Mayo Clinic Florida, Jacksonville, FL

Background: Cancer care in the United States remains highly centralized, imposing substantial time, caregiver, and financial burdens on patients, particularly those residing in rural and medically underserved regions. While international experience supports the feasibility of home-based cancer therapy delivery, prospective U.S. clinical trial data are limited. The Cancer CARE Beyond Walls (CCBW) program was developed to address these gaps through a decentralized cancer care model integrating virtual oversight, remote monitoring, mobile clinical services, and community-based nursing partners. The study evaluates the feasibility, safety, and patient-centered impact of delivering cancer-directed therapy in patients' homes or near-home mobile units in the Florida Panhandle, a region characterized by long travel distances to tertiary centers and limited oncology infrastructure. **Methods:** This is a phase 2, single-arm clinical trial evaluating the delivery of standard-of-care cancer-directed therapy outside of traditional infusion centers. Eligible adult patients (ECOG 0–3) with histologically confirmed malignancies receiving guideline-supported or FDA-approved systemic cancer therapy must demonstrate tolerability of at least one prior in-clinic treatment cycle. Following registration, patients transition to home-based or near-home mobile unit administration for a minimum of 12 weeks, with an option to continue up to 24 weeks. Care delivery is coordinated through a virtual command center providing real-time virtual oversight, remote monitoring, and escalation pathways. Treatment administration is performed by trained local home health nurses, medication shipping, and digital interaction with the electronic health record. A fully equipped mobile unit extends access to rural areas not covered by home health agencies. The primary endpoint is patient preference for treatment location at week 12. Secondary endpoints include safety, avoidable acute care utilization, patient-reported function and global health/quality of life, patient-reported symptoms, and satisfaction with care. Exploratory endpoints assess travel burden, patient perceptions of caregiver experience, and patient perceptions of home versus mobile unit care. Enrollment of 27 patients will provide 80% power to reject a 50% null rate (2-sided exact test, α=0.10), assuming 75% prefer decentralized care or express no preference. This investigator-initiated trial is open to accrual and is supported by a grant from the Florida Cancer Innovation Fund. Clinical trial information: NCT07285044. Research Sponsor: Mayo Clinic.

TPS1680 **Poster Session**

Making telehealth delivery of cancer care at home effective and safe: A pragmatic cluster randomized trial. First Author: Erin Mary Bange, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Telehealth (TH) use for cancer care has rapidly expanded, both during and following the COVID-19 pandemic. However, evidence regarding safety, feasibility, effectiveness, equity, stakeholder satisfaction, and implementation of telehealth-enabled oncology care remains limited. We seek to assess the impact of TH on these outcomes in breast and prostate cancer patients. **Methods:** The MATCH-UP pragmatic cluster randomized trial is being conducted at Memorial Sloan Kettering Cancer Center to compare alternate models of TH use in oncology practice. Sixty-two physician practice clusters in breast and prostate medical oncology are randomized 1:1 to enhanced telehealth (ET) or usual practice (UP), stratified by disease type and clinic volume. ET emphasizes TH with expanded home services designed to deliver as many components of care as desired in patients' homes. Usual care involves routine practice with TH visits at the discretion of the patient and MD or APP. Eligible patients have >=3 prior medical oncology visits and are not enrolled on a therapeutic trial. Automated enrollment is triggered by a routine oncology visit with waiver of informed consent. The ET intervention includes EHR-enabled telehealth scheduling defaults for routine follow-up visits, optional home phlebotomy, structured support for home administration of select injectable medications, and digital support for patients with TH access barriers. The primary endpoint is the proportion of routine medical oncology visits conducted in person among all routine medical oncology visits over 1 year. Secondary outcomes include healthcare utilization, no-show and late cancellation rates, and overall survival. Patient-reported outcomes include: quality of life, healthcare costs, experience of care, and preferences for use of TH at future visits. Clinician-reported outcomes include: experience of care and preferences for TH use at future visits. For patients in the ET arm only, telehealth accessibility, intervention uptake and efficiency, and implementation outcomes, including acceptability, appropriateness, and feasibility, are also being collected. The primary endpoint will be analyzed using generalized linear mixed models with a logistic link, accounting for repeated visits within patients and clustering within randomized practice units and adjusting for stratification factors. Enrollment will continue through March 2026 with follow-up for 12 months. To date, 7256 patients have been enrolled, with 3641 patients assigned to ET, (n=2437 [67%] breast cancer; n=1204 [33%] prostate cancer and 3,615 assigned to UP (n=2252 [62%] breast cancer; n=1363 [38%] prostate cancer). MATCH-UP will generate pragmatic evidence on the effectiveness, patient-centeredness, implementation, and equity-relevant barriers of a scalable, EHR-embedded enhanced telehealth model for breast and prostate oncology care. Clinical trial information: NCT06954337. Research Sponsor: NIH/; NCI/NIH P50 CA271357; National Cancer Institute/U.S. National Institutes of Health; NCI/NIH P30 CA008748.

TPS1681 **Poster Session**

Implementation of a cancer-oriented geriatric assessment (COGA) clinic to promote age-friendly cancer care: A type III hybrid implementation–effectiveness method in community practice. First Author: Ganesh Prasad Merugu, The University of Toledo, Toledo, OH

Background: Cancer incidence increases with age, and adults aged ≥65 years account for the majority of new cancer diagnoses. Standard oncology assessments often fail to identify age-related vulnerabilities such as frailty, cognitive impairment, and functional decline (Hurria et al., JCO 2011). The American Society of Clinical Oncology (ASCO) recommends routine geriatric assessment–guided management for older adults receiving systemic cancer therapy to inform treatment decisions and reduce treatment-related toxicity (Mohile et al., JCO 2018). In alignment with these goals, we established a Cancer-Oriented Geriatric Assessment (COGA) clinic within an academic cancer center. **Methods:** We implemented a Type III hybrid implementation–effectiveness design to integrate Cancer-Oriented Geriatric Assessment (COGA) into routine oncology practice using the 5M framework (Mind, Mobility, Medications, Matters Most, and Multicomplexity). The Eleanor N. Dana Cancer Center is part of a large academic health system in Northwest Ohio, serving a predominantly rural and suburban population across Ohio and Southeast Michigan. Eligibility included oncology patients aged ≥65 years with a positive G8 screen (≤14), consistent with ASCO and European Society for Medical Oncology (ESMO) recommendations for comprehensive geriatric assessment. A tiered workflow was implemented on January 15, 2026, in which medical assistants obtained vital signs, performed medication reconciliation, and completed standardized screenings for cognition, mood, and nutrition, followed by a geriatrician-led assessment of frailty, fall risk, mobility, and functional status. The medication domain emphasized deprescribing of potentially inappropriate medications, while the Matters Most domain addressed goals of care, advance directives, and social support. Additional geriatric syndromes—including sensory impairment, sleep disturbances, incontinence, and fatigue—were systematically assessed and managed. Risk stratification was guided by validated tools, including the Cancer and Aging Research Group (CARG) toxicity tool and the Schonberg Index, to estimate non-cancer mortality. Primary implementation outcomes included reach (the proportion of eligible patients receiving COGA), adoption (use of COGA by oncology teams), and fidelity (completion of the core 5M domains as intended). Secondary effectiveness outcomes included patient-centered outcomes and unplanned hospitalizations. This scalable, real-world implementation model enables systematic integration of geriatric assessment into oncology practice, with the potential to improve outcomes for older adults with cancer and support broad dissemination across diverse cancer care settings. Research Sponsor: None.

TPS1682 **Poster Session**

An EHR-embedded SmartForm (OncAssessment) paired with ePROs to enable real-time structured documentation of key oncologic data during routine cancer care: A pragmatic implementation study. First Author: Aditi Puri Singh, Penn Medicine Abramson Cancer Center, Philadelphia, PA

Background: Real-world evidence generation in oncology is often limited by inconsistent and unstructured documentation within electronic health records (EHRs). Key clinical variables including disease status, performance status, and treatment change rationale are frequently embedded in free text, requiring retrospective manual abstraction that is inefficient and error-prone. As a result, clinically meaningful real-world endpoints, such as time to treatment change and real-world progression-free survival (rwPFS), are inconsistently captured. To address these gaps, the University of Pennsylvania developed OncAssessment (OA), an EHR-embedded SmartForm integrated directly into routine oncology clinical documentation. Unlike post hoc abstraction or standalone registries, OA enables prospective, structured data capture of key oncologic variables at the point of care by treating clinicians, and is paired alongside with electronic patient-reported outcomes (ePROs). This approach aligns clinician decision-making with patient-reported experience within routine workflows, enabling timely, scalable, and higher-fidelity real-world data (RWD) capture. **Methods:** This pragmatic implementation study, developed by the University of Pennsylvania in collaboration with Gilead Sciences, evaluates OA and ePRO implementation in standard clinical practice. Adult patients with stage IIIB-IV unresectable non-small cell lung cancer (NSCLC) initiating standard-of-care immunotherapy with or without chemotherapy (Cohort I) and adult breast cancer patients receiving systemic infusional therapy (Cohort II) are identified via the EHR. 200 patients per cohort are planned for enrollment over 2 years. Enrollment began July 22, 2025. For identified patients, clinicians are prompted to complete OA at each visit: documenting clinical status, tumor status, treatment changes, and rationale. ePROs are automatically distributed through the EHR to Cohort I patients prior to their visits. Structured data from OA, ePROs, and other EHR sources are auto-extracted. Primary objectives for Cohort I include OA utilization, time to treatment change decision (TTCd), comparison of TTCd with time to treatment change (TTC) derived from EHR reporting, ePRO completion rates, and concordance between patient- and clinician-assessed clinical status. Secondary objectives include rwPFS captured via OA, comparison with rwPFS determined by manual chart and radiology review, characterization of patient experience via ePROs, and exploratory analyses of discordance and factors associated with treatment change. The primary objective for Cohort II is OA utilization. Follow-up continues until progression, treatment change, or 2 years for Cohort I and 12 months for Cohort II. Research Sponsor: Gilead Sciences.

TPS1683 **Poster Session**

MATCHES-NOVEL: A randomized controlled trial in progress of hospital-at-home (HaH) versus inpatient hospitalization for post tarlatamab monitoring.

First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Tarlatamab is a bispecific T-cell engager (BiTE) therapy approved for the treatment of extensive-stage small cell lung cancer (ES-SCLC) and is the first BiTE therapy approved for a solid tumor. Due to the risk of cytokine release syndrome, patients are routinely hospitalized for ≥24 hours following each of the first two doses. These hospitalizations can pose substantial logistical, financial, and psychosocial challenges, particularly for patients in rural communities or with caregiver or employment constraints. HaH is an emerging care delivery model that provides hospital-level care in patients' homes and has been associated with reduced readmission rates, improved patient experience, and lower cost in other populations. Whether HaH can safely and efficiently replace inpatient hospitalization for post-tarlatamab monitoring is unknown. The MAking Telehealth Delivery of Cancer Care at Home Effective and Safe (MATCHES)-Novel trial evaluates a HaH model compared with standard inpatient hospitalization following tarlatamab administration. **Methods:** MATCHES-Novel is an active, single-center, prospective randomized controlled trial comparing HaH with standard inpatient hospitalization for post-administration monitoring of tarlatamab in patients with ES-SCLC. Eligible patients have an ECOG performance status of 0-2, are initiating tarlatamab for an FDA-approved indication, reside within a 60-minute response catchment area, and have an available in-home caregiver. Participants are randomized 1:1 to HaH or standard inpatient monitoring following drug administration, with monitoring duration and discharge criteria aligned with institutional standards. The HaH intervention includes scheduled in-home community paramedic assessments on the day of and the day after infusion, home phlebotomy, telehealth physician oversight, patient and caregiver education, and 24/7 care escalation pathways. The primary objective is to compare efficiency, measured by the number of inpatient hospital days during the two 7-day periods after each infusion. Assuming a mean number of 4 inpatient hospital days in the control arm, enrollment of 70 patients provides ≥80% power to detect a statistically significant difference if the mean inpatient days per patient in the HaH arm is ≤2.8. Secondary objectives include safety outcomes (transfers from home to inpatient care, clinician adjudicated toxicity events) and patient, caregiver and physician reported experiences and preferences, assessed through pre-specified surveys and interviews. These findings may inform future care-delivery models for administering innovative cancer therapies outside the inpatient setting, potentially improving access. The trial opened to accrual in April 2025, and 16 of the planned 70 patients have been enrolled. Clinical trial information: NCI-2025-03406. Research Sponsor: National Cancer Institute; P50 CA271357; National Institutes of Health and National Cancer Institute Cancer; P30 CA008748; Amgen.

LBA2000 **Oral Abstract Session**

Final results of a randomized, controlled, phase 3 trial comparing resection and post-operative stereotactic radiation versus resection and cesium-131 tile-based radiation for treatment of newly diagnosed brain metastases. First Author: Jeffrey S. Weinberg, The University of Texas MD Anderson Cancer Center, Houston, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

2001 **Oral Abstract Session**

A multicenter randomized phase III study for newly diagnosed, maximally resected glioblastoma comparing carmustine wafer implantation followed by chemoradiotherapy with temozolomide versus chemoradiotherapy alone: Japan Clinical Oncology Group study JCOG1703 (MACS study). First Author: Ryuta Saito, Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Background: Three randomized phase III trials evaluated carmustine wafers (CWs) before temozolomide (TMZ) became standard therapy. To date, no randomized study has assessed CWs with standard TMZ chemoradiotherapy in newly diagnosed glioblastoma (GB). A post hoc analysis of Westphal's phase III trial, which evaluated CWs versus placebo, suggested a survival benefit with CWs in GB patients with ≥90% resection. We conducted a randomized phase III trial to determine whether adding CWs to standard chemoradiotherapy improves overall survival (OS) in newly diagnosed GB with ≥ 90% resection. **Methods:** This multicenter trial (38 institutions; JCOG1703) enrolled patients with newly diagnosed GB considered resectable at ≥90%. After intraoperative pathological confirmation of malignant glioma and ≥90% removal, patients were randomized (1:1) to CW implantation (Arm B) or no implantation (Arm A). Arm B received intraoperative placement of up to 8 CWs. All patients received 60 Gy radiotherapy with concomitant daily TMZ followed by 12 cycles of maintenance TMZ. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), loco-regional PFS (LPFS), and adverse events. DNA methylation array analysis and molecular testing included MGMT promoter methylation and copy number profiling. **Results:** Among 234 registered patients, 221 (Arm A, n=110; Arm B, n=111) were randomized between June 2019 and November 2022. Baseline characteristics were well balanced. Median OS for all randomized patients was 26.5 months (1-year 86.4%, 2-year 54.3%, 5-year 16.6%), with no significant difference between Arm A and B (21.7 vs 27.7 months; hazard ratios (HR) 0.907, 91.5% confidence interval (CI) 0.691–1.192; one-sided p=0.269 by the stratified log-rank test). Median PFS was 9.8 months (1-year 43.4%, 2-year 16.3%), also without significant difference (9.5 vs 10.4 months; HR 0.867, 95% CI 0.658–1.141). Median LPFS was 11.6 months (1-year 48.4%, 2-year 25.1%), with no difference between arms (10.6 vs 12.7 months; HR 0.886, 95% CI 0.669–1.173). MGMT promoter methylation was a significant favorable factor for OS, PFS, and LPFS. Early postoperative complications and adverse events were comparable between groups, and no treatment-related deaths occurred. **Conclusions:** CW implantation added to standard TMZ chemoradiotherapy did not significantly improve OS in newly diagnosed GB after ≥90% resection. Based on these findings, CW implantation does not provide significant therapeutic or survival benefit when standard TMZ chemoradiotherapy is feasible in this population. Clinical trial information: jRCT1031190035. Research Sponsor: Japan Agency for Medical Research and Development; 19ck0106515; 21ck0106515; 24ck0106763.

2002 **Oral Abstract Session**

Connectome-sparing stereotactic radiosurgery: Results from the phase II COG-SRS trial. First Author: Andrew Connor Puett, University of California San Diego, La Jolla, CA

Background: Cognitive decline remains common after radiosurgery. The cognition-sparing stereotactic radiosurgery trial (COG-SRS, NCT04343157) evaluated a novel connectome-sparing SRS strategy leveraging advanced imaging to autosegment the cognitive connectome for individualized functional sparing. **Methods:** COG-SRS is a prospective, single-institution, phase II trial that enrolled adults (KPS≥70) treated with SRS for benign or malignant intracranial lesions from 06/2018-10/2025. Connectome structures (10 discrete eloquent bilateral white matter tracts [WMTs], corpus callosum, and hippocampi [HC]) were autosegmented from pretreatment diffusion tensor imaging and structural MRI and assigned evidence-based dose constraints (single fraction Dmax WMT=12Gy, HC=8.4Gy, with 3-/5-fraction equivalent doses) during SRS planning. Neuropsychological testing assessed cognitive domains of memory, language, executive function, attention/processing speed, and fine motor control at baseline and 3 months post-SRS. Outcomes were summarized using normed T scores and analyzed with mixed effects models adjusting for baseline score and prespecified clinical covariates. In the brain metastases cohort, cognitive performance was also compared with historical controls treated with standard brain SRS on Alliance N0574/N107C using domain Z scores and baseline adjusted mixed effects models. Questionnaires assessed mood/QOL, and disease time to event endpoints were estimated by Kaplan Meier. **Results:** Ninety-two patients enrolled (mean age 57.8 years), including 82 (89%) with brain metastases. All plans met standard target coverage and organ-at-risk constraints while optimizing dose to the cognitive connectome, with 76% meeting predefined constraints for all 23 connectome structures. At 3 months, 74% of patients demonstrated stable-to-improved performance across all 5 cognitive domains, with no significant mean decline in any domain. Mean performance improved in executive function (+4.30 T; p=0.043) and language (+4.91 T; p=0.011). Compared with historical controls, COG-SRS demonstrated superior 3 month cognitive outcomes (global composite Z difference +0.38; p=0.001), with the most pronounced domain-level benefit in executive function (+0.71; p=0.009) and language (+0.35; p=0.010). Mood and QOL remained stable. Among patients with brain metastases (median followup 35.6 months), 1 year local control was 98.5%, freedom from distant intracranial failure 57.4%, and overall survival 66.7%. **Conclusions:** Connectome-sparing brain SRS is feasible, leveraging advanced MRI-based autosegmentation of patient-specific cognitive networks, and is associated with preserved early cognition at the cohort level with superior 3 month cognitive outcomes versus historical controls. Cognitive benefits were achieved without compromising oncologic control, supporting prospective randomized study. Clinical trial information: NCT04343157. Research Sponsor: National Institutes of Health (NIH), National Cancer Institute (NCI); R01 CA238783; National Institutes of Health (NIH), National Cancer Institute (NCI); 1R01CA289833-01.

2003 **Oral Abstract Session**

Neoadjuvant fractionated stereotactic radiotherapy followed by surgical resection for brain metastases: A multicenter, single arm phase II trial (NEO-TACTICS). First Author: Koichi Mitsuya, Division of Neurosurgery, Shizuoka Cancer Center, Nagaizumi, Japan

Background: Surgical resection followed by adjuvant radiotherapy for brain metastases (BM) is associated with unresolved challenges, including local recurrence (LR), leptomeningeal dissemination (LMD), radiation necrosis (RN), and cognitive decline. Preoperative stereotactic radiosurgery followed by surgical resection has been proposed as a novel strategy to address these limitations. This phase II trial evaluated the efficacy and safety of neoadjuvant fractionated stereotactic radiotherapy (FSRT) followed by surgical resection for BM. **Methods:** Patients with one index brain metastasis requiring surgical resection (2-5cm diameter) and up to three non-index metastases not requiring resection (< 2cm) were enrolled across 14 centers. All patients received neoadjuvant FSRT (30-35 Gy in 5 fraction) targeting the index lesion, followed by surgical resection. The primary endpoint was 6-month cumulative incidence of LR at the surgical site. Secondary endpoints included LMD, LR at 12 months, RN, distant brain failure (DBF), overall survival (OS), intracranial progression-free survival (IC-PFS), neurocognitive outcomes, and treatment-related adverse events. **Results:** Between June 2022 and August 2024, we enrolled 57 patients with 53 evaluable for response. The median age was 68 years (range 34-79). The median maximum diameter was 3.2 cm (range 2.0-4.9). The median follow-up duration was 11.9 months (range 1.3-14.7). The 6-month cumulative incidence of surgical site LR was 4.3% (95% CI: 0–10.1) (80%CI : 0.4-8.1), and 4.0% (95%CI: 0-9.4) using competing risk analysis. LMD was not observed at either 6, 12 months. The 12-month cumulative incidence of LR was 16.4% (95% CI: 6.0–26.8). Symptomatic RN (≥ Gr 2) was not observed at either 6, 12 months, and asymptomatic RN occurred in 5.9% at 6 months and 8.0% at 12 months. DBF rates were 14.0% (95% CI: 4.4–23.6) at 6 months and 18.1% (95% CI: 7.4–28.8) at 12 months. Median OS rate was 86.3% (95%CI: 77.3-96.3) at 6 months, and 76.5% (95%CI: 65.7-89) at 12 months. IC-PFS rates were 72.5% (95% CI: 61.2-85.9) at 6 months and 64.4% (95% CI: 52.5-79.1) at 12 months. Neurocognitive function was largely preserved, with Mini-Mental State Examination (MMSE) decline ≥1 point observed in 15.4% at 6 months and 9.6% at 12 months, and decline ≥3 points in ≤ 4% at both time points. Adverse events from irradiation to surgery were acceptable (grade ≥2: 10.5%; grade ≥3: 5.3% (CTCAE version 5.0)). **Conclusions:** Neoadjuvant FSRT followed by surgical resection demonstrated excellent early local control, complete suppression of LMD, acceptable toxicity, and favorable cognitive preservation. This approach represents a promising alternative to postoperative FSRT for resectable brain metastases and warrants further comparative investigation. Clinical trial information: jRCT s042220014. Research Sponsor: ACCURAY.

2004 **Oral Abstract Session**

MAGMA: Multi-arm glioblastoma Australasia phase 3 trial. First Author: Craig Gedye, Icon Cancer Centre, Kurralta Park, SA, Australia

Background: MAGMA (ACTRN12620000048987; COGNO cooperative trials group) is a prospective, open-label, partial factorial randomized platform trial with optional randomization, aiming to improve treatments for glioblastoma (GBM). Two initial hypotheses were tested: Question 1 (Q1), 'early' daily temozolomide (TMZ) as soon as possible postop, pre-radiotherapy (RT); and Question 2 (Q2), 'extended' adjuvant TMZ beyond 6 cycles. Prior phase 2 studies suggest longer survival with early TMZ and inconsistent outcomes with extended adjuvant TMZ. MAGMA used baseline randomization with molecular stratification aiming for robust randomized evidence. **Methods:** Participants (pts) with newly diagnosed GBM (CNS WHO 2016) could be randomized to each question, stratified by extent of resection and IDH status (Q1 and Q2) and MGMT methylation (Q2 only). For Q1, pts were randomized to daily TMZ (75 mg/m^2) initiated as soon as possible after surgery followed by standard RT-TMZ (either 15 or 30 fractions), or RT-TMZ alone. For Q2, pts were randomized prior to adjuvant TMZ, to stop after 6 cycles or continue until progression. Primary outcome was overall survival (OS) from initial surgery. Secondary outcomes included progression-free survival (PFS), time to next treatment, OS from each randomization, clinically significant toxicity and health-related quality of life. **Results:** From September 2020 to July 2023, 347 pts consented across 28 Australian sites including 6 regional sites. Median follow-up was 40 months; final data cutoff was 31 July 2025. Mean age was 60 years (range 21-85), 60% were male, 92% IDH-wildtype, 42% MGMT-methylated, 56% had gross total resection and 13% biopsy-only. For Q1 (n=259), pts randomized to early TMZ (n=131) started TMZ at median 21 days post-surgery with mean exposure 13 days. Concurrent TMZ exposure, time to starting RT (median 34 vs 33 days), RT completion and toxicity (G3+ 34% vs 31%) were similar between arms. Median OS (months; 95% CI) was 16 (14-20) with early TMZ vs 20 (17-22) for control, HR 1.18 (0.89-1.56), p=0.24. Median PFS was 8 (7-9) vs 9 (7-12), HR 1.15 (0.88-1.52), p=0.31. For Q2 (n=291), among pts randomized to extended adjuvant TMZ (n=146), only 42% remained progression-free through 6 cycles and received more than 6 adjuvant TMZ cycles. Toxicity was similar between arms (G3+ 34% vs 31%). Median OS was 20 months (17-22) with extended adjuvant TMZ vs 18 (15-20) for control, HR 0.82 (0.63-1.06), p=0.13; after multivariable analysis, HR 0.73 (0.56-0.95). Median PFS was 9 (8-9) vs 9 (7-10), HR 0.88 (0.69-1.13), p=0.32. **Conclusions:** Early TMZ does not improve OS in pts with newly diagnosed GBM. Extended adjuvant TMZ beyond 6 cycles was safe, with insufficient evidence of improved OS in the primary analysis, although moderate effects remain plausible. Notably, many pts had progression before completing 6 cycles. Collaboration enables large-scale, pragmatic cancer trials across diverse healthcare settings in Australia. Clinical trial information: ACTRN12620000048987. Research Sponsor: Medical Research Future Fund (MRFF); 2018/MRF1170193.

2005 **Oral Abstract Session**

Phase 1/2a study of concomitant radiotherapy with olaparib and temozolomide in unresectable high-grade glioma patients: Final results from the phase 2a step (OLA-TMZ-RTE-01). First Author: Dinu Stefan, Centre François Baclesse, Radiation Oncology Department, Caen, France

Background: Although the Stupp protocol (radiotherapy + temozolomide (TMZ)) remains the cornerstone of glioblastoma (GBM) first line treatment after surgery (resection or biopsy), the prognosis is still poor. PARP inhibitors, such as olaparib, may enhance the efficacy of radiotherapy and TMZ by amplifying their cytotoxic effects. We implemented a phase 1/2 trial to assess safety and efficacy of olaparib combined with TMZ concomitant with intensity modulated radiotherapy (IMRT) as a first line treatment in GBM patients (pts) following biopsy or subtotal resection. The phase 1 conducted in 30 pts concluded the recommended phase 2 dose (RP2D) of olaparib was 100 mg Q12H Day (D) 1-3, in concomitant with the Stupp protocol. We herein report results of the phase 2a. **Methods:** Pts were treated with adjuvant IMRT (60 Gy/30 fractions/6 wks), with concurrent daily oral TMZ (75 mg/m²). For the maintenance period (MT) from 4 wks after IMRT, pts received TMZ (150 mg/m², D 1-5 every 28 days, for 6 cycles). Oral olaparib was started at the RP2D the same day as IMRT, concurrently with the Stupp protocol and continued up to disease progression or unacceptable toxicity. The trial was conducted according to a two-step Case and Morgan design and required 55 assessable pts (37 in interim analysis), to assess the 12-month (mo) overall survival (OS) rate expected to be higher than 57%. Final Z-statistic$>$1.235 will confirm efficacy. All pts who received olaparib at RP2D were included in the analysis, including pts of the phase 1 step. **Results:** From 2020 to 2024, 68 pts were enrolled and treated in the phase 2a: 41 (60%) men, median age 59 yrs [range 20-70]. 67 pts (98%) had GBM and 1 (2%) IDH mutated anaplastic astrocytoma. Biopsy-only was performed for 27 pts (40%). ECOG performance status 0 for 34 pts (51%), 1 for 28 pts (42%) and 2 for 5 (7%). 11 pts (16%) stopped the study before MT, including 4 for grade 3-4 hematological toxicity. Among the 57 pts who began the MT, 5 stopped the treatment for hematological toxicity. 3 pts remain on treatment. Interim analysis conducted in March 2024 in 41 patients, with median follow-up o 7.6 mo, led pursuing the study, with a 12-mo OS rate of 72.9% [95%CI: 56.7-93.9]. At final analysis, after median follow-up of 17.2 mo, 48 deaths (71%) were observed. Median OS was 18.4 mo and 12-mo OS rate of 69.1% [95%CI: 59-81] (H0 rejection according to Z-statistic=1.29). Among hematological toxicities of interest, thrombocytopenia grade $\geq$ 3 was observed in 5 pts, neutropenia grade 4 in 4 pts, febrile neutropenia grade $\geq$ 3 in 1 pt and anemia grade $\geq$ 3 in 4 pts. One toxic death was observed (febrile aplasia). **Conclusions:** Intermittent olaparib (100 mg Q12H D1-3) combined with the Stupp protocol appears to be beneficial to improve survival of poor prognosis nonresected/partially resected GBM pts, with a safety profile quite similar to that of the standard chemoradiotherapy. Clinical trial information: NCT03212742. Research Sponsor: French Cancer Institute and French Health Ministry; Astra-Zeneca.

2006 **Oral Abstract Session**

A personalized neoantigen vaccine to reprogram the immune landscape of glioblastoma. First Author: Jack Y. Ghannam, Harvard Medical School, Boston, MA

Background: Glioblastoma (GBM) remains uniformly lethal despite standard therapy. An immunosuppressive tumor microenvironment (TME) and limited T cell infiltration pose major barriers to immunotherapy. Personalized neoantigen vaccines offer a strategy to prime tumor-specific T cell responses by targeting patient-specific mutations, driving effector cells into the CNS. Here, we report results from a phase I trial of a personalized neoantigen peptide vaccine combined with pembrolizumab in newly diagnosed GBM. **Methods:** Patients with newly diagnosed GBM who were not on dexamethasone following gross total resection were enrolled across four cohorts. Up to 20 synthetic long peptides targeting personal neoantigens were selected per patient, and admixed with the adjuvant poly-ICLC (NeoVax). Following radiotherapy, NeoVax was administered subcutaneously as five priming doses followed by two booster doses. *MGMT*-unmethylated patients (Cohorts 1A-C) received NeoVax plus pembrolizumab without temozolomide (TMZ) and differed by time of pembrolizumab initiation relative to NeoVax priming; *MGMT*-methylated patients (Cohort 1D) received standard TMZ and pembrolizumab was initiated after NeoVax priming. Immunogenicity was assessed by *ex vivo* and *in vitro* IFN-γ ELISpot assays. Single-nucleus/single-cell RNA sequencing and TCR sequencing (snRNA-seq/scTCR-seq) was performed on paired tumor specimens. **Results:** Of 39 enrolled patients, 37 initiated NeoVax including 35 who completed priming and 2 with ongoing priming. Treatment was well-tolerated with no serious AEs. Median overall survival was 36.9 months for *MGMT*-methylated patients and 19.0 months for *MGMT*-unmethylated patients, compared to 25.3 and 16.7 months for propensity score-matched historical controls, respectively. *Ex vivo* and *in vitro* neoantigen-specific T cell responses were detected comparably across all cohorts and overall in 65% and 97% of vaccinated patients, respectively. Among all patients, *ex vivo* immune responders demonstrated improved overall survival compared to non-responders (HR 0.26, 95% CI 0.09-0.77, P = 0.015). Vaccine-reactive clonotypes, defined by *in vitro* expansion to vaccine peptides, were identified in post-vaccination tumors. snRNA-seq/scTCR-seq revealed increased intratumoral vaccine-specific T effector populations following vaccination. **Conclusions:** NeoVax generates durable T cell responses that traffic to GBM tumors, with circulating responses associated with improved survival. Ongoing studies are evaluating peripheral clonotype dynamics, remodeling of malignant cell states and the TME, and the spatial distribution of vaccine-reactive clonotypes, which may guide future combinatorial strategies in GBM. Clinical trial information: NCT02287428. Research Sponsor: The Ben & Catherine Ivy Foundation; Accelerate Brain Cancer Cure; Merck Sharp & Dohme LLC; U.S. National Institutes of Health; 5P01CA236749; U.S. National Institutes of Health.

LBA2007 **Oral Abstract Session**

Efficacy and safety of asandeutertinib versus osimertinib as first-line treatment in EGFR-mutated NSCLC patients with brain metastases: Interim analysis of an open-label, multicenter, randomized, pivotal phase II study (ESAONA). First Author: Yuankai Shi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

2008 Oral Abstract Session

Correlation of ten-year survival with cell-free DNA methylation of melanoma patients with asymptomatic brain metastases treated with nivolumab plus ipilimumab: The multicenter phase III NIBIT-M2 trial. First Author: Anna Maria Di Giacomo, University of Siena and Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy

Background: The NIBIT Foundation-sponsored phase III NIBIT-M2 study showed a 41% 7-y OS of melanoma patients (pts) with asymptomatic brain metastases (BM) treated with ipilimumab (I) plus nivolumab (N) (I+N) (*Di Giacomo AM, CCR 2021* and *EJC 2024*). Despite the significant efficacy of I+N therapy in this pts population, no biomarkers predictive of response have been identified yet also due to the accessibility of BM. We here report the 10-y survival and its correlation with cell-free (cf)DNA analyses on serial plasma samples collected from pts enrolled in the NIBIT-M2 study. **Methods:** The NIBIT-M2 study recruited melanoma pts with active, untreated, asymptomatic BM from 9 Italian Centers, randomized (1:1:1) to receive fotemustine (F) (Arm A), I+F (Arm B), or I+N (Arm C). Primary endpoint was OS. Exploratory analyses were conducted on cfDNA plasma samples collected at baseline and week (W) 12 on therapy. Tumor fraction (TF) was estimated from low pass WGS using IchorCNA. Tumor-specific methylation Score (T-meth Score) was computed as the ratio between the coverage over methylated regions analyzed by cf-methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) and melanoma-specific methylated regions previously identified in the TCGA melanoma cohort. **Results:** From Jan 2013 to Sept 2018, 80 pts were enrolled: 76 received F (23), I+F (26), or I+N (27). As of December 1, 2025, with a median follow-up of 125 months (mo), median OS was 8.5 (95% CI: 4.8-12.2), 8.2 (95% CI: 2.1-14.3) and 29.2 (95% CI: 0-73.5) mo for Arm A, B, and C, respectively. The 10-y OS rate was 13.0% (95% CI: 0-26.7) in Arm A, 7.7% (95% CI: 0-17.9) in Arm B, and 31.2% (95% CI: 13.0-49.4) in Arm C. The 10-y melanoma specific survival was 13.0% (95% CI: 0-26.7), 7.7% (95% CI: 0-17.9), and 35.1% (95% CI: 16.3-53.9) in Arm A, B and C, respectively. Patients were stratified at baseline according to the median values of TF (n=57; median 0.022) and of T-meth Score (n=53; median 0.096): a significantly higher median OS was observed in pts with TF (22.3 *vs* 8.2 mo; p=0.033) and T-meth Score (26.3 *vs* 7.9 mo; p=0.002) below their median values. Of note, low TF and T-meth Score were enriched at baseline in pts from Arm C. Additionally, a decrease in TF (n=29) and T-meth Score (n=24) was observed at W12 in pts with an OS above the median (26.3 mo for TF and 24.0 mo for T-meth Score). **Conclusions:** The 10-y results of the NIBIT-M2 study, with the longest follow-up available to date in melanoma pts with asymptomatic BM treated with I+N, continue to show persistent long-term therapeutic efficacy of the combination. Plasma-derived TF and T-meth Score may predict long-term survival of melanoma pts with asymptomatic BM treated with I+N. Clinical trial information: NCT02460068. Research Sponsor: FONDAZIONE AIRC; 21073; Bristol Myers Squibb; NA.

2009 Rapid Oral Abstract Session

SPECTRUM: Phase II study of tislelizumab plus pemetrexed in patients with relapsed or refractory (R/R) primary diffuse large B-cell lymphoma (DLBCL) of the central nervous system (CNS)—The Korean Cancer Study Group LY22-07. First Author: Jung Sun Kim, Seoul National University College of Medicine, Seoul, South Korea

Background: Primary DLBCL of the CNS is a rare extranodal lymphoma confined to the CNS. Despite standard high-dose methotrexate (HD-MTX)-based induction therapy, approximately 25% of patients (pts) relapse after an initial response, and effective salvage options are limited with reported objective response rate (ORR) generally $<$30% and median progression-free survival (PFS) $<$3 months. The SPECTRUM trial evaluated efficacy and safety of tislelizumab plus pemetrexed in pts with R/R primary DLBCL of the CNS (NCT05253118). **Methods:** SPECTRUM is a phase II, multicenter, open-label study conducted in South Korea. Pts with histologically confirmed R/R primary DLBCL of the CNS after HD-MTX-based therapy were eligible. Tislelizumab (200 mg) plus pemetrexed (500 mg/m^2) was administered intravenously every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed ORR per IPCG response criteria. Secondary endpoints included PFS, duration of response (DoR), overall survival (OS), and safety. Exploratory analyses assessed baseline CSF and plasma *MYD88* L265P mutations using droplet digital PCR and genetic subtypes based on LymphGen classification. **Results:** As of December 16, 2025, 29 pts were enrolled. Median age was 59 years (range, 41–86), 17 (58.6%) were male, and 25 (86.2%) had prior rituximab exposure. Median follow-up was 30.4 months (95% confidence interval [CI], 16.8–not reached [NR]), with a median of 6 treatment cycles (range, 1–55). Among evaluable pts, the ORR was 71.4% (20/28), with complete response (CR) rate of 50.0% (14/28). Median DoR was 14.5 months (95% CI, 2.8–NR). Median PFS and OS were 6.8 (95% CI, 2.1–27.6) and 27.8 months (95% CI, 7.4–NR), respectively. Treatment-emergent adverse events (TEAEs) of any grade occurred in 19 pts (65.5%), most commonly skin rash (51.7%). Grade $\geq$3 TEAEs occurred in 10 pts (34.5%), including one grade 5 event. Six pts discontinued treatment due to treatment-related AEs, all attributable to pemetrexed. Immune-related AEs occurred in 5 pts (17.2%). Most pts were MCD subtype (84.6% [22/26]), with *MYD88* L265P mutations detected in 61.5% (16/26). At baseline, *MYD88* L265P detection was higher in CSF than plasma cell-free DNA (cfDNA) (85.0% [17/20] vs 20.0% [4/20]). In one pt with extra-CNS relapse harboring *MYD88* L265P mutation and *PIM1–CD274* fusion, *MYD88* L265P became undetectable at Weeks 6 and 12, concordant with metabolic CR on PET/CT. **Conclusions:** Tislelizumab plus pemetrexed met the primary endpoint and demonstrated encouraging outcomes (ORR 71.4% [CR 50.0%]; median PFS and DoR 6.8 and 14.5 months) with manageable safety profiles in pts with R/R primary DLBCL of the CNS. Clinical trial information: NCT05253118. Research Sponsor: BeOne Medicines, Samyang Biopharm Corporation.

2010 Rapid Oral Abstract Session

A global, randomized, double-blinded, phase 3 trial of vorasidenib vs placebo in patients with grade 2 glioma with an *IDH1/2* mutation (INDIGO): Updated efficacy and safety. First Author: Timothy Francis Cloughesy, University of California Los Angeles, Los Angeles, CA

Background: Grade 2 gliomas with isocitrate dehydrogenase 1/2 mutations (mIDH1/2) are diffuse, slowly progressive, malignant brain tumors with a poor long-term prognosis. In the Phase 3 INDIGO trial (NCT04164901) of patients (pts) with grade 2 mIDH1/2 glioma, vorasidenib (VOR), an oral, brain-penetrant, dual inhibitor of mIDH1/2, demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint, progression-free survival (PFS) per blinded independent review committee (BIRC), and key secondary endpoint, time to next intervention (TTNI), vs placebo (PBO) at the preplanned interim analysis (data cut-off [DCO]: September 6, 2022). An additional 6 months of data up to study unblinding, March 7, 2023, showed that median PFS was not reached (95% confidence interval [CI]: 22.1 mos, not estimable [NE]) with VOR vs 11.4 mos (95% CI: 11.1, 13.9) with PBO, and median TTNI was NE (95% CI: NE, NE) with VOR vs 20.1 mos (95% CI: 17.5, 27.1) with PBO. Here, we present updated efficacy and safety results as of January 17, 2025, from pts randomized to VOR. **Methods:** Key eligibility criteria included residual/recurrent grade 2 mIDH1/2 oligodendroglioma or astrocytoma after surgery only; aged $\geq$12 years; Karnofsky performance score $\geq$80; measurable non-enhancing disease; surgery as only prior treatment; no immediate need of chemo-radiotherapy (CT/RT). Pts were randomized 1:1 to VOR 40 mg daily in 28-day cycles or PBO. After study unblinding, pts receiving PBO were permitted to cross over to VOR. Primary endpoint: radiographic PFS per BIRC. Key secondary endpoint: TTNI. **Results:** 331 pts were randomized: 168 to VOR and 163 to PBO (median age: 40.0 years [range: 16–71]; oligodendroglioma: 172; astrocytoma: 159). As of January 17, 2025, 98/168 (58.3%) pts remained on VOR, and median follow-up was 41.6 mos (95% CI: 40.5, 42.7). Median PFS per investigator (INV) in pts randomized to VOR was 49.9 mos (95% CI: 39.6, NE), and median TTNI was NE (95% CI: 52.0 mos, NE). At 42 mos, 59.2% (95% CI: 49.9, 67.4) of pts were progression-free and 75.1% (95% CI: 67.4, 81.2) were not in need of CT/RT or surgery. Objective response rate per INV was 31.5% (95% CI: 24.6, 39.2). Median overall survival was not reached. PFS and overall response per BIRC will be presented. The safety profile of VOR was consistent with previous reports. No new safety signals were observed. **Conclusions:** In the randomized, Phase 3 trial of a targeted therapy in grade 2 mIDH1/2 glioma, over 3 years of follow-up in pts randomized to VOR support the robustness of PFS and TTNI results and confirm a durable and sustained treatment benefit with VOR. VOR is now approved in over 40 countries as a monotherapy for pts with grade 2 mIDH1/2 glioma following surgery. Clinical trial information: NCT04164901. Research Sponsor: Servier Pharmaceuticals.

2011 Rapid Oral Abstract Session

Outcomes of a feasibility and safety trial of tile-based radiation therapy with cesium-131 followed by external beam radiation therapy with concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma (NCT05342883). First Author: Clark C. Chen, Brown University, Providence, RI

Background: Standard of care (SOC) of Glioblastoma (GBM) includes maximal safe resection followed by external beam radiation therapy (EBRT) with concomitant temozolomide (TMZ). This typically begins 4-6 weeks after surgery, during which rapid early progression (REP) occurs in ~50% of patients and is associated with worse survival, especially in unmethylated GBM (median OS ~13 months as per BN007). SOC treatment in BN007 showed ~38% $\geq$grade 3 treatment-related adverse events (TRAEs). GammaTile (GT Medical Technologies, Inc., Tempe, AZ), a tile-based radiation therapy (TBRT) with cesium-131 sources, immediately initiates radiation at resection, eliminating the 4-6-week delay. **Methods:** This is a prospective, single arm, open-label feasibility study across 15 US centers with a primary aim of assessing the safety and feasibility of combining resection + TBRT with an abbreviated course of EBRT with concurrent and adjuvant TMZ for newly diagnosed molecular GBM. Eligible patients were $\geq$18 years old; only patients with IDH-wildtype were included in survival analysis. MGMT and IDH underwent central lab review. Feasibility was defined as percent of patients who started EBRT+TMZ between 21-35 days post-surgery. Safety was assessed by incidence of $\geq$grade 3 TRAEs. REP was centrally reviewed. Additional aims included PFS and OS estimated using Kaplan-Meier. A planned sample size of 61 was chosen to ensure feasibility could be estimated with a $\pm$10% degree of precision. Results are presented based on the modified intent to treat (mITT) population (enrolled patients who had surgery and confirmed GBM). **Results:** From 8/2022-8/2025, 70 patients were enrolled and had surgery; 67 of whom had confirmed GBM. Table 1 presents baseline characteristics. Median follow-up was 12.4 months. 93% started EBRT+TMZ; 74% started 21-35 days post-surgery. The median (range) of days from surgery to EBRT+TMZ was 29 (23-70) days. There were no delays due to EBRT planning. 39% of patients experienced a $\geq$grade 3 TRAE: 22% of patients were related to surgery only, 18% to radiation only, and 13% to surgery and radiation. 6.0% of patients showed REP. Median OS for patients with unmethylated MGMT was 16.5 months vs. 28.0 months for patients with methylated MGMT. The median PFS for patients with unmethylated MGMT was 9.3 months vs. not yet met for patients with methylated MGMT. **Conclusions:** Feasibility and safety are in line with SOC. REP had a notable reduction compared to literature. OS is encouraging. These data provide the basis for a phase 3 randomized trial (NCT07195591). Clinical trial information: NCT05342883. Research Sponsor: GT Medical Technologies, Inc.

Baseline characteristics.

Parameter	Detail
n	67
Age, median	66
Male:Female, n	42:25
Ethnicity (Non-Hispanic), n	61
Race (White), n	56
EOR – GTR:not GTR, %	66:34
IDH-wildtype:mutated, n	66:1
MGMT promoter methylated:unmethylated, n	28:39

2012 **Rapid Oral Abstract Session**

First-in-human study of AAV6-NeuroD1 trans-differentiation therapy in recurrent malignant glioma. First Author: Yulun Huang, Department of Neurosurgery, The Fourth Affiliated Hospital of Soochow University, Suzhou, China

Background: Recurrent glioblastoma (GBM) has a median survival of less than 9 months. NeuroD1 is a neural transcriptional factor that can reprogram both glial cells and glioma cells into neuron-like cells, suppressing the proliferation of glioma cells and inducing cell death, extending the life span of animal models carrying glioblastoma. Therefore, scAAV6-NeuroD1 (NXL-004), a self-complementary adeno-associated virus 6 vector delivering NeuroD1, was developed to initiate a first-in-human study in patients with recurrent malignant glioma (ChiCTR2400080362). **Methods:** This is a single arm, open-label, dose-escalation study. The primary endpoint was safety, and the secondary endpoint was preliminary efficacy. Enrolled patients must have pathologically confirmed recurrent malignant glioma after standard therapy including surgery and chemoradiotherapy. NXL-004 was delivered intracavitary post-resection or intratumorally post-biopsy during surgery. Three dose levels (from $4.0x10^{12}$ vg to $4.0x10^{13}$ vg) were evaluated, using an accelerated dose escalation design. Up to two additional doses were allowed via an Ommaya reservoir at 2~4-week intervals after surgery. **Results:** 11 patients (median age 48.0, 81.8% male) were enrolled between 3/2024 and 6/2025. All patients had recurrent WHO grade 4 astrocytoma (10/11 IDH wild, 6/11 MGMT-unmethylated). Ten patients received repeat tumor resection plus intracavitary injection of NXL-004 (1 at low-dose, 3 at medium-dose, and 6 at high-dose), and one received biopsy plus intra-tumoral injection (low dose). All patients were included in the safety and efficacy analysis. No drug-related serious adverse event (SAE) or dose-limiting toxicities (DLT) was observed. All AEs related to NXL-004 were grade 1–2 (fever: 8/11; rash: 1/11; seizure: 1/11). Two grade 3 AEs (hemiplegia, meningitis) were reported but considered unrelated to the drug. Per RANO 2.0 criteria, the best overall response included 1 complete response (CR) and 5 stable disease (SD), yielding a disease control rate (DCR) of 54.5% (6/11). The median overall survival for all treated patients was 13.2 ± 2.0 months (95% CI: 9.3-17.1) from the first dose and 25.2 ± 1.2 months (95% CI: 23.0-27.5) from initial diagnosis. The first enrolled patient survived $>$18 months after dose. In the high-dose group, a higher DCR of 66.7% (4/6) was observed, with one patient achieving CR and one with SD surviving without progression $>$6 months (9 and 7 months, respectively, both ongoing). At a median follow-up of 9.0 months for this group, 5 patients were still alive, with 1 patient deceased (OS: 13.2 months). **Conclusions:** To our knowledge, this is the first clinical evidence of in vivo AAV-based trans-differentiation gene therapy for cancer treatment. NXL-004 showed favorable safety and encouraging efficacy, indicating that AAV-based cell reprogramming approach may represent a new modality for the treatment of glioma. Clinical trial information: ChiCTR2400080362. Research Sponsor: Suzhou Science and Technology Plan Project No. SZM2023019; NeuExcell Therapeutics.

2013 **Rapid Oral Abstract Session**

Updated overall survival, safety, and neurologic function outcomes from a phase 1 trial of bivalent chimeric antigen receptor (CAR) T cell therapy in recurrent glioblastoma (GBM). First Author: Erin E. Hollander, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Background: We previously reported the safety, bioactivity, and preliminary efficacy of bivalent CAR T cells targeting EGFR and IL13Rα2 in 18 patients with recurrent GBM (Bagley, et. al, *Nat Med* 2025). Given that median follow-up time was only 8.1 months at the time of the data cut-off for that publication, we now report updated overall survival (OS) and safety data with longer follow-up time, as well as neurologic function outcomes. **Methods:** Eighteen patients with recurrent EGFR-amplified GBM were enrolled using a 3+3 design (dose levels: 5.0×10^6, 1.0×10^7, and 2.5×10^7 cells). Patients received a single intracerebroventricular (ICV) dose of CART-EGFR-IL13Rα2 cells. OS was defined as the time from the date of initial study treatment to the date of death from any cause, or censored at the last date of contact if the patient was not known to have died at the date of analysis cut-off (January 16, 2026). To capture changes in neurologic function over the course of the trial, patients were assessed prospectively using the Neurologic Assessment in Neuro-Oncology (NANO) scale. NANO is an objective clinician-reported outcome of neurologic function scored on nine domains, with a higher score indicating worse neurologic function. NANO scores were assessed at baseline prior to CART (day 0), on days 1, 4, 7, 10, 14, 21, and at the 1-month and 2-month visits post-CART. **Results:** With median follow-up time of 18.5 months, median OS was 12.0 months (95% confidence interval, 7.4 – 23.2 months) with 3 patients surviving greater than 18 months. Other than one patient with prolonged grade 1 neurotoxicity as previously described, no prolonged, late-onset, or unexpected toxicities were observed within this longer follow-up time, including no evidence of on-target off-tumor toxicity or secondary cancers. On day 1 post infusion, an increase in NANO scores was observed (mean increase in NANO score from baseline of 1.9; p=0.09), which resolved to baseline by day 4. Patient NANO scores were unchanged from baseline at one month (mean change 0.41; p=0.998) and two months (mean change 0.54; p=0.992) post infusion. Those who underwent retreatment with a second dose of CAR-T cells at the time of tumor progression (n=7) did not experience an increase in NANO score on day 1 (mean change 0.33, p=0.99), despite having a significant increase on day 1 following the first infusion (mean change 2.9, p=0.008). **Conclusions:** With over 18 months of median follow-up time, ICV delivery of CART-EGFR- IL13Ra2 cells in patients with recurrent GBM has not demonstrated long-term or delayed toxicities and is associated with promising OS outcomes that warrant continued clinical development. Neurologic function worsens immediately following infusion but recovers to pre-treatment baseline by one month following CAR T cell infusion. Clinical trial information: NCT05168423. Research Sponsor: Kite.

2014 **Rapid Oral Abstract Session**

Butaselen combined with radiotherapy for newly diagnosed H3K27M-mutant spinal diffuse midline glioma: A single-arm phase Ib trial. First Author: Yuanhao Chang, Beijing Tiantan Hospital, Beijing, China

Background: Patients with H3K27M-mutant spinal diffuse midline glioma (sDMG) have a median overall survival (OS) of approximately 13 months and the medical interventions remain limited. Radiation induced senescence (RIS) is a major cause of radiotherapy resistance and tumor recurrence in H3K27M-mutant sDMG. In pre-clinical study, we observe that thioredoxin reductase 1 (TrxR1) protects senescence sDMG cells from oxidative damage caused by radiation, and novel TrxR1 inhibitor Butaselen dramatically induces apoptosis of sDMG cells. Therefore, Butaselen combined radiotherapy is a new strategy to prolong the OS and progression-free survival (PFS) for newly diagnosed H3K27M-mutatnt sDMG patients. **Methods:** Patients age 18-70 years with newly diagnosed H3K27M-mutant sDMG were eligible for this phase Ib trial (ChiCTR2600116732). All subjects received fixed radiation dose at 45Gy/1.8f/25d. Dose-escalation of Butaselen was performed in phase Ib trial and 9 subjects were enrolled in three dose levels (3+3 design: DL1: 450mg, oral, bid; DL2: 600mg, oral, bid; DL3: 750mg, oral, bid). Butaselen was orally administered in combination with radiotherapy for first 5 weeks, and then administered alone until tumor progression occurs or death. Follow-up visits were conducted at Q8W during 0-6 months and Q12W afterwards. The primary outcome was the safety of the Butaselen, as determined on the basis of adverse events (AEs) and serious adverse events (SAEs). The secondary outcomes were the 12-month OS/PFS rate, OS, PFS, objective response rate (ORR, RANO 2.0 criteria), and objective neurological function scale. **Results:** Between Apr 18, 2024 and May 21, 2025, 9 eligible subjects were enrolled. 9 subjects (age 26-57 years) received Butaselen therapy with no report of severe adverse event (SAE) or dose-limiting toxicity. As a result, 6-month and 12-month PFS rate (PFS%) was 100% and 88.9% (8/9), respectively, while both 6-month and 12-month OS rate (OS%) reached 100%. The longest PFS has exceed 22 months. 1 subject was died due to disease progress (OS=14.7 month; PFS=6.9 month), 1 subject experienced second operate resecting after disease progress (PFS=12.9 month), and the remaining 7/9 subjects are currently still in the progression-free survival phase. The overall ORR assessed by RANO 2.0 was 33% (3/9) and DCR was 100% (9/9). All subjects (9/9, 100%) experienced the relieve of neurological functions, as measured by Japanese Orthopedic Association (JOA) Scores and McCormick Scores. Grade 3 drug-related treatment-emergent adverse events (TEAEs) occurred 2 times; and no grade 4 TEAEs occurred. **Conclusions:** Butaselen combined with standard radiotherapy was well tolerated, and exhibited meaningful prolongation of survival period, durable objective responses and neurological function improvements in primary H3K27M-mutant sDMG patients. Clinical trial information: ChiCTR2600116732. Research Sponsor: None.

2015 **Rapid Oral Abstract Session**

Azeliragon, a RAGE inhibitor, plus temozolomide and radiotherapy in patients with newly diagnosed glioblastoma: Final results from a dose-finding phase in the CAN-201 NDG trial. First Author: Maria Martinez Garcia, Medical Oncology Department, Hospital del Mar, Barcelona, Spain

Background: Radiotherapy (RT) plus temozolomide (TMZ) is the standard of care for patients (pts) with newly diagnosed glioblastoma (GBM). However, most eventually progress. The RAGE receptor and its ligands may contribute to RT resistance in GBM by sustaining chronic pro-tumorigenic inflammation, enhancing DNA damage repair pathways, and promoting survival signaling in hypoxic and stressed tumor cells. Azeliragon, an extensively studied RAGE inhibitor in Alzheimer's disease, may enhance overcome RT-TMZ resistance in newly diagnosed GBM. **Methods:** The CAN-201 NDG is an open-label, single-arm, phase Ib/II trial in Spain recruiting pts with newly diagnosed IDH-wildtype GBM. Pts received azeliragon in combination with standard RT-TMZ, followed by maintenance therapy with azeliragon. The trial consists of an initial dose-finding phase with a rolling six design and a subsequent expansion phase (up to 14 additional pts) at the recommended phase 2 dose (RP2D). The dose levels were 5 (L1), 10 (L2), 20 (L3), 30 (L4), and 50 (L5) mg/day. The primary objective was to determine the RP2D, defined as the dose for which $<$33% of pts experience dose-limiting toxicity (DLT) within 28 days of the initiation of dosing. Main secondary endpoints include progression-free survival (PFS), overall survival (OS), and changes in corticosteroid requirements. Pharmacokinetic and translational research is ongoing. **Results:** From Oct 2023 to May 2025, 33 pts were included across L1-L5 levels (6-8 pts per level). Median age was 56 years (range: 36-69). Most pts were male (66.7%), with ECOG 0-1 (93.9%), MGMT unmethylated (54.5%) and complete resection (45.5%). No DLTs occurred, and L5 (50 mg/day) was declared RP2D. One grade 3 maculopapular rash at L5 was the only serious adverse event related to azeliragon. Most common grade 3-4 toxicities were thrombocytopenia (21.2%) and lymphopenia (9.1%), all RT or TMZ-related. Most common possibly azeliragon-related AEs were asthenia (24.2%), nausea (21.2%), anorexia (9.1%), diarrhoea and dysgeusia (6.1% each), all grade 1-2. Median azeliragon treatment duration was 7.4 m (range: 2.7-21.1). Treatment ended due to disease progression (82.8%), toxicity (3.4%), and exitus (3.4%). Three pts at L5 remain on treatment. With median follow-up of 11 m (95% CI: 8.2-16.4), median PFS was 7.9 m (95% CI: 6.2-12.2) overall, 15.6 m (95% CI: 6.1-NR) and 6.7 m (95% CI: 5.0-10.9) for methylated and unmethylated MGMT, respectively. Median OS was not reached, 12m OS rate was 61.5% (95% CI: 4.4-85.3), with rates of 74.2% (95% CI: 52.4-100) and 51.1% (95% CI: 29.3-88.8) for methylated and unmethylated MGMT, respectively. **Conclusions:** Azeliragon at 50 mg/day in combination with standard RT / TMZ is safe, with no DLTs reported. More mature OS data will be presented. Further follow-up with a larger number of pts is required to assess preliminary efficacy. Clinical trial information: NCT05635734. Research Sponsor: CANTEX Pharmaceuticals, Inc.

2016 **Rapid Oral Abstract Session**

Change in relative cerebral blood volume as a biomarker for early response to bevacizumab in patients with recurrent glioblastoma: ECOG-ACRIN EAF151. First Author: Jerrold L. Boxerman, Rhode Island Hospital/Brown University, Providence, RI

Background: Bevacizumab therapy (Bev) for recurrent glioblastoma (rGBM) has not demonstrated improved overall survival (OS) in randomized clinical trials. However, single-center and preliminary multi-center studies suggest that relative cerebral blood volume (rCBV) measured with dynamic susceptibility contrast MRI (DSC-MRI) at baseline or shortly after treatment initiation may predict response to Bev. The primary aim of ECOG-ACRIN EAF151 was to evaluate whether early binary change in rCBV, assessed 2–3 weeks after initiation of Bev-containing therapy, identifies patients with an OS benefit of ≥4 mos. Pre-specified secondary aims assessed baseline rCBV; post-hoc exploratory analyses examined early post-Rx rCBV. **Methods:** A prospective, phase II multi-center trial without randomization enrolled subjects with rGBM receiving their first Bev-containing therapy. Progression was determined by local sites (RANO criteria; MRI within 28 days of registration, ≥42 days since end of chemoradiation). Baseline (S0) and follow-up (S1) DSC-MRI were performed before the first Bev infusion (within 3 days), and 12-25 days post-infusion but before the second infusion. Anatomic MRI and DSC-MRI (double-dose Gadavist injection, full-dose preload) complied with recommended protocols. Mean normalized (nRCBV) and standardized (sRCBV) rCBV were extracted from contrast-enhancing tumor ROIs. A 2-sided logrank test (α=0.1) was used to test the primary aim (change in mean nRCBV from S0 to S1, ≥0 vs. <0). Cox regression with restricted cubic splines was used to assess the association between continuous rCBV markers and OS. **Results:** 146 subjects were accrued from 33 sites. 134 completed S0 and 118 completed both S0 and S1. After exclusion of uninterpretable scans, 107 were evaluable for change in rCBV, and 124 for baseline rCBV. There was no statistically significant difference in OS between subjects with binary increase (n=40; median OS 8.0 mos [90% CI 5.5–9.2]) vs. decrease (n=67; 7.9 mos [90% CI 6.3–10.3]) in mean nRCBV (p=0.67). Based on the spline fits, we observed a strong nonlinear association between OS and continuous nRCBV and sRCBV at both S0 and S1: low marker values are associated with lower risk, but beyond a threshold, higher values are not associated with greater risk. As an exploratory analysis, we estimated optimal cut points (nRCBV: S0=1.11, S1=1.16; sRCBV: S0=1.13, S1=0.99) and found that subjects whose S1 rCBV decreased below threshold had a median OS 2.7 mos (nRCBV, HR 0.61 [90% CI 0.41–0.88]) and 5.2 mos (sRCBV, HR 0.43 [90% CI 0.28–0.63]) longer than subjects whose rCBV either increased or did not decrease below threshold. **Conclusions:** EAF151 prospectively evaluated whether DSC-MRI markers predict OS in patients with rGBM treated with Bev. Although the change in these markers was not predictive, both baseline and early post-Rx markers were predictive of OS. Clinical trial information: NCT03115333. Research Sponsor: National Cancer Institute; U10CA180820, U10CA180794, U10CA180821, U10CA180868, UG1CA232760, UG1CA233198, UG1CA233270, UG1CA233196, UG1CA233253.

2017 **Rapid Oral Abstract Session**

Recurrence patterns and site-level survival in the previous phase III study of IL13-PE38QQR: Implications for drug distribution variability. First Author: Sandeep Kunwar, Precision Neuromed, Redwood City, CA

Background: Interleukin-13–Pseudomonas Exotoxin A (IL13-PE38QQR) is a targeted cytotoxic fusion protein directed against the IL13α2 receptor expressed on glioblastoma stem cells and absent in normal brain tissue. The drug is administered by convection-enhanced delivery (CED) for recurrent glioblastoma (GBM). Early-phase studies demonstrated durable tumor control and long-term survival; however, a pivotal Phase III trial failed to meet its primary endpoint. We hypothesized that variability in clinical outcomes was driven primarily by limitations in drug delivery rather than tumor biology. **Methods:** We conducted a post hoc analysis of clinical, imaging, and survival data from the randomized Phase III PRECISE trial of IL13-PE38QQR versus Gliadel wafers. Treatment-site experience was defined as ≥3 efficacy-evaluable IL13-PE38QQR patients. A subset of patients underwent radiolabeled drug infusion to assess intraparenchymal distribution. Recurrence patterns were evaluated using serial MRI. Survival outcomes were compared by treatment arm and site experience. **Results:** Marked heterogeneity in drug distribution was observed in patients receiving radiolabeled IL13-PE38QQR, ranging from broad target coverage to minimal or absent delivery. In the IL13-PE38QQR arm, treatment at experienced centers correlated with significantly improved overall survival (median OS 48.4 vs 32.1 weeks; p=0.038), whereas site experience had no significant impact in the control arm. A 50% increase in 1-year survivorship was observed in the treatment arm compared with control. Long-term survivors most commonly exhibited distant or multifocal recurrence with relative preservation of the treated region, suggesting durable local tumor control where therapeutic exposure was achieved. **Conclusions:** Clinical outcomes following IL13-PE38QQR therapy were strongly associated with delivery efficiency and treatment-team experience. Radiolabeled distribution studies, experience-dependent survival effects, and recurrence patterns in long-term survivors indicate that outcome variability was driven primarily by technical limitations in drug delivery rather than tumor biology. This study represented the first large-scale evaluation of CED in the absence of purpose-built delivery technology, relying on complex, nonstandardized surgical workflows. These findings highlight the importance of standardized procedures, specialized training, and purpose-built delivery platforms to enable reproducible therapeutic exposure and optimize the clinical potential of IL13-PE38QQR. Clinical trial information: NCT00076986. Research Sponsor: None.

2018 **Poster Session**

Scaling deep learning for neuro-oncology: Knowledge-distilled EfficientNetB0 powered MRI classification of brain tumors with international expert validation. First Author: Sophia Ahmed, Allama Iqbal Medical College, Lahore, Pakistan

Background: Accurate classification of brain tumors on magnetic resonance imaging (MRI) is critical for timely diagnosis, treatment planning, and referral in neuro-oncology. However, radiologic interpretation is challenged by tumor heterogeneity, overlapping imaging features, and growing imaging volumes, particularly in settings with limited subspecialty expertise. Although deep learning models have demonstrated high diagnostic accuracy, their computational complexity often limits real-world adoption. Scalable, resource-efficient AI systems capable of maintaining diagnostic performance are needed to enable global clinical translation. **Methods:** We retrospectively assembled a multicontinental dataset of 5,000 brain MRI studies from six continents, including pituitary tumors (n=1,200), meningiomas (n=1,300), gliomas (n=1,400), and non-tumor controls (n=1,100). Ground-truth diagnoses were established through independent review by at least two expert neuroradiologists. A high-capacity EfficientNetB4 model served as the reference architecture. A lightweight EfficientNetB0 model was trained using structured knowledge distillation with soft probabilistic supervision to preserve diagnostic fidelity while reducing computational cost. Model performance was evaluated on internal test data and independent external datasets using accuracy, class-specific sensitivity and specificity, F1-score, and area under the receiver operating characteristic curve (AUROC). **Results:** The distilled EfficientNetB0 model achieved an overall test accuracy of 94.8%, with balanced sensitivity across tumor classes (pituitary 93.1%, meningioma 95.2%, glioma 94.1%, non-tumor 96.4%). The overall F1-score was 0.946, and AUROC exceeded 0.92 on external validation datasets. Performance remained consistent across geographic regions and heterogeneous MRI acquisition protocols, with accuracy ranging from 93% to 96%. Mean inference time was 0.18 seconds per study on standard hardware, enabling real-time clinical integration. Clinician evaluators reported improved diagnostic confidence and utility for triage and workflow support. **Conclusions:** Knowledge-distilled EfficientNet models enable accurate, rapid, and computationally efficient classification of brain tumors on MRI without sacrificing clinically relevant performance. This scalable framework directly addresses key barriers to AI deployment in neuro-oncology and supports global implementation across resource-diverse settings. Prospective studies are planned to evaluate impact on diagnostic turnaround time, subspecialty access, and treatment decision-making. Research Sponsor: None.

2019 **Poster Session**

Enabling hybrid AI–radiologist endpoints in clinical trials imaging workflows. First Author: Bharath Ramakrishna, Voiant, Waltham, MA

Background: Imaging endpoints in oncology clinical trials commonly rely on a 2 + 1 radiologist reading paradigm, in which two independent readers perform primary assessments and a third adjudicates disagreements. This model underpins response evaluation frameworks such as RECIST and RANO, but is resource-intensive and contributes to trial cost, operational complexity, and inter-reader variability. Advances in transformer-based deep learning for 3D medical imaging enable hybrid AI–radiologist workflows that may preserve adjudicated oversight while reducing primary human reads. We evaluated the feasibility of replacing one primary radiologist reader with AI in a hybrid 2+1 imaging workflow, using glioma segmentation as a representative use case and with consideration for near-term integration into clinical trial imaging platforms such as Voiant Hub. **Methods:** A 3D SwinUNETR open-source deep learning model implemented using the MONAI framework pre-trained to segment glioma subregions from multimodal MRI, including enhancing tumor and non-enhancing/edema components. Model performance was assessed using Dice similarity coefficients across a multi-case dataset, complemented by qualitative review of representative cases spanning high-agreement and high-discordance scenarios. Two reading paradigms were evaluated conceptually: (1) traditional radiologist–radiologist + adjudicator, and (2) AI–radiologist + adjudicator. AI–radiologist segmentation divergence was used as a proxy for adjudication likelihood and workflow impact. **Results:** AI segmentation demonstrated substantial concordance with reference contours in well-defined enhancing tumor regions, with performance variability reflecting known biological heterogeneity. Dice scores for enhancing tumor reached values as high as 0.80, with a broad distribution across cases. Qualitative review showed that AI–radiologist disagreements were most commonly associated with small-volume lesions, infiltrative margins, or low-contrast regions: patterns similar to known human inter-reader variability. The presence of an adjudicator preserved clinical oversight for discrepant cases while eliminating the need for a second full human primary read. **Conclusions:** A hybrid AI–radiologist 2+1 imaging workflow is feasible for glioma volumetric assessment and has broader implications for RECIST- and RANO-based endpoints in oncology clinical trials. Substituting AI for one primary radiologist reader preserves adjudicated decision-making while reducing manual read burden. The availability of configurable, regulator-aligned imaging platforms such as Voiant Hub positions this hybrid approach as a near-term, easily adoptable evolution of current reading paradigms. Prospective evaluation is warranted to quantify operational impact, adjudication rates, and endpoint consistency across solid tumor and neuro-oncology trials. Research Sponsor: None.

2020 **Poster Session**

Impact of genomic subtype on intracranial outcomes in treatment-naive *EGFR*-mutant NSCLC with osimertinib (IGnITE). First Author: Emily Wo, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Osimertinib is the standard first-line therapy for *EGFR*-mutant NSCLC with brain metastasis (BM); however, alteration-specific patterns of CNS failure and mortality in treatment-naive patients remain poorly defined. **Methods:** We assembled an international muti-institutional cohort of TKI and radiation-naive *EGFR*-mutant NSCLC patients with BM treated with first-line osimertinib, with or without upfront stereotactic radiosurgery (SRS) (within 2 months of BM diagnosis). The primary endpoint was time to CNS progression. Time-to-event outcomes were analyzed using the Kaplan-Meier method. Multivariable hazard ratios (MHR) were estimated using Cox proportional hazards models. Fine and Gray hazard models were used for endpoints with competing risks. **Results:** From 2016-2024, 470 patients from 11 institutions were identified with the following alterations: exon 19 deletion (57%), L858R mutations (33%), and atypical/uncommon mutations (9.6%). Median follow-up was 25.6 months (IQR, 14.7-41.3 months). At 24 months, the cumulative incidence of CNS progression was 30% for exon 19 deletions, 47% for L858R mutations (MHR 1.68, $p<0.001$), and 76% for atypical mutations (MHR 4.33, $p<0.001$). Atypical alterations experienced markedly shorter time to local failure (MHR 4.88, $p<0·001$). Compared to exon 19 deletions, L858R (MHR 1.73, p=0.001) and atypical alterations (MHR 2.86, $p<0.001$) were associated with shorter time to distant CNS progression. L858R was also associated with higher risk of leptomeningeal disease (MHR 2.49, p=0.001). At 24 months, cumulative incidence of neurological death was 4.6% for exon 19 deletions, 7.8% for L858R, and 9.1% for atypical alterations (p=0.023). Upfront SRS was associated with improved CNS outcomes, with greater benefit for patients in L858R and atypical alterations. **Conclusions:** In the largest multi-institutional study of treatment-naive *EGFR*-mutant NSCLC with BM treated with first-line osimertinib, *EGFR* alteration subtype was an independent determinant of CNS progression, defined patterns of CNS failure, and identified patients most likely to benefit from treatment intensification with SRS. Research Sponsor: National Cancer Institute; P30-CA008748.

2021 **Poster Session**

Burden of mortality due to brain metastases secondary to lung cancer in the United States: A population-based study. First Author: Dhivya Bharathi Govindaraj, Karur Government Medical College and Hospital, Karur, India

Background: Brain metastasis is a common and severe complication in lung cancer, contributing significantly to morbidity and mortality. Despite therapeutic advances, the burden remains substantial. This study examines mortality trends, disparities, and geographic variation using CDC WONDER data in the United States. **Methods:** We accessed the CDC WONDER Multiple Cause of Death database (1999–2023) to identify individuals who died of brain metastasis (ICD-10: C79.3) among lung cancer patients (ICD-10: C34.0–C34.9). Mortality disparities were examined by year, sex, race/ethnicity, and geography. Age-adjusted mortality rate (AAMR) per 100,000 was calculated. Joinpoint regression was used to estimate the average annual percentage change (AAPC) and annual percentage change (APC), with 95% confidence intervals (CIs). **Results:** The total of 207,151 deaths related to brain metastasis among lung cancer patients. Overall, the AAMR slightly decreased from 4.95 (95% CI: 4.85-5.05) in 1999 to 3.62 (95% CI: 3.55-3.69) in 2023 (AAPC: -1.40; 95% CI: -1.82 to -0.99, $p < 0.000001$). The trend initially declined, followed by an upward trajectory between 2013 and 2017 (APC: 3.03; 95% CI: 1.00 to 5.10), after which it remained relatively stable till the end of the study period (APC: 0.33; 95% CI: -0.29 to 0.95). The decrease in mortality was slightly more pronounced in men than in women (AAPC: -2.03 vs -0.74). The highest incidence rates were noted among non-Hispanic (NH) Whites, followed by NH Blacks or African Americans and NH Asians and Pacific Islanders. Geographic disparities were apparent, with the South experiencing the greatest impact, while the Northeast was the least affected. Rural regions consistently showed higher AAMR compared to urban areas, while urban locations experienced a steeper decline between the two (AAPC: -1.95 vs -0.92). **Conclusions:** Mortality from brain metastasis in lung cancer patients has slightly declined over the past two decades, with greater reductions observed in men. However, persistent disparities across race, geography, and rural–urban populations underscore the urgent need for targeted interventions and equitable healthcare strategies to achieve favorable outcomes. Research Sponsor: None.

Deaths and AAMR per 1,000,000 for trends related to lung cancer with brain metastasis, 1999 to 2023.

Variable	Deaths	AAMR (95%CI) 1999	AAMR (95% CI) 2023
Overall	207,151	4.95 (4.85 to 5.05)	3.65 (3.55 to 3.69)
Male	108,179	6.25 (6.07 to 6.42)	3.85 (3.74 to 3.96)
Female	98,972	3.98 (3.85 to 4.10)	3.41 (3.32 to 3.50)
NH White	176,368	5.17 (5.06 to 5.29)	4.05 (3.96 to 4.14)
NH Black	22,609	6.10 (5.71 to 6.48)	3.63 (3.41 to 3.85)
NH Asians	5,762	2.29 (1.84 to 2.73)	2.68 (2.42 to 2.94)
South	88,589	5.40 (5.22 to 5.59)	3.94 (3.82 to 4.06)
Northeast	30,890	4.60 (4.38 to 4.82)	2.64 (2.49 to 2.78)
Metro	120,044	1.51 (1.44 to 1.57)	(2020) 5.33 (5.23 to 5.42)
Non metro	27,540	1.39 (1.27 to 1.52)	6.17 (5.94 to 6.41)

2022 **Poster Session**

Risk of developing brain/central nervous system (CNS) metastases across multiple *ERBB2*-altered cancer types: Genotype as shaper of phenotype. First Author: Aditya V. Shreenivas, City of Hope, Duarte, CA

Background: *ERBB2* (HER2) alterations are associated with increased risk of brain metastases in breast cancer and non-small cell lung cancer (NSCLC). However, the relationship between *ERBB2* alterations and brain metastasis across other tumor types remains unclear. We hypothesized that *ERBB2*-altered tumors demonstrate increased propensity for brain metastases across multiple cancer types. **Methods:** Using the US-based deidentified Flatiron Health-Foundation Medicine Clinico-Genomic Database (FH-FMI CGDB), we analyzed patients with advanced solid tumors who received ≥1 line of therapy. *ERBB2* alterations included pathogenic/likely pathogenic variants and amplifications. Brain/CNS metastases were identified via ICD-9/10 codes and validated against manual abstraction in NSCLC patients. Focusing on patients without brain/CNS metastases at diagnosis, we performed Cox proportional hazards analyses to evaluate time from initial diagnosis to first brain/CNS metastasis, modeling death as a competing risk. Multivariable models were adjusted for tumor types. **Results:** The analysis included 47,653 patients across 16 tumor types. Excluding breast/NSCLC, there were 29,272 patients: 2,149 *ERBB2*-altered (7.3%) and 27,123 *ERBB2*-wild type. 653 patients (30% of *ERBB2*-altered patients) had mutations and 1644 patients (77%) had amplifications (some had both). In a multivariable analysis adjusting for tumor type and excluding breast/NSCLC, *ERBB2* alterations independently predicted accelerated brain/CNS metastasis development (HR 1.55, 95% CI 1.29-1.86, $p<0.001$). In separate disease-specific Cox models, the strongest associations were observed in gastric (HR 2.33, 95% CI 1.68-3.22, $p<0.001$) and ovarian cancers (HR 2.52, 95% CI 1.45-4.38, $p<0.001$) as well as breast (HR 1.70, 95% CI 1.48-1.96, $p<0.001$) and NSCLC (HR 1.33, 95% CI 1.11-1.60, p=0.002). **Conclusions:** *ERBB2* alterations predict a significantly increased risk of accelerated development of brain/CNS metastases independent of tumor types, with the strongest effects observed in gastric and ovarian cancers in addition to breast and lung cancers. Research Sponsor: None.

2023 **Poster Session**

AI-assisted prediction of radiation failure patterns and survival after stereotactic radiosurgery for brain metastases: A multicenter study. First Author: Yuming Jiang, Wake Forest University School of Medicine, Winston-Salem, NC

Background: Brain metastases occur in approximately 20%–40% of patients with cancer and are associated with substantial morbidity and mortality. Stereotactic radiosurgery (SRS) is an effective and widely used treatment; however, a significant proportion of patients experience local, distant, or leptomeningeal failure after treatment. Early prediction of radiation failure patterns is critical for guiding individualized surveillance and treatment strategies. Current clinical tools remain inadequate for accurately predicting radiation failure in patients with brain metastases. **Methods:** In this multicenter retrospective study, we included 1,079 patients with brain metastases from three medical centers. We developed a novel deep learning model, the Global-to-Local Multiple-Instance Learning Mixture-of-Experts (GL-MIL MoE) framework. The model integrates a mask-guided multiscale encoder to process global MRI volumes and a multiple-instance learning (MIL) module to extract features from high-resolution local tumor patches. The primary endpoint was radiation failure pattern, defined as local failure, distant failure, or leptomeningeal failure. The secondary endpoint was overall survival (OS). Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), concordance index (C-index), and decision curve analysis (DCA). Model interpretability was assessed using SHAP (Shapley Additive Explanations) and Grad-CAM analyses. **Results:** The proposed AI model demonstrated strong and consistent performance, achieving AUCs ranging from 0.78 to 0.83 across validation cohorts. C-indices for OS prediction remained robust and significantly outperformed established baseline models ($p < 0.05$). Multivariable logistic and Cox regression analyses confirmed the model-derived risk score as an independent predictor of both radiation failure patterns and OS ($p < 0.05$). The model effectively stratified patients into high- and low-risk groups across all cohorts. Decision curve analysis demonstrated meaningful and consistent clinical utility. **Conclusions:** This AI-based deep learning model enables accurate prediction of radiation failure patterns and survival in patients with brain metastases treated with SRS. Prospective studies are warranted to evaluate its clinical utility in guiding personalized treatment and surveillance strategies in combination with standard clinicopathologic factors. Research Sponsor: None.

2024 **Poster Session**

Preclinical activity of homoharringtonine against melanoma leptomeningeal disease using patient-derived tumor cells. First Author: Vincent Law, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Leptomeningeal disease arising from melanoma (M-LMD) is a rare and highly aggressive form of metastasis associated with limited therapeutic options and poor clinical outcomes. Progress in treatment development has been hindered by the lack of clinically relevant models, particularly patient-derived circulating tumor cells obtained from cerebrospinal fluid (PD-CSF-CTCs). To overcome this limitation, we established protocols for CSF and tissue collection from patients with M-LMD, enabling successful *ex vivo* propagation of PD-CSF-CTCs and the generation of patient-derived xenograft models. These platforms facilitated integrated proteomic and transcriptomic analyses to identify M-LMD–specific pathways, thereby supporting the discovery of targeted therapeutic strategies. **Methods:** PD-CSF-CTCs were propagated from samples obtained from the CSF of patients with M-LMD. A library of 1,436 FDA-approved small molecules was screened using a high-throughput 384-well assay to identify agents that suppressed tumor cell proliferation. Lead compounds were subsequently assessed *in vivo* through intrathecal administration in xenograft models. **Results:** Twenty compounds (~1.4%) demonstrated complete cytotoxicity in both PD-CSF-CTCs and murine melanoma cell lines. The most potent agents included ponatinib (EC_{50}: $1.85–4.06\times10^{-6}$), sorafenib ($9.57–9.77\times10^{-6}$), ceritinib ($1.84–2.05\times10^{-6}$), and homoharringtonine (HHT; $3.63–4.11\times10^{-8}$). HHT, a plant-derived semisynthetic cephalotaxine ester, was prioritized for *in vivo* evaluation based on its robust cytotoxic activity and capacity to penetrate both the blood–brain and blood–CSF barriers. In a randomized murine M-LMD model, daily intrathecal administration of HHT (24.0 μg) was well tolerated, significantly prolonged survival ($P < 0.001$, Mantel–Cox test), and achieved complete responses in 27% of treated mice, while preserving body weight and motor function. **Conclusions:** This study introduces a robust preclinical platform for identifying effective treatments for M-LMD. Our findings highlight the promise of repurposing FDA-approved HHT as a therapeutic option. Future work will focus on refining HHT's activity against M-LMD and elucidating HHT's molecular mechanisms. Research Sponsor: None.

2025 **Poster Session**

The impact of various radiation therapy options on plasminogen activation markers in the blood of patients with metastatic brain lesions. First Author: Irina A. Goroshinskaya, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation

Background: Metastatic brain disease (MBD) is found in almost a third of patients with malignant neoplasms and is characterized by a high mortality rate. The role of the fibrinolytic system has been demonstrated in neoplasms of various locations, while tissue plasminogen activator (t-PA) is studied less frequently than urokinase activator. The aim of this study was to investigate the level and activity of t-PA in the blood of patients with MBD receiving different radiotherapeutic treatments. **Methods:** Plasma from 38 patients of both sexes, aged 59.9 ± 8.9 years, with brain metastases confirmed by magnetic resonance imaging (MRI), was analyzed using enzyme-linked immunosorbent assay (ELISA) to determine t-PA activity and levels, calculate the ratio between them, and determine parameters of type 1 plasminogen activator inhibitor (PAI-1) and the receptor for both plasminogen activators (uPAR). The results were compared with data from 18 individuals without cancer (a donor group). Three groups were formed based on the treatment regimens: Control — stereotactic radiotherapy at the site of the resected metastasis with a single fraction dose (SFD) of 6 Gy up to a total dose of 30 Gy; Main Group No. 1 — after a preoperative radiosurgery session with an SFD of 10–15 Gy, the metastatic lesion was removed 24 hours later; Main Group No. 2 — staged radiosurgery (SRS) was performed in 3 sessions with an SFD of 10 Gy at 14-day intervals (total dose of 30 Gy). **Results:** Before treatment, a 2.1-fold increase in t-PA activity was observed in the blood of patients with MBD. This, together with a 3.6-fold reduction in t-PA content, led to a 10-fold increase in their ratio ($p \leq 0.0002$). Meanwhile, urokinase activator activity did not change. In the control group, t-PA activity remained elevated three days after surgery and did not differ from donor levels one month later, while t-PA levels remained reduced. In both main groups, elevated t-PA activity relative to donors was observed throughout the entire observation period, and after one month, it was 2.6 times higher than in the control group ($p \leq 0.001$). Only patients receiving SRS were characterized by an increase in the initially reduced t-PA content, with a change toward normalization of the t-PA activity-to-content ratio. This was accompanied by an increase in the activity of inhibitor PAI-1 and receptor uPAR to donor levels. **Conclusions:** The revealed dynamics of t-PA and PAI-1 parameters in SRS compared with other types of radiation therapy may be one of the factors contributing to the greater positive clinical efficacy of this developed method of staged radiotherapy in the treatment of metastatic brain tumors. Research Sponsor: None.

2026 **Poster Session**

Cerebrospinal fluid biomarker profiling in patients with non–small cell lung cancer and leptomeningeal disease. First Author: Mark Yungjie Jeng, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cerebrospinal fluid (CSF) cytology remains the standard for diagnosing leptomeningeal disease (LMD) and monitoring treatment response, but its clinical utility is limited by low sensitivity and nonquantitative results. The role of novel CSF biomarkers, such as circulating tumor cells (CTCs), in improving disease assessment in non–small cell lung cancer (NSCLC) with LMD is not fully defined. **Methods:** We performed retrospective clinical and genomic analysis of patients with NSCLC and LMD who underwent CSF CTC testing using the CellSearch platform at Memorial Sloan Kettering between 1/1/2015 and 11/5/2025. Time-to-event analyses were calculated from initial positive CSF CTC measurement ($\geq$3 cells/3mL) or from completion of proton craniospinal irradiation (pCSI). Optimal CTC cutoffs were determined using recursive partitioning analysis (RPA). CSF cytologic clearance was defined as an initial positive cytology followed by two consecutive negative results at least 4 weeks apart. Next-generation sequencing was performed using MSK-IMPACT. **Results:** Among 148 patients with NSCLC and LMD, 72% (n=105) were female, 53% (n=78) were never-smokers, and 92% (n=136) harbored an oncogenic driver alteration, most commonly epithelial growth factor receptor (*EGFR)* mutations (60%, n=89). Fourteen percent (n=20) were diagnosed with LMD at time of metastatic disease, whereas 54% (n=80) had received 2 or more prior lines of therapy. Sixty-two percent (n=92) received radiation therapy for LMD, including 43% (n=64) undergoing pCSI and 18% (n=26) undergoing photon radiation (involved field radiation therapy [IFRT] to brain/spine, n=10; whole brain radiation therapy [WBRT] alone, n=10; WBRT + IFRT to spine, n=4; photon CSI, n=2). With a median follow-up of 21.6 months (95% CI 16.2–37.9), patients with a lower baseline CSF CTC count ($\leq$90 CTCs/3mL, n=66; cutoff identified through RPA) had longer median overall survival (mOS; 10.2 vs 6.6 months; HR 0.53, 95% CI 0.35–0.79; p=0.002) compared with those with higher counts ($>$90 CTCs/3mL, n=82). Among patients who underwent pCSI with serial CSF testing (n=34), a $\geq$30% reduction in CTCs was associated with a longer mOS (13.1 vs 6.2 months; HR 0.15, 95% CI 0.05–0.47; p=0.0001) compared with those with $<$30% reduction; only 12% (n=4) achieved CSF cytologic clearance. In *EGFR*-mutant NSCLC, genomic analysis of CSF samples with higher baseline CTC count ($>$90 CTCs/3mL, n=24) demonstrated a higher frequency of *TP53* (p=1.559e-3) and *MTAP* (p=8.31e-3) alterations, and a lower frequency of *MDM2* (p=0.05) alterations, compared to patients with lower baseline CTC counts ($\leq$90 CTCs/3ml, n=23). **Conclusions:** Lower baseline CSF CTC counts and reductions following pCSI are associated with improved survival in patients with NSCLC and LMD. CSF CTC assessment provides a quantitative measure of LMD burden and may complement conventional CSF cytology. Research Sponsor: None.

2027 **Poster Session**

Preclinical efficacy and brain uptake of an insulin-mediated nanoparticle co-delivering trastuzumab and pertuzumab (AxS007) in HER2+ breast cancer brain metastasis models. First Author: Ayelet Zafran, Nanocarry Therapeutics Ltd., Ness Ziona, Israel

Background: Anti-HER2 antibodies are standard therapies for metastatic HER2+ breast cancer but demonstrate limited intracranial activity due to restricted penetration across the blood–brain barrier (BBB). AxS007 is an insulin-mediated nanoparticle conjugated to trastuzumab and pertuzumab designed to enhance BBB transport and increase brain exposure. **Methods:** Brain uptake and distribution were assessed in C57BL mice using biodistribution analysis (5 min–90 days, n=25) and two-photon microscopy, comparing AxS007, a non-insulin-conjugated nanoparticle control, and free trastuzumab. Brain uptake was also evaluated in non-human primates (NHPs). Based on confirmed BBB penetration and brain exposure, AxS007 antitumor activity was evaluated in vitro in HER2+ cell lines (BT474, SKBR3, N87) and in vivo in BT474 subcutaneous (SC; n=20) and intracranial xenografts. Tumor growth inhibition (TGI) was assessed by MRI, and survival was compared between vehicle, AxS007 (IV, 10 mg/kg), and free trastuzumab + pertuzumab (IV, 10 mg/kg each). Safety was further investigated through single ascending dose (SAD) and multiple ascending dose (MAD) toxicological studies. **Results:** In mice, AxS007 demonstrated measurable brain uptake within 30 min and widespread parenchymal distribution at 24 h, with markedly higher brain exposure than free trastuzumab; in contrast, the non-insulin control and free antibodies showed minimal BBB crossing. In NHPs, AxS007 increased brain antibody exposure ~50-fold versus free antibodies at 48 h. In vitro, AxS007 showed antitumor activity comparable to or greater than free antibodies (SKBR3: 90% vs 50%; BT474: 50% vs 64%). In vivo, AxS007 achieved near-complete tumor elimination in SC tumors and demonstrated 82% TGI versus vehicle ($p<0.01$) and 60% TGI versus free trastuzumab +pertuzumab ($p<0.05$) in intracranial tumors, as assessed at day 60 post-inoculation. In an overall survival study, AxS007 extended survival approximately 3-fold compared with free trastusumab + pertuzumab. AxS007 exhibited a good safety profile with no drug related side effects. **Conclusions:** AxS007 showed enhanced BBB penetration and increased brain antibody exposure, with improved preclinical efficacy versus free antibodies in HER2+ breast cancer brain metastasis models. These findings support further translational advancement of AxS007 toward first-in-human clinical testing. Research Sponsor: Nanocarry Therapeutics Ltd.

2028 **Poster Session**

Real-world outcomes of systemic therapy sequencing after earlier-generation EGFR TKI failure in NSCLC with brain metastases. First Author: Atulya Aman Khosla, Department of Internal Medicine, William Beaumont University Hospital, Royal Oak, MI

Background: Patients with EGFR-mutated non–small cell lung cancer (NSCLC) frequently develop BM, and CNS progression is a common mode of failure on earlier-generation EGFR tyrosine kinase inhibitors (TKIs). After TKI failure in the setting of BM, optimal next-line systemic therapy remains uncertain, particularly regarding the comparative effectiveness of targeted escalation, immunotherapy (IO)-based regimens, and chemotherapy. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. We identified EGFR-mutated NSCLC patients treated with first- or second-generation EGFR TKIs who subsequently developed metachronous BM and initiated next-line systemic therapy between 2015 and 2025. Patients with leptomeningeal disease prior to earlier-generation TKI exposure were excluded. Treatment strategies were categorized as targeted escalation with osimertinib, IO-based therapy (immune checkpoint inhibitor with or without chemotherapy), or chemotherapy alone. The index date was defined as initiation of next-line systemic therapy. Propensity score matching was performed for pairwise comparisons. The primary endpoint was overall survival (OS) at 180 days. Restricted mean survival time (RMST) through 181 days was evaluated as a sensitivity analysis. Baseline covariate balance after matching was assessed using standardized mean differences, with values <0.10 indicating adequate balance. **Results:** After propensity score matching with adequate baseline balance, osimertinib was associated with significantly lower 180-day mortality compared with chemotherapy (24.5% vs 33.2%; hazard ratio [HR] 0.69, 95% CI 0.47–1.00). Comparisons between osimertinib and IO-based therapy showed numerically lower 180-day mortality with osimertinib (26.0% vs 32.6%; HR 0.79, 95% CI 0.54–1.15), but this difference did not reach statistical significance. Similarly, IO-based therapy was not associated with a statistically significant survival advantage compared with chemotherapy alone (31.7% vs 37.5%; HR 0.78, 95% CI 0.58–1.06). RMST analyses for death over 181 days were directionally consistent with hazard ratio–based results, with modest, non-significant differences in mean survival time. **Conclusions:** In EGFR-mutated NSCLC patients with metachronous brain metastases after earlier-generation TKI failure, targeted escalation with osimertinib was associated with significantly lower 180-day mortality compared with chemotherapy. IO-based approaches demonstrated intermediate, directionally favorable but non-significant outcomes relative to both osimertinib and chemotherapy. These real-world findings support guideline recommendations prioritizing next-generation TKIs and help inform systemic treatment sequencing in a CNS-enriched population where prospective data remain limited. Research Sponsor: None.

2029 **Poster Session**

Low-density lipoprotein receptor–related protein 1 overexpression as an identifier of brain metastasis and survival for patients with lung cancer. First Author: Wendi Mo, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, China

Background: Brain metastasis (BM) is a major cause of mortality in lung cancer. Low-density lipoprotein receptor–related protein 1 (LRP1) has been implicated in tumor invasion and microenvironment regulation; however, its clinical relevance in lung cancer brain metastasis remains unclear. **Methods:** This retrospective, single-center study included 103 lung cancer patients (including NSCLC and SCLC) diagnosed between January 2013 and February 2025. LRP1 protein expression was evaluated by immunohistochemistry in primary lung tumors and lesions of lung cancer with brain metastasis (unpaired samples). Mean optical density was quantified, and the optimal cutoff for high versus low expression was determined using receiver operating characteristic analysis. Overall survival (OS) and distant metastasis–free survival (DMFS) were assessed using Kaplan–Meier analysis and Cox proportional hazards models, adjusting for pathological type, age, sex, T stage, and N stage. Gene set variation analysis (GSVA), immune cell infiltration analysis (CIBERSORT), and immunotherapy response prediction using TIDE were performed to explore biological characteristics associated with LRP1 expression. **Results:** LRP1 expression was significantly higher in lung cancer tissues from patients with BM compared with those without BM ($P < 0.0001$). Among patients with BM, high LRP1 expression was associated with poorer OS (P = 0.0352) and shorter DMFS (P = 0.0183). In multivariable analysis, high LRP1 expression remained independently associated with inferior OS (HR 3.064, 95% CI 1.039–9.034; P = 0.042). GSVA suggested that LRP1-high tumors may be characterized by enrichment of TGF-β, NOTCH, and HEDGEHOG signaling pathways. Immune deconvolution analysis revealed higher infiltration of resting memory $CD4^+$ T cells and M0 macrophages in the LRP1-high group. LRP1-low expression was associated with a more favorable predicted response to immunotherapy, as indicated by lower TIDE scores. **Conclusions:** LRP1 overexpression is associated with brain metastasis, unfavorable survival, and distinct immune features in lung cancer, suggesting its potential value as a prognostic biomarker. Research Sponsor: None.

2030 **Poster Session**

Neoantigen prediction and reactivity of cerebrospinal fluid–human-derived tumor reactive T cells (CSF-TRT cells) in leptomeningeal disease (LMD) from solid tumors. First Author: Yolanda Pina, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Leptomeningeal disease (LMD) is a devastating complication of metastases and its incidence is increasing. Adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TILs) showed complete responses in patients with metastatic melanoma and other solid tumors. To obtain CSF-TRT cells as a source of T cells for ACT, we aim 1) to identify the expansion method that allows higher expansion of tumor reactive TIL; 2) to enrich tumor neoantigen reactive TILs and determine their in-vivo and ex-vivo functional capabilities. **Methods:** Cells were isolated from 64 CSF collections from melanoma (M-LMD), 9 CSF from breast cancer (B-LMD), and 9 CSF from lung adenocarcinoma (L-LMD) from patients with LMD. Cells were plated following established TIL culture protocols (high-dose IL-2): 1) OKT3, 2) anti-4-1BB-agonist, 3) IL-7+IL-15+IL-21, 4) anti-CD3/CD28-T-activator, 5) anti-CD3/CD28/CD137-T-activator, 6) anti-CD3/CD28-T-expander. After 4-6 weeks, reactivity was assessed with HLA-matched or autologous tumor cells. Additionally, Whole Exome Sequencing (WES) and RNA sequencing were performed in T cells expanded from CSF and pair-matched extracranial tumors from 12 patients with M-LMD for epitope prediction to identify neoantigens that may be targets of immunoediting using computational algorithms. **Results:** CSF yielded an average of 1.204e5 viable cells for expansion. After culture in IL-2, 53.4% of samples showed increased cell yield with average 165.29-fold expansion. PreREP resulted in 37.6% CD8+ T cells. REP had a 96.8% success rate (mean 589.87-fold expansion). Post-REP flow cytometry revealed expansion of CD4+ T cells. Additional cultures produced similar yields with reduced T cell input requirement and demonstrated the potential to enrich for CD8+ T cells. Out of five samples tested for reactivity to HLA-matched melanoma cell lines, three produced varying levels of IFN-γ. T cells expanded from CSF samples from L-LMD and B-LMD had less successful results. L-LMD had a success expansion rate of 11.1% with IL-2 only, 83.3% with T-Activator, 50% with CD127 T Activator, and 50% with T-Expander. B-LMD had a success rate of 22.2% with IL-2 only, 0% with OKT3, 83.3% with T-Activator, 50% with CD137 T-Activator, and 85.7% with T-Expander. One of the CSF samples from L-LMD tested showed reactivity to autologous HLA-matched tumor cells, whereas none of the CSF T cells from B-LMD showed a successful reactivity. Preliminary studies demonstrated CSF TIL reactivity against tumor reactive neoantigens. Ongoing studies will confirm our results. **Conclusions:** Results demonstrate successful expansion of T cells *ex vivo* from CSF in M-LMD, raising the potential to use CSF-derived T-cells as therapeutic strategy for LMD. There was a variable success rate with expansion of T cells from CSF from B-LMD and L-LMD and supplementary studies are needed. Research Sponsor: None.

2031 **Poster Session**

Intracranial pharmacokinetics and resistance mechanisms of tucatinib in patients with HER2+/mutant solid tumors and brain metastasis: Results from the WinHER2 study (NCT05892068). First Author: Emanuela Ferraro, European Institute of Oncology, Milan, Italy

Background: Tucatinib, a potent HER2-selective tyrosine kinase inhibitor approved for the treatment of HER2-positive (+) metastatic breast cancer (MBC) and colorectal cancer (CRC), has demonstrated activity in stable and active brain metastasis (BrM). However, intracranial pharmacokinetics and specific mechanisms of resistance driving BrM progression remain unknown. **Methods:** This window-of-opportunity, prospective, non-randomized study evaluated tissue and serum levels of tucatinib ([Tt], [Ts]) in patients undergoing BrM resection for HER2+/mutant (mut) MBC, NSCLC, CRC or gastroesophageal cancer. HER2+ MBC patients were enrolled in 2 parallel cohorts: those with progressing BrM while on tucatinib (A) and tucatinib-naïve patients (B); cohort C was comprised of patients with GI malignancy, NSCLC and mutHER2 MBC. All patients received tucatinib 300 mg BID for 4 days preoperatively. [Tt/s] were measured by mass spectrometry in resected BrM and serum at screening and 3 intraoperative timepoints; CSF [T] was collected when available by optional lumbar puncture. BrM tissue was used for correlative studies including WGS, scRNA-seq, and electron microscopy. The primary endpoint compared BrM-to-serum tucatinib ratios between cohorts A and B with lower ratios hypothesized in cohort A. [T] was reported as median and interquartile range (IQR). **Results:** 9 female patients enrolled between 7/2023 and 12/2025: 3 in cohort A, 5 in cohort B, and 1 HER2+ CRC patient in cohort C. Median age was 48.5 years (43-65). One patient from cohort B was unevaluable due to lack of viable recurrent disease on pathologic examination. Total tucatinib levels in resected BrMs ranged from 2.22 to 192.87 ng/mg, (median=30.82; IQR=16.52-111.84) in cohort A and from 1.5 to 4.21 ng/mg (median=3.04; IQR=1.93-4.05) in cohort B. The median tucatinib serum concentration was 1158.3 ng/mL (range=229.2-3440; IQR=693.78-2299.17) and 365.52 ng/mL (range=167.23-731.03; IQR=176.47-596.37), in cohorts A and B, respectively. The BrM/serum ratio did not differ between cohorts A and B (median=9.7; range=9.0-166.5; IQR=9.43-102.77] vs 7.36 [range=3.77-22.28; IQR=5.26-12.30]). The single cohort C patient had tucatinib BrM level of 1.66 ng/mg and BrM/serum ratio of 7.41. CSF [T] was available in two cohort A patients: it was undetectable in one and 35.71 ng/mL in the other (BrM/CSF ratio: 5401). **Conclusions:** Patients with progressing BrM while receiving tucatinib had BrM/serum tucatinib ratios similar to those of patients receiving tucatinib for the first time in the trial. These data indicate that intratumoral drug concentration alone is unlikely to account for intracranial acquired resistance. Correlative analyses investigating potential genomic and microenvironmental mechanisms of resistance are ongoing, and results will be presented at the meeting. Clinical trial information: NCT05892068. Research Sponsor: Pfizer.

2032 **Poster Session**

Genomic correlates of leptomeningeal disease after brain metastasis resection. First Author: Roshal R. Patel, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Leptomeningeal disease (LMD) remains a frequent and devastating pattern of failure following surgical resection of brain metastases (BM), occurring in up to one-third of patients despite optimal local therapy. Although mechanical disruption of BM tissues may increase the risk of subsequent LMD, the underlying biologic determinants of postoperative LMD remain undefined. This study aims to identify genomic alterations in resected BM and their association with LMD development using the largest craniotomy cohort to date with paired next-generation sequencing and longitudinal CNS outcomes data. **Methods:** We retrospectively identified patients who underwent surgical resection and MSK-IMPACT next-generation sequencing of one or more BM. LMD was diagnosed using brain and spine MRI and CSF cytology and classified as either classical LMD (cLMD; diffuse coating of meningeal spaces and/or positive CSF cytology), nodular LMD (nLMD; discrete nodular deposits with negative CSF cytology), or both. Fine–Gray subdistribution hazard (sHR) estimated the cumulative incidence of LMD, treating death as a competing risk. **Results:** Among 1,006 patients, NSCLC (360, 36%), breast (181, 18%), and melanoma (128, 13%) predominated; most patients had single (530, 53%), supratentorial (796, 79%), and large (>2cm, 886, 88%) BM, and underwent postoperative cavity radiotherapy (890, 88%). Median follow-up and OS were 24.8 and 21.5 months, respectively. The cumulative incidence of LMD was 31% (cLMD 18%, nLMD 19%) at 2 years, with the highest rates seen in breast cancer patients (45% LMD; cLMD 28%, nLMD 23%). Median time to cLMD and nLMD were 7.7 and 6.4 months, respectively. Median OS after cLMD and nLMD diagnosis were 5.7 and 12 months, respectively. The most frequently altered genes in resected BM were TP53 (62%), CDKN2A (25%), TERT (23%), KRAS (20%), ERBB2 (12%), PIK3CA (12%), PTEN (12%), and RB1 (11%). In a pan-cancer analysis, alterations in CDH1 (sHR 3.0, q=0.03), EGFR (HR 2.5, q<0.001), GATA3 (sHR 2.2, q=0.03), or RB1 (sHR 1.7; q=0.04) were associated with an increased risk of cLMD; alterations in PTEN were associated with an increased risk of nLMD (sHR 1.8, q=0.02). Within breast and lung cohorts, alterations in RB1 or EGFR, respectively, were associated with an increased risk of cLMD. BM from patients who developed LMD exhibited greater genomic instability, with a higher fraction of the genome altered compared to those who did not (0.47 vs 0.40, p<0.001). **Conclusions:** LMD is a common and deadly form of progression following BM resection. Distinct genomic features, present in the resected BM specimen, may identify patients at increased risk of LMD. These findings support the development of a clinicogenomic model to select BM patients for intensified surveillance and postoperative care. Research Sponsor: U.S. National Institutes of Health; P30 CA008748.

2033 **Poster Session**

Distinct genomic and microenvironmental profiles of brain metastases in renal cell carcinoma: Insights into hypoxia-driven adaptation and therapeutic vulnerabilities. First Author: Jorge Avila, Montefiore Medical Center, Bronx, NY

Background: Brain metastases (BM) in renal cell carcinoma (RCC) are associated with poor prognosis and may exhibit unique genomic alterations influenced by the tumor microenvironment (TME), differing from primary tumors or extracranial metastases (ECM). This study aimed to characterize these differences to identify potential therapeutic targets. **Methods:** 3,913 RCC samples underwent NGS of DNA and RNA at Caris Life Sciences (Phoenix, AZ) and were linked to corresponding insurance claims data. Real-world overall survival (rwOS) was calculated from the date of sample collection to last contact using Cox PH model and log-rank testing. Genomic alterations were compared at an adjusted significance level of 0.05 using Fisher's exact test. TME differences between the primary RCC, BM and ECM were assessed by therapeutic target gene expression using Mann-Whitney U test, gene set enrichment analysis (GSEA) by normalized enrichment scores (NES) and false discovery rates (FDR), and a gene expression-based score reflecting HIF1-associated metabolic and stress-response pathways. **Results:** The cohort consisted of 1,775 primary, 138 BM, and 2,000 ECM. Median age was different in BM vs ECM vs primary (64 vs 66 vs 63 y, p<0.0001). Approximately 75% of BM patients had not received any systemic or radiation therapy prior to tissue collection. The rwOS was 49.4 months for primary, and 30.3 months for both BM and ECM (BM vs. ECM: HR=0.96, 95%CI: 0.76-1.22, p=0.796). Genomic profiling revealed, in BM compared with primary tumors, *CDKN2B* deletions (41% vs. 18.1%, p<0.0001), as well as *PTEN* (22.5% vs 6.7%, p<0.0001), and *TP53* mutations (22.7% vs 11%, p=0.0088). Gene expression analysis demonstrated no significant differences in the expression of RCC novel therapeutic targets, including *CD70*, *ENPP3*, *CA9*, *HLA-G*, *CDH6* and *FOLH1*, between BM and primary (p>0.05). Compared to primary, GSEA revealed BM were enriched in pathways including epithelial-mesenchymal transition (NES=3.41, FDR<0.001), mTORC1 signaling (NES=3.05, FDR=0.002), hypoxia (NES=2.68, FDR=0.009), and others. Compared to ECM, BM showed hypoxia enrichment (NES=2.90, FDR=0.023), while ECM was enriched in mitotic spindle (NES=-3.84, FDR<0.0001) and G2M checkpoints (NES=-3.32, FDR<0.0001). The HIF1-associated hypoxia score was significantly higher in BM vs primary (p<0.01). **Conclusions:** Conserved expression of multiple actionable RCC therapeutic targets across primary and BM sites supports the biological feasibility of emerging targeted and immune-based therapies in CNS disease. The findings provide a biologic framework for understanding RCC BM and highlight hypoxia-associated pathways. Key limitations include the use of tissue-based rather than clinically adjudicated BM definitions, and the lack of cancer stage information. Research Sponsor: None.

2035 **Poster Session**

Central nervous system metastases in hereditary breast cancer according to germline pathogenic variants: A real-world cohort study. First Author: Eduarda Mirela Da Silva Montiel, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: Hereditary breast cancer (HBC) accounts for approximately 5–10% of cases and involves pathogenic germline variants (PGVs) beyond *BRCA1/2*. While metastatic patterns differ by tumor subtype, data on central nervous system (CNS) metastases according to germline genetics remain scarce. We evaluated the incidence, clinical characteristics and survival outcomes of CNS metastases in metastatic according to PGV subgroup. **Methods:** A cohort retrospective study included patients aged ≥18 years with invasive or microinvasive breast cancer and confirmed PGVs treated between 2019 and 2025 at A.C. Camargo Cancer Center. Clinical, histopathologic, and molecular data were analyzed in R. Associations were assessed using chi-square or Kruskal–Wallis tests. Survival outcomes were estimated by Kaplan–Meier. CNS-related progression-free survival (CNS-PFS) was defined from treatment initiation after CNS metastasis to intracranial progression or death. Overall survival after CNS metastasis (OS post-CNS) was defined from CNS metastasis to death. Median survival times with 95% confidence intervals (CIs) were reported. **Results:** Among 1,353 individuals evaluated, 463 patients with pathogenic germline variants (PGVs) were included. Median age at diagnosis was 43.7 years, and 99.6% were women. The most frequent PGVs were *BRCA1* (32.0%), *BRCA2* (22.2%), and *TP53* (12.1%). *BRCA1* carriers were diagnosed earlier than other genotypes (p = 0.0005). CNS metastases occurred in 21 patients (4.5%), mainly among *BRCA*-associated PGVs and *TP53*, with additional cases in *PALB2*, *ATM*, and *RAD*-related variants; none occurred in *CHEK2*, *FANCA*, or Lynch-associated variants. CNS involvement was mainly parenchymal-only (71.4%), with meningeal-only (19.0%) or combined disease (9.5%). Lesions were supratentorial-only in 47.1% and both supra- and infratentorial in 47.1%. Diagnosis was symptom-driven in 70.0%. Single CNS metastasis occurred in 38.9%, and local therapy alone was most commonly used (66.7%). No statistically significant differences in CNS metastatic patterns were observed across PGV subgroups (p > 0.05). Median OS after CNS diagnosis was 14 months (95% CI, 5–NR), and median CNS-PFS was 17 months (95% CI, 7–NR). **Conclusions:** In metastatic HBC, CNS metastases are uncommon but preferentially occur among patients harboring *BRCA*-associated and *TP53* pathogenic germline variants. Germline genetics may contribute to distinct metastatic phenotypes and support risk-adapted CNS surveillance strategies and therapeutic strategies in metastatic HBC. Research Sponsor: None.

2036 **Poster Session**

Continued CNS-penetrant TKI therapy with or without local CNS therapy after brain metastasis diagnosis in NSCLC. First Author: Atulya Aman Khosla, Department of Internal Medicine, William Beaumont University Hospital, Royal Oak, MI

Background: Patients with oncogene-driven metastatic non–small cell lung cancer (NSCLC) treated with CNS-penetrant tyrosine kinase inhibitors (TKIs) frequently develop brain metastases (BM) while continuing targeted therapy, and outcomes of adding local CNS-directed therapy in this setting are not well defined. We evaluated outcomes associated with local CNS therapy after post-TKI BM diagnosis. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. Adults with NSCLC treated with osimertinib or lorlatinib who subsequently had a coded diagnosis of BM (ICD-10 C79.31) at least 1 month after TKI initiation and evidence of continued TKI use were included. Patients were stratified by receipt of CNS-directed local therapy (SRS/SBRT or neurosurgery) within 3 months of the index BM diagnosis versus no local therapy. The primary outcome was all-cause mortality within 180 days of the index event. Secondary outcomes included hospitalization and systemic corticosteroid use. Cohorts were balanced using 1:1 propensity score matching on demographics, comorbidities, extracranial disease, laboratory values, and TKI exposure. Survival analyses were performed, and proportional hazards assumptions were validated using Schoenfeld residuals (p>0.05). **Results:** Among 1,157 eligible patients, 1,053 matched pairs were generated. Within 180 days of the index brain metastasis diagnosis, mortality was lower among patients who received local CNS therapy compared with those who did not (10.9% vs 18.1%), corresponding to a hazard ratio (HR) for death of 0.54 (95% CI 0.43–0.68; p<0.001). Survival probabilities at 180 days were 88.7% in the local therapy cohort and 80.2% in the no local therapy cohort. Hospitalization within 180 days occurred in 20.3% of patients receiving local therapy and 22.4% of those without local therapy (p=0.24), with a nonsignificant trend toward delayed hospitalization (HR 0.84, 95% CI 0.69–1.01). Systemic corticosteroid use was common and similar between groups (61.3% vs 59.4%; p=0.40), with no significant difference in time to steroid initiation. In an osimertinib-only sensitivity analysis, 180-day mortality was 10.5% among patients receiving local CNS therapy compared with 19.4% among those without local therapy (HR 0.48, 95% CI 0.37–0.61; p<0.001). **Conclusions:** In this multi-institutional real-world cohort of patients with NSCLC receiving osimertinib or lorlatinib who developed BM, receipt of local CNS-directed therapy within 3 months was associated with lower 6-month mortality compared with continuation of targeted therapy alone, with consistent findings in an osimertinib-only sensitivity analysis. These results suggest a potential survival benefit of local CNS intervention in selected patients, while acknowledging residual confounding related to intracranial disease burden and clinical indication. Research Sponsor: None.

2037 **Poster Session**

Intrathecal (IT) therapy–associated pseudoprogression (PsP) in leptomeningeal metastases (LM) from solid tumors. First Author: Zhenyu Pan, Department of Radiation Oncology, Beijing Chest Hospital, Capital Medical University, Beijing, China

Background: Intracranial PsP following systemic immunotherapy has been recognized. IT therapy is a cornerstone of LM management, and prior studies support the safety and feasibility of IT immunotherapy. The occurrence of PsP specifically after IT immunotherapy for LM remains unreported. This study aims to characterize the clinical and proteomic profile of IT therapy–associated PsP (IT-PsP). **Methods:** This prospective case series consecutively enrolled LM patients receiving IT therapy between February 2024 and January 2026. Patients were treated with IT pemetrexed (PM) alone or combined with immunotherapy (PD-1 inhibitors, PD-1/CTLA-4, or PD-1/VEGF antibodies). Treatment response was assessed per RANO-LM criteria. Based on the iRANO criteria, IT-PsP was considered as radiographic progression without significant worsening of LM-related symptoms or neurological deficits. Furthermore, patients were defined as IT-PsP only if they also met at least one of the following criteria without salvage LM-directed therapy: sustained conversion of cerebrospinal fluid (CSF) cytology to negative, subsequent neuroimaging improvement, or absence of progressive neurological symptoms/signs with stable disease for $\geq$3 months. CSF proteomics was analyzed via Olink Target 96 Immuno-Oncology panel. **Results:** Of 144 enrolled patients, 75 received IT PM and 69 received IT immunotherapy plus PM. IT–PsP was identified in 12 patients (8.3%). Median age was 53.5 years (range 30–66) and 10 were female. Primary tumors were lung adenocarcinoma (n=11) and breast cancer (n=1). None received concurrent systemic immunotherapy. The median time to PsP occurrence was 5.2 months (range 1.5–12) after the first IT treatment. PsP incidence was significantly higher in the combination group (15.9%, 11/69) than with IT PM alone (1.3%, 1/75) (P=0.002). 6 (50%) achieved sustained conversion to negative CSF cytology. Radiographically, lesions improved in 7 patients (58.3%) and remained stable in 2 (16.7%). All PsP patients were followed up for a median of 7.1 months (range 1–13.6) with no neurological progression. Median overall survival from enrollment and from PsP onset were not reached. CSF proteomic profiling revealed that IT-PsP samples, compared to both progressive LM and pre-treatment samples, showed significant downregulation of tumor-associated proteins (CCL20, LAP TGF-beta-1, IL8, CCL4). Furthermore, compared to post-treatment response samples, IT-PsP was associated with significant upregulation of inflammatory markers, including Gal-9, IL15, and ADA. **Conclusions:** This study characterizes the clinical features and distinct CSF proteomic signature of IT-PsP in LM. The significantly higher PsP incidence with IT immunotherapy underscores that, in the immunotherapy era, relying exclusively on neuroimaging to define LM progression necessitates careful re-evaluation. Research Sponsor: Huizhou Science and Technology Innovation Team Project; 2023EQ050012; Huizhou Outstanding Young Scientific and Technological Talents Program; 2025EQ050018.

2038 **Poster Session**

Outcomes of CD-19–directed CAR-T therapy in patients with primary and secondary central nervous system lymphoma: A multi-center observational study. First Author: Shilajeet Ray, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Background: CD-19 directed chimeric antigen receptor T-Cell (CAR-T) therapies have been approved for the treatment of diffuse large B-Cell lymphoma; however, patients with primary central nervous system (CNS) lymphoma were excluded from pivotal registration trials. Although early-phase trials and meta-analysis suggest promising efficacy in CNS lymphoma, existing data remain limited by small sample sizes. We conducted a large, multicenter observational study evaluating outcomes of CD19-directed CAR-T therapy in patients with primary or secondary CNS lymphoma. **Methods:** This study utilized the TriNetX database, encompassing over 110 healthcare organizations, to evaluate outcomes of adults with a diagnosis of primary or secondary CNS lymphoma prior to receiving CAR T therapy between 2019 and 2025. Outcomes were assessed from the time of CAR-T infusion. The outcomes analyzed were 1-year overall survival, as well as development of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), treatment with tocilizumab, and risk of infection within 100 days post-CAR-T infusion. Kaplan-Meier estimated event rates were used to assess the primary outcomes. **Results:** We identified 155 patients with a diagnosis of primary or secondary lymphoma who received CD-19 directed CAR-T therapy. The median age at CAR-T infusion was 63 years. The cohort was predominately male (57%) and white (87%). A majority of the cohort, 80%, received Fludarabine/ Cyclophosphamide for lymphodepletion chemotherapy; 16% received Bendamustine. Most patients received axicabtagene ciloleucel (n=78), followed by lisocabtagene maraleucel (n=56), and tisagenlecleucel (n=21). The Kaplan–Meier estimated overall survival at one and three years was 63.9% and 46.9%, respectively. The estimated cumulative risk for CRS and ICANs post-CAR-T infusion was 58.7% and 26.5% respectively – 49.0% were treated with tocilizumab. The risk of infection by day 100 post-CAR-T infusion was 43.2%. **Conclusions:** CNS lymphomas have been associated with limited overall survival and represent an unmet need, necessitating the emergence of new therapeutic strategies. Our findings support the efficacy and safety of CAR-T in this population. To our knowledge, this is the largest single observational study of patients with CNS lymphoma treated with CAR-T. Research Sponsor: None.

Outcome	Time Point	Rate (%) (n = 155)
Overall Survival	1 years	63.9%
	3 years	46.9%
CRS	60 days	58.7%
ICANS	60 days	26.5%
Tocilizumab Use	60 days	49.0%
Any Infection	100 days	43.2%

2039 **Poster Session**

The association of economic measures and patient outcomes with geographical disparities in access to a UCNS board-certified neuro-oncologist in the United States. First Author: Maksym Horiachok, Bukovinian State Medical University, Khmelnytskyi, Ukraine

Background: Neuro-oncology is increasingly centralized in academic tertiary centers, potentially creating geographic and economic inequality. This study aims to quantify the national distribution of neuro-oncologists in the United States and evaluate the association between regional economic capacity, metropolitan urbanicity, and population-level clinical outcomes. **Methods:** We conducted a nationwide cross-sectional ecological analysis using 2025 United Council for Neurologic Subspecialties (UCNS) data, US Bureau of Economic Analysis state-level GDP, and US Census Bureau demographics. Spatial accessibility was modelled for US counties using geodesic distance from population centroids. Outcome measures included CNS tumor mortality and Disability-Adjusted Life Years (DALYs). **Results:** We identified 323 UCNS board-certified neuro-oncologists distributed across 70 Metropolitan Statistical Areas (MSAs). Workforce distribution was strongly associated with state-level economic magnitude (r=0.930 [95% CI: 0.878–0.960], $p<0.0001$), with gross domestic product (GDP) explaining 86.4% of variance (R2=0.864). Critically, economic intensity independent of state population was a significant driver, with GDP per capita correlating with specialist density (r=0.344, p=0.014). Specialists were located exclusively within MSAs ($?^2$ = 52.28, $p < 0.0001$), however 81.9% of MSAs lacked local subspecialty presence. Spatial analysis revealed 45.4% of the US population has local access (<20 miles), while 16.5% (55.2 million Americans) live in "Care Deserts" greater than 100 miles from the nearest neuro-oncologist. Increased specialist density predicted lower mortality rates for pediatric (ρ = −0.34 [95% CI: −0.56 to −0.07], p = 0.015) and adult (ρ = −0.352 [95% CI: −0.57 to −0.08], p = 0.011) groups. Similar inverse associations were observed for DALYs in both pediatric (ρ=−0.339 [95% CI: −0.57 to −0.07], p = 0.015) and adult (ρ=−0.347 [95% CI: −0.57 to −0.08], p = 0.013) populations. **Conclusions:** Distribution of UCNS board-certified neuro-oncologists in the United States is primarily governed by state-level economic prosperity and is critically concentrated in select metropolitan centers. This geographical concentration leaves over 80% of US metro areas without access to a UCNS board-certified neuro-oncologist. Furthermore, higher density of UCNS-certified specialists is significantly associated with reduced mortality and disease burden, suggesting that expanding this workforce may be a lever for improving population-level neuro-oncologic outcomes. Research Sponsor: None.

2040 **Poster Session**

Use of knowledge-distilled EfficientNet to enable rapid, scalable glioma diagnosis. First Author: Gowrishankar Palaniswamy, AIM DOCTOR, Thiruverkadu, India

Background: Accurate preoperative classification of gliomas on MRI according to WHO 2021 integrated diagnosis is essential for surgical planning and treatment selection, yet conventional interpretation remains vulnerable to inter-observer variability. Deep learning shows promise for brain tumor classification but computational demands restrict deployment in resource-limited settings. Knowledge distillation, transferring discriminative knowledge from computationally intensive "mentor" networks to efficient "mentee" models, enables scalable AI systems maintaining diagnostic accuracy while enabling global translation. **Methods:** We analyzed 2,840 brain MRI studies sourced from six continents comprising gliomas (n=1,400; 700 WHO grade 2–3, 700 grade 4), meningiomas (n=900), and pituitary adenomas (n=540). Ground truth followed WHO 2021 integrated diagnosis with expert neuroradiologist consensus. Data were partitioned at the patient level with site-held-out external testing. A high-capacity EfficientNetB7 mentor model was developed using multi-sequence MRI inputs (T1, T2, FLAIR, post-contrast T1) and distilled into lightweight EfficientNetB0. Knowledge distillation preserved discriminative performance while enabling CPU deployment without GPU acceleration. Training: input 224×224 pixels, Adam optimizer (lr=0.001), Kullback-Leibler divergence loss (temperature T=4), twelve epochs. Performance metrics included accuracy, sensitivity, specificity, F1-score, and AUROC. Independent clinical feasibility involved 52 board-certified neuroradiologists across 11 geopolitical regions. **Results:** For WHO grade 2–3 versus grade 4 stratification, distilled EfficientNetB0 achieved 97.2% accuracy, 98.1% sensitivity, 96.3% specificity, and AUROC 0.993. Differential diagnosis accuracy: 95.3% (glioma vs. meningioma), 96.1% (glioma vs. pituitary). Site-held-out external validation showed consistent performance (93–97% grading, 94–96% differential). Mean inference time: 0.19 seconds on CPU. Distilled model: 3.9 million parameters (97% reduction), 2.1 billion FLOPs (94% reduction). Neuroradiologist assessment: 94.7% rated system valuable for diagnostic confidence and surgical triage. Inter-rater agreement: 96.8% (κ=0.951, 95% CI 0.941–0.961). **Conclusions:** Knowledge-distilled EfficientNetB0 achieves 97.2% accuracy for glioma grading and 95–96% for differential diagnosis while reducing parameters by 97% and enabling CPU deployment. Global validation across six continents and clinical assessment by 52 neuroradiologists establish real-world feasibility. The architecture supports translation as a decision-support tool for preoperative glioma stratification, particularly in resource-constrained settings. Prospective clinical trials evaluating impact on surgical decision-making are warranted. Research Sponsor: None.

2041 Poster Session

Phase 1, first-in-human (FIH) study evaluating safety and efficacy of ABBV-706: Results from patients with high-grade central nervous system (CNS) tumors. First Author: Maria Vieito, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Patients (pts) with primary high-grade CNS tumors, especially those with glioblastoma (GBM), face poor clinical outcomes (GBM 5yr OS 5–10%). Seizure-related 6 homolog (SEZ6) is overexpressed in many tumor types, including primary CNS tumors. ABBV-706 is a SEZ6-targeting antibody-drug conjugate with topoisomerase 1-inhibitor payload that has shown a manageable safety profile in pts with small cell lung cancer. We present safety and efficacy data from a phase 1, FIH study evaluating ABBV-706 in pts with CNS tumors. **Methods:** This phase 1, FIH study (NCT05599984) enrolled pts ≥18 years with histologically/cytologically confirmed advanced relapsed/refractory GBM (IDH-wildtype, Grade [G] 4) or astrocytoma (IDH-mutant, G 3/4). Pts had ECOG performance score ≤1, and ≥1 measurable lesion per Response Assessment in Neuro-Oncology (RANO). Pts had prior surgical resection and progressed after receiving standard of care treatment. During dose escalation and expansion, pts received 1.3–3.5 mg/kg and 2.5 mg/kg ABBV-706, respectively. Treatment was every 3 weeks until disease progression or intolerable toxicity. Endpoints included safety and efficacy determined by RANO criteria. **Results:** As of Sep 27, 2025, 48 pts with primary CNS tumors (GBM, n=41; astrocytoma, n=6; missing indication, n=1) received ABBV-706 (1.3 mg/kg, n=1; 2.5 mg/kg, n=44; 3.0 mg/kg, n=1; 3.5 mg/kg, n=2). Among all pts, median age was 50 years (range 18–78), 58% were male, and the median number of prior lines of therapy was 2 (range 1–5). Median follow-up was 13.7 and 13.2 months for pts with GBM and astrocytoma, respectively. Treatment-related adverse events (TRAEs) were observed in 90% of pts. Most common toxicities were hematological (65%) and gastrointestinal (52%) events. G ≥3 TRAEs were observed in 60% of pts; most commonly anemia (40%). TRAEs led to treatment discontinuation, dose interruption, and dose reduction in 4%, 38%, and 27% of pts, respectively. No G 5 TRAEs were reported. One pt had pneumonitis (2.5 mg/kg, G 2). Among all pts, ORR was 8%, and 2 pts (4%) had a confirmed complete response. Efficacy data for GBM are shown in the Table. SEZ6 IHC expression was similar between GBM pts with (n=4) and without (n=31) an objective response. **Conclusions:** In pts with previously treated primary CNS tumors, ABBV-706 had a comparable safety profile to that observed in other tumors and showed encouraging antitumor activity. Clinical trial information: NCT05599984. Research Sponsor: AbbVie Inc.

Efficacy of ABBV-706.[a]

	Pts with GBM 2.5 mg/kg ABBV-706 (n=41)
BOR, n (%)	
CR[b]	2 (5)
PR[b]	4 (10)
SD	21 (51)
PD[b]	9 (22)
NE/not assessed	5 (12)
ORR[c], n (%), 95% CI	4 (10), 3–23
CBR, n (%), 95% CI	
>5 weeks	26 (63), 47–78
>6 months	5 (12), 4–26
Median PFS, months (95% CI)	2.7 (2.3-5.4)
Probability at 9 months, % (95% CI)	10 (3-24)
Median OS, months (95% CI)	6.4 (5.4–8.3)
Probability at 12 months, % (95% CI)	17 (6–33)

[a]By investigator per RANO.
[b]Including confirmed + preliminary.
[c]Confirmed.

2042 Poster Session

Initial analysis of adoptive neoantigen-specific T-cell immunotherapy for MGMT-unmethylated glioblastoma (TVI-AST-008): Signals amid control arm attrition. First Author: Tolga Tuncer, Department of Neurosurgery, Division of Medical Oncology, University of Kansas Health System, Kansas City, KS

Background: MGMT-unmethylated (MGMT-u) glioblastoma (GBM) confers resistance to alkylating agents and poor overall survival (OS). Limited options beyond Standard of Care (SOC) drive patient pursuit of experimental therapies, complicating randomized controlled trials (RCTs). TVI-AST-008 evaluates safety and efficacy of adding autologous neoantigen-specific T-cell immunotherapy to SOC in this high-risk population. **Methods:** In this prospective RCT, newly diagnosed MGMT-u GBM patients were randomized 1:1 post-resection to Immunotherapy + SOC or SOC alone, stratified by age, residual tumor, and sex. The investigational arm used patient tissue to manufacture an autologous vaccine and undergo tumor cell vaccination to induce antigen-specific priming. Following leukapheresis, harvested lymphocytes undergo *ex vivo* T-cell activation/expansion (TVAX). On completion of SOC (radiation/temozolomide), manufactured cells undergo adoptive transfer with low-dose IL-2. Primary endpoint: OS. **Results:** As of September 2025, 21 subjects (median age 60) were randomized: Treatment (n=11) or Control (n=10). Control arm retention was challenging: 4/10 withdrew post-randomization to pursue other experimental therapies, leaving 6 evaluable Controls. Six Treatment subjects completed infusion. Despite limited statistical power, survival divergence emerged: mean OS for Controls (n=6) was 6.6 months versus 10.6 months for infused Treatment patients (n=6), with survivors followed at a median of 14 months (2 died at 9 and 10 months). Safety was favorable; adverse events were Grade 1–2 (pyrexia, rash) consistent with immune activation. No SAEs attributed to the investigational product. **Conclusions:** Early TVI-AST-008 data suggest adoptive neoantigen-specific immunotherapy is feasible, safe, and early signals suggest possible improved survival in MGMT-u GBM. High post-randomization withdrawal in Controls highlights challenges of SOC-controlled trials in this setting. Future validation may require synthetic controls or crossover allowances to ensure trial viability. Clinical trial information: NCT05685004. Research Sponsor: FDA/HHS; R01FD007259.

2043 Poster Session

Impact of vorasidenib vs placebo on seizure rates and quality of life: Exploratory analysis from the phase 3 INDIGO study. First Author: Wolfgang Wick, Universitätsklinikum Heidelberg & German Cancer Research Center, Heidelberg, Germany

Background: Grade 2 diffuse gliomas with isocitrate dehydrogenase 1/2 mutations (mIDH1/2) are incurable brain tumors with poor long-term prognosis and tumor-related symptoms, eg seizures, that negatively impact patients' (pts) quality of life (QoL). Vorasidenib (VOR) is an oral, brain-penetrant, dual inhibitor of mIDH1/2 approved in >40 countries for treating grade 2 mIDH1/2 gliomas following the positive clinical outcomes, including tumor volume reduction, shown in the Phase 3 INDIGO study (NCT04164901). We investigated the effect of long-term VOR treatment on seizure activity and QoL in pts with mIDH1/2 glioma in INDIGO. **Methods:** Pts aged ≥12 years with grade 2 mIDH1/2 glioma, no prior glioma treatment other than surgery and with controlled seizures were randomized 1:1 to receive VOR 40 mg or placebo (PBO) daily. Data from the pre- and post-unblinding periods were used; PBO pts after crossover were excluded from the analyses. Exploratory analyses for the number of on-treatment seizures were conducted in pts with ≥1 seizure in the baseline or on-treatment periods using a negative binomial regression model. Seizure severity was self-reported (1 [not bad] to 10 [as bad as imaginable]). QoL was measured using the Functional Assessment of Cancer Therapy – Brain (FACT-Br) scale and FACT-Br brain cancer subscale (BrCS), and changes were estimated with time-to-event analysis. **Results:** During the study, 110/331 pts (33.2%) reported ≥1 seizure (VOR n=55; PBO n=55). VOR treatment showed a constant and sustained effect on seizure control, reflected by significantly lower seizure rates per person per year than in the PBO group (Table), and lower number and severity of seizures over time. In addition, in pts with a seizure burden (≥1 seizure), VOR significantly delayed time to first worsening of FACT-Br and FACT-Br BrCS scores (hazard ratio [95% confidence interval]: FACT-Br, 0.38 [0.15, 1.00], *P*=0.0435; FACT-Br BrCS, 0.32 [0.11, 0.91], *P*=0.0263). **Conclusions:** In pts with mIDH glioma and ≥1 on-study seizure, long-term VOR treatment generally led to a sustained decrease in seizure activity and severity and delayed worsening of QoL. These results suggest that VOR may have an additional benefit on QoL in pts who experience seizures. Clinical trial information: NCT04164901. Research Sponsor: Servier.

Exploratory analyses of VOR treatment and seizure rate in pts who reported ≥1 seizure in the baseline or on-treatment periods in INDIGO.

	VOR (n = 56)		PBO (n = 56)
Patients with ≥1 on-treatment seizure, n (%)	55 (98.2)		55 (98.2)
Rate of on-treatment seizures per person-year* (95% CI)	13.2 (5.8, 29.8)		64.9 (26.5, 159.1)
Ratio of rates: VOR vs PBO (95% CI)		0.20 (0.08, 0.52)	
Two-sided *P* value†		**0.0008**	

*Estimated using negative binomial regression model adjusted by number of seizures and tumor size at baseline.
†Not prespecified and not adjusted for multiplicity; should be interpreted with caution. Data cut-off: January 17, 2025. CI, confidence interval; PBO, placebo; VOR, vorasidenib.

2044 Poster Session

Tumor treating fields therapy in patients with newly diagnosed glioblastoma and poor performance status: Real-world analysis of patients treated in the US. First Author: Omar H. Butt, Washington University in St. Louis, St. Louis, MO

Background: TTFields therapy is an FDA-approved treatment for patients with newly diagnosed glioblastoma, showing benefit in overall survival (OS) when added to maintenance temozolomide (TMZ). While device effectiveness was demonstrated regardless of performance status (PS) in the EF-14 study, only patients with Karnofsky Performance Status (KPS) of ≥70 were eligible for the study. This study investigates real-world outcomes of patients with newly diagnosed glioblastoma and poor PS who were treated with TTFields. **Methods:** Electronic medical records of patients initiating treatment with TTFields in the US commercial setting between January 1, 2019 and December 31, 2021 were accessed via the xCures real-world data platform and Novocure systems, from which clinical data were extracted. To be included in the analysis, patients needed to have a documented new diagnosis of glioblastoma occurring within 180 days of initiating TTFields and have KPS ≤60 or ECOG PS ≥2 within 3 weeks of treatment initiation. IDH status was ascertained where data were available. Device usage was calculated as the average percentage of time the device was used within the first 3 months of therapy, as recorded by the device log files. Patients were divided into high and low usage groups. High usage was defined as usage ≥50% and treatment duration ≥30 days, and low usage as usage <50% or treatment duration <30 days, excluding patients with a death event within 30 days of initiating TTFields. Demographics, disease characteristics, and survival outcomes were evaluated. Data cutoff for analysis was Jan 7, 2026. **Results:** The study included 306 patients, of whom 198 (65%) were high users and 108 (35%) low users. Baseline characteristics were balanced between the two groups. Although most patients had KPS of 60 or ECOG PS of 2 (n=204, 67%), the study included 102 patients (33%) who had KPS ≤50 or ECOG PS ≥3. The entire cohort had median OS from diagnosis of 13.3 months (95% CI, 12.4–14.5). Median OS was 14.1 months (95% CI, 12.8–15.9) in the high-use group compared with 11.9 months (95% CI, 9.6–13.3) in the low-use group (HR, 0.69 [95% CI, 0.53–0.89]; P=0.005). Similar results were observed regardless of the performance scale utilized. Further subgroup analysis showed a consistent usage effect for patients ≥65 and <65 years of age (HR, 0.71 [0.49–1.02], P=0.067 and HR, 0.69 [0.47–1.00], P=0.049, respectively). **Conclusions:** Patients with newly diagnosed glioblastoma and poor performance status receiving TTFields therapy in the real-world setting appear to have favorable survival when compared with historical data. Usage is associated with improved survival in this population, including among elderly patients for whom treatment options are limited. Additional studies examining TTFields in this high-need population with limited trial options are warranted. Research Sponsor: None.

2045 **Poster Session**

Beyond survival: Longitudinal prognostication in glioblastoma using conditional survival—A population-based study. First Author: Obuli Srinivasan Gurunathan, United Health Services Hospitals, Johnson City, NY

Background: Glioblastoma multiforme (GBM) carries a poor prognosis, and the initial survival projections provided at diagnosis do not accurately depict the evolving risk that exists for all GBM survivors. Conditional survival (CS), defined as the probability of surviving an additional period after having lived to a specific time point, provides a much more accurate way of defining prognosis for these patients. We evaluated conditional survival patterns in a large population-based cohort of patients with glioblastoma. **Methods:** Adult patients who were diagnosed with primary glioblastoma between 2000 and 2022 were identified from the SEER 17 Registries. The estimated overall survival (OS) was determined by using the Kaplan-Meier method. We also calculated one year and two-year conditional survival (CS) probabilities at multiple landmark times (0-24 months). In addition, we stratified the conditional survival by the status of surgical resection and whether or not the patient received radiation therapy. **Results:** There were 52,125 patients in our sample. As expected, the median OS was very poor, dropping from 37.3% at 12 months to 16.0% at 24 months. Nevertheless, the conditional survival was significantly better than overall survival. One-year CS increased from 40.4% at diagnosis to 57.2% among patients surviving 24 months, while two-year CS improved from 17.3% to 39.4% over the same landmarks. Patients who underwent surgical resection had higher early CS compared with biopsy or no surgery, though differences diminished at later landmarks. Similar trends were found in CS rates in patients who received radiation therapy, indicating survivorship selection over time as opposed to a decrease in the effectiveness of treatments. **Conclusions:** Conditional survival in glioblastoma improves markedly with increased time of survival. Therefore, it is essential to use CS in place of traditional survival statistics to provide more accurate prognoses for glioblastoma patients. Research Sponsor: None.

Landmark Time (Months)	Overall Survival	1-Year Conditional Survival	2-Year Conditional Survival	1-Year CS (Resection)	1-Year CS (No resection/Biopsy)	1-Year CS (RT Yes)	1-Year CS (RT No/Unknown)
0	92.4%	40.4%	17.3%	46.7%	17.1%	48.7%	14.1%
6	56.3%	42.0%	20.9%	43.2%	32.3%	42.5%	37.9%
12	37.3%	42.9%	24.5%	43.1%	40.7%	42.4%	47.9%
18	23.7%	49.8%	31.7%	49.9%	48.7%	49.2%	56.0%
24	16.0%	57.2%	39.4%	57.1%	57.2%	56.5%	63.2%

RT: Radiotherapy.

2046 **Poster Session**

A phase I study to assess the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of KH617 for patients with advanced solid tumors (including diffuse gliomas of adulthood). First Author: Wenbin Li, Department of Neuro-Oncology, Cancer Center, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Background: Outcomes in patients (pts) with recurrent glioblastoma (rGBM) are poor, with historical median overall survival (mOS) of 7-8 months. KH617 is a sesquiterpene compound that exhibits a wide spectrum of anti-cancer properties, has low toxicity, and is capable of traversing the blood-brain barrier. It can inhibit the growth, proliferation, and migration of tumors via multiple mechanisms, mitigate the malignant phenotype of tumor cells, and facilitate the transdifferentiation of tumor cells into normal cells. This is a phase I study of KH617 in pts with advanced solid tumors (including diffuse gliomas of adulthood). Here, we report the results of the dose escalation stage. **Methods:** Pts with histologically confirmed advanced solid tumors (including diffuse gliomas of adulthood) that were no longer responding to standard therapies were enrolled. The Bayesian Optimal Interval (BOIN) design was used for dose escalation, having explored in 7 successive cohorts (5-60mg/kg). **Results:** As of Dec, 30 2025, 32 pts were enrolled across 7 dose levels, including 23 pts with rGBM, 7 with non-glioblastoma, and 1 each with adenocarcinoma and spinal cord ependymoma. The median age was 51 years, and 19 (59.4%) pts were male. No dose-limiting toxicity (DLT) or treatment-related serious adverse events (TRSAEs) were observed, and the maximum tolerated dose (MTD) was not reached. The most frequently reported ($\geq$10%) treatment-related serious adverse events (TRAEs) were white blood cell count decreased, neutrophil count decreased, lymphocyte count decreased, abnormal ECG T wave, and sinus bradycardia. Only 1(3.13%) pt reported grade $\geq$3 adverse event. Efficacy signals were observed especially in the 23 rGBM pts, who were administered KH617 across 7 doses (n = 1, 1, 3, 2, 8, 7, 1 in 5, 10, 17, 25, 33, 45, 60mg/kg cohorts, respectively), the mOS was 16.07 months. At the recommended phase 2 dose (RP2D) of 33mg/kg, 8 rGBM pts were included in the efficacy evaluation, objective response rate (ORR) was 12.5%, median progression-free survival (PFS) was 1.84 months, mOS exceeded 21 months (3 died and 5 were still alive). In the pharmacokinetic (PK) study, C_{max} no longer increased with escalating doses from 25 mg/kg to 45 mg/kg, indicating that the peak plasma concentration had already reached the maximum plateau level under the current dosing. Combined the efficacy data with the PK data, 33 mg/kg was confirmed as the RP2D. **Conclusions:** KH617 has shown significantly superior antitumor activity compared to the historical mOS in pts with rGBM, while also being well-tolerated. Clinical trial information: CTR20223286. Research Sponsor: Sichuan Honghe Biotechnology Co., Ltd.

2047 **Poster Session**

Interrupting HEG1/Cx43 interaction to promote cuproptosis via inhibiting gap junction to overcome glioblastoma radioresistance. First Author: Lanlan Guo, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University., Guangzhou, Guangdong, China

Background: Glioblastoma (GBM) is the most common and aggressive primary malignant tumor of the central nervous system. Its intrinsic radioresistance leads to suboptimal therapeutic outcomes. A prior clinical trial by our team revealed that mutations in the *HEG1* gene lead to upregulated protein expression, a key factor limiting the benefit from standard radiotherapy in GBM patients. As a form of non-classical programmed cell death induced by radiotherapy, we hypothesized that high HEG1 expression reduces the susceptibility of GBM cells to cuproptosis, thereby promoting radiotherapy resistance. **Methods:** Cellular functional assays were performed to evaluate the impact of HEG1 expression on cuproptosis sensitivity and radiotherapy response in GBM cells. Molecular techniques were used to assess intracellular and intercellular copper ion flow. Co-immunoprecipitation and inhibition of protein degradation pathways were employed to investigate the direct interaction between HEG1 and the gap junction protein Connexin 43 (Cx43), and its inhibitory effect on Cx43 degradation via the endolysosomal pathway. Structural modeling combined with virtual screening of a drug library was conducted to identify potential compounds disrupting the HEG1-Cx43 interaction. Site-directed mutagenesis and kinase activity modulation were used to elucidate the mechanism by which c-Kit kinase promotes HEG1-Cx43 binding by phosphorylating HEG1 at tyrosine residue Y1350. Functional validation was performed both in vitro and in vivo using GBM models. **Results:** High HEG1 expression facilitated intercellular copper ion flow, dampened intracellular copper ion fluctuations, and consequently blocked the propagation of cuproptosis. Mechanistically, HEG1 directly interacted with Cx43, inhibiting its degradation via the endolysosomal pathway and sustaining gap junction establishment. Virtual screening identified several multi-target tyrosine kinase inhibitors capable of disrupting the HEG1-Cx43 interaction. Mechanistic studies revealed that c-Kit kinase promoted this interaction by phosphorylating HEG1 at Y1350. Both in vitro and in vivo functional validation demonstrated that targeting the HEG1-Cx43 interaction reactivated cuproptosis and sensitized GBM to radiotherapy. **Conclusions:** Our findings elucidate the regulatory role of the "HEG1-Cx43-cuproptosis" axis in GBM radioresistance, offering new insights for treatment. The combination of multi-target tyrosine kinase inhibitors and cuproptosis inducers may represent a promising novel therapeutic strategy for GBM. Research Sponsor: National Key R&D Program of China; Natural Science Foundation of China; Cancer Innovative Research Program of Sun Yat-sen University Cancer Center; Natural Science Foundation of Guangdong Province; Young Talents Program of Sun Yat-sen University Cancer Center; Guangzhou Science and Technology Plan; Guangzhou Basic and Applied Basic Research Foundation.

2049 **Poster Session**

Histopathology-verified comparison of FET PET and contrast-enhanced MRI for tumor visualization in glioblastoma. First Author: Roman Stuerzl, Department of Nuclear Medicine, LMU University Hospital, LMU Munich, Munich, Germany

Background: In glioblastoma, precise visualization is a prerequisite for optimal resection strategies and accurate radiotherapy volume definition. In routine practice, contrast-enhanced MRI (CE-MRI) is most commonly used; however, it can underestimate tumor extent when viable tumor is present without blood–brain barrier disruption and therefore without contrast uptake. The present study examined whether amino acid PET with O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET) can better visualize the true distribution of tumor tissue and thereby improve preoperative assessment. **Methods:** In this prospective, biopsy-validated single-center study, in 61 patients with IDH-wildtype glioblastoma (44 newly diagnosed, 17 recurrent) 472 biopsies spatially correlated with preoperative FET PET and CE-MRI were histopathologically evaluated. Diagnostic metrics were calculated and compared between modalities using McNemar and Chi² tests ($p = 0.05$). **Results:** Overall, FET PET identified tumor tissue with significantly higher sensitivity than CE-MRI (91.2% vs. 55.7%; $p < 0.001$). When benchmarked against T2/FLAIR, FET remained more sensitive (85.3%; $p = 0.012$) while also demonstrating a pronounced gain in specificity (82.5% vs. 33.3%; $p < 0.001$). Remarkably, there was the high reliability of FET in regions without MRI contrast enhancement: biopsies taken from FET-positive areas without contrast enhancement showed a positive predictive value of 98.3%. Subgroup analyses consistently demonstrated the advantage of FET across clinical and histological strata, including newly diagnosed and recurrent disease ($p < 0.001$), as well as within cohorts with resection ($p < 0.001$; specificity $p = 0.03$) or biopsy ($p < 0.001$). Importantly, performance advantages were also observed regardless of histological tumor cell density, with FET exceeding CE-MRI in both histological strata (infiltration zone and solid tumor, both $p < 0.001$). **Conclusions:** FET PET demonstrated significant diagnostic superiority over CE-MRI for the visualization of glioblastoma tissue. Comparable positive predictive values in contrast-enhancing and non-enhancing regions indicate that FET PET detects tumor reliably, independent of the blood–brain barrier integrity. These findings support the integration of amino acid PET as an important component in target definition for both surgical and radiation planning in glioblastoma. Research Sponsor: None.

2050 Poster Session

Caregiver professional employment and its impact on glioblastoma patient survival: Results from two prospective studies. First Author: Vincenzo Di Nunno, Nervous System Medical Oncology Department, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto delle Scienze Neurologiche di Bologna, Bellaria Hospital., Bologna, 40139, Italy

Background: Caregiver burden is a crucial factor to consider in the diagnosis and care of patients with glioblastoma (GBM). Despite growing interest in caregiver issues, data on caregiver burden and, in particular, professional and working burden are limited, as well as the potential effect of caregiver burden on patients' survival. **Methods:** We collected caregiver data from two prospective observational studies (ISES 1 and ISES 2) investigating the impact of socioeconomic variables (SES) in GBM patients. In particular, we collected data on the presence and type of caregiver, the caregiver's professional situation, and any professional modifications after the GBM diagnosis at time of adjuvant treatment start and after six months (in patients enrolled in ISES 2 study). **Results:** Overall, 511 GBM isocitrate dehydrogenases wild-type (IDH-wt) patients were included. The median follow-up period was 55.2 months (95% CI, 44.3–86.3), and the median overall survival was 15.7 months (95% CI, 14.8–17.2). A caregiver was present for 472 patients (92.4%), consisting mainly of partners or daughters and sons. At the start of adjuvant treatment, 158 caregivers (30.9%) reduced their working hours, and 55 caregivers (10.8%) stopped working. For 232 patients, a longitudinal assessment of caregiver condition was collected, and 71 caregivers (30.6%) reduced their working hours, while 33 patients (14.2%) stopped their work activities. Patients whose caregivers were in stable employment had a longer life expectancy than those whose caregivers were not (multivariate - HR 0.76, 95% CI 0.60–0.94, p = 0.03), regardless of other known prognostic factors, as confirmed by a multivariate analysis (Table 1). **Conclusions:** Our study revealed that GBM diagnosis often leads to a negative impact on caregiver work activities. A stable caregiver employment translates independently to a long-life expectancy of patients with GBM, regardless of other recognized prognostic factors. Policies supporting the professional and social activities of caregivers could improve not only the quality of care for GBM patients but also their clinical outcomes. Clinical trial information: 0321-3733778. Research Sponsor: None.

VARIABLES	Univariate analyses Hazard Ratio (95%CI) p value	Multivariate analyses Hazard Ratio (95%CI) p value
MGMT		
Unmethylated vs methylated	2.23 (1.79 – 2.77) p < 0.001	0.43 (0.34-0.55) p < 0.001
SURGERY		
Biopsy	Ref	Ref
Partial resection	0.51 (0.38-0.69)	0.62 (0.43-0.88)
Complete resection	0.50 (0.37-0.69) p <0.001	0.61 (0.42-0.89) p = 0.008
TREATMENT		
RT (40Gy)/CT ->CT vs RT (60Gy)/CT ->CT	1.31 (1.04-1.73) p = 0.02	1.04 (0.77-1.49) p = 0.8
ECOG		
0 vs 1 or more	0.67 (0.54-0.82) p <0.001	0.72 (0.56-0.91) p = 0.007
STEROIDS		
Yes vs No	1.94 (1.57-2.40) p < 0.001	1.75 (1.31-2.13) p < 0.001
AGE		
(As continuous for year)	1.02 (1.01-1.03) p < 0.001	1.01 (1.0009-1.03) p = 0.04
CAREGIVER		
(professional condition) Employed vs other	0.73 (0.59-0.90) p = 0.005	0.76 (0.60-0.94) p = 0.03

2051 Poster Session

Expression patterns of circulating microRNAs in classification models: New opportunities in brain tumor diagnosis. First Author: Dmitry Yu. Gvaldin, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation

Background: Diffuse gliomas are the most common primary brain tumors and, according to the 2021 WHO classification, are divided into three main types: IDH-wild-type glioblastomas, IDH-mutant astrocytomas, and IDH-mutant oligodendrogliomas with 1p/19q codeletion. Oligodendrogliomas are neuroepithelial tumors of the central nervous system that have histological and molecular characteristics distinct from other subtypes of diffuse gliomas. The problem of early diagnosis of oligodendrogliomas, due to their location, requires the search for accessible and informative markers. Circulating microRNAs in blood plasma appear to be the most promising in this aspect. The purpose of the study was to develop a model for the diagnosis of oligodendrogliomas based on the expression profiles of microRNAs circulating in blood plasma. **Methods:** The study included 251 participants: 84 patients with glioblastomas, 51 patients with astrocytomas, 12 patients with oligodendrogliomas, 47 patients with meningiomas, 14 patients with lung cancer metastases, 25 patients with breast cancer metastases, and 18 healthy donors. The miRNeasy Serum/Plasma Kit (Qiagen, Germany) was used to isolate the microRNA fraction from blood plasma. The expression levels of hsa-miR-30c-5p, hsa-miR-186-5p, hsa-miR-194-5p, hsa-miR-484, hsa-miR-19b-3p, hsa-miR-431-5p, hsa-miR-363-3p, hsa-miR-128-3p, hsa-miR-3168, hsa-miR-192-5p, hsa-let-7c-5p, hsa-miR-340-5p, hsa-miR-182-5p and hsa-miR-144-5p were measured by stem loop RT-qPCR. **Results:** The model for diagnosing cases with oligodendrogliomas was as follows: K_o=-1.59×hsa-miR-128-3p-1.97×hsa-miR-194-5p+1.78×hsa-miR-19b-3p-2.47×hsa-miR-3168+3.41×hsa-let-7c-5p+0.91×hsa-miR-192-5p+1.39×hsa-miR-340-5p-1.8, where K_o is the coefficient used to differentiate cases with oligodendrogliomas from other cases. The optimal cut-off value for K_o was 0.38 with a Youden index of 0.86. Model validation on the test dataset revealed that cases with oligodendrogliomas typically have calculated coefficient values $\geq$ 0.38. ROC analysis yielded the following model metrics: sensitivity – 100%, specificity – 85.7%, accuracy – 92.9%, and AUC – 0.93. **Conclusions:** The developed model opens up new opportunities for the early diagnosis of oligodendrogliomas and may eventually become part of a test system for the differential diagnosis of brain tumors. Research Sponsor: None.

2052 Poster Session

Global validation of a brain cancer liquid biopsy. First Author: James Munro Cameron, Dxcover Ltd, Glasgow, United Kingdom

Background: Delayed diagnosis of brain cancer leads to approximately two-thirds of patients being identified only after presentation to the emergency department with advanced symptoms or established neurological deficits. Implementation of a simple liquid biopsy test as a rule-out test prior to confirmatory imaging, could facilitate earlier and more efficient triage of patients presenting with non-specific symptoms suggestive of brain cancer, enabling prioritization for those most at-risk and accelerate diagnostic pathways. **Methods:** Presented here is the clinical validation of the Dxcover Brain Cancer Liquid Biopsy Platform obtained to support regulatory approvals. The multi-centre and observational 'Early and tiMely detection of BRAin CancEr' ('EMBRACE') study was conducted with prospective patient recruitment across seven sites in Europe. The target population consisted of patients with symptoms indicative of brain cancer. Test performance was assessed by comparison of the liquid biopsy result to diagnostic imaging. Furthermore, the liquid biopsy test was then independently tested on an additional clinical dataset obtained from a US patient population (n=234) as part of a CLIA laboratory validation study. **Results:** In the EMBRACE performance evaluation, 2554 patients were enrolled across the seven collection sites; 2324 were deemed eligible and taken forward for test assessment. There were 697 brain tumours in total, of which 395 were malignant, and 1627 non-tumour diagnoses. In the intended use population, the reported diagnostic performance was 86% sensitivity for brain cancer detection with 44% specificity, and a 99% negative predictive value (NPV). Notably, for the most prevalent and most aggressive brain cancer, glioblastoma, 86% of cases were successfully identified. Additionally, 94% of patients with central nervous system lymphoma, and 90% of brain metastases were predicted correctly as having tumours. The test has gained regulatory approval for use in the UK and in Europe, gaining UKCA and CE – IVDR certification respectively. The CLIA validation has provided additional confirmation of the clinical utility of the liquid biopsy test in the US population. **Conclusions:** Existing symptom-based referral pathways are ineffective for the detection of brain cancer, and there is an urgent need for new tests to help with clinical decision making. With a NPV of 99%, the Dxcover Liquid Biopsy test could aid with the efficient stratification of patients toward diagnostic imaging. Research Sponsor: None.

2053 Poster Session

Genomic determinants of radiation necrosis in diffuse glioma patients. First Author: Michael Kienhöfer, University Hospital Heidelberg, Heidelberg, Germany

Background: Diffuse gliomas are the most common primary brain tumors, requiring multimodal therapy. Radiotherapy (RT) represents a key pillar of treatment; however, radiation-induced brain toxicities remain a major challenge. Radiation necrosis (RN) is a delayed complication that can impair clinical outcomes and quality of life. Emerging evidence suggests that tumor biology, together with clinical factors, can influence radiation toxicity in a variety of cancer entities. However, in diffuse gliomas, tumor-intrinsic biomarkers predisposing to radiation toxicities remain poorly defined. We hypothesized that integrating clinical features with tumor genomic data could identify patients at increased risk of developing RN. **Methods:** We analyzed a cohort of 943 adult patients with diffuse gliomas treated between 2014 and 2024 at MD Anderson. All tumors were classified according to the WHO 2021 criteria into three diagnoses: GBM, astrocytoma (astro), and oligodendroglioma (OD). RN occurring at least 12 weeks after completion of RT was identified based on pathology and/or advanced brain tumor imaging (ABTI), which included conventional MRI, perfusion imaging and spectroscopy. A multivariate regression model was employed to identify clinical or genetic predictors for RN. Included covariates were demographics, diagnosis, and common genetic alterations. To address missing values, multiple imputation was utilized. **Results:** Sixty patients with RN were identified: 51 GBM (85%), 6 astro (10%), and, 3 OD (5%); compared with 883 controls: 682 GBM (77%), 140 astro (16%), and 61 OD (7%). Age, gender, and diagnoses were not associated with RN. We evaluated the top 22 altered genes and *MGMT* status. In the overall cohort, *IDH1* (OR 0.15 [95% CI, 0.02–0.93]; p=0.042) and *MDM2* (OR 0.11 [95% CI, 0.01–1.00]; p=0.050) alterations were associated with reduced RN risk, while *ATR* alterations were associated with increased RN risk (OR 6.05 [95% CI, 0.85–33.1]; p=0.049) on multivariable analysis. In the GBM subgroup, *CDK4* (OR 3.32 [95% CI, 1.04–9.97]; p=0.042) and *MSH6* alterations (OR 6.05 [95% CI, 1.12–33.1]; p=0.037) were associated with increased RN risk, whereas *MDM2* alterations remained associated with reduced risk (OR 0.07 [95% CI, 0.01–0.69]; p=0.023). In the *IDH*-mutant diffuse glioma subgroup (RN n=9; controls n=201), *ATRX* alterations were associated with lower RN risk (OR 0.10 [95% CI, 0.01–0.73]; p=0.023). *MGMT* status was not associated with RN risk. **Conclusions:** In this cohort, RN risk was not associated with demographic factors, tumor diagnosis, or MGMT status, but was associated with specific tumor genomic alterations. The enrichment of DNA damage response–related genes among those associated with RN suggests a potential biological link between tumor genomics and RN toxicity. Prospective validation will be required to determine the utility of these findings for genome-based risk stratification. Research Sponsor: None.

2054 Poster Session

Direct oral anticoagulants versus low-molecular-weight heparin for venous thromboembolism in primary brain tumors: A TriNetX real-world analysis. First Author: Medina Esenbekova, UPMC Harrisburg, Harrisburg, PA

Background: Venous thromboembolism (VTE) is a common complication in patients with primary brain tumors and is associated with poor outcomes. Although therapeutic anticoagulation is required for VTE treatment, its use in this population is challenging because of the increased risk of intracranial hemorrhage (ICH). Optimal anticoagulant selection remains uncertain, as concerns regarding ICH have limited randomized trial data in patients with primary brain tumors. Therefore, comparing ICH risk between direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH) is critical to optimizing anticoagulation in this high-risk group. **Methods:** This retrospective cohort study used the TriNetX Global Collaborative Network to identify adults (≥18 years) with primary malignant brain tumors who developed VTE within one year of tumor diagnosis. Patients with secondary malignant neoplasms were excluded. Cohorts included patients treated with DOACs (apixaban, rivaroxaban, edoxaban, or dabigatran) or LMWH (enoxaparin, dalteparin, or tinzaparin) after VTE diagnosis. The index date was defined by cohort entry criteria, and outcomes were assessed over 180 days. 1:1 propensity score matching was performed across demographic and clinical characteristics, including age, sex, race, cardiovascular disease, diabetes, kidney disease, coagulation disorders, obesity, and substance use. Intracranial hemorrhage and all-cause mortality were evaluated using risk estimates and Kaplan-Meier survival analyses. **Results:** After propensity score matching, 6,114 patients were included in each cohort. DOAC therapy was associated with a significantly lower risk of intracranial hemorrhage compared with LMWH over 180 days (3.9% vs 7.3%; risk ratio, 0.54; 95% CI, 0.46–0.64; $p<0.001$). In addition, all-cause mortality at 180 days was significantly lower in the DOAC cohort than in the LMWH cohort (24.8% vs 31.3%; risk ratio, 0.79; 95% CI, 0.75–0.84; $p<0.001$). These findings were consistent across the matched population, demonstrating improved safety and survival outcomes associated with DOAC use in patients with primary malignant brain tumors and VTE. **Conclusions:** In this large real-world cohort of adults with primary brain malignancy and VTE, DOAC treatment was associated with a lower intracranial hemorrhage risk and reduced mortality at 180 days compared with LMWH after propensity score matching. These findings support the safety of DOACs in patients with primary brain tumors and warrant further prospective evaluation of anticoagulant selection in this high-risk population. Research Sponsor: None.

2056 Poster Session

Development of human B7H3/IL13Ra2 bispecific armored CAR-T for treatment of glioblastoma. First Author: Keming Zhang, Elpis Biopharmaceuticals, Lexington, MA

Background: Glioblastoma (GBM) remains a highly lethal malignancy driven by infiltrative growth, molecular complexity, immune evasion, and therapeutic resistance. The limited efficacy of current treatments reflects antigen heterogeneity, an immunosuppressive tumor microenvironment, and restricted delivery across the blood–brain barrier with targeted therapy. Although earlier CAR-T therapies demonstrated preliminary activity in GBM, durable efficacy remains elusive. We have developed EPC-003, a fully human bispecific B7-H3/IL13Rα2 CAR-T engineered with a multi-mechanism armor to mitigate antigen heterogeneity, modulate the tumor microenvironment, and enhance persistence via central memory T-cell enrichment. **Methods:** Human anti-IL13Rα2, anti-B7-H3, and anti-PD-L1 scFvs were discovered from proprietary human B-cell libraries using mRNA display platform. A multi-mechanism armor was engineered by fusing the anti-PD-L1 scFv to a fine-tuned, immune cell-type specific IL-2 variant, identified through the unique cytokine engineering platform. These binding and functional modules were systematically optimized to generate EPC-003, a bispecific tandem CAR targeting IL13Rα2 and B7-H3 and incorporating a secreted multi-mechanism armor. CAR mechanisms, anti-tumor activity, and preclinical toxicity were evaluated. A proprietary clinical manufacturing process was established to produce a central memory T cell enriched CAR-T product. **Results:** The secreted armor of EPC-003 suppressed regulatory T-cell activation while selectively activating central memory T-cells, with the potential to enhance CAR-T cell persistence. In a 7-day G-Rex manufacturing process, EPC-003 demonstrated promising druggability with robust and reproducible CAR expression, and the proprietary cytokine cocktail consistently enriched the product to >65% central memory CAR-T cells. In orthotopic GBM models, intracranial administration of EPC-003 (0.4×10^6 and 1.2×10^6 CAR-T cells) induced tumor regression and showed dose-dependent anti-tumor activity. In preclinical toxicity studies, EPC-003 exhibited a favorable safety profile, with no body weight loss, cytokine release syndrome, or systemic clinical signs. No treatment-related pathological changes were observed across 25 examined organs. Immunohistochemistry revealed no evidence of brain hemorrhage in treated groups, with minimal monocyte infiltration in the pia mater observed only at the high dose. **Conclusions:** EPC-003, a multi-mechanism armored bispecific CAR-T, demonstrated favorable preclinical safety, developability, robust anti-tumor activity, and potential durability. These data support its advancement into an investigator-initiated clinical trial for the treatment of glioblastoma. Research Sponsor: None.

2057 Poster Session

Which treatment is best? A systematic review and Bayesian network meta-analysis of adjuvant treatments for low-grade glioma. First Author: Amit Kumar Chowdhry, AdventHealth Cancer Institute, Orlando, FL

Background: The standard of care for low-grade glioma (LGG) includes resection with or without adjuvant treatment. It is currently unknown which adjuvant strategy is best. **Methods:** A systematic review of PubMed and EMBASE for randomized controlled trials (RCTs) evaluating adjuvant treatment for LGG published on or before 6/2/2025 was conducted as pre-registered (CRD420251072899). Study eligibility and data extraction were reviewed by two authors independently, and risk of bias was assessed via Cochrane RoB2. Two Bayesian network meta-analyses profiling *de novo* LGG were conducted with uninformative priors adjusting for baseline characteristics of each trial cohort. The pre-specified outcome measure was the distribution of posterior HR_{PFS} (primary meta-analysis) and HR_{OS} (secondary meta-analysis) for each identified treatment against observation. Posterior distributions were summarized with the posterior median hazard ratio (HR), and 95% equal-tailed credible interval (CrI). Further the probability of major benefit (HR≤0.6) and any magnitude harm (HR>1.0) were reported for each meta-analysis. **Results:** Six RCTs (all with low risk of bias) profiling 1,757 participants were identified for the primary meta-analysis (PFS). Seven RCTs (6 with low risk of bias 1 with high risk of bias) profiling 1,392 patients were identified for the secondary meta-analysis (OS). In total, six adjuvant treatment strategies were identified: radiotherapy (RT) + procarbazine/CCNU/vincristine (PCV), RT + temozolomide (TMZ), RT + CCNU alone, high-dose RT (HDRT, >54Gy), low-dose RT (LDRT; ≤54Gy), and TMZ. The posterior median HRs and 95% CrIs are reported in Table 1. For all profiled treatments, the probability of any benefit (HR<1.0) on the endpoint of PFS was >98% and >76% for OS. Additionally, the probability of major benefit (P1) and any magnitude harm (P2) were reported as clinically significant summary measures of all posterior distributions (Table 1). **Conclusions:** Based on the identified RCTs, RT+PCV was found to have the most favorable probability efficacy and RT+TMZ a similar distribution of treatment effect. RT+PCV and RT+TMZ had a >98% probability of any benefit for both endpoints. The probability of major benefit for RT+PCV and RT+TMZ was >99.9% and 84.8% for PFS and 71.3% and 63.3% for OS. Research Sponsor: NIH/NCI CCR Intramural Research Program.

Probability of benefit/harm of adjuvant therapy for low-grade glioma.

	PFS	$P1_{PFS}$	$P2_{PFS}$	OS	$P1_{OS}$	$P2_{OS}$
PT+PCV	0.29 (0.19-0.43)	>99.9%	<0.1%	0.53 (0.32-0.84)	71.3%	0.4%
RT+TMZ	0.45 (0.27-0.76)	84.8%	0.2%	0.55 (0.33-0.91)	63.3%	1.1%
RT+CCNU	-		-	0.63 (0.28-1.42)	46.0%	13.4%
HDRT	0.59 (0.41-0.83)	55.0%	0.2%	0.86 (0.57-1.30)	4.4%	23.0%
LDRT	0.58 (0.44-0.76)	59.0%	<0.1%	0.89 (0.63-1.24)	1.4%	23.4%
TMZ	0.67 (0.47-0.97)	26.9%	1.4%	-	-	-
Observation	1 (Ref.)	-	-	1 (Ref.)	-	-

P1, probability HR≤0.6; P2, probability HR>1.0.

2058 Poster Session

Characterization of contemporary practice patterns in the management of *IDH*-mutant glioma: A multidisciplinary multi-institutional survey. First Author: Luis Nicolas Gonzalez Castro, Dana-Farber Cancer Institute, Boston, MA

Background: The management of isocitrate dehydrogenase (IDH) mutant glioma is rapidly evolving following the recent FDA approval of the mutant IDH inhibitor, vorasidenib. Optimal treatment decisions for many specific clinical scenarios remain undefined leading different neuro-oncology providers to recommend different treatment approaches. The aim of this study was to characterize how clinicians collectively approach different clinical scenarios and evaluate how demographic and professional backgrounds influence decision-making in IDH-mutant glioma. **Methods:** An online survey was developed by a team of neuro-oncologists and radiation oncologists and distributed via email and X to clinicians treating patients IDH-mutant glioma. The survey included demographic questions and multiple case-based clinical scenarios with standardized response options. We compared the responses of neuro/medical oncologists, radiation oncologists, and neurosurgeons, and performed univariable regression to identify predictors of treatment preference, as well as to understand familiarity and enthusiasm with the use of IDH inhibitors. **Results:** A total of 153 clinicians (58% neuro/medical-oncologists, 34% radiation oncologists, 8% neurosurgeons) completed the online survey. Five of ten scenarios reached consensus (>75% agreement on a treatment option), while the remainder demonstrated heterogeneity of treatment approaches. Compared to neuro/medical oncologists, radiation oncologists were less likely than neuro/medical oncologists to recommend IDH inhibitor therapy (IRR 0.57, $p<0.001$) and more likely to recommend radiotherapy (IRR 1.54, $p<0.001$) or chemo-radiotherapy (IRR 1.47, $p<0.001$). Neuro-oncologists and neurosurgeons reported the most and least familiarity, respectively, with the use of IDH inhibitors whereas medical oncologists and radiation oncologists reported the most and least enthusiasm for IDH inhibitor use, respectively. **Conclusions:** Our survey results evidence substantial variation in real-world management of IDH-mutant glioma across specialties and institutions. While several clinical scenarios demonstrated strong therapeutic consensus, others revealed diverse approaches, underscoring the need for ongoing multidisciplinary collaboration and further advancement of evidence-based consensus to guide clinical decisions. Research Sponsor: None.

2059 **Poster Session**

Rituximab pre-conditioning in a phase I study of CARv3-TEAM-E for recurrent glioblastoma (GBM): The INCIPIENT trial. First Author: Bryan D. Choi, Massachusetts General Hospital, Boston, MA

Background: Chimeric Antigen Receptor (CAR) T cells for glioblastoma (GBM) have been limited by the challenge of targeting a single tumor antigen in a heterogeneous disease. To address this barrier, we generated a novel engineered T-cell product (CARv3-TEAM-E) that targets the EGFRvIII antigen while also secreting T-cell-Engaging Antibody Molecules (TEAMs) against wild-type EGFR. **Methods:** The INCIPIENT clinical trial is a first-in-human study of CARv3-TEAM-E in patients with GBM (NCT05660369). Patients with recurrent GBM were treated with intraventricular CARv3-TEAM-E T cells (10E6 cells per infusion) and one of three pre-treatment regimens: no lymphodepletion (N=3), lymphodepleting chemotherapy with cyclophosphamide and fludarabine (LDC) (N=7), or cyclophosphamide, fludarabine, and rituximab (LDC+R) (N=3). The primary objective was safety and tolerability. Immune cells were profiled in the cerebrospinal fluid (CSF) and peripheral blood by flow cytometry. **Results:** CAR T manufacturing was successful for all patients. There were no dose-limiting toxicities (DLT). Three patients were treated without LDC; all developed anti-CAR and/or anti-TEAM antibodies (i.e., anti-therapy antibodies) after a single infusion of CARv3-TEAM-E. Subsequently, 7 patients were treated with LDC prior to CARv3-TEAM-E, 5 of which underwent serial infusions (range 2-5 infusions). Four patients had reinfusions after which CAR T cells were not detected in the CSF. We therefore added rituximab to the LDC regimen. In the 3 individuals pre-treated with LDC+R, CAR T cells were detected in CSF not only after initial infusion (range 21-28 days) but also following repeat infusion in all patients (range 3-15 days post-reinfusion). Anti-therapy IgG was not detected in patients treated with LDC+R, as compared to 9/10 patients who developed an antibody response when rituximab was not administered. As of 12/15/2025, 10/13 patients are alive 6-30 months after first infusion, with 7 alive $>$14 months. **Conclusions:** Intraventricular CARv3-TEAM-E infusions were well-tolerated after LDC+R pre-conditioning and no DLTs were noted. The addition of Rituximab abrogated anti-therapy antibody formation and prolonged CAR T-cell persistence in 3/3 patients. Survival data reflect continued promise of CARv3-TEAM-E in patients with recurrent glioblastoma. Clinical trial information: NCT05660369. Research Sponsor: None.

2060 **Poster Session**

Real-world outcomes from 3D-PREDICT glioma chemosensitivity testing of primary CNS tumors. First Author: Aidan Jones, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: 3D-Predict Glioma is an *ex vivo* chemosensitivity assay that predicts response to 12 systemic agents using patient-derived 3D cell cultures. Prospective studies showed predictive accuracy, but real-world data linking assay-guided therapy selection to clinical outcomes remain limited. We analyzed outcomes at a tertiary cancer center. **Methods:** This retrospective–prospective chart review included patients with primary CNS tumors who underwent chemosensitivity testing at an urban cancer center since 3/2023. Demographics, tumor characteristics, assay results for the 12-drug panel, treatment selection, and clinical outcomes were abstracted. Drug response was categorized as response, moderate response, or no response. Survival analyses were performed using the Kaplan–Meier method. **Results:** Among the 96 patients, ECOG was 0 in 21 (22.1%), 1 in 37 (38.9%), 2 in 26 (27.4%), and 3 in 11 (11.6%). Insurance coverage included private (69, 71.9%), Medicaid/Medicare (14, 14.5%), Private plus Medicaid/Medicare (12, 12.5%), or self-pay (1, 1.0%). At the time of analysis, 85 patients (88.5%) were alive. Median age was 64 years (range 25–86; IQR 56–71), and 53 (55.2%) were female. Most were diagnosed with adult-type diffuse glioma (92, 95.8%), including 84 (87.5%) glioblastoma. Chemosensitivity testing failed in 10 (10.4%) cases due to insufficient tissue quantity or quality control. All remaining cases yielded 1 or more drugs with assay-predicted responses. Response rates for each drug are detailed in the Table. Mean time to results was 8.8 days (range 5–15). Assay-guided therapy was selected in 59.5%, predominantly temozolomide. The remaining patients received other agents on trial, standard-of-care physician's choice, no further therapy, or transferred care. Key endpoints analyzed included progression-free survival (PFS), PFS at 6 months, overall survival (OS), OS at 12 months, and time-to-progression (TTP) ratio. **Conclusions:** In a real-world CNS tumor cohort, 3D-Predict Glioma identified potentially active agents and influenced treatment selection in more than half of patients. Our series suggests that chemosensitivity-guided therapy is feasible in routine neuro-oncology practice. Research Sponsor: None.

Response rates by drug.

Drug	Newly Diagnosed	Progression	Pseudoprogression	All
Abemaciclib	17 (37.8)	10 (47.6)	2 (100.0)	29 (42.6)
Carboplatin	30 (60.0)	11 (50.0)	2 (100.0)	43 (58.1)
Dabrafenib	4 (8.0)	4 (17.4)	0 (0.0)	8 (10.7)
Etoposide	13 (25.5)	5 (21.7)	0 (0.0)	18 (23.7)
Everolimus	44 (100.0)	22 (100.0)	2 (100.0)	68 (100.0)
Irinotecan	23 (45.1)	9 (34.6)	0 (0.0)	32 (40.0)
Lomustine	2 (3.9)	1 (4.3)	0 (0.0)	3 (3.9)
Osimertinib	8 (17.4)	5 (23.8)	0 (0.0)	13 (18.8)
Procarbazine	50 (100.0)	23 (95.8)	2 (100.0)	75 (98.7)
Rucaparib	43 (86.0)	17 (73.9)	2 (100.0)	62 (82.7)
Temozolomide	20 (39.2)	10 (40.0)	2 (66.7)	32 (40.5)
Trametinib	20 (44.4)	6 (28.6)	0 (0.0)	26 (38.2)

Denominators defined by available results per drug; N (%).

2061 **Poster Session**

Neoadjuvant treatment of recurrent high-grade gliomas with camrelizumab in combination with apatinib: A prospective phase II clinical study. First Author: Cheng-Cheng Guo, Department of Neurosurgery/Neuro-Oncology, Sun Yat-sen University Cancer Center, Collaborative Innovation Center for Cancer Medicine, State Key Laboratory of Oncology in South China, Guangzhuo, China

Background: High-grade gliomas exhibit extremely recurrent and resistant to treatments, and require urgent therapeutic innovation. This phase II trial presents preliminary results of neoadjuvant camrelizumab (PD-1 inhibitor) combined with apatinib (VEGFR2 TKI) for recurrent high-grade gliomas. **Methods:** This single-center, single-arm, phase II trial (NCT04588987) enrolled patients (age $>$18, KPS $\geq$60) with recurrent high-grade gliomas suitable for re-resection after prior STUPP therapy. Patients received i.v. camrelizumab 200mg (D1) and oral apatinib 250mg (D1-D7). Surgery was performed 1 week post-drug discontinuation. Adjuvant treatment with i.v. camrelizumab 200 mg every two weeks (from 2 weeks $\pm$ 5 days post-surgery) in combination with continuous oral apatinib 250 mg/d (from 4 weeks post-surgery) was administered until death/unacceptable toxicity. Primary endpoint: overall survival (OS). Secondary endpoints: 1-year OS rate, 6-/12-month PFS rates, time to progression (TTP), KPS, and adverse events (AEs). **Results:** From October 2020 to December 2024, 28 patients were enrolled (median age 42 years [range 23-62]; 22 glioblastoma, 4 anaplastic astrocytoma, 1 anaplastic oligodendroglioma, 1 gliosarcoma). The 27 patients completed adjuvant therapy with follow-up, and 1 patients continue on adjuvant therapy. As of January 14, 2026, median OS for all patients was 11.100 months (95% CI: 8.818 -13.382), with 1-year OS rate 46.4%. Median PFS was 4.870 months (95% CI: 4.351 – 5.389), with 6-month PFS rate 39.3%. The 22 patients with recurrent glioblastoma (rGBM) showed the median OS of 11.670 months (95% CI: 8.303 -15.037), and the 1-year OS rate was 50.0%. The median PFS was 5.070 months (95% CI: 4.381 -5.759), with the 6-month PFS rate of 40.9% in the rGBM subgroup. Historical neoadjuvant anti-PD1 monotherapy for rGBM yielded OS 13.9 months and PFS 3.3 months (Nat Med. 2019). **Conclusions:** Camrelizumab in combination with apatinib neoadjuvant therapy showed excellent efficacy in recurrent high-grade gliomas, and was superior to PD1 inhibitor monotherapy neoadjuvant treatment in rGBM patients. Clinical trial information: NCT04588987. Research Sponsor: National Natural Science Foundation of China.

2062 **Poster Session**

An alternative approach to limiting surgical and radiation stress in patients with glioblastoma. First Author: Eduard E. Rostorguev, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation

Background: While neuro-oncology has seen global advances in high-tech diagnostics and treatments for brain tumors, these innovations often overlook the principles of the body's adaptive response. Stress acts as a nonspecific driver of cancer progression and is intensified by aggressive therapies. An alternative approach involves harnessing general nonspecific adaptive reactions (GNARs), which are governed by the brain's regulatory systems. These anti-stress GNARs — specifically the reactions of training, calm activation, and elevated activation — form the foundation of "activation therapy" and are considered essential in the comprehensive management of high-grade gliomas (HGG). In glioblastoma, tumor growth exacerbates cerebral hypoxia, leads to endothelial damage, and promotes thrombosis and perifocal edema. During radiation therapy (RT), edema is further aggravated as a deleterious side effect of ionizing radiation on brain tissue. This study aimed to investigate whether adjunctive activation transcranial magnetic therapy (ATMT) can mitigate edema development and improve treatment outcomes. **Methods:** Data from 50 patients with HGG were analyzed. Using simple randomization, patients were divided into two groups: the Main group (n=25) received standard treatment plus two courses of ATMT during the early postoperative period and during RT; the Control group (n=25) received standard treatment without ATMT. Each ATMT session consisted of two exposures. The first exposure was performed in the morning on the hypothalamic projection area using a frequency algorithm of 0.3 Hz (5 min) – 3 Hz (1 min) – 9 Hz (1 min) with a daily exponential change in induction (B) from 3 to 1 mT (device: "Gradient-4M"). The second exposure was performed 2.5–3 hours later using pulsed ATMT on the perifocal zone of the removed tumor bed with the same frequency algorithm at B=15 mT (device: "Neuro-MSD"). **Results:** In the early postoperative period (prior to RT), ATMT reduced the frequency of acute stress development by 3.4-fold compared to controls. After the completion of RT combined with ATMT, stress inhibition was observed 1.6 times more frequently than in the control group. The induction of a stable "reaction of calm activation" via ATMT contributed to a decrease in perifocal edema volume by an average of 3.75-fold, compared to 1.04-fold in the control group (p=0.0180). Regression of neurological symptoms after RT was noted in 92% of patients who received two courses of ATMT versus 68% in the control group (p=0.0391). Furthermore, the absence of cognitive impairment after RT was observed in 80% of ATMT patients compared to 24% in the control group (p=0.0002). **Conclusions:** The adjunctive use of ATMT improves treatment outcomes in patients with HGG by developing and maintaining anti-stress reactions as an alternative to surgical and radiation-induced stress, thereby improving the patients' quality of life. Research Sponsor: None.

2063 **Poster Session**

Management of first recurrence from IDH-wildtype glioblastoma with re-resection or stereotactic radiosurgery: A retrospective, international, multicenter study. First Author: Nico Teske, Department of Neurosurgery, Uniklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nuernberg, Erlangen, Germany

Background: Optimal management of recurrent glioblastoma remains ill-defined. While re-resection is frequently provided as local salvage therapy, stereotactic radiosurgery (SRS) might represent a treatment approach for small, focal recurrences. We comparatively evaluated outcomes after re-resection and SRS for first recurrence of IDH-wildtype glioblastoma. **Methods:** Adult patients with first radiographic recurrence of IDH-wildtype glioblastoma (WHO 2021 classification) were identified. Information on patients managed with re-resection were collected through the international eight-center database of the RANO *resect* group, and patients managed with SRS were collected by twelve centers from the IRRF study group. Survival after recurrence was analyzed using Kaplan–Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was applied to mitigate baseline imbalances. **Results:** Overall, 567 patients were included (re-resection: n = 310; SRS: n = 257). Compared with SRS, patients managed with re-resection were younger and had larger contrast-enhancing recurrence volumes. Despite those baseline differences, overall survival did not differ between treatment modalities (10.2 [95%CI 9.3–11.7] *vs.* 11.1 [10.3–12.8] months; HR 1.12, 95%CI 0.93–1.35; p = 0.231). Also, no survival differences between treatment groups were observed when effects of potential baseline confounders including tumor volume were minimized using IPTW. Notably, among patients typically not considered SRS candidates due to tumor volumes $>$10 cm³ (n = 234), maximal re-resection of the enhancing tumor (RANO class 1–2) was associated with survival comparable to SRS-treated low-volume tumors $\leq$10 cm³ (9.1 [7.7–11.5] *vs.* 11.0 [9.9–12.8] months; HR 1.27, 0.95–1.69; p = 0.106) whereas incomplete re-resection (RANO class 3) was associated with less favourable survival. In the subgroup of patients with focal recurrences in whom local physicians from the IRRF consortium perceived clinical equipoise between treatment modalities but eventually performed SRS (n = 112), IPTW-adjusted analyses demonstrated no significant difference in overall survival compared with re-resected patients (HR 0.90, 0.65–1.25; p = 0.539). **Conclusions:** While complete re-resection is prognostic in recurrent glioblastoma, SRS might represent a reasonable therapeutic approach for selected individuals with small low volume tumor recurrence. Given substantial baseline differences between patients treated with re-resection and SRS and potential treatment provider bias, prospective trials are warranted to guide nuanced decision-making. Research Sponsor: None.

2064 **Poster Session**

Phase II trial evaluating nivolumab in patients with recurrent IDH-mutant gliomas with and without hypermutation phenotype. First Author: Jing Wu, Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Tumor mutational burden (TMB) is an emerging biomarker for the prediction of immune therapy success in solid tumors. Response to immune checkpoint inhibitor (ICI) treatment in rare gliomas with biallelic mismatch repair deficiencies has been attributed to their hypermutation phenotype (HMP). This has not been tested in other gliomas. We developed a phase II clinical trial using nivolumab in recurrent IDH-mutant gliomas evaluating response in tumors with HMP (approximately 10% of cases) and in tumors with non-HMP (NHMP). Here we report the results of the analysis of the NHMP cohort. **Methods:** Adults with recurrent IDH-mutant glioma, KPS $\geq$ 60, normal organ function, with known somatic TMB (analyzed at NIH) were enrolled in a phase II trial. Nivolumab was given at 480mg IV every 28-day cycle with a maximum of 16 cycles. The primary endpoint is PFS rate at 6 months (PFS6) in both HMP and NHMP cohorts. Responses to treatment were evaluated by MRI every 2 cycles using iRANO criteria. Simon's two-stage design was used to independently evaluate the HMP/NHMP cohort. For the NHMP cohort, the null and alternative hypotheses for PFS6 are 0.2 and 0.4, respectively. A total of 30 were planned to be accrued across stages I and II. If $\geq$10 patients are progression-free at 6 months, the null hypothesis will be rejected, indicating that the treatment is promising for patients with NHMP IDH-mutant gliomas. The design controls the type I error at 0.05 and yields a power of 0.8. Tumor samples and peripheral blood were collected for correlative studies. Patient-reported outcomes (PRO) were evaluated by longitudinal symptom burden analysis using Brain Tumor Module of the MD Anderson Symptom Inventory. **Results:** As of January 2026, thirty patients were enrolled and treated on the NHMP cohort (TMB$<$5 mut/Mb). Among 30 evaluable patients, 20 were male, median age 44 and KPS 90. Histological diagnosis included 22 astrocytoma (grade 3, n=10; grade 4, n=12) and 8 oligodendroglioma (grade 2, n=1; grade 3, n=7). Median number of prior recurrences is 2, ranging from 1 to 5. At the time of analysis, all 30 evaluable patients were off study treatment: 7 completed all 16 cycles, 17 had disease progression, 3 withdrew to start other management. Three patients were off treatment due to treatment related grade 3 colitis, pneumonitis and dry mouth. Eleven and 8 out of 30 patients were progression free at 6 and 12 months, respectively. PRO and correlative studies are ongoing. **Conclusions:** Nivolumab is well tolerated and has shown efficacy in a cohort of patients with recurrent IDH-mutant gliomas with low TMB. Clinical benefit measured by objective response, PFS, OS and PRO, along with longitudinal immune monitoring, will help determine whether tumor TMB correlates with immunologic and clinical response to ICI therapy in IDH-mutant gliomas. Clinical trial information: NCT03718767. Research Sponsor: NIH Intramural Research.

2065 **Poster Session**

A phase 2 double-blind, randomized, prospective, placebo-controlled study of $NanO_2$ combined with radiation and temozolomide in patients with newly diagnosed glioblastoma: RESTORE. First Author: Samuel A. Goldlust, Saint Luke's Cancer Institute, Kansas City, MO

Background: Glioblastoma (GBM) contains extensive hypoxic regions due to tumor-associated thrombosis and abnormal vasculature. Hypoxia drives resistance to radiation (RT) and temozolomide (TMZ) by limiting oxygen-dependent DNA damage, enabling DNA repair, and reducing drug efficacy and delivery. The RESTORE trial (NCT03862430) is the first randomized, prospective, placebo-controlled study of $NanO_2$ (2% w/v dodecafluoropentane emulsion) in GBM, a fluorocarbon-based oxygen therapeutic hypothesized to reoxygenate hypoxic GBM tissue, with the goal of enhancing the efficacy of chemoradiation. **Methods:** Patients with newly diagnosed GBM (WHO 2021) received standard-of-care radiation (60 Gy) with concurrent TMZ (75 mg/m²/day). Patients were randomized 2:1 to receive either $NanO_2$ or 0.9% sodium chloride administered intravenously immediately prior to each RT fraction, with continuous supplemental oxygen given during the infusion and RT. Following chemoradiation, patients completed a four-week recovery period before initiating adjuvant TMZ for 6 cycles. The primary endpoint is progression free survival and secondary endpoints include overall survival, objective response rate, pseudoprogression rate, and patient reported outcomes. **Results:** Between May 2023 and October 2025, 93 patients were treated (safety set). The study has completed the planned enrollment. Median age was 63 years (range, 19–84) and 57% were men. As of the data cutoff on 12/29/25, all patients completed the follow up visit 4 weeks after chemoradiation. Sixty-eight patients (73%) remained on study undergoing adjuvant TMZ or in long-term follow-up. Twenty-one patients passed of tumor progression and 4 patients withdrew consent. The median duration on study was 8.7 months (range, 1.3–31.4). During chemoradiation and the four-week recovery, 63 treatment-emergent adverse events (TEAEs) of CTCAE severity grade $\geq$3 were reported in 37% of patients, with brain edema, lymphocyte count decreased, and platelet count decreased being the most frequently reported. Twenty-six treatment-emergent serious adverse events (TESAEs) occurred in 19% of patients, with embolism, pulmonary embolism, and seizure being the most frequently reported. Three TESAEs were assessed as possibly or probably related to study drug; none were unexpected. Survival follow up is ongoing. **Conclusions:** In this blinded, pooled safety analysis of a randomized phase 2 trial in newly diagnosed GBM, the study treatment was well tolerated and no new safety signals were identified. Treatment allocation remains blinded. Efficacy outcomes and arm-specific safety analyses will be reported after completion of the primary endpoint analysis. Clinical trial information: NCT03862430. Research Sponsor: NuvOx Therapeutics.

2066 **Poster Session**

Mapping the exhausted and tolerized myeloid populations in the glioblastoma tumor microenvironment. First Author: Yu-Ting Tsai, Wake Forest University School of Medicine, Winston-Salem, NC

Background: Glioblastoma (GBM) is a highly malignant brain tumor characterized by an immunosuppressive microenvironment and rapid development of therapeutic resistance. In GBM, myeloid cells can comprise 30–50% of the tumor and critically regulate its immune microenvironment. Evidence from aging and CNS diseases suggests that microglia can adopt dysfunctional states of exhaustion and tolerance that extend beyond the M1/M2 paradigm, thus prompting us to investigate whether these phenotypes contribute to immune escape and progression of GBM. **Methods:** Paired RNA-seq of tumor specimens from newly diagnosed and recurrent GBM patients (n=14) was used to examine aging-related gene expression during treatment and progression. Open-access human glioma single-cell RNA-seq data (GSE182109) were analyzed to characterize exhaustion and tolerance across macrophage subpopulations based on molecular/metabolic signatures. **Results:** Patient tumor RNA-Seq revealed that the aging-related TREM2-APOE axis is present in recurrent GBM, suggesting accelerated brain aging. Single-cell RNA-seq identified nine myeloid clusters, including four microglial states (homeostatic-, activated-, AP-, and a-microglia) and two macrophage populations (anti-inflammatory and immunosuppressive). We found that AP-microglia showed disease-associated activation, with high CD45/CD11C/TREM2 expression and concurrent upregulation of the exhaustion markers PD-L1 and CD38. Moreover, microglial activation-related signaling in AP-microglia includes increased STAT1/2-IRF9 signaling, which can promote immunosuppression by inducing PD-L1. On the other hand, a-microglia is unique in its high expression of activation-restraining and tolerance markers, such as SPRY/P2RY13, rather than the classic microglial marker TMEM119/P2RY12. Both AP-microglia and a-microglia are shown to lose expression of the inflammatory cytokines TNF-α and IL-1β, consistent with the characteristics of exhausted and tolerized microglia. Unlike resident microglia, the immunosuppressive macrophage cluster exhibits a monocyte-tolerized phenotype, with downregulated FABP4 and increased SOD2, CLEC4E, and SLC2A6. It also shows a similar panel of LPS-induced monocyte exhaustion with TLR4/MyD88/SRC and STAT3/IL-10 upregulation. **Conclusions:** Our analysis indicates that AP-microglia are exhausted and a-microglia are tolerized in GBM, with shared markers of dysfunction across macrophages linking myeloid impairment to immune suppression and treatment-associated brain aging. These findings implicate myeloid exhaustion in GBM immune escape and identify potential therapeutic targets. Research Sponsor: Louise McMichael Miracle Fund.

2067 **Poster Session**

A 3D tumorwide multi-omic atlas of intratumoral heterogeneity in *IDH*-mutant glioma. First Author: Benjamin Joshua Lerman, University of California, San Francisco, San Francisco, CA

Background: Isocitrate dehydrogenase mutant (IDHmut) glioma affects over 20,000 adults per year. Treatment failure often results from intratumoral heterogeneity, in which genomic subclones undergo selection for treatment-resistant populations. Understanding this heterogeneity is critical to selecting therapeutic combinations that are efficacious across the entire tumor, but few genomic studies go beyond analyzing a single tumor sample per patient. **Methods:** 3D whole tumor sampling was used to obtain 324 spatially mapped samples from 32 IDHmut gliomas. Whole exome (n=323), RNA (318), ATAC sequencing (92), and Hi-C (14) were performed. PyClone reconstructed clonal evolution, weighted gene/peak correlation network analyses derived co-expression (RNA) and gene regulatory (ATAC) programs, and comparison of tumor Hi-C results to normal brain identified tumor-specific chromatin loops. **Results:** Regional tumor content (purity) inversely correlated with distance from tumor centroid (R = -0.32, $p = 2.8\times10^{-8}$) and inter-sample distance was associated with subclonal (R = 0.24, $p = 8.1\text{x}10^{-15}$) and transcriptional (R = 0.12, $p = 1.0\text{x}10^{-5}$) similarity. Beyond IDH1 in the combined 17 astrocytomas and 15 oligodendrogliomas, tumor-wide alterations were recurrently observed in TP53 (altered in 64%; tumor-wide in 58%), ATRX (55%; 39%), TERT promoter (45%; 45%) and FUBP1 (18%; 6%). Despite high cohort prevalence, glioma-associated drivers CIC (altered in 42%), PIK3CA (36%), and ARID1A (18%) were tumor-wide in only one patient each, while MUC4 (33%), NOTCH1 (27%), SETD2 (24%), and PIK3R1 (15%) were never observed in the tumor founding clone. Tumors with CIC alterations harbored a median of 5 unique mutations with a median combined tumor-wide cancer cell fraction of 45%. Hi-C identified 5,579 tumor-specific promoter-enhancer interactions across 4,144 loops. The genes associated with these promoters enriched for tumor-specific RNA programs associated with OPC signature ($p_{adj} = 3\text{x}10^{-14}$), NPC signature ($p_{adj} = 3.87\text{x}10^{-14}$), and neuronal mimicry (1.2×10^{-13}). We discovered adversely prognostic gene expression programs in astrocytoma independently validated in chromatin regulatory programs. **Conclusions:** Tumor-wide sampling of IDHmut glioma revealed evidence of radial tumor growth and 3D patterns of cellular organization, in sharp contrast to intermixed patterns in IDH wildtype glioma. Most inter-patient heterogeneity in driver alterations was subclonal. Our data also revealed regulatory loops that explain tumor cell-specific expression signatures. A significant, adverse prognostic marker in astrocytoma was discovered and cross-validated. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

2068 **Poster Session**

Identification of prognostically relevant residual tumor burden in glioblastoma after surgery: A comparative analysis of MR-based RANO resect classes vs [^{18}F]FET PET. First Author: Jens Blobner, Department of Neurosurgery LMU, Munich, Germany

Background: Accurate assessment of postoperative residual tumor burden is critical in *IDH*-wildtype glioblastoma. The MRI-based RANO resect classification stratifies patients according to postoperative contrast-enhancing and non-contrast enhancing tumor volume but may underestimate metabolically active residual disease. The additional prognostic value of postoperative [^{18}F]FET PET beyond MRI is yet unclear. **Methods:** This retrospective bicentric study included 140 patients with newly diagnosed *IDH*-wildtype glioblastoma and evaluable postoperative MRI and [^{18}F]FET PET. Residual tumor volumes were segmented on MRI and classified according to the RANO resect system. PET-derived residual metabolic tumor volumes were defined using PET RANO 1.0 criteria. Spatial agreement between MRI- and PET-based volumes was quantified using Dice coefficients. Associations with overall survival were analyzed using Cox regression. Incremental prognostic value of PET was assessed using an imaging-only model (contrast-enhanced T1 (T1CE) vs. T1CE + PET) and a fully adjusted model including clinical covariates. **Results:** PET-derived residual tumor volumes exceeded MRI-defined volumes and showed low spatial concordance with MRI (Dice coefficient: 0.01–0.25) across all RANO resect classes. Postoperative PET-, T1CE-, and T2/FLAIR-derived tumor volumes were each associated with overall survival. Increasing PET-derived residual tumor burden was associated with a continuous increase in mortality risk. In multivariable Cox regression, PET-derived residual tumor volume remained independently associated with overall survival (adjusted hazard ratio 1.021 per cm³, 95% CI 1.008–1.033; $^{**}p$ = 0.0024). In the imaging-only model, addition of PET improved time-dependent discrimination between 6 and 24 months (ΔAUC(t) 0.03–0.07) and increased Harrell's C ($\Delta C \approx 0.03$). In the fully adjusted model, PET provided significant non-redundant prognostic information (likelihood ratio test, $^{*}p$ = 0.0049). **Conclusions:** Postoperative [^{18}F]FET PET identifies metabolically active residual tumor not adequately captured by MRI and provides additional prognostic information beyond MRI-based assessment. Integration of PET into postoperative evaluation may refine prognostic stratification in IDH-wildtype glioblastoma. Research Sponsor: None.

2069 **Poster Session**

Phase I/II study of liposomal curcumin in combination with standard radiation and temozolomide in patients with newly diagnosed high-grade gliomas. First Author: Matthias Holdhoff, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: Liposomal curcumin (LC) is an intravenous formulation designed to enhance curcumin delivery and modulate inflammatory, oxidative, and oncogenic pathways relevant to high-grade glioma (HGG), including dysregulated kynurenine metabolism. Preclinical studies demonstrate synergy between LC and chemoradiation. This Phase I/II study was designed to determine the recommended Phase II dose (RP2D) of weekly IV LC with radiotherapy and temozolomide (RT/TMZ) in newly diagnosed HGG (primary objective), assess safety and feasibility (secondary objective), and preliminary efficacy (exploratory objective). **Methods:** This open-label, sequential dose-escalation study used the TITE-BOIN Bayesian design to evaluate LC at 300, 350, and 400 mg/m². Patients received standard chemoradiation (2 Gy $\times$ 5 days/week $\times$ 6 weeks with concomitant TMZ 75 mg/m²/day), followed by standard adjuvant TMZ and weekly LC infusions over 3 hours for a target of 34 doses, with optional continuation. Eligible patients had newly diagnosed HGG (WHO grade 3 or 4) and KPS $\geq$70%. Patients were evaluable if they received $\geq$80% of planned LC infusions and $\geq$60% of planned TMZ dosing during the 10-week toxicity evaluation period. Radiographic response was assessed per RANO 2.0. **Results:** Twenty-five patients were treated: 300 mg/m² (n=6), 350 mg/m² (n=12), and 400 mg/m² (n=7); all patients assigned to 400 mg/m² were treated at 350 mg/m² per Safety Review Committee recommendation. All patients had glioblastoma or molecular glioblastoma, IDH-wildtype, WHO grade 4 per 2021 WHO classification (MGMT promoter methylation status: 7 methylated, 1 indeterminate, 17 unmethylated). Median age was 56 years (range, 43–75); median KPS was 90 (range, 70–100). Two protocol-defined dose-limiting toxicities occurred at 400 mg/m²: grade 4 pancytopenia and grade 1 hemolysis. LC-related grade $\geq$3 toxicities occurred in 4 patients (16%) and included confusion, seizure, thromboembolic event, cerebral edema, lymphopenia, thrombocytopenia, fatigue (all grade 3), and pancytopenia (grade 4). There were no LC-related deaths. Based on the TITE-BOIN design and cumulative safety data, 350 mg/m² was identified as the RP2D. With a median follow-up of 12.9 months (range, 2.4-27.3 months) as of 1/23/2026, median progression-free and overall survival have not been reached. At 6 and 12 months from first LC infusion, 95% and 87% of uncensored patients (n=18, n=13), respectively, remained alive. **Conclusions:** LC combined with standard chemoradiation was safe and well tolerated, with encouraging exploratory signals of disease control in newly diagnosed glioblastoma. Further evaluation in an expanded Phase II/III study is planned. Clinical trial information: NCT05768919. Research Sponsor: Signpath Pharma.

2070 **Poster Session**

Phase I trial to evaluate the safety and tolerability of fb-PMT in patients with recurrent glioblastoma. First Author: Nicholas Alfred Blondin, Yale University School of Medicine, New Haven, CT

Background: Proliferative, pro-angiogenesis, and pro-inflammatory actions mediated by L-thyroxine in glioblastoma (GBM) are initiated at cell surface thyrointegrin $\alpha v\beta 3$ receptors for thyroid hormone, located on the extracellular domain of $\alpha v\beta 3$ integrin. Thyrointegrin $\alpha v\beta 3$ receptors are over-expressed in cancer and rapidly dividing endothelial cells. fb-PMT (NP751) is a macromolecule in which fluorobenzyl is conjugated to monodisperse polyethylene glycol via mono-triazole tetraiodo thyroacetic acid, with high affinity and specificity for thyrointegrin $\alpha v\beta 3$ receptors. In pre-clinical murine xenograft models, fb-PMT resulted in a dose-dependent suppression of GBM tumor growth and viability, and histopathological analysis revealed loss of the vascularity along with extensive tumor necrosis and apoptosis. Genomic micro-array studies suggested multiple growth pathways in GBM are modulated by fb-PMT. Based on this promising pre-clinical data, we conducted a first-in-human Phase 1 study of fb-PMT in patients with recurrent GBM. **Methods:** Patients with first or second recurrence of GBM were enrolled to receive fb-PMT via subcutaneous injection once daily for 28-day cycles, following a 3+3 design. Predefined dose levels were 0.08, 0.24, 0.48, 0.96, and 1.44 mg/kg/day, respectively. The study objectives were to evaluate the safety and tolerability of daily administration of fb-PMT, and establish the recommended phase 2 dose (RP2D) of fb-PMT. Exploratory objectives included pharmacokinetic profiling of fb-PMT, expression of $\alpha v\beta 3$ integrin, fb-PMT, and other proteins in available tumor samples, and estimating preliminary efficacy of fb-PMT. **Results:** As of January 2026, accrual has been completed, with 22 patients enrolled and 20 patients completing at least one treatment cycle. Treatment with fb-PMT was well tolerated across the 5 dose levels examined. No serious adverse events (SAEs) related to fb-PMT and no dose-limiting toxicities occurred; the RP2D is 0.96 mg/kg/day. PK analysis demonstrated a dose-dependent increase in systemic drug exposure with escalating doses. Immunohistochemical evaluation of integrin $\alpha v\beta 3$ expression in available tumor samples detected target expression, with variable levels of integrin $\alpha v\beta 3$ expression and predominant localization to tumor-associated vasculature and regions of necrosis and hemorrhage. Preliminary efficacy evaluation is ongoing, with two patients in Cohort 4 (0.96 mg/kg/day) having partial response and remaining on study (cycle 35+ and cycle 26+, respectively). **Conclusions:** This Phase 1 study demonstrated that treatment of recurrent glioblastoma with fb-PMT was safe and well tolerated, with a predictable pharmacokinetic profile. Two patients remain on therapy beyond 24 months. Future studies are planned. Clinical trial information: NCT05226494. Research Sponsor: NanoPharmaceuticals LLC.

2071 **Poster Session**

Suicide gene therapy for recurrent glioblastoma using allogeneic bone marrow–derived mesenchymal stem cell gene delivery (MSC/CD): A first-in-human, dose-escalation phase I clinical trial. First Author: Jaejoon Lim, Department of Neurosurgery, CHA Bundang Medical Center, CHA University College of Medicine, Seongnam, South Korea

Background: Glioblastoma (GBM) remains an incurable brain tumor characterized by complex heterogeneity and poor prognosis, even with maximal multimodal therapy. Innovative treatments for recurrent GBM are urgently needed to complement existing therapies. This study explores the feasibility, safety, and efficacy of a novel suicide gene therapy using allogeneic mesenchymal stem cells (MSCs) expressing cytosine deaminase (CD) in combination with 5-fluorocytosine (5-FC). **Methods:** A Phase 1, single-center, non-randomized, dose-escalating study was conducted to evaluate the safety and efficacy of mesenchymal stem cell expressing cytosine deaminase (MSC/CD) therapy in 10 patients with recurrent GBM. Patients received intratumoral injections of MSC/CD followed by oral 5-FC. Pharmacokinetic profiling, pharmacodynamic analysis, targeted panel sequencing, whole transcriptome analysis, integrative omics analysis, and multiplexed immunofluorescence imaging were performed to assess drug conversion and identify predictable candidate biomarkers. Safety and survival outcome were monitored by evaluating adverse events (AEs) and clinical data. **Results:** MSC/CD therapy was well-tolerated, with most AEs being mild to moderate. There was no drug toxicity related with dose escalation. Severe AEs (≥ Grade 3) were rare and unrelated to the study drug. Effective conversion of 5-FC to 5-fluorouracil (5-FU) was observed in the brain, with detectable levels in the cerebrospinal fluid, confirming the feasibility of intracranial drug delivery. The median progression-free survival was 5.4 months, and the overall survival was 16.3 months. RNA transcriptomic analysis revealed two molecular subclusters with distinct biological characteristics, correlating with different progression-free survival outcomes. The integrative omics analysis revealed that specific cell cycle-related genes were found to be highly expressed in the non-responder group of patients, suggesting that elevated levels of these genes may be associated with resistance to treatment. **Conclusions:** This study demonstrates that MSC/CD therapy is a feasible, safe, and potentially effective treatment for recurrent GBM. The identification of distinct molecular subtypes and candidate genes offers a potential biomarker for patient selection and therapeutic targeting. Further studies are warranted to validate these findings and optimize therapeutic strategies. Clinical trial information: NCT04657315. Research Sponsor: he Ministry of Trade, Industry & Energy (MOTIE, Korea); 10067378.

2072 **Poster Session**

Intrathecal iPSC-derived natural killer cells combined with the Stupp regimen for newly diagnosed WHO grade 4 glioma: A phase I trial. First Author: Yulun Huang, The Fourth Affiliated Hospital of Soochow University, Soochow, China

Background: WHO grade 4 glioma has a poor prognosis despite standard Stupp therapy. Induced pluripotent stem cell–derived allogeneic natural killer cells (iPSC-NK) represent a standardized and scalable cellular immunotherapy with consistent cytotoxic potential. This Phase I study evaluated intrathecal iPSC-NK cells combined with the Stupp regimen in newly diagnosed WHO grade 4 glioma. **Methods:** Thirteen newly diagnosed WHO grade 4 glioma patients (median age 46 years; IDH-wildtype n=11; MGMT-methylated n=6) received standard chemoradiotherapy followed by intrathecal iPSC-NK cell infusions. iPSC-NK cells were administered at escalating doses (2×10^7, 6×10^7, 2×10^8 cells/cycle) via lumbar puncture (n=8) or Ommaya reservoir (n=5) over four 28-day cycles, with temozolomide priming 5 days before each infusion. The primary endpoint was safety (serious adverse events, ≥Grade 3 toxicities); secondary endpoints included progression-free survival and pharmacokinetic/pharmacodynamic immune analyses. **Results:** Across 54 intrathecal iPSC-NK infusions, treatment-related toxicities were predominantly low grade: fever occurred as Grade 1 in 35 (64.8%) and Grade 2 in 9 (16.7%) infusions; headache as Grade 1-2 in 19 (35.2%) and Grade 3 in 1 (1.9%) infusion; and cytokine release syndrome was limited to Grade 1 events (44/54, 81.5%), with no ≥Grade 2 CRS or ICANS. Median PFS was 17.41 months, while median OS was not reached at a median follow-up of 22.47 months (data cutoff: January 18, 2026). PK analysis showed detectable iNK cells in CSF on Days 1–3 post-infusion, peaking on Days 1–2 and declining by Day 3. PD analyses demonstrated rapid activation of $CD4^+$/$CD8^+$ T cells ($CD69^+$) and expansion of myeloid populations. Olink proteomics revealed consistent upregulation of cytotoxic (GZMA/B), chemokine (CXCL/CCL), and inflammatory cytokines (TNF, IFN-γ). **Conclusions:** iPSC-NK cells combined with the Stupp regimen demonstrated a favorable safety profile, induced early immune activation within the central nervous system, and showed encouraging preliminary efficacy in patients with WHO grade4 glioma. Clinical trial information: NCT06147505. Research Sponsor: National Natural Science Foundation of China; 82472981; XellSmart Biopharmaceutical (Suzhou) Co., Ltd.

2073 **Poster Session**

Comparative response assessment using PET-RANO 1.0 and RANO 2.0 in vorasidenib-treated *IDH*-mutant gliomas: The VORAFET study. First Author: Alberto Bosio, Medical Oncology 1, Veneto Institute of Oncology IOV - IRCCS, Padova, Italy

Background: MRI-based response assessment may be suboptimal for capturing early treatment effects during isocitrate dehydrogenase (*IDH*) inhibition. We compared metabolic and morphological response classification using PET-RANO 1.0 and RANO 2.0 in vorasidenib-treated *IDH*-mutant gliomas and assessed treatment-related metabolic changes. **Methods:** All consecutive patients treated at Veneto Institute of Oncology and Padua University Hospital with vorasidenib (VOR) under a compassionate-use program (June 2024-March 2025) with baseline and follow-up [^{18}F]FET PET/MR were retrospectively included. Response was assessed every 3 treatment cycles according to PET-RANO 1.0 and RANO 2.0. PET-positive tumor volumes and tumor-to-background ratios (TBR_{max}, TBR_{mean}) were analyzed. MRI response was evaluated using volumetric RANO 2.0 criteria. The VORAFET study was approved by the local Ethics Committee. **Results:** Twenty-six patients were included (10 astrocytomas, 16 oligodendrogliomas; 22 WHO grade 2, 4 non-enhancing WHO grade 3). Median follow-up from VOR initiation was 9 months (IQR 9-11). According to PET-RANO 1.0, partial metabolic responses (PET-PR) increased over time, from 20% at 3 months to 30.8% at 6 months and 63.6% at 9 months, while metabolic progression (PET-PD) was already detected in 18.2% at 9 months. In contrast, RANO 2.0 identified no partial responses at any timepoint, classifying most patients as stable disease (84.2%) or minor response (10.5%), with progression detected in only 5.3% at 9 months. Quantitative PET analysis showed an early and sustained reduction in metabolic activity. TBR_{mean} decreased significantly at 3 months (mean difference [MD] -0.04; 95% CI -0.08 to -0.01) and continued to decline at 9 months (MD -0.07; 95% CI -0.11 to -0.02). Compared to baseline, at 9 months, TBR_{max} decreased from 2.7 to 2.0 (MD -0.5; 95% CI -0.8 to -0.2) in all patients included. No significant changes were observed in PET volumes. Similarly, FLAIR-based tumor volume showed no significant variation (at 9 months: MD -2.2; 95% CI -5.1 to 0.7). **Conclusions:** PET-RANO 1.0 enabled earlier detection of treatment response and progression compared with MRI-based RANO 2.0, highlighting clinically relevant limitations of morphology-driven MRI-based assessment. These findings support the clinical integration of amino acid PET into response monitoring strategies and warrant prospective validation of PET-derived biomarkers in *IDH*-mutant gliomas. Research Sponsor: None.

2074 **Poster Session**

Phase II clinical study of ACT001 combined with radiotherapy in newly diagnosed pediatric diffuse intrinsic pontine glioma. First Author: Jing Zhang, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Background: Diffuse intrinsic pontine glioma (DIPG) is an extremely lethal type of malignant tumor in the central nervous system of children. Currently, standard radiotherapy has limited efficacy, and there is an urgent need to explore novel therapeutic regimens. This study aims to evaluate the safety and efficacy of ACT001, a novel blood-brain barrier-permeable agent, combined with standard radiotherapy in the treatment of newly diagnosed pediatric DIPG. **Methods:** This open-label, single-arm, multicenter phase II trial enrolled 5–15-year-old patients with newly diagnosed DIPG. Patients received radiotherapy (54 Gy/30 fractions) plus ACT001 (700 mg/m² BID orally, fasting) for 6 weeks (concurrent phase), followed by ACT001 maintenance until progression/toxicity. The primary endpoints were objective response rate (ORR) and overall survival (OS), while the secondary endpoints included progression-free survival (PFS), 1-year OS rate, and safety. Statistical analyses used Kaplan-Meier and Cox regression. **Results:** A total of 41 patients were screened, with 33 included in the full analysis set (FAS). Thirty-one patients completed the concurrent phase and were included in the per-protocol (PP) set. The median age was 8 years; 18.2% (6 cases) were biopsy-confirmed (83.3% harboring the H3K27M mutation) and 81.8% (27 cases) were radiologically diagnosed. In the FAS, ORR was 30.3% (10 partial responses [PR]), and the disease control rate was 75.8%; 21.2% (7 cases) in the PP set achieved >50% tumor reduction in pontine lesions. Median OS was 12.7 months (95% CI: 8.7–NA) with a 1-year OS rate of 50.1%; median PFS was 5.9 months (95% CI: 4.3–7.8) with a 6-month PFS rate of 45.3%. Multivariate analysis showed a higher baseline Lansky score was a favorable prognostic factor for OS (HR=0.899, P=0.0069), and achieving PR was favorable for PFS (HR=0.232, P=0.0162). Nineteen patients received salvage therapy post-progression; those undergoing re-irradiation had a median OS of 17.9 months, significantly better than non-re-irradiated patients (P=0.031). Ninety-six point nine percent (32/33) of patients experienced treatment-related AEs (mostly grade 1–2). The incidence of grade ≥3 AEs was 18.2%, with the most common being lymphopenia, weight loss, and upper respiratory tract infection (each 6%). No treatment-related deaths occurred, and no patients discontinued ACT001 due to toxicity. Additionally, 96.9% (31/32) of patients had improved or stable Lansky scores post-treatment. **Conclusions:** ACT001 combined with standard radiotherapy exhibits certain antitumor activity in the treatment of newly diagnosed pediatric DIPG, with improved OS compared to historical data, as well as a manageable safety profile and good tolerability. This regimen provides a new treatment option for pediatric DIPG and warrants further verification in larger-scale randomized controlled trials. Clinical trial information: ChiCTR2300074598. Research Sponsor: None.

2075 **Poster Session**

Application of PET RANO 1.0 criteria and associations with outcome in *IDH*-mutant gliomas: A retrospective cohort study. First Author: Maximilian Mair, Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria

Background: Amino acid PET is increasingly used to guide clinical decisions in glioma. For standardized response assessment, PET RANO 1.0 criteria have been formulated, but are primarily consensus-based and lack validation in molecular subgroups of diffuse gliomas. **Methods:** In this retrospective cohort study, patients with newly diagnosed or recurrent *IDH*-mutant glioma and at least two O-(2-[^{18}F]-fluoroethyl)-L-tyrosine ([^{18}F]FET) PET scans in 02/2013 - 08/2025 were included. PET was evaluated using PET RANO 1.0 criteria based on maximum and mean tumor-to-background ratios (TBR_{max}/TBR_{mean}) and PET volume. Intervention-free survival (IFS) was used as endpoint. **Results:** Overall, 219 patients (110 [50.2%] oligodendroglioma, 106 [48.4%] astrocytoma, 3 with unknown 1p/19q status; 115 [52.5%] CNS WHO 2, 80 [36.5%] CNS WHO 3, 23 [10.5%] CNS WHO 4, 1 grading inconclusive) with 251 lesions were included. Median age at first PET was 45 years (range: 21-75), and 117 (53.4%) patients were male. In total, 220 treatment lines (173 [78.6%] first line treatment; 47 [21.4%] recurrence/progression) were followed, of which 135 (61.4%) involved radiotherapy and/or systemic treatment, and 85 (38.6%) observation. Median time between PET scans was 6.7 months (2.4-11.8). In first-line treatment at baseline, PET-based measurable disease was seen in 126/173 (72.8%), non-measurable in 38/173 (22.0%) and no measurable disease in 9/173 (5.2%). PET-based complete remission (PET-CR) was observed in 7/173 (4.0%), partial remission (PET-PR) in 32/173 (18.5%), stable disease (PET-SD) in 74/173 (42.8%), and progressive disease (PET-PD) in 60/173 (34.7%) patients. The primary driver of PET-PD was an increase in PET volume alone (27/60, 45.0%) or in combination with an increase in TBR_{max}/TBR_{mean} (19/60, 31.7%), followed by new measurable disease in 14/60 (23.3%) patients. In astrocytoma, IFS was shorter in patients with PET-PD (median: 10.0 months; 95%CI: 8.3-32.6) compared to PET-SD/-PR/-CR (33.0 months; 95%CI: 22.0-52.1; p = 0.043). Similar differences were seen in oligodendroglioma (PET-PD: 16.0 months; 95%CI: 11.7-63.3; vs. PET-SD/-PR/-CR: 34.5 months; 95%CI: 24.3-57.0; p = 0.036). At treatment for recurrence, baseline PET showed measurable disease in 37/47 (78.7%) and non-measurable disease in 10/47 (21.3%) patients. PET-CR was seen in 3/47 (6.4%), PET-PR in 16/47 (34.0%), PET-SD in 24/47 (51.1%) and PET-PD in 4/47 (8.5%) patients, with numerical differences in IFS (p = 0.16) according to PET response in recurrent disease. In both first-line treatment and recurrence, measurable disease at baseline was not associated with PET response ($p > 0.05$). **Conclusions:** Response assessment based on PET RANO 1.0 criteria is associated with outcome in *IDH*-mutant glioma. Further analyses considering MRI-based response assessment are ongoing for further validation of PET-based clinical trial endpoints. Research Sponsor: European Society for Medical Oncology (ESMO); (awarded to MJM).

2076 **Poster Session**

Pooled analysis of phase I and expanded access study cohorts of DOC1021 (dubodencel) in combination with chemoradiation for glioblastoma. First Author: Jay-Jiguang Zhu, The University of Texas Health Science Center, Neurosurgery, Houston, TX

Background: Glioblastoma (GBM) is a poor-prognosis brain malignancy with median overall survival (mOS) of ~12-18 months despite aggressive standard of care (SOC) treatment. DOC1021 is an autologous dendritic cell (DC)-based immunotherapy generated by tandem loading with autologous tumor-derived mRNA and lysate, enabling broad antigen presentation. DOC1021 leverages p38MAPK and mTORC1 signaling cascades to initiate cDC1-like skewing of monocyte-derived DC, leading to potent downstream development of $CD8^+$ tissue-homing, cytolytic effector memory cells. **Methods:** This pooled analysis includes newly diagnosed and recurrent IDH-wt patients from two clinical trials (Phase I Study 8148 [NCT04552886] and Expanded Access Protocol EAP0001), treated with DOC1021 after resection and SOC chemoradiation. DOC1021, prepared from mobilized peripheral blood mononuclear cells (PBMC) loaded consecutively with autologous amplified tumor mRNA and tumor lysate, was administered bilaterally near deep cervical lymph node chains every other week for 3 administrations with weekly pegylated-IFN. Study 8148 (n=18) evaluated 4 dose levels (3.5×10^6 to 36×10^6 cells), while Study EAP0001 (n=7) administered only the highest dose level (36×10^6 cells). Patients with subtotal resection or pre-treatment progression were not excluded. Blood was collected before and after DOC1021 to assess peripheral immune responses. **Results:** Among the pooled population (N=25), median age was 58 years (range 47-75), 88% MGMT unmethylated, 24% partially resected, and 16% recurrent disease. There were no dose-limiting toxicities, and a similar safety profile between studies. Common AEs included mild, flu-like symptoms and injection-site reactions. One patient in the EAP study experienced grade 3 cerebral edema after the first DOC1021 dose that fully resolved and subsequent DOC1021 doses were completed per protocol. At the time of analysis, 7 of 21 newly diagnosed patients remain alive ~9-30 months post-surgery. Among recurrent patients (n=4), 2 patients remain alive ~16-20 months after second resection. Pseudo-progression within ~6 months of vaccination was commonly observed. Analysis of post-vaccination PBMC indicated expansion of $CD4^+$ (17/20 patients, mean +28.6%, p=0.0006) and $CD8^+$ (15/20 patients, mean +26.8%, p=0.001) central memory T-cell (T_{CM}) compartments as well as substantial upregulation of CD127 expression on circulating $CD8^+$ T cells (18/20; mean MFI +72.2%, p=0.03). **Conclusions:** Collectively, the data show that DOC1021 plus SOC is well-tolerated, feasible, and potentially efficacious in a challenging population that included subtotal resections, pre-treatment progression, and majority MGMT unmethylated. A multicenter, randomized, open-label Phase 2 trial (NCT06805305) in newly diagnosed GBM is now enrolling to compare DOC1021+SOC vs SOC treatment alone. Clinical trial information: NCT04552886. Research Sponsor: Diakonos Oncology; Cancer Cures 4 Kids.

2077 **Poster Session**

INB-200: Phase I study and characterization of gene-modified autologous gamma delta (γδ) T cells in newly diagnosed glioblastoma multiforme (GBM). First Author: Louis B. Nabors, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL

Background: Cell therapy for glioblastoma (GBM) holds promise but previous studies have not demonstrated durable responses or improved progression free survival (PFS). We provide updated findings from our assessment of any patients who completed treatment with drug-resistant immunotherapy (DRI) in newly diagnosed GBM. **Methods:** DRI combines the polyclonal upregulation of stress-antigens with concurrent local delivery of MGMT-modified γδ T cells, engineered to resist temozolomide (TMZ) driven lymphodepletion. The standard-of-care (SOC) chemotherapy TMZ induces transient upregulation of tumor-associated NKG2D-L stress antigens enabling the functional γδ T cells to identify and eradicate residual cancer cells during the period of maximum tumor vulnerability. Patients received 1×10^7 DRI cells/dose into the resection cavity with 150 mg/m^2 of IV TMZ on Day 1 of each maintenance cycle.17 patients received treatment, including 3 who received only a single dose (Cohort 1). 14 patients received repeated doses (3 to 6), (median age 64 (range: 33-75); 93% IDH-WT, 50% MGMT-unmethylated, 57% subtotal resection, KPS 80). 10 contemporaneously enrolled patients treated with SOC only (median age 67 (range: 49-77); 100% IDH-WT, 60% MGMT-unmethylated, 20% subtotal resection, KPS 80) were examined as a control cohort. **Results:** No DLTs, CRS, ICANS or treatment related deaths were reported. As of December 31, 2025, the median PFS for DRI repeat dose patients (N=14) is 13.0 months (m), vs. SOC control (N=10) of 6.6m (+97%) demonstrating prolonged disease control in newly diagnosed GBM. The median overall survival (OS) for repeat dose patients will be updated, as it is still climbing at 17.2m+ vs. SOC control of 13.2m. Notably, 8/14 (57%) of the repeat dose patients had PFS that exceeded their expected OS based on age and MGMT-status, compared to only 1/10 (10%) of SOC control patients. One patient with a grade-4, IDH-mutant tumor remains progression free for 4.6 years with no additional maintenance therapies. Gene expression profiling of pre- and post-manufactured cell products revealed upregulation of cytotoxicity-associated markers of activation and immune cell trafficking (e.g., *IFN-g, GZMB, PRF1*). Patient correlate analysis showed that CRS associated serum cytokines *IL-6, IL-1B*, *CCL2*, and *TNF-a* were not increased over baseline during DRI + maintenance-phase TMZ. Peripheral γδ and total T cell levels, however, improved incrementally with each dose frequency cohort, suggesting an influence on systemic immune reconstitution through local DRI delivery. T cell persistence was demonstrated in recurrent GBM biopsies from patients that revealed significant γδ T cell infiltration and necrosis well beyond the final dose of TMZ and DRI γδ T cells. **Conclusions:** These findings demonstrate a manageable safety profile and a positive trend in PFS and OS from treatment with DRI cells. Clinical trial information: NCT04165941. Research Sponsor: IN8Bio, Inc.

2078 **Poster Session**

Regorafenib in recurrent glioblastoma: Real-world outcomes from a Colombian cohort (REGOMA-COL). First Author: Javier Jacobo, Luis Carlos Sarmiento Angulo Cancer Treatment and Research Center - CTIC, Bogotá, Colombia

Background: Therapeutic options for recurrent glioblastoma (GBM) remain limited, with historically poor outcomes following first progression. The phase II REGOMA trial demonstrated an overall survival benefit of regorafenib compared with lomustine, prompting its adoption in selected patients. However, real-world data from Latin America are scarce, where differences in patient characteristics, access to molecular testing, and treatment patterns may influence outcomes. We evaluated the effectiveness and safety of regorafenib in a Colombian cohort of patients with recurrent high-grade gliomas (HGG - WHO 4). **Methods:** REGOMA-COL is a retrospective, single-center cohort study including adult patients with histologically confirmed HGG treated at a tertiary referral center in Bogotá, Colombia. All patients received standard first-line therapy consisting of maximal safe resection followed by IMRT/VMAT with concomitant and adjuvant temozolomide, and subsequently progressed. Regorafenib was administered in the second- or third-line setting at a starting dose of 160 mg daily (3 weeks on, 1 week off), with dose modifications permitted for toxicity. Survival outcomes were estimated using the Kaplan–Meier method. Adverse events were graded according to CTCAE v5.0. Subgroup analyses examined progression-free survival (PFS) by molecular and clinical characteristics. **Results:** Twenty-six patients were included. The median age at diagnosis was 49.3 years, and 80.8% had an ECOG performance status of 1. Most tumors were IDH–wild type (84.6%), and MGMT promoter methylation was present in 38.5%. Regorafenib was administered as second-line therapy in 53.8% of patients and as third-line therapy in 57.7%. Median PFS from regorafenib initiation was 4.9 months (95% CI 3.9–5.7), and median OS from regorafenib was 11.3 months (95% CI 9.3–13.2) (Figure 1). Disease control rate (DCR) with regorafenib was achieved in 69.2% of patients. Toxicity was predominantly low-grade, with fatigue, mucositis, and diarrhea as the most common adverse events. **Conclusions:** In this real-world cohort, regorafenib demonstrated meaningful clinical activity and a favorable safety profile in patients with recurrent HGG. Survival outcomes compared favorably with those reported in pivotal and observational studies, particularly in a relatively young population with preserved performance status. These findings support regorafenib as an important therapeutic option in selected HGG cases and highlight the need for broader Latin American real-world data. Research Sponsor: None.

2079 Poster Session

Lucicebtide (ST101) plus chemoradiation in newly diagnosed GBM patients: Efficacy, pharmacodynamics, and safety from phase 2 window-of-opportunity study. First Author: Fabio M. Iwamoto, Columbia University Irving Medical Center, New York, NY

Background: Glioblastoma (GBM) is a lethal brain malignancy with no cure. Recurrent GBM (rGBM) is enriched in a mesenchymal-like state, and the tumor microenvironment (TME) is enriched in immune-suppressive tumor-associated myeloid cells (TAMs). C/EBPß is a master regulator of the mesenchymal GBM state and in sustaining immunosuppressive TAMs. Lucicebtide (ST101) is a first-in-class peptide antagonist of C/EBPß with demonstrated anti-tumor activity and TAM reprogramming in preclinical models. **Methods:** The WoO study enrolled 2 cohorts; 9 pts with rGBM that received 2-4 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide after surgery to progression and 9 ndGBM pts that received 2-3 doses of lucicebtide 500mg QW prior to surgery and resumed lucicebtide + chemoradiation after surgery until progression. Endpoints include efficacy parameters of PFS and OS, safety as a single agent and in combination with chemoradiation, and pharmacodynamic (PD) analyses including spatial transcriptomics and TME characterization. **Results:** Lucicebtide was well-tolerated alone and in combination with chemoradiation. Tissue analysis indicates BBB penetration, tumor uptake, and C/EBPß target engagement. Lucicebtide + chemoradiation in ndGBM extended PFS beyond historic benchmarks, with the majority of patients remaining on study without progression beyond 21 months. As of January 27, 2026, mOS could not be evaluated; 18- and 24-months OS of 67% and 44% respectively exceeded the historic 39-45% and 26-31% respectively from Stupp 2005 and 2017. In rGBM, lucicebtide improved mPFS of 4.0 months and mOS to 12.3 months, exceeding historical data with chemotherapy (historic mPFS ~ 2 months and mOS 5.6-9.8 months). Spatial transcriptomics revealed significant reductions in C/EBPß regulon activity in tumor cells and macrophages, resulting in a dramatic reduction in the mesenchymal signature in tumor cells. Importantly, lucicebtide altered the infiltration patterns and phenotypes of the TME, including increased effector $CD8^+$ infiltration and an increase in the M1/M2 ratio that were associated with disease control. **Conclusions:** Lucicebtide is well-tolerated as monotherapy and in combination with SoC. Improvements in PFS and OS have been seen in GBM patients following lucicebtide exposure. Analysis of tumor resections demonstrate penetration across the BBB and target engagement, and on-target pharmacodynamic activity, including a dramatic reduction in mesenchymal gene signature in tumor cells and a remodeling towards a more permissive immune TME. These data provide the safety, efficacy and mechanistic rationale for continued clinical evaluation of lucicebtide as a novel approach for patients with GBM. Clinical trial information: NCT04478279. Research Sponsor: Ivy Foundation.

2080 Poster Session

Tumor recurrence or treatment effect? Large multi-institutional evaluation of an AI risk assessment model in glioma and brain metastases. First Author: Dheerendranath Battalapalli, University of Wisconsin Madison, Madison, WI

Background: Distinguishing true tumor recurrence (TuR) from radiation necrosis (RN) on post-treatment MRI scans remains a major neuro-oncology challenge. We hypothesized that an integrated Spatial, Morphologic, and Textural radiomics risk (SMART-risk) model that comprehensively captures local and spatial organization of lesion heterogeneity, can unravel distinct biology across TuR and RN, on clinical MRI; and improve distinction over a data-driven ResNet50 deep learning model. **Methods:** We retrospectively collected multi-institutional post-treatment MRI cohorts: brain metastases (233 studies; from Cleveland Clinic (CCF), University Hospitals Cleveland (UH), University of Wisconsin (UW); and glioma (340 studies from Indiana University (IU), Dana-Farber Cancer Center, Thomas Jefferson University (TJU), and CCF). Over 80% of the studies were pathologically confirmed as TuR or RN. Institution-held-out external testing was performed (metastases: train CCF+UH, test UW; glioma: train IU+TJU+Dana-Farber Cancer Center, test CCF). Following segmentation, 944 radiomic features/lesion were extracted including graph-based spatial organization of tumor heterogeneity (GrRAiL), local gradient texture heterogeneity (COLLAGE), Haralick, and morphology. LASSO-selected features were integrated in a Random Forest classifier. Performance metrics included cross validation accuracy (CV), test accuracy, F1 score, and AUC; interpretability used SHAP. Comparison was performed with a ResNet50 baseline model. **Results:** SMART-Risk demonstrated consistent discrimination on the institution-held-out external test set (Table 1) with ~80% accuracy; ~10-15% improvement over a ResNet50 model. SHAP analysis indicated that features corresponding to spatial organization and local heterogeneity, i.e. average path length, node count and entropy measures, were dominant contributors (Mann–Whitney U test, $p \leq 0.001$). Recurrent tumors showed higher spatial complexity and greater heterogeneity than RN. **Conclusions:** SMART-Risk may provide a noninvasive approach to distinguish TuR from RN on routine post-contrast T1-weighted MRI. By integrating spatial-organization (GrRAiL), texture (COLLAGE/Haralick), and morphology features, SMART-Risk captures complementary signatures and may improve discrimination compared with any single feature family. An AI-based SMART-Risk approach may reduce diagnostic ambiguity, support earlier treatment decisions, and avoid unnecessary invasive procedures. Research Sponsor: NIH / NCI / ITCR; 1U01CA248226-01; NIH / NCI; R01CA277728-01A1; NIH / NCI; 1R01CA264017-01A1; NIH / NCI / ITCR; U01CA248226-03S1.

Test set performance of SMART-Risk vs ResNet50 for TuR vs RN classification.

Cohort (external test site)	Model	CV accuracy	Test accuracy	F1 score	AUC
Metastatic cohort (UW)	SMART-Risk	0.78 ± 0.08	0.79	0.78	0.86
Metastatic cohort (UW)	ResNet50	0.70 ± 0.09	0.60	0.67	0.63
Glioma (CCF)	SMART-Risk	0.83 ± 0.06	0.80	0.84	0.87
Glioma (CCF)	ResNet50	0.69± 0.10	0.65	0.77	0.70

2081 Poster Session

Decision support for treatment of patients with glioblastoma: A systems biology approach enabled by explainable AI. First Author: Thomas D. Brown, Institute of Systems Biology, Seattle, WA

Background: Glioblastoma (GBM) patients (pts) have median survival of 15 months and 5-year survival <7% with standard therapy. Current clinical decision-making relies on IDH mutation and MGMT methylation status, which provide limited guidance for most pts. We developed SATGBM (SYGNAL Analytics Test for GBM), a systems biology-based test that integrates tumor mutations and gene expression to identify causally dysregulated gene networks and predict treatment response. **Methods:** SATGBM uses Systems Genetics Network AnaLysis (SYGNAL) to mine pts' molecular profiles (RNASeq, WES and NGS) and build disease network maps to single out an individual pt's molecular tumor profile and identify unique causal mechanisms that drive the progression of disease. Treatment predictions integrate network activity scores, deep learning scores, and historical objective response rates from clinical trials. We validated SATGBM in two independent cohorts: (1) 43 pt-derived glioma stem-like cells (PDGSC) screened against 28 anticancer drugs; (2) 83 GBM pts from XCELSIOR open registry observational study with documented treatment outcomes including progression-free survival (PFS) and time on treatment (TOT). **Results:** In PDGSC high throughput screening, SATGBM successfully predicted treatments with greatest drug sensitivity in each of the cell cultures. SATGBM predictions separated responders vs non-responders: median IC50 2.70×10^{-7} vs 1.00×10^{-3}, Mann–Whitney $p=2.1\times10^{-41}$, Pearson r = -0.38, AUC = 0.79. In the XCELSIOR cohort (n=31 drug courses), SATGBM correctly predicted the effective response of individual pts to 6 second-line therapies (including off-label drugs). Pts who stayed on SATGBM-recommended treatments remained on therapy 5-times longer compared to predicted non-responders, demonstrating real-world clinical validity and improved outcomes. SATGBM predictions yielded median TOT of 260 vs 50.5 days, p=0.0021; sensitivity/specificity were 60.0% / 95.2% and AUC = 0.79 (benefit = ToT ≥120 days). **Conclusions:** SATGBM demonstrated statistically significant prediction of treatment outcomes in independent preclinical and clinical validation cohorts. Network-based analysis provided superior predictive accuracy compared to mutation-only or expression-only approaches and provided insights beyond standard GBM biomarkers. These findings support clinical utility of mechanistic network analysis for personalizing GBM treatment decisions and warrant prospective validation in clinical trials. Research Sponsor: U.S. National Institutes of Health; R01-CA259469; U.S. National Science Foundation; NSF-2150265; U.S. National Institutes of Health; R01-NS119650; Washington Research Foundation; Andy Hill Cancer Research Endowment (CARE) Fund; the Burroughs Wellcome Career Award for Medical Scientists; Discovery Grant from the Kuni Foundation; the Ben and Catherine Ivy Foundation; Swedish Medical Center Foundation.

2082 Poster Session

Germline HLA class II diversity as a predictor of survival selectively in MHC-silenced gliomas. First Author: Om H. Gandhi, Centre for Immuno-Oncology, University of Oxford, Oxford, United Kingdom

Background: $CD4^+$ T cell help is central to durable anti-tumour immunity and predicts response to neoantigen vaccination. Antigen presentation to $CD4^+$ T cells is governed by HLA class II molecules, yet the class II landscape in glioma remains poorly defined. Germline HLA diversity can influence immunity only if tumours retain antigen-presentation capacity. We hypothesised that the prognostic impact of HLA class II heterozygosity in glioma is conditional on tumour MHC-II expression. **Methods:** We performed germline HLA class II typing (DRB1, DQB1, DPB1) in 893 TCGA gliomas (388 glioblastoma, 505 lower-grade glioma) using a weighted consensus of four algorithms (HLA-HD, hla-genotyper, SOAP-HLA, Kourami). Tumour MHC-II expression was quantified using a nine-gene antigen-presentation signature. The primary analysis tested the interaction between germline heterozygosity and tumour MHC-II status on overall survival using multivariable Cox regression. Allele-level survival analyses were exploratory. **Results:** Gliomas showed extensive class II polymorphism (54 DRB1, 28 DQB1, 47 DPB1 alleles), with 35.9% of patients homozygous at one or more loci. The most frequent alleles were DRB107:01 (12.7%), DQB103:01 (20.7%), and DPB1*04:01 (38.7%). Germline heterozygosity was not prognostic in unstratified analyses (HR 1.04, 95% CI 0.83–1.32, p = 0.72). However, a significant interaction with tumour MHC-II expression was observed (p-interaction = 0.044). In MHC-II–low tumours, germline heterozygosity independently predicted improved survival (HR 0.71, 95% CI 0.52–0.97, p = 0.031), whereas no effect was seen in MHC-II–high tumours (p = 0.89). Tumour MHC-II expression itself was independently prognostic (p = 0.004). Exploratory allele-level analysis identified DRB1*03:01 (10.2%) as nominally associated with worse survival (median 23.7 vs 34.9 months, uncorrected p = 0.041). **Conclusions:** Germline HLA class II diversity influences survival in glioma only when tumour antigen presentation is impaired. Combined tumour MHC-II loss and limited germline diversity identify a biologically and clinically high-risk group with compounded antigen-presentation deficits. These findings have direct implications for neoantigen vaccine design and patient stratification, suggesting that restoration of antigen presentation may be required prior to immunotherapy in selected patients. The adverse association with DRB1*03:01 merits mechanistic investigation. Independent validation in 322 glioblastoma patients is ongoing. Research Sponsor: None.

2083 **Poster Session**

Knowledge distillation for glioma diagnosis: ResNet-based deep learning for WHO grade stratification with real-world deployment optimization. First Author: Sravani Bhavanam, Brookdale University Hospital and Medical Center, New York, NY

Background: Gliomas are the most common primary CNS malignancies. WHO 2021 classification stratifies diffuse gliomas into molecularly-defined grades with vastly different treatment pathways: grades 2–3 (median survival 7–10 years) versus grade 4 glioblastoma (median survival 15 months untreated). Accurate preoperative grading is critical for surgical planning and treatment intensity. However, 5–8% of gliomas are initially misdiagnosed as meningiomas or pituitary adenomas, delaying definitive treatment by 3–6 months. Automated systems achieving high accuracy while remaining deployable in resource-limited settings could substantially reduce diagnostic error. **Methods:** Retrospective cohort: 2,840 brain MRI studies (1,400 gliomas: 700 grade 2–3, 700 grade 4; 900 meningiomas; 540 pituitary adenomas) from six continents. Ground truth used WHO 2021 classification; expert neuroradiologist consensus confirmed diagnoses. ResNet152 (60.2M parameters; 224×224 input; 28.6 GFLOPs) optimized for multi-sequence fusion (T1, T2, FLAIR, post-contrast) served as reference. ResNet18 (11.7M parameters; 224×224 input; 1.8 GFLOPs; 81% parameter reduction) underwent structured knowledge distillation—soft probability targets from ResNet152 with temperature-scaled softmax and regularized cross-entropy loss. Model performance evaluated on accuracy, sensitivity, specificity, F1-score, AUROC. Differential diagnostic accuracy assessed. Deployed globally; 52 neuroradiologists evaluated across six continents. **Results:** Glioma grading: ResNet18 achieved 96.9% accuracy for grade 2–3 vs. grade 4 (sensitivity 97.8%, specificity 96.0%, AUROC 0.991). Differential diagnosis: 95.1% for glioma vs. meningioma; 96.0% for glioma vs. pituitary. External validation confirmed consistent performance (93–97% grading; 94–96% differential diagnosis). Deployment advantage: ResNet18 inference time 38ms/image (ResNet152: 320ms), enabling real-time clinical integration on standard hospital GPU servers. Global deployment: 94.6% of neuroradiologists rated the system clinically valuable. Knowledge distillation preserved 99.2% of teacher diagnostic accuracy while reducing computational cost by 93.7%. **Conclusions:** Knowledge distillation enables ResNet18 to achieve ResNet152-comparable diagnostic accuracy for glioma grading and differential diagnosis while reducing parameters by 81% and computational cost by 94%. This framework solves critical deployment barriers in resource-limited healthcare systems. ResNet18's efficiency enables real-time inference on standard hardware, rapid diagnostic turnaround, and scalable global implementation. This system merits prospective evaluation to reduce time-to-diagnosis and eliminate glioma misclassification worldwide. Research Sponsor: None.

2084 **Poster Session**

Transcriptomic signature of temozolomide treatment-effect heterogeneity in IDH-wildtype glioblastoma. First Author: Amirhossein Zare, Tehran University of Medical Sciences, Tehran, Iran

Background: Adjuvant temozolomide (TMZ) is standard of care for IDH-wildtype glioblastoma (GBM), yet clinical benefit is heterogeneous and not fully explained by MGMT promoter methylation. We developed a transcriptomic signature specifically predicting TMZ benefit rather than overall prognosis using a causal inference framework. **Methods:** Transcriptomic and clinical data from 448 patients with histologic grade 4 IDH-wildtype GBM treated with radiotherapy alone or radiotherapy plus TMZ across six cohorts were analyzed. A training set (N=322; TCGA, CGGA-325/693, GLASS) and an independent validation set (N=126; GSE7696, CGGA-301) were used. Data were normalized, batch-corrected, and screened for outliers. To address non-random treatment assignment, inverse probability of treatment weighting (IPTW) based on propensity scores from age, sex, and MGMT status was applied. A 15-gene Temozolomide Sensitivity Score (TSS) was derived using univariate prognostic filtering followed by LASSO modeling of gene-by-treatment interactions. Final gene weights were obtained from a doubly adjusted multivariable Cox model incorporating IPTW and clinical covariates. Performance was assessed by comparing adjusted hazard ratios (HRs) for TMZ benefit across TSS-defined subgroups. **Results:** Five genes emerged as significant independent modulators of TMZ response: C2CD4A, SLC35E3, and DNASE1L3 predicted sensitivity, whereas APOBEC3B and PMAIP1 predicted resistance. In the training cohort, TSS-sensitive patients derived significant benefit from TMZ (median overall survival, 21.0 vs 7.7 months; adjusted HR, 0.20; 95% CI, 0.10–0.39; P<0.001), whereas TSS-resistant patients did not (14.4 vs 13.1 months; adjusted HR, 0.89; 95% CI, 0.53–1.51; P=0.674), with a significant difference in treatment effect (P<0.001). Validation confirmed these findings: TSS-sensitive patients benefited (21.9 vs 12.8 months; adjusted HR, 0.32; 95% CI, 0.16–0.62; P<0.001), while TSS-resistant patients did not (13.7 vs 15.1 months; adjusted HR, 1.25; 95% CI, 0.70–2.23; P=0.453), showing differential efficacy (P=0.003). Age, sex, and MGMT status were balanced between groups. **Conclusions:** A 15-gene transcriptomic signature developed through causal inference and interaction modeling is associated with differential temozolomide benefit in IDH-wildtype glioblastoma independent of MGMT status. This signature may identify patients less likely to benefit from temozolomide, offering a promising tool for de-escalation strategies and enrollment in precision clinical trials. Research Sponsor: None.

2085 **Poster Session**

Gene–treatment interaction modeling to identify temozolomide-sensitive *IDH*-mutant diffuse gliomas. First Author: Seyed Reza Salarikia, Tufts University School of Medicine, Boston, MA

Background: IDH-mutant diffuse gliomas are biologically heterogeneous. While radiotherapy is standard, temozolomide (TMZ) is variably used in a risk-adapted manner and preferentially administered to patients with adverse features, introducing substantial indication bias in observational cohorts. Existing molecular markers are largely diagnostic or prognostic rather than predictive of chemotherapy benefit. We aimed to develop a transcriptomic signature identifying differential TMZ benefit while correcting for treatment-selection bias using causal inference. **Methods:** IDH-mutant, histologic grade 2–3 glioma patients treated with radiotherapy or radiotherapy + TMZ were analyzed in a training cohort (N=438; TCGA, CGGA325/693) and an independent validation cohort (N=62; CGGA301). To mitigate non-random treatment allocation, inverse probability of treatment weighting (IPTW) was applied using propensity scores from age, sex, histologic grade, 1p/19q codeletion, and MGMT promoter status. A 10-gene temozolomide sensitivity score was derived using univariate filtering followed by LASSO modeling of gene–treatment interactions. Final weights were estimated from a doubly adjusted multivariable Cox model incorporating IPTW and clinical and molecular covariates. Performance was assessed by comparing adjusted hazard ratios (HRs) for TMZ benefit across score-defined subgroups. **Results:** Clinical and molecular baseline characteristics were well balanced between treatment groups. In the training cohort, TMZ-sensitive patients derived significant benefit from TMZ (median overall survival 114.0 vs 85.7 months; adjusted HR 0.58, 95% CI 0.35–0.96; P=0.035). In contrast, TMZ-resistant patients demonstrated an elevated adjusted HR (2.98, 95% CI 1.63–5.45; P<0.001), consistent with residual confounding from preferential TMZ use in patients with poorer prognosis rather than evidence of treatment harm. A significant difference in treatment effect was observed between subgroups (P<0.001). External validation confirmed differential treatment effects: TMZ-sensitive patients showed a concordant trend toward benefit (HR 0.51, 95% CI 0.13–1.94; P=0.323), with lack of significance attributable to limited sample size, while TMZ-resistant patients exhibited a resistant trajectory (HR 6.04, 95% CI 1.56–23.38; P=0.009), with the difference in treatment effect remaining significant (P=0.011). **Conclusions:** Using causal inference and gene–treatment interaction modeling, we developed and validated a 10-gene signature that predicts heterogeneity of TMZ benefit in IDH-mutant, histologic grade 2–3 gliomas. This approach distinguishes patients likely to derive substantial benefit from TMZ from those with limited benefit and provides a robust methodological framework for predictive biomarker discovery in non-randomized oncologic datasets. Research Sponsor: None.

2086 **Poster Session**

Preclinical evaluation of intrathecal TRP1-targeted CAR T cells: Effects on durable antitumor immunity in melanoma leptomeningeal disease. First Author: Peter A.J. Forsyth, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Melanoma leptomeningeal disease (LMD) is fatal, with median survival under 3 months and no effective immune-based therapies. Direct cellular immunotherapy of the cerebrospinal compartment has not been systematically explored. Tyrosinase-related protein 1 (TRP1) is a conserved melanocytic lineage antigen expressed across mouse and human melanoma, including CNS involvement. We evaluated the efficacy, durability, and safety of intrathecal TRP1-directed CAR T cell therapy in aggressive melanoma models. **Methods:** TRP1 CAR T cells were generated and evaluated in vitro and in vivo using syngeneic B16 melanoma model, including a leptomeningeal disease setting. CAR T cells were administered intrathecally. Antitumor activity was assessed by bioluminescent tumor burden and survival. Durability of response was evaluated by secondary tumor rechallenge. Toxicity was assessed by longitudinal neurologic monitoring and body weight. Human TRP1 CAR T constructs were evaluated in vitro using real-time cell adhesion (RTCA) assays across multiple donors using TRP1-positive melanoma cell lines to assess antigen-dependent functional activity. scRNAseq data from CSF of melanoma patients were analyzed to determine TYRP1 expression. **Results:** Intrathecal administration of TRP1 CAR T cells resulted in significant tumor control and prolonged survival in aggressive M-LMD models compared with controls (+CTX OS=18%, median survival:18 days; +1x-PBS OS=15%, median survival:17 days). Approximately 40% of treated animals achieved durable remission following intrathecal infusion of CAR Ts (OS=40%, median survival: 32 days, P<0.0001). Long-term survivors (eg. more than 60 days) demonstrated functional immune memory, with approximately 36% rejecting secondary tumor rechallenge (OS=36%, median survival: 41 days vs. naïve control OS=17%, median survival: 15 days, P<0.0001). Treatment was well tolerated, with no detectable neurologic toxicity or weight loss. RTCA data showed that human TRP1-CAR T cells across donors recognize TYRP1 antigen in target melanoma cells inducing killing. scRNAseq data revealed that 50% of 12 patient samples expressed TYRP1(33,3% were M-LMD, 8.3% were primary intradural spinal melanoma, and 8.3% from 1 autopsy). Surface expression of TYRP1 is being determined using our Rapid Tissue Donation in LMD Core. Together, our data supports translational relevance. **Conclusions:** Intrathecal TRP1-targetedCAR T cell therapy induces potent and durable antitumor immunity in aggressive disease-LMD with a favorable safety profile. These findings represent the first clear demonstration of intrathecal CAR T cell therapy in melanoma LMD and establish proof of concept for CNS-directed CAR T strategies targeting a melanocytic lineage antigen. This work provides a rational foundation for systematic optimization and IND-enabling development. Research Sponsor: None.

2087 **Poster Session**

Efficacy of high-dose chemotherapy in adult patients with relapsed or refractory medulloblastoma. First Author: Nurlan Mammadzada, Ankara Gülhane Eğitim ve Araştirma Hastanesi, Ankara, Turkey

Background: Adult medulloblastoma (MB) is rare, and there is no standard salvage approach for relapsed or refractory cases. High-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) has shown potential, but evidence in adults remains limited. This study evaluated the response rate, survival and toxicity after HDC with ICE regimen followed by ASCT in MB, with further focusing on post-ASCT response and pretransplant intracranial residual disease (ICRD). **Methods:** We retrospectively analyzed adult patients with relapsed/refractory MB who underwent HDC with the ICE regimen followed by ASCT. Baseline features, treatment response, progression-free survival (PFS), overall survival (OS), and treatment-related toxicity were evaluated. Subgroup analyses focused on post-ASCT response and pretransplant intracranial residual disease (ICRD). **Results:** The study included 23 patients (median age: 24 years; male: 52%, with 43% classic subtype and 61% pretransplant ICRD). The overall and complete response (CR) rates to HDC was 73.9% and 48%, respectively. The median PFS was 12.8 months, and OS was 45.1 months, with 2-year PFS and OS rates of 31% and 63%, respectively. Patients achieving CR after ASCT had significantly longer OS (NR vs 16.4 months; HR, 0.15; 95% CI, 0.03–0.72; P=.02), corresponding to an 85% reduction in mortality risk compared with non-CR patients. OS was markedly shorter in patients with pretransplant intracranial residual disease compared with those without (22.5 vs. 74.0 months; HR, 7.08; 95% CI, 1.3–36.3; p = 0.008).The large cell/anaplastic subtype remained the poorest prognostic group despite ICE induction. Toxicity was dominated by universal grade 4 myelosuppression and febrile neutropenia, but no transplantation-related mortality occurred. **Conclusions:** This study showed that HDC with ICE followed by ASCT is feasible in adults with relapsed/refractory MB, with encouraging survival and manageable toxicity. Pretransplant ICRD clearance and achievement of CR were major prognostic determinants, while non-CR patients remained at high risk, highlighting the need for treatment intensification in this subgroup. Research Sponsor: None.

2088 **Poster Session**

Molecular characterization of WHO grade II atypical meningioma using the AACR Project GENIE database. First Author: Aden V. Chudziak, Arizona State University, Tempe, AZ

Background: Atypical meningioma (AM) is a WHO grade II neoplasm arising from meningeal arachnoid cap cells and is distinguished from WHO grade I meningiomas by parenchymal invasion and rapid proliferation. AM demonstrates recurrence rates up to 52% following gross total resection and >90% after subtotal resection. The absence of FDA-approved systemic treatments for AM underscores the need to define oncogenic drivers for targeted therapies. This study leverages the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database to characterize the genomic landscape of AM and identify key genetic drivers for therapeutic targets. **Methods:** The AACR GENIE database was accessed from cBioPortal (v18.0-public) on December 12, 2025 to identify all AM patient samples. Fisher's exact test and non-parametric tests (Mann-Whitney U) were used with Benjamini-Hochberg False Discovery Rate correction to analyze most common genetic mutations, demographic correlations, and mutual exclusivities. Unknown values were excluded from analysis. **Results:** The cohort identified 402 AM samples from 394 patients. The cohort was slightly female-predominant (52.8%) and largely adult (94.0%). Most patients were White (47.2%), followed by Asian (7.4%) and Black (3.6%). Most samples (n=307, 76.4%) were primary tumors and 48 (11.9%) were metastatic. *NF2* was the most prevalent mutation (n=228; 56.7%), followed by *TERT* promoter mutations (n=52; 12.9%). Chromatin-modifying genes, including *KMT2D* (n=24; 6.0%), *KMT2A* (n=19; 4.7%), and *KMT2C* (n=16; 4.0%), were frequently altered. Additional recurrent mutations were observed in *SPTA1* (n=21; 5.2%), *MT-ND5* (n=20; 5.0%), *FAT1* (n=20; 5.0%), *PRKDC* (n=18; 4.5%). Sex-stratified analysis revealed male-exclusive mutations in *DAXX* (n=9), *IL6ST* (n=4), *TMPRSS2* (n=4), *SMARCE1* (n=4), and *COL2A1* (n=5) that reached statistical significance (all $p<0.05$). *TSC2* and *DNMT3A* mutations were significantly more frequent in males, whereas *BRCA1* mutations were uniquely observed in females ($p<0.05$). *NF2* mutations were enriched in Asian patients ($p<0.001$), while *TERT*, *KDR*, *PTPRB*, *SPEN*, and *KMT2C* were enriched in Black patients (all $p<0.05$). *NF2* and *TERT* demonstrated significant mutual exclusivity ($p<0.05$). Co-occurrence was observed between *ROS1*/*ATM* and *KMT2D*/*TSC2* ($p<0.05$). Metastatic tumors were enriched for *BRCA1*, *IKBKE*, and *PALB2*, with *MDM4* exclusive to metastatic disease ($p<0.001$). **Conclusions:** To our knowledge, this is the first GENIE study to identify *NF2* and *TERT* as central genomic drivers of AM, with their observed mutual exclusivity suggestive of divergent oncogenic pathways. Race-associated mutations, such as enrichment of *NF2* in Asian patients and *TERT* in Black patients, emphasize demographic consideration in targeted therapies. These findings prioritize *NF2* and *TERT* as targets for precision therapeutics in AM. Research Sponsor: None.

2089 **Poster Session**

Long term outcomes of central neurocytoma in a multi-institutional cohort: The role of radiotherapy and Ki-67. First Author: Yufan Yang, University of Michigan, Ann Arbor, MI

Background: Central neurocytomas (CNs) are rare, WHO grade 2 brain tumors that can have relatively high recurrence rates following surgical resection. Owing to the rarity of CNs and limited robust data, the optimal use and timing of radiotherapy (RT) remain undefined, particularly in young adults with low mortality. Tumor proliferation index (Ki-67) may also predict CN recurrence rates, but there is no consensus on its utility in clinical practice. The present collaboration between Northwestern University and the Mayo Clinic describes long-term outcomes of CN as it relates to RT timing and Ki-67 level. **Methods:** Patients established between 1990-2025 with a tissue diagnosis of CN at Northwestern University and the Mayo Clinic were reviewed. Demographic, treatment, and tumor characteristics (histologic/molecular) were recorded. Recurrence free survival (RFS) and overall survival (OS) were calculated according to the Kaplan Meier-method. **Results:** Fifty-one patients with CN (51% male, 49% female)—with a median age of 26 years and 9.7 years median follow-up—were included. RFS at 2, 5, and 10 years for the cohort was 79%, 65%, and 59% respectively; OS at 10 years for the cohort was 94%, and no deaths were attributed to uncontrolled CN. Subtotal resection (STR) yielded 2- and 5-year RFS of 74% and 65%, while gross total resection (GTR) yielded 2- and 5-year RFS of 90% and 66%. Median Ki-67 of the cohort was 3%; RFS at 2 and 5 years for Ki-67 <3% was 82% and 76%, compared to 76% and 43% for Ki-67 ≥3% ($p<0.02$). In patients who underwent resection without adjuvant RT (n=35), those with STR had a 2- and 5-year RFS of 61% and 45%, and those with GTR had a 2- and 5- year RFS of 88% and 61%. Additionally, without adjuvant RT, RFS at 2 and 5 years for Ki-67 <3% was 73% and 64% versus 71% and 24% for Ki-67 ≥3%. Among patients without adjuvant RT and Ki-67 ≥3% (n=14), 2-year RFS was 60% after STR and 78% after GTR. Salvage RT after first recurrence (n=16) had a 5-year RFS of 81%, with a median follow-up of 4.1 years. **Conclusions:** We report one of the largest cohorts of CN with long-term follow-up. STR and/or Ki-67 ≥3% were associated with shorter RFS. Salvage RT at recurrence achieved durable long-term tumor control, and long-term (~10-year) mortality was low. In appropriately selected patients, observation after resection may be a reasonable initial strategy, with RT reserved for salvage. Research Sponsor: None.

General cohort characteristics (n=51) with Ki-67 (n=39).

Variable	Number (%)
Median Age (years)	26 (range: 5-57)
Gender, Male:Female (M/F)	26:25 (51/49)
Subtotal Resection	29 (57)
Gross Total Resection	22 (43)
Adjuvant Radiotherapy	16 (31)
Salvage Radiotherapy	16 (31)
No Radiotherapy	19 (38)
Ki-67 ≥3	21 (56)
Ki-67 <3	18 (44)

2090 **Poster Session**

Final results of a single-arm, open-label, multicenter phase 2 study of the radiopharmaceutical [^{177}Lu]Lu-DOTA-TATE and [^{68}Ga]Ga-DOTA-TATE in adults with advanced intracranial meningioma. First Author: Sylvia Christine Kurz, Yale University School of Medicine, New Haven, CT

Background: A subset of meningiomas has an aggressive clinical course requiring multimodal therapies. Yet, treatment options beyond surgery and radiation are limited. Somatostatin receptor 2 (SSTR2) is uniformly expressed in meningiomas and can be targeted by the radiopharmaceutical agent [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-Dotatate). [^{68}Ga]Ga-DOTA-TATE (^{68}Ga-Dotatate) PET is emerging as a promising imaging modality to assess treatment response in SSTR2-expressing tumors. However, prospective clinical data supporting the use of ^{177}Lu-Dotatate and ^{68}Ga-Dotatate in treatment-refractory meningiomas is limited. **Methods:** In this multicenter, open-label, phase 2 clinical study (NCT03971461), adult patients with progressive intracranial meningiomas received ^{177}Lu-Dotatate at 7.4 GBq (200 mCi) every 8 weeks for 4 doses. The primary endpoint was 6-month progression-free survival (PFS-6). Up to 5 meningioma lesions per patient were assessed by gadolinium-enhanced T1 MRI every 12 weeks. ^{68}Ga-Dotatate PET was obtained before/after ^{177}Lu-Dotatate treatments. Lesional ^{68}Ga-Dotatate PET activity was assessed relative to liver/spleen or superior sagittal sinus (SSS). **Results:** 32 patients (female = 21, male = 11) with progressive meningiomas (WHO grade 1 = 7, grade 2 = 24, grade 3 = 1) were enrolled. Median age was 65.5 (range 41-78) years. All patients had at least one prior tumor surgery and at least one course of radiation. Overall, ^{177}Lu-Dotatate was well tolerated and the most common grade 3/4 adverse events were transient cytopenia in 15 patients (47%). One patient (3%) discontinued treatment due to grade 4 thrombocytopenia. PFS-6 was reached in 22 patients (69%), which includes 5 of 7 (71%) with grade 1 and 17 of 24 (71%) with grade 2 meningiomas. Best radiographic response by MRI was partial response (PR) in 5 (16%) and stable disease (SD) in 20 (63%) patients. Eight patients (16 lesions) were evaluable by paired MRI and ^{68}Ga-Dotatate PET pre- and post-treatment. Referenced to SSS, ^{68}Ga-Dotatate avidity reduced by ≥50% in 2 lesions (PR), 25-49% (minor response, MR) in 3 lesions and remained stable (< 25% reduction and < 25% increase) in 11 lesions. Using liver/spleen as a reference (6 patients, 14 lesions), ^{68}Ga-Dotatate uptake was reduced in 9 lesions and stable in 5 lesions. ^{68}Ga-Dotatate PET assessments were generally concordant with MRI-based treatment response assessments. **Conclusions:** The primary endpoint (PFS-6) was met in this phase 2 study with 69% of patients achieving PFS-6, thereby surpassing established historical benchmarks. ^{177}Lu-Dotatate was generally well tolerated and deserves further study in patients with advanced meningiomas. Exploratory ^{68}Ga-DOTATATE PET studies showed decreased uptake in a subset of lesions and bears promise as an imaging biomarker to assess treatment response. Clinical trial information: NCT03971461. Research Sponsor: None.

2091 **Poster Session**

Long-term outcomes of CNS lymphoma patients treated with glucarpidase. First Author: Lauren Webb, Memorial Sloan Kettering Cancer Center, New York, NY

Background: High-dose methotrexate (HD-MTX) is the backbone of potentially curative therapy for central nervous system lymphoma (CNSL) but requires inpatient admission for hydration and monitoring to minimize toxicity. Glucarpidase is a recombinant bacterial enzyme that rapidly clears systemic MTX without crossing the blood-brain barrier. It is FDA-approved as a rescue agent in the setting of MTX toxicity. Exploration of use beyond this indication has been limited, in part, due to concerns about immunogenicity and effect on MTX efficacy. We previously demonstrated the safety of repeated low-dose glucarpidase. Here, we report long-term outcomes of CNSL patients treated with MTX and glucarpidase on clinical trial NCT03684980. **Methods:** NCT03684980 is a multicenter, open-label trial that prospectively enrolled primary (PCNSL) or secondary (SCNSL) lymphoma patients across different cohorts to receive repeated doses of MTX (3-8 g/m²) and glucarpidase (1000-2000u). Patients who received ≥ 6 of 8 planned doses were included. Patients had indication for MTX for newly diagnosed (ND) or relapsed/refractory (r/r) disease. There were no restrictions on post-MTX therapy or consolidation. Objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) were assessed. **Results:** Twenty-two enrolled patients met inclusion criteria; 10 (45%) were women. Median age was 70 years, and median Karnofsky Performance Status was 80. PCNSL accounted for 20/22 (91%) of cases; 5/22 (23%) were treated for r/r disease. Following MTX-based induction, patients achieved complete response (CR) (n=10, 45%), CR unconfirmed (n=2, 9%), partial response (n=6, 27%), stable disease (n=2, 9%), or progressive disease (n=2, 9%) for an ORR of 18/22 (82%). Responding patients received consolidation with cytarabine (n=10), autologous stem cell transplant (ASCT) (n=5), ibrutinib maintenance (n=1), or unknown (n=2). Median follow-up was 55.5 months. Median PFS and OS were not reached overall. PFS and OS were not reached for PCNSL, versus 7.3 and 21.0 months for SCNSL. PFS was not reached for ND patients versus 12.4 months for patients with r/r disease; OS was not reached for either group. **Conclusions:** Repeated low-dose glucarpidase does not appear to adversely impact long-term outcomes in CNSL. Outcomes were superior in PCNSL and ND disease compared to SCNSL and r/r disease. These findings support further exploration into the use of glucarpidase to facilitate MTX clearance without compromising efficacy. Clinical trial information: NCT03684980. Research Sponsor: None.

TPS2093 **Poster Session**

Phase I trial of trastuzumab deruxtecan in combination with stereotactic radiosurgery for brain metastases from HER2-positive breast cancer. First Author: Zouina Sarfraz, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Brain metastases (BM) develop in nearly 40-50% of patients with HER2-positive breast cancer. Stereotactic radiosurgery (SRS) provides effective local control of treated lesions but does not prevent the development of new BM, while whole-brain radiation therapy is associated with significant neurocognitive toxicity. Trastuzumab deruxtecan (T-DXd) is a HER2-targeted antibody-drug conjugate (ADC) that has demonstrated significant systemic and intracranial activity in patients with HER2-positive breast cancer. Preclinical and clinical data suggest that combining HER2-directed therapy with radiation may enhance intracranial disease control. However, there is conflicting information about the rate of radiation necrosis in patients treated with T-DXd and SRS. We hypothesize that the combination of T-DXd and stereotactic radiosurgery may be safe and provide effective intracranial disease control in patients with HER2-positive breast cancer BM. **Methods:** This is a prospective, single-arm, multicenter, open-label, ongoing phase I clinical trial evaluating the safety, tolerability, and maximum tolerated dose of T-DXd in combination with SRS in patients with BM from HER2-positive breast cancer. Eligible participants are adults (≥18 years) with histologically confirmed HER2-positive breast cancer, Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function, and 1–10 newly diagnosed BM who are candidates for SRS. Any number of prior systemic therapies is permitted, except prior exposure to T-DXd. Key exclusion criteria include leptomeningeal metastases, clinically significant intra- or peri-tumoral hemorrhage, prior cranial radiation therapy, active or prior interstitial lung disease or pneumonitis, and BM within 5 mm of the optic apparatus. Participants receive SRS to all eligible lesions with concurrent intravenous T-DXd every 3 weeks. A standard 3+3 dose de-escalation design is used, starting at 5.4 mg/kg with planned de-escalation to 4.4 mg/kg and 3.2 mg/kg. Dose-limiting toxicities are assessed during a 3-week post–SRS evaluation period. The primary endpoint is safety, tolerability, and determination of the maximum tolerated dose. Secondary endpoints include intracranial and extracranial progression-free survival, overall survival, and objective response rate assessed by RECIST v1.1. Exploratory endpoints include intracranial response assessed using RANO-BM criteria and longitudinal changes in neurocognitive function. Upon determination of the maximum tolerated dose, an expansion cohort will enroll up to 20 participants. The trial has been approved by the Institutional Review Board and is currently enrolling participants. Research Sponsor: None.

TPS2094 **Poster Session**

Randomized phase 2 trial of ruxolitinib in combination with radiation and temozolomide compared to radiation and temozolomide for newly diagnosed glioblastoma. First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Glioblastoma is the associated with poor outcomes despite treatment with radiation and temozolomide. Therapeutic resistance and disease recurrence are driven in part by glioma stem cell populations and activation of oncogenic signaling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Aberrant JAK/STAT signaling has been implicated in tumor proliferation, stem cell maintenance, immune modulation, and resistance to radiation and alkylating chemotherapy in glioblastoma in preclinical models. Ruxolitinib is an oral JAK1/2 inhibitor with established clinical use in myeloproliferative neoplasms. Preliminary activity has also been reported in high-grade glioma; in the phase 1, non-randomized CRUX study. **Methods:** This is a randomized, multicenter, open-label, ongoing phase II clinical trial enrolling adults (≥18 years) with newly diagnosed, histologically confirmed IDH-wildtype glioblastoma and Karnofsky performance status ≥70. Eligible patients must have adequate organ function and available tumor tissue for molecular characterization. Participants are randomized 1:1 and stratified by MGMT promoter methylation status, performance status, sex, and extent of resection. Patients assigned to the experimental arm receive oral ruxolitinib 20 mg administered twice daily in combination with standard radiation therapy (60 Gy delivered in 30 fractions) and concurrent temozolomide at 75 mg/m², followed by adjuvant temozolomide at 150-200 mg/m² with continuous ruxolitinib at 20 mg bid. Patients in the control arm receive radiation therapy with concurrent and adjuvant temozolomide per standard of care. Treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, or completion of protocol-defined therapy. The primary endpoint is overall survival (OS). Secondary endpoints include progression-free survival (PFS), objective response rate (ORR), duration of response (DOR), and safety. Tumor response is assessed using modified Radiologic Assessment in Neuro-Oncology (mRANO) criteria. Exploratory objectives include correlative analyses evaluating tumor tissue biomarkers associated with treatment response or resistance. The planned sample size is 190 participants across multiple institutions in the United States. The statistical analysis is a sequential design with one interim look at 50% events on one-sided log rank test, an overall sample size of 172 participants (86 in the control group and 86 in the treatment group) needed to achieve 80 % power at a 0.1 significance level to detect a hazard ratio of 0.68182 when the control group median survival time is 15 months. The trial has been approved by the Institutional Review Board (IRB) and is currently enrolling patients. Clinical trial information: NCT06991101. Research Sponsor: None.

TPS2095 **Poster Session**

CLARITY-GBM: A phase II, multi-centered, open-label, single-arm study to evaluate the safety and efficacy of cetuximab and lomustine (CCNU) in adult patients with recurrent high-grade glioblastoma. First Author: Zoya Peelay, SunAct Cancer Institute Private Limited, Mumbai, India

Background: Recurrent glioblastoma (GBM) has a poor prognosis with no universally accepted systemic standard of care. Lomustine (CCNU) remains a commonly used benchmark, achieving 6-month progression-free survival (PFS-6) rates of approximately 20%. Epidermal growth factor receptor (EGFR) amplification is present in a substantial proportion of GBMs and represents a biologically relevant therapeutic target. Cetuximab, an anti-EGFR monoclonal antibody, has demonstrated preclinical activity and limited clinical efficacy in EGFR-driven high-grade gliomas. CLARITY-GBM evaluates the safety and preliminary efficacy of combining cetuximab with lomustine in adults with recurrent high-grade glioblastoma. **Methods:** CLARITY-GBM is a prospective, open-label, multicenter, single-arm Phase II study conducted at four tertiary cancer centres in India. Eligible patients are adults (≥18 yrs) with histologically confirmed WHO grade 4 glioblastoma at first or second recurrence following standard chemoradiation, ECOG performance status 0–2, and measurable disease per RANO criteria. Participants will receive cetuximab intravenously 500 mg/m² every 2 weeks in combination with oral lomustine 110 mg/m² every 6 weeks. Treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, or investigator decision. Tumour assessments are performed every 6 weeks using MRI and evaluated according to RANO criteria. The study uses an exact single-stage Phase II design testing the null hypothesis that PFS-6 ≤20% versus the alternative hypothesis that PFS-6 ≥40%, with a one-sided alpha of 0.10 and 80% power. A total sample size of 25 patients is planned to ensure 24 evaluable patients for the primary analysis. The regimen will be considered promising if at least 8 patients are progression-free at 6 months. A single interim futility analysis is planned after 15 evaluable patients. The primary endpoint is PFS-6. Secondary endpoints include progression-free survival, overall survival, objective response rate, duration of response, safety and tolerability (CTCAE v5.0), corticosteroid-sparing effect, and health-related quality of life (EORTC QLQ-C30 and BN20). Exploratory analyses evaluate correlations with EGFR amplification, EGFRvIII status, and MGMT promoter methylation. Clinical trial information: CTRI/2026/01/100794. Research Sponsor: None.

Design and key methodological features of the CLARITY-GBM trial.

Characteristic	Description
Study Design	Phase II, open-label, single-arm
Population	Adults with recurrent WHO grade 4 GBM
Sample Size	25 planned (24 evaluable)
Treatment	Cetuximab q2w + Lomustine q6w
Primary Endpoint	PFS-6
Statistical Design	One-sample exact binomial
Null/Alternative	PFS-6 ≤20% vs ≥40%
Power/Alpha	80%, one-sided 0.10
Interim Analysis	After 15 evaluable patients
Exploratory Biomarkers	EGFR, EGFRvIII, MGMT

TPS2096 **Poster Session**

TTFields with maintenance temozolomide (TMZ) and pembrolizumab versus TTFields with maintenance TMZ and placebo for newly diagnosed glioblastoma: The phase 3 EF-41/KEYNOTE D58 trial. First Author: David D. Tran, Department of Neurological Surgery, Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, CA

Background: Glioblastoma remains a lethal disease with limited treatment options. With current standard-of-care, consisting of maximal safe resection followed by radiotherapy with concurrent TMZ, then maintenance TMZ plus TTFields, median overall survival (OS) is 20.9 months, as reported in the pivotal EF-14 trial completed more than a decade ago. While immune checkpoint inhibitors (ICIs) have improved outcomes in multiple malignancies, they have not demonstrated meaningful clinical benefit in glioblastoma, in part because the tumor microenvironment (TME) is typically profoundly immunosuppressive. Strategies that reprogram the TME toward immune activation may therefore enable ICIs to elicit more effective anti-tumor immunity. Beyond antimitotic effects, TTFields have shown preclinical evidence of inducing immunogenic cell death and activating type 1 interferon signaling via DNA sensor inflammasomes, with downstream increases in dendritic cell activation and cytotoxic T cell infiltration. In a single-arm phase 2 study (NCT03405792), TTFields plus TMZ and pembrolizumab was associated with improved progression-free survival (PFS) and OS compared to historical controls in newly diagnosed glioblastoma. Here, we describe the design of a randomized phase 3 trial evaluating this regimen. **Methods:** EF-41/KEYNOTE D58 is a randomized, double-blind, placebo-controlled, phase 3 study (NCT06556563). Eligible patients have newly diagnosed glioblastoma (WHO 2021 Classification), have completed concurrent chemoradiotherapy, and can initiate treatment 4–7 weeks thereafter. Additional criteria include ECOG performance status 0–1 and availability of tumor tissue for central MGMT methylation analysis. Key exclusion criteria include prior anti-PD(L)1 or anti-PDL2 therapy and ongoing dexamethasone $>$2 mg/day. Patients are randomized 2:1 to TTFields (200 kHz for $\geq$18 hours/day) plus maintenance TMZ (150–200 mg/m^2/day PO, days 1-5 of each 28 day cycle for 6-12 cycles) with either pembrolizumab 200 mg IV Q3W (up to 35 cycles) or matching placebo. TTFields is continued until second progression. At first progression, TTFields therapy is maintained and patients may receive standard salvage therapy, including re-resection and/or radiotherapy as well as systemic therapy. The target enrollment is 741 patients, providing 85% power to detect an OS improvement at a two-sided alpha of 0.05 using a 2-sided log-rank test. The primary endpoint is OS. Secondary endpoints include PFS per RANO 2.0 and RANO, PFS6 and PFS12 rates (RANO 2.0), PFS2 (RANO 2.0), 1- and 2-year survival rates, EORTC QLQ-C30 with BN20 module score, and safety. MRI assessments are performed every 9 weeks and evaluated per RANO 2.0. Adverse events are monitored throughout the study. Enrollment is ongoing. Clinical trial information: NCT03405792. Research Sponsor: None.

Key inclusion criteria.

Surgically resected and histologically proven ND-GBM
Tumor EGFR status by local test using commercially available or CLIA certified assay
Part 1: any pathogenic EGFR alteration
Part 2: EGFRvIII-positive by NGS
Unmethylated MGMT tumor status (Part 2 only)
No treatment for ND-GBM other than surgery followed by chemoradiation
≥4 weeks after chemoradiation therapy with post-radiation MRI showing no progression

TPS2097 **Poster Session**

Resection and intracranial implant of (Z)-*n*-butylidenephthalide wafer followed by temozolomide as treatment for recurrent glioblastoma: A randomized phase IIb/III trial. First Author: Clark C. Chen, Legorreta Cancer Center Warren Alpert Medical School of Brown University, Providence, RI

Background: Glioblastoma, an isocitrate dehydrogenase (IDH)–wildtype diffuse glioma, remains highly lethal despite standard therapy, and the absence of an effective treatment at recurrence highlights a critical unmet clinical need. (Z)-*n*-butylidenephthalide ((Z)-BP) is a multimodal anti-glioblastoma agent that inhibits key mechanisms mediating oncogenic signaling including epidermal growth factor receptor (EGFR), AXL-1 receptor, and c-mesenchymal epithelial transition factor (c-Met) receptor, as well as DNA repair (MGMT) and immune suppression (programmed death-ligand 1, PD-L1). To enable sustained local delivery of (Z)-BP, an interstitial controlled-release polymer wafer was developed and advanced through Phase I and Phase IIa evaluation, demonstrating feasibility, a favorable safety profile, and early indications of survival signals. Building on these findings, a randomized Phase IIb/III study has been initiated to further evaluate intracranial (Z)-BP implantation using this controlled-release platform. **Methods:** The trial (NCT07349693) is an open-label, randomized study that aims to determine the efficacy of tumor resection with implantation of the (Z)-BP wafer, followed by temozolomide treatment in the setting of recurrent glioblastoma. With a sample size of 175, the study is designed to observe 116 overall survival events to achieve 80% power. Eligible adults must have histologically confirmed glioblastoma at first or second recurrence following standard first-line therapy and maintain a Karnofsky Performance Status $\geq$ 70. Furthermore, candidates require measurable disease per response assessment in neuro-oncology (RANO) 2.0 criteria (lesion $\geq$ 1 cm) that is deemed suitable for gross total resection. Subjects are excluded if they present with oligodendroglioma, mixed glioma, specific genetic markers (IDH or H3K27M mutations, 1p19q co-deletion), or prior bevacizumab treatment with uncontrollable progression. Patients with MRI findings showing multi-focal disease, diffuse dissemination, lesions $>$ 6 cm, or tumor locations deemed unsuitable for safe resection and wafer implantation will also be excluded. Subjects are randomized in a 2:1 ratio to either resection with 6 (Z)-BP wafers implantation or resection only (control arm). All enrolled patients subsequently receive six cycles of temozolomide. The primary endpoint is median overall survival (OS). Secondary endpoints include progression-free survival (PFS), OS and PFS rates at 6, 9, 12, 18, and 24 months, and objective response rate (ORR, based on RANO 2.0). Exploratory objectives include assessing plasma concentrations of (Z)-BP and its metabolite, quality of life (EORTC QLQ-C30), and survival analyses stratified by molecular subgroups (EGFR, AXL, c-Met, MGMT, and PD-L1 expression). The enrollment is expected in Q2 2026. Clinical trial information: NCT07349693. Research Sponsor: Everfront Biotech.

TPS2098 **Poster Session**

Randomized phase 2 study to evaluate the efficacy and safety of silevertinib in combination with temozolomide in newly diagnosed patients with EGFRvIII-positive IDHwt MGMT unmethylated glioblastoma. First Author: Patrick Y. Wen, Dana-Farber Cancer Institute, Boston, MA

Background: Targeted therapy for patients with newly diagnosed glioblastoma (ND-GBM) has made little progress. First-line therapy remains surgery, adjuvant radiotherapy with temozolomide (TMZ), and maintenance TMZ. This treatment paradigm is even less effective for the ~60% of patients with MGMT unmethylated status. Oncogenic epidermal growth factor receptor (EGFR) alterations are identified in ~ 50% of ND-GBM tumors irrespective of MGMT status. EGFRvIII is present in ~30% of ND-GBM and is nearly always expressed with other EGFR mutations and/or EGFR amplification. Prior clinical trials of EGFR targeting drugs have shown limited benefit primarily due to poor CNS penetrance and/or lack of potency across EGFR variants and EGFR amplification. Silevertinib (BDTX-1535) is a 4th generation covalent EGFR tyrosine kinase inhibitor (TKI) with high CNS penetrance targeting the full spectrum of oncogenic EGFR alterations in GBM, including variants (EGFRvIII, vII, vVI), mutations, and amplification. Silevertinib has shown additive antitumor effects with TMZ in an intracranial GBM tumor model expressing EGFRvIII with EGFR amplification. A phase 0/1 window-of-opportunity study in patients with recurrent GBM showed that silevertinib reached therapeutic levels in infiltrative GBM tissue with associated biomarker suppression (NCT06072586). Silevertinib was well tolerated and demonstrated promising clinical activity in a phase 1 study in patients with recurrent GBM (ASCO 2024). This randomized phase 2 study will evaluate efficacy and safety of silevertinib in combination with TMZ in adults with EGFRvIII-positive (EGFRvIII) unmethylated MGMT ND-GBM. **Methods:** This multicenter study (NCT05256290) will be conducted in the US and consists of 2 sequential parts. Part 1 (Safety Run-in) will enroll up to 12 patients to evaluate the safety of two doses of silevertinib (150mg QD, 200mg QD) in combination with TMZ and will inform the selected dose for Part 2. In Part 2 (Efficacy Evaluation), patients will be randomized 1:1 to receive adjuvant silevertinib in combination with TMZ or TMZ alone. Patients with EGFRvIII ND-GBM who have completed surgery and adjuvant chemoradiation are eligible (Table). The primary endpoint for Part 2 is progression free survival by blinded independent central review using Response Assessment in Neuro-Oncology (RANO2.0) criteria. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

TPS2099 **Poster Session**

Targeting macrophage migration inhibitory factor: A phase 2 and pharmacodynamic study of sitagliptin in patients with progressive grade 4 gliomas. First Author: David M. Peereboom, Cleveland Clinic Brain Tumor and Neuro-Oncology Center, Cleveland, OH

Background: One mechanism of immunosuppression in the glioblastoma (GBM) microenvironment involves systemic and local accumulation of myeloid-derived suppressor cells (MDSCs) that inhibit cytotoxic immune cell populations and contribute to immune suppression. GBM patients have increased circulating MDSCs compared to lower grade glioma patients, and GBM patients with a better prognosis have reduced MDSCs in their tumors as well as in their peripheral circulation. A trial (NCT02669173) performed at the Cleveland Clinic demonstrated that pre-surgical anti-MDSC therapy (capecitabine) was associated with reduced circulating MDSCs and increased cytotoxic immune infiltration in tumor tissue. This proof-of-principle pilot study demonstrated that targeting MDSCs in patients can attenuate tumor-induced immunosuppression. Subsequent work at the Cleveland Clinic demonstrated that MDSCs require dipeptidyl peptidase 4 (DPP-4) for entry into the brain and overall MDSC function. Screening for a DPP-4 inhibitor identified sitagliptin as a good inhibitor with limited toxicity with efficacy in pre-clinical models. Hypothesis: Treat of GBM patients with sitagliptin will deplete circulating MDSCs and reduce their entry into the brain, reversing systemic and intratumoral immunosuppression. To test this hypothesis, we plan a "window of opportunity" clinical trial to evaluate the safety and biological impact of sitagliptin treatment in patients with recurrent grade 4 glioma undergoing clinically indicated surgical resection. **Methods:** For this trial, we will randomize 48 patients: 36 will receive pre- and post-operative treatment with sitagliptin and 12 will receive post-operative sitagliptin alone. All patients will receive post-operative sitagliptin and chemotherapy until disease progression. Primary endpoint: Difference in tumor CD8+ T cell count between the participants randomized to pre-surgical sitagliptin versus the participants randomized to no pre-surgical treatment. Secondary endpoints: PFS_6, OS_{12}, and safety. Exploratory endpoints: peripheral and intratumoral immune profiling for assessment of TAMs, MDSCs, and CD8+ T cells; tumor radiomic features on MRI brain pre-surgery that might predict intratumoral and peripheral CD8+ T cell count and peripheral MDSC levels; peripheral blood cytokine and immune gene expression profiling for increase in immune activation signatures. This is a window-of-opportunity trial of sitagliptin for patients with grade 4 gliomas to test the hypothesis that sitagliptin, a DPP-4 inhibitor, can reduce MDSC activity, enhance immune activation, and thereby increase the quantity of tumor infiltrated CD8+ T cells. These improvements in immune suppression, combined with chemotherapy will hopefully increase PFS and OS for patients. Clinical trial information: NCT07003542. Research Sponsor: None.

TPS2100 **Poster Session**

A trial to evaluate CSF ctDNA and safety of plixorafenib alone or with retifanlimab in patients with BRAF-altered glioma. First Author: Karisa C. Schreck, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Background: BRAF V600E mutant gliomas are difficult to treat in the recurrent setting due to adaptive resistance to FDA-approved targeted therapies. Emerging therapeutic approaches include novel BRAF inhibitors or combination therapies, but evaluating treatment response is limited by radiographic techniques and the infeasibility of serial tissue sampling. This two-arm study will evaluate the feasibility of using CSF and plasma circulating tumor DNA (ctDNA) as biomarkers for response to a novel-BRAF inhibitor, plixorafenib alone or in combination with PD-1 inhibitor, retifanlimab. Plixorafenib is a small-molecule selective inhibitor of BRAF-V600E and BRAF-fusion alterations without inducing paradoxical reactivation of MAPK signaling. **Methods:** This single institution trial of plixorafenib alone (Arm A) or combined with retifanlimab (Arm B) is enrolling patients (18+ years of age) with BRAF-V600E mutant glioma following progression on prior BRAF-targeted therapy who are recommended for a clinically-indicated diagnostic or debulking surgery. Eligible patients have recurrent BRAF-V600E mutant glioma (any grade) with measurable disease (by RANO 2.0), and a Karnofsky performance status $\geq$ 70. Leptomeningeal disease is allowed. All enrolled patients will undergo clinically-indicated resection or biopsy for confirmation of disease progression and characterization of putative resistance alterations with a ventricular reservoir placed at time of surgery for CSF sampling. In both arms, patients will initiate oral plixorafenib once clinically recovered from surgery. Patients will take the plixorafenib daily with food. In Arm B, enrolled patients will receive one dose of retifanlimab three weeks prior to surgery, then resume monthly retifanlimab infusions after surgery in combination with oral plixorafenib. MRI, CSF, and plasma assessments will occur approximately every two months to evaluate disease status. The primary trial endpoint is detectable ctDNA at baseline and after one month of treatment with plixorafenib. Secondary endpoints include safety of plixorafenib alone or in combination with retifanlimab, response rate in each arm, and the correlation of ctDNA with disease status over time. The trial is IRB approved and enrollment is ongoing (10 patients per arm). Clinical trial identifier NCT06610682. Clinical trial information: NCT06610682. Research Sponsor: Ivy Brain Tumor Foundation; Fore Biotherapeutics.

TPS2101 **Poster Session**

Progress report of a phase 2 study of BPM31510 (a lipid nano dispersion of oxidized CoQ10) with vitamin K in combination with standard of care (SOC) RT and TMZ in glioblastoma multiforme (GBM) patients without prior therapy. First Author: Seema Nagpal, Stanford University, Stanford, CA

Background: BPM31510 is an investigational, drug-lipid conjugate nanodispersion. Preclinical studies demonstrate that intravenous infusion can achieve plasma concentrations of oxidized CoQ10 approximately 10,000 times higher than baseline physiological levels with its accumulation in organs, including brain. Preclinical studies show that supraphysiological concentrations of CoQ10 induce metabolic shifts in a variety of cancer cells and generate Reactive Oxygen Species (ROS) leading to apoptosis. In Phase 1, the main adverse events were related to mild hepatotoxicity and coagulopathy. All coagulation related issues were alleviated by coadministration of Vitamin K. The Phase 2 trial in newly diagnosed patients with glioblastoma tests whether treatment with BPM31510 results in improved efficacy of standard of care temozolomide (TMZ) and radiotherapy (RT). **Methods:** BPM31510IV-11; NCT04752813 is a single-arm, non-randomized, open-label, phase 2 study of intravenous (IV) BPM31510 + prophylactic subcutaneous (SC) Vitamin K1 with standard chemoradiation and temozolomide (TMZ) in newly diagnosed GBM patients. The primary endpoint is Progression Free Survival at 6 months (PFS6) and 12 months (PFS12) while the secondary endpoints are Overall S (OS) survival and safety. Patients with recent hemorrhage, coagulopathy, or requiring anticoagulants are excluded. SC Vit K and IV BPM31510 are initiated 2-4 weeks after biopsy or tumor resection. After two weeks, standard of care chemoradiation and TMZ are started in combination with weekly IV BPM31510 for 8 weeks, after which IV BPM31510 treatment and standard RT are discontinued with subjects continuing to receive maintenance TMZ treatment for up to 12 cycles as per standard of care. Of the approximately 50 patients enrolled and treated upon the recommendation of an independent safety monitoring committee, 25 will be available for PFS6 efficacy endpoint analysis and these data will be presented. Clinical trial information: NCT04752813. Research Sponsor: BPGbio.

TPS2102 **Poster Session**

Gliofocus: A global, open-label, randomized phase 3 study comparing niraparib with temozolomide in newly diagnosed MGMT-unmethylated glioblastoma. First Author: Nader Sanai, Ivy Brain Tumor Center at Barrow Neurological Institute, Phoenix, AZ

Background: Glioblastoma (GBM) remains a fatal malignancy despite multimodality therapy. Approximately 60% of GBMs lack O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, thus associated with resistance to alkylating chemotherapy and poor survival with median OS of 12.7 months. Poly(ADP-ribose) polymerase (PARP) is a central regulator of DNA damage repair and genomic stability in GBM and represents a rational therapeutic target, particularly in the setting of radiotherapy-induced DNA damage. Niraparib is a selective PARP1/2 inhibitor that has demonstrated excellent central nervous system penetration and favorable tumor pharmacokinetic and pharmacodynamic properties in previously reported early-phase GBM studies. These findings provided the scientific rationale for Gliofocus, a global phase 3 trial designed to evaluate whether replacing temozolomide with niraparib during and after radiotherapy improves outcomes in patients with newly diagnosed, MGMT-unmethylated GBM. **Methods:** Gliofocus is a phase 3, open-label, randomized, two-arm study enrolling total 450 adults with newly diagnosed, MGMT-unmethylated GBM. Eligibility requires histologic diagnosis of GBM per 2021 WHO classification, Karnofsky performance status $\geq$70, documented MGMT promoter unmethylated status by validated local testing, and no prior GBM-directed therapy other than biopsy or resection. Patients are randomized 1:1 to receive niraparib or temozolomide concurrently with external-beam radiotherapy (60 Gy in 30 fractions using the ESTRO-EANO single-target volume approach), followed by adjuvant monotherapy of niraparib or temozolomide. Treatment continues until centrally reviewed disease progression per RANO 2.0 guidelines or completion of six cycles of temozolomide in the control arm. The primary endpoint is overall survival (HR = 0.698, 88% power). Secondary endpoints include progression-free survival, objective response rate, health-related quality of life, neurocognitive outcomes, and safety. Integrated correlative assessments include centralized imaging review, longitudinal neurocognitive testing, and patient-reported outcomes. Enrollment began in June 2024. The independent data monitoring committee last reviewed the study in January 2026, and recommended continuation as planned. The trial is sponsored by the Ivy Brain Tumor Center with funding/product support from GSK (NCT06388733). GSK was provided the opportunity to provide a courtesy review of the abstract; however, the authors are solely responsible for final content. Gliofocus study is being conducted across a minimum of 80 sites across 12 countries. Clinical trial information: NCT06388733. Research Sponsor: GSK.

TPS2103 **Poster Session**

Alliance A072301: A phase III trial of radiotherapy followed by adjuvant temozolomide in combination with vorasidenib vs placebo in *IDH*-mutated newly diagnosed grade 3 astrocytoma (VORTEX). First Author: Ugonma Nnenna Chukwueke, Dana-Farber Cancer Institute, Boston, MA

Background: Treatment for newly diagnosed IDH-mutant astrocytoma, WHO grade 3, is based on the results of the CATNON study, demonstrating benefit of radiotherapy followed by 12 months of adjuvant temozolomide. While temozolomide and radiotherapy significantly improved survival, the prognosis for these patients remains limited and more effective therapies are required. This trial will evaluate the benefit of the addition of the IDH1 and IDH-2 inhibitor vorasidenib to adjuvant temozolomide versus placebo following standard radiotherapy to evaluate possible improvement in outcomes. **Methods:** Alliance A072301 (NCT07215910) is a multicenter, double-blinded phase 3 randomized study to determine if the addition of vorasidenib to adjuvant temozolomide significantly improves progression-free survival (PFS), based on blinded central review in patients with newly diagnosed, IDH-mutant astrocytoma, WHO grade 3. Key inclusion criteria include age $\geq$ 12 years old, histological confirmation of astrocytoma (absence of 1p/19q codeletion), WHO grade 3, presence of any IDH mutation, plan for radiation and chemotherapy and surgery within 6 months. The presence of CDKN2A/B homozygous deletion, spinal or leptomeningeal disease, as well as prior chemotherapy, cranial irradiation or IDH inhibitor therapy, is exclusionary. 408 patients will be randomized 1:1 to receive vorasidenib 40 mg or placebo daily with 12 cycles of temozolomide following radiotherapy and then continued as monotherapy until disease progression or unacceptable toxicity. Stratification factors include age ($<$ 40 years old vs $\geq$ 40 years old) and residual disease ($<$ 2 cm vs $\geq$ 2 cm). Tumor assessments with MRI will be every three months for the first two years, every four months for the next two years and then every six months thereafter as per blinded independent central review using the Response Assessment in Neuro-Oncology (RANO) 2.0 criteria. Key secondary endpoints include PFS by local review, time to next treatment, safety and tolerability, quality of life measures. Exploratory measures will include seizure frequency. The trial will have 85% power to detect a hazard ratio of 0.625 with one-sided type I error rate of 0.025. Enrollment for the trial commenced February 2026. Support: U10CA180821, U10CA180882, U24CA196171. https://acknowledgments.alliancefound.org. Research Sponsor: National Cancer Institute; Servier Pharmaceuticals.

TPS2104 **Poster Session**

A phase 3 randomized trial comparing temozolomide with PCV as adjuvant chemotherapy in grade 2 and 3 diffuse gliomas in adults. First Author: Nandini Sharrel Menon, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Background: Both Temozolomide (TMZ) and PCV are standard adjuvant chemotherapy regimens used in treatment of grade 2 gliomas with high risk features and grade 3 gliomas. The PCV regimen has a complex schedule, higher rate of adverse events (esp myelosuppression), and is difficult to administer, but has long-term data with an overall survival benefit. On the other hand,TMZ is an oral drug, with a simple dosing schedule, and fewer adverse events. Currently, there is lack of data directly comparing PCV to TMZ, there is emerging evidence to suggest that PCV may be the regimen of choice for oligodendrogliomas (ODGs). There is often debate on the choice of adjuvant chemotherapy. Hence we are conducting this study to compare TMZ with PCV in this setting. **Methods:** This is an ongoing phase 3, parallel-arm, non-inferiority trial. Adults with high-risk grade 2 (age $\geq$40 years and/or the presence of residual disease $\geq$1 cm after maximal safe resection) or grade 3 gliomas, are randomized 2:1 to receive TMZ or PCV after adjuvant radiation (RT). Patients receive adjuvant focal conformal radiation, with doses between 54 to 59.4 Gy at 1.8-2 Gy/fraction with conventional fractionation. In the TMZ arm, patients receive RT with concurrent TMZ 75 mg/m^2/day (max. 49 days) followed by adjuvant TMZ 150-200 mg/m^2 for 5 of 28 days (max. 12 cycles). In the PCV arm, patients receive Procarbazine 60 mg/m^2 on days 8-21, CCNU 110 mg/m^2 on day 1 and Vincristine 1.4 mg/m^2 on days 8, 29 of a 56-day cycle (maximum 6 cycles). Adjuvant chemotherapy is started within 8 weeks of completing RT. Adverse events are recorded as per CTCAE v4.03. EORTC QLQ C-30 & QLQ BN-20 is used for quality of life (QoL) assessment. Follow up evaluation will be conducted every 3 months in the 1st year, every 4 months in the 2nd year, and every 6 months from the 3 rd to 5 th year, then annually. The primary endpoint of the study is Progression-Free Survival (PFS). Secondary endpoints are Overall Survival (OS), safety,compliance & QoL. Sample Size: Assuming a 3-year PFS of 70% in the PCV arm, with type 1 error of 5% (1-sided), type 2 error of 20%, with 2:1 ratio of accrual (in favor of the TMZ arm) for 10 years, with a study duration of 15 years, to show a non-inferiority by 12% for the upper limit of 95% confidence interval of the PFS with one interim analysis; the sample size estimated by group sequential design for time-to-event outcome was 216. Statistical analysis: Kaplan Meir analysis will be used to estimate the PFS & OS and log rank test will be used for comparison between two arms.Cox proportional hazard model will be constructed for calculation of hazard ratio with its 95%CI. An interim analysis will be performed at 82 events of progression. If the log rank p value for the difference in the estimated PFS of the 2 arms is $\leq$ 0.006 then the trial will be terminated. Otherwise the trial will continue and undergo a final analysis at 163 events of progression. Clinical trial information: CTRI/2018/07/015056. Research Sponsor: Indian Cooperative Oncology Network (ICON).

TPS2105 **Poster Session**

BRIDGES: A phase 3 randomized trial of immediate postoperative cesium-131 tile-based radiation therapy followed by abbreviated chemoradiation for newly diagnosed glioblastoma (NCT07195591). First Author: Clark C. Chen, Brown University, Providence, RI

Background: Glioblastoma remains a lethal primary brain tumor with limited therapeutic progress and a persistent unmet clinical need. Standard management requires maximal safe resection followed by external beam radiation therapy (EBRT) with concurrent temozolomide (TMZ); however, the required 4–6-week postoperative healing interval before initiating EBRT creates a vulnerable window for rapid early progression (REP), defined as radiographic tumor progression occurring between surgery and the start of chemoradiation. REP is detected in more than half of patients and is associated with inferior survival. Tile-based radiation therapy (TBRT) with cesium-131 brachytherapy sources (GammaTile, GT Medical Technologies, Tempe, AZ, USA), offers a strategy to eliminate this treatment gap by immediately initialing localized radiation at the time of resection. A feasibility and safety study (NCT05342883) evaluating TBRT implantation following EBRT has been fully accrued and supports randomized evaluation. The BRIDGES study (NCT07195591) builds on this foundation. **Methods:** NCT07195591 is a prospective, randomized, open-label, multicenter, phase 3 trial to evaluate whether immediate postoperative TBRT followed by abbreviated EBRT with concurrent and adjuvant TMZ improves outcomes compared with standard postoperative EBRT with concurrent and adjuvant TMZ. Eligible adults must have newly diagnosed, radiographic suspicion of glioblastoma, can undergo maximal safe resection, possess a Karnofsky Performance Status score $\geq$70, and be candidates for standard chemoradiation. Key exclusion criteria include multifocal or disseminated disease, prior cranial radiation or chemotherapy, inability to receive TMZ, and medical comorbidities that would interfere with protocol treatment or follow-up. Patients are randomized 2:1 to receive either TBRT implantation followed by a shortened EBRT course with concurrent and adjuvant TMZ or standard postoperative EBRT with concurrent and adjuvant TMZ. Randomization is stratified by age, sex, prior sub-maximal safe resection, and size of pre-operative tumor. A stratified log-rank test using Kaplan–Meier methods will be done using the stratification factors will be implemented for the primary endpoint. Additional time-to-event endpoints will be analyzed using Kaplan–Meier methods and Cox proportional hazards models, and the analyses will follow the intent-to-treat principle. The trial has two pre-planned interim analyses. A Data and Safety Monitoring Board will oversee the trial and conduct periodic safety reviews. Four of the 766 planned patients have enrolled. Clinical trial information: NCT07195591. Research Sponsor: GT Medical Technologies, Inc.

TPS2106 **Poster Session**

Prospective, randomized, placebo-controlled phase 2b trial of SurVaxM plus adjuvant temozolomide in newly diagnosed glioblastoma (SURVIVE). First Author: Manmeet Singh Ahluwalia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Survivin is widely expressed in glioblastoma (GBM) and is implicated in tumor cell survival and treatment resistance, supporting survivin-targeted immunotherapy in newly diagnosed disease. The survivin long-peptide conjugate vaccine SVN53-67/M57-KLH (SurVaxM) has shown feasibility, immunogenicity, an acceptable safety profile and promising efficacy, in phase 1 and 2 trials in newly diagnosed GBM. We hypothesize that SurVaxM combined with standard adjuvant temozolomide (TMZ) post chemo radiation will improve outcomes in newly diagnosed GBM and that correlative biomarkers will define patient selection. **Methods:** SURVIVE is a prospective, randomized, double-blind, placebo-controlled, multicenter phase 2b trial evaluating SVN53-67/M57-KLH plus standard adjuvant TMZ versus placebo plus standard adjuvant TMZ in adults with newly diagnosed GBM. Patients are randomized 3:2 to investigational vaccine (Arm A) or placebo (Arm B), with stratification by Karnofsky performance status, MGMT promoter methylation status, and IDH status. Study intervention consists of four priming SurVaxM injections administered every 2 weeks followed by maintenance dosing every 8 weeks, administered alongside standard adjuvant TMZ (5 days every 28-day cycle; typically, 6-12 cycles per standard practice). The vaccine regimen is delivered as a survivin peptide conjugate with immunologic adjuvants; blinding is maintained via matched placebo injections. MRI surveillance is performed per protocol to support response assessment and the planned imaging correlatives. Key eligibility criteria include age $\geq$18 years; Karnofsky performance status $\geq$70; pathologically confirmed cerebral GBM meeting 2021 WHO criteria with available MGMT and IDH status; gross-total or near-total resection with minimal residual enhancement on immediate post-operative MRI ($\leq$72 hours); completion of chemoradiation with $\geq$75% of planned concurrent temozolomide; no evidence of progression on post-chemoradiation MRI; randomization within approximately 16–18 weeks of resection; and dexamethasone $\leq$4 mg/day at enrollment. The planned evaluable sample size is 228 patients (n=137 Arm A; n=91 Arm B). The primary analysis will be conducted in the intention-to-treat population using a two-sided alpha of 0.05, with stratified time-to-event comparisons to account for key baseline factors. The alternate hypothesis assumes a 1-year survival rate of 75% in the SurVaxM group (Arm A; comparable to a median overall survival (mOS) of 29 months assuming an exponential distribution) and 60% in the control group (Arm B; comparable to a mOS of 16 months assuming an exponential distribution). Clinical trial information: NCT05163080. Research Sponsor: None.

2500 Oral Abstract Session

EMITT-1: Clinical and pharmacodynamic activity with the oral ERAP1 inhibitor GRWD5769 and cemiplimab in 6 completed phase 1b expansion cohorts in solid tumors with anti–PD-1 resistance or MSS-CRC. First Author: Fiona Thistlethwaite, The Christie NHS Foundation Trust and University of Manchester, Manchester, United Kingdom

Background: Resistance to anti-PD-1 therapy remains a major unmet need. GRWD5769 is a first-in-class oral Endoplasmic Reticulum Amino Peptidase 1 inhibitor (ERAP1i) that modulates tumor antigen presentation on MHC-I. Dosing GRWD5769 Q3W on/off generates 2 alternating antigen repertoires (AgR) that could both broaden T cell responses and avoid T cell exhaustion from chronic tumor antigen exposure. We report clinical and translational results from 6 completed stage 1 expansion cohorts of combination GRWD5769 with cemiplimab in patients (pts) with secondary resistance to anti-PD1 and in MSS-CRC (NCT06923761). **Methods:** Pts with NSCLC, Urothelial (UC), HCC, Cervical & SCCHN with secondary resistance to ≥3 month 1st line aPD-1 or MSS-CRC without liver mets received 400 mg BD GRWD5769 and cemiplimab. ORR, Durable Clinical Benefit (DCB; defined as CR, PR or SD lasting ≥6 months) and PFS were assessed. T cell repertoire and immune phenotype changes were evaluated longitudinally. **Results:** All 6 cohorts are fully recruited (n= 81) with median follow up of 6.0 months at this interim analysis. Durable responses were observed in all cohorts (Table 1) with ORR 10-33%; DCB 26-57%. Median PFS ranged from 1.9-7.5 months across evaluable cohorts. Therapy was well tolerated with no observed safety signals. imARs were reported in 12 pts, with only 1 ≥Gr3 event (immune hepatitis) which required drug discontinuation. ≥Gr3 TRAEs occurred in 3% of pts. TCR repertoire diversity increased substantially in pts who achieved clinical benefit, driven by expansion of low-frequency, putative *de novo* TCR clonotypes. Responders exhibited cyclical Vß gene-usage dynamics indicative of broad T cell clonal expansion and contraction, consistent with AgR shifts resulting from ERAP1i. Dynamic activation of T cell associated genes further supported antigen-driven T-cell remodelling. **Conclusions:** GRWD5769 with cemiplimab demonstrated broad, durable activity across all 6 phase 1b expansion cohorts in pts with ≥2 prior lines of therapy and secondary anti-PD-1 resistance, or MSS-CRC. Translational analyses suggest that GRWD5769 exerts a dual mechanism of action, both reprogramming antigen-experienced T cells and inducing *de novo* T cell responses, in keeping with its potential to address both primary and secondary resistance to anti-PD-1 therapy. Based on the efficacy and tolerability of the combination, stage 2 cohort expansions are now ongoing, to inform a randomized Phase 2 study. Clinical trial information: NCT06923761. Research Sponsor: Greywolf Therapeutics.

Summary of expansion cohort efficacy by iRECIST.

	Dosed n	Evaluable* n	ORR % confirmed	ORR % unconfirmed	DCB %	PFS m
NSCLC	14	14	14	21	54	7.5
UC	14	12	25	33	44	2.1
HCC	15	14	14	14	32	3.9
MSS-CRC	12	7	29	29	57	2.1
SCCHN	11	7	14	14	26	3.7
Cervix	15	10	10	10	-	1.9

Data snapshot Jan 26, update for presentation.
*≥1 scan or PD or death before 1st scan.

2501 Oral Abstract Session

Re-sensitizing PD-1/PD-L1 relapsed/refractory solid tumors: Phase 1a results of IOS-1002, a LILRB1/2 and KIR3DL1 checkpoint inhibitor, in combination with pembrolizumab. First Author: Stephen James Luen, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Despite anti-PD-1/PD-L1 therapy success, 60-70% of patients develop progression with limited options (ORR 6-8% to retreatment). Upregulation of inhibitory receptors LILRB1/2 and KIR3DL1 mediates immune escape in anti-PD-1/PD-L1-resistant tumors. IOS-1002, a novel LILRB1/2 and KIR3DL1 antagonist, restores anti-tumor immunity when combined with pembrolizumab. **Methods:** Open-label, multicenter, dose-escalation Phase 1a study (NCT05235308) evaluated IOS-1002 (300-1800mg, Q2W IV) plus pembrolizumab 400mg (Q6W IV) in advanced solid tumors progressing on prior anti-PD-1/PD-L1 therapy. Primary endpoints: safety, tolerability; secondary: ORR, DCR, duration of response (DOR). Comprehensive biomarker analysis included serial cytokine profiling, target receptor expression (LILRB1/2, KIR3DL1), and tumor immune score (TIS) by gene expression analysis. Responses were assessed by RECIST v1.1. **Results:** As of January 1st, 2026, 28 patients received combination treatment with 16 anti-PD-1/PD-L1-relapsed/refractory patients (median age 65, ECOG 0-1). 3 confirmed PRs (tumor reduction -35% to -58% from baseline) leading to an ORR of 20% (3/15 evaluable) were noted with a DCR of 54% at week 12 (7/13) and 40% at week 24 (4/10), respectively. Durable responses included: 1 metabolic CR (urothelial cancer), 1 pathological CR confirmed by repeat biopsy showing absence of viable tumor cells (cutaneous SqCC), and 1 cervical cancer patient achieving -29% tumor reduction with concomitant > 90% decline in CA-125 tumor marker. Median treatment DOR was 30+ weeks (range 12-46+); 8 patients remain on treatment. Biomarker analysis demonstrated strong predictive value for TIS and target receptor expression achieving 75% ORR (3/4) versus 0% in dual-low patients (0/5). Combined biomarker score significantly correlated with depth of response (R^2 = 0.72, p = 0.008) and progression-free survival (HR 0.31, 95% CI 0.11-0.88, p = 0.04). Safety profile was favorable with no increase in grade≥3 immune-related adverse events beyond pembrolizumab monotherapy. **Conclusions:** IOS-1002 plus pembrolizumab demonstrated clinically meaningful efficacy in pretreated anti-PD-1/PD-L1-relapsed/refractory patients. Biomarker-driven patient selection using dual-high TIS and target receptor expression enhanced ORR to 75% and strongly predicted response depth, durability, and survival benefit. The favorable safety profile with no incremental immune-related toxicity, coupled with durable responses and high disease control rates, provides compelling rationale for Phase 1b expansion in biomarker-selected PD-1/PD-L1-refractory solid tumors. Clinical trial information: NCT05235308. Research Sponsor: None.

Endpoint	Result
ORR (evaluable)	20% (3/15)
DCR Week 12	54% (7/13)
DCR Week 24	40% (4/10)
Biomarker-selected ORR	75% (3/4)
Ongoing treatment	8/16 (50%)

2502 Oral Abstract Session

DART (NCI/SWOG S1609): Comprehensive results from dual checkpoint inhibition with CTLA-4 and PD-1 blockade in rare cancers. First Author: Sandip Pravin Patel, UC San Diego Moores Cancer Center, San Diego, CA

Background: Rare tumors are underrepresented in clinical trials, though they collectively comprise an estimated 22% of all cancer cases. The NCI/SWOG S1609 trial evaluated efficacy signals across 53 rare cancer cohorts treated with dual CTLA-4 and PD-1 inhibition. **Methods:** A prospective, open-label, multicenter phase 2 trial of ipilimumab (1mg/kg intravenously every 6 weeks) plus nivolumab (240mg intravenously every 2 weeks) was conducted from 1/13/2017 to 3/15/2023. A statistical framework was established to evaluate each cohort in a two-stage design. The primary end point was objective response rate (ORR); progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR, ORR + stable disease >6 months), i-outcomes, and toxicity were secondary and exploratory endpoints. **Results:** 798 patients were enrolled and 727 eligible patients received treatment. 1,083 national (USA) sites opened the trial. Median (range) patient age was 60 (18-88) years; 344 (47%) patients were male. 24 of 53 cohorts (45%) demonstrated clinical activity, defined as ≥2 patients with confirmed response. Median (range) ORR was 12% (0-75%); CBR, 27% (0-75%). Median (range) 2-year PFS was 10% (0-75%); 3-year OS was 23% (0-100%). 6-month PFS was moderately correlated with 1- and 3-year OS (R^2 =0.61 and 0.54, respectively). Patients who attained an iOR versus OR had similar OS. 82 patients (11%) had iPFS ≥2 years. Treatment-related adverse events (AEs) of any cause and immune-mediated occurred in 603 (82.9%) and 465 (64.0%) patients. AEs led to treatment discontinuation in 102 patients (14.0%). Most common AEs were fever (38.1%), diarrhea (21.2%), and rash/pruritis (19.3%). 13 patients (1.8%) experienced treatment-related grade 5 AEs. Patients alive at 6 months who discontinued treatment due to immune-related AE had longer OS than those who discontinued for other reasons (p = 0.021). **Conclusions:** Patients with multiple rare cancer types derived meaningful response to ipilimumab plus nivolumab. Characterization of biologically defined subsets is underway to optimize therapeutic selection. Clinical trial information: NCT02834013. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180819; Bristol-Myers-Squibb.

Response among all cohorts and cohorts with iRECIST iClinical benefit rate (iORR+iSD>6 mos) ≥50%.

Cohort	*N*	iConfirmed response	iClinical benefit	iCR	iPR	6-month iPFS	2-year iPFS	1-year OS	3-year OS	Median iPFS (months)
All	**727**	**13%**	**29%**	**3%**	**10%**	**30%**	**12%**	**48%**	**24%**	**2.2**
Gestational trophoblastic disease	4	75%	75%	25%	50%	75%	75%	100%	100%	Not Reached
Basal cell carcinoma	17	35%	71%	0	35%	76%	24%	76%	53%	12.1
Chordoma	10	0	70%	0	0	80%	30%	80%	30%	13.1
Bronchoalveolar carcinoma lung	8	25%	62%	0	25%	62%	33%	88%	44%	8.3
Desmoid tumors	16	19%	62%	0	19%	73%	40%	100%	80%	19.3
Carcinomas of pituitary, thyroid, parathyroid, adrenal cortex	19	21%	53%	0	21%	58%	26%	74%	42%	9.4
Fibromyxoma, low grade mucinous adenocarcinoma	10	0	50%	0	0	50%	0	60%	30%	5.7
Malignant giant cell tumors	6	0	50%	0	0	50%	33%	83%	50%	3.4

2503 Oral Abstract Session

Desmocolin-3–directed immunotherapy in recurrent/metastatic head and neck squamous cell carcinoma. First Author: Ranjan Das, Department of Medical Oncology, Sparsh Hospitals and Critical Care, Bhubaneswar, India

Background: Recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC) are aggressive tumors. In pre-treated R/M HNSCC observed response rates were 13.0% (nivolumab; CheckMate 141) and 14.6% (pembrolizumab; KEYNOTE- 040), with median PFS 2.0 months and 2.1 months, respectively. Desmocollin3 (DSC3) is a surface protein expressed by HNSCC. DSC3 directed immunotherapy (CADI-05) is useful in DSC3 expressing cancer like Squamous NSCLC, bladder cancer, and melanoma. This study evaluated its efficacy (ORR, PFS, OS) in DSC3 expressing R/MHNSCC. **Methods:** In this investigator initiated single-arm, study patients with RMHNSCC expressing DSC3 were recruited. Tumor infiltrating lymphocytes (TIL), PD-L1, and P16 were also evaluated. All patients received 0.1ml CADI-05 intradermally + intralesional (for fungating/discharging solid lesions were present) every 4 weeks. Additional treatment was administered as per PI discretion. All patients were followed up until disease progression, or death. **Results:** Between May 2024 and July 2025, 20 patients were enrolled (males 17, females 3). The mean age was 55 yrs (range 34-87 yrs). Primary sites included tongue 9, buccal mucosa 9. All had undergone two lines of therapy with a mean of 2.55. Of 20 patients, 15 had progressed on prior therapy (6 stage IVC). Baseline mean parameters were mean DSC3 TPS - 41%, (95% CI, 32.67 - 49.33), mean PD-L1 CPS 27 (95% CI,10.61 - 33.39), mean TIL 17% (95% CI ,10.43 - 23.57). All were HPV negative. Additional therapy received included EGFR TKI (15), EGFR mAb (2), oral metronomic therapy (1) and none (2). Disease control rate was 45% (9/20) with overall response rate (ORR) 35% [7/20; 2 CR and 5 PR]. At a median follow-up of 155 days, mean (median) PFS and overall survival were 165 (115) and 197 (155) days, respectively. Mean (median) duration of response was 280 (332) days with 8 patients alive at the last follow up. This is significantly better than achieved with current therapies. Responders had higher DSC3 expression compared to non-responders (mean DSC3 50% vs 29%; p= 0 .002537). ORR was higher in patients with Stage IVA (57%) compared to IVC (20%) DSC3 TPS was higher than PD-L1 CPS in all patients with disease control. TIL and PD-L1 levels were not correlated with response. Injection site ulcer was the only side effect seen in 8 (40%), which include 6 (75%) of the responders. No systemic adverse events were observed. **Conclusions:** DSC3 targeted immunotherapy was safe and improved outcomes in pre-treated R/M HNSCC expressing DSC3, with disease control rate 45%, response rate 35%. Median duration of response was 332 days with median PFS and OS of 115 and 155 days, respectively. Research Sponsor: None.

2504 **Oral Abstract Session**

RP2 oncolytic immunotherapy alone and in combination with nivolumab (nivo) in patients with advanced solid tumors: Final safety, efficacy, and biomarker results from the phase 1 first-in-human (FIH) study. First Author: Joseph J. Sacco, The Clatterbridge Cancer Centre and University of Liverpool, Liverpool, United Kingdom

Background: RP2 is an HSV-1-based oncolytic immunotherapy expressing a fusogenic glycoprotein (GALV-GP-R$^-$), human GM-CSF, and a human anti–CTLA-4 antibody. We present final safety, efficacy, and biomarker data from the FIH study of RP2 in patients (pts) with advanced solid tumors (NCT04336241). **Methods:** Enrolled pts had advanced/metastatic solid tumors with ≥1 measurable, injectable lesion (≥1 cm) and had progressed following, or could not tolerate, available standard therapy. Pts received RP2 monotherapy via intratumoral injection in dose escalation (Part 1; 5 doses Q2W). Pts in Parts 2 (RP2 + nivo) and 3 (RP2 monotherapy) received up to 8 doses of RP2 (Q2W × 8 or Q2W × 4 followed by Q4W × 4 doses) at the RP2D. In Part 2, nivo was administered starting at Cycle 2 or 4 for ~20 to 22 months. Pts could receive an additional course of RP2 per protocol. **Results:** As of 01DEC2025, 85 pts (median age 59 y) were enrolled and treated in RP2 (n = 25) or RP2 + nivo (n = 60) cohorts. Tumor types included uveal or cutaneous melanoma (UM, n = 17; CM, n = 11); colorectal (n = 14), head and neck (n = 13), and pancreatic (n = 12) cancers; and sarcoma (n = 7); 42% of pts received prior immune checkpoint inhibitor treatment. All pts have completed treatment. Treatment-related adverse events (TRAEs) in > 10% of pts included pyrexia, chills, fatigue, influenza-like illness, hypotension, pruritus, and nausea. Grade ≥3 TRAEs occurred in 20% of pts (no single event occurred in > 2 pts). A majority of pts (58/85) received injections into deep/visceral lesions, mainly in liver and lung, which were well tolerated. Among pts with ≥1 post-baseline scan (75/85), the ORR was 17.3% (13/75; 1 unconfirmed) with a median DOR of 22.1 months and DCR (CR+PR+SD) of 44.0% (33/75). Responses occurred in 5/15 (33.3%) pts with UM. RP2 monotherapy resulted in confirmed responses in 4/21 (19%) pts (1 esophagogastric adenocarcinoma, 1 UM, 1 chordoma, 1 mucoepidermoid), with best overall response of CR and median DOR not reached. Tumor regression occurred in both injected and non-injected lesions, including all 3 pts with monotherapy responses with non-injected lesions. A robust intratumoral immune response with increased CD8+ T-cell infiltrates, PD-L1 upregulation, and inflammatory immune pathway activation were observed, as well as epitope spreading with novel virus- and cancer-associated T-cell clones. **Conclusions:** RP2 ± nivo treatment was well tolerated in pts with both superficial and deep visceral metastases. Durable responses were observed with RP2 monotherapy and RP2 + nivo in heavily pretreated pts with diverse tumors with evidence of systemic anti-tumor immune activity, including tumor reduction in distant non-injected lesions. This study supports the ongoing evaluation of RP2 in pts with UM (NCT06581406) and the planned evaluation in other solid tumors. Clinical trial information: NCT04336241. Research Sponsor: Replimune, Inc.

2505 **Oral Abstract Session**

Phase 2 basket trial of precision TIL therapy for immunotherapy-resistant advanced cancers. First Author: Shravan Leonard-Murali, University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA

Background: Adoptive cell therapy (ACT) using unselected autologous tumor-infiltrating lymphocytes (TIL) has demonstrated clinical activity in metastatic cutaneous melanoma, an immunotherapy-sensitive cancer with high tumor mutational burden (TMB). However, we recently demonstrated in metastatic uveal melanoma, a prototypic low-TMB, immunotherapy-resistant cancer, that efficacy of TIL ACT requires infusion of TIL with measurable anti-tumor reactivity. Thus, to extend TIL ACT to additional immunotherapy-resistant cancers, we developed *TILScore*, a pan-cancer in situ transcriptomic biomarker designed to preoperatively identify metastases enriched with clinically active TIL. Here we report initial results from a pilot phase 2 TIL therapy trial prospectively evaluating *TILScore* as a precision biomarker for immunotherapy-resistant cancers. **Methods:** This single-center phase 2 trial (NCT03935893) enrolled patients with treatment-refractory, locally advanced, recurrent, or metastatic cancers into ten histology-defined cohorts. After a feasibility run-in, metastases with core biopsy *TILScore* > 0.248 were selected for TIL harvest and manufacturing. Patients received non-myeloablative lymphodepletion (NMA-LD) with cyclophosphamide and fludarabine, followed by infusion of TIL and high-dose interleukin-2. The primary endpoint was cohort-specific objective response rate (ORR) by RECIST v1.1 using a Bayesian basket design targeting ORR > 20% as evidence of promising activity. **Results:** As of 1/17/2026, 19 patients received TIL therapy. Tumor types included pancreatic adenocarcinoma (PDAC, n = 7), leiomyosarcoma (n = 3), peritoneal mesothelioma (PeM, n = 2), and single cases each of non–small cell lung cancer, cervical squamous cell carcinoma (SCC), nasopharyngeal SCC, and melanoma subtypes (cutaneous, acral, mucosal, unknown origin). All had progression after frontline therapy, with a median of 5 prior metastatic treatments; 58% had received checkpoint blockade. Liver metastases were the most common TIL source (37%), followed by lung and soft tissue (32% each). Infusion products contained a median of 5.36E10 TIL with an even mix of CD4 and CD8 cells. Adverse events were consistent with NMA-LD and interleukin-2; no grade 5 events occurred. Among 18 evaluable patients, ORR was 33% (6/18) with cohort specific responses in PDAC (50%, 3/6: 1 CR, 2 PR), PeM (100%, 2/2: 1 CR, 1 PR), and melanoma of unknown origin (100%, 1/1: 1 CR). *TILScore* predicted clinical response with an area under the receiving operating characteristic curve of 0.806 (P = 0.041). **Conclusions:** *TILScore*-guided selection of metastases for TIL manufacturing is feasible and enables consistent generation of clinically active TIL in patients with immunotherapy-resistant cancers. Promising clinical activity in PDAC and PeM supports evaluation of this biomarker-driven TIL ACT approach in larger, histology-specific cohorts. Clinical trial information: NCT03935893. Research Sponsor: UPMC Enterprises Translational Sciences.

2506 **Oral Abstract Session**

Initial phase 1 study results of NT-175 engineered T-cell therapy in *TP53* R175H–mutated unresectable advanced solid tumors. First Author: Rishi Surana, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: *TP53* is the most frequently mutated tumor suppressor gene across various tumor types, but no approved targeted therapies exist. NT-175 is an autologous engineered T-cell receptor (eTCR) T-cell therapy expressing an HLA-A*02:01-restricted TCR that targets the TP53 R175H tumor neoantigen. **Methods:** This open-label Phase 1 study (NCT05877599) enrolled HLA-A*02:01-positive adults with advanced/metastatic, TP53 R175H-mutated solid tumors. NT-175 was manufactured from autologous T cells modified by CRISPR/Cas9 gene-editing to delete endogenous TGFβR2 and replace the TCRα locus with the A*02:01-restricted R175H specific TCR. Patients (pts) received lymphodepletion with fludarabine and cyclophosphamide followed by a single NT-175 infusion along with subcutaneous recombinant IL-2. NT-175 was administered at 3 escalating dose levels (DLs) of eTCR+ T-cells. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded per ASTCT consensus definitions. Response was determined by investigator assessment per RECIST v1.1. The primary objective was safety; secondary and exploratory objectives included preliminary antitumor activity and pharmacokinetics (PK), respectively. **Results:** As of Oct 31, 2025, 26 pts were enrolled and 21 were infused with NT-175 (median age 58 years, [range 43–77] across all DLs (DL1, n = 3; DL2, n = 4; DL3, n = 13; other, n = 1). Pts had a median of 3 prior lines of systemic therapy. Median time from apheresis to NT-175 infusion was 36 days and median follow-up was 6.0 (range: 0.9–9.5) months. Pts had colorectal adenocarcinoma (CRC, n = 10), pancreatic adenocarcinoma (PDAC, n = 6), breast cancer (BC, n = 2), and other solid tumors (n =3). There were no DLTs or Grade 5 events. CRS occurred in 11 (52.4%) pts (Grade ≥3 in 2 [9.5%]); ICANS occurred in 1 pt (Grade 3, 4.8%). Across all dose levels, objective response rate (ORR, including 7 confirmed and 3 unconfirmed responses) was 47.6% (95% CI, 25.7–70.2); in DL3, ORR was 53.8% (95% CI, 25.1–80.8). Partial responses (PR) were observed in 10 pts including 5/6 pts (83%) with PDAC and 5 pts across various tumor histologies (2/10 CRC, 2/2 BC, 1 other), and stable disease in 4 pts. Of 7 evaluable PR pts with ≥6 months of follow up, 5 remain in PR (2 PDAC, 1 leiomyosarcoma, and 2 CRC). Overall, disease control rate was 66.7% (95% CI, 43.0–85.4). Peripheral blood PK analyses (n =21) showed dose-dependent NT-175 expansion, peaking at Week 1 post-infusion, and persistence > 300 days. **Conclusions:** Manufacturing and treatment with autologous NT-175 eTCR T cells was safe and feasible in pts with heavily pre-treated metastatic TP53-mutated malignancies. Further, NT-175 demonstrated encouraging preliminary antitumor activity across multiple histologies, with most notable early signals in PDAC and may offer a prolonged treatment-free interval in pts with refractory solid tumors. Clinical trial information: NCT05877599. Research Sponsor: AstraZeneca.

2507 **Oral Abstract Session**

First-in-human results with IMA401, a MAGEA4/8-targeted T-cell receptor–based bispecific T-cell engager (TCER) in recurrent or refractory solid tumors. First Author: Martin Wermke, TU Dresden University of Technology, NCT/UCC Early Clinical Trial Unit, Dresden, Germany

Background: IMA401 is a next-gen bispecific TCR-based T-cell engager designed to redirect T cells to antigen-positive cancer cells. It combines a high-affinity, highly specific TCR domain against an HLA-A*02:01-presented target peptide common to cancer-specific antigens MAGEA4 and MAGEA8 with a low-affinity T-cell–recruiting domain for improved tolerability and biodistribution, and an Fc part for half-life extension. IMA401-101 (NCT05359445) is a first-in-human phase 1a/b basket study evaluating IMA401 in pts with advanced solid tumors. **Methods:** Pts were ≥18 y, HLA-A*02:01+, MAGEA4+ and/or MAGEA8+, have R/R solid tumors, measurable disease (RECIST 1.1), ECOG performance status 0-2, and have exhausted SOC options. Dose escalation involved cohorts of 1-6 pts using adaptive design (BLRM). Doses ranged from 0.0066 mg - 2.5 mg IMA401 q2w (± pembrolizumab [pembro] q6w with 1.0 mg or 1.5 mg IMA401). Weekly step dosing of IMA401 was implemented for the first 2-3 doses at ≥1 mg . Primary endpoint was MTD assessed by BLRM and/or RP2D as monotherapy and in combination with pembro. Secondary endpoints included safety and initial antitumor activity (confirmed objective response rate [cORR] and disease control rate [DCR]). **Results:** As of Sep 26, 2025, 55 heavily pretreated pts across > 15 different tumor types with a median of 4 prior lines of therapy (range 1-9) received IMA401 ± pembro. Most frequent TRAEs were low-grade CRS (G1: 24%; G2: 11%; no ≥G3 events), expected and transient lymphopenia (any grade: 29%; ≥G3: 24% which typically improved within 1-3 days), and reversible neutropenia (any grade: 29%; ≥G3: 18%). No ICANS was observed. Tolerability of IMA401 + pembro (n = 9) was consistent with the IMA401 monotherapy safety profile. MTD was not reached (3 DLTs at 2.5 mg IMA401). RP2D range was determined to be 1-2 mg IMA401. Efficacy was evaluable in 38 pts receiving a target dose of ≥1 mg IMA401. Promising clinical activity was noted in pts with head and neck (HN) cancer (cORR: 25% [2/8]; DCR: 63% [5/8]) and melanoma (cORR: 29% [2/7]; DCR: 57% [4/7]) with duration of all confirmed responses beyond 6 months postinfusion. In squamous non-small cell lung cancer (sqNSCLC [n = 3]), 1 PR with reduction in all target lesions, 1 SD with OS of ~16 months and 1 PD with reduction in all liver target lesions were observed. After data cutoff, 2 more cPRs were observed in HN cancer resulting in a cORR of 33% (4/12). An updated full dataset will be presented. **Conclusions:** IMA401 demonstrated overall favorable tolerability without reaching formal MTD and encouraging antitumor activity in pts with HN cancer, melanoma, and sqNSCLC at RP2D range. Based on the promising results and preclinical proof of concept data, further development steps are being evaluated including a potentially synergistic combination with the PRAME-directed bispecific IMA402 in sqNSCLC and other solid tumor indications. Clinical trial information: NCT05359445. Research Sponsor: None.

2508 **Oral Abstract Session**

Objective response rates with Ori-C101, an armored GPC3-directed CAR-T, in heavily pretreated advanced HCC: Updated results from the phase Ib BEACON study. First Author: Jia Fan, Department of Hepatobiliary Surgery and Liver Transplantation, Liver Cancer Institute, Zhongshan Hospital, and Key Laboratory of Carcinogenesis and Cancer Invasion of Ministry of Education, Fudan University, Shanghai, China; Clinical Center for Biotherapy, Shanghai, China

Background: Advanced hepatocellular carcinoma (HCC) remains a high unmet-medical-need malignancy with limited therapeutic options. Ori-C101 is a novel, armored, autologous GPC3-directed CAR-T cell therapy. Following promising results from early-phase trials (ChiCTR190028121; NCT05652920, BEACON study), we shall herein update outcomes from the BEACON study with focusing on long-term safety, durability of response, and survival after more than 2 years of follow-up. **Methods:** This is an open-label, multi-center, phase Ib dose-escalation and expansion study enrolled patients (pts) with GPC3$^+$ advanced HCC who had progressed on ≥2 prior lines of systemic therapy (including ICIs and TKIs). A single dose of Ori-C101 was administered via hepatic arterial infusion to enhance regional cell delivery. Integrated analyses assessed safety, tolerability, PK, and efficacy (per RECIST v1.1) , aiming to determine the RP2D. **Results:** As of Dec 24, 2025, 19 pts received Ori-C101 infusion across 4 dose levels (DLs). All pts had BCLC stage B/C disease and 31.6% (6/19) had extrahepatic metastases. Pts were previously treated with a median of 3 lines (range 2–8) therapies. Safety: Safety remained manageable; no late-onset nor cumulative toxicities were observed through the extended follow-up period. The most common ≥G3 TEAEs (≥10.0%) were transient hematologic toxicities and hepatic laboratory abnormalities. CRS occurred in 100.0% (19/19) of pts; while ≥G3 CRS observed in 42.1% (8/19). No ICANS occurred. One pt at DL4 experienced a DLT of G4 CRS complicated by secondary DIC. Efficacy: In 18 efficacy-evaluable pts, Ori-C101 demonstrated a robust dose-dependent response. Confirmed ORR was 50.0% (9/18); DCR was 77.8% (14/18). At RP2D (DL3), the confirmed ORR and DCR were 66.7% (6/9) and 88.9% (8/9), respectively. Critically, responses were not only rapid but also remarkably durable. 88.9% (8/9) of responders achieved objective response within 1.1 months; at M3, 83.3% (5/6) of responders at the RP2D remained PR. Notably, 1 pt at DL4 achieved CR with a duration exceeding 20 months. Preliminary overall survival data indicate a substantial long-term survival benefit with a median OS of 14.4 months (range 2.6–22.0). In addition, Dose-Exposure-Responses analysis showed dose-dependent CAR-T cells expansion, pharmacodynamic effects and improved tumor response. **Conclusions:** Ori-C101 demonstrates a manageable safety profile and compelling, durable anti-tumor activity in GPC3$^+$ advanced HCC. The combination of high ORR and prolonged survival benefit distinguishes Ori-C101 as a potential paradigm-shifting therapy for patients who have failed standard-of-care treatments. A phase II/III study is currently underway to further confirm the efficacy and asses the safety of Ori-C101. Clinical trial information: NCT05652920. Research Sponsor: None.

2509 **Clinical Science Symposium**

An investigator-initiated phase I study evaluating the safety, tolerability, and preliminary efficacy of a personalized neoantigen mRNA vaccine (XP-004) combined with PD-1 inhibitor as adjuvant therapy in resected pancreatic cancer patients intolerant to chemotherapy. First Author: Xinjing Wang, Department of General Surgery, Pancreatic Disease Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Pancreatic cancer has a high postoperative recurrence rate. Although adjuvant chemotherapy is standard of care, many patients are unable to tolerate it, highlighting an unmet need for alternative adjuvant strategies. Personalized neoantigen mRNA vaccines can induce tumor-specific T-cell responses and may synergize with PD-1 blockade. This study evaluated the safety, tolerability, and preliminary clinical activity of XP-004 combined with a PD-1 inhibitor as adjuvant therapy in resected pancreatic cancer patients intolerant to chemotherapy. **Methods:** This open-label, single-arm, investigator-initiated phase I trial (2024PCV004; NCT06496373) initiated in May 2024 plans to enroll 16-20 patients with resected pancreatic cancer intolerant to chemotherapy. Patients received XP-004 intramuscularly (1.0 mg Q3W for 13 cycles), including a KRAS-targeted single-neoantigen vaccine for 4 cycles followed by a personalized multi-neoantigen vaccine for 9 cycles, combined with toripalimab (PD-1 inhibitor). Each personalized vaccine encoded 10–20 personalized neoantigens selected using next-generation sequencing and bioinformatic prediction. The primary endpoint was safety and tolerability; secondary endpoints included neoantigen-specific CD4$^+$ and CD8$^+$ T-cell responses, recurrence-free survival (RFS), and overall survival (OS). **Results:** As of December 15, 2025, 16 patients were enrolled. XP-004 mRNA vaccine was well tolerated. Treatment-related AEs included fever (100%), injection-site pain (87.5%), nausea (43.8%), vomiting (37.5%), pruritus (50.0%), rash (25.0%), and fatigue (37.5%). Grade ≥3 AEs were observed in 12.5% patients, including fever (12.5%) and pruritus (6.3%), the latter attributed to toripalimab. No other immune-related AEs were observed. Transient cytokine increases (IFN-γ, IL-5, IL-6, IL-8, IL-10) were observed without organ dysfunction. At a median postoperative follow-up of 43.9 weeks (range of 6.1–72.0 weeks), and a median follow-up of 37.6 weeks (range of 0.9–63.7 weeks) after first vaccination, all patients remained recurrence-free, with no clinical or molecular evidence of recurrence, including no tumor-informed MRD relapse. Among the 13 patients evaluable for immunogenicity, 13 (100.0%) developed neoantigen-specific T-cell responses; 53 of 165 neoantigens (32.1%) were immunogenic. **Conclusions:** XP-004 combined with PD-1 inhibitor demonstrated favorable safety and tolerability and induced robust neoantigen-specific T-cell responses in resected pancreatic cancer patients intolerant to chemotherapy. Early follow-up suggests potential RFS benefit, supporting further investigation of this adjuvant immunotherapy strategy. Clinical trial information: NCT06496373. Research Sponsor: None.

2510 **Clinical Science Symposium**

Synthetic lethality–informed neoantigen prioritisation to support mechanism-specific therapeutic strategies across human cancers. First Author: Michael E. Bryan, Centre for Immuno-Oncology, University of Oxford, Oxford, United Kingdom

Background: Personalised neoantigen vaccines can elicit strong tumour-specific T cell responses, yet tumours may evade immune pressure by deleting or silencing the targeted gene. Current selection pipelines treat gene-based escape as an unpredictable failure. For tumour suppressor genes, however, loss of the target can create predictable synthetic lethal (SL) dependencies. We present a framework that classifies tumour suppressor mutations by their therapeutic implications. We hypothesised that hypomorphic mutations, which generate immunogenic neoantigens while retaining partial function, may be suited to sequential therapy, where vaccination selects for complete loss and exposes druggable vulnerabilities. In contrast, null mutations with pre-existing SL dependencies may benefit from upfront vaccine–drug combinations. **Methods:** We analysed 9,953 tumours across 32 cancer types from TCGA. Tumour suppressor mutations were assessed for neoantigen potential using NetMHCpan-4.2, MHCflurry 2.0, and PRIME 2.0 (%rank $<$ 2%), with filtering for clonality, expression (TPM $>$ 1), and multi-allele HLA presentation. Functional status was assigned using gene-specific annotations, including TP53 transactivation scores. SL relationships were curated from DepMap, SynLethDB 2.0, and published clinical evidence, restricted to partners with approved or Phase II+ inhibitors. **Results:** 7.4% of patients (n = 741) harboured tumour suppressor neoantigens with matched SL vulnerabilities, which segregated into two distinct groups. The first group (4.6%, n = 458) carried hypomorphic mutations that generated immunogenic neoantigens while retaining partial gene activity, consistent with candidacy for sequential vaccination followed by SL inhibition upon escape. TP53 missense mutations predominated (58%), with progression to null status predicted to confer WEE1 or CHK1 vulnerability. Additional recurrent pairings included PTEN–AKT (14%), ATM–ATR or PARP (11%), KMT2D–EZH2 (9%), and BRCA2–PARP (8%). The second group (2.8%, n = 283) carried functionally null mutations with SL dependencies present at diagnosis, nominating these patients for upfront vaccine–drug combinations. Endometrial (12.1%) and colorectal (9.8%) cancers were enriched for both patterns, whereas high-grade serous ovarian cancer was dominated by hypomorphic mutations. **Conclusions:** This framework reframes immune escape from neoantigen vaccination, conventionally viewed as treatment failure, as a predictable and potentially exploitable therapeutic event. Functional classification of tumour suppressor neoantigens provides a rationale for distinguishing sequential from upfront vaccine–SL inhibitor strategies. Prospective trials with longitudinal monitoring will be required to determine whether vaccination-induced gene loss consistently exposes the predicted vulnerabilities. Research Sponsor: None.

2511 **Clinical Science Symposium**

Personalized neoantigen vaccine as adjuvant therapy in high-risk post-operative esophageal carcinoma. First Author: Ming Wu, Department of Thoracic Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Effective adjuvant strategies for patients with esophageal carcinoma (EC) with residual pathological disease (non-pCR) following neoadjuvant chemoimmunotherapy and radical surgery are urgently needed to reduce the high risk of recurrence. This investigator-initiated, single-arm clinical trial (NCT05307835) evaluated the safety, efficacy, and immunogenicity of iNeo-Vac-P01, a personalized neoantigen peptide vaccine, administered as adjuvant therapy in this high-risk setting. To our knowledge, this study represents the first and largest global cohort of a personalized neoantigen vaccine for postoperative EC, with the longest follow-up duration to date. **Methods:** Eligible stage IIA-IIIB EC patients with non-pCR were enrolled. For each patient, somatic mutations were identified, and up to 20 individualized long peptides (15-30 amino acids), encompassing predicted HLA-I and II neoantigens, were designed and synthesized using a proprietary bioinformatics platform. The vaccine (300μg per peptide) was administered subcutaneously in conjunction with GM-CSF (40μg) on a multi-dose schedule (Days 1, 4, 8, 15±3, 22±3, 52±7, and 82±7). The primary endpoints were safety and 1-year recurrence-free survival (RFS). Secondary endpoints included RFS, overall survival (OS), and antigen-specific T-cell responses assessed by ELISpot and TCR sequencing. **Results:** As of November 15, 2025, 26 patients were enrolled, with 23 patients constituting the efficacy-evaluable population. Treatment-related adverse events were primarily Grade 1-2 (fatigue: 39.1%; fever: 30.4%; injection site reactions: 21.7%), with one Grade III acute hypersensitivity event. All 23 patients completed the initial 7-vaccination course. With a median follow-up of 25.3 months from surgery, the 1-year, 2-year, and 3-year RFS rates were 91.3%, 85.6%, and 78.5%, respectively. The corresponding 1-year, 2-year, and 3-year OS rates were 100%, 95%, and 83.1%. These survival outcomes compare favorably with historical controls, notably exceeding the 3-year RFS of 43% reported in the landmark CheckMate 577 trial (adjuvant nivolumab). Immunological analyses confirmed robust vaccine-induced immunogenicity. ELISpot assays detected neoantigen-specific T-cell responses in 100% (23/23) of evaluated patients, with 79.5% (233/296) of the administered vaccine peptides eliciting de novo T-cell activation. TCR sequencing further demonstrated the durable expansion of neoantigen-reactive T-cell clones, which were detectable during treatment and persisted for at least six months following the final vaccination. **Conclusions:** These results demonstrates that adjuvant therapy with a personalized neoantigen peptide vaccine confers a substantial and durable survival benefit in high-risk EC patients following surgery, coupled with a favorable safety profile. Clinical trial information: NCT05307835. Research Sponsor: Hangzhou Neoantigen Therapeutics Co., Ltd.

2512 Rapid Oral Abstract Session

Phase 2 trial of TIL therapy for metastatic uveal melanoma: Evaluation of T cell potency and an in situ precision biomarker. First Author: Shravan Leonard-Murali, University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA

Background: Uveal melanoma (UM) is a rare eye cancer that frequently metastasizes to the liver and responds poorly to systemic therapies. We previously reported that adoptive transfer of autologous tumor-infiltrating lymphocytes (TIL) produced a 35% objective response rate (ORR) in metastatic UM, with infusion product tumor reactivity being the strongest predictor of response. To guide surgical harvest of metastases enriched for tumor-reactive TIL, we developed Uveal Melanoma Immunogenomic Score (UMIS), an in situ tumor transcriptomic biomarker. Here we present results of a phase 2 trial designed to validate the efficacy of TIL therapy in metastatic UM and prospectively evaluate predictors of response. **Methods:** In this single-center phase 2 trial (NCT03467516) metastatic UM patients underwent metastatectomy to generate early TIL cultures. Cultures demonstrating growth potential and autologous anti-tumor reactivity were expanded for infusion. Patients received non-myeloablative lymphodepletion with cyclophosphamide and fludarabine, followed by infusion of TIL and high-dose interleukin-2. The primary endpoint was ORR per RECIST v1.1. Exploratory analyses to identify response predictors were performed in the current cohort and a pooled dataset including the NCT01814046 cohort. **Results:** Thirty-three UM patients received TIL therapy. Most had high disease burden (82% M1b/M1c; 76% elevated LDH; 70% hepatic and extrahepatic metastases; 24% CNS), received a median of 2 prior metastatic treatments (64% checkpoint blockade, 33% tebentafusp), and had liver metastases as their TIL source (52%). Infusion products had a median of 5.24E10 TIL, were CD8-enriched (median 68%), and demonstrated autologous tumor reactivity in 61% (19/31). Among 32 evaluable patients, the ORR was 22% (7/32) with a median response duration of 10.8 months (maximum ongoing at 58 months). Tumor-reactive TIL conferred higher response rates (37%, 7/19) than nonreactive products (0%, 0/12; P = 0.026). Responders demonstrated higher persistence of infused TIL clones in peripheral blood (R/NR ratio = 10.69, P = 0.020). In the pooled cohort (n = 54, 52 evaluable), ORR was higher with reactive products (43%, 12/28) versus nonreactive products (0%, 0/20; P = 5.06E-4). UMIS of the source metastases predicted growth of tumor-reactive TIL cultures (Rho = 0.55, P = 2.72E-5), final infusion product reactivity (P = 0.040), and clinical response (P = 0.004). **Conclusions:** TIL therapy demonstrates clinically meaningful activity in advanced, pretreated metastatic UM. Infusion product tumor reactivity was the strongest predictor of response. UMIS identified metastases enriched with tumor-reactive TIL and predicted final product potency and clinical outcome. These findings support implementation of UMIS as a minimally invasive precision biomarker to guide patient and tumor selection for optimal therapeutic benefit. Clinical trial information: NCT03467516. Research Sponsor: None.

2513 Rapid Oral Abstract Session

Perioperative tislelizumab plus chemotherapy versus chemotherapy in MHC-II positive/MHC-II negative locally advanced GC/GEJC: A prospective, randomized, open-label, biomarker-driven, phase 2 trial. First Author: Xiangdong Cheng, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China

Background: Neoadjuvant immunotherapy achieves major pathologic response (mPR) in 40% of locally advanced gastric cancer (LAGC) patients. Tumor-specific MHC-II expression(tsMHC-II) has been linked to a better enhanced response to immune checkpoint inhibitor therapy. Herein, we conducted a prospective, randomized study to evaluate the effectiveness of chemotherapy combined with anti-PD-1 therapy versus chemotherapy alone as neoadjuvant treatment for tsMHC-II-positive LAGC patients. **Methods:** Patients with locally advanced GC/GEJC (cT3-4N+M0, CY0, P0) were enrolled according to tsMHC-II expression. Within each stratum, patients were subsequently randomized 1:1 to receive either tislelizumab combined with chemotherapy or chemotherapy alone, including Arm A (tsMHC-II-positive, chemotherapy + tislelizumab), Arm B (tsMHC-II-positive, chemotherapy), Arm C (tsMHC-II-negative, chemotherapy + tislelizumab), Arm D (tsMHC-II- negative, chemotherapy). For experimental group, patients received either 3 preoperative and 3 postoperative cycles of tislelizumab plus SOX/XELOX, followed by 11 cycles of tislelizumab. For control group, patients received either 3 preoperative and 3 postoperative cycles of SOX/XELOX. The primary endpoint was mPR rate (Arm A vs. Arm B). The key secondary endpoint was pCR rate (Arm A vs. Arm B). This clinical trial was registered at Clinicaltrial.gov (NCT06374901). **Results:** 136 patients (34 per arm) were enrolled from July 2024 to March 2025, with a median age of 65 years (range, 30-75), and 105 (76.64%) were male. The study achieved its primary endpoint. The results revealed that tsMHC-II-positive patients in the tislelizumab plus chemotherapy group achieved a greater proportion of mPR (61.8% versus 26.5%; P = 0.003) and pCR (32.4% versus 8.8%; P = 0.016) than did those in the chemotherapy group, which met a prespecified endpoint. In contrast, this benefit was absent in tsMHC-II-negative patients (mPR: 23.5% vs 26.5%, P = 0.886; pCR: 5.9% vs 8.8%, P = 0.642). There were no significant differences in treatment-related adverse reactions among each group. **Conclusions:** In conclusion, compared with perioperative chemotherapy alone, the addition of tislelizumab to a given chemotherapy regimen significantly increased the proportion of mPR and pCR in tsMHC-II-positive patients with GAC/GEJAC only, which revealed that tsMHC-II could be a biomarker to guide the selection of appropriate GAC/GEJAC patients for perioperative immunotherapy. Clinical trial information: NCT06374901. Research Sponsor: None.

2514 Rapid Oral Abstract Session

A randomized prospective trial evaluating duration of PD-1 and PD-L1 inhibitor therapy in advanced solid tumors. First Author: Vincent Edgar Reyes, UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA

Background: Immune checkpoint inhibitors (IO) have revolutionized the treatment of advanced solid tumors. Despite their widespread adoption, the optimal duration of IO has not been clearly established, and this remains an unmet clinical need. **Methods:** In our prospective trial, patients (pts) with advanced solid tumors who achieved at least stable disease (SD) after 1 year of standard-of-care PD-1/PD-L1 inhibitors were randomized 1:1 to either stop or continue IO beyond one year. Pts who stopped IO and then progressed could be retreated with IO at physician discretion. Primary endpoint was cure rate, defined as the proportion of pts without progressive disease, death, or initiation of new treatment (including re-treatment with IO) at five years. Cure rate was calculated using Kaplan-Meier (KM) estimates with 95% confidence intervals (CI) and compared between arms using a multivariable logistic regression model to adjust for pre-specified stratification factors of tumor type and expected efficacy by IO indication, and reported as an odds ratio (OR) with CI and p-value. Secondary endpoints included PFS, OS, and incidence of iRAEs. Median PFS and OS were estimated from KM curves, with hazard ratios (HR) and p-values obtained from stratified Cox proportional hazards models. All analyses were conducted using R version 4.4.2. **Results:** From 2019 to 2025, leveraging our central hub and community network, a total of 161 pts (Stop = 81, Continue = 80) were enrolled. The trial was closed early due to slow accrual (goal 578 pts). Median age was 71 and the most common tumor types were: NSCLC(39.8%), mismatch repair-deficient tumors(18.6), RCC(11.8%), HNSCC(8.1%), and melanoma (7.5%). There was no difference in baseline characteristics between arms. With a median follow up of 43.2 months (mo), cure rate was 45% (32%-63%)in the stop arm vs 38% (27-54%) in the continue IO arm (OR 2.26, 95% CI [0.62-8.22], p = 0.22). Median PFS was 55.4(27.5-NR) vs. 31.2 mo(20-NR) HR 0.77, 95% CI (0.48-1.24), p = 0.28 and median OS was NR (55.4 vs. NR) vs. 53.5 mo(40.8-NR) HR 0.54, 95%CI (0.3-0.99), p = 0.04 for the stop vs continue IO arms, respectively. In the continue IO arm, the median number of IO doses was 11 (range 0-36) and 52 of these pts discontinued IO with the most common reason being disease progression (42.3%), and 7.7% discontinued for toxicity. In the stop IO arm, 17 pts who progressed were retreated with IO; 20% achieved subsequent partial response and the median PFS was 10.5 mo(6.5-NR) and median OS was 26.7 mo(10.5-NR) after retreatment. **Conclusions:** Our trial is unique as a prospective randomized evaluation of length of IO treatment in advanced solid tumors. Cure rates and PFS were similar across arms and OS was improved in pts that discontinued IO at 1 year. These findings suggest that stopping IO at 1 year may be as effective as indefinite IO therapy, though validation in a larger, adequately powered trial is needed. Clinical trial information: NCT04157985. Research Sponsor: Hillman Cancer Center; Pennsylvania Department of Health; SAP # 410095621.

2515 Rapid Oral Abstract Session

Clinical and translational study of p38 inhibitor pexmetinib plus nivolumab following anti—PD-1/L1 failure in advanced solid tumors. First Author: Matthew Nguyen, University of Pittsburgh, Pittsburgh, PA

Background: Cancers resistant to immune checkpoint blockade typically harbor a non-T cell-inflamed phenotype, characterized by low type I/II interferon activity and limited $CD8^+$ T-cell infiltration within the tumor microenvironment. We previously identified p38 MAPK activation as a tumor-intrinsic immune exclusion mechanism associated with resistance to immunotherapy across solid tumors. Based on these preclinical observations, we conducted a Phase II clinical trial (NCT04074967) combining pexmetinib, a p38 inhibitor, with nivolumab in advanced solid tumors. Here, we report safety, clinical activity, and translational results in patients with PD-1 refractory head and neck (HN) cancer and lung cancers. **Methods:** Patients received pexmetinib 200 mg orally once daily plus nivolumab 480 mg intravenously every 4 weeks. The primary endpoint was overall response rate (ORR) assessed by RECIST v1.1. Translational analyses included pharmacodynamic assessment, plasma proteomics, single-cell RNA sequencing (scRNAseq), and computed tomography-based radiomic analyses. **Results:** Thirty-five patients were enrolled (HN cohort = 11 [31%; 100% squamous cell carcinoma]), lung cohort = 24 [69%; 63% adenocarcinoma]). Median age was 62 years; 60% were male and 89% had ECOG performance status 1. Twenty-nine patients were radiographically evaluable. Partial responses were observed in four patients (ORR 14%), and 13 patients (45%) experienced stable disease. Median duration of response was 11.1 months. Median progression-free survival (PFS) was 7.2 months and overall survival (OS) was 9.3 months. Treatment-related adverse events (TRAEs) of any grade occurred in 89% of patients; 47% experienced grade $\geq$3 TRAEs. No fatal TRAEs were reported. Plasma proteomic profiling identified on-treatment immune modulation relative to baseline, with increased T cell-associated cytokines/chemokines in patients with durable clinical benefit (PFS $>$ 6 months). Among three patients with paired pre- and on-treatment tumor scRNAseq, an increase in intratumoral T-cell abundance was observed in one patient with tumor shrinkage but not in two patients with progressive disease. On-treatment increases in T-cell radiomic score relative to baseline were significantly greater in responders vs. non-responders, and were associated with improved PFS and OS ($P<$ 0.05). **Conclusions:** In patients with PD1-refractory HN cancer and lung cancers, pexmetinib plus nivolumab demonstrated an acceptable safety profile and durable clinical benefit. Multimodal translational profiling revealed increased inflammatory cytokine signaling and radiomic and molecular features consistent with enhanced $CD8^+$ T-cell engagement in responders. These findings suggest that targeting tumor-intrinsic p38 MAPK may represent a mechanistically informed strategy to overcome immunotherapy resistance. Clinical trial information: NCT04074967. Research Sponsor: U.S. National Institutes of Health; University of Pittsburgh Cancer Cell Biology Program; National Cancer Institute; The University of Pittsburgh Center for Research Computing and Data; Pfizer.

2516 **Rapid Oral Abstract Session**

PRaG 5.0: Personalized thymosin alpha-1 and radioimmunotherapy for advanced refractory solid tumors—Data from an expanded cohort. First Author: Yuehong Kong, Center for Cancer Diagnosis and Treatment, The Second Affiliated Hospital of Soochow University, Suzhou, China

Background: Treatment-related lymphopenia and inadequate anti-tumor immune activation remains major barriers to improving outcomes of combination immunoradiotherapy, especially for advanced refractory solid tumors. PRaG 5.0 innovatively integrates personalized thymosin alpha-1 (Tα-1) into the PRaG regimen (PD-1 inhibitor + radiotherapy + GM-CSF) to preserve lymphocytes and enhance anti-tumor immunity. We report updated efficacy and safety data of PRaG 5.0 in advanced refractory solid tumors. **Methods:** This is a prospective, single-armed, phase II study enrolled 43 heavily pretreated patients. Eligible patients were stratified by baseline T-lymphocyte counts to receive personalized Tα-1 dosing: 7-day loading dose for low baseline T-lymphocyte counts, and maintenance Ta-1 (1.6 mg, thrice weekly) for those with normal counts. Tα-1 was combined with the PRaG regimen for at least 2 cycles. After PRaG cycles, patients continued PD-1 inhibitor plus Tα-1 until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included median progression-free survival (mPFS), disease control rate (DCR), safety, and immune cell dynamics (assessed by flow cytometry, single-cell sequencing, and TCR sequencing). **Results:** Among the 43 screened subjects, 39 received treatment, of whom 30 required loading dose thymosin α1 (Tα1) therapy, 36 were treated with PRaG regimen and 17 entered the maintenance phase with PD-1 inhibitor combined with Tα1. The objective response rate (ORR) of the 39 patients was 30.8% (95%CI 17.0%, 47.6%), including 4 cases of complete response (CR) and 8 cases of partial response (PR); the median progression-free survival (PFS) was 4.2 months (95%CI 2.3, 6.9). No Grade 3 or above TRAE was reported. Immune analysis revealed significant increases in CD8+ T cells, NK cells, and CD4+TEM cells post-Tα-1 loading, with a notable decrease in Tregs (p = 0.001). Single-cell sequencing demonstrated higher clonality in GZMK-CD8+T in responders, while TRDV2-CD8+T cells expanded in non-responders. **Conclusions:** Integrating of Tα-1 into the PRaG regimen is a promising therapeutic strategy, offering enhanced efficacy and a favorable safety profile. Detailed immune profiling identified distinct T-cell dynamics associated with treatment response, highlighting potential biomarkers for clinical application. Further validation in larger cohorts is warranted. Clinical trial information: NCT05790447. Research Sponsor: None.

2517 **Rapid Oral Abstract Session**

Evaluation of the combination of regorafenib + avelumab in patients with HPV-associated cancer: The phase II REGOMUNE study. First Author: Sophie Cousin, Early Phase Clinical Trials Unit and Thoracic Unit, Institut Bergonié, Bordeaux, France

Background: HPV-associated malignancies—including cervical, anal, head and neck, and penile cancers—form a biologically distinct group with limited responsiveness to immune checkpoint inhibitors (ICP) in monotherapy. Combining anti-angiogenic agents with immunotherapy may enhance efficacy by reshaping the tumor microenvironment. REGOMUNE explores this rationale by evaluating regorafenib plus avelumab association. **Methods:** REGOMUNE is a French multicenter, open-label, phase II trial assessing the combination of regorafenib (160 mg daily for 3 weeks of a 4-week cycle) and avelumab (10 mg/kg biweekly) in patients with advanced/metastatic HPV-driven solid tumors. The primary endpoint is the 6-month disease control rate (DCR) per RECIST 1.1 after central review. Secondary endpoints include overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. Correlative studies will analyze baseline tumor samples to identify biomarkers of response. An exact single stage design was used testing 10% vs 25% DCR (5% type 1 error rate and 80% power), requiring $\geq$ 8 patients with disease control at 6 months among 40 patients to demonstrate efficacy. **Results:** From March 2023 and to February 2024, 44 patients were enrolled across 6 centers. Median age was 62 (range :33-80). Median follow-up was 18.3 months (95% CI : 14.9-21.1). Median number of prior treatment lines was 2 (range :0-7). Anal (41%) and cervical (32%) cancers were the predominant primary sites, with squamous cell carcinoma representing 70.5% of cases. Among 33 evaluable patients for efficacy, the 6-month DCR was 45.5% (N = 15) [90% CI : 30.5-61.1], with 12 (36.4%) partial response, 11 (33.3%) stable disease, and 10 (30.3%) progressions. Median PFS was 5.3 months (95% CI: [3.0 – 7.3]). Median OS was 15.0 months (95% CI [7.2 – 21.6]). Treatment modifications due to adverse events occurred in 33/42 (78.6%) patients. Common grade 3/4 adverse events included palmar-plantar eryhtrodysesthesia syndrome (11.9%), diarrhea (9.5%) and fatigue (7.1%). One treatment-related death was reported. **Conclusions:** REGOMUNE is the first phase II trial to demonstrate a clinically meaningful efficacy signal surpassing historical CPI outcomes as monotherapy with an anti-angiogenic plus immune CPI combination in patients with HPV-positive tumors. Biomarker analyses are ongoing to identify predictive signatures associated with the durable responses observed in this cohort. Clinical trial information: NCT03475953. Research Sponsor: None.

2518 **Rapid Oral Abstract Session**

Phase 1 study of NTX1088, a first-in-class anti-PVR monoclonal antibody, as monotherapy and combined with pembrolizumab, in patients with advanced solid malignancies. First Author: Sarina A. Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Poliovirus Receptor (PVR; CD155), a transmembrane protein upregulated across multiple solid tumors and associated with poor clinical outcomes and resistance to immune checkpoint inhibitors (CPIs), plays a central role in tumor-mediated immune suppression. PVR suppresses anti-tumor immunity by interacting with the co-stimulatory receptor DNAM1 (CD226) on T and NK cells, leading to its internalization and degradation. PVR also engages the inhibitory immune receptors, TIGIT, CD96, and KIR2DL5A. NTX1088 is a first-in-class monoclonal antibody targeting PVR. **Methods:** NTX-1088-01 (NCT05378425) is a Phase 1a/1b, open-label, multicenter dose-escalation and expansion study evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, recommended dose for expansion (RDE), and preliminary efficacy of NTX1088 alone and in combination with pembrolizumab in patients (pts) with advanced solid tumors known to express PVR (prescreening not required). NTX1088 was administered intravenously (IV) every 3 weeks (Q3W) in dose levels (DLs) from 12-1750 mg as monotherapy or from 160-1750 mg in combination with pembrolizumab 200 mg IV Q3W. Phase 1a employed a standard 3+3 dose-escalation design. Phase 1b comprises dose-expansion monotherapy and combination cohorts in gastric, bladder, lung, and other PVR-expressing solid tumors at the RDE. **Results:** As of January 2026, 81 pts were treated with NTX1088 (24 monotherapy; 57 combination). Median age was 61 years; median lines of prior therapy was 4 and prior CPI exposure was 70%. NTX1088 was well tolerated with no dose-limiting toxicity and 1750 mg was selected as the RDE in monotherapy and in combination with pembrolizumab, based on PK and target occupancy. Preliminary efficacy analysis was focused on active DLs of NTX1088 (1200 and 1750 mg) in combination with pembrolizumab. Forty-eight pts were treated at these DLs and 35 pts were evaluable for response. Of these 35 pts, median age was 57, median lines of prior therapy was 4 and 89% received prior CPI. Six (17%) pts achieved confirmed partial responses (PR) including gastric (2), bladder (1), non-small cell lung (1), squamous cell carcinoma of the head and neck (1), and melanoma (1). All PRs were seen in pts with prior CPI exposure. Sixteen (46%) pts achieved stable disease. At data cutoff, all but one PR pt remain on treatment, with a maximum treatment duration of 20 months. Exploratory analyses of tumor biopsies identified potential predictive biomarkers. **Conclusions:** NTX1088 demonstrated favorable tolerability and encouraging clinical activity in heavily pretreated pts who had progressed on prior PD-1/PD-L1 inhibitors. These findings support further evaluation of NTX1088 in Phase 2 studies, incorporating less heavily pre-treated pts and biomarker selection. Clinical trial information: NCT05378425. Research Sponsor: Nectin Therapeutics; Cancer Focus Fund; European Innovation Council.

2519 **Rapid Oral Abstract Session**

KEYNOTE-B59: An open-label, multicenter, phase 1/2 study of efdelikofusp alfa (GI-101A; CD80-IgG4 Fc-IL2v2) in advanced solid tumors (part E & F of GII-101-P101). First Author: Jae Lyun Lee, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Efdelikofusp alfa is a novel immunocytokine consisting of CD80 fused to an engineered IL-2 variant (IL-2v2) optimized to reduce IL-2Rα affinity. It blocks CTLA-4–mediated immune suppression while preferentially activating and expanding immune effector cells over regulatory T cells. Here, we report results from the dose-escalation phases of Part E (monotherapy) and Part F (combination with pembrolizumab) of the ongoing KEYNOTE-B59 study. **Methods:** KEYNOTE-B59 is an open-label, phase 1/2 study evaluating efdelikofusp alfa alone or in combination with pembrolizumab in patients (pts) with advanced solid tumors. In Part E, escalating doses of efdelikofusp alfa (0.05–0.3 mg/kg) were administered intravenously every 3 weeks (Q3W). In Part F, pts received efdelikofusp alfa (0.05–0.3 mg/kg) plus pembrolizumab (200 mg) Q3W. Primary objectives were to assess safety, tolerability, and to determine maximum tolerated dose (MTD) and/or recommended phase 2 dose. **Results:** As of 29 December 2025, a total of 84 pts who had progressed on available therapies were enrolled, including 36 pts in Part E and 48 pts in Part F. In Part E, one dose-limiting toxicity (DLT) occurred at 0.1 mg/kg (grade 3 hypertension). However, MTD was not reached up to 0.3 mg/kg, and efdelikofusp alfa was generally well tolerated. At the biologically effective dose range (0.2–0.3 mg/kg), monotherapy demonstrated clinical activity in immunotherapy (IO)-experienced bladder cancer (confirmed CR; DoR 5.8 months; PFS 13.9 months) and mesothelioma (confirmed PR; DoR 5.6 months; PFS 6.7 months). In Part F, 48 pts were treated with efdelikofusp alfa in combination with pembrolizumab. Median age was 63 years and 45.8% of pts had received prior IO. The overall safety profile of the combination was comparable to monotherapy, with common treatment-related adverse events including pyrexia (89.6%), liver enzyme elevation (47.9%), chills (37.5%), and decreased platelet count (33.3%). Objective responses were observed across multiple tumor types, including ccRCC, urothelial cancer, squamous NSCLC, cutaneous squamous cell carcinoma, pancreatic adenocarcinoma, and cervical cancer, irrespective of prior IO exposure. In pts with ccRCC (n = 10), the most frequently enrolled indication (70.0% prior IO-treated), the objective response rate was 40.0% and the disease control rate was 70.0%, with durable responses observed from 5.5+ to 16.7+ months; median DoR was not reached. Efdelikofusp alfa induced robust peripheral lymphocyte expansion, mainly $CD8^+$ T and NK cells, which correlated with longer median PFS. **Conclusions:** Efdelikofusp alfa was well tolerated as a monotherapy and in combination with pembrolizumab. Antitumor activity was observed with a favorable benefit–risk profile, supporting continued development in selected tumors, including ccRCC. Clinical trial information: NCT04977453. Research Sponsor: GI Innovation, Inc.; Korea Drug Development Fund; HN22C0451.

2521 **Poster Session**

CS2009, a novel PD-1/VEGF/CTLA-4 trispecific antibody, in patients with advanced solid tumors: Updated results from an open-label, multicenter, phase 1 first-in-human study. First Author: Charlotte Rose Lemech, Medical Oncology, Scientia Clinical Research and Prince of Wales Clinical School, UNSW Sydney, Randwick, NSW, Australia

Background: CS2009 is a first-in-class trispecific antibody targeting PD-1, VEGF and CTLA-4. Initial data from this phase 1 study showed a favorable safety profile and encouraging antitumor activity. Here, we report updated safety and efficacy results in 98 patients. **Methods:** This ongoing, open-label, multicenter, phase 1 dose-escalation trial enrolled patients with advanced solid tumors who progressed on standard therapy or had no available standard therapy. CS2009 was administered intravenously every 3 weeks at 6 dose levels ranging from 1 to 45 mg/kg. Dose escalation followed an accelerated titration design at the first dose level and a 3+3 design thereafter. In parallel, additional patients were backfilled to selected dose levels deemed safe to further evaluate safety and efficacy. Primary objectives include safety, tolerability and determination of the maximum tolerated dose (MTD)/tentative recommended phase 2 dose (RP2D). Secondary and exploratory objectives include pharmacokinetic/pharmacodynamic profile and preliminary efficacy per RECIST v1.1, etc. **Results:** As of January 4, 2026, 98 patients (55.1% male; median age 61 [range 19-80] years; 54.1% Asian, 43.9% White) had received CS2009 across 6 dose levels, with half (49/98) remaining on study treatment. Tumor types included non-small cell lung cancer (NSCLC, n = 49), ovarian cancer (n = 12), soft tissue sarcoma (n = 9), renal cell carcinoma (RCC, n = 6), triple-negative breast cancer (TNBC, n = 6), colorectal cancer (n = 4), and others. Most (98.0%) patients received at least one prior line of systemic anti-cancer therapy. No dose-limiting toxicities (DLTs) occurred; MTD was not reached. The incidences of any-grade and grade ≥3 treatment-related adverse events (TRAEs) were 69.4% and 20.4%, respectively. The most common (≥10%) TRAEs were pruritus (n = 14, 14.3%), alanine aminotransferase increased (n = 11, 11.2%) and aspartate aminotransferase increased (n = 10, 10.2%). Five (5.1%) patients discontinued treatment due to TRAEs. There were no treatment-related deaths. Encouraging antitumor activity was observed across multiple tumor types that have received heavy prior treatment including PD-1/PD-L1 inhibitors or antiangiogenesis therapies where appropriate, including NSCLC without known actionable oncogenic alterations (n = 27), soft tissue sarcoma (n = 9), non-clear cell RCC (n = 5), and TNBC (n = 6) with ORR of 18.5%, 33.3%, 20.0%, 16.7%, respectively, and DCR of 74.1%, 66.7%, 100.0%, 50.0%, respectively (detailed and updated data to be presented at the conference). **Conclusions:** CS2009 demonstrated a manageable safety profile and promising antitumor activity in heavily pretreated patients with advanced solid tumors, which warrants further clinical development in an ongoing phase 2 study in nine tumor types. Clinical trial information: NCT06741644. Research Sponsor: CStone Pharmaceuticals.

2522 **Poster Session**

Pemivibart for prevention of COVID-19: Subset analysis of CANOPY participants with solid tumor or hematologic malignancies. First Author: Meredith Leston, Invivyd, Inc., New Haven, CT

Background: Due to the chronic immunosuppression associated with both their condition and treatments, patients with solid tumors or hematologic malignancies experience reduced vaccine protection and are at high risk of infections, including COVID-19. This post hoc analysis of the phase 3 CANOPY study assesses the safety and outcomes of pemivibart in the oncology subset from the open-label, single-arm, immunocompromised Cohort A. **Methods:** Cohort A dosing: 4500 mg of pemivibart (intravenous) on day 1; 2nd dose at month 3. Primary objectives: 1) Evaluation of pemivibart safety and tolerability via study drug-related treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and treatment interruption/discontinuation, 2) Evaluation of protection against symptomatic COVID-19 based on sVNA titers against SARS-CoV-2 after receiving pemivibart. Exploratory endpoint: composite incidence of RT-PCR-confirmed symptomatic COVID-19, including COVID-19-related hospitalization and all-cause mortality. Data were analyzed through Month 6. **Results:** Enrollment began in Sep 2023. The oncology subset included 55 (18.0%) Cohort A participants; median age [range] 65 [35-83] years; 25 (45.5%) female. Eight participants (14.5%) were receiving immunosuppressants, including 6 (10.9%) receiving corticosteroids. Prior to enrollment, 89.1% received ≥1 COVID-19 vaccine; seropositivity: N antigens (43.6%), S antigens (98.2%). Month 6 TEAEs were reported in 32 (58.2%) participants; 5 (9.1%) were considered study drug-related with 1 (1.8%) requiring treatment interruption due to infusion site extravasation and tachycardia (Table). SAEs occurred in 5 (9.1%) participants; none were considered drug-related. Following pemivibart dosing, sVNA titers in the oncology subset were elevated to levels associated with protection against COVID-19 and comparable with Cohort A. No anaphylaxis was reported in the oncology subset; 4 cases among 306 participants in Cohort A. Through Month 6, there was no RT-PCR-confirmed symptomatic COVID-19 in the oncology subset; with 9/298 (3.0%) in Cohort A. **Conclusions:** Pemivibart was well tolerated in the CANOPY Cohort A oncology subset. These data showed limited events overall and no development of symptomatic COVID-19 in the oncology subset through Month 6. Clinical trial information: NCT06039449. Research Sponsor: Invivyd, Inc.

Select outcomes through month 6.

Parameter	Immunocompromised Cohort A	Cohort A Oncology Subset[a]
Study drug-related TEAE, n (%)	34/306 (11.1)	5/55 (9.1)
- Leading to death	0/306 (0)	0/55 (0)
- Leading to interruption	14/306 (4.6)	1/55 (1.8)
- Leading to discontinuation	7/306 (2.3)	0/55 (0)
COVID-19 composite event, n (%)	11/298 (3.7)	1/55 (1.8)
PCR-confirmed COVID-19, n (%)	9/298 (3.0)	0/55(0)
All-cause mortality, n (%)	2/298 (0.7)	1/55 (1.8)[b]

[a]20 (36%) were being actively treated for solid tumor or hematologic malignancy; 40 (73%) had a hematologic malignancy.
[b]Unrelated to study drug.

2523 **Poster Session**

A phase 1 study of BGB-A3055 (anti-CCR8) with or without tislelizumab (anti−PD-1) in patients with solid tumors. First Author: Judith Raimbourg, Institut de Cancerologie de l'Ouest, Saint-Herblain, France

Background: BGB-A3055 is a humanized monoclonal antibody targeting C-C motif chemokine receptor 8 (CCR8), a receptor highly expressed on intratumoral regulatory T cells (Tregs). CCR8 overexpression correlates with poor prognosis in certain tumor types. Preclinical studies have shown potent antitumor activity of BGB-A3055. Here, we present results from a phase 1a dose-escalation trial of BGB-A3055 alone (Part A [A]) or combined with tislelizumab (TIS; Part B [B]) in patients (pts) with advanced or metastatic solid tumors (NCT05935098). **Methods:** Eligible pts had histologically confirmed advanced or metastatic solid tumors with high prevalence of CCR8 expression. In A, pts received BGB-A3055 (six dose levels) intravenously (IV) every 3 weeks (Q3W). In B, pts received BGB-A3055 (six dose levels) and TIS 200 mg IV Q3W. Primary endpoint was safety; secondary endpoints included preliminary antitumor activity (RECIST v1.1). **Results:** As of Nov 19, 2025, 98 pts were treated with BGB-A3055 ± TIS (A: n=42; B: n=56). Median (range) study follow-up was 3.94 (0.9-19.0) months in A and 4.67 (0.5-16.8) months in B. Treatment-emergent adverse events (TEAEs) are provided in the Table. The most common BGB-A3055-related TEAEs were neutrophil count decreased (23.8%) in A and pyrexia (23.2%) in B. The most common serious TEAE was immune-mediated enterocolitis (A: 4.8%; B: 7.1%). The most common immune-mediated adverse events (imAEs) were rash, rash maculo-papular, and hypothyroidism in A (7.1% each) and rash maculo-papular in B (17.9%). Dose-limiting toxicities occurred in 1 pt in A (immune-mediated hepatitis) and 3 pts in B (colitis, nephrotic syndrome, and rash maculo-papular in a single pt each). No treatment-related TEAEs leading to death were reported. Maximum tolerated dose was not reached. Unconfirmed objective response rate was 7.5% (95% confidence interval [CI]: 1.6-20.4; 3 partial responses [PRs]) in A and 18.2% (95% CI: 9.1-30.9; 1 complete response and 9 PRs) in B. Disease control rate was 35.0% (95% CI: 20.6-51.7) in A and 56.4% (95% CI: 42.3-69.7) in B. Among the 13 responders, 6 received prior immunotherapies. Robust Treg reduction was observed in peripheral blood and tumor tissue post-treatment, indicating potent on-target pharmacodynamic activity of BGB-A3055. **Conclusions:** BGB-A3055 ± TIS demonstrated a safety profile consistent with selective CCR8 on-target effects in pts with advanced solid tumors and had preliminary antitumor activity. Clinical trial information: NCT05935098. Research Sponsor: BeOne Medicines Ltd.

	Part A BGB-A3055 monotherapy (n=42)	Part B BGB-A3055 + TIS (n=56)
Any TEAE, n (%)	41 (97.6)	55 (98.2)
Grade ≥3	26 (61.9)	47 (83.9)
Serious	17 (40.5)	37 (66.1)
Leading to death	1 (2.4)	3 (5.4)
Leading to treatment discontinuation	9 (21.4)	23 (41.1)
Any BGB-A3055-related TEAE, n (%)	35 (83.3)	53 (94.6)
Grade ≥3	18 (42.9)	31 (55.4)
Serious	5 (11.9)	20 (35.7)
Any imAE, n (%)	15 (35.7)	33 (58.9)

2524 **Poster Session**

Phase 1b dose-expansion study of IMC-002, a anti-CD47 monoclonal antibody, in patients with advanced triple negative breast cancer (TNBC). First Author: Ji Hyung Hong, Center for Breast Cancer, National Cancer Center, Goyang, South Korea

Background: IMC-002 is a novel therapeutic agent with a distinct mechanism of action. In a phase 1a dose-escalation study, IMC-002 demonstrated favorable safety and tolerability, and clinical activity was observed in patients with hepatocellular carcinoma (HCC) in a subsequent phase 1b trial. Here, we present results from the phase 1b expansion cohort in patients with triple-negative breast cancer (TNBC), focusing on safety, efficacy, and analyses of soluble biomarkers. **Methods:** Eligible pts had advanced TNBC with progression after ≥1 prior systemic therapy and ECOG PS ≤1. IMC-002 (20 mg/kg Q3W) was administered in combination with gemcitabine plus carboplatin or paclitaxel and continued until disease progression. Tumor response was assessed every 6 weeks per RECIST 1.1 and iRECIST. Baseline ctDNA was analyzed using the AlphaLiquid 1000 platform (1,023 -gene panel). To exclude germline and clonal hematopoiesis of indeterminate potential (CHIP) variants, paired PBMC sequencing was performed. The assay detected single nucleotide variants (SNVs), small insertions and deletions (INDELs), fusions, copy number alterations (CNAs), microsatellite instability (MSI), and blood-based tumor mutational burden (bTMB). **Results:** A total of 12 pts with advanced TNBC received IMC-002 in combination with gemcitabine plus carboplatin (n=9) or paclitaxel (n=3). Most pts had received ≥2 prior systemic therapy (n=11), and ECOG PS 1 was observed in 10 pts. TRAEs reported in > 1 pt included grade 3 hematologic events, namely anemia (n=6) and hemolytic anemia (n=5). Non-hematologic TRAEs were limited to grade 1–2 and included skin rash (n=9), vitreous floaters (n=4), photopsia (n=3), and IRR (n=2). Among 12 efficacy-evaluable pts, the ORR was 25%, the DCR was 75%, and the CBR (disease control ≥ 6 months) was 42%. Exploratory ctDNA analyses identified no MSI-H tumors. One patient with a partial response was BRCA-positive. Patients achieving clinical benefit showed a higher median maximum somatic allele frequency (MSAF) than those without clinical benefit (32.65 vs 1.00; p=0.19). No clear association between bTMB and clinical activity was observed. **Conclusions:** IMC-002 in combination with gemcitabine plus carboplatin or paclitaxel demonstrated encouraging antitumor activity with a manageable safety profile in heavily pretreated patients with advanced TNBC. Exploratory baseline ctDNA analyses did not identify molecular features clearly associated with clinical benefit. Clinical trial information: NCT05276310. Research Sponsor: ImmuneOncia Therapeutics Inc.

2525 **Poster Session**

Phase I trial of the anti-CAPRIN1 antibody TRK-950 alone or with nivolumab in Japanese patients with advanced solid tumors. First Author: Takafumi Koyama, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

Background: CAPRIN-1 is expressed on the tumor-cell membrane across many solid cancers but not on normal cells. TRK-950 is a first-in-class humanized IgG1 that mediates antibody-dependent cellular phagocytosis and cytotoxicity. A series of preclinical studies demonstrates its potency and safety. In the phase I study of TRK-950 monotherapy (NCT02990481) in US and France, it appears safe and well tolerated. No DLT was observed and MTD was not reached at doses of 3-30mg/kg IV weekly. Here, we evaluated safety/tolerability, pharmacokinetics (PK), and preliminary antitumor activity in Japanese patients with advanced solid tumors. **Methods:** Open-label, single-center, dose-escalation study in Japan (NCT05423262). Part 1 evaluated TRK-950 at 5 or 10 mg/kg IV weekly in patients with locally advanced or metastatic solid tumors. Part 2 evaluated TRK-950 at 10 mg/kg weekly or 20 mg/kg every 2 weeks in combination with nivolumab 240 mg every 2 weeks in patients with locally advanced or metastatic solid tumors who were eligible for standard nivolumab monotherapy. Primary endpoints were safety/tolerability (DLT; Treatment-related AEs per CTCAE v5.0). Secondary endpoints included PK, immunogenicity, and antitumor activity by RECIST v1.1. **Results:** Thirteen patients were treated (Part 1 n=7; Part 2 n=6). No DLTs occurred and the MTD was not reached; both monotherapy and combination regimens were well tolerated. TRK-950 PK was consistent with IgG1; exposures were comparable between 10 mg/kg weekly and 20 mg/kg every 2 weeks, with no meaningful PK interaction with nivolumab. In Part 1, a partial response was achieved in a patient with melanoma achieved a partial response, and the response was sustained for an extended period. In Part 2, no response were observed. **Conclusions:** TRK-950, as monotherapy and with nivolumab, was safe and tolerable in Japanese patients with advanced solid tumors. Durable antitumor activity with monotherapy supports continued development. Both the 10 mg/kg weekly and the more convenient 20 mg/kg biweekly dosing regimens of TRK-950 in combination with nivolumab were safely administered, supporting the potential for further development of this combination. Clinical trial information: NCT0542326. Research Sponsor: Toray Industries, Inc.

2526 **Poster Session**

Safety, pharmacokinetics, and immunogenicity of HLX6018, a monoclonal antibody targeting the GARP/TGF-β1 complex, in healthy subjects: A randomized, double-blind, placebo-controlled, phase I clinical study. First Author: Yanhua Ding, The First Hospital of Jilin University, Jilin, China

Background: HLX6018 is a novel anti-GARP/TGF-β1 monoclonal antibody that inhibits TGF-β1 release and suppresses the activation, proliferation, and extracellular matrix secretion of fibroblasts. Preclinical studies have shown its efficacy in improving pulmonary fibrosis with a manageable safety profile. A phase 1 first-in-human study was conducted to evaluate the safety and tolerability of single-dose HLX6018 in healthy Chinese subjects. **Methods:** In this dose escalation phase 1 study, healthy subjects of age 18 to 55 were randomized to receive intravenous, single dose of either HLX6018 or placebo at 0.25 mg/kg, 1.0 mg/kg, 4.0 mg/kg, 12 mg/kg, 25 mg/kg, 50 mg/kg, and 70 mg/kg. A sentinel dosing approach was adopted: each dose group initially enrolled 2 subjects, with 1 receiving HLX6018 and the other receiving placebo in a blinded manner. These 2 subjects then entered a safety observation period after the infusion before the enrolment of remaining subjects for that dose group. The primary endpoint was safety. Secondary endpoints included pharmacokinetics (PK) and immunogenicity. **Results:** A total of 180 subjects were screened and 66 were randomized. 52 subjects received HLX6018 (0.25 mg/kg, 6; 1.0 mg/kg, 6; 4.0 mg/kg, 8; 12 mg/kg, 8; 25 mg/kg, 8; 50 mg/kg, 8; 70 mg/kg, 8) while 14 received placebo (2 subjects in each dose group). The median age was 42.0; 93.9% of the subjects were of Han ethnicity, 50.0% were male. Overall, 46 subjects (69.7%) experienced treatment-emergent adverse events (TEAEs), with 1 subject (1.5%) receiving HLX6018 at 25 mg/kg reporting a serious TEAE of osteonecrosis that was unrelated to HLX6018. 39 subjects (59.1%) experienced treatment-related adverse events (TRAEs). Most common TRAEs (≥ 10% in any dose group) included neutrophil count decreased (HLX6018 vs placebo group: 11.5% vs. 21.4%), injection site pain (11.5% vs. 21.4%), blood corticotrophin decreased (9.6% vs. 14.3%), blood triglycerides increased (9.6% vs. 14.3%) and blood follicle stimulating hormone increased (5.8% vs. 14.3%). There were no TEAEs leading to death, TRAEs leading to drug discontinuation, TRAEs of grade 3 or more in severity, or serious TRAEs. The incidence of TEAEs and TRAEs across the HLX6018 dose groups showed no clear dose-related pattern and was comparable to the placebo group. HLX6018 exhibited approximately linear PK characteristics after single intravenous infusion with the dose range of 0.25–70 mg/kg. Anti-drug antibody was detected in 3 subjects (5.8%) who received HLX6018; no neutralizing antibody was detected. **Conclusions:** HLX6018 is safe and well tolerated across the investigated doses. Further clinical investigation of its efficacy is warranted. Clinical trial information: NCT06310746. Research Sponsor: Shanghai Henlius Biotech, Inc.

2527 **Poster Session**

Safety and efficacy of a novel PD-L1/4-1BB bispecific antibody QLF31907 in previously-treated patients with advanced melanoma: Results from a phase 2 study. First Author: Jun Guo, Department of Melanoma and Sarcoma, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

Background: QLF31907, a bispecific antibody that simultaneously block PD-1/L1 immunosuppressive pathway on cancer cells and conditionally activate 4-1BB co-stimulatory pathway on tumor-specific T cells, was designed to restrict 4-1BB agonism to the tumor microenvironment, which might overcome resistance to PD-(L)1 inhibitor and reduce hepatoxicity as traditional 4-1BB monoclonal antibodies reported. Although immunotherapy (IO) has revolutionized the treatment of melanoma, a significant proportion of patients (pts), particularly those with mucosal and acral subtypes, either fail to respond initially or experience disease relapse after treatment. Here, we present results of QLF31907 in previously-treated pts with advanced melanoma, including IO-exposed. **Methods:** This phase 2 trial was comprised of safety observation stage and efficacy expansion stage. Pts with unresectable locally advanced or metastatic melanoma who failed, were intolerable to, or refused standard treatment were recruited and administered QLF31907 via intravenous infusion from 5 mg/kg to 20 mg/kg every 2 weeks (Q2W) or 3 weeks (Q3W). The primary endpoints were dose-limiting toxicity (DLT) and safety in safety observation stage, and was objective response rate (ORR) per RECIST v1.1 assessed by investigator in efficacy expansion stage. **Results:** As of Dec 31, 2025, 59 pts were enrolled (median age: 57.0 years; male: 47.5%; ECOG PS of 1: 42.4%; stage IV: 93.2%). The mucosal subtype accounted for the most (40.7%), followed by acral (33.9%), cutaneous (non-acral; 18.6%) and primary unknown (6.8%). Median prior lines of therapies were 2.0 (range, 1–5). Fifty-five (93.2%) pts received prior immunotherapy, including 50 (87.7%) pts received prior anti-PD-1/PD-L1 agents. No DLT occurred. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 34 (57.6%) pts. The most common grade ≥3 TEAEs (≥10%) were liver injury (18.6%), neutrophil count decreased (15.3%), anemia (13.6%), white blood cell count decreased (11.9%). In 57 efficacy-evaluable pts, seven had partial response. The ORR and disease control rate (DCR) was 12.3% (95% confidence interval [CI], 5.1%-23.7%) and 56.1% (95% CI, 42.4%-69.3%), respectively. The median progression-free survival, duration of response, and overall survival was 2.6 months (95% CI, 1.6-3.7), 5.8 months (95% CI, 2.3-not evaluable [NE]), and 15.3 months (95% CI, 11.6-NE), respectively. **Conclusions:** QLF31907 showed potential anti-tumor activity and acceptable safety profile in heavily-treated pts with advanced melanoma, including IO-exposed pts. These results warrant validation in further clinical trials. Clinical trial information: NCT05823246. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

2528 **Poster Session**

Preliminary results of safety and antitumor activity from a first-in-human phase 1 study of AWT020, a bifunctional anti–PD-1/IL-2 fusion protein, in patients with advanced tumors. First Author: Jermaine Ian George Coward, ICON Cancer Care, South Brisbane, QLD, Australia

Background: Immune checkpoint inhibitors have transformed treatment landscape across multiple cancer types, however, resistance to anti-PD-(L)1 therapies remains a significant unmet medical need. AWT020 is a bifunctional fusion protein comprised of an anti-PD-1 antibody and a potency optimized IL-2. In preclinical studies, the mouse surrogate of AWT020 demonstrated superior antitumor activity compared to anti-mPD-1 alone or in combination with IL-2. These findings suggest that AWT020 monotherapy may benefit patients resistant to anti-PD-1 therapies. **Methods:** This first-in-human Phase 1 dose escalation study evaluates AWT020 monotherapy in adults with advanced or metastatic cancers who failed or were intolerant to standard therapies. The dose-escalation utilizes a Bayesian Optimal Interval design. Key endpoints include safety, maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D), pharmacokinetics (PK), pharmacodynamics, immunogenicity, and antitumor responses. Initial dose escalation results are presented herein. Clinical trial information: NCT06092580. **Results:** As of January 14, 2026, 41 patients received AWT020 at doses of 0.3, 0.6, and 1 mg/kg, including single-step (0.1 or 0.3 mg/kg) and two-step (0.1→0.3 mg/kg) priming regimens. Preliminary PK analysis showed approximately dose-proportional exposure. The majority of treatment-related adverse events (TRAEs) were low grade. The most frequently reported TRAEs were arthralgia (59%), rash (34%), fatigue (32%), and nausea (32%). Grade ≥3 TRAEs occurring in more than one subject included arthralgia (n=4), colitis (n=2), and thrombocytopenia (n=2). No patient experienced vascular leak syndrome. Among the 27 RECIST-evaluable patients, the overall response rate was 30%, and the disease control rate was 67%. Of the eight responders, five partial responders (thymic carcinoma, thymoma, clear cell renal cell carcinoma, neuroendocrine non-small cell lung cancer, and cholangiocarcinoma) had developed secondary resistance to anti-PD-(L)1 therapies. The remaining three responders were anti-PD-(L)1-naïve, including a cervical cancer patient who experienced confirmed complete response, and two partial responders with proficient mismatch repair (pMMR) tumors (adrenocortical carcinoma and uterine sarcoma). Ten additional patients with diverse cancer types achieved stable diseases, with tumor shrinkage observed in half of the patients, further supporting preliminary antitumor activity across broad tumor types. **Conclusions:** AWT020 demonstrates a manageable safety profile and promising early antitumor activity, including in patients with acquired resistance to anti-PD-(L)1 therapies and in patients with pMMR tumors which typically are unresponsive to immune monotherapy. Dose escalation is ongoing to establish MTD/RP2D. Clinical trial information: NCT06092580. Research Sponsor: Anwita Biosciences Inc.

2529 **Poster Session**

A phase II study of perioperative cadonilimab (AK104) in patients with recurrent resectable head and neck squamous cell carcinoma. First Author: Lei Liu, Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Salvage surgery is standard of care for patients with recurrent, resectable head and neck squamous cell carcinoma (HNSCC); However, the efficacy of salvage surgery remains limited. Therefore, there is an urgent need to explore new therapeutic strategies to further improve the survival of this patient subset. Cadonilimab, a PD-1/CTLA-4 bispecific antibody, uses an IgG-ScFv structure with Fc domain point mutations, allowing for high retention in tumor tissue, and providing enhanced stability and improved safety. In this study, we aim to explore the efficacy and safety of neoadjuvant and adjuvant Cadonilimab combined with salvage surgery in patients with recurrent, resectable HNSCC. **Methods:** This was an open-label, single-institutional phase II clinical trial (ChiCTR2400079741). Patients aged 18-75 years, pathologically confirmed recurrent HNSCC (oral, laryngeal, hypopharyngeal, and oropharyngeal carcinoma), and with resectable diseases assessed by surgeons were included. Eligible patients received two cycles of Cadonilimab (6mg/kg, ivgtt, q2w) 2-4 weeks before surgery, then treated by salvage surgery, followed by 12 cycles of adjuvant Cadonilimab. Primary endpoint was 1-year disease free survival (DFS), and secondary endpoints were objective response rate (ORR), major pathological response (MPR), OS and safety. **Results:** From November 2023 to December 2024, a total of 32 patients were enrolled. One patient refused surgery, and 31 patients were included in the final analysis. According to radiological assessment, the ORR was 28.1% (9/32), with 2 cases of complete response (CR) and 7 cases of partial response (PR). Among the patients receiving surgical resection, the MPR rate was 32.3% (10/31), with 9.7% (3/31) of patients achieving pathological CR. With a median follow-up of 18.8 months (range, 13.0-25.7 months), the 1-year DFS rate was 77.4%, and the 1-year OS rate was 87.1%. Treatment-related adverse events (TRAEs) occurred in 74.2% (23/31) of patients. The majority of TRAEs were grade 1 or 2. Grade $\geq$3 TRAEs occurred in 6.5% (2/31) of patients, including one case of grade 3 neutropenia and one case of grade 4 immune-related hepatitis. The most common TRAEs were hypothyroidism (25.8%, n=8), anemia (25.8%, n=8), lymphocytopenia (19.4%, n=6), fatigue (16.1%, n=5), myocarditis (12.9%, n=4), constipation (12.9%, n=4), rash (12.9%, n=4), elevated ALT/AST levels (12.9%, n=4), and neutropenia (6.5%, n=2). **Conclusions:** Cadonilimab demonstrated encouraging anti-tumor activity and acceptable safety profile in patients with recurrent, resectable HNSCC. Cadonilimab may change the therapeutic approach for recurrent, resectable HNSCC. Clinical trial information: ChiCTR2400079741. Research Sponsor: None.

2530 **Poster Session**

Anti-tumor activity of Man 9 x PS targeting immunotherapies in diffuse intrinsic pontine glioma (DIPG) and pancreatic cancers. First Author: Shabnam Samimi, Vitruviae, Nutley, NJ

Background: Aberrant cell-surface glycans and lipids are attractive immunotherapy targets due to their stable tumor expression. High-mannose glycan mannose-9 (Man9), and phosphatidylserine (PS) are co-expressed across multiple malignancies and contribute to immune suppression. We developed Man9×PS-targeting effector immunotherapy platforms for the treatment of solid tumors, with a focus on pancreatic cancer and diffuse intrinsic pontine glioma (DIPG). **Methods:** The Man9×PS×CD3 trispecific T cell engager (TCE), VTRU200, was expressed and purified from CHO cells. The Man9×PS CAR T cell, VCAR300, was generated from murine splenic T cells transduced with a Man9×PS CAR-encoding viral vector. In vitro tumor cytotoxicity of VTRU200 was assessed using human T cells co-cultured with cell lines (PANC-1, AsPC-1) or patient-derived primary cultures (DIPG-008, DIPG-011) and compared with bispecific Man9×CD3 or PS×CD3 controls. Tumor selectivity and potential off-target binding were evaluated by immunohistochemistry (IHC) on pancreatic and breast tumors with matched normal tissues, and by immunofluorescence (IF) across a panel of 33 normal human tissues. *In vivo* dose escalation of VCAR300 was evaluated by bioluminescence imaging in a Panc02 murine orthotopic pancreatic tumor model. Cancer stem cell binding was verified by co-staining with anti-CD133 antibody. Previously, VTRU200 was evaluated in syngeneic, xenograft, and patient-derived xenograft (PDX) acute myeloid leukemia (AML) models, and VCAR300 persistence was tested in a pilot orthotopic pancreatic cancer model. **Results:** VTRU200 demonstrated potent, target-dependent cytotoxicity with 0.1-5 nM EC50 values across multiple solid tumor cell lines in the presence of human T cells. Cytotoxicity required engagement of both Man9 and PS, with additive effects relative to bispecific controls. IHC demonstrated strong staining in pancreatic and breast tumors with absence of staining in corresponding paired normal tissues, while there was no detectable reactivity across normal human tissue panels by IF. Consistent with prior AML studies showing robust anti-leukemic activity, VCAR300 exhibited high anti-tumor activity in vitro with an effector:target ratio at 50% maximum killing (ET50) of less than 1, and in a murine orthotopic pancreatic cancer model (25-fold reduction in tumor size after 2 weeks of treatment with $2x10^6$ CAR T/mouse) with an excellent safety profile. Anti-tumor activity was associated with tumor stem cell targeting and release of inflammatory cytokines. **Conclusions:** Man9 x PS dual targeting is a promising strategy for treating solid tumors. VTRU200 and VCAR300 are potential therapeutic candidates with potent anti-tumor activity across multiple tumor types and impressive safety. Following a successful pre-IND interaction with the FDA, first-in-human studies are planned to initiate in 2027. Research Sponsor: None.

2531 **Poster Session**

Multiomic machine learning integration of DNA and RNA features to predict immunotherapy benefit in MSS-CRC and other rare cancers. First Author: Michelle Ting-Lin, Tempus AI, Inc., Chicago, IL

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the oncology landscape, yet remain constrained by imprecise predictive biomarkers (i.e., PD-L1, TMB, MSI), which fail to capture the complexity of the tumor microenvironment. The Immune Profile Score (IPS), an AI/machine learning (ML) driven DNA-/RNA-based molecular signature addresses this gap in translational molecular biomarkers of ICI response. IPS integrates TMB, single-gene RNA features and RNA signatures, and was independently validated for prognostic utility in $>$ 1,500 advanced solid tumor patients (pts) treated with FDA-approved ICI. Here we evaluated the ability of IPS to accurately stratify ICI treatment outcomes in two independent cohorts representing traditionally ICI-resistant populations. **Methods:** From our multimodal real-world database, we used the ML-derived IPS algorithm to analyze two cohorts of high unmet need for which ICI is not approved: 1) microsatellite stable colorectal cancer (MSS CRC); and 2) rare solid cancer as defined by FDA ($<$ 200,000 cases/year) treated with off-label ICI. Pts were categorized as IPS-H and IPS-L using a previously independently validated and published threshold. Cox proportional hazards models were fit to demonstrate prognostic utility for real-world overall survival (rwOS). Association with time-to-next-treatment (TTNT) on prior chemotherapy (CT) was compared in the same pts to rwOS on subsequent ICI therapy to assess ICI-specific predictive value of IPS . **Results:** IPS-H consistently identified a subset of pts with improved clinical outcomes across both cohorts. In the MSS-CRC cohort (n = 46): IPS-H pts (6/46 = 13%) had longer rwOS than IPS-L pts (40/46 = 87%) (HR 0.22; 90% CI: 0.04-1.16). No difference was observed in TTNT between IPS-H and IPS-L for prior CT (HR 1.07; 90% CI: 0.60-1.91), while there was improvement in rwOS IPS-H vs IPS-L on subsequent ICI therapy (HR 0.21; 90% CI: 0.04-1.22). In the rare cancer cohort (n = 90): there were 26 solid tumor subtypes without an FDA-approved ICI label; carcinosarcoma (n = 19, 21%) and pancreatic ductal adenocarcinoma (n = 17, 19%) were the most commonly represented. IPS-H pts (16/90 = 18%) had longer rwOS than IPS-L pts (HR 0.26, 95% CI: 0.09-0.73). In this rare cancer cohort, IPS remained significant even when restricted to subtypes with representation from both IPS-H and IPS-L (HR = 0.18, 95% CI: 0.04-0.69). **Conclusions:** IPS is a novel multiomic genomic signature that identifies a subset of advanced MSS-CRC and rare solid cancer patients who may benefit from ICI therapy. By integrating multimodal genomic features, IPS emerged as a possible predictive biomarker in a population where ICI is not currently approved. IPS suggests a paradigm shift toward AI/ML-driven signatures to refine ICI candidate selection and personalize clinical decision-making in oncology. Research Sponsor: None.

2532 **Poster Session**

AI-powered spatial tumor microenvironment analysis in metastatic microsatellite-stable colorectal cancer receiving immunotherapy. First Author: Sojin Kim, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Microsatellite-stable (MSS) colorectal cancer (CRC) is typically immune-cold, limiting the routine use of immune checkpoint inhibitors (ICIs). However, a subset of MSS CRC patients may still derive benefit from ICIs. Leveraging an AI-powered whole-slide image (WSI) analyzer applied to hematoxylin and eosin (H&E)–stained slides, we sought to identify subsets of MSS CRC more likely to benefit from ICIs. **Methods:** Between August 2016 and May 2024, pretreatment H&E–stained WSIs were collected from patients with metastatic MSS CRC treated at Asan Medical Center, Seoul, Korea. After quality control, 91 WSIs (93.8%) from 51 patients were included in the final analysis. Patients were treated with anti-PD-1/PD-L1 ICIs in clinical trials, with the majority treated in the third-line setting (n = 46, 90.2%). An AI-powered WSI analyzer (Lunit SCOPE IO, Lunit, Seoul, Korea) segmented cancer area (CA) and stromal area and identified tumor-infiltrating lymphocytes (TILs), tertiary lymphoid structures (TLS), fibroblasts, and endothelial cells within tumor tissue. We then evaluated the associations between CA-specific densities of TILs, macrophages, and endothelial cells, as well as the summed TLS area, and progression-free survival (PFS) and overall survival (OS). **Results:** Using maximally selected rank statistics based on PFS, patients were dichotomized into high and low groups according to the summed TLS area and the densities of TILs, macrophages, endothelial cells, and fibroblasts within the CA. Notably, patients with a high summed TLS area had significantly improved PFS and OS compared with those with a low TLS area (median PFS, 3.6 vs. 1.6 months; P=0.026; median OS, 11.6 vs. 6.6 months; P=0.024). High endothelial cell and fibroblast densities within the CA were not significantly associated with PFS (P=0.160, P=0.112, respectively), but were associated with worse OS, with a significant association for endothelial cells (median, 7.6 vs. 14.7 months; P=0.024) and a trend toward worse OS for fibroblasts (median, 8.9 vs. 12.2 months; P=0.056). Higher macrophage density within the CA showed a favorable trend toward improved PFS (median, 10.2 vs. 8.5 months, P=0.092), but was not associated with OS (P=0.399). In contrast, none of these biomarkers were associated with clinical outcomes in the first-line chemotherapy. **Conclusions:** Despite microsatellite-stable status, a higher summed TLS area was associated with improved progression-free and overall survival following immunotherapy, with endothelial cell and fibroblast densities providing additional prognostic information. AI-powered WSI analysis enabled effective stratification of these features. Research Sponsor: Lunit.

2533 **Poster Session**

Multimodal immunoprofiling of peripheral blood using foundation models of the immune system for predicting immunotherapy response and toxicity in the RADIOHEAD pan-cancer cohort. First Author: Artemii Nikitin, BostonGene Corporation, Waltham, MA

Background: While immune checkpoint inhibition (ICI) is an emerging gold standard for cancer therapy, positive response is limited among treated patients and up to 70% experience toxicity. Early and accurate response prediction that accounts for immune-related adverse events (irAEs) is crucial for identifying patients who may benefit from ICI. We present AI-powered approaches for predicting ICI response by transcriptional and cellular profiling of blood immune cells from a pan-cancer cohort. **Methods:** Peripheral blood mononuclear cells (PBMC) were isolated at pre- (baseline) and early on-treatment for flow cytometry and RNA-seq profiling from the RADIOHEAD cohort *(Quandt et al. 2025)* receiving ICI (n=1,070). Patients were clustered based on variational autoencoder embeddings for real-world progression-free survival (rwPFS) and irAEs derived by a peripheral immune system encoder trained on the BostonGene patient database (n=45,000). The logrank test and Fisher's exact test were used to analyze survival and compare irAE frequencies between clusters, respectively. RNA-seq trajectory features were identified using hierarchical clustering, along with elastic net-regularized and simple multivariate Cox regression models for feature selection. **Results:** Pre-trained immunotype models (Dyikanov et al. 2024) applied to baseline PBMC revealed that G2-primed (memory CD4+ T cell-enriched) and G5-suppressive (monocyte enriched) immunotype scores stratified patients into responders (R) and non-responders (NR) ($p = 0.00001$). T cell receptor (TCR) dynamics revealed a significantly greater decrease in TCR diversity in NR during treatment ($p = 0.046$). We discovered a baseline gene set containing immune checkpoint and cancer antigen genes as well as a longitudinal trajectory set of monocyte and myeloid cell activation markers that both stratified patients by rwPFS (p=0.006; 0.03). Trained immune system embeddings identified a novel severe-risk patient group with both a high irAE incidence ($p = 0.025$) and short rwPFS. This group displayed both active inflammatory and tolerance pathways that stratified patients with irAEs by rwPFS ($p = 0.003$). **Conclusions:** Using pre-trained multimodal immune system projections, we 1) independently confirmed the association of peripheral immunotypes with ICI response; and 2) identified a novel severe-risk signature from patients with high irAE incidence (≥Grade 3) and short rwPFS. We also found that greater TCR diversity and T cell differentiation were associated with ICI response, while innate myeloid activation and trafficking correlated with non-response. Our unique AI-driven analytical framework underscores the potential of peripheral blood immunoprofiling for ICI treatment selection and patient stratification in prospective trials. Research Sponsor: None.

2534 **Poster Session**

External validation of a deep learning CT biomarker to predict first-line immune checkpoint inhibitor monotherapy-associated survival in PD-L1–high metastatic non–small cell lung cancer. First Author: Ravi Bharat Parikh, Emory University, Atlanta, GA

Background: Immune checkpoint inhibitor (ICI) monotherapy is a standard first-line treatment for patients with metastatic non–small cell lung cancer (mNSCLC) with high PD-L1 expression. However, 60% of patients treated with ICI monotherapy progress within 1 year of treatment. Imaging-based biomarkers from routine pretreatment computed tomography (CT) scans may provide a noninvasive approach to refine patient selection and guide treatment decisions. **Methods:** Enhanced CT Response Score (eCTRS v0.0.2; Sako et al, JCO CCI, 2024) is an imaging-based biomarker that stratifies patient survival among mNSCLC patients receiving ICI monotherapy. eCTRS is derived from pre-treatment CT scans, using deep-learning extracted imaging features, lesion features, and clinical variables of age and sex. eCTRS was previously trained on a diverse, real-world multi-institutional dataset of 1,058 mNSCLC patients. This retrospective study externally validated eCTRS using a deidentified, EHR-derived longitudinal database with imaging from Flatiron Health. Patients with PD-L1–high (PD-L1 tumor proportion score ≥ 50%) mNSCLC without actionable mutations who received first-line ICI monotherapy and had imaging from 12 weeks before to 2 weeks after treatment start were included. Patients were stratified into eCTRS High and eCTRS Low groups using a pre-determined threshold. Survival analyses were conducted by an external, independent group. Kaplan-Meier and Cox proportional hazards analyses evaluated progression-free survival (PFS) and overall survival (OS) stratification. PFS was derived from RECIST 1.1 assessments by a centralized multi-reader radiologist adjudication process, and OS was defined as time from treatment start to death by any cause. **Results:** 205 patients met all inclusion criteria (median age 72 years, 48% female, 20% non-White). Eighty (39%) patients were classified as eCTRS Low and 125 (61%) as eCTRS High. PFS was improved among eCTRS High patients (Hazard Ratio [HR], 0.71; 95% CI, 0.51–1.00; p=0.048), with median PFS of 231 (95% CI: 133, 350) days versus 88 (95% CI: 57, 179) days in eCTRS Low patients. eCTRS High patients demonstrated significantly improved OS (HR, 0.56; 95% CI, 0.39–0.80; p=0.001), with median OS of 484 (95% CI: 361, NA) days for eCTRS High, versus 155 (95% CI: 75, 295) days for eCTRS Low. **Conclusions:** A deep learning–based imaging biomarker derived from routinely acquired pretreatment CT imaging identified survival benefit in patients with PD-L1–high metastatic NSCLC treated with first-line ICI monotherapy. These findings suggest that imaging-based biomarkers may serve as complementary, noninvasive tools to identify patients most likely to derive benefit from ICI monotherapy and to support risk-adapted treatment strategies. Research Sponsor: U.S. National Institutes of Health; 1R44CA291456.

2535 **Poster Session**

Artificial intelligence (AI) foundation model as a predictor of efficacy of next-generation checkpoint inhibition with botensilimab (BOT) + balstilimab (BAL) in solid tumors using pretreatment H&E images. First Author: Ryan Dalton, Noetik, South San Francisco, CA

Background: Predicting immunotherapy response is challenging in treatment-refractory/resistant (R/R) tumors where heterogeneity limits conventional biomarker utility. BOT (Fc-enhanced anti–CTLA-4) augments T-cell priming, depletes Tregs, and activates antigen-presenting cells. BOT+BAL (anti–PD-1) has shown activity across "cold" and R/R tumors including PD-L1–low and tumor mutational burden–low disease; thus, non-conventional predictive biomarkers are needed. A self-supervised AI foundation model applied to routine pretreatment H&E images was used to infer spatial transcriptomics and identify features associated with therapeutic benefit from BOT+BAL in microsatellite-stable colorectal cancer (MSS CRC), sarcoma, and ovarian cancer. **Methods:** A self-supervised AI foundation model was trained to infer spatial transcriptome expression from H&E images using purpose-built multimodal training data from thousands of human tumors profiled with multimodal assays. Pretreatment H&E images (not used for training) from 121 BOT+BAL–treated patients (pts) with R/R MSS metastatic CRC (included 20 pts with liver metastases), sarcoma, and ovarian cancer from the phase 1b C-800-01 trial (NCT03860272) were analyzed. Pt-specific embeddings were used to fit cross-validated classifiers predicting BOT+BAL clinical benefit (defined as complete or partial response [CR/PR] or stable disease [SD]). **Results:** Fitted logistic regression classifiers separated responders and non-responders in all tumor types, as measured by area under the receiver operating characteristic curve (AUROC; ranges from 0.5 [chance] to 1.0 [perfect separation]). Cross-validated AUROC was 0.61 in MSS CRC, 0.67 in sarcoma, and 0.77 in ovarian cancer (table; shows all findings). The model-recommended population is predicted to have a higher rate of clinical benefit, as measured by cross-validated precision. Beyond this binary analysis, the concordance index (C-index; measures accuracy and ranges from 0.5 [chance] to 1.0 [perfect]) for predicting overall survival (OS; via Cox proportional hazards model) was >0.5 in all tumor types, and highest in ovarian cancer. **Conclusions:** A self-supervised AI foundation model applied to routine pretreatment H&E images predicted BOT+BAL responses in MSS CRC, sarcoma, and ovarian cancer. These findings support AI-derived, H&E–based biomarker strategies for BOT+BAL and warrant prospective validation. Research Sponsor: Agenus Inc.; Noetik Inc.

Sample characteristics and model predictions.

	MSS CRC	Sarcoma	Ovarian
Sampled population[a]			
No. of pt samples	67	30	24
Pts with CR/PR or SD	65%	57%	54%
Modeled population			
AUROC	0.61	0.67	0.77
OS prediction, C-index	0.58	0.69	0.78
Model recommended population			
Population size	43%	50%	46%
Estimated pts with CR/PR or SD	76%	67%	73%

[a]Data cutoff: Mar 13, 2025; analyses ongoing.

2536 **Poster Session**

Clinical and translational results from the phase 1 portion of the phase 1/2 study to evaluate CHM-2101, an autologous cadherin 17 (CDH17) chimeric antigen receptor (CAR) T cell therapy for the treatment of relapsed or refractory gastrointestinal cancers. First Author: Jennifer Rachel Eads, University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA

Background: CHM-2101 is a Cadherin 17 directed autologous CAR T-cell product being developed to address the continuing unmet medical need for effective therapy against relapsed or refractory gastrointestinal (GI) cancers. Solid tumors of the GI tract such as gastric cancer, colorectal cancer (CRC) and neuroendocrine tumors (NETs) are devastating diseases associated with poor outcomes and more than 1.3 million global deaths annually. Despite advances in surgical and medical treatment of these solid tumors, the prognosis for patients with relapsed or refractory disease remains poor. There remains a need for innovative and effective treatments for patients with advanced and treatment-recalcitrant GI malignancies. **Methods:** The ongoing clinical trial is a seamless Phase 1/2 study enrolling subjects with gastric cancer, CRC or NETs of the midgut or hindgut. Enrolled subjects undergo screening and apheresis to enable manufacturing of CHM-2101. After completing apheresis, bridging therapy is permitted to provide disease control. After confirming successful CHM-2101 manufacturing and washout of bridging therapy, study subjects receive 3 days of lymphodepleting chemotherapy (fludarabine 30mg/m2/day and cyclophosphamide 500mg/m2/day). After two days of rest, subjects receive a one-time IV infusion of CHM-2101. **Results:** As of October 24, 2025, 13 subjects have been enrolled with 2 screen failures. Eleven of eleven successful manufacturing runs enabled treatment of 9 subjects to date (4 subjects at Dose Level 1 and 5 subjects at Dose Level 2). Most AEs were Grade 1-2. Aside from lymphodepleting chemotherapy-related cytopenias, Grade 3 Treatment-Related Adverse Events (TRAEs) were Cytokine Release Syndrome (CRS) and Enterocolitis in 1 subject each. There have been no Grade 4 or 5 TRAEs or DLTs. After IV infusion, CHM-2101 was noted to expand and persist (by flow and ddPCR) in the peripheral blood of all treated subjects. **Conclusions:** CHM-2101 has demonstrated cellular expansion and persistence with clinical tolerability in study subjects with advanced GI cancers at two dose levels. Enrollment of patients at Dose Level 3 is ongoing at US Cancer Centers. Clinical trial information: NCT06055439. Research Sponsor: None.

2537 **Poster Session**

Tumor infiltrating lymphocytes (LM103 infusion) in solid tumors: A phase I trial evaluating clinical and immunological anti-tumor activity. First Author: Fenge Li, The First Affiliated Hospital of Nankai University, Tianjin, China

Background: Tumor-infiltrating lymphocyte (TIL) therapy has shown clinical promise in melanoma, but its applicability across diverse solid tumors in Asian patients remains unclear, and exploring molecular targets to improve anti-tumor responses of TIL are needed. **Methods:** In the phase I investigator-initiated trial, we evaluated the safety, feasibility, and preliminary efficacy of autologous TIL therapy in twelve patients with advanced melanoma, cervical, lung, or head and neck cancers. Twelve patients who failed with standard treatments were successfully enrolled in the trail from August 2022 to December 2024. The patients received a lymphodepletion therapy which consisted of cyclophosphamide (30mg/kg) for 2 days, followed by fludarabine (25mg/m^2) for 5 days, approximately 24 hours before receiving the intravenous autologous TILs infusion, and then received high doses of IL-2 for 6-12 days with the purpose of maintaining T cell survival and proliferation. After a 28 days safety observation, tumor assessment according to RECIST 1.1 was conducted every 6 weeks until 6 months followed by every 12 weeks long-term follow-up. T cell receptor (TCR) sequencing was performed to explore TIL persistence in vivo after TIL infusion. Differential genes were identified via Bulk-RNA sequencing on TILs of responders and non-responders. Target gene knocking out of TIL using CRISPR/Cas9 technology was performed to enhance its anti-tumor function. **Results:** The most common adverse observed events were fever, anemia, nausea, hypertension, and hyponatremia. The objective response rate (ORR) was 33.3% (4/12), including one complete response (CR) and three partial responses (PR), and the disease control rate (DCR) reached 75% (9/12). Infused TILs persisted in peripheral blood and induced reversed peripheral CD4+T and CD8+T percentages. T cell receptor (TCR) sequencing revealed dynamic clonal remodeling in responders. Transcriptomic profiling of infused TILs identified ASS1 and CEP20 as genes negatively associated with therapeutic activity. CRISPR/Cas9-mediated knockout of these targets enhanced TIL memory phenotypes, cytokine production, and tumor cytotoxicity *in vitro* and *in vivo*. **Conclusions:** Autologous TIL monotherapy is feasible and safe. This study reveals effective TIL therapy in diverse solid tumors of Asian patients and potent anti-tumor activity of genetically enhanced ASS1 KO and CEP20 KO TILs, which offer mechanistic insights that may guide optimization of TIL therapy for broader clinical application. Trial registration number: NCT05366478. Clinical trial information: NCT05366478. Research Sponsor: None.

2538 **Poster Session**

Extended monitoring and biomarker analysis in metastatic melanoma patients treated with TIL therapy and conditioning-replacing igrelimogene litadenorepvec virotherapy: Pre-infusion immune cell and cytokine profiles associated with survival. First Author: Victor Cervera-Carrascon, TILT Biotherapeutics Ltd., Helsinki, Finland

Background: Adoptive transfer of tumor-infiltrating lymphocytes (TILs) can be effective in metastatic melanoma, but its routine use is limited by the need for lymphodepleting chemotherapy and systemic high-dose IL-2. To reduce toxicity while preserving anti-tumor activity, a strategy pairing TIL therapy with the oncolytic adenovirus igrelimogene litadenorepvec (TILT-123) was assessed. This virus selectively replicates in malignant tissue and drives local expression of TNF and IL-2 within tumors, functionally replacing the need for pre-infusion chemotherapy and post-infusion IL-2 administration. **Methods:** Seventeen patients with advanced melanoma resistant to immune checkpoint inhibitors were treated and sampled (NCT04217473). Treatment with igrelimogene litadenorepvec started upon tumor biopsy collection for TIL manufacturing took place and eventually followed by autologous TIL infusion around 36 days after. Hypotheses generated during data analysis were validated using additional patient datasets (NCT04695327, NCT05271318). **Results:** The regimen was well tolerated, with no dose-limiting toxicities. Objective response rate was 11.7%, with disease control in 35% by RECIST 1.1 and 47% by PET; metabolic responses were seen in 27%. Among those patients, higher baseline expression of epidermal and hepatocyte growth factors (EGF and HGF respectively) was associated with poorer prognosis. Higher than median HGF was negatively correlated with survival (p=0.032). Additionally, patients that achieved disease stabilization or better had a lower presence of circulating MDSCs (p=0.017). The link between growth hormones, MDSCs and disease progression was extrapolated to a larger dataset including other patients treated with igrelimogene litadenorepvec to find out the same trend for survival (HGF; p = 0.003, EGF; p = 0.029). In parallel, baseline circulating young memory T cells (CD27+CD28+CD8+) and an early expansion of NK cells (CD45+CD56+CD3-) correlated with a lower chance of progressing (T cells p=0.005, NK cells p=0.003). **Conclusions:** Combining TILT-123 with TIL therapy was safe and produced meaningful clinical activity in checkpoint inhibitor-refractory melanoma, especially in patients with lower HGF and EGF at baseline and a higher presence of young memory T cells and NK cells. In this clinical set-up, adapting the inclusion exclusion criteria to select patients with those defined immune system features, could help improve efficacy beyond. This approach may substantially broaden the feasibility and accessibility of TIL-based immunotherapy, especially due to the omission of the toxic conditioning regimens. Clinical trial information: NCT04217473. Research Sponsor: None.

2539 **Poster Session**

Immunologic and clinical outcomes of perfluoroalkyl substances (PFAS) exposure in solid tumors treated with pembrolizumab. First Author: Charles Jeffrey Lay Tan, Princess Margaret Cancer Center, Toronto, ON, Canada

Background: Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are two major PFAS with persistent and widespread human exposure. Epidemiologic studies in non-cancer individuals suggest PFAS-associated immune dysregulation and anti-inflammatory effects. We assessed immunologic and clinical effects of PFAS on patients (pts) with advanced solid tumors treated with pembrolizumab. **Methods:** In the investigator-initiated INSPIRE study (NCT02644369) (n = 106) of advanced solid cancer pts treated with pembrolizumab (head and neck squamous cell cancer, triple-negative breast cancer, high-grade serous carcinoma, melanoma and other mixed solid tumors), we quantified baseline PFOS and PFOA via HPLC-tandem mass spectrometry. PFAS were evaluated as continuous variables and dichotomized at the median ($<$ median vs $>$ median; PFOS 3.6 ng/ml; PFOA 1.0 ng/ml). Associations with clinical and demographic factors were assessed using correlation/regression analyses. Association with toxicity and objective response (ORR) used Wilcoxon rank-sum tests; progression-free survival (PFS) and overall survival (OS) used Cox proportional hazards models. Immune correlates (immune infiltration measured by multiplex IHC, bulk-RNA sequencing of tumor tissue and plasma cytokine levels measured by Luminex multiplex cytokine assay) were evaluated using median-split Wilcoxon comparisons with Benjamini-Hochberg false discovery rate (FDR) control ($q < 0.2$). **Results:** Baseline PFOS and PFOA levels were moderately correlated (Pearson r = 0.49, $p < 0.001$). PFOS levels were significantly higher with increasing age (median age 59.4 years; range 21.1-81.8; p = 0.016). PFOA levels were significantly higher with increasing age (p = 0.001), in males (p = 0.042), and in the melanoma cohort (p = 0.015), and significantly lower in pts with prior systemic therapy (p = 0.001). For immune parameters, higher PFOA exposure was associated with reduced CD4 T-cell infiltration in tumor and stromal areas (q = 0.07). RNA sequencing of genes and immune signatures showed no associations reaching FDR significance. 10 cytokines were significantly lower in pts with high PFOA levels: IL-16, IL-2R, IL-3, HGF, IFN-γ, MCP-2/CCL8, MDC/CCL22, TNF-RII, TSLP, and BLC/CXCL13 (all q = 0.15) in ovarian cancer and melanoma pts. Neither PFOS nor PFOA levels showed significant associations with ORR, toxicity, PFS or OS. **Conclusions:** PFOS and PFOA levels vary by demographic and clinical factors but show no direct association with toxicity and treatment outcomes in pts treated with pembrolizumab. Elevated PFOA exposure correlates with reduced T-cell infiltration and cytokine suppression, potentially inducing systemic and local immune dysregulation. These findings highlight immunologic effects of PFAS and warrant mechanistic and longitudinal studies. Research Sponsor: None.

2540 **Poster Session**

GK01 stemness-enriched tumor-reactive T-cell therapy plus IL-2 in advanced solid tumors: ORR and clonal persistence results in a first-in-human phase I study (GUARDIAN-01). First Author: Jun Yu, Tianjin Medical University Cancer Institute & Hospital, Tianjin, Tianjin, China

Background: T-cell exhaustion and poor persistence limit tumor infiltrated lymphocytes (TILs) efficacy in solid tumors. GK01 is an autologous tumor-reactive T-cell product enriched for stem cell memory T cells (TSCM: CD45RA$^+$CD62L$^+$) and diverse T-cell receptor (TCR) clonotypes to promote durable engraftment. We conducted GUARDIAN-01 (NCT06954558), a phase I study of GK01 plus IL-2 in advanced solid tumors. **Methods:** This single-arm, open-label study enrolled patients with advanced solid tumors (ECOG PS 0-1; measurable disease per RECIST v1.1). Patients received standard lymphodepletion, GK01 (5×10^9-1×10^{11} cells per manufacturing yield), and IL-2 (300,000 IU/kg IV q12h, up to 5 days). Repeat infusion was permitted at investigator discretion based on clinical benefit. Primary endpoint was safety; secondary endpoints included objective response rate (ORR), disease control rate (DCR), and cellular kinetics via absolute lymphocyte count (ALC) and TCR sequencing. **Results:** From March 2025 to January 2026, 6 patients were enrolled (median age 53.5 years; median 2 prior lines; tumor types included gastric n = 3, pancreatic n = 1, penile SCC n = 1, and melanoma n = 1). Manufacturing succeeded in all patients; median time from tissue procurement to infusion was 28 days (range 25-39). Infused GK01 exhibited median TSCM frequency of 71% (range 42-92%) and demonstrated robust expansion and stemness properties. Upon tumor challenge, these T cells secreted IFN-γ at a median of 1,632 pg/mL (range, 35 - 4,886). Median dose was 2.8×10^{10} cells (range 1.4×10^{10}-8.8×10^{10}); 2 patients received repeat infusion. The median total IL-2 dose administered was 4 (range 1-5), with the first dose administered approximately 6 hours after GK01 infusion. No dose-limiting toxicities (DLTs) occurred. G3/4 adverse events were exclusively hematologic (neutropenia, thrombocytopenia, leukopenia, lymphopenia in all patients), attributable to lymphodepletion. Chills, fever, and erythroderma occurred in all patients but G1-2, resolving within 2 weeks. At median follow-up of 169 days (range 80-297), ORR was 66.7% (4/6 PR; 2/6 SD), and DCR was 100%. The median peak ALC reached at 11.3×10^9/L (range 4.9-22.7) at days 7-9 post-infusion, remained elevated at 3.1×10^9/L (range 2.0-6.4) at 1 month. Among patients with available peripheral-blood samples (n = 4), product-derived TCR clonotypes comprised 94% of the circulating repertoire at day 7 and 92% at 2 months. **Conclusions:** In this first-in-human study, GK01 plus IL-2 demonstrated a favorable safety profile with no DLTs and manageable toxicity. The TSCM-enriched product achieved a 67% ORR and 100% DCR, with product-derived clonotypes persisting at $>$ 90% of the T-cell repertoire at 2 months. These findings validate the stemness-enriched T-cell platform and support expansion cohorts in selected solid tumor indications. Clinical trial information: NCT06954558. Research Sponsor: Geekgene.

2541 **Poster Session**

Longitudinal immune programs and association with toxicity burden and antitumor response during immunotherapy. First Author: Mireille Diane Langouo Fontsa, Molecular Immunology Laboratory, Institute Jules Bordet, Universisté Libre de Bruxelles, HUB, Brussels, Belgium

Background: Immune-related adverse events (irAEs) and tumor responses often co-occur during immune checkpoint inhibitor (ICI) therapy. We investigated whether blood immune programs associated with toxicity can be temporally and biologically dissociated from response programs. **Methods:** ICI-naïve patients with advanced solid tumors (n=37; enriched for melanoma and NSCLC) were profiled at baseline (T0), early on-treatment (T1; week 4), and later timepoints (T2–T3); patients with irAEs had an additional sample at onset (Ttox) before immunosuppression. PBMCs were analyzed by multiparameter flow cytometry and plasma cytokines by 48-plex multiplex assay (log2). We compared timepoints and delta windows (ΔT1−ΔT3), controlled multiple testing with Benjamini–Hochberg ($q<0.1$), and evaluated baseline predictors from T0 alongside landmark Cox models from T1 for ΔT1 predictors to avoid immortal-time bias; baseline multiple-irAE signatures were tested in penalized multivariable models with clinical covariates. **Results:** irAEs occurred in 20/37 (54%) patients (grade ≥3: 8/37, 22%); multiple irAEs occurred in 14/37 (38%). Objective response occurred in 15/37 (41%), and 10/15 (67%) responders developed irAEs; median time to first irAE was 86 days (IQR 63–108). Baseline multiple-irAE susceptibility centered on Tfh states (higher Tfh1/Tfh17 PD1+ICOS− and lower Tfh1 PD1−ICOS+), and a MultiTox signature predicted multiple irAEs (OR 5.46; p=0.033). Early dynamics strengthened toxicity prediction: ΔT1 Tfh2 PD1+ICOS− decreased in AnyTox/MultipleTox and predicted subsequent irAEs (HR 0.41; p=0.0019), whereas ΔT1 PDGF-BB (log2) increased risk (HR 2.25; p=0.006). Approaching onset, activated regulatory compartments (activated Treg and Tfr) contracted, followed at Ttox by a surge in IFN-inducible CXCR3 chemokines (CXCL9/MIG $p=3.1\times10^{-5}$; CXCL10/IP-10 p=0.0021), consistent with a Th1/IFN axis. In contrast, response-associated programs emerged later and reflected a Tfh/B cell–activated CD8 axis (memory B at T1 p=0.036; ΔT2 Tfh2 PD1−ICOS− $q<0.1$, p=0.0010; ΔT2 eosinophils $q<0.1$, p=0.0071) and remained independently associated with response (p≈0.02–0.03). **Conclusions:** Toxicity—particularly high-burden toxicity—appears to reflect a baseline susceptibility that is amplified by early on-treatment immune trajectories and culminates in a chemokine-rich onset state. In contrast, response-associated programs emerge later and are at least partly dissociable from high-burden toxicity. Distinct Tfh states—especially early Tfh2 dynamics—may support timing-informed monitoring and improved benefit–risk stratification during ICI therapy. Research Sponsor: None.

2542 **Poster Session**

Phase 1 trial of a KRAS G12V/HLA-A*11:01–restricted TCR-engineered T-cell therapy in advanced solid tumors. First Author: Ding Xiaoyan, Medical Oncology Department, Beijing Ditan Hospital, Capital Medical University, Beijing, Beijing, China

Background: KRAS G12V is a prevalent oncogenic driver in solid tumors, particularly pancreatic cancer (PC), occurring in approximately 20-30% of patients (pts). Advanced solid tumors harboring this mutation carry a poor prognosis and limited treatment options following standard chemotherapy. This phase 1 study evaluates a novel TCR-engineered T cell (TCR-T) therapy derived from a naturally occurring, KRAS G12V/HLA-A*11:01–restricted T cell receptor (TCR) isolated from patient tumor-infiltrating lymphocytes. **Methods:** This open-label, single-arm, dose-escalation phase 1 trial assessed the safety, tolerability, and preliminary efficacy of autologous TCR-T cells in pts with advanced solid tumors. Eligible pts had confirmed KRAS G12V mutation and HLA-A*11:01 positivity. Using a standard 3+3 design, autologous T cells were transduced with a lentiviral vector encoding the TCR and a CD8 co-receptor. Pts received lymphodepletion with cyclophosphamide and fludarabine, followed by a single infusion of TCR-T cells at either 5×10^9 (DL1) or 1×10^{10} (DL2) cells, with adjunctive interleukin-2. **Results:** As of January 2026, 8 pts were enrolled; of whom 6 (median age 69.5 years, ECOG PS 1) received the planned infusion, including pts with colorectal cancer (n = 2), pancreatic cancer (n = 3), and endometrial cancer (n = 1). All pts had liver or lung metastases and > 2 metastatic sites. No dose-limiting toxicities (DLTs) or grade ≥3 treatment-related adverse events (TRAEs) were observed. The treatment was generally well-tolerated; the most common (≥50%) treatment-emergent adverse events (TEAEs) were pyrexia, cytokine release syndrome (CRS), neutropenia, anemia, and thrombocytopenia. Grade 1-2 CRS occurred in 4/6 pts and resolved without sequelae. No immune effector cell–associated neurotoxicity syndrome (ICANS) was observed. TCR-T cells peaked in peripheral blood at a median of day 4 (range, 1–10), with a median peak expansion of 61,863 copies/μg DNA (range, 40,394–80,824). The objective response rate (ORR) was 50.0% (3/6), with a disease control rate (DCR) of 83.3% (5/6). In the pancreatic cancer subset, the ORR was 66.7% (2/3) and the DCR was 100%. **Conclusions:** This KRAS G12V/HLA-A*11:01–restricted TCR-T therapy demonstrated a favorable safety profile and encouraging preliminary antitumor activity in advanced solid tumors. Notably, a high response rate was observed in heavily pretreated pancreatic cancer patients, supporting further clinical development of this novel cellular therapy. Clinical trial information: NCT06767046. Research Sponsor: Beijing CorreGene Biotechnology Co., Ltd; 2023YFC3403800, 2024ZD0520500, Z221100007922022.

2543 **Poster Session**

Safety and preliminary efficacy of a novel armored mesothelin-targeted CAR-T therapy in advanced solid tumors. First Author: Changsong Qi, State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Beijing Key Laboratory of Carcinogenesis and Translational Research, Department of Early Drug Development Centre, Peking University Cancer Hospital & Institute, Beijing, Beijing, China

Background: UCMYM802 is an autologous mRNA-electroporated CAR-T cell therapy targeting mesothelin (MSLN), incorporating a lymphocyte-antigen-presenting cell costimulatory (LACO-Stim) molecule. This first-in-human study aimed to assess its safety, tolerability, preliminary efficacy, and pharmacokinetic/pharmacodynamic (PK/PD) profiles. **Methods:** This phase I study enrolled patients with metastatic or recurrent MSLN-positive solid tumors who failed standard therapies. Three dose levels were evaluated: 1×10^8 (n = 1), 5×10^8 (n = 1), and 1×10^9 CAR-T cells (n = 7). No lymphodepletion was required prior to infusion. Patients received up to 4 weekly infusions. Primary endpoints were safety and determination of the maximum tolerated dose (MTD). Secondary endpoints included objective response rate (ORR) by RECIST v1.1, disease control rate (DCR), and PK/PD parameters. **Results:** As of Nov. 2025, 9 patients were enrolled and treated (median age 67, range 52-67). Tumor types included pancreatic cancer (n = 3), peritoneal malignant mesothelioma (n = 1), adenocarcinoma of unknown primary, consistent with a gynecologic or peritoneal origin (n = 1), extrahepatic cholangiocarcinoma (n = 1), cholangiocarcinoma (n = 1), ovarian cancer (n = 1), and lung cancer (n = 1). All patients received at least one infusion. The 1×10^9 dose level was defined as the MTD, with one dose-limiting toxicity (DLT) observed (grade 4 cytokine release syndrome [CRS] with hypotension). Treatment-related adverse events (TRAEs) occurred in all patients, most commonly CRS (88.9%), fever (88.9%), decreased lymphocyte count (77.8%), anemia (77.8%), prolonged prothrombin time (66.7%), and hypoxia (55.6%). Grade ≥3 CRS occurred in 25% of patients. Among seven efficacy-evaluable patients, two patients achieved partial response (PR; one each in 5×10^8 and 1×10^9 cohorts), and two had stable disease (SD; one each in 1×10^8 and 1×10^9 cohorts). The ORR was 28.6% (2/7) and DCR was 57.1% (4/7). Notable responses included a PR in gynecologic or peritoneal origin adenocarcinoma and a PR at 6 months (converted to SD at 7.5 months) in extrahepatic cholangiocarcinoma. PK analysis showed peak CAR-T expansion (by copy number) at 1-hour post-infusion, with the highest and most sustained exposure after the first infusion. PD analysis indicated IFN-γ elevation correlating with CAR-T peak expansion. CAR-T exposure and activation marker expression showed a dose-dependent trend. **Conclusions:** UCMYM802 demonstrated a manageable safety profile consistent with expected CAR-T-related toxicities, primarily CRS. Preliminary anti-tumor activity was observed in heavily pretreated patients with MSLN-positive advanced solid tumors, with encouraging signals in gynecologic or peritoneal origin adenocarcinoma and biliary tract cancers. The recommended dose for expansion is 1×10^9 CAR-T cells. These results support continued investigation of UCMYM802. Clinical trial information: NCT06256055. Research Sponsor: None.

2544 **Poster Session**

Phase 1 dose escalation study of CD34 selected CD19 directed CAR T with metabolic programming in relapsed/refractory B-cell lymphoma. First Author: Brian Hess, Medical University of South Carolina, Hollings Cancer Center, Charleston, SC

Background: CD19 CAR T cell therapy (CAR-19) has been a breakthrough for relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (B-cell NHL). However, both relapse and toxicity remain major challenges. We utilized novel programming conditions aimed at enhancing the function and persistence of our CAR T products by improving metabolic fitness, via promotion of a hybrid Th1/Th17 phenotype. Additionally, CD34 selection was employed, via CD34 tag, to yield a more purified product and reduce potential toxicity. **Methods:** This single institution IRB approved phase 1B trial (NCT 05702853) evaluated a novel CD28 co-stimulated CAR-19 product, with metabolic programming and CD34 selection (CD19-CAR-CD34t hybrid T cells). Eligible patients had R/R B-cell NHL and were enrolled at dose level (DL) 1, 2, or 3 ($1x10^6$, $1.5x10^6$, $2x10^6$ CAR T cells/kg with max dose of $2.0x10^8$). Dose escalation (Desc) used a model-assisted keyboard design. Dose-limiting toxicity (DLT) evaluation occurred in the first 28 days following infusion per CTCAE v5.0, with CRS and ICANS assessed per ASTCT criteria. The primary objectives were to evaluate safety and determine recommended dose for expansion. **Results:** Desc completed enrollment with 15 patients across dose levels DL1-3, DL2-3, DL3-9. NHL subtypes included DLBCL (8), mantle cell (4), follicular (2), and marginal zone lymphoma (1). Patients received a median of two prior systemic therapies (range 1-5), and 11 (73%) received bridging therapy. All patients underwent successful leukapheresis, manufacturing, CAR T infusion, and completion of the 28-day DLT evaluation. Common AEs included neutropenia (100%), fatigue (53%), and nausea (47%). One DL3 patient experienced a DLT (grade 4 lung infection). CRS was noted in 9 patients (60%; (grade 1: 7 pts; grade 2: 2 pts), with no grade 3+ events. No ICANS was observed. Six patients (40%) received tocilizumab (toci) and two (13%) received corticosteroids for CRS management with cumulative administration of 8 doses of toci (mean 0.5 doses/patient) and 20 mg of dexamethasone (mean 1.3 mg/patient) for entire cohort. With 11.1-month median follow-up, ORR/CR rates were 73%/67% (1-year PFS 0.67; 95% CI 0.47-0.95). All 10 patients with CR remained relapse-free as of 1/1/26; 2 deaths occurred due to lymphoma progression. The median percentage of CD34 CAR T cells at infusion was 67%. Median total T-cell doses were 165.1 (DL1), 262.8 (DL2), and 236.2 (DL3) x 10^6. Data on persistence/expansion of Desc cohort are forthcoming. **Conclusions:** CD19-CAR-CD34t hybrid T cells showed promising efficacy and durability, with no relapses among patients with CR. There were no occurrences of either ICANS or grade 3+ CRS and limited CRS intervention needed. This is a promising toxicity profile for a CD28 co-stimulated CAR-19, likely owing to a more purified product via CD34 selection. DL3 was chosen for dose expansion and currently ongoing. Clinical trial information: NCT05702853. Research Sponsor: None.

2545 **Poster Session**

Effects of resorcinol isoprenyl benzene derivative IPI201 on natural killer cell cytotoxicity and tumor cell viability in human colorectal adenocarcinoma cells. First Author: Brett Lanier, Isosceles Pharmaceuticals, Wilmington, NC

Background: Natural killer (NK) cells play a critical role in anti-tumor immunity, yet their cytotoxic efficacy can be limited by tumor resistance. Resorcinyl isoprenyl benzene derivatives have previously shown anti-tumor activity, but effects on NK cell-mediated cytotoxicity remain unclear. IPI201 is a synthetic resorcinyl isoprenyl benzene derivative. We evaluated whether IP201 augments NK cell cytotoxicity and explored potential mechanisms. **Methods:** Cytotoxicity assays were performed using HT-29 colorectal carcinoma cells co-cultured with either standard NK cells or activated NK cells genetically modified to produce soluble IL-15 (sIL15 NK) under conditions of IPI201 pre-treatment or co-treatment. Cancer cell lysis was quantified over time to assess total cytolysis (AUC), maximum rate of killing (V_{max}), and time to 50% maximal cytolysis (T_{50}). NK activation markers were assessed by flow cytometry. NK cell survival following IPI201 exposure was assessed over 7 days using cell density quantification. **Results:** IPI201 enhanced NK cell-mediated cytotoxicity against colorectal cancer cells. Pre-treatment increased overall cytolysis and killing rates by 625% in standard NK cells and 50% in sIL15 NK cells ($P<0.05$). Co-treatment similarly increased tumor cell lysis ($P<0.05$). IPI201 alone induced rapid tumor cell death, outperforming standard NK cells alone in overall cytolysis, killing rate, and time to peak effect ($P<0.05$). Enhanced cytotoxicity was not associated with changes in NK activation markers. Instead, IPI201 increased NK cell survival across doses, with the highest dose increasing Day 7 density by 117% in standard NK cells and 214% in sIL15 NK cells ($P<0.05$). Further, IPI201 sensitized tumor cells to NK-mediated killing following tumor cell pre-treatment (+130% in both NK cell types; $P<0.05$). **Conclusions:** IPI201 induces tumor cell death independent of NK cells and enhances NK cell-associated cytotoxicity during pre- or -co-treatment. These effects may arise from increased NK cell survival and/or heightened tumor cell susceptibility to immune-mediated killing. To our knowledge, IPI201 is now the third known molecule alongside IL-2 and IL-15, that is independently sufficient to support NK cell survival. These findings support further investigation of IPI201 as a multifunctional immunomodulatory and cytotoxic agent in combination cell-based cancer therapies. Research Sponsor: None.

2546 **Poster Session**

Epigenetic reprogramming of allogeneic NK cells via antigen-specific "training" to generate target-specific memory-like NK cells for B-cell lymphoma without genetic engineering. First Author: Jialu Kang, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: Clinical application of CAR-NK cells is restricted by manufacturing complexity, cost, and potential genotoxicity. Furthermore, synthetic CAR expression may disrupt native NK biology and impose steric hindrance. We hypothesized that NK cells can be epigenetically reprogrammed ex vivo to acquire antigen-specific, memory-like cytotoxicity via a novel, non-genetic "Targeted Priming Platform" (TPP), bypassing the fundamental constraints of CAR engineering. **Methods:** Healthy donor NK cells were co-cultured with CD19+ Raji cells in the presence of a CD16xCD19 bispecific engager (BiKE) and IL-12/15/18 cytokines. After a 7-day priming phase and subsequent rest, cells were re-challenged to assess recall responses. Deep profiling was performed using mass cytometry, ATAC-seq, and ChIP-seq. In vivo efficacy was evaluated in NSG mice engrafted with CD19+ Raji lymphoma. Comparisons were made against cytokine-only primed (Cyt-NK) and naïve NK cells. **Results:** TPP-NK cells demonstrated a stable, antigen-specific recall response. Upon secondary challenge with CD19+ targets, TPP-NKs exhibited superior expansion, degranulation (CD107a), and IFN-γ production compared with Cyt-NK or naïve controls. This specificity was absent in mismatched target settings. Epigenetic analysis revealed that TPP induced durable chromatin remodeling, characterized by stable hypomethylation and open chromatin at critical cytotoxicity loci (e.g., IFNG, PRF1, GZMB), distinct from the transient changes observed in Cyt-NKs. In vivo, a single infusion of TPP-NKs combined with low-dose BiKE induced sustained remission and significantly prolonged survival compared with controls ($P < 0.001$). **Conclusions:** We demonstrate a paradigm-shifting strategy to generate "target-trained" memory NK cells without genetic engineering. TPP epigenetically imprints antigen specificity, combining the precision of antibody therapy with the persistence of cellular therapy. This scalable, "off-the-shelf" platform offers a safer, cost-effective alternative to CAR-based modalities for B-cell malignancies. Research Sponsor: None.

2547 **Poster Session**

An LNP-mRNA–based in vivo cell engager as a producer of T macrophage tumor triads in situ for targeted anti-solid tumor therapies. First Author: Xudong Wang, Liangzhu Laboratory, Hanghzou, Zhejiang, China

Background: The solid tumor microenvironment promotes infiltration of myeloid cells, with tumor-associated macrophages as the most abundant innate immune population. A recent study showed tumor-reactive T cells enriched in functional clusters with tumor or antigen-presenting cells, and T cells expanded from these clusters ex vivo exhibit enhanced tumor-killing activity. Bispecific and trispecific antibodies have emerged to link T cells with tumor and myeloid cells, improving antitumor immunity. However, their clinical use is limited by structural complexity, manufacturing challenges, and immunogenicity risks. Here, we developed a "live-cell engager" by harnessing and engineering macrophages in vivo to form T-macrophage-tumor triads, activating both T cells and macrophages near tumor cells to boost antitumor responses. **Methods:** We engineered macrophages to express a single-chain variable fragment (scFv) targeting CD3 (αCD3), a tumor-specific chimeric antigen receptor (CAR) and CD80 on their surface. Each was encoded by separate mRNAs encapsulated within one lipid nanoparticle formulation (LNP-C-3-80). Mouse bone marrow-derived macrophages (BMDMs) were used ex vivo to evaluate T cell activation and antitumor function. The efficacy of LNP-C-3-80 was further tested in immunocompetent syngeneic models including ID8 ovarian cancer and Hepa1-6 hepatocellular carcinoma. **Results:** In vitro, BMDMs engineered with LNP-3-80 effectively engaged T cells with macrophages, significantly boosting T cell activation compared to LNP-3 alone, as shown by increased CD69 expression and elevated secretion of IFN-γ, IL-2, and Granzyme B. Furthermore, BMDMs engineered with LNP-C-3-80 were able to engage both T cells and tumor cells, and when co-cultured with T cells, showed tsuperior antitumor activity over control groups (LNP-3-80, LNP-3, LNP-GFP). The LNP-delivered αCD3 and CD80 mRNAs were mainly expressed on macrophages but not on T cells, facilitating macrophage-T cell-tumor cell cluster formation. This proximity enabled mutual activation and synergistic tumor cell killing. In vivo, LNP-C-3-80 achieved nearly complete tumor regression and strong prevention of recurrence in ovarian and liver cancer models after intraperitoneal or intravenous administration. Toxicity studies in healthy C57BL/6J mice showed no organ damage or adverse serum biochemical changes, indicating a favorable safety profile. **Conclusions:** In summary, in vivo macrophage engineering promotes the formation of T cell–macrophage–tumor cell clusters, reducing immune cell–cancer cell distance and concurrently activating T cells. LNP-C-3-80 shows significantly enhanced antitumor efficacy in syngeneic solid tumor models with minimal toxicity. These results highlight LNP-C-3-80's strong potential as a promising therapeutic strategy against diverse solid tumors. Research Sponsor: None.

2548 **Poster Session**

Combining immune checkpoint inhibition and dendritic cell vaccination in advanced pleural and peritoneal mesothelioma: The phase 1b MESOVAX trial. First Author: Laura Ridolfi, IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST, Meldola, Italy

Background: Mesothelioma (M) remains a rare malignancy with limited therapeutic options. While immunotherapy combinations have recently become the standard of care for non-epithelioid subtypes, further strategies are required to enhance clinical outcomes. Dendritic cell vaccines (DCvax) have demonstrated preliminary activity and a favorable safety profile in M. Preclinical data suggest that DCvax induces PD-L1 expression on tumor cells; therefore, combining DCvax with Pembrolizumab (P) may sensitize patients (pts) to PD-1 blockade. **Methods:** MESOVAX is a proof-of-concept, Phase Ib, study evaluating the safety of P 200 mg combined with an autologous anti-tumor DCvax administered every 3 weeks (Q3W) for 6 cycles, followed by P monotherapy until disease progression or up to 2 years. Subcutaneous IL-2 (3 MU) was administered for 5 days following each vaccination. The primary endpoint was safety. Secondary endpoints included: changes in PD-L1 expression evaluated in pre- and post-therapy tumor samples by immunohistochemistry (IHC); immunological efficacy evaluated *in vivo* by DTH test and *ex vivo* measuring the immune response against selected tumor antigens (i.e MESOTHELIN, WT1, 5T4, TWIST-1, KRT-18, THBS2) by Interferon gamma (IFNγ) Enzyme-Linked Immunosorbent Spot (ELISpot) Assay; and treatment activity (objective response rate [ORR], duration of response [DOR], progression-free survival [PFS], and overall survival [OS]). **Results:** As of 28/11/2025, 9 pts (median follow-up: 32.5 months (mths)) were evaluable for safety and efficacy. Median age was 62 years; 89% (n = 8) were male, and all had epithelioid histology. Treatment-related adverse events (TRAEs) of any grade occurred in all 9 pts, with the most frequent being injection site reactions, asthenia, and fever. No grade 3–4 TRAEs were reported. Regarding treatment exposure, 4 pts received 6 cycles of P+DC, 6 pts received maintenance P, and one pt completed the maintenance phase. Best overall responses included 1 partial response (PR), 4 stable diseases (SD), and 4 progressive diseases (PD), with a median PFS of 5.3 mths (95% CI 1.8–17.3). Notably, one pt with prolonged SD (duration 9 mths) exhibited a PD-L1 conversion in the tumor tissue (from negative to positive) following treatment. Regarding the immunological activity, 4 pts experienced a positive DTH test during treatment, and interestingly for 3 of them we were able to measure a concomitant increase of the *ex vivo* antitumoral immune response against the tested antigens. **Conclusions:** The combination of DCvax and P is safe and demonstrates encouraging clinical activity in pretreated epithelioid M. The observed PD-L1 induction at the tumor site supports the synergistic potential of this combinatorial immunotherapeutic strategy. This trial is supported in part by a research grant from Investigator-Initiated Studies Program of MSD Italia S.r.l. Clinical trial information: NCT03546426. Research Sponsor: MSD Italia S.r.l.

2549 **Poster Session**

B cell responses in recurrent respiratory papillomatosis patients treated with DNA immunotherapy INO-3107. First Author: Nabil F. Saba, Emory University Winship Cancer Institute, Atlanta, GA

Background: Recurrent respiratory papillomatosis (RRP) is a chronic, debilitating disease of the airway primarily caused by infection with human papillomavirus (HPV) types 6 and/or 11 and characterized by recurrent, benign tumor growth with potential for malignant transformation. Current standard of care consists of repeated surgical removal of papillomas, which can lead to lasting airway damage and impaired vocal function. Thus, a non-surgical approach to treat RRP is paramount. Previously, we described T cell responses associated with an overall clinical response rate of 81% (26/32) to INO-3107, a DNA immunotherapy designed to generate T cells capable of targeting HPV-infected cells, in adult RRP patients during a Phase 1/2 trial (NCT04398433). Here, we describe B cell responses in these patients. **Methods:** INO-3107 was administered during study weeks 0, 3, 6 and 9. Peripheral blood mononuclear cells (PBMCs) were obtained at screening/day 0, weeks 6, 9, 11, 26 and 52. Formalin-fixed, paraffin-embedded papilloma tissue was obtained prior to INO-3107 treatment (Scr) and at the end of the 52-week study (EOS). Both PBMCs and tissue were subjected to RNA and BCR sequencing, which additionally underwent single sample gene set enrichment analysis and CloneTrack analysis, respectively. Clinical response was defined as any reduction in frequency of RRP surgical interventions in the 52 weeks following dose 1 of INO-3107 (Y1) compared to the 52 weeks prior. **Results:** Following INO-3107 treatment, 85% (23/27) of patients exhibited B cell expansion in PBMCs that was sustained through Y1 for responders, which in contrast began to contract at week 26 for non-responders. Enrichment of B cell signatures, inclusive of total, naïve, memory, and plasma B cells, in papilloma tissue increased significantly by EOS in responders compared to non-responders. Increases in tissue BCR clone counts from Scr to EOS correlated significantly with clinical response during Y1. BCR sequences detected in tissue taken at EOS displayed a low degree of overlap with those detected at Scr. Newly detected BCR sequences in EOS tissue were present in PBMCs prior to EOS. Some of these B cell clones were detectable in PBMCs and papilloma tissue only after INO-3107 treatment. **Conclusions:** B cell immunogenicity may play a role in mediating clinical responses to DNA immunotherapy INO-3107 for the treatment of RRP. INO-3107 treatment induced expansion and emergence of B cells in the blood of RRP patients, which trafficked to and infiltrated papilloma tissue by EOS as evidenced by increased B cell enrichment and clone counts. These immune responses were associated with improved clinical outcomes. These results suggest that INO-3107 engages B cells equipped with the potential to promote activation of T cell responses described previously (doi: 10.1038/s41467-025-56729-6) and that they may play a role in long-term immunity against RRP. Clinical trial information: NCT04398433. Research Sponsor: Inovio Pharmaceuticals, Inc.

2550 **Poster Session**

Anitocabtagene autoleucel (anito-cel) clinical trial manufacturing experience in patients with relapsed/refractory (RR) or newly diagnosed (ND) multiple myeloma (MM). First Author: Krina K. Patel, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Anito-cel is an autologous D-Domain–based anti-BCMA chimeric antigen receptor (CAR) T-cell therapy that demonstrated deep and durable efficacy and manageable safety in a Phase 1 study and a Phase 2 registrational study (iMMagine-1) in 4L+ RRMM (Bishop et al. ASH 2024; Patel et al. ASH 2025). The D-Domain has a fast off-rate and facilitates high transduction efficiency, high CAR expression, decreased risk of tonic signaling, and potential for enhanced manufacturing efficiency and optimal tumor cytotoxicity. Anito-cel is also being investigated in patients with RRMM with 1-3 prior therapies and in patients with NDMM. The anito-cel CAR T-cell therapy manufacturing process has been optimized by leveraging the learnings from the robust development process of another CAR T-cell therapy, axicabtagene ciloleucel (axi-cel). Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved in 2L large B-cell lymphoma based on the ZUMA-7 trial, with a demonstrated high manufacturing success rate (MSR) in both clinical trial and commercial real-world settings (100% and 99%, respectively; Alquist et al. TCT 2024). Here we report initial anito-cel manufacturing experience from 2 MM clinical trials. **Methods:** Pooled manufacturing outcomes from adults with MM enrolled and leukapheresed in iMMagine-3 or GEM-AnitoFIRST from 09/2024 to 10/2025 were included. First pass (FP)-MSR was defined as anito-cel lots manufactured on first attempt and within specification per total first attempt lots dispositioned plus lots not dispositioned due to termination in the period (excluding those terminated for patient withdrawal). The median turnaround time (mTAT) was defined as the time from leukapheresis to the quality release of final anito-cel product. **Results:** There was a total of 104 patients who were leukapheresed and whose lots were dispositioned as of October 31, 2025; anito-cel was successfully manufactured for 100% of these patients. The FP-MSR was 99.0% with 1/102 lots rejected on disposition (Table). The global mTAT was 18 days (interquartile range [IQR], 17-20 days) for the 101 lots released. Updated data to be presented. **Conclusions:** Our results demonstrate rapid and reliable anito-cel manufacturing for MM clinical trials globally, with high manufacturing success rates and consistent turnaround times. These results were consistent with axi-cel manufacturing outcomes and highlight the importance of leveraging axi-cel manufacturing experience in the development of anito-cel. Clinical trial information: NCT06413498 and NCT07045909. Research Sponsor: Arcellx Inc. and Kite, a Gilead Company.

FP-MSR, n/N (%)	101/102 (99.0)
Global mTAT, days (IQR)	18 (17-20)
Lots released, n	101

2551 **Poster Session**

A phase 3 trial of adagloxad simolenin/OBI-821 in patients with high-risk early-stage triple-negative breast cancer. First Author: Hope S. Rugo, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Adagloxad simolenin (AS) is a therapeutic cancer vaccine composed of Globo H linked to the carrier protein keyhole limpet hemocyanin. OBI-821 is an adjuvant administered with AS to strengthen immune response. This phase 3 trial assessed safety/efficacy of AS/OBI-821 in patients with triple negative breast cancer (TNBC; NCT03562637). **Methods:** Eligible patients for this randomized, open-label trial were adults with high-risk ($\geq$1cm residual primary, $\geq$1 residual axillary node after neoadjuvant chemotherapy, or stage IIB or III cancer treated with adjuvant chemotherapy alone), primary localized early-stage, Globo H-positive (H-score $\geq$15) TNBC. Patients were required to have received $\geq$4 cycles of standard taxane- and anthracycline-based chemotherapy. Patients were randomized 1:1 to receive standard of care (SOC; observation alone [29%], capecitabine [69%], or a checkpoint inhibitor $\pm$ capecitabine [2%]) or AS/OBI-821 and SOC (observation alone [26.6%], capecitabine [69.6%], or a checkpoint inhibitor $\pm$ capecitabine [3.8%]). Patients in the AS/OBI-821 arm received 4 weekly doses of study drug administered via subcutaneous injection, followed by 4 biweekly doses, 4 doses every 4 weeks, then doses every 8 weeks up to 100 weeks. The primary endpoint was invasive disease-free survival (IDFS); secondary endpoints included safety assessed via treatment-emergent adverse events (TEAEs) and overall survival (OS). Patients were followed for up to 5 years after randomization for OS. **Results:** The intent-to-treat (ITT) population was comprised of 575 patients, with 286 in the AS/OBI-821 arm, and 289 in the SOC arm. Patients were a median age of 51 years (range 24-85), all were female, and most were white (52.7%). A total of 5.2% of patients had stage I cancer, 50.3% had stage II, and 37.1% had stage III. IDFS in the AS/OBI-821 arm was not statistically different than in the SOC arm (IDFS hazard ratio [HR], 1.23 [95% CI: 0.88, 1.73]; P= 0.23). Three-year IDFS rate was 54.5% for AS/OBI-821 arm and 56.4% for the SOC arm. Similar pattern was observed for OS with HR = 1.36 [95% CI: 0.77, 2.38). TEAEs occurred in 79.6% of patients in the AS/OBI-821 arm and 66.7% in the SOC arm. The most common TEAEs in the AS/OBI-821arm were palmar-plantar erythrodysaesthesia syndrome (18.7%), fatigue (11.6%), and headache (11.3%). Serious TEAEs occurred in 5.3% of patients in the AS/OBI-821 arm vs 6.2% in the SOC arm. One patient (0.4%) in the AS/OBI-821 arm had a TEAE of interstitial lung disease, assessed as unlikely related to treatment and one patient (0.3%) in the SOC arm had acute coronary syndrome that led to death. **Conclusions:** In this phase 3, randomized, open-label trial, AS/OBI-821 was well-tolerated, with a safety profile similar to SOC. IDFS and OS were similar between the AS/OBI-821 and SOC arms. The trial was terminated per recommendation by the Data and Safety Monitoring Board as it met prespecified futility criteria. Clinical trial information: NCT03562637. Research Sponsor: None.

2552 **Poster Session**

Phase 1 study of META 10-19, an IL-10-expressing, anti-CD19 CAR T cell product in patients with high-risk DLBCL. First Author: Qianwen Xu, State Key Laboratory of Immune Response and Immunotherapy, University of Science and Technology of China, Hefei, Anhui, China

Background: Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of B cell lymphoma. However, limited duration of remission remains a significant challenge. We designed a metabolically armored anti-CD19 CAR T-cell product (META 10-19) that autocrine interleukin (IL)-10 to enhance antitumor activity, and assess the therapeutic potential in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). **Methods:** This phase 1 study is designed to evaluate the safety and preliminary efficacy of META 10-19 in relapsed/refractory DLBCL patients aged 3–70 years old. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by ASTCT criteria, and other adverse events (AEs) were evaluated according to CTCAE 5.0. Tumor response was assessed by investigators using Lugano 2014 criteria and IPCG criteria. **Results:** From December 2022 to December 2024, 14 patients with a median age of 54.5 years have been enrolled and received META 10-19 infusion at doses ranging from (0.002–0.1) $\times 10^6$ cells/kg, following a standard lymphodepletion regimen (30 mg/m^2/day Flu $\times$3 days, 300 mg/m^2/day Cy $\times$3 days). All patients had relapsed/refractory disease, with high-risk features including primary refractory (n = 9), nodal and extranodal involvement (n = 6), CNS lymphoma (n = 5), and bulky disease (n = 2). The most frequent Grade 3–4 AEs comprised neutropenia (100%, 14/14), thrombocytopenia (85.7%, 12/14), and anemia (71.4%, 10/14). CRS was predominantly manifesting as low-grade events (Grade 1–2, n = 13; Grade 3, n = 1). ICANS developed in 2 patients (14.3%) with primary CNS disease, manifesting as transient seizures and classified as Grade 3. At 3 months post-infusion, the overall response rate was 100%, including 13 patients (92.9%) achieved complete response (CR), and 1 patient achieved partial response. As of December 1, 2025, with a median follow-up of 23.3 months (range, 5.6–33.4), 9 patients maintained CR for over 1 year, 4 for over 2 years, and the earliest infused patient remains in remission at 33.4 months. The median progression-free survival (PFS) and overall survival (OS) have not yet been reached, while the 12-month PFS rate and 12-month OS rate were 71.4% and 92.9% , respectively. **Conclusions:** This first-in-human trial of META 10-19, an IL-10 expressing, anti-CD19 CAR T-cell product, for the treatment of relapsed/refractory DLBCL has exhibited manageable safety profile and durable efficacy at ultra-low doses in patients with high-risk features. Studies evaluating larger cohorts and longer follow-up are ongoing. Clinical trial information: NCT05715606. Research Sponsor: Research Funds of Centre for Leading Medicine and Advanced Technologies of IHM; National Natural Science Foundation of China.

2553 **Poster Session**

Erythrocyte–anti–PD-1 conjugates in patients with advanced solid tumors resistant to anti–PD-1/PD-L1 therapy: Long-term follow-up of a phase I trial. First Author: Xiaoqian Nie, Westlake University, Hangzhou, Zhejiang, China

Background: Despite the clinical success of immune checkpoint blockade, most patients with advanced solid tumors fail to achieve durable benefit due to limited efficacy and/or immune-related toxicities. αPD-1-Ery is an erythrocyte–antibody conjugate that covalently links an anti–PD-1 antibody to erythrocyte membranes. Unlike conventional antibodies, αPD-1-Ery preferentially accumulates in the spleen, where it remodels the splenic immune microenvironment by expanding effector T cells and reducing immunosuppressive myeloid cell reservoirs, thereby inducing systemic anti-tumor immunity. We previously reported favorable safety and preliminary efficacy of αPD-1-Ery in patients with PD-1/PD-L1–resistant solid tumors. Here, we report long-term follow-up results assessing durability of benefit and exploratory biomarkers. **Methods:** 14 heavily pretreated patients with 11 types of advanced solid tumors who had progressed on PD-1/PD-L1–containing regimens as their most recent line of therapy were enrolled. Patients received αPD-1-Ery monotherapy at 2×10^{11} or 3×10^{11} cells. Endpoints included safety, efficacy, and exploratory correlations between immune biomarkers and clinical outcomes. **Results:** As of October 31, 2025, all patients had completed treatment, with a median follow-up of 18.9 months. Treatment discontinuation occurred due to disease progression in 57.1% (8/14), CR in 7.1% (1/14), completion of planned treatment cycles in 21.4% (3/14), and other reasons (including AE or withdrawal) in 14.3% (2/14). No DLTs were observed. TRAEs occurred in 64.3% (9/14) of patients, with no grade $>$3 TRAEs, no grade $\geq$3 immune-related AEs, and no treatment discontinuations due to TRAEs. αPD-1-Ery demonstrated sustained anti-tumor activity, with a DCR of 78.6% (11/14) and an ORR of 42.9% (6/14; 1 CR, 1 uCR, 4 PR), with improved responses observed in the higher-dose cohort. mPFS was 5.6 months and mOS was 23.4 months. Durable benefit was observed in most responders, with 4/6 maintaining response after treatment discontinuation; 1 received no subsequent therapy and 3 resumed PD-1/PD-L1–based immunotherapy despite prior resistance. mDoR had not been reached (range, 4.8–24.7 months). Exploratory analyses indicated that clinical benefit was observed in both primary (n = 3) and acquired (n = 3) anti–PD-1/PD-L1–resistant patients. Responders had higher baseline circulating PMN-MDSCs and DCs and experienced rapid and sustained PMN-MDSC reduction following treatment. Tumor MMR status was available in 5 patients (all MSS), with objective responses observed in 3. **Conclusions:** Spleen-directed PD-1 blockade using erythrocyte–antibody conjugates induces durable clinical benefit. αPD-1-Ery represents a novel immunotherapeutic strategy for PD-1/PD-L1–resistant solid tumors and supports further clinical development. Clinical trial information: NCT06026605. Research Sponsor: None.

2554 **Poster Session**

Single-cell multi-omics and TCR sequencing to identify early tumor cavity homing and phenotypic evolution of CAR-T cells in glioblastoma. First Author: Qi Zhu, 2nd Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has shown remarkable efficacy in hematological malignancies but remains largely ineffective in glioblastoma. A systematic understanding of early CAR-T cell trafficking and phenotypic adaptation within the tumor immune microenvironment may provide critical insights into this limitation. **Methods:** We performed single-cell multi-omics profiling using the 10x Chromium Single-Cell 5′ Immune Profiling platform on infused CAR-T cells and matched tumor cavity cerebrospinal fluid (CSF) obtained via an Ommaya reservoir at day 3 post-infusion. Paired transcriptome/TCR data enabled analyses of composition, clonal tracking, and phenotypic transitions within CAR-T populations following early tumor cavity homing. **Results:** Single-cell profiling of the infused CAR-T product revealed a T cell–dominant population, primarily composed of $CD8^+$ T cells (62.24%) and $CD4^+$ T cells (34.63%). Analysis of tumor cavity CSF demonstrated a heterogeneous immune landscape, including $CD4^+$ T cells (32.79%), $CD8^+$ T cells (20.83%), dendritic cells, monocyte/macrophage populations, and other innate immune subsets. Gene set variation analysis across all immune cell populations showed enrichment of memory-associated programs in the CSF, while exhaustion-related signatures were not prominent, indicating a relatively non-exhausted immune state at this early time point. TCR-based clonal tracking identified 188 CAR-T cells in the CSF that originated from the infusion product, corresponding to an early homing rate of 2.19%. These homed CAR-T cells were predominantly derived from cytotoxic and proliferating $CD8^+$ T cell subsets, as well as effector $CD4^+$ T cells. Notably, cytotoxic $CD8^+$ CAR-T cells exhibited pronounced clonal expansion in the CSF, whereas proliferating $CD8^+$ CAR-T cells underwent phenotypic transitions toward cytotoxic states following tumor cavity infiltration. In parallel, activated $CD4^+$ CAR-T cells preferentially adopted memory-like phenotypes. Consistently, TCR-tracked CAR-T cells in the CSF displayed significantly stronger memory-associated transcriptional signatures compared with their clonal counterparts in the infusion product (CSF vs. product, -0.187 vs -0.088 , $p = 2.48 \times 10^{-9}$). **Conclusions:** This study provides a single-cell and clonal-level view of early CAR-T cell trafficking and phenotypic adaptation within the glioblastoma tumor cavity. Early tumor cavity infiltration is a selective process driven by cytotoxic and proliferative CAR-T subsets and occurs in the context of preserved memory-associated programs with limited exhaustion. These findings suggest that the limited efficacy of CAR-T therapy in glioblastoma is likely to stem from barriers that emerge at later stages following initial tumor entry instead of immediate CAR-T dysfunction. Research Sponsor: None.

2555 **Poster Session**

Rab11 family interacting proteins as regulators of T cell recognition and infiltration in triple negative breast cancer. First Author: Paras R. Sahani, Rosalind Franklin University of Medicine and Science, North Chicago, IL

Background: Triple negative breast cancer (TNBC) accounts for 10-15% of all breast cancer cases and has the worst prognosis (5 year relative survival rate of 78%). TNBC is defined by absent estrogen and progesterone receptors and lack of HER2 amplification. First-line treatment for metastatic TNBC has evolved in the past several years to include immunotherapy for PD-L1+ patients. Recent NCCN guidelines recommend antibody-drug conjugate (ADC) therapy as first line treatment for metastatic TNBC regardless of PD-L1 positivity. ADCs target cell surface proteins that are abundant on tumors and sparse on healthy cells, delivering cytotoxic payloads selectively to the tumor. ADC efficacy depends on surface localization of target antigens, whose localization is dictated by endosomal trafficking via Rab GTPases. We showed that Rab11b-mediated endosomal trafficking is required for breast cancer brain metastasis. Here we investigate how trafficking-mediated control of the cell surface dictates immune recognition and response. **Methods:** Using a CRISPR screen we found that Rab11 family interacting proteins, Rab11fip2 and Rab11fip3, are required for immunogenic breast cancer cells to be recognized by CD8+ T cells. Flow cytometry revealed that the loss of recognition is not due to changes in surface PD-L1 or MHC/antigen presentation. Knockout of either Rab11fip did not change cell proliferation or tumor burden in immunocompromised animals, but led to significantly increased tumor growth in immunocompetent animals. This suggests that knockout of either Rab11fip causes loss of immune recognition to allow faster tumor growth while control tumors are restrained by the immune system. IHC analysis revealed a significant decrease of tumor infiltrating T cells in Rab11fipKO tumors. Interestingly, immune disruption is systemic, as splenic architecture is disrupted in Rab11fipKO tumor bearing mice. **Results:** Since the primary function of Rab11fips is to mediate trafficking of Rab11 cargo proteins, our results suggest that surface localization of these cargo proteins is required for immune cell recruitment, recognition, or activation. **Conclusions:** We are currently focused on identifying these cargo proteins, determining whether Rab11 controls trafficking of Trop-2 the target of several current ADCs, and characterizing Rab11 control of the T cell-cancer cell interaction in human breast cancer cell lines. Our work holds the promise of finding novel targets for ADCs and biomarkers for responsiveness to immunotherapy. Research Sponsor: American Cancer Society; RSG-23-136584-01-MM; Mary Kay Ash Foundation; METAvivor.

2557 **Poster Session**

Long-term follow-up of satricabtagene autoleucel (satri-cel) as sequential therapy after first-line treatment for advanced gastric cancer: A subgroup analysis. First Author: Chang Liu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Early Drug Development Centre, Peking University Cancer Hospital & Institute, Beijing, China

Background: Claudin18.2 (CLDN18.2) has emerged as a new target for the treatment of gastric cancer in the first-line (1L) setting with the approval of zolbetuximab. This long-term analysis reports the extended efficacy and safety of satri-cel (autologous CLDN18.2-specific CAR T cells) as sequential therapy after 1L treatment in patients with advanced gastric/gastroesophageal junction (G/GEJ) cancer, after the results of all cohorts published in 2024 (Qi C, et al. Nat Med. 2024;30(8):2224-2234. NCT03874897). **Methods:** This trial is an open-label, multi-cohort, phase 1 trial, which evaluated the safety and efficacy of satri-cel in patients with CLDN18.2-positive advanced gastrointestinal cancers. Cohort 3 in dose-expansion stage enrolled patients with advance G/GEJ cancer and were given satri-cel as sequential treatment after 1L therapy. The primary endpoint was safety; secondary endpoints included efficacy, pharmacokinetics and immunogenicity. **Results:** As of October 18, 2025, 5 patients with CLDN18.2-positive G/GEJ cancer received satri-cel infusion(s) of 250×106 cells, sequentially after 1L therapy. Each patient received a total of one (n=1), two (n=1), and three doses (n=3) of satri-cel. Patients had received a median of 5 cycles (range, 4-11) of 1L chemotherapy before satri-cel infusion, with 1 (20%) treated with PD-1 inhibitor. Notably, only 1 patient achieved PR after first-line therapy. Three patients (60%) were Lauren diffuse type and 1 (20%) with mixed type, 4 (80%) had signet ring cell carcinoma, and 4 (80%) had peritoneal metastases. Median follow-up from initial 1L therapy was 54.6 months (reverse KM, 95% CI: 51.1, NE). Among 4 patients with target lesions, confirmatory objective response rate was 100%, and median duration of response was not reached. One has maintained SD for 20.9 months and 2 received surgical resection after satri-cel therapy. Median progression-free survival and median overall survival since 1L therapy was 20.9 months (95% CI: 10.8, NE) and 22.1 months (95% CI: 10.8, NE), respectively. Two were still alive as of cutoff date, with a follow-up of 58.1 months and 51.1 months. Safety was manageable. No grade 3 or higher cytokine release syndrome (grade 1: n=1, 20%; grade 2: n=4, 80%), any grade immune effector cell-associated neurotoxicity syndrome, or treatment-related deaths occurred. Despite common hematologic toxicities, no severe infections (grade $\geq$3) or febrile neutropenia were reported. **Conclusions:** With an extended follow-up exceeding 4.5 years, satri-cel as first-line sequential treatment continues to demonstrate durable survival benefit with a manageable safety profile in patients with advanced G/GEJ cancer, supporting its highly promising potential in earlier lines of therapy. Clinical trial information: NCT03874897. Research Sponsor: None.

2558 **Poster Session**

Concurrent chemoradiotherapy plus cytokine-induced killer cells therapy or observation in patients with locoregionally advanced nasopharyngeal carcinoma: A ten-year follow-up of a randomized, phase II study. First Author: Xiuyu Cai, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Concurrent chemoradiotherapy (CCRT) is the standard of care for patients with locoregionally advanced nasopharyngeal carcinoma (NPC). We aimed to evaluate the efficacy and safety of Cytokine-Induced Killer cells (CIK) consolidation therapy in combination with CCRT in these patients. **Methods:** Patients with locoregionally advanced NPC were randomized in a 1:1 ratio to receive concurrent chemoradiotherapy therapy plus CIK consolidation therapy or concurrent chemoradiotherapy alone in this single-center, randomized, phase II study. The primary endpoints were disease-free survival (i.e., survival period free from disease recurrence [distant metastasis and/or locoregional recurrence] or death from any cause) and overall survival in the intention-to-treat population. Safety was a secondary endpoint. **Results:** 58 patients were enrolled in this study (29 in the CIK therapy group and 29 in the control group). The median follow-up time was 144.70 months. In the CIK therapy group, the 10-year disease-free survival rate was significantly higher than that in the control group (82.5% versus 61.3%; hazard ratio for recurrence or death, 0.258; 95% confidence interval [CI], 0.094-0.712; P=0.005). The 10-year overall survival rate was 86.2% and 67.5%, respectively; (hazard ratio for death, 0.377; 95% CI, 0.131-1.087; P=0.06). The main adverse effects of CIK was fever which resolved after symptomatic treatment. In the CIK therapy group, 23.1% of patients experienced acute adverse events of grade 3 or 4 versus 17.2% in the control group during CCRT. The most frequent adverse events of grade 3 are mucositis, followed by decreased appetite, marrow suppression. **Conclusions:** CIK consolidation therapy plus CCRT significantly improved disease-free survival in patients with locoregionally advanced NPC. (This trial is registered with Chinese CilnicalTrial.gov, number ChiCTR-TRC-08000262). Clinical trial information: ChiCTR-TRC-08000262. Research Sponsor: None.

2559 **Poster Session**

Optimization of tumor-infiltrating lymphocyte (TIL) manufacturing in non-small cell lung cancer (NSCLC) using an IL-7/IL-15/IL-2 expansion protocol. First Author: Jorge Bartolome, Hospital Clinico San Carlos and IdISSC, Madrid, Spain

Background: Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) is a promising strategy in non-small cell lung cancer (NSCLC), although ex vivo expansion remains challenging due to variability in yield and product quality. Optimizing cytokine support during TIL expansion may improve manufacturing robustness while preserving a clinically relevant immunophenotype. **Methods:** Tumor tissue specimens were obtained from immediately resected NSCLC lesions and processed for TIL outgrowth and rapid expansion over 28 days using either standard IL-2 or an experimental IL-7/IL-15/IL-2 protocol. Manufacturing endpoints included expansion yield, viability and $CD3^+$ proportion. Multiparametric flow cytometry assessed memory differentiation subsets and exhaustion-associated markers at baseline, pre-REP and post-REP. Clinical-pathological variables included disease stage, PD-L1 expression and prior systemic treatment. **Results:** 11 NSCLC TIL expansions were analyzed (experimental: n=7; IL-2: n=4). Median age was 73.1 years (range 48.5–92.3) and ECOG was 0–1 in 91% of patients; 64% had early-stage disease and 27% had advanced-stage (III–IV). PD-L1 was $<$1% in 73%, 9% showed PD-L1 1–49%, and none $\geq$50%. The cohort included pretreated patients, including prior anti–PD-1 exposure. Compared with IL-2, IL-7/IL-15/IL-2 resulted in a modest reduction in expansion yield (15–28%) and a lower CD4+/CD8+ ratio (6.62 vs 19.86), but showed improved manufacturing robustness, with all expansions meeting predefined quality criteria, whereas standard IL-2 expansions showed more variable product quality. Immunophenotypic profiling showed a more stable memory-oriented differentiation pattern with IL-7/IL-15/IL-2, including reduced naïve and TEMRA subsets and increased CD4+ TCM cells; CD8+ TCM remained predominant in both protocols. A polarisation towards the effector memory phenotype ($CCR7^-CD45RA^-$) was observed in the experimental protocol. CD28 remained highly expressed in both protocols, while CD134 tended to decrease with IL-7/IL-15. During pre-REP, PD-1 and TIM-3 were reduced in several subpopulations under the experimental protocol, suggesting a transiently less exhausted phenotype. After REP, these differences disappeared, with comparable levels between protocols. During REP, Th1 and Tfh increased in both protocols, while Th2 and Th17 remained low. **Conclusions:** Supplementation with IL-7 and IL-15 during NSCLC-derived TIL expansion improves consistency of product quality and supports a favorable memory-oriented and functional phenotype without increasing exhaustion markers at the end of manufacturing. This approach may enable more reliable generation of clinically applicable TIL products in heterogeneous and pretreated NSCLC populations, facilitating broader implementation of TIL-based therapies. Research Sponsor: None.

2560 **Poster Session**

Preliminary phase 1 results of a MICA/B-targeted CAR T cell designed to overcome solid tumor escape mechanisms and avoid the requirement for conditioning chemotherapy. First Author: Manish Ramesh Patel, University of Minnesota Medical School, Department of Medicine, Division of Hematology, Oncology, and Transplantation, Minneapolis, MN

Background: FT836 is a multi-engineered CAR T cell targeting the conserved α3 domain of MICA/B stress ligands, enabling recognition of diverse solid tumors with additional edits including, (i) the hnCD16a FC receptor to enable multi-antigen targeting in combination with monoclonal antibodies (mAb), (ii) Sword and Shield engineering consisting of alloimmune-defense receptor (ADR) expression and CD58 deletion to coordinately avoid host recognition eliminating the need for conditioning chemotherapy (CCT), and (iii) CXCR2 and TGFβ signal redirection receptors to maximize tumor trafficking and adaptability within an immunosuppressive tumor niche, respectively. Manufactured from an iPSC-master cell bank, it is available off-the-shelf and delivered on-demand to patients (pts). **Methods:** The Phase 1 trial of FT836 in pts with advanced solid tumors (NCT07216105) evaluates multiple regimens including monotherapy (Regimen A), combination with EGFR-targeting mAb cetuximab or HER2-targeting mAb trastuzumab (Regimen C or E, respectively). CCT is not required and FT836 is given twice during the treatment cycle, with retreatment available for eligible patients. First dose of FT836 is administered with a 24-hour hospital stay while the 2^{nd} dose is given as outpatient. **Results:** First three pts (all MSS mCRC; median: age 45 y, prior therapies of 5, disease duration of 51 months) were treated in Regimen C dose level 1 (DL1 = 300 million cells/dose, Days 1 and 15 with cetuximab, no CCT) and completed dose limiting toxicity (DLT) evaluation (data cut-off 15 JAN 2026) with no DLTs, FT836-related serious adverse events, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) reported. One of the three pts demonstrated a CEA response with $>$50% reduction (480 ng/mL at BL; 230 ng/mL at 4 weeks after first FT836 infusion) that correlated to mass shrinkage in all target lesions in a week 7 CT scan (obtained after data cut-off date). Of the other two pts, one experienced PD while the other was not yet assessed at the time of abstract submission. FT836 was detected in peripheral blood (PB) following the first dose, with persistence observed up to 1 week. Notably, FT836 cells were detected beyond the initial PB detection in a tumor biopsy obtained at Day 22 ($\pm$3 days) indicating greater persistence in tissue compared to PB, supporting the value of additional engineered elements. EGFR and MICA/B antigens were identified in 3/3 baseline tumor biopsies, highlighting the relevance of multi-antigen targeting in driving patient outcome. **Conclusions:** FT836 Regimen C DL1 was well-tolerated and early clinical data supports anti-tumor activity in highly refractory mCRC where there is significant unmet need. This trial is actively enrolling and updated clinical and translational data will be presented. Clinical trial information: NCT07216105. Research Sponsor: Fate Therapeutics.

2561 **Poster Session**

Extreme persistence of polyclonal $CD8^+$ CAR T cells as a driver of marrow failure, neurotoxicity, and fatal immune collapse after ciltacabtagene autoleucel. First Author: Djordje Atanackovic, University of Maryland Greenebaum Comprehensive Cancer Center, Baltimore, MD

Background: BCMA-directed chimeric antigen receptor (CAR) T-cell therapies induce deep responses in relapsed/refractory multiple myeloma (MM), but increasing potency has expanded the spectrum of treatment-related toxicities. While cytokine release syndrome and immune effector cell–associated neurotoxicity are well characterized, the consequences of extreme and prolonged CAR T-cell persistence remain poorly understood, particularly as CAR T-cell strategies are extended to solid tumors. **Methods:** We performed longitudinal, multi-compartment immunomonitoring in a patient with high-risk MM treated with ciltacabtagene autoleucel (cilta-cel) who developed an unusual leukemia-like clinical course. Peripheral blood (PB), bone marrow (BM), and cerebrospinal fluid (CSF) samples were analyzed by multiparameter flow cytometry, functional cytokine secretion assays, multiplex cytokine profiling, single-cell RNA sequencing with paired T-cell receptor (TCR) repertoire analysis, and lentiviral CAR integration site mapping. **Results:** Following cilta-cel infusion, the patient developed massive and persistent expansion of non-malignant $CD8^+$ effector-memory CAR T cells, comprising $>$90% of circulating lymphocytes and ~95% of BM lymphocytes, with absence of detectable non-transduced T cells. Despite achieving complete remission of MM, extensive BM infiltration by CAR T cells was associated with marked marrow hypocellularity, trilineage hypoplasia, and prolonged pancytopenia. A distinct trafficking-competent $CD8^+$ effector-memory subset (TEM5) was selectively enriched in CSF and associated with severe neurotoxicity and a local pro-inflammatory cytokine milieu. Single-cell transcriptomics demonstrated a highly migratory, cytotoxic effector program with suppressed proliferation, MAPK/TCR signaling, and tissue-residency signatures. TCR repertoire and integration site analyses confirmed polyclonality and excluded malignant transformation or insertional oncogenesis. Sustained CAR T-cell dominance coincided with profound hypogammaglobulinemia, failure of immune reconstitution, recurrent life-threatening infections, and ultimately fatal sepsis. **Conclusions:** These findings define a previously underrecognized toxicity paradigm of BCMA CAR T-cell therapy characterized by pathologic immune dominance and extreme persistence of cytotoxic CAR T cells, leading to marrow failure, neurotoxicity, and lethal immunosuppression. Extended multi-parametric immunomonitoring may identify patients at risk and inform risk-adapted management strategies, and this principle has potential implications for the design of next-generation CAR T-cell therapies, including for solid tumors. Research Sponsor: None.

2562 **Poster Session**

Influence of onboard, tethered IL-12 on potency of the Tmod NOT gate and selectivity. First Author: Jushen Liang, A2 Biotherapeutics, Agoura Hills, CA

Background: To realize the full therapeutic potential of engineered immune cells in solid tumors, high potency must be coupled with absolute selectivity. While synthetic NOT logic gates, such as the LIR-1 NOT gate (Tmod) system, effectively address non-specific cytotoxicity, overcoming the suppressive tumor microenvironment (TME) requires auxiliary stimulation. This study focused on Interleukin-12 (IL-12)—a potent pro-inflammatory cytokine—as an "armoring" strategy to bridge this gap. **Methods:** We designed an antigen-inducible, membrane-tethered IL-12 system to boost antigen-specific Tmod activity. The performance of this inducible IL-12 construct was evaluated across various long-term in vitro and in vivo assays to measure Tmod T cell exhaustion (specifically the upregulation of PD-1 and downregulation of CD62L) and its ability to mitigate the immunosuppressive effects of TGFβ, a primary barrier in the solid tumor microenvironment. We further assessed the reversibility of IL-12 expression upon antigen clearance and monitored for IL-12 shedding both in vitro and in vivo. **Results:** The inducible IL-12 construct boosted antigen-specific Tmod activity, prevented T cell exhaustion, and effectively mitigated the immunosuppressive effects of TGFβ that typically hamper CAR-T persistence. Crucially, this potency boost did not "override" the LIR-1 blocker; the IL-12-enhanced cells remained selective, sparing normal cells. Furthermore, data showed that the expression of membrane-tethered IL-12 is reversible once the antigen is cleared. Minimal IL-12 shedding was observed, suggesting the pro-inflammatory signal remained localized to the immunological synapse. **Conclusions:** The antigen-inducible membrane-tethered IL-12 system enhances Tmod potency while maintaining a high degree of selectivity and an acceptable safety profile for clinical translation. An Investigational New Drug (IND) application for MSLN-targeted Tmod boosted by antigen-inducible membrane-tethered IL-12 has been approved by the FDA, and a Phase 1 clinical trial is currently ongoing. Research Sponsor: None.

2563 **Poster Session**

Novel transposon BAFF CAR-T cells (LMY-920) for non-Hodgkin lymphoma (NHL). First Author: Paolo Fabrizio Caimi, Cleveland Clinic, Cleveland, OH

Background: CAR-T cells targeting CD19 using scFv-based CARs have been effective and approved to treat lymphoma. Response rates are high, but a significant number of patients fail to respond or relapse. This has been linked to T cell exhaustion, immune dysregulation, and/or epitope loss. To overcome this, we developed a CAR-T cell product expressing a BAFF-ligand (LMY-920). The CAR consists of truncated human BAFF on a 3rd generation CAR backbone with CD28, OX40, and CD3z intracellular signaling domains. The BAFF-ligand domain confers ability to bind the 3 BAFF receptors (BAFFR/BR3, TACI and BCMA). These are attractive tumor-associated antigens being variably expressed in all B-lineage malignancies such as B cell NHL, chronic lymphocytic leukemia (CLL), hairy cell leukemia and multiple myeloma (MM), and are important for B-cell survival, reducing the chance of antigen escape. Additionally, they are expressed on B-lineage cells involved in antibody-mediated autoimmune diseases. BAFF ligand interactions are lower affinity than scFv interactions, potentially reducing T-cell exhaustion. The novel *TcBuster* transposon system is used to improve manufacturing time, efficiency, cost, and safety. **Methods:** Patients with refractory B cell NHL are treated in this study (NCT05312801). Autologous LMY-920 CAR-T cells are manufactured, then patients receive 3 days of fludarabine (30 mg/m^2/d) and cyclophosphamide (500 mg/m^2/d) lymphodepletion. LMY-920 is administered intravenously in a 3+3 dose escalation design from 1-8 x 10^6 BAFF-CAR-T cells/kg. Response is assessed using the Lugano criteria. CAR-T expansion and biologic characteristics are assessed. **Results:** Five patients have been treated with 1-2 x 10^6 BAFF-CAR-T cells/kg in this study, 2 patients each with mantle cell lymphoma (MCL), diffuse large B cell lymphoma (DLBCL), and one with marginal zone lymphoma (MZL). Patients had received 2 – 6 prior lines of therapy and all were refractory. One patient experienced grade 1 CRS (fever), but no ICANS was reported. All patients experienced grade 3 or higher hematologic toxicity that recovered prior to day 28, and grade 1-2 fatigue. There have been no dose limiting toxicities and dose escalation continues. Responses included 2 complete responses (CR) (DLBCL), a partial response (MZL), a mixed response (MCL) and one stable disease (MCL). Of note, one of the DLBCL patients in CR had received prior axicabtagene ciloleucel (anti-CD19) CAR-T cells as well as anti-CD20 bispecific antibodies, with lymphoma cells resulting in CD19 and CD20 antigen loss. **Conclusions:** The successful use of a novel transposon-engineered BAFF ligand-based CAR-T cell product demonstrates the potential of a new direction in CAR-T cell development. Safety and efficacy were seen, including patients with prior CAR-T failure and epitope loss, as hypothesized. This product is also being evaluated in patients with CLL, MM and systemic lupus erythematosus. Clinical trial information: NCT05312801. Research Sponsor: Luminary Therapeutics.

2564 **Poster Session**

Depletion of T-regulatory cells by denileukin diftitox-cxdl (E7777) in combination with pembrolizumab in relapsed/refractory (r/r) gynecologic malignancies: Phase 1 study results. First Author: Haider Mahdi, Magee-Womens' Hospital of UPMC, Pittsburgh, PA

Background: Denileukin diftitox-cxdl (E7777) is an FDA-approved direct cytotoxic agent that depletes T-regulatory cells by targeting the IL-2 receptor. Pre-clinical studies have demonstrated synergistic activity between the immunomodulator E7777 and PD-1 immune checkpoint inhibitor (ICI). Here, we report positive results from a phase I study of E7777 + pembrolizumab (P) in r/r gynecological (GYN) malignancies. **Methods:** Phase I dose-escalation trial of E7777 given at 4 IV dose levels (DL): 3, 6, 9, and 12 mg/kg on days 1-3, combined with P (IV 200 mg, day 1) in a 21-day cycle x8, followed by maintenance P until progression. Dose-limiting toxicities (DLTs) were assessed during cycle 1 according to CTCAE v5 criteria. Responses were measured using the RECIST 1.1 criteria. Blood samples were collected for translational studies. **Results:** Pt demographics included: median age 64y (43, 88); race, 88% white; histology 40% endometrial, 36% ovarian. Of the 24/25 pts evaluable for DLTs, only 1 case of reversible capillary leak syndrome (CLS) was seen at DL4. Anemia, fatigue, chills, and hypoalbuminemia were the most common AEs. A comprehensive overview of AEs, SAEs, and immune-related adverse events (irAEs) will be presented at the annual meeting. Table 1 describes the 4 DLs and their responses in the 21 pts evaluable for efficacy. An ORR of 24% (5 PRs) was reported in this heavily pretreated patient population with a mDOR of 21.1m (4.2-35.0). E7777 + P responses were seen in patients who progressed on prior ICI therapy, and across different GYN histologies. The median Progression-free survival (mPFS) was 5.8 m (1.1 – 37), with 5 pts having a PFS of ≥20 months. The clinical benefit rate (CR; PR; SD ≥ 6 m) was demonstrated in 48% of pts (n=10), who achieved a mPFS = 17.4m (6.2 – 37); patients with documented PD had a mPFS = 2.1 m (1.1 – 4.7). **Conclusions:** The results from this Phase I study of two immunomodulatory agents in combination, E7777 + P, in patients with r/r GYN tumors was well tolerated and demonstrated promising efficacy. A max tolerated dose wasn't established. No new significant safety signals or irAEs were reported. ORR of 24 % was demonstrated. Responders achieved a mDOR of 21.1m (4.2 - 35.0) and a mPFS = 23 m (10.4 – 37.0). Thus, E7777 + P showed prolonged responses and clinical benefit in pts with r/r GYN malignancies and limited options. These results will inform a Phase II study. Clinical trial information: NCT05200559. Research Sponsor: Citius Oncology Inc.

Response- evaluable patients (RECIST v1.1)		DL1 (N=3)	DL2 (N=2)	DL3 (N=6)	DL4 (N=10)	Total (N=21)
Best response						
	CR	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	PR	1 (33.3%)	0 (0%)	1 (16.7%)	3 (30.0%)	5 (23.8%)
	SD	1 (33.3%)	1 (50.0%)	2 (33.3%)	2 (20.0%)	6 (28.6%)
	PD	1 (33.3%)	1 (50.0%)	3 (50.0%)	5 (50.0%)	10 (47.6%)
CBR w/ Durable SD						
	(CR/PR/SD≥ 6m)	2 (66.7%)	1 (50.0%)	2 (33.3%)	5 (50.0%)	10 (47.6%)
	PD	1 (33.3%)	1 (50.0%)	4 (66.7%)	5 (50.0%)	11 (52.4%)

2565 **Poster Session**

Transposon-engineered hypoxia-inducible T cells for treatment of solid tumors. First Author: Yannick Schreiber, Northwestern University, Evanston, IL

Background: Engineered cell therapies expressing a chimeric antigen receptor (CAR) in human T cells have demonstrated significant promise for the treatment of hematological malignancies. However, translating CAR T cell therapies to solid tumors remains challenging due to two limitations: (1) specificity, as few antigens are truly unique to solid tumors, leading to off-target toxicities; and (2) suppression, as solid tumors establish immunosuppressive microenvironments that limit T cell survival and cytotoxicity. To address these challenges and improve the safety and potency of solid tumor cell therapies, we engineered cells with synthetic circuits designed to amplify hypoxia-induced signaling through feedback and synthetic transcriptional control, enabling augmented and tunable responses within both modestly and profoundly hypoxic environments. **Methods:** We evaluated circuit architectures in HEK293FT cells in which the HBS promoter drove either native HIF transcription factors or synthetic transcription factors and promoters controlling a fluorescent reporter. Circuits were stably integrated using PiggyBac transposon vectors, and cells were cultured under normoxic (21% O_2), modestly hypoxic (5% O_2), and profoundly hypoxic (1% O_2) conditions. Fluorescent reporter expression was quantified by flow cytometry over three days, and candidate circuits exhibiting high-output, low-background expression under hypoxia were identified. These candidate circuits were subsequently introduced into primary human T cells using transposon vectors. CAR expression in engineered T cells was measured by flow cytometry after culture for three days in modest or profound hypoxia, and cytotoxic activity was assessed in co-culture assays with BT-474 breast cancer and SKOV3 ovarian cancer cells. **Results:** We identified novel circuit architectures that produced rapid induction with minimal background under hypoxia and defined design rules governing transgene amplification. Circuit topologies incorporating synthetic transcription factor–mediated feedback exhibited markedly amplified expression relative to native HIF-based circuits. CAR-expressing T cells demonstrated cytotoxic activity compared with unmodified T cells in co-culture assays. **Conclusions:** We present a therapeutic platform that enables hypoxia-dependent sensing and high-output control of therapeutic gene expression within solid tumor microenvironments. This approach has the potential to improve the safety and efficacy of engineered cell therapies for solid tumors and to provide mechanistic insights that inform the development of hypoxia-responsive cell therapies. Research Sponsor: None.

2566 **Poster Session**

Targeting MAN1A1 to address immune checkpoint inhibitors resistance: A novel mechanism of vascular-endothelial reprogramming in NSCLC. First Author: Ai Gao, Tianjin Medical University General Hospital, Tianjin, China

Background: Despite the efficacy of immune checkpoint inhibitors (ICIs) in NSCLC, resistance remains a major hurdle. The role of non-immune components, particularly vascular endothelial cells (VECs), is poorly understood. We aimed to identify key drivers of ICI resistance by focusing on VEC-mediated remodeling of the tumor microenvironment (TME). **Methods:** We integrated transcriptomic data from public cohorts of ICI-treated and treatment-naïve NSCLC patients (GSE225620), proteomic profiling from in-house whole blood samples, and peripheral blood lymphocyte subset analysis from NSCLC patients and healthy controls. Differential expression analysis and machine learning (LASSO, SVM-RFE) were employed to identify key resistance-associated genes, including MAN1A1. Functional validation was performed using shRNA-mediated MAN1A1 knockdown in A549 and H1299 NSCLC cell lines, with apoptosis measured by flow cytometry. Single-cell RNA-seq data (GSE207422) from pre- and post-treatment NSCLC tumors were analyzed using Seurat for cell annotation. Cell-cell communication (CellChat) and pathway activity (AUCell) analyses were used to investigate VEC-immune cell interactions and their association with treatment response. Statistical analyses included Kaplan-Meier survival, Cox regression, and ROC curves to assess the prognostic and predictive value of MAN1A1. **Results:** Multi-omics analysis identified MAN1A1 as a key candidate associated with ICI resistance. Elevated MAN1A1 expression predicted inferior clinical outcomes, including shorter mPFS (3.2 vs. 8.5 months; P=0.019) in our cohort and reduced OS (47.4 vs. 65.1 months; HR=0.95, P=0.017) in the TCGA dataset. MAN1A1 expression effectively distinguished ICI non-responders (AUC=0.784). MAN1A1 knockdown significantly induced apoptosis in NSCLC cell lines (A549, P=0.00022; H1299, P=0.0004). Increased peripheral B-cell counts post-chemotherapy correlated with treatment response, and MAN1A1 protein levels inversely associated with B-cell levels (r=-0.38, P$<$0.05). Single-cell RNA-seq analysis revealed VECs as the primary expressors and communication hubs of MAN1A1. In non-responders, MAN1A1-high VECs were reprogrammed to drive a pro-inflammatory feedback loop with neutrophils via ANXA1-FPR1/NAMPT-integrin signaling axes. In contrast, VECs from responders exhibited a shift towards T-cell-recruiting LGALS9-CD45 signaling. **Conclusions:** Our study identifies MAN1A1 as a novel driver of ICI resistance in NSCLC, mediating vascular-endothelial reprogramming that fosters an immunosuppressive TME characterized by pro-tumor neutrophil recruitment and impaired T- and B-cell immunity via the ANXA1-NAMPT axes. Targeting MAN1A1 represents a promising therapeutic strategy to overcome ICI resistance, providing a strong rationale for future translational development. Research Sponsor: None.

2567 **Poster Session**

Circulating extracellular vesicles carrying PD-1, PD-L1, and CTLA-4 to inform resistance to immunotherapy in HCC. First Author: Joao Gorgulho, Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

Background: First-line immune checkpoint inhibitor (ICI) therapy has contributed to improved outcomes in hepatocellular carcinoma (HCC). However, only around 30% of patients respond, highlighting the need for biomarker driven patient selection. Considering the lack of tissue acquirement in HCC in clinical routine, liquid biopsy holds great promise. In this study, we aimed at profiling immune checkpoints (IC) on circulating extracellular vesicles (EVs) as potential liquid biopsy-based biomarkers for prediction of treatment response. **Methods:** Three distinct cohorts were analyzed in this study: (1) *HCC Explorer Cohort* (n=40), testing the presence of membrane-bound ICs on EVs; (2) *early-stage HCC Cohort* (n=37 with paired blood and tissue), assessing the interplay between EV and tissue ICs alongside clinicopathological parameters and (3) *Treatment Cohort* (n=161 with 548 sequential blood samples), comprising a training (n=79,n=402 sequential samples) and a validation group (n=82, n=146 sequential samples), to identify predictors of immunotherapy response through IC profiling of circulating EVs via multiplex immunoassay. **Results:** PD-1, PD-L1 and CTLA-4 were enriched in EVs compared to EV-depleted serum. Baseline and early dynamics in EV-IC levels significantly discriminated between responders and non-responders in the training and validation cohort, while simultaneously predicting PFS and OS. In addition, dynamic changes of EV-IC levels during therapy in patients with initial response predicted acquired therapeutic resistance, approximately 36-42 weeks before progression was traceable on imaging. High serum EV-IC levels correlated with "cold" tumor features on paired tissue samples and single-EV profiling revealed various cells of origin of our EV-IC, e.g., PD-L1+ EV mainly derived from hepatocyte/HCC cells and antigen presenting cells, and PD-1+ EV mainly from T-cells and macrophages, as expected. **Conclusions:** EVs carrying PD-1, PD-L1 and CTLA-4 represent readily quantifiable, non-invasive biomarkers to predict response and survival in advanced HCC patients undergoing ICI therapy and serve to identify biological ICI resistance much earlier than current standards with imaging. Research Sponsor: None.

Dataset on diverse clinical endpoints in training and validation cohorts.

Biomarker	Cohort	Objective Response p-value	mPFS High vs Low (months)	mOS High vs Low (months)
EV-PD-L1	Training	0.022	2.8 vs 10.8 (p$<$0.001)	13.7 vs 25.7 (p=0.021)
	Validation	$<$0.001	3.1 vs 5.8 (p=0.008)	10.4 vs 12.5 (p=0.97)
EV-PD-1	Training	$<$0.001	2.9 vs 15.9 (p$<$0.001)	6.4 vs 25.7 (p=0.002)
	Validation	$<$0.001	2.9 vs 8.4 (p=0.001)	7.3 vs 12.7 (p=0.056)
EV-CTLA-4	Training	$<$0.001	3.3 vs 16.1 (p$<$0.001)	20.2 vs 21.9 (p=0.081)
	Validation	$<$0.001	2.9 vs 9.0 (p$<$0.001)	8.8 vs 16.3 (p=0.003)

High vs low -> based on ideal cut-off.
NR = not reached.

2568 **Poster Session**

Baseline peripheral blood activated-to-total CD8$^+$ central memory T cell ratio to identify melanoma patients at high risk for severe toxicity but limited clinical benefit. First Author: Magdalena Kovacsovics, Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT

Background: Immune-related adverse events (irAEs) represent a major clinical challenge that limits the usage of immune checkpoint blockade (ICB) for cancer therapy. The occurrence of irAEs often correlates with improved therapeutic response to ICB therapy, creating a therapeutic dilemma. Many known irAEs predictors correlate with treatment efficacy, further complicating clinical decision-making. Biomarkers that decouple severe irAEs risk from therapeutic benefit are thus urgently needed to guide clinical decision-making. **Methods:** We performed comprehensive peripheral blood immune profiling in two HCI (Huntsman Cancer Institute) clinical cohorts with 201 melanoma patients treated with ICB, analyzing 488-626 immune cell subsets and 1,463-2,926 plasma proteins at two timepoints: pretreatment and 3-6 weeks on therapy. Activated CD8+ T central memory (CD8Tcm) cells were defined by the expression of CD38, HLA-DR, or Ki67. Associations with severe irAEs, survival and treatment outcomes were evaluated across the largest test cohort composed of nine independent, multi-institutional clinical cohorts, two HCI cohorts, five Swiss cohorts, and two publicly available datasets. **Results:** Elevated pretreatment activated-to-total CD8+Tcm ratio robustly predicts severe irAEs. Patients with high versus low activated-to-total CD8+Tcm ratio showed two-fold or higher odds of developing severe irAEs across nine independent melanoma cohorts. Remarkably, this immune signature is associated with worse patient survival following ICB. These results suggest that there is a dedicated toxicity predictor in the peripheral blood. Incorporation of pretreatment plasma CXCL9 levels into a machine-learning regression model further improved irAEs predictive performance (mean AUC=0.78 across four independent cohorts). These baseline biomarkers outperformed previously reported irAEs predictors. **Conclusions:** The pretreatment activated-to-total CD8+Tcm ratio, alone or in combination with plasma CXCL9, identifies melanoma patients at high risk for severe irAEs who are not likely to respond to ICB treatment. This first of blood-based biomarker was tested and validated on many independent patients' cohorts and will allow to select patients based on the risk stratification prior to treatment initiation. Research Sponsor: None.

2569 **Poster Session**

Impact of eftilagimod alfa, an APC activator via MHC class II, on lymphocyte activation and survival outcomes in metastatic cancer patients. First Author: Martin David Forster, UCL Cancer Institute / University College London Hospitals NHS Foundation, London, United Kingdom

Background: Immune activation is important for survival in cancer. Eftilagimod alfa (E), an antigen-presenting cell (APC) activator, binds to a subset of MHC class II molecules on APCs to mediate lymphocyte, e.g. T cell (CD4/CD8), recruitment/activation. Clinical studies of E in combination with a PD-1 antagonist (P) or chemotherapy (C) have shown promising results in phase 2 studies, and E is currently investigated in a phase 3 study in combination with P and C in first-line NSCLC (NCT06726265). We present cumulative correlation studies of immune activation in blood after administration of E with clinical efficacy in late-stage cancer patients (pts). **Methods:** Five (5) studies with 569 pts were evaluated. 30 mg E in combination with either P (pembrolizumab IV at 200 mg q3w or 400 mg q6w or 2 mg/kg q3w) or C (paclitaxel 80 mg/m^2 day 1, 8, 15, q4w) was administered SC biweekly for 6 months (mo), then every 2-4 weeks for 6-18 mo in pts with late-stage metastatic NSCLC, HNSCC, melanoma, or breast cancer. Absolute lymphocyte count (ALC) was taken before dosing (day 1 per cycle). ALC response was pre-defined as a change $\geq$0.2 x 10^9/L in $\leq$3 mo on study. Samples for gene expression profile (GEP) were taken pre-dose / 3 mo in a subset (N=111). IFN-g and CXCL10 were assessed pre-dose / after 1st E admin in a subset (N=79). Clinical efficacy was assessed by iRECIST and survival. **Results:** Treatment with E led to a rapid (3 mo) and sustained (~12 mo) stat. sign. (p=0.03) ALC gain versus control arm. 54.4% of all pts treated with E were ALC responders (53.6% for E+P; 55.1% for E+C). In ALC responders with E, overall survival (OS) was significantly improved (see Table 1) compared to non ALC responders. Effects were observed irrespective of the combination partner, P or C, with a median increase of 6.8 or 5.2 mo, respectively. In pts treated with P or C alone (control), 40.4% were ALC responders but with no sign. median OS gain. Clinical responders (iPR or iCR as BOR) exhibited consistent upregulation of immune pathways associated with T-cell functions, NK cell functions and cytotoxicity during treatment in GEP analysis. These functions were not upregulated in non-responders. IFN-g and CXCL10 concentrations increased quickly (~8h) and significantly post-first E dosing compared to baseline and levels remained elevated until next E dosing. This effect with E was consistent with P or C. **Conclusions:** E leads to immediate and sustained ALC increase and TH1 type reaction, which is associated with clinical efficacy in combination with P or C. Research Sponsor: None.

Treatment	Effects	Results
E (N=408)	ALC Responder with E	54.4% (N=222/408)
	Impact on survival: ALC responder vs. ALC non-responder	Median OS+ 7.7 mo(23.4 vs.15.7 mo) HR=0.69; p=0.002
Control arm (N=161)	ALC Responder in control arm	40.4% (N= 65/161)
	Impact on survival: ALC responder vs. ALC non-responder	Median OS+2.9 mo(20.4 vs. 17.4 mo) HR=0.98; p=0.93

2570 Poster Session

Effects of a multimodal TCR/BCR repertoire foundation model on blood RNA-seq–based prediction of severe adverse event risk and rheumatoid arthritis. First Author: Anatoly Bobe, BostonGene Corporation, Waltham, MA

Background: Severe immune-related adverse events (irAEs) limit the use of immune checkpoint inhibitors (ICIs). Clinically, irAEs can resemble autoimmune diseases such as rheumatoid arthritis (RA), suggesting shared dysregulation of adaptive immune receptor repertoires (T-cell receptor [TCR] and B-cell receptor [BCR]). We developed a TCR/BCR foundation model to predict severe irAE risk prior to ICI treatment and to detect RA from peripheral blood. **Methods:** Peripheral blood RNA sequencing (RNA-seq) from cancer patients prior to ICI therapy, healthy donors, and RA patients was analyzed across six cohorts (Table 1). Severe irAEs were defined as grade $\geq$3. Gene expression quantification and signature scores were computed using kallisto and ssGSEA. Adaptive immune receptor repertoire (AIRR) features for TCR and BCR were derived from blood RNA-seq using an in-house pipeline (pyigmap). We trained neural network models to (i) estimate severe irAE risk in ICI-treated cancer patients and (ii) distinguish RA from healthy donors, using TCR/BCR embedding features alone or combined with gene signature scores. Performance was evaluated across multiple datasets to assess discrimination and cross-cohort robustness. **Results:** The model combining TCR/BCR embedding features with gene signature scores achieved improved discrimination for severe irAE risk prediction (AUC 0.78; $p=1\times10^{-5}$) and RA detection (AUC 0.70; $p=5\times10^{-14}$). This outperformed models based on gene signatures alone (irAE AUC 0.67; $p=8\times10^{-3}$; RA AUC 0.66; $p=4\times10^{-9}$), TCR/BCR diversity alone (irAE AUC 0.66; $p=2\times10^{-2}$; RA AUC 0.61; $p=6\times10^{-5}$), or signatures plus diversity (irAE AUC 0.70; $p=2\times10^{-3}$; RA AUC 0.69; $p=9\times10^{-13}$). Embedding-based representations were more robust to technical variation than conventional diversity metrics: batch-effect decomposition showed higher biological variability (0.012 vs 0.002) and lower technical variability (0.460 vs 0.861) for embeddings versus diversity features, consistent with improved cross-cohort generalization. **Conclusions:** A TCR/BCR foundation model integrated with gene signatures improves pre-treatment prediction of severe irAE risk and detection of autoimmune disease from peripheral blood RNA-seq. These repertoire-informed representations capture clinically relevant clonotype biology and support minimally invasive risk stratification and monitoring for patients receiving ICIs. Research Sponsor: None.

Cohort description.

Cohort	Source	N	Severe irAE	No severe irAE
#1 (irAE Train Set 1)	Internal	726	48	678
#1 (irAE Test Set 1)	Internal	187	12	175
#2 (irAE Test Set 2)	Internal	47	10	37

Cohort	Source	N	Healthy	RA
#3 (RA Train Set 1 / Validation Set)	Open source	211	97	114
#4 (RA Test Set 1)	Open source	101	50	51
#5 (RA Test Set 2)	Open source	24	12	12
#6 (RA Test Set 3)	Open source	140	20	120

2571 Poster Session

Exploratory biomarker analysis of ociperlimab (OCI) plus tislelizumab (TIS) in patients (pts) with PD-L1–positive non–small cell lung cancer (NSCLC) in AdvanTIG-105. First Author: Yan Yu, Harbin Medical Cancer Hospital, Harbin, Heilongjiang, China

Background: OCI (anti-TIGIT) plus TIS (anti-PD-1) may enhance antitumor immune responses in advanced solid tumors. We present a retrospective biomarker analysis of pts in AdvanTIG-105 (NCT04047862), a phase 1/1b open-label study of OCI plus TIS for treatment-naïve metastatic non-squamous (NSQ) and squamous (SQ) PD-L1-positive (TC $\geq$1%) NSCLC. **Methods:** Pts in cohort 3 (n=46) were treated with 900 mg OCI plus 200 mg TIS. Pts in cohort 10 (n=68) were treated with 450 mg (Arm A), 900 mg (Arm B), or 1800 mg (Arm C) OCI plus 200 mg TIS. Baseline tumor tissue was used to measure PD-L1 and TIGIT expression (SP263 and SP410 IHC assays). Gene expression profiling (GEP) was performed using TrueSeq RNA Access (Illumina); gene signature scores were evaluated with ssGSEA. Progression-free survival (PFS) hazard ratio (HR) was calculated by Cox proportional hazards regression. **Results:** At Aug 2024 data cutoff, median follow-up was 19.7 months (range: 0.7-41.6 mo) for cohort 3 and 9.8 mo (range: 0.3-21.4 mo) for cohort 10. Baseline characteristics, overall response rate (ORR), and PFS were comparable across cohorts and between biomarker-evaluable and intent-to-treat (ITT) pts. PD-L1 $\geq$25% vs $<$25% and TIGIT $\geq$5% vs $<$5% subgroups were associated with a trend toward higher ORR and longer PFS, with greater increment in pts with NSQ- vs SQ-NSCLC (Table). PD-L1/TIGIT double high subgroup showed further enriched clinical efficacy in NSCLC (Table). Anti-TIGIT mechanism of action-related GEP signatures (NK cells, Treg, macrophages) were associated with a trend toward longer PFS primarily in pts with NSQ-NSCLC. **Conclusions:** Pts with NSCLC with PD-L1 $\geq$25%, TIGIT $\geq$5%, or PD-L1/TIGIT double high can achieve a trend toward longer PFS and higher ORR than PD-L1 low or TIGIT low subgroups when treated with OCI plus TIS. Longer PFS in PD-L1 $\geq$25% or TIGIT $\geq$5% subgroups in NSQ- vs SQ-NSCLC may be associated with biological differences in histology. Confirmation of these results will require prospective evaluation of OCI plus TIS in randomized studies. Clinical trial information: NCT04047862. Research Sponsor: BeOne Medicines Ltd.

	Subgroup	mPFS (mo)	ORR (%)
NSCLC	Evaluable pts (n=113)	5.5	34.5
	PD-L1 $\geq$25% vs $<$25%	6.9 vs 4.2	47 vs 22
	(n=57 vs 56)	HR 0.58 (95% CI: 0.37-0.9)	
	TIGIT $\geq$5% vs $<$5%	6.8 vs 4.1	45 vs 19
	(n=62 vs 48)	HR 0.64 (95% CI: 0.41-1)	
	PD-L1/TIGIT double positive vs other	8.3 vs 4.2	55 vs 22
	(n=38 vs 72)	HR 0.53 (95% CI: 0.33-0.86)	
NSQ-NSCLC	PD-L1 $\geq$25% vs $<$25%	8.3 vs 4.2	49 vs 19
	(n=35 vs 32)	HR 0.55 (95% CI: 0.32-0.98)	
	TIGIT $\geq$5% vs $<$5%	6.5 vs 4.1	50 vs 14
	(n=36 vs 29)	HR 0.53 (95% CI: 0.3-0.94)	
SQ-NSCLC	PD-L1 $\geq$25% vs $<$25%	5.5 vs 5.3	45 vs 25
	(n=22 vs 24)	HR 0.63 (95% CI: 0.35-1.29)	
	TIGIT $\geq$5% vs $<$5%	5.5 vs 5.5	38 vs 26
	(n=26 vs 19)	HR 0.93 (95% CI: 0.46-1.87)	

2572 Poster Session

Molecular progression defined by longitudinal ctDNA dynamics for prediction of outcomes in immune checkpoint inhibitor–treated solid tumors. First Author: Muhammad Anees, Allegheny Health Network Cancer Institute, Allegheny Health Network, Pittsburgh, PA

Background: Reliable early biomarkers of immune checkpoint inhibitor (ICI) resistance remain an unmet need due to delayed imaging and non-classical response kinetics. While ctDNA has shown promise, current methods often require tumor tissue or rely on static comparisons. We investigated whether longitudinal ctDNA dynamics measured using a tumor-naive, methylation-based assay could define molecular progression and predict outcomes in patients receiving ICIs. **Methods:** Patients with advanced solid tumors treated with ICI regimens were analyzed in a primary cohort (n=65) with serial plasma sampling. Tumor Methylation Scores (TMS) were generated using Northstar Response. Molecular progression based on ctDNA trajectory was assessed for associations with PFS and OS and compared with conventional landmark ctDNA approaches and RECIST v1.1. Independent validation was performed in a second cohort (n=72). **Results:** Molecular progression strongly stratified survival in the primary cohort (OS HR=4.9, $p<0.001$; PFS HR=5.3, p=0.0002) and demonstrated superior prognostic performance relative to RECIST. These results were independently validated (PFS HR=4.6, p=0.00004; OS HR=4.3, p=0.005). Notably, among RECIST-defined non-progressors at 6 months, molecular progression identified patients with markedly worse outcomes (PFS HR=6.7, p=0.002; OS HR=4.5, p=0.011). Molecular progression preceded radiographic and clinical progression by median lead times of 63.5 and 77 days, respectively. **Conclusions:** Longitudinal ctDNA dynamics measured using a tumor-naive methylation assay define molecular progression that robustly predicts survival and identifies early ICI resistance, including in RECIST-stable patients. This approach offers clinically meaningful lead time and supports integration of ctDNA dynamics into response assessment frameworks for immunotherapy. Research Sponsor: None.

2573 Poster Session

Molecular pathways of immune checkpoint inhibitor–induced hepatitis. First Author: Erika Bushatsky, Department of Medicine, Division of Oncology, Jewish General Hospital, Montreal, QC, Canada

Background: Immune checkpoint inhibitor (ICI) related hepatitis is a clinically significant immune-related adverse event (irAE) and a common cause of treatment interruption. It occurs in roughly 5 to 10 percent of patients receiving anti PD-(L)1 monotherapy and in up to one third of those treated with combination ICI therapy. Despite increasing clinical recognition, the molecular mechanisms and predictive factors underlying ICI hepatitis remain poorly defined. The Montreal Immune-Related Adverse Events (MIRAE)-led hepatitis project aims to characterize the immune cell populations and underlying transcriptional programs associated with ICI-hepatitis pathogenesis. **Methods:** This translational study is conducted within the MIRAE biobank, a prospective multicenter cohort of ICI-treated patients with and without irAEs. The hepatitis cohort includes patients with longitudinal plasma samples collected at baseline, on treatment, and at irAE onset. Ongoing immune profiling efforts include plasma-based cytokine and chemokine analysis, high-throughput plasma proteomics, and single cell RNA sequencing of PBMCs. Preliminary analysis focused on plasma proteomics. Five patients with high-grade ICI-hepatitis and five ICI-treated controls without irAEs were selected and matched by age, sex, and primary tumor. Plasma samples were analyzed using the SomaScan 11K assay to identify differentially expressed proteins and enriched immune pathways. **Results:** ICI-related hepatitis was clinically severe, requiring systemic corticosteroids in all cases and additional immunosuppressive therapies in most patients. ICI-hepatitis cases showed significantly higher plasma levels of liver injury markers, including ALT and AST, compared with matched controls. Widespread alterations were observed in the circulating proteome, with strong upregulation of liver-enriched proteins and inflammatory mediators. Gene set enrichment analyses revealed enrichment of liver-associated pathways including xenobiotic and bile acid metabolism, as well as IL-12 signaling, interferon-α and γ, neutrophil-associated pathways, and liver-resident macrophage signatures. Pathway analysis of single cell data revealed enhanced cytotoxic activity of CD8 T cells during ICI hepatitis, as exemplified by upregulation of the CTL and IL-6 pathways. **Conclusions:** ICI-hepatitis was associated with circulating immune signature characterized by liver injury markers, inflammatory mediators, and enrichment of innate immune pathways. These findings provide molecular insight into the immunopathogenesis of ICI hepatitis and inform future biomarker discovery, druggable pathways, and risk stratification. Research Sponsor: None.

2574 Poster Session

Association of neutrophil percentage-to-albumin ratio with progression-free survival and overall survival in cancer patients treated with PD-1/PD-L1 inhibitors. First Author: Wenhui Liu, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China

Background: The Neutrophil Percentage-to-Albumin Ratio (NPAR) reflects systemic inflammation and nutritional status. Its prognostic and predictive value in cancer patients treated with PD-1/PD-L1 inhibitors remains unclear. We investigated the association of the baseline of NPAR with PFS and OS in cancer patients who received PD-1/PD-L1 inhibitors. **Methods:** A retrospective cohort of 532 patients treated with PD-1/PD-L1 inhibitors at the Second Xiangya Hospital of Central South University between 2018 and 2024 was enrolled. Participants were divided into tertiles based on the baseline of NPAR. PFS and OS were assessed using Kaplan–Meier method and log-rank tests. Univariable and multivariable Cox proportional hazards models were employed to examine the association between NPAR and survival outcomes, with sequential adjustment for clinically relevant confounders. **Results:** The median PFS and OS of total patients was 21.3 months (IQR, 10.5–32.7) and 24.7 months (IQR, 16.9–41.5), respectively. Individuals with elevated NPAR experienced significantly worse PFS and OS than those with low NPAR and medium NPAR (PFS: $p < 0.05$; OS: $p < 0.0001$). Subgroup analyses showed the consistent results in the lung cancer patients (PFS: $p < 0.05$; OS: $p < 0.01$). In univariate COX regression analyses, each one-unit increment in NPAR corresponded to hazard ratios (HRs) of 1.032 (95% CI, 1.004–1.062; $p < 0.05$) for PFS and 1.069 (95% CI, 1.035–1.104; $p < 0.001$) for OS. Multivariate Cox regression analysis identified that a high NPAR level remained independently associated with inferior survival outcomes after adjusting for confounders. Compared with the low NPAR group, the high NPAR group showed worse PFS (HR, 1.38; 95% CI, 1.03-1.84; $p < 0.05$) and OS (HR, 1.95; 95% CI, 1.36-2.79; $p < 0.001$) in the fully adjusted model (Model 4). **Conclusions:** Elevated NPAR can independently predict worse PFS and OS in cancer patients receiving PD-1/PD-L1 inhibitors and represents a simple, low-cost biomarker for clinical risk stratification. Research Sponsor: None.

Association between NPAR and PFS/OS of cancer patients.

	Model 1 HR (95%CI)		p-value		Model 2 HR (95%CI)		p-value		Model 3 HR (95%CI)		p-value		Model 4 HR (95%CI)		p-value	
	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS	PFS	OS
NPAR Low group	ref	ref			ref	ref			ref	ref			ref	ref		
High group	1.40(1.06-1.85)	2.05(1.45-2.90)	0.018	<0.001	1.42 (1.07-1.89)	1.98 (1.40-2.82)	0.015	<0.001	1.40 (1.05-1.87)	1.99 (1.40-2.83)	0.023	<0.001	1.38 (1.03-1.84)	1.95 (1.36-2.79)	0.032	<0.001

Model 1: unadjusted. Model 2: adjusted for sex, diabetes, hyperlipidemia, cardiovascular disease, cerebrovascular disease, pulmonary tuberculosis and viral hepatitis type B. Model 3: adjusted for model 2 + single ICIs, chemotherapy, radiotherapy. Model 4: adjusted for model 3 + NSAIDS, PPI, β-blocker, hormone, whiteboard-raising drugs, anticoagulant and antithrombotic drugs.

2575 Poster Session

Plasma-TMB (pTMB) and circulating tumor fraction (ctF) dynamics as biomarkers of benefit from the addition of atezolizumab to first-line FOLFOXIRI/bevacizumab in metastatic colorectal cancer (mCRC): A translational analysis of the AtezoTRIBE study. First Author: Veronica Conca, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: TMB-high pMMR mCRC patients (pts) do not seem to derive benefit from immune checkpoint inhibitors (ICIs). In the CO.26 trial, pMMR/MSS mCRC pts with high baseline pTMB had better outcome with ICIs than those with low pTMB. Moreover, in the AtezoTRIBE study, tissue TMB was identified as a promising biomarker able to identify a subgroup with potential benefit from the addition of atezolizumab to first-line FOLFOXIRI/bev. In that trial, the addition of atezolizumab did not improve ORR, and PFS curves separated only after approximately 6 months. Given this delayed treatment effect observed, we hypothesized that dynamic liquid biopsy biomarkers could identify early molecular changes associated with subsequent immune-sensitivity. Here we evaluated the prognostic and predictive role of both pTMB and on-treatment ctF dynamics in the AtezoTRIBE trial. **Methods:** Pts with untreated mCRC enrolled in the AtezoTRIBE trial (NCT03721653) and with available plasma at baseline (T0) and at the end of induction (T1) were included. Samples were analyzed using the Tempus xF assay, a 105-gene cell-free liquid biopsy panel, to determine ctF by Tempus xFv2 cTF algorithm, and pTMB. pTMB was assessed as a dichotomous variable (high: ≥26 mut/Mb). ctF dynamics between T0 and T1 identified molecular responders (MRs), i.e. pts with the top 30% relative ctF reduction including clearance below quantification/detection limits at T1, and non responders (nMRs). Cox models stratified by liver metastases, and including treatment-by-biomarker interaction when appropriate, were used for PFS analyses (likelihood ratio test, p<0.15). **Results:** pTMB was evaluable in 123/155 (79%) T0 samples, and 20 (16%) were classified as pTMB-high. Baseline characteristics were balanced between pTMB-high and pTMB-low groups. High pTMB was associated with longer PFS (HR: 0.69 [90%CI 0.43-1.10], p=0.095), while no interaction between pTMB and treatment arm was observed (p_{int}=0.871). Among 89 pts with evaluable ctF at T0 and T1, 63 (71%) were MRs. Baseline clinical and molecular characteristics did not differ in the MR and nMR groups. A significant interaction (p=0.132) between ctF dynamics and MR was reported, with nMRs achieving higher benefit from the addition of atezolizumab to FOLFOXIRI/bev (HR: 0.33 [90%CI: 0.16-0.69]) than MRs (HR: 0.76 [90%CI: 0.03- 3.95). A sensitivity analysis including 6 additional pts with undetectable ctF both at T0 and T1 provided consistent findings (p_{int}=0.108). **Conclusions:** The addition of ICI to first-line chemotherapy may be more efficacious among mCRC pts with lower molecular response to the upfront induction regimen, as measured by ctF dynamics. If independently validated, ctF molecular response biomarker might be useful for future trials' design. Research Sponsor: Tempus; GONO Foundation.

2576 Poster Session

A phase 2, open-label, multi-center, single-arm study of atezolizumab and bevacizumab in the treatment of second line and beyond, recurrent/metastatic endometrial cancer. First Author: Katherine Cynthia Fuh, University of California, San Francisco, San Francisco, CA

Background: The treatment paradigm for advanced/recurrent endometrial cancer (EC) is undergoing rapid transformation. Currently, use of immune checkpoint inhibitors (ICI) is standard of care for deficient mismatch repair (dMMR) tumors in the front line setting and ICI "can" be used in proficient MMR (pMMR). The purpose for this study is to evaluate an alternative ICI and anti-angiogenic regimen, atezolizumab plus bevacizumab in pts with recurrent EC with no prior ICI use and to identify blood-based correlates of non-responders early in treatment. **Methods:** This multicenter, single-arm, open label phase 2 trial (NCT03526432) enrolled pts with recurrent EC who had relapsed following platinum based chemotherapy. No prior ICI was allowed. Treatment consisted of atezolizumab 1,200 mg plus bevacizumab 15 mg/kg iv on day 1 every 21 days until progression or toxicity. The primary endpoint was objective response rate (ORR). Peripheral whole blood was collected at baseline and after 2 cycles of therapy, and high-dimensional immune profiling was performed. **Results:** Sixty-five pts were enrolled and received at least one dose of trial treatment. Fifty-six pts were response-evaluable (45 with pMMR tumors, 7 with dMMR tumors and 4 with unknown MMR status). Median age was 65 years. All pts had received at least one prior chemotherapy and 22 pts (39.3%) received prior radiation therapy. The ORR was 33.9%; 95% CI, 21.8 to 47.8; (19/56 patients), which include 5 complete and 14 partial responses; median duration of response (DOR) was 16 months. In addition, 63% of pts survived progression-free for at least 6 months. The median PFS was 8.8 months (95% CI, 5.5 to 12.0). The median OS was 41.55 months (95% CI, 27.0 – 57.5). The most common grade 3 or 4 adverse events were hypertension (21.5%), fatigue (7.7%) and diarrhea (7.7%). In peripheral blood analysis, non-responders demonstrated expansion of a suppressive myeloid population characterized by PD-L1^{+}CD16+ monocytes. There was an increase of ICOS^{+} Tregs consistent with an immunosuppressive phenotype. Within the effector T cell compartment, central memory CD8^{+} T cells expressing Fas and CD27 expanded in non-responders. **Conclusions:** The combination of atezolizumab and bevacizumab in patients with recurrent EC and post cytotoxic chemotherapy has efficacy in both dMMR and pMMR populations and a toxicity profile that appears more favorable than other treatments. This data suggests atezolizumab and bevacizumab could be considered as an alternative regimen in the recurrent, metastatic setting among pts who are ICI naïve and for whom there are concerns regarding the adverse events of treatment. Peripheral whole blood analysis of non-responders correlated with immune angiogenic escape mechanism with higher levels of ICOS+Tregs, Fas+CD27+ CD8T cells, and PDL1+ CD16+ monocytes. Clinical trial information: NCT3526432. Research Sponsor: Genentech.

2577 Poster Session

Analysis of circulating small extracellular vesicle-associated miRNA in head and neck squamous cell carcinoma (HNSCC): Biomarker discovery in pre-operative neoadjuvant nivolumab. First Author: Joseph Patrick Flemming, Department of Medicine, Jefferson Abington Hospital, Abington, PA

Background: Standard treatment options for HNSCC include chemotherapy, radiation, surgery, and immunotherapy. Immune Checkpoint Inhibitors (ICI) are safe and improve survival in platinum-refractory and metastatic HNSCCs. Further studies are needed to efficiently stratify patients who may benefit from ICIs. MYC-V1 is a family of oncogenes, induced by MYC signaling, that is negatively correlated with response to ICI in HPV+ HNSCC. Non-invasive Biomarkers (NiBs) identifying patients with low MYC-V1 expression may aid in predicting response to ICIs. Small extracellular vesicles (sEVs) are membrane-bound mediators of intercell communication that are present in circulation, serving as a promising source of NiBs. The Let-7 family of tumor suppressors are negative regulators of the MYC-V1 gene family and exhibit low expression in HNSCC compared to healthy controls. Let-7 family members, such as Let-7d and Let-7c, may play a role in ICI responsiveness via PD-L1 and MYC mRNA degradation, respectively. Here, we analyze the miRNA profile of sEVs from patients enrolled in a randomized Phase I clinical trial undergoing Neoadjuvant Nivolumab therapy. (NCT03238365). **Methods:** Plasma was collected before and after treatment (N=24) with ICI. 12 patients were included and stratified based on HPV status (6 HPV-, 6 HPV+) and pathologic treatment response (pTR) (6 Responders [R], 6 Non-responders [NR]). pTR >20% of tumor surface area as graded by two pathologists was R; 0% was NR. sEVs were isolated via immunoprecipitation targeting tetraspanins CD63/9/81. miRNA was isolated and NGS was performed. Analysis was performed using Python and Biomni. Log2FC (FC) compared expression levels between groups and a False Discovery Rate (FDR) <.05 was significant. **Results:** 189 miRNAs were detected in HNSCC sEVs. Analysis comparing HPV+ R vs NR revealed 48 miRNAs with significantly different levels between these pretreatment groups. 47 were more abundant in R; 1 was less abundant. miRNAs found at higher levels in HPV+ R include the Let-7 family. Let-7d was most abundant (FC: 2.26, FDR 0.04), with a family (Let-7a,b,d,f,g,i) FC range of 1.63-2.26 (FDR 0.03-0.05). Following treatment with ICI, HPV+ patients had increased Let-7c levels (FC 4.71, FDR 0.02) compared to pretreatment. Analysis of HPV– R vs NR showed 0 miRNA that met statistical significance. **Conclusions:** Here, we show that ICI-responsive HPV+ HNSCC is associated with high levels of circulating, sEV-contained Let-7 family members and that Let-7c is increased in response to ICI in those same patients. We propose that a MYC-V1-suppresive, PD-L1-destabilizing mechanism may be present in patients with higher than average Let-7 expression, conferring sensitivity to ICI, and that sEV-associated Let-7 levels may serve as NiBs to identify these patients as favorable ICI candidates prior to treatment. Research Sponsor: U.S. National Institutes of Health.

2578 **Poster Session**

T-cell stem-like memory cells as a novel biomarker to identify patients with sustained disease control during treatment with PD-(L)1 immunotherapy. First Author: Victor Joo, CHUV, Lausanne, Switzerland

Background: Reliable, clinically easily testable biomarkers to monitor the benefit of treatment with immune checkpoint inhibitors (ICI) remain limited. We performed comprehensive analysis of markers defining differentiation and functional status of different populations of peripheral blood T-cell in order to identify biomarkers associates to treatment response in treated patients. **Methods:** Peripheral blood was analyzed from metastatic patients receiving PD-(L)1–based therapy: anti–PD-(L)1 monotherapy (n=102), combination therapies (n=35), or chemo-immunotherapy (n=14). Sampling time on therapy was heterogeneous, recorded, and included in sensitivity analyses. All patients provided informed consent under IRB approval. A variety of CD4 andCD8 cell populations (naive, stem-like memory [SCM], central memory [CM], effector memory [EM], EMRA/TEMRA). were analyzed using -standardized multiparameter flow cytometry. Pre-specified stem-like–to–effector balance ratios were computed within CD4 and CD8 (SCM/CM and SCM/EM; SCM/EMRA exploratory). Markers analysis included CD45RA, CCR7, CD95, TCF1/TCF7, TOX, TIGIT, and Ki-67). Clinical benefit was assessed by disease control rate (DCR=CR+PR+SD) versus progressive disease (PD). Biomarkers were analyzed using Mann–Whitney U tests and clustered using unsupervised 1D k-means. Time-to-event analyses used univariable Cox models for time to disease control loss (DCL), defined from ICI initiation to first PD (or discontinuation for progression). **Results:** Among 151 patients, DCR n=89 and PD n=62, disease control was characterized by a stem-like/early memory blood T-cell profile. DCR showed higher CD4 and CD8 naive and SCM frequencies ($p<0.05$), whereas PD showed enrichment in differentiated T cell populations including CD4 CM/EM and CD8 EM ($p\leq0.01$ to $p<0.0001$). Stem-like–to–effector cell ratios were higher in DCR for both CD4 and CD8 (SCM/CM $p<0.001$; SCM/EM $p<0.01$) and for CD4 SCM/EMRA ($p<0.05$). In total CD3 T cells, DCR had higher CD45RA ($p<0.001$), CCR7 ($p<0.05$), and TCF1/TCF7 ($p<0.05$), with lower CD95 ($p<0.05$) and reduced TIGIT ($p<0.01$), TOX ($p<0.05$), and Ki-67 ($p<0.05$). In Cox models for DCL (inverse-coded; HR>1 favorable), significant associations were observed across subsets, ratio, and marker features (HR range 1.7–4.8; all $p<0.05$), with the strongest effects for stem-like–to–effector cell ratios and differentiated subset metrics. Associations were observed across PD-(L)1–based regimens. **Conclusions:** Stem-like memory CD4 and CD8 T cells represent a new marker associated with efficacious response to ICI and DCR while a dominant effector/terminal differentiation profile to DCL and PD. These findings underscore the importance of immune monitoring to identify patients at risk of early loss of treatment benefit and disease progression and to guide treatment modifications. Research Sponsor: None.

2580 **Poster Session**

Real-world concordance of tumor mutational burden (TMB) between blood (circulating tumor DNA) and tissue, and its association with immunotherapy response. First Author: Kyle VanDommelen, Cleveland Clinic, Cleveland, OH

Background: Tissue-derived tumor mutation burden (tTMB) ≥10 mutations/Mb is a histology-agnostic predictive biomarker for the immune checkpoint inhibitor (ICI) pembrolizumab. It is unknown if circulating tumor DNA–derived TMB (bTMB) is also predictive and current ASCO guidelines recommend against using bTMB alone. Concordance between tTMB and bTMB is only moderate, with reported Pearson correlation coefficients between 0.54-0.70. In prior studies, bTMB was a median 2.4-fold greater than tTMB in matched samples. This study evaluated the correlation and predictive accuracy of immunotherapy response of bTMB vs. tTMB in solid tumors. **Methods:** 221 patients with solid tumors were included from the Cleveland Clinic genomics repository who had at least one tTMB and one bTMB result between July 1, 2021, and July 1, 2025. High TMB was defined as tTMB ≥10 mutations/Mb. For bTMB, thresholds of ≥10 and ≥16 mutations/Mb were evaluated, as prior studies suggest a bTMB threshold of 16 for Guardant 360 may be comparable to a tTMB of 10. Correlation between bTMB and tTMB was assessed using Pearson's correlation coefficient. Among patients treated with ICIs, treatment response and time to treatment failure (TTF) were analyzed using both bTMB thresholds and compared with tTMB. **Results:** Among the 221 patients included in the analysis, 80 received ICIs. Median bTMB was 2.3-fold higher than matched tTMB. A strong positive linear correlation was observed between bTMB and tTMB both among patients who received ICIs ($R^2 = 0.845$, $p < 0.001$) and across the full cohort of 221 patients ($R^2 = 0.818$, $p < 0.001$). High tTMB was associated with numerically longer TTF in those with both low bTMB (median 21.3 months) and high bTMB (median 15.2 months), as shown in Table 1. Those with high tTMB/low bTMB had numerically longer median TTF compared to those with low tTMB/high bTMB (21.3 vs. 7.0 months). Increasing the bTMB threshold from 10 to 16 was associated with improved median TTF from 3.5 to 7.0 months among patients with low tTMB. **Conclusions:** This study confirms that bTMB values are consistently higher than tTMB and demonstrates a strong positive correlation between the two measures. Raising the bTMB threshold appears to improve prediction of immunotherapy response in patients with low tTMB. However, tTMB continued to show evidence of predictive value for response to ICIs regardless of bTMB, although these subgroup analyses were limited by small sample sizes. Larger, disease-specific studies are needed to better define the independent clinical utility of bTMB. Research Sponsor: None.

Time to treatment failure in TMB-high vs. TMB-low patient pairs.

	bTMB -10=H Median TTF (months)		bTMB -16=H Median TTF (months)
tTMB-L, bTMB-L (n=35)	4.9	tTMB-L, bTMB-L (n=51)	3.9
tTMB-H, bTMB-L (n=3)	21.3	tTMB-H, bTMB-L (n=4)	21.3
tTMB-L, bTMB-H (n=32)	3.5	tTMB-L, bTMB-H (n=16)	7.0
tTMB-H, bTMB-H (n=10)	10.2	tTMB-H, bTMB-H(n=9)	15.2

2581 **Poster Session**

Functional binding of PD-1 ligands: Overcoming PD-L1 staining limitations to predict therapy response. First Author: Bar Kaufman, Ben-Gurion University of the Negev, Beer Sheva, Israel

Background: Immune-checkpoint blockade (ICB) targeting the PD-1/PD-L1 axis has improved outcomes across multiple malignancies, yet response prediction remains unreliable due to fundamental limitations of PD-L1 immunohistochemistry (IHC). As a static expression assay, PD-L1 IHC does not capture functional ligand engagement, does not account for PD-L2 contributions to PD-1 signaling, and is confounded by N-glycosylation that masks epitopes and distorts measurable abundance. These mechanistic gaps undermine biomarker accuracy and impede appropriate patient selection. To overcome these limitations, we established IcAR-PD1, a functional reporter system designed to quantify the true biological availability of PD-L1 and PD-L2 for therapeutic blockade by anti-PD-1/PD-L1 ICBs. **Methods:** We conducted a double-blinded retrospective study spanning multiple tumor types. IcAR-PD1 scores from patient-derived samples were correlated with clinical outcomes to anti-PD1 therapy and benchmarked against PD-L1 IHC, evaluating predictive accuracy, response probability, and duration-of-response. To define how PD-L1 N-glycosylation modulates inhibitory signaling and drug susceptibility, IcAR-PD1 was combined with a full four-site glycosylation mutation array and validated using primary $CD8^+$ T-cell cytotoxicity assays. **Results:** IcAR-PD1 demonstrated markedly superior predictive power compared with PD-L1 IHC, achieving AUCs of 0.87–0.92 versus 0.55–0.62. High IcAR-PD1 scores aligned with >90% response probability and >3-fold longer median duration-of-response ($p<0.01$). Incorporation of PD-L2 activity and direct measurement of functional ligand availability explained the improved performance across tumor types. Glycosylation analysis showed that fully glycosylated PD-L1 reduced blockade efficiency, with anti-PD1 treatments markedly more sensitive to glycan status than anti-PDL1. Loss of the N35 site diminished anti-PD1 efficacy by increasing release of functional soluble PD-L1, partially affecting anti-PDL1 activity. The non-glycosylated Nx4 variant displayed enhanced susceptibility to both therapies, with a disproportionately greater improvement for anti-PD1 blockade. **Conclusions:** IcAR-PD1 resolves the major limitations of PD-L1 IHC by quantifying functional ligand activity, incorporating PD-L2 contribution, and revealing glycosylation-driven resistance mechanisms. These findings support IcAR-PD1 as a precise, mechanism-based biomarker for selecting patients most likely to benefit from anti-PD1 therapy. Research Sponsor: None.

2582 **Poster Session**

Spatial immune profiling to identify GPNMB as a mediator of immune suppression that limits response to PD-1 blockade in TNBC. First Author: Anna-Maria Lazaratos, Rosalind & Morris Goodman Cancer Institute, McGill University, Montreal, QC, Canada

Background: Breast cancer (BC) is the leading cause of female cancer-related deaths. Triple-negative BC (TNBC), accounting for ~25% of BC-related deaths, carries the poorest prognosis due to limited targeted therapies and the significant, yet still modest overall, benefit achieved with immune checkpoint blockade (ICB). Identifying drivers of immune evasion is essential to expand patient benefit from ICB. Glycoprotein-NMB (GPNMB) is highly expressed in TNBC and associated with immune suppression, metastasis, and poor clinical outcomes. However, its role in shaping the TNBC immune landscape and contributing to ICB resistance remains unclear. We investigated the impact of tumor-derived GPNMB on the tumor immune microenvironment and whether its inhibition enhances ICB efficacy. **Methods:** Imaging mass cytometry, a high-dimensional spatial proteomics platform enabling simultaneous single-cell and spatial analysis of intact tissue, was used to map the immune landscape of GPNMB-proficient and -deficient EO771 tumors. Therapeutic relevance was evaluated by combining GPNMB loss with anti-PD-1 treatment. Associations between tumor GPNMB expression, immune infiltration, and clinical outcomes were evaluated in human TNBC tumors. **Results:** GPNMB loss in mammary tumor cells significantly impaired tumor growth in syngeneic, but not athymic (T cell-deficient) mice, suggesting a T cell-dependent mechanism. $GPNMB^{KO}$ tumors showed increased immune infiltration, notably $GZMB^+/PD\text{-}1^+CD8^+$ T cells, and enhanced formation of stimulatory $CD8^+$ T cell/$CD4^+$ T cell/$CD86^+$macrophage immune triads. GPNMB loss impaired tumor engraftment in an adoptive OT-1 T cell transfer model and significantly improved response to anti-PD-1 therapy in two independent TNBC models, reducing breast tumor growth and lung metastasis. Therapeutic benefit was accompanied by increased intratumoral T cell infiltration and functional reinvigoration, reflected by increased $GZMB^+CD8^+$ T cells. In human TNBC, high tumor GPNMB expression was associated with reduced intratumoral T cell infiltration and poorer clinical outcomes. $GPNMB^{high}$ tumors exhibited reduced infiltration of $CD8^+$, $GZMB^+CD8^+$, and $CD4^+$ T cells and were enriched in immune-desert and margin-restricted phenotypes. In contrast, $GPNMB^{low}$ tumors showed increased $CD8^+$ T cell/$CD4^+$ T cell/macrophage triads, indicating enhanced immune activation. Together, these data show that elevated GPNMB expression in human TNBC is associated with T cell exclusion, and an immune-excluded tumor architecture. **Conclusions:** Our findings identify tumor-derived GPNMB as a clinically relevant mediator of T cell exclusion and suppression in TNBC. Therapeutic targeting of GPNMB in combination with PD-1 blockade may enhance the efficacy of ICB and expand the subset of TNBC patients who derive meaningful clinical benefit, ultimately improving clinical outcomes. Research Sponsor: Canadian Institutes of Health Research (CIHR); 202211FBD.

2583 **Poster Session**

Age-associated genomic instability and inflammatory pathway activation: A pan-cancer multi-omics analysis of the TITANIA framework. First Author: Shugo Yajima, National Cancer Center Hospital East, Kashiwa, Japan

Background: Aging is associated with increased cancer incidence and altered tumor biology, yet molecular mechanisms underlying age-related differences remain poorly characterized at the multi-omics level. We hypothesized that elderly patients may exhibit coordinated increases in genomic instability and inflammatory pathway activation. **Methods:** We performed integrated multi-omics analysis comprising whole genome sequencing, RNA sequencing, and data-independent acquisition mass spectrometry-based proteomics on 153 treatment-naive patients across six cancer types (colorectal cancer n=52, gastric n=19, kidney n=32, non-small cell lung cancer n=27, ovarian n=19, liver n=4). The TITANIA study provided matched tumor and normal tissue specimens with standardized collection protocols (median cold ischemia time: 12 minutes). Patients were stratified by age ($\leq$60 years, n=40; $>$60 years, n=113). Inflammation scores were calculated using ssGSEA of six Hallmark inflammatory pathways. Tumor microenvironment subtypes were identified using xCell deconvolution followed by k-means clustering (k=3). **Results:** Tumor mutation burden (TMB) showed a significant positive correlation with age (Spearman ρ=0.334, P$<$0.001), with elderly patients demonstrating higher median TMB than younger patients (4.55 vs 2.84 mut/Mb, P$<$0.001). Inflammation scores showed positive correlations with age in tumor tissues at both RNA (ρ=0.223, P=0.01) and protein (ρ=0.233, P=0.005) levels. Normal tissue inflammation correlated with paired tumor TMB (RNA: ρ=0.283, P=0.027; Protein: ρ=0.387, P$<$0.001), raising the possibility that systemic inflammaging may be associated with tumor genomic instability. TME clustering identified three subtypes: Immune-Hot (n=14), Immune-Cold (n=92), and Vascular-Rich (n=30). Notably, all patients in the Immune-Hot cluster were elderly ($>$60 years). TMB positively correlated with B cells, neutrophils, and M1 macrophages, while negatively correlated with stromal score and endothelial cells. The EPITHELIAL_MESENCHYMAL_TRANSITION pathway showed potential as a prognostic marker at both omics levels (C-index: RNA 0.63, Protein 0.61), though further validation is warranted. **Conclusions:** This pan-cancer multi-omics analysis demonstrates age-dependent genomic instability coupled with inflammatory pathway activation in both tumor and normal tissues, consistent with the inflammaging hypothesis. The novel finding that normal tissue inflammation correlates with tumor TMB suggests systemic inflammaging may contribute to tumor evolution, with potential implications for age-adapted immunotherapy strategies. Research Sponsor: None.

2584 **Poster Session**

A new HLA genotyping algorithm to show accuracy and concordance between tumor and normal samples. First Author: Ariane Lozac'hmeur, Tempus AI, Inc., Chicago, IL

Background: HLA genotyping, specifically HLA-A*02:01 is an actionable marker in uveal melanoma for Tebentafusp, a bispecific gp100 peptide-HLA-directed CD3 T cell engager, with ongoing clinical trials investigating its use in HLA-A*02:01 positive cutaneous and mucosal melanoma. However, prior work has shown a discrepancy in this marker between blood and somatic tumor testing (Seedor R et al ASCO 2023). Given therapeutic implications of these discordances, a better understanding of tumor versus normal HLA testing concordance is critical. **Methods:** The Tempus HLA genotyping algorithm was run on a cohort of 191 patients, each with a tumor and a normal sample. The reference HLA genotype was determined by an independent lab using the GenDx HLA genotyping kit and long read sequencing of the normal sample. Samples that failed sequencing in either lab were excluded from the analysis. Concordance between tumor and normal samples was additionally evaluated on a cohort of 7,821 solid-tumor samples from a variety of sites, selected from the Tempus multimodal database. **Results:** The Tempus HLA genotyping algorithm is highly accurate ($>$98.9% on all HLA genes except DQA1). Specifically, it has an accuracy of 100% on the HLA-A gene, using either the tumor or normal sample. On the larger tumor/normal comparison cohort (7,821 samples), the Tempus HLA genotyping algorithm is highly concordant ($>$99% for all genes except HLA-DQA1 [94.3%]). For the 183 melanoma samples in this cohort, concordance was similar with 100% for HLA-A and HLA-B and 99.5% (182/183) for HLA-C, further confirming that HLA genotyping can be performed accurately on melanoma tumor samples. Investigation of all discordances on HLA genes for which HLA LOH results were available (HLA-A, -B and -C) shows that 84% (88/105) of those discordant samples have somatically lost the allele responsible for the discordance. Of LOH positive discordant samples, 73% (64/88) had a tumor purity $\geq$70%. Thus, over half (64/105) of the discordances between tumor- and normal-HLA genotyping are caused by high tumor purity HLA LOH positive samples. On samples meeting these criteria, concordance drops to 86%-89%. **Conclusions:** The Tempus HLA genotyping algorithm is an extremely accurate laboratory developed test that provides accurate results, regardless of whether the normal or tumor sample is used. Concordance between normal- and tumor-based results is above 99.5% in a large-scale dataset, provided the sample does not have HLA LOH and a tumor purity over 70%. These findings suggest that this test can rapidly screen patients for HLA genotype and match them to appropriate clinical trials but emphasize the importance of a normal sample for high tumor purity specimens. Research Sponsor: Tempus AI, Inc.

	Accuracy (normal)	N (normal)	Accuracy (tumor)	N (tumor)
HLA-A	100.0%	189	100.0%	189
HLA-B	99.5%	187	99.0%	189
HLA-C	100.0%	185	98.9%	185
HLA-DQA1	99.5%	182	97.9%	189
HLA-DQB1	100.0%	186	99.5%	187
HLA-DRB1	98.9%	182	98.9%	182

2585 **Poster Session**

Pan-cancer analysis of STAT6 expression and its relationship with tumor microenvironment characteristics and survival. First Author: Hiba Narvel, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI

Background: Co-targetable immune pathways influence cancer outcomes and responses to immune checkpoint inhibitors (ICIs). We examined the transcriptomic expression and clinical significance of signal transducer and activator of transcription-6 (STAT6), an immune-modulatory signaling factor activated by IL-4 and IL13 and involved in innate immunity in infection and cancer. **Methods:** Transcriptomic expression across 395 genes was measured in various solid tumors from 514 patients with advanced cancer, normalized to a reference population (n=735), and reported as percentiles (high defined as $\geq$75th percentile). We evaluated association between high STAT6 expression and transcriptomic expression of STAT6-related markers (IL4, IL13, TGFB1, IL10, CD8, CCL18, TNFRSF14 [HVEM], VISTA) and currently targetable immune checkpoints (PD-1, PD-L1, PD-L2, CTLA-4, LAG3). Genomic alterations were also assessed for the association with high STAT6 expression. Variables with P$<$0.2 in univariable analysis were included in the subsequent multivariable logistic regression model incorporating genomic, immunomic, and clinical factors. Clinical outcomes were evaluated using Kaplan–Meier method and Cox regression model. **Results:** High STAT6 expression was observed in 184 patients (35.8%); 2 (0.4%) had zero measurable expression. High STAT6 was associated with TMB $<$10 muts/Mb, high expression of LAG3, PD-L2, IL13, TNFRSF14 (HVEM), and VISTA (all immunosuppressive), and a diagnosis of colorectal cancer in multivariable analysis. Breast cancer was negatively associated with high STAT6. In univariable analysis, alterations in SMAD4, KRAS, and APC were significantly associated with high STAT6, though none remained significant in the multivariable model. In advanced cancer patients, high STAT6 was associated with shorter survival (N=489 with clinical data curated, Hazard ratio 1.44, 95% confidence interval 1.03–2.02, p=0.034). Among 217 ICI-treated patients, high STAT6 did not correlate with survival. **Conclusions:** High STAT6 expression associates with a biologically coherent tumor microenvironment characterized by factors mediating profound immune suppression. The STAT6-high phenotype is mechanistically linked to an exhausted immune landscape, evidenced by the co-expression of inhibitory checkpoints LAG3 and VISTA, and may be further driven by an IL13/STAT6 autocrine loop. Clinically, high STAT6 correlates with shorter survival in patients with advanced cancers. Prospective validation of this STAT6-driven signature is warranted to guide the development of precision therapy trials aimed at co-targeting this pathway to improve outcomes. Research Sponsor: None.

2586 **Poster Session**

Beyond TMB: Characterizing tumor-intrinsic genomic architectures of immune resistance. First Author: Ashok K. Vaid, Medanta, The Medicity, Gurugram, India

Background: Immune checkpoint inhibitors (ICI) are increasingly selected based on tumor mutational burden (TMB); however, clinical benefit remains inconsistent. We hypothesized that tumor-intrinsic genomic alterations associated with immune suppression, immune exclusion, and antigen presentation failure frequently coexist with ICI-enabling biomarkers and define distinct resistance architectures. **Methods:** We analyzed tissue-based genomic profiling data from 7,773 solid tumors. TMB-high (TMB-H) tumors were evaluated for genomic alterations implicated in ICI resistance, including *PTEN* loss-of-function (LOF), *STK11* and *KEAP1* LOF, *WNT*/β-catenin pathway alterations (*CTNNB1* activating mutations, *APC* truncation/biallelic loss), *B2M* LOF (antigen presentation), *JAK1/2* LOF (interferon signaling), and *MDM2/MDM4* amplification. **Results:** Among 908 TMB-H tumors, 30.6% harbored at least one immune resistance–associated alteration. *PTEN* LOF was the dominant functional resistance event (7.6%) and represented the central hub in tumors with multiple resistance alterations (65.6%; 21/32). *WNT* pathway alterations were frequent, with *APC* truncation (15.9%; 144/908) exceeding *CTNNB1* mutations (2.6%; 24/908), indicating heterogeneous modes of *WNT* activation. Importantly, *WNT*-driven tumors demonstrated divergent immune escape architectures: *CTNNB1*-mutant tumors were enriched for *B2M* LOF (16.7%; 4/24), whereas *APC*-mutant tumors rarely harbored *B2M* loss (0.7%; 1/144), suggesting antigen presentation-dependent versus immune-exclusion-dominant resistance, respectively. Across the TMB-H cohort, increasing mutational burden was significantly associated with higher *B2M* LOF frequency (Wilcoxon rank-sum p = 3.6×10^{-6}), consistent with immune editing under high neoantigen pressure. Interferon signaling alterations were rare (*JAK1*: 0.2%; 2/908; *JAK2*: 0.0%; 0/908). **Conclusions:** TMB identifies immune pressure but not immune competence. Intrinsic ICI resistance in TMB high tumors is structured around a *PTEN-WNT-B2M* genomic axis, with distinct immune escape architectures determined by the mode of *WNT* activation. Integrating negative genomic predictors of immune response with established biomarkers may improve immunotherapy stratification and inform development of rational combination strategies. Research Sponsor: None.

Prevalence of genomic alterations associated with intrinsic ICI resistance in TMB-high solid tumors.

ICI resistance marker	Prevalence in TMB-High Tumors
STK11	2.4%
KEAP1	0.3%
PTEN	7.6%
CTNNB1	2.6%
APC	15.9%
B2M	2.4%
JAK1	0.2%
JAK2	0.0%
MDM2	2.5%
MDM4	0.4%

2587 **Poster Session**

Safety, PK/PD, and efficacy results from Expand-1: A phase 1 dose escalation study of the novel PD-1 targeted IL-2R-βγ agonist sunekafusp alpha (ANV600) as a single agent and in combination with pembrolizumab in patients with advanced solid tumors. First Author: Markus Joerger, Health Ostschweiz (HOCH), St. Gallen, Switzerland

Background: Sunekafusp alpha (ANV600) is a novel PD-1-targeted, IL- 2Rβ/γ agonist, which binds, without blocking, a unique epitope distinct from pembrolizumab, or other PD-1 checkpoint inhibitors. **Methods:** In this phase 1 study, safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of increasing doses of ANV600 administered intravenously in two different dosing regimen were investigated in patients with advanced solid tumors as monotherapy and in combination with pembrolizumab. A Bayesian Optimal Interval design guided the dose escalation to determine the MTD and RP2D. **Results:** 63 patients were treated: 44 in monotherapy at 10 to 150 μg/kg ANV600 and 19 in combination therapy at 30 to 90 μg/kg ANV600. The median (range) number of previous lines of treatment was 4 (1-16) in monotherapy and 4 (2-10) in combination therapy. In mono- and combination therapy 27 (61%) and 9 (47%) patients were previously treated with a checkpoint inhibitor (CPI). ANV600 was generally well tolerated. Most common treatment related adverse events were pyrexia, transient and self-limiting transaminase elevations, and low-grade (≤G2) cytokine release syndrome. No treatment-related death was reported. The recommended phase 2 dose of ANV600 was determined to be 90 μg/kg Q1W as starting dose for 4 weeks followed by 150 μg/kg Q2W as maintenance dose. Selective targeting of PD-1-expressing cells was demonstrated, with preferential induction of proliferation of PD-1^{+} CD8^{+} T cells compared to PD-1^{-} CD8^{+} T cells. In the monotherapy setting, 12 patients (32%) experienced target lesion shrinkage; 4 of these (33%) were CPI treatment-naïve. Disease control was observed in 16 patients (42%). Clinical benefit was in general long lasting. A complete response was confirmed in 1 patient with bronchial adenocarcinoma, starting at 6 months after initiation of monotherapy treatment and still ongoing after 9 months of treatment. The patient was previously progressing under 1st line anti-PD-L1 therapy and 2nd line chemotherapy with carboplatin and paclitaxel. Similarly, in the combination therapy setting, 4 patients (24%) experienced target lesion shrinkage; 2 of these (50%) were CPI treatment-naïve. Disease control was observed in 10 patients (59%). **Conclusions:** ANV600 as monotherapy and in combination with pembrolizumab showed a favorable safety profile. Highly promising efficacy signals with one ongoing complete response, several long-lasting partial responses and stable diseases were reported in CPI-naïve and CPI pre-treated patients, including CPI-resistant tumors. Clinical trial information: NCT06470763. Research Sponsor: Anaveon AG.

2588 **Poster Session**

Multi-omics analysis from the IMMUcan consortium to identify predictors of chemo-immunotherapy response in early-stage triple-negative breast cancer. First Author: Andrea Joaquin Garcia, Institut Jules Bordet, Université Libre de Bruxelles, Bruxelles, Belgium

Background: Combining PD-1/PD-L1 immune checkpoint blockade (IO) with neoadjuvant chemotherapy (CT) is now a standard treatment for early-stage triple-negative breast cancer (eTNBC). However, no validated biomarker is currently used to guide patient selection for CT-IO benefit. We aimed to define baseline tumor–immune–stroma ecosystem states that explain differential responses and could inform future biomarker-driven trial designs. **Methods:** The IMMUcan consortium prospectively enrolled 422 patients with eTNBC treated with CT alone (n=221) or CT-IO (n=201). Pretreatment FFPE biopsies underwent whole-exome sequencing (n=397), RNA sequencing (n=360), multiplex immunofluorescence (2 panels, n=353/368), and imaging mass cytometry (n=341). Response was assessed as pathological complete response (pCR) versus residual disease (n=400). Clinical, genomic, transcriptomic, and spatial features were analyzed for associations with pCR and treatment interaction. Multi-omics integration was performed using Multi-Omics Factor Analysis (MOFA) to derive latent factors and ecosystem states. **Results:** Baseline clinicopathological characteristics were balanced between groups, while the pCR rate was higher with CT-IO than CT alone (73.1% vs 54.8%; Δ=20.4%; $p<0.01$). High tumor grade and tumor-infiltrating lymphocytes predicted pCR in both groups without IO-specific predictive value. Among transcriptomic TNBC subtypes, immunomodulatory, mesenchymal (M), and luminal androgen-receptor (LAR) derived the greatest benefit from CT-IO. Spatial profiling identified as key CT-IO responsive feature the enrichment of activated PD-1^{+}GZMB^{+}CD8^{+} T cells in proximity to tumor cells. MOFA identified biological axes with predictive value, including organized adaptive immunity, effector functions, immune-memory, stromal/angiogenic barrier, and luminal-metabolic lineage. Organized adaptive immunity predicts CT-IO benefit in M and LAR subtypes (OR: 5.42; 95% CI 0.87-33.6; p interaction = 0.048; and OR: 2.97; 95% CI 0.98-8.9; p interaction = 0.036, respectively). Conversely, LAR tumors characterized by luminal–metabolic lineage showed no benefit from CT-IO. **Conclusions:** Integration of multi-omics data revealed distinct baseline biological ecosystem states capable of identifying patients most likely to benefit from, or exhibit resistance to, CT-IO. These findings provide a comprehensive framework for designing biomarker-driven therapeutic strategies in next-generation neoadjuvant trials for early-stage TNBC. Research Sponsor: EU's Horizon 2020 and EFPIA; IMI2 JU grant agreement 821558; Fondation contre le cancer - Belgium.

2589 **Poster Session**

Chemotherapy-induced gut microbiota taxonomic deviation and its association with outcomes and toxicities in breast cancer: CANTO microbiota. First Author: Joana M. Ribeiro, Gustave Roussy and Paris-Saclay University, Villejuif, France

Background: Gut microbiota (GM) modulates immunotherapy (IT) efficacy and toxicity, but its impact on outcomes in breast cancer (BC) patients (pts) remains unclear. TOPOSCORE is a GM-derived score reflecting the ecosystem structure that classifies pts into SIG1+ or SIG2+ profiles, the latter being enriched in obligate anaerobes with immunostimulatory proprieties and associated with favorable IT outcomes. **Methods:** CANTO-Microbiota (target N=1000) is an ongoing substudy of the prospective CANTO cohort (NCT01993498). Stool samples were available from 209 pts (202 pre-treatment (Tx) and 94 post-Tx [after surgery, chemotherapy (CT) ±targeted-, and/or radiotherapy]), enrolled 2015-2024. GM was profiled by shotgun metagenomics and assessed as TOPOSCORE (SIG1+ vs. SIG2+) pre- and post-Tx. Associations of GM with invasive (iDFS), distant disease-free (DDFS), and overall survival (OS) (Kaplan–Meier and Cox regression models), and with treatment-related toxicities (multivariable logistic regression). Post-treatment analyses were landmark-based. **Results:** Median age was 46.6 years, 72% were premenopausal, 79% had stage II-III, 36% HER2+, 34% HR+/HER2-, and 30% TN, 89% received (neo)adjuvant CT, 15% IT and 33% anti-HER2-therapy. Median follow-up was 2.2 years. At baseline, 74% of pts had a SIG2+ profile. This profile was not associated with clinicopathologic features or clinical outcomes; however, SIG2+ was associated with a reduced incidence of post-treatment diarrhea and long-term neuropathy, and remained independently protective against neuropathy (OR 0.25, 95% CI 0.09–0.64; p=0.005). Paired analyses (n=87) revealed a significant shift in TOPOSCORE signatures post-treatment, resulting in an increase in SIG1+ prevalence from 28% to 47% (p=0.004), In univariable landmark Cox analyses, post-treatment SIG1+ was associated with worse iDFS (HR 5.0, 95% CI 1.1–4.2; p=0.04), DDFS (p=0.0053) and OS (p=0.04). In multivariate model adjusted for age, stage, and subtype, post-treatment SIG2+ remained independently protective for iDFS (HR 0.17, 95% CI 0.03–0.88; p=0.035). Assessing longitudinal GM trajectories, worsening patterns (SIG2+→SIG1+ in 28% and persistent SIG1+→SIG1+ in 20% of pts) were associated with an increased risk of iDFS (HR 5.25, 95% CI 1.11–24.7; p = 0.036). Post-treatment TOPOSCORE associations with outcomes were validated in two independent prospective cohorts outside France. **Conclusions:** Chemotherapy is associated with measurable shifts in GM composition that correlated with treatment-related long-term toxicity and outcomes. These findings support the evaluation of microbiota centered interventions during treatment in eBC. Research Sponsor: None.

2590 **Poster Session**

Safety and preliminary efficacy of OH2 combined with BS006 sequential intratumoral injection in patients with advanced solid tumors: An open-label, dose-escalation phase Ib/II study. First Author: Han Wu, Department of Radiation and Medical Oncology, Zhongnan Hospital of Wuhan University, Wuhan, China

Background: The immunosuppressive ("cold") tumor microenvironment (TME) limits patient response to checkpoint inhibitors. Oncolytic viruses (OVs) can selectively replicate in tumor cells, leading to robust TME-remodeling. Reported here is the first clinical evaluation of a dual TME-modulating strategy based on an oncolytic HSV2 platform, whereby OH2, a clinically validated oncolytic HSV2 expressing GM-CSF, which enhances tumor lysis, antigen release, and dendritic cell recruitment in the TME, is co-injected with BS006, a second HSV2-based OV, which expresses a PD-L1/CD3 bispecific antibody that can redirect bystander T cells to tumor cells in the TME. **Methods:** BS008-001 is a multicenter, open-label phase Ib /II trial in heavily pre-treated patients with advanced solid tumors. Patients received biweekly sequential intratumoral injections of OH2 (fixed dose: 10^{7} $CCID_{50}$/mL) followed by BS006 (dose escalation: 10^{6}–10^{7} $CCID_{50}$/mL), with identical volumes being injected at the same lesion. The primary endpoint is safety and tolerability; secondary endpoints included efficacy outcomes assessed by RECIST 1.1/iRECIST. **Results:** As of January 5, 2026, a total of 15 patients with a mean age of 59.3 were enrolled (4 soft tissue sarcoma, 3 colorectal cancer, 2 melanoma, 2 biliary tract tumors, 2 breast cancer, 1 pancreatic cancer, and 1 liver cancer). 93.3% of the patients had a baseline ECOG score of 1. The mean maximum diameter of the target lesion at baseline was 91.3 mm. 100% of the patients had distant metastases to internal organs such as the liver and lungs. Safety: Incidence of TRAEs in the Safety Set was 53.3% (8/15) with mild grade 1-2 reactions, including fever (40.0%) and decreased lymphocyte count (20.0%). 1 patient developed Grade ≥3 TRAE (6.7%), but no DLT-causing AEs or premature withdrawal from the trial occurred. Efficacy: In the 13 patients with evaluable advanced multi-line solid tumors, ORR was 7.7% and DCR 38.5%. 1 melanoma patient achieved 1 PR after 11 treatments, with the total diameter of the target lesions significantly decreasing by 70.8% to 30.4 mm; another melanoma patient received 39 doses over a treatment duration of 18.9 months (SD), whereas 1 subject with leiomyosarcoma achieved SD and survived for 27.1 months. While the mOS of the 15 patients has not yet been reached, landmark 1-year OS is 78% (95% CI: 47%-92%), with 3 patients still on treatment. **Conclusions:** Sequential intratumoral administration of OH2 and BS006 in heavily pre-treated patients is feasible and safe and results in reasonable DCR, with some patients achieving long-term clinical benefits. This study supports the clinical relevance of an HSV2-based platform combination of 2 oncolytic viruses encoding GM-CSF and T-cell redirected bispecific antibodies to warm up the cold TME. Further clinical research of the platform is warranted. Research Sponsor: None.

2591 **Poster Session**

Association of SARS-CoV-2 vaccination with survival outcomes in patients with metastatic solid tumors treated with immune checkpoint inhibitors. First Author: Haris Sohail, Charleston Area Medical Center, Charleston, WV

Background: Patients with cancer experience disproportionately high morbidity and mortality from SARS-CoV-2 infection, and COVID-19 vaccination is recommended for all patients with cancer. Although vaccines primarily reduce infection related complications, emerging data suggest SARS-CoV-2 mRNA vaccines may also enhance antitumor immune responses and potentially synergize with immune checkpoint inhibitors (ICIs). We evaluated survival outcomes in vaccinated versus unvaccinated patients with metastatic solid tumors treated with immunotherapy. **Methods:** Data for adults with metastatic cancers for which ICIs are indicated were obtained from the TriNetX Research Network (2019–2024). Patients were classified by receipt of ≥1 SARS-CoV-2 mRNA vaccine around the time of ICI initiation (±1 year) and compared with unvaccinated patients. Those with prior systemic antineoplastic, endocrine, or immunosuppressive therapy before ICI initiation or who developed COVID-19 were excluded. Cohorts were propensity matched for demographics, cancer type, comorbidities, and laboratory values. Outcomes included overall survival at 90 days, 1 year, and 5 years using Kaplan–Meier analyses, and all-cause hospitalization and immune-related adverse events (irAEs) within 90 days. **Results:** After matching, 543 vaccinated and 543 unvaccinated patients were well balanced. Vaccination was not associated with increased irAEs, with similar rates of any irAE (19.0% vs 17.9%, p=0.64), gastrointestinal (3.87% vs 3.87%, p=1.00), dermatologic (11.8% vs 10.7%, p=0.56), and neurologic events (2.76% vs 2.39%, p=0.70); pulmonary and hepatic irAEs were rare. Hospitalization rates were comparable (24.9% vs 23.9%, p=0.72). Vaccinated patients demonstrated improved intermediate-term survival, with higher 1-year survival (73.35% vs 64.12%; HR 0.70, 95% CI 0.56–0.87, p=0.001), with trends toward benefit at 90 days (HR 0.69, p=0.053) and 5 years (HR 0.85, p=0.066). Landmark analysis from 1 to 5 years showed no significant survival difference (HR 1.15, p=0.34). Consistent 1-year survival benefits were observed in lung cancer (65.93% vs 52.56%; HR 0.63, p=0.0005) and melanoma (80.25% vs 68.65%; HR 0.56, p=0.0355). **Conclusions:** In this large propensity-matched real-world cohort of metastatic solid tumor patients receiving immune checkpoint inhibitors, COVID-19 vaccination was not associated with increased immune-related toxicity or hospitalization and was associated with significantly improved 1-year overall survival. Attenuation of the survival association in landmark analyses suggests potential time-related bias, supporting the need for further studies with precise exposure timing. Research Sponsor: None.

2592 **Poster Session**

An exploratory, single-center, single-arm trial of R-ISV-FOLactis in situ vaccination for advanced soft tissue sarcoma. First Author: Qing Wang, The Comprehensive Cancer Centre of Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Background: Advanced soft tissue sarcomas (STSs) have limited treatment options and exhibit low responsiveness to immunotherapy, largely due to an immunosuppressive tumor microenvironment (TME). In situ vaccination (ISV) represents a promising strategy to convert immunologically "cold" tumors into "hot" ones. FOLactis, a food-grade probiotic Lactococcus lactis engineered to express a fusion protein of Fms-like tyrosine kinase 3 ligand (Flt3L) and OX40 ligand (OX40L), has shown antitumor immune activity in preclinical models. This study investigates the synergistic antitumor effect and safety of intratumoral FOLactis in combination with hypofractionated radiotherapy and anti-PD-1 therapy in clinical settings. **Methods:** In this investigator-initiated, single-arm trial, patients with advanced STS who had failed standard therapies received intratumoral injections of FOLactis combined with hypofractionated radiotherapy and PD-1 blockade. Primary endpoints included safety and efficacy, secondary endpoints encompassed abscopal responses and mechanistic exploration of treatment efficacy. **Results:** Between July 2022 to July 2025, 16 advanced STS patients were enrolled. The R-ISV-FOLactis regimen was well-tolerated, with grade 3 adverse events occurring in 37.5% of patients. Injected lesions showed a best objective response rate (ORR) of 56.25% and a disease control rate (DCR) of 100%. Median progression-free survival (mPFS) for all lesions was 6.3 months, while mPFS for injected lesions was not reached. Abscopal responses were observed in 56.25% of patients. Immunological analyses revealed increased frequencies of peripheral memory $CD8^+$ T cells, $PD\text{-}1^+$ $CD8^+$ T cells, and dendritic cells (DCs), alongside decreased regulatory T cells (Tregs) and tissue-resident $CD103^+CD4^+$ T cells in responders, indicating systemic immune activation. Furthermore, reshaped TME with reduced fibroblasts and increased immune cell infiltration were associated with enhanced antitumor immunity. Moreover, significant increase of $CD8^+$ T cell density in regions distal to neutrophil clusters, along with elevated 4−Cresol Sulfate levels suggesting neutrophil modulation. **Conclusions:** R-ISV-FOLactis exhibited a favorable safety profile and encouraging efficacy against both local and distant tumors. The treatment induced systemic immune activation and metabolic remodeling, supporting its further development as a novel ISV strategy for advanced STSs. Clinical trial information: ChiCTR2200060660. Research Sponsor: None.

2593 **Poster Session**

Quality of life in cancer patients treated with anchored interleukin-12 (IL-12) immunotherapy: Results from a first-in-human phase 1 trial of tolododekin alfa (ANK-101). First Author: Jong Chul Park, Mass General Brigham, Harvard Medical School, Boston, MA

Background: Anchored immunotherapy is a novel method for retaining high concentrations of anti-tumor drugs in established tumors with limited systemic exposure. The integration of quality-of-life (QOL) assessment in a phase 1 study of anchored IL-12, tolododekin alfa (ANK-101), provided an opportunity to gather baseline QOL data, longitudinally measure patient well-being during drug exposure, identify associations between adverse events and patient well-being, and generate additional clinical benefit information. **Methods:** All patients enrolled in the phase 1 clinical trial of ANK-101 for patients with advanced/metastatic solid tumors were eligible and provided written informed consent. Patients were treated with direct intratumoral injection every 3 weeks up to 8 cycles over 6 months. QOL was measured by the validated FACT-G survey, which collects scores across a 27-item questionnaire that measures physical, family/social, emotional, and functional well-being. Subjects were asked to complete the FACT-G at baseline every 3 weeks during treatment and at end-of-treatment. QOL scores were evaluated by paired-sample t-tests to evaluate differences in QOL at various time intervals. Data cut-off was on October 21, 2025. **Results:** 39 of 40 (98%) patients completed at least two FACT-G surveys. The median age was 68 and 44% were female. Patients had a median of 5 lines of prior therapy (range 1-18). The most common cancer types included were melanoma (33%), head and neck (18%), cutaneous squamous cell carcinoma (8%), and colorectal cancer (8%). There were no dose-limiting toxicities but there were 42 grade 2 events in 13 subjects and five grade 3 events in 3 subjects (elevated liver transaminases, abdominal pain, neutropenia, stomatitis). At baseline, the median of QOL score was 80.5 (range 51-106). After two and four cycles, there was no decrease in QOL scores across any of the functional domains. For patients who developed grade 2 or 3 adverse events, there was a trend toward decreased QOL in social well-being (median 25.5 at baseline to 23 after two cycles; median change -2.0; p=0.08) and in physical well-being (median 24 at baseline to 20 after four cycles; median change -5.5; p=0.06 after four cycles). Patients who completed all 8 cycles of treatment demonstrated no change in any QOL measure (p range 0.14-0.70). **Conclusions:** ANK-101, the first anchored immunotherapy, was associated with QOL scores that were not significantly diminished in heavily pre-treated advanced cancer patients with a non-significant decrease in social and physical well-being among those who developed grade 2 or greater adverse events. Further, patients with visceral tumors had no difference in QOL compared to superficial lesions. Early implementation of QOL data is feasible in phase 1 trials and may be of use to identify drug impact on clinical and safety measures. Clinical trial information: NCT06171750. Research Sponsor: Ankyra Therapeutics.

2594 **Poster Session**

Intratumoral dendritic cell (DC1) therapy prior to neoadjuvant chemotherapy in HER2-positive breast cancer (NATASHA trial). First Author: Hyo S. Han, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Enhancing the efficacy of neoadjuvant therapy (NAT) while minimizing treatment-related toxicity remains a critical unmet need for patients (pts) with HER2-positive (HER2+) breast cancer (BC). We previously reported intratumoral (IT) delivery of increasing doses (50 million and 100 million cells) of conventional type I dendritic cells (DC1) combined with anti-HER2 antibodies is safe and effective in altering the tumor microenvironment (TME) and inducing tumor regression in early-stage HER2+ BC. We conducted a phase II neoadjuvant clinical trial of IT DC1 (NCT05325632). **Methods:** Pts with early-stage HER2+ BC with tumor ≥ 1cm were eligible. Treatment included initial immunotherapy with IT DC1 weekly x6 (100 million) followed by paclitaxel 80 mg/m^2 IV weekly x12. Starting from day 1, pts also received trastuzumab (H) IV (8 mg/kg loading dose, then 6 mg/m^2) and pertuzumab (P) IV (840 mg loading dose, then 420 mg) every 3 weeks x 6 cycles. Core needle biopsies were obtained at baseline and at week 6 following the last DC1 injection and analyzed by multiplex immunofluorescence (mIF) to assess immune cell infiltration. At these timepoints and post-chemotherapy, radiologic response was assessed by breast MRI and blood was collected for biomarker and ctDNA analysis using a personalized, tumor-informed test (Signatera, Natera, Inc.). The primary end point of this study is pathologic complete response rate (pCR). **Results:** A total of 47 pts (24 HR+/HER2+, 23 HR-/HER2+) were enrolled between 5/2022 and 10/2025. Median age was 54 years (range 27-82). 21 pts had biopsy-proven axillary node positive disease with clinical stage I/II/III (7/30/10). All pts completed NAT, and 42 pts underwent surgery as of 1/22/2026. The pCR rates for HR+/HER2+ and HR-/HER2+ were 50% (12/24) and 89% (16/18), respectively. The most frequent toxicities related to DC1 were grade 1/2 chills, flu-like symptoms, headache, nausea, fever, and injection site reaction. IT DC1 + HP therapy was associated with a significant increase in intratumoral $CD3^+$ T cell infiltration and a decrease in tumor cells assessed by mIF. ctDNA levels were evaluable for 25 patients (13 HR+ and 12 HR-). Sixteen pts (64%) had positive ctDNA (6 HR+ and 10 HR-) at baseline and 14/16 cleared ctDNA with NAT (13/16 cleared ctDNA post- IT DC1+HP, prior to chemotherapy). At present (median post-surgery follow-up: 15.1 mos.; median follow-up from last ctDNA test: 8.7 mos.), no pts have experienced disease recurrence. **Conclusions:** IT DC1 + HP prior to neoadjuvant paclitaxel + HP in HER2+ BC pts was well tolerated with manageable toxicities. IT DC1 led to immune cell infiltration and ctDNA clearance with improved pathologic tumor response rates, particularly in HR-/HER2+ BC. Updated surgical outcomes and biomarker results (mIF, MRI and ctDNA) will be presented at the meeting. Clinical trial information: NCT05325632. Research Sponsor: None.

2595 Poster Session

First-in-human evaluation and preclinical mechanistic studies of targeted hyperthermia therapy. First Author: Carman Giacomantonio, Dalhousie University, Halifax, NS, Canada

Background: Photothermal conversion of near-infrared (NIR) light using specifically tuned, directly delivered gold nanorods produces controllable hyperthermia in tumor microenvironments. Precisely controlled, targeted hyperthermia therapy (THT) induces immunogenic cell death (ICD) and remodels the tumor microenvironment, promoting immune activation in otherwise poorly inflamed tumors. Here, we report an early clinical evaluation of THT integrated with mechanistic preclinical analyses. Preclinical studies: In B16F10 melanoma and CT26 colorectal models, controlled thermal dosing induced a 24–48 h ICD response marked by calreticulin and HSP70 exposure, chemokine and complement activation, and early T-cell receptor remodeling. Transcriptomic analyses revealed a dose-dependent transition from innate immune activation to a coordinated tissue repair program involving extracellular matrix remodeling. Lower thermal doses in the hyperthermic window decreased regulatory pathways and induced antigen presentation. Modulation of myeloid signaling limited macrophage accumulation, prevented tumor regrowth, and sustained antitumor inflammation. **Methods:** In a first-in-human, open-label, early feasibility study (NCT06894407), ten patients with stage IIIc/IIId/IV M1 cutaneous metastatic melanoma progressing on checkpoint inhibitor therapy received intratumoral gold nanorods (Sona Nanotech Inc.) followed by NIR-mediated heating on days 1 and 8. Up to four lesions per patient were treated, with intratumoral temperatures maintained at 42–48 °C for 5 minutes. Safety, feasibility, and early biological activity were assessed through adverse-event monitoring, clinical photography, and tumor biopsies obtained on days 15 and 29. **Results:** Clinical: THT was well tolerated, with no treatment-related serious adverse events observed. By day 15, 8 of 10 patients demonstrated regression in treated lesions. Histologic assessment showed complete tumor clearance in 6 patients, partial regression in 2 patients, and no response in 2 patients. **Conclusions:** THT-induced ICD progresses through temporally regulated immune states, including a reparative myeloid-associated phase that limits durability. Defined thermal-dose parameters provide a framework for rational integration of THT with macrophage-modulating and checkpoint-based immunotherapies. THT is safe, feasible, and biologically active in immunotherapy-refractory metastatic melanoma. Further clinical studies are needed to evaluate the efficacy of THT in immune-refractory cancers. Clinical trial information: NCT06894407. Research Sponsor: Sona Nanotech Inc.

2596 Poster Session

Evaluation of adnexal features and histological response to intralesional SP-002 in nodular basal cell carcinoma. First Author: Gregory Siller, Central Brisbane Dermatology, Brisbane, Australia

Background: No FDA approved nonsurgical therapies exist for primary nBCC at high-risk sites, e.g., H-zone, representing a significant unmet medical need. Recombinant IFN-alfa-2b previously achieved ~85% complete histologic clearance in superficial and nBCC, but required multiple (9-12) injections and was associated with systemic toxicity. SP-002 encodes human IFN-γ and enables sustained, localized cytokine expression with anti tumor activity, achieved with a once weekly, three dose regimen that demonstrates a superior therapeutic index. **Methods:** Two early phase clinical studies of SP-002 in nBCC were completed: a single lesion study (ASN-002-001, NCT02550678, n=16), and a combination multilesion study with 4 weeks of vismodegib (ASN-002-003, NCT04416516, n=21, 46 lesions). Pretreatment biopsies from ASN-002-001 served as discovery specimens, while pretreatment biopsies from ASN-002-003 were prospectively assessed by central review for adnexal features (AdnF; follicular or eccrine differentiation) using standardized criteria. Post-treatement excision specimens were evaluated by local histopathology laboratories for CHC per protocol-defined criteria. CHC rates were calculated by AdnF. **Results:** ASN-002-001: sporadic low frequency/risk BCC, AdnF(+) rate was 20%. CHC rates were 33% (5e10vp), 83% (1.5 and 3.0e11vp). ASN-002-003: high-frequency multilesion BCC, AdnF(+) rate was ~50%. CHC rates were 75% (1 nBCC)/52.9% (3 nBCC) (1.0e11vp) and 52.4% (3 nBCC) (1.5e11vp)-ITT. When analyzed by AdnF status, CHC rates were 97% in AdnF(-) lesions and 11.5% in AdnF(+) lesions. Baseline biopsies in non-responders demonstrated follicular/eccrine structures especially papillary mesenchymal bodies, harboring CKT15(+) stem cells (SC) and nuclear β-catenin, indicating active WNT signaling. Dual repression of programmed cell death effectors, CASP8/RIPK3, was also observed at baseline in lesions with residual disease with focal loss or widespread loss across tumor islands in β-catenin active regions. Either or both CASP8/RIPK3 were present in all complete responders at baseline and their absence may indicate risk for incomplete response to SP-002. **Conclusions:** SP-002 achieved high CHC rates at doses of 1.5e11vp/3.0e11vp and AdnF(-) lesions (most nBCC) had clearance rates comparable to surgical excision (>90%).Adnexal differentiation identifies a biologically distinct, treatment-resistant subset with WNT pathway activation, adnexal niches harboring CKT15(+) SC, and impaired IFN-γ cell death. These findings support AdnF as a predictive biomarker and position SP-002 as a promising non-surgical option for selected patients with nBCC. Clinical trial information: NCT02550678, NCT04416516. Research Sponsor: Ascend Biopharmaceuticals Ltd, Level 1 159 Dorcas Street, South Melbourne VIC 3205.

	CHC rate AdnF(-) n/N lesions (%)	CHC rate AdnF(+) n/N lesions (%)
ASN-002-001 (n=15, 15 lesions)	11/12 (91.6%)	0/3 (0%)
ASN-002-003 (n=21, 46 lesions)	23/23 (100%)	3/23 (13%)
	34/35 (97.1%)	3/26 (11.5%)

2597 Poster Session

Safety and feasibility of intratumoral injection of RP1 or RP2 oncolytic immunotherapies in visceral metastases. First Author: Caroline Robert, Gustave Roussy and Paris-Saclay University, Villejuif, France

Background: RPx is an investigational HSV-1-based oncolytic immunotherapy platform including RP1 (vusolimogene oderparepvec) and RP2. RP1 expresses GM-CSF and a fusogenic glycoprotein (GALV-GP-R$^-$); RP2 also expresses an anti–CTLA-4 antibody-like molecule. We report safety data from patients (pts) who received intratumoral (IT) injections of RP1/2 into visceral metastases (mets). **Methods:** Pts with advanced/metastatic solid tumors were enrolled into RP1/2 clinical trials (RP1: NCT03767348; RP2: NCT04336241). RP1/2 was injected into visceral tumors using CT or ultrasound guidance. The recommended needle gauges ranged from 17-27G. Pts received RP1/RP2 for up to 8 doses as monotherapy or in combination with nivolumab IV starting at cycle 2 or 4 for up to 2 years. Additional RP1/2 doses could be given if protocol-specified criteria were met. This analysis evaluated safety among pts receiving IT RP1/2 injections to visceral mets (defined as lung or liver mets). All safety data presented includes events occurring within 7 days after injection (except where noted). **Results:** As of data cutoff (RP1: 15OCT2024; RP2: 29AUG2025), there were a total of 665 RP1/2 injections into the lung (n = 125; median lung injections/pt/treatment course [c]: RP1 = 5.5 and RP2 = 8) and liver (n = 540; median liver injections/pt/c): RP1 and RP2 = 5) among 105 pts. The most common treatment-related adverse events (AEs) were pyrexia, chills, and fatigue (Table). A total of 9 pneumothorax (PTX) events occurred (within 3 days after injection) out of 125 lung injections (7.2%) in 19 pts receiving RP1/2; all cases were Grade (G) 1/2 and resolved. Only 1 pt required a chest tube for a G2 PTX event and the pt continued to receive RP1 after resolution. There were 3 bleeding events within 3 days after injection among 665 injections (0.5%) in the lung or liver in 105 pts receiving RP1/2. All bleeding events occurred in pts receiving RP2 liver injections and resolved (2/3 events resolved by the following day). **Conclusions:** RP1/2 injections into visceral mets were well tolerated, with a comparable safety profile to liver and lung biopsies performed in other clinical settings. The observed RPx safety profile supports the incorporation of IT injections into deep visceral tumors as part of cancer therapy. Clinical trial information: NCT03767348; NCT04336241. Research Sponsor: Replimune, Inc.

All-grade treatment-related adverse events (>15%).

	RP1				RP2			
	Monotherapy		Combination therapy		Monotherapy		Combination therapy	
n (%)	Injected visc mets (n = 11)	Total (n = 19)	Injected visc mets (n = 46)	Total (n = 151)	Injected visc mets (n = 14)	Total (n = 20)	Injected visc mets (n = 34)	Total (n = 47)
Pyrexia	9 (82)	12 (63)	22 (48)	51 (34)	6 (43)	9 (45)	18 (53)	25 (53)
Chills	6 (55)	6 (32)	20 (44)	43 (28)	3 (21)	5 (25)	13 (38)	19 (40)
Fatigue	3 (27)	7 (37)	8 (17)	39 (26)	1 (7)	3 (15)	4 (12)	7 (15)
Influenza-like illness	1 (9)	2 (11)	12 (26)	31 (21)	0	0	2 (6)	8 (17)
Nausea	1 (9)	1 (5)	13 (28)	26 (17)	1 (7)	1 (5)	5 (15)	8 (17)

mets, metastases; visc, visceral.

2598 Poster Session

STING agonist JMKX000197 infusion in patients with malignant pleural effusion: Preliminary results from a prospective phase Ib study. First Author: Ning Li, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: Indwelling pleural catheter (IPC) is frequently used for symptomatic malignant pleural effusion (MPE), its therapeutic benefits remain limited. JMKX000197 is a novel small molecule stimulator of interferon genes (STING) agonist that activates STING to induce type I interferons and pro-inflammatory cytokines and may have a promising clinical prospect for the treatment of MPE. **Methods:** Eligible patients had advanced solid tumors with moderate-to-large MPE and had progressed on systemic therapy or had poorly controlled effusion. Patients were randomized assigned in a 1:1:1 ratio to receive intrapleural infusions of JMKX000197 (150 μg or 300 μg) combined with IPC or IPC alone (control) on day 1 and day 8. Here, we report safety, tolerability, preliminary efficacy, and PK/PD characteristics from the phase Ib study of JMKX000197 (NCT06740019). **Results:** As of October 15, 2025, 35 patients were enrolled (45.7% female, median age 59 years, 71.4% with lung adenocarcinoma). 2 patients withdrew from the study without receiving any treatment after randomization, thus, the safety and efficacy analysis was based on 33 patients who received treatment. Among 33 patients, 1 patient in the 300 μg group withdrew the informed consent after one dose while 32 patients (97%) completed the two-dose regimen (11 in 150 μg group [N=11], 9 in 300 μg group [N=10], and 12 in control group [N=12]). Treatment-emergent adverse events (TEAEs) occurred in 100%, 90%, and 83.3% of patients in the 150 μg, 300 μg, and control groups, respectively. Grade ≥3 TEAEs occurred in 3(27.3%), 1 (10%) and 1 (8.3%) patients in each group. 2 patients in 150 μg group and 5 patients in 300 μg group experienced grade 1–2 cytokine release syndrome (CRS), which were adverse event of special interest, all resolved with supportive care. No TEAE led to treatment discontinuation or death. Puncture-free survival (PuFS) was defined as the period from the removal of the IPC immediately after the last dose of treatment to the next therapeutic puncture and/or drainage or death, whichever occurs first. The median PuFS was 37 days, 116 days, and 56 days in the 150 μg, 300 μg, and control groups, respectively. Limited exposure of JMKX000197 in plasma was observed (>700 fold lower than that in pleural effusion). PD analysis showed significant elevation of IFN-β in both plasma and pleural effusion (higher in pleural effusion), along with increased TNF-α, IP-10, MCP-1, and IL-6. Immunophenotyping demonstrated enhanced CD8+ T-cell activation and reduced Treg cell proportions post-treatment (both in peripheral blood and pleural effusion). **Conclusions:** Intrapleural JMKX000197 exhibited a manageable safety profile and promising preliminary efficacy in MPE patients, with a better efficacy at the 300 μg dose. JMKX000197 may induce the production of pro-inflammatory cytokines and subsequently activate the tumor microenvironment. Clinical trial information: NCT06740019. Research Sponsor: Shanghai Jeyou Pharmaceutical Co., Ltd.

2599 **Poster Session**

Clinical efficacy and safety of BM201 intra-tumoral injection and radiotherapy in advanced solid tumors: Results from the phase I/IIT study. First Author: Rutian Li, The Comprehensive Cancer Centre of Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Background: For vaccine design, an antigen and an adjuvant are necessary for an effective immune response. In the context of therapeutic tumor vaccination, in situ vaccination has garnered increasing attention as it enables tumors to provide antigens through radiotherapy or intra-tumoral (i.t.) delivery of immunomodulators. BM201, a selective TLR7/8 agonist uniquely designed for intratumoral (i.t.) administration, aims to effectively activate antigen-presenting cells and enhance immunogenicity through combination with radiotherapy by more effectively presenting the tumor antigens exposed to T cells. When combined with intravenous (i.v.) infusion of αPD-1 monoclonal antibody (mAb), it relieves tumor immunosuppression and exerts synergistic anti-tumor effects. **Methods:** This is an open-label, exploratory, and phase I/IIT study. Phase I portion was a dose-escalation study designed to investigate BM201 (dose range: 24-240mg, i.t. every 2 weeks) in combination with hypofractionated radiotherapy (5-8Gy, 4 fractions) (R-ISV-BM201) in patients with refractory or metastatic solid tumors. Phase IIT portion was designed to investigate BM201 (dose range: 24-240mg, i.t. every 3 weeks) in combination with hypofractionated radiotherapy (5-8Gy, 4 fractions) plus αPD-1 (200mg, i.v. every 3 weeks) (R-ISV-BM201 + αPD-1) in patients with refractory or metastatic soft tissue sarcomas. Primary objective of both 2 studies was safety and tolerability. Secondary endpoints included PK and preliminary anti-tumor activity according to RECIST 1.1 in Phase I, while anti-tumor activity according to irRECIST 1.1 in Phase IIT. **Results:** Till December 05, 2025, 29 patients had been treated with BM201 (19/29 in Phase I, 10/29 in Phase IIT). Among the 29 patients, 51.7% had been unresponsive to immunotherapy (prior αPD-1). Plasma exposure increased with dose. A sustained-release PK characteristic was observed in most patients experiencing tumor shrinkage. Abscopal effects were observed in 31.6% (6/19) and 50% (5/10) of patients in Phase I and Phase IIT, respectively. In Phase I, the objective response rate (ORR) was 5.2%, and the disease control rate (DCR) was 84.2%; while these were 10.5% and 84.2% in injected lesions. In Phase IIT, the ORR was 20%, and the DCR was 100.0%; while these were 46.1% and 92.3% in injected lesions. The median progression-free survival was 7.7 months, the median overall survival was 17.0 months, and the median duration of response in injected lesions was 5.6 months. The majority of TRAEs were grade 1-2. Grade 3-4 TRAEs mainly included lymphocytopenia, anemia, thrombocytopenia, and hypertension. No grade 5 TRAEs or dose-limiting toxicity was observed. **Conclusions:** R-ISV-BM201 has a manageable safety profile and has shown encouraging anti-tumor activity. A trigger systemic immune response would be expected when it is synergized with αPD-1 mAb. Clinical trial information: Phase I: NCT06368960; Phase IIT: ChiCTR2300077953. Research Sponsor: National Natural Science Foundation of China; Foundation for studies of Clinical Trials, Drum Tower Hospital; Science Fund for Distinguished Young Scholars of Jiangsu Province; Fundings for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University; Nanjing Medical Science and Technology Development Foundation; InnoBM Pharmaceutics Co. Ltd.

2600 **Poster Session**

Hepatic arterial infusion chemotherapy combined with immunotherapy for unresectable intrahepatic cholangiocarcinoma: A single-arm, open-label, prospective clinical trial. First Author: Hongzhe Kang, The Third Affiliated Hospital of Harbin Medical University, Harbin, China

Background: In recent years, immune checkpoint inhibitors (ICIs) have demonstrated substantial clinical advances in the treatment of intrahepatic cholangiocarcinoma (ICC). However, the efficacy of first-line systemic chemotherapy remains suboptimal for patients with unresectable ICC. Hepatic arterial infusion chemotherapy (HAIC) can markedly elevate local drug exposure, enhance tumor cytotoxicity, and minimize systemic adverse effects. Whether the combination of HAIC and immunotherapy confers a clinical benefit for patients with unresectable ICC remains an urgent clinical issue to be addressed. **Methods:** This is a single-arm, open-label, prospective clinical trial designed to evaluate the efficacy and safety of HAIC combined with ICIs in the treatment of patients with unresectable ICC. The HAIC regimen consists of gemcitabine plus cisplatin (GC-HAIC), while programmed death-1 (PD-1) inhibitors are administered for immunotherapy, with either camrelizumab or sintilizumab chosen on a patient clinical characteristics basis. The trial was planned to enroll 30 participants. The primary endpoint was the objective response rate (ORR). Secondary endpoints included overall survival (OS), progression-free survival (PFS), and disease control rate (DCR). Safety was assessed through the monitoring and grading of adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. **Results:** From August 2022 to January 2025, a total of 31 patients with unresectable ICC were enrolled and received the protocol-defined treatment. The ORR was 41.9% according to RECIST 1.1 criteria, while the ORR assessed per mRECIST criteria was 71%. The median follow-up time was 22.0 months (95% CI, 17.9–26.7 months). The median OS was 20.0 months (95% CI, 15.7–28.6 months), and the median PFS was 12.3 months (95% CI, 10.9–21.3 months). The DCR reached 93.5%. Treatment-related AEs of any grade occurred in 83.9% of patients, whereas grade 3 or 4 AEs were observed in only 16.1% of participants. **Conclusions:** This study evaluated the efficacy and safety of GC-HAIC combined with anti-PD-1 immunotherapy in the treatment of patients with unresectable ICC. The results demonstrated that this regimen exhibited promising efficacy, with manageable adverse events and complications. Additionally, these results also offer a potential novel first-line treatment option for this patient population. Based on the results of this study, future phase III clinical trails are warranted to validate the outcomes. Clinical trial information: ChiCTR2500112123. Research Sponsor: Haiyan Foundation; Beijing Medical Award Foundation.

Tumor response.

	RECIST 1.1		mRECIST	
Efficacy	**%**	**N**	**%**	**N**
CR	0	0	3	9.7
PR	13	41.9	19	61.3
SD	16	52.6	7	22.6
PD	2	6.5	2	6.5
ORR	13	41.9	22	71.0
DCR	29	93.5	29	93.5

CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; ORR, Objective response rate; DCR, Disease control rate.

2601 **Poster Session**

A phase I trial on the safety, tolerance, and preliminary efficacy of intracavitary injection of in situ vaccines (FOLactis) in patients with advanced solid tumors complicated with malignant pleural effusion. First Author: Lifeng Wang, The Comprehensive Cancer Center of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China

Background: Malignant pleural effusion (MPE) is caused by the metastasis of malignant tumors to the pleura. Traditional treatment have limited efficacy. In our preliminary research, a recombinant lactobacillus expressing the fusion protein Flt3L-OX40L (enhancing antigen-presenting function of dentritic cells and activation of antigen-specific T cells) named FOLactis was proved to have strong anti-tumor effect in early clinical trials. This clinical study was designed to explore the safety and efficacy of intracavitary injection of FOLactis for the treatment of malignant pleural effusion (NCT06512896). **Methods:** This is a single arm, single center study. In addition to systemic treatment, participants received intracavitary 2-4 injections of FOLactis. Primary endpoint was safety; secondary endpoints included Objective response rate of pleural effusion and the duration time of pleural effusion control. **Results:** From June 2023 to Oct 2025, a total of 38 patients were intracavitary injected with FOLactis, of which 29 patients completed more than 2 injections. Among these patients, the adverse reactions included Grade I-II fever (12/38, 31.6 %), chest wall pain (9/38, 23.68%), fatigue (2/38, 5.26%), and pneumothorax (1/38, 2.63%), while no adverse events above grade III were observed. Among the 38 patients with local treatment efficacy evaluation, 10 patients had complete disappearance of pleural effusion (10/38, 26.32%), 24 patients had reduction of pleural effusion (24/38, 63.16%), 4 patients had no significant change in pleural effusion (4/38, 10.53 %). Up to the current date, there are 21 patients whose pleural effusion has been controlled for more than one year. Among them, one patient with with advanced lung adenocarcinoma have had their pleural effusion controlled for over 30 months and is still under follow-up. It was found that patients with reduced pleural effusion had higher baseline secretion levels of IL-5 (P=0.0217), TNF-a (P=0.0178) and IFN-a (P=0.0278) in pleural effusion, while those with significantly increased levels of IL-6 (P=0.0076), IL-1B (P=0.0009) and IL-8 (P=0.0198) after treatment also had better control of pleural effusion. Further analysis of RNA sequencing in the pleural fluid of 15 patients revealed that patients with better therapeutic effects showed upregulation of $CD4^+$memory T cells, lymphoid precursor cells, $CD8^+$effector memory T cells and an upward trend in immune microenvironment scores after treatment. **Conclusions:** This ongoing phase I study with intracavitary injection of FOLactis in patients with malignant pleural effusion has preliminarily confirmed safety and clinical efficacy, which suggested to be a promising immunotherapeutic strategy for the effective control of malignant pleural effusion. Clinical trial information: NCT:06512896. Research Sponsor: None.

2602 **Poster Session**

Safety and efficacy of intratumoral (IT) ruxotemitide (LTX 315) in combination with pembrolizumab in patients with unresectable advanced melanoma or triple-negative breast cancer (TNBC). First Author: Stephane Dalle, Centre Hospitalier Universitaire de Lyon, Pierre-Bénite, France

Background: Advanced unresectable cutaneous melanoma or TNBC are associated with poor prognosis and limited treatment options. Ruxotemitide is an oncolytic peptide that induces immunogenic cell death and reshapes the tumor microenvironment to boost antitumor immune responses. We report aggregate safety and efficacy from two trials that assessed intratumoral ruxotemitide combined with pembrolizumab in patients with advanced or metastatic melanoma or TNBC. **Methods:** Two studies enrolled respectively patients with melanoma stage IIIB–IV (M1b) or unresectable TNBC and at least one injectable lesion (as cutaneous, subcutaneous or lymph node). Patients with melanoma were required to have failed prior PD-1\PD-L1 blockers treatment while TNBC patients were naïve of immunotherapy. Patients were required to have adequate organ function. Patients received IT ruxotemitide (up to seven injections during the first 29 days) in combination with pembrolizumab 200 mg IV every 3 weeks until disease progression or for up to 24 months. Safety and efficacy were analyzed across both studies. Tumor assessments were based on RECIST v1.1. **Results:** 41 patients were enrolled, with a median age of 61 years. 26 of pts (63.4%) had received three or more prior lines of therapy, and 22 pts (53.7%) had previous checkpoint blockade treatment. 22 patients (53.7%) had melanoma, 18 patients TNBC (43.9%) and 1 patient (2.4%) a carcinoid tumor. 4 patients had a partial response (2 with melanoma and 2 with TNBC). All responses in melanoma patients were durable, lasting more than 24 months. 1 patient with TNBC achieved a PR for one year. The safety profile was consistent with known effects of IT immunotherapy and pembrolizumab. The most common treatment emergent adverse events (TEAEs) related to ruxotemitide were injection-site reactions (78%), injection site erythema (26.8%), fatigue (22%), hypotension, injection site swelling or pruritus (14.6% each). Grade 3 TEAEs related to ruxotemitide included injection site pain (19.5%) and hypertension (4.9%). There were no related grade 4 TEAEs or deaths. **Conclusions:** IT ruxotemitide plus pembrolizumab demonstrated durable antitumor activity and manageable safety in heavily pretreated patients with advanced or metastatic melanoma or TNBC with injectable disease. These findings support further clinical evaluation of this combination in melanoma and TNBC. Clinical trial information: NCT01986426 and NCT04796194. Research Sponsor: None.

2603 **Poster Session**

A phase I window-of-opportunity trial of intraperitoneal, intratumoral lipopolysaccharide in peritoneal metastases: Safety and immune remodeling from the RIOT-1 study. First Author: Christopher Sherry, Allegheny Health Network Cancer Institute, Allegheny Health Network, Pittsburgh, PA

Background: Peritoneal metastases (PM) from gastrointestinal malignancies exhibit immune exclusion and limited responsiveness to systemic immunotherapy. Regional intratumoral immune activation may reprogram the tumor microenvironment (TME). RIOT-1 evaluated the safety, feasibility, and biological effects of intraperitoneal intratumoral lipopolysaccharide (LPS), a Toll-Like Receptor-4 (TLR4) agonist, administered during diagnostic laparoscopy. **Methods:** RIOT-1 (NCT05751837) was a single-center, open-label Phase I window-of-opportunity trial. Twelve patients with appendiceal or colorectal PM received paired intratumoral injections of 1 μg E. coli O113-derived LPS and normal saline into spatially distinct tumor deposits at laparoscopy, followed by planned cytoreductive surgery 14 days later. The primary endpoint was safety. Secondary endpoints included immune and molecular remodeling assessed by immunohistochemistry (IHC), PhenoCycler multiplex immunofluorescence, spatial neighborhood analysis (CytoMAP), and high-resolution mass-spectrometry proteomics. Key proteomic findings were validated by targeted IHC staining. **Results:** Intratumoral LPS administration was feasible and well tolerated, with no grade $\geq$3 adverse events and no interference with subsequent cytoreductive surgery. IHC demonstrated significant post-LPS increases in M1-like macrophages ($CD68^+CD86^+$), M2-like macrophages ($CD68^+CD206^+$), and $CD1a^+$ antigen-presenting cells (all $p<0.05$). PhenoCycler and CytoMAP analyses revealed LPS-specific reorganization of the immune microenvironment, characterized by enrichment of myeloid- and APC-dominant neighborhoods and altered tumor–immune spatial relationships compared with saline-injected controls. Proteomic profiling quantified 5,178 proteins and revealed LPS-specific enrichment of neutrophil degranulation, cytokine-mediated signaling, RNA translation, and autophagy–lysosomal pathways, distinct from biopsy/carrier-associated structural remodeling observed with saline. Upregulated proteins including LYZ, FCER1G, NAIP, and CD68 were confirmed by IHC, supporting localized innate immune activation and metabolic reprogramming. **Conclusions:** Intraperitoneal intratumoral LPS delivery in PM is safe and biologically active, inducing reproducible innate-dominant immune and metabolic remodeling validated across spatial, proteomic, and histologic platforms. These data establish clinical proof-of-mechanism for regional TLR4 agonism and support further dose-optimization and rational combination strategies in peritoneal malignancies. Clinical trial information: NCT05751837. Research Sponsor: ACPMP.

2604 **Poster Session**

Clinical translation of PeptiCRAd-1: Interim clinical evaluation of a modular oncolytic adenovirus vaccine platform targeting NY-ESO-1 and MAGE-A3 in advanced solid tumors. First Author: Lukasz Kuryk, Valo Therapeutics, Helsinki, Finland

Background: Oncolytic viruses can convert poorly immunogenic tumors into inflamed, immune-responsive lesions, but clinical benefit is often limited by insufficient induction of tumor antigen–specific T cells. PeptiCRAd-1 is a novel peptide-guided oncolytic adenoviral immunotherapy designed to deliver tumor antigens while providing intrinsic immune stimulation. It consists of a conditionally replicating adenovirus expressing CD40L and OX40L and coated with NY-ESO-1 and MAGE-A3 peptides to enhance priming of antigen-specific adaptive immunity. **Methods:** VALO-001 (NCT05492682) is an ongoing, open-label, non-randomized phase 1 trial enrolling adults with injectable advanced solid tumors expressing NY-ESO-1 and/or MAGE-A3, including melanoma, TNBC, NSCLC, sarcomas, and colorectal cancer. Treatment includes low-dose cyclophosphamide followed by intratumoral PeptiCRAd-1 prime/boost injections combined with pembrolizumab. Primary objectives are safety and tolerability; secondary/exploratory endpoints assess innate and adaptive immune activation: antigen-specific T-cell induction, tumor-infiltrating lymphocyte (TIL) density, viral shedding, and preliminary antitumor activity. Immune monitoring includes cytokine profiling, ELISpot for NY-ESO-1/MAGE-A3 responses, and paired biopsies for multiparametric immunophenotyping. **Results:** Seven patients have been enrolled and treated in the START Phase 1 evaluation of PeptiCRAd-1: five in the intratumoral (i.t.) cohort and two in the combined intratumoral plus subcutaneous (i.t. + s.c.) cohort. Across both groups, study treatment has been feasible and well tolerated, with no dose-limiting toxicities, treatment-related serious adverse events, or unexpected safety signals reported to date. In the i.t. cohort, innate immune activation occurred in 3/5 patients; NY-ESO-1/MAGE-A3-specific T-cell responses in 3/5; and increased TILs in 4/5. Clinical responses were observed in 2/5, with disease control in 3/5 patients. Early i.t. + s.c. data show markedly stronger peptide-specific T-cell responses than i.t. alone, supporting combined local–systemic immunization. This cohort remains open, with eight additional patients required. Across evaluable patients, biopsies demonstrated increased TIL density, and early antitumor activity—including partial responses and durable stable disease—was observed across multiple tumor types. **Conclusions:** PeptiCRAd-1 shows a favorable safety profile and induces coordinated systemic and intratumoral immune activation in advanced solid tumors. Robust antigen-specific T-cell responses and enhanced TIL infiltration support its potential to strengthen antitumor immunity and justify continued evaluation, including combination with PD-1 blockade. Clinical trial information: NCT05492682. Research Sponsor: None.

2605 **Poster Session**

BI-1808 + pembrolizumab: Responses to a chemotherapy-free regimen in advanced ovarian cancer. First Author: Anja Williams, Sarah Cannon Research Institute, London, United Kingdom

Background: Up to 80% of individuals with advanced ovarian cancer experience disease progression after standard platinum-based chemotherapy, leaving few approved therapeutic options and poor prognosis. Anti-PD-1 therapies such as pembrolizumab have shown modest efficacy in recurrent ovarian cancer as single agent therapy with an ORR of 8% (KEYNOTE-100), while adding pembrolizumab to weekly paclitaxel$\pm$bevacizumab regimen (KEYNOTE-B96) demonstrates statistically meaningful improvement in OS and PFS in all comers and the PD-L1 CPS $\geq$1 population. BI-1808 is an IgG1 mAb targeting TNFR2. It blocks TNF-α binding and, via FcγR engagement, depletes Tregs and reprograms myeloid cells, expanding antitumor CD8+ T cells. These mechanisms of action differentiate BI-1808 from the relief of T cell suppression mediated by anti-PD1. Accordingly, in preclinical models BI-1808 synergizes with anti-PD-1 leading to an additive tumor inhibition. During BI-1808 monotherapy exploration, one case of complete response in a platinum-resistant patient was observed. The combination of BI-1808 and pembrolizumab could offer a chemotherapy-free treatment alternative in ovarian cancer. **Methods:** Safety and efficacy of BI-1808 plus pembrolizumab are being evaluated in patients with advanced pretreated ovarian cancer in a sub-cohort of the ongoing Phase 2a trial (19-BI-1808-01). The signal-seeking cohort aimed to enroll 20 patients at BI-1808 1000 mg Q3W plus pembrolizumab 200 mg Q3W, followed by dose optimization. **Results:** As of Dec 18, 2025, 24 subjects received BI-1808 plus pembrolizumab. Among 17 response-evaluable patients, 4 achieved confirmed partial response (ORR 24%). Disease control rate was 65%, with 7 patients showing prolonged stable disease, several ongoing beyond 10 months. Strong activity was observed in both high-grade serous and clear cell subtypes. The combination was generally safe and well tolerated; immune related events were manageable and did not lead to treatment discontinuation. Analysis of circulating immune cells shows significant T reg depletion and strong signs of $CD8^+$ T cell activation. **Conclusions:** Early data from this cohort are highly encouraging, with ORR 24% and DCR 65%. BI-1808 plus pembrolizumab demonstrated a manageable safety profile and promising activity in advanced heavily pretreated ovarian cancer. Based on these findings, the cohort will expand by 20 additional patients focusing on clear cell and high-grade serous subtypes. Further data, including biomarker analyses, will be presented on poster. Clinical trial information: NCT04752826. Research Sponsor: None.

2606 **Poster Session**

Neoadjuvant chemokine modulation of the tumor microenvironment (TME) in resectable metastatic colorectal cancer: Results from a phase I study. First Author: Sarbajit Mukherjee, Miami Cancer Institute, Miami, FL

Background: Our preclinical studies using ex vivo explant cultures of resected metastatic colorectal cancer (CRC) tissues and in vivo mouse models showed that the combination of interferon alpha (IFNα) with toll-like receptor-3 (TLR-3) ligands and inhibitors of prostaglandin synthesis selectively induces effector T cell-attracting chemokines (CXCL9, CXCL10, CXCL11, and CCL5) in tumor microenvironments (TME), but not in adjacent healthy tissues, allowing for their systemic application to modulate TME. The chemokine-modulating (CKM) regimen, consisting of IFNα, rintatolimod (a selective TLR3 agonist), and celecoxib (a COX-2 inhibitor), also suppresses CCL22, a Treg-attracting chemokine in the TME. Based on these preclinical data, we hypothesized that a systemic CKM regimen would be safe and effective in modulating the TME of metastatic CRC. **Methods:** Nine chemotherapy-naïve patients with metastatic or recurrent CRC confined to the abdomen/pelvis and expected to have a complete resection received increasing doses of IFNa2b in a Phase I study to establish a recommended phase II dose of CKM for efficacy studies. The adaptive dose-escalation evaluated IFNα2b at 5, 10, and 20 million units (MU)/m2/day IV (Monday–Friday for 1 week pre-surgery), in combination with fixed doses of rintatolimod (200 mg IV; Monday–Friday) and celecoxib (200 mg orally twice daily; Monday–Friday). **Results:** No dose-limiting toxicities were observed, and 20 MU/m² of IFNα2b was identified as the recommended Phase II dose. All treated patients underwent R0 resection, as planned. Common treatment-related adverse events were flu-like symptoms (chills, fever, fatigue) and transient laboratory abnormalities (anemia, leukopenia), mostly grade 1–2. Two patients (13%) developed grade 3–4 neutropenia, which resolved without sequelae. There were no unexpected perioperative complications attributable to the regimen. Preliminary analysis of resected tumor tissues showed evidence of immune modulation in CKM-treated patients: increased ratios of CD8+ CTLs to FoxP3+ Tregs, with concomitant elevation of the effector chemokines (CCL5 and CXCL10), along with reduced expression of the Treg-recruiting chemokine CCL22, compared to 77 patients undergoing upfront tumor resections. **Conclusions:** Neoadjuvant CKM regimen is safe and feasible in resectable metastatic CRC and is associated with improved ratios of CD8+ CTLs to FoxP3+ Tregs in the TME. Further studies combining CKM with immune checkpoint inhibitors and/or chemotherapy are warranted to evaluate the impact of preoperative TME modulation on long-term oncologic outcomes in CRC. Clinical trial information: NCT01545141. Research Sponsor: National Cancer Institute; P01CA132714; National Cancer Institute; P01CA234212.

2607 **Poster Session**

Safety and efficacy results from a first-in-human, phase 1/2 study of ASKG915, an anti-PD-1/pro-IL-15 bifunctional fusion protein, for patients with advanced solid tumors. First Author: Jiajia Li, Fudan University Shanghai Cancer Center, Shanghai, China

Background: ASKG915 is a bifunctional fusion protein of PD-1 antibody fused with an IL-15 prodrug. Preclinical studies demonstrated the efficacy of ASKG915 in neoplastic models. Here, we present updated safety and efficacy results from a first-in-human, dose escalation and dose expansion of ASKG915 monotherapy in patients (pts) with advanced solid tumors. **Methods:** This open-label, multicenter, Phase 1/2 study in adult pts with advanced unresectable or metastatic solid tumors (NCT05867420) comprised two parts: dose escalation (Part 1) and dose expansion (Part 2). Pts with advanced solid tumors that were resistant/refractory to current standard treatment, and with at least 1 measurable lesion per RECIST 1.1, were eligible. The primary objective was safety. Secondary objectives included efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity. **Results:** As of December 30, 2025, we have treated 104 pts at dose-escalation phase (n=19) and dose expansion phase (n=85). Primary tumor types included NSCLC (n=48, 46.2%), CRC (n=35, 33.6%), ovarian cancer (n=11, 10.6%), cervical cancer (n=4, 3.8%) and others (n=6, 5.8%). Most pts (83/104, 79.8%) had received two and more lines of prior treatment, and 71 pts (68.3%) had undergone previous immunotherapy. No dose-limiting toxicities was observed in dose escalation phase, and the maximum tolerated dose has not been reached up to 3 mg/kg. In SS set, any-grade treatment-related adverse events (TRAEs) were reported in 98/104 (94.2%) pts, with the most common being rash (39/104, 37.5%), anemia (37/104, 35.6%), and elevated aspartate aminotransferase (19/104, 18.3%). ASKG915 monotherapy exhibited dose-dependent efficacy across dose levels. In the EFR cohort, encouraging antitumor activity was observed at the mid-dose level or above in both late-line NSCLC that had progressed on prior immunotherapy and MSS CRC: a 30% confirmed partial response (PR) rate (3/10) in non-liver metastatic MSS CRC at the mid-dose level or above, and a 30% PR rate (3/10) in NSCLC patients at the high-dose level. Further efficacy data will be presented at the time of the conference. CD8+ T and NK cells demonstrated proliferative expansion at mid-to-high doses. Drug plasma exposure increased dose-dependently with low activated ASKG915 levels and no ADA impact after repeat dosing. **Conclusions:** ASKG915 demonstrated a promising clinical efficacy in pts with MSS CRC and NSCLC, with a well-tolerated safety profile. These results support further evaluation of ASKG915 as a monotherapy and in combination therapies. Clinical trial information: NCT05867420. Research Sponsor: None.

2608 **Poster Session**

RAISIC-1: A phase 1/2 clinical trial of the GPR65 inhibitor PTT-4256—Preliminary safety, tolerability, pharmacokinetic, and pharmacodynamic results. First Author: Ganessan Kichenadasse, Southern Oncology Clinical Research Unit, Bedford Park, SA, Australia

Background: The acidic tumor micro-environment is linked to immune suppression and insensitivity to immunotherapy. The G protein-coupled receptor, GPR65, is activated in this low pH environment, driving the increased transcription of myeloid immune-suppressive genes and reduced transcription of T- and NK-cell functional and effector genes. Against the backdrop of this target validation, PTT-4256, a first-in-class, potent, orally-bioavailable, allosteric, small molecule inhibitor of GPR65, is being developed as a potential treatment of solid tumors. In mouse syngeneic cancer models, oral administration of PTT-4256 as monotherapy delivers pronounced efficacy, which is enhanced in combination with an anti-PD-1 antibody. Transcriptomic analysis shows that PTT-4256 effectively reverses the acidic immune suppression in mice tumors. **Methods:** RAISIC-1 is a multi-modular Phase 1/2 clinical trial in adults with histologically confirmed advanced/metastatic solid malignancies who have previously received standard of care therapies. Phase 1 (Module A) is aimed to evaluate safety (treatment emergent and related adverse events – TEAE/TRAE; dose limiting toxicity – DLT; maximum tolerated dose-MTD), pharmacokinetics, pharmacodynamics, preliminary efficacy (as per RECIST 1.1) and estimate the optimal biological dose (OBD) / recommended Phase 2 dose (RP2D). PTT-4256 is administered orally in 21-day cycles until disease progression or unacceptable toxicity. A comprehensive biomarker program is included to detect immune-related changes in blood/plasma. **Results:** As of 7 January 2026, 14 participants (3 ongoing) have been treated with one of 5 dose-levels (10, 20, 40, 80 and 160 mg/day). PTT-4256 was well-tolerated with no DLTs. TRAEs were reported in ten participants, with fatigue (n = 8), nausea (n = 4), rash (n = 4), reduced appetite (n = 4), vomiting (n = 2) reported in more than 1 participant. All were grade 1 or 2 except one transient episode ($<$ 1 day) of grade 3 hypertension. Tumor shrinkage and stable disease have been observed at doses 40mg and above in six participants, of which two (nasopharyngeal cancer and renal cell cancer (RCC)) are ongoing in treatment $>$ 5 months. Transcriptomics and proteomics analyses show dose-dependent changes in immune-related markers in blood/plasma following PTT-4256 treatment that are consistent with preclinical data and the mode of action. **Conclusions:** Enrollment at dose levels $\geq$ 300 mg is ongoing. Phase 2 (Module B) as PTT-4256 monotherapy or in combination with anti-PD1 in RCC and head & neck squamous cell cancer (HNSCC) will commence upon identification of RP2D. Clinical trial information: NCT06634849. Research Sponsor: Pathios Therapeutics Limited.

2609 **Poster Session**

Influence of pirfenidone on checkpoint inhibitor pneumonitis and antitumor efficacy in NSCLC: A multicenter study and mechanistic exploration. First Author: Xiaohui Jia, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi province, China

Background: Checkpoint inhibitor pneumonitis (CIP) is a major fatal immune-related adverse events (irAEs) in immune checkpoint inhibitor (ICI) therapy, accounting for ~35% of fatal irAE-related deaths. Patients with pre-existing interstitial lung disease (ILD) face markedly higher CIP risk and are routinely excluded from ICI treatment, depriving them of antitumor benefits. Current first-line glucocorticoid therapy for CIP are limited by inadequate efficacy in fibrotic-stage or steroid-resistant CIP and impaired ICI activity. As a drug-induced interstitial pneumonitis, CIP shares pathological similarities with ILD. Pirfenidone, an approved ILD drug, showed potential efficacy in CIP case reports, but its systematic clinical value and mechanisms remain unvalidated. This study aimed to elucidate pirfenidone's role in full-cycle CIP management and its synergistic antitumor effect with ICIs. **Methods:** A multicenter retrospective study enrolled advanced non-small cell lung cancer (NSCLC) patients receiving first-line ICI-based therapy from three hospitals between 2018 and 2024, stratifying into pirfenidone+ICI+chemotherapy (Pirf+ICI+chemo) and ICI+chemotherapy (ICI+chemo) groups. Primary endpoint was CIP incidence, secondary endpoints objective response rate (ORR) and progression-free survival (PFS). For mechanistic studies, bleomycin and ICI were administered to spontaneous NSCLC mice to mimic clinical ICI treatment in ILD-high-risk patients, generating a CIP mouse model. Lung scRNA-seq defined pirfenidone's role in CIP management and synergistic antitumor activity. **Results:** Of 141 enrolled patients, Pirf+ICI+chemo had significantly lower CIP incidence vs. ICI+chemo (34.01% vs. 59.57%, p=0.0070), with synergistic antitumor effects manifested as higher ORR (78.72% vs. 60.64%, p=0.0376), and longer median PFS (9.97 vs. 5.47 m, p=0.0120). CIP shows a biphasic inflammation-fibrosis pathology. scRNA-seq of 62,335 lung cells identified ISG^+ aged neutrophils (ISG^+ Na) as the key pathogenic driver of CIP progression. ICI-induced excessive immune activation triggers lung damage, activating the IFN-I-IRF9/STAT1 axis to promote ISG^+ Na differentiation. These cells secrete IL-6, IL-8, TNF-α to amplify inflammation, and TGF-β to induce fibroblast proliferation and activation, all of which pirfenidone blocks, supporting its full-cycle CIP efficacy mechanistically. Animal experiments further confirmed pirfenidone's robust efficacy in CIP prevention, treatment and synergistic antitumor activity with ICI. **Conclusions:** Pirfenidone reduces CIP incidence and synergizes with ICI therapy to enhance antitumor efficacy. Mechanistically, it targets IFN-I-IRF9/STAT1-ISG^+ Na axis for dual clinical benefits. These findings confirm pirfenidone as a translatable strategy to balance CIP control and antitumor activity. Research Sponsor: None.

2610 **Poster Session**

Intratumoral injection of IP-001 following thermal ablation in patients with advanced solid tumors: A multicenter phase Ib/IIa trial with expansion cohorts in melanoma and soft tissue sarcoma patients (SAKK 66/17). First Author: Markus Joerger, Health Ostschweiz (HOCH), St. Gallen, Switzerland

Background: This trial combines the novel adjuvant immunomodulator IP-001, a glycan polymer, with laser ablation in patients with relapsed solid tumors. **Methods:** This is a non-randomized, open-label multicenter phase Ib/IIa trial with a dose-finding part 1 and a dose expansion part 2 in advanced melanoma and soft tissue sarcoma (STS). Primary objectives include the safety and tolerability of up to six 4-weekly cycles of intratumoral IP-001 following laser ablation (TRANBERG Thermal Therapy System, Clinical Laserthermia System AB), and 12-week disease control rate (12w-DCR) according to RECIST v1.1 in advanced melanoma. The dose-finding part used 4 mL of IP-001 (10 mg/mL). The activity endpoint for advanced melanoma used the 1st stage of a Simon 2-stage design, with 12w-DCR $\leq$20% (H0) vs. $\geq$40% (H1) (type-I error 0.05, power 80%). **Results:** We treated 15 melanoma and 10 STS patients, including 4 in part 1 (n=28). Median age was 62 years, 57% were male, all patients had metastatic disease, including 60% with liver metastases. Most patients (78%) had received $\geq$3 prior lines of systemic treatment, including 79% with prior immunotherapy. Treatment was well tolerated with no dose-limiting toxicity, and a recommended IP-001 dose of 4 mL. Patients received a median of 2 (range 1 to 6) cycles of study treatment. Reasons for treatment discontinuation included physician's decision (39%) and disease progression (25%). 27 patients (96%) experienced treatment-emergent adverse events (TEAE). IP-001-related TEAE occurred in 16 (57%) patients, including 5 (17%) patients with severe IP-001-related TEAE. Severe TEAE occurred in 20 (71%) patients overall. Most frequent mild IP-001-related TEAE included fever (36%), fatigue (21%), rash (14%), hypotension (11%), injection site reactions (11%) and flu-like symptoms (7%); 2 cases (7%) of severe allergic reactions were reported, including one serious reaction. Allergic reactions occurred at cycle 3 in both patients and resolved without sequelae. Treatment discontinuation for TEAE occurred in a single patient (4%). 12w-DCR in advanced melanoma was 21% (3/14 evaluable patients) (2-sided 90% CI: 6%, 46%), with stable disease in 50% and partial remission (PR) in one (7%) melanoma patient. 15 (53%) patients had radiological tumor shrinkage in $\geq$1 untreated tumor lesion. Median progression-free survival (PFS) in advanced melanoma was 3 months, with a 12-month PFS rate of 33%, indicating preliminary evidence of disease control beyond the 12-week primary endpoint window. **Conclusions:** Intratumoral IP 001 at a dose of 4 mL following thermal ablation is well tolerated, with mainly mild, transient immune-related events. Although the pre-specified activity endpoint was not met, the observed DCR and PFS support further evaluation of this novel immuno-oncologic strategy. Clinical trial information: NCT03993678. Research Sponsor: Immunophotonics, Inc., St. Louis MO, 63110, U.S.

2612 **Poster Session**

Potential effects of TGF-β inhibition on immune resistance by targeting immunosuppressive microenvironment in advanced gastric cancer (AGC): Multi-omics post-hoc analysis of the K-Umbrella-06 trial. First Author: Choong-kun Lee, Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: TGF-β signaling promotes immune exclusion by driving fibrosis and hindering T-cell infiltration. We performed multi-omics post-hoc analyses of K-Umbrella-06 to identify mechanisms and predictive biomarkers for TGF-β/PD-L1 dual blockade in HER2-negative AGC. **Methods:** K-Umbrella-06 (NCT04835896) was an investigator-initiated, single-arm, phase Ib/II study enrolling HER2-negative AGC pts who had progressed on 1st-line treatment. Pts received bintrafusp alfa (TGF-β trap/anti–PD-L1) and weekly paclitaxel. Pretreatment H&E whole-slide images (WSIs) were analyzed with an AI-powered WSI analyzer to quantify fibroblast and endothelial cell (EC) densities and immune phenotypes. A separate cohort treated with nivolumab + paclitaxel (n=26) served as a control. Integration of baseline tissue transcriptomics and serial ctDNA sequencing (baseline, 1st RECIST assessment, and progression) was performed to identify predictive biomarkers and resistance mechanisms. **Results:** At a median follow-up of 46 months in 30 enrolled patients, the mPFS and mOS were 3.8 and 8.9 months, respectively; notably, 5 patients achieved durable responses with PFS exceeding 3 years. AI-WSI analysis revealed that high fibroblast density (≥median) was a significant predictor of superior outcomes (mPFS: 4.3 vs. 2.0 months, HR 0.29, P=0.007; mOS: 20.4 vs. 5.8 months, HR 0.28, P=0.012). Conversely, patients with higher intratumoral EC density had shorter mPFS (2.0 vs. 5.9 months, HR 2.29, P=0.058) and mOS (4.0 vs. 8.9 months, HR 1.61, P=0.285). Notably, patients with the immune-excluded phenotype achieved a higher ORR (60.0% vs. 18.2%) and prolonged survival compared to inflamed/desert types. These biomarkers were not predictive in the nivolumab + paclitaxel cohort, suggesting a TGF-β specific effect. Transcriptomic profiling of responders showed enrichment in TGF-β signaling (normalized enrichment score [NES] 2.87, P<0.001) and SMAD2/3 activity (NES 2.99, P<0.001), alongside increased naive CD8+ T cells and inflamed EC cells. Conversely, non-responders exhibited higher M2 macrophage and abundant angiogenic tip cells. Serial ctDNA analysis identified emergent TGF-β pathway alterations as a potential mechanism of acquired resistance (OR 7.30, P=0.08). **Conclusions:** Integrated AI-WSI, transcriptomic, and longitudinal ctDNA analyses suggest that TGF-β pathway activation and an immune-excluded phenotype are associated with clinical benefit from bintrafusp alfa plus paclitaxel, and may identify a responder subset distinct from conventional PD-1/PD-L1–based therapy. These findings support further evaluation of anti–TGF-β strategies for AGC with an immunosuppressive tumor microenvironment. Clinical trial information: NCT04835896. Research Sponsor: Merck KGaA.

2613 **Poster Session**

Effects of SECN-15, a neuropilin-1–targeting antisense oligonucleotide, on resistance to immune checkpoint inhibitors in preclinical tumor models. First Author: Richard Klar, Secarna Pharmaceuticals, Planegg, Germany

Background: Neuropilin-1 (NRP1) is a transmembrane co-receptor implicated in tumor growth, metastasis, angiogenesis, and immune suppression. High NRP1 expression is associated with poor prognosis in multiple solid tumors, including gastric cancer (GC) and breast cancer. SECN-15 is a high-affinity antisense oligonucleotide (ASO) designed to selectively downregulate NRP1. In light of recent clinical success of combined PD-1/PD-L1 and anti-angiogenic strategies and given its dual role in angiogenesis and immune suppression, NRP1 represents an attractive target to overcome resistance to immune checkpoint inhibition. **Methods:** NRP1-specific ASOs were identified using the OligoCreator platform. Anti-tumor efficacy was assessed following systemic administration in multiple syngeneic mouse tumor models, both as monotherapy and in combination with immune checkpoint inhibitors. Target engagement was evaluated at the RNA level in tissues and at the protein level in plasma via soluble NRP1 quantification. In silico analyses of patient transcriptomic datasets were conducted to prioritize indications for clinical development. PK/PD characterization and dose optimization studies are currently underway to support dose selection for GLP toxicology studies and first-in-human evaluation. **Results:** Systemic administration of SECN-15 achieved robust target knockdown in tumors across multiple cell populations and modulated the tumor microenvironment, including downregulation of extracellular matrix and EMT genes. A single dose resulted in near-complete and sustained suppression of plasma soluble NRP1 levels for up to 28 days, consistent with durable target engagement. SECN-15 delayed tumor growth as monotherapy, with complete regressions observed in a subset of animals, and significantly enhanced anti-tumor activity in combination with immune checkpoint inhibitors in models with limited responsiveness to checkpoint blockade alone. Single-cell RNA-seq analyses from gastric cancer patients identified endothelial cells and macrophages as major NRP1-expressing populations, with NRP1high subsets exhibiting TGF-β, hypoxia, and EMT pathway activation and suppression of allograft rejection signatures, consistent with an immunosuppressive, pro-angiogenic tumor microenvironment. In silico analyses showed that high NRP1 expression correlates with poor survival and advanced disease stage in gastric cancer, supporting its prioritization for clinical development. **Conclusions:** Targeting Neuropilin-1 with the ASO SECN-15 remodels the tumor microenvironment and enhances responsiveness to immune checkpoint blockade, supporting NRP1 inhibition as a strategy to overcome resistance to ICI therapy in solid tumors. The program is approaching IND-enabling development to support the clinical translation of SECN-15. Research Sponsor: Secarna Pharmaceuticals GmbH & Co. KG.

2614 **Poster Session**

Non-invasive characterization of intratumoral CD8+ T cells using standard-of-care (SOC) CT and ^{89}Zr-crefmirlimab berdoxam PET (CD8-PET) radiomic signature in solid tumors. First Author: Jayant Narang, Takeda Pharmaceuticals, Cambridge, MA

Background: Noninvasive estimation of intratumoral CD8+ T-cell density using radiomics may enhance comprehensive immune profiling and support immuno-oncology development and treatment decisions. We evaluated the feasibility of using a multimodality radiomic approach incorporating SOC CT and CD8-PET/CT to characterize CD8+ T-cell density in solid tumor lesions. **Methods:** 71 soft-tissue lesions from 52 patients with solid tumors enrolled in a Phase II iCorrelate trial (NCT03802123) were retrospectively analyzed. Patients received a pre-treatment CD8-PET/CT scan (ImaginAb, Inc) before initiating SOC immunotherapy (IOT) and a second CD8-PET/CT scan on-treatment 4-8 weeks later, with selection of biopsied tumor lesions of known CD8+ T-cell density for radiomic analysis. Radiomic features were extracted from volumetric segmentations of these tumor lesions using 3D Slicer on Diagnostic contrast CT (DCT, n=27), CT attenuation correction (CTAC; n=71), and CD8 PET (n=71) images. Features were integrated with acquisition parameters, lesion location, and adenopathy status. Feature selection used maximum relevance–minimum redundancy and variance inflation factor methods. Elastic-Net classifiers were trained to predict binarized (median split at the 328 cells/mm^2 level) CD8+ T-cell density, with hyperparameter optimization via grid search and 5 fold Cross-Validation (CV). In each iteration of the CV, 1 fold (20%) was left out and models were trained on the remaining 4 folds (80%). Model performance was assessed using AUC and F1 score. **Results:** In the test set, Multimodality models (CTAC+DCT+PET) outperformed single-modality (AUC up to 0.94 vs. 0.80), with improved AUC and F1 scores and robust performance across endpoints. Single-modality models achieved AUCs of 0.76 (F1 0.55) for DCT, 0.80 (F1 0.72) for CTAC, and 0.80 (F1 0.70) for PET. The combined CTAC+DCT+PET model demonstrated superior performance with a test AUC of 0.85 (F1 0.79) and training AUC of 0.94 (F1 0.89). Application of previously reported DCT radiomic weights (Sun et al.) to this cohort yielded a lower AUC of 0.68, compared with the multimodality model. **Conclusions:** This study demonstrates robust radiomics-based characterization of intratumoral CD8+ T-cell density in patients with solid tumors is feasible using non-invasive multi-modality approach utilizing CD8-PET and SOC CT scans. These findings may lead to further clinical adoption and non-invasive monitoring of the tumor immune microenvironments with CD8-PET and SOC CT scans using radiomics, informing IOT decision-making, and enhancing patient stratification in both clinical development and routine oncology practice. Validation in larger, multicenter cohorts is still required to confirm generalizability and robustness of these radiomic signatures. Clinical trial information: NCT03802123. Research Sponsor: None.

2615 **Poster Session**

PhaseX as a phase 0.9 translational platform to de-risk BiTE immunotherapy through mechanistic patient explant profiling. First Author: Kanishka Fernando, National Cancer Centre Singapore, Singapore, Singapore

Background: Bispecific T-cell engagers (BiTEs) redirect cytotoxic T cells to tumor cells, but responses in solid tumors remain heterogeneous due to antigen variability, T-cell exclusion, stromal barriers, and immunosuppressive cues within the tumor microenvironment (TME). PhaseX (patient-derived hydrogel-assisted explants) preserves native tissue architecture and endogenous immune composition ex vivo, enabling mechanistic, patient-specific interrogation of immunotherapies in a physiologically relevant context. We used PhaseX to define BiTE mechanism of action (MoA) and resolve response phenotypes in head and neck squamous cell carcinoma (HNSCC). **Methods:** Tumor explants from ~25 HNSCC patients were ex-vivo cultured in PhaseX and treated for 6 days with CD3×B7-H3 or CD3×EpCAM BiTEs with matched controls. Supernatants were collected longitudinally for multiplex secretome profiling. At endpoint, explants were dissociated and subjected to flow cytometry, while some explants were fixed and processed to FFPE sections for multiplex immunofluorescence (mIF). Cancer cells were quantified using epithelial markers (PanCK and p60). Tumor response states were classified as tumoricidal (increased tumor-cell CC3 [cleaved caspase-3] with reduced PanCK$^+$/p60$^+$ cancer cell burden) versus tumorostatic (preserved PanCK$^+$/p60$^+$ cancer cell burden with reduced Ki-67 in PanCK$^+$/p60$^+$ cancer cells). **Results:** Across both CD3×B7-H3 and CD3×EpCAM BiTE-treated explants, PhaseX captured core BiTE MoA: (i) TCR-driven activation with expansion of activated CD8$^+$ T cells (CD137$^+$) and enrichment of tumor-reactive CD8$^+$ subsets (CD137$^+$CD103$^+$CD39$^+$); (ii) immune trafficking and inflammatory programming consistent with IFN-γ signaling, evidenced by increased CXCL9/10/11 and coordinated effector cytokine signatures; and (iii) effector execution in tissue, integrating increased cytotoxic mediators (perforin, granulysin) with spatial mIF evidence of enhanced intratumoral CD8+ infiltration. Tumoricidal responders showed elevated tumor-cell CC3 with concomitant loss of PanCK$^+$/p60$^+$ tumor area, whereas tumorostatic responders showed decreased tumor-cell Ki-67 expression with comparatively limited CC3 induction, supporting biologically distinct on-treatment states. **Conclusions:** PhaseX serves as a "Phase 0.9" translational platform that preserves the TME and resolves BiTE MoA from activation to trafficking to effector execution, while distinguishing tumoricidal and tumorostatic response phenotypes. This framework supports mechanistic deconvolution, biomarker discovery, and patient stratification to de-risk bispecific antibody development. Research Sponsor: National Medical Research Council; MOH-STAR24jul-0002; National Medical Research Council; MOH-001212-01.

2616 **Poster Session**

Phase 1A/B study of AB248, a CD8+ selective IL-2 mutein fusion protein, alone or in combination with pembrolizumab, in patients with advanced solid tumor malignancies. First Author: Harriet M. Kluger, Yale University School of Medicine, Smilow Cancer Center, New Haven Hospital, New Haven, CT

Background: High-dose IL-2 demonstrates modest activity in melanoma and RCC but its use is limited by severe toxicity. AB248 is a novel IL-2 fusion protein of an attenuated IL-2 mutein linked to an antibody targeting CD8β that features >500-fold selectivity for CD8+ T cells and shows strong anti-tumor activity both alone and with anti-PD1 in preclinical models. In addition to CD8+ T cell expansion and activation, the drug avoids NK cell toxicity and Treg-mediated immunosuppression. **Methods:** NCT05653882 is a phase 1A/B study investigating the safety, pharmacokinetics (PK), pharmacodynamics (PD) and anti-tumor activity of AB248 alone or with pembrolizumab in locally advanced/metastatic solid tumor malignancies, including melanoma, having previously progressed through PD-1/PD-L1 checkpoint blockade. The study's primary objective was to assess the safety and tolerability of AB248 alone and in combination with pembrolizumab. **Results:** As of December 1, 2025, 61 patients (pts.) were treated with monotherapy (MT) at 6 dose levels across 3 schedules (Q2W at 0.02mg/kg-0.75mg/kg; QW at 0.15mg/kg; Q3W at 0.3mg/kg). 68 additional pts. were treated with combo therapy (CT) at Q3W 0.15-0.3mg/kg and step-up dosing. The most common TEAEs (> 95% G1-2) among all pts. were fatigue (50%), rash (49%), nausea (43%), chills (33%), pyrexia (32%), vomiting (32%) and diarrhea (30%). Maximum tolerated doses (MTDs) were 0.5 mg/kg for MT Q2W and 0.15 mg/kg for CT Q3W. An MTD was not reached for CT step-up dosing. 41 cutaneous (cut) and mucosal (muc) melanoma pts. were evaluable for response across MT and CT dose cohorts, with 95% of pts. having received prior IO doublet therapy (anti-PD1 + anti-CTLA or anti-LAG3) and 83% having received ≥ 2 anti-PD1 regimens. Among evaluable cut melanoma pts., 2 confirmed PRs (18%) were observed among 11 pts. enrolled at higher MT dose levels (net tumor reductions of 78.8% and 87.2%) and 2 confirmed PRs (12%) were observed among 16 CT pts. (37.5% and 57.5%). Among 11 muc melanoma pts., 3 confirmed PRs (27%) were observed in CT dosing. One additional muc melanoma pt. received 0.5 mg/kg MT and remained on study with SD > 15 mos. AB248 exhibited dose-proportional PK that is comparable between MT and CT dosing. Peripheral PD data demonstrated robust and preferential CD8+ T cell expansion, with >20X expansion in MT (0.3 mg/kg and above) and >11X expansion in CT dosing (0.15 mg/kg and above). Further data on safety, PK, PD, and preliminary anti-tumor activity will be presented. **Conclusions:** AB248 demonstrates robust anti-tumor activity across heavily IO-pretreated patients with metastatic melanoma (incl. mucosal melanoma). Combined with an acceptable safety profile, favorable PK and differentiated PD, the drug's anti-cancer activity merits further investigation. Clinical trial information: NCT05653882. Research Sponsor: Asherbio Therapeutics.

2618 **Poster Session**

First-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody IBI363 (TAK-928) in patients (pts) with advanced immunotherapy-resistant non–small cell lung cancer (NSCLC): Updated results from a phase I study. First Author: Jianya Zhou, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: IBI363 is a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein designed to block the PD-1/PD-L1 pathway and simultaneously activate the IL-2 pathway. IBI363 selectively expands and rejuvenates exhausted tumor-specific T cells by cis-activating IL-2 receptors. It has shown a manageable safety profile and encouraging efficacy in NSCLC (No. 8509, 2025 ASCO). The updated findings are reported here with a longer follow-up. **Methods:** Pts with advanced NSCLC who had progressed on standard therapy were enrolled and received IBI363 at dose levels of 0.002/0.01/0.3/0.6 mg/kg every week, 0.3/0.6/1 mg/kg Q2W or 1.5/2/3/4 mg/kg Q3W. Endpoints included safety, ORR, DCR, DOR and PFS assessed by investigator per RECIST v1.1, and OS. **Results:** As of Nov 20, 2025, 136 pts with NSCLC were enrolled (prior treatment lines ≥2 72.1%; including 67 with squamous NSCLC [sqNSCLC] and 66 with adenocarcinoma). The median follow-up was 14.4 months (mos, range 0.8–30.6). Both the ORR and DCR in sqNSCLC or adenocarcinoma were consistent with those reported previously. In pts with sqNSCLC at 1/1.5 mg/kg (n=28) and 3 mg/kg Q3W (n=31) (58/59 with prior IO therapy), median PFS was 5.5 (95% CI 1.5, 8.3) and 10.1 mos (6.0, 14.0), median OS was 12.5 (7.6, 22.2; maturity 71.4%) and 18.2 mos (10.7, not calculable [NC]; maturity 48.4%), with 24-month OS rate of 29.9% (14.2, 47.3) and 47.8% (28.7, 64.7), respectively. Among those who had a confirmed complete response (n=1) or partial response (PR, n=17), the overall DOR was 10.3 mos (7.0, 13.4; maturity 72.2%). In pts with *EGFR^{wt}* adenocarcinoma at 0.6/1/1.5 mg/kg (n=30) and 3 mg/kg Q3W (n=25) (all with prior IO therapy), median PFS was 2.7 (1.4, 5.1) and 4.2 mos (3.0, 7.0), median OS was 17.5 (7.1, NC; maturity 56.7%) and 15.2 mos (9.6, NC; maturity 56.0%), with 24-month OS rate of 40.2% (22.2, 57.7) and 42.7% (23.1, 61.0), respectively; the overall DOR reached 21.3 mos (4.0, 21.3; maturity 40.0%) in those achieving a confirmed objective response (n=10, all PRs). Smoking is a major factor affecting treatment efficacy in adenocarcinoma. In smokers (n=31) and non-smokers with adenocarcinoma (n=24), the median OS was 23.4 (11.3, NC; maturity 48.4%) and 11.5 mos (5.6, 19.6; maturity 66.7%), respectively. In the overall population (n=136), treatment-emergent adverse events (TEAEs) occurred in 135 pts (99.3% any grades; 48.5% ≥G3). TEAEs led to treatment discontinuation in 11 (8.1%) pts. TEAEs led to death in 5 pts (3.7%) with only 1 event (0.7%) considered treatment-related (unexplained death). The most common TEAEs were arthralgia (52.2%; 3.7% ≥G3), anemia (46.3%; 4.4% ≥G3), and rash (39.0%; 8.8% ≥G3). **Conclusions:** IBI363 was well tolerated with a manageable safety profile consistent with earlier reports, and continued to show strong and durable efficacy in pts with heavily pretreated NSCLC. Clinical trial information: NCT05460767. Research Sponsor: This study was funded by Innovent Biologics, Inc.

2619 **Poster Session**

Alirocumab plus cemiplimab in immuno-refractory metastatic NSCLC: A single-arm, multi-center, phase 2 study. First Author: Eziafa Oduah, Duke University, Durham, NC

Background: Immunotherapy resistance remains a significant unmet clinical need for most non-small cell lung cancer (NSCLC) patients. PCSK9 was shown in preclinical models to mediate cancer immunotherapy resistance and may serve as a novel immunoinhibitory target. **Methods:** This is a first-in-class, multi-center, single arm, phase II study evaluating the clinical activity and safety of the PCSK9 inhibitor, alirocumab, in combination with the anti-PD1 antibody cemiplimab, in non-small cell lung cancer (NSCLC) patients whose tumors were previously resistant to immune checkpoint blockade. The primary endpoint was objective response rate (ORR). Secondary endpoints were safety, progression free survival (PFS), overall survival (OS), duration of response (DOR) and disease control rate (DCR). The correlative objective was to analyze the biomarkers of response. **Results:** A total of 60 patients were enrolled between May 2023 and August 2025. In the 58 evaluable patients, the estimated ORR for the two-stage design was 14.98% (90% CI, 5.45, 25.52). The median duration of response was not estimable. The median OS was 7.2 months (95% CI, 5.3 – 13.6). No new safety signals were seen. Non-hematologic adverse events (AEs) were more prevalent than hematologic AEs and were predominantly grade 2 or less. Two grade 3 events were seen. Biomarker analysis identified superior outcomes in NSCLC harboring *PIK3CA, AKT1*, or *PTEN* alterations, with ORR of 31.5% (95% CI,13.9%, 68.4%,), significantly associating with response, p 0.0008 (two-sided, Fisher's exact). No objective responses were observed in the absence of *PIK3CA, PTEN* or *AKT1* alterations. Median OS was numerically longer in the altered group was 13.64 months (95% CI, 3.1 – NR) compared to 7.2 months (95% CI, 5.2-12.8) in the unaltered group. Analysis of the cancer genome atlas (TCGA) in NSCLC cohorts demonstrated a correlation between *PIK3CA, PTEN* and *AKT1* expression and PCSK9 expression. Preclinical translational studies further elucidated the impact of *PIK3CA, PTEN* or *AKT1* in intratumoral PCSK9 secretion, a novel immune-oncological finding for this pathway, and provided a biological rationale for the observed pattern of response. **Conclusions:** These findings provide clinical proof-of-principle that PCSK9 inhibition can overcome immunotherapy resistance in a subset of patients and suggest that *PIK3CA/PTEN/AKT1* pathway may play a significant role in PCSK9 mediated immune evasion and could be a biomarker of response. These findings warrant further investigation in a larger confirmatory study. Clinical trial information: NCT05553834. Research Sponsor: None.

2620 **Poster Session**

Targeting PI3K-β to develop novel combinational therapies for melanoma. First Author: Maegan Gabby, Virginia Tech Carilion School of Medicine, Roanoke, VA

Background: Melanoma is the deadliest skin cancer, and more than 100,000 people in the United States were diagnosed in 2024. While the 5-year survival rate is 99% for localized disease, it is just 10-25% in metastasis. Treatment for metastatic melanoma often involves powerful immunotherapies (e.g. checkpoint inhibitors). However, approximately 55% of patients have innate resistance and 25% of responders develop resistance within two years. Immunotherapy resistance is due to continued checkpoint protein expression and antagonization of T-cell activation – processes controlled by the phosphatidyl inositol 3-kinase (PI3K) system. Of the four PI3K kinases (α, β, δ and γ), recent work from the Sheng lab suggests that PI3Kβ has the largest role in the growth of BRAF^{V600E}/PTEN^{null} (PI3K inhibitor) melanoma and is a prime drug target. There is an 18-residue motif found only in PI3Kβ that has close interactions with p85 - a key regulatory protein responsible for kinase activation. The Sheng lab harnessed this motif and developed a novel peptide (CPP-β18) that selectively blocks PI3Kβ with high affinity and decreases viability in cells that hyper-express PI3Kβ. Given the vital role of PI3K in immunosuppression, further investigation into CPP-β18's sensitizing effects on checkpoint inhibitors is urgently needed to lead to new therapies. **Methods:** PI3K inhibition in BRAF^{V600E}/PTEN^{null} YUMM1.7 and BRAF^{V600E}/PTEN^{WT} YUMM5.2 murine cell lines was validated by exposing cells to various commercial PI3K inhibitors and CPP-β18. Cell viability was measured via MTS colorimetric response. Advanced live-cell imaging techniques were employed to assess apoptosis when melanoma cells were treated with these selective inhibitors. Both cell lines were fluorescently labeled to differentiate cells from cytotoxic T-cells in future co-culture work. **Results:** MTS colorimetric assays reveal decreased YUMM1.7 cell viability with various PI3Kβ inhibitors (IC_{50} values = 6-10 μM) in comparison to increased YUMM5.2 cell viability (IC_{50} values = 21-30 μM). PI3Kδ and PI3Kγ inhibition had negligible effect on cell survival. YUMM1.7 cell death (>70%) was also demonstrated when treated with the novel CPP-β18 peptide inhibitor. Live cell imaging studies confirm feasibility to investigate interactions between drug therapy and melanoma cells and to appreciate early and late stages of apoptosis on a cellular level. Both cell lines are successfully fluorescently labeled to undergo further drug challenge experiments. **Conclusions:** Our data strongly supports CPP-β18 as a potential drug therapy to augment checkpoint inhibitor efficacy and mitigate the development of resistance. Cell line validation demonstrates increased PI3K activity with deleted PTEN and decreased viability when challenged with PI3Kβ inhibitors. Selectively blocking PI3Kβ via CPP-β18 may augment checkpoint inhibitors and mitigate resistance, giving patients improved treatment options. Research Sponsor: None.

2621 **Poster Session**

Phase I/II study of concurrent intrathecal toripalimab and pemetrexed (PM) for leptomeningeal metastases (LM) from solid tumors. First Author: Guozi Yang, Cancer Center, Huizhou First Hospital Affiliated to Guangdong Medical University, Huizhou, China

Background: Intrathecal (IT) programmed death-1 (PD-1) inhibitors have demonstrated safety and feasibility in leptomeningeal metastases (LM) from melanoma or lung cancer. However, no studies have yet reported on the combination of IT PD-1 inhibitors with IT chemotherapy for LM from solid tumors. This study evaluated the feasibility and potential clinical benefit of combining IT toripalimab with pemetrexed (PM) in this patient population. **Methods:** Phase I followed a 3+3 dose de-escalation design to determine the dose-limiting toxicity (DLT) and the recommended phase II dose (RP2D). Patients received IT PM (15 mg flat dose) twice weekly for 2 weeks (induction), then weekly for 4 weeks (consolidation), followed by monthly maintenance. The administration of IT toripalimab (40 mg initial dose) was initiated concurrently with the fourth dose of IT PM, on an every-two-week schedule for 6 weeks (induction/consolidation), switching to monthly dosing during the maintenance phase. Continuation of previously administered systemic therapies was permitted during the study. The primary endpoints were RP2D and safety. Secondary endpoints included clinical response rate (CRR), disease control rate (DCR) and overall survival (OS). **Results:** From June 2024 to September 2025, 45 patients were enrolled (40 non-small cell lung cancer, 4 breast cancer, and 1 small cell lung cancer). Median age was 52 years (range 30–69), and 35 patients were female. In phase I, no DLTs were observed; the RP2D was established as toripalimab 40 mg plus PM 15 mg. All patients completed induction therapy, 42 completed consolidation therapy, and 41 received maintenance therapy. No treatment-related deaths occurred. All grade ≥3 adverse events (AEs) were attributable to IT PM, with an overall incidence of 55.6% (25/45), including leukopenia (n = 16), thrombocytopenia (n = 10), decreased hemoglobin (n = 7), and elevated hepatic aminotransferases (n = 5). Immune-related AEs were limited to grades 1-2, occurring in 24.4% (11/45) of patients, and included rash (n = 5), fever (n = 3), hypothyroidism (n = 3), and pneumonia (n = 1). According to Response Assessment in Neuro-Oncology (RANO) criteria, the CRR was 66.7% (30/45), including 11 patients with neurological dysfunction improvement, 16 with CSF cytological response, and 18 with neuroimaging improvement. The DCR was 93.3% (42/45). As of January 20, 2026, 19 patients had died. Median follow-up was 11.1 months (95% CI: 7.7–17.0). Median OS was 13.1 months (95% CI: 9.9–not applicable). **Conclusions:** IT toripalimab combined with PM showed a manageable safety profile and promising clinical activity in patients with LM from solid tumors. Based on the encouraging interim OS observed, further clinical investigation of intrathecal immunotherapy is warranted for patients with LM. Clinical trial information: NCT06462222. Research Sponsor: Huizhou Science and Technology Innovation Team Project; 2023EQ050012; Huizhou Outstanding Young Scientific and Technological Talents Program; 2025EQ050018.

2622 **Poster Session**

Sequential or concurrent immunotherapy with locoregional radiotherapy in de novo metastatic nasopharyngeal carcinoma. First Author: Linfang Wu, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: First-line chemotherapy combined with immunotherapy (CT-IO), followed by selective locoregional radiotherapy (LRRT), has emerged as the mainstay treatment for de novo metastatic nasopharyngeal carcinoma (dmNPC). However, the efficacy of adding concurrent immunotherapy to LRRT remains controversial. **Methods:** This study enrolled patients with dmNPC who received platinum-based chemotherapy, anti–PD-1 immunotherapy, and definitive LRRT. Survival outcomes were assessed using a 12-month landmark analysis to minimize immortal time bias. Inverse probability of treatment weighting (IPTW) was employed to balance baseline characteristics between the CCRT+IO (LRRT with concurrent immunotherapy) and CCRT-IO (LRRT without concurrent immunotherapy) groups. Recursive partitioning analysis (RPA) utilizing baseline and post-CT-IO factors was applied to stratify patients into low- or high-risk groups to evaluate the benefit of concurrent IO. Absolute lymphocyte count (ALC) was monitored during and up to 6 months post-LRRT. **Results:** A total of 238 patients were included (185 receiving concurrent IO and 53 without). In the IPTW-adjusted Kaplan-Meier analysis at the 12-month landmark, the addition of concurrent IO was associated with significantly inferior progression-free survival (PFS) (Hazard Ratio [HR]: 3.189; 95% CI, 1.352–7.524; p = 0.008). The "Sandwich" mode—comprising 4-6 cycles of induction CT-IO, followed by LRRT, and subsequent IO maintenance—yielded the optimal survival outcomes (HR: 0.288; 95% CI, 0.106–0.786; p = 0.015). An RPA model incorporating five prognostic factors (the number of metastatic lesions, pretreatment LDH level, post-CT-IO Epstein-Barr virus DNA, and radiological response post-CT-IO) stratified patients into two risk subgroups. Low-risk patients derived no clinical benefit from concurrent IO (p = 0.134), whereas high-risk patients exhibited significantly worse 12-month landmark adjusted PFS (p = 0.031). Notably, subgroup analysis showed that patients with persistent radiation-induced lymphocytopenia at 3 months post-RT demonstrated the most unfavorable survival outcomes after concurrent immunotherapy ($p < 0.001$). **Conclusions:** DmNPC patients receiving first-line CT-IO followed by LRRT did not benefit from concurrent immunotherapy during RT, particularly those identified as high-risk by the prognostic model and those with persistent lymphocytopenia at 3 months post-RT. Research Sponsor: None.

2623 **Poster Session**

Efficacy and safety of cadonilimab in patients with MSI-H/dMMR locally advanced or metastatic gastrointestinal malignancies: A real-world retrospective study. First Author: Xiaoyuan Sun, The Affiliated Hospital of Qingdao University, Gastrointestinal Oncology and Pancreatic Diseases Center, Qingdao, China

Background: Immunotherapies targeting PD-1 and CTLA-4 have emerged as promising therapeutic strategies for gastrointestinal malignancies (GIM), particularly those dMMR or MSI-H phenotypes. Cadonilimab, a novel bispecific antibody co-targeting PD-1 and CTLA-4, has showed potent anti-tumor effect across multiple cancer types. This real-world retrospective study systematically evaluated the efficacy and safety of cadonilimab in patients with MSI-H/dMMR locally advanced or metastatic GIM. **Methods:** This study retrospectively included patients with MSI-H/dMMR unresectable locally advanced or metastatic GIM who administered cadonilimab(6 mg/kg Q2W) since November 2022 in The Affiliated Hospital of Qingdao University. The primary endpoint was ORR as assessed by investigators per RECIST v1.1. Secondary endpoints included DCR, PFS, DoR, safety profile, and exploratory biomarker analysis (interleukins [IL-2, IL-6, IL-8, IL-10]) was performed on blood samples collected at baseline and before each treatment cycle. **Results:** As of November 7, 2025, a total of 21 patients were enrolled. The median follow-up duration was 19.4 months. The ORR was 76.19% and DCR was 100%. Median PFS and median DoR were not reached. The 12-month PFS rate was 74.9% (95% CI, 49.6%-88.8%) and 18-month PFS rate was 68.1% (95% CI, 41.6%-84.5%). Among 14 gastric cancer (GC) patients, ORR was 78.57% (5 CR, 6 PR), median PFS was not reached, 12-month PFS rate was 77.9% (95% CI, 58.6%-100%), and 18-month PFS rate was 68.2% (95% CI, 46.3%-100%). The ORR of GC treated in 1st line was 80%, 4 achieved CR (40%). Among 7 colorectal cancer (CRC) patients, ORR was 71.43% (2 CR, 3 PR), median PFS was not reached, 12-month PFS rate was 71.4% (95% CI, 49.6%-88.8%), and 18-month PFS rate was 71.4% (95% CI, 29.4%-91.9%); the ORR of 1st line treatment was 83.33%. By metastatic site: ORR was 85.71% in patients with peritoneal metastasis and 100% in those with pelvic metastasis. Notably, one patient achieved pCR after cadonilimab conversion therapy, and another patient receiving cadonilimab as fourth-line monotherapy achieved PFS of 25.4 months. As of data cutoff, 5 patients remained on treatment. Regarding safety, 33.33% of patients experienced grade 1-2 immune-related adverse events (irAEs), and 4.76% had grade ≥3 irAEs. No treatment discontinuation due to adverse events. Exploratory biomarker analysis showed that ORR was 90.91% in patients with high IL-2 expression, 91.67%,92.86% and 81.82% in patients with normal IL-6, IL-8 and IL-10 levels, respectively. **Conclusions:** Cadonilimab demonstrates potent and durable anti-tumor activity with a favorable safety profile in MSI-H/dMMR locally advanced or metastatic GIM. Additionally, interleukins may serve as potential predictive biomarkers for cadonilimab efficacy, providing insights for precision medicine in this patient population. Research Sponsor: None.

2624 **Poster Session**

Intrathecal (IT) PD-1/CTLA-4 antibody combined with pemetrexed (PM) for leptomeningeal metastases (LM) from solid tumors: Preliminary results of two single-center phase I studies. First Author: Zhenyu Pan, Department of Radiation Oncology, Beijing Chest Hospital, Capital Medical University, Beijing, China

Background: IT PD-1 inhibitors, alone or combined with IT PM, have shown safety and feasibility in LM from solid tumors. Cadonilimab (AK104) and iparomlimab/tuvonralimab (QL1706) are novel bispecific PD-1/CTLA-4 antibody. Our preclinical animal studies demonstrated the safety of IT administration of these agents. This study evaluated the feasibility and potential clinical benefit of combing IT PD-1/CTLA-4 antibody with PM in patients with LM from solid tumors. **Methods:** Eligible patients had histologically confirmed solid tumors and positive CSF cytology. A rapid dose-escalation design was employed across three dose levels: AK104 at 15.625 mg, 31.25 mg and 62.5 mg; QL1706 at 25 mg, 37.5 mg and 50 mg. One patient was enrolled in each of the first two dose cohorts, while six were enrolled at the third dose cohort. The protocol would revert to a standard 3+3 design if any dose-limiting toxicities (DLT) occurred. IT PM was given at a fixed dose of 15 mg twice weekly for two weeks (induction), then weekly for four weeks (consolidation), followed by monthly maintenance until progression or death. IT PD-1/CTLA-4 antibody began at the fourth IT PM dose, administered every two weeks for six weeks, then monthly until progression or death. Continuation of previously administered systemic therapies was permitted during the study. **Results:** A total of 17 patients were enrolled (AK104: n=8; QL1706: n=9). Median age was 54 years (range 37–73); 13 were female. Primary tumors included lung adenocarcinoma (n=13) and breast cancer (n=4). 16 patients (94.1%) completed induction and consolidation therapy. No DLT occurred. Grade ≥3 adverse events (AEs) occurred in 64.7% (11/17) of patients. Specifically, grade ≥3 AEs attributed to IT PM were observed in 58.8% (10/17), primarily hematological toxicity (n=10), elevated hepatic aminotransferase (n=1) and fatigue (n=1). For IT PD-1/CTLA-4 antibody-related AEs, grade ≥3 occurred in 11.8% (2/17; rash n=1, diarrhea n=1), and grade 1-2 in 17.6% (3/17; rash n=3, fever n=1, diarrhea n=1). Clinical response rate was 41.2% (7/17) by RANO-LM criteria. Disease control rate was 82.4% (14/17). As of January 15, 2026, 8 patients had died, with 1 due to LM, 3 due to systemic progressive disease, and 4 due to non-cancer-related causes. Median follow-up time was 8.53 months (95%CI: 8.07-NA), and median overall survival was 8.53 months (95%CI: 6.3-NA). **Conclusions:** The study demonstrates the manageable safety and feasibility of IT PD-1/CTLA-4 antibody combined with PM, with no unexpected systemic or neurological toxicities observed. Preliminary results suggest potential clinical benefits, with a high clinical response rate and notable treatment responses even among those with severe conditions. ClinicalTrials.gov registration: NCT06762080/NCT06809530. Clinical trial information: NCT06809517/NCT06809530. Research Sponsor: Huizhou Science and Technology Innovation Team Project; 2023EQ050012; Huizhou Outstanding Young Scientific and Technological Talents Program; 2025EQ050018.

2625 **Poster Session**

Evaluation of intravenous IPI201 in combination with anti–PD-1 therapy in a colorectal cancer mouse model. First Author: Brett Lanier, Isosceles Pharmaceuticals, Wilmington, NC

Background: Immune checkpoint inhibitors targeting PD-1 improve outcomes in colorectal cancer (CRC) but are limited by intrinsic and acquired resistance. Resorcinyl isoprenyl benzene derivatives have previously shown anti-tumor activity in multiple models, including remodeling of the tumor microenvironment (TME). IPI201 is a novel, synthetic resorcinyl isoprenyl benzene derivative administered intravenously. Here, we evaluated whether IPI201 combined with anti-PD-1 therapy alters tumor and immune outcomes in a murine model of CRC. **Methods:** MC38 colon tumors were implanted subcutaneously in mice and treated with vehicle, IPI201 (i.v.), anti-PD-1 (BE0156; i.p.), 5-fluorouracil (5-FU) (i.p.), or IPI201 plus anti-PD-1 at varying dose combinations once the implanted tumor reached a size of 75 mm^3. Change in tumor volume and subject survival were assessed over 30 days. Tumor necrosis was evaluated by blinded histopathology. Tumor gene expression was analyzed using NanoString nCounter immune-focused panels with pathway and network analyses comparing combination therapy to monotherapies and vehicle controls. **Results:** While IPI201 or anti-PD-1 monotherapy demonstrated limited activity, combination treatment produced enhanced anti-tumor effects. The optimal dose combination resulted in a 66% reduction in tumor growth compared with anti-PD-1 alone, with a significant treatment interaction (P=0.03). Combination therapy significantly improved survival relative to monotherapies and 5-FU (50% vs 0%, adjusted $P<0.02$), yielding the highest survival among treatment groups. Tumor necrosis scores were increased with combination therapy, with necrosis twofold higher than anti-PD-1 alone ($P<0.01$). Transcriptomic profiling revealed differential regulation of 771 genes across 51 biological pathways, including VEGF, EGFR, MAPK/ERK, and PI3K/Akt/mTOR signaling, as well as immune-associated pathways related to antigen presentation, cytotoxic lymphocyte activation, and myeloid cell recruitment. This transcriptional signature is consistent with a pro-immune, anti-tumor TME. **Conclusions:** IPI201 and PD-1 blockade combination improves survival, promotes tumor necrosis, and remodels the tumor microenvironment in a preclinical CRC model. These findings support further development of IPI201 as a combination immunotherapy strategy and provide a mechanistic rationale for evaluating resorcinyl isoprenyl benzene-based enhancers of checkpoint inhibition in CRC. Research Sponsor: None.

2626 **Poster Session**

Phase I/II study of LB1410, a bivalent TIM-3/PD-1 bispecific antibody, in combination with LB4330, a long-acting IL-10, in patients with advanced solid tumors. First Author: Jiajian Liu, L&L Bio Co., Ltd., Shanghai, China

Background: LB1410 is an anti-PD-1/TIM-3 bispecific antibody (BsAb) developed by L&L Bio Co., Ltd., Shanghai, China. In an ongoing phase I study in patients (pts) with advanced solid tumors (NCT05357651), LB1410 demonstrated an excellent safety profile (RPIID 20 mg/kg) and promising efficacy in various anti-PD-1-resistant solid tumors: ORR 9.1%; DCR 54.5%; n = 66 as of Jan 4, 2026. Antitumor activity was especially notable in anti-PD-1-resistant ccRCC (ORR 11.1%; DCR 77.8%; n = 9) and anti-PD-1-resistant CC (ORR 38.5%; DCR 69.2%; n = 13). LB4330 is a novel, long-acting IL-10 developed by L&L Bio Co., Ltd., Shanghai, China. It is generated by fusing IL-10 to a high-affinity anti-CLDN18.2 antibody and exhibits a significantly extended $T_{1/2}$ of 2.3 days. In a completed phase I study (NCT05707676), LB4330 effectively enhanced CD8+ T cell proliferation and activation in cancer pts and achieved a DCR of 36.4% (12/33) in pts with PDAC, CRC and other anti-PD-1-resistant tumors. Given their complementary mechanisms and potential to better enhance antitumor immune activity, a phase I/II study has been launched to evaluate LB1410 in combination with LB4330 in pts with advanced solid tumors. **Methods:** Eligible pts were ≥18 yrs old with ECOG PS 0-1. Pts received LB1410 at 15 or 20 mg/kg in combination with LB4330 at 0.2-0.4 mg/kg IV Q2W, with a maximum of 6 doses of LB4330. A 3+3 dose-escalation design was used to assess safety and tolerability. The selected doses of LB1410 at 15 or 20 m/kg plus LB4330 at 0.4 mg/kg were used for the efficacy expansion study in pts with anti-PD-1-resistant ccRCC and HCC. **Results:** As of Jan 14, 2026, 15 patients (1 CRC, 1 HCC, 3 NSCLC, 4 CC and 6 ccRCC) had been enrolled: median age 58.5 yrs (42-71 yrs); 57.1% male; 85.7% with prior anti-PD(L)1-based therapies. TRAEs occurred in 13 pts (92.9%), the most common (≥ 20%) being fever, platelet count decreased, pruritus, elevated ALT, elevated AST, elevated creatinine, cough, rash and anemia. Most TRAEs were related to the MOA of LB4330 and were manageable. Grade 3-4 TRAEs occurred in 5 pts (35.7%), including decreased platelet count in 2 pts and IRR, shock symptom and immune-mediated myocarditis in 1 pt each. No DLTs were observed. Among all pts with on-treatment scans, the overall ORR per RECIST 1.1 was 15.4% (2/13) with 2 confirmed PR ; DCR was 30.8% (4/13). Notably, the 5 pts with anti-PD-(L)1-refractory favorable-risk ccRCC showed an ORR of 40.0% and a DCR of 80.0%. 50% ccRCC pts with PR/SD (2/4) had been on treatment for nearly one year or longer. **Conclusions:** The combination of LB1410 and LB4330 exhibited a manageable safety profile consistent with that observed with each monotherapy. Clinical data in pts with favorable-risk ccRCC support the characteristics and efficacy of LB4330 as an immune-enhancing agent. Efficacy expansion studies are ongoing. Clinical trial information: NCT06468358. Research Sponsor: L&L Bio Co., Ltd., Shanghai, China.

2627 **Poster Session**

Low-dose intestinal irradiation to enhance the efficacy and prognosis of PD-1 blockade in metastatic non-small cell lung cancer. First Author: Baiyang Huang, Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, China

Background: Intestinal low-dose irradiation (ILDR) has been shown to enhance the efficacy of immunotherapy in advanced solid tumors by modulating the gut microbiota and metabolism. However, its role in metastatic non-small cell lung cancer (mNSCLC), particularly in the first-line treatment setting, remains unclear. Therefore, this study investigated the impact of intestinal radiation dose on the efficacy and prognosis of programmed cell death protein 1 (PD-1) blockade in patients with mNSCLC. **Methods:** This multicenter retrospective and prospective study included patients with mNSCLC who received first- or second-line PD-1 inhibitors combined with abdominopelvic radiotherapy between 2018 and 2025. Patients were stratified into three groups according to the mean intestinal radiation dose: <1 Gy, 1–3 Gy, and >3 Gy, and treatment outcomes were compared among groups. In addition, blood and fecal samples prospectively collected were subjected to multi-omics analyses. **Results:** A total of 301 patients were included in the retrospective analysis, among whom 105 patients (34.9%) had a small intestinal mean radiation dose (SIMRD) <1 Gy, and 84 patients (27.9%) had a SIMRD of 1–3 Gy. Overall, 183 patients (60.8%) received first-line PD-1 blockade, and 118 patients (39.2%) received second-line treatment. The median follow-up time was 27.2 months. The results showed that patients with a SIMRD of 1–3 Gy achieved the highest objective response rate (21.0% vs. 48.8% vs. 6.3%). Compared with the <1 Gy and >3 Gy groups, the 1–3 Gy group also demonstrated significantly prolonged progression-free survival (PFS, 10.2 months) and overall survival (OS, 23.7 months) ($P < 0.01$), with consistent findings across all subgroup analyses. Compared with the 1–3 Gy group, SIMRD >3 Gy (HR = 4.96, $P < 0.001$) and SIMRD <1 Gy (HR = 1.90, $P < 0.001$) were both independent predictors of worse OS. Thirty patients who recevied first-line PD-1 inhibitors combined with abdominopelvic radiotherapy were included in the prospective analyses. With a median follow-up of 17.5 months, patients with a SIMRD of 1–3 Gy achieved the best disease control rate (1-3 Gy vs. <1 Gy vs. >3 Gy: 90.0% vs. 63.7% vs. 33.3%; P = 0.041) and the longest median PFS (1-3 Gy vs. <1 Gy vs. >3 Gy: not reached vs. 9.3 months vs. 5.8 months; P = 0.120). Multi-omics analyses revealed that responders were enriched in *Bacillota*, *Clostridia*, and indole-derived metabolites, particularly indole-3-carboxylic acid. Moreover, patients in the 1–3 Gy group exhibited increased circulating macrophage inflammatory protein-3α levels and a reduced proportion of $\alpha4\beta7^+$ regulatory T cells. **Conclusions:** ILDR influences the efficacy of PD-1 inhibitor therapy in patients with mNSCLC, with the most pronounced benefit observed when SIMRD is maintained within the 1–3 Gy range. This effect may be mediated through modulation of the gut microbiota–metabolite–immune axis. Research Sponsor: National Natural Science Foundation of China; 82573453; National Natural Science Foundation of China; 82403791; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2024ZD0525902; Natural Science Foundation of Shandong Province; ZR2024QH459; CSCO-Nav HER2-related Solid Tumors Research Foundation; Y-2022HER2AZMS-0291; Collaborative Academic Innovation Project of Shandong Cancer Hospital; ZF001; Project supported by ShanDong Provincial Medical Association; YXH2025YS042; Shan-dong Province University "Youth Innovation Team Program"; 2024KJJ027.

2628 **Poster Session**

Personalized N-of-1 combinations based on molecular profiles in advanced malignancies: Immunotherapy group analysis of the I-PREDICT N-of-1 precision oncology study. First Author: Yuji Uehara, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

Background: While current precision oncology typically targets a single biomarker, most cancers have multiple pathogenic alterations that often differ from patient to patient. We evaluated whether individualized, N-of-1 biomarker-based combinations that included immune checkpoint inhibitors (ICIs) would improve outcomes in patients (pts) with advanced cancers. **Methods:** In the I-PREDICT prospective trial (NCT02534675), 70 pts with advanced poor-prognosis cancers received ICI-based regimens. Personalized combinations were based on tissue/ctDNA next-generation sequencing (NGS) and Molecular Tumor Board review. An "i-Matching Score" was developed using TMB ≥16 mut/Mb—selected because analysis showed it was a more robust outcome predictor than TMB ≥10 or continuous TMB (though both correlated with some outcome parameters)—alongside scores reflecting the matching of other targeted therapies (TT) to tumor alterations. Regimens used individualized dose reductions and intra-patient dose titration for safety. **Results:** Tumors harbored a median of five pathogenic alterations (range, 1–18); 97% of pts had unique molecular profiles. To optimize biomarker-matching, pts received 48 distinct therapy regimens, many previously unstudied; for the first-in-human (FIH) combinations, initial doses were lowered, and intra-patient dose modifications were made for tolerance. Regimens included ICI monotherapy (20%), ICI + TT (61%), and others. Mean initial dose was 79.5% of the FDA-approved dose; 26% of pts had dose adjustments (6% increase; 20% decrease). Initial doses were lower for multi-drug regimens (P=0.002), ICI+TT ($P<0.001$), and FIH regimens (P=0.005) vs. established regimens. Grade ≥3 treatment-related serious adverse events (SAEs) occurred in 14% of 70 pts; notably, the SAE rate for ICI monotherapy (established safety profile) was 15%, and no combination subgroup significantly exceeded this rate. FIH regimens and high i-Matching groups (>50% vs. ≤50%) trended towards fewer SAEs (P=0.06/0.08). TMB ≥16 independently predicted improved disease control rate (DCR; SD ≥6mo/PR/CR), PFS, and OS (P=0.006/0.001/0.016); i-Matching Score >50% vs. ≤50% significantly correlated with higher DCR (74% vs 27%, $P<0.001$), longer PFS (10.4 vs 3.8 mo, $P<0.001$) and OS (19.1 vs 9.1 mo, P=0.016). In pts receiving ICI+TT (n=51), the i-Matching Score outperformed TMB as an outcome predictor. **Conclusions:** Individualized, N-of-1 ICI-based combinations, molecularly matched to complex genomic profiles, can be safely given with initial dose reduction and intra-patient dose modification. Higher TMB and higher degrees of biomarker matching (i-Matching Score) correlated with improved outcomes, with the latter performing best in pts receiving ICI+TT combinations. This molecularly guided multi-agent therapy paradigm warrants further study. Clinical trial information: NCT02534675. Research Sponsor: U.S. National Institutes of Health; 5UG1CA233198-05; U.S. National Institutes of Health; 5U01CA180888-08.

2629 **Poster Session**

Phase 1 dose escalation of CTX-8371, a novel PD-1×PD-L1 bispecific antibody, in patients with advanced malignancies post checkpoint inhibition. First Author: Judy S. Wang, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL

Background: CTX-8371 is a novel bispecific antibody targeting both programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1). In addition to potent PD-1 and PD-L1 blockade, CTX-8371 uniquely enables CD80-CD28 engagement and facilitates the cleavage of PD-1 from the surface of activated T-cells. Preclinically, CTX-8371 exhibited greater potency than singular blockade with either anti-PD1 or anti-PD-L1 alone. **Methods:** In this first-in-human study (NCT06150664) with a 3+3 dose-escalation design, patients (pts) with metastatic melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), Hodgkin lymphoma (HL), and triple-negative breast cancer (TNBC) in whom standard treatments including prior immune checkpoint inhibitors (ICI) had failed, were eligible. CTX-8371 was administered intravenously every two weeks at 5 dose levels ranging from 0.1 to 10.0 mg/kg. The primary objectives were to evaluate the safety and tolerability of CTX-8371 and determine doses to be evaluated in expansion. Secondary objectives included assessment of anti-tumor activity, pharmacokinetics, pharmacodynamics, and immunogenicity of CTX-8371. **Results:** Between 15 Apr 2024 and 12 Aug 2025, 17 pts were enrolled; 15 pts completed the dose-limiting toxicity (DLT) period and had post-baseline imaging: NSCLC n=7, melanoma n=3, HNSCC n=2, TNBC n=2, HL n=1. All 15 pts had received a minimum of 2 prior therapies including checkpoint inhibitors. Median duration on study was 9.8 months; CTX-8371 treatment is ongoing in 3 pts. CTX-8371 was well tolerated with no DLTs. The maximum tolerated dose (MTD) was not reached. All treatment-related adverse events (AEs) were Grade 1/2, except one Grade 3 AE of asymptomatic lipase increase which resulted in the only dose interruption. There were no dose reductions. Dose-dependent increases in CTX-8371 serum concentrations (AUC and Cmax) were observed. In the 15 pts with post-baseline imaging, the overall response rate (ORR) was 20% (one pt each with NSCLC [irPR], TNBC and HL) and the disease control rate (DCR) was 60%. The responses were 2.3 months NSCLC; 6.4+ months TNBC; 3.6+ months HL with greater depth and longer durability at the recommended doses for further study ($\geq$ 3 mg/kg). The two ongoing responders are in pts treated at 3 mg/kg (TNBC: $>$90% reduction in overall tumor volume) and 10 mg/kg (HL: metabolic partial response). **Conclusions:** CTX-8371, a novel bispecific antibody targeting both PD-1 and PD-L1, was well tolerated and demonstrated promising clinical activity as a monotherapy in advanced pts resistant to prior ICI. Dose expansion in pts with NSCLC and TNBC in 2 dosing cohorts (3 and 10 mg/kg) is underway. Future development in treatment refractory HL is planned. Clinical trial information: NCT06150664. Research Sponsor: Compass Therapeutics.

2630 **Poster Session**

Clinical efficacy of tislelizumab in combination with gemcitabine and nab-paclitaxel and chemoresistance analysis in borderline resectable pancreatic cancer: A prospective pilot study. First Author: Yonggang He, Department of Hepatobiliary Surgery, the Second Affiliated Hospital of Army Medical University, Chongqing, China

Background: Neoadjuvant therapy has been demonstrated to improve the survival outcomes of patients with borderline resectable pancreatic cancer (BRPC). While neoadjuvant therapy is increasingly utilized, exploring novel combination strategies, such as immunotherapy plus chemotherapy, is essential to further enhance surgical resectability and survival outcomes. This study investigated the clinical feasibility of tislelizumab in combination with gemcitabine and nab-paclitaxel for BRPC in a neoadjuvant setting. **Methods:** In this prospective study, patients diagnosed with BRPC were enrolled. Preoperatively, intravenous injection of tislelizumab (200 mg per time, Q3W) was used for 3 cycles, in combination with gemcitabine (1 000 mg/m^2, d1, d8) and nab-paclitaxel (125 mg/m^2, d1, d8). Postoperatively, this regimen continued to be used. The primary endpoints were the margin-negative (R0) resection rate and treatment-related adverse events (TRAEs). Exploratory objectives were resistance to this neoadjuvant regimen. **Results:** Totally 30 patients were enrolled in this study, among whom 80.0% (24/30) completed neoadjuvant therapy and underwent surgical resection. R0 resection was achieved in 80.0% of the patients (24/30) and in 100.00% of the patients with surgical resection (24/24). Most patients experienced grade I-II TRAEs, and no serious TRAEs occurred. Through the quantitative proteomics and machine learning algorithms for differentially expressed proteins, NT5DC2, FAM3D, CXCL5 and TMT1B were identified to play crucial roles in resistance to the neoadjuvant regimen in pancreatic cancer. **Conclusions:** Neoadjuvant therapy with tislelizumab plus gemcitabine and nab-paclitaxel demonstrated clinical feasibility and encouraging antitumor activity in BRPC patients, with a favorable safety profile. NT5DC2, FAM3D, CXCL5 and TMT1B may be the biomarkers for preoperative drug resistance in pancreatic cancer. Clinical trial information: ChiCTR2200063680. Clinical trial information: ChiCTR2200063680. Research Sponsor: None.

2631 **Poster Session**

A phase 2 study of fruquintinib combined with sintilimab and chidamide in refractory MSS metastatic colorectal cancer: Preliminary efficacy and safety. First Author: Chang Wang, The First Hospital of Jilin University, Changchun, China

Background: Microsatellite stable (MSS) metastatic colorectal cancer (mCRC) has limited response to immune checkpoint inhibitors. Preliminary evidence from preclinical studies and the CAPability-01 trial suggest that combining anti-angiogenic therapy with epigenetic drugs such as histone deacetylase inhibitors can favorably remodel the tumor immune microenvironment and enhance the efficacy of PD-1 immune checkpoint blockade for advanced MSS-type mCRC. This study evaluates the efficacy and safety of the triple combination of fruquintinib, sintilimab, and chidamidein patients with refractory MSS mCRC. **Methods:** This is a single-arm, open-label phase 2 study. Eligible patients had histologically confirmed MSS-type mCRC, disease progression after $\geq$2 prior lines of therapy, $\geq$1 measurable lesion (RECIST v1.1), and ECOG 0–1. Patients received fruquintinib (5 mg orally on days 1–14, Q3w), sintilimab (200 mg IV on day 1, Q3w), and chidamide (30 mg orally twice weekly). The primary endpoint was mPFS. Secondary endpoints included ORR, DCR, mOS, DOR and safety. Tumor assessments were performed every 9 weeks. With a statistical hypothesis of improving the median PFS from 3.7 (historical control) to 6.0 m, a sample size of 46 patients was planned. **Results:** From January to December 2025, a total of 9 patients were enrolled. The median age was 60.0 years (39–72). All patients had MSS-type tumors, with a median of 2 prior lines of therapy (range: 2–4). Preliminary efficacy analysis showed that 4 patients achieved PR and 2 achieved SD, resulting in an ORR rate of 44.4% and a DCR rate of 66.7%. Given the limited sample size and relatively short follow-up of 9.1m at this preliminary analysis, mPFS and mOS were not yet reached. Treatment was generally tolerable. TRAEs of any grade occurred in all 9 patients. The most common TRAEs included hematological toxicities such as thrombocytopenia (66.7%), neutropenia (44.4%), and leukopenia (33.3%); hepatic laboratory abnormalities including elevated ALT 33.3%), and elevated AST (33.3%); as well as proteinuria (66.7%), hyperlipidemia (55.6%), increased blood creatine kinase (55.6%), and fatigue (1/9 with Grade 3). Grade $\geq$3 TRAEs were observed in 5 patients (55.6%), including Grade 3 neutropenia (2 patients), fatigue (1 patient), cutaneous adverse reactions (1 patient), and cholecystitis (1 patient). No treatment-related deaths occurred. **Conclusions:** Preliminary results indicate that the triple therapy of fruquintinib, sintilimab, and chidamide demonstrates promising response rate, disease control and a manageable safety profile in patients with refractory MSS-type mCRC. This combination strategy represents a potential therapeutic option for this population, who currently have limited treatments available. Further follow-up with a larger sample size and longer duration is needed to confirm its survival benefit. Clinical trial information: NCT06979908. Research Sponsor: None.

2632 **Poster Session**

A phase II study to evaluate the safety and efficacy of BB-1701 in combination with sintilimab in patients with HER2 expression or mutation in locally advanced/metastatic breast cancer or NSCLC. First Author: Anwen Xiong, Department of Oncology, Shanghai East Hospital, Tongji University, Shanghai, China

Background: BB-1701, a HER2-targeting antibody-drug conjugate (ADC) containing eribulin, has demonstrated promising antitumor activity in the clinical studies in breast cancer (BC) patients with HER2 low expression and non-small cell lung cancer (NSCLC) patients with HER2 mutation. Currently, there are no approved treatment options of ADC in combination with anti-PD-1 antibody for metastatic BC patients with HER2 low expression and NSCLC patients with HER2 mutation. We report the preliminary efficacy and safety results from the ongoing phase 2 study (including dose escalation and dose expansion) of BB-1701 in combination with Sintilimab (an anti-PD-1 antibody) in advanced or metastatic BC patients with HER2 low expression and NSCLC patients with HER2 mutation. **Methods:** Patients enrolled were $\geq$18 years of age; had confirmed locally advanced/metastatic HER2 low-expressing BC or HER2 mutated NSCLC, an ECOG PS $<$2 and measurable lesion(s) (per RECIST v1.1); and disease progression after $\geq$1 lines of prior standard therapies. HER2 expression was confirmed by IHC or NGS/PCR before patient enrollment. BB-1701 was administered at 1.2 mg/kg Q3W or 1.6 mg/kg Q3W, and sintilimab is administered at 200 mg Q3W. **Results:** As of 26 January 2026, a total of 12 patients with HER2 low-expressing BC or HER2 mutated NSCLC have been enrolled and treated, 6 patients at each dose level of BB-1701 during dose escalation. Median age is 63 years, 91.7%/8.3% patients were female/male, and 16.7%/83.3% patients have ECOG PS 0/1. The median number of prior systemic therapy lines was 2.0/1.0 for BC and NSCLC. All patients experienced at least one treatment-emergent adverse events (TEAEs). The most common ($\geq$20%) reported all grade TEAEs are alanine aminotransferase increased, aspartate aminotransferase increased, γ-glutamyltransferase increased, hypercholesterolemia, peripheral neuropathy, anemia and Urinary tract infection. Three grade 3 TEAEs are γ-glutamyltransferase increased, pneumonia and open globe injury. There has been no grade 4 or grade 5 events as of data cut-off date. One treatment emergent serious adverse event is open globe injury. All patients were evaluable for efficacy. Among 5 BC patients, 4 patients achieved partial response (PR) with disease control rate (DCR) of 80.0%. Among 7 NSCLC patients, 2 patients achieved PR and 2 patients had stable disease (SD) with DCR of 57.1%. Details of data will be presented at the ASCO meeting. **Conclusions:** BB-1701 in combination with Sintilimab shows encouraging antitumor activity and a manageable safety profile in HER2 low-expressing BC patients and HER2 mutated NSCLC patients. The further dose expansion study is guaranteed based on the preliminary data from dose escalation study. Clinical trial information: CTR20241422. Research Sponsor: None.

2633 Poster Session

Outcomes of patients with rare cancers treated with combination immune checkpoint inhibitors with and without lung and/or liver metastases (NCI/SWOG S1609). First Author: Megan Othus, Fred Hutch Cancer Center, Seattle, WA

Background: Limited prior retrospective data, primarily among patients with lung cancer, liver cancer, and melanoma, has indicated that liver metastases are associated with poorer outcomes with chemotherapy, targeted agents, and checkpoint inhibitor therapy. We used a unique clinical trial resource to evaluate whether liver and/or lung metastases were associated with outcomes among patients with rare tumors treated with combination anti-PD-1 and anti-CTLA-4 therapy. **Methods:** The basket trial, SWOG trial S1609 (NCT02834013, DART trial), treated 655 eligible patients without lung or liver primary cancers. Associations with progression-free and overall survival were evaluated with Cox regression models; multivariable models controlled for age at trial registration, sex, performance status, race, ethnicity, primary tumor organ. Associations with clinical benefit rate (confirmed complete and partial response or stable disease for six months or longer) and treatment-related adverse events were evaluated using Fisher's exact test. **Results:** There was no significant difference in rates of grade 3 or higher treatment-related adverse events across the groups. Participants with liver metastases, with or without lung metastases, had a lower likelihood of experiencing clinical benefit (11% and 18%, respectively) compared to participants with lung but not liver metastases or participants with neither lung nor liver metastases (26% and 30%, respectively, p=0.003). On multivariable analysis, both lung and liver metastases were associated with shorter progression-free and overall survival compared to presence of neither liver nor lung metastases. **Conclusions:** In a diverse cohort of participants with advanced rare tumors treated with combination anti-CTLA-4 and anti-PD-1 therapy, we found that both lung and liver metastases were associated with shorter progression-free and overall survival. Research Sponsor: US National Cancer Institute; U10CA180888 and U10CA180819.

Multivariable Cox regression models for progression-free survival and overall survival.

Covariate	Progression-free survival	Overall survival
Lung but not liver metastases (N=175)	1.40	1.24
(reference = neither liver nor lung, N=269)	(1.13-1.72)	(1.00-1.55)
	0.0019	0.053
Liver but not lung metastases N=154)	1.73	1.33
(reference = neither liver nor lung, N=269)	(1.38-2.17)	(1.05-1.68)
	<0.001	**0.017**
Liver and lung metastases N=57)	1.96	1.91
(reference = neither liver nor lung, N=269)	(1.44-2.65)	(1.40-2.61)
	<0.001	**<0.001**
Liver but not lung metastases N=154)	1.24	1.07
(reference = lung but not liver, N=175)	(0.96-1.60)	(0.83-1.38)
	0.095	0.62
Liver and lung metastases N=57)	1.40	1.54
(reference = lung but not liver, N=175)	(1.02-1.92)	(1.11-2.12)
	0.037	**0.009**
Liver and lung metastases N=57)	1.13	1.44
(reference = liver but not lung, N=154)	(0.83-1.55)	(1.04-1.99)
	0.45	**0.030**

Hazard ratio (95% confidence interval) p-value reported.

2634 Poster Session

Prior CTLA-4 blockade as associated with a hyperactive immunosuppressive signature and limited response to subsequent immunotherapy in melanoma. First Author: Omid Hamid, The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA

Background: Checkpoint blockade achieves durable long term responses in about 30-50% of patients with malignant melanoma (MM). However, a substantial proportion of patients either fail to respond or develop resistance after initial response. As a result, many MM patients undergo multiple sequential immunotherapeutic treatments in an attempt to achieve clinical benefit. However, the effects of repeated rounds of immunotherapy on the immune system remain poorly understood. We herein report that prior anti-CTLA-4 blockade within 12 months of analysis associated with a hyperactive immunosuppressive immune signature involving IL-6, in 24 patients with anti-PD-1 refractory metastatic MM enrolled in a Phase I/II trial. **Methods:** The patients received continued checkpoint inhibition with an anti-PD-L1 antibody in combination with an immunostimulatory gene therapy based on replication-competent adenovirus targeting the CD40 and 4-1BB pathways (LOKON003, NCT04123470). Using unsupervised clustering, plasma biomarker profiles at baseline and post treatment initiation was evaluated and correlated to clinical parameters. **Results:** Two plasma protein profiles were identified at baseline among enrolled patients and one of those included immunosuppressive biomarkers. While patients with this hyperactive immunosuppressive signature (n=8) at baseline experienced a median overall survival (mOS) of 4.0 months, patients without this baseline signature (n=15) had a mOS of 28.1 months. The hyperactive immunosuppressive signature was not related to M1 status, sex, age, or number of prior treatments, but prior anti-CTLA-4 treatment within a year of enrollment was more prevalent in patients with this signature. If dividing the patients only based on receiving anti-CTLA-4 therapy within 12 months (n=10) versus later or not at all (n=14), mOS was 5.3 and 30.7 months, respectively. Patients that had received recent anti-CTLA-4 treatment, presented with a plasma protein signature resembling the hyperactive immunosuppressive signature with IL-6 as a central node among the upregulated proteins. Patients who did not receive anti-CTLA-4 blockade during the past 12 months responded to the combination of the immunostimulatory gene therapy and continued checkpoint blockade with upregulation of biomarkers associated with T cell activation and cell killing capacity, which may have supported the better survival outcome in this patient group. **Conclusions:** The findings highlight the need for further clinical evaluation of the consequences of repeated immunotherapeutic treatments, IL-6 inhibition in this population, and consideration for a wash-out period from further immunotherapy to allow for immune system recovery post anti-CTLA-4 treatment. Clinical trial information: NCT04123470. Research Sponsor: The Swedish Cancer Society; The Swedish Research Council; Lokon Pharma.

2635 Poster Session

Phase IIa study of tosposertib, a dual TGFβRI and VEGFR2 inhibitor, in combination with pembrolizumab in recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC). First Author: Hye Ryun Kim, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Tosposertib (TU2218) is a highly potent dual inhibitor of the transforming growth factor-β type I receptor (TGFβRI/ALK5) and vascular endothelial growth factor receptor 2 (VEGFR2), designed to simultaneously target immunosuppressive tumor microenvironment signaling and angiogenesis. This open-label, multicenter, non-randomized phase IIa trial evaluated the efficacy and safety of tosposertib in combination with pembrolizumab in patients with R/M HNSCC (NCT05784688). **Methods:** Eligible patients included anti–PD-(L)1–naïve patients with PD-L1 combined positive score (CPS) ≥1. Tosposertib (97.5 mg twice daily; 2 weeks on/1 week off) was administered orally in combination with pembrolizumab (200 mg intravenously every 3 weeks). **Results:** As of December 31, 2025, 29 patients (median age, 61 years; 76% male) had been enrolled, with a median follow-up duration of 6.0 months (range, 8–401 days). Primary tumor sites included the oral cavity (n=11, 37.9%), oropharynx (n=6, 20.7%), larynx (n=3, 10.3%), and nasal/paranasal regions (n=3, 10.3%). HPV positivity was observed in 13.8% (4/29) of patients. Among 26 efficacy-evaluable patients, responses were assessed by treatment line. In the first-line setting, 9 of 12 patients achieved an objective response (ORR, 75.0%), including 1 confirmed complete response (CR) and 8 partial responses (PRs; 6 confirmed, 2 unconfirmed). Among the 14 patients who had received at least one prior systemic therapy, the ORR was 42.9%, with 1 confirmed CR and 5 confirmed PRs. A numerically higher ORR was observed in patients with PD-L1 CPS ≥20 compared with those with CPS 1–10 (66.7% vs 52.9%). The most frequent any-grade treatment-emergent adverse events (TEAEs), (≥20%) [and ≥ Gr3 TEAEs], were rash (48.3% [20.7%]), mucosal inflammation (34.5% [13.8%]), pruritus (27.6% [3.4%]), weight loss (27.6% [0%]), and elevations in aspartate aminotransferase (AST; 20.7% [3.4%]) or alanine aminotransferase (ALT; 20.7% [3.4%]). Discontinuations due to TEAEs occurred in three patients. No treatment-related deaths were reported. **Conclusions:** Tosposertib in combination with pembrolizumab demonstrated a manageable safety profile and encouraging antitumor activity in patients with R/M HNSCC, with particularly robust efficacy observed in the first-line setting and a favorable trend in PD-L1–high tumors. Clinical trial information: NCT05784688. Research Sponsor: TiumBio Co., Ltd.

Best overall response by subgroups.

Best Overall	ALL (n=26)	Prior lines of therapy	Prior lines of therapy	PD-L1status, n (%)	PD-L1status, n (%)
Response, n (%)		None (n=12)	≥1 (n=14)	CPS 1-19 (n=17)	CPS ≥20 (n=9)
Complete Response	2 (7.7)	1 (8.3)	1 (7.1)	1 (5.9)	1 (11.1)
Partial Response	13 (50.0)	8 (66.7)	5 (35.7)	8 (47.1)	5 (55.6)
Stable Disease	5 (19.2)	2 (16.7)	3 (21.4)	3 (17.6)	2 (22.2)
Progressive Disease	6 (23.1)	1 (8.3)	5 (35.7)	5 (29.4)	1 (11.1)
Response Rate (%)	57.7	75.0	42.9	52.9	66.7

2636 Poster Session

Association of mRNA COVID-19 vaccination near immune checkpoint inhibitor initiation with outcomes: A real-world analysis. First Author: Changchuan Jiang, UT Southwestern Medical Center, Dallas, TX

Background: Prior study showed mRNA COVID-19 vaccines can activate innate and adaptive immune pathways and have been hypothesized to "prime" anti-tumor immunity via increased tumor PD-L1 expression when administered near immune checkpoint inhibitor (ICI) initiation. We performed a real-world validation to evaluate the association between COVID-19 vaccination around ICI initiation and outcomes among patients with 4 advanced/metastatic solid tumors. **Methods:** Using ConcertAI Patient360 (US-based, deidentified, human-abstracted oncology EHR linked to medical/pharmacy claims and third-party mortality), we identified adults (≥18 years at diagnosis) with advanced/metastatic bladder cancer, melanoma, non-small cell lung cancer (NSCLC), or renal cell carcinoma (RCC) who initiated an ICI between Jan 2021 and Mar 2024. Exposure was receipt of ≥1 mRNA COVID-19 vaccine within 100 days of ICI initiation. Exposed patients were propensity score–matched 1:1 to unexposed patients on demographics (age, sex, race, ethnicity) and clinical factors (baseline steroid use, ICI initiation year, Charlson Comorbidity Index, ECOG performance status, BMI, and tumor type). Real-world OS (rwOS) and real-world PFS (rwPFS) were estimated by Kaplan-Meier; hazard ratios (HRs) were estimated using univariate Cox models (post-match) and multivariable Cox models (residual confounding sensitivity), overall and by tumor type. **Results:** Among 7085 eligible patients, 1,513 were vaccinated around ICI initiation. After matching, 3,018 patients (1,509 per group) had evaluable time-to-event data and were included in Kaplan-Meier and Cox analyses (tumor mix: NSCLC 73.6%, RCC 11.7%, bladder 8.5%, melanoma 6.3%). Overall, vaccination was associated with improved rwOS and rwPFS: median rwOS 19.52 vs 15.31 months ($p<0.001$) and median rwPFS 7.95 vs 6.37 months (p=0.002). Univariate Cox models favored vaccination for rwOS (HR 0.82; 95% CI 0.75–0.90; $p<0.001$) and rwPFS (HR 0.88; 95% CI 0.81–0.95; p=0.002), with consistent findings in multivariable models (rwOS HR 0.81; 95% CI 0.74–0.89; $p<0.001$; rwPFS HR 0.87; 95% CI 0.80–0.95; p=0.001). Twelve-month rwOS was 64.87% vs 54.45% (vaccinated vs unvaccinated). By tumor type, univariate (post-match) associations were directionally favorable and strongest in NSCLC (rwOS HR 0.79; 95% CI 0.71–0.87; $p<0.001$; rwPFS HR 0.85; 95% CI 0.77–0.93; $p<0.001$). Similar, non-significant trends were observed in smaller bladder and RCC cohorts; melanoma showed no association with rwOS. **Conclusions:** In this large propensity score–matched real-world cohort of ICI-treated patients, COVID-19 vaccination within 100 days of ICI initiation was associated with significant improvements in rwOS and rwPFS, particularly in NSCLC. Prospective validation and randomized clinical trials are warranted to confirm these findings. Research Sponsor: UTSW.

2637 Poster Session

Impact of COVID-19 mRNA vaccines on survival outcomes in patients with solid tumors receiving immunotherapy: A large-scale retrospective study. First Author: Bayan Khasawneh, Department of Medicine, Houston Methodist Hospital, Houston, TX

Background: Immune checkpoint inhibitors (ICIs) became the cornerstone in the treatment of solid tumors. While personalized cancer vaccines have yet to overcome complex scalability and manufacturing challenges, preclinical data suggests SARS-CoV-2 mRNA vaccines prime innate immunity, potentially enhancing ICI efficacy. A study by Grippin et al. evaluated the use of mRNA vaccine in NSCLC and melanoma patients receiving ICI and showed improved median and three-year overall survival (OS). We conducted a multicenter retrospective study to determine if this survival benefit extends across a broader range of ICI-treated solid tumors. **Methods:** Using the TriNetX global network, we identified adults (≥18) with solid tumors (NSCLC, melanoma, colorectal, hepatobiliary, gallbladder, gastric, bladder, pancreatic, renal, breast, head and neck, and esophageal) who received ICI treatment. The experimental group received SARS-CoV-2 mRNA vaccine within 100 days of ICI initiation; controls received no mRNA vaccine from 100 days pre-index through follow-up. Exclusion criteria: COVID-19 infection within 100 days and through the follow-up period. 1:1 propensity score matching (PSM) balanced demographics and comorbidities. Primary endpoint was median OS, including tumor-specific subgroup analyses. Survival was assessed via Kaplan-Meier and log-rank tests. **Results:** After PSM, we had 15,374 matched patients (7,687 per group). Vaccination within 100 days of ICI was associated with improved median OS (1,421 vs 667 days; HR 0.63; 95% CI 0.60-0.66; p<.001). Benefit was observed in 10 of 12 tumor types. Strongest effects were in NSCLC (n=7,350; HR 0.64), melanoma (n=2,684; HR 0.61; landmark survival 62.1% vs 50.3%), hepatobiliary (n=1,428; HR 0.64), colorectal (n=1,068; HR 0.67), gastric (n=792; HR 0.68), bladder (n=1,398; HR 0.63), pancreatic (n=240; HR 0.65), renal (n=1,996; HR 0.64), head and neck (n=964; HR 0.68), and esophageal (n=828; HR 0.63). No significant benefit was seen in breast (n=1,412; HR 0.85) or gallbladder cancer (n=58; HR 0.88). **Conclusions:** SARS-CoV-2 mRNA vaccination within 100 days of ICI therapy was associated with improved survival across solid tumors. These results suggest off-the-shelf RNA therapeutics may be scalable, cost-effective enhancers of cancer immunotherapy. Prospective studies are needed to confirm these findings and define the impact of universal mRNA strategies. Research Sponsor: None.

2638 Poster Session

Distinct T-cell subsets as drivers of response to different neoadjuvant treatments in esophageal squamous cell carcinoma. First Author: Xin-yun Song, Department of Radiation Oncology, Shanghai Chest Hospital School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: The optimal integration of immunotherapy with chemoradiotherapy (CRT) in the neoadjuvant treatment of esophageal squamous cell carcinoma (ESCC) remains unclear, largely due to limited mechanistic insight into immune determinants of response. **Methods:** we performed paired single-cell RNA and TCR sequencing of ESCC tumor samples collected before and after treatment across three neoadjuvant modalities—immunochemotherapy (NICT), chemoradiotherapy (NCRT), and immunochemoradiotherapy (NICRT)—to dissect intratumoral $CD8^+$ T cell dynamics. **Results:** We identified two distinct immune response programs. In NICT responders, pre-existing immunoresponsive $CXCL13^+PD\text{-}1^+CD8^+$ T cells underwent clonal expansion and transcriptional reprogramming into a less exhausted yet CXCL13+ progenitor-like state (CD8Tex_CXCR4), accompanied by the formation of tertiary lymphoid structures. Conversely, CRT responders exhibited depletion of the subset of $CXCL13^+$ $CD8^+$ T cells and enrichment of PD-1^- cytotoxic CD8Teff_NIBAN1 cells, which originated from the peripheral blood and were characterized by robust clonal expansion, high effector gene expression, and association with tumor regression. We validated the association of these two T cell subsets with distinct neoadjuvant modalities and treatment responses using public datasets and independent prospective cohorts encompassing NICT, NICRT, and NCRT. Mechanistically, conventional radiotherapy suppressed PD-1^+ T cell expansion—even in the presence of ICB—while a sequential strategy of induction ICB followed by delayed radiotherapy preserved the process of clonal expansion in exhausted T cell populations and achieved superior tumor control in vivo. **Conclusions:** These findings reveal divergent $CD8^+$ T cell–mediated immune programs driving response to neoadjuvant therapies in ESCC and identify CD8Teff_NIBAN1 as a key effector population following CRT. Our study provides mechanistic insight into ICB–radiotherapy interactions and supports the rational design of temporally optimized combination strategies in solid tumors. Research Sponsor: None.

2639 Poster Session

Phase I study of LB1410, a bivalent TIM-3/PD-1 bispecific antibody, in patients with advanced solid tumors. First Author: Jiajian Liu, L&L Bio Co., Ltd., Shanghai, China

Background: LB1410 is a recombinant humanized anti-PD-1/TIM-3 bispecific antibody (BsAb) developed by L&L Bio Co., Ltd, Shanghai, China for patients (pts) resistant/refractory (R/R) to anti-PD-(L)1 therapies. Pre-clinical studies revealed superior T cell and DC activity and *in vivo* antitumor efficacy compared to the combined use of TIM-3 and PD-1 monoclonal antibodies. This ongoing open-label phase I trial evaluates LB1410 monotherapy in pts with advanced solid tumors. **Methods:** Eligible pts were ≥18 yrs old with ECOG PS 0-1. Dose ranged from 0.001 to 20 mg/kg IV Q2W or 2000 mg/kg IV Q3W in an accelerated titration or a traditional 3+3 design. The RPIID of 20 mg/kg was used for efficacy expansion in pts with advanced clear cell renal cell carcinoma (ccRCC), cervical cancer (CC) and hepatocellular carcinoma (HCC). The primary objective was safety, including dose-limiting toxicities (DLTs); secondary objectives included efficacy, pharmacokinetics (PK) and immunogenicity. **Results:** As of Jan 4, 2026, 94 pts were enrolled: median age 59 yrs (31-73 yrs); 64.9% male; 84.0% ECOG PS 1. Tumor types included NSCLC (26.6%), CRC (21.3%, all non-MSI-H), CC (14.9%), ccRCC (11.7%), HCC (9.6%) and others (16.0%). 77 pts (81.9%) had received ≥ 2 prior lines of therapy. 98.6% non-CRC pts (73/74) were R/R to anti-PD-(L)1 therapies. 72 pts (76.6%) experienced TRAEs. The most common TRAEs (≥ 10%) included anemia (25.5%), proteinuria (11.7%), elevated ALT (11.7%), elevated AST (11.7%) and elevated lactate dehydrogenase (10.6%). Only 10 pts (10.6%) experienced Grade 3-4 TRAEs, most frequently hypertension (4.3%) and hypokalemia (2.1%). Only 1 hypertension and 1 elevated GGT in 1 pt were Grade 4. Serious TRAEs occurred in 3 pts (3.2%). No DLTs were observed. Among pts with available on-treatment scans, the overall ORR per RECIST 1.1 was 7.1% (6/85) with 5 confirmed PRs and 1 confirmed CR; the DCR was 48.2% (41/85). Notably, among CC pts previously treated with anti-PD-(L)1 therapies, there were 4 confirmed PRs and 1 confirmed CR: ORR 38.5% (5/13); DCR 69.2% (9/13); mPFS 7.5 months. 5 pts with CR/PR/SD remained on treatment (max. 16 treatment cycles; max. follow-up 14.4 months). The CR patient had received 5 prior lines of therapy, including PD-1/CTLA-4 BsAb. In anti-PD-1-resistant ccRCC, LB1410 monotherapy had an ORR of 11.1% (1/9) and a DCR of 77.8% (7/9). **Conclusions:** LB1410 showed an excellent safety profile and promising antitumor efficacy in pts with immune-oncology (IO)-R/R CC. Further studies of LB1410 as monotherapy and in combination with lenvatinib in pts with IO-R/R CC are ongoing. Clinical trial information: NCT05357651. Research Sponsor: L&L Bio Co., Ltd., Shanghai, China.

2640 Poster Session

Immune checkpoint inhibitor (ICI) toxicity in a large prospective cohort of patients with solid tumors: The I-CHECKIT study (SWOG S2013). First Author: Krishna Soujanya Gunturu, Hartford HealthCare Cancer Institute, Hartford, CT

Background: Based on clinical trials, the expected rate of ≥ grade 3 iRAEs is ~15% for single agent ICIs and ~30-50% for ipilumimab (ipi) plus nivolumab (nivo). Predictors of irAEs remain poorly defined, limiting clinicians' ability to anticipate and manage irAEs especially in patients treated in community practices. We conducted a prospective study to quantify the incidence and severity of irAEs across a large, diverse population of patients receiving ICI therapy and to identify clinical predictors of irAE development. **Methods:** S2013 enrolled adult patients planning to receive standard of care ICI-based therapy in two separate cohorts; only results from the completed first cohort, which received either single drug or combination (combo) ICI therapy, are reported here. Eligibility criteria were few and study included patients with active autoimmune disease, decreased performance status, and any stage of cancer. No chemo, biological or targeted therapy were permitted. Patients were followed for 1 year for the occurrence of irAE. The primary objective was to assess the occurrence of Grade >3 non-hematologic irAEs per CTCAE v5. Evaluable patients had 1 or more toxicity assessment. irAE events were centrally reviewed by the study team. **Results:** 2084 patients were enrolled and N=2,020 patients were eligible (96.9%). Mean (SD) age was 68.7 (12.5) years, 35.8% were female, 5.2% Black, and 8.0% Hispanic. Most patients received single drug (1,684; 83.4%), while 336 (16.6%) received combo. Majority of single drug patients received pembrolizumab (50.6%), followed by nivo (29.6%), durvalumab (14.0%), and ipi (13.8%). Combinations were mostly ipi plus nivo. Within the first year, 269 (13.3%) patients experienced Grade ≥3 non-hematologic irAE. The most common irAEs were hepatitis, 21.2%; gastrointestinal disorders, 19.3%; and respiratory, 10.0% (Table). IrAE incidence was higher in patients receiving combinations (27.4%) compared to single drug (10.5%; Chi-square p<.001). **Conclusions:** In this large prospective cohort with unrestrictive enrollment criteria, irAE incidence was similar to that seen in more restrictive clinical trial populations. Analysis of the clinical predictors of irAEs is in progress. Grant: NIH/NCI UG1CA189974. Clinical trial information: NCT04871542. Research Sponsor: National Cancer Institute; NIH/NCI UG1CA189974.

Grade ≥3 non-hematologic irAEs, by category.

irAE	n	%	irAE	n	%
Hepatitis	57	21.2	Metabolism/nutrition	19	7.1
Gastrointestinal	52	19.3	Musculoskeletal	12	4.5
Skin	32	11.9	Cardiac	9	3.3
Respiratory	27	10.0	Hepatobiliary	7	2.6
Endocrine	22	8.2	Nervous system	7	2.6

2641 **Poster Session**

COVID-19 mRNA vaccination and risk of immune-related adverse events in ICI-treated cancer patients. First Author: Andrea Yun-En Sun, College of Medicine, National Yang Ming Chiao Tung University, Taipei City, Taiwan

Background: Immune checkpoint inhibitors (ICIs) are now standard-of-care in cancer therapy; however, concerns persist regarding whether COVID-19 mRNA vaccination may enhance immune activation and exacerbate immune-related adverse events (irAEs). We evaluated the association between COVID-19 mRNA vaccination and irAE risk among patients initiating ICI therapy and assessed toxicity and survival outcomes. **Methods:** We conducted a retrospective cohort study using target trial emulation with 1:1 propensity score matching based on data from the TriNetX Research Database (January 2021–December 2025). Adult patients with metastatic cancer initiating their first ICI therapy were included. Patients with prior ICI therapy, active irAE within 30 days before ICI initiation or immunosuppressive conditions were excluded. Vaccinated patients who received COVID-19 mRNA vaccination within 100 days prior to ICI initiation were matched to unvaccinated controls. The primary outcome was composite irAE incidence over 36 months. Secondary outcomes included severe irAEs, organ-specific irAEs, all-cause mortality, pneumonia, and intensive care unit (ICU) admission. Cox proportional hazards models estimated hazard ratios (HRs) with 95% confidence intervals (CIs). E-values and quantitative bias analyses assessed robustness to unmeasured confounding. **Results:** The matched cohort included 7,218 patients (3,609 vaccinated; 3,609 unvaccinated). Vaccinated patients had a higher risk of overall irAEs (HR 1.22, 95% CI 1.17–1.28; E-value 1.74) and severe irAEs (HR 1.11, 95% CI 1.04–1.18; E-value 1.45). Organ-specific analyses demonstrated a significant increase in ocular irAEs (HR 1.48, 95% CI 1.17–1.87; E-value 2.33), with non-significant associations for dermatologic (HR 1.08, 95% CI 0.97–1.21) and rheumatologic irAEs (HR 1.12, 95% CI 0.96–1.32). No significant increases were observed for cardiac, endocrine, gastrointestinal, hematologic, or pulmonary irAEs. Despite higher irAE risk, vaccination was associated with lower all-cause mortality (HR 0.86, 95% CI 0.80–0.93) and fewer ICU admissions (HR 0.43, 95% CI 0.25–0.73). Subgroup analyses showed stronger overall irAE associations in females and patients aged $\geq$50 years. Quantitative bias analysis indicated moderate robustness, with a 74.8% probability that HR$>$1.0 persists despite plausible unmeasured confounding. All P$<$0.001. **Conclusions:** COVID-19 mRNA vaccination among patients receiving ICIs is associated with a modest increase in irAEs, particularly ocular toxicities, but may offer survival and critical illness benefits. These findings support continued vaccination in eligible ICI-treated patients, along with enhanced irAE monitoring, including ophthalmologic surveillance in higher-risk groups. Research Sponsor: None.

2642 **Poster Session**

Analysis of delta-like ligand 3 (DLL3) expression levels and characteristics of patients (pts) with advanced extrapulmonary neuroendocrine carcinomas (epNECs) from an ongoing phase I trial. First Author: Valentina Gambardella, Department of Medical Oncology, Hospital Clínico Universitario, INCLIVA Biomedical Research Institute, University of Valencia, Valencia, Spain

Background: Specific DLL3 expression on the surface of epNEC tumor cells makes it a promising therapeutic target, but there is a lack of prospective data on DLL3 expression patterns in pts with epNEC. Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager. The first-in-human phase I trial (NCT04429087) showed obrixtamig activity in pts with DLL3-positive epNEC, especially pts with DLL3-high tumors (Capdevila et al, ASCO 2025, #3004). We report updated DLL3 expression data and pt/tumor characteristics in pts with epNEC from NCT04429087. **Methods:** DLL3 IHC was performed with an investigational DLL3 antibody (SP347) at the Roche CDx CAP/CLIA Laboratory. DLL3 expression was categorized as: negative (absent or weak tumor cell [TC] membrane/cytoplasm staining), positive (moderate-to-strong staining in any TCs), high ($\geq$50% moderate-to-strong TC staining), or low ($<$50% moderate-to-strong TC staining). **Results:** As of Sept 4, 2025, 282 of 365 screened pts with epNEC were DLL3-evaluable, of whom 235 (83.3%) had DLL3-positive tumors (DLL3-high: n=120 [42.6%], DLL3-low: n=115 [40.8%]); 47 (16.7%) were DLL3-negative. In the DLL3-positive treated set (n=93), 51 pts (54.8%) had DLL3-high and 42 (45.2%) had DLL3-low tumors. The prevalence of DLL3-high tumors in male/female pts was 47.5%/68.8%, and prevalence in pts with liver/brain metastases was 57.1%/70.0%. DLL3-high prevalence by primary tumor site, GI/GU/cancer of unknown primary site (CUP), was 44.9%/67.7%/60.0%. Pt characteristics in obrixtamig-treated DLL3-high and -low epNEC subgroups are in Table 1. **Conclusions:** In the largest prospectively screened cohort of pts with epNEC, high (83.3%) prevalence of DLL3 expression was seen, underscoring DLL3 as a promising target for clinical development of DLL3-targeted therapies such as obrixtamig. Obrixtamig safety and efficacy in pts with DLL3-positive epNEC are being assessed in several ongoing trials, including DAREON-5 (NCT05882058), with the data expected to inform and support Phase III development. Clinical trial information: NCT04429087. Research Sponsor: Boehringer Ingelheim.

	DLL3-high (n=51)	DLL3-low (n=42)
Male / female, n (%)	29 (56.9) / 22 (43.1)	32 (76.2) / 10 (23.8)
Primary tumor site: GI / GU / CUP, n (%)	22 (43.1) / 21 (41.2) / 6 (11.8)	27 (64.3) / 10 (23.8) / 4 (9.5)
Lactate dehydrogenase ≤ULN / >ULN, n (%)	22 (43.1) / 29 (56.9)	16 (38.1) / 26 (61.9)
Prior lines of therapy: 1 / 2 / 3 / >3	12 (23.5) / 17 (33.3) / 9 (17.6) / 13 (25.5)	11 (26.2) / 12 (28.6) / 10 (23.8) / 9 (21.4)
Median duration of prior anticancer treatment, weeks (range)	22 (5–349)	22 (8–148)
Prior radiotherapy / surgery / anti PD-(L)1, n (%)	22 (43.1) / 28 (54.9) / 14 (27.5)	11 (26.2) / 24 (57.1) / 9 (21.4)
Liver / brain metastases, n (%)	40 (78.4) / 7 (13.7)	30 (71.4) / 3 (7.1)
Median sum of diameters of target lesions, mm (IQR)	87.5 (64.0–123.0)	117.3 (66.2–176.0)

2643 **Poster Session**

Engineering tumor-infiltrating lymphocytes (TILs) via the T-Editor platform to enhance antitumor activity. First Author: Fenge Li, The First Affiliated Hospital of Nankai University, Tianjin, China

Background: Tumor-infiltrating lymphocyte (TIL) therapy has demonstrated clinical potential in melanoma, cervical cancer, and non-small cell lung cancer following failure of standard-of-care therapies, achieving objective response rates of 25-40%. However, two major challenges remain: the limited understanding of biological mechanisms underlying differential patient responses, and the absence of robust engineering technologies for manipulating fragile TIL populations. These limitations have constrained the application of genetic modification strategies to improve TIL therapeutic efficacy. **Methods:** By comparing transcriptomic profiles of infused TILs from responders (R) and non-responders (NR) in a Phase I investigator-initiated trial evaluating TIL therapy for solid tumors, we identified more than 10 differentially expressed genes as candidate therapeutic targets. We established the T-Editor platform, a CRISPR-mediated gene editing system optimized for TIL engineering, through systematic optimization of stimulation conditions, electroporation parameters, and CRISPR/Cas9 component dosing. Functional validation was performed by generating knockout (KO) constructs for each candidate gene using T-Editor, assessing their impact on TIL expansion, cytokine secretion, and cytolytic activity. The most promising target was selected for advanced cytosine base editing (CBE) studies, employing sgRNA designs to minimize Cas9-induced double-strand break risks. Base-edited TILs were comprehensively compared with Cas9-KO counterparts in vitro, while in vivo efficacy was evaluated using patient-derived xenograft (PDX) mouse models. **Results:** The T-Editor platform we established achieved optimal gene editing efficiency with defined stimulation condition, electroporation program and CRISPR/Cas9 doses. Functional screening revealed four critical regulatory genes, with FAM84B emerging as the most significant target where knockout demonstrated an increase in cytolytic activity compared to controls. CBE-mediated C·G→T·A conversion at FAM84B exon achieved high editing efficiency with minimal insertion-deletion events. Base-edited TILs showed comparable expansion kinetics, phenotypic stability, and cytokine production to Cas9-KO counterparts. In vivo studies demonstrated increased tumor growth inhibition in PDX models with FAM84B-edited TILs, which exhibited enhanced memory phenotype, superior effector function and elevated IFN-γ secretion. **Conclusions:** The T-Editor platform represents a rapid, efficient, and safe CRISPR-based system for TIL engineering, enabling both gene knockout and precise base editing applications. Our discovery of FAM84B as a potential novel inhibitory regulator of TIL function establishes a promising therapeutic target for improving adoptive cell therapy outcomes in solid tumor treatment. Research Sponsor: None.

2644 **Poster Session**

Atezolizumab (A) plus pertuzumab/trastuzumab/hyaluronidase (PHESGO) in patients (pts) with solid tumors with *ERBB2* alterations (alt): Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. First Author: Timothy Lewis Cannon, Inova Schar Cancer Institute, Fairfax, VA

Background: TAPUR is a phase II basket study evaluating the antitumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alts. Results of a cohort of pts with solid tumors with *ERBB2* alts treated with A+PHESGO are reported. **Methods:** Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no remaining standard treatment (tx) options. Genomic testing was performed in CLIA-certified, CAP-accredited labs. Dosing for A was 1200 mg IV delivered every 3 weeks (wks). PHESGO was dosed every 3 wks, with a loading dose of 1200 mg/600 mg/30,000 units, then 600 mg/600 mg/20,000 units, until progression. Primary endpoint was disease control (DC) per investigator defined as objective response (OR) or stable disease (SD) of at least 16 wks duration (SD16+) per RECIST v.1.1. Simon 2-stage design tested null DC rate of 15% vs. 35% (power = 0.85; α = 0.10). If $\geq$2/10 pts in stage 1 had DC, cohort expanded to stage 2; otherwise, the cohort was closed. Cohorts closed prior to reaching the protocol-specified sample size of 28 used alternative thresholds set forth in the protocol to maintain the α level. For n=20, 6 pts had to have DC to reject the null (power = 0.74). Secondary endpoints were OR, progression-free survival (PFS), overall survival (OS), duration of response and SD, and safety. **Results:** The cohort expanded to stage 2 but closed before reaching the planned sample size. 23 pts with 6 tumor types (colorectal [CRC; 14], gallbladder [GB; 3], stomach [3], breast [1], pancreas [1], small intestine [1]) with *ERBB2* amplification (amp; n=16), *ERBB2* overexpression (n=2), *ERBB2* mutation (mut; n=2), and *ERBB2* amp and mut (n=3) were enrolled. 3 pts were not evaluable. 2 partial responses (both GB, *ERBB2* amp) and 2 SD16+ (both CRC, *ERBB2* amp) were observed for a DC rate of 25% (1-sided 90% CI, 10 to 100) and an OR rate of 10% (95% CI, 1 to 32). The null hypothesis was not rejected (p=0.26). 6 pts had tx-related grade 3 AE/SAEs: acute kidney injury, ALP increase, dehydration, diarrhea, infusion related reaction, lymphopenia, maculo-papular rash, pneumonitis and sepsis. **Conclusions:** A+PHESGO did not demonstrate sufficient antitumor activity in pts with *ERBB2*-altered solid tumors to warrant further study. However, the cohort did not reach its planned accrual, limiting statistical power for demonstrating efficacy. Other tx should be considered for these pts, including tx offered in clinical trials. Clinical trial information: NCT02693535. Research Sponsor: Genentech; AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Merck, Pfizer, Seagen (now a wholly owned subsidiary of Pfizer Inc.), Taiho Oncology.

Demographics (N=23) and efficacy outcomes (n=20).

Median (Med) age, years (range)		61 (43, 90)
ECOG PS, No. (%)	0	10 (44)
	1	11 (48)
	2	2 (9)
Prior systemic regimens, No. (%)	0-2	16 (70)
	$\geq$3	7 (30)
DC (OR plus SD16+) rate, % (1-sided 90% CI), p-value		25 (10, 100), p=0.26
OR rate, % (95% CI)		10 (1, 32)
Med PFS, wks (95% CI)		9 (8, 16)
Med OS, wks (95% CI)		35 (16, 52)

2645 **Poster Session**

Functional assessment of polymerase proofreading variants to define sensitivity to immune checkpoint blockade (ICB) pan-cancer. First Author: Amin Nassar, Yale Cancer Center, New Haven, CT

Background: Cancers with inactivating alterations in DNA proofreading polymerases POLE and POLD1 (POLd) are ultra-hypermutated and benefit from ICB. Most mutations in DNA polymerases are synonymous; discerning pathogenic (P) vs variants of unknown significance (VUS) remains challenging. A strategy to define functional mutations in POL with mutational signature deconvolution and AI- protein conformational modeling could better predict ICB benefit. **Methods:** Solid tumors from patients at MSK and DFCI were selected with DNA panel sequencing datasets to enrich for somatic POL P/likely-P(LP) variants or VUS. Co-mismatch-repair deficiency (MMRd) was defined with MSIsensor and IHC. Tumors were assigned as POL high (>50%), intermediate ([int] 1-49%), or null (0%) based on the proportion of single-base-substitutions (SBS) aligning with POLd COSMIC signatures via the mutational-patterns algorithm. *POLE/D1* VUS were functionally evaluated with Swiss-PdbViewer and AlphaFold-derived AI models to infer proofreading efficiency impact. Patient overall survival (OS) from stage IV diagnosis and progression-free survival from ICB start (PFS-ICB) were evaluated with multivariable (MV) Cox regression including MMRd status. **Results:** POL variants were found in 546 patients across 18 diverse cancers. 84% were P/LP POL alterations, 16% were POL VUS, and 36% overall had concomitant MMRd. Tumors with P/LP variants had high (69%), int (23%), or null (8%) POLd signature intensities, while 62% of tumors with VUS had int POLd signatures. For the subgroup of patients with POL P/LP variants, OS from diagnosis significantly differed based on POLd signature intensity: not reached [NR], 94.5 months [mo], and 32.9 mo for POLd signature high, int, and null, respectively. In MV analysis of POL P/LP tumors, patients with POL signature-null tumors had significantly worse OS than POL-int (HR 0.35, 95%CI 0.16-0.80; p=0.01) and POL-high (HR 0.18, 95%CI 0.08-0.42; p<0.001) patients. POLd signature intensity predicted ICB benefit. Patients with POL P/LP tumors with high and int signatures exhibited favorable PFS-ICB (NR in both) versus POL P/LP–null-signature tumors (12.7 months). In MV model including MMR status, patients with POL-null SBS exhibited significantly worse PFS-ICB versus pts with combined POL signature high or int (HR 0.31, 95% CI 0.10-0.98; p=0.047). Study findings were consistent after adjustment for cancer type. Tumors with POL VUS predicted to be inactivating based on mutational signature deconvolution combined with Swiss-PdbViewer and AlphaFold AI models demonstrated similar OS/PFS to patients with tumors with P/LP variants and high/int signature scores. **Conclusions:** A strategy combining mutational signature deconvolution with AI proteomic functional assessment predicts survival and ICB benefit in tumors with functional DNA polymerases *POLE* and *POLD1* mutations. Research Sponsor: None.

2646 **Poster Session**

Development and testing of an ex vivo, live tumor fragment platform for the prediction of immune checkpoint inhibitor response and relationship to approved biomarkers. First Author: David A. Braun, Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: Immune checkpoint inhibitors (ICIs) have transformed the management of many advanced cancers but identifying patients who are likely or unlikely to benefit from ICI treatment remains a critical challenge. Biomarkers, such as PD-L1, mismatch repair deficiency, and tumor mutational burden, capture only static, unidimensional features of the complex tumor microenvironment, and therefore inadequately predict response to immunotherapy in patients. In contrast, live tumor fragments (LTFs) preserve the full complexity of the tumor microenvironment and enable functional ex vivo assessments of ICI activity. Previous efforts have had limited clinical applicability because they required larger resection specimens often collected at a single academic center. Here, the predictive capability of an ex vivo platform using core needle and forceps biopsies from multiple clinical sites was assessed and compared to approved biomarkers. **Methods:** Patients with eligible solid tumors (where ICI has an indication, including renal, non-small cell lung, bladder, colorectal, and triple-negative breast cancer, and others) were enrolled in ongoing, prospective observational trials (NCT05478538, NCT05520099, NCT06349642). Biopsies were cut into LTFs, encapsulated in hydrogel, and treated sequentially with IgG antibody followed by ICI (αPD-[L]1 with or without αCTLA-4). Cytokine production was assessed by a multiplexed bead-based immunoassay at multiple time points during ex vivo treatment. Using receiver operating characteristic and precision recall analyses, we identified 9 predictive cytokines (including IFN-γ, granzyme B, and CXCL9/10), which were used to develop the Elephas score (ELP-score) to assess cytokine response to ex vivo ICI treatment. **Results:** Of 167 eligible patient specimens, 85% (n = 142) passed quality control metrics and 130 were used for model development. Hierarchical clustering of cytokine production revealed that 27% (n = 35) of patient specimens exhibited a cytokine response to ICI. In a validation set of 20 tumors, collected from patients who were subsequently treated with ICI, ELP-score positivity correctly identified 9 of 11 patients (82%) who had an objective response (PR/CR) to ICI, including 2 patients who were negative for FDA-approved standard-of-care ICI biomarkers. Furthermore, 5 of 5 patients (100%) with clinical progressive disease were correctly characterized as ELP-score negative. **Conclusions:** Using routine biopsy specimens, the ex vivo live tumor platform accurately identifies patients with clinical response to ICI therapy, including those incorrectly identified by conventional biomarkers. Ongoing efforts will test these findings in an additional validation set. If confirmed, the ex vivo LTF platform could enable the identification of patients likely to benefit from ICI therapy. Clinical trial information: NCT05478538, NCT05520099, NCT06349642. Research Sponsor: Elephas.

2647 **Poster Session**

Mitochondrial DNA (mtDNA) expression as used to define metabolic and immune states in colorectal cancer (CRC). First Author: Michela Bartolini, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

Background: CRC exhibits metabolic reprogramming driven by the Warburg effect; however, active mitochondria and oxidative phosphorylation (OXPHOS) often remain crucial for tumor growth. mtDNA encodes critical OXPHOS components and influences the balance between OXPHOS and glycolysis, with effects on tumor microenvironment and response to immune checkpoint inhibitors (ICIs). We evaluated whether mtDNA gene expression predicts metabolic phenotype, immune contexture and benefit from ICIs. **Methods:** 30,887 CRC cases with DNA/RNA sequencing were analyzed from Caris Life Sciences. Expression of mtDNA-encoded OXPHOS genes (*MT-ND1–6, MT-ND4L, MT-CO1–3, MT-ATP6, MT-CYB*) was summarized as a composite Z-score due to correlation (r>0.9). Tumors were stratified into quartiles (n=7,722 each), mtDNA-high (MT-H, top quartile) and mtDNA-low (MT-L, bottom quartile) cohorts. Overall Survival (OS) was calculated in months (m) from first treatment to last contact. Hazard ratios (HRs) were calculated using Cox proportional hazards models and p-values by log-rank tests. Gene set enrichment analysis (GSEA) was performed to evaluate pathway differences. **Results:** MT-H tumors were enriched for Consensus Molecular Subtype (CMS) 2 compared to MT-L (44.2% vs 21.9%) and CMS3 (24.5% vs 8.7%), whereas CMS4 was markedly enriched in MT-L tumors (MT-H 16.5% vs MT-L 52.2%); all p<0.001. GSEA showed a trend toward higher OXPHOS activity in MT-H tumors (NES 1.19, FDR q=0.472), while glycolysis was significantly downregulated (NES -2.43, FDR q=0.002), with low immune/inflammatory signaling (interferon signaling and inflammatory response, among others) and reduced immune cell infiltration. These associations persisted in microsatellite stable (MSS) CRC, including CMS (CMS2/CMS3 46.3%/24.9% in MT-H vs CMS4 55.6% in MT-L) and immune signatures (all q<0.05). MT-L was prognostic for improved OS vs MT-H (median OS [mOS] 30.1 vs 27.2 m; HR 0.87, 95% CI 0.84-0.91, p<0.001). In ICI-treated patients (pts), MT-L showed amplified effect (mOS 24.3 vs 13.5 m; HR 0.69, 95% CI 0.58-0.83, p<0.001), including in CMS1 (mOS 39.3 vs 26.0 m; HR 0.71, 95% CI 0.53-0.96, p=0.024), CMS4 (mOS 19.3 vs 10.7 m; HR 0.61, 95% CI 0.40-0.94, p=0.024), MSS (mOS 13.8 vs 9.02 m; HR 0.67, 95% CI 0.54-0.84, p<0.001) and in pts with liver metastases (mOS 13.4 vs 7.93 m; HR 0.65, 95% CI 0.44-0.97, p=0.034). Multivariate analysis adjusting for age (>65 years), sex, liver metastases, MSI status, *BRAF V600E* status and CMS confirmed MT-L to be independently associated with improved OS in ICI-treated pts (p=0.01). No survival association was observed in pts treated with other therapies. **Conclusions:** mtDNA-encoded OXPHOS expression defines biologically distinct CRC subsets with distinct metabolic states and immune infiltration, with MT-L linked to improved OS and enhanced benefit from immunotherapy, including in MSS and liver metastases where ICI sensitivity is limited. Research Sponsor: None.

2648 **Poster Session**

Pan-cancer long mononucleotide repeat microsatellite instability testing for detection and immunotherapy selection. First Author: Ruchi Shah, Department of Medicine, University of Wisconsin-Madison, Madison, WI

Background: Microsatellite instability (MSI) and mismatch repair deficiency (dMMR) are crucial biomarkers to inform potential for hereditary risk and eligibility for immunotherapy across multiple cancers. While current standard of care testing can identify most MSI-high (MSI-H)/dMMR patients, improved testing sensitivity for MSI-H status could identify more patients who may benefit from immunotherapy. Recent studies have indicated potential for more sensitive testing using a long mononucleotide repeat (LMR)-based multiplex MSI-detection assay. **Methods:** Patients were identified and consented as part of an IRB-approved protocol (UW15068) based on MSI status, MMR gene variants, or high tumor mutation burden (TMB). Patient tissues, normal and tumor, were formalin-fixed and slides were prepared for pathologist annotation and immunohistochemistry (IHC) for CD8. CD8+ tumor infiltrating lymphocytes (TILs) were quantified/high powered field (HPF). Slides were scraped for DNA isolation. MSI testing was performed on the resultant DNA using the LMR MSI Analysis System (Promega, Madison, WI) and the OncoMate MSI Dx Analysis system (OM, Promega) per manufacturer protocols. LMR MSI status and score were compared with other testing methods, TMB, CD8+ TILs/HPF, immunotherapy response, progression-free survival (PFS), and overall survival (OS). **Results:** A cohort of 202 patients (median age: 64 (range: 24-80+)) with 20+ different cancer types (lung 27.2%, colorectal 18.8%, skin 9%, esophageal 5.9%, uterine 5.9%) and across disease stages, mutation profiles, and immunotherapy treatment regimens were consented. At least one test identified a case as dMMR/MSI-H in 31.6% of cases. In 9.4% of cases, a discrepancy between testing methods was observed. LMR detected 9 cases as MSI-H that were not detected by clinical NGS or OM. 4 cases were detected as MSI-H by LMR and OM alone, one case by OM alone, and one case by LMR and clinical NGS alone. Additionally, 2 cases were dMMR by IHC but not LMR, OM, or clinical NGS and 2 cases were dMMR by IHC and MSI-H by clinical NGS, but not LMR or OM. LMR score positively correlated with TMB (r^2 = 0.57) for MSI-H, but not MSS patients (r^2 = 0.002). LMR score weakly correlated with CD8+ TILs/HPF (r^2 = 0.16) in MSI-H, but not MSS cases (r^2 <0.001). LMR MSI-H cases have a 52.6% complete response rate compared to 6.12% of LMR MSS subjects (p<0.001). Patients identified as MSI-H by LMR testing had an increased PFS (median PFS (days) MSI-H: 711, MSS: 178; hazard ratio (HR) 0.25 [95% CI 0.13-0.50; p<0.001]) and OS (median OS (days) MSI-H: 926, MSS: 402; HR 0.43 [95% CI 0.22-0.82; p=0.015]) compared to LMR MSS patients. **Conclusions:** Variability can be observed between dMMR/MSI testing methods indicating that multiple methods should be considered for each patient. LMR testing demonstrates promising sensitivity and correlation with immunotherapy efficacy. Research Sponsor: Promega.

2649 **Poster Session**

Are all tumor-agnostic biomarkers equally tissue-independent? Comparative cross-histology efficacy analysis of MSI-H/dMMR versus *BRAF* V600E. First Author: Victor Andres Castillo, Autonomous University of Baja California, Tijuana, BJ, Mexico

Background: FDA tumor-agnostic approvals for pembrolizumab/dostarlimab (MSI-H/dMMR) and dabrafenib-trametinib (BRAF V600E) assume uniform cross-histology efficacy. However, MSI-H/dMMR depends on immune checkpoint blockade—potentially influenced by tissue-specific microenvironments—while BRAF V600E represents oncogene addiction with essential MAPK dependencies. We hypothesized these biomarkers differ in tissue independence, with MSI-H/dMMR demonstrating greater histology-dependent response variability. **Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. PubMed, Embase, and the Cochrane Central Register owere searched from inception to January 2026 to identify prospective basket trials enrolling adults ($\geq$18 years) with advanced or metastatic solid tumors harboring FDA-approved tumor-agnostic biomarkers. Eligible trials evaluated pembrolizumab or dostarlimab in MSI-H/dMMR tumors, or dabrafenib plus trametinib in BRAF V600E-mutant tumors, and reported objective response rates (ORR) stratified by tumor histology. Studies were required to include $\geq$3 distinct tumor histologies (not subtypes) with a minimum of 10 patients per histology cohort. Phase I trials, retrospective case series, pediatric-only populations, and studies without histology-specific efficacy data were excluded. Primary outcome was ORR heterogeneity across tumor types within each biomarker platform, quantified using the I^2 statistic and coefficient of variation (CV). Pooled analyses were performed using random-effects models. Effect estimates are expressed as ORR percentages with 95% confidence intervals. **Results:** Four trials included: KEYNOTE-158 (pembrolizumab, n=373), GARNET (dostarlimab, n=363), ROAR (dabrafenib-trametinib, n=215), VE-BASKET (vemurafenib, n=62); 1,013 patients across 12 tumor histologies. MSI-H/dMMR platform (n=736, 8 tumor types): mean ORR 35.1% (range 0-57.1%); endometrial 57.1%, gastric 45.8%, colorectal 43.5%, small intestine 42.1%, cholangiocarcinoma 40.9%, ovarian 33.3%, pancreatic 18.2%, brain 0%; CV=0.513. BRAF V600E platform (n=277, 4 tumor types): mean ORR 45.0% (range 37.1-53%); anaplastic thyroid 53%, biliary tract 47%, glioma 42.9%, NSCLC 37.1%; CV=0.149. MSI-H/dMMR demonstrated 3.4-fold greater heterogeneity than BRAF V600E (CV 0.513 vs 0.149). **Conclusions:** Tumor-agnostic biomarkers exhibit differential tissue independence. MSI-H/dMMR showed 3.4-fold greater response heterogeneity (CV=0.513) than BRAF V600E (CV=0.149), indicating immune checkpoint efficacy remains tissue-dependent while oncogene addiction confers uniform predictivity. These findings challenge the assumption of biomarker-driven tissue-agnostic efficacy and necessitate histology-specific outcome counseling and trial stratification. Research Sponsor: None.

2650 **Poster Session**

Pan-cancer landscape of oncogenic POLE and POLD1 alterations. First Author: Lawrence W. Wu, Columbia University Irving Medical Center, New York, NY

Background: POLE and POLD1 encode key enzymes for DNA proofreading. Oncogenic alterations in POLE and POLD1 associated with defective proofreading can lead to tumor hypermutation and increased sensitivity to immune checkpoint inhibition. Prior studies have identified enrichment of POLE and POLD1 alterations in colorectal and endometrial cancers. However, characterization of POLE and POLD1 alterations in the pan-cancer setting has been limited. Utilizing the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) v19.0, we performed a comprehensive analysis of oncogenic POLE and POLD1 alterations across tumor types. **Methods:** The AACR GENIE v19.0 database was used to select tumor samples that were profiled for molecular alterations (somatic mutations, structural variants, copy number alterations) in POLE or POLD1. POLE and POLD1 alterations were annotated by OncoKB to determine if they were oncogenic. Tumor samples were analyzed for co-occurring molecular alterations. Categorical variables were compared using chi-square or Fisher exact tests, as appropriate. P-values were adjusted with Benjamini-Hochberg correction to control false discovery rate (significance for $q<0.05$). **Results:** Across 188,863 tumor samples that were profiled for POLE or POLD1, there were known oncogenic alterations in 786 samples (0.4%). Of note, there were 18,170 molecular alterations in POLE and POLD1 that were classified as variants of unknown significance at time of analysis. The most common tumor types with oncogenic alterations were endometrial (n=374 of 7573 samples profiled; 4.9%), colorectal (143/17821; 0.8%), glioma (49/12795; 0.4%), NSCLC (35/30542; 0.1%), ovarian (26/7728; 0.3%), breast (25/16813; 0.2%), bladder (25/6433; 0.4%), cancer of unknown primary (19/6544; 0.3%), melanoma (13/7965; 0.2%), and pancreatic (10/10369; 0.1%), and esophagogastric (9/6503, 0.1%). The most common mutations in POLE were V411L, E18K, P286R, S297F, and A456P. The most common mutations in POLD1 were R1016H, R1016C, R689W, L606M, and D402N. Oncogenic alterations in POLE and POLD1 were enriched in endometrial cancer (OR 22.8; $q<0.001$) and colorectal cancer (OR 2.14; $q<0.001$), with no other tumor types showing enrichment. Within the oncogenic POLE/POLD1 cohort, the most common co-occurring molecular alterations were in PIK3CA (n=561, 71.4% in altered vs 12.9% in unaltered, $q<0.001$), APC (n=526, 68.7% vs 11.8%, $q<0.001$), ATM (n=523, 67.8% vs 7.3%, $q<0.001$), and PTEN (n=523, 66.5% vs 8.7%, $q<0.001$). **Conclusions:** To our knowledge, this study represents the largest molecular analysis of oncogenic POLE and POLD1 alterations in a pan-cancer setting. These findings suggest that oncogenic POLE and POLD1 alterations may be rarely identified in a broad range of tumor types. Further studies are needed to classify the functional implication of many variants of unknown significance in POLE and POLD1. Research Sponsor: None.

2651 **Poster Session**

Phase Ib evaluation of a recombinant overlapping peptide survivin immunotherapy: Safety, immunogenicity, and immune–clinical associations in advanced solid tumours. First Author: Shisong Jiang, Department of Oncology, University of Oxford, Oxford, Oxfordshire, United Kingdom

Background: Survivin (BIRC5) is a tumour-associated self-antigen broadly expressed in solid malignancies but subject to immune tolerance, limiting its value as an immunotherapy target. OVM-200 is a recombinant overlapping peptide (ROP) survivin immunotherapy designed to enhance antigen processing and presentation through both MHC class I and II pathways, thereby overcoming HLA restriction. A Phase Ia study established safety and the recommended regimen. Here we report novel Phase Ib data evaluating extended immunisation and immune–clinical associations. **Methods:** Phase Ib enrolled a total of 24 patients with advanced NSCLC, ovarian, or prostate cancer who had progressed on standard therapies. Patients received OVM-200 at the recommended regimen (2 mg) with extended immunisation schedules (3–11 immunisations). The primary endpoint was safety and the secondary endpoint was immunogenicity. Survivin-specific antibodies were measured by IgG ELISA and T-cell responses by IFN-γ ELISpot. Tumour response was assessed using RECIST 1.1, with best overall response (BOR) classified as stable disease (SD) or progressive disease (PD). Immune responses were analysed longitudinally and in relation to BOR. **Results:** The primary endpoint of safety was met, with OVM-200 well tolerated and no dose-limiting toxicities or treatment-related serious adverse events. Survivin expression was detected in tumour tissue in 17 patients prior to immunisation; however, baseline survivin-specific antibody and T-cell responses were low or undetectable, consistent with immune tolerance. The secondary endpoint of immunogenicity was achieved. Mean peak anti-survivin antibody titres increased from 1:143 pretreatment to >1:160,000 post-treatment ($p < 0.001$), and mean peak T-cell responses increased from 211 to 859 net SFU/10^6 PBMCs ($p < 0.00001$). Antibody responses were durable, rising through Days 113–169, whereas T-cell responses peaked at Day 57 and remained significantly above baseline. Extended immunisation (>5 immunisations) maximised humoral responses, while T-cell magnitude was comparable across schedules. Patients with BOR of SD showed higher and more sustained survivin-specific humoral and cellular immune responses than those with PD. **Conclusions:** Phase Ib results demonstrate that OVM-200 is safe and immunogenic, achieving both the primary safety and secondary immunogenicity endpoints. OVM-200 overcomes immune tolerance to survivin and induces durable humoral and cellular immune responses. The observed association between stronger immune responses and BOR of SD supports further clinical evaluation and rational combination strategies. Clinical trial information: NCT05104515. Research Sponsor: Oxford Vacmedix.

2652 **Poster Session**

Monitoring blood-based biomarkers as early predictors of progression-free survival in a randomized Bria-ABC phase 3 trial for advanced metastatic breast cancer: An ongoing analysis. First Author: Daniel L. Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ

Background: Circulating Tumor Cells (CTCs) are prognostic for poor outcomes in metastatic Breast Cancer (mBC), however CTCs are uncommon in mBC (<20%) and many pts without CTCs often progress. Cancer associated macrophage-like cells (CAML) are prognostic inflammatory pro-tumorigenic PD-L1 expressing macrophages common in mBC pt blood (>90%). In a previous randomized phase II trial, CTC & CAML decreases post Bria-IMT induction correlated with clinical benefit. Bria-IMT is an allogenic whole cell vaccine engineered to express tumor associated antigens & GM-CSF, promoting adaptive & innate immune responses. The ongoing Bria-ABC (NCT06072612) phase 3 study compares Bria-IMT to physician's choice (TPC) in late stage mBC. We present interim results, without treatment arm comparison, for Progression Free Survival (PFS) by CTC & CAML changes as the exploratory part of the trial. **Methods:** This still blinded ongoing multicenter randomized open label Phase 3 trial evaluates Bria-IMT+ checkpoint inhibitor (CPI) vs TPC in mBC pts lacking approved therapies. Pts are randomized 1:1:1 to Bria-IMT+CPI, TPC, or Bria-IMT monotherapy (discontinued after 150 pts). The Bria-IMT consists of cyclophosphamide, irradiated SV-BR-1-GM cells, micro-dose pegylated α IFN at each inoculation site. CPI is administered day -3 to 3. TPC followed standard of care. Blinded anonymized blood was taken at baseline (BL), prior to therapy & 2nd (T1) taken at cycle 3 (~4 weeks post initiation). CTCs & CAMLs, and PD-L1 expressions, were quantified using LifeTracDx liquid biopsy with analysis of PFS by censored univariate analysis. **Results:** At time of analysis, >250 consented, >170 randomized, 119 had BL and 78 had T1. Median age 56 yrs [34–83], median 6 [2–13] prior lines of therapy, 31% TNBC, 62% ER+/PR+, & 15% HER2+. $\geq$1 CTCs were found in 25% (30/119) at BL & 22% (17/78) at T1. $\geq$1 CAMLs were found in 93% (111/119) at BL & 95% (74/78) at T1. At BL, $\geq$1 CTC was not significant for PFS (HR=1.7, CI95% 1.0-2.9, p=0.0513), but $\geq$2 CTCs was significant for worse PFS (HR=1.8 CI95% 1.1-3.1, p=0.0480). At T1, $\geq$1 CTCs nor $\geq$2 CTCs correlated with PFS (HR=0.9, p=0.8392) & (HR=1.6, p=0.1079), respectively. Further, a decrease in CTCs was seen in 11 pts but did not correlate with PFS (HR=0.7, p=0.6552). $\geq$1 CAML at BL nor T1 correlated with PFS (HR=1.2 CI95% 0.7-2.0, p=0.6811) or (HR=0.9 CI95% 0.7-2.5, p=0.5307), respectively. However, 51 pts (65%) had a decrease or stable CAML counts between BL & T1 which did significantly correlate with better PFS (HR=2.2 CI95% 1.2-3.9, p=0.0154). **Conclusions:** In an ongoing analysis of a heavily treated mBC pts, we observed that in the entire blinded population, 65% of pts had stability/drop in CAMLs significantly correlated with better PFS. Treatment arm specific comparisons will not be unblinded until completion of the designated milestone (144 mortalities). Clinical trial information: NCT06072612. Research Sponsor: Creatv Microtech; BriaCell Therapeutics Corp.

2653 **Poster Session**

Off-target HLA matches for prediction of response in personalised cancer vaccines: A multi-trial retrospective analysis. First Author: Om H. Gandhi, Centre for Immuno-Oncology, University of Oxford, Oxford, United Kingdom

Background: Personalized neoantigen vaccines aim to match epitopes to a patient's HLA genotype, yet many peptides bind promiscuously across multiple HLA alleles. Promiscuous binding may reflect intrinsic peptide properties, including enhanced processing efficiency and structural stability, that drive immunogenicity independent of any single HLA match. We hypothesized that peptides with broader HLA binding profiles would show higher clinical immunogenicity, even when restricted to the patient's own HLA alleles. **Methods:** We curated 17 neoantigen vaccine trials (174 patients) and selected five with per-epitope $CD8^+$ T cell immunogenicity data for primary analysis. Across 571 neoantigen sequences (3,806 derived peptides), we predicted binding and presentation using NetMHCpan-4.2, MHCflurry 2.0, and PRIME-2.0, and estimated peptide–MHC stability with NetMHCstabpan. A reference panel of 62 common HLA class I alleles (>95% global coverage) was used to quantify incidental coverage, defined as predicted binding (IC50 <500 nM) to non-patient HLA alleles. Mixed-effects models adjusted for patient-specific binding affinity, predicted stability, mutation type, neoantigen length, and trial structure, with Bonferroni correction for 5 pre-specified hypotheses. **Results:** Off-target HLA binding independently predicted clinical immunogenicity. Among peptides selected for vaccination, 35.2% bound at least one non-patient HLA allele, with the most promiscuous peptides binding up to 37 alleles. After adjusting for patient-specific binding affinity and stability, peptides from immunogenic neoantigens showed greater incidental coverage than non-immunogenic peptides (mean 2.46 vs 1.80 additional HLAs; p=0.0034). This association was consistent across tumour types and prediction methods. Among immunogenic peptides, the breadth of off-target binding correlated with response magnitude (Spearman ρ=0.46, p=0.034), with the strongest effect observed in glioblastoma. High-affinity off-target matches (IC50 <50 nM) and high-stability interactions showed the most robust associations with immunogenicity. **Conclusions:** Promiscuous HLA binding independently predicts neoantigen immunogenicity in clinical trials, beyond binding affinity and stability to the patient's own HLA alleles. These results point to peptide-intrinsic properties linked to MHC stability and processing that are overlooked by current selection pipelines. Explicit modelling of HLA promiscuity and stability may improve neoantigen prioritisation, particularly in low–mutation burden tumours and patients with rare HLA genotypes. Research Sponsor: None.

2654 **Poster Session**

Ranking neoantigens for escape-resilience rather than predicted immunogenicity: Associated changes in vaccine design. First Author: Michael E. Bryan, Centre for Immuno-Oncology, University of Oxford, Oxford, United Kingdom

Background: Personalised neoantigen vaccines induce detectable $CD8^+$ T cell responses for fewer than one-third of selected peptides. Current pipelines prioritise candidates by predicted immunogenicity and select peptides independently, overlooking two constraints: efficacy depends on the peptide set as a whole, and tumours adapt antigen processing under immune pressure. We developed a framework that optimises peptide combinations for resilience to tumour escape and tested whether escape-resilience predicts clinical immunogenicity. **Methods:** We modelled peptide susceptibility to five antigen-processing escape mechanisms: TAP downregulation, immunoproteasome-to-constitutive proteasome switching, aminopeptidase upregulation, tapasin loss, and HLA loss of heterozygosity. Selection was formulated as a minimax optimisation, maximising predicted efficacy under worst-case tumour adaptation. We analysed five neoantigen vaccine trials with per-epitope $CD8^+$ T cell response data, consisting of 571 neoantigens, 3,806 peptides, and 174 patients. Mixed-effects models tested associations between escape-resilience and immunogenicity, adjusting for binding affinity (NetMHCpan-4.1 %rank), pMHC stability (NetMHCstabpan), mutation type, and clonality. Six hypotheses were pre-registered with Bonferroni correction. **Results:** Escape-resilience predicted immunogenicity independently of established features. After adjustment, vulnerability to TAP loss (OR 0.42 per SD, 95% CI 0.24–0.71, p=0.0018) and proteasome switching (OR 0.54 per SD, 95% CI 0.34–0.86, p=0.0089) were associated with failure to elicit $CD8^+$ responses. Among peptides with comparable predicted binding affinity, escape-resilient peptides were significantly more likely to be immunogenic. Composite escape-resilience scores discriminated immunogenic from non-immunogenic peptides (AUC 0.71, 95% CI 0.66–0.76), outperforming binding affinity alone (AUC 0.58) and an affinity-stability model (AUC 0.64). Adding escape-resilience improved discrimination (ΔAUC 0.07, p=0.003). Retrospective re-ranking altered 38% (95% CI 31–45%) of vaccine compositions, replacing high-affinity but escape-vulnerable peptides with lower-affinity, processing-robust alternatives. Associations were stronger for truncal mutations (OR 2.8, 95% CI 1.6–4.9) than subclonal mutations (OR 1.4, 95% CI 0.8–2.4; interaction p=0.041), indicating that processing robustness is most consequential for clonally dominant neoantigens. **Conclusions:** Optimising neoantigen selection against tumour escape identifies peptides more likely to elicit $CD8^+$ T cell responses, independent of binding affinity and stability. The stronger effects in truncal mutations suggest escape-aware ranking may be particularly valuable for durable, clone-targeted vaccination strategies. Prospective trials are needed to assess clinical impact. Research Sponsor: None.

2655 **Poster Session**

The differentiated SIRPα–IgG4 Fc fusion protein HCB101 in monotherapy and combination therapy. First Author: Fangling Ning, Binzhou Medical University Hospital, Binzhou, China

Background: The CD47–SIRPα axis is a central innate immune checkpoint that enables tumor immune evasion. No prior CD47-directed program has demonstrated meaningful monotherapy activity, limited by on-target hematologic toxicity, constraining development. HCB101 is a differentiated SIRPα–IgG4 Fc fusion protein engineered to maintain macrophage-mediated phagocytosis while reducing red-blood-cell binding. This study assesses whether HCB101 can overcome historical class limitations by achieving a wide therapeutic safety margin and durable monotherapy antitumor activity, while also serving as a backbone for combination immunotherapy efficacy across standard-of-care (SOC) regimens. **Methods:** HCB101-101 (NCT05892718) is a first-in-human Phase 1 monotherapy dose-escalation study evaluating weekly IV dosing from 0.08 to 36 mg/kg. HCB101-201 (NCT06771622) is a Phase 1b/2a multi-cohort trial assessing HCB101 combined with SOC agents across 9 solid tumor types, including gastric cancer (GC), triple-negative breast cancer (TNBC), colorectal cancer, head and neck squamous cell carcinoma (HNSCC), hepatocellular carcinoma, ovarian cancer, and small cell lung cancer. Primary endpoints are safety, tolerability, and determination of the recommended Phase 2 dose; secondary and exploratory endpoints include pharmacokinetics (PK), pharmacodynamics, efficacy, and biomarkers. **Results:** In HCB101-101, 36 mg/kg has been reached. To 09JAN2026, 2 confirmed partial responses (HNSCC: −42% at 5.12 mg/kg, durable > 44 weeks; marginal zone lymphoma), and 9 stable diseases (SD) have been observed. PK was dose-proportional ($T_{1/2}$ ~2.9 days) with receptor occupancy plateauing at > 99% by ≥8 mg/kg. In HCB101-201, 2L-GC treated with HCB101 plus ramucirumab and paclitaxel demonstrated 8 PRs and 5 SDs, with two additional patients at 12 mg/kg pending first assessment. In mid-dose cohorts (5.12–8 mg/kg), 8 of 10 subjects achieved PRs and 100% achieved disease control, with regressions up to −78.2%. In 1L HER2+ GC, 4 subjects showed 3 PR (up to −57.6%) and 1 SDs. In 1L-TNBC, 6 of 6 subjects achieved disease control, including 3 PRs. Across cohorts, HCB101 demonstrated manageable safety with reversible cytopenias and no unexpected immune-mediated toxicities. **Conclusions:** HCB101 demonstrates a class-distinguishing profile for a macrophage checkpoint inhibitor, with durable monotherapy antitumor activity and a wide therapeutic window up to 36 mg/kg, addressing long-standing limitations of CD47-directed therapies. The early and reproducible combination activity across multiple solid tumors, including GC, HER2+ GC, and TNBC, has supported rapid cohort expansion. These data position HCB101 as a next-generation innate immune checkpoint backbone with broad clinical applicability and a clear rationale for future combination-based registrational development. Clinical trial information: NCT05892718. Research Sponsor: None.

2656 **Poster Session**

Low-dose nivolumab in patients at high risk of immune-related adverse events: A retrospective cohort study. First Author: Lisa May Ling Tachiki, University of Washington, Seattle, WA

Background: Immune checkpoint inhibitors (ICIs) are relatively contraindicated in patients with prior severe immune-related adverse events (IRAEs) and/or have pre-existing serious auto-immune diseases (AID). Such patients are generally excluded from immunotherapy trials due to toxicity concerns, and data on ICI (re)exposure is limited. Our correlative data [Tachiki L 2024 SITC] suggest that low-dose (LD) nivolumab (Nivo; 40 mg) achieves PD-1 receptor occupancy comparable to standard-dose (SD) Nivo (240 or 480 mg), suggesting a potentially similar risk of developing IRAEs. However, faster serum clearance observed with LD Nivo may allow easier management of IRAEs when they occur. Based on this rationale, we have offered LD Nivo to high-risk patients after careful clinical discussion. In this study, we present the outcomes of our institutional experience. **Methods:** This single institution, retrospective cohort study included patients with advanced skin cancers who received LD Nivo (40 mg) due to a high-risk of IRAEs, including those with a previous history of IRAEs from SD ICIs or ICI-naïve patients with pre-existing AID. We analyzed efficacy and safety endpoints, including best objective response rates (BORR) per RECIST v1.1 and rates of IRAE with SD and LD ICIs. Outcomes were analyzed using descriptive statistics and stratified Cox models. **Results:** From 2015 – 2025, 23 patients with advanced skin cancers (22-Melanoma; 1-Merkel cell carcinoma) received LD Nivo due to an elevated IRAE risk. Sixteen patients had a history of treatment-limiting IRAEs on SD ICIs ("Prior-IRAE" cohort: 7 SD anti-PD-1 monotherapy; 9 SD combination ICI), and 7 patients were ICI-naïve with pre-existing AID ("AID" cohort). In the Prior-IRAE cohort, treatment hold/discontinuation due to IRAEs occurred in 100% with SD ICI versus 43.8% with LD Nivo (p = 0.032). Among the 7 patients previously treated with SD anti-PD-1 monotherapy, the incidence of grade ≥2 IRAEs was 100% (median duration 75 days; range, 12–217) on SD therapy versus 42.8% (median duration 43 days; range, 23–146) on LD Nivo. In the AID cohort, 100% patients experienced at least one grade 2 IRAE, but no grade 3 or 4 events were observed. In patients with evaluable disease (measurable and progressing at LD Nivo initiation), BORR was 57.1% (4/7; 1 complete response [CR], 3 partial responses) in the Prior-IRAE cohort and 33.3% (2/6; both CR) in the AID cohort. **Conclusions:** LD Nivo demonstrates biological activity, as evidenced by both anti-tumor responses and toxicities, in patients at high risk of IRAEs. Compared to SD ICI, LD Nivo may offer an advantage in toxicity management, potentially enabling more consistent treatment delivery with fewer interruptions and reduced need for immunosuppressive interventions. This strategy warrants further evaluation in prospective clinical trials. Research Sponsor: Winn Career Development Award; Kuni Foundation.

2657 **Poster Session**

Association of PCSK9 inhibitors with clinical outcomes in patients with cancer receiving immune checkpoint inhibitors: A real-world analysis. First Author: Chuan Angel Lu, UT Southwestern Medical Center, Dallas, TX

Background: Although developed as lipid-lowering agents, PCSK9 inhibitors (PCSK9i) have shown preclinical potential to synergize with immune checkpoint inhibitors (ICIs) by increasing tumor antigen presentation and overcoming ICI resistance. However, there is limited evidence describing their use and associated outcomes in real-world oncology practice. We aimed to explore the clinical outcomes in relation to PCSK9i use in patients with cancer receiving ICIs. **Methods:** This propensity score-matched (PSM) cohort study utilized the TriNetX research network, encompassing real-time electronic health records from > 70 U.S. healthcare organizations. The study population included adults (aged ≥18 years) diagnosed with non-small cell lung cancer, melanoma, renal cell carcinoma, or breast cancer, who underwent concurrent ICI therapy (e.g., pembrolizumab, nivolumab, atezolizumab, durvalumab) plus PCSK9i (e.g., evolocumab, alirocumab; with or without statins) or high-intensity statins alone (atorvastatin ≥ 40 mg, or rosuvastatin ≥ 20 mg) between 01/01/2011 (the earliest year of ICI approval) and 01/01/2025 for hyperlipidemia. The primary outcome was overall survival (OS). Secondary outcomes included emergency room (ER) visits, all-cause hospitalization, ICU admission, and 4-point (acute myocardial infarction, heart failure, stroke, and unstable angina) major adverse cardiovascular event (MACE). A 1:1 PSM was applied to balance potential confounders, including demographics, socioeconomic status, cancer site, Charlson-Comorbidity-Index comorbidities, and laboratory parameters [Albumin, LDL, AST/ALT, and BMI]. Time-to-event analyses were performed using Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with log-rank test for significant survival differences. Follow-up began at the initiation of concurrent ICI plus PCSK9i or statin and continued until 01/05/2025, or until the occurrence of the study outcomes. **Results:** A total of 254 patients in PCSK9i cohort were matched to 254 patients from the statin-only cohort (n = 13734). Patients receiving PCSK9i demonstrated significantly improved OS compared with those receiving statins alone (HR 0.67, 95% CI 0.52-0.88) and associated with lower risk of ER visits (HR 0.64, 95% CI 0.49-0.83), hospitalization (HR 0.68, 95% CI 0.54-0.85), and ICU admission (HR 0.69, 95% CI 0.50-0.95; all $p<0.01$). No significant difference was observed for MACE outcomes (HR 0.79, 95% CI 0.59-1.07, p=0.13). **Conclusions:** In this large, real-world analysis, the use of PCSK9i in patients with cancer and hyperlipidemia treated with ICIs was associated with improved overall survival and reduced healthcare utilization. These findings support ongoing prospective clinical trials evaluating the potential synergistic effects of PCSK9 inhibition with ICI therapy. Research Sponsor: None.

2658 **Poster Session**

Modulation of PD-1 and PD-L1 expression on peripheral blood T-cells by novel rotavirus variants. First Author: Svetlana Yu Filippova, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation

Background: Promising oncolytic viruses are typically evaluated based on their direct cytotoxic effects on cancer cells. However, the therapeutic benefit of virotherapy may also stem from its immunomodulatory actions, particularly through influencing immune checkpoint molecules like PD-1 and PD-L1. This study aimed to investigate the effect of unclassified apathogenic rotavirus strains RVK100 and RVK228 on the expression of PD-1 and PD-L1 on T-cells derived from the peripheral blood of patients with breast cancer. **Methods:** Mononuclear cells of peripheral blood were isolated on a ficoll gradient, cultured in RPMI 1640 (Gibco, USA) without serum at 37 °C, 5.0% CO2 in 4 variants of the experiment: 1) negative control without viruses; 2) positive control of activation with the addition of PHA; 3) experience with the addition of 107 particles per 1 ml of the RVK100 strain; 4) experience with the addition of 107 particles per 1 ml of the RVK100 strain RVK228. After 24 and 72 hours of cultivation, the expression of PD-1 (CD279) and PD-L1 (CD274) was determined on T cells by flow cytometry. The study used antibodies conjugated with fluorochromes: anti-CD4 (PE), anti-CD8 (APC Cy7), anti-CD279 (FITC), anti-CD274 (PerCP-Cy5–5) (Becton Dickinson, USA). **Results:** After 24 hours, we observed increases in PD-1 expression on CD4+ (PHA—40.5%, RVK100—42.3%, RVK228—37.5%; vs. control—18.1%) and CD8+ cells (PHA—41.7%, RVK100—46.4%, RVK228—42.6%; vs. control—27.7%). Similarly, PD-L1 expression rose on CD4+ cells (RVK100—67.0%, RVK228—58.6%, PHA—75.1%; vs. control—44.8%) and CD8+ cells (RVK100—63.4%, RVK228—58.4%, PHA—52.8%; vs. control—46.2%). At 72 hours, PD-1 levels decreased significantly in CD4+ cells exposed to RVK100 (from 42.3% to 21.6%) and CD8+ cells (from 46.4% to 17.4%). Conversely, PD-L1 expression increased across all groups on CD8+ cells, reaching 67–79%, while minimal change occurred on CD4+ cells except for a minor decline in the RVK100 group. **Conclusions:** Both strains, like the non-specific T-mitogen PHA, caused the stimulation of the expression of immune checkpoint receptors PD-1 and PD-L1 on T-helpers and CTL after 24 hours of cultivation. After 72 hours of cultivation, RVK100, unlike RVK228, was revealed ability to reduce the expression of PD-1 on these cells. Research Sponsor: None.

2659 **Poster Session**

Preclinical investigations and first-in-human phase I trial of KP-483 in solid tumors: Safety, antitumor activity, and preliminary efficacy. First Author: Noboru Yamamoto, Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

Background: KP-483 is a novel small-molecule antagonist of the E-type prostanoid receptor 4 (EP4) that potentially exerts antitumor effects by modulating the tumor microenvironment and restoring antitumor immunity. Based on preclinical and phase I studies, this report presents the pharmacological properties, safety, and preliminary efficacy of KP-483. **Methods:** In preclinical studies, the pharmacodynamic profile of KP-483 was characterized *in vitro* and *in vivo*. Antitumor activity was evaluated in tumor-bearing mice, and tumor infiltrating $CD8^+$ and $CD163^+$ cells were quantified. A first-in-human phase I study (jRCT2031220311) using a 3+3 dose-escalation design enrolled patients with solid tumors who had progressed after standard treatments or for whom no appropriate standard treatment was available. KP-483 was administrated orally once daily, with dose escalation across five cohorts (50, 100, 200, 400, and 800 mg). The primary endpoints were dose-limiting toxicities (DLTs) and safety profiles. Plasma concentrations of KP-483 were also measured. Preliminary efficacy was evaluated according to RECIST criteria, and the antitumor mechanisms were explored by flow cytometry analysis of tumor tissue. **Results:** KP-483 exhibited greater EP4 antagonist activity than existing antagonists (IC_{50}: 1.0 nmol/L in human) and had higher binding affinity to the EP4 receptor and a longer dissociation half-life than PGE_2 *in vitro*. In mouse models, KP-483 exhibited dose-dependent antitumor effects following 14 days of oral administration at doses of 3, 30, and 300 mg/kg once daily. The number of $CD8^+$ T cells in tumor tissue increased while that of $CD163^+$ cells decreased in a dose-dependent manner. In addition, combination treatment with KP-483 (15 mg/kg, twice daily) and either anti-PD-1 or anti-PD-L1 antibodies enhanced antitumor effects compared with either monotherapy. In the phase I study, safety was assessed in a total of 19 patients. The median treatment duration was 43 days (range: 24–713 days), and no DLTs were observed. The most common treatment-emergent adverse events were anemia and nausea (each 26.3%), with only one study-drug-related grade ≥3 event (anemia). Systemic exposure to KP-483 increased with dose, and the plasma half-life of KP-483 ranged from 7.9 to 12.8 hours on treatment day 15. Best overall responses included stable disease in four patients and partial response in one patient. Flow cytometry analysis of tumor tissue showed a trend toward increased activated cytotoxic T cells, dendritic cells, and M1-like macrophages. **Conclusions:** KP-483 is a potent EP4 antagonist that exerts antitumor effects through modulation of the tumor immune microenvironment. Given its favorable safety and pharmacokinetic profiles, KP-483 represents a promising EP4 receptor–targeted therapeutic strategy with potential for combination with immune checkpoint inhibitors. Clinical trial information: jRCT2031220311. Research Sponsor: KAKEN Pharmaceutical Co., LTD.

2660 **Poster Session**

Enrichment of the germline *NLRC5^{Pro191Leu}* variant in patients with immune checkpoint inhibitor–induced hepatitis. First Author: Shira Gabizon Peretz, Yale University School of Medicine, Medical Oncology, New Haven, CT

Background: Immune checkpoint inhibitor–induced hepatitis (ICI-hepatitis) is a clinically significant immune-related adverse event (irAE) that may require treatment interruption and immunosuppressive therapy. Predictors of susceptibility to irAEs remain poorly defined. NLRC5 is a key regulator of MHC class I antigen presentation and $CD8^+$ T-cell–mediated immune activation. We previously identified a germline missense variant at the NLRC5 gene (*$NLRC5^{Pro191Leu}$*) that is associated with ICI-related endocrinopathies, and increased expression of downstream genes involved in antigen presentation. Our purpose was to determine whether the variant has a broader role in immune-related toxicity. **Methods:** We evaluated the prevalence and clinical associations of the germline *$NLRC5^{Pro191Leu}$* variant in patients with grade ≥2 ICI-hepatitis. Sanger sequencing was performed to assess the *$NLRC5^{Pro191Leu}$* (rs74439742) germline variant. Hepatitis severity was graded according to CTCAE criteria. Clinical data included irAE co-occurrence, duration of corticosteroid therapy, and requirement for additional immunosuppression. Variant prevalence was compared with the general population using data from the 1000 Genomes Project. **Results:** Among 39 patients with ICI-hepatitis, the cohort was predominantly composed of patients with metastatic melanoma receiving ipilimumab plus nivolumab. The variant was significantly enriched in the ICI-hepatitis cohort compared with the general population (30.0% vs 12.8%; p = 0.007, odds ratio [OR] = 2.9). Variant carriers also more frequently developed co-occurring endocrine irAEs, particularly thyroid dysfunction and hypopituitarism. Conversely, co-occurrence of hepatitis and colitis was more frequent among wild-type patients (p = 0.06, OR = 7.6), suggesting distinct immunopathogenic toxicity patterns. The severity of hepatitis was assessed by a composite outcome of maximal grade 4 hepatitis and prolonged steroid use (≥120 days). Variant carriers showed a trend toward increased hepatitis severity that did not reach statistical significance (Fisher's exact p = 0.06; OR = 4.9). **Conclusions:** Germline *$NLRC5^{Pro191Leu}$* is significantly more common in patients who develop ICI-hepatitis than in the general population and is associated with distinct immune-related toxicity patterns. This suggests that host genetic factors may inform toxicity surveillance and early management strategies. Larger multi-center studies are needed to validate these observations and define the clinical utility of *$NLRC5^{Pro191Leu}$* as a predictor of immune-related toxicity risk. Research Sponsor: Davidoff Fund.

Prevalence of *$NLRC5^{Pro191Leu}$* variant in the ICI-hepatitis cohort.

Group	NLRC5 WT, n (%)	*NLRC5Pro191Leu*, n (%)
ICI-hepatitis cohort (n=39)	27 (70.0)	12 (30.0)
Odds ratio		2.9
p value		0.007
General population (1000 Genomes Project) (n=694)	605 (87.2)	89 (12.8)

2661 **Poster Session**

Systemic third generation allosteric STING agonist CRD3874-SI, a novel immunotherapy, in patients with advanced solid tumors: Results from a single-agent phase I study. First Author: Ciara M. Kelly, Memorial Sloan Kettering Cancer Center, New York, NY

Background: CRD3874-SI is a first in class, systemically administered, allosteric STING agonist that blocks STING's proton channel activity differentiating it from previously developed STING agonists. The drug has demonstrated pre-clinical anti-cancer activity in several murine tumor models and has pharmacological properties distinct from earlier generation STING agonists. **Methods:** This is a single institution, open-label, phase I study of CRD3874-SI in patients with advanced solid tumors. The dose escalation study follows a standard 3+3 design. CRD3874-SI is administered intravenously once per week for 2 cycles. Cycle duration is 28 days. From cycle 3 onwards, continuous weekly treatment +/- one week break (week 4) may be considered. The primary objective is to assess the safety of CRD3874-SI by determining the maximum tolerated dose, recommended phase 2 dose and schedule of administration. Secondary objectives include examining the pharmacokinetics and pharmacodynamics (IP10 analysis) of CRD3874-SI and evaluating the efficacy of CRD3874-SI as determined by best objective response rate per RECIST v 1.1. Clinical trial information: NCT06021626. Research sponsor: Curadev Pharma, Inc. **Results:** As of January 5th 2026, 21 patients (sarcoma n=20, adenoid cystic carcinoma n=1) received treatment at four escalating dose levels (0.1-1.8mg/kg). The median number of prior lines of treatment was 4 (1-11). The median duration of treatment was 7 weeks (range: 1-32 weeks). 2 patients continue treatment. Reasons for treatment discontinuation include: progression of disease (n=16), toxicity (n=2), patient withdrawal (n=1). Treatment emergent adverse events (TEAEs) were manageable and reversible. Only low-grade cytokine related symptoms were reported. TEAEs possibly related to study treatment reported in $>$20% of participants and were mostly low grade include: fatigue (43%), chills (38%), nausea (38%), diarrhea (33% (G3 (10%)), headache (29%) and flu-like symptoms (24%). Low grade colitis not typical of auto-immune mechanism, responding well to temporary treatment pause +/- oral budesonide, were reported in 4 patients. One DLT at dose level 4 (G3 dyspnea) was observed. 19 patients are evaluable for efficacy. The best objective response per RECIST v1.1: confirmed partial response, n=1 (malignant phyllodes tumor); stable disease, n=9; progressive disease, n=9. Dose level 3 (0.9mg/kg) represents a biologically active dose (one confirmed PR and a second case with -27% tumor regression was observed). Dose proportional increase in AUC with concomitant increase in plasma CXCL10 levels were observed. **Conclusions:** CRD-3874-SI has demonstrated clinical activity with manageable safety. Dose level 0.9mg/kg is biologically and clinically active. A dose expansion phase at this dose level in is planned in $>$5 histology specific cohorts. Clinical trial information: NCT06021626. Research Sponsor: Curadev Pharma.

2662 **Poster Session**

Effect of IL7 on ImmTAC-mediated killing by T cells in vitro and T-cell fitness in patients. First Author: Joseph J. Sacco, The Clatterbridge Cancer Centre and University of Liverpool, Liverpool, United Kingdom

Background: A blood T cell fitness (TCF) signature, reflecting properties of naïve and stem cell memory T cells, was strongly associated with clinical benefit from tebentafusp (gp100 $\times$ CD3) and brenetafusp (PRAME $\times$ CD3) ImmTAC bispecific therapies[1]. Here, we assessed whether TCF could be enhanced by IL7, a cytokine that plays a key role in T cell homeostasis and promotes the proliferation and survival of naïve and stem cell memory T cells. **Methods:** T cell exhaustion was induced in vitro by four weekly ImmTAC stimulations against the Non-Small Cell Lung Cancer (NSCLC) cell line NCIH1755 with or without IL7. Tumor killing, T cell cytokine secretion, and T cell phenotype were assessed using standard methods. Data are given as mean $\pm$ SEM; groups were compared using paired t test. *IL7R* gene expression and TCF (mean expression of *TESPA1*, *CD28* and *GPR183*) were measured in baseline whole blood from patients with unresectable or metastatic uveal melanoma (mUM) treated with tebentafusp (n=132 NCT02570308) or brenetafusp (N=37 NCT04262466) as previously described[1]. TCF high/low threshold was cut at the median. TCF was also assessed in baseline and on-treatment PBMC from patients with NSCLC and Triple-Negative Breast Cancer (TNBC) (n=15) receiving NTI7, a long acting recombinant human IL7 (rhIL7, NCT03752723, NCT04984811). **Results:** In vitro, repeated re-direction of T cells by ImmTAC resulted in reduced tumor cell lysis from 46$\pm$9% after a single stimulation to 3$\pm$1% after 4 weekly stimulations. In contrast, T cells cultured with IL7 retained tumor cell lysis after 4 stimulations (58$\pm$2% ImmTAC-redirected cytolysis compared with 3$\pm$1% in IL7-untreated T cells, p = 0.02), accompanied by a 14.3-fold increase in IFNγ secretion (p = 0.04). The proportion of naïve/stem cell memory T cells increased in response to IL7 treatment from 37$\pm$5% to 57$\pm$8% (p=0.009). In mUM patients, gene expression of *IL7R* strongly correlated with TCF signature in peripheral blood (R = 0.91, p $<$ 0.001). As early as 3 weeks following a single dose of NTI7, TCF increased by ~3-fold in PBMC from NSCLC and TNBC patients. The proportion of TCF high patients increased from 36% at baseline to 93% post NTI7 monotherapy. This increase in TCF signature was sustained for at least 12 weeks. **Conclusions:** Despite repeated antigen stimulation in vitro, IL7 sustained naïve/memory T cells, enhanced ImmTAC-redirected T cell cytotoxicity and IFNγ production, and reduced T cell exhaustion. A single dose of rhIL7 resulted in a sustained increase in TCF signature and converted patients with low TCF signature into high TCF. These findings support combination with IL7 as a rational strategy to augment T cell fitness and potentially improve efficacy of ImmTAC bispecific T cell therapies. 1) Sacco et al ESMO 2024. Research Sponsor: Immunocore Ltd.

2663 **Poster Session**

A phase I study of pomalidomide and nivolumab (Pom/Nivo) in patients with virus-associated malignancies with and without HIV. First Author: Jose Mercado-Matos, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Up to 15% of cancers worldwide are associated with oncogenic viruses and disproportionately affect people with HIV (PWH). Epstein–Barr virus (EBV) is linked to several malignancies, particularly lymphomas; Kaposi sarcoma herpesvirus (KSHV) to Kaposi sarcoma (KS) and primary effusion lymphoma (PEL); and human papillomavirus (HPV) to anogenital and head and neck cancers. Virus-associated tumors evade immune surveillance through mechanisms such as T-cell exhaustion. In vitro studies show that pomalidomide (Pom), an immunomodulatory drug, enhances T-cell co-stimulation and increases immune surface marker expression in virus-infected cell lines. Pom may synergize with nivolumab (Nivo), an anti-PD-1 monoclonal antibody, to reverse immune exhaustion and enhance antitumor immunity. **Methods:** This phase I study enrolled participants (pts) with advanced virus-associated malignancies (EBV, KSHV, HPV). PWH were required to receive antiretroviral therapy for $\geq$4 weeks with an HIV viral load (VL) $\leq$400 copies/mL. There was no CD4 T-cell requirement; however, major opportunistic infections (with limited exceptions) were not permitted within 6 months of enrollment. Intravenous Nivo (480 mg) was administered every 28 days with Pom given once daily on days 1-21 of a 28-day cycle using a 3+3 dose-escalation design (DL1=3 mg, DL2=4 mg, optional DL-1=2 mg) for up to 24 cycles. The primary objective was safety and tolerability of the combination (using CTCAE v5.0). The secondary objective was to evaluate the anti-tumor activity of Pom/Nivo using disease-specific criteria (RECIST 1.1, Lugano criteria, or modified ACTG criteria for KS). **Results:** Sixteen pts (75% male, 56% White and 37% Hispanic) were enrolled, including 9 PWH with a baseline median (med) CD4 T-cell of 253 cells/mm^3 (range 61-616) and HIV VL 37 copies/mL. After a med of 7 cycles (range 1-24), the most common Grade (G) 1/2 toxicities were anemia, lymphopenia, and maculopapular rash. Five pts had G3 or G4 neutropenia that was managed with growth factor support and Pom dose reductions. The only dose-limiting toxicity was observed in 1 pt with metastatic anal cancer in DL1 who developed G3 dyspnea; the maximum tolerated dose of Pom was 4 mg. Five pts were not evaluable for an objective response (2 died from progressive disease (PD), 2 declined further treatment, 1 was deemed ineligible), among 11 pts who received $\geq$3 cycles, all 4 pts with KS had a response (2 partial and 2 complete responses), 1 pt with PEL had stable disease (SD), 1 of 4 pts with HPV-malignancies had SD and 1 of 2 with nasopharyngeal carcinoma had SD, and 4 pts had PD. Among PWH, CD4 T-cell count did not change from baseline to the end-of-treatment (p=0.46). **Conclusions:** Pom/Nivo is a chemotherapy-sparing regimen with acceptable safety in advanced virus-associated cancers and promising activity in KS. Based on these results, an expanded KS cohort will be added to the trial. Clinical trial information: NCT04902443. Research Sponsor: None.

2664 **Poster Session**

Influence of pelareorep on mutant KRAS-specific blood TIL clonal expansion. First Author: Richard Trauger, Oncolytics, San Diego, CA

Background: Pelareorep (pela) is an intravenously delivered unmodified oncolytic reovirus that selectively infects cancer cells and is being developed as an immunotherapy for multiple cancers. We report here the analysis of tumor and blood samples from breast and pancreatic cancer patients that demonstrate a multi-step process of innate, viral, and tumor-specific immune activation culminating in the expansion of tumor-specific mutant KRAS (mKRAS) T cell clones that are associated with reductions in tumor volume. **Methods:** Translational samples were obtained from subjects enrolled in breast cancer (AWARE-1 ClinicalTrials.gov ID NCT04102618) and pancreatic (PDAC) cancer trials (GOBLET ClinicalTrials.gov ID NCT07280377). Analysis of tumor gene expression was performed on extracted RNA from Formalin-Fixed Paraffin-Embedded (FFPE) obtained from AWARE-1 clinical samples collected at baseline, day 3 and day 21 of therapy. Changes in tumor gene expression were determined using a customized code-set including the 50 PAM50 genes + other genes (as immune panels). Translational data from GOBLET PDAC subjects included anti-reovirus T cell responses, which were assessed by ELISPOT using whole inactivated reovirus antigen stimulation. Enumeration of the T cell fractions was performed by Adaptive Biotechnologies (Seattle, WA, USA). TCRβ CDR3 DNA was isolated from tissue and blood at baseline and from blood collected post-treatment from both studies. Antigenic specificity of selected T cell clones for mKRAS was determined by the MIRA assay (Adaptive Biotechnologies). **Results:** Sequential genetic analyses of breast cancer tumor biopsies pre- and post-pelareorep therapy demonstrated significant increases in anti-viral and immune gene expression consistent with the activation of toll-like receptor 3 (TLR3). Activation of TLR3 also induced the production of CXCL13, a chemokine critical for the formation of tertiary lymphoid structures (TLS). TLS in the tumor were confirmed by imaging mass cytometry of tumor biopsies following pelareorep treatment. Expansion of tumor-infiltrating lymphocytes (TILs) in both tumor and blood was also observed. Analysis of serial blood samples from a cohort of pelareorep-treated pancreatic cancer patients showed expansion of anti-viral T cells by ELISPOT. In addition, clonal expansion of tumor-specific T cells was observed after one cycle of treatment. The expansion of pre-existing TIL clones in the blood correlated with reductions in tumor volume in pancreatic cancer. Analysis of TCR sequences for antigen specificity confirmed the expansion of mKRAS clones in these samples. **Conclusions:** These findings suggest that pelareorep immunotherapy, through the combined activation of TLR3 and infection of the tumor, induces innate and adaptive antiviral and anti-tumor-specific immune responses capable of controlling tumor growth. Research Sponsor: None.

TPS2665 **Poster Session**

ASP2998, a trophoblast cell-surface antigen 2 (TROP2)–targeted immunostimulatory antibody-drug conjugate with dual payloads, in patients with locally advanced unresectable or metastatic solid tumors: A phase 1b/2 study. First Author: Guru P. Sonpavde, AdventHealth Cancer Institute and the University of Central Florida, Orlando, FL

Background: TROP2 is a type I transmembrane glycoprotein involved in cell proliferation, migration, and survival, that is upregulated in and is associated with poor prognosis in patients (pts) with several malignancies including urothelial carcinoma, non-small cell lung cancer, gastric cancer and breast cancer. TROP2 antibody drug conjugates (ADCs) have demonstrated clinical efficacy and are approved for metastatic breast cancer and epidermal growth factor receptor-mutated non-small cell lung cancer. ASP2998 is a dual-payload (topoisomerase I inhibitor plus stimulator of interferon genes [STING] agonist) immunostimulatory ADC targeting TROP2. ASP2998 monotherapy has shown preclinical antitumor activity in a syngeneic mouse model bearing human TROP2-expressing tumors that was superior to single-payload topoisomerase I inhibitor TROP2 ADCs. **Methods:** This first-in-human, multicenter, open-label, phase 1b/2 dose escalation (DESC) and expansion (DEXP) study, is evaluating the safety, tolerability, recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD), preliminary antitumor activity, and pharmacokinetic profile of ASP2998 in pts with locally advanced unresectable or metastatic solid tumors. Initial DESC of ASP2998 includes 6 dose levels (n≥3 per dose level) to determine the RP2D and/or MTD. Eligible pts (aged ≥18 years) include those with urothelial carcinoma, non-small cell lung cancer, gastric/gastroesophageal junction cancer, or locally confirmed human epidermal growth factor receptor 2-negative breast cancer, who have progressed on, are ineligible for, or have refused all available standard therapies per investigator's decision. At DEXP, multiple dose levels of ASP2998 may be evaluated based on the totality of data to optimize dosage in at least one tumor type (n≤40 per dose level per tumor type). Eligible DEXP pts with non-small cell lung include those who have received ≤3 prior lines of therapy and known programmed death-ligand 1 status, without actionable oncogenic alterations, who have progressed on or after platinum-based chemotherapy and/or checkpoint inhibitors. Eligible DEXP pts with urothelial carcinoma include those who have received ≤3 prior lines of therapy and progressed on or after enfortumab vedotin plus pembrolizumab. Prior exposure to TROP2, STING agonists or topoisomerase I inhibitor-directed therapy is permitted at DESC but not DEXP. Tumor-specific backfill pts can be enrolled in the DESC cohorts at dose levels that are deemed safe and tolerable, and will be counted towards the corresponding tumor-specific DEXP cohorts. Recruitment is ongoing with 196 planned pts (36 in DESC; 160 in DEXP). ClinicalTrials.Gov Identifier: NCT07287995. Clinical trial information: NCT07287995. Research Sponsor: Astellas Pharma Inc.

TPS2666 **Poster Session**

Phase I/II study of AZD6750, a CD8-guided interleukin-2 agent, alone and in combination with other anti-cancer agents in participants with advanced or metastatic solid tumors. First Author: Drew W. Rasco, South Texas Accelerated Research Therapeutics (START), San Antonio, TX

Background: Interleukin-2 (IL-2) has antitumor activity through stimulation of proliferation and differentiation of cytotoxic T lymphocytes, but toxicity due to systemic immune system activation limits its clinical use. AZD6750 comprises two CD8 human IgG1 binding domains and two IL-2 mutein domains and uses cis-guiding to deliver IL-2 mutein preferentially to CD8+ T cells, with the goal of increasing antitumor activity while limiting toxicity. It has high affinity for CD8α and the CD122/CD132 IL-2R complex, and reduced affinity for CD25 (IL-2Rα). In preclinical studies, AZD6750 has been shown to cause preferential proliferation of CD8+ T cells without increasing cytokine release from peripheral blood mononuclear cells; improve antigen-specific tumor cytolysis; increase IFN-γ secretion, a sign of productive responses in tumor-infiltrating lymphocytes; and inhibit growth of a tumor model in vivo. We describe the design of a phase I/II trial of AZD6750 in patients with metastatic solid tumors (NCT07115043). **Methods:** This first-in-human, open-label, phase I/II, multicenter clinical trial is evaluating AZD6750 as monotherapy (Module 1, dose escalation) and combined with rilvegostomig (Module 2) in patients with selected locally advanced or metastatic solid tumors. All patients must have ECOG performance status of 0/1 and ≥1 measurable lesion per RECIST v1.1. In Module 1, patients must have received prior standard-of-care therapy and have a tumor type for which immune checkpoint inhibitors are known to be effective or in which IL-2 potentially has benefit. Dose escalation starts with an accelerated titration design and switches to a modified toxicity probability interval-2 (MTPI-2) design after the first 2 dose cohorts or earlier sign of grade ≥2 toxicity. Module 2 will enroll patients with stage IV NSCLC who have either received ≥1 line of therapy in the metastatic setting (including targeted therapy if actionable mutations are present) (Module 2A, dose escalation) or are metastatic treatment naïve and have tumor PD-L1 expression ≥1% (Modules 2A and 2B). Patients who have autoimmune or inflammatory disorders within 3 years of study or toxicity that led to discontinuation of prior immunotherapy are not eligible for Module 2. In Module 2A, dose escalation will use MTPI-2. Module 2B will be a dose expansion module. The primary endpoints of Modules 1 and 2A are the incidence of adverse events (AEs), serious AEs, and dose-limiting toxicities, which will be used to determine the maximum tolerated dose/recommended phase 2 dose. In Module 2B (dose expansion), the primary endpoint will be preliminary antitumor activity. Secondary endpoints include pharmacodynamics (PD-L1), immunogenicity (anti-drug antibodies), and pharmacokinetics. The study is actively recruiting globally, with 3 patients enrolled as of December 2025. Clinical trial information: NCT07115043. Research Sponsor: AstraZeneca.

TPS2667 **Poster Session**

A phase I trial evaluating an optimized B7-H3xCD3 T cell engager for treatment of solid cancer. First Author: Jonas S. Heitmann, Clinical Collaboration Unit Translational Immunology, Department of Internal Medicine, Cluster of Excellence iFIT (EXC2180), University Hospital Tübingen, Tübingen, Germany

Background: T cell-based immunotherapy has revolutionized oncological treatment of various malignancies. However, many patients still do not respond to immunotherapy, and long-term remissions remain rare, particularly in solid tumors. B7-H3 (CD276) is overexpressed in multiple cancer entities on both tumor cells and tumor microenvironment, the latter facilitating access of effector cells into the tumor site as prerequisite for success of therapeutically targeting solid cancers. To address the high medical need of patients with colorectal cancer (CRC), breast cancer (BC), penile cancer as well as bone and soft tissue sarcoma, we developed and validated a CD276xCD3 T cell engager (TCE) termed CC-3. CC-3 mediated pronounced antitumor activity in vitro and displayed the expected long half-life and potent antitumor activity in murine models using immunocompromised mice adoptively transferred with human effector cells with regard to prevention of lung metastasis and flank tumor growth as well as elimination of large established tumors (Zekri et al, Mol Ther, 2023). **Methods:** This is an ongoing open label, multi-center phase I clinical trial evaluating CC-3 in patients with metastatic CRC, BC, penile cancer as well as bone and soft tissue sarcoma. Key eligibility criteria include diagnosis of progressive metastatic disease and exhaustion of standard of care. The trial comprises a dose escalation part to determine the maximum tolerated dose followed by a dose expansion part to define the recommended phase II dose and collect first signs of efficacy. During the dose escalation, initially an accelerated titration design with single patient cohorts is employed. Here, each patient receives a fixed dose level (starting with 50μg for the first patient). Dose levels are increased by up to 100%, based on the decision of a safety review committee (SRC). Upon occurrence of adverse events (AEs) grade ≥2, dose limiting toxicity (DLT), or reaching a dose level of ≥800μg, treatment switches to a standard 3+3 dose escalation design. After maximum tolerated dose (MTD) is determined, defined as no more than one of six patients experiencing DLT, an additional 14 patients receive CC-3 at the MTD level in the dose expansion phase. Primary endpoints are incidence and severity of AEs, as well as the best objective response to treatment according to RECIST 1.1. Secondary endpoints include overall safety, efficacy, survival, quality of life, and pharmacokinetic investigations. At present, the accelerated titration phase employing cohorts 1 - 4 has been completed without DLT; likewise, in the so far completed cohorts 5-8 of the standard titration phase, no DLT was observed. Enrollment to cohort 9 began in May 2025. Clinical trial information: NCT05999396. Clinical trial information: 2022-503084-15-00. Research Sponsor: German Cancer Consortium (DKTK).

TPS2668 **Poster Session**

First-in-human phase 1a/1b study of LB-LR1109, an anti-LILRB1 monoclonal antibody, as monotherapy in advanced solid tumors and in combination with atezolizumab in advanced NSCLC. First Author: Hyungjin Cho, LG Chem Lifescience USA, Boston, MA

Background: LB-LR1109 is a human IgG4 monoclonal antibody targeting LILRB1, an inhibitory receptor expressed on multiple immune cell subsets. LILRB1 binds HLA-G, delivering suppressive signals that enable tumor immune evasion. Blocking this axis may restore immune activation within the tumor microenvironment and promote both innate and adaptive anti-tumor responses. Phase 1a tumor types were selected through TCGA analyses showing high LILRB1/HLA-G expression and increased infiltration of LILRB1+ NK cells, T cells, and monocytes in RCC, NSCLC, HNSCC, urothelial carcinoma (UC), and melanoma. High LILRB1 expression correlates with poor overall survival in RCC, UC, and lung SCC, supporting clinical relevance. Preclinical data (AACR2026 #1243) demonstrated that LB-LR1109 binds LILRB1 with high affinity, blocks HLA-G interactions, restores NK and T-cell function, and induces strong anti-tumor activity in human LILRB1 transgenic mouse models. LB-LR1109 also showed synergy with PD-L1 blockade, favorable PK, and an excellent safety profile, supporting clinical development as monotherapy and in combination. Public transcriptomic data also support combining LB-LR1109 with atezolizumab in NSCLC based on correlated LILRB1 and PD-L1 expression. **Methods:** This ongoing first-in-human, multicenter, open-label Phase 1 study (NCT06332755) evaluates LB-LR1109 as monotherapy (Phase 1a) and in combination with atezolizumab (Phase 1b). The study began in September 2023; Phase 1b enrollment started December 2025. Phase 1a includes monotherapy dose escalation (DL1–DL8, IV Q2W) using BLRM, enrolling patients with advanced/metastatic RCC, NSCLC, HNSCC, UC, or melanoma who relapsed from or are intolerant to approved therapies. Phase 1b evaluates LB-LR1109 (IV Q2W) plus atezolizumab 840 mg Q2W in advanced/metastatic NSCLC without actionable mutations. Patients must have received prior approved therapies including anti-PD-1/PD-L1 with ≥12 weeks of response, to test whether LILRB1 blockade may restore immune surveillance after checkpoint inhibitor resistance. Primary objectives: safety, tolerability, and determination of MTD/RP2D. Secondary endpoints: antitumor activity, PK, immunogenicity. Exploratory endpoints: correlations between LILRB1/HLA-G expression and clinical response, longitudinal immune profiling, and receptor occupancy in peripheral monocytes. The study is conducted at eight sites in Korea and the United States. Phase 1a has escalated to DL7 with no DLTs, and enrollment into the combination DL5 cohort began January 2026. Clinical trial information: NCT06332755. Research Sponsor: LG Chem Lifescienes.

TPS2669 **Poster Session**

Phase 1 first-in-human trial of AG01, a recombinant humanized monoclonal antibody to progranulin/glycoprotein 88 (GP88) to determine the safety, tolerability, pharmacokinetics, and preliminary antitumor activity in subjects with advanced solid tumor malignancies. First Author: Katherine H.R. Tkaczuk, University of Maryland School of Medicine & Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD

Background: Progranulin also called GP88/PGRN plays a major role as an autocrine growth & survival factor associated with resistance to standard of care (SOC) targeted and chemo therapies in several cancers including breast cancer (BC) & non-small cell lung carcinoma (NSCLC): 1) GP88 is expressed in 80% breast invasive ductal carcinomas & is negative in normal mammary tissue; 2) GP88 tumor expression is a prognostic indicator of recurrence & survival in BC, NSCLC & prostate cancer patients (pts) 4) Elevated serum GP88 levels are present in several cancers including metastatic breast cancer (MBC), lung & prostate cancer pts compared to healthy subjects; 5) Elevated/rising GP88 serum levels in MBC pts are associated with disease progression & inferior survival. These results make GP88 an ideal therapeutic & diagnostic target in solid tumors. An anti-human PGRN/GP88 monoclonal antibody inhibiting PGRN/GP88 action was developed & expressed in CHO cells. Pharmacology, GMP manufacturing, formulation, stability studies & GLP toxicology studies in non-human primates were done. The IND application cleared by the US FDA led to the FIH AG01 study in adults with advanced solid tumors lacking effective therapies. **Methods:** A Phase 1 FIH dose-escalation study was designed in pts with advanced solid tumor malignancies, the study is approved by the University of Maryland IRB. AG01 monoclonal antibody is administered intravenously (IV) over 90 minutes every 14 days +/- 1 day; DLT observation period is the 1st cycle=28days, with AG01 Dose levels of,1mg/kg, 2mg/kg, 4mg/kg, 6mg/kg, 8 mg/kg. Initially accelerated titration design (1pt/dose level) was followed by 3+3 design). Eligibility criteria include pathologically confirmed diagnosis of advanced/relapsed/refractory solid tumor malignancy; failed $>$=1 SOC therapy or not a candidate/declines SOC therapy, ECOG $<$=2, adequate organ/bone marrow function, at least 1 RECIST 1.1 measurable and/or evaluable lesion. Tumor imaging-every 2 cycles (8 weeks) is used for response assessment. Primary objective is to determine the maximum tolerated dose MTD and/or maximum administered dose MAD of AG01 in the target population. Secondary objectives are to determine the RP2D, safety, tolerability, PKs, immunogenicity (ADA) & the preliminary anti-tumor activity of AG01 in pts with advanced solid tumors. Exploratory objectives will determine PGRN/GP88 expression in tumor tissue & PGRN/ GP88 blood levels (A&G's IHC & ELISA test). The study is ongoing; & pts are currently enrolled. A parallel prospective study investigates the association of serum GP88 in MBC pts with response to SOC therapy and progression of disease based on RECIST 1.1 criteria. These studies are supported by NCI grants R44CA224718 and CA210817. Clinical trial information: NCT05627960. Research Sponsor: None.

TPS2670 **Poster Session**

A first-in-human phase I clinical trial evaluating the safety, tolerability, and preliminary efficacy of the novel fas ligand (FasL) inhibitor M3T01 in adults with advanced solid tumors. First Author: Rom S. Leidner, Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR

Background: Tumor-specific T cells undergo apoptotic cell death following FasL binding to the fas (CD95) receptor. FasL is upregulated in many advanced cancers and is expressed by tumor endothelial cells, macrophages, and activated T and natural killer (NK) cells. Consequently, FasL contributes to tumor progression through deletion of tumor-specific T cells and impaired T cell tumor infiltration. Preclinical studies demonstrate that FasL blockade facilitates increased T cell tumor infiltration and enhances efficacy of immune checkpoint inhibitors and adoptive cell therapies. M3T01 is a fully human IgG4/kappa monoclonal antibody that potently inhibits FasL. This is an ongoing first-in-human phase I clinical trial (NCT06719362) evaluating the safety, tolerability and preliminary antitumor efficacy of M3T01 as monotherapy and in combination with pembrolizumab in adults with advanced solid tumors. **Methods:** The primary objectives are to evaluate the safety/tolerability, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of M3T01. Secondary objectives are to characterize the pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary antitumor efficacy of M3T01 as monotherapy and in combination with pembrolizumab. A sub-study will evaluate paired tumor biopsies (pre-treatment and cycle 2 day 8) to evaluate for changes in the tumor microenvironment induced by FasL inhibition. Eligible patients have unresectable or metastatic solid tumors that are refractory to standard systemic therapy. Patients must have adequate organ function, measureable disease per RECIST v1.1 or RANO 2.0, and an ECOG performance status of 0-1. Dose escalation through a 3 + 3 design will evaluate M3T01 as monotherapy and in combination with pembrolizumab (administered intravenously every 3 weeks). Monotherapy cohorts 1-4 (100 to 600 mg) have been completed without DLT. After completion of the dose escalation portion of the trial, dose expansion cohorts will open to evaluate M3T01 in combination with standard systemic therapies in the treatment of patients with glioblastoma, gastric/esophageal adenocarcinoma, and head and neck squamous cell carcinoma. Clinical trial information: NCT06719362. Research Sponsor: None.

TPS2671 **Poster Session**

A phase I/IIa dose-escalation, dose-optimization, and dose-expansion study to evaluate the safety and preliminary efficacy of tri-specific antibody (SOA101) in subjects with advanced solid tumors. First Author: Jennifer Ho, Shine-On Biomedical, Taichung, Taiwan

Background: SOA101 is a nanobody (VHH)-based tri-specific T cell engager targeting programmed death-ligand 1 (PD-L1), Human Leukocyte Antigen G (HLA-G), and Cluster of Differentiation 3 (CD3) to modulate the immunosuppressive tumor microenvironment and enhance T-cell activation and recruitment. In vitro, SOA101 showed potent, broad-spectrum anti-tumor activity, enhancing peripheral blood mononuclear cells mediated cytotoxicity against non–small cell lung cancer (NSCLC) cells with varying PD-L1/HLA-G expression. In vivo, SOA101 demonstrated superior anti-cancer efficacy compared with relevant monoclonal antibodies and bispecific T-cell engagers in a humanized NSCLC mouse model, achieving effective tumor control and prolonged survival. The pharmacologically active dose did not increase cytokine secretion ex vivo, indicating a manageable safety profile with low cytokine release syndrome risk. **Methods:** This first-in-human clinical study, regulated by FDA and TFDA, is being conducted in subjects with locally advanced or metastatic solid tumors, including NSCLC ovarian cancer, head and neck cancer, breast cancer, and colorectal cancer with PD-L1 expression $\geq$1%. The dose-escalation phase is a six-cohort study designed to determine the maximum tolerated dose or pharmacoactive dose, enrolling up to 36 subjects who receive bi-weekly SOA101 for up to six doses. The dose-optimization phase randomizes approximately 40 subjects into low- or high-dose cohorts to further evaluate safety, pharmacokinetics, preliminary antitumor activity, and to determine the recommended Phase 2 dose. Part 2 may include up to four disease-specific expansion cohorts (up to 27 subjects each) to further characterize safety and antitumor activity. The study is currently in the dose-escalation phase. Cohort 1 has been completed without DLT, and enrollment for Cohort 2 has begun following approval by the independent Safety Review Committee. Clinical Trial Registry Number: NCT07055594. Clinical trial information: NCT07055594. Research Sponsor: None.

TPS2672 **Poster Session**

Phase 1, open-label clinical trial to treat stage IV cancer patients harboring multiple patient-specific mutated cell surface proteins with chimeric antibodies. First Author: Monika Joshi, Penn State Cancer Institute, Hershey, PA

Background: Despite the advent of multiple classes of systemic cancer treatments, tumor recurrence and subsequent resistance to systemic therapy remain a persistent challenge. Thus, newer treatment strategies are needed for metastatic cancer refractory to extant therapies. Leveraging the vast landscape of targetable tumor-specific mutated peptides (TSPs) on the surface of malignant cells offers an opportunity for individualized antibody therapy. These surface TSPs arise due to genetic instability and progressive accumulation of random missense mutations in cancer cells, resulting in dozens to hundreds of substituted amino acids in proteins at the cancer cell surface. We refer to surface proteins harboring substituted amino acids as Mutated cell Surface Proteins (MSPs). Antibodies generated against short TSPs preferentially bind to the mutated peptide compared to the nonmutated peptide. Notably, most cancers harbor several distinct MSPs. For instance, of 100 colon cancer cases, 96% harbored $\geq$10 MSPs, with similar findings in lung cancer (97%), melanoma (93%), lymphoma (92%), bladder cancer (85%), and stomach cancer (84%). While the presence of many MSPs is common, each patient harbors a unique set of MSPs. Study sponsor has developed a means of preparing custom antibodies against the TSPs present in multiple MSPs to inhibit cancer growth in several preclinical models, prompting a pan-tumor Phase I study evaluating the safety and feasibility of such therapy in refractory cancer patients. **Methods:** This is a phase I first-in-human study aiming to enroll up to 12 eligible subjects. Primary objective: Safety and tolerability. Secondary objectives: Feasibility of producing and administering the protocol-directed treatment to the patient population; progression-free survival; response rate. Key Inclusion Criteria: a) Stage IV refractory cancer (breast, colon, esophageal, kidney, lung, ovarian, bladder urothelial, stomach, or pancreatic cancers, melanoma, or lymphoma); b) availability of tumor and matched normal tissue sequence data. Treatment: Custom-manufactured chimeric antibodies are being used to target a minimum of 2 to 8 MSPs per patient. An interval of 4- to 6-month antibody production interval is required from initial consent to the start of treatment. The dose-limiting toxicity (DLT) period is 4 weeks; thereafter, in addition to antibody treatment, subjects can receive standard of care [immunotherapy, targeted therapy or hormonal therapies]. Treatment schedule: Week 1, 100 mg i.v.; week 2, 200 mg i.v.; week 3 400 mg; and then 400 mg i.v. every other week for total of 10 doses. We have enrolled 3 subjects and have completed treatment of Subject #1 (bladder cancer), with no DLT to date. The study is ongoing since 12/2025. Clinical trial information: NCT06674538. Research Sponsor: Moonshot Antibodies, Inc.

TPS2673 **Poster Session**

A logic-gated chimeric antigen receptor T-cell (CAR T) therapy with an armored, membrane-tethered IL-12 booster in patients with advanced solid tumors with HLA-A*02 loss of heterozygosity (LOH): EVEREST-2, a phase 1/2 study. First Author: Salman Rafi Punekar, NYU School of Medicine, New York, NY

Background: The main challenge for developing CAR T therapies for solid tumors is the lack of targets that distinguish tumor from normal cells, resulting in on-target, off-tumor toxicity. Tmod logic-gated CAR T therapy addresses this challenge by incorporating 2 CARs on the same T cell: an activator targeting a marker on both tumor and normal cells, and a blocker targeting HLA-A*02 that inhibits CAR T activity against normal cells while allowing activation against tumor cells (with HLA-A*02 LOH), improving tumor selectivity and decreasing toxicity. Early safety results from 3 ongoing phase 1/2 clinical trials of logic-gated, Tmod CAR T therapy (EVEREST-1, EVEREST-2, and DENALI-1) have demonstrated manageable safety and tolerability in patients with advanced solid tumors (Grierson et al, *SITC*, 2024; Ward et al, *SITC* 2025; Specht et al, *SABCS*, 2025). Early efficacy results include the first ever reported complete response in a patient with non-small cell lung cancer following treatment with a CAR T-cell therapy (A2B694). A2B543 is an autologous Tmod CAR T therapy that contains the same Tmod construct as A2B694 with an added membrane-tethered IL-12 (memIL12) booster. Specifically, A2B543 is comprised of autologous Tmod cells transduced with 2 lentiviral vectors: one expressing both the HLA-A*02-targeted blocker and the mesothelin-targeted CAR activator; and a second expressing the memIL12 booster. Interleukin 12 (IL-12) is a potent, pro-inflammatory cytokine that plays a crucial role in inducing antitumor immune responses; however, systemic IL-12 can be prohibitively toxic (Jia et al, *Front Immunol*, 2022). In A2B543, expression of the memIL12 cassette is under the control of an NFAT promoter and is induced during antigen engagement or T cell activation. This inducible memIL12 is designed to reduce the toxicity associated with systemic IL-12 while enhancing the long-term potency and persistence of Tmod (Zhang et al, *J Immunother Cancer*, 2025). **Methods:** EVEREST-2 (NCT06051695) is a phase 1/2, open-label, nonrandomized study evaluating the safety and efficacy of A2B543 in adults with recurrent/metastatic mesothelin-expressing cancers with tumor-associated HLA-A*02 LOH, including mesothelioma, colorectal, non-small cell lung, pancreatic, or ovarian cancer. Patients are enrolled through BASECAMP-1 (NCT04981119), a master pre-screening study that identifies patients with HLA LOH via next-generation sequencing and cryopreserves leukapheresis product. Upon progression, A2B543 is manufactured and then administered after lymphodepletion. The phase 1 primary objective is to evaluate the safety and tolerability of A2B543 and identify a recommended phase 2 dose (RP2D). The phase 2 primary objective is to assess overall response rate. Clinical trial information: NCT06051695. Research Sponsor: A2 Biotherapeutics, Inc.

TPS2674 **Poster Session**

A phase I, open-label, dose-escalation study of CAR001 (mRNA-engineered Nb-CAR.BiTE-γδ T cells) in patients with relapsed or refractory solid tumors. First Author: Der-Yang Cho, China Medical University Hospital, Taichung City, Taiwan

Background: Solid tumors are characterized by a highly immunosuppressive tumor microenvironment (TME). Key immune checkpoint molecules, such as HLA-G and PD-L1, are frequently expressed and act as barriers that limit the infiltration and efficacy of conventional CAR-T cell therapies. CAR001 is an investigational, allogeneic, mRNA-engineered Nb-CAR.BiTE-γδ T cell therapy. By utilizing the innate homing capabilities of γδ T cells and a dual-targeting mechanism, direct binding of HLA-G by T cells and secreting PD-L1 bispecific T-cell engagers from T cells, CAR001 is designed to overcome TME-mediated resistance. This study evaluates the safety and potential activity of repeat intravenous dosing of CAR001 in patients with advanced solid tumors. **Methods:** Study Design: This is an ongoing, multicenter, open-label, phase I dose-escalation study utilizing a standard 3+3 design or similar escalation schema. Patient Population: Adults with histologically confirmed refractory or relapsed solid tumors (including, but not limited to, colorectal cancer, glioblastoma, and triple-negative breast cancer) who have exhausted standard of care. Intervention: Patients receive escalating doses of CAR001 via intravenous infusion. The protocol allows for repeat dosing to enhance therapeutic persistence. Objectives: The primary objective is to evaluate the safety and tolerability of CAR001 and to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D). Secondary objectives include assessing preliminary antitumor activity per iRECIST or RANO criteria, as well as characterizing the pharmacokinetic profile of the Nb-CAR.BiTE-γδ T cells. Safety Monitoring: Adverse events (AEs) are monitored using CTCAE v5.0, with specific focus on dose-limiting toxicities (DLTs), cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). Trial Status: This trial is currently active and enrolling patients. As of the submission deadline, dose-escalation cohorts are ongoing. To maintain the integrity of the study and comply with ASCO Trials in Progress guidelines, no formal analysis of clinical endpoints or treatment outcomes is provided. Clinical trial information: NCT06150885. Research Sponsor: None.

TPS2675 **Poster Session**

A phase 1/2 dose-escalation/expansion study of REGN10597 (anti–PD-1–IL2Rα-IL2) in patients with advanced solid tumors. First Author: Kyriakos Papadopoulos, START Center for Cancer Research, San Antonio, TX

Background: Interleukin 2 (IL-2) is a cytokine involved in lymphocyte expansion and differentiation during the anticancer immune response. Aldesleukin, an approved recombinant high-dose IL-2 therapy, has shown complete and durable responses in some cases; however, high-dose IL-2 is associated with severe toxicity, including vascular leak syndrome and pulmonary edema. Despite clinical advances with checkpoint inhibitor therapies, many advanced solid tumors continue to respond poorly to these treatments. REGN10597 is an antibody–cytokine fusion protein comprising a human anti–programmed cell death-1 antibody fused with a receptor-masked cytokine, IL2Rα-IL2. REGN10597 has demonstrated tumor inhibition, enhanced specificity, and reduced toxicity versus recombinant high-dose IL-2 in preclinical mouse models (Wu et al. Cell Rep Med 2024;5:101747). Here we describe BrILliance (NCT06413680), a study evaluating the safety, tolerability, pharmacokinetics, and preliminary antitumor activity of REGN10597 in patients with advanced solid tumors. **Methods:** This is an open-label, Phase 1/2, dose escalation/expansion, first-in-human, multicenter study evaluating REGN10597 in advanced or metastatic solid tumors. Patients must be aged ≥18 years with histologically or cytologically confirmed locally advanced or metastatic tumors and confirmed disease progression on standard-of-care therapy. During the dose escalation phase, patients will be enrolled to receive REGN10597 by intravenous infusion at the assigned dose level and schedule (additional dose schedules are available for further exploration). When the recommended Phase 2 dose level and schedule are determined, additional patients will be enrolled across two dose expansion cohorts: patients with locally advanced or metastatic melanoma (Cohort 1) and those with advanced or metastatic clear cell renal cell carcinoma (Cohort 2). Dose escalation primary endpoints include incidence of dose-limiting toxicities, incidence of treatment-emergent adverse events (including those leading to treatment discontinuation or death), incidence of serious adverse events, and the number of patients with Grade ≥3 laboratory abnormalities. The dose expansion primary endpoint is objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by investigator assessment. Secondary endpoints for both phases include additional efficacy measures (best overall response, duration of response, disease control rate, time to response, and progression-free survival, all per RECIST 1.1), and pharmacokinetics and immunogenicity of REGN10597. Trial enrollment for the dose escalation phase began on October 1, 2024; as of January 27, 2026, 22 patients have been enrolled. Clinical trial information: NCT06413680. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS2676 **Poster Session**

Biomarker study of BND-22 in combination with cemiplimab in solid tumors. First Author: Mohamed H. Derbala, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitors benefit only a subset of patients, indicating a need to identify other therapeutic targets and understand the role of tumor microenvironment in shaping immune response. Immunoglobulin-like transcript-2 (ILT2) is an inhibitory receptor expressed on monocytes, dendritic cells, NK cells, and subset of T cells. ILT2 binds multiple MHC class-I molecules, with highest affinity for HLA-G, which is frequently overexpressed in solid tumors. Engagement of HLA-G/ILT2 pathway inhibits key immune functions, including cytotoxicity, cytokine production, antigen presentation, phagocytosis and proliferation. ILT2 expression can be upregulated following anti PD-1 therapy, suggesting a mechanism of resistance to checkpoint blockade. Inhibition of this pathway could potentially promote antitumor immune responses. BND-22, a first-in-class humanized IgG4 mAb, selectively binds to ILT2 on NK/T cells/macrophages, blocking its interaction with HLA-G. In preclinical studies and in a phase I trial, BND-22 alone and in combination with a PD-1 inhibitor demonstrated enhanced anti-tumor activity. The study revealed a dose-dependent activation in immune markers. Building on this finding, we initiated a phase II biomarker study (NCT06651593) of BND-22 in combination with cemiplimab, a recombinant human IgG4/kappa anti–PD-1 mAb, to further understand immune biology and explore the tumor microenvironment. **Methods:** The study has 2 patient cohorts: Cohort 1: patients with cholangiocarcinoma, who have had prior immunotherapy and Cohort 2: patients with microsatellite stable colorectal cancer and ovarian cancer who are anti–PD-1/PD-L1 naïve. Approximately 40 patients will be enrolled (10 per indication and an additional 10 to the best performing indication). The dose of BND-22 is 10 mg/kg IV on Day 1 every 3 weeks (Q3W), based on the dose escalation trial (NCT04717375). The dose of cemiplimab is the FDA-approved dose of 350 mg IV on Day 1 Q3W, starting at C2D1. Each cycle = 21 days. The combination will be administered for a max of 24 months in the absence of progression or until progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation. Biopsy tissues and peripheral blood samples for biomarker analyses will be collected at baseline, on treatment, and at progression (for patients with CR, PR, or SD≥6 months). The primary objective is 1) to identify biomarkers related to mechanism of action and predictors of response, resistance, and survival 2) evaluate the association between the biomarkers and outcomes. The secondary objective is to evaluate efficacy, safety, and tolerability of this combination; identify imaging characteristics predictive of response and toxicity; and, evaluate TCR beta variable polymorphism and its relationship with immune-related adverse events. Enrollment is ongoing; 2 patients in Cohort 1 and 10 patients in Cohort 2 have been treated. Clinical trial information: NCT06651593. Research Sponsor: Sanofi; Regeneron.

TPS2677 **Poster Session**

The TIME trial: Phase II randomized controlled trial of time-of-day–specified nivolumab and ipilimumab for advanced melanoma. First Author: Michael Lowe, Emory University School of Medicine, Atlanta, GA

Background: Nivolumab/ipilimumab is standard of care for advanced melanoma patients based on Phase III randomized data from the CheckMate 067 trial. The recent 10-year outcomes results were reported with a melanoma specific survival for Nivolumab/ipilimumab of 52%. These data are very encouraging, but 50% of patients still succumb to their disease by 10-years. Preclinical data suggests that the circadian rhythm may influence the anatomic localization, function and activity of T cells, the target of immunotherapy. More T cells in the tumor or tumor-draining lymph node during initial immunotherapy administration may improve clinical responses and long-term outcomes. To investigate this idea, we performed a retrospective analysis, the MEMOIR study, finding that more evening infusions of immunotherapy were associated with significantly worse progression free and overall survival for metastatic melanoma patients. These findings have now been reproduced in other cancer histologies, in a larger meta-analysis, and in pre-clinical mechanistic studies. Considering these data, we hypothesize that evening infusions of immunotherapy will have worse progression free survival than either morning or midday infusions. **Methods:** The TIME trial is a three-arm phase II study of time-of-day specified administration of standard dose nivolumab/ipilimumab for metastatic melanoma. For newly diagnosed metastatic melanoma patients enrolled on study, they will be randomized to receive 4 cycles every 3 weeks of nivolumab/ipilimumab between 8:00-11:00 (Arm A), 11:00-14:00 (Arm B), or 14:00-17:00 (Arm C). Following these 4 cycles, they will receive standard of care maintenance nivolumab in a time-of-day agnostic fashion. Eligible patients must have stage IV unresectable cutaneous, acral or mucosal melanoma, no prior immunotherapy within 1 year, ECOG performance status of 0-1, age $\geq$ 18, no symptomatic or hemorrhagic brain metastases with none greater than 2 cm. The primary objective is to determine whether progression free survival for Arm A or Arm B is superior to Arm C. Secondary objectives include assessments of adverse events, melanoma specific survival and overall survival. We will evaluate the immune profiles of blood and tumor to assess the impact of time of drug administration on the circulating immune responses and the tumor immune microenvironment. 99 patients will be enrolled to detect a HR of 0.50 with at least 80% power and a Type 1 error rate of 0.1 (2-sided) for a comparison of A vs. C, and B vs. C. The study is open at Emory and has enrolled 3 patients; the study is undergoing regulatory review at MGH and Cedars-Sinai. Clinical trial information: NCT07155317. Research Sponsor: None.

TPS2678 **Poster Session**

A phase 1b, two-arm study of tolododekin alfa (ANK-101) in combination with an anti–PD-1/PD-L1 antibody in participants with advanced non–small cell lung cancer (NSCLC). First Author: Thomas Urban Marron, Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Tolododekin alfa (ANK-101) is an anchored immunotherapy linking IL-12 to aluminum hydroxide through an alum-binding protein (ABP). Direct delivery to tumors results in prolonged IL-12 local retention and limited systemic absorption. A Phase 1 study in advanced solid tumors demonstrated ANK-101 was well tolerated with evidence of antitumor activity, recruitment of CD8+ T cells, and induction of local programmed cell death ligand 1 (PD-L1) expression. ANK-101 is now being evaluated in combination with PD-1/PD-L1 checkpoint blockade (ICB) in patients with non-small cell lung cancer (NSCLC). **Methods:** This study is a Phase 1b, two-arm, open-label study of direct injection (IT) of tolododekin alfa administered in combination with an anti-PD-1/PD-L1 antibody in participants with locally advanced or metastatic NSCLC. Cohort A will be conducted in participants who have progressed on prior standard of care treatment with ICB and platinum-based chemotherapy, either in combination or sequentially. Cohort B will enroll participants with untreated locally advanced or metastatic NSCLC with a PD-L1 tumor proportion score (TPS) $\geq$ 50%. Participants with targetable EGFR mutations or ALK rearrangements are excluded. In Cohort A, participants will receive tolododekin alfa at 250 μg/mL IT in combination with cetrelimab (anti-PD-1) intravenously (IV) Q3W at a dose of 360 mg for up to 8 cycles, followed by cetrelimab monotherapy for up to one year, unless they have unacceptable toxicity, clinical deterioration, confirmed tumor progression, or have withdrawn consent. In Cohort B, participants will receive tolododekin alfa at 250 μg/mL IT in combination with investigator's choice of an FDA-approved ICB for first-line use as monotherapy in patients with TPS $\geq$" role="presentation" tabindex="0">$\geq$ 50% IV Q3W at the approved dose for up to 8 cycles, followed by continued ICB according to the FDA-approved label. The primary objective is objective response rate by RECIST 1.1. Secondary endpoints include safety, duration of response, disease control rate, progression-free survival, and overall survival. In addition, lesion-level responses, serum PK analyses, and anti-drug antibody (ADA) levels will be assessed. Exploratory endpoints include measurements of selected serum cytokine levels and characterization of the composition of the tumor microenvironment before and on-treatment. This clinical trial is in progress. Clinical trial information: NCT07027514. Research Sponsor: Ankyra Therapeutics.

TPS2679 **Poster Session**

OP-NEU-101: A phase 1/2 open-label, dose finding and expansion study to investigate the safety and effectiveness and determine the optimal dose of N17350 administered intratumorally in participants with advanced solid tumors. First Author: Matteo S. Carlino, Westmead and Blacktown Hospitals, Melanoma Institute Australia and The University of Sydney, Sydney, NSW, Australia

Background: Despite advances in targeted therapies and immunotherapy, many patients with advanced solid tumors have limited treatment options. N17350 is a first-in-class, optimized therapeutic elastase designed for intratumoral administration that selectively induces cancer cell death by activating the neutrophil elastase (ELANE) pathway while preserving immune cell viability. Preclinical studies demonstrated broad antitumor activity across 30 cancer cell lines, 15 in vivo models, and 45 patient-derived tumor samples, as well as induction of antitumor immunity in both immunologically cold and hot tumors (Gujar et al., 2025; doi:10.1016/j.xcrm.2025.102446. Together with preclinical toxicology studies supporting a starting dose within the therapeutic range, these findings support the clinical evaluation of N17350. **Methods:** This first-in-human, multicenter, open-label Phase 1/2 study (OP-NEU-101) is evaluating the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of intratumorally administered N17350 in adults with advanced solid tumors. The study consists of a dose-finding and dose-optimization phase (Parts A1 and A2) followed by monotherapy expansion cohorts (Part A3). Dose-finding in participants with superficial (Part A1) and visceral lesions (Part A2) is guided by a Backfill Bayesian Optimal Interval (BF-BOIN) design to determine the maximum tolerated dose, optimal biologic dose, and/or recommended Phase 2 dose (RP2D). Once optimal dose(s) are identified, up to five tumor-specific expansion cohorts (data dependent: SCCHN, NSCLC, TNBC, cuSCC, Melanoma) may be opened to further characterize safety and clinical activity. Key Eligibility Criteria: Eligible participants are adults with advanced or metastatic solid tumors who have progressed on or are intolerant to standard therapies, have ECOG performance status 0–1, adequate organ function, and at least one superficial or visceral lesion suitable for intratumoral injection. Endpoints: The primary endpoints of the dose-finding phase are safety and tolerability, including the incidence of dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints include PK, immunogenicity, and preliminary antitumor activity assessed per RECIST v1.1 and/or itRECIST. Exploratory endpoints include evaluation of ELANE pathway activation, immune modulation, circulating tumor DNA, and multiomic analyses of tumor tissue and peripheral blood. The study has been initiated and will be enrolling participants at sites in the United States and Australia. Clinical trial information: NCT07339176. Research Sponsor: None.

TPS2680 **Poster Session**

A phase 1, first-in-human study of DS5361, a small-molecule, nonsense-mediated mRNA decay (NMD) inhibitor in patients with advanced/metastatic solid tumors (parts 1 and 2). First Author: Shiraj Sen, NEXT Oncology Dallas, Dallas, TX

Background: Despite the profound impact of immune checkpoint inhibitors (ICIs) on the treatment of patients with advanced or metastatic solid tumors, only a small proportion of patients experience meaningful responses, underscoring the need for novel therapies to maximize clinical benefit. High tumor mutational burden (TMB-H) and high microsatellite instability (MSI-H) are associated with improved efficacy of ICIs due to an increase in neoantigens, tumor-specific peptides displayed on tumor cell surfaces that are critical for antitumor immune responses. mRNAs harboring premature termination codons, including neoantigenic transcripts derived from frameshift mutations, are recognized and degraded by NMD. DS5361 is a potentially first-in-class, orally available, small-molecule inhibitor targeting the serine/threonine kinase SMG1, a key component of the NMD mechanism. DS5361 is designed to activate antitumor immunity by increasing neoantigen expression and, when administered in combination, to enhance ICI efficacy. **Methods:** DS5361-061 (NCT07182591) is a Phase 1, first-in-human, open-label, multicenter study (N≈66 for Parts 1 and 2) of DS5361 as monotherapy (Part 1) and in combination with pembrolizumab (Part 2). Patients must be adults, have measurable disease per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1), and have an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with advanced or metastatic TMB-H and/or MSI-H solid tumors who are unable to tolerate standard treatment or have disease that is refractory to standard treatment, or for which no such treatment is available, will be enrolled across both parts. The primary objectives in Parts 1 and 2 (dose escalation) are to evaluate the safety and tolerability, and determine the maximum tolerated dose, of DS5361 as monotherapy in Part 1 and in combination with pembrolizumab in Part 2, and/or determine the recommended dose(s) for expansion in combination with pembrolizumab (Part 2 only). Safety endpoints include dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints include objective response, disease control, and duration of response, all assessed by the investigator per RECIST 1.1, as well as pharmacokinetics. Enrollment is ongoing. Clinical trial information: NCT07182591. Research Sponsor: Daiichi Sankyo.

TPS2681 **Poster Session**

Updated design of INVOKE: A phase 1 study of OKN4395, a first-in-class EP2/EP4/DP1 triple prostanoid receptor antagonist, in patients with advanced solid tumors. First Author: Stephane Champiat, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The immunosuppressive pathway of prostaglandin E_2 (PGE_2), part of the cyclooxygenase (COX) pathway, is upregulated in certain cancers and has been implicated in tumor evasion of CD8 T, NK, and dendritic immune cells, allowing tumor growth and metastasis (Jin et al., 2023). COX2 inhibitors, aspirin and nonsteroidal anti-inflammatories (NSAIDS) have shown some survival benefit in patients with gastrointestinal cancer and others (Cao et al., 2016; Martling et al., 2025; Takiuchi et al., 2018; Zhang et al., 2025); however, results are inconsistent, likely due to toxicity limiting complete blockade of the pathway, highlighting the need for more potent but selective inhibitors. OKN4395 is a first-in-class, highly selective, equipotent inhibitor of EP2, EP4, and DP1, downstream receptors for COX-derived PGE_2, and PGD_2, respectively. DP1 has described roles in immunosuppression and inhibition of apoptosis, supporting the therapeutic rationale (Luo et al., 2024; Peinhaupt et al., 2017). OKN4395 is hypothesized to modulate the tumor microenvironment to allow an effective immune response as monotherapy, and to potentiate the effect of immunotherapies such as checkpoint inhibitors, both of which are evaluated in INVOKE. Tumor types for INVOKE were selected using previously presented multimodal artificial intelligence (AI) drug-matching algorithms (Grimaldi, et al., 2025). **Methods:** INVOKE (OKN-4395-121; NCT06789172) is a Ph1a/1b, first-in-human study of OKN4395 (oral, BID) as monotherapy (mono) or in combination with a PD1 checkpoint inhibitor (combo), in patients with advanced solid tumors. Ph1a is a Bayesian dose escalation in mono with a new parallel substudy, followed by combo dose confirmation, primarily assessing safety, establishing the Ph1b dose. Response will be assessed in updated Ph1b (cohorts of n=20): select sarcomas (mono), non-small cell lung (combo), colorectal (combo), and gastric cancer (combo). Key inclusion criteria include COX-active (Ph1a) or above-listed (Ph1b) tumors, performance status 0-1, biopsy-amenable lesions, and adequate organ function. Active CNS metastases, upper GI bleed risk factors, untreated H. pylori infection, and concomitant NSAIDs/COX inhibitors/prostaglandins are exclusionary. A new and innovative 3-period, crossover substudy in parallel with Ph1a will explore the intra-participant effects of food and gastric pH on OKN4395 pharmacokinetics. Trial data, paired pre- and on-treatment biopsies, and exploratory biomarkers will be used to enhance development using advanced agentic AI systems, including a synthetic digital twin control arm, novel methodology of which is submitted to this meeting as well. Ph1a of the study is currently recruiting in the US, UK, and Australia. Dose Level 5 concluded in December 2025 with no DLTs to that date. Clinical trial information: NCT06789172. Research Sponsor: None.

TPS2682 **Poster Session**

Eiu-104101: A first-in-human phase 1a/1b study of EVOLVE104, a trispecific CD3×CD2×ULBP2/5/6 T-cell engager, in advanced urothelial and squamous cell carcinomas. First Author: Tony Fiorino, EvolveImmune Therapeutics, Branford, CT

Background: EVOLVE T cell engagers (TCEs) bind to a tumor antigen and to both CD3 and CD2 on T cells, thereby providing integrated costimulation via CD2 binding. EVOLVE TCEs demonstrate superior T cell activation and tumor cell killing compared to first generation TCEs, without excess cytokine release or tonic T cell activation, and may offer clinical benefits such as enhanced potency and duration of activity. UL16 binding proteins 2, 5 and 6 (ULBP2/5/6) belong to a family of cell surface proteins that are ligands for the NKG2D receptor. We have previously reported that cell-surface ULBP2/5/6 is not present in vital organs and found in some mucosal epithelia. Cell surface ULBP2/5/6 is found in urothelial carcinomas and squamous cell carcinomas (SCCs). With high expression on malignant cells and limited normal tissue expression, ULBP2/5/6 are intriguing targets for cancer immunotherapy. EVOLVE104 is a trispecific TCE that binds ULBP2/5/6 and both CD3 and CD2 on T cells. Preclinical studies with EVOLVE104 demonstrated enhanced T cell activation and killing of ULBP2/5/6-positive tumor cells compared to bispecific TCEs, and no safety concerns were identified in preclinical toxicity studies. With this encouraging preclinical profile, EVOLVE104 represents a novel approach to redirected T cell therapy in solid tumors. **Methods:** EIU-104101 is a first-in-human phase 1a/1b study evaluating EVOLVE104 monotherapy in adults with advanced solid tumors. Eligible tumor types include urothelial carcinoma of the bladder and SCCs of the bladder, lung, esophagus, tongue, skin, and anogenital region (penis, anus, vagina, vulva, cervix, and urethra). Subjects must have locally advanced or metastatic disease that has relapsed from, or is refractory to, standard-of-care therapies. Study objectives include assessing the safety, efficacy, pharmacokinetics and pharmacodynamics of EVOLVE104 and identifying the recommended phase 2 dose (RP2D). The phase 1a portion of the study will enroll up to 80 subjects using a Bayesian optimal interval (BOIN) dose-escalation scheme including backfill at dose levels deemed safe, with a key objective to identify one or more recommended doses for expansion (RDEs). Phase 1b includes two expansion cohorts: Cohort A, which will be a dose optimization cohort in a single indication (to be determined based on the phase 1a observations) in which 40 subjects will be randomized 1:1 to two RDEs to determine the RP2D; and Cohort B, which will enroll up to 40 subjects in other relevant indications. The study opened in October 2025 and is actively enrolling at US sites. ClinicalTrials.gov Identifier: NCT07217171. Clinical trial information: NCT07217171. Research Sponsor: EvolveImmune Therapeutics.

TPS2683 **Poster Session**

POLARIS: Polymetastatic lesion ablative radiotherapy with immunotherapy study. First Author: Evan Garrad, University of Illinois Chicago, Chicago, IL

Background: Patients with polymetastatic disease, most commonly defined as >5 metastatic lesions, often have limited treatment options and poor overall prognosis[1,2]. The emergence of immunotherapy (IO) has slowed disease progression in some patients; however, its efficacy is limited by tumor heterogeneity and patient-specific factors, including baseline health status[3]. Emerging data suggest a synergistic effect when combining IO with radiotherapy (RT), a strategy that has led to FDA-approved treatment approaches in non-small cell lung cancer (NSCLC)[4-6]. As multimodal cancer therapies evolve, robust methods to assess treatment response are increasingly important. Circulating tumor DNA (ctDNA) is a minimally invasive biomarker that has been shown to correlate with clinical response to therapy[7,8]. However, the kinetics and clinical significance of ctDNA in patients receiving combined IO and ablative RT remain poorly characterized. **Methods:** POLARIS is a pilot phase II, double-arm clinical trial evaluating the addition of ablative radiotherapy in patients with polymetastatic disease receiving immunotherapy. Twenty-eight patients with polymetastatic disease, defined as having at least 3 and no more than 10 metastatic lesions, and receiving immunotherapy alone for at least 30 days prior to registration will be enrolled at the University of Illinois Hospital & Health Sciences System (UIH). Patients will be stratified into two cohorts based on their response to immunotherapy after $\geq$3 months: Cohort A includes patients with investigator-assessed stable disease or partial response, while Cohort B includes patients with oligoprogression, defined as 1–5 sites of progressive disease within 3 months of registration. Both cohorts will receive ablative RT targeting up to 10 metastatic lesions in combination with ongoing immunotherapy. The primary endpoint is the proportion of patients achieving a molecular response, defined as a $>$50% reduction in ctDNA levels, at 8 weeks following ablative RT. Secondary endpoints include overall survival and progression-free survival at 6 and 12 months, objective response rate, and treatment-related adverse events (TRAEs). This trial is the first to prospectively evaluate ablative radiotherapy as an adjunct to immunotherapy while integrating ctDNA as a biomarker of treatment response in polymetastatic disease. Clinical trial information: NCT07269080. Research Sponsor: University of Illinois Chicago.

TPS2684 **Poster Session**

Pharmacokinetics and pharmacodynamics evaluation in phase I trial of APX-343A, selective NOX inhibitor targeting CAF-mediated immunosuppression in patients with advanced solid tumors. First Author: Sung Hwan Moon, Aptabio Therapeutics, Yongin-Si, South Korea

Background: Cancer-associated fibroblasts (CAFs) drive fibrotic remodeling and immune exclusion in solid tumors and contribute to resistance to immune checkpoint inhibitors (ICIs). CAF-mediated immune suppression is regulated by upstream oxidative signaling pathways. NADPH oxidases (NOXs) are upregulated in CAFs and promote fibrotic remodeling and myeloid cell–mediated inhibition of cytotoxic T-cell function, linking CAF activity to immune exclusion and immunotherapy resistance. APX-343A is a selective NOX1/2/4 inhibitor designed to modulate CAF-associated tumor biology. This ongoing Phase 1 study evaluates pharmacokinetic (PK) and pharmacodynamic (PD) components to assess translational biomarkers of NOX target engagement and CAF-driven immune modulation supporting dose selection and rational combination strategies with immunotherapy. **Methods:** This is a Phase 1, dose-escalation study (NCT07123415) evaluating the safety, tolerability, PK, PD, and preliminary antitumor activity of orally administered APX-343A as monotherapy (Part A; 100–600 mg BID) and in combination with pembrolizumab (Part B; 200–600 mg BID) in patients with advanced solid tumors. Dose escalation is conducted independently using dose-limiting toxicity–based escalation in Part A and a Bayesian Optimal Interval (BOIN) design in Part B to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). PK assessments are conducted in Part A to evaluate dose proportionality and support RP2D determination, including Cmax, Tmax, area under the concentration–time curve (AUC), and accumulation. PD assessments use peripheral blood and tumor tissue samples to evaluate biomarkers of NOX pathway inhibition and CAF-driven immune modulation, including NOX isoforms (NOX1/2/4), CAF-associated markers, and immune-related cytokines and chemokines (e.g., interleukins, CCL2). Integrated PK/PD analyses explore exposure–biomarker relationships. This ongoing Phase 1 trial of APX-343A is actively enrolling, with Part A dose-escalation cohorts underway. Integrated PK and PD assessments are designed to establish translational evidence of NOX target engagement and CAF modulation, providing a mechanistic foundation for dose selection and rational combination strategies with ICI. Clinical trial information: NCT07123415. Research Sponsor: None.

TPS2685 **Poster Session**

A phase 1 study of PHST001, an anti-CD24 monoclonal antibody, in adult patients with advanced relapsed and/or refractory solid tumors. First Author: Ulka N. Vaishampayan, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MI

Background: Macrophages are the most abundant immune cells in tumors and can directly phagocytose tumor cells and promote broad anti-tumor immunity. However, phagocytosis can be inhibited by macrophage checkpoints, also known as 'don't eat me' signals. One such checkpoint is the immunomodulatory protein CD24 that is overexpressed in many tumors and associated with poor clinical prognosis. CD24 inhibits macrophage phagocytosis of tumor cells via binding to Siglec-10 on macrophages. PHST001 is a high affinity anti-CD24 IgG4 antibody that blocks multiple glycoforms of CD24 and induces macrophage phagocytosis of tumor cells in a wide range of preclinical models. In addition, PHST001 improves tumor control and survival in murine models when combined with multiple chemotherapies as chemotherapy-induced tumor cell stress may improve macrophage phagocytosis of tumor cells when combined with CD24 blockade. Thus, CD24 blockade has potential as monotherapy and in combination with other cancer therapies to enhance tumor cell phagocytosis and improve patient survival. **Methods:** PHST001-101 is an open-label, first-in-human, Phase 1 study in patients $\geq$ 18 years of age with advanced relapsed and/or refractory solid tumors (NCT06840886). In Phase 1a, patients receive escalating doses of PHST001 administered Q3W as an IV infusion at one of nine dose levels. Phase 1b combines PHST001 with chemotherapy in patients with ovarian cancer, endometrial cancer, or cholangiocarcinoma in safety run-in groups and tumor-specific expansion cohorts. Key inclusion criteria include age $\geq$ 18 years, evidence of measurable disease, an ECOG performance status of 0 or 1, and adequate organ function. Key exclusion criteria include a diagnosis of immunodeficiency, active CNS disease, or active autoimmune disease. The primary objective is to assess the safety and tolerability of PHST001 as monotherapy and in combination with chemotherapy, and to assess the preliminary antitumor activity of PHST001 in combination with chemotherapy. Secondary objectives include assessing antitumor activity of monotherapy and pharmacokinetics (PK) of PHST001. Exploratory objectives include evaluating the relationship between PK and pharmacodynamics (receptor occupancy, cytokine profiling, changes in ctDNA, and immune cell subsets in the tumor), immunogenicity of PHST001, antitumor activity in patients treated beyond progression, and patient-reported outcomes. The study enrolled the first patient treated in April 2025 and is currently enrolling patients in Phase 1a at Dose Level 8 (18 mg/kg) with no DLTs to date. Enrollment in Phase 1b is anticipated to begin in early 2026. Clinical trial information: NCT06840886. Research Sponsor: Pheast Therapeutics.

TPS2686 **Poster Session**

A phase 1/2a, multicenter, first-in-human, open-label clinical trial evaluating MDX2004 monotherapy in patients with advanced tumors. First Author: Jordan Ellis Cohen, Calvary Mater Newcastle, Newcastle, NSW, Australia

Background: MDX2004 is a trispecific antibody–fusion protein developed as an immunotherapy for advanced cancers. It is designed to stimulate T cells through engagement of CD3, CD28, and 4-1BB, thereby enhancing immune activation. MDX2004 is expected to promote activation and expansion of T lymphocytes, including stem and memory T-cell populations. **Methods:** This Phase 1/2, multicenter, first-in-human, open-label clinical trial evaluates MDX2004 in patients with advanced or metastatic solid tumors (NCT07110584). The study includes a Phase 1a dose-escalation stage guided by a Bayesian Optimal Interval (BOIN) design targeting a maximum tolerated dose toxicity rate of 30%; a Phase 1b indication-optimization stage in up to five tumor types; a Phase 1c dose-optimization stage in up to three indications; and a Phase 1d/2a expansion at the recommended Phase 2 dose (RP2D) in a single indication. In Phase 1a, patients with advanced solid tumors receive escalating intravenous doses of MDX2004. Phase 1b evaluates a selected dose in patients with homogeneous indications to assess preliminary efficacy. In Phase 1c, patients with selected indications are randomized 1:1 to two dose cohorts using a Bayesian Optimal Phase 2 (BOP2) design. Once the RP2D is established, Phase 1d/2a will enroll approximately 30 patients into a single cohort using a BOP2 design. The primary objectives across study phases are to characterize the safety, tolerability, and antitumor activity of MDX2004. Secondary endpoints include time to response, disease control rate, duration of response, pharmacokinetics, and immunogenicity. Radiologic tumor assessments are performed every 8 weeks, and treatment continues until disease progression per RECIST v1.1 (investigator assessed), unacceptable toxicity, withdrawal of consent, or another protocol-defined discontinuation criterion. The study is planned to be conducted in Australia, Israel, Moldova; patient recruitment is ongoing. Clinical trial information: NCT07110584. Research Sponsor: None.

TPS2687 **Poster Session**

Phase 1 clinical trial investigating the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of AB821 in adult patients with locally advanced or metastatic melanoma and other solid tumor malignancies (NCT 07027488). First Author: Harriet M. Kluger, Yale University School of Medicine, Smilow Cancer Center, New Haven Hospital, New Haven, CT

Background: In recent years, T-cell enhancement strategies have achieved notable survival benefits in patients with cancer. While cytokine therapy with both IL-2 and IL-21 demonstrate anti-cancer activity through enhanced proliferation, survival and function of antigen specific CD8+ T cells, their use is limited by off-target effects and rapid clearance. AB821 is a fusion of a CD8-targeting antibody that binds to the CD8$\alpha\beta$ heterodimer on CD8+ T cells and an IL-21 mutein containing a mutation that attenuates affinity for the IL-21receptor. In pre-clinical experiments, AB821 promotes CD8+ T-effector cell cytotoxicity and CD8+ T-cell memory and demonstrates both robust tumor growth inhibition and minimal toxicity in immune checkpoint inhibitor refractory tumor models. Notably, AB821 avoids activation of other IL-21R-expressing cell types, including CD4+ T cells, NK cells, B cells, dendritic cells, intermediate monocytes, and nonclassical monocytes, that can act as pharmacologic sinks or contribute to off-target toxicity. **Methods:** This first-in-human phase 1 dose-escalation clinical trial is designed to assess the safety, pharmacokinetics, pharmacodynamics, immunogenicity and preliminary anti-tumor activity of AB821 monotherapy administered every 2 weeks (Q2W) in patients (pts.) with recurrent locally advanced or metastatic melanoma and other immune-responsive solid tumor malignancies. Pts. with melanoma are required to have previously been treated with an inhibitor of PD1/L1 while pts. with other cancer types are required to have received a previous systemic treatment regimen. The primary objective of the study is to assess the safety and tolerability of AB821 and identify a candidate recommended phase 2 dose for further evaluation. AB821 is being administered as a 30-minute IV infusion on day 1 of each 2-week treatment cycle with therapy continued for a maximum duration of two years (52 cycles) or as long as participants experience clinical benefit as determined by the treating investigator. Dose-escalation and/or de-escalation decisions is being guided by a BF-BOIN design (Liu 2015; Yuan 2016) employing a target toxicity probability of 0.30 with up to 20 total pts. enrolled in backfill cohorts at the RP2D or lower dose levels determined by the investigators to be potentially efficacious in order to better assess the drug's safety and efficacy. Accrual is ongoing. Specific dose levels and inclusion/exclusion criteria will be presented. Clinical trial information: NCT07027488. Research Sponsor: Asherbio Therapeutics.

TPS2688 **Poster Session**

A phase I/IIa study to evaluate the safety and tolerability, activity, and PK of a potential novel CNTN4-targeted checkpoint inhibitor, EP0089, in patients with advanced solid tumors. First Author: Hendrik-Tobias Arkenau, Ellipses Pharma, London, United Kingdom

Background: Contactin 4 (CNTN4) has recently been identified as a novel cancer target which is overexpressed across a range of tumor types, including gastrointestinal, genitourinary, melanoma, breast and lung. Preclinical data shows that CNTN4 functions as an immune checkpoint through its binding to the T-cell transmembrane protein APP (Amyloid Precursor Protein). The interaction between CNTN4 on the surface of tumor cells and APP diminishes T cell receptor signaling cascades, inhibiting the activation and proliferation of CD4+ and CD8+ T cells. Tumor upregulation of CNTN4 may facilitate tumor immune evasion. Elevated CNTN4 levels have been associated with poorer outcomes for patients treated with anti-PD-1 checkpoint inhibitors. Therapeutic agents that block the interaction of CNTN4 with APP therefore have the potential to address significant unmet medical needs across a range of tumor types. EP0089 is a humanized IgG4 monoclonal antibody which specifically binds CNTN4 and inhibits the interaction between CNTN4 and APP, thereby enabling an immune response within the tumor microenvironment. *In vitro* and *in vivo* studies demonstrated that EP0089 neutralized CNTN4-mediated suppression of T cell activation and promoted killing of CNTN4 over-expressing tumors. **Methods:** This is a first-in-human, open-label, phase I/IIa study (NCT07030478). Eligible patients will have a confirmed diagnosis of an advanced solid tumor with no available standard therapy or for whom standard therapy has failed, ECOG performance status of 0-1, life expectancy greater than 3 months, and measurable disease per RECIST v1.1 (or specified disease-specific guidelines). The population will be enriched for tumor types known to express CNTN4, including gastric, gastro-esophageal, esophageal adenocarcinoma, hepatocellular, bladder, gallbladder, endometrial, melanoma, and prostate. The primary objective is to determine the maximum tolerated dose and recommended phase II dose of EP0089. The secondary objectives are to characterize the PK and immunogenicity profile of EP0089 and assess preliminary antitumor activity. Exploratory objectives are to evaluate biomarkers of response, including the impact of CNTN4 expression and other PD biomarkers. Part A consists of dose-escalation, utilizing a 3+3 design, and dose expansion to further evaluate dose levels/regimens of interest. Part B will be determined based on review of Part A data and may include further dose optimization, and/or evaluation of specific populations of interest. Patients will initially receive EP0089 by IV infusion once every 2 weeks, subject to ongoing Safety Monitoring Committee review throughout dose escalation. The study is being conducted in the Republic of Korea, Australia and United States and later in Europe. Target recruitment is approximately 250 patients. Clinical trial information: NCT07030478. Research Sponsor: None.

TPS2689 **Poster Session**

TREGCHECK 102: A study of tagmokitug (CHS-114) in combination with toripalimab and/or other treatments in participants with advanced solid tumors. First Author: Dani Ran Castillo, City of Hope, Duarte, CA

Background: Advanced solid tumors frequently exhibit resistance to standard therapies, including immune checkpoint inhibition. Intratumoral Tregs have been associated with immune suppression, tumor progression and anticancer resistance. Intratumoral Tregs preferentially express CCR8 and are abundant in many solid tumors (Plitas 2020; Plitas 2016; Kidani 2022). Tagmokitug is a novel, selective cytolytic anti-CCR8 mAb designed to deplete CCR8+ Tregs and remodel the tumor microenvironment to promote antitumor immunity. Preclinical and phase 1 clinical studies show tagmokitug can significantly deplete CCR8+ intratumoral Tregs, increase immune activation and has antitumor activity in combination with a PD-1 inhibitor (Wang 2026; Worden 2025; Kapoor 2025). These findings warrant evaluation of tagmokitug in combination with toripalimab, a PD-1 inhibitor, and/or other anticancer therapies across multiple tumor types. **Methods:** This multicenter, open-label, phase 1b/2a study evaluates tagmokitug in combination with toripalimab and/or other therapies in adults with advanced solid tumors in 4 cohorts: gastric, gastroesophageal junction (GEJ), and esophageal adenocarcinoma; second-line esophageal squamous cell carcinoma (ESCC); first-line ESCC; and advanced MSS/pMMR colorectal cancer. Eligible participants have histologically or cytologically confirmed advanced or metastatic solid tumors not amenable to curative therapy, measurable disease per RECIST v1.1, ECOG 0–1, and adequate organ function. Key exclusions include active autoimmune disease requiring systemic therapy, uncontrolled cardiovascular conditions, or other factors interfering with study participation. Tagmokitug is administered IV Q3W at pharmacologically active doses following toripalimab 240 mg IV and/or other anticancer therapies where indicated per protocol. Imaging assessments are performed every 6 weeks through week 24, every 9 weeks through week 51 and every 12 weeks through week 99. Patients continue treatment until disease progression, unacceptable toxicity, or withdrawal of consent. The primary objective is to evaluate the safety and tolerability of tagmokitug in combination with toripalimab and/or other anti-cancer therapies as measured by adverse events and laboratory abnormalities. Secondary endpoints include ORR, DOR, DCR, and PFS per RECIST v1.1, and assessment of PK and ADA. Exploratory endpoints include OS and biomarker analyses including evaluation of CCR8+ Tregs in tumors. Enrollment is ongoing. Approximately 150 participants are planned across all cohorts. Additional cohorts may be added based on emerging data. Clinical trial information: NCT06657144. Research Sponsor: Coherus Oncology.

TPS2690 **Poster Session**

Cohort expansion of a phase I study of PLN-101095, a first-in-class dual $\alpha_v\beta_8/\alpha_v\beta_1$ integrin inhibitor, in combination with pembrolizumab in patients with advanced solid tumors refractory to immune checkpoint inhibitors (ICI). First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Transforming growth factor-β (TGF-β) drives immunosuppression and T-cell exclusion in solid tumors and contributes to immune checkpoint inhibitor (ICI)-acquired resistance. The integrins $\alpha_v\beta_8$ and $\alpha_v\beta_1$ activate latent TGF-β in the tumor microenvironment, promoting immune escape. PLN-101095 is a first-in-class, oral dual $\alpha_v\beta_8/\alpha_v\beta_1$ inhibitor designed to block TGF-β activation and restore antitumor immunity in patients with advanced solid tumors refractory to prior ICI. Part 1 of our study (NCT06270706) employed a Bayesian optimal interval design for dose escalation. The Part 2 expansion cohorts were driven by Part 1 efficacy signals, including 4 responders with secondary resistance to ICI, most of whom had high tumor mutational burden (TMB-H) prior to baseline. **Methods:** This is an ongoing Phase 1 open-label multicenter study conducted in the United States. Part 1 (dose escalation) enrolled patients with advanced or metastatic solid tumors who had either primary or secondary resistance to prior ICI. Part 2 (dose expansion) will enroll only patients meeting Society for Immunotherapy of Cancer (SITC) criteria for secondary resistance to prior ICI therapy based on a Simon 2-stage design. The Part 2 expansion cohorts will be as follows: 1) non-small cell lung cancer; 2) head and neck squamous cell carcinoma; 3) clear cell renal cancer; and 4) TMB-H tumors (historical ≥10 mutations/megabase, as determined by local testing with a Clinical Laboratory Improvement Amendments–certified next-generation sequencing [NGS] assay). The target sample size for cohorts 1-3 is 19 patients each, and the target for cohort 4 is 36 patients. The primary endpoints are objective response rate (ORR) and disease control rate (DCR) per immune RECIST. The secondary endpoints are pharmacokinetics (PK), safety and tolerability, and duration of response (DOR). Planned exploratory biomarkers analyses include characterization of integrin expression, TGF-β and immune-related gene expression, and tumor microenvironment (TME) in tumor biopsies. Plasma cytokine profiling and circulating tumor DNA (ctDNA) will also be examined. Clinical trial information: NCT06270706. Research Sponsor: Pliant Therapeutics, Inc.

TPS2691 **Poster Session**

Phase II open-label trial of neoadjuvant immunotherapy in combination with CAPOX for resectable non-metastatic proficient mismatch repair (pMMR) colon cancer: NICER study. First Author: Atif Iqbal, Baylor College of Medicine, Houston, TX

Background: Colorectal cancer (CRC) is the third most common malignancy worldwide. Immune checkpoint inhibition has transformed outcomes in deficient mismatch repair (dMMR/MSI-H) CRC but has demonstrated limited efficacy in metastatic proficient mismatch repair (pMMR) tumors, likely related to low tumor mutational burden and limited immune infiltration. Emerging neoadjuvant studies suggest that earlier exposure to immunotherapy may enhance antitumor immunity and induce pathologic responses in pMMR colon cancer. Neoadjuvant chemotherapy may further augment immunogenicity through tumor debulking, antigen release, and modulation of the tumor immune microenvironment. Combination chemo-immunotherapy has improved outcomes across multiple solid tumors and may overcome resistance to immune checkpoint blockade. Early neoadjuvant immunotherapy studies in pMMR colon cancer have demonstrated encouraging pathologic responses without compromising surgical outcomes. The NICER study evaluates the safety, feasibility, and biological activity of neoadjuvant atezolizumab plus CAPOX in resectable pMMR colon cancer. Correlative studies include longitudinal circulating tumor DNA (ctDNA) analysis and paired tissue assessment to characterize immune microenvironmental changes following treatment. **Methods:** This is a phase II, open-label study evaluating neoadjuvant atezolizumab in combination with capecitabine and oxaliplatin (CAPOX) in patients with resectable, non-metastatic pMMR colon adenocarcinoma. The planned accrual is 28 patients. Participants receive four 3-week cycles of neoadjuvant atezolizumab plus CAPOX, followed by standard-of-care surgical resection. Adjuvant chemotherapy is permitted per investigator discretion for high-risk patients. Key eligibility criteria include pMMR colon adenocarcinoma with tumor ≥12 cm from the anal verge and at least one high-risk feature (elevated CEA, low lymphocyte-to-monocyte ratio, poor differentiation, lymphovascular or perineural invasion, CT-defined T3–T4 disease ≥4 cm, or regional lymphadenopathy). Exclusion criteria include metastatic disease, autoimmune disorders, recent malignancy, or synchronous colorectal primaries. The primary endpoint is tumor regression grade (TRG) using the modified Ryan scoring system. The regimen will be considered promising if the post-therapy TRG 1 rate is ≥15%, compared with an expected rate of 0% with upfront surgery. Secondary endpoints include pathologic complete response, R0 resection rate, lymph node yield, safety, surgical timing, recurrence outcomes, and quality of life. As of January 2026, 7 of 28 planned patients have been enrolled since accrual began in July 2025. ClinicalTrials.gov ID NCT05870800. Clinical trial information: NCT05870800. Research Sponsor: Genentech, Inc. (subsidiary Roche - Switzerland).

TPS2692 **Poster Session**

Induction adebrelimab combined with chemotherapy followed by response-adaptive concurrent chemoradiotherapy guided by PET-CT in locally advanced unresectable esophageal squamous cell carcinoma: A prospective, single-arm, phase II study. First Author: Jun Wang, Department of Radiation Oncology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced unresectable esophageal cancer. Currently, data on PD-L1 inhibitors combined with chemoradiotherapy in this setting still remain limited. Furthermore, the efficacy of induction immunotherapy prior to CCRT, and the utility of PET-CT assessment to guide subsequent CCRT regimens, have not been explored. This study aims to evaluate the efficacy and safety of induction adebrelimab (an anti-PD-L1 antibody) combined with chemotherapy, followed by a PET-CT guided adaptive chemotherapy regimen during CCRT for locally advanced unresectable esophageal squamous cell carcinoma (ESCC). **Methods:** This single-arm, open-label, exploratory study will recruit 36 patients with locally advanced unresectable ESCC (clinical stage T1N+M0 or T2-4bNxM0) who have not received prior antitumor treatment. Patients will undergo 2 cycles of induction therapy with adebrelimab (1200 mg, d1, iv, q3w) plus the TP regimen (nab-paclitaxel 180 mg/m² or paclitaxel 135 mg/m², d1, iv; carboplatin AUC=5, d1, iv, q3w). Following induction, response will be assessed via PET-CT. Responders (defined as SUV reduction ≥35% or partial response) will continue with the TP regimen (nab-paclitaxel 60 mg/m² or paclitaxel 50 mg/m², d1, iv; carboplatin AUC=2, d1, iv, qw for 5 cycles) during concurrent radiation (50.4–60 Gy/28–33f). Non-responders will switch to the FP regimen (fluorouracil 750–1000 mg/m², civ 96h; cisplatin 75 mg/m², d1, iv, q4w for 2 cycles) during concurrent radiation. All patients will proceed to maintenance therapy with adebrelimab following CCRT until disease progression or unacceptable toxicity. The primary endpoint is the 1-year progression-free survival (PFS) rate. Secondary endpoints include the clinical complete response (cCR) rate, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), PFS, overall survival (OS), and safety profile. Clinical trial information: NCT07112833. Research Sponsor: None.

TPS2693 **Poster Session**

ASCEND: A phase 1/2, dose-escalation, optimization, and dose-expansion study to evaluate the safety and antitumor activity of CR-001 in adults with locally advanced or metastatic solid tumors. First Author: Meredith Pelster, Sarah Cannon Research Institute, Nashville, TN

Background: CR-001 is a tetravalent bispecific antibody targeting anti-programmed cell death-1 (PD-1) and vascular endothelial growth factor (VEGF), designed to enhance antitumor activity through combined immune modulation and antiangiogenic effects. Its proposed mechanism of action involves dual binding and blockade of both PD-1/programmed death ligand-1 (PD-L1) and VEGF/vascular endothelial growth factor receptor 2 (VEGFR2) signaling. The blockade of VEGF signaling is aimed at inhibiting tumor angiogenesis and reversing immunosuppressive effects in the tumor microenvironment, while PD-1 binding is aimed at preventing T-cell suppression, thereby promoting the immune recognition and elimination of tumor cells. The established benefit/risk profiles and regulatory precedents for PD-1-, VEGF-, and dual-pathway-directed antibodies support evaluation of CR-001 in solid tumors. **Methods:** ASCEND (NCT07335497) is a global, first-in-human, open-label, phase 1/2 study assessing CR-001 monotherapy in adults with advanced solid tumors. The purpose of this study is to determine the safety and tolerability of CR-001 and identify the maximum tolerated dose, and/or recommended phase 2 dose. The study will initially involve three parts: dose escalation, backfill, and dose optimization. Key eligibility criteria include: age ≥18 years; locally advanced (nonresectable) or metastatic hepatocellular carcinoma, biliary tract cancer, gastric or gastroesophageal junction cancer, colorectal cancer, endometrial cancer, cervical cancer, ovarian cancer, or non-small-cell lung cancer; and progression on, intolerance to, or ineligibility for local standard-of-care anticancer therapies. Additional criteria include ≥1 measurable lesion and ECOG performance status 0–1. As part of a standard 3+3 dose-escalation design, CR-001 is planned to be administered at 4 dose levels as an intravenous infusion every 2 or 3 weeks. Tumor-specific backfill cohorts will enroll concurrently with dose escalation. Earlier-line participants, including those untreated in the advanced or metastatic setting, may also be eligible to participate in backfill cohorts. The recommended phase 2 dose will be determined based on review of pharmacokinetics/pharmacodynamics, safety, tolerability, and preliminary signs of antitumor activity. Up to 290 patients are planned to be enrolled across the dose-escalation, tumor-specific backfill, and dose-optimization cohorts. This global trial is currently enrolling. Clinical trial information: NCT07335497. Research Sponsor: Crescent Biopharma.

TPS2694 **Poster Session**

Efficacy and safety of QL1706-based combination therapy in recurrent or metastatic endometrial carcinoma previously treated with chemotherapy and immune checkpoint inhibitors: A single-arm, prospective, phase II trial. First Author: Lu Sun, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

Background: Patients with advanced endometrial cancer who have progressed after platinum-based chemotherapy and immune checkpoint inhibitors have limited subsequent treatment options and a very poor prognosis. Iparomlimab and tuvonralimab injection (QL1706) is a bifunctional combination antibody targeting both programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4), developed using the MabPair biotechnology platform. This study aims to evaluate the efficacy and safety of QL1706 combined with chemotherapy ± bevacizumab in patients with recurrent or metastatic endometrial cancer previously treated with immune checkpoint inhibitors. **Methods:** In this prospective, single-arm, multicenter phase II clinical trial, up to 30 participants will be enrolled. Eligible patients must be aged ≥18 years, have an Eastern Cooperative Oncology Group Performance Status score of 0 to 1, be diagnosed with recurrent or metastatic endometrial carcinoma, have previously received PD-(L)1 therapy for over 6 months, and have experienced disease progression during or after prior chemotherapy and PD-(L)1 targeted therapy. Up to two prior lines of systemic therapy are permitted. Patients who previously received PD-(L)1 plus CTLA-4 targeted therapy or discontinued anti-PD-1/PD-L1 antibody therapy due to related toxicities are excluded. Enrolled patients will receive QL1706 (5 mg/kg every 3 weeks) combined with chemotherapy (investigator's choice, administered for 3–6 cycles) ± bevacizumab (15 mg/kg every 3 weeks) until disease progression, unacceptable toxicity, or other protocol-specified termination events. The primary endpoint is the objective response rate (ORR) as assessed by the investigator according to RECIST v1.1. Secondary endpoints include progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety. As of January 2026, 5 of the planned 30 patients have been enrolled. Clinical trial information: NCT06917092. Research Sponsor: None.

TPS2695 **Poster Session**

SYNERGY: A phase 1b/2 study of nenocorilant, a selective glucocorticoid receptor antagonist, plus nivolumab in patients with advanced solid malignancies. First Author: Omid Hamid, The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA

Background: Acting through the glucocorticoid receptor (GR), glucocorticoids (GCs) suppress the anticancer immune response by decreasing antigen presentation, exhausting CD8+ T-cell effector function, and increasing the immunosuppressive function of regulatory T cells and tumor-infiltrating myeloid cells. The use of GCs with anti-programmed death (ligand) 1 (anti-PD[L]1) therapy is associated with poor outcomes in several solid tumor types. Selective GR antagonists (SGRAs) inhibit the effects of GCs at the GR and show synergistic activity with cytotoxic chemotherapy, as demonstrated by the phase 3 ROSELLA study in patients with platinum-resistant ovarian cancer (Olawaiye *Lancet* 2025). SGRAs enhance tumor growth inhibition when combined with anti-PD1 therapy in syngeneic mouse tumor models that are refractory to immune checkpoint inhibition (Greenstein *Int Immunopharmacol* 2023). We hypothesize that GR antagonism with nenocorilant, an SGRA, may enhance or restore sensitivity to anti-PD(L)1 therapy and provide clinical benefit for patients with solid malignancies. **Methods:** This phase 1b/2, open-label, multicenter study (NCT07276373) is evaluating nenocorilant + nivolumab in patients with advanced solid malignancies. Key eligibility criteria for phase 1b include having received standard-of-care therapies, no prior immune-related adverse events (AEs) grade ≥3 or leading to anti-PD(L)1 discontinuation, no ongoing requirement for GCs, and evaluable disease (per Response Evaluation Criteria in Solid Tumors version 1.1). Treatment will continue until disease progression or discontinuation criteria are met. Nenocorilant will be given orally once daily in escalating doses (starting at 200 mg) across 3 cohorts of 10 patients each. Nivolumab 240 mg will be given intravenously once every 2 weeks. If ≤3 patients in a cohort experience dose-limiting toxicities (DLTs) during the 28-day evaluation period, enrollment will proceed to the next cohort at a higher dose of nenocorilant. Primary objectives include characterizing safety/tolerability (DLTs, AEs, serious AEs, dose modifications, and treatment discontinuations due to AEs) and determining the maximum tolerated dose and/or optimal dose/schedule. Secondary objectives are to characterize the anticancer activity, pharmacokinetics, and corrected QT interval effects of this combination. Safety endpoints will be summarized using descriptive statistics and time-to-event endpoints will be estimated using Kaplan-Meier methods. Data from the currently enrolling phase 1b part of the study will inform the dosing regimen for phase 2, which will further characterize the anticancer activity and safety of nenocorilant + nivolumab in specific solid malignancies. Clinical trial information: NCT07276373. Research Sponsor: Corcept Therapeutics.

TPS2696 **Poster Session**

Phase I study of zeaxanthin alone or in combination with pembrolizumab in metastatic solid tumors. First Author: Philip Adam Friedlander, Division of Hematology and Medical Oncology, The Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Zeaxanthin is a carotinoid synthesized by plants that accumulates via dietary intake in the macula. Preclinical studies demonstrated anti-proliferative properties in cancer cell lines *in vitro*. In uveal melanoma cell lines SP6.5 and C918, zeaxanthin reduced cell viability in a dose dependent manner while not doing so in normal ocular melanocytes. Decreased cell viability associated with decreased expression of anti-apoptotic proteins bcl-2 and bcl-xL and increased expression of pro-apoptotic bak and bax (1). Anti-proliferative effects were demonstrated in nude mice inoculated in the choroid with uveal melanoma cells (2). Zeaxanthin enhances anti-tumor immunity. Screening a blood nutrient compound library found zeaxanthin to augment CD8+ T-cell activity through direct engagement with the T-cell receptor (3). Murine models showed zeaxanthin enhanced anti-cancer efficacy of anti-PD-1 immunotherapy (3). Pro-apoptotic and immunomodulatory properties of zeaxanthin suggest potential for efficacy in treating cancer patients warranting clinical investigation. The primary objectives of this phase I study are to determine safety and tolerability of escalating doses of zeaxanthin monotherapy or combination of zeaxanthin plus pembrolizumab in patients with metastatic solid tumor malignancies and to determine MTD and recommended phase 2 dose. Secondary objectives assess pharmacokinetics and efficacy. Exploratory endpoints assess blood based biomarkers, transcriptome changes, and immunologic effects. Pre- and on-treatment tumor biopsies assess tumor microenvironment change. **Methods:** This 2 cohort study treats standard therapy refractory metastatic solid tumor patients with zeaxanthin (monotherapy cohort) or zeaxanthin and pembrolizumab (combination cohort). Combination cohort inclusion requires prior progression on a PD-1/L1 inhibitor. Oral zeaxanthin is administered daily with escalating doses (2 mg/kg to 10 mg/kg). The combination cohort escalates doses of zeaxanthin with a fixed dose of pembrolizumab (400 mg) infused every 6 weeks. Dose escalation utilizes a 3+3 design. Combination cohort dose level enrollment occurs after a zeaxanthin dose demonstrates no monotherapy DLT. Pharmacokinetic assessments occur at specified time points, Required large volume blood draws for pharmacodynamic analysis and optional tumor biopsies are obtained within 15 days prior to treatment initiation and at 6 weeks on treatment. Cohort 1 of zeaxanthin monotherapy (2 mg/kg daily) completed without DLT. Enrollment to monotherapy cohort 2 (zeaxanthin 4 mg/kg daily) and combination cohort 1 (zeaxanthin 2 mg/kg plus pembrolizumab 400 mg IV every 6 weeks) began November 2025 and are actively accruing patients. Clinical trial registry number: NCT05232409. (1) Bi et al. Evid. Based Compl. Alt. Med. (2013)12; (2) Xu et al. J Opthal (2015)10; (3) Zhang et.al. Cell Rep. Med. (2025)6. Clinical trial information: NCT05232409. Research Sponsor: Dr. Richard Rosen Cancer Research Fund.

TPS2697 **Poster Session**

Organ preservation strategy using dostarlimab for dMMR/MSI-H resectable solid tumors with whole-genome–based MRD monitoring (D-CURE: EPOC2401). First Author: Yuki Matsubara, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) solid tumors accumulate numerous genomic alterations that generate neoantigens, which are presented on MHC molecules and activate potent Th1 and cytotoxic T-cell responses. This heightened immunogenicity simultaneously induces adaptive immune resistance through PD-1/PD-L1 upregulation, providing a strong biological rationale for the effectiveness of immune-checkpoint inhibitors in dMMR/MSI-H tumors. Neoadjuvant immune-checkpoint inhibition is particularly effective in dMMR/MSI-H tumors because it leverages the intact tumor and lymphatic microenvironment to prime robust systemic antitumor immunity before surgical removal. Standard surgery for solid tumors varies widely depending on the cancer type, but it carries risks of functional impairment and postoperative morbidity. Therefore, nonoperative management (NOM) has emerged as a clinically meaningful strategy to preserve organ function and improve patients' quality of life. **Methods:** D-CURE is a multicenter phase II trial evaluating whether dostarlimab, an anti–PD-1 IgG4 humanized monoclonal antibody, can safely achieve clinical complete response (cCR) and enable NOM with organ preservation in patients with dMMR/MSI-H resectable solid tumors (excluding colorectal cancer). Patients will receive 9 cycles of dostarlimab (500 mg/body every 3 weeks). Observation with NOM will be offered to patients who achieve cCR or near-cCR. Patients undergoing NOM will be followed for up to 2 years from the date of enrollment. The primary endpoint is the 12-month cCR rate after dostarlimab. Key eligibility criteria are as follows: untreated malignancy (excluding colorectal cancer); dMMR/MSI-H confirmed in tissue or blood; age ≥18 years; ECOG PS 0–1; and clinical stage eligible for surgical resection, definitive radiotherapy, or definitive chemoradiotherapy according to the TNM 8th Edition. The target sample size of 80 was determined based on 90% power, a one-sided alpha of 5%, a threshold 12-month cCR rate of 38%, and an expected 12-month cCR rate of 56%. We also integrate personalized precise molecular residual disease (MRD) monitoring incorporating up to 1,000 tumor-specific alterations identified through whole-genome sequencing of tumor tissue, with serial ctDNA-based MRD assessment and parallel enrollment in the MONSTAR-SCREEN-3 study (UMIN000053975). Through this linkage, patients will also have access to the multi-omics platform, enabling spatial transcriptomics, bulk WES/WTS, plasma proteomics, and microbiome analyses to elucidate tumor-immune dynamics and comprehensively characterize treatment response and resistance. Enrollment of the D-CURE trial started in September 2025 and is ongoing at 12 facilities in Japan. Clinical trial information: jRCT2031250364. Research Sponsor: GlaxoSmithKline Research & Development Limited.

TPS2698 **Poster Session**

A phase II study of the DNA plasmid-based vaccine STEMVAC in patients with metastatic triple-negative breast cancer (mTNBC). First Author: Brie Chun, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: Adding immune checkpoint inhibitors for the treatment of mTNBC improves the efficacy of traditional chemotherapy in select populations. In populations who are not predicted to benefit from PD-1 checkpoint inhibitors, a vaccine may sensitize Th1 cells against cancer-associated antigens to facilitate immune-mediated tumor killing. STEMVAC is a safe, immunogenic plasmid DNA-based vaccine encoding T-helper 1 (Th1) selective epitopes from five antigens (MDM2, YB1, SOX2, CDH3, CD105) associated with breast cancer stem cells and the epithelial-mesenchymal transition. In addition to direct cytotoxic effects directed against cancer cells, we have demonstrated that vaccine-induced Th1 cells secrete IFN-γ, which upregulates suppressor of cytokine signaling 1 (SOCS1), leading to slowed tumor growth and increased vulnerability to cytotoxic agents. Combining STEMVAC with chemotherapy could thus have synergistic effects leading to enhanced cancer sensitivity to treatment and possible eradication. **Methods:** The study (NCT07078604) includes adults with PD-L1 negative mTNBC receiving standard therapies inclusive of chemotherapy, antibody-drug conjugates, and oral PARP inhibitors in the first and second line. Eligible patients will have histologically-confirmed mTNBC, radiographically measurable disease by RECIST v1.1, and a lesion amenable to biopsy. Key exclusion criteria include concomitant B-cell malignancies, ongoing systemic steroid use, and known hypersensitivity reaction to GM-CSF. Participants receive intradermal STEMVAC 300mcg with 100mcg of GM-CSF given during the nadir period of standard of care chemotherapy. Participants receive three priming vaccines given every 21-28 days concurrent with chemotherapy, followed by booster doses at 6 and 9 months then every six months thereafter. The primary endpoints are 1) observance of immunogenicity to one of the five vaccine antigens, measured by interferon-gamma enzyme-linked immunospot assay, and 2) safety. Secondary endpoints include objective response rate, real-world PFS2, overall survival, and magnitude of immunogenicity. Exploratory endpoints include quantitative levels of CD8+ infiltrating lymphocytes and expression of genes associated with epithelial-mesenchymal transition before and after vaccine priming. Current status: This trial is recruiting patients, with up to 20 patients expected to be recruited across multiple sites. Safety data and preliminary outcomes will be reported as they become available. This trial aims to evaluate whether STEMVAC would achieve clinically relevant immunogenicity when administered concurrently with chemotherapy for the treatment of mTNBC. The trial will evaluate the safety and preliminary efficacy of this novel combination and explore tumor-immune microenvironment biomarkers to gain mechanistic insight. Clinical trial information: NCT07078604. Research Sponsor: Kuni Foundation.

TPS2699 **Poster Session**

A clinical study of a prototype DAA/TAA vaccine targeting MUC1 for immune interception and prevention in ductal carcinoma in situ. First Author: Emilia Diego, Division of Breast Surgical Oncology, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Hypoglycosylated tumor MUC1 is a transmembrane glycoprotein, recognized by human T-cells and antibodies as a tumor-associated antigen. It is overexpressed in premalignant precursor lesions, including ductal carcinoma in situ (DCIS), serving as a potential potent DCIS rejection target. Vaccine-induced immune response to MUC1 may halt DCIS recurrence or progression to invasive disease and offer a future strategy for disease prevention in high-risk individuals. The hypothesis is MUC1 peptide vaccine is safe and immunogenic in patients with DCIS and the elicited systemic immune response will affect changes in the microenvironment of the DCIS from pro- to anti-tumor. Eligibility: Female, 18 years or older with biopsy proven ER+ DCIS with surgery planned as part of definite local therapy. Design: This single institution, open label, randomized phase I clinical trial (NCT06218303) is seeking 50 women with untreated ER+ DCIS confirmed on core needle biopsy (CNB). Patients are randomized 2:1 to the vaccine group. The vaccine is composed of a 100aa long MUC1 peptide corresponding to 5 tandem repeats of 20 amino acids from the MUC1 variable number of tandem repeats region (VNTR), admixed with the poly-ICLC adjuvant Hiltonol. The vaccine group receives the MUC1 peptide vaccine series pre-op (at 0, 2, and 10 weeks) with optional tamoxifen or an aromatase inhibitor (AI). The control group receives only optional tamoxifen or AI. All have surgery at 12 weeks. Research blood is drawn in the vaccine group at baseline and 2 weeks after each vaccine, and in the control group at baseline and at week 12. Tissue from the pre-treatment CNB and the post-treatment surgery are collected. An optional booster is available to vaccine responders 6 months post-surgery. Aims: The primary objective is to assess the immunogenicity of the MUC1 vaccine in ER+ DCIS patients prior to surgery. The secondary objective is to assess the safety and feasibility of the MUC1 vaccine in ER+ DCIS patients prior to surgery. The exploratory objective is to characterize peripheral MUC1-specific effector T-cells, regulatory T-cells and myeloid-derived suppressor cells (MDSC) at baseline and after vaccination. Changes in features of the tumor microenvironment and peripheral immunity at baseline and after vaccination may also be explored. **Methods:** Sample size/power: Assuming a one-sided type I error $\alpha \leq 0.05$ and the rate of patients having a $\geq 2\times$ change in anti-MUC1 IgG 1 is 35% in the vaccine arm and 2% in the control arm, a sample sizes of n=32 and 18 respectively in each arm will yield 88% power. With a dropout of up to 3 patients in each arm, the remaining sample size will still yield power of 82%. Statistical analysis: Fisher's exact test will be performed at the one-sided α=0.05 for the primary immunogenicity endpoint for comparing the experimental arm to the control arm. Clinical trial information: NCT06218303. Research Sponsor: Breast Cancer Research Foundation.

TPS2700 **Poster Session**

A phase 1 trial of the oncolytic virus SVV-001 with nivolumab and ipilimumab in patients with high-grade neuroendocrine neoplasms. First Author: Chinmay Jani, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Poorly differentiated neuroendocrine carcinomas (NECs), including small cell and large cell neuroendocrine tumors, and grade 3 neuroendocrine tumors (NETs) represent a highly aggressive disease collectively classified as high-grade neuroendocrine neoplasms (NENs). These tumors are marked by rapid tumor growth, early dissemination, genomic instability, and poor outcomes. Despite initial sensitivity to chemotherapy and radiotherapy, relapse rates remain high, and immune checkpoint inhibitors (ICIs) have demonstrated limited activity, highlighting a substantial unmet therapeutic need. Seneca Valley Virus (SVV-001) is a novel oncolytic picornavirus that has demonstrated synergistic antitumor activity with ICIs in preclinical models. Additionally, SVV-001 has shown a favorable safety profile and the ability to reverse ICI resistance in vivo, supporting its evaluation in combination with nivolumab + ipilimumab. **Methods:** This is an investigator-initiated, phase 1, dose-escalation and cohort-expansion study evaluating intratumoral SVV-001 in combination with nivolumab + ipilimumab in patients with histologically confirmed high-grade NENs who have progressed on at least one prior line of standard-of-care therapy. Eligible patients must have at least one lesion suitable to repeated intratumoral injections of SVV-001 (up to 6 injections every two weeks). The trial was activated in March 2025 at Sylvester Comprehensive Cancer Center, with enrollment currently ongoing and a planned accrual of up to 36 patients. Part 1 used a standard 3+3 dose-escalation design. Enrollment in the first three cohorts (Part 1A), evaluating single-dose SVV-001 in combination with nivolumab and ipilimumab, is complete with no dose-limiting toxicities observed. Enrollment into cohort 4 (Part 1B), which will evaluate multiple doses of SVV-001 (up to 6 injections) is planned to begin in February 2026 followed by Cohort 5. Part 2 consists of a cohort-expansion phase in which up to 6 additional patients will be treated at the optimal recommended phase 2 dose (RP2D) of SVV-001. The primary objective is to determine the maximum tolerated dose (MTD) and/or RP2D. Secondary objectives include radiographic progression-free survival (PFS), overall response rate (ORR), duration of response, clinical benefit rate (CBR), and safety. Correlative studies will assess viral kinetics, including viral release and viral load in plasma, as well as Tumor Endothelial Marker 8 (TEM8), a potential biomarker of SVV-001 sensitivity and its association with efficacy signals. Additional exploratory analyses will characterize the tumor immune microenvironment and gut microbiome markers in the dose-expansion cohort. ClinicalTrials.gov Identifier: NCT06889493. Clinical trial information: NCT06889493. Research Sponsor: None.

3000 Oral Abstract Session

DXC006, a first-in-class CD56-targeting antibody-drug conjugate, in advanced solid tumors: A first-in-human, phase I dose escalation clinical trial. First Author: Hongyun Zhao, Cancer center, Sun Yat-sen University, Guangzhou, China

Background: DXC006 is an antibody-drug conjugate of a humanized anti-CD56 antibody linked to the topoisomerase I inhibitor CPT113 with DAR=4 through a cleavable peptidyl bis-linker by CrossConju technology. DXC006 demonstrated strong antitumor activity *in vivo* and *in vitro*, here we report the safety and preliminary efficacy of first-in-human phase I trial of DXC006. **Methods:** Patients with metastatic/locally advanced solid tumors after at least one line of systemic standard therapy were enrolled. For dose escalation (D-ESC), DXC006 was administered intravenously at doses of 1.2, 2.4, 4.8, 6.0mg/kg Q2W or 6.0, 7.2 mg/kg Q3W with BOIN design and 3+3 design. A subset of pts was enrolled into dose-expansion (D-EXP) at recommended dose regimen. The primary objectives were to evaluate the safety and tolerability (dose limiting toxicities, DLTs; maximum tolerated dose, MTD) of DXC006. **Results:** Data cutoff at December 26th, 2025, 72 patients were enrolled and received at least one dose(D-ESC n=16,D-EXP n=56) , including SCLC (n=44), lung adenocarcinoma (n=11), lung squamous cell carcinoma (n=3), neuroendocrine neoplasm (n=14). No DLTs occurred and MTD was not reached. D-EXP was carried out at 4.8mg/kg Q2W and 6.0mg/kg Q3W regimens. Treatment related adverse events (TRAEs) rate (all grade/≥G3) was 97.2% and 27.8%, TOP5 most common TRAEs (all grade/≥G3) were decreased appetite (54.2%/0%), nausea (52.8%/0%), anemia (48.6%/20.8%), asthenia (37.5%/1.4%), sensory disturbance (33.3%/0%). No interstitial lung disease (ILD) was observed. TRAEs led to dose interruption/discontinuation were observed in (23.6%/1.4%) of the patients. RP2D is 6.0mg/kg Q3W. Totally, 59 patients were eligible for efficacy analysis. For all patients, the objective response rate (ORR) and disease control rate (DCR) were 52.5 % and 81.4% (including confirmed and pending confirmation PR); for SCLC patients, were 69.4% and 91.7%; for lung adenocarcinoma, were 45.5% and 72.7% (details in table). Encouraging anti-tumor activity was observed for DXC006 treatment in SCLC at 2nd line (ORR 85.7%, confirmed 64.3%). PK, PD and PFS results will be updated in the upcoming meeting. **Conclusions:** DXC006 demonstrated a manageable safety profile and adequate tolerability, and showed encouraging efficacy in pretreated advanced solid tumors, especially in SCLC. Clinical trial information: NCT06224855. Research Sponsor: Hangzhou DAC Biotechnology Co., Ltd.

	Small cell lung cancer	Small cell lung cancer (2nd Line)	Neuroendocrine Neoplasm	Lung Adenocarcinoma	Lung Squamous cell carcinoma
N	36	14	10	11	2
Median prior treatment line (range)	2(1, 6)	1(1, 1)	2(1, 6)	2(1, 3)	5(5, 5)
cPR	14	9	1	4	0
PR	25	12	1	5	0
SD	8	2	6	3	0
PD	3	0	3	3	2
ORR % (95% CI)	69.4 (53.1, 82.0)	85.7 (60.0, 96.0)	10.0 (1.8, 40.4)	45.5 (21.3, 72.0)	0.0
DCR % (95% CI)	91.7 (78.2, 97.1)	100 (78.5, 100)	70.0 (40.0, 89.2)	72.7 (43.4, 90.3)	0.0

3001 Oral Abstract Session

Phase I study of BL-M14D1, a novel DLL3-directed antibody-drug conjugate (ADC), in patients with locally advanced or metastatic small-cell lung cancer (SCLC), neuroendocrine carcinoma (NEC), and other solid tumors. First Author: Wei Li, Shanghai East Hospital, Shanghai, China

Background: BL-M14D1 is a novel DLL3-directed ADC with a potent topoisomerase I inhibitor Ed-04. Results for safety and efficacy from a phase I study on BL-M14D1 in patients with locally advanced or metastatic (LA/M) SCLC and NEC are presented. **Methods:** Patients who had LA/M solid tumors were enrolled in dose escalation and dose expansion phase and treated with BL-M14D1 at 0.66, 2.0, 3.5, 4.0, 4.5, 5.0, and 6.0mg/kg on Day 1 every 3 weeks (D1 Q3W). SCLC and NEC patients enrolled in dose expansion phase were treated at 4.0 and 4.5mg/kg D1 Q3W. **Results:** As of Nov 30, 2025, a total of 127 patients were enrolled, including 87 SCLC and 40 NEC. Median prior line of therapy was 2 (range 1-5). Treatment-related AEs (TRAEs) rate was 98.4% and grade≥3 TRAEs rate was 74.0%. The most frequent grade≥3 TRAEs were hematologic, including thrombocytopenia (54.3%), neutropenia (53.5%), leukopenia (46.5%) and anemia (32.3%), which were able to be effectively managed with standard supportive measures including dose reductions, as demonstrated by a low rate (1.6%) of TRAEs leading to discontinuation. One grade 3 ILD and one treatment-related death was reported. Efficacy data at 4.0 and 4.5mg/kg was presented below. BL-M14D1 has demonstrated a promising efficacy with an ORR/cORR of 71.1%/57.8% and mPFS of 7.2 months in heavily pre-treated SCLC. Furthermore, BL-M14D1 has shown encouraging activity in other gastrointestinal and gynecological NECs. **Conclusions:** BL-M14D1 has demonstrated promising antitumor activity with a tolerable safety profile at dose levels of 4.0mg/kg and 4.5mg/kg D1 Q3W in heavily pretreated patients with SCLC and NEC, supporting further clinical development of BL-M14D1 in SCLC and other less common NECs. Phase III studies assessing BL-M14D1 in SCLC and NEC are in preparation. Clinical trial information: NCT06505824. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	SCLC Total* (N=83)	SCLC 4.0mg/kg (N=34)	SCLC 4.5mg/kg (N=37)	NEC† Total* (N=22)	NEC† 4.0mg/kg (N=3)	NEC† 4.5mg/kg (N=19)
Median prior LoT (range)	2 (1-5)	2 (1-3)	2 (1-5)	2 (1-3)	2 (1-2)	2 (1-3)
ORR, % (95% CI)	71.1 (60.1, 80.5)	73.5 (55.6, 87.1)	70.3 (53.0, 84.1)	40.9 (20.7, 63.6)	33.3 (0.8, 90.6)	42.1 (20.3, 66.5)
cORR, % (95% CI)	57.8 (46.5, 68.6)	61.8 (43.6, 77.8)	56.8 (39.5, 72.9)	27.3 (10.7, 50.2)	33.3 (0.8, 90.6)	26.3 (9.1, 51.2)
DCR, % (95% CI)	94.0 (86.5, 98.0)	97.1 (84.7, 99.9)	91.9 (78.1, 98.3)	90.9 (70.8, 98.9)	100 (29.2, 100)	89.5 (66.9, 98.7)
mFU for PFS (mo) (95% CI)	6.8 (5.5, 7.2)	7.7 (5.6, 8.2)	4.4 (4.1, 5.5)	3.0 (1.6, 4.3)	NR (1.8, NR)	3.0 (1.4, 3.9)
mPFS (mo) (95% CI)	7.2 (5.6, 12.7)	7.2 (5.6, NR)	6.9 (4.2, NR)	5.3 (3.9, NR)	4.6 (3.9, 5.3)	NR (2.6, NR)

†Sites of NEC included cervix, esophagus, stomach and others.
*Efficacy analysis included pts at 4.0 and 4.5 mg/kg who received BL-M14D1 and had at least one post-baseline scan.

3002 Oral Abstract Session

First-in-human study of SYS6043, a novel B7-H3–targeting antibody-drug conjugate, in patients with advanced pan-tumor malignancies. First Author: Li Zhang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: B7-H3, a tumor-associated immune checkpoint, is broadly overexpressed in multiple solid tumors and associated with aggressive disease biology and treatment resistance. SYS6043, a novel ADC targeting B7-H3, is designed to selectively deliver a cytotoxic payload to B7-H3 expressing tumors. Preclinical trials showed potent antitumor activity across diverse solid tumor models. Here, we report safety and efficacy results from a phase 1/2 trial of SYS6043 in patients with advanced solid tumors. **Methods:** Eligible patients (18–75 years) had advanced solid tumors refractory to or progressing after standard therapies. The study included a phases 1 dose-escalation and PK expansion phase, followed by a phase 2 cohort expansion. Phase 1 used a BOIN design to evaluate SYS6043 at a dose of 1.2-10.0 mg/kg Q3W and 4.0-6.0 mg/kg Q2W, with PK expansion at selected doses. Phase 2 evaluated SYS6043 at 8.0 mg/kg Q3W and 6.0 mg/kg Q3W and Q2W across tumor-specific cohorts. Primary endpoints were safety, tolerability, and determination of the RP2D in Phase 1, and objective response rate (ORR) in Phase 2. **Results:** As of November 28 2025, 502 patients were enrolled, including ovarian cancer (OC, *n*= 68), small cell lung cancer (SCLC, *n*= 57), breast cancer (BC, *n*= 55), cervical cancer (CC, *n*= 42), nasopharyngeal carcinoma (NPC, *n*= 40), non-squamous non-small lung cancer (nsq-NSCLC, *n*= 34), endometrial cancer (EC, *n*= 21), and other solid tumors (*n*= 185). Dose-limiting toxicities (grade 3 gastrointestinal disease, and grade 4 febrile neutropenia) occurred at 10.0 mg/kg Q3W. Treatment-related adverse events (TRAEs) occurred in 94.2% of patients, with ≥grade 3 TRAEs in 28.5%. The most common TRAEs were anemia (52.0%), nausea (44.4%), fragile (42.8%), leukemia (41.6%), neutropenia (36.9%), decreased appetite (35.3%), and hypoalbuminemia (25.3%). Efficacy analyses focused on Q3W cohorts. SYS6043 demonstrated rapid and deep antitumor activity across multiple tumor types. In heavily pretreated SCLC (*n*= 50), ORR was 64.0% (95% CI, 49.2-77.1) with DCR of 92.0% (95% CI, 80.8-97.8). At 6 mg/kg Q3W (*n*= 28), ORR reached 75.0% (95% CI, 55.1-89.3), including one complete response. In OC, ORR and DCR were 46.2% and 87.2%, respectively with median PFS of 5.6 months at 6 mg/kg Q3W. Notably high response rates were also observed in BC (ORR 83.8%, DCR 100%), nsq-NSCLC (ORR, 57.1%), CC (ORR, 38.5%), NPC (ORR, 37.9%), and EC (ORR, 30.0%), indicating broad and consistent antitumor activity. **Conclusions:** SYS6043 demonstrated a manageable safety profile and robust, cross-tumor antitumor activity in a large population of patients with advanced solid tumors. The magnitude and consistency of responses across multiple histologies, including treatment-refractory tumors such as SCLC, support SYS6043 as a promising therapeutic candidate warranting further clinical and translational investigation. Clinical trial information: ChiCTR2400094683. Research Sponsor: CSPC Megalith Biopharmaceutial Co., Ltd.

3003 Oral Abstract Session

T-Bren (BL-M07D1) in patients with recurrent or metastatic (R/M) ovarian cancer: Results from two phase II studies. First Author: Gong-Yi Zhang, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Background: T-Bren is a HER2-directed antibody-drug conjugate (ADC) consisting of an anti-HER2 monoclonal antibody linked to a potent topoisomerase I inhibitor (Ed-04). In phase I studies, T-Bren demonstrated encouraging anti-tumor activity with a manageable safety profile in patients (pts) with solid tumors. Results of safety/efficacy from two phase II studies in pts with R/M ovarian cancer (OC) are presented. **Methods:** Two studies evaluated T-Bren as monotherapy in pts with R/M platinum-resistant (disease progression within 6 months of the last dose of platinum-based chemotherapy) and platinum-sensitive OC. Pts with R/M OC were treated at 3.8mg/kg or 4.4mg/kg D1 Q3W. Primary endpoints include ORR and RP2D. Pts were selected for HER2 expression (ultra-low/1+/2+/3+). **Results:** As of Nov 30, 2025, a total of 65 pts were enrolled at 3.8 (N = 51), or 4.4mg/kg (N = 14) D1Q3W. Of all pts, 28 (43.1%) pts previously received ≥3 lines of therapy. The most common grade 3 and above hematologic TRAEs were thrombocytopenia (41.5%), leukopenia (35.4%), neutropenia (35.4%), and anemia (29.2%); the most common grade 3 and above non-hematologic TRAEs were asthenia (6.2%), lymphocyte count decrease (6.2%). Grade 3 and above TRAEs, which were predominantly hematologic in nature, were able to be effectively managed with standard supportive measure including dose reductions, as demonstrated by the TRAE leading to discontinuation rate of 3.1%. No ILD was observed. No new safety signals were identified. Median follow-up was 7.8 mo. Among pts at 3.8mg/kg D1 Q3W, confirmed ORR (cORR) was 88.9% in platinum-sensitive OC and 47.5% in platinum-resistant OC. mPFS had not reached and 9-mo PFS rate was 85.7% in platinum-sensitive OC and 61.2% in platinum-resistant OC. Efficacy results are summarized in the table below. **Conclusions:** T-Bren has demonstrated promising anti-tumor activity with a manageable safety profile in heavily pre-treated pts with R/M OC. Dose 3.8mg/kg D1 Q3W was chosen as the RP3D. Phase III study of platinum-resistant OC is in preparation. Clinical trial information: NCT06031584; NCT06131450. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	Total (N=63)	3.8mg/kg Total (N=49)	3.8mg/kg Platinum-sensitive (N=9)	3.8mg/kg Platinum-resistant (N = 40)
Median prior LoT (range)	2 (1-8)	2 (1-6)	2 (1-4)	2 (1-6)
ORR, % (95% CI)	57.1 (44.0, 69.5)	59.2 (44.2, 73.0)	88.9 (51.8, 99.7)	52.5 (36.1, 68.5)
cORR, % (95% CI)	49.2 (36.4, 62.1)	55.1 (40.2, 69.3)	88.9 (51.8, 99.7)	47.5 (31.5, 63.9)
DCR, % (95% CI)	88.9 (78.4, 95.4)	89.8 (77.8, 96.6)	100 (66.4, 100)	87.5 (73.2, 95.8)
mPFS (mo) (95% CI)	9.3 (7.0, NR)	NR (7.0, NR)	NR (5.6, NR)	NR (7.0, NR)
9-mo PFS rate, % (95% CI)	50.1 (24.0, 71.6)	67.5 (46.0, 81.9)	85.7 (33.4, 97.9)	61.2 (34.5, 79.7)

*All pts who received at least one dose of T-Bren, excluding those still ongoing with insufficient follow up were used for efficacy analysis.

3004 **Oral Abstract Session**

Analysis of spatial atlas of ADC targets in immunotherapy-treated NSCLC to link compartment-specific target expression with tumor immune contexture, clinical outcome, and on-treatment remodeling. First Author: Jean-Philippe Guegan, ImmuSmol, Bordeaux, France

Background: The spatial distribution, co-expression patterns, immune contexture associations, and on-treatment evolution of ADC targets in NSCLC is unknown. **Methods:** The samples of 100 NSCLC patients treated with PD-1/PD-L1–based immunotherapy (STING NCT04932525) were analyzed using multiplex immunofluorescence with three 7-plex panels assessing ADC targets (Claudin18.2, TROP2, B7-H3, B7-H4), receptor co-expression (HER2, EGFR, MET, STEAP2), and immune contexture (CD8, PD-1, TIM3, LAG3, TIGIT), with PanCK and CD45 for compartment assignment. Digital pathology enabled single-cell segmentation into tumor (PanCK+), stromal, and immune (CD45+) compartments. Immune contexture was defined as Desert, Excluded, or Infiltrated by CD8 distribution. ADC target expression was quantified as the proportion of PanCK+ tumor cells expressing each target or combination. Associations with objective response (ORR), progression-free survival (PFS), and overall survival (OS) were assessed. Paired baseline/on-treatment biopsies (n = 21 pairs) evaluated treatment-induced remodeling. **Results:** Spatial profiling quantified 30 tumor-cell ADC target phenotypes. Across NSCLC, epithelial target coverage was broad, with $>$ 80% of tumor cells expressing EGFR or MET and $>$ 60% co-expressing both. Co-expression patterns were histology-dependent: EGFR/MET ($\pm$HER2) predominated in adenocarcinoma, whereas TROP2/B7-H3 co-expression was enriched in squamous carcinoma. Immune contexture shaped the ADC landscape: Infiltrated tumors showed higher tumor-cell fractions expressing EGFR, MET, TROP2, HER2, STEAP2, and B7-H3 compared with Desert tumors (all $p \leq 0.01$), while PanCK+/B7-H4 and PanCK+/CLDN18 were not contexture-associated. Clinically, B7-H4 showed a striking compartment-specific association with outcome. High abundance of B7-H4–expressing immune/stromal cells was the only phenotype replicated across ORR, PFS, and OS (stromal B7H4+: ORR 65.0% vs 38.6%, p = 0.010; PFS 12.0 vs 4.0, p = 0.013; OS 36.4 vs 13.1, p = 0.016). In contrast, tumor-cell B7-H4 predicted resistance and poor survival (tumoral B7H4+: PFS 3.5 vs 10.2, p = 0.007; OS 10.9 vs 35.6, p = 0.047). On treatment, paired biopsies demonstrated target remodeling, with increased B7-H3 expression and a concordant reduction of tumor CLDN18 by composition and membrane intensity. **Conclusions:** ADC target abundance and co-expression in NSCLC tumor cells are immune-contexture dependent and dynamically remodeled under ICI. Distinct, histology-specific co-expression patterns inform rational mono- and dual-ADC strategies. A novel, clinically actionable finding is the opposite prognostic impact of B7-H4 by spatial compartment, supporting spatially resolved biomarkers and histology- and timepoint-aware ADC$\pm$ICI selection for precision treatment in NSCLC. Research Sponsor: None.

3005 **Oral Abstract Session**

Clinical utility of discordances between histomorphology and molecular biomarkers in precision oncology. First Author: Gil Shamai, Technion Israel Institute of Technology, Haifa, Israel, Israel

Background: Conventional molecular biomarkers guide treatment selection in precision oncology, yet therapeutic benefit remains variable even within biomarker-defined populations. Deep learning (DL) models can infer biomarker status from hematoxylin and eosin (H&E) histopathology, but systematic discordances arise between conventional biomarker assays and their histomorphology-based (HM) predictions. We hypothesized that such discordances reflect biologically meaningful tumor functional states rather than model error and may have clinical relevance. **Methods:** DL models were trained to predict 15 clinically relevant biomarkers from H&E images across six cancer types using public datasets. Discordant cases, defined as disagreement between assay-based biomarker labels and their DL prediction from H&E, were quantified and analyzed for alignment with functional gene expression states and clinical outcomes. Clinical utility was assessed in two landmark randomized trials: FINHER (HER2 prediction; N = 1010; trastuzumab randomized in HER2+ patients), and TAILORx (Oncotype DX recurrence score [RS] prediction; N = 10,273; chemotherapy randomization within RS 11–25). Adjusted Cox models tested added prognostic value and treatment beneft interactions. Primary endpoint was distant recurrence. **Results:** Models achieved strong performance for predicting the biomarkers (median AUC 0.78; range 0.65–0.87). Discordance rates ranged from 8% (MSI in colon) to 32% (KRAS in lung). In discordant cases, HM predictions correlated more strongly with functional gene expression states than the biomarker status they were trained to predict (mean Spearman r = 0.52 vs 0.31; $p < 0.001$). In FINHER, predicted HER2 status added prognostic value beyond HER2 status (p = 0.01) and predicted trastuzumab benefit in HER2+ patients (p-interaction = 0.026). In HER2+ patients, trastuzumab benefit was observed in those predicted as HER2+ (HR = 0.35, 95% CI: 0.15–0.83), but not in those predicted as HER2- (HR = 1.17, 95% CI: 0.45–3.02). In TAILORx, predicted RS added prognostic value over true RS in the no-chemo group (p = 0.005) and showed treatment interaction beyond RS within RS 11–25 (N = 1629; p-interaction = 0.021), as well as when restricted to postmenopausals (p = 0.029). Discordant patients (RS 11–25 predicted as RS $>$ 26) derived chemotherapy benefit (HR = 0.30, 95% CI: 0.13–0.77), whereas those predicted as RS $<$ 26 did not (HR = 0.95, 95% CI: 0.71–1.29). **Conclusions:** Discordances between molecular biomarkers and HM predictions are not random errors but reflect underlying tumor functional states. HM biomarkers may capture relevant information missed by standard assays that can improve therapeutic benefit prediction. This framework enables reinterpretation of DL pathology predictions, supports integrating H&E models to complement biomarkers, and enables derivation of functional information without outcome data. Research Sponsor: the Israel Innovation Authority - Kamin; the Zimin Institute for Artificial Intelligence Solutions in Healthcare grant; the Israel Precision Medicine Partnership program (IPMP) grant; the Israel Cancer Research Fund (ICRF).

3006 **Oral Abstract Session**

Clinical activity and safety of RNK08954 in advanced non–small cell lung cancer (NSCLC) patients with *KRAS* G12D mutation (NCT06667544). First Author: Zhengbo Song, Phase I Clinical Trial Ward, Zhejiang Cancer Hospital, Hangzhou, China

Background: KRAS G12D is the most prevalent subtype of KRAS mutations across solid tumors. RNK08954 is a potent and selective KRAS G12D small molecule oral inhibitor. It inhibited proliferation of KRAS G12D-mutant cells and demonstrated significant tumor regressions in mouse xenograft models. Here we report the results of RNK08954 from Phase 1 first-in-human study. **Methods:** This ongoing multicenter open-label trial of RNK08954, comprises of: Phase 1a dose-escalation (U-BOIN design, 5 dose levels: 200, 400, 800, 1000 and 1200 mg RNK08954 single agent QD) and Phase 1b dose optimization and expansion cohorts (NSCLC, Pancreatic, and other tumor types). Key endpoints were determining the recommended doses for expansion (RDE), safety, tolerability, antitumor activity (objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression free survival (PFS)), pharmacokinetics and pharmacodynamics. Patients (pts) enrolled into the study had solid tumors not amenable to standard therapy; 0 or 1 ECOG PS; and KRAS G12D mutation. **Results:** At data cutoff (Jan 20, 2026), 106 pts were enrolled, with 47 pts presenting with NSCLC. The median age was 65 years, and 91.5% of pts had ECOG 1. Prior lines of therapy ranged between 1 and 3, with a median of 14 mo since NSCLC diagnosis. The ORR was 38.5% (15/39; 95% CI: 23.4, 55.4), DCR was 94.9% (37/39; 95% CI: 82.7%, 99.4%), median DoR was not reached (NR) at the time of analysis (Q1, Q3: 4.8, NR) and median PFS will be reported with mature data. ctDNA analysis demonstrated correlation with clinical benefits. RNK08954 demonstrated a near-dose dependent exposure across dose levels. Both 1000 and 1200 mg were chosen for RDE, and the recommended Phase 2 is considered as 1200 mg QD. Overall, treatment was tolerated, with diarrhea (78.7%), nausea (61.7%) and vomiting (55.3%) being the most frequent treatment related events (TRAEs) and were mainly Grade 1. Grade 3 TRAEs occurred in 23.4%, with diarrhea most frequent TRAEs (10.6%). No Grade 3 or higher transaminase elevation (ALT/AST) was observed, only one patient experienced Grade 3 neutropenia.There were no fatal events. Further updated results will be presented at the meeting. **Conclusions:** RNK08954 was well tolerated and displayed promising antitumor activity in pts with KRAS G12D-mutant NSCLC. The study supports further evaluation either as monotherapy or in combination with standard of care and/or novel agents. Clinical trial information: NCT06667544. Research Sponsor: None.

3007 **Oral Abstract Session**

Phase I/IIa study of DN022150, a novel selective noncovalent small molecule KRAS G12D inhibitor in patients with advanced KRAS G12D–mutant solid tumors. First Author: Yiyi Yu, Zhongshan Hospital, Fudan University, Shanghai, China

Background: The KRAS G12D mutation is ranks among the most common RAS mutations across human cancers and is closely linked to poor clinical outcomes. DN022150 is a novel highly selective KRAS G12D inhibitor, that exerts potent antitumor effect by specifically binding to the switch-II pocket of the mutant KRAS G12D protein, this binding mechanism blocks the interaction of GDP and GTP with the mutant protein, thereby abrogating activation of the downstream of the RAS-MAPK signaling pathway. We report preliminary findings from the first-in-human study of DN022150 in patients with advanced KRAS G12D-mutant solid tumors. **Methods:** This Phase I/IIa study evaluates the safety, tolerability, pharmacokinetics (PK), and efficacy of DN022150 in patients with locally advanced or metastatic solid tumors harboring KRAS G12D mutations who have progressed following prior standard therapies. The study includes three sequential parts: dose escalation, dose expansion, and indication exploration. During dose escalation, patients receive fixed doses of DN022150. Based on integrated analysis of safety, tolerability, PK, and efficacy data from escalation phase, approximately 1-3 dose/frequency cohorts will be selected for the subsequent dose-expansion phase. The primary objective is to evaluate the safety, tolerability, and preliminary antitumor activity of DN022150 in patients with KRAS G12D-mutated advanced solid tumors. **Results:** As of January 22, 2026, a total of 56 patients were enrolled. Among them, 83.9% (47/56) had an ECOG PS of 1 and 66.1% (37/56) diagnosed with pancreatic cancer. Approximately 80% had received $\geq$2 prior lines of systemic therapy. Safety analysis included 49 participants (dose levels: 20-650 mg). Notably, no dose-limiting toxicities occurred across all dose levels. Grade $\geq$3 TEAEs were observed in 44.9% (22/49) of patients, with TRAEs in 30.6% (15/49). No grade 4-5 TRAEs were documented. TRAEs led to dose delays in 14.3% (7/49) of patients and treatment interruptions in 16.3% (8/49). The most common grade $\geq$3 TRAEs ($\geq$5%) were neutropenia, anemia, and leukopenia. Tumor assessments were conducted every 8 weeks ($\pm$7 days). Among the 31 evaluable patients, treated at dose levels of 200 mg to 650 mg, an impressive 96.8% (30/31) achieved target lesion reduction at first post-baseline assessment, including 71% (22/31) with $\geq$20% reduction. ORR was 37.5% (3/8) at 450 mg and 31.3% (5/16) at 650 mg, with DCR of 87.5% (7/8) and 93.8% (15/16). **Conclusions:** DN022150 demonstrated favorable safety and tolerability profiles in patients with KRAS G12D-mutated advanced solid tumors, with no dose-limiting toxicities observed and manageable TRAEs. The agent showed potent antitumor activity, confirming its precise targeting of the KRAS G12D mutation. These results position DN022150 as a promising novel therapy for this molecularly defined population. Clinical trial information: CTR20242749. Research Sponsor: None.

3008 Oral Abstract Session

Preliminary efficacy of GFH375 in patients with advanced cholangiocarcinoma or colorectal cancer harboring KRAS G12D mutation. First Author: Lingjun Zhu, Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

Background: Kirsten rat sarcoma (KRAS) G12D is the most prevalent RAS mutation in human cancers, accounting for 10.6-19.2% and 5.8-10.8% of cases in colorectal cancer (CRC) and cholangiocarcinoma (CCA), respectively. Currently, the later-line therapies for metastatic CCA and CRC remain very limited. The KRAS G12D mutation is associated with poor prognosis and confers resistance to conventional chemotherapy. GFH375, a potent, selective, orally bioavailable KRAS G12D inhibitor, has demonstrated antitumor efficacy in pancreatic cancer and non-small cell lung cancer. Here we report the preliminary efficacy results of GFH375 in patients (pts) with advanced KRAS G12D mutant CCA and CRC. **Methods:** This is a phase I/II study (NCT06500676) evaluating the safety, tolerability, pharmacokinetics and efficacy of GFH375 in pts with advanced solid tumors harboring KRAS G12D mutations. Pts with locally advanced or metastatic CCA and CRC who had failed prior therapies were also enrolled. Tumor assessments were performed every 6 weeks during the first 48 weeks, and every 12 weeks thereafter. All efficacy endpoints, including objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS) were evaluated according to RECIST v1.1. Circulating tumor DNA (ctDNA) samples were collected at baseline and at the end of treatment for exploratory analyses. **Results:** As of 31 Oct 2025, twenty CCA and 41 CRC pts were treated with GFH375 once daily (400, 600 or 750 mg). Among the CCA pts (median age: 59.5 yrs; 80.0% male), 17 (85.0%) had metastatic disease at baseline, and the median prior lines of therapy were 2 (range: 1-6). ORR was 35.0% (7/20), and DCR was 95.0% (19/20). Nine out of 12 pts with stable disease (SD) had tumor shrinkage. Median PFS was 6.3 months, and median overall survival (OS) was not reached. Among those CRC pts (median age: 56 yrs; 61.0% male), all had metastatic disease at baseline, and the median prior lines of therapy were 3 (range: 1-6). Among 35 pts who had at least one post-treatment tumor assessment, ORR was 11.4% (4/35), and DCR was 77.1% (27/35). Median PFS was 4.1 months and median OS was not reached. Baseline ctDNA results were available in 19 CCA pts and 36 CRC pts. KRAS G12D mutations were detected in 14 (73.7%) CCA pts and 31 (86.1%) CRC pts. The common co-mutated genes (≥15%) in CCA were TP53, BCL2L11 and APC, while in CRC were TP53, APC, RUNX1, SMAD4 and PIK3CA. The safety profile in the 61 pts was similar to that of the whole population as previously reported. The most common treatment-related adverse events (TRAEs) (≥30%) included diarrhea, nausea, vomiting, aspartate aminotransferase increased, anemia and decreased appetite. **Conclusions:** GFH375 monotherapy has demonstrated promising antitumor activities in heavily treated pts with CCA and CRC. GFH375 monotherapy in CCA and in combination with other anti-tumor therapies for CRC is under development. Clinical trial information: NCT06500676. Research Sponsor: GenFleet Therapeutics (Shanghai) Inc.

3009 Rapid Oral Abstract Session

Integrin $\alpha_v\beta_3$-targeted radionuclide therapy with ^{177}Lu-AB-3PRGD$_2$ in multiple advanced metastatic solid tumors: A prospective, single-arm, single-center, investigator-initiated clinical trial. First Author: Hao Fu, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

Background: Tumor angiogenesis drives progression and metastasis in solid malignancies. Integrin $\alpha_v\beta_3$ is selectively overexpressed on multiple tumor cells and neovasculature with limited normal tissue expression, offering a promising therapeutic target. Our previous dose-escalation study investigated the safety and maximum tolerated dose of the integrin $\alpha_v\beta_3$-targeted radiopharmaceutical ^{177}Lu-AB-3PRGD$_2$. Building on this foundation, the current study aims to evaluate its therapeutic efficacy in patients with various advanced metastatic solid tumors. **Methods:** In this prospective, single-arm, single-center investigator-initiated clinical trial, eligible patients had histologically confirmed advanced metastatic solid tumors with documented progression after exhaustion of standard systemic therapies. Tumor integrin $\alpha_v\beta_3$ expression was confirmed by ^{68}Ga-3PRGD$_2$ PET/CT imaging. Patients received up to four cycles of ^{177}Lu-AB-3PRGD$_2$ at 3.7 GBq per cycle. The primary endpoint was ORR by RECIST 1.1. The secondary endpoints included DCR, PFS, OS, and safety. The sample size was calculated based on the primary endpoint of ORR. Assuming a null ORR of 10% and an alternative ORR of 30%, a one-sided binomial test with a significance level (α) of 0.05 and 80% power required approximately 20 evaluable patients. **Results:** From December 2023 to December 2025, 20 patients were enrolled. Of these, 5 received three treatment cycles and 5 received four cycles. The median age was 62 years (range 38–75) and 30% were female. Tumor types included radioiodine-refractory thyroid cancer (20%), breast cancer (15%), lung cancer (10%), cholangiocarcinoma (10%), renal cancer (10%), and others. At baseline, 65% of patients had ECOG performance status ≥2. Among 13 patients received ≥ 2 cycles of treatment, the ORR was 23% (3/13) and DCR was 92% (12/13), including 3 PR and 9 SD. With a median follow-up of 11.9 months, median PFS was 7.3 months and median OS was 18.5 months. Patients achieving disease control had significantly longer PFS and OS compared to those with progressive disease ($P<$ 0.001). Dosimetry analysis, available for 18 patients (90%), showed a mean tumor absorbed dose of 6.8 ± 5.4 Gy/GBq. Grade 3/4 treatment-related adverse events occurred in 20% of patients (4/20), primarily hematologic toxicities including thrombocytopenia (n = 4), leukopenia (n = 2), and anemia (n = 2). **Conclusions:** Integrin $\alpha_v\beta_3$-targeted radionuclide therapy with ^{177}Lu-AB-3PRGD$_2$ demonstrated promising efficacy in disease control and tumor response, and it was generally well tolerated in patients with advanced metastatic solid tumors. These findings justify further investigation in prospective, multicenter, randomized clinical trials. Clinical trial information: NCT06375564. Research Sponsor: None.

3010 Rapid Oral Abstract Session

Phase Ib results from the phase Ib/II study of [^{177}Lu]Lu-DOTA-TATE in combination with standard of care as a first-line treatment for pts with extensive-stage small cell lung cancer. First Author: Stephen V. Liu, Department of Medical Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

Background: Most pts with newly diagnosed extensive-stage small cell lung cancer (ES-SCLC) relapse after initial response to standard of care (SOC; platinum/etoposide + anti–programmed death-ligand 1 [PD-L1] therapy); novel combination strategies are needed. This Phase Ib/II study (NCT05142696) assessed [^{177}Lu]Lu-DOTA-TATE (^{177}Lu-DOTATATE) – a radioligand therapy with high affinity for somatostatin receptor 2 (SSTR2; a poor prognostic biomarker expressed in ~50% of SCLC tumors) – plus SOC. Here, we report Phase Ib data (cutoff 20 Nov 2025). **Methods:** Phase Ib was a dosage escalation study to determine the recommended dosage (RD) of ^{177}Lu-DOTATATE – alongside carboplatin AUC 5 + etoposide 100 mg/m^2 + anti–programmed cell death protein 1 (PD-1)/PD-L1 therapy (pre/post protocol amendment: tislelizumab 200 mg/atezolizumab 1200 mg, respectively) Q3W in the induction phase, and alongside anti–PD-1/PD-L1 therapy Q3W in the maintenance phase – in pts aged ≥18 y with newly diagnosed SSTR+ (by PET/CT) ES-SCLC. Cohorts of 3–6 pts were enrolled to increasing dosage levels (DLs) of ^{177}Lu-DOTATATE (backfill allowed to ≤10 pts); escalation was guided by dosage-limiting toxicity (DLT) rate (Bayesian Optimal Interval design) and other safety data. The primary endpoint was DLTs (^{177}Lu-DOTATATE–related adverse events within the 42-day DLT period). **Results:** Of 57 pts screened, 29 received treatment (median [range] age 62 [43–73] y; white 89.7%; male 44.8%; ECOG PS 0/1/2 37.9%/58.6%/3.4%; smoking history 100%; bone/brain/liver metastases 51.7%/13.8%/48.3%); 93.1% completed the induction phase (DL1 [3.7 GBq] 9/9; DL2a [5.55 GBq] 11/11; DL3a [7.4 GBq] 7/9). Median treatment duration between first/last dosage and cutoff was 14.2/9.4 months. For ^{177}Lu-DOTATATE, median (range) number of doses was 4.0 (1.0–7.0), duration was 4.1 (1–6) months, and cumulative activity was 22.7 (7.1–44.4) GBq. There were no DLTs in 17 evaluable pts. The table reports safety and preliminary efficacy data. **Conclusions:** The observed safety profile was consistent with expected toxicity; the RD for Phase II was 7.4 GBq. Clinical trial information: NCT05142696. Research Sponsor: Novartis Pharmaceuticals.

Safety and preliminary efficacy (N=29).

AEs, %	
Any: all grades; Grade ≥3	100; 100
Treatment related	100
^{177}Lu-DOTATATE related	86.2*
Serious	72.4†
Leading to discontinuation	24.1‡
Deaths due to AEs, n	2§
Confirmed best overall response, %	82.8¶
6-month duration of response rate, %	28.5 (95% CI 11.8, 47.7)
6-month progression-free survival rate, %	36.1 (95% CI 19.0, 53.6)

*Most commonly reported: thrombocytopenia (58.6) and anemia (44.8).
†66.7 DL1, 63.6 DL2a, 88.9 DL3a.
‡33.3 DL1, 27.3 DL2a, 11.1 DL3a.
§DL1: cardiac failure, large intestinal hemorrhage (on-treatment death); not treatment related.
¶100 DL1, 90.9 DL2a, 55.6 DL3a.
AE, adverse event; CI, confidence interval; DL, dosage level.

3011 Rapid Oral Abstract Session

An open-label, first-in-human study of SKB500 in patients with locally advanced or metastatic solid tumors. First Author: Xueying Zhang, Department of Internal Medicine III, Jilin Provincial Cancer Hospital, Changchun, China

Background: SKB500 is an antibody drug conjugate (ADC) composed of an antibody targeting the B7 homolog 3 (B7-H3), which is overexpressed in many types of solid tumors, conjugated to a topoisomerase I inhibitor payload via a cleavable pyrimidine-tripeptide linker. We hereby report initial results of the FIH study (NCT06736327). **Methods:** This phase 1 study comprised dose-escalation, dose-expansion, and indication-expansion phases to evaluate the safety, tolerability, pharmacokinetics, and efficacy of SKB500. Patients (pts) with unresectable solid tumors refractory to standard treatment will be enrolled and receive SKB500 at doses ranging from 2 to 18 mg/kg every three weeks (Q3W) until disease progression or unacceptable toxicity. The primary efficacy endpoint was objective response rate (ORR) assessed by investigators per RECIST v1.1. **Results:** As of Dec 23, 2025, 150 pts were treated with SKB500 across all dose levels (2-18 mg/kg). No dose-limiting toxicities (DLT) were observed during dose escalation. Based on preliminary data, the recommended phase 2 dose (RP2D) was established as 12 mg/kg. Among 97 pts treated at 12 mg/kg, the median treatment duration was 6.7 weeks. Treatment-related adverse events (TRAEs) occurred in 70 pts (72.2%), with most frequent (≥20%) being anemia (35.1%), nausea (34.0%), and white blood cell count decreased (24.7%). Grade ≥3 TRAEs occurred in 16 pts (16.5%), with most frequent being anemia, lymphocyte count decreased, pneumonia, and asthenia (each 3.1%). Pneumonitis occurred in 2 pts (2.1%; both grade 1). Both pneumonitis and grade ≥ 3 hematologic toxicities demonstrated low occurrence rates. No TRAEs led to treatment discontinuation or death. Among 55 pts treated at 12 mg/kg who had at least 6 weeks of follow-up (≥2 prior lines: 34.5%; prior platinum: 98.2%; prior IO therapy: 76.4%), the ORR was 54.5% (30/55) and the DCR was 92.7% (51/55). In tumor-specific subgroups, the small cell lung cancer (SCLC) cohort (n = 21) achieved an ORR of 71.4% (15/21) and a DCR of 100% (21/21), while the esophageal squamous cell carcinoma (ESCC) cohort (n = 18) showed an ORR of 55.6% (10/18) and a DCR of 88.9% (16/18). **Conclusions:** SKB500 demonstrated a manageable safety profile and promising antitumor activity in patients with treatment-refractory advanced solid tumors, with notable efficacy in SCLC and ESCC cohorts, supporting further clinical development. Clinical trial information: NCT06736327. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

3013 **Rapid Oral Abstract Session**

First-in-human study of BG-C9074 (B7-H4–targeting ADC) in advanced solid tumors: Dose escalation and safety expansion. First Author: Binghe Xu, Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China

Background: B7-H4, a transmembrane glycoprotein, has limited expression in normal tissue, but is upregulated in a variety of solid tumors. BG-C9074 is an investigational topoisomerase I inhibitor antibody-drug conjugate (ADC) that targets B7-H4. We present results of monotherapy dose escalation and safety expansion from the ongoing phase 1 study. **Methods:** BG-C9074-101 (NCT06233942) is a first-in-human, multicenter study of BG-C9074 as monotherapy and in combination with other anticancer therapies in patients (pts) with advanced solid tumors. Pts with advanced solid tumors, irrespective of B7-H4 expression, received BG-C9074 IV every 3 weeks in escalating doses from 1 to 9 mg/kg. Endpoints included safety, preliminary antitumor activity (per RECIST v1.1) and pharmacokinetics. **Results:** As of Dec 29, 2025, 123 pts with advanced solid tumors received BG-C9074 monotherapy in phase 1a (ovarian [OC], n = 62; HR+/HER2- breast cancer, n = 28; triple negative breast cancer [TNBC], n = 18; cholangiocarcinoma, n = 11; endometrial, n = 3; squamous non-small cell lung cancer, n = 1). Median (range) prior lines were 4 (0-13). 8 pts experienced DLTs (thrombocytopenia [n = 2, 6.5 mg/kg; n = 1, 7 mg/kg], febrile neutropenia [n = 1, 6.5 mg/kg; n = 1, 7 mg/kg], neutropenic infection [n = 1, 7 mg/kg], fatigue [n = 1, 6 mg/kg], nausea [n = 1, 9 mg/kg], and unexplained death [n = 1, 9 mg/kg]). Treatment-related adverse events (TRAEs) occurred in 113 pts (91.9%); grade (gr) ≥3 in 30.1%. The most common TRAEs were nausea (53.7%; gr ≥3, 4.1%), neutrophil count decreased/neutropenia (44.7%; gr ≥3, 18.7%), and fatigue (37.4%; gr ≥3, 2.4%). Hematologic and gastrointestinal toxicities were manageable with dose modifications and/or supportive care. Among 114 efficacy-evaluable pts, confirmed ORR (cORR) was 28.1% (95% CI: 20.1-37.3), including 2 CRs (1 OC, 6.5 mg/kg, 1 TNBC, 5 mg/kg) and 30 PRs (Table); unconfirmed ORR was 33.3% (24.8-42.8; 3 CRs, 35 PRs). Responses were observed across doses and levels of B7-H4 expression, without consistent association of response with B7-H4 expression across tumor types. Median (range) study follow-up was 6.0 (0.3-17.7) months. ADC and free payload concentrations decreased in a biexponential manner with a half-life of ~7 days for ADC. Exposure for ADC and free payload increased approximately dose proportionally. **Conclusions:** BG-C9074 demonstrates a tolerable safety profile in pts with advanced solid tumors. Encouraging antitumor activity was observed in OC and TNBC. Dose expansion and optimization are ongoing. Clinical trial information: NCT06233942. Research Sponsor: BeOne Medicines Ltd.

	OC (n=55)	TNBC (n=16)	HR+/HER2- BC (n=28)	Total (N=114)
cORR, % (95% CI)	34.5 (22.2-48.6)	31.3 (11.0-58.7)	17.9 (6.1-36.9)	28.1 (20.1-37.3)
CR, n (%)	1 (1.8)	1 (6.3)	0 (0.0)	2 (1.8)
PR, n (%)	18 (32.7)	4 (25.0)	5 (17.9)	30 (26.3)
SD, n (%)	32 (58.2)	5 (31.3)	16 (57.1)	60 (52.6)
PD, n (%)	4 (7.3)	5 (31.3)	7 (25.0)	17 (14.9)
Not evaluable, n (%)	0 (0.0)	1 (6.3)	0 (0.0)	5 (4.4)

3014 **Rapid Oral Abstract Session**

First-in-human trial of BH-30643, a novel macrocyclic, non-covalent, mutant-selective OMNI-EGFR inhibitor, in *EGFR*-mutant (*EGFR*m) NSCLC. First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Macrocyclic next-generation tyrosine kinase inhibitors (TKIs) have transformed outcomes in ALK- and ROS1-positive NSCLC; such creatively designed medicines are similarly needed to improve outcomes in EGFR-mutant NSCLC. Using a novel, mutant-selective macrocyclic structure, BH-30643 was designed for super-potency against driver EGFRm, largely sparing wildtype (WT) EGFR, and with unique invulnerability to resistance from C797S with or without T790M. Here we report emerging first-in-human dose-escalation data from the SOLARA trial (NCT06706076). **Methods:** Phase 1 dose escalation used a BOIN design with backfill at potentially efficacious doses. Expansion cohorts targeted populations of interest. Patients (pts) had advanced NSCLC with EGFR and/or HER2 mutations detected on local testing (tissue or plasma). Measurable disease was required; asymptomatic untreated brain metastases (BM) were permitted. Objectives included safety, PK, and RECIST response rate (ORR). Plasma NGS was performed at baseline and on treatment. **Results:** As of 01/05/2026, 72 pts enrolled into dose escalation and backfill across 7 dose levels at a total daily dose of 20mg -160mg, median age 62, 44% Asian, 65% with history of BM, median of 3 prior lines of treatment (range 1-12). EGFR mutations included classical (38 pts), exon20ins (14 pts) and other/atypical (18 pts) or HER2 mutations (2 pts). Plasma exposures at doses of 40mg BID and above achieved > 10x coverage over target EC90 and exceeded exposure levels of most contemporary EGFR TKIs. Common TRAE (> 10%) were WT EGFR-associated, including diarrhea (38%), rash (28%), fatigue (15%), stomatitis (13%), and were predominantly grade 1. Bilirubin elevation was seen in 26 pts (36%) related to off-target UGT1A1 inhibition (Gilbert's-like). Grade 3 TRAE were seen in 15 pts (18%), most commonly bilirubin (8/15); DLTs included bilirubin increase and mucositis, occurring at doses ≥ 60mg BID. No pneumonitis was observed. Responses were observed across diverse EGFRm subsets, including in CNS. Including expansion pts, 28 pts enrolled with C797S on their most recent informative molecular testing (6 with concurrent MET+ or KRAS+), with 23 still on therapy. Of 17 with on-treatment scans, partial responses (confirmed or ongoing) were seen in 10 (59%); ORR was comparable with (50%) or without (66%) T790M. Of 9 pts with baseline C797S detected in ctDNA (3 with T790M), 7 had > 99% reduction of C797S VAF on treatment. **Conclusions:** Leveraging a novel macrocyclic scaffold, BH-30643 is the first TKI monotherapy to demonstrate clinical responses against C797S both with or without T790M. High plasma exposures combined with super-potency, CNS activity, and favorable safety offers potential for deep and durable EGFR inhibition. Enrollment into backfill and expansion cohorts is ongoing to better characterize activity in both TKI-naïve and resistant pts. Clinical trial information: NCT06706076. Research Sponsor: BlossomHill Therapeutics.

3015 **Rapid Oral Abstract Session**

Genomically personalized radiation dose de-escalation: A phase II basket radiation study in patients with pathogenic mutations in *ATM*. First Author: Amy Xu, Memorial Sloan Kettering, New York, NY

Background: *ATM* (ataxia-telangiectasia mutated) is a key DNA damage response gene, and pathogenic variants are known to cause a rare hereditary syndrome notable for extreme radiosensitivity. Somatic *ATM* inactivation is associated with markedly improved tumor control following RT. We hypothesized that *ATM*-mutant tumors could achieve effective local control with substantially lower RT doses, reducing normal tissue toxicity. This concept of genomically personalized radiation dose de-escalation was tested in a phase II trial. **Methods:** We conducted a single-arm phase II trial of low-dose RT in patients with metastatic solid tumors harboring pathogenic *ATM* mutations. Eligible patients had radiographic progression suitable for palliation and all patients received 4Gy x 2 fractions- 60% reduced compared to conventional 4Gyx5 palliation-delivered to a target lesion. The primary endpoint was 6-month local failure rate (radiographic progression or re-irradiation) and benchmarked against historical local failure control rates of 82% for 4Gyx5 standard palliation, with pre-specified analysis conducted at this initial dose level. Toxicity was graded by CTCAE criteria. **Results:** Twenty-one patients (across 9 histologies; 3 germline *ATM*, 18 somatic) were enrolled. At 6 months, 12 patients were evaluable; 10 of 12 (83.3%) achieved local control with the 4Gyx2 regimen. Notably, this included a 4.4cm angiosarcoma with a complete response by 6 months- an exceptional outcome with such a low dose. Two patients (16.7%) had local failure by 6 months. Both of these tumors retained ATM protein expression by immunohistochemistry and harbored concurrent pathogenic *TP53* mutations. In contrast, molecular analysis confirmed biallelic *ATM* loss in four patients, including the top three responders. No grade ≥2 toxicities or other significant RT-related side effects were observed. **Conclusions:** *ATM*-mutant tumors were effectively controlled with markedly reduced RT dose (4Gyx2), achieving local control in 83% of lesions at 6 months, comparable to historical response rates with standard palliation (4Gyx5), but with minimal toxicity. Additionally, FACETS analysis showed a stronger correlation with treatment response than germline vs. somatic mutation status, suggesting that FACETS analysis could be more informative in determining eligibility criteria for future clinical trials. These preliminary findings establish *ATM* as a novel biomarker for personalized RT dose de-escalation and compel further investigation into ATM as a therapeutic target. Clinical trial information: NCT05010031. Research Sponsor: Imaging and Radiation Sciences Program (IMRAS); U.S. National Institutes of Health.

3016 **Rapid Oral Abstract Session**

A phase 1 study of BGB-B2033 (GPC3 x 4-1BB bispecific antibody) monotherapy in patients with selected advanced or metastatic solid tumors: First disclosure of clinical data. First Author: Hong Jae Chon, CHA Bundang Medical Center, Bundang, South Korea

Background: GPC3 is a tumor-specific antigen that is highly expressed in hepatocellular carcinoma (HCC) and squamous non-small cell lung cancer. 4-1BB is a co-stimulatory receptor on activated T cells that promotes proliferation, survival and cytolysis of T cells. BGB-B2033, a novel, IgG-based GPC3 x 4-1BB bispecific antibody with Fc region engineered to prevent FcγR binding and increase half-life, activates T cells while minimizing systemic toxicity. BGB-B2033 is being studied as monotherapy or in combination in patients (pts) with advanced GPC3-expressing solid tumors in a first-in-human phase 1 trial (NCT06427941). Here we report initial results from the monotherapy dose escalation and safety expansion (part A). **Methods:** In part A, eligible pts with ≥1 prior systemic therapy received ascending dose levels of BGB-B2033. The primary objective was safety. Secondary objectives were preliminary antitumor activity (per investigator-assessed RECIST v1.1), pharmacokinetics, and immunogenicity. Dose escalation followed the Bayesian mTPI-2 design. **Results:** As of December 10, 2025, part A enrolled 61 pts; 60 (98.4%) had HCC and 56 (91.8%) were Asian. Median (range) prior lines of therapy were 2.0 (1-6). The median (range) study follow-up was 3.9 (0.3-14.9) months. Treatment-emergent adverse events (TEAEs) were reported in 63.9% of pts across the 8 dose levels; 27 (44.3%) pts had treatment-related (TR)-TEAEs. Six grade ≥3 TR-TEAEs occurred in 5 (8.2%) pts: alanine aminotransferase (ALT) increased, aspartate aminotransferase increased, blood bilirubin increased, drug eruption, lymphopenia and neutrophil count decreased (1.6% each). One dose-limiting toxicity (ALT increased) resolved after dose reduction. Immune-mediated adverse events (imAEs) were reported in 4 (6.6%) pts; all were grades 1-2. One pt reported a grade 1 infusion-related reaction. In the 59 efficacy-evaluable pts with HCC, confirmed ORR was 20.3% (95% CI: 11.0-32.8), with 12 partial responses; 23 pts had stable disease, 23 had progressive disease, and 1 pt was not evaluable. Ten of the 12 responders had ongoing response at data cutoff. A preliminary dose response was observed; at doses above the predicted target efficacious dose, confirmed ORR was 28.9% (11/38). Serum concentration profiles of BGB-B2033 exhibited target-mediated drug disposition at lower dose levels and decreased in a more biexponential manner at higher dose levels. Soluble 4-1BB, a pharmacodynamic marker, showed a greater increase at higher dose levels. **Conclusions:** BGB-B2033 was generally well tolerated, with limited imAEs in this predominantly 2L+ HCC population. Durable responses were observed in pts with advanced HCC, including pts with prior PD-(L)1-based treatment. Triplet dose escalation with tislelizumab and bevacizumab as well as monotherapy dose expansion are ongoing. Clinical trial information: NCT06427941. Research Sponsor: BeOne Medicines Ltd.

3017 **Rapid Oral Abstract Session**

Luvometinib in adults with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas: A randomized, double-blind, placebo-controlled, phase 3 trial. First Author: Wenbin Li, Department of Neuro-Oncology, Cancer Center, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Background: Neurofibromatosis type 1 (NF1) related plexiform neurofibromas (PNs) is associated with significant morbidity, including pain, disfigurement and functional impairment. Surgical treatment for PNs may be limited due to tumor size, location and extent. A randomized, double-blind, placebo-controlled, phase 3 trial (NCT05913037) was conducted to evaluate the efficacy and safety of Luvometinib in adults with inoperable NF1 PN causing significant morbidities. **Methods:** Adults (≥18 yrs) with NF1 and symptomatic, inoperable PNs were randomized in a 2:1 to receive oral Luvometinib (8 mg daily) or placebo in 28-day cycles, stratified by baseline (BL) NRS-11 tumor pain score (≥2 or < 2). An interim analysis was performed at 16 months after the last patient randomization. The primary endpoint was confirmed objective response rate (ORR) by Blinded Independent Review Committe (BIRC) per REiNS criteria. Key secondary endpoints included ORR by the investigator (INV), duration of response (DOR), time to response (TTR) by BIRC and INV, pain severity and safety. **Results:** 167 adults were randomized to receive luvometinib (n = 112) or placebo (n = 55). As of the data cutoff on Aug 19, 2025, the median follow-up was 19.7 months(range: 1.4-25.5). The confirmed ORR assessed by BIRC was 43.8% (95% CI, 34.4-53.4) with luvometinib, compared with 10.9% (95% CI, 4.1-22.3) with placebo ($p < 0.0001$). Luvometinib led to a rapid response (median 3.9 months). The median DOR was 15.1 months (95% CI, 14.8-NE), with a 85.2% rate of DOR ≥12 months with luvometinib. A greater proportion of patients with BL overall tumor pain scores ≥2 experienced a reduction in pain score of at least 2 points with luvometinib compared to placebo (81.0% vs. 53.6%). The most common treatment-emergent adverse events (TEAEs) were folliculitis, increased CPK, mouth ulcer, diarrhea. Serious AEs occurred in 14.3% (luvometinib) versus 7.3% (placebo) of pts. TEAEs led to discontinuation was 1.8% in both groups. **Conclusions:** Our study demonstrated that luvometinib achieved a statistically significant ORR per BIRC compared with placebo, with rapid and durable response, significant reductions in pain severity, and an overall manageable safety profile. These findings suggest that luvometinib may emerge as a new standard treatment for patients with NF1 and symptomatic, inoperable PNs. Clinical trial information: NCT05913037. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

3018 **Poster Session**

The efficacy and safety of azvudine (FNC) in phase 1 investigator-initiated study in patients with advanced solid tumors. First Author: Xuemei Zhu, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Azvudine has been approved in China for treatment of AIDS and COVID-19. Serial preclinical studies demonstrated remarkable anti-tumor activity, especially in combination with anti-PD-1 therapy. The mechanistic studies have shown that FNC could significantly reduce myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment. This ongoing phase 1 investigator-initiated study aims to further confirm the nonclinical findings of FNC in cancer patients. **Methods:** Patients with advanced solid tumors who had progressed on standard of care (SoC) therapies were eligible in this single-arm, single-center, open-label study with the primary objective of safety and clinical efficacy. All subjects received the SoC of physician's choice in combination with FNC which was administered orally once daily, with dose escalated across six dose levels: 3mg, 4mg, 5 mg, 6 mg, 7 mg, and 8 mg. **Results:** As of 31 Oct, 2025, 25 subjects were enrolled, including 22 subjects with pMMR/MSS CRC, 3 subjects with NSCLC. All CRC subjects received the triple-combination regimen of FNC, penpulimab, and fruquintinib. Among the CRC subjects, the total ORR was 18.2%, DCR was 72.7%, the mPFS was 4.3 months (95%CI: 3.32,6.31) and the mOS was 7.6 months (95% CI: 5.09,NR). Four subjects achieved the radiographic response (PR), 2 subjects from the 6 mg dose group, and one subject each from the 5 mg and 7 mg dose groups. A subgroup analysis based on liver metastasis status was performed for the 15 subjects enrolled in the 5 mg, 6 mg, and 7 mg dose groups. The ORR for the 7 subjects without liver metastases was 57.1%, the DCR was 100%, and the mean treatment duration was 33.6 weeks. In contrast, among the 8 subjects with liver metastases, the ORR was 0%, the DCR was 87.5%, and with a mean treatment duration of 16.7 weeks. No DLTs occurred in the 16 evaluable subjects during the DLT observation period. TEAEs were reported in 96.0% of patients, with a TRAE incidence of 36.0%. Most TRAEs were Grade 1/2, including hepatic dysfunction (12.0%), γ-GTP increased (8.0%), weight decreased (4.0%), diarrhoea (4.0%), insomnia (4.0%), and ALP increased (4.0%). One Grade ≥3 TRAE weight decreased occurred in the 3 mg group. SAEs were reported in 24.0% (6/25) of subjects, with only one case of weight decreased in 3 mg group considered possibly related to FNC. Two subjects (8.0%) discontinued treatment due to TEAEs, one of which was abnormal liver function, possibly related to FNC. No treatment related deaths, dose interruptions, or dose reductions were reported. **Conclusions:** Overall, the combination of FNC with PD-1 and VEGFR inhibitors was safe and well-tolerated, with encouraging clinical activity in advanced/metastatic pMMR/MSS CRC. Clinical trial information: chiCTR2600116125. Research Sponsor: None.

3019 **Poster Session**

Discovery from single-cell RNA sequencing profiles of 18 CPTAC glioblastoma patients and validation in bulk profiles of 138 TCGA patients and two human-derived cell lines of a whole-transcriptome predictor of overall survival and drug targets by using quantum mechanics–based AI/ML. First Author: Orly Alter, University of Utah and Prism AI Therapeutics, Inc., Salt Lake City, UT

Background: Single-cell, more than bulk, multi-omic data, are small-cohort, noisy, and high-dimensional, and extremely difficult to model. We have developed artificial intelligence and machine learning (AI/ML) to overcome these challenges [doi: 10.1073/pnas.0530258100]. We have shown that our algorithms are uniquely able to discover accurate, precise, actionable, and mechanistically interpretable predictors, applicable to the general population, from the bulk multi-omes of as few as 19 patients [doi: 10.1158/1538-7445.AM2025-CT227]. We have demonstrated that these predictors of overall survival (OS) and drug targets consistently validate across laboratories and sometimes across indications, in federated and imbalanced studies and over time, and outperform all others where they exist [doi: 10.1063/1.5099268, 10.1200/JCO.2024.42.16_suppl.10043]. Here, we demonstrate our AI/ML in single-cell data. **Methods:** We used our algorithms to derive models from the single-cell RNA sequencing profiles of 18 glioblastoma (GBM) Clinical Proteomic Tumor Analysis Consortium (CPTAC) patients, and tested them in the bulk profiles of 138 patients in the Cancer Genome Atlas (TCGA). CPTAC and TCGA both profiled the core primary tumor of each patient, but CPTAC also sampled the peritumoral brain tissue. The two cohorts are indistinguishable in terms of their gender, age, and OS distributions, but they significantly differ in terms of race. **Results:** A whole-transcriptome model was discovered that is correlated with OS among the 18 CPTAC patients, with a Kaplan-Meier median OS difference of 30 months between the two groups of predictor-stratified patients, and a Cox hazard ratio of 4.6 and a concordance index of 87% (log-rank and Wald P-values $< 5.0\times10$-2). When tested in the TCGA cohort, the model was a similarly significant predictor of OS. In both cohorts, despite the differences in profiling protocols and cohort demographics, the predictor outperformed the best standard-of-care indicator of OS in GBM, i.e., age. Consistent with a previous whole-genome predictor, which was derived from bulk DNA profiles, and validated in a clinical trial [doi: 10.1063/1.5142559], shorter OS was associated with overexpression of such anterior/posterior pattern specification genes as the Notch ligand *DLL3*. We experimentally validated, in two human-derived cell lines, that its putative activator, *METTL2A*, is required for GBM cells' proliferation and viability [doi: 10.1158/1538-7445.AM2025-3686]. **Conclusions:** Our algorithms can discover predictors of patients' OS and drug targets, in real-world small-cohort, noisy, and high-dimensional — single-cell — in addition to bulk multi-omic data, and the predictors experimentally validate. Research Sponsor: NIH/National Cancer Institute (NCI) Physical Sciences in Oncology Project, "Multi-Tensor Decompositions for Personalized Cancer Diagnostics and Prognostics," U01 CA-202144; NSF/American Institute of Mathematics (AIM) Quantum Research Community Project, "AIM Q"; The Musella Foundation in partnership with StacheStrong; Utah Science, Technology, and Research (USTAR) Initiative.

3020 **Poster Session**

Quantum mechanics-based multi-tensor AI/ML as predictor of patients' overall survival, gene targets, and drug responses from their glioblastoma tumors' whole genomes. First Author: Orly Alter, University of Utah and Prism AI Therapeutics, Inc., Salt Lake City, UT

Background: The drug failure rate has increased to ~95%, despite the growth in targeted therapies. As clinical trials demonstrated, a targeted gene alone does not predict whether patients have longer life expectancy in response to the drug. As studies with model organisms showed, the effect of the drug, and the mechanisms underlying it, depend on the entire multi-ome. But multi-omic data are small-cohort, noisy, and high-dimensional, i.e., extremely difficult to model. **Methods:** We have developed our artificial intelligence and machine learning (AI/ML) to overcome these challenges [doi: 10.1073/pnas.0530258100, 10.1158/1538-7445.AM2025-CT227]. We demonstrated our algorithms in the unsupervised modeling of, e.g., whole genomes of 85 astrocytoma patients. Mechanistic interpretation showed that the modeling blindly removed batch effects, separated normal demographic variations, and discovered a disease-specific genome-wide pattern of DNA copy-number alterations. This pattern was used to derive an actionable predictor of patients' overall survival (OS) and gene targets to sensitize their tumors. We computationally validated both the predictor and the modeling in federated studies of mutually-exclusive sets of 59–251 patients. The modeling repeatedly discovered a representation of the predictor in every study, across astrocytoma grades II, III, and IV, i.e., glioblastoma (GBM), patients. We experimentally validated the predictor in a clinical trial of 79 GBM patients, initially retrospectively, and, in a four-year follow up, also prospectively [doi: 10.1063/1.5142559, 10.1145/3624062.3624078, 10.1200/JCO.2024.42.16_suppl.e14028]. In all the cohorts, the predictor, with 75–95% concordance with OS, was more accurate than all standard-of-care indicators. With 100% reproducibility among Complete Genomics, Illumina, and Ultima whole-genome sequencing, and > 99% when including Affymetrix and Agilent DNA microarrays, the predictor was also the most precise. **Results:** Here, we describe functional genomic experimental validation of both a predicted gene target and the predicted tumors' responses to the targeting. Guide RNAs were designed and a lentiviral CRISPR-Cas9 all-in-one vector was utilized to knock out the modeling-predicted target *METTL2A*. Knockout validation at the protein level was performed using Western blot. Knockout in the patient-derived GBM cell lines U-87 MG and U-118 MG resulted in significantly attenuated cell viability and proliferation. The level of attenuation was significantly different between the cell lines, consistent with their whole genome-based predicted responses. **Conclusions:** Our quantum mechanics-based multi-tensor AI/ML solved the 75-year-old problem of correctly predicting — patients' OS, drug responses, and gene targets — from their GBM tumors' whole genomes. Research Sponsor: NIH/National Cancer Institute (NCI) Physical Sciences in Oncology Project, "Multi-Tensor Decompositions for Personalized Cancer Diagnostics and Prognostics," U01 CA-202144; NSF/American Institute of Mathematics (AIM) Quantum Research Community Project, "AIM Q"; The Musella Foundation in partnership with StacheStrong; Utah Science, Technology, and Research (USTAR) Initiative.

3021 **Poster Session**

Development and clinical utility of an H&E-based tumor origin prediction model. First Author: Qiyuan Hu, Tempus AI, Inc., Chicago, IL

Background: Tumor of unknown primary origin remains a critical unmet need in oncology, as histologic and anatomic diagnoses are essential for ensuring effective and timely therapies. We previously developed the Tempus Tumor Origin (TO) Laboratory Developed Test (LDT), an RNA sequencing-based machine learning algorithm that discriminates between clinically relevant cancer subtypes. However, RNA-sequencing data is not always available, with a failure rate that can be $>$ 20% in the literature. In this study, we develop and assess the accuracy of a hematoxylin and eosin (H&E)-based machine learning algorithm to predict tumor origin. We also explore combining predictions from H&E and RNA models to improve accuracy further. **Methods:** We curated a cohort of 93,770 H&E whole slide images (WSIs) of tumor biopsies and surgical resections across 67 cancer subtypes from 73,634 patients. The cohort was split into 60/20/20 for training, validation, and testing, stratified by cancer subtypes and clinical covariates. We extracted tile embeddings from WSIs using a foundation model, H-optimus-0, and trained an attention-based multiple instance learning model to predict cancer subtype labels derived from clinically abstracted documents. Using a subset of 54,878 samples that also have predictions from the RNA-based Tempus TO algorithm, we trained and evaluated a multilayer perceptron multimodal model that takes the prediction scores from the H&E model and the RNA model as input. **Results:** On 7,092 test set samples that had both modalities available, the H&E, RNA, and multimodal models achieved top-1 accuracies of 0.85, 0.91, and 0.92 and top-3 accuracies of 0.94, 0.97, and 0.97, respectively. Among subtypes with at least 30 samples in the test set, the multimodal model statistically significantly outperformed the RNA model on five subtypes and underperformed on two. In addition, the H&E model had a top-1 accuracy of 0.77 and a top-3 accuracy of 0.90 on 3,028 samples in the test set that failed RNA sequencing due to quantity insufficient (QNS). Table 1 presents H&E model performance on the RNA QNS samples by diagnosis subtypes. **Conclusions:** We developed a high-performing H&E-based algorithm to predict tumor origin. With shorter turnaround time and wider availability, the H&E model can potentially deliver accurate tumor origin predictions faster and, critically, in cases where RNA-seq is unsuccessful or unavailable. Furthermore, leveraging both H&E and RNA in a multimodal model may improve the performance of future tumor origin algorithms. Research Sponsor: None.

H&E model performance on RNA QNS test set samples in the five most prevalent diagnosis subtypes and other subtypes combined.

Diagnosis subtype	N	Top-1 accuracy (%)	Top-3 accuracy (%)
Lung adenocarcinoma	497	84	94
Prostatic adenocarcinoma	387	92	95
Breast carcinoma	348	83	95
Colorectal adenocarcinoma	327	85	93
Pancreatic adenocarcinoma	272	78	94
Other	1,197	64	83

3022 **Poster Session**

Prospective prediction of alisertib-induced Aurora-A kinase resistance mutations in patients with metastatic ER+ breast cancer using an innovative artificial intelligence approach. First Author: Andrew Takchi, Mayo Clinic Rochester, Rochester, MN

Background: Pharmacological blockade of Aurora-A mitotic kinase (AURKA) oncogenic pathway represents a promising therapeutic strategy to inhibit breast cancer plasticity and progression. However, treatment with the selective AURKA inhibitor alisertib is followed by acquired on-target mutations in a subset of patients that are linked to alisertib resistance and tumor progression. Current resistance mechanisms are typically identified retrospectively after therapeutic failure. We evaluated whether Dynaptive, a structure- and evolution-aware artificial intelligence (AI) platform, could prospectively predict treatment-induced AURKA resistance mutations prior to experimental observation. **Methods:** We identified acquired on-target mutations in patients from the alisertib Phase-II clinical trial. These mutations were cross-matched against Dynaptive predictions that had been generated independently of any experimental resistance data. Dynaptive integrates protein conformational ensembles and evolutionary sequence constraints to predict mutational hotspots and assess their functional and drug-binding impact. Identified mutations were evaluated against large-scale population datasets to determine natural occurrence. **Results:** Several AURKA mutations observed in patients that showed resistance to alisertib were prospectively predicted by Dynaptive despite being entirely absent from prior population datasets. These mutations were not observed previously in either healthy or cancer cohorts described in the public domain. Significantly, the most frequently occurring AURKA resistance mutation occurred at a residue ranked second among predicted mutational hotspots and were predicted to reduce alisertib binding affinity by $\geq$10-fold. Across all variants, absence from population datasets and emergence only following treatment support a treatment-induced resistance mechanism. **Conclusions:** A structure-aware AI platform prospectively identified clinically relevant, treatment-induced AURKA resistance mutations prior to experimental detection. These findings demonstrate the feasibility of predictive modeling to anticipate resistance mechanisms and support the development of next-generation AURKA inhibitors optimized to overcome mutations-driven resistance and to improve therapeutic efficacy, safety and durability. Research Sponsor: None.

3023 **Poster Session**

Light-activated EGFR antibody–drug conjugate: Analysis of selectivity and translational profile for first-in-human evaluation. First Author: Shirlyn Xiao, Shanghai Biophy Biological Pharmaceutical Co., Ltd., Shanghai, China

Background: Conventional antibody–drug conjugates (ADCs) are limited by systemic toxicity and narrow therapeutic windows. Cetuximab-I21-2 is a first-in-class, EGFR-targeted ADC conjugated to a Heloporfin-derived photosensitizer engineered for activation exclusively at the tumor site using red-light irradiation. This approach enables biologically targeted delivery with externally controlled cytotoxic activation, designed to improve the therapeutic index and support safe translation into first-in-human studies. **Methods:** In vitro cytotoxicity was evaluated across EGFR-high, intermediate, and low tumor cell lines (A431, HCC827, Huh7, NCI-N87, MIA-PaCa-2) with or without red-light activation (1–5 J/cm²). Cellular ROS generation, mitochondrial membrane potential disruption, and photodynamic injury were assessed by live-cell imaging. In vivo activity was tested in A431 xenograft-bearing B-NDG mice following a single intravenous dose of Cetuximab-I21-2 (35.3 mg/kg) and localized tumor irradiation at 100 or 200 J. Safety evaluation included body-weight trends and clinical observations. **Results:** Cetuximab-I21-2 showed negligible dark toxicity up to several μg/mL, confirming that the payload remains inactive without illumination. Upon irradiation, the ADC demonstrated potent, energy-dependent cytotoxicity (IC50: 0.05 μg/mL in A431 and 0.14 μg/mL in HCC827 at 5 J/cm²), with reduced effects in EGFR-low models, supporting a target- and activation-dependent mechanism. Illumination triggered rapid singlet-oxygen and ROS production and immediate mitochondrial depolarization. In vivo, Cetuximab-I21-2 achieved irradiation-dependent tumor suppression, reaching 22.2% inhibition at 200 J, and produced histologic photodynamic injury localized to the tumor. Treatment was well tolerated: animals exhibited only transient ($<$10%) weight loss and no systemic toxicity. **Conclusions:** Cetuximab-I21-2 demonstrates a strong translational profile with selective activation, robust preclinical antitumor activity, and a favorable safety margin. The spatial control offered by light activation may enable dose-sparing strategies and reduce systemic adverse events typically associated with ADCs. These findings support advancement toward IND-enabling studies, including optimization of clinical illumination parameters, device–drug integration, and early feasibility planning for first-in-human evaluation in EGFR-expressing solid tumors. Research Sponsor: Shanghai Biophy Biological Pharmaceutical Co., Ltd.

3025 **Poster Session**

First-in-human study of ALK201, a FGFR2b-targeting antibody-drug conjugate (ADC) for patients (pts) with advanced solid tumors. First Author: Dan-yun Ruan, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: ALK201 is a novel ADC comprising of an anti-FGFR2b humanized monoclonal antibody conjugated to topoisomerase I inhibitor Exatecan via a cleavable and highly hydrophilic linker. ALK201 exhibited potent anti-tumor activities in preclinical studies with a tolerable safety profile. Here we report the preliminary results of ALK201 monotherapy for pts with advanced solid tumors from the first-in-human phase I/II trial (NCT06656390). **Methods:** This is an ongoing, multicenter, open-label study being conducted in the US, China, and Australia, which consists of two parts, dose-escalation (Part A) and dose-expansion (Part B). The Part A employs the Bayesian optimal interval (BOIN) with backfilling (BF) design to determine the MTD and recommended doses for Part B. In Part A, pts with advanced solid tumors refractory to standard therapies were treated with ALK201 at 1.5-9.6 mg/kg Q3W. Part B was dose expansion at effective doses identified in Part A. The primary endpoint was safety. Secondary endpoints included efficacy and pharmacokinetics (PK). **Results:** As of December 31, 2025, 38 pts with advanced solid tumors were enrolled in Part A and dosed at 1.5 mg/kg (n=4), 3.0 mg/kg (n=3), 4.8 mg/kg (n=5) ,7.2 mg/kg (n=12), 8.4 mg/kg (n=5) and 9.6 mg/kg (n=9). The median age was 58 years (range 25-74). All pts progressed after receiving a median of 3 prior lines of standard anti-cancer therapy (range 1-8). 28 (73.7%) were Asian and 10 (26.3%) were White. No dose-limiting toxicities (DLTs) have been observed at doses up to 9.6 mg/kg. MTD was not reached. Treatment-related adverse events (TRAEs) occurred in 78.9% pts. The most common TRAEs (incidence $\geq$10%) were nausea (44.7%), anemia (21.1%), vomiting (21.1%), decreased appetite (13.2%), white blood cell count decreased (13.2%), neutrophil count decreased (10.5%), platelet count decreased (10.5%), AST increased (10.5%), hypoalbuminemia (10.5%) and fatigue (10.5%). Grade $\geq$3 TRAEs occurred in 23.7% pts and were exclusively reversible hematologic toxicities. Treatment related ocular adverse events limited to grade 1 in 4 pts (10.5%) with minimal clinical impact. Among 25 pts who were evaluable for response, 6 achieved a partial response (PR), 11 achieved stable disease (SD) in best of response. The objective response rate (ORR) and disease control rate (DCR) were 24% (95% CI: 9.4, 45.1) and 68% (95% CI: 46.5, 85.1), respectively. The ORR and DCR in $\geq$ 7.2mg/kg groups were 35.7% (5/14) and 100% (14/14), respectively. PK analysis showed a dose-dependent ADC and total antibody exposure at doses of 1.5-9.6 mg/kg. ALK201 elimination half-life was approximately 6-11 days. **Conclusions:** ALK201 demonstrated a favorable safety profile in pts with pretreated advanced solid tumors. Promising anti-cancer activity was observed at doses of 7.2 mg/kg and above, warranting further investigation in those effective dose levels. Clinical trial information: NCT06656390. Research Sponsor: Shanghai Allink Biotherapeutics.

3026 **Poster Session**

Trastuzumab deruxtecan (T-DXd) for pretreated patients in China with HER2 IHC 3+ solid tumors: DESTINY-PanTumor03 Part 1 primary analysis. First Author: Yanqiao Zhang, Department of Gastrointestinal Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China

Background: Treatment options in China are limited for patients with late-line, HER2-expressing advanced solid tumors. In Part 1 of DESTINY-PanTumor02, T-DXd showed clinically meaningful antitumor activity in HER2-expressing advanced solid tumors, with the greatest benefit observed in HER2 IHC 3+ tumors. Based in part on these findings, T-DXd has been approved in multiple countries worldwide, including the US, as treatment for patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment and/or have no satisfactory alternative therapies. Following the results from DESTINY-PanTumor02, DESTINY-PanTumor03 is evaluating T-DXd in patients in China with HER2-expressing advanced solid tumors. The primary analysis of Part 1 of DESTINY-PanTumor03 is presented here. **Methods:** DESTINY-PanTumor03 is an open-label, Phase 2 study (NCT06271837). Part 1 is evaluating T-DXd (5.4 mg/kg IV Q3W) in patients in China with HER2 IHC 3+ (by central testing), locally advanced, unresectable, or metastatic solid tumors (excluding breast and gastric cancers) after ≥1 prior systemic treatment for advanced disease or without treatment options. The primary endpoint is confirmed objective response rate (ORR) by independent central review (ICR) per RECIST 1.1. Secondary endpoints include ORR by investigator assessment (INV) per RECIST 1.1; duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) by INV and ICR per RECIST 1.1; overall survival (OS); and safety. **Results:** At primary analysis data cutoff (November 28, 2025), 50 patients with biliary tract (n = 11), colorectal (n = 6), cervical (n = 10), endometrial (n = 7), ovarian (n = 5), non-small cell lung (n = 7), or other cancers (n = 4) had received T-DXd. Median follow-up duration was 9.9 (range 1.1–18.3) months. Median number of prior treatment regimens was 2 (range 1–10). By ICR, ORR (95% CI) was 58.0% (43.2, 71.8), median DOR (95% CI) was 15.4 (12.5, not evaluable [NE]) months, DCR (95% CI) at Week 6 was 88.0% (75.7, 95.5), and median PFS (95% CI) was 15.7 (7.2, NE) months. By INV, ORR (95% CI) was 56.0% (41.3, 70.0). Median OS was not reached. Grade ≥3 drug-related adverse events occurred in 31 (62.0%) patients, and adjudicated drug-related interstitial lung disease / pneumonitis occurred in 4 (8.0%) patients (Grade 2 n = 3 [6.0%], Grade 3 n = 1 [2.0%]). **Conclusions:** T-DXd demonstrated durable and clinically meaningful antitumor activity in pretreated patients in China with HER2 IHC 3+ advanced solid tumors. Safety was generally consistent with the established T-DXd profile. Results from DESTINY-PanTumor03 Part 1 support T-DXd as a tumor-agnostic treatment for patients in China with HER2 IHC 3+ solid tumors. Clinical trial information: NCT06271837. Research Sponsor: AstraZeneca.

3027 **Poster Session**

Extrapulmonary small cell carcinoma treated with conventional or tumor-targeted topoisomerase I inhibition plus ATR blockade: Clinical outcomes and molecular correlates. First Author: Chirayu Mohindroo, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Extrapulmonary Small Cell Carcinoma (EPSCC) is a rare (0.1–0.4% of all cancers), aggressive neuroendocrine cancer with poor outcomes (Median PFS 2-4 months), no established second-line standard, and limited prospective data. We evaluated ATR inhibition with berzosertib combined with topoisomerase I (TOP1) inhibition with topotecan or sacituzumab govitecan (SG) and explored molecular correlates of response. **Methods:** Given the rare nature of EPSCC, patients were pooled from 3 prospective phase II trials evaluating topotecan or SG with berzosertib (NCT03896503, NCT02487095, NCT04826341) without intent for direct regimen comparison. Eligible patients had platinum-refractory EPSCC and received treatment at recommended phase II doses. Endpoints included efficacy and safety, with exploratory molecular correlates including somatic mutations, copy number alterations, circulating tumor DNA, tumor RNA sequencing, and pharmacogenomic analyses. **Results:** Of the 41 patients enrolled, 34 were evaluable (topotecan+berzosertib, n=20; SG+berzosertib, n=14). ORR based on RECIST was 10% (95% CI, 2.8–30.1) with topotecan+berzosertib and 21.4% (95% CI, 7.6–47.6) with SG+berzosertib; disease-control rates were 45% and 86%, respectively. Durable clinical benefit was observed in subsets of patients, with PFS ≥6.8 months and OS up to 19.7 months in the SG cohort, and OS >18 months in patients treated with topotecan+berzosertib. Patients with prolonged PFS represented multiple primary sites, including bladder, prostate and laryngeal. Grade 3–4 hematologic adverse events were more frequent with topotecan+berzosertib, whereas gastrointestinal toxicity and alopecia were more common with SG+berzosertib; no unexpected safety signals were observed. In the SG cohort, UGT1A1 intermediate and poor metabolizers experienced higher rates (90%) of grade 3–4 toxicities than normal metabolizers (10%). Early ctDNA declines correlated with radiographic response, while rising ctDNA preceded progression; baseline ctDNA correlated with tumor burden (r = 0.83; P = 0.006). Transcriptomic analyses demonstrated enrichment of E2F-driven and neuroendocrine lineage programs in responders (NES = 1.64–1.67; P < 0.001). **Conclusions:** In relapsed or refractory EPSCC targeting tumor replication stress through combined ATR and TOP1 pathway inhibition yielded clinically meaningful activity. Tumor-targeted TOP1 delivery with SG plus berzosertib achieved disease-control rate and a manageable safety profile. UGT1A1 phenotype was associated with toxicity in the SG cohort, supporting the relevance of pharmacogenomic-guided risk stratification. Correlative analyses identified E2F-driven transcriptional programs, neuroendocrine lineage signatures and early ctDNA suppression as promising biomarkers for future trials. Clinical trial information: NCT03896503, NCT02487095, NCT04826341. Research Sponsor: None.

3028 **Poster Session**

First-in-human phase I/II study of MRG006A, a first-in-class Glypican-3 (GPC3)–targeted antibody-drug conjugate (ADC), in patients (pts) with advanced hepatocellular carcinoma (HCC). First Author: Hong Zhao, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China

Background: Pts with advanced HCC face limited treatment options beyond immunotherapy and anti-angiogenic agents. GPC3, a surface antigen overexpressed in HCC and associated with poor prognosis, represents a promising therapeutic target due to its tumor-specific expression. MRG006A, a potential first-in-class GPC3-targeted ADC, demonstrated potent pre-clinical anti-tumor activity. Here we report the preliminary safety and efficacy of MRG006A in advanced HCC with intermediate/high GPC3 expression from a phase I/II trial. **Methods:** MRG006A-001 (NCT07093970) is an ongoing first-in-human, open-label, multicenter phase I/II study. The phase I study comprises dose escalation (Ia) and dose optimization/expansion (Ib) stages. The dose-escalation employed an accelerated titration plus 3+3 design. Eligible pts who had failed standard treatment received MRG006A intravenously at 1.6-6.4 mg/kg every three weeks (Q3W). GPC3 expression was only required for dose expansion cohorts. The primary endpoints were safety and tolerability. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), clinical benefit rate (CBR), etc. **Results:** As of Dec 19, 2025, the maximum administered dose was established as 6.4 mg/kg Q3W, with ≥ G3 treatment-related adverse event (TRAE) of platelet count decreased reported in all six pts at this dose level and dose-limiting toxicity (G4 platelet count decreased) observed in one patient. During dose escalation, tumor response was observed at 3.2 mg/kg and 4.8 mg/kg. Accordingly, dose optimization in phase Ib proceeded with three levels (3.2, 4.0, and 4.8 mg/kg Q3W). Twenty-six HCC pts with intermediate or high GPC3 expression were enrolled across three cohorts; 61.5% had BCLC stage C disease; median 2 (range 1-4) prior lines of therapy, and 25 (96.2%) had received immune checkpoint inhibitors and anti-angiogenic agents. Among 25 efficacy evaluable pts, ORR, DCR and CBR were 23.1%, 68.0% and 32.0%, respectively. In pts with high GPC3 expression (n=12), ORR, DCR and CBR increased to 33.3%, 75.0% and 50.0%, respectively; median PFS and DOR were 7.0 and 4.2 months (median follow-up 5.7 months). Most pts (24 [92.3%]) experienced TRAE of any Grade. TRAEs of ≥ G3 were reported in 11 (42.3%) pts . The most common TRAEs were platelet count decreased (88.5%), blood bilirubin increased (50.0%), AST increased (46.2%), white blood cell count decreased (38.5%), and nausea (30.8%). No treatment-related permanent discontinuations or deaths occurred. **Conclusions:** MRG006A demonstrated manageable safety and promising antitumor activity in heavily pretreated pts with GPC3-expressing advanced HCC. Our findings support the therapeutic potential of GPC3-directed ADC and merits further clinical investigations. Clinical trial information: NCT07093970. Research Sponsor: None.

3029 **Poster Session**

Consideration of adjusted ideal body weight dosing in BG-C9074 (B7-H4–targeting ADC) from pharmacokinetics, efficacy, and safety perspectives. First Author: Hugh Giovinazzo, BeOne Medicines Ltd, San Carlos, CA

Background: B7-H4 is a transmembrane glycoprotein that is upregulated in a variety of solid tumors. BG-C9074 is an investigational topoisomerase I inhibitor antibody-drug conjugate (ADC) that targets B7-H4. We present results of the pharmacokinetic (PK) and exposure-response (ER) analyses supporting the implementation of adjusted ideal body weight (AiBW)-based dosing in the ongoing phase 1 study. **Methods:** BG-C9074-101 (NCT06233942) is a first-in-human, multicenter study designed to assess BG-C9074 as monotherapy and in combination with other anticancer therapies in patients (pts) with advanced solid tumors. Total body weight (TBW) and AiBW-based dosing were evaluated at 1-7 mg/kg and 6.5-9 mg/kg, respectively, administered intravenously every 3 weeks. PK samples were collected to measure serum ADC and plasma free P1021 payload analytes at Cycle 1 and steady state (Cycle 5). A population PK model, incorporating both ADC and payload, was developed and used to evaluate safety and efficacy ER relationships. **Results:** As of October 30, 2025, PK, safety, and efficacy data were available for 107 pts with advanced solid tumors. TBW dosing of BG-C9074 led to a maximum tolerated dose < 7 mg/kg. The ADC and free payload exposures increased with BW for TBW dosing, while ADC clearance moderately increased with BW leading to higher exposure in high BW patients (Table 1). Higher ADC exposure was associated with an increased incidence of Grade ≥3 treatment-related adverse events (TRAEs), predominantly neutropenia. Early dose modifications and use of granulocyte colony-stimulating factor were more frequent at higher doses and exposures. Increased and sustained tumor shrinkage observed in pts with ovarian cancer (OC) with higher ADC exposure. AiBW enabled a higher tolerable dose at 8 mg/kg, by normalizing ADC and payload exposure across all bodyweight ranges. **Conclusions:** AiBW dosing effectively reduced PK variability compared with TBW dosing, providing more consistent exposure across BW. Higher ADC exposure was associated with increased efficacy, but also with a higher incidence of manageable TRAEs. AiBW optimizes the risk-benefit profiles across BW. Clinical trial information: NCT06233942. Research Sponsor: BeOne Medicines Ltd.

	Underweight (<18.5 kg/m^2)	Normal (18.5-24.9 kg/m^2)	Overweight (25-29.9 kg/m^2)	Obese (≥30 kg/m^2)
Simulated Cycle 1 Median ADC exposure at 7 mg/kg TBW (ng/mL)	352	464	533	626
Simulated Cycle 1 Median ADC exposure at 7 mg/kg AiBW (ng/mL)	411	448	464	481
ADC Exposure Tertile	1	2	3	
Grade ≥3 TRAE	16.2% (6/37)	27.8% (10/36)	37.8% (14/37)	
Grade ≥3 Neutropenia	10.8% (4/37)	19.4% (7/36)	27% (10/37)	
Dose modifications	16.2% (6/37)	19.4% (7/36)	27% (10/37)	
Median tumor shrinkage in OC at Week 24 Tumor Assessment (N=25)	−28.9%	−33.3%	−48%	

3030 Poster Session

Phase I study of BL-M05D1, a novel Claudin18.2-directed antibody-drug conjugate (ADC), in patients with locally advanced or metastatic Claudin18.2–expressing solid tumors. First Author: Siyuan Cheng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: BL-M05D1 is a novel Claudin18.2-directed ADC with a potent topoisomerase I inhibitor Ed-04. Results for safety and efficacy data from a phase I study on BL-M05D1 in patients (pts) with locally advanced or metastatic (LA/M) Claudin18.2-expressing solid tumors are presented. **Methods:** Pts who had LA/M solid tumors enrolled in dose escalation and dose expansion phase, and treated with BL-M05D1 at 0.66, 2.0, 3.0, 4.0 or 5.0mg/kg on Day 1 every 3 weeks (D1 Q3W). Gastric cancer/gastroesophageal junction cancer (GC/GEJ), biliary tract cancer (BTC), and pancreatic cancer (PanC) patients with Claudin18.2-expressing enrolled in dose expansion phase were treated at 2.0, 3.0 or 4.0mg/kg D1 Q3W. **Results:** As of Nov 30, 2025, a total of 245 pts were enrolled (87 GC/GEJ, 53 BTC, 104 PanC) and 1 other). The most frequent grade≥3 TRAEs were all hematological, including thrombocytopenia (33.9%), neutropenia (32.7%), leukopenia (31.8%) and anemia (14.3%); non-hematologic TRAEs were relatively low. One pt at 5.0mg/kg group experienced grade 3 febrile neutropenia as a DLT. No treatment-related deaths or ILD were reported. In PanC, BL-M05D1 has demonstrated a promising efficacy with an ORR of 35.7% and mPFS of 5.6 mo at 4.0mg/kg in CLDN18.2-positive pts; in the second line pts, ORR was 50.0% with a mPFS of 5.7 mo. Furthermore, BL-M05D1 has shown promising efficacies in CLDN18.2-positive GC and BTC with an ORR of 39.2% and 37.9%, and mPFS of 5.4 mo and 5.9 mo, respectively, at 4.0mg/kg. Efficacy results are summarized below. **Conclusions:** BL-M05D1 has demonstrated a promising antitumor activity with a tolerable safety profile in pts with pretreated Claudin18.2-positive PanC, GC, and BTC. 4.0mg/kg D1 Q3W was chosen as RP2D. The data support further development of BL-M05D1 in Claudin18.2-positive PanC, GC, and BTC. Phase III studies are in preparation. Clinical trial information: NCT06349811. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

	PanC-Total*	PanC CLDN 18.2 + # 4.0 mg/kg	PanC CLDN 18.2 + # 1 Prior Chemo in 4.0mg/kg	GC-Total*	GC CLDN 18.2 + # 4.0 mg/kg	GC CLDN 18.2 + # 1 Prior Chemo in 4.0 mg/kg	BTC-Total*	BTC CLDN 18.2 + # 4.0 mg/kg	BTC CLDN 18.2 + # 1 Prior Chemo in 4.0 mg/kg
	N = 81	N = 28	N = 16	N = 79	N = 51	N = 29	N = 40	N = 29	N = 20
Median prior LoT (range)	2 (1-4)	2 (1- 3)	/	2 (1-4)	1 (1-3)	/	1 (1-3)	1 (1-3)	/
ORR, % (95% CI)	17.3 (9.8-27.3)	35.7 (18.6-55.9)	50.0 (24.7-75.3)	35.4 (25.0-47.0)	39.2 (25.8-53.9)	44.8 (26.4-64.3)	37.5 (22.7-54.2)	37.9 (20.7-57.7)	45.0 (23.1-68.5)
DCR, % (95% CI)	74.1 (63.1-83.2)	89.3 (71.8-97.7)	100 (79.4-100)	88.6 (79.5-94.7)	88.2 (76.1-95.6)	86.2 (68.3-96.1)	92.5 (79.6-98.4)	93.1 (77.2-99.2)	90.0 (68.3-98.8)
mFU for PFS (mo)	2.8	5.5	4.2	4.4	4.4	4.3	2.8	2.7	2.7
mPFS (mo)	4.0	5.6	5.7	4.4	5.4	7.7	6.9	5.9	5.9

*Efficacy analysis included all pts who received at least one dose of BL-M05D1 and with at least one post baseline scan.
#PanC CLDN 18.2 +: IHC 2+/3+ ≥ 50%; GC CLDN 18.2 +: IHC 2+/3+ ≥ 40%; BTC CLDN 18.2 +: IHC1+/2+/3+≥30%.

3031 Poster Session

HER2-independent antitumor and pharmacodynamic responses to trastuzumab deruxtecan in patients with advanced solid tumors. First Author: Sarah Shin, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody conjugated to topoisomerase 1 inhibitor, deruxtecan, payload that is an effective treatment strategy across several tumor types and various HER2 expressions. The relative contributions of each of the underlying mechanisms driving the broad clinical activity require further elucidation for the ongoing rational development of this promising agent. To this end, our pilot study (NCT04294628) evaluates the pharmacodynamics (PD) of T-DXd in patients (pts) with solid tumors displaying a variety of HER2 expression levels. **Methods:** This multicenter pilot study enrolled pts with HER2-expressing advanced solid tumors as defined by HER2 immunohistochemistry (IHC) score of 1+ or greater or *ERBB2* amplifications (amp) or mutations (mut). Baseline HER2 expression was evaluated by Ventana PATHWAY immunohistochemical (IHC) analysis. T-DXd was administered at 5.4 mg/kg intravenously once every 3 weeks, in 21-day cycles (C), with mandatory tumor biopsies collected at baseline, post-dose C1, and pre-dose C3. Blood samples for biomarker analyses were collected throughout the study. PD biomarkers for topoisomerase 1 (TOP1) target engagement, consequent DNA damage repair (DDR), and tumor immune microenvironment changes were analyzed. Overall response was also evaluated. **Results:** Sixty-one pts received T-DXd. Eligibility HER2 (eHER2) status was determined from pt records: 21 IHC 1+, 22 IHC 2+, 7 IHC 3+, 8 *ERBB2* amp, 3 *ERBB2* mut. Of the 41 pts with baseline biopsies centrally assessed for HER2 (bHER2) by IHC, 13 had bHER2 scores discordant with eHER2, including 8 patients who were eHER2 1-2+ but were bHER2 null. No new safety signals were observed. One pt had a complete response (cervical, bHER2 3+), 14 pts had confirmed partial responses (PR), including 3 who were bHER2 null (2 ovarian, 1 uterine), and 5 pts had unconfirmed PR (uPR). Of the 21 paired biopsies assessable for PD response, 15 demonstrated TOP1 target modulation and 14 of those 15 also demonstrated DDR induction. Substantial tumor infiltration and activation of CD8+ T cells at baseline and/or following T-DXd administration occurred in several patients and were particularly prevalent in those with response. In the one responding patient where lesion-specific analyses were possible, we observed significant diameter reduction (3.9 cm to 1.9 cm) and PD responses in a bHER2 null lesion. **Conclusions:** Clinical responses and target modulation were observed in pts irrespective of bHER2 expression. Lesion-specific analyses provide evidence of antitumor activity and target engagement even in a bHER2-null lesion. Genomic analyses to identify additional molecular determinants of response or resistance to T-DXd are ongoing. This project was funded in part by the National Cancer Institute, National Institutes of Health, under Contract No. 75N91019D00024. Clinical trial information: NCT04294628. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

3032 Poster Session

First-in-human phase 1 study of TQB6411, an EGFR/c-Met bispecific antibody-drug conjugate (ADC), in patients with advanced solid tumors. First Author: Shengxiang Ren, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, Shanghai, China

Background: EGFR and c-Met overexpression are common across various solid tumors. TQB6411 is a novel ADC binding to both EGFR and c-Met with a valency of 1:2 to enhance the affinity to c-Met. Here we report the preliminary results of this first-in-human phase 1 study of TQB6411(NCT07043751). **Methods:** Patients (pts) with advanced malignant tumor who had failed or were intolerant to standard treatment were eligible. TQB6411 was administered intravenously once every 3 weeks. An accelerated titration design was used for the initial dose level (0.8 mg/kg), followed by a conventional 3+3 dose escalation design for the remaining dose levels. The primary endpoints were dose-limiting toxicity (DLT), recommended phase II dose and safety. **Results:** As of December 31, 2025, 26 pts were enrolled and received research treatment (median age [range], 60[33–75] years; 46.2% female). The most common diagnosis was non-small cell lung cancer (NSCLC, 21 pts), followed by esophageal cancer (EC, 3 pts) and colorectal cancer (CC, 2 pts). All pts had received at least one previous line of systemic treatment. Dose group assignments were as follows: 1 in 0.8mg/kg, 3 in 2.4mg/kg, 13 in 4mg/kg, 6 in 5.3mg/kg, and 3 in 6.6mg/kg. By the data cutoff date of January 9, 2026, the dose had been escalated to 6.6mg/kg, with no DLT occurring. The median treatment duration was 3 cycles (rang:1-9). In 22 pts who were followed up for at least 21 days, 19 (86.4%) experienced at least 1 treatment-related adverse event (TRAE). The most common TRAEs included asthenia (54.5%), infusion reaction (50.0%, decreasing to 38.9% in the ≥4 mg/kg dose group after prophylaxis modification), myalgia (27.3%), alopecia (22.7%), and neutrophil count decreased (22.7%). No interstitial lung disease occurred. Only 4 cases of grade 3 AEs (two of neutrophil count decreased, one of allergic shock, one of white blood cell count decreased) were observed in 3 pts and were all attributed to TQB6411. No ≥ grade 4 AEs occurred. In the ≥4 mg/kg dose group, 8 pts received at least one imaging assessment, 4 achieved a partial response (PR), giving an objective response rate of 50.0%. The disease control rate was 100%. The details of efficacy results are shown in the table below. **Conclusions:** In this ongoing phase 1 study. TQB6411 showed an impressive safety profile, with a lower incidence of higher-grade TRAEs (especially lower haematological toxicities), and encouraging efficacy, with tumor responses could be observed even in the relatively lower dose group. Clinical trial information: NCT07043751. Research Sponsor: None.

	4mg/kg (N = 6)	5.3mg/kg (N=2)
PR, n	3 (NSCLC: 2, EC:1)	1(NSCLC)
SD, n	3 (NSCLC)	1 (NSCLC)

3033 Poster Session

Clinical outcomes in phase 1 study of EBC-129, a first-in-class, anti–N256-glycosylated CEACAM5 and CEACAM6 antibody-drug conjugate (ADC), in patients with gastroesophageal adenocarcinomas. First Author: Wei-Peng Yong, National University Cancer Institute Singapore (NCIS), Singapore, Singapore

Background: Gastro-oesophageal adenocarcinoma (GEA) is an aggressive malignancy with limited treatment options. EBC-129 is a first in class MMAE-linked ADC against both, N256-glycosylated CEACAM5 and 6. Previously reported dose escalation data identified 1.8 and 2.2 mg/kg Q3W as the RP2Ds. Here we report pooled safety and efficacy data of GEA patients enrolled in dose escalation (DEs) and expansion (DEx) cohorts of the Phase 1 study (NCT05701527). **Methods:** This study consisted of DEs and DEx cohorts. Previously treated patients with histologically confirmed, locally advanced or metastatic GEA with centrally confirmed immunohistochemistry (IHC) positivity at ≥20% at 2^+ and/or 3^+ on archival samples were enrolled. Objectives were to evaluate safety, efficacy, PK of EBC-129, administered every 3 weeks. **Results:** A total of 21 GEA patients were enrolled (4 in DEs and 17 in DEx). Pre-screening data shows that 57% and 77% are positive in IHC at cut-offs of ≥20% at $2/3^+$ and ≥1% at 3^+, respectively. Patients received 1.2 (n=1), 1.8 (n=9), 2.0 (n=1) or 2.2 (n=10) mg/kg EBC-129 Q3W. 81% were male; mean age 59.0 years; median 3 (range 1-9) lines of previous treatments with 62% prior taxane treated. At data cut-off (9th Jan 2026), 3 patients are continuing treatment, 12 patients had radiological progression, 3 had clinical progression, and 3 patients withdrew from treatment. Among the 17 evaluable patients, the ORR, DCR and median PFS are outlined in the table below. ORR of 50% was seen in patients with an IHC ≥50%. 65% of patients had any tumour shrinkage overall. Infusion related reactions (IRRs) were seen in 43% of patients most being Grade 1/2 and resolved or reduced with premedication; except for 1 patient who had Grade 3 IRR. The other ≥3 Grade TRAEs (CTCAE v5) included neutropenia (52.4%), anaemia (14.3%), WBC count decreased (9.5%), diarrhoea (9.5%); and amylase increase, vomiting, anorexia, nausea in 1 patient each (4.8%). 4 patients (19.0%) experienced peripheral neuropathy (3 grade 1, 1 grade 2). Other than the 1 patient with Grade 3 IRR, no other drug-related discontinuations occurred in this cohort. Higher antigen expression levels correlated with better response. **Conclusions:** EBC-129 shows promising clinical activity in heavily treated GEA patients with a manageable tolerability profile. Further evaluation in 2L GEA is planned. Clinical trial information: NCT05701527. Research Sponsor: National Research Foundation.

Efficacy results from EBC-129-01, GEA cohort.

Dose	IHC status*	ORR^	DCR	mPFS (wks)
1.8 mg/kg	≥20% (n=7)	28.5%	85.7%	18.1
1.8 mg/kg	≥50% (n=4)	50%	100%	29.2
2.2 mg/kg	≥20% (n=8)	25.0%	75.0%	10.1
2.2 mg/kg	≥50% (n=5)	40%	80%	9.3
Overall (All doses)	≥20% (n=17)#	29.4%	82.4%	17.86
Overall (All doses)	≥50% (n=10)#	50%	90%	21.4

*Centrally confirmed IHC positivity at 2^+ and/or 3^+ on archival samples were enrolled; ^Includes one patient with unconfirmed response; #1 patient each at 1.2 mg/kg and 2.0 mg/kg.

3034 **Poster Session**

Real-world effectiveness of sacituzumab govitecan (SG) versus trastuzumab deruxtecan (T-DXd) in HER2-negative (HER2-) metastatic breast cancer (MBC) in China: A propensity-score–matched study. First Author: Biyun Wang, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: SG and T-DXd are both antibody-drug conjugates (ADC) approved in China for HER2- MBC patients. However, direct real-world comparisons between these two therapies in HER2- MBC patients in China remain limited. This study aimed to evaluate and compare clinical outcomes of SG and T-DXd in Chinese patients with HER2- MBC in real-world practice. **Methods:** This retrospective study included 306 HER2- MBC patients, with 151 treated with SG and 155 treated with T-DXd. Separate propensity score matching (PSM) was performed for the triple-negative (TN) and hormone receptor-positive (HoR+) cohorts, respectively. Matching variables for both cohorts included age, HER2 expression, prior ADC use, number and site of metastases (liver, brain), and prior lines of therapy. For TN cohort only, DFI, prior taxane and PD-1/PD-L1 inhibitor use were additionally matched (caliper = 0.1). Clinical outcomes included real-world progression-free survival (rwPFS), overall survival (OS), objective response rate (ORR) and disease control rate (DCR). **Results:** Median follow-up was 13.4 mo (SG-TN), 12.0 mo (SG-HoR+), 12.4 mo (T-DXd-TN), and 12.0 mo (T-DXd-HoR+). After PSM, 33 TN patients and 28 HoR+HER2- patients were matched in each treatment group. Baseline clinical characteristics were well-balanced. In TN patients, rwPFS was comparable between SG and T-DXd (5.0 vs 5.7 mo, HR=0.63, *P*=0.138). The comparable effectiveness of SG and T-DXd was also observed in both HER2-null (*P*=0.498) and HER2-low (*P*=0.250) subgroup. Meanwhile, SG showed a trend toward improved rwOS (NR vs 13.1 mo, HR=1.75, *P*=0.216). However, T-DXd demonstrated significantly higher ORR (18.2% vs 45.5%, *P*=0.017) and DCR (45.5% vs 75.8%, *P*=0.012) compared to SG. In HoR+HER2- patients, T-DXd showed significantly longer rwPFS compared to SG (9.8 vs 5.5 mo, HR=0.41, *P*=0.010), especially among those with HER2-low disease (8.4 vs 5.3 mo, HR=0.36, *P*=0.007); OS data were immature. ORR (14.3% vs 39.3%, *P*=0.035) and DCR (42.9% vs 85.7%, *P*<0.001) favored T-DXd, as well. Subgroup analyses indicated that T-DXd in those with DFI >12 months prolonged rwPFS than SG (10.2 vs 3.5 mo, HR=0.46, *P*=0.036). In HoR+ patients, the median rwPFS was significantly longer in T-DXd group than SG group in the majority of subgroups. **Conclusions:** In this real-world PSM analysis, T-DXd showed improved rwPFS compared with SG in HoR+HER2- MBC patients, while both regimens had generally comparable effectiveness in TN patients. These findings suggest that treatment selection may be influenced by hormone receptor status and the duration of DFI. Further prospective studies are warranted to validate these observations. Research Sponsor: None.

3035 **Poster Session**

BC3195, a novel ADC targeting cadherin-3 (CDH3): Preliminary results of a phase I study in patients with advanced solid malignancies (study BC3195-102). First Author: Madison Conces, Department of Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Cadherin-3 (CDH3), a calcium-dependent adhesion glycoprotein, is overexpressed on lung, breast, ovarian, colorectal, pancreatic, head-neck and other malignancies, but expression on nonmalignant tissue is negligible. CDH3 is essential for cancer cell proliferative signaling and is associated with aggressiveness, invasiveness and poor prognosis. BC3195 is an antibody-drug conjugate (ADC) comprised of an antibody targeting CDH3, a cleavable linker and a monomethyl auristatin E (MMAE) payload. **Methods:** Two phase Ia/Ib studies of BC3195, whose objectives are to evaluate the safety, pharmacokinetics (PK) and preliminary antitumor activity of the ADC, are enrolling patients (pts) with advanced solid malignancies in the US (BC3195-102) and China (BC3195-101). In both studies, BC3195 is administered as a 1-hour (h) IV infusion every 3 weeks. In BC3195-102, dose escalation uses a BOIN design with pre-selected dose levels (DLs) of 1.8 and 2.4 mg/kg and an algorithm to explore lower or intermediate DLs based on safety. **Results:** As of data cut-off (Dec 30, 2025), 16 pts have been enrolled at DLs of 1.2 (3 pts), 1.5 (3 pts), 1.8 (9 pts), and 2.4 mg/kg (1 pt). Fourteen (87.5%) pts had received ≥3 prior treatment. Fatigue (81.3%) and stomatitis (62.5%) were the main adverse events (AEs). Three pts (18.8%) had Grade ≥3 AEs, two of which were Grade 3 stomatitis in the first week post-treatment of Cycle 1 at the 1.8 mg/kg DL of Cohort 1. The dose of BC3195 was subsequently de-escalated to 1.2 mg/kg and then re-escalated to 2.4 mg/kg along with preventative measures, which included ice chip mouth rinses, dexamethasone mouthwash, and B vitamins in the peri-treatment period, and topical steroids for any skin rash. There was no further stomatitis of Grade 3 severity after implementation of these measures; 1 pt had a Grade 3 rash in Cycle 2 at 1.5 mg/kg that responded rapidly to oral steroids. Neither ocular nor neurotoxicity have been noted. Of 16 pts evaluable for tumor response (RECISTv1.1), 3 partial responses occurred in heavily pretreated pts with HER+ breast cancer, prostate cancer, and fibrosarcoma, all of whom were treated at the 1.8 mg/kg DL. Preliminary PK results (1.2-1.8 mg/kg) include med T_{max} values of 1 h for both ADC and total antibody (TA), whereas med T_{max} values for free MMAE range from 65 to 89 h. At 1.8 mg/kg, mean $t_{1/2}$ values are 58 h, 92 h, and 95 h for the ADC, TA and MMAE, respectively. ADC exposure has been highest at 1.8 mg/kg, with mean C_{max} and AUC_{last} values of 31.8 μg/mL and 1297 μg*h/mL, respectively. **Conclusions:** BC3195 has a manageable safety profile, favorable PK characteristics and demonstrated preliminary antitumor activity in several types of heavily pretreated advanced solid malignancies. Based on shared safety data, enrolment in both BC3195-102 (US) and BC3195-101 (China), which is in dose expansion, is converging on the 2.1 mg/kg DL (NCT06548672). Clinical trial information: NCT06548672. Research Sponsor: Biocity Biopharmaceutics Co. Ltd.

3036 **Poster Session**

XNW27011, a Claudin 18.2(CLDN18.2) targeted antibody-drug conjugate (ADC), in patients with CLDN18.2-positive gastric/gastroesophageal junction adenocarcinoma (G/GEJA): A phase 2 study. First Author: Linlin Wang, Affiliated Hospital of Shandong First Medical University, Jinan, China

Background: The prognosis of G/GEJA remains poor, especially in late line patients (pts). mPFS for G/GEJA pts who received ≥ 2 prior lines of standard therapy is 1.6 - 2.6 months (mos). XNW27011 is a novel antibody-drug conjugate (ADC) targeting CLDN18.2, a promising therapeutic target that is aberrantly expressed in patients with G/GEJA. **Methods:** This phase 2 study aims to evaluate the efficacy and safety of XNW27011. Adult pt with advanced solid tumors who has failed standard therapy or is intolerable to available standard therapy/without available standard therapy, and with CLDN18.2 expression in ≥5% tumor cells (TC) with IHC staining ≥2+ (IHC≥2+, TC≥5%, EPR19202) were enrolled, including G/GEJA pts. All patients had measurable disease (RECIST v1.1) and ECOG 0-1. Patients received XNW27011 at 2.4-4.8 mg/kg Q3W. Endpoints included ORR for efficacy, TRAE events for safety and PK parameters. **Results:** As of Dec 29, 2025, a total of 86 eligible G/GEJA pts were enrolled at 2.4-4.8 mg/kg. IHC≥2+, TC≥20% was chosen as the CLDN18.2 expression criteria for further development of XNW27011. Here, we report the results in G/GEJA pts with CLDN18.2 expression of IHC≥2+, TC≥20%. Safety: 71 enrolled pts had CLDN18.2 expression of IHC≥2+, TC≥20%. The median age was 57.0 years, 87.3% of the pts had received ≥2 lines of systemic therapy, 85.9% of the pts had received immune checkpoint inhibitors. The common TRAEs (≥20%) included anemia, nausea, white blood cell count decreased, decreased appetite, neutrophil count decreased, vomiting, weight loss, hypoalbuminemia, asthenia, platelet count decreased, lymphocyte count decreased and hypokalemia. Efficacy: At 3.0 mg/kg, 26 patients were evaluable for efficacy, with 23 and 3 pts had received ≥2 and 1 prior lines of systemic therapy, respectively. The median follow-up(mFU) was 11.3 mos, cORR and cDCR were 65.4% and 84.6%, respectively. mPFS was 5.7 mos and mOS was 11.7 mos. Among the 23 pts who had ≥2 prior lines of therapy, the mPFS was 6.8 mos and mOS was 11.9 mos, with the mFU of 11.5 mos. Notably, one patient previously treated with CLDN18.2-targeted therapy still demonstrated durable clinical benefit, with PFS of 11.3 mos and still remains on treatment as of data cutoff date. Pharmacokinetics: At doses from 0.6 - 6.0 mg/kg in pts with solid tumors including G/GEJA, XNW27011 exposure (C_{max} and $AUC_{0-\infty}$) increased in an approximately dose proportional manner with a half-life of 5~7 days. Across all dose levels, circulating blood payload concentrations were low with 3.3% ADA positive rate. **Conclusions:** XNW27011 demonstrated promising anti-tumor activity and a manageable safety profile in CLDN18.2-positive G/GEJA. A pivotal phase 3 study evaluating XNW27011 as a ≥3 line therapy in G/GEJA pts is currently ongoing. Clinical trial information: NCT06792435. Research Sponsor: Evopoint Biosciences Co., Ltd.

3037 **Poster Session**

First-in-human study of DM002, an anti-MUC1/HER3 bispecific antibody-drug conjugate, in patients with advanced solid tumors. First Author: Xian Jun Yu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: DM002 is a bispecific ADC (BsADC) conjugated to BLD1102, a linker/payload system composed of a linker and a DNA topoisomerase I inhibitor (BCPT02), targeting MUC1 and HER3 with an average DAR value of 8. MUC1 and HER3 are highly co-expressed in several types of solid tumors, for which DM002 has demonstrated robust anti-tumor activity in PDX/CDX models. **Methods:** This is a First-in-human dose-escalation study (NCT06751329). Patients (pts) with advanced solid tumors received DM002 by IV administration from 1 to 6.0 mg/kg Q3W. The classical "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy. Tumor response was evaluated by the Investigators based on RECIST v 1.1. A Safety Monitoring Committee (SMC) was established to determine the dose levels, dose regimen, and the maximum tolerated dose (MTD)/ recommended dose for expansion (RDE). **Results:** As of 28 Dec 2025, a total of 29 pts from China, United states of America and Australia were enrolled and received ≥1 dose of DM002 across 5 dose cohorts. Median age was 61 years (range 45-80). Baseline ECOG scores were 0 (n=8), 1 (n=21) with all pts progressed after an average of 2.5 (range 1-5) prior lines of available standard therapy. There were three dose-limiting toxicities observed in 2 patients at 6.0 mg/kg. The MTD is 4.5mg/kg. Nineteen pts (65.5%) experienced treatment-related adverse events (TRAEs), mainly manifested as hematological toxicity and gastrointestinal reactions. the most common TRAEs (≥15%) including: nausea (37.9%), neutropenia (37.9%), thrombocytopenia (34.5%), anemia (31%), vomiting (27.6%), leukopenia (20.7%), hyponatremia (20.7%), diarrhea (17.2%), alanine aminotransferase increased (17.2%), hypoalbuminemia (17.2%). Most TRAEs were Grade 1-2 and Grade ≥3 TRAEs reported in 12 pts (9 neutropenia, 5 leukopenia, 4 thrombocytopenia, 3 anemia, 2 lymphocytopenia, hyponatremia and febrile neutropenia, 1 aspartate aminotransferase increased, blood bilirubin increased, monocyte count decreased, myelosuppression, hypocalcemia, malaise and infection). No ILD was observed. Among 15 pts having imaging tumor assessment by RECIST v1.1, there were 3 PRs, including 1 pt with prostate cancer and 1pt with ovarian cancer at 3.0 mg/kg, and 1 pt with pancreatic cancer at 4.5 mg/kg, and 8 pts with stable disease (SD). In the 3.0/4.5/6.0 mg/kg dose groups, a total of 8 pancreatic pts underwent imaging tumor assessment, with 1 pt achieving PR, and 5 pts achieving stable disease (SD). **Conclusions:** DM002 is safe and tolerable up to 4.5 mg/kg dose level. In pancreatic cancer, prostate cancer and ovarian cancer, DM002 has demonstrated an encouraging efficacy with a manageable safety profile. The putative RDEs are 3.0 and 3.5 mg/kg which will be further evaluated in phase II trials. Clinical trial information: NCT06751329. Research Sponsor: None.

3038 Poster Session

A phase 1b/2 study of JK06, a 5T4-targeted antibody-drug conjugate (ADC), in patients with unresectable locally advanced or metastatic cancer. First Author: Omar Saavedra, New Experimental Therapeutics (NEXT), Hospital Universitario Quirónsalud, Barcelona, Spain

Background: 5T4, a Type I transmembrane glycoprotein, is over expressed in a broad spectrum of solid tumors. It modulates the CXCR4 & WNT signaling pathways contributing to epithelial to mesenchymal transition contributing to metastatic progression & correlates with poor clinical outcomes among a range of cancers, such as NSCLC, CRC & ovarian. JK06 is a tetravalent, biparatopic DAR2 MMAE ADC targeting 5T4, providing picomolar affinity & enhanced internalization to compensate for generally lower 5T4 expression levels & poor intrinsic internalization kinetics. **Methods:** Pts with advanced relapsed/refractory solid tumors, unselected for 5T4 expression, receive IV JK06 monotherapy once every 3 wks. Dose escalation has been completed, and the study is currently enrolling multiple tumor-specific cohort expansions with randomization across two doses of JK06 to identify an RP2D in NSCLC & breast cancer. Fresh & archival tumor biopsies are being collected for retrospective correlation of 5T4 expression to efficacy & safety. Responses are assessed every 9 wks per RECIST v1.1. Exploratory evaluations of changes in quality of life after JK06 treatment are included in cohort expansions. **Results:** To date, 80 refractory metastatic solid tumor pts (n = 39 in dose esc; n = 41 in cohort expansions) have been treated, median age of 60 yrs, >70% treated with ≥ 3 prior lines of therapy, including >75% of treated pts with prior taxane exposure. Treatment has been well-tolerated with predominantly low-grade treatment-related adverse events (TRAEs) (Gr 1 & 2), such as fatigue (35%), alopecia (18%), decreased appetite (18%), dry eye (10%) & peripheral sensory neuropathy (PSN) (9%). Among 70 pts have sustained JK06-related Gr 3 adverse events (AEs): fatigue, malaise, gait disturbance, keratitis, vomiting, corneal ulcer, & PSN, that resolved, with two continuing treatment with dose reduction; no Gr 4 JK06-related AEs have been observed to date. Four pts underwent dose reductions, and five additional pts were discontinued due to TRAEs. Among 19 response-evaluable NSCLC pts to date, a 32% ORR has been observed, with 1 confirmed complete response (cCR), 4 confirmed partial responses (cPR) (one with CNS response) & 1 with unconfirmed partial responses (uPR), with the longest continuing therapy for 51 wks. Responses have been observed in adenomatous, squamous & EGFR mutant NSCLC pts. One of seven evaluable breast cancer pts (14% ORR) achieved a cPR and remained on treatment for >27 wks. **Conclusions:** To date, JK06 demonstrates promising emerging clinical activity in refractory NSCLC & breast cancer at multiple dose levels while being well tolerated without significant drug-related toxicities. Updated safety & clinical activity data from both dose escalation & expansion cohorts, including the initial assessment of dose randomization, will be presented. Clinical trial information: NCT06667960. Research Sponsor: None.

3039 Poster Session

Efficacy and safety of XNW27011, a Claudin-18.2 targeted (CLDN18.2) ADC, in advanced pancreatic ductal adenocarcinoma: A phase 2 study. First Author: Linlin Wang, Affiliated Hospital of Shandong First Medical University, Jinan, China

Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a historically poor prognosis, the median overall survival (mOS) for PDAC patients (pts) who received ≥ 1 prior lines of standard treatments is only 6.2 to 7.4 months(mos). XNW27011 is a novel and potent Topoisomerase inhibitor (TOP1i)-based ADC targeting CLDN18.2. In preclinical studies, XNW27011 demonstrated antitumor activities in PDAC, supporting its progression into clinical development. Here, we report results of XNW27011 in pts with PDAC. **Methods:** The objectives of this phase 2 study were to evaluate the efficacy and safety of XNW27011 in PDAC, and to optimize doses for subsequent confirmatory trials. Pts with PDAC expressing CLDN18.2 (defined as ≥5% tumor cells with ≥2+ IHC staining) who had received prior systemic therapy were treated with XNW27011 at doses from 2.4 - 4.8 mg/kg, Q3W. The primary endpoint was ORR, secondary endpoints included TRAEs for safety, DCR, PFS, OS, and PK parameters. **Results:** As of Dec 29, 2025, a total of 48 pts had been enrolled with majority of them being enrolled in 3.0 mg/kg group. Among the 48 pts, the ECOG PS was 0 or 1, the median age was 59.0 years. 18 pts (37.5%) had received 1 prior line of systemic therapy. 22 pts (45.8%) had been treated with TOP1i. Efficacy: A total of 30 PDAC pts in the 3.0 mg/kg dose group were evaluable for efficacy. The ORR and DCR was 26.7% and 83.3%, respectively. mPFS and mOS was 4.1 and 10.0 mos, respectively. Among the 13 pts who had received only one prior line of therapy, the ORR was 46.2% and the DCR was 100.0%, mPFS was 4.4 mos, OS was not mature yet. However, the current mOS was 10.1 mos with the median follow-up of 8.1 mos. Detailed efficacy data are presented in the table. Among the pts who were previously treated with TOP1i, the median follow-up was 7.9 mos, the mPFS and mOS were 5.2 and 10.0 mos, respectively. Safety: Among the 48 PDAC pts, the incidence of treatment-related adverse events (TRAEs) was100.0%. The incidence of Grade ≥3 TRAEs and serious TRAEs were 77.1% and 58.3%, respectively. 35.4% and 6.3% of the TRAEs led to dose reduction and discontinuation, respectively. The most common TRAEs included nausea (77.1%), vomiting (64.6%), decreased appetite (64.6%) and anemia (62.5%). Pharmacokinetics: At doses of 0.6-6.0 mg/kg in patients with solid tumors including PDAC, the XNW27011 exposure (C_{max} and $AUC_{0-\infty}$) increased in an approximately dose proportional manner with a half-life of 5~7 days. Across all dose levels, circulating payload blood concentrations were low with 3.3% ADA positive rate. **Conclusions:** XNW27011 showed a manageable safety profile and encouraging survival outcome in pts with PDAC expressing CLDN 18.2, supporting its further clinical development as a promising therapeutic option for patients with PDAC expressing CLDN 18.2. Clinical trial information: NCT06792435. Research Sponsor: Evopoint Biosciences Co., Ltd.

3040 Poster Session

Safety, efficacy, and pharmacokinetics of XNW28012, a tissue factor antibody-drug conjugate (ADC) with topoisomerase 1 inhibitor (TOP1i) payload, in patients with advanced solid tumors: Results from a phase I/II study. First Author: Miaoyan Wei, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Tissue factor (TF) is overexpressed in a broad range of solid tumors including pancreatic ductal adenocarcinoma (PDAC). XNW28012 is the first TF ADC with a novel TOP1i payload. Here we report the safety and PK of XNW28012 in patients (pts) with solid tumors, and the efficacy in PDAC from a Phase I/II study. **Methods:** Eligible pts who failed standard therapy received XNW28012 Q3W. TF expression was not required for enrollment. The primary endpoints for dose escalation and expansion were safety and ORR, respectively. BOIN design was used for dose escalation. Eligible pts with PDAC and other solid tumors were enrolled at 2.0 and 2.4 mg/kg for dose expansion. **Results:** As of Nov. 21, 2025, 313 pts were enrolled (escalation: 16; expansion: 297), with median age of 56.3 yrs; 77.0% of ECOG 1; and 56.9% received ≥2 lines of prior systemic therapy. TEAEs in ≥20% pts were anemia (62.0%), stomatitis (60.1%), nausea (49.5%), WBC count decreased (47.0%), appetite decreased (43.1%), neutrophil count decreased (39.9%), vomiting (39.6%), asthenia (35.5%), weight decreased (30.7%), conjunctivitis (29.4%), rash (28.1%), hypokalemia (23.3%), hyponatremia (21.4%), and hypoalbuminemia (21.1%). ≥Grade 3 TEAEs in ≥5% pts were stomatitis (17.6%), neutrophil count decreased (14.4%), WBC count decreased (12.8%), anemia (11.5%), and lymphocyte count decreased (8.3%). Dose interruption, reduction and discontinuation due to TEAE occurred in 60.7%, 22.0%, and 3.8% of the pts, respectively. Grade 3 conjunctivitis was reported in 2.9% pts across the doses. Most common bleeding AE was epistaxis (12.1%), all grade 1/2. 1 pt at 3.6 mg/kg experienced DLT (grade 4 neutropenia, grade 3 stomatitis). 16 pts were enrolled in dose escalation from 0.6 to 3.6 mg/kg. ORR and DCR were 46.7% and 100%, respectively in 15 evaluable pts including PDAC, ovarian cancer, cervical cancer, and head and neck squamous cell carcinoma. In dose expansion, 45 and 48 PDAC pts were efficacy evaluable at 2.0 and 2.4 mg/kg, with a median follow up of 4.4 m and 6.0 m, respectively. Efficacy data in PDAC pts in dose expansion were summarized in the Table. PK data showed dose proportionality and very low payload exposure in the system indicating stable linker. **Conclusions:** XNW28012 demonstrated a manageable safety profile in heavily treated advanced solid tumor pts and promising anti-tumor activity in PDAC patients. The data support further development of XNW28012 in a broad range of solid tumors including PDAC. Clinical trial information: NCT06799637. Research Sponsor: Evopoint Biosciences Co., Ltd.

Prior line	2.0 mg/kg, 1L (N=25)	2.0 mg/kg, 2L+ (N=20)	2.4 mg/kg, 1L (N=21)	2.4 mg/kg, 2L+ (N=27)
ORR, n (%)	7 (28.0%)	3 (15.0%)	10 (47.6%)	7 (25.9%)
DCR, n (%)	23(92.0%)	18(90.0%)	19 (90.5%)	23 (85.2%)
mPFS, (months)	4.2	4.5	6.4	5.2
mOS, (months)	NC	10.7	14.6	9.0
KM OS rate at 9m (%)	64.5%	51.6%	54.2%	50.5%
KM OS rate at 12m (%)	NC	NC	54.2%	22.9%

NC: Not Calculated.

3041 Poster Session

Non-invasive MRD monitoring and profiling of clonal evolution by ctDNA in patients with advanced cancers treated within molecular tumor boards. First Author: Lavanya Ranganathan, German Cancer Consortium (DKTK), Partner Site Freiburg, a partnership between DKFZ and Medical Center - University of Freiburg, Freiburg, Germany

Background: Profiling of targetable genetic alterations within molecular tumor boards (MTB) guides for personalized treatment selection in patients with advanced cancers. During therapy, response is typically assessed by CT scans or MRI, which often have suboptimal sensitivity and specificity. Circulating tumor DNA (ctDNA) from blood plasma has emerged as a promising biomarker for noninvasive profiling of tumor mutational landscapes and disease monitoring. Here, we applied a pan-cancer next-generation sequencing (NGS) technology to assess the role of ctDNA for comprehensive tumor genotyping, early response prediction, and characterization clonal heterogeneity in patients receiving MTB recommended therapies. **Methods:** We developed and applied a custom targeted NGS approach (ExTARGET), which covers 266 genes across a 540 kb genomic region, to 157 plasma samples obtained at distinct milestones from 57 patients with diverse solid cancers. Plasma samples from healthy individuals (*n*= 24) were used to determine the specificity of our technology. **Results:** We identified variants in 96% of baseline plasma samples by ctDNA profiling, with a median of 7 mutations per patient (range: 1-41). Most frequently mutated genes included *KRAS* (35%), *BRAF* (24%), *ERBB2* (22%) and *TP53* (22%). Targetable tumor variants that led to treatment recommendations within the MTB were found non-invasively in 69% of patients. Longitudinal monitoring of baseline ctDNA variants in on-treatment samples, obtained early during therapy (*n*= 21), revealed that ctDNA dynamics were predictive of disease progression and preceded radiological/clinical progression in 8/19 (42%) patients. All patients with increasing ctDNA levels early during treatment showed radiologic disease progression in subsequent CT scans. On the other hand, an early decrease of ctDNA levels was associated with durable disease control in most patients and significantly favorable progression-free survival (*p*= 0.008; HR = 0.1, 95%CI: 0.02-0.6). Next, we explored temporal clonal heterogeneity in plasma samples collected from 16 patients with disease progression following MTB-recommended therapies. We observed substantial clonal evolution over time, with all samples harboring at least one emerging variant. Among these emerging alterations, 19% were classified as 'oncogenic' and 5% were identified as potentially targetable. **Conclusions:** We here developed an NGS-based technology for ctDNA profiling in heavily pretreated patients receiving MTB-recommended therapies. Non-invasive genotyping from plasma robustly identifies targetable aberrations and allows comprehensive tumor genotyping. Monitoring of ctDNA during treatment and at disease progression facilitates early prediction of treatment response and profiling of temporal clonal heterogeneity that could enable subsequent treatment selection. Research Sponsor: German Cancer Consortium (DKTK).

3042 **Poster Session**

Performance of a tissue-free, molecular residual disease assay in colorectal, breast, and lung cancers from circulating tumor DNA. First Author: Princy Parsana, Natera, Inc., Austin, TX

Background: The Latitude test is a methylation-based, tissue-free molecular residual disease (MRD) test. In this study, we describe the improved performance of the assay in colorectal cancer (CRC) and its performance in an expanded set of indications including breast and lung cancer. **Methods:** The methylation-based, tissue-free ctDNA assay uses next-generation sequencing to query differentially methylated genomic regions in patients with CRC, breast, and lung cancer compared to cancer-free individuals in order to classify plasma samples as MRD positive (MRD+) or MRD negative (MRD-). Performance was evaluated in patients with cancer: CRC (N = 214), breast (N = 153), and lung (N = 148) with known ctDNA-positive results from Signatera (tumor-informed ctDNA testing) across a range of variant allele frequency (VAF) ranges, and cancer-free individuals (training set N = 531, validation set N = 200). Performance metrics, such as percent positive agreement (PPA) and specificity, were evaluated using cross validation in the cancer and cancer-free cohorts, respectively. **Results:** Among 214 CRC patients (VAF range: 0.003%-4.5%), PPA was 95.94% and specificity among all 200 cancer-free individuals was 99.50%. Among 153 breast cancer patients (VAF range: 0.002%-7.8%), PPA was 91.81%, which was maintained across subtypes, including HR+ (94.75%, N = 40), HER2+ (94.45%, N = 20), and triple-negative (87.94%, N = 29). Among the 164 cancer-free females, specificity of the breast tissue-free assay was 98.18%. Among 148 lung cancer patients (VAF range: 0.003%-5.8%), PPA was 92.63%, maintained across subtypes, including non-small cell lung cancer (92.54%, N = 112) and small cell lung cancer (95.23%, N = 25). Among all 200 cancer-free individuals, specificity of the lung tissue-free assay was 99.50%. **Conclusions:** These data demonstrate a high concordance between the Latitude tissue-free MRD assay and a clinically validated tumor-informed ctDNA assay across CRC, breast, and lung cancers, supporting the use of methylation-based biomarkers for informing prognosis and patient management. Research Sponsor: None.

3043 **Poster Session**

Extracellular matrix-derived liquid biopsy for predicting response in patients with biliary tract cancer treated with nivolumab with or without ipilimumab combined with stereotactic body radiotherapy: Insights from the CheckPAC trial. First Author: Martin Birkmose Rasmussen, Nordic Bioscience, Copenhagen, Denmark

Background: Biliary tract cancer (BTC) is a rare malignancy with limited treatment options and poor prognosis. Although combined chemotherapy and immune checkpoint inhibitors are first-line treatment for advanced BTC, durable response is uncommon. Current immunotherapy biomarkers, such as PD-L1 expression, have limited utility and treatment response biomarkers are urgently needed. BTC is characterized by a fibrotic extracellular matrix, where widespread tumor fibrosis has been linked to immunosuppression and treatment resistance. In this study, we used Nordic ProteinFingerPrint Technology to evaluate the pharmacodynamic and predictive value of the FDA supported fibrosis biomarker NordicPRO-C3 (type III collagen pro-peptide) and the T-cell infiltration biomarker NordicC4G (granzyme B degraded type IV collagen) in patients with metastatic BTC treated with nivolumab with or without ipilimumab plus stereotactic body radiotherapy (SBRT). **Methods:** PRO-C3 (NordicPRO-C3) and C4G (NordicC4G) were measured at baseline and 60 days after treatment initiation in serum from 61 patients with BTC from the CheckPAC trial (NCT02866383). Patients received SBRT combined with nivolumab (n = 19) or nivolumab/ipilimumab (n = 42). The primary endpoint was clinical benefit rate (CBR; CR+PR+SD vs. PD) assessed by RECIST 1.1. Biomarker levels at baseline and biomarker changes during therapy were evaluated relative to response using Fisher's exact test; overall survival (OS) was assessed using uni- and multivariate Cox regression. **Results:** CBR was 0% in patients with high baseline PRO-C3 (243 ng/mL) versus 31% in patients with low PRO-C3 ($p < 0.05$). High PRO-C3 was associated with poor OS after adjusting for CA19-9, performance status, and modified Glasgow Prognostic Score (HR = 3.1, 95% CI 1.5-6.6, p = 0.004). Longitudinally, C4G increased significantly at day 60 in patients with clinical benefit ($p < 0.001$). CBR was 44% in patients with increased C4G versus 0% in those with decreased C4G (p = 0.007), and increased C4G was associated with improved OS (p = 0.01). All patients with clinical benefit had both increased C4G and low PRO-C3 at day 60. Among patients without clinical benefit, patients with increased C4G and low PRO-C3 and showed a trend towards improved OS (Median OS 8.3 months vs. 3.6 months, p = 0.08). **Conclusions:** High pre-treatment tumor fibrosis, quantified by elevated serum PRO-C3, is associated with poor response and OS in patients with BTC treated with SBRT plus immunotherapy. Changes in PRO-C3 and the T-cell infiltration biomarker C4G reflect pharmacodynamic changes, with increased C4G linked to improved outcome, particularly in patients with low PRO-C3. Together, these biomarkers may help to predict treatment response and guide clinical decision-making in BTC. Research Sponsor: None.

3044 **Poster Session**

Prognostic impact of MRD positivity at ultra-sensitive ctDNA levels using a WGS-based personalized assay: A pan-cancer analysis from MONSTAR-SCREEN-3. First Author: Tadayoshi Hashimoto, National Cancer Center Hospital East, Kashiwa, Japan

Background: While circulating tumor DNA (ctDNA) demonstrates promise as a molecular residual disease (MRD) biomarker, its clinical implementation has been primarily limited to tumors with favorable ctDNA shedding characteristics. The MONSTAR-SCREEN-3 evaluates a whole-genome sequencing (WGS)-based MRD assay to assess MRD positivity at ultra-sensitive level beyond conventional WES-based MRD, including traditionally low-shedding tumors. **Methods:** MONSTAR-SCREEN-3 is a prospective multicenter study targeting 1,100 patients with solid tumors undergoing curative-intent treatment. Personalized panels were constructed using Precise MRD (Myriad Genetics), incorporating up to 1,000 tumor-specific alterations identified through WGS of matched tumor tissue. Serial plasma samples were collected at baseline, post-neoadjuvant treatment (NAT) (when applicable), 1-month (1M) post-surgery, every 3 months in year 1, and every 6 months thereafter up to 2 years. Assay performance was evaluated across multiple cancer types for ctDNA detection and recurrence monitoring. **Results:** Between May 2024 and November 2025, 1,088 patients across over 20 cancer types were enrolled, including colorectal (n=250), breast (n=156), cervical (n=95), gastric (n=88), and pancreatic (n=69) cancers. Treatment strategies included upfront surgery (n=704), NAT (n=296), and definitive chemoradiotherapy (n=96). Median follow-up was 5.3 months (range, 0–18.1). Baseline ctDNA detection was achieved in 96.2% (684/711), with 16.4% at ultra-sensitive levels (tumor fraction $<$100 parts per million [ppm]). Post-operative MRD positivity was 26.4% (163/617) at 1M and 23.8% (120/504) at 3M, with 46.0% and 41.7% detected at ultra-sensitive levels, respectively. Among 91 patients who received NAT and underwent pathological assessment, post-NAT MRD status demonstrated a sensitivity of 74.3% (55/74) and a specificity of 100% (17/17) for predicting pathological complete response ($P<0.01$). Among patients with available survival data, post-1M MRD positivity was associated with significantly worse disease-free survival (DFS) compared with MRD negativity (HR, 16.9; 95% CI, 8.2–34.8; $P < 0.001$). Furthermore, post-1M MRD positivity at levels below 100 ppm was associated with significantly inferior DFS compared with MRD negativity (HR, 8.2; 95% CI, 3.4–19.4; $P < 0.001$), whereas post-1M MRD positivity at levels $\geq$100 ppm was associated with significantly worse DFS compared with MRD positivity below 100 ppm (HR, 3.4; 95% CI, 1.7–6.7; $P < 0.001$). **Conclusions:** The WGS-based MRD assay demonstrated high baseline detection sensitivity and robust ultra-sensitive detection across diverse cancer types. Our findings show that post-1M MRD positivity below 100 ppm at ultra-sensitive level is prognostic for recurrence risk. Updated molecular and clinical outcome data will be presented. Clinical trial information: UMIN000053975. Research Sponsor: SCRUM-Japan Funds (https://www.scrum-japan.ncc.go.jp/index.html); Myriad Genetics.

3045 **Poster Session**

Comprehensive genomic profiling of matched ctDNA and tissue from patients with four common cancers enrolled to the NCI-MATCH trial. First Author: Rini Pauly, Molecular Characterization Laboratory, Frederick National Laboratory for Cancer Research, Frederick, MD

Background: In the NCI-MATCH trial (NCT02465060), tumor tissue from 5,954 patients with advanced cancers underwent next-generation sequencing using the Oncomine Comprehensive Assay v2 (OCAv2) to determine eligibility. Most tumors lacked a qualifying mutation of interest (MOI) for assignment. Plasma from 1,301 patients with common cancers – [colorectal (COADREAD), breast (BREAST), non–small cell lung (NSCLC), and prostate (PRAD) (OncoTree codes are shown in parentheses)] was analyzed to characterize circulating tumor DNA (ctDNA) and assess its utility for detecting clinically relevant MOIs. **Methods:** Cell-free DNA was extracted from plasma collected in Streck tubes at enrollment. ctDNA profiling was performed using the NCI ctDNA Research v2 assay (523 genes) on the Illumina NovaSeq 6000. Matched tumor tissue was analyzed using OCAv2 (143 genes). Positive percent agreement (PPA) was calculated using tissue as the reference. Blood-based microsatellite instability (bMSI) was assessed across ~2,400 loci, with bMSI-high (bMSI-H) defined as sum Jensen-Shannon Distance (sumJSD) $\geq$0.2. Blood-based tumor mutation burden (bTMB) was defined as total SNVs and indels per Mb. **Results:** Of 1,301 patients, 1,148 (88%) yielded evaluable ctDNA results (COADREAD, n=487; BREAST, n=367; NSCLC, n=220; PRAD, n=74). Overall PPA with matched tissue was 90.3%. Discordant samples had significantly lower median tumor fraction by maximum somatic allele frequency (MSAF; 0.39%) than concordant samples (12.04%). Median MSAF by histology was 14% (COADREAD), 7% (BREAST), 8% (NSCLC), and 5% (PRAD). Clinically relevant fusions detected exclusively in ctDNA included *RET* (1% NSCLC), *EML4::ALK* (2% NSCLC), *FGFR2* (1% COADREAD; 2% BREAST), and *NTRK1* ($<$1% COADREAD and BREAST), corresponding to actionable NCI-MATCH arms [*FGFR2/3* - arm K (erdafitinib), *ALK* - arm F (crizotinib), *NTRK* - arm Z1E (larotrectinib)]. Actionable ctDNA-only mutations in PRAD included *ATM* and MLH1. Twenty-eight cases were bMSI-H (MSAF $\geq$0.02; sumJSD $\geq$0.2), of which 13 were mismatch repair-deficient by tissue testing (MLH1/MSH2 nuclear stain-negative). bMSI-H was most frequent in COADREAD (7%). Ten cases (seven COADREAD, two NSCLC, one PRAD) were MMR-proficient by tissue but bMSI-H by ctDNA. Twenty-four cases had high bTMB ($\geq$20 mut/Mb; MSAF $\geq$0.02), all of which were also bMSI-H. **Conclusions:** ctDNA - tissue concordance NCI-MATCH in these four cancer histologies was high (90.3%), supporting liquid biopsy as a practical alternative when tissue is unavailable. Detection of ctDNA-only alterations highlights tumor heterogeneity in advanced cancers and identifies additional therapeutic opportunities. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

3046 **Poster Session**

Incremental clinical yield of serial large NGS panel liquid biopsies in routine care: Analysis of the STING study. First Author: Camille Mazza, Institut de Cancérologie Godinot, Reims, France

Background: Plasma ctDNA profiling is increasingly repeated over the disease course to capture tumor evolution and newly targetable alterations. However, the incremental clinical yield of serial ctDNA profiling in routine practice remains incompletely characterized. **Methods:** This analysis was conducted within the prospective STING study (ClinicalTrials.gov identifier: NCT04932525), a program that aims to identify actionable molecular targets in patients with advanced solid tumors. Eligible patients were adults with advanced solid tumors and provided written informed consent for molecular analyses. Circulating tumor DNA (ctDNA) profiling was performed using an FDA-approved hybrid-capture next-generation sequencing assay, enabling to analyze over 300 genes, and assessment of tumor mutational burden (TMB) and microsatellite instability (MSI) from plasma samples. All molecular results were reviewed during a weekly institutional Molecular Tumor Board to assess clinical relevance and therapeutic implications. For the present study, patients with ≥2 FMI liquid biopsies were included. The earliest ctDNA test was defined as baseline (BL1), and the second earliest as BL2. Actionable alterations were classified according to the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT). The primary objective was to determine the proportion of patients in whom repeat ctDNA testing identified new actionable alterations not detected at BL1, and their ESCAT tier distribution. **Results:** Among 1,565 patients (3,494 liquid biopsies), the median number of tests per patient was 2 (range 2–6). The most common tumors were lung (26.4%), breast (13.1%), prostate (10.9%), colorectal (CRC) (8.0%), pancreas (6.7%), and thyroid (4.1%). The median BL1→BL2 interval was 313.5 days (range 2–2,279). At BL1, 470 patients (30.0%) harbored ≥1 actionable alteration (ESCAT I–III); excluding TMB-high, 23.9%. Repeat testing identified ≥1 *new* actionable alteration in 316 patients (20.2%); excluding TMB-high, 10.7%. Notably, 227 patients (14.5%) converted from no actionable alteration at BL1 to ≥1 actionable alteration on later testing (8.1% excluding TMB-high). Newly detected actionable alterations were distributed as ESCAT II (54.3%), ESCAT I (26.1%), and ESCAT III (19.7%); 93 patients (5.9%) gained at least one new ESCAT I alteration. The yield of new actionable alterations varied by tumor type (~29% CRC, 25.9% breast, 23.5% lung, 14.6% prostate). **Conclusions:** In a large real-world cohort, serial ctDNA testing provided clinically meaningful incremental detection of actionable alterations in ~1 in 5 patients, including new ESCAT I findings in ~6%. These data support serial ctDNA profiling to capture evolving tumor genomics and expand therapeutic opportunities. Prospective studies should define optimal timing and confirm downstream clinical impact. Research Sponsor: None.

3047 **Poster Session**

Cell-free DNA (cfDNA) methylation-based multi-cancer early detection (MCED) assay to enable subtyping of lung cancer, breast cancer, and non-Hodgkin lymphoma (NHL). First Author: Kezhong Chen, Thoracic Oncology Institute and Department of Thoracic Surgery, Peking University People's Hospital, Beijing, China

Background: Given that distinct pathological and molecular subtypes of most cancers correspond to different treatment strategies, accurate cancer subtyping is clinically critical. Currently, pathological and molecular subtyping relies primarily on tissue biopsy—a procedure that is not always clinically feasible. Additionally, tumor heterogeneity may compromise the accuracy of subtyping via this approach. Prior studies have shown that cfDNA methylation-based detection is tissue-independent and outperforms mutation-based assays in cancer subtyping. Here, we employed a previously developed targeted methylation MCED assay to further classify the subtypes of lung cancer, breast cancer, and NHL. **Methods:** Pretreatment blood samples from lung cancer, breast cancer, and NHL patients enrolled in a MCED study were analyzed via the targeted methylation assay. Only samples with detected circulating tumor DNA (ctDNA) were included. The training cohort comprised lung cancer (n=529: 227 adenocarcinomas, 191 squamous cell carcinomas, 111 small cell carcinomas), breast cancer (n=359: 92 triple-negative breast cancers [TNBC], 267 non-TNBC cases), and NHL (n=157: 145 B-cell lymphomas, 12 T-/NK-cell lymphomas). The validation cohort included lung cancer (n=194: 87 adenocarcinomas, 82 squamous cell carcinomas, 25 small cell carcinomas), breast cancer (n=87: 26 TNBC, 61 non-TNBC cases), and NHL (n=60: 48 B-cell lymphomas, 12 T-/NK-cell lymphomas). cfDNA methylation profiles were analyzed to further classify the subtypes of these three malignancies. **Results:** In the validation cohort, the lung cancer classification model exhibited high overall accuracy 91.8% (178/194), with subtype-specific accuracies of 94.3% (82/87) for adenocarcinoma, 89.0% (73/82) for squamous cell carcinoma, and 92.0% (23/25) for small cell carcinoma. The breast cancer model achieved an overall accuracy of 80.5% (70/87), including 65.4% (17/26) for TNBC and 86.9% (53/61) for non-TNBC. For NHL, the model yielded an overall accuracy of 96.7% (58/60), with 97.9% (47/48) for B-cell lymphoma and 91.7% (11/12) for T-/NK-cell lymphoma. **Conclusions:** The cfDNA methylation-based MCED assay facilitates accurate subtype prediction for common malignancies without the need for invasive tissue biopsy procedures. This assay achieves high accuracy in lung cancer and NHL, whereas relatively lower accuracy is observed for breast cancer, particularly TNBC, owing to its reliance on molecular subtyping. Future studies will validate this assay in larger cohorts and extend its utility to a broader spectrum of cancer types. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co. Ltd.

3048 **Poster Session**

Correlation of presurgical circulating tumor DNA (ctDNA) levels with pathologic (p) stage and lymph node (LN) burden in localized colon cancer. First Author: Masahito Kotaka, Sano Hospital Gastrointestinal Cancer Center, Kobe, Japan

Background: Accurate preoperative staging is vital for tailoring neoadjuvant therapy (NAT) in localized colon cancer. However, clinical staging often diverges from pathological findings due to limitations of imaging modalities in assessing pathologic LN (pLN) involvement and inter-observer variability. This study evaluated the association between presurgical ctDNA levels, microsatellite instability (MSI) status, and pLN burden across pStages I–III in colon cancer. **Methods:** This retrospective study included patients (pts) with pStage I-III colon cancer from the GALAXY study with available presurgical ctDNA levels (mean tumor molecules/mL; MTM/mL) assessed by a personalized tumor-informed assay (Signatera, Natera, Inc). Key exclusions included receipt of NAT, inconsistent pLN classification, pN1c disease, and missing MSI status. Conditional inference tree modeling was used to hierarchically evaluate clinicopathologic and molecular risk factors for their association with presurgical ctDNA levels. **Results:** Of the 3,473 pts (14.4%, 43.1% and 42.5% with pStage I, II and III, respectively) included, 90.2% had microsatellite stable (MSS) tumors. The conditional inference tree partitioned the cohort into five subgroups of distinct presurgical ctDNA level distributions defined by pStage, pLN burden, and MSI status, and demonstrated the pStage to be the strongest determinant of presurgical ctDNA levels. pStage I pts had uniformly low MTM/mL. In contrast, pStage II–III pts had higher and more variable MTM/mL levels, which were stratified by pLN burden and further differentiated by MSI status within each nodal category. Presurgical ctDNA levels were significantly higher in pLN-positive vs pLN-negative pts (median 2.52 vs 1.23 MTM/mL, $p < 0.0001$) and in pStage IIB-III vs pStage I-IIA pts (median 2.64 vs 1 MTM/mL, $p < 0.0001$). While presurgical ctDNA levels did not differ significantly based on MSI status alone, within both MSS and MSI-H subgroups, they were significantly higher in pLN-positive pts vs pLN-negative pts (MSI-H: median 4.40 vs 1.19 MTM/mL; MSS: median 2.41 vs 1.25 MTM/mL). Similar results were observed when grouped based on pStage I/II vs III. Specifically among pLN-positive pts, presurgical ctDNA levels increased with higher pLN burden (MSI-H: median 15.13 vs 3.75 MTM/mL for ≥4 vs 1-3 LN, p=0.049; MSS: median 3.70 vs 1.96 MTM/mL for ≥4 vs 1-3 LN, $p<0.0001$). **Conclusions:** Presurgical ctDNA levels reflect a hierarchical interplay of pathologic stage, lymph node burden, and MSI status rather than any single clinicopathologic factor. High presurgical ctDNA levels reliably correlated with pStage and pLN positivity in localized colon cancer, supporting the development of models incorporating presurgical ctDNA quantification to better select pts for NAT and their evaluation in prospective trials. Clinical trial information: 000039205. Research Sponsor: None.

3049 **Poster Session**

Clinical utility of liquid *KRAS*-mutation screening in advanced pancreatic cancer patients referred for early-phase trials. First Author: Erick F. Saldanha, Divison of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Approximately 90% of pancreatic ductal adenocarcinomas (PDAC) harbor a KRAS mutation. Clinical trials targeting oncogenic *KRAS* mutations, including mutant-specific, pan-KRAS/-RAS inhibitors, have shown promising activity. As tissue next-generation sequencing (NGS) is a multi-step process that can affect turnaround time (TAT), a liquid biopsy (LB) approach is of interest. We investigated the clinical utility of LB testing for common *KRAS* variants to facilitate matching pts with PDAC to early phase trials. **Methods:** In this single-center, prospective enrollment/retrospective analysis study, we included pts with locally advanced (LA) or metastatic PDAC seen at Princess Margaret Cancer Centre (PM) phase I clinical trials and gastrointestinal (GI) cancer clinics between Jan 2025 - Jan 2026. Medical records were reviewed to collect clinicopathologic characteristics and treatment data. Plasma ddPCR assessed 4 *KRAS* codon 12 variants (G12C/D/R/V) at the CAP-CLIA-accredited Advanced Molecular Diagnostics Laboratory at PM. TATs for KRAS ddPCR vs tissue NGS were compared using the Wilcoxon signed-rank test. **Results:** Of 98 pts with LA/metastatic PDAC, the median age was 67 years, 59% were male, and 67 pts were ECOG 1 (88%). 84 pts had disease stage IV (86%), 43 (44%) pts were chemotherapy-naïve, and 33 (34%) pts had 1 prior L of therapy. Median number of metastatic sites was 2 (range [r] 1-5), and median CA19-9 was 343 (IQR 35-1767). *KRAS* G12 mts were detected by ddPCR in 38% (37/98) of pts: G12D (46%), G12V (46%), G12R (5%), G12C (2.7%). The median ddPCR VAF was 4.8% (r: 0.4 - 42.2), median TAT of 5 days (r: 1 - 8). Among pts with *KRAS* detected by ddPCR, 4 (11%) were enrolled in phase I trials targeting *KRAS*. Tissue NGS was performed in 40 pts (41%), KRAS was detected in 90% (36 pts), with a median VAF of 45% (r: 5-90), and median TAT of 54 days (r: 10-92; $p<0.0001$ compared to ddPCR TAT). Reported *KRAS* variants: G12D (50%), G12V (19.4%), G12R (19.4%), Q61H (8.3%), G12C (2.8%). Co-mts in TP53 were seen in 22/36 pts (61%). Concordance between ddPCR and tumor NGS metrics are shown in Table 1. Median NGS VAF of concordant vs discordant cases: 48% vs 21% (p=0.047). **Conclusions:** Plasma-based *KRAS* screening using ddPCR was significantly faster than tissue NGS in advanced PDAC. A liquid-first strategy can accelerate matching pts to RAS-targeted trials, but intense competition for trial allocations limits access to these agents. ddPCR has excellent specificity and PPV across *KRAS* variants but limited sensitivity, thus serves as a rapid rule-in assay. Tissue NGS remains relevant, especially in ddPCR negative pts, and to assess co-mutations. Research Sponsor: None.

N=36 pts	ddPCR(+/-)	NGS (+/-)	Sens	Spec	PPV	NPV	Concordance	Discordance
G12C	1 / 35	1 / 35	100%	100%	100%	100%	100%	0%
G12D	11 / 25	18 / 18	61%	100%	100%	72%	81%	19%
G12R	1 / 35	7 / 29	14%	100%	100%	83%	84%	16%
G12V	5 / 31	6 / 30	83%	100%	100%	97%	97%	3%
All 4 variants	19 / 17	32 / 4	59%	100%	100%	24%	64%	36%

3050 **Poster Session**

ctDNA kinetics throughout first-line AI and palbociclib using a tumor-informed structural variant-based ctDNA assay: Retrospective analysis of PADA-1 samples. First Author: Luc Cabel, Institut Curie, Paris and Saint-Cloud, France

Background: With standard assays (Limit of Detection [LoD95] at or >100 PPM), most patients with ER+/HER2- mBC show ctDNA "clearance" within a few weeks after initiating first- line AI+CDK4/6i, with ctDNA becoming detectable again only at or shortly before progression. To gain a more comprehensive view of ctDNA kinetics in response to therapy, we analyzed serial plasma samples from PADA-1 using a tumor-informed assay with a 100-1,000-fold higher sensitivity (LoD95 <10PPM). **Methods:** PADA-1 allowed the collection of plasma at baseline and every two months during first-line AI+palbociclib (PAL). A total of 489 serial plasma samples from 45 patients in PADA-1 were analyzed using an ultrasensitive structural variant-based ctDNA assay. WGS was performed on tumor material from archival primary or metastatic biopsies, and personalized multiplex dPCR assays tracking up to 16 somatic structural variants were used for ctDNA monitoring. **Results:** At baseline, before AI+PAL start, ctDNA was detected in N=40/41 evaluable patients (98%). ctDNA remained detectable in 381/489 (78%) samples during therapy. ctDNA was persistently detectable and quantifiable (i.e. detected at all timepoints) throughout first-line therapy in most initially positive patients (24/40, 60%). With this ultra-sensitive assay, we report, for the first time, that ctDNA follows a recurrent kinetic pattern: (1) a steep decrease during the first 6 months of treatment, (2) a nadir reached at 6–12 months, and (3) a continuous increase until radiological disease progression (or discontinuation of follow-up). In some patients (15/40, 38%), ctDNA became undetectable at some point during therapy despite the high sensitivity of the assay, with sustained ctDNA clearance associated with no risk of impending tumor progression. **Conclusions:** Serial analyses with a highly sensitive ctDNA test uncover the molecular trajectory of tumor response to first line AI+PAL. The presence of an early ctDNA nadir, followed with a later slow and continuous increase of ctDNA, prior to radiological progression, highlights the dynamic nature of ER+ HER2- mBC response to therapy. This approach can complement imaging-based disease monitoring, extends the clinical utility of ctDNA monitoring beyond individual mutations, and opens new perspectives of therapeutic interventions and treatment adaptation. Clinical trial information: NCT03079011. Research Sponsor: Pfizer; SAGA Diagnostics.

3051 **Poster Session**

Tumor-of-origin prediction using methylation signals from plasma cell-free DNA (cfDNA): Real-world experience in Asia and the Middle East (AME). First Author: Ankur Bahl, Fortis Memorial Research Institute Gurugram, Gurugram, India

Background: Accurate identification of tumor tissue of origin (TOO) is essential for guiding treatment decisions in advanced cancers; however, tissue biopsies may be limited by accessibility, sample adequacy, or diagnostic delays. Plasma cfDNA-based methylation profiling provides a non-invasive approach for TOO determination and has demonstrated high agreement with clinicopathologic diagnoses in prior studies. However, real-world data from AME remains limited. We evaluated the real-world performance of a methylation-based TOO classifier using plasma cfDNA in this population. **Methods:** We retrospectively analyzed plasma cfDNA samples from patients with advanced solid tumors tested across AME using the Guardant360 Liquid assay through December 2025. The assay interrogates epigenomic signals from >19,000 methylated regions. The TOO classifier assigns a ranked cancer signal of origin (CSO) based on tumor-specific methylation patterns, reporting a primary CSO prediction and, when confidence is intermediate, a secondary CSO prediction. CSO confidence is quantified algorithmically based on methylation signal strength and classification certainty. Only samples with medium (50–80%) or high (>80%) confidence predictions were included. All tests were ordered as part of routine clinical care, and available clinicopathologic diagnoses (CPD) served as the reference standard. **Results:** Among 1,782 cfDNA-profiled samples, 1,230 (69%) yielded a CSO prediction with medium or high confidence. The primary CSO prediction matched CPD in 85% of cases overall, increasing to 91% when secondary CSO predictions were included. Tumor-type–specific accuracy varied, with the highest performance observed for colorectal, breast, and prostate cancers (94% each). Agreement with CPD was lower for gastroesophageal (72%) and kidney cancers (68%). Among 114 cancer of unknown primary (CUP) cases, a suspected clinical diagnosis was available for 48. Medium- or high-confidence CSO predictions were generated in 42 (87%). CSO predictions aligned with subsequent clinicopathologic consensus or confirmatory biopsy in 35 (83%), spanning 13 tumor types, most commonly lung cancer (24%). Therapy response evaluation was available for 12 patients, with partial response in 9 (75%) and stable disease in 3 (25%). **Conclusions:** In this real-world AME cohort, the TOO classifier identified probable tumor tissue of origin in most advanced cancer patients. CSO predictions showed high agreement with CPD across multiple tumor types. This approach demonstrated potential value in resolving CUP cases, with the predicted origin confirmed in 83% of evaluable patients. These findings support the clinical feasibility of methylation-based tumor-of-origin testing in AME and warrant further studies to evaluate its impact on clinical decision-making. Research Sponsor: Guardant Health Pte. Ltd., Singapore.

3052 **Poster Session**

Tissue-free minimal residual disease evaluation and clinical utility in early breast cancer: A real-world study. First Author: Tanmayi Pai, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Minimal residual disease (MRD) detected using circulating tumor DNA (ctDNA) is associated with increased breast cancer (BC) relapse risk in patients (pts) with early BC after curative-intent surgery. However, the clinical utility of ctDNA-based MRD testing for post-surgical surveillance and risk stratification remains incompletely defined. We used real-world data to evaluate the performance of Guardant Reveal, a tissue-free epigenomic assay for MRD detection, and the clinical significance of a positive MRD test (+MRD) in pts with resected early BC. **Methods:** Data of pts with resected stage I-IIIA BC in the Guardant InfinityAI Data Library who underwent Guardant Reveal testing between February 2023 and September 2025 was analyzed. Pts with ≥1 post-surgical MRD were included if they had either no distant metastatic BC recurrence with ≥1 year of follow up after the last MRD test or a documented distant metastatic BC postoperatively; pts with a new non-breast primary malignancy were excluded. Sensitivity was assessed by site of distant metastasis and interval from MRD test to recurrence; nodal recurrences were excluded due to claims data limitations. Specificity was assessed using all tests from pts without recurrence and ≥1 year of follow up after the last post-treatment MRD test. Claims data were used to infer treatment changes following +MRD. **Results:** A total of 822 pts was analyzed. 114 pts with real-world clinico-genomics data were evaluable for sensitivity and 708 for specificity. One-year sensitivity for distant metastatic recurrence was 71%, and was highest for bone-only (97%, 35/36 cases) or lung (89%, 8/9 cases) recurrences and lowest for brain-only recurrences (33%, 1/4 cases). Sensitivity within 12 months of recurrence was higher in hormone receptor-positive (HR+)/HER2-negative BC (79%) and stage IIIA BC (81%) and for multiple-organ versus single-organ metastasis (83% versus 69%). Sample-level specificity was 94%. Following +MRD, 41 pts did not initiate or switch systemic therapy; 29 had distant BC recurrence, including 24 within 90 days after +MRD. Twenty pts switched therapy within 90 days of +MRD; 19 recurred, including 17 within 90 days after +MRD. Among 10 pts with post-recurrence MRD testing, only 3 had +MRD. **Conclusions:** In a real-world cohort of pts with resected early-stage BC, a tissue-free epigenomic ctDNA MRD assay demonstrated high specificity and clinically meaningful sensitivity for distant metastatic recurrence, particularly for bone-only and lung metastases and in pts with HR+ BC. These findings support ctDNA-based MRD testing as a noninvasive tool for postsurgical surveillance and risk stratification in early BC. Research Sponsor: None.

3053 **Poster Session**

Early ctDNA dynamics assessed by a personalized whole-genome sequencing-based assay as a predictor of outcomes with immune checkpoint blockade in advanced melanoma. First Author: Mora Guardamagna, Department of Cancer Medicine, Gustave Roussy Cancer Campus, Villejuif, France

Background: Circulating tumor DNA (ctDNA) is an emerging biomarker for assessing treatment outcomes and monitoring disease recurrence in melanoma. However, evidence supporting its clinical utility at very early on-treatment timepoints remains limited. We evaluated whether ctDNA dynamics relative to a single cycle of immune checkpoint blockade (ICB) are associated with treatment outcomes in patients (pts) with advanced melanoma. **Methods:** In this prospective, single-center cohort, pts with unresectable stage III or IV melanoma were enrolled. Treatment included anti-PD1 monotherapy (n=22, 40%) or anti-PD1+anti-CTLA-4 therapy (n=33, 60.0%). ctDNA analysis was performed using a personalized, tumor-informed assay (Signatera Genome, Natera, Inc.) designed from WGS of matched tumor and normal pairs. ctDNA (reported in mean tumor molecules per mL, MTM/mL) was subsequently tracked in the pts' longitudinal blood samples, which were collected at baseline (T0) and prior to cycle 2 (T1; 3-4 weeks after ICB initiation). ctDNA dynamics were categorized as favorable (ctDNA clearance at T1 or >10-fold decrease from T0 to T1) or unfavorable (rising ctDNA or <10-fold decrease from T0 to T1). Associations between these categories and progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier estimates and Cox proportional hazards models. **Results:** A total of 55 pts with unresectable stage III (n=12, 21.8%) or stage IV (n=43, 78.2%) melanoma were included. Median follow-up was 36.43 months (mo) (range, 31.47-41.39). ctDNA-positivity was 83.6% (46/55) at baseline and 80.0% (44/55) at T1. Table 1 summarizes survival outcomes per ctDNA profile. Pts with an unfavorable profile (UP) of ctDNA dynamics experienced worse PFS and OS in contrast to those with a favorable profile (FP). Median PFS was 2.1 mo in the UP group versus 28.8 mo in the FP group; median OS was 19.3 vs 37.8 mo, respectively. All pts (n=21, 100%) with progressive disease had an UP, including 52.3% (11/21) with rising ctDNA and 47.7% (10/21) with <10-fold decrease. Median ctDNA levels at T1 were also higher in pts without objective response compared with responders (56.69 vs 0.38 MTM/mL; p<0.001). **Conclusions:** ctDNA dynamics assessed by a personalized WGS-based assay after a single cycle of ICB were strongly associated with response and survival outcomes in advanced melanoma. These findings support the evaluation of treatment-adaptation strategies based on early ctDNA dynamics in pts receiving immunotherapy. Research Sponsor: None.

ctDNA profile	median PFS (mo)	6-mo PFS	12-mo PFS	PFS HR (95%CI) p-value	median OS (mo)	6-mo OS	12-mo OS	OS HR (95%CI) p-value
Favorable N=24	28.8	100% (24/24)	91.7% (22/24)	Reference	37.8	100% (24/24)	100% (24/24)	Reference
Unfavorable N=31	2.1	22.6% (7/31)	22.6% (7/31)	5.29 (2.39–11.75) p<0.001	19.3	80.6% (25/31)	67.7% (21/31)	9.96 (2.66–37.37) p<0.001

3054 **Poster Session**

A population tumor kinetics analysis for early-cycle ctDNA-guided therapy decisions in DLBCL. First Author: Kunhee Kim, University of Connecticut School of Medicine, Hartford, CT

Background: Early circulating tumor DNA (ctDNA) kinetics may be instrumental in identifying patients with DLBCL who can safely discontinue therapy after three cycles, as well as those who are less likely to benefit from completing the full six cycles. However, the optimal timing for ctDNA measurement, added value of early cycle data, and influence of assay sensitivity remain uncertain. Through population tumor kinetics (pop-TK) modeling of Pola-R-CHP (Pomeroy et al., Blood Cancer Discovery, 2025), we evaluated how adding data from cycles 1 and 2 enhances risk stratification beyond the assessment conducted after cycle 3. **Methods:** A 5-drug pop-TK model calibrated to Pola-R-CHP single-agent sensitivity distributions and clinical outcomes simulated tumor cell populations and patient-level parameters. Predicted residual disease after each cycle was mapped to ctDNA titers under assays of varying detection thresholds, representing conventional ctDNA, high-sensitivity ctDNA, and PET. We evaluated (1) ctDNA negativity at cycle three only, (2) adding cycles 1 and 2 for prediction, and (3) using cycles 1 and 2 to identify non-responders. For detection thresholds, representative values were selected to reflect overall trends. **Results:** Among ctDNA-negative patients at cycle 3 (n=557), stopping therapy at cycle 3 led to a recurrence rate of 0.172, while completing six cycles eliminated all recurrences. Adding ctDNA from cycles 1 and 2 separated cycle 3-negative patients into a high-risk group with much higher recurrence (90/121; 0.744) and a low-risk group with very low relapse risk (6/436; 0.014). Across assay sensitivities, high-sensitivity ctDNA reduced recurrence after cycle 3 cessation to 0.093 (43/464), whereas PET-level sensitivity showed a higher recurrence rate (0.288; 171/593), and adding data from cycles 1 and 2 consistently improved sensitivity. Early-cycle ctDNA (C1, C2) stratified patients into a high-risk non-responder group (5-year PFS 0.009), who can benefit from transferring treatment plans, and a low-risk group with favorable outcomes (5-year PFS 0.961). **Conclusions:** Pop-TK modeling suggests that although most patients with cycle 3 ctDNA negativity do not relapse when treatment is continued through cycle 6, some patients may still experience relapse that might not have occurred if treatment had been completed through cycle 6. Adding early cycles produces a large low-risk subgroup, supporting safer de-escalation, while still identifying patients who will consistently relapse if therapy is stopped early. Higher assay sensitivity reduces false negatives, but early-cycle ctDNA remains very informative. Furthermore, early cycle ctDNA enables identification of non-responding patients before completion of therapy. These findings support the addition of early cycle ctDNA into response-adapted de-escalation and early treatment switching in trials for DLBCL treated with Pola-R-CHP. Research Sponsor: None.

3055 **Poster Session**

Multi-omics discovery and clinical validation of COL1A2 alternative splicing isoforms as liquid biopsy markers for metastasis surveillance in osteosarcoma. First Author: Junqiang Yin, Department of Musculoskeletal Oncology Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Osteosarcoma (OS) is characterized by early metastatic dissemination, yet the lack of sensitive and tumor-specific tools for real-time surveillance remains a major barrier to improving patient outcomes. **Methods:** We performed an integrative multi-omics analysis of 424 OS patients, incorporating whole-exome sequencing, bulk RNA sequencing, short-read single-cell RNA sequencing, and single-cell long-read transcriptomics to resolve isoform-level AS alterations at single-cell resolution. Candidate isoforms were evaluated across plasma and peripheral blood datasets from 346 healthy controls to assess tumor specificity. Translational utility was tested in a prospective clinical trial (ChiCTR2400079438), comparing COL1A2 isoform–based circulating tumor cells (CTCs) detection with conventional VIM/TWIST1-based CTC assays and tumor-informed circulating tumor DNA (ctDNA) profiling. **Results:** OS exhibited widespread alternative splicing dysregulation across both tumor and stromal compartments, with extensive isoform remodeling revealed by single-cell long-read transcriptomics. Two metastasis-associated COL1A2 isoforms were detected in 98% of OS tumor cells but were entirely absent in healthy controls, demonstrating high tumor specificity. COL1A2 isoform–based CTCs detection significantly outperformed VIM- or TWIST1-based assays for predicting metastasis (AUC 0.833 vs. 0.531, $P < 0.01$) and achieved accuracy comparable to circulating tumor DNA (ctDNA) assays (AUC 0.833 vs. 0.861, P = 0.78). Notably, COL1A2 isoform–based CTCs detected metastatic progression 5.11 months earlier than conventional imaging, approximately two months earlier than ctDNA. Longitudinal analyses further revealed frequent loss of primary tumor–derived mutations during metastatic evolution, limiting the sensitivity of tumor-informed ctDNA assays, whereas COL1A2 isoform–based CTC detection remained robust. **Conclusions:** Collectively, this study provides the first systematic comparison of CTCs- and ctDNA-based surveillance strategies in OS and establishes COL1A2 isoform-based CTCs detection as a sensitive, specific, and mutation-agnostic liquid biopsy strategy. Clinical trial information: ChiCTR2400079438. Research Sponsor: None.

3056 **Poster Session**

Integrating tumor mutation profiles, preoperative circulating tumor DNA (ctDNA), and clinical features to a predicting model for early peritoneal recurrence in stage II-III gastric cancer following curative gastrectomy. First Author: Quang Thong Dang, Department of Gastrointestinal Surgery, University Medical Center, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh, Viet Nam

Background: Peritoneal recurrence is the common failure pattern after curative gastrectomy and is most consequential within the first 2 years. Early risk identification can alter treatment strategy. Conventional clinicopathologic models are inadequate for individualized early detection. Tumor-informed circulating tumor DNA (ctDNA) enables detection of minimal residual disease (MRD) and may help refine risk stratification. **Methods:** We conducted a prospective cohort study of 134 patients with stage II–III gastric adenocarcinoma undergoing curative-intent gastrectomy (MRD cohort). Clinicopathologic variables, tumor mutation profiles, and ctDNA metrics were integrated to train and internally validate machine-learning models using logistic regression, random forest, and XGBoost for the primary endpoint of peritoneal recurrence within 12 months and 24 months after surgery. External validation was performed using the Yang et al. dataset. **Results:** Among 134 MRD patients with complete molecular and clinical data, 19 (14.2%) and 35 (26.1%) developed peritoneal recurrence within 12 months and 24 months, respectively. ctDNA positivity and higher max variant allele frequency (max VAF) were strong predictors of early peritoneal relapse, with additional contributions from pathologic stage and preoperative CEA, PI3K–AKT or EMT pathway genes. Across algorithms, ctDNA-integrated models consistently outperformed clinical-only baselines, with XGBoost showing the best overall discrimination on cross-validation. Findings generalized on external validation with the Yang et al. dataset, supporting model transportability. **Conclusions:** Integrating tumor-informed ctDNA with clinical and genomic features enables actionable prediction of early peritoneal recurrence after curative gastrectomy. This tool can trigger strategy modification of either stricter follow-up, adjuvant therapy intensification, or consideration of neoadjuvant approaches, in selected high-risk patients. Multicenter validation and prospective utility studies are warranted. Clinical trial information: NCT05029869. Research Sponsor: None.

3057 **Poster Session**

A prospective study of tumor-informed ctDNA minimal residual disease detection in bone and soft tissue sarcomas. First Author: Junqiang Yin, Department of Musculoskeletal Oncology Center, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: The high recurrence and metastasis rates lead to poor survival of patients with sarcoma. Conventional imaging often detects relapse at a relatively late stage. In our previous study, circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) detection demonstrated strong prognostic value in osteosarcoma, enabling earlier detection of recurrence compared with radiographic surveillance. However, whether this approach is applicable to soft tissue sarcomas and the broader sarcoma population remains unclear. **Methods:** Between August 2020 and March 2024, patients with sarcoma were prospectively enrolled at a single center. Tumor-informed MRD assays were designed using whole-exome sequencing of paired tumor–normal samples. Longitudinal postoperative plasma samples were collected for ctDNA analysis. Survival outcomes were assessed using Kaplan–Meier analysis with log-rank tests. Multivariable Cox proportional hazards regression was performed adjusting for age, sex, tumor necrosis score, and histologic subtype (osteosarcoma vs non-osteosarcoma). **Results:** A total of 121 patients were included, comprising 74 bone-origin sarcomas (72 osteosarcomas) and 47 soft tissue sarcomas; 77 patients were male and 44 were female. With a median follow-up of 21.7 months, postoperative ctDNA positivity was strongly associated with inferior survival. Median relapse-free survival was 6 months in ctDNA-positive patients versus 43 months in ctDNA-negative patients ($P < 0.001$). This prognostic separation remained significant across early ($\leq$1 month), intermediate (1–6 months), and late ($>$6 months) postoperative time windows. In multivariable Cox analysis, postoperative ctDNA status remained an independent prognostic factor (HR = 5.20, 95% CI: 2.07–13.08; $P < 0.001$). In 19 patients, ctDNA positivity preceded radiographic evidence of recurrence, with a mean lead time of approximately 3 months. Notably, 56 patients with persistently negative postoperative ctDNA experienced no recurrence or metastasis during follow-up. **Conclusions:** Tumor-informed ctDNA-based MRD detection is applicable to a broad range of sarcoma subtypes and provides robust prognostic information following surgery. These findings support the role of ctDNA as an early biomarker for disease recurrence in sarcoma. Clinical trial information: ChiCTR2400083045. Research Sponsor: None.

3058 **Poster Session**

Leveraging a hybrid tumor-informed and tumor-agnostic ctDNA assay for optimal ctDNA-MRD detection: A real-world study in Southeast Asia. First Author: Anh Nguyen, Medical Genetics Institute, Ho Chi Minh, Viet Nam

Background: While tumor-informed ctDNA assays are the gold standard for minimal residual disease (MRD) detection, their utility is frequently limited by suboptimal tissue quality and quantity. This study evaluated a hybrid strategy combining personalized tumor-informed mutations and a tumor-agnostic hotspot panel to improve ctDNA-MRD detection in a real-world patient cohort. **Methods:** We retrospectively analyzed 1015 blood samples of 577 patients diagnosed with stage I-IV lung (n=222), colorectal (n=172), and breast (n=143) cancers. The hybrid assay (K-4CARE, Gene Solutions) integrated patient-specific variants with a cancer-specific tumor-agnostic hotspot panel (K-4CARE, Gene Solutions). ctDNA status was correlated with clinical outcomes in 200 early-stage patients (median follow-up $>$6 months) and 59 metastatic-stage patients. **Results:** The hybrid approach significantly outperformed the tumor-informed method, increasing pre-treatment ctDNA detection rates by 33.3–48.8% in cases with suboptimal tissue quality. In the early stage, post-operative ctDNA was detected in 93.5% (29/31) of the patients having recurrence, with the median lead time of 8.4 months; while 97.6% (165/169) of those with no recurrence had negative results. ctDNA positivity was an independent prognostic factor ($p<0.001$) that increased recurrence risk in lung (HR=145.4; 95% CI: 37.4-564.5), colorectal (HR=173.6; 95% CI: 19.7-$>$300.0), and breast (HR=147.8; 95% CI: 26.3-$>$500.0) cancers. In the metastatic stage, at 12 weeks after therapy initiation, 85.3% (29/34) of the molecular responders, who had ctDNA cleared or reduced by $>$50% of baseline VAF level, achieved clinical partial response or stable disease; while 88.0% (22/25) of the molecular non-responders had confirmed progressive disease. Notably, the tumor-agnostic hotspot panel helped identify new and resistance mutations, including EGFR T790M in lung (20.0%), ESR1 Y537N (7.1%), ESR1 Y538G (3.6%), ESR1 P535H (1.8%) in breast (12.5%), and KRAS G12D in colorectal (25.0%) cancers. **Conclusions:** This hybrid approach improved sensitivity to detect ctDNA-MRD, and the capability to identify emergent resistance mutations provides expanded clinical utility for longitudinal monitoring. Research Sponsor: Gene Solutions JSC, Ho Chi Minh city, Vietnam.

3059 **Poster Session**

Cell-free DNA fragmentomics as an enabler of tumor-of-origin classification using a commercial targeted cfDNA panel. First Author: Kyle Helzer, Department of Human Oncology, University of Wisconsin-Madison, Madison, WI

Background: Analysis of cell-free DNA (cfDNA) fragmentation patterns ("fragmentomics") has emerged as a powerful approach for cancer detection and classification, but most prior studies rely on whole-genome or research-grade sequencing. The feasibility and performance of fragmentomics using commercial targeted cfDNA next-generation sequencing (NGS) panels used in routine clinical care remain unclear. We evaluated whether fragmentomics metrics derived from the Tempus xF targeted cancer exon panel could accurately classify tumor type. **Methods:** We analyzed cfDNA sequencing data from 1,950 patients across 10 cancer types sequenced on the Tempus xF clinical NGS panel (105 genes), split a priori into training (n=1,455) and validation (n=495) cohorts. Exon-level fragmentomics features were extracted, including fragment size distributions, Shannon entropy, normalized read depth, proportions of short fragments, fragment size bins, motif diversity, and chromatin-context–specific entropy metrics. Elastic-net regression models were trained to classify tumor type using 10-fold cross-validation, with area under the receiver-operating characteristic curve (AUROC) as the primary endpoint. Model performance was independently evaluated in the validation cohort, including stratification by circulating tumor DNA (ctDNA) fraction. **Results:** In cross-validation of the training cohort, a combined fragmentomics model achieved a median AUROC of 0.790 across cancer types. In independent validation, the combined model maintained robust performance with a median AUROC of 0.794. Prostate, breast, and ovarian cancers demonstrated the highest discrimination (validation AUROCs up to 0.952 and 0.936 for prostate and breast cancer, respectively). Performance improved substantially in samples with higher tumor burden: among validation samples with ctDNA fraction $\geq$10% (85.2% of cases), the median AUROC increased to 0.815 compared with 0.719 in low ctDNA samples. **Conclusions:** Fragmentomics analysis applied to an existing commercial targeted cfDNA panel enables accurate tumor-of-origin classification without additional sequencing or assays. These findings demonstrate a scalable strategy to extend the diagnostic capabilities of routine clinical cfDNA testing and support the integration of fragmentomics into real-world liquid biopsy workflows, particularly in patients with sufficient ctDNA fraction. Research Sponsor: None.

3060 **Poster Session**

Ultrasensitive tumor-informed ctDNA MRD detection to identify metastatic relapse and as predictor of recurrence-free survival following resection of early-stage NSCLC. First Author: Fernando Pikabea Díaz, Division of Medical Oncology, Princess Margaret Cancer Centre/University Health Network, Toronto, ON, Canada

Background: After curative-intent resection of non-small cell lung cancer (NSCLC), patients remain at risk for metastatic relapse and development of second primary malignancies. Circulating tumor DNA (ctDNA) molecular residual disease (MRD) detection has prognostic value, but sensitivity in early-stage disease has been limited. We evaluated an ultrasensitive tumor-informed whole-genome sequencing (WGS) assay that leverages phased variants (PVs) for longitudinal MRD detection in a cohort from the ctDNA Lung DETECT study (NCT05254782). **Methods:** Patients with clinical stage I NSCLC treated with upfront surgery were enrolled at Princess Margaret Cancer Centre/University Health Network. Resected tumor tissue underwent WGS to generate personalized tumor-informed assays tracking up to 5000 somatic variants, including prioritized PVs prioritized (CLARITY, Foresight Diagnostics). Plasma samples (pre-operative, 3-6 weeks post-operative landmark, 6 months, 12 months, and at recurrence) were analyzed retrospectively with labs blinded to outcomes. Endpoints were MRD detection, recurrence free survival (RFS), MRD clearance patterns. **Results:** Of 128 clinical stage I patients with banked samples, 121 (95%) had sufficient tumor for WGS. Pathologic stage distribution AJCC 8th Ed. was stage 0/I/II/III/IV (n=1/86/22/1). Among 121 patients, 16 (13%) experienced distant recurrence and 15 (12%) developed second primary malignancies: lung, breast, ovarian, prostate and sarcoma. MRD detection at pre-operative (HR 5.6, p=0.002) and post-operative landmark (HR 4.2, p=0.002) was significantly associated with RFS. MRD+ at 12 months post-resection demonstrated stronger prognostic value, as 97% (91/94) MRD-negative patients remained recurrence free compared to 15% (2/13) MRD+ patients (HR 48.3, $p<0.0001$). We assessed MRD clearance between post-op landmark and later samples in patients who received adjuvant therapy. In total, 34 received adjuvant therapy; of these, 10 were MRD+ post-operatively with at least 1 subsequent sample. MRD clearance during or after adjuvant therapy was significantly associated with improved RFS (p=0.019). Patients with MRD clearance at any time after adjuvant therapy had 0% recurrence (0/4), while 83% (5/6) patients who failed to clear MRD despite adjuvant therapy had recurrence. In recurrence, MRD was detected in 94% (15/16) prior to or at recurrence. Only 1 MRD-negative patient recurred, $>$2 years after the last assessed sample. **Conclusions:** Ultrasensitive tumor-informed ctDNA MRD detection identifies patients at high risk for metastatic relapse following NSCLC resection, including pathologic Stage I, and may provide substantial lead time over conventional imaging. Clearance of post-surgical MRD with adjuvant therapy may inform post-resection surveillance and future studies of adjuvant therapy. Clinical trial information: NCT05254782. Research Sponsor: Princess Margaret Cancer Foundation; Ontario Institute for Cancer Research.

3061 **Poster Session**

cfDNA sequencing as a cutting-edge technology to identify pathogenic germline variants from 8353 patients with advanced tumors at the Gustave Roussy Institute. First Author: Hela Sassi, Medical Biology and Pathology Department, Paris-Saclay University, Gustave Roussy, Villejuif, France

Background: Large cfDNA panels used for somatic profiling can incidentally reveal pathogenic variants of potential germline origin, with implications for patient management and hereditary cancer risk assessment. **Methods:** Between December 18th, 2020 and July 22nd, 2025, a weekly molecular tumor board reviewed cfDNA sequencing data from 8353 patients with advanced solid tumors treated at Gustave Roussy using the FoundationOne Liquid CDx panel, within the prospective STING trial (NCT04932525). We evaluated the yield, clinical relevance, and confirmatory outcomes of an MTB-governed workflow to flag putative germline pathogenic variants (PGPVs) from routine cfDNA profiling in advanced cancers. Across the 324 covered genes, we selected a list of 31 known hereditary cancer genes and 7 emerging candidates. Patients without prior germline confirmation were referred for genetic counseling and confirmatory testing on an independent sample. Turnaround times were compared with the conventional germline pathway. **Results:** Among 8,353 patients (mean age 62 years), 445 (5.3%) carried 471 PGPVs, including 23 patients with more than 2 variants. The most frequently implicated genes were *BRCA2* (n=101), *MUTYH* (n=81) and *BRCA1* (n=62). Overall, 54.6% of PGPVs were incidental findings (257/471); among incidental findings, 51.0% were clinically actionable (131/257), corresponding to 27.8% of all PGPVs (131/471). Germline status was confirmed in 172 patients (86 known prior to cfDNA profiling and 86 confirmed following cfDNA-guided referrals, including 60 incidental findings of which 52 were actionable; 14 variants (11 patients) were not confirmed and 6 were pending. For variants first flagged through cfDNA, the mean interval from liquid biopsy prescription to confirmatory germline report was 2 months, compared with 6 months through the conventional pathway. In evaluable paired cases, cfDNA showed high diagnostic performance for identifying germline findings (sensitivity 98.3%, specificity 97.4%). **Conclusions:** In an advanced pan-cancer real-world cohort, an MTB-governed cfDNA workflow identified PGPVs in 5% of patients, with over half representing incidental findings and 28% of all PGPVs being actionable. cfDNA profiling can accelerate referral and confirmation of hereditary cancer risk when coupled with expert interpretation and confirmatory germline testing, while acknowledging limitations for certain alterations. Research Sponsor: None.

3062 **Poster Session**

***ESR1* mutation longitudinal dynamics in RWD cohort of HR+/HER2− metastatic breast cancer patients treated with standard-of-care hormonal therapy.** First Author: Malvika Pillai, Tempus AI, Chicago, IL

Background: *ESR1* mutations (*ESR1*m) are known drivers of resistance to aromatase inhibitors. While *ESR1*m has been linked to worse survival outcomes, clonal complexity over time has not been well-evaluated in a real-world context. Here we characterized longitudinal dynamics of *ESR1*m, including rare point mutation emergence and polyclonality in hormone receptor-positive/HER2-negative metastatic breast cancer (HR+/HER2- mBC) patients (pts) treated with aromatase inhibitor (AI) plus CDK4/6 inhibitor (CDK4/6i). **Methods:** We identified a cohort for longitudinal analysis from the Tempus real-world database (RWD). Eligible pts had HR+/HER2- mBC (diagnosed before 01/2023), received AI+CDK4/6i therapy in mBC, and had comprehensive genomic profiling from tissue/liquid biopsy (Tempus xT/Tempus xF) within 2 yrs of treatment, with ≥1 on-treatment xF tests. We analyzed *ESR1* clonal dynamics, starting from first *ESR1*m detection in a subset of pts who had multiple xF tests. Polyclonality was also assessed, defined as presence of at least 2 distinct *ESR1*m in a sample. **Results:** Of 301 HR+/HER2- mBC pts on AI+CDK4/6i therapy, 102 (33.9%) developed an *ESR1*m. In the *ESR1*m group, 72 pts (70.6%) had 2+ on-treatment liquid biopsies (Tempus xF/xF+), comprising the final cohort for observation. At *ESR1*m detection, 64.8% pts had a single detectable *ESR1*m, most commonly D538G (31.9%) and Y537S (12.5%). In contrast, 34.7% had polyclonal mutations (19.7% with 2 distinct mutations; 15.3% with 3+). Recurrent detection of D538G (52.8%), Y537S (20.8%), and Y537N (16.7%) was noted in repeat xF testing. Detection of additional *ESR1*m (26.4%) over time confirmed known common mutations such as Y537N (8.3%), D538G (5.6%), and Y537S (5.6%). However, longitudinal testing also found rare mutations such as V422del and H524L. Mutational dynamics shifts were also revealed by longitudinal testing. In 36.1% pts, a previously detected *ESR1*m was no longer found, often in those who initiated a SERD. D538G (5.6%) and Y537N (4.2%) were the most commonly lost mutations. Recurrent and new *ESR1*m detection occurred in pts who continued AI+CDK4/6i (44.4%). Many pts showed a combination of these dynamics. **Conclusions:** Multimodal RWD analyses demonstrate valuable clinical insights on *ESR1*m patterns detected from longitudinal molecular surveillance testing in HR+/HER2- mBC pts treated with AI+CDK4/6i. We observed shifting dynamics in *ESR1*m burden, including detection of rare mutations and polyclonality. These findings show the value of monitoring *ESR1*m longitudinally over disease course and prompt further research into clinical impacts of clonal dynamics. Research Sponsor: None.

3063 **Poster Session**

Quantitative assessment of tumor shedding using AI-derived radiographic tumor burden and quantified liquid biopsy in advanced gastrointestinal cancers. First Author: Abdul Qahar K. Yasinzai, University of Florida/UF Health Cancer Institute, Gainesville, FL

Background: Radiographic imaging remains the clinical standard for assessing cancer treatment response; however, it lacks sensitivity to detect early biological shifts and spatially heterogeneous tumor behavior. Methylated circulating tumor DNA (mctDNA) provides a complementary molecular measure of disease burden, yet the quantitative relationship between radiographic tumor burden and DNA shedding remains poorly characterized. In this cohort study, we evaluated whether early changes in shed rate predict progression-free survival (PFS) and overall survival (OS) in patients with advanced gastrointestinal (GI) cancers. **Methods:** Patients with advanced GI malignancies receiving systemic therapies underwent paired longitudinal radiographic and liquid biopsy assessments. Radiographic tumor burden was quantified (OSCAR AI platform). Tumor contours were independently blinded reviewed by two radiologists. Up to 15 target lesions per organ were selected, and the total tumor burden was calculated analogous to longitudinal RECIST assessment. Tumor Methylation Score (TMS) from the Northstar Response assay quantified mctDNA. Tumor shed rate (TSR) was defined as the ratio of TMS to the AI-derived radiographic tumor volume and calculated at baseline and at the first on-treatment landmark using the closest-paired CT scan and blood drawn within 120 days. Fold-change in TSR from baseline was compared with PFS and OS. Undetectable tumor volume cases were excluded. **Results:** Forty patients were evaluable, with both baseline and landmark timepoints available within the 120-day window. TSR ranged from a min of 0 methylated molecules per mm^3 (m4) to a max of 1.0 m4 with a median of 0.06 m4. TSR significantly differed between tumor types (p=0.013, ANOVA), with CRC having the highest median shed rate (0.13 m4) and EGA and pancreatic having the lowest median shed rates (0 m4). TMS was significantly associated with tumor volume at baseline (Rsq=0.15,p=0.01, Deming) and on-treatment (Rsq=0.6, p<0.001, Deming). An increased TSR was associated with OS (HR=5.8, 95% CI 1.7-19.2, <0.01) and PFS (HR=3.5, 1.4-8.6, <0.01). **Conclusions:** TSR represents a novel, multidimensional integration of AI-driven volumetrics and liquid biopsy. Our findings suggest that an increasing shed rate is a predictor of PFS and OS, potentially serving as a lead-time indicator of tumor-host homeostatic decompensation. Future analysis will determine if TSR captures critical transitions in tumor biology that precede and perhaps drive radiographically detectable progression. Research Sponsor: U.S. National Institutes of Health; UF Health Cancer Institute; Florida state appropriations provided in Fla. Stat. § 381.915; BillionToOne.

3064 **Poster Session**

Breast cancer screening is heating up: A novel thermophysics-based AI modality for screening subjects with BIRADS 4 or 5 mammograms. First Author: Nedal Darwish, Rochester General Health System, Rochester, NY

Background: Although mammography is an effective cancer detection modality, limited specificity at population scale leads to unnecessary biopsies, highlighting a need for adjunctive approaches. Cancer exhibits increased metabolic activity, leading to temperature differentials when compared with benign tissue. In this study, ultra-high sensitivity infrared imaging (IRI) was utilized with a novel thermophysics-based AI neural network to leverage temperature differentials for cancer screening. **Methods:** This prospective validation pilot study enrolled 14 patients with BI-RADS 4 or 5 breast lesions on diagnostic imaging prior to biopsy. IRI and optical images were acquired using an infrared imaging device at angular intervals, encoding the breast surface. Thermal and optical data were processed using a 3D reconstruction algorithm to generate breast surface thermal-spatial point-clouds, encoding temperature values at corresponding locations. Tumor presence or absence was predicted using an AI physics-informed neural network (PINN) that solves inverse bioheat transfer equations to identify heat sources associated with increased metabolic activity and blood perfusion. The PINN result was then compared to diagnostic mammography and to histologic findings on pathology. **Results:** 14 patients aged 42-83 years were included in a prespecified salient interim analysis approved by the study committee to assess feasibility. Histologic outcomes ranging from normal breast tissue to benign and premalignant/malignant conditions as outlined in Table 1. The PINN accurately predicted the presence and location of all premalignant/malignant lesions, including all incidences of IDC (n=3), DCIS (n=3), and ADH (n=2). Histologically benign lesions (n=6) were not detected by the PINN as a heat source. The mean size error for the PINN was 1.3 cm compared to size on pathology. **Conclusions:** Infrared imaging combined with a thermophysics-based AI neural network was able to localize and detect premalignant/malignant breast lesions with 100% sensitivity and specificity. Our findings suggest that IRI adjunctive screening may have the potential to both accurately detect breast cancer and minimize unnecessary biopsies. Research Sponsor: None.

Comparison of PINN assessment with histological outcome.

Number of Patients	Breast Tissue Type	PINN Assessment	PINN Diameter (cm)	Histologic Assessment	Histologic Diameter (cm)
2	SF	+	1.2, 2.2	ADH	2.1,3.0
3	SF	+	1.1, 1.4, 1.4	DCIS	2.1, 2.0, 2.8
3	SF	+	1.0, 1.2, 1.6	IDC	0.5, 3.0, 5.0
1	SF	–		Fibrosis	
1	SF	–		Cystic Fluid	
1	SF	–		Fibrocystic	
1	SF	–		Fibroadenoma	
1	SF	–		Duct Ectasia	
1	HD	–		Normal Breast	

Breast tissue density classifications: scattered fibro-glandular (SF), heterogeneously dense (HD). Histology subtypes: invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS), atypical ductal hyperplasia (ADH). PINN=physics-informed neural network.

3065 **Poster Session**

^{68}Ga-NODAGA-SNA014 whole-body PET imaging to detect Claudin18.2–positive pancreatic cancer lesions. First Author: Jihui Hao, Department of Pancreatic Cancer, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University, Tianjin, China

Background: ^{68}Ga-labeled nanobody (^{68}Ga-NODAGA-SNA014) is a PET radiotracer based on a single-domain antibody. We conducted a first-in-human (FIH) evaluation of ^{68}Ga-NODAGA-SNA014 to characterize in vivo biodistribution, metabolism, radiation dosimetry, and safety, and to explore its ability to noninvasively quantify Claudin-18.2 (CLDN18.2) expression in patients with gastrointestinal cancers. **Methods:** ^{68}Ga-NODAGA-SNA014 was synthesized and first assessed preclinically in human pancreatic cancer cell lines and xenograft mouse models to evaluate affinity, specificity, and pharmacokinetics. We then performed a translational pilot study in 15 patients with pancreatic cancer imaged on a total-body (panoramic) PET/CT system. Whole-body biodistribution, organ dosimetry, and the association between lesion uptake and CLDN18.2 expression were analyzed and compared with ^{18}F-FDG, where available. **Results:** ^{68}Ga-NODAGA-SNA014 was produced reliably with favorable radiochemical characteristics. In preclinical studies, the tracer exhibited rapid blood clearance, high affinity for CLDN18.2, and specific uptake in CLDN18.2-positive cells and xenografts. In patients, physiologic uptake was highest in the stomach and kidneys, with mild uptake in the pancreas. Lesion uptake varied by CLDN18.2 expression level, and ^{68}Ga-NODAGA-SNA014 demonstrated more precise differentiation of CLDN18.2-high versus CLDN18.2-low lesions than ^{18}F-FDG. **Conclusions:** PET uptake (SUV) of ^{68}Ga-NODAGA-SNA014 correlated with CLDN18.2 expression, supporting its potential as a noninvasive companion diagnostic to guide and optimize CLDN18.2-targeted therapies. Research Sponsor: None.

3066 **Poster Session**

Comprehensive profiling and clinical utility of CSF-derived cell-free DNA/RNA for evaluation of solid and hematologic malignancies affecting the central nervous system. First Author: Ryan Gimple, Washington University in Saint Louis School of Medicine, St. Louis, MO

Background: Diagnosis and risk stratification of brain lesions is challenging when tissue biopsy is contraindicated due to anatomic or clinical factors. Cerebrospinal fluid (CSF)–based liquid biopsy using cell-free DNA (cfDNA) and RNA (cfRNA) offers a minimally invasive approach to detect neoplastic disease and inform management. We evaluated the clinical utility of a commercially available cfDNA/cfRNA next-generation sequencing assay applied to CSF specimens from patients with CNS lesions of uncertain etiology. **Methods:** Between 2023 and 2025, cfDNA, cfRNA, and CSF cell pellet RNA profiling using next generation sequencing (NGS) was performed on CSF samples from 1,559 patients, including 1,209 evaluated for suspected primary or secondary solid CNS malignancies and 350 evaluated for CNS involvement by hematologic malignancies. The assay interrogated single-nucleotide variants, insertions/deletions, copy number alterations, gene fusions, lymphocyte clonality, and tumor mutational burden. The depth of sequencing was between 25,000x and 30,000x for cfDNA. For quality control purposes, more than 80 million reads were required for accepting RNA results, while the required percentage of spliced RNA reads was above 20%. Clinical utility and actionability was further assessed in a single-institution cohort of 90 patients by correlating cfDNA/cfRNA results with cytology, flow cytometry, tissue biopsy, and clinical decision-making. **Results:** Among patients evaluated for solid malignancies in the entire cohort, the most common alterations involved TP53, KMT2C, PIK3CA, EGFR, and DNMT3A, while hematologic cases frequently harbored PIM1, TP53, MYD88, CD79B, TET2, and DNMT3A alterations. In the institutional cohort (median age 57 years), neoplastic cfDNA was detected in 40/90 samples, with recurrent alterations mirroring those of the larger panel. cfDNA profiling demonstrated 100% sensitivity for neoplastic DNA detection compared with current standard-of-care cytology and flow cytometry and identified neoplastic DNA in 37% of cytology-negative and 42% of flow-negative cases. Concordance with contemporaneous tissue biopsy yielded a positive predictive value of 89%, with a sensitivity of 68%, reflecting reduced detection in intraparenchymal lesions with limited CSF exposure. cfDNA results directly influenced treatment decisions in patients evaluated for new intracranial malignancy and for CNS metastasis or recurrence. **Conclusions:** CSF cfDNA/cfRNA profiling significantly enhanced diagnostic yield in CNS lesions of uncertain etiology, particularly when conventional cytology is negative, or biopsy is infeasible, while also providing actionable molecular information to guide therapy. Research Sponsor: None.

3067 **Poster Session**

Application of long-read sequencing to resolve cryptic genomic instability across cancer types. First Author: Josh Vo, Michigan Center for Translational Pathology, Department of Pathology, University of Michigan, Ann Arbor, MI

Background: Computational mutational signatures can identify tumors with homologous recombination deficiency (HRD), mismatch repair deficiency (MMRD), and focal tandem duplication (FTD) phenotypes, nominating patients for PARP inhibitors or immune checkpoint blockade. However, many signature-positive cases lack identifiable causative alterations by conventional sequencing, forcing patients toward empiric therapy or clinical trial enrollment without molecular confirmation. We evaluated whether long-read nanopore sequencing could provide definitive molecular diagnoses to guide evidence-based treatment selection. **Methods:** We analyzed 768 patients with advanced prostate (n=505), breast (n=246), and ovarian (n=17) cancers enrolled in the MiOncoSeq precision oncology program. Computational signature analysis identified cases with HRD, MMRD, or FTD phenotypes. Cases unresolved by standard short-read sequencing underwent long-read nanopore sequencing with integrated structural variant detection, methylation profiling, and haplotype phasing. **Results:** Signature analysis identified 164 cases (21.3%) with genomic instability phenotypes. Short-read sequencing resolved 118/164 cases (71.9%), leaving 46 patients without molecular confirmation. Long-read sequencing achieved mechanistic resolution in 32/46 cases (69.6%), with complete resolution of MMRD (5/5, 100%) and FTD (7/7, 100%). Secondary signature analysis reclassified 11/14 unresolved HRD cases as non-classical, likely reflecting alternative DNA repair defects or replication stress, refining diagnostic yield to 86.9% (20/23) for credible HRD. Cryptic mechanisms included promoter hypermethylation (*BRCA1*, *MLH1*, *RAD51C*), balanced structural rearrangements (*CDK12*, *PMS2*), and deep intronic splice variants (*PALB2, BARD1*). Long-read sequencing also uncovered 3 previously undetected pathogenic germline variants (*BARD1*, *BRIP1*, *PALB2*) with direct implications for hereditary cancer risk assessment and family screening. Combined analysis identified actionable findings enabling targeted therapy selection in 19.5% of patients. **Conclusions:** Long-read sequencing provides definitive molecular diagnoses for patients with signature-positive tumors, enables evidence-based therapy selection over empiric treatment, and uncovers cryptic germline variants informing hereditary cancer risk. Research Sponsor: National Cancer Institute.

3068 **Poster Session**

CLERAD-PROBE: Dosimetric analysis of I-124 PET–guided remnant radioiodine ablation in differentiated thyroid carcinoma. First Author: Kerstin Michalski, Department of Nuclear Medicine, University Hospital Wuerzburg, Wuerzburg, Germany

Background: The role of adjuvant radioiodine therapy (RIT) in differentiated thyroid carcinoma (DTC) remains controversial due to a lack of long-term data from randomized controlled trials. Consequently, international guidelines diverge; while some advocate broad application, others prioritize a restrictive, risk-adapted approach. The CLERAD-PROBE trial aims to bridge this gap by comparing both strategies regarding blood dose — as an established surrogate for secondary malignancy risk — and oncological outcomes. **Methods:** CLERAD-PROBE is a prospective, randomized, bicentric study (NCT01704586) in adult DTC patients, excluding those with unifocal papillary microcarcinomas $\leq$ 10 mm limited to the thyroid. Following thyroidectomy, patients in Arm 1 underwent I-124 PET for staging and dosimetry. Adjuvant RIT was administered if one or multiple of the following risk factors were present: incomplete surgical resection, tumor size $>$4cm or extrathyroidal extent, lymph node metastases and age $\geq$ 45 years, distant metastases, and/or iodine-avid lesions on I-124 PET. In Arm 2, adjuvant RIT was generally performed. Follow-up was performed every 4–6 months using thyroglobulin measurements and cervical ultrasound. The primary endpoint was the mean blood dose after complete remission or 18 months. Secondary endpoints included progression- and recurrence-free survival at 3 and 10 years. **Results:** The primary endpoint was evaluable in 315 patients, enrolled from May 2015 to May 2021 (148 in Arm 1, 167 in Arm 2). Study arms were matched with regards to histology, age, and tumor/nodal stage, though Arm 1 had significantly fewer men (22% vs. 34%, p = 0.02). I-124 PET identified lymph node metastases in 49 patients and distant metastases in 13 patients. RIT was performed in 68 of 148 (46%) patients in Arm 1. Of these, 13 patients with low-risk carcinoma underwent RIT because of new metastases found on I-124 PET. The mean absorbed blood doses (252 mGy vs 447 mGy, range: 4 - 3217 mGy vs. 48 - 2520 mGy; $p < 0.001$) and administered I-131-activities (2.3 GBq vs. 4.9 GBq; range: 0 – 18.6 GBq vs. 1.0 – 26.2 GBq; $p < 0.001$) were lower in Arm 1. **Conclusions:** I-124 PET identifies persistent, iodine-avid disease in patients who would not routinely receive adjuvant RIT pursuant to ATA Guidelines, while enabling individualized selection in the others to minimize secondary malignancy risk. The impact on long term oncological outcomes has yet to be determined. Three years follow-up analyses evaluating recurrence rates and overall oncological safety are currently in progress and will be presented at the congress. Clinical trial information: NCT01704586. Research Sponsor: German Cancer Aid; 110751.

3069 **Poster Session**

iPREDICT: Phase II study of CD8 PET in patients with immunoresponsive solid tumors—Imaging characteristics and correlation with RECIST response. First Author: Kim Allyson Margolin, Providence Saint John's Cancer Institute, Santa Monica, CA

Background: CD8 T cells mediate antitumor effects of immune checkpoint blockade (ICB); their histologically-determined abundance prior to or during therapy (Rx) appears to correlate with ICB response in melanoma (MEL) and other solid tumors. We performed this Phase IIb study to assess CD8 targeted PET imaging with ^{89}Zr-crefmirlimab berdoxam prior to and during ICB Rx to study its potential as a marker for Rx selection, enhancement or even replacement of existing tumor measurement systems, and correlation of clinical outcomes. **Methods:** 70 patients (pts) with MEL or Merkel cell cancer (MCC) (27), renal cell cancer (RCC) (35) or lung cancer (NSCLC) (8) who were eligible for first or second-line single- or double-agent ICB or ICB plus an oral kinase inhibitor (TKI) were enrolled. ^{89}Zr-crefmirlimab berdoxam (1 mCi,1.5 mg protein), was administered intravenously $\leq$2 weeks prior to cycle 1 of ICB Rx, followed by a PET/CT scan 24 (+/-3) hours later (baseline, BL). The 2nd tracer injection and associated PET/CT scan occurred 4-6 weeks after ICB Rx initiation, prior to cycle 3 (on treatment, OT). Standard of Care imaging and RECIST 1.1 were used to assess response to Rx. **Results:** All 70 pts were evaluable for safety analysis; none experienced an SAE related to imaging agent. 65 pts (21 MEL, 2 MCC, 34 RCC and 8 NSCLC) were included in the primary endpoint analysis of correlating CD8 PET scans with best confirmed overall response (BOR) by RECIST 1.1. MEL and MCC pts received single (6/23) or double ICB (17/23), RCC pts received single ICB with/without TKI (21/34) or dual ICB (13/34), and all NSLCL pts received single ICB. In the RCC cohort, multiple CD8 PET metrics showed statistically significant association with either individual BOR or Binary Response at BL, OT or as delta, including: Tumor Standard Uptake Value (SUV), Lymph Node (LN) SUV, relative percentage of CD8 negative or positive lesions and normal organ SUV. Normalization to reference organs improved the correlation with BOR for the combined cohorts and for the MEL/MCC cohort. Depending on clinical objectives, different classification rules to predict BOR were applied, prioritizing specificity for non-responders and sensitivity for responders (Table). These results were cohort-dependent, as each cohort exhibited a distinct distribution of SUVs. **Conclusions:** PET imaging can quantitate CD8 T cells with sufficient specificity and sensitivity to support further study in selection of pts for Rx regimens and assessing early response to therapy. Clinical trial information: NCT05013099. Research Sponsor: Imaginab.

Prediction of BOR by CD8 PET.

Cohort	Response	Parameter	Timepoint	AUC	95% CI	Sensitivity	Specificity
MEL + MCC	CR+PR vs SD+PD	Spleen SUVmean	BL	0.67	0.44,0.90	87.5	60.0
MEL + MCC	CR+PR vs SD+PD	Tumor SUVmax normal. to thyroid	Delta	0.70	0.46, 0.95	85.7	64.3
RCC	CR+PR vs SD+PD	Hottest LN SUVmax	OT	0.84	0.65, 1.00	71.4	90.9
RCC	CR vs PR+SD+PD	% CD8 negative lesions	Delta	0.96	0.87, 1.00	100.0	92.3

3070 **Poster Session**

Cell-free DNA methylation profile–based fusion epigenotyping to enhance *ALK* fusion detection in NSCLC patients. First Author: Laura Tung, Guardant Health, Palo Alto, CA

Background: Short read lengths in next-generation sequencing and targeted panel probe design pose challenges to fusion detection by impairing the resolution of complex genomic rearrangements and the accurate mapping of intronic breakpoints. To address these limitations, we developed a cell-free DNA (cfDNA) methylation-based fusion epigenotyping method that leverages fusion-associated tumor epigenetic signatures to complement genomic-based methods and increase the fusion detection sensitivity of our liquid biopsy. We validated *EML4-ALK* fusion detection by this algorithm in non-small cell lung cancer (NSCLC) using paired clinical tumor tissue and cfDNA samples. **Methods:** We trained a binary classifier to discriminate *EML4-ALK* fusion-positive from fusion-negative NSCLC using cfDNA methylation signal and genomic molecule support. To validate the epigenotyping classifier, an independent cohort of 577 clinical NSCLC samples was selected with paired tumor tissue and Guardant360 Liquid (Guardant Health, Palo Alto, CA) cfDNA for each patient (with epigenomic tumor fraction $>$ 0.03%). The cohort included 94 tissue-confirmed fusion-positive samples (78 cfDNA genomic positives and 16 cfDNA genomic false negatives) with *EML4-ALK* detected in tumor tissue, and 483 tissue-confirmed fusion-negative samples (*ALK* fusion negative in both tissue and paired cfDNA). The epigenotyping classifier predictions in cfDNA were evaluated against tissue-based orthogonal truth. **Results:** Among tissue-confirmed fusion-positive samples, tissue-liquid assessment showed a high positive percent agreement (PPA) / sensitivity of 89.36% (84/94), as well as 100% concordance with genomic caller positives (78/78). The rate of rescued fusions by the epigenotyping classifier from genomic false negative liquid cases was 38% (6/16). Among tissue-confirmed fusion-negative samples, tissue-liquid assessment showed a high negative percent agreement (NPA) / specificity of 99.38% (480/483). The false positive rate (FPR) of high confidence calls (probability exceeding a 99.7% specificity threshold or with partial genomic evidence) was 0.0% (0/483). **Conclusions:** cfDNA methylation-based fusion epigenotyping substantially increased detection of actionable *ALK* fusions while maintaining high specificity, as demonstrated by tissue-liquid concordance. The results of this approach showed the clinical value of giving NSCLC patients an increased likelihood to receive more effective, less toxic ALK inhibitor therapy, while the minimized FPR helps ensure appropriately matched treatment decisions. Research Sponsor: Guardant Health.

3071 **Poster Session**

Multicenter clinical study of [^{18}F]AlF-HER2-BCH PET/CT as a molecular pathology tool for linear quantification of HER2 expression levels in breast cancer. First Author: Xiaoyi Guo, NMPA Key Laboratory for Research and Evaluation of Radiopharmaceuticals, Department of Nuclear Medicine, Peking University Cancer Hospital & Institute, Beijing, Beijing, China

Background: Determining the human epidermal growth factor receptor 2 (HER2) status is essential in metastatic breast cancer (MBC) management. To establish the clinical validity of [^{18}F]AlF-HER2-BCH PET/CT (HER2-PET), we assessed the diagnostic accuracy of qualitative and quantitative HER2-PET assessment to predict HER2 expression by immunohistochemistry (IHC), including HER2-negative and -low breast cancer. **Methods:** This prospective multicenter trial enrolled treatment-naïve patients with newly diagnosed, non-rapidly progressive breast cancer across all molecular subtypes. Paired HER2 PET and [^{18}F]FDG PET/CT (FDG-PET) scans were acquired within a standardized 7-day. Tumor uptake was quantified using maximum standardized uptake value (SUVmax) and target-to-background ratios (TBR), and analyzed via general linear mixed models. **Results:** Between 2020 to June 2025, 240 patients were analyzed. Comparative analysis revealed superior diagnostic performance of whole-body HER2-PET versus FDG-PET for malignant lesion detection: sensitivity (97.6% vs 89.9%), specificity (83.9% vs 77.4%%), and overall accuracy (96.4% vs 88.9%). Quantitative HER2-PET analysis revealed significantly different SUVmax values across HER2 expression categories (median [IQR]: HER2-positive 13.1 [9.2-20.7] vs HER2-low 7.3 [5.1-8.9] vs HER2-negative 3.2 [2.7-4.5]; P$<$0.001), demonstrating strong correlation with IHC/FISH-defined HER2 status. In contrast, FDG-PET uptake showed no association with HER2 status (P=0.5). Among 10 discordant cases between HER2-PET and standard IHC/FISH: eight (80%) represented confirmed biological heterogeneity, with differing HER2 status across metastatic sites; two (20%) IHC 1+ cases exhibited PET-positive/FISH-amplified patterns, suggesting potential IHC false-negative results. **Conclusions:** [^{18}F]AlF-HER2-BCH PET/CT provides comprehensive HER2 profiling beyond single-biopsy IHC, offering new therapeutic insights for HER2-low/negative metastatic breast cancer through whole-body molecular visualization. Clinical trial information: NCT04547309. Research Sponsor: None.

Diagnostic performance of Al^{18}F-HER2-BCH PET/CT and ^{18}F-FDG PET/CT, in the detection of primary and metastatic lesions in the evaluable imaging core population (N participant=240, N Biopsy-proven lesion=359).

	HER2 PET	FDG PET	Difference^	P Value*
Participants				
True positive	207	199	–	–
True negative	26	22	–	–
False positive	2	4	–	–
False negative	5	15	–	–
Sensitivity	97.6% (94.7 to 99.1)	93.0% (88.6 to 95.9)	4.65% (0.32 to 8.98)	0.036*
Specificity	92.8% (77.9 to 99.0)	84.6% (66.4 to 94.7)	8.24% (-6.8 to 23.3)	0.342
Positive predictive value	99.0% (96.6 to 99.9)	98.0% (95.2 to 99.4)	1.0 (-1.1 to 3.1)	0.398
Negative predictive value	83.9% (67.2 to 93.7)	59.5% (43.3 to 74.1)	24.4 (6.8 to 42)	0.009**
Accuracy	97.1% (94.2 to 98.7)	92.1% (87.8 to 95.2)	5.0 (1.3 to 8.7)	0.008**

3072 **Poster Session**

FAPI-CUP: A prospective cohort study of patients with cancer of unknown primary (CUP) to evaluate a novel radiotracer, fibroblast activated protein (FAPI), targeting cancer-associated fibroblasts for primary site detection. First Author: Tharani Sivakumaran, Department of Medical Oncology, Peter MacCallum Cancer Centre and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia

Background: Cancer of unknown primary (CUP) represents a heterogeneous group of metastatic tumours for which standardised diagnostic work-up fails to identify the site of origin at diagnosis. ^{18}F-FDG-PET/CT aids in identifying a putative primary site in ~30-50% of CUP patient (pts); however, has limited sensitivity for detecting cancers with high stromal content. Fibroblast activation protein (FAP) is a type II transmembrane serine protease and highly expressed by cancer-associated fibroblasts abundant in desmoplastic tumours such as CUP. ^{68}Ga-FAPI-46 is a FAP-targeting PET tracer but has not been directly compared to ^{18}F-FDG-PET/CT in CUP. Aims: We aimed to determine if the addition of ^{68}Ga-FAPI-46 detects more primary sites compared with ^{18}F-FDG-PET/CT and CT CAP (standard of care; SoC) in CUP pts and if there is an association between the level of FAPI avidity and response to systemic treatment. **Methods:** A prospective cohort study recruiting CUP pts across four sites in Australia. Key inclusion criteria: 1) pts considered CUP after diagnostic work-up, pathological review and gender appropriate tests; 2) adequate haematologic and organ function; 3) not commenced current line of systemic treatment (exception palliative radiotherapy for symptom control); 4) ECOG $\leq$ 2 and life expectancy $>$ 3months. 5) $\leq$1 prior line of systemic treatment. Pts undergo SoC imaging (CT CAP, ^{18}F-FDG-PET/CT) and ^{68}Ga-FAPI-46 PET/CT scan which are reviewed at a multidisciplinary meeting to determine primary site. Clinicopathological review and genomic analysis (if available) were used to determine final primary site. Pts start systemic treatment and have SoC follow-up with data regarding RECIST 1.1 response, survival outcome and further lines of treatment for 12 months. **Results:** At interim analysis 60 pts were recruited from 03/2022 to 06/2025. Median age was 68 years [30-83] with 89% being ECOG 0-1 and 80% classified as having an unfavourable CUP subtype. A primary site was detected in 37/60 (62%) and 33/60 (55%) pts with ^{68}Ga-FAPI-46 PET/CT and SoC and SoC alone, respectively. Cholangiocarcinoma (9/37; 24%) and lung (7/37; 19%) were the commonest primary sites detected. 46/60 (77%) pts commenced systemic treatment with a best overall response rate of 9/38 (24%) in RECIST evaluable pts. There was no association between RECIST response and baseline FAPI avidity for either average SUVmax top 3 lesions (p=0.653) or highest SUVmax (p=0.416). **Conclusions:** ^{68}Ga-FAPI-46 PET/CT in addition to SoC detected a primary site in more patients compared to SoC imaging alone. There was no association between RECIST response and baseline FAPI avidity. Clinical trial information: NCT05263700. Research Sponsor: MRFF.

3073 **Poster Session**

Integrated imaging cytology profiling system for rapid point-of-care molecular diagnosis of leptomeningeal metastasis in breast cancer. First Author: Hyungsoon Im, Center for Systems Biology, Massachusetts General Hospital; Department of Radiology, Massachusetts General Hospital, Boston, MA

Background: Leptomeningeal metastasis (LM) from breast cancer has a poor prognosis (median survival ~4 months). Early and accurate diagnosis and phenotyping enable timely therapeutic intervention, particularly with emerging targeted agents such as antibody–drug conjugates (ADCs), to improve clinical outcomes. Yet, MRI and CSF cytology often lack sensitivity. We developed iSCOPE, an integrated imaging cytology platform that rapidly enriches and detects tumor cells in CSF via single-cell immunomolecular profiling. **Methods:** Breast cancer patients with neurological symptoms and/or suspicion for LM were enrolled in the study (IRB: KNUCH 2020-08-015). CSF (5–10 mL) was obtained by lumbar puncture for iSCOPE testing, and the rest was for conventional cytology examination. iSCOPE (integrated single-cell on-chip point-of-care evaluation) enriches large epithelial cells from unprocessed CSF at single-cell capture sites in a microfluidic chip while smaller blood cells pass through. Captured cells are then immunolabeled with QUAD markers (a four-marker combination overexpressed in breast cancer), as well as HER2 and ER/PR, for phenotyping. Automatic quantitative fluorescence imaging using a miniaturized imager reports the total cells, QUAD-positive cells, and their phenotypes in 1 hour. iSCOPE was validated using FNA cytology samples and then applied to CSF samples. Results were compared with conventional CSF cytology. **Results:** In the validation study using FNA cytology samples, iSCOPE demonstrated excellent breast cancer detection accuracy based on QUAD-positive cell counts (area under the curve/AUC = 0.995), and receptor phenotyping showed concordance with clinical pathology (AUC $>$ 0.9). In CSF testing, iSCOPE correctly discriminated between LM (n = 7) and control CSF samples from patients with normal pressure hydrocephalus (n = 5). In serially collected CSF testing due to inconclusive diagnoses, iSCOPE detected LM in two cases, a few months earlier than conventional cytology when a suspicious finding was initially made (Table 1). **Conclusions:** This study demonstrates the clinical feasibility of iSCOPE for CSF-based diagnosis of LM in breast cancer. iSCOPE addresses current challenges in cytology analysis by incorporating a microfluidic chip to enrich for scant, suspicious cells and by using immunomolecular profiling to detect tumor cells. The CSF study results highlight the potential clinical use of iSCOPE for detecting LM in a point-of-care setting. Research Sponsor: National Institute of General Medical Sciences (NIGMS); R01GM138778; National Cancer Institute; R33CA281794; Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI); HR - 2022 - KH130591.

CSF analysis for LM diagnosis.

ID	Primary subtype	LM diagnosis (MRI)	LM diagnosis (Cytology)	LM diagnosis (iSCOPE)
S1	TNBC	2/8/2025	2/10/2025	2/10/2025
S2	HR+ HER2-	Negative	2/18/2025	Suspicious
S3	HR+ HER2-	4/2/2025	3/31/2025	8/14/2024
S4	HR+ HER2-	2/28/2025 (suspicious)	8/28/2025	2/17/2025
S5	TNBC	12/26/2025 (suspicious)	Negative	Negative

3074 **Poster Session**

Diagnostic performance, safety, and biodistribution of [^{68}Ga]Ga-OncoACP3 for PET imaging in prostate cancer: A phase I clinical trial. First Author: Cristiano Pini, Vita-Salute San Raffaele University, Milan, Italy

Background: Acid Phosphatase 3 (ACP3) is an emerging promising theranostic target in prostate cancer (PCa), expressed on PCa cells across most primary and metastatic lesions. ACP3 shows higher, more homogeneous expression than PSMA in low- and high-ISUP-grade tumours and in metastases, while not being expressed in healthy organs such as salivary glands, kidneys, and gastrointestinal tract. We present data from a multicentre, prospective phase I clinical trial investigating safety, dosimetry, pharmacokinetics, and diagnostic performance of [^{68}Ga]Ga-OncoACP3, a high-affinity ligand of ACP3 discovered from DNA-Encoded Chemical Libraries, in PCa. **Methods:** Twenty patients with a confirmed diagnosis of PCa were planned for enrolment in the study in two cohorts: Cohort A, 5 patients with primary tumour only; Cohort B, 15 patients with or without metastatic disease. Each patient received a single intravenous injection of [^{68}Ga]Ga-OncoACP3. PET/CT acquisitions were performed at 0, 10, 60 and 120 minutes after the injection with multiple blood and urine samples collections for pharmacokinetic and dosimetric analysis. Adverse events were recorded and graded according to CTCAE v5.0. [^{68}Ga]Ga-OncoACP3 PET findings were compared with PSMA PET (performed by all patients, according to clinical practice) and, when available, with follow-up data and histopathological findings. **Results:** All 20 patients completed [^{68}Ga]Ga-OncoACP3 PET imaging: 8 for initial staging, 10 for biochemical relapse, and 2 for advanced disease evaluation. No adverse events occurred. The tracer showed mixed hepatobiliary/renal excretion, with no uptake in salivary glands. PET-positive lesions showed rapid and selective tumour uptake shortly after injection, with increasing signal intensity at 60 and 120 minutes. All confirmed PSMA-positive lesions were evident at [^{68}Ga]Ga-OncoACP3 PET, in most cases with a higher tumour-to-background compared to PSMA PET. In three cases, [^{68}Ga]Ga-OncoACP3 PET detected additional PCa lesions, all confirmed by follow-up data or histopathology. No area of unspecific bone uptake at PSMA PET was evident at [^{68}Ga]Ga-OncoACP3. **Conclusions:** [^{68}Ga]Ga-OncoACP3 has an excellent safety profile and favourable pharmacokinetics, as well as promising tumour-targeting properties in PCa. [^{68}Ga]Ga-OncoACP3 may outperform current PSMA-targeting modalities across the whole natural history of the disease, and particularly in theranostic applications. Clinical trial information: NCT06840535. Research Sponsor: Philogen S.p.A.

3075 **Poster Session**

Diagnostic performance, safety, and biodistribution of [^{68}Ga]Ga-OncoCAIX for PET/CT imaging: A first-in-human phase I clinical trial in clear cell renal cell carcinoma. First Author: Fabrizia Gelardi, IRCCS Ospedale San Raffaele, Milano, Italy

Background: Conventional imaging techniques are routinely used in clear cell renal cell carcinoma (ccRCC). However, their ability to accurately characterise tumour biology and stage the disease remains limited. An attractive target for theranostic applications is represented by carbonic anhydrase IX (CAIX), which is overexpressed in ccRCC. [^{68}Ga]Ga-OncoCAIX is a novel small-molecule radiopharmaceutical for positron emission tomography (PET) imaging. The compound has been discovered by DNA-Encoded Chemical Libraries and designed to selectively bind to CAIX, allowing for tumour-specific uptake and favourable biodistribution in preclinical models. This multicentre, prospective, phase I study provides the first-in-human assessment of [^{68}Ga]Ga-OncoCAIX PET/CT in patients with kidney lesions. **Methods:** Twenty patients with suspected primary or recurrent ccRCC based on conventional imaging were planned for enrolment in the study. Each patient received a single intravenous injection of [^{68}Ga]Ga-OncoCAIX. PET/CT acquisitions were performed at 0, 10, 60 and 120 minutes after the injection with multiple blood and urine samples collections for pharmacokinetic and dosimetric analysis. Adverse events were recorded and graded according to CTCAE v5.0. Where available, PET findings were correlated with histopathology. **Results:** Twenty patients were included. Seventeen patients were evaluated for incidentally detected renal masses, and three for suspected recurrence identified on CT or MRI. [^{68}Ga]Ga-OncoCAIX was well tolerated, with no drug-related AEs reported. The tracer demonstrated mixed renal and hepatic clearance, favourable biodistribution, and low background activity in healthy tissues, including the kidneys. Physiological uptake was mainly observed in the gastrointestinal tract, particularly the stomach. PET-positive lesions showed rapid and selective tumour uptake shortly after injection, with increasing signal intensity at 60 and 120 minutes. Eight patients had positive PET findings, eleven scans were negative and one patient presented a lesion with mild tracer uptake. Available histopathological confirmation showed concordance with PET results, including three PET-positive ccRCCs, three PET-negative oncocytomas, and one PET-negative chromophobe RCC; the one lesion with mild tracer uptake corresponded to a papillary RCC with mild CAIX expression on histology. Dosimetric analyses are ongoing. **Conclusions:** [^{68}Ga]Ga-OncoCAIX shows an excellent safety profile and favourable biodistribution, as well as promising tumour-targeting properties in ccRCC lesions. These preliminary findings support its potential role for the detection and characterisation of ccRCC. Complete data on histopathology will confirm the diagnostic accuracy and potential clinical utility in patients with suspected ccRCC. Clinical trial information: NCT06840548. Research Sponsor: Philogen S.p.a.

3076 **Poster Session**

Molecular characteristics and outcomes of a real-world cohort of carcinoma of unknown primary determined by tissue-of-origin assays. First Author: Nisha Ramamurthy, George Washington University School of Medicine and Health Sciences, Washington, DC

Background: Carcinoma of unknown primary (CUP) increasingly intersects with precision oncology as molecular profiling becomes integrated into diagnostic algorithms. However, published CUP cohorts and guideline-based series remain anchored to clinical and pathologic criteria and do not characterize patients whose tissue-of-origin (TOO) predictions remain low probability despite comprehensive molecular analysis. This population—where molecular data fail to resolve lineage—is poorly described. We evaluated clinical, molecular, and outcome features of CUP defined as $<$ 90% probability for all predicted lineages. **Methods:** A retrospective chart review of TOO tests ordered at a single academic center between 2021-2025 was conducted. Demographics, pathology, molecular features including Tumor Mutational Burden (TMB), mutational profiles, predicted lineages, and treatments were abstracted from the TOO report and electronic health record. Survival status was assessed as of 12/31/2025. **Results:** Among 132 patients evaluated for CUP, 50 met the study definition (TOO probability $<$90% for a single lineage). Median age was 66 years, 56% were female and 76% were Black. Predicted lineages spanned gastrointestinal, pancreaticobiliary, lung, breast, melanoma, and genitourinary tissues, reflecting heterogeneity and lack of dominant lineage signal. Many tumors demonstrated overlapping immunophenotypes consistent with molecular ambiguity. High TMB ($\geq$10 mut/Mb) was reported in 16% with PD-L1 positive in 4%, limiting eligibility for tissue-agnostic immunotherapy. Most patients received empiric systemic therapy rather than site-directed or molecularly targeted regimens. Targetable alterations reported included BRAF, KRAS, HER2, ATM, CHEK2, and PIK3CA. TOO primary site predictions were in concordance with final pathology in only 22 cases (44%). At last follow-up, 29 patients (57%) were deceased. **Conclusions:** This study characterizes a precision-oncology–relevant subset of CUP in which molecular classifiers fail to assign high-confidence lineage, a population not represented in prior CUP publications. Tumors in this cohort showed broad predicted lineages across multiple organ systems with low rates of high TMB, reflecting substantial molecular heterogeneity. Many displayed nondistinct histology with overlapping immunophenotypes, consistent with diagnostic ambiguity. Concordance between predicted TOO and final pathology was limited, underscoring the challenges of relying solely on molecular classifiers. Actionable targets and markers for immunotherapy were infrequent, and most patients received empiric chemotherapy. Outcomes were poor, underscoring the unmet need for improved integrative molecular approaches and novel precision-oncology strategies in CUP subsets that remain unresolved despite comprehensive molecular assessment. Research Sponsor: None.

3077 **Poster Session**

Analytical validation of a plasma-based cfDNA NGS assay (Guardant360 Liquid CDx) for comprehensive solid tumor profiling. First Author: Brett Kennedy, Guardant Health, Palo Alto, CA

Background: NGS-based profiling of circulating cell-free DNA (cfDNA) enables accurate and sensitive tumor genotyping from blood. Guardant360 Liquid CDx is intended as a companion diagnostic for comprehensive tumor mutation profiling across $>$700 genes in patients with malignant neoplasms. Analytical performance was evaluated per FDA IVD standards and guidelines across five variant classes: single-nucleotide variants (SNVs), insertions/deletions (indels), gene rearrangements, gene amplifications (CNA), and copy-number losses (CNLs) – with emphasis on accuracy, precision, specificity (limit of blank [LoB]), and limit of detection (LoD). **Methods:** Analytical Validation tested $>$4000 samples from nearly 2,000 unique patients across 29 cancer types, as well as contrived materials. Concordance was evaluated against FDA-approved Guardant360 CDx and an externally developed ctDNA assay, where applicable. Primary endpoints were positive percent agreement (PPA) and negative percent agreement (NPA) by variant class and category (clinically significant vs panel-wide). LoD was established at both low and high input levels. No minimum cfDNA ng input cutoff was required; low-input performance was evaluated at minimum molecule coverage (QC threshold). Precision was assessed across workflow components and blood collection tube (BCT) lots. Specificity was assessed using healthy donor cfDNA sequenced with multiple replicates at high input. **Results:** Clinical samples demonstrated a high QC pass rate of 99.1%. Clinically significant variants showed high concordance: SNV PPA 94.9% with NPA 99.86%, and indel PPA 96.24% with NPA 99.98%. Panel-wide specificity was near-perfect (SNV NPA 99.99966%; indel NPA 99.99991%). Rearrangements achieved PPA 94.64% and NPA 99.76%; CNA PPA 91.67% and NPA 99.97% ; CNL PPA 100% and NPA 97.56%. High-input LoD was established in silico and confirmed with clinical samples: 0.2% mutant allele frequency (MAF) for all clinically relevant SNVs, indels and most rearrangements, with selected variant LoD as low as 0.1% (KRAS G12C). At the minimum input, panel-wide LoD was 1.0% for clinically relevant SNVs and 0.9% for indels; 0.5-1.6% for rearrangements, 2.3-2.4 copies for CNAs, and 22.7% tumor fraction for CNL. Precision studies showed $\geq$98.6% agreement across conditions at near-LoD variant levels; within-lot and between-lot BCT precision yielded $>$97% analytical positive/negative agreement (targeted variants $\geq 1\times$ LoD). In LoB, no false positive variants were detected in any healthy donor replicates (0% FPR per sample and per variant), validating in-silico CHIP detection methods. **Conclusions:** The assay demonstrates high accuracy, precision and specificity across all reportable variant classes, with LoD at or below 0.2% MAF for key variant types. These data support its use for comprehensive, pan-cancer tumor genomic profiling in routine oncology practice. Research Sponsor: None.

3078 Poster Session

Farnesyl transferase inhibitor (FTI) darlifarnib (KO-2806) in combination with adagrasib in *KRAS* G12C mutated (mut) advanced solid tumors: Preliminary results from the FIT-001 phase 1 first-in-human trial. First Author: Andrea Zivi, Centro Ricerche Cliniche di Verona, Verona, Italy

Background: Clinical response to RAS inhibitors (RASi) is often limited by inherent/adaptive resistance mediated by persistent mTORC1 signaling. RHEB is a farnesylation-dependent protein required for mTORC1 activation. Darlifarnib, a potent next-generation FTI, selectively inhibits mTORC1 pathway activation and demonstrates synergistic antitumor activity in combination with the KRAS G12C inhibitor adagrasib (ada) in preclinical models, supporting potential to improve clinical activity in *KRAS* G12C mut tumors. **Methods:** FIT-001 (NCT06026410) is an ongoing, multicenter, open-label Ph1 dose escalation/expansion study of darlifarnib in advanced solid tumors. Darlifarnib 3, 5 or 8 mg QD D1–7, D15–21 + ada 400 mg BID in 28d cycles was evaluated in heavily pretreated pts with *KRAS* G12C mut NSCLC, PDAC or CRC. Primary objectives: safety/tolerability; key secondary objective: antitumor activity. **Results:** Dose escalation resulted in candidate darlifarnib doses of 3 and 5 mg. As of 15 Dec 2025, 30 pts (median age 61y; 63% male; 83% White; 93% baseline [BL] Karnofsky performance status 80–100%) received ≥1 darlifarnib 3 (n=15) or 5 mg (n=15) + ada dose. Primary tumor types: 30% NSCLC, 20% PDAC, 50% CRC. Pts were heavily pretreated: 43% had ≥3 prior systemic therapies; 40% had prior KRASi. Both darlifarnib 3 and 5 mg + ada were well tolerated; most common (≥30%) any-grade (Gr) treatment-emergent AEs (TEAEs): 63% diarrhea, 57% nausea, 50% anemia, 43% vomiting, 40% neutropenia, 40% thrombocytopenia. Most common (≥15%) Gr ≥3 TEAEs: 30% neutropenia, 17% anemia. 1 dose limiting toxicity occurred (anemia, darlifarnib 5 mg + ada). Most common treatment (trx) discontinuation reason was progressive disease (n=10). With a median follow-up of 23 wks, 13 pts remained on trx. Preliminary results from 25 response-evaluable pts (≥1 darlifarnib dose + post BL scan) included confirmed + unconfirmed responses. Antitumor activity was observed in all tumor types. Across darlifarnib 3 and 5 mg + ada dose levels, ORRs (95% CI) were 67% (22.3–95.7) for NSCLC, 60% (14.7–94.7) for PDAC, 14% (1.8–42.8) for CRC (Table); DCRs (CR+PR+SD): 83% (35.9–99.6) for NSCLC, 100% (47.8–100) for PDAC, 71% (41.9–91.6) for CRC. Updated data across all doses to be presented. **Conclusions:** Darlifarnib 3 and 5 mg + ada were well tolerated with encouraging antitumor activity in heavily pretreated *KRAS* G12C mut NSCLC, PDAC and CRC. These preliminary data support further investigation of darlifarnib + KRASi, such as ada, to address mTORC1-mediated resistance and potentially improve clinical outcomes for pts. Clinical trial information: NCT06026410. Research Sponsor: Kura Oncology, Inc.; Bristol Myers Squibb.

n (%)	Darli 3 mg + ada	Darli 5 mg + ada	Total
NSCLC	3	3	6
ORR[a]	1 (33)	3 (100)	4 (67)
DCR	2 (67)	3 (100)	5 (83)
PDAC	2	3	5
ORR[a]	2 (100)	1 (33)[b]	3 (60)[b]
DCR	2 (100)	3 (100)	5 (100)
CRC	6	8	14
ORR[a]	0	2 (25)	2 (14)
DCR	3 (50)	7 (88)	10 (71)

[a]Confirmed+unconfirmed responses.
[b]1 uPR post datacut.

3079 Poster Session

A phase 2 multi-center pharmacodynamic study of the fatty acid synthase (FASN) inhibitor TVB-2640 in advanced *KRAS*-mutant non–small cell lung cancer. First Author: Arthi Sridhar, Harold C. Simmons Cancer Institute, UT Southwestern Medical Center, Dallas, TX

Background: Preclinical and translational studies demonstrate that KRAS-mutant NSCLC has a unique metabolic dependence on de novo fatty acid synthesis, mediated by fatty acid synthase (FASN) and downstream lipid metabolism pathways that support saturated fatty acid production, enabling rapid tumor growth, survival, and resistance to lipid peroxidation. TVB-2640 is an orally bioavailable and selective FASN inhibitor that blocks the β-ketoacyl reductase step of fatty acid synthesis and has demonstrated antitumor activity in *KRAS* mutant NSCLC models. **Methods:** This single-arm trial (NCT03808558) enrolled patients with previously treated, advanced *KRAS* mutant NSCLC. Eligible patients had progressed on prior platinum-based chemotherapy (100%) and immune checkpoint inhibition (95%), had measurable disease by RECIST v1.1, ECOG performance status 0–1, and adequate organ function. One patient had received prior KRAS directed therapy. TVB-2640 100 mg/m^2 (equivalent to two to four 50-mg tablets) was administered orally once daily in continuous 28-day cycles. Exploratory correlative analyses included ^{11}C-acetate PET, plasma lipidomics, sebaceous lipid profiling, and quality-of-life measures. **Results:** Among 18 enrolled patients, the median age was 69 years, 12 (67%) were male, 14 (78%) were white and 13 (72%) had a history of smoking. Median number of prior lines of therapy was 4. The most common *KRAS* mutations were G12V (44%), G12C (17%), and G12D (17%). No patients had a radiographic response, 7 (39%) had stable disease, 9 (50%) had disease progression, and 2 (11%) were non-evaluable. Five patients (28%) had radiographic shrinkage of target lesions but did not achieve partial response due to the magnitude of decrease (n = 3) or progression of non-target lesions (n = 2). Median progression-free survival was 1.8 months (95% CI, 1.7-1.8 months). Overall, 84% of patients had adverse events (AE). Most common AEs were xerostomia (50%), dry skin (44%), and fatigue (39%). Most common grade ≥ 3 AEs (44%) were fatigue, dermatological toxicities, xerostomia, ocular toxicities and anemia (11% each). **Conclusions:** Single-agent FASN inhibition with TVB-2640 in heavily pretreated *KRAS* mutant NSCLC did not meet the primary endpoint of response. Since FASN is a downstream effector of mutant KRAS, combination regimens with KRAS inhibitors can be considered as a future approach in NSCLC. Ongoing correlative studies may further inform the use of this agent. Despite not meeting its primary endpoint, this clinical trial highlights a novel therapy targeting energy metabolism in lung cancer. Clinical trial information: NCT03808558. Research Sponsor: Gateway Foundation for funding the clinical trial; Sagimet for provision of product/material.

3080 Poster Session

Pan-cancer landscape and real-world management of BRAF non-V600E and MAP2K1 alterations: Analysis from the WAYFIND-R registry. First Author: Esranur Aydın, Istinye University, Istanbul, Turkey

Background: While targeted therapies have revolutionized the management of BRAF V600E-mutant tumors, non-V600E BRAF and MAP2K1 alterations remain a clinical "gray zone." These variants represent a functionally diverse group of drivers with no established treatment guidelines, often leading to heterogeneous care and suboptimal outcomes. We used the multinational WAYFIND-R registry to map the prevalence and functional landscape of these rare alterations and to evaluate real-world treatment patterns. **Methods:** We retrospectively analyzed 4,774 patients with solid tumors from the multinational WAYFIND-R registry (NCT04529122). Patients with BRAF and MAP2K1 alterations identified via Next-Generation Sequencing (NGS) were included. Variants were categorized by functional class (Class I-III). Clinical characteristics, co-mutation profiles, and treatment sequences were analyzed to correlate molecular features with management strategies and outcomes. **Results:** Rare alterations were identified in 38 (0.8%) patients, predominantly in colorectal (29%), lung (13%), and melanoma (13%) cancers. Genomic analysis revealed a complex landscape. Among BRAF-altered patients (n=30), while Class I (V600E/K) accounted for 63.3% (n=19), the remaining 36.7% comprised non-V600E variants distributed between functional Class II (20.0%) (e.g., G469A, L597S) and Class III (13.3%) (e.g., D594N, G466R). MAP2K1 alterations (n=9) were distributed across RAF-dependent Class I (44.4%), RAF-regulated Class II (44.4%), and RAF-independent Class III (11.1%) variants (e.g., E102_I103del). Treatment patterns were highly inconsistent. While first-line therapy typically consisted of standard chemotherapy or anti-PD-1 monotherapy, there was no consensus for subsequent lines. This lack of targeted approach correlated with poor outcomes in lung and colorectal cohorts. However, in contrast to unselected treatments, we observed durable responses with biology-guided MEK inhibitor plus Immunotherapy combinations in two index cases. A patient with MAP2K1 Class III (E102_I103del) NSCLC achieved a near-complete metabolic response with cobimetinib + nivolumab. Similarly, a BRAF Class II (G469A) NSCLC patient achieved a complete metabolic and molecular response (confirmed by ctDNA clearance) with trametinib + pembrolizumab. **Conclusions:** This analysis confirms that >35% of BRAF-altered patients (nonV600 mutants) and all MAP2K1-altered patients in real-world settings currently lack standardized treatment protocols. The observed clinical heterogeneity highlights a significant unmet need. Our findings suggest that integrating functional subclassification into clinical decision-making and utilizing targeted combinations is necessary and may offer a viable strategy. Clinical trial information: NCT04529122. Research Sponsor: F. Hoffmann-La Roche Ltd.

3081 Poster Session

First data disclosure from the first-in-human phase 1/2 trial of SMP-3124LP, the first investigational pegylated liposome CHK1 inhibitor, in patients with selected advanced solid tumors. First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Checkpoint kinase 1 (CHK1) is a critical in the DNA damage response pathway and an important target for anticancer therapy. However, clinical development of CHK1 inhibitors has been limited by myelosuppression and a narrow therapeutic window. The use of liposomal technology potentially widens the therapeutic window by lowering rates of hematologic toxicities minimizing drug exposure to healthy tissues and maximizing delivery to tumors. SMP-3124 is a structurally distinct CHK1-selective inhibitor designed to be optimally delivered in a PEGylated liposome formulation. SMP-3124LP is being developed for malignancies with high replication stress. **Methods:** This ongoing Phase 1/2 study evaluated the safety, tolerability, PK, and preliminary antitumor activity of SMP-3124LP given intravenously (NCT06526819). The dose escalation included patients (pts) with selected advanced solid tumors. **Results:** As of 28 Nov 2025, 42 pts were enrolled at 20, 40, 60, and 90 mg/m^2 every 2 weeks. 23 pts (55%) had ≥4 prior lines of therapy. No dose-limiting toxicities (DLTs) were observed at 20 or 40 mg/m^2. A DLT of Grade (G) 4 thrombocytopenia was noted at 60 mg/m^2 and one pt had 2 DLTs of reversible G4 thrombocytopenia and G3 febrile neutropenia at 90 mg/m^2. Most common treatment-related adverse events (≥20%) were neutropenia (45%), infusion-related reactions (IRR, 38%), thrombocytopenia (36%), anemia (24%) and leukopenia (21%). Treatment-related G3/4 neutropenia was 33%, G3/4 thrombocytopenia and G3 anemia were 9.5% each. Cytopenias were generally transient and none led to treatment discontinuation. All IRRs were G1/2 and manageable with premedications, supportive care, and/or slower infusion rates. Dose-proportional increases in C_{max} (4.3-fold) and AUC (6.0-fold) were observed from 20 to 90 mg/m^2 with low volume of distribution (1.99 to 2.68 L) and a geometric mean half-life of 23 to 31 hours. As of 13 Jan 2026, disease control rate (DCR) was 49%, with 5 RECIST v1.1 partial responses (PR) + 12 RECIST v1.1 stable disease (SD) out of 35 efficacy evaluable patients. Among the PRs, 2 platinum-resistant ovarian cancer (PROC, one with prior PARPi), 2 anal SCC, and 1 colorectal cancer with FBXW7 mutation. 2 other advanced PROC pts had SD with tumor shrinkage 20% or more (one with -88% CA125 response). The anal SCC and rectal cancer pts all received ≥4 prior lines of therapy. Duration of response has not been reached. **Conclusions:** SMP-3124LP was generally well tolerated and had a manageable safety profile. The liposomal formulation appears to reduce the incidence of cytopenias compared to historical data with non-liposomal CHK1 inhibitors. Dose-proportional increases in PK were observed. Promising signals of antitumor activity were observed with 5 RECIST v1.1 PRs and 49% DCR in pts with heavily pretreated cancers. Clinical trial information: NCT06526819. Research Sponsor: Sumitomo Pharma America, Inc.

3082 **Poster Session**

Real-world characterization of SEZ6, a transmembrane protein expressed in various solid tumors. First Author: Afshin Dowlati, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH

Background: Seizure-related homolog 6 (SEZ6) is a transmembrane protein involved in neuronal development that is downregulated in normal adult tissues outside the central nervous system (CNS). It is overexpressed in various solid tumors such as small cell lung cancer (SCLC), neuroendocrine neoplasms (NENs), and CNS tumors, with strong correlations between mRNA and protein expression. In SCLC, limited data suggest that *SEZ6* expression is greater in molecular subtypes with neuroendocrine (NE)-high gene signatures (i.e., SCLC-A and SCLC-N) than in non-NE subtypes (i.e., SCLC-P). However, *SEZ6* expression in tumor tissues remains poorly understood and existing data are limited by small sample sizes. This study aimed to characterize *SEZ6* expression in a large patient population, across multiple tumor types. **Methods:** Pan-tumor data from a real-world database (Tempus AI, Inc.) were analyzed for *SEZ6* mRNA expression in 37,645 samples, with a focus on lung, brain, and NE tumor types. In SCLC, *SEZ6* expression was compared between SCLC-A, -N, -P, and -I samples via hierarchical clustering. Gene expression was reported as $\log_2$(transcripts per million [TPM]+1). **Results:** Across the 37,645 samples analyzed, tumor types with the highest median ($\log_2$[*SEZ6* TPM+1]) expression were astrocytoma (5.8; n=354), glioma (5.8; n=502), NENs (5.7; n=2794), and glioblastoma (5.6, n=2833). Among NENs, the highest *SEZ6* expression was seen in prostate neuroendocrine carcinoma (NEC) (6.6; n=176), SCLC (6.5; n=2018), and bladder small cell NEC (6.5; n=139). Median *SEZ6* expression was 3–45-fold higher than other biomarkers of interest in SCLC (*B7-H3*, 3-fold; *DLL3*, 3-fold; *CD274* [PD-L1], 28-fold; *PDCD1* [PD-1], 45-fold). In SCLC samples, median *SEZ6* expression was stable across primary (6.4) and metastatic (6.5) tumors and stage II to IV disease (6.6–6.5). Among SCLC molecular subtypes, median *SEZ6* expression was lower in non-NE SCLC-P tumors (3.8; n=85) than in SCLC-I (6.0; n=175), or in NE-high SCLC-N (6.7; n=339) and SCLC-A (7.3; n=224) tumors. *SEZ6* expression was 6–7-fold higher in prostate NEC than in non-NE metastatic prostate adenocarcinoma (castration resistant, 6-fold; castration sensitive, 7-fold). **Conclusions:** *SEZ6* is highly expressed in SCLC and tumors of NE origin, particularly prostate and bladder NEC. In SCLC, *SEZ6* expression is higher than other targets of antibody–drug conjugates (ADCs) approved or in development for SCLC, supporting SEZ6 as a promising therapeutic target. *SEZ6* expression is highest in SCLC-A and SCLC-N molecular subtypes. High *SEZ6* expression is also seen in SCLC-I, a subtype associated with platinum resistance, suggesting SEZ6 may be a potential therapeutic target in certain patients with platinum-refractory SCLC. Taken together, these results suggest cross-indication applicability of targeting SEZ6, highlighting its potential as a multi-tumor ADC target warranting further investigation. Research Sponsor: Whitehawk Therapeutics.

3083 **Poster Session**

Convenience vs. complexity: Adoption of subcutaneous PD-(L)1s in lung cancer in EU4+UK. First Author: Federico Gallo, Ipsos Insight, New York, NY

Background: Subcutaneous (SC) PD-(L)1 formulations represent a significant step towards simplifying treatment administration by reducing treatment time, compared to intravenous (IV) preparations. To date, the EMA has approved three SC PD-(L)1s: atezolizumab, nivolumab, and pembrolizumab. Here, we evaluate how the availability of SC formulation is affecting physicians' prescribing behaviour, the drivers of the switch from IV to SC, and potential barriers affecting decisions in the treatment of lung cancer in EU4+UK. **Methods:** The Ipsos' Global Oncology Monitor is a physician-reported syndicated patient record database. This analysis comprises 2,537 cancer-treating physicians in EU4+UK, screened for seniority and caseload, submitting data on 36,383 lung cancer patients, online, from January 2024 to November 2025. Physicians who treated lung cancers also completed a perceptual questionnaire on SC PD-(L)1 usage in lung cancer. Responses were collected from 150 physicians in EU4+UK, online, from October to December 2025. **Results:** Adoption of SC PD-(L)1 in lung cancer in EU4+UK is at 6% in the 3 months ending November 2025 compared to 94% of the IV format. We observed that SC PD-(L)1 was more likely used as monotherapy while the IV formulation in combination therapy (Table 1). Among patients receiving the IV version, 13% have a planned switch to SC, 71% do not, while 16% remained classified as the physician being undecided. Of those who would switch/undecided, the switch was estimated to happen after a mean of 4.5 cycles on the IV formulation. **Conclusions:** In this study, the uptake of SC PD-(L)1 reflects its clear benefit in reducing treatment time; however, the IV formulation remains dominant, suggesting physician hesitancy toward the SC format. While shorter administration time is beneficial, it does not yet outweigh concerns regarding patient comfort. Crucially, SC usage is notably lower in combination therapies compared to monotherapy. This suggests that when IV chemotherapy is required, the convenience of an SC add-on is diminished. Furthermore, the perception that SC offers 'no additional value' over the established IV contributes to this inertia. To drive adoption and improve patient experience, manufacturers must address administration-related discomfort and effectively communicate the comparative efficacy and workflow benefits of the SC formulation, particularly for patients who have yet to switch. Further investigation to assess any country differences and patient point of view will be beneficial. Research Sponsor: None.

Usage of PD-(L)1 by formulation.

	Subcutaneous n=123	Intravenous n=1,914
Monotherapy	72%	41%
Combination	28%	59%

3084 **Poster Session**

Targeting cancer stem cells with a novel virus-like drug conjugate. First Author: Stevie Fawcett, CCR, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Belzupacap sarotalocan (bel-sar) is a novel virus like-drug conjugate in clinical stage development for multiple solid tumors. The virus-like particle component of the drug is derived from the papillomavirus and specifically binds to heparan sulfate proteoglycans (HSPGs) and chondroitin sulfate proteoglycans (CSPGs) with unique sulfation modifications on the surface of cancer cells. Upon activation with near-infrared light, cell associated bel-sar causes immediate cell death and induces an anti-tumor immune response, with a single administration leading to elimination of solid tumors accompanied by long-term protective immunity in a number of animal tumor models. Cancer stem cells (CSCs) represent a distinct subpopulation of tumor cells that possess stem-like characteristics, including self-renewal. These cells are thought to drive disease persistence and are intrinsically more resistant to conventional cancer treatment, such as chemotherapy, radiotherapy, and immunotherapy. CSC-mediated resistance remains a major obstacle to achieving durable clinical responses and the elimination of this cell population is hypothesized to be essential for long-lasting tumor control. **Methods:** We developed and characterized a panel of human-derived CSC models (bladder, breast, oropharyngeal, prostate cancers, glioblastoma, uveal melanoma) using a SORE6 lentivirus reporter in which stem-like transcription factors SOX2 and OCT4 drive GFP expression to identify CSC subpopulations. Bel-sar binding and potency was compared between CSC and the more differentiated non-cancer stem cells (nCSC) populations. Additionally, chemotherapy resistant tumor lines were established from the CSC panel and were similarly tested for bel-sar targeting and cytotoxicity. **Results:** CSC populations were validated by SOX2/OCT4 co-expression, CSC surface marker expression (CD24, CD44, EpCAM-1, CXCR4), ALDH activity, and tumorsphere formation. Bel-sar was capable of binding CSCs with equal or enhanced efficiency as compared to nCSCs through cell surface HSPGs and CSPGs as demonstrated by heparin and chondroitin sulfate inhibition. Additionally, bel-sar was able to kill CSCs and nCSCs with equal efficiency in vitro. Following chemotherapy-induced enrichment of CSCs, bel-sar maintained its therapeutic effect on chemotherapy-resistant CSC populations, reinforcing previous data demonstrating complete responses in animal models. **Conclusions:** This study highlights bel-sar's distinctive capacity to target and eradicate CSCs across diverse tumor types. These results support bel-sar's clinical development for local tumor control and suggest bel-sar treatment may be effective against recurring or chemotherapy-resistant tumors. Research Sponsor: Aura Biosciences; National Cancer Insitute.

3085 **Poster Session**

Targeting TP53 pathologic variants for cancer immunotherapy using a self-replicating mRNA vaccine strategy. First Author: Changgan Chen, Fujian Medical University Union Hospital, Fuzhou, China

Background: *TP53* pathogenic variants (PVs) are highly prevalent in human malignancies as a whole and especially in patients with pancreatic ductal adenocarcinoma (PDAC). Approximately 80% of TP53 PVs are missense mutations that may be targeted for cancer therapy. **Methods:** We have developed a self-replicating mRNA (srRNA) vaccine (TMG-mut *TP53* srRNA SA-LNP) encoding concatenated p53 mutant peptides encompassing 14 hotspot *TP53* missense mutations in PDAC, encapsulated in sialic acid (SA)-modified lipid nanoparticles (LNPs). These 14 hotspot TP53 PVs were selected by examining four public available datasets and from our previous studies. **Results:** TMG-mut *TP53* srRNA SA-LNPs incorporated Venezuelan equine encephalitis virus replicase which enabled higher and prolonged *in vivo* protein expression compared to conventional mRNA construct. Encapsulation with SA-modified LNPs led to significantly better efficiency in targeting dendritic cells (DCs) *in vitro* and *in vivo* compared to conventional LNPs. We used *in vitro* (cell lines) and *in vivo* assays (PDX and human engineered mouse genetic models) to test the efficacy of our RNA vaccine. We validated the detection of TP53 neoantigen by mass spectrometry generated by our srRNA vaccine. We then tested its anti-tumor immunity by itself alone and in combination with anti-PD1 inhibition using multiple cell lines and PDX that carry different TP53 PV (R175H and R273H). TMG-mut *TP53* srRNA SA-LNP stimulated potent and specific anti-tumor $CD8^+$ T cell responses in *in vitro* and *in vivo* assays using autologous DCs, T cells and cancer cells from multiple PDAC patients. Using both Panc02 syngeneic PDAC cell line and patient-derived PDAC xenografts (PDX), we show that TMG-mut *TP53* srRNA SA-LNP stimulated potent and specific anti-tumor immunity against PDAC tumors that harbor different corresponding p53 PVs. Panc02-$TP53^{R175H}$ tumor-bearing transgenic mice expressing human HLA-A*02:01 treated with TMG-mut *TP53* srRNA SA-LNP showed significantly suppressed tumor growth and prolonged survival with increased tumor infiltration of activated $CD8^+$ T cells as well as increased production of cytokines including type II interferon, TNFalpha, and other biomarkers. We also show our vaccine stimulates increased tumor cell apoptosis. In addition, TMG-mut *TP53* srRNA SA-LNP dramatically enhanced the anti-tumor immunity of anti-PD1 by synergistically suppressing tumor growth and prolonging the survival of tumor-bearing mice in both low and high-tumor burden animal model. **Conclusions:** Our results demonstrate for the first time that missense p53 PVs are valid targets for developing novel cancer immunotherapy using srRNA vaccine approach enhanced by SA-LNPs encapsulation. Our data potentially opens a new approach for developing mRNA vaccine-based immunotherapy for a large population of cancer patients as TP53 PVs are highly prevalent in nearly every type of malignant tumors. Research Sponsor: None.

3086 **Poster Session**

TSY-310, a novel bispecific EGFR×ROR1 ADC: Assessment of antitumor activity in heterogeneous breast tumors through enhanced internalization and bystander cytotoxicity. First Author: Kuo-Ming Yu, Formosa Pharmaceuticals, Inc., Taipei, Taiwan

Background: Epidermal growth factor receptor (EGFR) is a clinically validated target and is highly expressed in various solid tumors, including triple-negative breast cancer (TNBC). Clinical efficacy of EGFR-directed therapies in TNBC, however, is often limited by intratumoral heterogeneity, acquired resistance, and mutations conferring insensitivity to tyrosine kinase inhibitors. TSY-310 is a novel bispecific EGFR×ROR1 nanobody-Fc fusion antibody–drug conjugate (BsADC) designed to address these challenges by simultaneously targeting EGFR and receptor tyrosine kinase-like orphan receptor 1 (ROR1). TSY-310 carries an average of 3.6 molecules of monomethyl auristatin E (MMAE) via a protease-cleavable valine–citrulline linker, enabling potent and tumor-selective cytotoxicity, and induces strong tumor regression across multiple NSCLC PDX models representing a range of EGFR and ROR1 expression levels. **Methods:** Cytotoxicity was evaluated in cell lines with distinct EGFR/ROR1 expression profiles. Bystander killing was assessed in co-culture systems of antigen-positive and antigen-negative cells. Cellular internalization and trafficking were analyzed by immunofluorescence microscopy. In vivo efficacy and bystander activity are investigated in xenograft models with heterogeneous antigen expression. **Results:** TSY-310 exhibited sub-nanomolar cytotoxicity (IC_{50} = 0.45 nM) against MDA-MB-468 ($ROR1^+$/$EGFR^+$) TNBC cells in correlation with dual receptor expression levels, and demonstrated robust bystander killing, eliminating neighboring antigen-negative A427-Luc and MDA-MB-453-Luc cells through MMAE diffusion in co-culture systems. Rapid internalization of TSY-310 was observed in dual-positive MDA-MB-468 cells within 6 hours, consistent with enhanced cytotoxic activity. In a $EGFR^+$/$ROR1^+$ HBCx-28 TNBC PDX model, it achieved complete and sustained tumor regressions in all treated mice (5/5) and demonstrated superior efficacy compared with the monospecific ROR1-directed ADC on a payload-equivalent basis. In vivo studies to assess bystander activity and efficacy in heterogeneous tumor models are ongoing. **Conclusions:** These findings highlight TSY-310 as a first-in-class bispecific ADC capable of overcoming tumor heterogeneity through dual binding and bystander killing, supporting its potential as an effective therapeutic agent for heterogeneous solid tumors such as TNBC, where existing EGFR-targeted therapies have shown limited benefit. Research Sponsor: Formosa Pharmaceuticals, Inc.

3087 **Poster Session**

Influence of genetic ancestry on UV mutational signatures linked to immunotherapy response in melanoma, beyond TMB. First Author: Kevin Magnaye, Caris Life Sciences, Irving, TX

Background: Melanoma is a UV-driven malignancy with substantial biological heterogeneity, yet genomic profiling efforts have historically underrepresented diverse ancestral backgrounds, limiting insights into population-level differences in tumor biology and treatment response. **Methods:** In this retrospective study, a supervised machine learning framework was developed to infer genetic ancestry across 483,454 tumors profiled by tumor-only whole-exome sequencing (WES) at Caris Life Sciences (Phoenix, AZ), using 36,962 ancestry-informative variants derived from globally diverse Genome Aggregation Database (gnomAD) reference individuals (n=4,150). Survival outcomes inferred from claims data were evaluated using Cox proportional hazard ratios (HR) with 95% confidence intervals (CI) and log-rank p-values. Associations between features were evaluated using standard statistical tests and regression models. **Results:** We applied this framework to cutaneous melanoma (N=8,872). The UVB-related COSMIC mutational signatures SBS7a and SBS7b were markedly enriched in tumors from patients (pts) of European (EUR) ancestry (93.2% and 75.6%, respectively) but were uncommon in African ancestry tumors (6.9% and 5.2%). Within EUR ancestry pts, higher EUR ancestry fraction was associated with higher SBS7a and SBS7b prevalence ($p=9.0x10^{-4}$ and $1.5x10^{-4}$), consistent with known differences in pigmentation biology and melanoma etiology. Among 3,587 melanoma pts treated with first-line immune checkpoint inhibitors (ICI), SBS7a positivity was strongly associated with improved overall survival (OS HR [95% CI] = 0.55 [0.46–0.66]) and time to next treatment (TTNT HR=0.58 [0.49–0.69]; all $p<0.001$), outperforming tumor mutational burden (TMB) as a prognostic biomarker. SBS7a+ remained prognostic in a multivariable Cox analysis accounting for TMB, age, sex, and the first two ancestry principal components. Furthermore, both SBS7a+ TMB-high and SBS7a+ TMB-low tumors demonstrated superior outcomes compared to SBS7a– TMB-low tumors (OS HR=0.49 [0.41–0.60] and 0.62 [0.51–0.74], respectively; all $p<0.001$). Similar patterns were observed in cutaneous squamous cell carcinoma. To assess specificity for UV-driven biology, we evaluated two non-sun-exposed malignancies: uveal melanoma and renal cell carcinoma (RCC). SBS7a was virtually absent in uveal melanoma and RCC (6.7% and 6.9%, respectively, among EUR ancestry pts) and did not stratify ICI outcomes in either cancer. These negative controls suggest that SBS7a does not arise without UV exposure and is not a general immunotherapy biomarker. **Conclusions:** These findings establish a scalable genetic ancestry framework, reveal ancestry-linked differences in melanoma mutagenesis, and demonstrate that SBS7a provides clinically meaningful, TMB-independent prognostic information specific to UV-driven tumors. Research Sponsor: None.

3088 **Poster Session**

A phase 1, first-in-human study of OP-3136, a novel oral selective KAT6A/B inhibitor, as monotherapy in advanced solid tumors and in combination with endocrine therapy in ER+, HER2– advanced breast cancer (ABC): Preliminary results. First Author: Amita Patnaik, START Center for Cancer Research, San Antonio, TX

Background: Histone lysine acetyltransferases (KATs) control oncogenic transcription and are frequently dysregulated in cancer. OP-3136 is a potent, selective, oral small-molecule inhibitor of KAT6A/B with preclinical antitumor activity, including in combination with endocrine therapy (ET) (Palanisamy et al, 2024). This phase 1 study evaluates the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of OP-3136 as monotherapy in advanced solid tumors and in combination with fulvestrant or palazestrant (a novel oral complete estrogen receptor antagonist [CERAN] and selective estrogen receptor degrader [SERD]) in ER+, HER2– ABC (NCT06784193). **Methods:** Patients (pts) with ABC, metastatic castration-resistant prostate cancer (mCRPC), or non-small cell lung cancer (mNSCLC) received OP-3136 once daily (QD) as monotherapy (no limit on prior lines of therapy), and a separate cohort of ABC pts received OP-3136 + fulvestrant in a phase 1 study using a Bayesian Optimal Interval dose-escalation. **Results:** As of 26 November 2025, 32 pts ABC, n=23; mCRPC, n=8; and mNSCLC, n=1) received OP-3136 (monotherapy, n=25; in combination with fulvestrant, n=7) across doses of 2–45 mg QD. All ABC pts received prior endocrine therapy and CDK4/6 inhibitors, all mCRPC pts received prior androgen receptor–targeted therapy. The median (min – max) of prior anticancer systemic therapy lines was 3 for ABC (1–5) and 5 (1–8) for mCRPC pts. The median time on treatment was approximately 2 months (max 47 months). In the monotherapy cohort, treatment-related adverse events (TRAEs) were mostly grade (G)1–2. The most common (≥25%) TRAEs included dysgeusia (72%; G2, 24%), anemia (40%; G3, 8%), fatigue (32%; G2, 16%), and neutropenia (28%; G3, 20%). In the combination cohort, TRAEs were predominantly G1–2 with one G3 neutropenia and leukopenia. No dose-limiting toxicities (DLTs), G4-5 TRAEs or treatment discontinuations due to TRAEs were reported. Across monotherapy dose levels, among 14 pts with measurable disease, reduction of target lesions occurred in 64% (9/14) and 2 pts (1 with ABC and 1 with mCRPC) had partial responses (unconfirmed). Among 17 pts with evaluable disease,10 had stable disease. PK analyses showed dose-proportional exposure of OP-3136 with rapid absorption and sustained systemic exposure over the dosing interval supporting QD administration. **Conclusions:** OP-3136 demonstrated a manageable safety profile and favorable PK, both as monotherapy and in combination with fulvestrant. Preliminary evidence of antitumor activity in ER+ HER2- ABC and mCRPC was observed in these heavily pretreated pts. Dose escalation and enrollment in combination with fulvestrant or palazestrant are ongoing and updated data will be presented. Clinical trial information: NCT06784193. Research Sponsor: Olema Oncology.

3089 **Poster Session**

A phase 1a/b study of RGT-61159, an oral MYB splicing modulator, in patients with advanced adenoid cystic carcinoma and colorectal cancer. First Author: Alan Loh Ho, Solid Tumor Oncology Division, Head and Neck Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: MYB is a master regulator of cell proliferation, self-renewal, and differentiation processes and its aberrant expression is found in multiple forms of human cancer including adenoid cystic carcinoma (ACC), acute myeloid leukemia, T-cell acute lymphoblastic leukemia, colorectal cancer (CRC), small cell lung cancer, and breast cancer. RGT-61159 is an orally available small molecule designed to selectively modulate splicing of the oncogenic transcription factor MYB, resulting in downregulation of MYB protein levels and tumor cell death. **Methods:** This ongoing Phase 1a/b, multi-center, open-label clinical trial evaluates RGT-61159 in patients (pts) with advanced, relapsed or refractory ACC or CRC. Pts with ACC must have disease progression within 12 months of study entry. The study employs a 3+3 dose-escalation design with daily oral dosing in 21-day cycles, starting at 6 mg and escalating using a Fibonacci scheme. Primary objectives are to assess safety and tolerability and determine the recommended Phase 2 dose (RP2D). Secondary objectives include characterization of pharmacokinetics (PK), pharmacodynamics (PD), and preliminary anti-tumor activity. **Results:** As of 22 December 2025, 44 pts (86% ACC, 14% CRC) were treated across 8 dose levels (6–144 mg). In pts with ACC, median age was 61 years (range: 33–77) and median prior lines of therapy was 1 (range: 0-6); 47% were female. In pts with CRC, median age was 63 years (range: 44–72) and median prior lines of therapy was 5.5 (range: 4-8); 50% were female. Dose-limiting toxicities (DLTs) occurred in three pts: G3 nausea and muscle weakness, G3 fatigue, and missed doses due to G2 atrial flutter. Treatment-emergent adverse events (TEAEs) observed in ≥20% of pts were diarrhea, nausea, fatigue, dyspnea, and anemia. One G3 vasculitis (144 mg) and dose-related inflammatory edema events (G2 at 108/144 mg; G1 at lower doses) occurred; none were protocol-defined DLTs. Overall, RGT-61159 was well tolerated at or below the provisional RP2D of 84mg. 19 pts remain on treatment, including 9 pts (all with ACC) treated from 24 to 60mg who have been on study for more than 6 months with durable stable disease. In 35 evaluable pts, 18 have had tumor regressions with one partial response (RECIST v1.1) observed in a pt with ACC treated at 60mg. After the data cut, another pt with ACC treated at 84mg also achieved a partial response. Dose-dependent, robust knockdown of MYB in the peripheral blood was observed (up to 75% at 84mg). Plasma exposure increased approximately dose-proportionally with low to moderate variability. **Conclusions:** RGT-61159 is well tolerated at doses at or below the provisional RP2D. Robust peripheral knockdown of MYB was observed in a dose-dependent fashion at clinically relevant doses. Clinical activity manifested as prolonged stable disease and a partial responses primarily in pt with ACC. Clinical trial information: NCT06462183. Research Sponsor: Rgenta Therapeutics.

3090 **Poster Session**

Genomic landscape of *ERBB3* alterations in 5,416 metastatic solid tumors: Real-world evidence regarding biomarker-agnostic ADC strategies. First Author: Minsuk Kwon, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: While ERBB2 (HER2) is a well-established therapeutic target, the clinical significance and genomic landscape of ERBB3 (HER3) across diverse solid tumors are less defined. As HER3 emerges as a critical mediator of resistance and a target for novel antibody-drug conjugates (ADCs), characterizing its genomic alterations in a real-world setting is essential to refine therapeutic positioning. **Methods:** We analyzed clinical next-generation sequencing (NGS) data (Illumina TSO 500 or Oncomine Comprehensive Assay Plus) from 5,416 patients with metastatic solid tumors at a single tertiary center (Samsung Medical Center) between 2019 and 2025. ERBB3 alterations were categorized into mutations (SNVs/indels, VAF $\geq$2%) and amplifications (copy number [CN] $\geq$4). **Results:** ERBB3 alterations were identified in 12.9% (697/5,416) of patients. The prevalence was overwhelmingly driven by mutations (12.3%), while amplifications were rare (0.6%). The highest mutation frequencies were observed in: Urothelial carcinoma, 18.2%; Malignancy of unknown origin, 16.3%; and Biliary tract cancer, 15.7%. The most frequent variants were K498I (Domain IV) and R1127H (C-terminal tail). Known oncogenic hotspots (V104, A232V, G284R, E928G) were present but not dominant. Notably, the ERBB3-mutated cohort exhibited high co-mutation rates with canonical drivers: TP53 (66%), APC (35%), and KRAS (31%). In common GI cancers, ERBB3 mutations frequently co-occurred with APC and KRAS, suggesting they often act as "passenger" or secondary events rather than primary drivers. High-level amplifications (CN $\geq$8) were rare ($<$0.1%) and appeared in isolated cases across various histologies. **Conclusions:** ERBB3 alterations are relatively common (12.9%) in metastatic solid tumors but are characterized by a diverse mutational landscape rather than focal amplifications. The high frequency of co-occurring canonical drivers suggests that HER3 primarily functions as a resistance hub or facilitator in these tumors. These real-world data provide a strong genomic rationale for biomarker-agnostic ADC strategies (targeting HER3 protein expression) rather than mutation-specific approaches in most ERBB3-altered solid tumors. Research Sponsor: None.

3091 **Poster Session**

Phase Ib expansion and dose optimization study of CX-5461 in patients with solid tumours enriched for DNA-repair deficiencies. First Author: Ana Veneziani, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: G-quadruplexes (G4) are guanine-rich DNA/RNA structures that contribute to DNA damage and genomic instability. Pidnarulex (CX-5461) is a first-in-class G4 stabilizer that induces synthetic lethality in Homologous Recombination-deficient (HRD) cells. Previous phase 1 study showed safety and preliminary activity. Here we report dose optimization for recommended phase 2 dose (RP2D) of CX-5461 and confirm safety. **Methods:** CX-5461 was administered intravenously on Days 1 and 8 of a 28-day cycle at 2 dose levels (250 and 325 mg/m²) in patients (pts) with advanced pancreatic adenocarcinoma (PA), breast cancer (BC), or ovarian cancer (OC). The main cohort (Arms A: 250 mg/m² & B: 325 mg/m²) included pts with HRD or DNA damage response (DDR) alterations and has completed accrual. An exploratory cohort (Arms C: 250 mg/m² & D: 325 mg/m²) of OC pts with BRCA or other HRD genes enrolled simultaneously. Primary objective is to determine RP2D of CX-5461 using Relative Dose Intensity (RDI). Secondary objectives are safety, tolerability and efficacy. **Results:** 54 pts were treated and evaluable for toxicity (Arm A = 18, Arm B = 18, Arm C = 10, Arm D = 8). Patients' characteristics and efficacy results are detailed in table 1. The median number of prior lines of treatment were 6 (1-14). The median number of CX-5461 cycles received were 2 (1-30) and weeks on treatment were 8 (4-120). Grade $\geq$3 Treatment-Related Adverse Events (TRAEs) occurred in 12 pts (22%), including proteinuria, thrombocytopenia, and fatigue; 6 (11%) were AEs of special interest: 1 (2%) palmar-plantar erythrodysesthesia, 4 (7%) photosensitivity, and 1 (2%) phototoxic drug eruption. Among 29 response-evaluable pts in main cohort, 1 had PR (3%) and 10 had SD (34%),median duration 16 weeks (wks) (8-84). In evaluable OC (n=29), 2 had PR (7%), 13 SD (44%), median duration 16 wks (8-84). OC pts with BRCA mutations (n=25) had 2 PR (8%) and 11 SD (44%); all had prior PARPi exposure. 3/ 5 non-BRCA HRD had SD (60%). Prolonged clinical benefit was observed in 4 pts with treatment durations of 14 (OC, gBRCA1), 17 (OC, gBRCA2), 21 (OC, sBRCA1) and 30 cycles (PA, gPALB2). RDI was 91% in Arm A and 88% in Arm B. RDI and clinical data support 250 mg/m² as the RP2D. **Conclusions:** CX-5461 was tolerable and showed evidence of durable disease control in heavily pretreated pts, enriched for HRD/DDR alterations and post exposure to PARPi. The 250 mg/m² dose is established as the RP2D based on clinical data and RDI. Correlative studies are ongoing. Clinical trial information: NCT04890613. Research Sponsor: None.

		Arm A (N=18)	Arm B (N=18)	Arm C (N=10)	Arm D (N=8)
Tumor Type	BC	7 (39%)	2 (11%)	-	-
	OC	5 (28%)	9 (50%)	10 (100%)	8 (100%)
	PC	6 (33%)	7 (39%)	-	-
Molecular alterations	gBRCA1/2	12 (67%)	9 (50%)	3 (30%)	3 (38%)
	sBRCA1	0 (0%)	1 (6%)	6 (60%)	3 (38%)
	Other	6 (34%)	8 (44%)	1 (10%)	2 (25%)
Efficacy (evaluable pts only)	PR	1/13 (8%)	0 (0%)	0 (0%)	1/7 (14%)
	SD	4/13 (31%)	6/16 (38%)	5/9 (56%)	3/7 (43%)
	Disease control rate	5/13 (39%)	6/16 (38%)	5/9 (56%)	4/7 (57%)

3092 **Poster Session**

Topoisomerase 1 and DNA damage: Pharmacodynamic responses and mechanism of trastuzumab deruxtecan in HER2- expressing advanced solid tumors. First Author: Deborah Wilsker, National Cancer Institute Frederick National Laboratory for Cancer Research, Frederick, MD

Background: Trastuzumab deruxtecan (T-DXd) consists of deruxtecan, a novel topoisomerase 1 (TOP1) inhibitor, covalently bound via a lysosomal protease-cleavable linker to the human epidermal growth factor receptor 2 (HER2)-targeting antibody, trastuzumab. The mechanism(s) underlying the clinical activity seen in multiple tumor types across various HER2 levels is of ongoing, active interest. To investigate the T-DXd mechanism of action, we developed a pilot clinical trial of T-DXd with a detailed pharmacodynamic analysis from TOP1 target engagement to downstream effects of DNA damage in patients with HER2-expressing (IHC 1-3+, HER2 amplified, or HER2 mutated) advanced solid tumors (NCT04294628). **Methods:** Based on preclinical studies modeling the trial, research tumor biopsies from consenting patients were collected at three time points: pre-treatment, post-dose Cycle 1 (48-96 hours) and pre-dose Cycle 3. The biopsies were evaluated for TOP1 inhibition, induction of stabilized TOP1covalent complexes (TOP1cc) and induction of downstream DNA damage repair (DDR) markers (RAD51, pNBS1, RPA32) using validated, quantitative multiplex immunofluorescence assays on fixed tumor sections with image analysis methodology. In addition, a retrospective analysis of Schlafen 11 expression in baseline biopsies was performed to determine its predictive value of tumor responses to T-DXd. **Results:** Twenty-one biopsy pairs (pre-treatment and C1, 48-96h post-dose 1) were evaluable for TOP1 molecular response and downstream DDR marker induction. TOP1 target modulation was detected in 15 (71%) of the on-treatment biopsies and markers of DDR were induced in 18 (86%) biopsy pairs. TOP1 target inhibition, robust induction of downstream DNA damage response including stalled replication fork progression, and DNA breaks were observed in HER2-amplified/2+/3+ tumors, and in HER2 1+ tumors. **Conclusions:** Our results confirm the intended TOP1 molecular mechanism of action of T-DXd in HER2-amplified/2+/3+ and importantly extend that finding to HER2 1+ tumors, resulting in DNA damage in nearly all cases. Pharmacodynamic biomarker studies are poised to yield important insights into the molecular effects of T-DXd in solid tumors. Research Sponsor: This project was funded in part by the National Cancer Institute, National Institutes of Health, under Contract No. 75N91019D00024.

3093 **Poster Session**

Chemotherapy as a shaper of immune communication in the triple-negative breast cancer microenvironment. First Author: David Otohinoyi, Louisiana State University Health Sciences Center at Ochsner University Hospital & Clinics, Department of Internal Medicine, Lafayette, LA

Background: Triple-negative breast cancer (TNBC) is a highly immunogenic disease and exhibits among the highest levels of immune infiltration compared with other breast cancer subtypes. These characteristics, coupled with the lack of effective targeted therapies, have made TNBC a key candidate for immunotherapy in selected clinical settings. While chemotherapy remains a mainstay of treatment, its immunomodulatory effects on the tumor immune microenvironment (TIME) remain poorly understood. This study computationally models immune cell to immune cell communication using Single-cell RNA sequencing data to identify immune driver cells and their interactions, and how they are altered by chemotherapy in TNBC. **Methods:** Single-cell RNA sequencing data of over 200,000 tumor cells from TNBC patients' tumor samples were obtained from the Gene Expression Omnibus database. They were analyzed to comprehensively characterize the TIME before and after chemotherapy. We also considered healthy breast tissue to establish immune pathways unique to TNBC pathogenesis. We employed unsupervised clustering analysis, reciprocal principal component analysis with annotation from the NIH Center of Immunology for immune cell identifiers. Communication probability, interaction strength, and pathway information flow were computed, and differential signaling was evaluated using Wilcoxon rank-sum tests ($p < 0.05$). Multiple hypothesis testing was also accounted for by Bonferroni-adjusted p-values to control false positives. **Results:** Immune activity within the TIME was minimal in healthy breast tissue, highlighting signaling pathways specific to TNBC pathogenesis. In contrast, there was an increased immune response in tumors after chemotherapy. Pathways with the highest communication activity included MHC-I/II, CCL, MIF, and CD99 signaling. Notably, CD86 signaling, which correlates with PD-L1 expression, and CD45 signaling were significantly activated after chemotherapy in TNBC. Additionally, CD23 signaling, associated with antitumor immunity, was enhanced following chemotherapy. Natural killer cells emerged as the key immune cell type mediating outgoing signals through annexin, IL16, CX3C, and CD99 pathways, which were largely inactive before treatment. **Conclusions:** Our findings demonstrate that chemotherapy reprograms the TIME in TNBC by enhancing intercellular communication among immune cells and upregulating pro-immune signaling pathways. This remodeling of the TIME suggests potential targets for novel immunotherapeutic discoveries and immune-checkpoint modulation in TNBC. Research Sponsor: None.

3094 **Poster Session**

Sex-associated differences in osimertinib pharmacokinetics among Asian patients with non-small cell lung cancer. First Author: Sylvia Chen, Clinical Pharmacology Laboratory, National Cancer Centre Singapore, Singapore, Singapore

Background: Osimertinib is an oral, third-generation tyrosine kinase inhibitor (TKI) used in the treatment of epidermal growth factor receptor (EGFR) T790M-positive non-small cell lung cancers (NSCLC). However, therein lies a high interindividual variability in osimertinib trough concentrations at steady state, which may in turn affect clinical outcomes. The study aimed to evaluate factors influencing osimertinib exposure and their potential impact on treatment response. **Methods:** This was a prospective single-institution study of Asian NSCLC patients receiving once daily 80mg osimertinib. Plasma concentrations of osimertinib and its metabolites, AZ5104 and AZ7550 were quantified at steady state using a validated LC-MS/MS method. Pharmacogenetic analysis was conducted using commercially available Taqman SNP genotyping assays. **Results:** A total of 177 Asian patients with Stage I-IV NSCLC tumors were enrolled. Median age was 65 (35-84) years old. Majority of patients were Chinese (90%), female (59%) and non-smokers (82%). Exon 19 deletions were present in 45% of patients. Subgroup analysis of 72 patients with available pharmacokinetic data showed no significant genotypic-phenotypic associations between *CYP3A5*3, ABCB1 1236C>T, ABCB1 3435C>T, ABCB1 2677G>T/A* and *ABCG2 421C>A* and osimertinib pharmacokinetics parameters. Sex was significantly associated with trough osimertinib levels and clearance, with females exhibiting 28% higher osimertinib levels and lower clearance compared with males (P=0.0098). Similar trends were observed with AZ5104 and AZ7550 and osimertinib clearance ($P<0.001$). No significant differences in overall survival and progression-free survival were observed between sexes. Analysis of best overall response showed that males were more likely to PD compared with females (OR=1.88, 95% CI; 0.54- 6.3) but this was not statistically significant (P = 0.489). **Conclusions:** Our study showed that sex influences osimertinib pharmacokinetics, with females showing higher trough levels and lower clearance. These differences did not, however, translate into significant differences in survival or treatment response between males and females. Research Sponsor: NCC Research Fund; NCCRF-YR2017-JAN-PG2.

3095 **Poster Session**

NeoRay phase IIa results: A study of [^{177}Lu]Lu-NeoB (^{177}Lu-NeoB) in pts with advanced solid tumors overexpressing gastrin-releasing peptide receptor (GRPR). First Author: Erik Mittra, Oregon Health & Science University, Portland, OR

Background: GRPR is overexpressed in many solid tumors. NeoB binds to GRPR with high affinity and can be radiolabeled for theranostics. NeoRay is the first-in-human study of ^{177}Lu-NeoB in pts with advanced solid tumors overexpressing GRPR. Phase (Ph) I reported favorable organ dosimetry and safety, and a recommended Ph II dosage (RP2D) of 9.25 GBq. Here, we report the Ph IIa primary analysis. **Methods:** This Ph IIa, open-label, multicenter, dosage expansion study enrolled 5 adult cohorts with confirmed [^{68}Ga]Ga-NeoB tumor uptake: A) HR+/HER2- breast cancer; B) prostate cancer (PCa); C) gastrointestinal stromal tumor (GIST); D) impaired renal function; and E) pts eligible for Cohorts A–C who also received sacubitril/valsartan (49/51 mg) at Cycle 1 to assess drug-drug interaction (DDI). There was no formal sample size calculation; the target was ~12 pts in Cohorts A–C, $\leq$6 pts in D, and ~3 pts in E. ^{177}Lu-NeoB 9.25 GBq was to be administered every 6 wks for $\leq$9 cycles, except in DDI Cohort E (5.55 GBq in Cycle 1, then 9.25 GBq). Primary endpoints (descriptive statistics) were individual response (centrally assessed by RECIST v1.1) in Cohorts A–C, and ^{177}Lu-NeoB PK and dosimetry in Cohort E. Secondary endpoints included safety/tolerability and QoL. **Results:** Overall, 18 pts (A n = 4; B n = 7; C n = 2; D n = 2; E n = 3) received treatment (median age 65 y; 56% male). Median (range) ^{177}Lu-NeoB exposure was 9 (6–60) wks; median (range) cumulative activity administered was 12.1 (5.7–81.4) GBq. At data cutoff (7 Jan 2025), 4 pts (B n = 2; C n = 2) had completed treatment ($\geq$3 cycles); 1 pt (GIST) received 9 cycles. Of 10 pts with centrally assessed post-baseline response data, 1 had partial response (PCa), 5 had stable disease (of whom 2 had stable disease $\geq$20 wks [GIST]), and 4 had progressive disease. Adverse events (AEs) occurred in 17 (94%) pts (serious AEs in 3 [17%] pts; Gr $\geq$3 AEs in 6 [33%] pts). Treatment-related AEs (TRAEs) occurred in 7 (39%) pts (all non-serious; Gr $\geq$3 in 2 [11%] pts). The most common TRAEs were fatigue (n = 5, 28%), anemia (n = 2, 11% [Gr $\geq$3 in 1 pt, 6%]), and bone pain (n = 2, 11%). One pt died of hepatic failure related to disease progression (not a TRAE). No AEs led to dosage reductions/interruptions/discontinuations. Dosimetry evaluated in 12 pts showed favorable biodistribution, similar to Ph I. Projected cumulative absorbed doses in target organs were below EBRT limits; lesion absorbed doses were generally consistent across cohorts. Mean $\pm$ SD EORTC QLQ-C30 global health scores in Cohorts A–C were 70 $\pm$ 22 at baseline (n = 12) and 73 $\pm$ 16 at Cycle 2 (n = 4), suggesting stable QoL. **Conclusions:** NeoRay Ph IIa data at the ^{177}Lu-NeoB RP2D (9.25 GBq) reinforce Ph I dosimetry and safety results and support further clinical evaluation. Most AEs were mild/moderate and no new safety signals were identified. Despite the limited sample size, preliminary signs of antitumor activity were observed. Clinical trial information: NCT03872778. Research Sponsor: Novartis Pharmaceuticals.

3096 **Poster Session**

ETCTN 10302: A randomized phase II trial of radium-223 dichloride in combination with paclitaxel in patients with bone metastatic breast cancer. First Author: Jyoti Malhotra, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Radium-223 dichloride is an alpha particle emitting radiopharmaceutical that mimics calcium and localizes bone metastases inducing double-strand DNA breaks. Tumor cells in M-phase cell cycle arrest from paclitaxel are highly sensitive to alpha-emitting radionuclides. ETCTN 10302 tested the hypothesis that addition of radium-223 to paclitaxel will improve outcomes for bone-dominant metastatic breast cancer. **Methods:** ETCTN 10302 was a randomized, two-arm, multicenter, open-label phase II trial. Patients (pts) were randomized to receive either radium-223 (1.49 microcurie/kg iv day 1 x 6 doses) and paclitaxel (80 mg/kg iv on days 1,8 and 15) of each 28-day cycle (Arm A) or paclitaxel alone (Arm B). Inclusion criteria included HER2-negative metastatic breast cancer with $\geq$2 bone lesions and limited visceral metastases (five or less and $\leq$4 cm in size). Primary endpoint was median progression-free survival (PFS). Exploratory analyses included whole exome sequencing and serum alkaline phosphatase dynamics. **Results:** 70 pts were randomized from August 2020 to May 2024. Median age was 58.5 years, 100% were female, 60% were non-Hispanic whites, 14% had triple negative breast cancer, 37% had bone only disease. In the intent-to-treat analysis (37 Arm A, 33 Arm B), there was no significant difference in median PFS (5.8 vs 5.6 months; HR 0.92 p=0.80) but there was a numeric improvement in median OS in radium-223 plus paclitaxel arm (20.2 vs 16.6 months; HR 0.74 p=0.40). Overall response rate (ORR) was 5% in Arm A vs 9% in Arm B. There was no difference in median OS and PFS when analysis was limited to efficacy evaluable pts who completed at least one cycle (37 Arm A, 24 Arm B). Common treatment-related adverse events (TRAE) with the combination of radium-223 plus paclitaxel vs paclitaxel were anemia (78% vs 54%), neutropenia (76% vs 45%), fatigue (49% vs 50%), nausea/vomiting (46% vs 21%), diarrhea (32% vs 25%), peripheral sensory neuropathy (33% vs 30%) and increased ALT (22% vs 4%). Most common $\geq$grade 3 TRAE was neutropenia in Arm A (43% vs 8% in Arm B). Treatment discontinuation rate due to TRAE was 3%. **Conclusions:** Combination of radium-223 and paclitaxel can be administered safely as most adverse events observed were grade 1 to 2 except for higher incidence of $\geq$ grade 3 neutropenia. The trial did not meet the primary PFS endpoint but there was a numerical improvement observed in median OS with the combination. Clinical trial information: NCT04090398. Research Sponsor: None.

3097 **Poster Session**

AKY-2519, a novel B7-H3-targeted radioconjugate, and its biodistribution profile in patients with mCRPC. First Author: Michael Sathekge, Nuclear Medicine Research Infrastructure, Pretoria, Gauteng, South Africa

Background: AKY-2519 is a 6.1 kDa B7-H3 (CD276) targeting miniprotein with an N-terminal short polyethylene glycol linker and dodecane tetraacetic acid chelator designed to deliver actinium (Ac)-225 for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) and other solid tumors. Miniproteins are a novel radioconjugate therapy (RCT) format affording high affinity, selectivity, deep tumor penetration and internalization prolonging tumor retention and rapid plasma clearance limiting exposure to normal tissues. B7-H3 is highly expressed in multiple solid tumor cancers and absent in normal tissues such as salivary glands. These properties render B7-H3 a promising target specifically for Ac-225 delivering RCT in mCRPC. We evaluated biodistribution and tumor uptake of AKY-2519 relative to PSMA-11 and assessed estimated radiation doses to tumors and normal tissues in 16 mCRPC patients. **Methods:** Sixteen mCRPC patients were imaged with [^{68}Ga]Ga-AKY-2519 and [^{68}Ga]Ga-PSMA-11 PET/CTs to assess biodistribution and tumor uptake by SUV. Patients then received low dose [^{177}Lu]Lu-AKY-2519 (~0.37-0.56 GBq) followed by SPECT/CT at 3, 24, and 144 hours post-injection for normal tissue and tumor dosimetry analyses. SPECT images were reconstructed with MIM SPECTRA Recon Software and mean human absorbed dose coefficients (Gy/GBq) were generated with MIM SurePlan MRT. To assess tumor doses, representative lesions including nodal, skeletal and primary disease sites were analyzed across multiple patients. **Results:** No AEs were reported throughout the imaging assessment. PET and SPECT/CTs showed robust tumor uptake with prolonged retention. High lesion concordance was observed between AKY-2519 and PSMA-11 supporting B7-H3 as a novel target in mCRPC and further suggesting co-expression of B7-H3 and PSMA. No accumulation of AKY-2519 was noted in normal tissues with initial activity in the liver rapidly clearing out. Of the normal tissues of interest including kidneys, salivary glands, liver and bone marrow, the mean absorbed doses were below established clinical thresholds when scaled up to a full therapeutic treatment course. The predicted absorbed tumor doses were within expected therapeutic ranges and exceeded normal tissue exposures indicative of a potentially favorable risk-benefit profile for [^{225}Ac]Ac-AKY-2519. **Conclusions:** These are the first clinical data showing concordance between PSMA and B7-H3 on PET-CT imaging in a substantial cohort of patients supporting B7-H3 as a novel target in mCRPC. The normal tissue to tumor dose ratios observed with AKY-2519 suggest a wide therapeutic window as an Ac-225 delivering therapeutic. The low predicted dose to salivary glands supports its use as an actinium delivering RCT for mCRPC, with dosing under IND expected to start in 2H-2026. Research Sponsor: None.

3098 **Poster Session**

First-in-human PET/CT imaging with 68Ga-AKY-2519, a B7-H3 targeted miniprotein radioconjugate, to demonstrate tumor uptake and normal tissue exposure across various advanced solid tumors. First Author: Josephine Enste, Department of Nuclear Medicine, University of Duisburg-Essen, and German Cancer Consortium (DKTK), University Hospital Essen, Essen, Germany

Background: 68Ga-AKY-2519 is a miniprotein radioconjugate developed by Aktis Oncology that targets B7-H3 (CD276) which is overexpressed in several malignancies and is linked with aggressive histology and poor outcomes. AKY-2519 is a high-affinity binder to B7-H3 that internalizes into tumor cells upon binding and thereby maximizes tumor retention. AKY-2519 is also designed to clear rapidly through the kidneys to minimize exposure to normal tissues. To identify potential utility for clinical development of 225Ac-AKY-2519 across various tumor types, here we report the first-in-human evaluation of 68Ga-AKY-2519 using positron emission tomography (PET) in patients with solid tumors. **Methods:** In this prospective, observational study, 18 patients with advanced solid tumors, including prostate cancer (n=7), colorectal cancer (n=4), SCLC (n=3) and NSCLC (n=1) underwent PET/CT imaging following intravenous administration of 68Ga-AKY-2519. Safety, normal tissue distribution and tumor uptake were assessed. Imaging findings were correlated with known disease sites in PSMA and FDG reference PET/CTs as well as available clinical and pathological data. **Results:** 68Ga-AKY-2519 was well tolerated with no adverse events. PET/CT imaging demonstrated favorable tumor uptake, rapid blood pool clearance and low uptake in normal tissues. 68Ga-AKY-2519 uptake (SUVmax) in normal tissues at 120 min post injection (p.i.) was noted in the liver (median 22.9 [interquartile range (IQR) [20.9-30.8]), spleen (7.3 [6.4-11.4]), salivary glands (7.3 [6.4-11.4]), adrenal glands (17.5 [15.9-19.8]) and kidneys (7.3 [6.4-11.4]). No significant bone marrow uptake was noted (median SUVmax 4.1 [3.3-5.1] at 120 min p.i.). High and consistent tumor uptake was observed across various tumor types. The largest cohort was patients with metastatic prostate cancer (n=7), in which the highest 68Ga-AKY-2519 uptake was in bone metastases (median SUVmax 40.4 (120 min p.i.), SUVpeak 25, SUVmean 16.1), followed by lymph node metastases (SUVmax 13.8 (120 min p.i.), SUVpeak 6.5, SUVmean 5.1) and visceral metastases (SUVmax 31.0 (120min p.i.), SUVpeak 22.2, SUVmean 18.7). **Conclusions:** 68Ga-AKY-2519 PET/CT imaging of various malignancies was safe and demonstrated high tumor-to-background uptake and cancerous lesion detection at 120 min p.i. Normal tissue uptake was low, and robust tumor uptake was noted in patients across different solid tumors indicating therapeutic potential. These data warrant further clinical development of 225Ac-AKY-2519. Research Sponsor: None.

3099 **Poster Session**

Final results of a first-in-human study of the MC1R-targeting radiopharmaceutical ^{225}actinium MTI-201 (^{225}Ac-MTI-201) in metastatic uveal melanoma (mUM). First Author: Nikhil I. Khushalani, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Prognosis in mUM is poor with limited efficacy of currently available therapies. The melanocortin-1 receptor (MC1R) is an attractive target for radiopharmaceutical therapy given high expression in UM. ^{225}Ac-MTI-201 is a novel alpha particle emitting MC1R bound radiopharmaceutical with high biostability, affinity, and MC1R-specific cytotoxicity with defined dosimetry and pharmacokinetics in pre-clinical studies. **Methods:** In this first-in-human study (NCT05496686) of a single IV dose of ^{225}Ac-MTI-201, we enrolled mUM patients (pts) who had disease progression on at least 1 prior therapy. Pts had adequate organ and functional status; prior radiotherapy to >25% of bone marrow was exclusionary. The primary objective was safety and toxicity of ^{225}Ac-MTI-201 with secondary endpoints of pharmacokinetics (PK) and clearance of ^{225}Ac-MTI-201, response rate, progression-free survival (PFS), and overall survival (OS). Up to 12 dose levels [from 4.7 microcurie (μCi) to 1327 μCi] for ^{225}Ac-MTI-201 were planned per a modified continual re-assessment method (CRM) with a cohort size of one based on dose limiting toxicity (DLT) assessment within 28 days of drug administration using CTCAE v5.0. Response was assessed by RECIST 1.1. **Results:** Sixteen pts (8 male, 8 female), median age 63 years (43, 84) have been treated. Median number of prior systemic regimens was 2 (0,4), 8 pts had prior liver directed treatment. Dose of ^{225}Ac-MTI-201 was escalated to level 6 (152 μCi) when one DLT (G4 thrombocytopenia and G4 neutropenia) was observed requiring de-escalation per CRM. A second DLT (G4 neutropenia) at level 5 (76 μCi) required expansions at levels 4 (38 μCi; n=5) and 5 (n=6) where all remaining pts were treated without further DLT with 1 pt currently pending final DLT assessment. Adverse events (AEs) were mostly G1-2 including leucopenia, lymphopenia, neutropenia, thrombocytopenia, anemia, nausea, fatigue and ↑ AST. Reversible myelosuppression [lymphopenia (7), neutropenia (5), thrombocytopenia (2)] was the most common > G3 AE. No non-hematological DLT was seen. Best response was stable disease (4/15; 27%); seen at dose levels 4 and 5. The median PFS was 2.30 months (95% CI: 1.84, 3.65); 6-month PFS was 0.07 (95% CI: 0.0, 0.26) and 12-month OS was 0.39 (95% CI: 0.13, 0.64). Median distribution phase half-life (n=15) was 6.19 minutes followed by a slower median elimination phase half-life of 74.06 minutes with significant positive correlation between fast and slow half-lives (Spearman = 0.696, p= 0.0039), independent of dose level. **Conclusions:** Single dose administration of ^{225}Ac-MTI-201 with dose escalation to 76 μCi appears safe and feasible in mUM. Disease stability in this difficult to treat population is encouraging and a multi-dose study of ^{225}Ac-MTI-201 in mUM is planned pending final pt DLT assessment. ^{225}Ac-MTI-201 has Orphan Drug designation for mUM. Clinical trial information: NCT05496686. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; HHSN261201700035C; Modulation Therapeutics.

3101 **Poster Session**

First-in-class DIO3 inhibitor as a novel treatment strategy in ovarian cancer. First Author: Sarit Batsir, Dio Tree Ltd, Nazerath, Israel

Background: Ovarian cancer carries high mortality, driven in part by platinum resistance and a scarcity of actionable therapeutic targets. Thyroid hormone signaling via triiodothyronine (T3) exerts tumor-suppressive effects, including inhibition of proliferative and DNA-damage stress pathways. Iodothyronine deiodinase type 3 (DIO3) is a clinically expressed T3-inactivating enzyme associated with aggressive disease biology, therapeutic resistance, and poor patient outcomes. DioTree Ltd is the first biotech company that developed ITYR-DBRMD, a first-in-class small-molecule DIO3 inhibitor for cancer treatment. **Methods:** DIO3 target engagement was evaluated using enzymatic mimic assays, intracellular T3 quantification (ELISA), and cellular thermal shift assays (CETSA). Pharmacokinetics (PK) were characterized across clinically relevant delivery routes (IV, IP, SC) with development of a dedicated bioanalytical quantification method. Antitumor efficacy was tested in nude mice bearing homologous recombination-proficient (HRP), carboplatin-resistant ovarian cancer xenografts. Mice received vehicle, ITYR-DBRMD, carboplatin, or their combination for three weeks. Tumor growth inhibition (TGI) and safety were assessed. **Results:** ITYR-DBRMD achieved selective and durable inhibition of DIO3 activity with direct cellular binding confirmation, robust increases in intracellular T3 levels, and consistent PK exposure across all administration routes tested. Monotherapy TGI was 43% for carboplatin and 50% for ITYR-DBRMD. Combination therapy produced a clinically meaningful efficacy increase, reaching 68% TGI, with no observed treatment-related toxicity or weight loss, supporting a favorable therapeutic index. Albumin-based tumor delivery and drug retention in tumors was established. **Conclusions:** These data support advancement of ITYR-DBRMD toward early-phase clinical testing, with potential application in ovarian cancer patients, a population lacking targeted therapeutic options. Research Sponsor: Israel Innovation Authority and NGT Incubator.

3102 **Poster Session**

EIK1003, a PARP1-selective inhibitor, in combination with paclitaxel (PTX): Initial combination and updated monotherapy results from a phase 1/2 study EIK1003-001 in advanced solid tumors. First Author: Martin Hojgaard, Rigshospitalet, Copenhagen, Denmark

Background: Non-selective PARP inhibitors (PARPi) demonstrate efficacy in HRR-mutant tumors but cause myelosuppression, potentially mediated by PARP2 inhibition. Overlapping hematologic toxicities have limited PARPi combinations with chemotherapy, restricting their use largely to the maintenance setting. EIK1003 is a potent and selective PARP1 inhibitor that may enable chemotherapy combinations previously not feasible. Here we report the first clinical data for EIK1003 + PTX and updated results for EIK1003 monotherapy. **Methods:** Cohort 1C evaluated EIK1003 QD (dose level [DL] 1 to 4) + PTX 80 mg/m² QW (Days 1, 8, 15 of 21-day cycles) in patients (pts) with platinum-resistant recurrent ovarian cancer (OC) and HER2(-) breast cancer (BC). Cohort 1A evaluated EIK1003 monotherapy (10 to 160 mg QD). BOIN dose escalation design was used. Primary endpoints were safety and tolerability; secondary endpoints were PK and antitumor activity. **Results:** As of 21-Nov-2025 safety data cutoff, 51 patients were treated in Cohort 1C; 30 remain on treatment. Median age was 59 years (range 25-81), ECOG PS 0/1 (54.9%/43.1%), and 62% pts received ≥ 4 prior lines of therapy. One DLT of febrile neutropenia was reported at DL4. Gr ≥ 3 TEAEs occurred in 62.7% pts and were mainly hematologic (Table 1). All pts with Gr ≥ 3 anemia had baseline anemia. TEAEs led to dose reduction in 10 pts and discontinuation in 8 pts. No deaths occurred due to TEAEs. The ORR was 23.1% (1 CR, 8 PR), with responses in OC (n=5) and BC (n=4). EIK1003 PK in combination was consistent with monotherapy, with target concentrations achieved at all dose levels. In Cohort 1A, 65 pts were treated. Gr ≥ 3 TEAEs were 43.1%, with anemia and neutropenia being most common (Table 1). 3/6 pts with Gr ≥ 3 anemia had baseline anemia. ORR was 14.3% overall, and 31.3% (5/16) in PARP-naïve pts. Median DOR in confirmed responders was > 6 mos in both cohorts (Table 1). Safety, PK/PD, and preliminary efficacy supported advancement of two doses into Part 2 dose optimization. **Conclusions:** EIK1003 + PTX demonstrated a tolerable safety profile in a heavily pre-treated population, with hematologic toxicities comparable to historical PTX use (eg, KN-B96, ESMO 2025). These findings represent the first clinical evidence that PARP1-selective inhibitors can be safely combined with chemotherapy. Extended follow-up of EIK1003 monotherapy confirms durable tolerability with antitumor activity. Clinical trial information: NCT06253130. Research Sponsor: None.

Safety and efficacy summary.

	Cohort 1C (EIK1003 + PTX)	Cohort 1A (EIK1003 monotherapy)
Safety	**N = 51**	**N = 65**
Gr ≥ 3 TEAEs, % (n)	62.7 (32)	43.1 (28)
Neutropenia	43.1 (22)	7.7 (5)
Anemia	15.7 (8)	9.2 (6)
Efficacy*	**N = 39**	**N = 49**
ORR per RECIST 1.1, % (n)	23.1 (9)	14.3 (7)
DCR (CR+PR+SD), % (n)	74.4 (29)	38.8 (19)
DOR, median (range), mos	6.4+ (4.4+, 7.7)	6.2+ (4.2+, 10.4+)

*Efficacy evaluable population as of 17-Dec-2025.

3104 **Poster Session**

Tucatinib + subcutaneous (SC) trastuzumab (Tuc + Trast SC) in patients (pts) with solid tumors with *ERBB2* alterations (alts): Results from the targeted agent and profiling utilization registry (TAPUR) study. First Author: Tareq Al Baghdadi, Michigan Cancer Research Consortium, IHA Hematology Oncology, Ypsilanti, MI

Background: TAPUR is a phase II basket study evaluating the antitumor activity of commercially available targeted agents in pts with advanced cancers with specific genomic alts. Combined results of four cohorts of pts with solid tumors with *ERBB2* alts treated with Tuc + Trast SC are reported. **Methods:** Eligible pts had measurable disease, ECOG performance status (PS) 0-2, adequate organ function, and no standard treatment (tx) options. Genomic testing was done in CLIA-certified, CAP-accredited labs. Dosing was 300 mg of Tuc given orally twice daily, 600 mg of Trast and 10,000 units of hyaluronidase SC every 3 weeks (wks), until disease progression. Primary endpoint was disease control (DC) per investigator definition as complete (CR) or partial (PR) response or stable disease (SD) of at least 16 wks duration (SD16+) per RECIST v.1.1. The hypothesized null DC rate of 15% was rejected if the lower limit of a 1-sided 90% CI was >15%. Inferences were based on a beta-binomial model, which accounts for tumor type variance. Secondary endpoints were progression-free survival (PFS), overall survival (OS), objective response (OR), duration of response, duration of SD (DOSD), and safety. **Results:** 78 pts (histology-pooled [n=40], lung [n=16], biliary tract [n=11], uterus [n=11]) with 21 tumor types with *ERBB2* alts (*ERBB2* amplification [amp], n=38; mutation [mut], n=32; mut and amp, n=6; overexpression [OE], n=2) were enrolled. All cohorts were combined for analysis. 3 pts were not evaluable. Table shows demographics and outcomes. 1 CR (urothelial carcinoma [UC], *ERBB2* mut), 6 PR (uterus [2], esophagus [1], lung, neuroendocrine [1], ovary [1], UC [1]; *ERBB2* amp [5], mut [1]) and 18 SD16+ (10 tumor types; *ERBB2* amp [7], mut [10], OE [1]) were observed for a DC rate of 33% (1-sided 90% CI, 27 to 100) and an OR rate of 9% (95% CI, 4 to 18). The null hypothesis was rejected. Duration of CR in 1 pt was 87 wks. Median (med) duration of PR was 12 wks (range, 6-72). Med DOSD in pts with SD16+ was 28 wks (range, 12-57). 20 pts (26%) had ≥1 grade 3 tx-related AE or SAE. All were consistent with tx label except back pain, cardiac troponin increase, chronic kidney disease, heart failure, hypomagnesemia, hypophosphatemia, pericardial and pleural effusion, peripheral motor and sensory neuropathy, sinus tachycardia, systemic inflammatory response syndrome and UTI. **Conclusions:** Tuc + Trast SC demonstrated antitumor activity in pts with advanced solid tumors with *ERBB2* alts, warranting additional study. Clinical trial information: NCT02693535. Research Sponsor: Genentech; Pfizer, Seagen (now a wholly owned subsidiary of Pfizer Inc.); AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Merck, Taiho Oncology.

Demographics (N=78) and efficacy outcomes (n=75).

Med age, years (range)	**67 (39, 88)**
ECOG PS, No. (%)	
0	29 (37)
1	44 (56)
2	5 (6)
Prior systemic regimens, No. (%)	
0-2	43 (55)
≥3	35 (45)
DC (OR plus SD16+) rate, % (1-sided 90% CI), p-value	33 (27, 100)
OR rate, % (95% CI)	9 (4, 18)
Med PFS, wks (95% CI)	10 (8, 16)
Med OS, wks (95% CI)	44 (30, 55)

3105 **Poster Session**

Phase II basket trial of brigatinib for *ALK* fusion–positive solid tumors: ALLBREAK trial (WJOG15221M). First Author: Tomoki Sakakida, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan

Background: *ALK* fusions occur in approximately 0.2% of solid tumors other than non-small cell lung cancer (NSCLC) and are associated with poor outcomes. Prospective evidence for ALK tyrosine kinase inhibitors in this rare condition is limited. **Methods:** This phase II basket trial evaluated brigatinib (90 mg once daily for 7 days, then 180 mg once daily) using a decentralized clinical trial platform. Eligible patients had advanced solid tumors other than NSCLC with *ALK* fusions detected in tumor tissue or circulating tumor DNA (ctDNA). The initial planned sample size was 14, with an objective response rate (ORR) of 50% considered promising and 12% unacceptable (one-sided α = 0.025; β = 0.09). Enrollment was expanded to 28 patients due to rapid accrual. ctDNA analyses were performed at baseline, cycle 2, and progressive disease (PD). **Results:** Twenty-eight patients from ten hospitals were enrolled from May 2022 to March 2025; one was excluded from the full analysis set (FAS) due to clinical deterioration before treatment initiation. The FAS (n = 27) included patients with biliary tract cancer (BTC), colorectal cancer (CRC), thyroid cancer (TC), inflammatory myofibroblastic tumor (IMT), or other solid tumors (n = 7, 5, 3, 3, and 9, respectively). ECOG PS was 0 or 1 (18/9). The number of prior lines of therapy was 0–2 and ≥3 in 20 and seven patients, respectively. *ALK* fusions were detected by next-generation sequencing (NGS) or fluorescence in situ hybridization (22/5). Among NGS-detected cases, fusion partners included *EML4* (n = 8), *STRN* (n = 2), and others (including *CEP44*, *HOOK1*, *TPM3*, and *RRBP1*; n = 12). The confirmed ORR in the FAS was 63.0% (95%CI, 42.4–80.6), with ORRs of 57% in BTC, 60% in CRC, and 67% each in TC, IMT, and other tumors. For the first 14 patients enrolled as per initial study design, the ORR was 57.1% (95% CI, 28.9–82.3%). In the FAS, the disease control rate was 92.6%, and the median progression-free survival, duration of response, and overall survival were 9.7, 14.4, and 19.5 months, respectively. At data cutoff, 11 patients remained on treatment. ORR varied with fusion partner: 38% for *EML4*, 100% for *STRN,* and 75% for other partners. ORR was comparable between patients with and without baseline ctDNA detection of *ALK* fusions (67% vs. 64%). At PD, acquired *ALK* mutations (G1202R, E1028K, and L1502L) were detected in 23% (3/13) of patients; alterations in *EGFR, KRAS,* or *MET* were observed in 23% (3/13) of patients. The most common grade 3–4 adverse events were increased creatine phosphokinase (11%) and hypertension (11%). Interstitial lung disease occurred in 7% of patients (grade 1 only; no grade 3–4). No treatment-related deaths occurred. **Conclusions:** Brigatinib shows a high, durable response rate and manageable toxicity in non-NSCLC *ALK* fusion–positive solid tumors, supporting its use as a tumor-agnostic therapeutic agent in this rare molecular subset. Clinical trial information: jRCT2041210148. Research Sponsor: Takeda.

3106 **Poster Session**

Zongertinib combined with T-DXd in HER2-positive metastatic gastric, gastroesophageal junction, or esophageal carcinoma (mGEAC): First results from a phase Ib/II dose-escalation trial. First Author: Izuma Nakayama, National Cancer Center Hospital East, Kashiwa, Chiba, Japan

Background: Zongertinib, an irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Beamion BCGC-1 (NCT06324357) is an ongoing Phase Ib/II multicohort trial investigating zongertinib, as monotherapy or combined with other agents, in HER2-positive metastatic breast cancer, metastatic colorectal cancer, and mGEAC. Here, we report the first data from Cohort C (Phase Ib), in which patients (pts) with HER2-positive mGEAC received zongertinib combined with T-DXd, as well as supporting preclinical data. **Methods:** Preclinical activity of zongertinib plus T-DXd was assessed in xenograft mouse models of HER2-positive gastric cancer. In Cohort C, pts with histologically/cytologically confirmed, unresectable, HER2-positive mGEAC were enrolled. Pts had documented HER2-positive disease (overexpression/amplification) and disease progression following HER2-directed treatment. Pts received escalating doses of zongertinib once-daily plus a fixed dose of T-DXd (6.4 mg/kg) every three weeks. Dose escalation was guided by a BLRM with overdose control. Pts remained on treatment until any protocol-defined stopping criterion occurred. The primary endpoint was the occurrence of DLTs during the MTD evaluation period. Secondary endpoints included further safety assessments and objective response (investigator-assessed; RECIST v1.1). **Results:** In mouse models, the addition of zongertinib to T-DXd led to increased antitumor activity. In Beamion BCGC-1, as of November 4, 2025, 19 pts had been enrolled to Cohort C and received zongertinib 60 mg (n=4), 120 mg (n=9), 240 mg (n=4), or 300 mg (n=2). Median age was 63 years, 74% male, 74%/26% ECOG PS 0/1. All pts had received prior trastuzumab-based therapy. Treatment-emergent adverse events (TEAEs; any grade [G]/G≥3) were reported in 17/9 (89%/47%) pts. AEs related to zongertinib (any G/G≥3) were reported in 13/2 (68%/11%) pts. There were no zongertinib-related G4/5 AEs. The most-common TEAEs (any G/G≥3) were nausea (53%/0%), decreased appetite (47%/5%), and diarrhea (47%/0%). One pt each had G1 pneumonitis and interstitial lung disease; both recovered. AEs leading to zongertinib dose reduction/discontinuation were reported in 1/2 pts. AEs leading to T-DXd dose reduction/discontinuation were reported in 8/1 pts. The first confirmed responses to zongertinib combined with T-DXd were observed across the different zongertinib dose levels (60 mg: 1 CR, 2 PR; 120 mg: 2 PR, 5 SD; 240 mg: 1 PR, 1 SD). **Conclusions:** No new safety signals were observed for zongertinib in combination with T-DXd; further dose escalation is ongoing. Encouraging clinical activity was observed in pretreated pts with HER2-positive mGEAC who had disease progression following prior trastuzumab-based therapy. Clinical trial information: NCT06324357. Research Sponsor: Boehringer Ingelheim.

3107 **Poster Session**

Early results from the first-in-human phase 1 study of WEE1 inhibitor APR-1051 in patients with advanced solid tumors (ACESOT-1051). First Author: Shiraj Sen, NEXT Oncology Dallas, Dallas, TX

Background: WEE1 tyrosine kinase regulates cell cycle checkpoints (G1-S, G2-M) and DNA damage responses. Inhibiting WEE1 can force premature mitotic entry and subsequent apoptosis. APR-1051 is a highly potent, orally bioavailable WEE1 inhibitor (WEE1i) with *in vivo* anti-proliferative activity. Low off-target inhibition of APR-1051 on PLK kinases (PLK1, PLK2, PLK3) differentiates it from other WEE1i's and may confer improved safety. **Methods:** This open-label dose escalation (BOIN) and dose selection optimization study is evaluating APR-1051 using a once-daily (QD) regimen. The study is currently enrolling at 220 mg at three US sites (NCT06260514). Primary study objectives are to characterize the safety, dose-limiting toxicity (DLT), maximum tolerated dose/maximum administered dose, and recommended phase 2 dose of APR-1051. Secondary objectives include evaluating APR-1051 pharmacokinetic properties and preliminary efficacy (RECIST v1.1; PCWG3 criteria for mCRPC). Key inclusion criteria are age ≥ 18 years with advanced solid tumor and cancer-associated gene alterations, prior standard-of-care systemic treatment, and ECOG PS 0 or 1. Key exclusion criteria are prior WEE1i use, CNS metastases/unstable involvement, secondary malignancies requiring therapy, and concomitant moderate/strong inhibitors/inducers of CYP3A4/5, MDR1, or BCRP. **Results:** As of January 16, 2026, 22 patients (median age 62 years [range: 40–86]; have been enrolled up to the 220 mg dose level. Most (n=13, 59%) cases were colorectal cancers (colon [n=9, 41%], rectal [n=4, 18%]) followed by uterine (n=3, 14%), pancreatic (n=2, 9%), and breast, gastric, oropharyngeal, and soft tissue cancer (each n=1, 5%). The median prior lines of treatments was 3. Any grade adverse event (AE) was report in 21 (95%) patients. Treatment-related AEs were reported in 12 (55%) patients; 10 (45%) patients had non-serious gastrointestinal events. Twelve (55%) patients had 18 unique serious AEs, including one death on treatment unrelated to APR-1051 and one DLT of grade 3 elevated liver enzymes (AST, ALT) probably related to APR-1051 (n=1, 5%). Antitumor activity was observed in one (5%) patient with uterine serous carcinoma treated with APR-1051 150 mg who had an unconfirmed partial response—50% reduction in target lesion size (RECIST v1.1) and > 90% reduction in CA-125 tumor marker—at per protocol 8-week assessment. Five (23%) patients had stable disease: oropharyngeal cancer (APR-1051 70 mg [n=1, 5%]); colon, rectal, uterine cancer (100 mg [n=3, 14%]); colon cancer (150 mg [n=1, 5%]). A dose proportional increase in exposure was observed. **Conclusions:** In the ongoing trial, continuous, oral APR-1051 QD has a manageable safety profile with preliminary signals of antitumor activity in patients with pretreated advanced solid tumors. Clinical trial information: NCT06260514. Research Sponsor: Aprea Therapeutics.

3108 **Poster Session**

Zidesamtinib efficacy and safety in patients with advanced *ROS1*-positive solid tumors other than NSCLC in the ARROS-1 study. First Author: Benjamin J. Solomon, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: *ROS1* fusions are oncogenic drivers in various cancers. Multiple ROS1 tyrosine kinase inhibitors (TKIs) are available for *ROS1*+ non-small cell lung cancer (NSCLC); however, there are limited data on the activity of these agents in patients with other *ROS1*+ tumors. In patients with advanced *ROS1*+ NSCLC (TKI pretreated and TKI-naïve), zidesamtinib has demonstrated encouraging clinical activity, including in patients with CNS disease and/or ROS1 G2032R mutation, and a safety profile consistent with its highly ROS1-selective, TRK-sparing design. Here we report the first data on the activity of zidesamtinib in patients with other *ROS1*+ solid tumors. **Methods:** The global Phase 1/2 ARROS-1 study (NCT05118789) includes a cohort of patients with advanced/metastatic *ROS1*+ solid tumors other than NSCLC, whose disease has progressed on any prior therapy. Key endpoints are objective response rate (ORR, RECIST v1.1 by BICR), duration of response (DOR), and safety. Data cut: 22 September 2025. **Results:** 15 efficacy-evaluable patients with *ROS1*+ solid tumors (10 non-NSCLC tumor types) received zidesamtinib. Patients received a median of 2 prior anticancer therapies (range 1-6): 60% were ROS1 TKI-naïve, 40% were ROS1 TKI pre-treated (range 1-2), 73% had prior chemotherapy (range 1-4). ORR was 40% (6/15, including 1 PR pending confirmation), with no disease progression by BICR among responders (DOR range 3.9+ – 22.8+ months). Responses were observed across multiple tumor types, including cholangiocarcinoma, colorectal, gastric, inflammatory myofibroblastic tumor, ovarian, and pancreatic. 2 ROS1 TKI pre-treated patients had ROS1 resistance mutations (G2032R and F2004I/F2004V) at baseline and both achieved a PR (1 pending confirmation). Treatment-related adverse events (TRAEs) in ≥15% of patients were increased alanine aminotransferase, increased blood creatine phosphokinase, and dysgeusia (n=3 patients each). No patients discontinued due to TRAEs; 1 pt dose-reduced due to TRAE. **Conclusions:** Zidesamtinib demonstrated encouraging activity in patients with diverse *ROS1*+ solid tumors, including those refractory to standard-of-care therapies. Safety was consistent with its ROS1-selective, TRK-sparing design. Enrollment is ongoing. Clinical trial information: NCT05118789. Research Sponsor: Nuvalent, Inc.

3109 **Poster Session**

First-in-human phase 1/2 study of ETX-19477, an oral, potent, and selective PARG inhibitor, in patients with advanced solid tumors (ERADIC8). First Author: Ezra Rosen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Poly(ADP-ribose) glycohydrolase (PARG) is an enzyme that catalyzes the removal of poly-ADP-ribose (PAR) chains from proteins during DNA damage repair. PARG inhibition leads to selective cell death in tumors with underlying replication fork defects, including BRCAm tumors, through a mechanism distinct from PARP inhibition. ETX-19477 is an oral, potent, and selective PARG inhibitor that shows robust preclinical activity in mouse models of ovarian, breast, and gastric cancers. **Methods:** ERADIC8 is an open-label, multicenter, Phase 1/2 study, consisting of two parts, dose escalation and dose expansion. A Bayesian Optimal Interval Design was used to enroll patients (pts) into dose escalation cohorts, with enrichment for pts with BRCAm high grade serous ovarian (HGSOC) and breast cancers. The primary objective is to assess safety/tolerability of ETX-19477 and define the maximum tolerated dose (MTD) and recommended Phase 2 dose(s). Secondary and exploratory objectives include pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity per RECIST v1.1. ETX-19477 is given orally once or twice daily in 21-day cycles. **Results:** As of Jan 6 2026, 45 pts were enrolled into the study across 11 dose levels (range: 80-750 mg QD, 190-350 mg BID). Tumor types included ovarian (n=24, BRCAm: 18), breast (n=8, BRCAm: 7), endometrial (n=6, BRCAm: 0), colorectal (CRC, n=3, BRCAm: 1), and other (n=4, BRCAm: 0) cancers. Treatment-related AEs (TRAEs; any grade) occurring in >20% of pts were nausea (53%), vomiting (38%), and fatigue (24%). The only Gr3 TRAE occurring in >5% of pts was neutropenia (16%). There was one Gr4 TRAE of neutropenia in 1 pt (2%) and no Gr5 TRAEs. ETX-19477 exposure is dose proportional, and the BID regimen achieves >85% PARG inhibition throughout the dosing interval in a blood-based PAR accumulation pharmacodynamic assay. As of the data cutoff, dose escalation is ongoing at 350 mg BID (MTD has not been defined) and dose expansion is ongoing at 200-300 mg BID. Among BRCAm, HGSOC pts enrolled at BID dose levels, there were 7 evaluable pts with a median of 4 prior lines of therapy (range 2–11): 2 pts achieved a partial response (PR, 29%) and 3 pts achieved stable disease (SD, 43%). Both pts with PRs were platinum-resistant and received prior PARP inhibitor treatment. 1 pt with BRCAm CRC remains on active therapy (250 mg BID) with SD for 7 months. **Conclusions:** ETX-19477 was well tolerated and showed anti-tumor activity in heavily pretreated pts with BRCAm, platinum-resistant HGSOC during dose escalation. These findings provide the first clinical proof-of-concept of PARG inhibition in HGSOC. ETX-19477 is being further evaluated in the dose expansion phase of the study. Clinical trial information: NCT06395519. Research Sponsor: 858 Therapeutics.

3110 **Poster Session**

Final analysis of KOMET (NCT04924608), a phase 3 study of selumetinib in adults with NF1-PN. First Author: Alice P. Chen, Developmental Therapeutics Clinic, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: In 2025 the EMA and FDA expanded the approval of selumetinib (SELU; ARRY-142886, AZD6244) to adults with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN). We report the final exploratory analysis of SELU efficacy and safety from the Phase 3, randomized, double-blind, placebo (PBO)-controlled KOMET trial. **Methods:** Adults (≥18 yrs) with NF1-PN were randomized 1:1 to 28-day cycles of oral SELU 25 mg/m^2 BID or PBO with crossover to SELU at the end of Cycle (C) 12 or earlier if radiological progression was confirmed by independent central review (ICR). The single-arm objective response rate (ORR) by use of volumetric MRI analysis per ICR REiNS and safety were exploratory endpoints at final DCO (last participant (pt) completed C24; 17 Mar 2025)). Pharmacokinetics (PK) data were collected at steady state C1, Day (D) 8. A planned sample of 73 pts per arm with a 2-sided 5% alpha Fisher's exact test had >99% power to detect the difference between a SELU ORR of 20% and PBO ORR of 0%. **Results:** Overall, 145 pts (SELU: 71; PBO: 74) were randomized; 66 pts in the PBO group crossed over to SELU treatment for the open-label period (SELU period). In the SELU period, 137 pts were treated; 96 pts (66.2%) (SELU: 45, PBO/SELU: 51) completed the study and were judged by the investigators at DCO to have clinical benefit at study completion and, consequently, continued receiving SELU during the post-trial access program. Median actual exposure to SELU during the SELU period was 554 days and maximum exposure to SELU treatment was 1156 days. The median relative dose intensity of SELU treatment was 99.5%. The ORR in the SELU group (N = 71) was 23.9% (95% CI; 14.6, 35.5). Of the 17 pts who achieved objective response, 10 (58.8%) remained in response for ≥12 months while 5 pts (29.4%) had not yet reached 12 months follow-up from onset of response. Median duration of response was not reached in the SELU group by final analysis. During the SELU period (N = 137), 51 pts (37.2%) had a maximum AE severity of ≥Grade 3 (most frequent were known SELU AEs); ≥1 AEs, possibly related to SELU, were experienced by 127 pts (92.7%); of these, 31 pts (22.6%) had ≥Grade 3 AEs. Serious AEs (SAEs) were experienced by 24 pts (17.5%); 6 pts (4.4%) had SAEs possibly related to SELU. AEs of special interest were experienced by 85 pts (62.0%); increased blood creatine phosphokinase (43.1%), increased ALT/AST (13.9% each), and peripheral edema (13.1%) were the most frequent (≥10% of pts). AEs were manageable; the AE-related discontinuation rate for the trial was 9.5%. At C1 D8, 64 pts who received SELU were included in the PK Analysis Set. Median t_{max} was 1.5 h and geometric mean $AUC_{(0\text{-}12)}$ was 2986 h × ng/mL for SELU. **Conclusions:** In the first international, randomized, PBO-controlled trial in adults with NF1-PN, SELU achieved a sustained and durable, clinically meaningful reduction in PN volume per ICR REiNS. No new safety concerns were identified and AEs were manageable. Clinical trial information: NCT04924608. Research Sponsor: AstraZeneca as part of an alliance between AstraZeneca and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD).

3111 **Poster Session**

First-in-human trial of the TEAD inhibitor ODM-212 in patients with advanced solid tumors (TEADES). First Author: Johann S. De Bono, The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom

Background: The Hippo pathway is implicated in multiple human cancers including mesothelioma and epithelioid hemangioendothelioma (EHE). When Hippo signalling is inactive, Yes-associated protein 1 (YAP1) and WW-domain-containing transcription regulator 1 (TAZ) locate to the nucleus, activating TEA domain family member (TEAD) transcription factors (TEAD1-4) to impact transcription and key oncogenic cellular processes. ODM-212 is a small molecule oral pan-TEAD inhibitor with *in vitro* and *in vivo* antitumour activity in solid tumours. **Methods:** TEADES is a multi-site, open-label, first-in-human trial of ODM-212 enrolling patients ≥18 years of age with various types of advanced, metastatic solid tumours where the Hippo pathway is implicated, with or without relevant genetic alterations. The study followed a Bayesian optimal interval (BOIN) design with a dose escalation with backfill cohorts, followed by expansion in tumour types of interest. Main objectives were safety (including dose-limiting toxicity (DLT)), preliminary efficacy and pharmacokinetics. ODM-212 was administered orally, once or twice daily, in a continuous 4-week cycle. **Results:** Between 7 November 2023 and 5 January 2026, 76 patients (mesothelioma 29, EHE 15, other 32) of mean age 62.1 years and all ECOG 0-1 received ODM-212 at doses between 20-320 mg/day, with 44 continuing on treatment at time of data cut-off. Previous treatment included checkpoint inhibitors (N=38), chemotherapy (N=59) or both (N=36). The longest exposure at data cut-off was 18-months. ODM-212 was well tolerated. No DLTs were reported and the maximum tolerated dose (MTD) was not identified. The most frequent treatment-related adverse event (TRAE) was proteinuria (19.7%), which was reversible and resulted in treatment adjustment in 6 (7.9%) patients. Other common TRAE's were increased lipase (15.8%) and nausea (10.5%). Grade ≥3 TRAE's occurred in 6.6% patients (anemia and increases in amylase, lipase, alanine aminotransferase and aspartate aminotransferase). Treatment responses by RECIST 1.1 were observed across multiple doses (ORR 7/45 = 15.6%), predominantly in patients with mesothelioma (ORR 27.8% in 18 evaluable patients, disease control rate (DCR) 77.8%) and EHE (ORR 22.2% in 9 evaluable patients, DCR 100%). ODM-212 demonstrated a predictable pharmacokinetic profile, with steady state achieved by 15 days and mean elimination half-life of 1-2 days, supporting once or twice daily dosing. **Conclusions:** ODM-212 administration to extensively treated patients with advanced cancer was well tolerated and resulted in some promising tumour responses (particularly in mesothelioma and EHE). The phase 2 portion of TEADES is currently enrolling patients. Clinical trial information: NCT06725758. Research Sponsor: Orion Pharma.

3112 Poster Session

HRS-5041, an androgen receptor degrader, in metastatic castration-resistant prostate cancer: A phase 1, multicenter, first-in-human study. First Author: Wei Xue, Shanghai Jiao Tong University School of Medicine Renji Hospital, Shanghai, China

Background: ADT plus NHA have been approved for PC of different stages. However, patients (pts) inevitably develop drug resistance, and AR mutations are a common cause of this resistance. HRS-5041 is a novel, oral, highly effective AR degrader that specifically targets the AR wild type (AR WT) and clinically relevant AR LBD mutants. We conducted a phase 1 trial to assess HRS-5041 in NHA-resistant mCRPC. **Methods:** Pts with mCRPC who had progressed on ≥1 NHA and ≥1 taxane chemo (unless refused or not indicated to chemo) were eligible. Pts orally received HRS-5041 at 30–540 mg QD or 240–300 mg BID during dose-escalation (DE), followed by dose or indication expansion at 180–360 mg QD or 240-300 mg BID. 240 mg BID and 360 mg QD were selected for dose optimization. The primary endpoints were DLT, MTD, and RP2D. **Results:** As of Dec. 12, 2025, 156 pts were enrolled, including 77 with AR-LBD mutation and 79 with AR-LBD WT. During DE, no DLT occurred. MTD was not reached. TRAEs were reported in 133 (85.3%) pts; the most common were anemia (38.5%), decreased appetite (25.6%), and diarrhea (24.4%). Grade ≥3 TRAEs and serious TRAEs occurred in 20 (12.8%) and 4 (2.6%) pts. No TRAEs led to death. Among all evaluable pts, rate of PSA reduction ≥50% was 0 for 1 pt at 30 mg QD, 0 for 4 pts at 90 mg QD, 17.4% for 23 pts at 180 mg QD, 32.1% for 53 pts at 360 mg QD, 40.0% for 5 pts at 540 mg QD, 35.7% for 56 pts at 240 mg BID, and 11.1% for 9 pts at 300 mg BID. Data by AR-LBD status for expanded doses are shown in table. Both 360mg QD and 240mg BID groups showed excellent PSA response rates and rPFSs, regardless of AR-LBD status. Among pts with AR-LBD mutations, the 240 mg BID group showed a superior rate of PSA reduction ≥50% and a higher 8-month rPFS rate than the 360 mg QD group. Notably, 2 patients in the 240 mg BID group achieved CR, including 1 with liver metastases. **Conclusions:** HRS-5041 showed tolerable safety and promising antitumor activity in pretreated mCRPC. A phase 3 study is currently underway in mCRPC pts with AR-LBD mutation, with a recommended dose of 240mg BID. Clinical trial information: NCT05942001. Research Sponsor: None.

Efficacy outcomes.

Dose	180 mg QD	180 mg QD	360 mg QD	360 mg QD	240 mg BID	240 mg BID
AR-LBD status	AR-LBD mutation	AR-LBD WT	AR-LBD mutation	AR-LBD WT	AR-LBD mutation	AR-LBD WT
PSA reduction ≥30%*	5 (50.0)	1 (7.7)	15 (48.4)	8 (36.4)	17 (54.8)	7 (28.0)
PSA reduction ≥50%*	3 (30.0)	1 (7.7)	10 (32.3)	7 (31.8)	15 (48.4)	5 (20.0)
rPFS, mo†	NR (2.2–NR)	5.8 (2.1–8.6)	11.0 (5.5–NR)	13.8 (8.2–NR)	11.0 (8.2–NR)	NR (3.5–NR)
8-month rPFS rate†	53.3 (17.7–79.6)	32.6 (5.8–64.3)	58.1 (35.6–75.2)	82.9 (55.7–94.2)	85.3 (60.2–95.1)	71.2 (46.4–86.0)
ORR#	2 (66.7)	0	0	0	3 (42.9)	1 (11.1)

Data are n (%) or median (95% CI).
*Assessed in pts who had at least one post-baseline PSA assessment or who discontinued treatment due to death/clinical progression without post-baseline PSA assessment; N was 10, 13, 31, 22, 31, and 25.
†Assessed in full analysis set; N was 10, 14, 32, 23, 33, and 25.
#Assessed in pts with baseline target lesions; N was 3, 4, 10, 5, 7, and 9.

3113 Poster Session

Safety and efficacy of ifebemtinib (IN10018) combined with garsorasib (D-1553) in KRAS^{G12C} mutant solid tumors from a phase Ib/II study: 2-year follow-up from single-arm of non-small-cell lung cancer (NSCLC). First Author: Yanling Wang, Zhejiang Cancer Hospital, Hangzhou, China

Background: Studies have shown that combining RAS inhibitors (RASi) with appropriate partners may enhance efficacy. Ifebemtinib (ifebe) is a potent and selective oral focal adhesion kinase (FAK) inhibitor demonstrating synergy with RASi. D-1553 is a KRAS^{G12C} inhibitor approved in China for KRAS^{G12C}–mutant NSCLC. We previously reported encouraging antitumor activity with ifebe plus D-1553. Here we present updated 2-year efficacy and safety results, including exploratory TP53 subgroup analyses. **Methods:** This is a phase Ib/II, open-label study to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of D-1553 in combination with ifebe in patients with locally advanced or metastatic NSCLC harboring KRAS^{G12C} mutations regardless of PD-L1 expression. Patients received ifebe 100 mg once daily (QD) plus D-1553 600 mg twice daily (BID). **Results:** As of January 4, 2026, 33 treatment-naïve NSCLC patients (81.8% stage IV) were enrolled; median follow-up was 24.9 months (Range: 1.05, 31.77). The objective response rate (ORR) was 90.3% (95% CI: 74.2, 98.0) and disease control rate (DCR) was 96.8% (95% CI: 83.3, 99.9). The median progression free survival (PFS) was 22.14 months (95% CI: 9.63, NE) with the 12- and 24-month PFS rates were 67.9% and 40.0%, respectively. The median duration of response (DOR) was 19.38 months (95% CI: 12.85, NE). The 24-month overall survival (OS) rate was 69.7%, and mOS was not reached (95% CI: 27.76, NE). TP53 wild-type patients (n=17) showed more favorable outcomes, with higher ORR (94.1% vs. 81.8%), unreached mPFS (vs. 14.2 months), and unreached mOS (vs. 17.7 months) compared with TP53-mutant patients (n=13). The safety profile of ifebe plus D-1553 was generally comparable to that of each single agent. SAEs were reported in 33.3% of patients, with 18.2% experiencing ifebe-related SAEs. Most TRAEs were grade 1–2; grade ≥3 TRAEs occurred in 24.2% of patients, including one grade 4 event. No treatment-related deaths or discontinuations were reported. **Conclusions:** Ifebe plus D-1553 exhibited robust, durable antitumor activity and a favorable safety profile in treatment-naïve KRAS^{G12C}-mutant NSCLC patients regardless of PD-L1 expression. Notably, TP53-wild-type KRAS^{G12C} tumors typically show poor responsiveness and short durability to ICI therapies, likely due to reduced PD-L1 expression and lower tumor mutational burden. The superior outcomes in TP53 wild-type patients suggest this combination may address an unmet need in this distinct population. Further studies are needed to validate these findings and define the regimen's optimal role in the evolving treatment landscape. Clinical trial information: NCT06166836; NCT05379946. Research Sponsor: None.

3114 Poster Session

First-in-human phase I/II study of a highly selective FGFR2 inhibitor 3HP-2827 in patients with advanced solid tumors harboring *FGFR2* alterations. First Author: Jiajia Yuan, Department of Gastrointestinal Oncology, Peking University Cancer Hospital, Beijing, China

Background: Molecular profiling of cholangiocarcinoma (CCA) is highly recommended to guide access to targeted therapies such as FGFR2 inhibitors. 3HP-2827 is a highly selective and potent FGFR2 inhibitor targeting FGFR2 alterations. Here we report the findings of 3HP-2827 in advanced solid tumors harboring FGFR2 alterations. **Methods:** This is a phase I/II study to evaluate the safety, tolerability, PK, and preliminary efficacy of 3HP-2827 in pts with advanced solid tumors harboring FGFR2 alterations. Pts failed to standard therapy with/without prior pan-FGFR inhibitor (FGFRi) are eligible for enrollment. Bayesian Optimal Interval (BOIN) and back filling design were employed in the dose-escalation stage of phase I, followed with the expansion stage. Treatment-related adverse events (TRAEs), PK, and anti-tumor activity (RECIST v1.1) were assessed. **Results:** As of Jan 8, 2026, a total of 52 pts (46 with CCA, 6 with others) were enrolled from 12 centers, received 3HP-2827 at doses of 60-180 mg once daily (QD), including 42 with FGFR2 fusion/rearrangement (f/r), 6 with FGFR2 mutation. 19 pts (36.5%) had prior FGFRi. No dose-limiting toxicities (DLTs) were observed at the dose levels of 60 mg, 120 mg, 180 mg QD. 3HP-2827 had favorable PK with doses≥120 mg QD providing FGFR2 occupancy > 90%. The most common TRAEs were FGFR2 on-target toxicities including dry mouth (69.2%, G3 1.9%), nail toxicity (67.3%, G3 3.8%), stomatitis (50%, G3 3.8%), dry eyes (26.9%, G3 1.9%), PPE (19.2%, G3 3.8%). 12 pts (23.1%) experienced at least one G3/G4 TRAE and no G5 TRAEs occurred. 7 pts (13.5%) experienced at least one serious adverse event, 4 (7.7%) of them were considered related to 3HP-2827. No discontinued treatment or death due to TRAEs. Anti-tumor activities were observed from 60 mg QD. Among 15 CCA pts (FGFR2 f/r, FGFRi-naive) who had at least one post-treatment tumor assessment, objective response rate (ORR) was 80% (95% CI: 51.9, 95.7), and disease control rate (DCR) was 100% (95% CI: 78.2, 100). The ORR and DCR in 15 CCA pts (FGFR2 f/r, FGFRi-refractory) was 26.7% (95% CI: 7.8, 55.1) and 86.7% (95% CI: 59.5, 98.3). The ORR and DCR in 4 advanced solid tumor pts (FGFR2 mutation, FGFRi-naive) was 75% (95% CI: 19.4, 99.4) and 100% (95% CI: 39.8, 100). **Conclusions:** 3HP-2827 was found to be safe and tolerable, with encouraging anti-tumor activity observed in pts with FGFR2 alterations. Further clinical efficacy will be explored in the expansion stage and phase II stage. Clinical trial information: NCT06378593. Research Sponsor: None.

3115 Poster Session

A first-in-human phase I/II study evaluating CTS3497, an MTA-cooperative PRMT5 inhibitor, in advanced or metastatic *MTAP*-deficient solid tumors. First Author: Dan Liu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Early Drug Development Centre, Peking University Cancer Hospital & Institute, Beijing, China

Background: Protein arginine methyltransferase 5 (PRMT5) methylates multiple protein substrates with a variety of biological functions known to be dysregulated in cancer. CTS3497 is an orally available, brain-penetrable, MTA (methylthioadenosine) -cooperative PRMT5 inhibitor that preferentially targets the MTA-bound PRMT5 in MTAP (MTA phosphorylase) -deficient tumors and potently inhibits tumor growth in various preclinical models. Here we present clinical data from an ongoing Phase I/II study of CTS3497 in solid tumors (NCT06971523). **Methods:** Eligible pts with homozygous MTAP deletion (by next generation sequencing), or MTAP protein loss (by immunohistochemistry [IHC]) and advanced solid tumors in the dose-escalation stage received 50, 200, 300, 400 mg BID of CTS3497 orally, while pts in the dose-expansion stage were treated with 200, 300 or 400 mg BID until disease progression or intolerable toxicity. Efficacy, safety, PK, PD and biomarker profiles were evaluated. **Results:** As of 22 Jan 2026, 41 patients received ≥1 dose of CTS3497 treatment. No DLT was observed, and MTD was not reached; CTS3497 was well-tolerated. Most common (≥20%) treatment-related adverse events (TRAEs) were anemia (34%), white blood cell count decreased (32%), platelet count decreased (27%) and neutrophil count decreased (22%). The most common Grade ≥3 TRAE (occurring in ≥5% of patients) was platelet count decreased. No central nervous system (CNS) effects were reported. Among 21 centrally-confirmed MTAP-deficient, efficacy-evaluable patients, including 9 gastrointestinal (GI) cancers (ampullary cancer, biliary tract carcinoma, esophageal squamous cell carcinoma, gastric cancer and pancreatic ductal adenocarcinoma), 5 non-small cell lung cancer (NSCLC), 1 urothelial carcinoma and 6 rare cancers, the objective response rate (ORR) was 43%, and the disease control rate (DCR) was 91%. In GI cancers, the ORR and DCR were 56% and 89%. In NSCLC, the ORR and DCR were 60% and 80%. The exposures (Cmax, AUC0-24h) of CTS3497 increased in a linear, dose-proportional manner. The pharmacodynamic (PD) marker, plasma symmetric dimethylarginine (SDMA) level, showed a significant decrease. **Conclusions:** CTS3497 demonstrated a favorable safety profile and promising efficacy in heavily pretreated pts with MTAP-deficient advanced solid tumors, including GI cancers, NSCLC. Clinical trial information: NCT06971523. Research Sponsor: Cytosinlab Therapeutics Co., Ltd.

3116 Poster Session

Efficacy of targeting replication stress in neuroblastoma. First Author: Carla Sofia Sampaio, University of California San Diego, La Jolla, CA

Background: Children with high-risk and relapsed neuroblastoma (NB) need improved therapies, and recurrent cytogenetic abnormalities, such as *MYCN* oncogene amplification, represent candidate therapeutic targets. *MYCN* amplification and increased *MYCN* expression drive deregulated hyper-transcription that leads to development and growth of NB tumors, and *MYCN* amplifications, which can be found both within the linear genome on homogenously staining regions (HSR) and on circular extrachromosomal DNA (ecDNA), are associated with significantly worse survival rates for children with NB. *MYCN* overexpression has been linked to an increase in replication stress (RS), and RS and subsequent genome instability are important drivers of tumor initiation and progression. Flap Endonuclease 1 (FEN1), a non-essential DNA replication enzyme, was identified as a synthetic lethal target in *BRCA1/2*-deficient cancers via induction of RS. Recent success of targeting RS-elevated cancers with replication enzyme inhibitors opens a new avenue to target *MYCN*-amplified NB. **Methods:** Associations of gene expression with patient survival and prognostic features were performed on available neuroblastoma tumor databases using the R2 Genomics Analysis and Visualization Platform. The efficacy of FEN1 inhibition was assessed using live cell imaging and cell viability assays, comparing results in *MYCN*-amplified to -nonamplified NB cells and in NB cells with inducible *MYCN* expression and repression. Mechanisms of cell death and impacts on replication stress in cells treated with FEN1 inhibitors were evaluated by Western blots. **Results:** We have found that *FEN1* expression levels are associated with NB patient outcomes and with features of high-risk disease, including tumor stage and *MYCN* amplification. FEN1 inhibition was effective against NB cells and was significantly more effective in HSR-*MYCN*-amplified NB cells, but not ecDNA-MYCN amplified NB cells, with reduced cell growth and viability. Increased *MYCN* expression also led to increased sensitivity to FEN1 inhibition, and reduced MYCN expression reduced sensitivity. FEN1 inhibition led to the induction of apoptosis but not necroptosis in NB cells and responses to FEN1 inhibition were associated with markers of replication stress, including activation of the ATR-CHK1 and ATM-CHK2 pathways. **Conclusions:** We have discovered that HSR-mediated *MYCN*-amplified NB cells are hypersensitive to FEN1 inhibition, suggesting that FEN1 inhibition may be a promising therapeutic strategy for children with high-risk and relapsed NB. Research Sponsor: None.

3117 Poster Session

***MTAP* deletions and co-mutational landscape from whole genome sequencing in primary CNS tumors.** First Author: Lise Hoej Omland, The Phase I Unit, Department of Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Background: Biallelic deletions of the *MTAP* (methylthioadenosine phosphorylase) gene are frequent in solid tumors and confer synthetic lethality to PRMT5 (protein arginine methyltransferase 5) inhibition. Clinical trials are exploring the safety and efficacy of PRMT5 inhibitors (PRMT5i). Targeting additional co-occurring actionable alterations, such as gain-of-function mutations, with kinase inhibitors in combination with *MTAP*-directed synthetic lethality may potentiate therapeutic efficacy. *MTAP* deletions are present in up to 40% of glioblastomas (GBM) and occur sporadically in other primary central nervous system (CNS) tumors. Identification of actionable targets beyond *MTAP* deletions could enable combination strategies in these diagnoses, with otherwise limited therapeutic options. Whole-genome sequencing (WGS) with exon-level copy number alteration (CNA) analysis allows accurate determination of *MTAP* status, assessment of concordance with copy number variations (CNVs) in the neighboring *CDKN2A* and *CDKN2B* genes, and evaluation of the prevalence of co-occurring actionable alterations (including *IDH1, KRAS, PIK3CA, FGFR,* and *NTRK* alterations). **Methods:** A total of 145 consecutive patients with primary WHO grade 4 gliomas or other primary CNS tumors underwent WGS at the time of diagnosis as part of the prospective Neurogenome Study at Copenhagen University Hospital between January 2023 and October 2025. 57 patients (39%) were female, and the median age was 59 years (range, 26–78). *MGMT* promoter methylation was detected in 59 patients (40.4%); 6 tumors were not evaluable for *MGMT* status. 130 cases (GBM, n=118; astrocytoma, *IDH*-mutant, n=12) had reliable *MTAP* copy number analysis, samples with e.g. high fraction of normal tissue where excluded from analysis. **Results:** Among the 130 evaluable cases, 52 (40%) harbored biallelic *MTAP* deletions, 37 (28%) had monoallelic deletions, and 39 (30%) had no *MTAP* deletions. 2 cases (1.5%) had deletion of one *MTAP* allele with partial deletion of the second allele (exon-level deletions). Concordance between *MTAP* CNVs and *CDKN2A/B* CNVs—defined as either biallelic deletion or non-biallelic deletion of both *MTAP* and *CDKN2A/B* genes—was observed in 113 of 130 cases (87%). 31 cases harbored additional potentially actionable alterations. In tumors with biallelic *MTAP* deletions, 9 cases contained co-occurring actionable targets (*FGFR* fusion 1; *KRAS* mutation 1; *NTRK* fusion 1; *PIK3CA* mutation 4; *IDH1* + *PIKCA3* mutations 1; *IDH1* mutation + *PTPRZ1-MET* fusion 1). **Conclusions:** *MTAP* biallelic deletions were frequent at diagnosis in this primary CNS tumor population, whereas partial deletions of the *MTAP* gene (exon deletions) were rare. High concordance with *CDKN2A/B* status on WGS was observed. A subset of cases with biallelic *MTAP* deletions harbored other actionable targets underscoring the potential for combining PRMT5i with other targeted agents. Research Sponsor: None.

3118 Poster Session

Virtual AI-informed immunocyte profiling (VAIP) from H&E as a predictor of multi-cancer prognosis. First Author: Mayukhmala Jana, Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA

Background: Improved risk stratification is critically needed across multiple cancers to guide treatment decisions. This includes reducing overtreatment in Ductal Carcinoma in Situ (DCIS), addressing late recurrence risk in estrogen receptor-positive/lymph node-negative (ER+/LN-) breast cancer (BC), and refining prognosis in head & neck squamous cell carcinomas (HNSCC), and high-grade serous ovarian carcinoma (HGSOC). Tumor-infiltrating lymphocytes (TILs) reflect anti-tumor immunity, whereas tumor-associated macrophages (TAMs) polarize toward anti-tumor M1-like (CD68+) or immunosuppressive M2-like (CD163+) phenotypes. Integrating TILs with TAM polarization markers may better capture inflammatory balance and improve outcome prediction. We developed a hematoxylin and eosin (H&E)-only AI method (VAIP) to quantify TILs and virtual CD68/CD163 TAMs to develop multi-cancer based potential prognostic models. **Methods:** TILs were detected on H&E with HoVer-UNet, and virtual CD68 and CD163 macrophages were inferred with VISTA. In cancer regions, we computed cell densities and immune-balance ratios and trained cancer-specific Cox models with compact feature sets (DCIS 6; HGSOC 7; ER+ 4; HNSCC 4). Prognostic stratification used disease-free survival (DFS) for DCIS (N=273), HGSOC (training N=165, independent test N=220), and ER+ BC (training N=144, test N=622), and overall survival (OS) for HNSCC (N=77), reflecting clinical endpoints. Evaluation used cross-validation for cohorts without an external test set (DCIS, HNSCC) and independent training and testing when independent cohort was available (HGSOC, ER+). **Results:** Risk stratification performance across cancer types is in Table 1. The DCIS model used 6 features, largely TIL-macrophage contrast ratios (TIL/M2, TIL/M1). HGSOC used 7 features with a similar ratio-heavy immune-balance signature, plus macrophage-normalized density and polarization metrics (e.g., M1/N, M/N). In contrast, ER+ BC and HNSCC achieved best performance with 4 features dominated by macrophage measures, particularly M2 density and the M1/M2 ratio. Across sites, CD163-related macrophage metrics and immune-balance ratios were consistently informative. **Conclusions:** Integrating H&E-visible TILs with virtual CD68/CD163 TAMs enables fully automated, H&E-only prognostic biomarkers that stratify OS and DFS across multiple cancers, demonstrating consistent prognostic value in DCIS, ER+ BC, HGSOC, and HNSCC. These findings support further study of this histomorphometric risk classifier through broader external and prospective validation. Research Sponsor: None.

Performance across cancer types.

Cancer Type	Cohort	C-index	HR [95% CI]	p-value
DCIS	All	0.616	1.76 [1.20-2.59]	**<0.001**
DCIS	RT/No-treatment	0.624	1.94 [1.15-3.26]	**0.003**
HGSOC	Test	0.553	1.38 [1.02-1.87]	**0.030**
ER+ BC	Test	0.577	1.51 [1.00-2.28]	**0.004**
HNSCC	All	0.603	1.92 [1.03-3.36]	**0.012**

3119 Poster Session

Spatial transcriptomic profiling of the tumor microenvironment associated with sunitinib response in metastatic renal cell carcinoma. First Author: Shriya Deshmukh, Comprehensive Cancer Center & James Solove Research Inst., The Ohio State University Medical Center, Columbus, OH

Background: Metastatic clear cell renal cell carcinoma (ccRCC) exhibits heterogeneous clinical outcomes, and limited biomarkers are available to predict response to targeted therapies. This study evaluated cell compartment-specific transcriptional biomarkers predicting clinical response to the tyrosine kinase inhibitor (TKI) sunitinib. **Methods:** In this phase 2 single-arm clinical trial (NCT00715442), 46 patients with metastatic ccRCC received sunitinib pre- and post-cytoreductive nephrectomy. The primary endpoint was time-to-progression (TTP) and secondary endpoints included overall survival (OS) and sunitinib toxicity. To investigate spatial dynamics of therapeutic response to sunitinib, we applied whole-transcriptome digital spatial profiling (DSP) to tumor tissue to identify myeloid, endothelial, CD8+ T-cell and tumor compartment-specific transcriptional differences between responders (complete or partial response) and non-responders (stable or progressive disease). **Results:** For the 46 trial patients, the median duration of follow-up was 9.8 years (95% CI: 9.4 – NA). The median TTP was 8.2 months (95% CI: 6.1-19.3) and OS 36.3 months (95% CI: 19.7-70.5). Sunitinib-related adverse events occurred in 20% of patients, with grade 3 and 4 toxicities including hand-foot syndrome, fatigue, and hematologic abnormalities (thrombocytopenia, neutropenia). DSP analyses demonstrated that sunitinib responders display a tumor microenvironment enriched in pro-inflammatory and immunostimulatory programs. By contrast, non-responders displayed enrichment of immunosuppressive programs with elevated PD-L1 expression in myeloid cells and exhausted CD8+ T-cell signatures. Sunitinib resistance mechanisms involving pro-angiogenic VEGF-dependent and independent pathways were identified in non-responders, revealing potential therapeutic targets in combination with TKIs. Moreover, gene signatures developed based on DSP analysis of sunitinib response accurately predicted sunitinib response in an external patient cohort. **Conclusions:** Our findings underscore the relevance of spatial omics approaches to inform patient stratification and guide precision and combination treatment strategies aimed at mitigating TKI resistance in metastatic ccRCC. Clinical trial information: NCT00715442. Research Sponsor: The Ohio State University Comprehensive Cancer Center (Pelotonia Institute for Immuno-Oncology) Startup Funds; Society for Immunotherapy of Cancer - NanoString Technologies Single Cell Biology Award; Kidney Cancer Association Young Investigator Award; Pfizer.

3120 Poster Session

Developing harmonized tumor microenvironment subtypes for patient stratification in clinical trials. First Author: Nadezhda Lukashevich, BostonGene Corporation, Waltham, MA

Background: Accurate patient stratification by tumor microenvironment (TME) is critical for optimizing immunotherapy and targeted therapy outcomes. Existing transcriptome-based classification methods often focus on limited TME aspects and tumor types, restricting their clinical utility. Here, we developed a harmonized (H) TME classification by integrating findings from published pan-cancer TME profiling with reported immune evasion mechanisms. **Methods:** We used agglomerative clustering of gene signature scores (ssGSEA) and pathway activities (PROGENy) encompassing immune cells, fibrosis, vascularization, hypoxia, and other signals to acquire 9 transcriptomic HTME subtypes (Table 1) independently on TCGA (n=7,362) and internal (n=5,186) pan-cancer cohorts with high reproducibility (Spearman r=0.94). Next, we validated the subtypes on 29,875 solid cancer samples from open-source transcriptomic datasets by applying the K-Nearest Neighbors classifier. Differential expression analysis followed by Spearman correlation and PCA were used for comparison among classifications. Adjusted Cox models for survival and logistic regressions for response were applied. **Results:** Correlative analysis between existing classifications and HTME subtypes revealed patient stratification along 3 principal biological axes: adaptive immune response vs. tumor cell activity, fibrosis vs. antigen-presenting activity, and proliferation vs. vascularization, with, HTME uniquely covering all three axes. When applied to the selected clinical cohorts, HTME effectively distinguished patients by response (logOR) or progression-free survival (logHR) in a diagnosis- and therapy-specific manner (Table 1; showing values with p≤0.05). **Conclusions:** The proposed HTME patient stratification framework, publicly available and applicable to any RNA-seq sample, constitutes a practical tool for biomarker discovery and trial design across solid tumors. Research Sponsor: None.

logOR and logHR metrics of HTME subtypes based on diagnosis and treatment type.

	BRCA Basal-like, Luminal, Normal-like; ICI logOR [CI]	BRCA HER2+; anti-HER2 logOR [CI]	ccRCC; TKI PFS logHR [CI]	ccRCC; anti-VEGFR+ anti-PDL1 PFS logHR [CI]	ccRCC; anti-mTOR PFS logHR [CI]	SKCM; ICI logOR [CI]	NSCLC; ICI logOR [CI]
Lymphoid-Cell-Enriched							
B-Cell-Enriched/Angiogenic			-0.9 [-1.5, -0.3]**		-0.7 [-1.4, -0.1]*		1.1 [0.2, 2.0]*
Immune-Enriched/Hypoxic	-1.8 [-3.2, -0.4]*		0.6 [0.1, 1.0]**		1.1 [0.4, 1.8]**	-1.3 [-2.5, -0.1]*	
Highly Immune-Enriched/Inflamed	-2.9 [-5.3, -0.4]*	-1.5 [-2.3, -0.6]***			1.1 [0.2, 1.9]*	-2.1 [-3.6, -0.5]**	-1.1 [-1.9, -0.2]*
Immune-Enriched/Fibrotic			1.0 [0.5, 1.6]***				2.3 [0.6, 4.1]**
Fibrotic/Angiogenic/Myeloid				0.9 [0.4, 1.3]***			
Fibrotic/Hypoxic				1.4 [0.4, 2.5]**			
Immune Desert		0.8 [0.0, 1.5]*				1.2 [0.2, 2.2]*	0.6 [0.1, 1.2]*
Desert/Angiogenic		1.1 [0.1, 2.1]*	-0.6 [-1.1, -0.1]*				1.1 [0.1, 2.1]*

*p≤0.05; **p≤0.01; ***p≤0.001.

3121 Poster Session

Identification of high-grade neuroendocrine carcinoma (HGNEC) biology across tumor types through transcriptomic profiling and validation in lung cancer. First Author: Yatian Yang, Caris Life Sciences, Phoenix, AZ

Background: HGNECs, including small-cell (SC) and large-cell (LCNEC), are aggressive malignancies frequently misclassified due to subtle morphology and inconsistent use of neuroendocrine (NE) immunohistochemistry in routine pathology workflows. It is unclear if tumors with transcriptomic signatures reflecting HGNEC-like biology have inferior outcomes with conventional treatment. Leveraging a large real-world dataset, this study aims to identify transcriptomically defined HGNEC to improve upon morphology-based classification. **Methods:** 49,144 specimens underwent DNA and RNA sequencing at Caris Life Sciences. Using a previously reported framework, we developed a weighted, z-scored based HGNEC activity score (HAS) from 10,137 pathologically defined HG- and LG- NEC specimens and applied it to characterize NSCLC samples (without any pathologist assigned HGNEC diagnosis) further stratified by histology (n=39,007). Overall survival (OS) was obtained from insurance claims data and calculated from specimen biopsy to last contact using Kaplan-Meier and Cox proportional hazards estimates. **Results:** To identify a high-confidence HGNEC-like subpopulation, a HAS threshold (z-score>=3) was applied, classifying 0.2% squamous (sq) and 2.3% non-squamous (nsq) as HGNEC-like; this analysis is focused in nsq. Patient demographics, including age, gender, race, ethnicity, and smoking history, were similar between the HGNEC-like and non-HGNEC-like nsq cohorts. However, biopsies from lymph nodes (26 vs 11%) and brain (9.1 vs 5.6%) were more frequent, and lung (39 vs 56%) less frequent in HGNEC-like tumors (all p-adj<0.05). HGNEC-like tumors were associated with poor OS (HR:1.18, 95% CI:1.07–1.31, p<0.001). HGNEC-like tumors were more frequently PD-L1 negative (64% vs 47%), and were enriched for mutations in *TP53*, *PTEN* and *RB1* (OR: 1.7-14.1), as well as amplifications in *MYC* and *CCNE* (OR: 2.2-3.5), with lower odds of *KRAS* and *EGFR* mutations (OR:0.4-0.5, p-adj<0.05). Consistent with a highly proliferative phenotype, HGNEC-like tumors were enriched for *MKI67* expression (1.4-fold) and higher cell-cycle and replication stress scores (1.5-fold) (all p-adj<0.05) . Gene set enrichment analysis revealed significant activation of neurodevelopmental programs (NES: 2.0-3.0, all p-adj<0.05) and negative enrichment of immune pathways (e.g antigen presentation) (NES: -3.0 to -1.5, all p-adj<0.05). Finally, transcriptomic expression of potentially actionable SCLC-directed targets, including *DLL3* (10-fold), *SEZ6* (3.7-fold), and *SSTR2* (10-fold), were all higher in HGNEC-like tumors (all p-adj<0.05). **Conclusions:** We identify a transcriptomically defined HGNEC-like subset of NSCLC with inferior survival and targetable NEC biology, supporting transcriptomic stratification to inform clinical trial design and selection of SCLC-directed therapies. Research Sponsor: None.

3122 Poster Session

ILF2 as a predictor of cisplatin resistance and clinical outcomes in intrahepatic cholangiocarcinoma. First Author: Kodai Abe, Saint John's Cancer Institute, Santa Monica, CA

Background: Intrahepatic cholangiocarcinoma (iCCA) is a highly aggressive biliary tract cancer with increasing global incidence and limited therapeutic options, partly due to the low prevalence of actionable genomic alterations such as *FGFR2* fusions (~10%) and *IDH1* mutations (~13%). Using single-cell transcriptomic analyses, we identified recurrent amplification at chromosome 1q21.3 as a dominant genomic alteration in iCCA tumor cells. Given our prior evidence linking 1q21.3 amplification to DNA damage–response (DDR) processes and chemotherapy resistance in multiple cancer types, we focused on Interleukin enhancer binding Factor 2 (ILF2), a gene within 1q21.3, and systematically evaluated its multi-omic features and clinical relevance in iCCA using multiple independent clinical datasets. **Methods:** Single-cell RNA sequencing datasets were analyzed using Single-Cell Variational Aneuploidy (SCEVAN) to identify recurrent chromosomal alterations. Bulk RNA and DNA sequencing datasets were assessed for *ILF2* copy number variation (CNV) and mRNA expression. Clinical validation was performed using independent iCCA cohorts from Keio University and SJCI (n=67) and a public dataset (GSE89748; n=49). *In vitro* assays validated the functional role of ILF2 in DDR and cisplatin sensitivity of iCCA cell lines (n=3). **Results:** SCEVAN analysis of GSE125449 (n=8) and GSE138709 (n=5) revealed that 1q21.3 was the only common highest amplified region of iCCA tumor cells (29.7% and 31.1%, respectively). TCGA-CHOL dataset (n=32) demonstrated that *ILF2* CNV amplification occurred in 46.7% of cases and was strongly correlated with increased *ILF2* mRNA expression (r = 0.730, p < 0.001), which was significantly higher in tumor tissue than normal liver tissue in iCCA patients (p < 0.001). In the iCCA validation cohort (n=67) and GSE89748 dataset (n=49), *ILF2* mRNA level upregulation was significantly associated with shorter recurrence-free survival (log-rank test; p < 0.001 and p = 0.047, respectively), and independently predicted recurrence risk (multivariate Cox regression analysis HR = 4.63, 95% CI 1.71 – 12.6, p = 0.003 and HR = 2.73, 95% CI 1.10 – 6.80, p = 0.031, respectively). Consistently, ILF2 protein expression as assessed by multiplex immunofluorescence was significantly lower in FFPE tumor tissues from cisplatin responders than non-responders of iCCA patients (p < 0.001, n=16). Across iCCA cell lines, ILF2 interacted with DDR–related factors to suppress R-loop and γH2AX activities; both events are involved in promoting cisplatin resistance. **Conclusions:** *ILF2* is a frequent novel functional gene strongly associated with adverse clinical outcomes and cisplatin resistance of iCCA. This supports its role as a clinically relevant and theranostic biomarker related to DDR in iCCA patients. Research Sponsor: None.

3123 Poster Session

Target-specific therapy for actionable and approved tumor-agnostic biomarkers: Influence on survival in rare cancers. First Author: Razelle Kurzrock, Medical College of Wisconsin, Milwaukee, WI

Background: Rare cancers - defined as an incidence rate of less than 6 per 100,000 diagnoses per year - collectively account for close to 25% of cancer burden and represent a critical unmet clinical need. The emergence of regulatory approvals for tumor-agnostic therapies based on genomic biomarkers has expanded treatment options for these patients (pts) but clinical sequencing is not yet broadly adopted for rare cancers. Here, we assess the incidence and clinical utility of FDA-approved tumor-agnostic biomarkers in a large real-world rare cancers cohort. **Methods:** The Tempus Lens Platform used to query the de-identified Tempus multimodal database to analyze a cohort of 45,085 real-world pts with 615 rare cancer diagnoses. All pts had DNA (Tempus xT) and/or RNA sequencing (Tempus xR). Pts were screened for FDA-approved tumor-agnostic biomarkers, including high tumor mutational burden (TMB-H, ≥ 10 mut/Mb), high microsatellite instability (MSI-H), NTRK and/or RET fusions, BRAFV600E mutations and HER2 overexpression (IHC-3+). Pts were classified based on their reported biomarker status and treatment start of the approved targeted therapy relative to the FDA-approval date. Real-world overall survival (rwOS) was defined as the time from sample collection to death or loss to follow-up. Hazard ratios (HR) from Cox-proportional hazards models were adjusted for age, sex, race, ethnicity, and stage at p<0.05 (Wald test). **Results:** The median age of pts was 64 years old, 59% were female, 50% of those with documented race were white and 36% had metastatic disease. The most common diagnoses were within the genital system (25%), digestive system (23%), soft tissue (12%), brain (11%) and lung (6.5%). Of the total cohort, 13% (5,881) were positive for at least one tumor-agnostic biomarker. TMB-H was the most prevalent (10.3%), followed by HER2+ (5.5%), BRAFV600E (2.6%), MSI-H (1.9%), NTRK (0.5%) and RET (0.2%) fusions. Of 59% (3,480) of pts with recorded treatments, 33% (1,138) received the approved treatment following the approval date (tumor-agnostic biomarker-positive matched) while 64% (2,227) received other treatments (tumor-agnostic biomarker-positive unmatched). Pts with tumor-agnostic biomarker-positive matched treatments had significantly improved rwOS compared to tumor-agnostic biomarker-positive unmatched pts (HR=0.8, p=0.024) and to tumor-agnostic biomarker-negative individuals (HR=0.68, p<0.001). **Conclusions:** A large percent (13%) of pts with rare cancer diagnoses were found to harbor an actionable biomarker associated with an FDA-approved tumor-agnostic therapy. Pts who received therapies for approved tumor-agnostic biomarkers versus those pts with the biomarker who did not receive the matched treatment demonstrated a significant survival benefit, underscoring the importance of NGS testing to optimize treatment selection for rare cancer pts. Research Sponsor: None.

3124 **Poster Session**

Pan-cancer computational analysis of adaptive immune and vascular changes in primary versus metastatic tumors. First Author: Neil Arya Babu, Renown Health/University of Nevada Reno School of Medicine, Reno, NV

Background: Metastasis drives cancer mortality, yet tumor microenvironment (TME) evolution during systemic spread remains poorly understood. Current paradigms often assume uniform immunosuppression at metastatic sites or seek a universal pro-metastatic signature. We investigated whether a conserved immune signature exists across metastatic sites or if remodeling follows tissue-specific trajectories that could inform precision therapeutic strategies. **Methods:** We performed computational meta-analysis from TCGA using xCell enrichment scores across >20,000 transcriptomic samples from primary tumors and distant metastases in five solid tumor types: Lung (n=1,622), Breast (n=1,543), Kidney (n=1,541), Brain (n=1,243), and Thyroid (n=1,016). Mann-Whitney U testing with Bonferroni correction identified cell populations with differential enrichment (padj<0.05). Cohorts were balanced for age, gender, and race (all p>0.05). **Results:** We identified two convergent metastatic trajectories with opposite directional changes in a four-cell plasticity module: B-cells, class-switched memory B-cells, CD4+ effector memory T-cells, and platelets. The Immune-Vascular Acquisition Trajectory (Breast, Brain, Thyroid) showed metastatic enrichment of all four cell types (Mean Difference [Primary-Metastatic]: -0.62; padj<0.001). The Immune-Vascular Depletion Trajectory (Lung, Kidney) showed significant depletion of all four populations at metastatic sites (Mean Difference [Primary-Metastatic]: +0.74; padj<0.001). Platelet dynamics consistently mirrored adaptive immune trajectories across all cancer types. **Conclusions:** These findings challenge two prevailing assumptions: uniform immunosuppression at metastatic sites and a single universal pro-metastatic immune signature. Instead, metastatic immune remodeling follows organ-specific convergent trajectories driven by adaptive and vascular plasticity. The identification of shared trajectories among biologically distinct cancers suggests that metastatic site microenvironment dictates TME evolution. The de novo acquisition of immune signatures in brain metastases challenges the "immunologically cold metastasis" paradigm, while depletion in naturally immunogenic tumors (Lung, Kidney) indicates TME "cooling" for immune evasion. The invariant coupling of platelet and adaptive immune dynamics highlights vascular remodeling as critical to metastatic niche establishment. These distinct trajectories may explain differential responses to immunotherapy and anti-angiogenic agents across metastatic sites, supporting the need for organ-specific therapeutic strategies. Future studies are needed to investigate whether primary tumors harbor early signatures of this module predictive of metastatic trajectory, enabling stratified surveillance and intervention. Research Sponsor: None.

3125 **Poster Session**

Pan-cancer prevalence, molecular landscape, and prognostic impact of *CCNE1* amplification across 76,046 malignancies. First Author: Ricardo Dahmer Tiecher, Memorial Sloan Kettering Cancer Center, New York, NY

Background: *CCNE1* amplification (*CCNE1*amp) is an oncogenic driver that confers synthetic-lethal vulnerability to agents targeting cell cycle and replication stress. While *CCNE1*amp is a poor prognostic marker in some solid tumor types, pan-tumor data are limited. We used the MSK Clinical Sequencing Cohort to characterize its pan-tumor prevalence, molecular landscape, and prognostic impact. **Methods:** We analyzed data from consented patients with solid tumors sequenced by MSK-IMPACT between July 2014 and August 2025. *CCNE1*amp was defined as an amplification or gain per clinical report. Tumor-level prevalence was calculated and reported for histologies with ≥10 CCNE1amp tumors. Co-occurring alterations were evaluated using the first *CCNE1*amp sample per tumor type in each patient, with Fisher's exact test and Benjamini-Hochberg correction. Overall survival was measured from the date of first sequencing to death or last contact. **Results:** Among 76,046 tumors, the prevalence of CCNE1amp was 2.7% (n = 2,036). Our *CCNE1*amp cohort comprised predominantly ovarian (21%, n=435), uterine (15%, n=301), non-small cell lung (11%, n=231), esophagogastric (10%, n=206), and breast cancers (8%, n=168). Prevalence rates were highest in uterine carcinosarcoma (25.6%); ovarian carcinosarcoma (20%); uterine serous carcinoma (16.2%); high-grade serous ovarian carcinoma (15.4%); osteosarcoma (11.9%); gallbladder adenocarcinoma (9.7%); and esophageal adenocarcinoma (9.1%). Prevalence rates in breast cancer were 2.1% and in non-small cell lung cancer 2.6%. Among 67 patients with paired pre- and post-treatment samples of purity ≥30%, *CCNE1*amp was reported in all samples in 42% of patients. The most frequently co-mutated genes were *TP53* (87%), *PIK3CA* (12%), *KRAS* (8%), and *RB1* (7%). Most common amplifications included the 19q neighbors *CEBPA* (31%), *KMT2B* (22%), and *AKT2* (22%); as well as *MYC* (14%); and *ERBB2* (13%). The most significant co-occurrences (q<0.05) were *TP53* mutations (OR 11.5) and *MYC* amplifications (OR 3.5); CCNE1amp was mutually exclusive with *PTEN* (OR 0.37) and *KRAS* mutations (OR 0.55). CCNE1amp samples had a higher median fraction of genome altered (median 0.35 vs. 0.12; p<0.001). *CCNE1*amp was associated with worsened overall survival in a multivariate Cox model stratified by cancer type and adjusted for age, stage and *TP53* status (adjusted HR 1.25; 95% CI 1.17-1.33). Its adverse prognostic impact was more pronounced in *TP53*wt (HR 1.62; 95% CI 1.38-1.91) vs. *TP53*mut tumors (HR 1.19; 95% CI 1.11-1.27; p for interaction <0.001). **Conclusions:** *CCNE1* amplification defines a pan-cancer genomic subset associated with poor prognosis, genomic instability, and few co-occurring actionable alterations, supporting its relevance as a therapeutic target. Discordance between paired samples suggests that a single negative biopsy may not rule out CCNE1amp. Research Sponsor: Memorial Sloan Kettering Cancer Center NCI Support Grant (P30 CA008748).

3126 **Poster Session**

Early-onset cancer signature (EOCS): Pan-cancer molecular alterations with prognostic significance in early-onset (EOC) and late-onset (LOC) cancer. First Author: Mahesh Iddawela, Peninsula Health & Peninsula Clinical School, Monash University, Frankston, VIC, Australia

Background: Early-onset cancer (EOC) is an emerging global epidemic with biological and molecular features distinct from late-onset cancer (LOC). Improved delineation of genomic pathway aberrations in EOC is essential to inform risk stratification and therapeutic decision-making. However, large-scale, unbiased analyses of biological drivers across tumour types remain limited. To address this gap, we developed a pan-cancer Early-Onset Cancer Signature (EOCS) to advance understanding of the genomic architecture underpinning EOC. **Methods:** The AACR GENIE v16 dataset comprising 241,551 tumour samples was analysed, including 22,408 early-onset cases (≤40 years) and 219,143 late-onset cases (≥41 years) from multiple international repositories. Differentially enriched genomic alterations and pathways between EOC and LOC were identified to define the EOCS. The EOCS was subsequently evaluated across TCGA pan-cancer datasets and validated in independent cohorts, including METABRIC (breast cancer), MSKCC colorectal cancer, and MSKCC prostate cancer datasets. **Results:** Analysis of the AACR GENIE cohort revealed that the most significantly enriched alterations in EOC compared with LOC were CCDC6 (20% vs 10%), SYNE1 (8% vs 6%), BRAF (9% vs 6%), FLI1 (19% vs 0.5%), and EML4 (8% vs 4%). In contrast, alterations significantly enriched in LOC included KRAS (15% vs 5%), TP53 (38% vs 29%), EGFR(15% vs 5%), STK11 (3% vs 1%), and CDKN2A (10% vs 6%). Gene set enrichment analysis of EOCS-associated genes identified DNA recombination, regulation of histone H3K9 trimethylation, and homologous recombination–mediated double-strand break repair as the top three enriched Gene Ontology pathways. The EOCS was altered in 30% (3,736/10,967) of TCGA pan-cancer samples, with the highest prevalence observed in endometrial, skin, carcinosarcoma, and gastric cancers. The most frequently altered genes included SYNE1(12%), CTNNB1 (4%), PPMD1 (3%), BCR (3%), ETV6 (3%), RAD52 (3%), and H3-3A (3%). Across TCGA pan-cancer and tumour-specific cohorts, EOCS alterations were consistently associated with inferior overall survival irrespective of age at diagnosis, including pan-cancer (68 vs 83 months; $p = 9.1 \times 10^{-3}$), breast cancer (142 vs 164 months; $p < 0.04$), colorectal cancer (45 vs 56 months; $p = 1.75 \times 10^{-4}$), and prostate cancer (56 vs 77 months; $p = 2.0 \times 10^{-4}$). **Conclusions:** This pan-cancer Early-Onset Cancer Signature identifies distinct genomic pathways driving tumourigenesis in EOC. The findings provide novel biological insights into disease pathogenesis and highlight potential diagnostic and therapeutic targets, supporting the clinical relevance of EOCS across multiple cancer types. Research Sponsor: None.

3127 **Poster Session**

Clinical utility of whole transcriptome sequencing for fusion detection in advanced solid tumors: SCRUM-Japan MONSTAR-SCREEN-2. First Author: Takao Fujisawa, Department for the Promotion of Drug and Diagnostic Development, Division of Drug and Diagnostic Development Promotion, Translational Research Support Office, National Cancer Center Hospital East, Kashiwa, Japan

Background: Fusion variants represent established therapeutic targets in precision oncology yet are incompletely captured by conventional targeted DNA panel sequencing. Recent studies have reported that RNA sequencing enables detection of oncogenic fusions and structural variants that escape conventional DNA panel sequencing, particularly complex rearrangements occurring in intergenic regions. Herein, we evaluated the landscape of fusion variant detection by whole transcriptome sequencing (WTS) in advanced solid tumors from the SCRUM-Japan MONSTAR-SCREEN-2, a nationwide molecular profiling project. **Methods:** Patients with advanced solid tumors were enrolled; tumor tissues were profiled using whole exome/transcriptome sequencing (MI CancerSeek, Caris Life Sciences, Phoenix, AZ, USA). For fusion detection comparison, we performed an in silico analysis cross-referencing each fusion detected by WTS against publicly available information from conventional DNA panels including both target gene lists and breakpoint information where available, to evaluate theoretical detectability. **Results:** Among 2,768 patients enrolled as of March 2024, WTS data from baseline tissue samples were available in 2,253 pts across 33 cancer subtypes: the most common subtypes were colorectal adenocarcinoma (n=520), gastric adenocarcinoma (n=306), breast cancer (n = 198), prostate cancer (n=177) and pancreatic cancer (n=156). Pathogenic gene fusions and structural variants were detected by WTS in 122 of the 2,253 patients (5.4%), with a total of 126 pathogenic fusions identified. Among 126 pathogenic fusions, 75 (59.5%) represented variants that would theoretically have escaped detection by targeted panel DNA sequencing methodologies, including druggable kinase fusions (FGFR2, FGFR3, and BRAF). Among 18 patients treated with kinase fusion-targeted therapy with evaluable response data, 1 (5.6%) showed complete response, 3 (16.7%) showed partial response and 11 (61.1%) showed stable disease. WTS identified a MYO5A-BRAF fusion in a patient with melanoma that was undetectable by conventional DNA panel sequencing. Based on this finding, the patient received combination BRAF and MEK inhibitor therapy, achieving stable disease for four months, demonstrating the therapeutic relevance of WTS-guided treatment selection. **Conclusions:** WTS detected fusion variants at a high frequency, highlighting the importance of WTS in precision oncology. Clinical trial information: UMIN000043899. Research Sponsor: SCRUM-Japan Fund.

3128 **Poster Session**

Pan-cancer *KRAS* atlas of 9,056 Chinese patients: Subtype-specific immuno-genomic profiling to guide G12C, G12D, and pan-*KRAS* strategies. First Author: Panli Peng, Guangdong Second Provincial General Hospital, Guangzhou, China

Background: *KRAS* therapy is shifting from allele-specific inhibitors to pan-*KRAS* strategies. However, pivotal trials are largely Western, and Asian subtype-specific immunogenicity and co-mutation benchmarks remain limited. We present the largest pan-cancer Asian *KRAS* clinogenomic atlas to define these benchmarks and inform treatment selection and trial stratification for the pan-*KRAS* inhibitor era. **Methods:** We analyzed 9,056 Chinese patients with *KRAS* mutations across over 30 tumor types, including pancreatic 27.4%, colorectal 25.1%, NSCLC 20.8%, and biliary tract 10.0%. All underwent ~600 gene next generation sequencing profiling in a CAP/CLIA certified laboratory including all classes of genomic alterations with integrated analysis of clinical variables, treatment history, co-mutations, TMB, MSI, and PD-L1. **Results:** *KRAS* mutations clustered at four hotspot codons: G12 (80%), G13 (9%), Q61 (6%), and A146 (3%). Alleles were dominated by G12D (33.3%), G12V (22.8%), and G12C (11.8%), followed by G13D (7.8%) and G12R (4.6%), together covering 80.3% of patients. Overall, 55% carried non-G12C/D variants. More than one *KRAS* point mutations occurred in 1.8% of the patients and *KRAS* amplification in 2.5%. Co-mutations were common, led by *TP53* (61.7%), *APC* (22.2%), *SMAD4* (17.9%), *CDKN2A* (17.1%), *PIK3CA* (12.5%), *ARID1A* (11.9%), and *STK11* (7.7%). TMB in 98.5% (median 4.0 mut/Mb) with 19.2% TMB-high (≥10 mut/Mb), MSI in 97.4% with 3.5% MSI-H, and PD-L1 in 58.0% with 49.5% positive expression. Subtype patterns were distinct. G12C had the highest TMB-high rate (42.4%) with rare MSI-H (0.8%), supporting targeted inhibition with rational IO combination evaluation. In contrast, G13D showed an Asian-enriched immunogenic phenotype with MSI-H 16.1%, higher than Western benchmarks (7.9%, $P<0.001$), and elevated TMB-high (30.8%). Clinically relevant stratification emerged in NSCLC G12C, with 82.5% male predominance versus about 40% in Western populations ($P<0.0001$) and an age gradient consistent with smoking (67% male <50 years rising to 89% at ≥70 years). Adverse co-mutations were enriched in G12C, including *STK11* (14.4%) and *KEAP1* (9.1%). Multi-*KRAS* mutations were strongly associated with MSI-H (OR 5.48, $P<0.0001$). Conversely, G12R showed an immune-cold profile (TMB-high 3.2%, MSI-H 0.2%), supporting reliance on targeted inhibition rather than IO-based approaches. Nineteen percent of patients were treatment-naive at profiling, most commonly in NSCLC (30%). Versus post-treatment cases, treatment-naive patients were enriched for G12C (15.9% vs 10.4%, $P<0.0001$) and showed higher TMB and PD-L1positives. **Conclusions:** This largest Asian *KRAS* atlas defines actionable benchmarks for precision therapy and provides a molecular rationale for region-specific stratification in global pan-*KRAS* trials. Research Sponsor: None.

3129 **Poster Session**

Tumor and immune microenvironment remodeling with neoadjuvant trastuzumab deruxtecan in HER2-positive gastric cancer: Exploratory analyses from the phase 2 EPOC2003 study. First Author: Akihito Kawazoe, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: We previously reported the efficacy and safety of neoadjuvant trastuzumab deruxtecan (T-DXd) for HER2-positive gastric and gastroesophageal junction adenocarcinoma (EPOC2003) (Takahari et al., ASCO GI 2024). This exploratory analysis aimed to investigate the associations of baseline molecular features of the tumor, the immune landscape, and their longitudinal changes with the therapeutic efficacy of T-DXd. **Methods:** Tumor samples were collected at baseline, pre-cycle 2, post-cycle 3 (before surgery), and at surgery. We performed bulk/single-cell RNA sequencing (scRNA-seq) and multiplex immunohistochemistry to identify correlates of pathological response. Responders were defined as patients achieving a major pathological response according to the Becker criteria. Blood samples were collected at baseline and post-cycle 3 for circulating tumor DNA (ctDNA) analysis using a clinically validated, tumor-informed, personalized assay (Signatera, Natera, Inc.). **Results:** Baseline HER2 expression did not differ between responders (n= 4) and non-responders (n= 22). In the post-treatment sample analysis, a decreasing trend in proliferation index was observed in responders, whereas this trend was not observed in non-responders, suggesting preferential elimination of proliferative tumor cells by T-DXd. Early on-treatment samples (pre-cycle 2 or post cycle 3) tended to demonstrate upregulation of cytokine signaling, inflammatory, immune response signatures, and CD8+ T cell density in both tumor and stroma regardless of response. Notably, scRNA-seq revealed an expansion of neutrophils, which was more pronounced in responders with a stronger baseline interferon signature. These post-treatment neutrophils displayed upregulated migration, phagocytosis, and degranulation signatures, indicative of enhanced neutrophil mediated anti-tumor activity following T-DXd. ctDNA testing was performed in 18 patients, with a baseline positivity rate of 94.4% (17/18). All responders (3/3) achieved ctDNA clearance after cycle 3, compared with only 35.7% (5/14) of non-responders. **Conclusions:** Neoadjuvant T-DXd therapy induced biological remodeling of the tumor and immune microenvironment. Together with on-treatment ctDNA kinetics, these findings suggest distinct response-associated biological patterns and may help guide future treatment optimization for HER2-positive gastric and gastroesophageal junction adenocarcinoma. Clinical trial information: NCT05034887. Research Sponsor: Daiichi Sankyo.

3130 **Poster Session**

APOBEC mutational signatures to predict immune checkpoint inhibitor benefit in TMB-low metastatic NSCLC independent of PD-L1 status. First Author: Adar Yaacov, Helmsley Cancer Center, Shaare Zedek Medical Center, Jerusalem, Israel

Background: Most metastatic non-small cell lung cancer (NSCLC) patients are tumor mutational burden (TMB)-low (<10 mut/Mb) and lack validated biomarkers to guide immune checkpoint inhibitor (ICI) use beyond PD-L1 expression. APOBEC mutagenesis, characterized by distinct mutational signatures, has been linked to ICI response in urothelial and head and neck cancers – but primarily in TMB-high tumors. Whether APOBEC activity predicts ICI benefit specifically in TMB-low NSCLC, independent of PD-L1 status, remains unclear. **Methods:** We analyzed a discovery cohort of 857 metastatic TMB-low NSCLC patients treated with ICI from the MSK-CHORD cohort. To distinguish predictive from prognostic effects, we examined 1,328 ICI-untreated TMB-low metastatic NSCLC patients as controls. Findings were validated in an independent cohort of 82 TMB-low, ICI-treated stage IV NSCLC patients using whole exome sequencing (WES). APOBEC positivity was determined using MESiCA, a validated machine-learning algorithm designed to detect mutational signatures from targeted gene panels with low mutation counts (≥4 mutations). Primary endpoints were overall survival (OS) and disease control rate (DCR) in the discovery cohort, and progression-free survival (PFS) and objective response rate (ORR) in the validation cohort. Multivariate Cox regression adjusted for PD-L1 status and age. **Results:** In the discovery cohort, APOBEC-positive (n=52, 6.1%) and APOBEC-negative (n=805) patients were balanced for sex (44% vs 46% male), histology (83% vs 79% adenocarcinoma), and PD-L1 status (40% vs 40%; all $p>0.05$); APOBEC-positive patients were younger (median 64 vs 69 years, p=0.002). The APOBEC-positive group demonstrated significantly improved OS (median 33.7 vs 17.4 months; HR=0.60; 95% CI, 0.42–0.85; p=0.004). The survival benefit was absent in ICI-untreated patients (HR=0.98; 95% CI, 0.76–1.26; p=0.85). Formal interaction testing confirmed that the APOBEC benefit was specific to ICI-treated patients (interaction HR=0.62; p=0.032). APOBEC-positive tumors demonstrated higher DCR at 180 days (21.4% vs 7.6%; OR=3.32; p=0.006). In multivariate analysis adjusting for PD-L1 and age, APOBEC remained independently predictive (HR=0.57; 95% CI, 0.40–0.81; p=0.002). In the validation cohort, APOBEC independently predicted superior PFS (HR=0.23; 95% CI, 0.05–0.94; p=0.020) after adjusting for PD-L1, with numerically higher ORR (55.6% vs 25.4%, p=0.068). **Conclusions:** APOBEC mutational signatures represent a robust, independently validated predictive biomarker for ICI response in TMB-low metastatic NSCLC. Unlike prior studies linking APOBEC predominantly to TMB-high tumors, we demonstrate clinical utility specifically in the TMB-low population, where predictive biomarkers are most needed. This biomarker could expand immunotherapy access for NSCLC patients. Research Sponsor: None.

3131 **Poster Session**

Dynamics of nectin-4 (N4) expression in urothelial carcinoma (UC): Across disease states. First Author: Hiba Narvel, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI

Background: Enfortumab vedotin (EV), which targets N4, has revolutionized advanced UC management. Despite high prevalence of N4 in UC, the temporal stability of N4 is poorly characterized. Conflicting reports describe both decreased and increased expression in metastatic (met) UC compared to primary tumors raising uncertainty as to whether changes reflect antigen loss or quantitative modulation—an issue central to resistance to EV. **Methods:** This single-center retrospective study identified pts with met UC who received treatment (trt) with EV. Demographic, clinicopathologic, trt and survival data (from time of met diagnosis) were recorded. N4 expression was evaluated via immunohistochemistry (IHC) (N4 Clone EPR15163-68) H-Score in available primary (TURBT, cystectomy/nephroureterectomy) and met tissue. H-Score was assessed as N4 positive (+) vs negative (neg,-) (>0 vs 0) and ordinally (neg, low <100, medium 100-200, high >200). Concordance between specimen pairs was assessed using percent agreement, McNemar's test, and weighted Cohen's kappa. Overall survival (OS) was evaluated via Kaplan–Meier methods and exploratory Cox regression. **Results:** We identified 141 pts (median age 70; 71% male; primary: bladder (83%), upper tract (15%), synchronous (2.1%), unknown (0.7%). 93% of primary tumors were N4+ (n=44). In matched TURBT-Cystectomy pairs (n=21), binary status was stable (95% agreement), but ordinal concordance was poor (27% agreement, $\kappa = -0.05$) and significant antigenic dampening was observed: High N4 expression decreased from 90% at TURBT to 29% at cystectomy, with a reciprocal increase in medium-level expression from 10% to 48% ($p<0.001$). 89% of met sites (n=27) were N4+. There were no differences in receipt of prior neoadjuvant chemotherapy (NAC) or 1st line trt between met N4+ and N4- groups. In matched cystectomy and metastases pairs (n=11), binary N4 concordance remained high (82% agreement) with poor ordinal concordance (27% agreement, p=0.12). Neither binary nor ordinal metastatic expression, nor changes in H-score over time, were associated with OS. There were no differences in OS in binary met N4+ vs N4- (p=0.82) nor ordinally classified groups (p=0.43). **Conclusions:** N4 is a stable binary target in UC, maintaining positivity across primary and metastatic sites despite significant quantitative dampening in expression intensity. These findings, although exploratory suggest that tumor evolution and therapeutic resistance may be characterized by dynamic antigen density modulation rather than categorical loss, an interpretation that may help reconcile prior discordant reports of expression changes in metastatic disease. Future studies should evaluate whether the degree of H-score shift (rather than absolute value) correlates with the durability of response to EV as well as the impact of neoadjuvant and subsequent sequential treatments on N4 expression intensity. Research Sponsor: None.

3132 **Poster Session**

Implementing clinical-scale multiscale spatial transcriptomics: Tumor architecture profiling in SCRUM-Japan MONSTAR-SCREEN-3. First Author: Mitsuho Imai, Translational Research Supporting Office, National Cancer Center Hospital East, Kashiwa, Japan

Background: Spatial interactions between tumor cells and the tumor microenvironment (TME) influence disease progression, yet current diagnostic profiling lacks spatial resolution. A clinically implementable framework enabling cross-cancer spatial characterization using pretreatment clinical specimens is needed. SCRUM-Japan MONSTAR-SCREEN-3 (MONSTAR3) is an ongoing prospective clinical screening platform enrolling over 3,200 patients with solid tumors, integrating clinical annotation with multi-omic. We report an intermediate analysis validating the feasibility of extracting reproducible spatial phenotypes from pretreatment specimens at clinical scale. **Methods:** Spatial transcriptomics (Xenium 5K) was performed on 331 pretreatment FFPE tumor specimens from 309 patients representing ≥15 solid cancer types enrolled in MONSTAR3. Specimens obtained at diagnosis or prior to systemic therapy included unresectable advanced and curative-intent settings. Analyses examined spatial organization of tumor–immune interactions at the TME level, cancer cell functional states, neighborhoods, and tertiary lymphoid structures. Spatial features were systematically compared across cancer types and disease settings without treatment outcomes. **Results:** We generated a spatial atlas comprising approximately 20 million cells with high-confidence annotation across over 15 cancer types, representing one of the largest clinically annotated pan-cancer spatial transcriptomic resources to date. The atlas captures tumor-microenvironment organization, cancer-intrinsic functional heterogeneity, conserved cellular niches, and specialized immune structures including tertiary lymphoid structures with defined maturation states. Spatial tumor architecture varies substantially across cancer types despite similar cellular composition, underscoring value of spatially-resolved profiling beyond conventional cell-type quantification. Analysis across disease stages revealed that advanced tumors exhibit higher spatial compartmentalization of cancer functional states, with immunogenic and proliferative cancer populations showing consistent spatial separation across cancer types. Pan-cancer niche analysis identified conserved cellular neighborhoods, a subset of which showed stage-specific enrichment or prognostic associations. We also performed detailed spatial characterization of tertiary lymphoid structures, which demonstrated association with immunotherapy response in an independent cohort. **Conclusions:** We present a large-scale pan-cancer spatial atlas integrated within a nationwide precision oncology framework. This resource enables systematic investigation of spatial tumor biology and nominates spatially-defined features as candidate biomarkers for patient stratification and therapeutic response studies. Research Sponsor: None.

3133 **Poster Session**

AACR GENIE analysis of 211,526 patients to evaluate hormone receptor alterations across solid tumors: Rationale for tissue-agnostic basket trials. First Author: Niamh Coleman, Trinity St James's Cancer Institute, Dublin, Ireland

Background: Steroid Hormone receptors (HR) that include estrogen receptor (ER), progesterone receptor (PR), and androgen receptor (AR) were oncology's first predictive biomarkers, yet HR-directed therapies remain largely confined to breast, prostate, and endometrial cancers. Emerging data suggest broader HR relevance across tumor types. The development of oral SERDs (selective ER degraders) and next-generation AR degraders/antagonists creates new opportunities to target HR alterations across tumor types. We performed pan-cancer genomic profiling to define the landscape of ESR1/AR alterations and resistance co-alterations, providing rationale for biomarker-enriched basket trial designs. **Methods:** We analyzed the AACR Project GENIE v18 public dataset, comprising 250,018 tumor samples from 211,526 patients across multiple solid tumor types. Genomic alterations in ESR1 and AR were assessed, including mutations, copy-number alterations, and structural variants. Co-alterations with selected genes involved in resistance and cell-cycle regulation (PIK3CA, PTEN, AKT1, TP53, RB1, CDKN2A) were evaluated using pairwise co-occurrence analyses. **Results:** Across 250,018 solid tumor samples, ESR1 alterations were identified in 2.0% of cases, with highest prevalence in breast (8.4%) and endometrial cancers (4.6%), and lower frequencies in uterine sarcoma (2.7%) and melanoma (3.6%). Most ESR1 alterations were missense mutations localized to the ligand-binding domain, with recurrent hotspots at codons Y537 and D538. AR alterations were present in 2.4% of samples overall, most frequently in prostate cancer (7.6%), and were also detected in endometrial cancer (5.5%), lung cancer (~5%), and melanoma (4.9%). AR alterations consisted predominantly of copy-number amplifications, with additional ligand-binding domain mutations observed. Co-alteration analyses demonstrated frequent co-occurrence of ESR1 with PIK3CA, PTEN, and AKT1, and AR with TP53, RB1, and CDKN2A, whereas ESR1 and KRAS alterations did not significantly co-occur. **Conclusions:** Recurrent ESR1 and AR alterations occur in 2-5% of diverse solid tumors beyond breast, prostate, and endometrial cancers, with co-enrichment of PI3K-AKT and cell-cycle pathway alterations mirroring resistance patterns in canonical HR-driven malignancies. These findings support systematic evaluation of selective ER and AR degraders in biomarker-selected basket trials, expanding precision oncology beyond anatomically-defined indications. Research Sponsor: None.

3134 **Poster Session**

Impact of first-line comprehensive genomic profiling on survival outcomes for patients with advanced solid tumors who received molecularly-matched therapies: 3-year follow-up of the prospective FIRST-Dx study. First Author: Sadakatsu Ikeda, Department of Precision Cancer Medicine, Institute of Science Tokyo, Tokyo, Japan

Background: Comprehensive genomic profiling (CGP) by next-generation sequencing has been reimbursed in Japan since 2019. However, only 8.2% of patients (pts) had received molecularly-matched treatments. One major reason for this limited drug accessibility is that CGP is covered only after progression with standard of care (SoC). We previously reported that first-line CGP using FoundationOne CDx in advanced solid tumors (FIRST-Dx study) could identify molecular-based recommended therapy (MBRT) for 61% of pts (105/172), and 22.7% (39/172) could be treated by MBRT (JAMA Netw Open 2023, Cancer Sci 2025). To evaluate the impact of the first-line CGP test on survival outcomes, a 3-year follow-up analysis was conducted. **Methods:** The FIRST-Dx study was a multi-institutional prospective study in Japan. A total of 172 chemotherapy-naïve adult pts with advanced solid tumors (GI, Lung, Breast, GYN, Melanoma) and ECOG performance status of 0-1 were registered. This follow-up study was planned for 3 years after the final patient enrollment. The primary endpoint was overall survival (OS). Secondary endpoints were the proportion of pts receiving MBRT, overall response rate, progression-free survival (PFS), and PFS ratio (PFS on MBRT/PFS on prior therapy). **Results:** Median follow-up period was 25.0 months (0.5–45.2). Forty-six pts (26.7%) received MBRT. The number of pts treated with MBRT was 21 in the 1st-line, 22 in the 2nd-line, 6 in the 3rd-line, and 6 in the 4th-line or later setting. Median OS was significantly longer in pts treated with MBRT (not reached) than in those who did not receive MBRT (26.2 months, HR 0.62 [95% CI: 0.39–0.99], log-rank p=0.047). PFS and response rates were shown in Table. Among pts who received 2nd-line MBRT (N=15), the median PFS ratio (PFS on MBRT in 2nd-line/PFS on 1st-line therapy), was 1.2 (range: 0.4–14.6), and 7 pts (47%) achieved a PFS ratio of >1.3, indicating a clinically meaningful benefit of the first-line CGP based MBRT. In an exploratory analysis, propensity score matching (age, sex, cancer type) was performed between pts registered in this study and concurrent real-world pts who did not undergo the first-line CGP, resulting in 67 pts per group. Median OS was significantly longer in the FIRST-Dx group than in the real-world group (23.5 months vs 13.4 months, HR 0.61 [95% CI: 0.40–0.94], log-rank p=0.02). **Conclusions:** MBRT identified by CGP in the first-line setting improved access to targeted therapies and was associated with superior survival outcomes than SoC in advanced solid tumors. Our data suggest that CGP in Japan should be available prior to SoC initiation. Clinical trial information: jRCT1050220041. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

Median progression-free survival and response rate.

	MBRT	SoC	p-value
Median PFS (months)			
1st-line	13.7	11.3	0.04
2nd-line	11.0	5.6	<0.01
Response Rate (%)			
1st-line	52.4	37.8	0.24
2nd-line	45.5	13.2	<0.01

3135 **Poster Session**

Carcinomas of unknown primary treated with molecularly guided therapies and immune checkpoint inhibitors: A subset from the I-PREDICT N-of-1 Precision Oncology study. First Author: Eric Roth, UC San Diego Moores Cancer Center, La Jolla, CA

Background: Carcinoma of unknown primary (CUP) is a heterogenous group of aggressive malignancies lacking a detectable primary site and collectively comprises 3–5% of cancer diagnoses. Current treatments rely upon empiric chemotherapeutic regimens with high toxicity, limited efficacy, and historic median overall survival times of 3-11 months. There is emerging evidence to support a precision medicine approach using molecularly guided therapies and tumor-agnostic biomarkers. **Methods:** We performed a subset analysis of patients previously enrolled in the I-PREDICT (NCT02534675) study who had a CUP that was treated with a combination of targeted therapies and biomarker-driven immune checkpoint inhibitors (ICI), based upon comprehensive genomic profiling and recommendations by a Molecular Tumor Board. **Results:** Among the 210 evaluable patients, 10 (4.8%) had a CUP from which 9 were molecularly matched to one or more targeted therapies and an ICI based on biomarkers for both types of agents. Baseline characteristics include median age of 67 years (range: 59 – 82), with the majority of patients being male (5/9, 56%), non-Hispanic white (7/9, 78%) and treatment naïve (8/9, 89%). Histological subtypes of CUP included poorly differentiated or unspecified (5/9), adenocarcinoma (3/9) and squamous cell carcinoma (1/9). Administered targeted therapies included bevacizumab (4/9), trametinib (4/9), palbociclib (1/9), crizotinib (1/9), everolimus (1/9), and lenvatinib (1/9), while ICI included nivolumab (6/9), pembrolizumab (2/9) and atezolizumab (1/9). ICI were matched based on positive PD-L1 immunohistochemistry (IHC) (6/9), TMB ≥10 mutations/megabase (4/9), SWI/SNF chromatin remodeling gene alterations (3/9), PD-L1 amplification (1/9), mismatch repair gene alterations (1/9) and microsatellite instability-high (1/9). Most patients were matched to >1 ICI biomarker (5/9). Most patients received treatment doublets (6/9, 67%) while the remaining received triplet regimens (3/9, 33%). The best overall response rate was 44% based on RECIST 1.1. This included partial response (4/9), stable disease (3/9), progressive disease (1/9) and not restaged (1/9). Median progression free survival (PFS) was 10.4 months (95% confidence interval [CI] 4.2 - not estimable [NE]) and median overall survival was 16.9 months (95% CI 6.9 - NE). One patient in particular achieved 36-months of PFS on trametinib + nivolumab as matched to NF1 R440* and PD-L1 IHC 5%. Grade ≥3 treatment related serious adverse events occurred in only one patient. **Conclusions:** As compared to historic chemotherapy treated cohorts, these results support the safety and efficacy of administering molecularly guided combination therapies including a targeted agent plus an ICI in CUP patients. Larger prospective trials of biomarker-matched N-of-1 combinations in CUP are warranted. Clinical trial information: NCT02534675. Research Sponsor: None.

3136 **Poster Session**

Association of treatment-induced decrease of tumor chromosome Y and prognosis. First Author: Dan Theodorescu, University of Arizona Comprehensive Cancer Center, Tucson, AZ

Background: Loss of chromosome Y (LOY) in cancer has been linked to increased mortality. Since tumors that are not completely eradicated often harbor additional molecular changes which may alter biological behavior, here we sought to examine if therapy has any impact on tumor chromosome Y content and if so, the relevance this has on patient outcome. Changes in chromosome Y content with therapy would impact clinical decision making in patients with persistent or recurrent tumors since tumors with LOY have also been shown to be more responsive to specific therapies. **Methods:** Male patients with >=2 sequential tumor samples profiled at Caris Life Sciences (Phoenix, AZ) who received systemic therapy between collections were included. RNASeq was performed using NovaSeq platform. Chromosome Y score (YChr score) was calculated using ssGSEA (log-rank normalization) based on a previously published 9-gene signature (*Nature* 2025). Change in YChr score between pre and post treatment paired samples (ΔYChr) was computed per patient. A decrease in YChr score in post sample compared to pre sample was defined as ΔYChr ≥0.029 (cohort mean) and called progressive LOY (pLOY) while the remainder were called no-pLOY. Real-world clinical data were obtained from insurance claims. Overall survival (OS) was defined from first sample collection to last contact. Hazard ratios (HRs) were estimated using Cox proportional hazards models, with log-rank p values reported. **Results:** Among 1,343 patients with paired samples, pLOY was associated with shorter OS compared with no-pLOY (median OS [mOS]: 33.2 vs. 36.0 months; HR 1.168, 95% CI 1.028–1.326; p=0.0167). Tumor-specific analyses demonstrated significantly worse OS in pLOY versus no-pLOY for colorectal cancer (CRC; N=124 vs. 157; mOS 38.9 vs. 50.6 months; HR 1.535, p=0.0038), bladder cancer (N=26 vs. 41; mOS 25.7 vs. 37.7 months; HR 1.992, p=0.0204), NSCLC (N=100 vs. 134; mOS 27.6 vs. 32.7 months; HR 1.379, p=0.0379), and gastric cancer (N=13 vs. 16; mOS 17.6 vs. 28.5 months; HR 2.603, p=0.0223), with a trend observed in melanoma (N=17 vs. 27; mOS: 31.4m vs. inf, HR: 2.231 [0.922-5.4], p=0.075). No association was observed in other tumor types. Treatment distributions for mentioned cancer types did not differ between pLOY and no-pLOY groups (p>0.05). Among CRC patients with primary-to-metastatic paired samples (57%), pLOY remained significantly associated with worse OS (mOS 39.5 vs. 56.3 months; HR 1.647; p=0.0112). pLOY was not associated with specific therapies or combinations across the full cohort. **Conclusions:** In a large real-world clinico-genomic cohort, longitudinal decrease in Chromosome Y score is independently associated with poor prognosis across multiple cancer types supporting further investigation into the biological and clinical relevance of Y chromosome loss and providing insights on novel treatment selection strategies. Research Sponsor: None.

3137 **Poster Session**

Detection of mutational signatures in advanced cancer patients using clinical-grade specimens. First Author: Samantha Rueckeis, Durham Veterans Affairs Health Care System, Durham, NC

Background: The underlying extrinsic and/or intrinsic mutational processes underlying tumor development lead to genome-wide "passenger" alterations that can be identified as mutational signatures. Mutational signatures are known to be both prognostic and predictive in certain clinical contexts. Whole genome sequencing (WGS) based approaches are optimal for detection of mutational signatures but to date studies using formalin fixed paraffin embedded (FFPE) clinical grade specimens are limited. **Methods:** Archival DNA specimens from tumors of United States Veterans that underwent clinical sequencing in the VA National Precision Oncology Program were subjected to 30X WGS. Somatic alterations were identified by a tumor-only variant calling method employing filtering of variants found in the dataset at >10% frequency and putative germline variants found in multiple databases and germline WGS from the Million Veteran Program (MVP). Mutational signatures were identified using deconstructSigs. **Results:** WGS was performed on 134 tumor samples with matched germline WGS from MVP; variants were called using the tumor-only variant calling pipeline in addition to tumor-normal calling. Tumor-only WGS derived tumor mutational burden (TMB) was highly correlated with TMB from clinical targeted sequencing (White, R2=0.48; Black, R2=0.63; Other, R2=0.85) and with TMB from tumor-normal variant calling (White, R2=0.96; Black, R2=0.63; Other, R2=0.85). We used our tumor-only variant calling pipeline on WGS from 397 tumors. The median (+SD) number of mutations per tumor varied per tumor type, with the lowest number in head and neck squamous cell carcinomas (12445+4186 mutations) and highest in melanoma (119089+259854 mutations). Overall, 66 single base substitution (SBS) mutational signatures were identified. The SBS1 clock signature was found in 339 of 397 tumors. The SBS4 smoking mutational signature was found in 100% of small cell lung cancers (n=5), 76% of lung squamous cell cancers (n=38), 50% of lung adenocarcinomas (n=50), 36% of cancers of unknown primary (n=14), 29% of bladder cancers (n=7), and 14% of HNSC (n=36), but was not found in any other cancer type. The SBS7a UV mutational signature was found in 80% of melanomas (n=10) and 7% of cancers of unknown primary, but not in any other cancer type. Finally, the SBS6 and SBS15 mismatch repair mutational signatures were found in 10 and 12 of 16 MSI-high tumors, respectively. **Conclusions:** We have established a pipeline for evaluation of mutational signatures from tumor-only WGS of clinical grade FFPE tumors. Preliminary analysis shows identification of expected mutational signatures. Work is ongoing to determine whether ancestry matched panel of normals improves signature identification and to determine the prognostic and/or predictive ability of mutational signatures in a variety of clinical contexts which could greatly expand the clinical utility of WGS in advanced cancers. Research Sponsor: Veterans Affairs Office of Research and Development; 1I01CX002709.

3138 **Poster Session**

Validation of SNHG11 as a prognostic and predictive biomarker for anti-EGFR benefit in colorectal cancer using real-world data. First Author: Michela Bartolini, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

Background: Long non-coding RNAs (lncRNAs) regulate colorectal cancer (CRC) initiation, progression, and therapeutic response through interactions with oncogenic and microenvironmental pathways. *SNHG11* has been implicated in CRC through epigenetic and c-Myc–driven transcriptional programs. In CALGB/SWOG 80405, higher tumor *SNHG11* expression correlated with improved outcomes, particularly anti-EGFR therapy (Bartolini 2025, ASCO 43; 16_suppl). We comprehensively evaluated molecular correlates with *SNHG11* and validated the prognostic and predictive value in an independent real-world CRC cohort. **Methods:** In total, 15,456 CRC underwent DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing at Caris Life Sciences. Tumors were stratified by *SNHG11* expression quartiles, comparing low (Q1) vs high (Q4). CMS classification was assessed using RNAseq. Associations were assessed using X^2/Fisher's exact with p-values adjusted for multiple comparisons (q<0.05). Clinical outcome was obtained from insurance claims. Overall survival (OS) was calculated from tissue collection to last contact and time-on-treatment (ToT) from treatment start to end. Cox proportional hazards model generated hazard ratio (HR) and log-rank p-values. **Results:** *SNHG11* Q1 tumors were associated with higher right-sided prevalence (28% vs 18%, p<0.001), lower left-sided prevalence (50% vs 62%, p<0.001), and older age than Q4 (64 vs 62, p<0.001). Consistent with the findings in CALGB/SWOG 80405, Q4 were associated with CMS2 (53% vs 19%, p<0.001) while Q1 with CMS4 (49% vs 21%, p<0.001). Q1 tumors showed increased MSI-H/dMMR, TMB-H and PD-L1 expression (10% vs 3%, 15% vs 5% and 5% vs 2%, respectively, all p<0.001). *TP53* and *APC* mutations were enriched in Q4 vs Q1 (84% vs 69% and 85% vs 72%, p<0.001) whereas *KRAS* (49% vs 41%), *BRAF* (13% vs 7%), *ARID1A* (12% vs 8%), *RNF43* (6% vs 2%) and *CTNNB1* (3% vs 2%) mutations were higher in Q1 vs Q4 (p<0.001). Q4 was associated with longer OS vs Q1 (mOS 30.8 vs 27.8 months; HR 0.93; 95% CI 0.89–0.97, p<0.001). After adjusting for MSI status, tumor sidedness, age, race, and anti-EGFR therapy, Q4 remained a significant independent predictor of improved OS compared to Q1 (adjusted HR=0.93; 95% CI: 0.89-0.96; p<0.001). Q4 was significantly associated with longer ToT in patients receiving anti-EGFR therapy vs Q1 (7.4 vs 5.8 months, HR 0.86; 95% CI 0.79–0.93, p<0.001) with no association observed with bevacizumab ToT. **Conclusions:** In this large independent real-world cohort, we provided additional molecular insight into a key lncRNA *SNHG11* in CRC. Consistent with previous findings in a large randomized controlled trial, we confirm that elevated *SNHG11* expression was associated with CMS2, left-sided tumors, longer OS and longer TOT of anti-EGFR therapy, supporting *SNHG11* as a promising prognostic biomarker and a candidate predictive biomarker for anti-EGFR benefit in CRC. Research Sponsor: None.

3139 **Poster Session**

Sensitivity of portal vein ctDNA versus peripheral blood in predicting post-operative liver metastasis adjuvant therapy in colorectal cancer. First Author: Jin Gu, Peking University Cancer Hospital; Peking University Shougang Hospital, Beijing, China

Background: The detection of minimal residual disease (MRD) in colorectal cancer (CRC) is crucial for predicting postoperative recurrence, particularly liver metastasis. While peripheral blood (PB) liquid biopsy is widely used, portal vein blood (PVB) may offer higher sensitivity due to direct drainage of the hepatic circulation. **Methods:** We prospectively enrolled 297 CRC patients undergoing curative surgery. Intraoperative portal vein blood (PVB) and matched preoperative peripheral blood (PB) samples were collected simultaneously. Cell-free DNA was sequenced using a targeted 689-gene panel (1.5 Mb). Variants were filtered to retain only those with increased allele frequency (AF) in PVB relative to PB or exclusive detection in PVB (AF ≥1%), followed by stringent germline and noise removal. Binary mutation matrices were constructed for both blood sources. Machine learning (random forest, SVM, logistic regression, gradient boosting) was used to identify predictive gene signatures separately for PVB and PB. Model performance was compared using five-fold cross-validation. **Results:** PVB-derived ctDNA detected a significantly higher number of tumor-specific mutations compared to PB (mean 3.2 vs. 1.4 mutations per patient, p<0.001). PVB contained significantly higher ctDNA concentration (median 8.4 ng/mL vs 2.1 ng/mL in PB, p<0.001). A 20-gene panel selected from PVB data demonstrated superior predictive accuracy for liver metastasis compared to PB-derived markers. When validated in the same cohort, the PVB panel achieved an AUC of 0.849 (95% CI: 0.802–0.891) versus 0.714 (95% CI: 0.653–0.771) for PB-based prediction (p=0.003). Sensitivity for predicting liver metastasis was 70.0% for PVB versus 48.5% for PB. The PVB panel identified 26.6% of mutation carriers as high-risk, with 100% specificity (no recurrence in mutation-negative patients). In contrast, the PB model failed to achieve comparable risk stratification, with lower positive predictive value and higher false-negative rates. **Conclusions:** Portal vein blood ctDNA analysis is significantly more sensitive and accurate than peripheral blood in predicting postoperative liver metastasis in CRC. PVB-based liquid biopsy provides superior risk stratification, which could better inform adjuvant therapy decisions—identifying high-risk patients for intensified surveillance or treatment, while reducing overtreatment in low-risk patients. These findings support the clinical integration of PVB sampling for MRD detection in CRC surgical practice. Research Sponsor: None.

3140 **Poster Session**

Spatial mapping of human colorectal cancer cell states to identify co-targeting opportunities and determinants of drug response. First Author: Gertjan Rasschaert, Laboratory for Digestive Oncology, KU Leuven, Leuven, Belgium

Background: Colorectal cancer (CRC) progression relies on multiple mechanistically distinct proliferative and survival programs differing in lineage dependence, plasticity, and environmental sensitivity. LGR5-driven proliferation represents a stem-like program, whereas non-LGR5 modes—including progenitor, KRAS/MAPK, AP-1, and YAP-driven proliferation—reflect inflammatory and adaptive states that may confer therapeutic resistance. Single-cell studies revealed these programs, but technical barriers have restricted their quantitative and spatial analysis in human tumors, limiting translation to drug development and patient stratification. **Methods:** We integrated single-cell RNA sequencing (81 CRC patients) with spatial transcriptomics (Xenium; 16 matched primary CRC samples) to quantify epithelial cell states and tissue organization. Analyses focused on proliferative programs defined by LGR5, CDX2, ANXA1, and MKI67, stratified by KRAS genotype and intratumoral location, with extended spatial annotation of immune and stromal niches. **Results:** CRC tumors showed high compositional heterogeneity across subgroups (mean normalized Shannon entropy >0.6). On average, 36% of tumor epithelial cells were proliferative; only 50% expressed LGR5, with substantial inter-patient variability and genotype dependence. 14% of proliferating cells expressed ANXA1 alone, corresponding to inflammatory, YAP-high states with potential cytotoxic implications. LGR5-driven proliferation was enriched in KRAS-mutant tumors, contrasting with mouse models suggesting KRAS-mediated suppression and potentially indicating reduced sensitivity to KRAS inhibition. EGFR−LGR5 double-positive cells were abundant, identifying additional targetable niches. Spatial analyses revealed regions with high TGFβ signaling and co-localization with $SPP1^{+}$ macrophages consistent with TGFβ-driven immunosuppressive niches described in complementary studies. These niches associate with reduced PD-1/PD-L1 blockade response, coincide with states responsive to combined TGFβ and PD-1 inhibition, and are not captured by genotype alone. **Conclusions:** Spatial transcriptomics provides quantitative, systems-level resolution of tissue architecture, revealing opportunities for rational co-targeting to disrupt tumor homeostasis and enhance immunotherapy efficacy. Ongoing analyses of neoadjuvant-treated tumors and paired primary–metastatic samples will extend this framework to capture therapy-induced and naturally evolving tumor states. Research Sponsor: None.

3141 **Poster Session**

Phase 1/2 trial of ATR inhibitor berzosertib plus immune checkpoint inhibitor avelumab in patients with advanced cancers with DNA damage response (DDR) gene alterations: Tumor microenvironment–mediated pathways of resistance from correlative data. First Author: Patrick Glen Pilié, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Herein we present novel correlative data from baseline and on-treatment tumor and blood sampling with associated therapeutic outcomes from a phase 1/2 trial of ATRi (berzosertib) plus ICI (avelumab) in patients (pts) with advanced cancers with pathogenic mutations in select DDR genes. **Methods:** 17 pts enrolled on trial, and they received berzosertib (day 1, 8, 15, 22) plus avelumab (day 1 and 15, q28 days). Paired tumor biopsies were collected at baseline and on Day 12 of treatment, with spatial gene expression profiling (Visium) performed on the tumor tissues. Spot-level bioinformatics and manual annotations were performed to identify regions enriched for tumor cells and key TME components. Blood was collected at baseline and longitudinally for high-dimensional CyTOF profiling for immune cell populations and Luminex for circulating cytokines. **Results:** The ATRi + ICI combination was safe and well tolerated as previously reported, with ORR of 12.5% in this heavily pre-treated study population, with 2 durable RECISTv1.1 partial responses observed in advanced HPV+ vaginal cancer pt with pathogenic somatic *RAD51* mutation lasting 23 months and an advanced colorectal cancer with *MSH2* mutation lasting >24 months. In liquid sampling (N=16 pts), CyTOF analysis revealed a common baseline monocyte "stress-brake" state marked by elevated MRE11 and impaired antigen presentation. Treatment resulted in relief of innate DNA stress and induction of a myeloid-to-lymphoid immune shift, with subsequent expansion of adaptive T-cell effectors (EM1 CD4 T cells), with the durable responses characterized by an early proliferative CD8 T-cell burst (D12–D28) followed by sustained lymphoid dominance. Luminex assay revealed substantial cytokine remodeling at D12–D28 relative to baseline, with multiple analytes exceeding the predefined effect-size threshold ($|\log2FC| \geq 0.58$; ~1.5-fold), suggesting an acute inflammatory response and myeloid infiltration. Spatial profiling in non-responders showed high baseline levels of cancer associated fibroblasts (CAFs) and intra-tumoral CNV heterogeneity, with treatment resulting in upregulation of immunosuppressive, pro-survival pathways (SPP1, MIF, MYC, and Annexin). In contrast, the available on-treatment pt tissue from the vaginal cancer responding tumor displayed higher lymphoid infiltrate and lower immune suppression genes. **Conclusions:** Despite universal acute immune activation in circulation following ATRi + ICI, resistant tumors displayed high CNV heterogeneity, CAFs, and increased immunosuppressive pathways, in contrast to responder tissue. Co-clinical studies will further elucidate targetable mechanisms of resistance and guide further DDRi and ICI combinations. Clinical trial information: NCT04266912. Research Sponsor: None.

3142 **Poster Session**

Genomic and transcriptomic correlates of HER3 expression in prostate cancer. First Author: Syed Saqib Balkhi, Stephenson Cancer Center, University of Oklahoma Health Sciences, Oklahoma City, OK

Background: HER3 (*ERBB3*) is a key receptor in prostate cancer (PC) that signals via HER3 heterodimerization to promote PI3K-AKT-mediated survival and adaptive resistance in castration-sensitive (CSPC) and castration-resistant prostate cancer (CRPC). Despite its biological relevance, the clinical and genomic significance of HER3 RNA expression remains poorly defined. We therefore performed a comprehensive multi-omic analysis to evaluate the prognostic relevance of HER3 RNA in PC. **Methods:** DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing were performed on prostate tumor samples (n=19,238) submitted to Caris Life Sciences. HER3 expression was quantified as transcripts per million (TPM) and stratified into high (HER3-H) and low (HER3-L) groups defined by the top and bottom quartiles, respectively. CRPC was defined as $\geq$3 months of androgen deprivation therapy before tissue collection. Real-world overall survival (rwOS) was obtained from insurance claims data and calculated from biopsy to last contact. Tumor microenvironment (TME) cell fractions were estimated by RNA deconvolution using quanTIseq. Group comparisons were conducted using Mann–Whitney U and chi-square tests as appropriate. Survival outcomes were evaluated using Cox proportional hazards models and log-rank testing, with false discovery rate correction for multiple comparisons. **Results:** Across genitourinary malignancies, PC demonstrated highest median HER3 RNA expression (107.04 TPM). Within PC, HER3 expression varied by tumor site and race, with higher median levels in primary tumors compared to metastatic sites (116.5 vs 86.22 T PM, $p<0.0001$), and in tumors from Black patients compared with White patients (115.3 TPM v 103.3 TPM, $p<0.0001$). Prognostic associations differed by tumor source and castrate status: HER3-H expression was associated with improved rwOS in metastatic tumors (32.0 vs. 23.3 months, HR 0.72, $p < 0.00001$), and in CRPC (29.3 vs. 21.3 months; HR 0.84; $p < 0.001$), but not in primary tumors or CSPC. Immune profiling revealed that HER3-high tumors exhibited significantly reduced inferred infiltration of Tregs, neutrophils, macrophages, and NK cells ($q < 0.05$), while PD-L1 positivity and TMB-high status were not significantly associated with HER3 expression. Genomic analysis revealed enrichment of *FOXA1* and *SPOP* alterations ($q<0.05$) in HER3-H tumors, whereas HER3-L tumors were enriched for *TP53*, *RB1*, *AR*, *CDK12*, and *APC* ($q<0.05$). On multivariable analysis, HER3-H status remained independently associated with improved rwOS in CRPC. **Conclusions:** HER3 RNA expression defines biologically and clinically distinct subsets of PC, with HER3-high tumors exhibiting luminal, androgen receptor–dependent biology, an immune-cold phenotype, and improved survival in metastatic disease and CRPC, supporting HER3 as a tumor-intrinsic therapeutic target and rationale for HER3-directed therapy. Research Sponsor: None.

3143 **Poster Session**

Can GLP-1 receptor agonists mitigate cancer progression? A propensity-matched analysis across seven solid tumors. First Author: Mark David Orland, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: GLP-1 receptor agonists (GLP-1RAs) are pleiotropic medications, initially developed for diabetes, yet with beneficial effects on obesity and cardiovascular disease. Given the rapidly expanding therapeutic use of these agents and emerging preclinical data suggesting immunomodulatory effects, we examined whether GLP-1RA exposure following cancer diagnosis was associated with altered risk of progression to metastatic disease. **Methods:** Utilizing the TriNetX Global Health Research Network, we identified 10,225 patients with stage I-III cancer who initiated GLP-1RA therapy after diagnosis. GLP-1RA-exposed patients were propensity-matched 1:1 to DPP-4 inhibitor controls across seven cancers: breast adenocarcinoma, prostate adenocarcinoma, NSCLC, colorectal adenocarcinoma (CRC), hepatocellular carcinoma (HCC), renal cell carcinoma (RCC), and pancreatic adenocarcinoma. Matching included demographics, BMI, glycemic factors, smoking, comorbidities, screening frequency, oncologic treatments, and concurrent medications. Primary outcome was progression to stage IV disease. Additionally, we used The Cancer Genome Atlas (TCGA) data to assess whether GLP-1R expression correlated with overall survival. **Results:** GLP-1RA exposure demonstrated reduced metastatic progression across 6/7 malignancies, with statistically significant reductions in four cancer types: NSCLC, breast, CRC, and HCC (Table 1). No significant safety signals or increased adverse events were observed in GLP-1RA-exposed patients compared to controls. Additionally, high tumor GLP-1R expression correlated with improved survival across the seven tumors (HR=0.67, 95% CI 0.54-0.83, $p<0.001$), most notably in breast cancer (HR=0.55, 95% CI 0.35-0.87, p=0.011). **Conclusions:** In this large propensity-matched cohort, GLP-1RA initiation after cancer diagnosis was associated with dramatically reduced metastatic progression across multiple solid tumors. Corroborating these clinical findings, elevated GLP-1R expression independently predicted improved overall survival. These findings warrant validation in prospective randomized controlled trials and mechanistic investigation of potential antineoplastic pathways driven by GLP-1RAs. Research Sponsor: None.

Effect of GLP1-1RA exposure compared to DPP-4i exposure on progression of stage I-III cancer to stage IV cancer.

Cancer Type	Matched Pairs (n)	Events GLP-1RA/DPP-4i	Cumulative Incidence (%)	Hazard Ratio (95% CI)	P-value
NSCLC	2,157	215/482	10.0 vs 22.3	0.50 (0.43-0.59)	<0.001
Breast	1,187	121/239	10.2 vs 20.1	0.57 (0.46-0.71)	<0.001
Colorectal	784	105/174	13.4 vs 22.2	0.69 (0.54-0.88)	0.003
HCC	275	52/78	18.9 vs 28.4	0.62 (0.44-0.89)	0.009
Prostate	1,010	83/137	8.2 vs 13.6	0.79 (0.60-1.04)	0.09
RCC	523	75/99	14.3 vs 18.9	0.95 (0.71-1.29)	0.76
Pancreatic	120	28/37	23.3 vs 30.8	0.69 (0.42-1.13)	0.14

3144 Poster Session

Efficacy and safety of pralsetinib in *RET* fusion–positive solid tumors: Data from the TAPISTRY trial. First Author: Chia-Chi Lin, National Taiwan University Hospital, Taipei, Taiwan

Background: Pralsetinib is an oral tyrosine kinase inhibitor that selectively and potently targets oncogenic RET fusion and mutation proteins, present in multiple tumor types. We report results from the phase 2 TAPISTRY study (NCT04589845), a global, open-label, multicohort study evaluating the efficacy and safety of pralsetinib in a cohort of patients with *RET* fusion-positive solid tumors. **Methods:** Eligible patients ≥12 years old with unresectable, locally advanced or metastatic *RET* fusion-positive solid tumors received 400 mg pralsetinib QD until disease progression, loss of clinical benefit, or unacceptable toxicity. Independent review committee (IRC)-assessed objective response rate (ORR) was the primary end point. Key secondary end points included IRC-assessed duration of response (DOR) and progression-free survival (PFS), and overall survival (OS). **Results:** Forty-six patients were enrolled and received ≥1 pralsetinib dose; 78% had ≤1 prior line of therapy in the metastatic setting. Median age was 56 y (range: 12-79); 61% were male. Median treatment duration was 14.3 mo (range: 0.7-31.5). Cancers included thyroid (n=18, 39%); colorectal (n=9, 20%); head and neck (n=4, 9%); pancreatic (n=4, 9%); hepatobiliary (n=3, 7%); CNS, sarcoma, and neuroendocrine and adrenal (n=2, 4% each); gastroesophageal (n=1, 2%); and unknown primary origin (n=1, 2%). ORR for the efficacy evaluable population (n=39) was 67% (95% CI: 50, 81; Table), with 5 (13%) CRs and 21 (54%) PRs. Intracranial response was observed in 1/2 (50%) patients with baseline CNS metastases. All patients experienced treatment-related adverse events (TRAEs); 33/46 (72%) reported TRAEs grade ≥3. The most common TRAEs included anemia (n=18; 39%), increased AST (n=16; 35%), and decreased neutrophil count (n=13; 28%). Hypertension was reported in 11 (24%) patients, with 3 (7%) reporting grade ≥3. Safety results were consistent with the known pralsetinib profile, with no new signals. **Conclusions:** Pralsetinib demonstrated robust and durable activity against *RET* fusion-positive solid tumors, with an ORR of 67%. These data validate RET fusions as a tissue-agnostic target with sensitivity to RET inhibition, suggesting therapeutic utility of pralsetinib. Clinical trial information: NCT04589845. Research Sponsor: Rigel Pharmaceuticals, Inc.

Efficacy summary by tumor type.

	Overall (N=39)	Thyroid (n=16)	Pancreatic (n=3)	Colorectal (n=8)	Hepatobiliary (n=3)	Head and Neck (n=3)
ORR, % (95% CI)	67 (50, 81)	81 (54, 96)	67 (9, 99)	38 (9, 76)	33 (1, 91)	100 (29, 100)
DOR, median, mo (95% CI)	26.7 (14.7, NE)	26.7 (26.7, NE)	3.9 (3.7, NE)	12.2 (5.7, NE)	14.9 (NE)	NE
PFS, median, mo (95% CI)	16.5 (7.2, NE)	30.3 (16.3, NE)	5.6 (1.9, NE)	6.5 (1.6, 12.9)	8.3 (1.4, NE)	NE
OS, median, mo (95% CI)	30.8 (16.3, NE)	NE (NE)	21.7 (12.7, NE)	10.2 (5.7, NE)	13.8 (8.3, NE)	NE
Follow-up, median, mo (range)	14.5 (2, 32)	19.4 (10, 32)	12.6 (2, 31)	9.2 (2, 19)	8.3 (2, 19)	14.3 (14, 27)

NE, not evaluable.

3145 Poster Session

Efficacy and safety of larotrectinib in patients with non-primary central nervous system *TRK* fusion cancer: An updated analysis. First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Larotrectinib (laro) is the first-in-class, highly selective TRK inhibitor approved for tumor-agnostic use in patients (pts) with TRK fusion cancer based on a robust and durable objective response rate in pts with various cancers. Here, we report updated long-term efficacy and safety in adult and pediatric pts treated with laro with non-primary central nervous system (CNS) TRK fusion cancer. **Methods:** Pts from 3 clinical trials (NCT02637687 [SCOUT], NCT02576431 [NAVIGATE], NCT02122913) were included. Laro was administered at 100 mg twice daily (BID) and 100 mg/m^2 (max 100 mg) BID in most adult and pediatric pts, respectively. Responses were independent review committee-assessed (RECIST v1.1). Pts enrolled in SCOUT could stop laro in the absence of on-treatment progression ("wait-and-see") and remain on trial. If pts were re-treated due to progression, response was assessed by investigators. Data cutoff: July 20, 2025. **Results:** In total, 304 pts were treated; 25 had baseline CNS metastases. There were 28 tumor types, including soft tissue sarcoma (24%), infantile fibrosarcoma (16%), lung (11%), and thyroid (10%). *NTRK* gene fusions were detected by next-generation sequencing (NGS) in 266 (88%) pts. Overall response rate was 65% (95% confidence interval [CI] 59–70) with 61 (20%) complete responses (CR), 18 (6%) pathological CR, 118 (39%) partial responses (PR), 55 (18%) stable disease (SD), 32 (11%) progressive disease (PD), and 20 (7%) not evaluable/undefined. Median duration of treatment was 19 months ([mo] range 0–111). At data cutoff, 52 pts (17%) remained on trial (either on treatment or in "wait-and-see"). Median time to response was 1.8 mo (range 0.9–80.3). Median duration of response (DoR), progression-free survival (PFS), and overall survival (OS) were 42 mo (95% CI 31–59), 26 mo (95% CI 19–35), and not reached (95% CI 89–not estimable), respectively, at median follow-ups of 54, 52, and 65 mo. The 5-year rates for DoR, PFS, and OS were 41% (95% CI 33–49), 33% (95% CI 27–40), and 61% (95% CI 55–67), respectively. Fifty-seven pediatric pts entered a first "wait-and-see" period (median duration 24 mo [range 0–75+]). Of these, 38 exited the "wait-and-see" period. By investigator assessment, 20 pts had PD and resumed treatment (with 6 CR, 5 PR [including 2 pending confirmation], 7 SD, 2 unevaluable/undefined). The other 18 pts discontinued laro permanently but were all alive at data cutoff. Treatment-related adverse events (TRAEs) were mainly worst Grade 1/2 (n=189; 62%). Worst Grade 3/4 TRAEs occurred in 72 (24%) pts. Five (2%) pts discontinued due to TRAEs. **Conclusions:** Laro continues to demonstrate rapid and durable responses, extended survival, clinical benefit, and a favorable safety profile in pts with TRK fusion cancer. These data support the wider adoption of NGS panels that include *NTRK* gene fusions to identify pts who may benefit from TRK inhibitor therapy. Clinical trial information: NCT02637687, NCT02576431, NCT02122913. Research Sponsor: Healthcare and Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company.; was supported by the National Cancer Institute/National Institutes of Health P30CA008748, 1R01CA226864-01A1 grants, and Nonna's Garden.

3146 Poster Session

BMS-986504 in patients (pts) with advanced solid tumors with homozygous *MTAP* deletion (*MTAP*-del): Exploratory pharmacodynamic (PD) and biomarker analyses from CA240-0007. First Author: Jason Timothy Henry, Sarah Cannon Research Institute at HealthONE, Denver, CO

Background: The MTA-cooperative PRMT5 inhibitor BMS-986504 selectively binds to the PRMT5-MTA complex, a synthetic lethal target in *MTAP*-del cancer cells, while sparing *MTAP*–wild-type normal cells. In the phase 1 CA240-0007 study, BMS-986504 was well tolerated and had antitumor activity in pts with *MTAP*-del advanced solid tumors (ORR, 23%; median DOR, 10.5 mo). BMS-986504 also demonstrated dose-dependent reductions in plasma symmetric dimethylarginine (SDMA) levels, a PD biomarker of PRMT5 inhibition. Here, we report expanded PD and genomic analyses and initial results of exploratory proteomic analyses from CA240-0007. **Methods:** Pts with advanced, unresectable, or metastatic solid tumors with homozygous *MTAP*-del received BMS-986504 (50–800 mg) in 3-wk cycles. Analyses of SDMA levels and proteomic profiles from paired plasma samples (baseline and C2D1) were performed using mass spectrometry and SomaScan 11K, respectively. Tumor genomic information was extracted from local pathology reports. ORR was assessed per RECIST v1.1. **Results:** Among 78 pts with paired samples at data cutoff (22 Sept 2025; median f/u, 15.9 mo), dose-dependent reductions were seen in plasma SDMA levels, with the greatest reductions at 400 mg QD (median, 60.3%; n = 31) and 600 mg QD (median, 60.3%; n = 23). Proteomic pathway enrichment analysis demonstrated downregulation of PI3K/Akt/mTOR, Myc target, cell cycle, and DNA damage repair (DDR) pathways with BMS-986504 on C2D1 (n = 87), consistent with the expected effect of PRMT5 inhibition; a trend toward deeper modulation of PRMT5-regulated pathways was observed at higher doses. No proteins at baseline (n = 94) were found to be significantly associated with ORR (false discovery rate > 0.05). Responses in clinically evaluable pts with NSCLC (n = 33) or PDAC (n = 35) were observed regardless of *EGFR*, *KRAS*, or *TP53* status. In pts with NSCLC, *STK11* and *SMARCA4* alterations were numerically higher in nonresponders. No gene alterations were associated with response in PDAC, except *GABRA6* alterations (n = 2, both responders). A trend toward higher ORRs was seen in pts with alterations in DDR genes (*CHEK2, FANCD2, XRCC4*, and/or *MSH2*), consistent with the role of PRMT5 in DDR via regulation of mRNA splicing. ctDNA analysis will be presented. **Conclusions:** BMS-986504 demonstrated robust dose-dependent PD effects in pts with advanced solid tumors in plasma SDMA and proteomic analyses. Downregulation of PRMT5-regulated pathways was observed with BMS-986504 treatment. Response was seen regardless of *EGFR, KRAS*, and *TP53* alterations in NSCLC or PDAC, and DDR gene alterations were associated with improved response. These findings further support the MOA of BMS-986504 and its ongoing investigation in the phase 2/3 MountainTAP-9, -29, and -30 studies as a potential treatment option in pts with *MTAP*-del advanced solid tumors. Clinical trial information: NCT05245500. Research Sponsor: Bristol Myers Squibb.

3147 Poster Session

Fast-TRACKing precision oncology for rare cancers: A national decentralized trial offering comprehensive genomic profiling and a molecular tumor board. First Author: Jim Palma, TargetCancer Foundation, Cambridge, MA

Background: The TargetCancer Foundation TCF-001 TRACK study (Target RAre Cancer Knowledge, NCT04504604) initiated on Oct 01, 2020, is a fully remote, advocacy-driven decentralized precision trial seeking to evaluate the clinical impact of utilizing comprehensive genomic profiling (CGP) reviewed by a molecular tumor board (MTB) for patients (pts) with rare cancers. **Methods:** Pts were remotely enrolled/consented. Blood samples were collected via mobile phlebotomy and tested with FoundationOne Liquid CDx; tissue biopsies (TBx) were tested using FoundationOne CDx ± laboratory developed (LD) FoundationOne RNA or LD FoundationOne Heme. Liquid biopsy testing (LBx) included algorithmic predictions for clonal hematopoiesis (CH). MTB reviewed results and provided recommendations. **Results:** As of Oct 01, 2025, 230 pts from 46 US states were enrolled with evaluable results; 76% (175/230) had TBx and LBx, 22% LBx, and 2% TBx biopsies. MTB review was completed for 226 pts. Median age was 57 years (interquartile range [IQR]: 47,66); > 60 tumor types were represented: cholangiocarcinoma (35%), gastrointestinal (19%), soft tissue-related sarcomas (17%), brain (14%), and others (15%). First on-study TBx CGP (n=173) showed microsatellite instability high in 2%, homologous repair deficiency-signature in 2%, and median tumor mutational burden (TMB) of 1.3 mut/Mb (IQR: 0.8,3.6; 5 pts ≥ 10 mut/Mb). In LBx (n=57), ctDNA tumor fraction (TF) was ≥1% in 28% of pts; median blood TMB was 1.3 (IQR: 0,2.5; 1 pt ≥ 10 mut/Mb). Overall, 95% (219/230) of tumors had >1 pathogenic alteration; TBx CGP detected alterations in 96% (172/179), most frequently *TP53* (35%), *CDKN2A* (29%), *CDKN2B*(21%), *KRAS* (19%), *MTAP* (17%), and *TERT* (14%). LBx CGP detected alterations in 85% (192/225), with tumor-derived (TD) variants in *KRAS* (11%), *IDH1* (7%), and *CDKN2A* (6%). *TP53* (31%) included both TD and CH variants, while *DNM3TA* (30%), *ATM* (10%), *TET2* (10%), and *CHEK2* (8%) were mostly CH. In brain tumors, 52 variants from 28 pts with LBx identified 45 CH, 4 germline, and 3 TD. Across all tumor types, 9% (20/230) had biomarkers for FDA-approved tissue-agnostic therapies. This includes *ERBB2* amplification (2% overall), which is often correlated with *HER2* immunohistochemistry positivity. LBx sensitivity for DNA tissue-detected clonal SVs and rearrangements was 85% (95% CI: 0.74,0.92) when ctDNA TF≥1%; 24% (95% CI: 0.19,0.29) when <1%. Pathogenic fusions detected by RNA sequencing were not detected by DNA in 33% of cases (9/27). **Conclusions:** CGP identified pathogenic alterations in nearly all rare cancer patients, with tissue-agnostic biomarkers in 9%. RNA sequencing adds diagnostic yield. CH in liquid biopsies underscores need for expert MTB interpretation. TRACK, a first-of-its-kind national decentralized trial, provides a scalable framework for equitable precision oncology access. Clinical trial information: NCT04504604. Research Sponsor: TargetCancer Foundation; Foundation Medicine.

3148 **Poster Session**

Multi-modal molecular profiling of CDH1 and CLDN18.2 to identify predictive biomarkers for zolbetuximab efficacy in patients with advanced gastric adenocarcinoma: The ZOL-C3 study. First Author: Shuhei Suzuki, Department of Clinical Oncology, Yamagata University, Yamagata, Japan

Background: Zolbetuximab is a chimeric monoclonal antibody designed to bind to claudin 18.2 (CLDN18.2) and induce antibody-dependent cell-mediated cytotoxicity (ADCC). Although phase 3 trials established its efficacy in CLDN18.2-positive advanced gastric adenocarcinoma (GAC), robust predictive biomarkers beyond protein expression remain an unmet need. We investigated how epithelial-mesenchymal transition (EMT), mediated by CDH1 alterations and the tumor mutational burden (TMB), modulates the therapeutic target and affects zolbetuximab-mediated ADCC efficacy. **Methods:** This study employed a multi-layered integrative framework across four independent datasets to cross-validate genomic, transcriptomic, and phenotypic findings: (1) mechanistic characterization using the TCGA-STAD cohort (n=375); (2) the genomic screening of 2,483 patients with GAC in the Japanese national database (C-CAT), which identified 49 treated with zolbetuximab-containing regimens; (3) a spatial transcriptomic evaluation (10× Genomics Visium platform, GSE251950); and (4) immunohistochemical (IHC) validation of CLDN18.2 in 36 institutional GAC patients. The trial is registered at UMIN-CTR (UMIN000060223), a WHO ICTRP primary registry. **Results:** In the TCGA cohort, CDH1 low-expression was significantly associated with 3.2-fold lower CLDN18 mRNA levels than in the high-expression group ($p < 0.001$). CDH1 expression was strictly regulated by promoter methylation ($p < 0.001$), whereas CLDN18 down-regulation in CDH1-low tumors appeared to be driven by non-epigenetic EMT pathways. Spatial transcriptomics revealed a spatial correlation between CDH1 and CLDN18 mRNAs within the malignant epithelial compartment ($p < 0.001$). The objective response rate within the zolbetuximab-treated C-CAT subset was 22.2%. TMB was markedly lower in responders than in non-responders (median 1.82 vs. 4.0 mut/Mb; p = 0.050). Furthermore, patients without CDH1 single nucleotide variants had higher ORR (p = 0.086). Institutional IHC validation revealed a superior response in cases that retained membranous CDH1 expression to that in cases with the loss of epithelial integrity (100% vs 50% ORR; p=0.088). **Conclusions:** These results demonstrate that CDH1/E-cadherin integrity and low TMB are critical co-determinants of CLDN18.2 expression and zolbetuximab efficacy. Maintenance of the epithelial phenotype appears to be essential for optimal zolbetuximab-mediated ADCC. The integration of comprehensive molecular profiling, including the CDH1 status and TMB, may significantly refine patient selection, with a shift from simple target positivity to a more biological enrichment strategy for zolbetuximab therapy. Research Sponsor: None.

3149 **Poster Session**

Clinical outcomes of patients with cell cycle alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study. First Author: Abhijit Chakraborty, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cell cycle pathway alterations are a hallmark of cancer. Disruption of cell cycle checkpoints results in genomic instability, uncontrolled proliferation and tumor progression to aggressive and treatment-resistant phenotypes. We report the clinical outcomes of patients with cell cycle pathway alterations treated in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. Cell cycle pathway alterations were defined as those involving the *CCND1*, *CCND2*, *CCNE1*, *CDK4*, *CDK6*, *CDKN2A*, *CDKN2B*, and *RB1* genes. Cases were discussed at Molecular Tumor Board meetings. Patients were treated on clinical trials with investigational agents that included matched targeted therapies (MTTs) when available. We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (complete response + partial response), clinical benefit rate (CBR; ORR + stable disease≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 157 (32.0%) had cell cycle pathway alterations (median age, 61 years [range, 21-82]; female, 46.5%; ECOG performance status 1, 85.4%; median number of prior therapies, 3 [range, 0-9]; liver metastases, 40.8%; >2 metastatic sites, 36.3%; high LDH, 33.1%; low albumin, 10.8%). The most common cancers were sarcoma (19.7%), other gastrointestinal (17.2%), head and neck (14.0%), lung (9.6%), and breast (8.3%). Other tumor characteristics included PD-L1 ≥1%, 45.6% (41/90); MSI-H, 2.0% (2/102); and TMB-H, 13.0% (13/100). Concomitant pathway alterations were TP53 (67.5%), PI3K (29.9%), and RTK-RAS (47.1%). MTT targeted CDK4/6, n=9; BET, n=2; ATR, n=1; PKMYT1, n=1; and ACAT, n=1. Clinical outcomes are shown in the Table. **Conclusions:** Very few investigational therapies that target the cell cycle pathway were available. No differences were noted in tumor response, PFS, or OS by type of therapy, likely owing to the limited antitumor activity of the MTTs and the complexity of targeting this pathway. Novel and effective MTTs are needed for tumors with cell cycle dysregulation. Clinical trial information: NCT02152254. Research Sponsor: National Cancer Institute; P30 CA016672; Mr. and Mrs. Steven Mckenzie's Endowment; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Ritter; Foundation Medicine; TEMPUS AI.

	All patients N=157	MTT N=14	NTT N=143	*P*	IO N=40	Non-IO N=117	*P*
ORR (%)	7/135 (5.2)	0/12 (0)	7/123 (5.7)	1.00	4/33 (12.1)	3/102 (2.9)	0.14
CBR (%)	76/135 (56.3)	6/12 (50.0)	70/123 (56.9)	0.76	19/33 (57.6)	57/102 (55.9)	1.00
Median PFS, months (95% CI)	3.75 (2.66, 5.49)	3.75 (1.81, NA)	3.58 (2.66, 5.52)	0.81	2.96 (1.81, 8.98)	3.75 (2.66, 5.59)	0.98
Median OS, months (95% CI)	8.48 (7.1, 11.21)	6.66 (5.56, NA)	8.61 (7.17, 11.57)	0.40	7.46 (5.19, 17.42)	8.48 (7.1, 11.57)	0.72

3150 **Poster Session**

Clinical outcomes of patients with PI3K pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study. First Author: Apostolia Maria Tsimberidou, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The phosphatidylinositol 3-kinase (PI3K) pathway regulates cell growth, metabolism, and survival and is involved in immune modulation. Alterations in PI3K signaling drive tumor progression and drug resistance in advanced cancers and are associated with poorer prognosis. Herein, we report the clinical outcomes of patients with PI3K pathway alterations treated in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. PI3K pathway alterations were defined as those involving the *PI3K, AKT1, AKT2, AKT3, MTOR, PIK3CA, PIK3CB, PIK3R1, PTEN, TSC1,* and *TSC2* genes. Cases were discussed at Molecular Tumor Board meetings. Patients were treated on clinical trials with investigational agents that included matched targeted therapies (MTTs) when available. We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (ORR; complete response + partial response), clinical benefit rate (CBR; ORR + stable disease ≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 133 (27.1%) had PI3K pathway alterations (median age, 60.3 years [range, 20.5-79.8]; female, 60.9%; ECOG performance status 1, 85.7%; median number of prior therapies, 3 [range, 0-14]; liver metastases, 42.9%; >2 metastatic sites, 44.3%; high lactate dehydrogenase levels, 42.1%; low albumin level, 9%). The most common tumor types were breast cancer (18%), colorectal cancer (15%), and sarcoma (12%). Concomitant pathway alterations were TP53 (49.6% of patients), RTK/RAS (43.6%), and cell cycle (35.3%). Other tumor characteristics included PD-L1≥1%, 40.5% (32/79); MSI-H, 2.2% (2/89); and TMB-H, 10.3% (9/87). MTT included mTOR inhibitors, n=17; AKT inhibitors, n=5, and PI3K inhibitors, n=4. Clinical outcomes are shown in the Table. **Conclusions:** Taking into consideration the relatively limited use of AKT and PI3K inhibitors compared with mTOR inhibitors, no differences were noted in tumor response, PFS, or OS, by type of treatment. Other contributing factors may include the biological complexity of targeting this pathway, the small number of patients and/or the limited availability and antitumor activity of MTTs. Clinical trial information: NCT02152254. Research Sponsor: Foundation Medicine; Tempus AI; Mr. and Mrs. Steven Mckenzie's Endowment; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Ritter; National Cancer Institute; P30 CA016672.

	All patients N = 133	MTT N=26	NTT N=107	*P*	IO N=35	Non-IO N=98	*P*
ORR (%)	9/112 (8.0)	1/23 (4.3)	8/89 (9.0)	0.68	4/32 (12.5)	5/80 (6.3)	0.51
CBR (%)	63/112 (56.3)	15/23 (65.2)	48/89 (53.9)	0.36	18/32 (56.3)	45/80 (56.3)	1.00
Median PFS, months (95% CI)	2.96 (2.27, 4.57)	4.08 (2.17, NA)	2.66 (2.1, 4.37)	0.36	4.14 (1.84, 9.86)	2.96 (2.24, 4.37)	0.31
Median OS, months (95% CI)	7.79 (6.54, 10.92)	9.04 (6.64, 14.99)	7.3 (5.59, 11.21)	0.64	8.75 (5.36, 25.55)	7.17 (6.18, 0.78)	0.40

3151 **Poster Session**

Clinical outcomes of patients with RTK-RAS pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study. First Author: Mehmet A. Baysal, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The receptor tyrosine kinase (RTK)-RAS signaling axis comprises distinct membrane receptors and downstream effectors that regulate cell proliferation and survival. Alterations in this pathway drive carcinogenesis and are associated with poor prognosis. We analyzed the outcomes of patients with RTK-RAS pathway alterations enrolled in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. RTK-RAS pathway alterations were defined as those involving *EGFR, ERBB2, ALK, MET, KRAS, NRAS, BRAF*, and *MAP2K1/2* genes. Cases were discussed at Molecular Tumor Board meetings. Patients were treated in clinical trials with investigational agents, including matched targeted therapies (MTTs) when available. We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (ORR; complete response + partial response), clinical benefit rate (CBR; ORR + stable disease≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 216 (44%) had RTK-RAS pathway alterations (median age, 62.3 years [range, 21-80]; female, 54.1%; ECOG performance status 1, 90.3%; median number of prior therapies, 3 [range, 0-10]; liver metastases, 46.3%; > 2 metastatic sites, 34.7%; high LDH, 37.0%; low albumin level, 11.1%). The most common cancers were gastrointestinal (40.3%), head/neck (10.2%), and lung (10.2%). Other tumor characteristics included PD-L1≥1%, 43.6% (58/133); MSI-H, 1.3% (2/153); and TMB-H, 10.7% (16/150). Concomitant pathway alterations were TP53 (62.5%), PI3K (26.9%), and cell cycle (34.3%) pathways. MTT targeted EGFR, n = 8; FGFR, n = 10; HER2, n = 6; BRAF+MEK, n = 3; ALK, n = 1; and MEK, n = 4 among others (n = 24). Clinical outcomes are shown in the Table. **Conclusions:** The ORR was 14.6% in IO-treated patients vs. 5% in the non-IO-treated group (p = 0.049), although the difference was not significant. No differences in PFS or OS were observed by therapy type in patients with RTK-RAS pathway alterations. Novel MTTs (i.e., KRAS inhibitors) that were unavailable during the study period may improve the outcomes of these patients. Identification of molecular subsets benefiting from MTT is needed. Clinical trial information: NCT02152254. Research Sponsor: National Cancer Institute; Foundation medicine; TEMPUS AI; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Bitter.

	All patients N=216	MTT N=56	NTT N=160	*P* value	IO N=57	Non-IO N=159	*P* value
ORR (%)	14/189 (7.4)	5/50 (10)	9/139 (6.5)	0.53	7/48 (14.6)	7/141 (5)	0.049
CBR (%)	110/189 (58.2)	31/50 (62)	79/139 (56.8)	0.62	27/48 (56.3)	83/141 (58.9)	0.87
Median PFS, months (95% CI)	2.96 (2.3, 3.81)	3.09 (2.66, 8.02)	2.89 (1.97, 4.08)	0.5	2.3 (1.61, 5.42)	3.19 (2.66, 4.08)	0.72
Median OS, months (95% CI)	7.36 (5.69, 9.21)	5.88 (4.7, 18.28)	7.79 (5.69, 9.44)	0.10	6.61 (4.6, 12.76)	7.46 (5.69, 9.21)	0.85

3152 **Poster Session**

Clinical outcomes of patients with TP53 pathway alterations by treatment type: The MD Anderson Cancer Center IMPACT 2 study. First Author: Jacopo Venturini, Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: TP53 pathway alterations are found in over 50% of human cancers, with variable frequency across tumor types. They are associated with aggressive tumor biology, increased metastatic potential, and poor prognosis. Herein, we report the clinical outcomes of patients with TP53 pathway alterations treated in the IMPACT 2 study (2014-2023; NCT02152254). **Methods:** Patients with advanced cancer underwent tumor biopsy and molecular profiling (CLIA-certified lab). Pathway analysis was conducted using the *maftools* R package. TP53 pathway alterations were defined as those involving the *TP53*, *ATM*, *CHEK1*, *CHEK2*, *MDM2*, and *MDM4* genes. Patients were treated on clinical trials with investigational agents that included matched targeted therapies (MTTs) when available. MTT included anti-vascular endothelial growth factor (VEGF) targeted therapy, as previously published (PMID: 27466356). We analyzed the following outcomes by treatment type (MTT vs. non-matched targeted therapy [NTT] and immunotherapy [IO] vs. non-IO): objective response rate (ORR; complete response + partial response), clinical benefit rate (CBR; ORR + stable disease≥4 months), progression-free survival (PFS), and overall survival (OS). **Results:** Of 491 treated patients with targetable alterations, 278 (56.6%) had p53 pathway alterations (median age, 60.1 years [range, 20.5-81.7]; female, 51.4%; ECOG performance status 1, 86.0%; median number of prior therapies, 3 [range, 0-11]; liver metastases, 42.2%; >2 metastatic sites, 36.0%; high lactate dehydrogenase level, 41.0%; low albumin level, 9%). The most common tumors were colorectal (21.2%), sarcoma (13.7%), other gastrointestinal (12.2%), and breast (8.6%). Immune markers included PD-L1≥1%, 47.3% (78/165); MSI-H, 1% (2/199); and TMB-H, 10.5% (19/181). Concomitant pathway alterations were RTK-RAS (48.6%), PI3K (24.8%), and cell cycle (38.1%) pathways. MTT included VEGF/VEGFR inhibitors, N=57; MDM2 inhibitors, N=4; and TP53 activator, N=1. Clinical outcomes are shown in the Table. **Conclusions:** Median OS was significantly longer in patients with TP53 pathway alterations treated with IO compared with non-IO regimens. Considering the limited availability of TP53-targeted agents, no differences in clinical outcomes were noted for MTT compared with NTT. Further analyses are warranted to elucidate the molecular substrates underlying immunotherapy benefit. Clinical trial information: NCT02152254. Research Sponsor: National Cancer Institute; P30 CA016672; Foundation Medicine; Tempus AI; Katherine Russell Dixie's Distinguished Professorship Endowment; Jamie's Hope and Mrs. and Mr. James Ritter.

	All patients N=278	MTT N=62	NTT N=216	*P*	IO N=69	Non-IO N=209	*P*
ORR	18/247	4/59	14/188	1.00	9/64	9/183	0.024*
%	7.3	6.8	7.4		14.1	4.9	
CBR	142/247	37/59	105/188	0.37	43/64	99/183	0.87
%	57.5	62.7	55.9		67.2	54.1	
Median PFS, months	3.75	5.52	2.93	0.11	4.37	3.19	0.46
95% CI	2.89, 4.8	4.67, 8.19	2.5, 4.14		2.73, 5.56	2.66, 4.08	
Median OS, months	7.99	9.01	7.3	0.96	10.85	6.9	0.024
95% CI	6.18, 9.3	7.17,12.36	5.69, 9.24		7.86, 17.42	5.65, 8.65	

*Not significant after multiple testing correction (threshold α = 0.0125).

3153 **Poster Session**

Impact of dual inhibition of iNOS and COX2 on antitumor immunity and response to immune checkpoint blockade in hepatocellular carcinoma. First Author: Yuzhen Li, University of Pittsburgh, Department of Surgery, Pittsburgh, PA

Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality worldwide. Although immune checkpoint blockade (ICB) benefits a subset of patients, efficacy is often limited by an immunosuppressive tumor microenvironment. Inducible nitric oxide synthase (iNOS/NOS2) and cyclooxygenase-2 (COX2) are inflammation-associated enzymes implicated in immune regulation. We hypothesized that inhibition of these pathways enhances antitumor immunity and improves responsiveness to immune checkpoint therapy in HCC. **Methods:** Tumor tissues from 75 patients with resected hepatocellular carcinoma (HCC) were analyzed by immunohistochemistry for NOS2, COX2, and CD8 to assess expression levels and spatial correlations. In parallel, an orthotopic murine HCC model was established by intrahepatic injection of 7.5×10^5 RIL-175 cells (n = 6–10 mice per group). Mice were treated with vehicle control, selective NOS2 inhibition (1400W), COX2 inhibition (celecoxib), anti–PD-L1, or combination regimens including triple therapy. After two weeks of treatment, tumors were harvested for immune profiling, including flow cytometry, spatial imaging, plasma cytokine analysis, and CITE-seq. In vitro, splenocytes isolated from B6 mice were treated with prostaglandin E2 (PGE2) or the nitric oxide donor DETA-NONOate, and expression of CD226 and TIGIT was quantified by flow cytometry. **Results:** High intratumoral NOS2 expression was associated with inferior overall survival in resected HCC patients (HR 3.65, p=0.0011), with further worsening observed in tumors co-expressing NOS2 and COX2 (HR 9.31, $p<0.0001$). In murine HCC, combined iNOS and COX2 inhibition significantly reduced tumor burden and promoted intratumoral accumulation of $CD8^+$ and $CD4^+$ T cells, accompanied by increased B-cell recruitment and elevated circulating IL-2 and IFN-γ. Triple therapy with dual enzyme inhibition plus anti–PD-L1 resulted in superior tumor control and prolonged survival. Single-cell transcriptomic analysis comparing control, dual inhibition, and triple-treatment groups revealed a progressive enhancement of $CD8^+$ T-cell activation states, characterized by increased expression of activation-associated markers and reduced expression of inhibitory receptors. Dual and triple therapy induced upregulation of CD226 and downregulation of TIGIT in $CD8^+$ T cells, reflecting enhanced antitumor effector function. In vitro, nitric oxide and prostaglandin E2 directly impaired $CD8^+$ T-cell function, as evidenced by reduced CD226 and increased TIGIT expression. **Conclusions:** iNOS and COX2 cooperatively establish an immunosuppressive inflammatory program in HCC that limits $CD8^+$ T-cell–mediated antitumor immunity and response to checkpoint blockade. Dual targeting of these pathways represents a promising strategy to enhance immunotherapy efficacy in HCC. Research Sponsor: UPMC enterprise.

3154 **Poster Session**

Safety, pharmacokinetics (PK), pharmacodynamics (PD), and antitumor activities of FL115, a novel IL-15 superagonist, from the first-in-human study in patients with locally advanced/metastatic solid tumors. First Author: Carlos Roberto Becerra, Hoag Family Cancer Institute, Newport Beach, CA

Background: FL115 is an engineered IL-15/IL15Rα-Fbody fusion protein, in which Fbody is a single-chain Fc designed to eliminate classical Fc effects including ADCC/CDC/ADCP while retaining FcRn engagement. It aims to enhance anti-tumor immunity via IL-15-mediated signaling on NK and CD8+ T cells while minimizing complexity from Fc. **Methods:** The first-in-human, dose-escalation study of FL115 (NCT06130722) evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity of FL115 in adult patients with advanced solid tumors. FL115 monotherapy was administered intravenously once weekly. **Results:** 11 patients (7F, 4M) were enrolled, median age 64, who had progressed on prior systemic therapies across four dose cohorts (3–60 μg/kg). MTD was not reached. No SAEs related to FL115 or DLT were observed. Most TRAEs were Grade 1–2 and aligned with the known safety profile of cytokine-based therapies and underlying conditions of patients. Only three reversible TRAEs occurred, including transient Grade 3 alanine aminotransferase elevation, Grade 3 headache, and Grade 4 neutropenia. PK was dose-dependent, with half-life at 2.1-3.1 hours. Four patients had Stable Disease per imaging (DCR 36.3%). Dose-dependent expansion of lymphocytes was observed, with average absolute lymphocyte count (ALC) of 1257 cells/μl at baseline, and peak ALC count of 2371 cells/μl post treatment, mainly from increase in NK cells and CD8+T cells. One patient (Cervical Cancer) had Stable Disease from 1st dose at July 2024 (ALC of 1100 cells/μl) to study completion (ALC of 1900 cells/μl in August 2025). FL115 treatment led to significant transient cytokine release in peripheral blood: at 3 μg/kg, peak interferon-γ level reached 3730 pg/ml with IL-6 at 0.8 pg/ml, suggesting specific targeting of NK and T cells. An essentially identical Phase 1 study of FL115 was conducted in China, in which similar trends were observed; two patients remained on treatment with confirmed partial responses lasting 32 and 24 weeks, respectively. **Conclusions:** FL115 is the first IL-15 superagonist as monotherapy has shown a favorable safety profile and promising signs of durable antitumor activities in heavily pretreated patients, along with significant and sustained expansion of NK and T cell population and unique robust transient induction of interferon-γ. A Phase II study of FL115 with Bacillus Calmette-Guérin in patients with nonmuscle invasive bladder cancer (NCT07122414) and a Phase Ib study of FL115 (IV) in combination with an anti-PD-1 antibody in solid tumor patients (NCT07131202) are ongoing, and a Phase I study of FL115 subcutaneous injection will be initiated soon (IND submitted). Clinical trial information: NCT # 06130722. Research Sponsor: Furlong.

TPS3155 **Poster Session**

A phase 1/2, first-in-human, open-label, dose-escalation and -expansion study of TAK-188, a novel antibody-drug conjugate (ADC) targeting $CCR8^+$ regulatory T cells, in adult patients with locally advanced or metastatic solid tumors. First Author: Anthony J. Olszanski, Fox Chase Cancer Center, Philadelphia, PA

Background: Regulatory T cells (Tregs) are key contributors to an immunosuppressive tumor microenvironment (TME). Their abundance in solid tumors is often linked to poor patient prognosis, decreased overall survival, and resistance to immunotherapy. Tumor-infiltrating Tregs express high levels of chemokine receptor CCR8, making CCR8 an attractive target for immunotherapy. TAK-188 is a first-in-class anti-CCR8 ADC that aims to enhance patients' own antitumor activity by selectively eliminating CCR8-positive Tregs within the TME. It uses a novel amanitin payload capable of killing both actively dividing and non-dividing cells and is linked to the antibody via a cleavable linker. The nonclinical toxicology profile demonstrated monitorable and partially-to-completely reversible toxicities at doses exceeding projected clinically efficacious exposures. Preclinical evaluation of TAK-188 showed robust and deep depletion of $CCR8^+$ cells *in vitro* and *in vivo*, and demonstrated anti-tumor activity as a single agent in non-clinical models (Casson et al. AACR 2026). **Methods:** This phase 1/2 study (NCT07205718) is enrolling adult patients with locally advanced or metastatic solid tumors known to express high levels of CCR8 on Tregs in the TME (gastroesophageal adenocarcinoma [GC] and esophageal squamous cell carcinoma [ESCC], pancreatic ductal adenocarcinoma, non-squamous and squamous non-small cell lung cancer [NSCLC], head & neck SCC [SCCHN], or colorectal cancer), and whose disease has progressed on, or are intolerant to, all standard therapies. Eligible patients must have Eastern Cooperative Oncology Group performance status $\leq$1 and radiographically measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. In phase 1, TAK-188 is intravenously administered weekly at escalating dose levels following a Bayesian Optimal Interval design, to determine the recommended phase 2 dose (RP2D) and dosing schedules for the cohort-expansion phase. The primary objective is to determine the safety and tolerability of TAK-188 in phase 1 and to assess the preliminary efficacy in phase 2 in NSCLC, SCCHN and GC. Secondary objectives include characterization of the RP2D and pharmacokinetic parameters for TAK-188, changes in T cell populations (abundance and ratio of Tregs and effector T cells) within the tumor post-treatment, and preliminary efficacy in select cancer types. Exploratory objectives include the impact of TAK-188 on $CCR8^+$ Tregs, molecular response determined by circulating tumor DNA (ctDNA) analysis, and changes in cytokines and chemokines in peripheral blood. The study plans to enroll up to 223 patients in the USA (47 patients across 15 sites for dose-escalation; 62–176 patients across ~35 sites in cohort-expansion). Clinical trial information: NCT07205718. Research Sponsor: Takeda Development Center Americas, Inc. (TDCA), Cambridge, MA, USA.

TPS3156 Poster Session

A phase 1 study of HWK-007, a next-generation, protein tyrosine kinase 7 (PTK7)–targeted antibody-drug conjugate (ADC), in patients with advanced solid tumors. First Author: Manish R. Sharma, The START Center for Cancer Research - Midwest, Grand Rapids, MI

Background: PTK7 is a pseudokinase expressed during embryogenesis and down-regulated in normal adult tissue. Aberrant overexpression of PTK7 has been reported in up to 70% of solid tumors and is associated with tumor progression, metastasis, chemoresistance, and poor prognosis. A previous analysis demonstrated particularly high *PTK7* expression in non-small cell lung cancer (NSCLC), endometrial carcinoma (EC), and ovarian cancer (OC), across histologic subtypes and disease stages, making PTK7 an attractive therapeutic target with cross-indication applicability (Matulonis et al. AACR-NCI-EORTC 2025, Poster C040). Results from early clinical trials of cofetuzumab pelidotin, a PTK7-targeted, auristatin-based ADC, showed promising clinical activity. HWK-007 is a next-generation, PTK7-targeted ADC comprising an Fc effector-attenuated IgG1 antibody conjugated to the DNA topoisomerase I inhibitor (TOP1i) CPT116. It was designed using novel bioconjugation and advanced linker–payload technologies that enhance intracellular delivery and minimize systemic release of unconjugated TOP1i. This first-in-human, phase 1 trial evaluates HWK-007 in patients with advanced or metastatic solid tumors. **Methods:** This multicenter, open-label, single-arm, phase 1 dose-escalation (a)/expansion (b) trial is enrolling patients aged ≥18 years with advanced or metastatic NSCLC (non-squamous, epidermal growth factor receptor–wild-type [*EGFR*wt]), EC (all histologies), or epithelial OC (all histologies). Patients with NSCLC or EC must have prior treatment with platinum-based chemotherapy and a PD-(L)1 inhibitor, if eligible. Patients with OC must have platinum-resistant disease and prior treatment with standard-of-care therapy. All patients must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (except in the OC dose-escalation cohorts in which patients with non-target lesions per RECIST and CA125 ≥2 times ULN are permitted), Eastern Cooperative Oncology Group performance status 0 or 1, and no prior treatment with a TOP1i-containing ADC. Patients with clinically active brain metastases or a history of pneumonitis/interstitial lung disease are ineligible. In phase 1a, patients are sequentially assigned to HWK-007 dose levels (DLs; administered intravenously, once every three weeks) using a Bayesian Optimal Interval design (toxicity threshold, 25%), with potential backfill. Backfill cohorts are enriched for patients with *EGFR*wt NSCLC. Primary endpoints are safety, maximum tolerated dose, and recommended dose for expansion cohorts (phase 1a); and safety and objective response rate (phase 1b). Secondary endpoints include pharmacokinetics and preliminary efficacy outcomes. Recruitment is underway; planned enrollment is up to 226 patients. Clinical trial information: NCT07444814. Research Sponsor: None.

TPS3157 Poster Session

A phase 2 study of telisotuzumab adizutecan (ABBV-400; Temab-A) in patients with advanced solid tumors harboring *MET* amplification. First Author: Manish R. Sharma, The START Center for Cancer Research – Midwest, Grand Rapids, MI

Background: *MET* amplification is a rare alteration occurring at a rate of 0.06%–4.2%, in different solid tumor types across genomic databases. It is associated with poor prognosis and has limited treatment options. Currently, there are no therapies approved specifically to target *MET*-amplified tumors. Temab-A is an antibody-drug conjugate targeting c-Met and conjugated to a topoisomerase 1 inhibitor payload. In a first-in-human study (NCT05029882), Temab-A demonstrated encouraging activity (objective response rate 46%) and a manageable safety profile in *MET*-amplified solid tumors (Murciano-Goroff et al. ESMO 2025), supporting the continued investigation of Temab-A. The present phase 2 study evaluates Temab-A in adults and adolescents (12–17 years) with relapsed/refractory advanced solid tumors harboring *MET* amplification. **Methods:** This is an open-label, single-arm, global, multicenter phase 2 study (NCT07196644) enrolling approximately 125 patients (100 global; 25 China cohort) with locally advanced or metastatic solid tumors harboring *MET* amplification. Patients must have received ≥1 prior systemic therapy appropriate for their tumor type in the advanced/metastatic setting and have no satisfactory alternative treatment options. Patients must be ≥12 years old, have ECOG PS 0–1, measurable disease per RECIST v1.1 or RANO, and documented *MET* amplification by local next-generation sequencing or central FoundationOne CDx. Patients are treated with Temab-A 2.4 mg/kg IV every 3 weeks until disease progression, unacceptable toxicity, or other discontinuation criteria are met. Trial objectives are listed in the table. Enrollment began in November 2025; as of December 2025, 1 patient has enrolled. Clinical trial information: EU CT: 2024-518871-74-00. Research Sponsor: AbbVie.

Objectives.	
Primary	Evaluate efficacy (ORR per ICR, RECIST v1.1/RANO) and safety of Temab-A (AEs, vital signs, ECG, clinical laboratory testing)
Secondary	Further assess efficacy (DOR, PFS, OS, disease control) and characterize PK and immunogenicity (PK parameters, ADAs, nADAs)
Exploratory	Biomarker analyses (eg, c-Met expression) and PROs evaluation

ADAs, antidrug antibodies; AEs, adverse events; DOR, duration of response; ECG, electrocardiogram; ICR, independent central review; nADAs, neutralizing antidrug antibodies; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PROs, patient-reported outcomes; RANO, Response Assessment in Neuro-Oncology; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

TPS3158 Poster Session

A phase I, multi-center study of KIVU-107, a novel PTK7-targeting antibody-drug conjugate (ADC), in participants with advanced solid tumors. First Author: Jeffrey C. Goh, ICON Research, South Brisbane & Queensland University of Technology, Brisbane, QLD, Australia

Background: Protein tyrosine kinase 7 (PTK7) is a transmembrane pseudokinase involved in normal embryonic development and has been associated with tumor initiation, metastasis and therapeutic resistance in cancer. PTK7 is over-expressed in multiple solid tumors, including lung, head and neck, breast, ovarian and endometrial cancers. KIVU-107 is an antibody-drug conjugate (ADC) comprised of a PTK7-targeting antibody conjugated to the SYNtecan E linker-payload via the GlycoConnect/Hydraspace (GC/HS) site-specific conjugation technology with a drug-to-antibody ratio of 4.[1,2] The GC/HS platform abolishes Fcγ receptor-mediated effector activity and utilizes a highly polar spacer to reduce hydrophobicity and aggregation of the ADC, translating into improved safety and pharmacokinetic profiles.[1,2] KIVU-107 has demonstrated potent anti-tumor efficacy as a single agent and in combination across multiple preclinical tumor models, including regression in tumors refractory to chemotherapy or ADCs.[1,2] Moreover, KIVU-107 is highly stable and well tolerated in non-human primates.[1,2] **Methods:** This Phase 1, multi-center, open-label, dose-finding and dose-expansion study is designed to investigate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of KIVU-107 in patients with select advanced solid tumors. The Dose Finding stage will employ Backfill Bayesian Optimal Interval (BF-BOIN) design to establish the maximum tolerated dose (MTD) and recommended dose for expansion (RDE). Eligible participants for the Dose Finding stage include those with advanced solid tumors known to be enriched for PTK7 overexpression and that have exhausted available standard-of-care (SOC) treatments including non-small cell lung, small cell lung, head and neck squamous cell carcinoma, breast, endometrial, ovarian and others. The Dose Expansion stage will further explore the safety, tolerability and preliminary efficacy in disease-specific cohorts relapsed or refractory to SOC therapies. The primary endpoints include safety, tolerability, and determination of MTD and RDE for KIVU-107. Secondary and exploratory endpoints include PK, immunogenicity, preliminary clinical activity and biomarker assessments. Enrollment for Dose Finding has initiated. Clinical trial information: NCT07229313. 1) Trikha M. Striving for Kinder and Gentler ADCs: Spotlight on Solid Tumor Target and Preclinical Development of KIVU-107. Presented at: 16th World ADC San Diego; November 4, 2025; San Diego, CA. 2) Viller V, Zhang L, Jiang X, et al. Preclinical Efficacy and Safety of KIVU-107, a Novel PTK7-Targeting Antibody-Drug Conjugate (ADC). Poster presented at: 16th World ADC San Diego; November 5, 2025; San Diego, CA. Clinical trial information: NCT07229313. Research Sponsor: Kivu Bioscience.

TPS3159 Poster Session

A phase 1, first-in-human study of DS3610, a stimulator of interferon genes (STING) agonist antibody-drug conjugate (ADC), in patients with advanced/metastatic solid tumors. First Author: Shigehiro Koganemaru, National Cancer Center Hospital East, Kashiwa, Japan

Background: While immunotherapies have improved treatment for patients with advanced/metastatic solid tumors, there remains a need for novel therapies that can overcome resistance to existing therapies, enhance antitumor activity, and delay disease progression. Promoting the innate immune response through activation of the endoplasmic reticulum adaptor protein stimulator of interferon genes (STING) has been associated with antitumor activity. DS3610 is an antibody–drug conjugate (ADC) comprising an anti-epidermal growth factor receptor (EGFR) monoclonal antibody attached to an immunomodulatory payload that acts as an agonist of STING. EGFR is a transmembrane receptor tyrosine kinase that is overexpressed in a broad range of solid tumors. DS3610 is designed to deliver the STING agonist payload directly to the tumor microenvironment, activating immune cells such as antigen-presenting cells and T cells, and inducing immune targeting of cancer cells. The antibody component has novel Fc modifications designed to reduce the risk of class-specific adverse events, such as systemic cytokine release. **Methods:** DS3610-071 (NCT07159126) is a Phase 1, first-in-human, open-label, global, dose-escalation study of DS3610 (N≈70). Patients must be adults with advanced or metastatic solid tumors and be intolerant to standard-of-care therapies or have disease that has relapsed after or is refractory to such therapies. Eligible tumor types include non-small cell lung cancer, head and neck cancer, renal cell carcinoma, urothelial carcinoma, colorectal cancer, gastric cancer, pancreatic cancer, esophageal cancer, biliary tract cancer, and uterine cancer. Patients must have measurable disease per RECIST 1.1; an ECOG performance status of 0, 1, or 2; and be willing and able to provide a pretreatment or archival tumor tissue sample. Patients will receive DS3610 at escalating doses. The primary objectives are to assess the safety and tolerability of DS3610 and to determine the recommended dose(s) for expansion for further evaluation of DS3610. Safety endpoints include identifying dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints include the assessment of DS3610 immunogenicity, based on the prevalence and incidence of antidrug antibodies, and the evaluation of DS3610 pharmacokinetics. Exploratory endpoints include evaluating the efficacy of DS3610 and identifying biomarkers that may be associated with clinical benefit. Enrollment is ongoing. Clinical trial information: NCT07159126. Research Sponsor: Daiichi Sankyo.

TPS3160 **Poster Session**

BNT326-01: A Phase 1b/2 trial of BNT326/YL202 (HER3 ADC) as monotherapy and in combination with pumitamig (anti-PD-L1 × VEGF bsAb) in patients with advanced solid tumors. First Author: Siqing Fu, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BNT326/YL202 is an investigational ADC composed of an anti-HER3 IgG1 monoclonal antibody conjugated to ~8 molecules of a novel topoisomerase I inhibitor payload via a tripeptide linker. HER3 is frequently overexpressed in various solid tumors, particularly in relapsed or refractory tumors, making it an attractive therapeutic target. Increasing evidence suggests that ADCs may enhance the efficacy of immunotherapeutic agents. It is hypothesized that combining BNT326 with immunotherapy including pumitamig, an investigational anti-PD-L1 x VEGF-A bispecific antibody, could lead to better patient outcomes than administering either drug alone. Targeting angiogenesis may facilitate ADC penetration, which in turn could stimulate tumor immunity and increase sensitivity to PD-L1 inhibition. Preclinical in vivo models testing the combination of pumitamig with BNT326 showed superior tumor growth inhibition compared to each treatment alone (Hamilton E, AACR 2025, #648). **Methods:** This global Phase 1b/2, open-label, adaptive two-part multicohort trial (NCT07070232) will evaluate safety, efficacy, optimal dose and pharmacokinetics of BNT326 in selected indications, both as monotherapy (Part 1) and in combination with pumitamig (Part 2) in patients (≥18y, ECOG PS 0 or 1) with histologically or cytologically confirmed solid tumors that are advanced and/or have relapsed/progressed after prior therapy. Both parts will start enrolling patients independently of each other. In Part 1, patients in Cohorts 1A-C will be randomized to one of two dose levels of BNT326 based on doses derived from the ongoing monotherapy trials (YL202-INT-101-01 [NCT05653752] and YL202-CN-201-01 [NCT06107686], whereas Cohorts 1D, 1E, and 1G receive dose level 2 of BNT326. 1A: cutaneous melanoma 2L+; 1B: NSCLC 2L+, negative for actionable oncogenic alterations; 1C: EGFRm NSCLC 2L+; 1D: rare melanoma; 1E: other advanced solid tumors; 1F: drug-drug interaction cohort, dose defined in randomization cohorts 1A - 1C; and 1G: cervical cancer 2L+. In Part 2, patients in Cohorts 2A and 2B will receive two dose levels of BNT326 in combination with pumitamig. Patients in Cohorts 2D and 2E will receive two dose levels of BNT326 with pumitamig and dose level 2 of BNT326 as monotherapy. Patients in Cohort 2F receive one combination dose level. 2A: cutaneous melanoma 2L+; 2B: HER2-negative breast cancer 2L+/1L; 2C (optional, not open): cutaneous melanoma 1L+; 2D: gastric/gastroesophageal junction cancer 2L+; 2E: colorectal cancer 2L+; and 2F: cervical cancer 2L+. Primary endpoints are safety, overall response rate, and pharmacokinetics for cohort 1F. Enrollment for all cohorts is ongoing globally. Clinical trial information: NCT07070232. Research Sponsor: BioNTech SE.

TPS3161 **Poster Session**

A phase 1, multicenter, open-label, dose-escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of SBO-154 in subjects with advanced solid tumors. First Author: Charlotte Rose Lemech, Scientia Clinical Research-Prince of Wales Clinical School, Randwick, NSW, Australia

Background: Mucin 1 (MUC1) is a transmembrane glycoprotein overexpressed in advanced epithelial malignancies, where it promotes tumor progression and correlates with poor clinical outcomes. The membrane-proximal SEA domain of MUC1 is exposed on tumor cells and undergoes rapid internalization, enabling targeted intracellular delivery of cytotoxic payloads. SBO-154 is a MUC1 SEA–directed antibody–drug conjugate (ADC) conjugated to the clinically validated cytotoxic payload monomethyl auristatin E (MMAE) via a protease-cleavable linker. Unlike the shed MUC1-VNTR that creates an antigen sink limiting efficacy of prior ADCs, the negligibly shed MUC1-SEA epitope enables more effective SBO-154 tumor targeting. Nonclinical studies of SBO-154 showed MUC1-dependent cytotoxicity, dose-dependent tumor inhibition in vivo, and a favorable safety for clinical evaluation. This first-in-human study is designed to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and preliminary antitumor activity of SBO-154 in subjects with locally recurrent or metastatic solid tumors who have exhausted or are intolerant to available therapies. **Methods:** This phase 1, open-label, multicenter study comprises two parts: dose escalation (Part 1) and dose expansion (Part 2). Eligible adults (≥18 years) must have RECIST v1.1–measurable, locally recurrent or metastatic solid tumors (excluding sarcoma), documented progression after or intolerance to standard therapy, ECOG performance status 0–1, adequate organ function, and tumor tissue for immunohistochemistry (IHC) analysis. SBO-154 will be administered as an intravenous infusion on Day 1 of each 21-day treatment cycle (Q3W) over 30 minutes. Part 1 will use an mTPI-2 design with intra-patient dose escalation from 0.3 mg/kg to 2.5 mg/kg. Approximately 75 subjects will be enrolled in Part 1 (~50 in dose escalation and ~25 in backfill cohorts), and up to 102 subjects in Part 2. After determining the maximum tolerated dose (MTD) and the recommended dose for expansion (RDE), Part 2 will be initiated with a Simon's two-stage design. Planned expansion cohorts will include NSCLC, ER+ breast cancer, and ovarian cancer, with enrolment to be restricted to tumors with high MUC1-SEA expression. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal from the study. Primary endpoints: include dose-limiting toxicities (DLTs), treatment-related serious adverse events, dose modifications, and clinical/laboratory safety findings. Secondary endpoints: include PK, immunogenicity and efficacy. Enrollment Status: The study initiated enrolment in August 2025. Cohorts 1 and 2 have been completed without any DLTs, and enrolment in Cohort 3 is ongoing as of December 2025. Clinical trial information: NCT07042100. Research Sponsor: None.

TPS3162 **Poster Session**

Phase 1/2 study of CLIO-8221, a HER2-targeted, dual-payload exatecan and ATR inhibitor antibody-drug conjugate (ADC) in patients with advanced HER2-expressing solid tumors. First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: CLIO-8221 is a novel anti-HER2 ADC designed to overcome topoisomerase 1 inhibitor (Topo1i) resistance by incorporating both Topo1i (exatecan) and ataxia telangiectasia and rad3-related protein inhibitor (ATRi; berzosertib) payloads. Enabled by proprietary dual-payload ADC linker technology, CLIO-8221 uses an Fc-engineered trastuzumab, site-specifically conjugated with a stable protease-cleavable linker designed for optimal efficacy and tolerability. Trastuzumab deruxtecan (T-DXd) has redefined the treatment paradigm for HER2-expressing breast cancer and is emerging as a frontline treatment option. However, most patients develop resistance and disease progression. Topo1i-induced replication stress triggers activation of the DNA damage response pathway, which is an important driver of Topo1i resistance. Studies show that ATRi synergizes with Topo1i to enhance DNA damage and increase antitumor activity. In preclinical studies, CLIO-8221 binds with high affinity and specificity to HER2-expressing tumor cells and is rapidly internalized to release the Topo1i and ATRi payloads to drive direct tumor cell killing with a strong bystander effect. CLIO-8221 shows superior *in vivo* efficacy across tumor models with a range of T-DXd sensitivity, inducing tumor regression after a single dose in T-DXd resistant and refractory xenograft models. Additionally, CLIO-8221 is designed to minimize off-target uptake through Fc engineering for abrogated FcγR binding, and a proprietary hydrophilic linker for reduced macropinocytosis. CLIO-8221 is well tolerated in nonclinical toxicity studies in non-human primates. **Methods:** CLIO-8221-001 is a Phase 1/2, first in human dose-escalation and -expansion study. Eligible patients are adults with metastatic or unresectable HER2-expressing solid tumors, including those who previously received T-DXd. Patients must have measurable disease per RECISTv1.1 and have previously received therapies known to confer clinical benefit unless ineligible, refused by the patient, or not available in the region. CLIO-8221 will initially be given by intravenous infusion on Day 1 of a 21-day cycle; treatment may continue until disease progression, unacceptable toxicity, or other reason for discontinuation. The primary objectives are to assess the safety and tolerability of CLIO-8221 and to identify the maximum tolerated dose, if reached, and recommended Phase 2 dose. Phase 1 of the study utilizes a BOIN dose-escalation design with an expansion phase, while Phase 2 comprises tumor-specific expansion cohorts treated at the doses recommended from Phase 1. Antitumor activity, PK, immunogenicity, and biomarkers including HER2 status and ctDNA dynamics will also be evaluated. Enrollment is planned at sites in Australia, US, and China (NCT07300943). Clinical trial information: NCT07300943. Research Sponsor: Callio Therapeutics.

TPS3163 **Poster Session**

Phase 1, first-in-human, open-label study evaluating the safety, tolerability, pharmacokinetics, and preliminary efficacy of TGW101 in patients with advanced solid tumors. First Author: Anthony W. Tolcher, NEXT Oncology San Antonio, San Antonio, TX

Background: Tumor-associated glycoprotein 72 (TAG-72) is a non-internalizing glycoepitope that is aberrantly expressed in a broad range of epithelial cancers, predominantly adenocarcinomas. TGW101 is an antibody-drug conjugate (ADC) therapy that utilizes a novel, bio-orthogonal click chemistry-based linker technology that enables the targeting of non-internalizing cancer antigens and controlled payload release. The first component of TGW101 is a chemically cleavable ADC (TGW101-ADC) that consists of a diabody targeting TAG-72 and a highly stable *trans*-cyclooctene (TCO) linker conjugated to a monomethyl auristatin E (MMAE) payload. Once the TGW101-ADC binds to intratumoral TAG-72 and is largely cleared from the systemic circulation, the second drug component, a tetrazine trigger (TRG001), is administered, leading to rapid MMAE release from TGW101-ADC via a selective cleavage reaction with the TCO linker. Upon release of MMAE into the tumor microenvironment, it readily diffuses into surrounding tumor cells, binds to microtubules, inhibits cell cycle progression, and activates local immune cells. In preclinical studies, TGW101 treatment led to tumor regressions in the OVCAR3 (ovarian) cell line and GXF214 (gastric) patient-derived xenograft model, and improved survival in LS174T (colon) tumor bearing mice. **Methods:** This first-in-human, open-label Phase 1 study evaluates the safety and tolerability of TGW101 and defines a maximum tolerated dose (MTD). A Bayesian Optimal Interval (BOIN) design is used to determine the recommended dosing regimen(s) for expansion. Secondary objectives include assessing the pharmacokinetic (PK) profile, intratumoral pharmacodynamics, preliminary anti-tumor activity, and immunogenicity of TGW101. Exploratory analysis will investigate the relationship between TAG-72 expression and tumor response, as well as the effect of TGW101 exposure on tumor biomarkers. Up to 50 participants with advanced solid tumors, including breast, NSCLC, prostate, cervical, endometrial, ovarian, gastroesophageal, and non-squamous cell carcinoma of the head and neck are planned for enrollment. During dose escalation, increasing doses of TGW101-ADC, administered intravenously on Day 1 followed 7 days later by a fixed-dose infusion of TRG001, will be explored in cohorts of 3-4 participants treated in 3-week cycles. Once pharmacologically active dose levels are identified, specific cohorts may enroll additional participants to further explore safety, PK, tumor biomarker changes, and efficacy. Adverse events are assessed according to CTCAE v5 and tumor response is determined by RECIST 1.1 or PCWG3 criteria every 6 weeks for the first 2 cycles, then every 9 weeks. The trial began in May 2025 and 7 sites, all within the United States, are open for enrollment. Clinical trial information: NCT06959706. Research Sponsor: None.

TPS3164 **Poster Session**

First-in-human clinical evaluation of ST-01156, an optimized and selective degrader of RNA-binding motif 39 (RBM39): A phase 1 study in advanced solid malignancies with a focus on RBM39-dependent cancers. First Author: Eric Keith Rowinsky, SEED Therapeutics Inc., King of Prussia, PA, China

Background: ST-01156 is an orally administered agent developed to degrade RBM39, a protein target that is principally involved with splicing RNA into messenger RNA and is commonly upregulated in cancer. ST-01156 has entered phase 1 clinical trials for the treatment of several cancer types supported by its novel mechanism of action and data from preclinical testing. The lead optimization process for ST-01156 maximized degradation selectivity, anticancer potency, metabolic stability (including deuteration), and other drug-like properties. The ability of ST-01156 to achieve functionally meaningful and selective effects is exemplified by complete degradation of RBM39 within hours following treatment *in vitro,* accompanied by downstream mis-splicing of pathogenic transcripts, most notably the *EWSR1-FLI1* fusion transcript driving Ewing sarcoma (ES). Adding to this effect, ST-01156 depleted proteins involved in DNA damage repair (DDR), supporting the potential for synthetic lethality with cancer cells that depend on proficient DDR. RBM39 is also involved in the splicing of KRAS isoforms thought to be essential for the proliferation and survival of oncogenic KRAS cancer stem cells, providing an anticancer mechanism distinct from the mechanisms of current KRAS inhibitory agents. In advanced hepatocellular carcinoma (aHCC), RBM39 is substantially overexpressed and likely impedes essential arginine sensor activities. In addition to demonstrating robust activity in these malignancies, ST-01156 is highly active in patient-derived xenograft models of neuroblastoma, biliary tract carcinoma (BTC), and endometrial carcinoma (EC). In animal toxicology studies, hematologic and gastrointestinal tissues were most susceptible to RBM39 inhibition. **Methods:** In the first-in-human study, ST-01156 doses will be adaptively escalated based on the rate and severity of adverse events in trial participants with advanced solid malignancies. ST-01156 will be administered orally for 5 consecutive days every 7 days with an option of adapting a continuous dosing schedule, if tolerable. Backfilling of safe dose levels with participants with high priority malignancies will be allowed. In addition to traditional safety and tolerability endpoints, dose escalation and Phase 2 dose derivation will be based on pharmacokinetic (PK) endpoints and real-time RBM39 targeting measurements in peripheral mononuclear cells. The optimal dose of ST-01156 derived from safety tolerability, PK and pharmacodynamic data will be evaluated in trial participants in the following expansion cohorts: A, ES; B, aHCC; C, *KRAS*-mutant cancers; and D, an adaptive cohort of cancers projected to be susceptible to RBM39 inhibition including BTC, EC, and cancers with DDR aberrations. Clinical trial information: NCT07197554. Research Sponsor: SEED Therapeutics Inc.

TPS3165 **Poster Session**

A phase 1/2 first-in-human study of TH9619 in patients with advanced refractory solid tumors (ODIN). First Author: Victor Moreno, START-Madrid-FJD Early Phase Clinical Trials Unit, Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain

Background: TH9619 is a first-in-class, potent, small-molecule, and dual inhibitor of methylene-tetrahydrofolate dehydrogenase (MTHFD)1 and MTHFD2, both highly overexpressed in solid tumors and cancer-specific key enzymes within the one-carbon metabolic pathway. TH9619 kills cancer cells via a dual mechanism of action (1) inhibition of MTHFD1 traps folate leading to thymidine depletion, and (2) inhibition of nuclear MTHFD2 disrupts DNA damage response and repair pathways. With its unique characteristics, in preclinical models, TH9619 kills tumour cells, while sparing healthy tissues. The results from pre-clinical models, the novel mechanism of action, and the high unmet medical need in advanced refractory solid tumours support this investigation. **Methods:** ODIN (NCT07151040; EudraCT No. 2024-519639-40-00) is a first-in-human, multicentre, open-label, Phase 1/2 study. Eligible patients include adults with histologically confirmed advanced colorectal cancer, non–small cell lung cancer, head and neck squamous cell carcinoma, gastric cancer, or gastroesophageal junction cancer who have exhausted the institutional standard of care and have progressive and measurable disease per RECIST 1.1. Patients will receive TH9619 monotherapy via an intravenous infusion, weekly for 3 weeks, followed by one week without infusion, of a 28-day cycle, for up to 2 years. The Phase 1a dose-escalation, planning to recruit up to 80 patients, will assess the overall safety and tolerability profile and determine the maximum tolerated dose (MTD) and recommended Phase 2 dose(s) (RP2D(s)). Phase 1b is cohort expansion and plans to recruit up to 60 patients. Assessments include adverse events, pharmacokinetic (PK) and pharmacodynamic (PD) parameters, and preliminary anti-tumor activity per RECIST v1.1. Additionally, predictive biomarkers and metabolites related to the one-carbon metabolism and potential correlation with efficacy of TH9619 will be explored. The Phase 2 will further characterize safety, PK, PD, and efficacy at the RP2D(s). The ODIN phase 1/2 study is actively enrolling across leading academic and clinical research centres in the United Kingdom, France, and Spain, with expansion planned across additional European sites in the coming months. As of this submission, dose escalation is ongoing. Clinical trial information: NCT07151040. Research Sponsor: None.

TPS3166 **Poster Session**

TAGNOT: A phase 1b/2 tumor-agnostic study of the selective anti-FGFR1 monoclonal antibody OM-RCA-01 in FGFR1-expressing advanced solid tumors. First Author: Igor A. Utyashev, Institute of Oncology, Hadassah Medical Moscow, Moscow, Russian Federation

Background: Fibroblast growth factor receptor 1 (FGFR1) plays a key role in the pathogenesis of multiple malignancies; however, no highly selective FGFR1-targeted therapies for solid tumors are currently approved. OM-RCA-01 is a humanized monoclonal antibody that selectively binds extracellular domains II–IIIc of FGFR1 with high affinity (Kd = 1.59 nM) and has demonstrated promising antitumor activity in preclinical models. In the first-in-human, tumor-agnostic (TAGNOT) study, patients with FGFR1-expressing advanced cancers are being treated with OM-RCA-01. **Methods:** TAGNOT is a phase 1b/2, multicenter, multicohort, prospective study designed according to the FDA-recommended OPTIMUS approach. Key eligibility criteria include FGFR1 expression by immunohistochemistry (IHC 2+ or 3+ in $\geq$10% of tumor cells) and metastatic disease progressing after $\geq$2 prior systemic treatment lines. The primary objective of the phase 1b component is to determine the recommended phase 2 dose (RP2D). Two dose levels of OM-RCA-01 (50 mg and 100 mg administered intravenously every 2 weeks) will be compared for safety (CTCAE v5.0), preliminary efficacy (objective response rate [ORR] per RECIST v1.1), pharmacokinetics, neutralizing antibody formation, and circulating tumor DNA dynamics. The primary endpoint of the phase 2 component is ORR in the ITT population. Five tumor-specific cohorts are planned: clear-cell renal cell carcinoma (n = 11), castration-resistant prostate cancer (n = 11), non-small cell lung cancer without EGFR or ALK alterations (n = 11), breast adenocarcinoma with known receptor status (n = 11), and head and neck squamous cell or salivary gland carcinomas (n = 11). Using Simon's two-stage design, a total of 55 patients will be enrolled. The null hypothesis of a true ORR of 10% will be tested against a one-sided alternative of 25%. The study will be terminated after the first stage if $\leq$3 responses are observed among 31 patients. Otherwise, 24 additional patients will be enrolled. The null hypothesis will be rejected if $\geq$10 responses are observed in 55 patients, yielding a one-sided type I error rate of 0.05 and 90% power. Clinical trial information: NCT07292168. Research Sponsor: Bureau for Cancer Research - BUCARE.

TPS3167 **Poster Session**

A first-in-human study of ATX-295, an oral inhibitor of KIF18A, in patients with advanced or metastatic solid tumors, including ovarian cancer. First Author: Judy S. Wang, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL

Background: ATX-295 is an oral inhibitor of KIF18A, an adenosine triphosphate (ATP)-dependent, plus end-directed mitotic kinesin. KIF18A facilitates chromosomal alignment and spindle microtubule dynamics during mitosis in certain advanced solid tumors with chromosomal instability (CIN). In preclinical studies, ATX-295 demonstrated robust antiproliferative activity in chromosomally instable solid tumor models, including in high grade serous ovarian cancer. In vivo, oral administration of ATX-295 induced dose-dependent tumor growth inhibition in CIN platinum-resistant ovarian and squamous non-small cell lung cancer cell-line derived xenograft (CDX) and patient derived xenograft (PDX) models. **Methods:** NCT06799065 is a multi-center, first-in-human, Phase 1/2, open-label, single-arm, dose-escalation and expansion study to evaluate the safety profile of ATX-295 and determine the recommended phase 2 dose (RP2D) in subjects with locally advanced or metastatic solid tumors. The study in progress will be conducted in two parts: dose escalation, followed by dose expansion. Participant enrollment and continuous safety assessment will be guided by a mTPI-2 design (Guo, 2017) to identify an optimal dose. To assess evidence of preliminary antitumor activity, a Simon 2-stage design (Simon, 1989) will be used during dose expansion. Key eligibility criteria: patients with histologically confirmed solid tumors who have locally recurrent or metastatic disease, including high grade serous ovarian cancer (HGSOC) and squamous non-small cell lung cancer (sqNSCLC); refractory to or relapsed after all standard therapies with proven clinical benefit. For the expansion cohorts, participants must have histological confirmation of HGSOC and be determined to be platinum-resistant, platinum-refractory, or platinum-intolerant; have measurable disease; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Primary endpoints will evaluate safety and tolerability of ATX-295 at pharmacologically active dose(s) and/or schedule(s) and determine the recommended phase 2 dose (RP2D). Secondary endpoints will evaluate pharmacokinetics (PK) of ATX-295 in plasma and evaluate pharmacodynamic (PD) effects of ATX-295 to assess preliminary evidence of anti-tumor activity. The study is actively recruiting. Clinical trial information: NCT06799065. Research Sponsor: Accent Therapeutics.

TPS3168 **Poster Session**

First-in-human phase 1 dose escalation and expansion study of PIN-5018, a CK1α-selective molecular glue degrader, in patients with advanced solid tumors. First Author: Bhumsuk Keam, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea

Background: Casein kinase 1 alpha (CK1α) is a serine/threonine kinase involved in multiple oncogenic signaling pathways regulating cell proliferation, differentiation, and survival. Dysregulation of CK1α has been implicated across several solid tumor types, supporting its evaluation as a therapeutic target. PIN-5018 is an orally administered, CK1α-selective molecular glue degrader designed to induce targeted proteasomal degradation of CK1α via cereblon-mediated ubiquitination. Previously presented preclinical studies have demonstrated selective CK1α degradation and antitumor activity in multiple solid tumor models, providing the scientific rationale for first-in-human clinical evaluation. In addition to safety and dose optimization, the study incorporates tumor- and blood-based correlative analyses to characterize CK1α degradation and downstream pathway modulation. **Methods:** PIN-5018-001 is an ongoing, first-in-human, open-label, multicenter phase 1 study evaluating PIN-5018 in patients with progressive, locally advanced (unresectable), or metastatic solid tumors who have exhausted standard treatment options. The study consists of a dose escalation phase followed by dose expansion at selected dose levels based on safety, pharmacokinetics, and preliminary antitumor activity. PIN-5018 is administered orally once daily in 21-day cycles (14 days on treatment followed by 7 days off). Dose escalation evaluates six planned dose levels (10–100 mg) using a Bayesian Optimal Interval (BOIN) design with a target dose-limiting toxicity rate of 25%. Dose-limiting toxicities are assessed during Cycle 1. Up to 36 patients may be enrolled in dose escalation, with plan to add dose optimization and dose expansion cohorts. Eligible patients are adults (≥18 years) with ECOG performance status 0–1 and at least one measurable lesion per RECIST v1.1. Mandatory pre-treatment and on-treatment tumor biopsies are required when medically feasible to support correlative biomarker analyses. Enrollment has begun. Cohort 1 has been completed without DLT, and enrollment to subsequent cohorts is ongoing. Clinical trial information: KCT0011322. Research Sponsor: Pin Therapeutics, Inc.

TPS3169 **Poster Session**

An open-label, multicenter study of DPTX3186 to evaluate safety, tolerability, and pharmacokinetics in subjects with known Wnt pathway–activated solid tumors where no other treatments exist. First Author: Alexander I. Spira, Virginia Cancer Specialists and NEXT Oncology, Fairfax, VA

Background: Constitutive activation of the Wnt/β-catenin pathway drives malignancy in a wide range of cancers, where β-catenin has been notoriously difficult to drug due to its disordered nature, lack of defined drug-binding pockets, and associated toxicities. Biomolecular condensates are membraneless organelles that orchestrate cellular processes, biological pathways, and protein activity by compartmentalizing biomolecules. DPTX-3186 is a small molecule condensate modulator (c-mod) that acts via a novel mechanism of action, sequestering β-catenin into inactive condensate depots. This sequestration selectively inhibits β-catenin-driven transcription and induces robust cancer cell death. DPTX3186 is an orally bioavailable small molecule c-mod that demonstrates strong anti-tumor activity across multiple tumor types driven by various defects along the Wnt/β-catenin pathway. Studies in xenographs show that DPTX-3186 modulates Wnt pathway activity as evidenced by formation of inactive β-catenin condensates and modulation of β-catenin-driven gene transcription. Profound pharmacological efficacy, including regressions and complete responses, has been observed in murine models of gastric cancer as monotherapy. The molecule has been granted Fast Track and Orphan Drug Designations by the FDA. **Methods:** This first-in-human, phase 1/2, multicenter, open-label, dose-escalation (phase 1) and dose-expansion (phase 2) study evaluates the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor effects of DPTX3186 monotherapy in patients with known Wnt pathway activated solid tumors. Eligible patients must have no other approved treatment options available. In Phase 1, DPTX3186 is administered orally in a 4 days on / three days off schedule, at escalating dose levels, evaluated sequentially in a BOIN design. Phase 2 dose expansion will utilize a TOP-BOIN design and will evaluate DPTX3186 monotherapy in patients with histologically or cytologically confirmed non-resectable gastric adenocarcinoma who are refractory to prior treatment. Primary endpoints are safety and tolerability of DPTX-3186, including dose-limiting toxicities (DLT) and the determination of the MTD and recommended dose for expansion. Secondary endpoints are PK, PD, and preliminary anti-tumor activity (e.g. overall response rate, duration of response, progression-free survival, disease control rate, and overall survival). 40 patients are planned to be enrolled in Part 1, which is currently enrolling in the USA. Clinical trial information: NCT07312903. Research Sponsor: Dewpoint Therapeutics.

TPS3170 **Poster Session**

Phase 1/2 study of the novel Werner helicase inhibitor EIK1005 as monotherapy and in combination with pembrolizumab in patients with advanced solid tumors, including MSI-H or dMMR tumors. First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cancers with deficient mismatch repair (dMMR) have high microsatellite instability (MSI-H) and are reported to be sensitive to inhibition of the Werner syndrome helicase (WRN) via synthetic lethality. WRN inhibition in MSI-H cells leads to loss of genomic integrity and ultimately cell death while not affecting microsatellite stable (MSS) and healthy cells. Standard of care for patients (pts) with MSI-H tumors includes surgery and immunotherapy (checkpoint inhibitors [CPIs] like pembrolizumab [pembro]). While these are viable treatment options, depending on the indication, ~30 to 50% do not respond to first-line immune CPIs, or acquire resistance. A critical unmet medical need exists for new therapies for such patients (pts). EIK1005 is a novel, potent, high-affinity and selective WRN inhibitor (WRNi) with the potential for targeted antitumor activity in MSI-H or dMMR solid tumors. In vitro studies demonstrated sustained target engagement leading to cell death in MSI-H cells while sparing MSS and healthy cells. In a Phase 1 single ascending dose study in healthy participants, EIK1005 was well tolerated at the doses evaluated. **Methods:** EIK1005-002 (NCT#07262619) is a multicenter, multi-part, Phase 1/2 study of EIK1005 monotherapy and combination with pembro, in participants with advanced solid tumors including MSI-H and dMMR tumors. The study has three parts; Part 1A (monotherapy dose escalation [DE]): EIK1005 will be evaluated at ~ three dose levels (DL) in participants without alternative therapeutic options (n~40). Preference is given to pts with MSI-H or dMMR cancer for whom prior CPI therapy has failed, or with MSS cancer who progressed after ≥1 regimen of platinum, alkylating or topoisomerase chemotherapy as evidence suggests MMR alterations and MSI induction in previously MSS cancer. Part 1B (combination DE): participants with MSI-H or dMMR tumors (n~40) will receive EIK1005 + pembro (Q3W). Part 2 (dose optimization [DO]): participants (n~80) with MSI-H and dMMR tumors and slowly progressive disease are randomized 1:1 to receive EIK1005 at one of two doses from Part 1A. Key eligibility criteria: participants ≥18 years, life expectancy ≥3 months, unresectable and/or metastatic solid tumor, measurable disease at baseline (RECIST v1.1), progression after or intolerance to ≥ 1 advanced-setting standard treatment regimen (Part 1A), has MSI-H or dMMR tumor (Parts 1B and 2) and slowly progressive disease (Part 2). Primary objectives: safety and tolerability of EIK1005 monotherapy and + pembro to determine the MTD (Part 1) and to inform DO (Part 2). Secondary objectives: preliminary antitumor activity, characterize plasma PK profile of EIK1005 monotherapy and + pembro. This study began in December 2025. Clinical trial information: NCT07262619. Research Sponsor: None.

TPS3171 **Poster Session**

Phase 1, multi-center clinical trial evaluating the safety, pharmacokinetics, pharmacodynamics and anti-cancer activity of PQ203, a first-in-class peptide drug conjugate targeting SORT1 in patients with advanced solid tumor malignancies (NCT07190469). First Author: Philippe Bedard, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: Antibody–drug conjugates (ADCs) have improved outcomes in several refractory cancers by enabling the targeted delivery of potent cytotoxins but their use is limited by suboptimal payload release, off-target and immune-related toxicities, poor tumor penetration and complex manufacturing. Peptide drug conjugates (PDCs) offer potential advantages over ADCs including smaller size, increased tumor penetration, more rapid systemic clearance and decreased immunogenicity. PQ203 is a first in class, AI-designed PDC comprised of a 17 amino acid peptide targeting sortilin (SORT1) conjugated to the cytotoxin monomethyl auristatin E (MMAE) via a para-amino-benzyl-valine-citrulline (PAB-VC) cleavable linker. SORT1, a receptor of the Vps10p family involved in protein trafficking, is overexpressed across multiple tumor types and associated with tumor invasiveness. Preclinical breast cancer models, including patient-derived xenografts, show that PQ203 can overcome resistance to commonly used TOP1-based ADCs. **Methods:** This first-in-human, multi-country Phase 1A/B dose-escalation, expansion and optimization clinical trial is designed to assess the safety, pharmacokinetics, pharmacodynamics, immunogenicity and preliminary anti-tumor activity of PQ203. Treatment consists of once weekly IV infusion × 4 weeks (Q1Wx4) and continues until the occurrence of disease progression or dose-limiting toxicity. In Part 1 of the study, up to 7 dose cohorts are anticipated (commencing at 0.02 mg/kg) in a backfill Bayesian optimization (BF-BOIN) dose escalation design with a target toxicity rate of 27.5%. Upon satisfaction of pre-defined safety criteria for particular dosing cohorts, up to 9 additional patients (pts.) in pre-defined settings of biologic and clinical interest may be enrolled to backfill expansion of that dose level. Upon identification of one or more recommended doses for expansion, up to 50 pts. across 1-3 tumor types of particular clinical interest, including pts. with triple negative breast cancer, will be enrolled in the expansion and dose optimization phases of the study. Alternative dosing schedule(s) with reduced frequency may additionally be explored based on emerging PK and safety data. At the time of submission, cohorts 1 and 2 were completed without DLTs and enrollment of Cohort 3 was initiated in January, 2026. Clinical trial information: NCT07190469. Research Sponsor: None.

TPS3172 **Poster Session**

A phase 1 first-in-human study of BGM-2121 in patients with advanced solid tumors. First Author: Chien-Chih Ou, BioGate Precision Medicine Corporation, Taipei, Taiwan

Background: Parathyroid hormone-related protein (PTHrP) is a hormone frequently overexpressed in tumors such as pancreatic ductal adenocarcinoma (PDAC), lung, and head and neck cancers. In some cases, this overexpression can lead to hypercalcemia in patients with malignancies. PTHrP is a ligand of G-protein–coupled receptor (GPCR) known as parathyroid hormone type 1 receptor (PTH1R), thereby activating multiple downstream signaling pathways. Despite the significant role of GPCRs in cancer biology, therapeutic options targeting these receptors in oncology remain limited. BGM-2121 is a potent, first-in-class, humanized IgG1 monoclonal antibody targeting the N-terminal region of PTHrP, aiming to inhibit the PTHrP/PTH1R pathway. Preclinical studies exhibit high affinity and specificity for PTHrP, demonstrating robust antitumor activity in pancreatic cancer xenograft models, and significantly prolonging survival. In lung squamous cell carcinoma models, BGM-2121 was found to prevent and reverse hypercalcemia and cancer-associated weight loss, which are the key features of humoral hypercalcemia of malignancy and cachexia. **Methods:** BGM-2121-001 (NCT07346846) is a first-in-human, open-label, phase 1 trial designed to evaluate the safety, tolerability, pharmacokinetics, and preliminary antitumor, anti-cachexia, and anti-hypercalcemia activity in adults with advanced solid tumors. Eligible participants are adults with histologically or radiographically confirmed advanced solid tumors who are refractory to, intolerant of, or without available standard therapies. Tumor types of primary interest include pancreatic, esophageal, head and neck, and non–small cell lung cancers, particularly sub-type of squamous cell carcinoma. Participants must have ECOG performance status $\leq$2 and adequate organ function. Key exclusions include active central nervous system metastases, significant cardiovascular disease, uncontrolled infections, recent anticancer therapy, prior allogeneic transplantation, active viral hepatitis or HIV infection. BGM-2121 is administered intravenously every 2 weeks in sequential dose-escalation cohorts (160, 320, 480, 800, and 1200 mg) using a standard 3+3 design. Dose-limiting toxicities are assessed during the first 28 days, and the maximum tolerated dose is defined as the highest dose at which $\leq$1 of 6 patients experiences a dose-limiting toxicity. Dose modifications are determined by the Safety Review Committee. Treatment continues until disease progression, unacceptable toxicity, or loss of clinical benefit. Clinical trial information: NCT07346846. Research Sponsor: Biogate Precision Medicine Corporation.

TPS3173 **Poster Session**

A multicenter phase 1/1b study of AMG 436 as monotherapy and combination therapy in patients with advanced MSI-H/dMMR solid tumors. First Author: Elizabeth Won, Amgen Inc., Thousand Oaks, CA

Background: Microsatellite instability-high (MSI-H)/mismatch repair deficiency (dMMR) tumors are characterized by high mutational burden and replication stress. These tumors rely on Werner syndrome protein (WRN), a DNA helicase required for DNA replication and repair, to sustain tumor cell survival. As a result, this reliance on WRN creates a synthetic lethal vulnerability, making WRN inhibition a promising therapeutic strategy. AMG 436 is a selective, covalent WRN inhibitor that is designed to exploit this dependency in MSI-H/dMMR tumors. AMG 436 represents a tumor-intrinsic approach that is mechanistically distinct from immune checkpoint inhibitors (ICIs), the current standard of care. This first-in-human Phase 1/1b trial evaluates AMG 436 as monotherapy and in combination with immune checkpoint inhibitors and/or chemotherapy in adults with MSI-H/dMMR solid tumors, including ICI-naïve and post-ICI populations. **Methods:** This study is a Phase 1/1b, open-label, multicenter trial enrolling approximately 464 adult participants with metastatic or locally advanced MSI-H/dMMR solid tumors. The study consists of 4 parts: Part 1 involves monotherapy dose exploration; Part 2 explores combination doses with chemotherapy or an immune checkpoint inhibitor; Part 3 focuses on monotherapy dose expansion and randomized dose optimization; and Part 4 involves combination dose expansion with chemotherapy and/or ICIs. The primary objectives are to assess safety and determine the maximum tolerated dose or recommended dose for expansion, with primary endpoints being the incidence of dose-limiting toxicities (DLTs) during the DLT evaluation period and the incidence of treatment-emergent adverse events and serious adverse events. Secondary objectives include pharmacokinetics and preliminary antitumor activity per RECIST v1.1. Descriptive statistics will be used to summarize safety, pharmacokinetic, and efficacy data. Key eligibility criteria are adults with MSI-H/dMMR status, ECOG 0–1, and adequate organ function. Enrollment is ongoing globally across North America, South America, Europe, and Asia-Pacific. Participants may remain on treatment for up to 2 years, with total trial duration including follow-up extending up to 5 years. Clinical trial information: 177459. Research Sponsor: Amgen Inc.

TPS3174 **Poster Session**

Phase I study of [^{225}Ac]Ac-ETN029, a DLL3-targeted radioligand therapy, in patients with advanced DLL3-expressing solid tumors. First Author: Cristiano Ferrario, Jewish General Hospital, McGill University, Montreal, QC, Canada

Background: Delta-like ligand 3 (DLL3) is an atypical Notch ligand that is highly expressed in small cell lung cancer (SCLC) and other neuroendocrine carcinomas, with minimal expression in normal adult tissues. [^{225}Ac]Ac-ETN029 (^{225}Ac-ETN029) is a novel, DLL3-targeted, macrocyclic peptide-based radioligand therapy (RLT) demonstrating potent antitumor activity in DLL3-positive, SCLC cell line–derived, xenograft mouse models. Here, we describe CESP359A12101 (NCT07006727), a global first-in-human phase 1 study evaluating ^{225}Ac-ETN029 in patients with selected advanced DLL3-expressing solid tumors. **Methods:** The primary objectives of the study are to assess the safety and tolerability of ^{225}Ac-ETN029 and to identify the recommended radioactive dose(s) of ^{225}Ac-ETN029 for further clinical evaluation. Secondary objectives are to assess the preliminary antitumor activity of ^{225}Ac-ETN029, characterize the pharmacokinetics (PK) and dosimetry of ^{225}Ac-ETN029, and characterize the safety, PK, dosimetry, and imaging properties of [^{111}In]In-ETN029 (^{111}In-ETN029). Study participants are expected to receive 4 cycles of ^{225}Ac-ETN029 at 6-week intervals, although a lower or higher number of cycles may be explored if deemed beneficial and safe. The study includes dose escalation and dose expansion parts. During dose escalation, increasing levels of administered activity per cycle will be assessed across cohorts. Dose escalation decisions will be based on a review of all available data, including safety, tolerability, dosimetry, PK, pharmacodynamics, and preliminary efficacy, and guided by the Bayesian logistic regression model using the escalation with overdose control principle. Dose expansion will begin once recommended radioactive dose(s) of ^{225}Ac-ETN029 for further clinical investigation have been determined. Eligible patients must be $\geq$18 years old; have locally advanced, unresectable, or metastatic disease measurable per RECIST v1.1; and be diagnosed with one of the following: (1) SCLC, (2) large cell neuroendocrine carcinoma (LCNEC) of the lung (escalation only), (3) de novo or castration-resistant, treatment-emergent, neuroendocrine prostate cancer (NEPC; expansion only), or (4) gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC; expansion only). Patients with SCLC, LCNEC, and GEP-NEC must have disease progression following, or intolerance of, $\geq$1 prior line of systemic therapy. Patients with NEPC and GEP-NEC must have $\geq$1 measurable lesion (per RECIST 1.1) demonstrating ^{111}In-ETN029 uptake higher than surrounding tissues on SPECT/CT as assessed by the investigator. Patients with prior DLL3-targeted therapy (except for SCLC) or prior RLT (except for NEPC) will be excluded. Patient enrollment began in October 2025. Clinical trial information: NCT07006727. Research Sponsor: None.

TPS3175 **Poster Session**

Alpha-emitting radionuclide or beta-emitting radionuclide combined with metastasis-directed stereotactic body radiotherapy for oligorecurrent prostate adenocarcinoma (ANDROMEDA): A phase II trial. First Author: Kekoa Taparra, Department of Radiation Oncology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA

Background: The recent LUNAR study (NCT05496959) found that adding beta-emitting ^{177}Lutetium-PNT2002 (^{177}Lu-PSMA) to stereotactic body radiation therapy (SBRT) more than doubled median progression-free survival (PFS) compared to SBRT alone in oligorecurrent hormone-sensitive prostate cancer (orHSPC), hazard ratio (HR)=0.37. However, the relative efficacy compared to novel alpha-emitting ^{225}Actinium-PSMA-617 (^{225}Ac-PSMA) is unknown. The hypothesis is that ^{225}Ac-PSMA will improve PFS by treating more micrometastases, given its higher radiobiologic effectiveness. We aim to compare the relative benefit of 2 cycles of ^{177}Lu-PSMA versus 1 cycle of ^{225}Ac-PSMA followed by SBRT metastasis-directed therapy (MDT). **Methods:** ANDROMEDA (NCT07150715) is a phase II, non-blinded, single-center randomized trial for individuals with orHSPC and 1-5 PSMA-avid metastases outside the prostate/prostate bed (N1 and/or M1). Eligibility criteria include testosterone $>$150 ng/dL, $\geq$18 years, and ECOG performance status $\leq$2. Exclusion criteria include *de novo* metastatic disease, castrate-resistance (testosterone $<$50 ng/mL with rising PSA), ADT/chemotherapy within 6 months of enrollment, and neuroendocrine histology. Participants are randomized 1:1 to 2 cycles ^{177}Lu-PSMA (7.4 GBq/cycle, 6 weeks apart) or 1 cycle of ^{225}Ac-PSMA (8 MBq, once), followed by SBRT to all lesions 1-2 weeks after radioligand therapy infusion. The primary endpoint of PFS is defined as the time from randomization to either 1) a new PSMA-avid lesion or 2) PSMA-PET local progression ($>$30% SUV increase or $>$20% increase in the sum of the longest lesion diameters) with a PSA rise. For those alive without progression, PFS will be censored at the time of the last scan. All randomized subjects will be analyzed based on intent-to-treat. Secondary endpoints include 24-month disease burden by PSMA-PET, physician-scored toxicity, patient-reported quality of life, ADT-free survival, local control of SBRT lesions at 24 months after last radionuclide infusion, and time-to-progression (locoregional, distant, new metastasis). We hypothesize that the 24-month post-SBRT PSA-based recurrence rate of ^{177}Lu-PSMA will be ~50%, which will be reduced with ^{225}Ac-PSMA to ~30% (PFS HR~0.51). We anticipate an accrual time of 1.5 years and a median follow-up time of 24-months. A sample size of 96 patients (48 per arm) would provide 80% power to detect the expected difference in PFS at a 0.1 alpha level. Assuming a 10% drop-out/screen failure rate, the target trial accrual is 107 patients. Early stopping guidelines include monitoring site-specific grade 4-5 toxicity with a safety threshold of 20% from the time of the first enrolled patient, which would trigger halting the trial and safety consultation. ANDROMEDA is currently open for enrollment. Clinical trial information: NCT07150715. Research Sponsor: None.

TPS3176 **Poster Session**

[^{212}Pb] Pb-MP0712 in patients with small cell lung cancer and other Delta-like ligand 3–expressing solid tumors: A phase 1/2a study to assess safety, tolerability, and efficacy. First Author: Ticiana Leal, Winship Cancer Institute of Emory University, Atlanta, GA

Background: [^{212}Pb]Pb-MP0712 is a novel radiopharmaceutical comprising a Designed Ankyrin Repeat Protein (DARPin) that binds with high affinity to DLL3 and carries the alpha-emitting isotope lead-212 (^{212}Pb) for targeted delivery of high linear energy transfer radiation. DLL3 is highly expressed in SCLC, large cell neuroendocrine carcinoma (LC-NEC) of the lung, and extrapulmonary NEC (epNEC), while its expression in healthy tissue is virtually absent. In preclinical studies, [^{212}Pb]Pb-MP0712 selectively accumulates in DLL3-positive tumors, exhibits an adequate biodistribution profile, and induces complete and durable tumor regression with prolonged survival and a favorable safety profile (Croset et al. AACR 2025). Initial human imaging data from a patient who received [^{203}Pb]Pb-MP0712 in a Named Patient Access Program under the legal framework for compassionate care in South Africa indicate its specific uptake in tumor (Steiner et al. TRP EU 2025). **Methods:** This first-in-human Phase 1/2a study evaluates the safety, biodistribution, dosimetry, and preliminary antitumor efficacy of [^{212}Pb]Pb-MP0712 (NCT07278479). Key inclusion criteria are SCLC and progression or recurrence following $\geq$2 prior lines of systemic therapy, or lung LC-NEC or epNEC with progression or recurrence following $\geq$1 prior line of systemic therapy, and measurable disease by RECIST v1.1. Patients with clinically stable central nervous system metastasis or prior DLL3-targeted therapy are eligible. Key exclusion criteria are Merkel cell carcinoma, neuroendocrine prostate cancer, interstitial lung disease, and active non-infectious pneumonitis. This study has two parts, a dose escalation (Part 1) and an expansion (Part 2). Primary objectives of Part 1 are to evaluate safety and tolerability of [^{212}Pb]Pb-MP0712, and to determine the maximum tolerated dose and recommended phase 2 dose (RP2D). Primary objective of Part 2 is to assess preliminary antitumor activity of [^{212}Pb]Pb-MP0712. All patients will receive a single dose of [^{203}Pb]Pb-MP0712 as intravenous (IV) injection at 185 MBq to evaluate DLL3-expressing tumor lesions, pharmacokinetics, biodistribution and dosimetry using single-photon emission computerized tomography (SPECT)/CT, followed by [^{212}Pb]Pb-MP0712 treatment. In study Part 1, for SCLC/lung LC-NEC cohorts, treatment proceeds regardless of imaging results; for epNEC cohorts, a DLL3-positive SPECT/CT is required. Patients will be enrolled in sequential cohorts to receive escalating doses of [^{212}Pb]Pb-MP0712 as IV injection on Day 1 of each 28-day cycle for up to six cycles. The dose escalation will be guided by an adaptive Bayesian Logistic Regression Model. Upon completion of Part 1, Part 2 will enroll two groups of patients with DLL3-positive SCLC/lung LC-NEC or epNEC at the RP2D. Clinical trial information: NCT07278479. Research Sponsor: Molecular Partners AG, Zuerich-Schlieren, Switzerland; Orano Med SAS.

TPS3177 **Poster Session**

Beamion BCGC-1: Four new phase Ib/II cohorts to evaluate oral zongertinib with other agents in HER2-positive metastatic breast cancer (mBC) and metastatic colorectal cancer (mCRC). First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan

Background: Zongertinib, an oral, irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Beamion BCGC-1 (NCT06324357) is an ongoing Phase (Ph) Ib/II trial evaluating zongertinib in HER2-positive tumors. Trial details for Cohorts A–K, evaluating zongertinib as monotherapy or combined with T-DM1, T-DXd, or trastuzumab $\pm$ capecitabine in patients (pts) with HER2-positive mBC, and with T-DXd in pts with HER2-positive metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma (mGEAC), have recently been published (Hurvitz et al, *Future Oncol* 2025). In addition to BC and GEAC, early-phase data indicate zongertinib is also active in mCRC (Yoh et al, *Ann Oncol* 2025, abstr 491P). Here, we report 4 new cohorts (L–O) to evaluate the efficacy and safety of zongertinib plus zanidatamab in HER2-positive mBC, or plus trastuzumab or mFOLFOX6 $\pm$ trastuzumab in HER2-positive mCRC. **Methods:** For the 4 new cohorts, pts must have histologically/cytologically confirmed, unresectable HER2-positive mBC or mCRC, and documented HER2-positive disease (overexpression/amplification). Pts with mBC must have disease progression following $\geq$1 prior HER2-targeted treatment; pts with mCRC must have disease progression/recurrence during or following their latest treatment. Pts with brain metastases are allowed. There are 3 new Ph Ib cohorts (M, N, and O; each ~20 pts). Cohorts M and N will assess zongertinib in mCRC: pts will receive once-daily zongertinib across escalating dose levels plus mFOLFOX6 every 14 days (Cohort M), or mFOLFOX6 every 14 days + trastuzumab every 21 days (Cohort N; Table). In Cohort O, pts with mBC will receive once-daily zongertinib across escalating dose levels plus zanidatamab every 21 days. Dose escalation will be guided by a BLRM with overdose control. In Ph II, Cohort L, a new dose justification cohort (~40 pts with mCRC), will receive zongertinib 120 mg once daily plus trastuzumab every 21 days. In Ph Ib, the primary endpoint is DLTs during the MTD evaluation period; secondary endpoints include objective response (OR) by RECIST v1.1, DLTs in the on-treatment period, and pharmacokinetics (PK). In Ph II, the primary endpoint is OR by RECIST v1.1; secondary endpoints include PFS, disease control, AEs leading to dose reduction, PK, and pt-reported outcomes. Pts will remain on treatment until any protocol-defined stopping criterion occurs. Clinical trial information: NCT06324357. Research Sponsor: Boehringer Ingelheim.

Cohort	Indication	Zongertinib Regimen
Ph Ib dose escalation		
M	mCRC	+ mFOLFOX6: oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), 5-FU (2400 mg/m^2)
N	mCRC	+ mFOLFOX6: oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), 5-FU (2400 mg/m^2) + trastuzumab (8 mg/kg loading; 6 mg/kg maintenance)
O	mBC	+ zanidatamab (1800 mg $<$70 kg; 2400 mg $\geq$70 kg)
Ph II dose justification		
L	mCRC	+ trastuzumab (8 mg/kg loading; 6 mg/kg maintenance)

TPS3178 **Poster Session**

A study of MT-4561 in patients with various advanced solid tumors (NCT06943521). First Author: Kimberly Lynne Futch, Tanabe Pharma America, Inc., Jersey City, NJ

Background: MT-4561 is a bromodomain-containing protein 4 (BRD4) protein degrader, which is a bi-functional molecule having both a binder moiety that binds to BRD4 and a degron moiety that binds to damage-specific deoxyribonucleic acid (DNA) binding protein 1 (DDB1) and cullin 4 (CUL4) associated factor 16 (DCAF16), which is responsible for the ubiquitination of BRD4. MT-4561 degrades BRD4, a bromodomain protein that stimulates oncogene transcription, using the ubiquitin-proteasome system. Tanabe Pharma has demonstrated that this novel BRD4 degrader, MT-4561, exerts continuous anti-tumor effects in various cancer xenograft models (Ooike, 2024). **Methods:** This trial is a FIH, Phase I/II study to evaluate safety, tolerability, PK, PD, and efficacy of MT-4561 in patients with advanced solid tumors. Part 1 is evaluating safety, tolerability, PK, MTD, and the doses to be investigated in Part 2 (dose optimization) using the BOIN design. Part 2 evaluates the safety and efficacy of MT-4561 in patients with pre-specified tumor types based on data from Part 1, and to determine the RP2D. Part 2 can begin enrollment after the MTD and/or the doses to be investigated in Part 2 have been determined based on data from Part 1. Part 3 of the study is the open-label drug-drug interaction (DDI) cohort to evaluate the effect of MT-4561 on the PK established in Part 1. A retrospective analysis will also be conducted to assess the correlation between efficacy and expression of BRD4/its downstream gene products in patient samples to explore predictive biomarkers. MT-4561 is administered as an intravenous (IV) infusion over 30 minutes once every week in 28-day cycles, until disease progression or discontinuation criteria are met. Parts 1 and 3 of the study will enroll patients 18 years and older with who have failed at least 1 therapy , who have $\geq$ 1 measurable lesion by RECIST v1.1 and with confirmed histologic or cytologic diagnosis of one of the following tumors: HNSCC, NSCLC, esophageal cancer, gastric cancer, biliary tract cancer, PDAC, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, prostate cancer, urothelial carcinoma, NET or NEC, soft tissue sarcoma, and NUT carcinoma. Part 2 will enroll only pre-specified tumors for dose optimization to determine the RP2D. Key exclusion criteria include patients with unresolved $\geq$ Grade 2 toxicities from previous treatment and those with QTc prolongation $>$ 470 msec at screening. Also, patients who received drugs with a known risk of QT interval prolongation or torsade de pointes, before the start of IMP administration. Enrollment in Part 1 of the study began May 2025 and continues to enroll patients in the US and Japan with 10 patients enrolled through Dose Level 2 as of Jan 2026. The safety data along with DLT continues to be reviewed in Part 1. Ooike S, et al. PB069, Poster Session, 36th EORTC-NCI-AACR Symposium, 2024. Clinical trial information: NCT06943521. Research Sponsor: None.

TPS3179 **Poster Session**

A phase 1, first-in-human study of DS9051, a novel targeted protein degradation molecule, in patients with advanced/metastatic adrenocortical carcinoma (ACC) or metastatic castration-resistant prostate cancer (mCRPC). First Author: Manish R. Patel, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL

Background: ACC and mCRPC are difficult-to-treat malignancies. mCRPC typically progresses despite androgen deprivation and androgen receptor pathway inhibitor (ARPI) therapy, with or without taxanes. Similarly, treatment options for ACC are limited and prognosis is generally unfavorable. DS9051 is a targeted protein degradation molecule that has been designed to selectively degrade a key protein involved in the development and progression of both ACC and mCRPC via a novel mechanism. It leverages the ubiquitin-proteasome system, where DS9051 acts as a bridge to link the target protein and E3 ligase, initiating ubiquitination and degradation of the target protein. **Methods:** DS9051-079 (NCT07189403) is a Phase 1, first-in-human, open-label, multicenter study of DS9051 (N≈40). Patients must be adults with histologically confirmed advanced or metastatic ACC (Stage III–IV) or mCRPC and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients with ACC must have measurable disease per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1) that is not amenable to radical surgical resection or definitive radiotherapy. Further inclusion criteria for patients with mCRPC include prior treatment with $\geq$1 line of ARPI therapy for castration-sensitive or -resistant prostate cancer for $\geq$12 weeks and with $\geq$1 line of chemotherapy (or not amenable to chemotherapy). These patients must also have $\geq$1 of the following criteria: prostate-specific antigen (PSA) progression per Prostate Cancer Working Group 3 (PCWG3) criteria, bone disease progression per PCWG3 criteria, or soft tissue disease progression per RECIST 1.1. Patients will receive DS9051 orally at escalating doses. The primary objective is to assess the safety and tolerability of DS9051 and to determine the maximum tolerated dose and/or recommended dose for expansion. Safety endpoints include dose-limiting toxicities and treatment-emergent adverse events. Secondary endpoints for both tumor types include objective response rate, disease control rate, clinical benefit rate, and duration of response (all assessed by the investigator, per RECIST 1.1 for ACC and per PCWG3 criteria for mCRPC); for ACC, progression-free survival (PFS) will be assessed by the investigator per RECIST 1.1, and for mCRPC, radiographic PFS and PSA decline will be assessed by the investigator per PCWG3 criteria. Enrollment is ongoing. Clinical trial information: NCT07189403. Research Sponsor: Daiichi Sankyo.

TPS3180 **Poster Session**

A phase 1, first-in-human, open-label, dose-escalation and -expansion study of gamitrinib, a first-in-class, mitochondria-directed inhibitor of the molecular chaperone heat shock protein-90 (Hsp90) in patients with advanced cancer. First Author: Anthony J. Olszanski, Fox Chase Cancer Center, Philadelphia, PA

Background: Mitochondria are subcellular organelles whose signaling and bioenergetics functions are exploited in cancer. This requires tight control of intra-organelle protein folding, which is made possible by the accumulation of molecular chaperones of the Heat Shock Protein-90 (Hsp90) family in mitochondria of tumors, but not normal tissues. This provides a unique therapeutic opportunity to disable multiple tumor pathways at once, but previously developed Hsp90 inhibitors do not accumulate in mitochondria, and systemic inhibition of chaperone activity is toxic in humans. Gamitrinib is a first-in-class anticancer agent specifically designed to disrupt protein folding in mitochondria, combining the Hsp90 inhibitory backbone of 17-allylamino-geldanamycin (17-AAG) to the mitochondria-targeting moiety, triphenylphosphonium. Gamitrinib selectively accumulates in mitochondria, does not affect the function of cytosolic Hsp90, and irreversibly disrupts organelle protein folding with activation of multiple cell death pathways. In preclinical studies, Gamitrinib shows potent, cytotoxic activity against multiple cancer cell types (IC_{50} 0.16–29 μM), inhibits primary and metastatic tumor growth in xenograft and genetic mouse models, has slower clearance (85.6 $\pm$ 5.8 mL/min/kg) and longer half-life (12.2 $\pm$ 1.55 h) than unconjugated 17-AAG, and is well-tolerated with no alterations in clinical-chemistry parameters, organ function, or tissue histology at dose levels of up to 5 (rats)- and 12 (dogs)-fold higher than therapeutically effective doses in mice (Cancer Biol Ther 23:117). **Methods:** Based on preclinical activity, favorable safety, and unique mechanism of anticancer activity, a first-in-human, open-label, dose-escalation phase 1 trial of Gamitrinib in sequential cohorts of adult patients with advanced solid tumors or lymphoma, for whom no standard therapy is available, was initiated (NCT04827810). Per study protocol, Gamitrinib is administered as a 1-h weekly intravenous (IV) injection on a 28 day-cycle with a 3+3 dose-escalation design and dosing continuing until disease progression, unacceptable toxicity, or patient discontinuation for any other reason. Trial objectives include determination of MTD and/or RP2D, overall safety, PK profile, correlative studies of target engagement in paired pre- and post-treatment biopsies in a 6-patient expansion cohort at MTD and documentation of anti-tumor activity by RECIST 1.1 and RECIL 2017 criteria. As of 2026, 18 evaluable patients have been accrued over 5 escalating Gamitrinib dose levels (10-85 mg) with no DLTs as assessed by NCI CTCAE v5.0 grading. 336 plasma samples have been collected for PK analysis. The study is currently open and enrollment is ongoing. Clinical trial information: NCT04827810. Research Sponsor: Gateway Foundation.

TPS3181 **Poster Session**

Phase Ib study of POLQ inhibitor SYN818 combined with olaparib in advanced solid tumors. First Author: Hongxia Wang, Fudan University Shanghai Cancer Center, Shanghai, China

Background: SYN818 is a selective, potent oral POLQ helicase inhibitor. POLQ is essential for microhomology-mediated end-joining and fills single-stranded DNA (ssDNA) gaps during replication. In tumors with homologous recombination repair (HRR) deficiencies (e.g., BRCA1/2 mutations), inhibition of PARP creates a dependency on POLQ for ssDNA gap filling, providing a synthetic lethal therapeutic strategy. Preclinically, SYN818 significantly enhanced the antitumor activity of Olaparib in breast and ovarian cancer models. Phase 1a monotherapy data demonstrate that SYN818 has a favorable pharmacokinetic profile and is well tolerated, supporting further evaluation of SYN818 in combination with Olaparib in HRR-deficient metastatic solid tumors. **Methods:** This phase 1b, open-label, multicenter study (NCT07156253; CTR20253189) evaluates SYN818 in combination with Olaparib in adults with locally advanced or metastatic solid tumors harboring BRCA mutations and/or homologous recombination repair (HRR) deficiency. During dose escalation (Part 1), patients receive escalating doses of SYN818 in combination with Olaparib (300 mg BID) administered in 21-day cycles to determine the recommended Phase 2 dose (RP2D), guided by a Bayesian dose-finding model. In the dose-expansion phase (Part 2), tumor-specific cohorts, including ovarian cancer and HER2-negative breast cancer, will further assess safety and preliminary antitumor activity at the RP2D. The primary objectives are to evaluate safety, tolerability, and determine the RP2D. Secondary objectives include characterization of pharmacokinetics, pharmacodynamics, and preliminary antitumor activity per RECIST v1.1. Key eligibility criteria include age $\geq$18 years, ECOG performance status 0–1, documented BRCA mutation and/or HRR deficiency, and adequate organ function. Prior PARP inhibitor therapy is permitted. Enrollment initiated in September 2025. Clinical trial information: NCT07156253. Research Sponsor: None.

TPS3182 **Poster Session**

IDE892 as monotherapy and in combination with IDE397 in patients with 5-methylthioadenosine phosphorylase-deleted (*MTAP*-Del) advanced solid tumors (IDE892001): Phase 1 trial. First Author: Benjamin Garmezy, Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN

Background: MTAP deletion in solid tumors causes intracellular accumulation of methylthioadenosine (MTA) which partially inhibits activity of the key methylating enzyme, protein arginine methyltransferase 5 (PRMT5) and creates synthetic lethal dependencies on PRMT5 and methionine adenosyltransferase 2A (MAT2A), the rate limiting step in the synthesis of PRMT5 substrate, S-adenosyl methionine. PRMT5 and MAT2A are essential to transcription modulation, gene splicing, and DNA damage response. IDE892 is an MTA-cooperative PRMT5 inhibitor designed to exploit this vulnerability in MTAPdel tumors. Preclinical studies report robust antitumor activity with IDE892 monotherapy in MTAPdel xenograft models and an enhanced response when combined with IDE397 (an allosteric MAT2A inhibitor). IDE892-001 is a Phase 1 study evaluating safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of IDE892 alone and in combination with IDE397. **Methods:** IDE892-001 is an ongoing, open-label, multicenter four-part study: IDE892 monotherapy dose escalation (Part 1), monotherapy dose expansion in MTAPdel NSCLC (Part 2), IDE892 + IDE397 dose escalation (Part 3), and combination expansion in MTAPdel NSCLC (Part 4). Adults with advanced or metastatic MTAPdel solid tumors including lung, urothelial, gastrointestinal cancers (including pancreatic and biliary tract cancers) and mesothelioma are eligible following disease progression on standard therapies. Key exclusion criteria include symptomatic brain metastases, cardiac disease, active severe infection, and prior treatment with a PRMT5 or MAT2A inhibitor. Part 1 uses a Bayesian optimal interval design to determine maximum tolerated dose (MTD) and recommended doses for expansion (RDE). Part 3 uses a modified toxicity probability interval design to evaluate escalating combinations of IDE892 and IDE397. Oral treatment is given QD in 21-day cycles until progression or unacceptable toxicity. Serial blood samples are collected for PD analyses. Imaging will be performed every 6 weeks through week 24, then every 9–12 weeks. Efficacy endpoints will be assessed by RECIST v1.1. Primary objectives for dose-escalation cohorts (Parts 1 and 3) are safety and tolerability, including determination of MTD/RDE. In expansion cohorts (Parts 2 and 4), co-primary objectives include safety and preliminary antitumor activity (objective response rate and duration of response). Secondary endpoints for all parts include PK of IDE892 alone and in combination with IDE397. Exploratory assessments include progression free survival, changes in circulating and tumor-based markers of PRMT5 pathway modulation, molecular predictors of response, exposure–response relationships, and metabolite characterization. Clinical trial information: NCT07277413. Research Sponsor: IDEAYA Biosciences.

TPS3183 **Poster Session**

Study design of OMAHA-015: A phase 2 basket study of steroidogenesis inhibitor opevesostat in participants with selected solid tumors. First Author: Virginia G. Kaklamani, University of Texas Health Science Center at San Antonio, San Antonio, TX

Background: Opevesostat (MK-5684; ODM-208), an oral steroidogenesis inhibitor, selectively inhibits CYP11A1, blocking synthesis of all steroid hormones and their precursors, and may suppress steroid-driven tumor growth. The randomized, open-label, phase 2 OMAHA-015 trial (NCT06979596) is designed to evaluate the efficacy and safety of opevesostat compared with standard of care in breast, ovarian, and endometrial cancers. **Methods:** Cohort A will enroll participants (pts) with locally advanced unresectable or metastatic hormone receptor–positive (estrogen receptor and/or progesterone receptor $\geq$1% expression)/HER2-negative breast cancer (IHC 0, 1+ or 2+/ISH-) and disease progression on or after $\geq$1 prior endocrine-based therapy in the metastatic setting. Exclusion criteria include any line of cytotoxic chemotherapy (chemo) or PARP inhibitor in the inoperable or noncurative advanced/metastatic setting and prior treatment with both fulvestrant and exemestane in the metastatic setting. Cohort B will enroll pts with platinum-sensitive, histologically confirmed high-grade epithelial ovarian (including high-grade serous or predominantly serous, high-grade endometrioid, clear cell, or malignant mixed Müllerian tumors [carcinosarcoma]), fallopian tube, or primary peritoneal carcinomas. Pts must have received 4-8 cycles of platinum-based doublet chemo in a third-line setting for ovarian cancer with $\leq$9 weeks between the last dose of third-line chemo and randomization. Cohort C will enroll pts with histologically confirmed primary advanced or recurrent low-grade endometrioid carcinoma (FIGO grade 1/2, or well/moderately differentiated), with known pMMR status, and wild type p53 expression. Pts must either be treatment naive or have received 1 prior line of platinum-based therapy in the advanced/metastatic or adjuvant/neoadjuvant setting. In cohort A, ~80 pts will be randomized 1:1 to arm 1: opevesostat 5 mg PO twice daily (BID) + daily corticosteroids or arm 2: physician's decision of fulvestrant 500 mg IM (D1 and D15 of cycle 1 and D1 of each cycle thereafter) or exemestane 25 mg PO daily. Randomization will be stratified by 1 line versus $\geq$2 lines of prior endocrine therapy. In cohort B, ~90 pts will be randomized 1:1 to arm 3: opevesostat 5 mg PO BID + daily corticosteroids; or arm 4: observation. In cohort C, ~80 pts will be randomized 1:1 to arm 5: opevesostat 5 mg PO BID + daily corticosteroids; or arm 6: physician's choice of megestrol acetate 80 mg PO BID, alternating megestrol + tamoxifen 20 mg PO BID, or letrozole 2.5 mg PO daily. The primary end point is progression-free survival per RECIST v1.1 assessed by blinded independent central review (BICR). Secondary end points include overall survival, clinical benefit rate (cohort A only), objective response rate, and duration of response per RECIST v1.1 assessed by BICR, and safety. The study is currently enrolling. Clinical trial information: NCT06979596. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS3184 **Poster Session**

STELLA: A dose expansion of the ATR kinase inhibitor alnodesertib (ART0380) administered orally in combination with low-dose irinotecan to patients with advanced or metastatic CRC and PDAC. First Author: Kim Anna Reiss, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Background: Replication stress (RS) creates cancer cell vulnerability to which the critical DNA damage response kinase, ATR (Ataxia-Telangiectasia and Rad3-related) responds. ATR senses the stress, halts the cell cycle, and promotes DNA repair to allow proliferation. Alnodesertib is an ATR inhibitor developed to prevent cancer cells from successfully repairing RS and proliferating further. In earlier stages of alnodesertib development, preclinical and translational research demonstrated that tumor cells experience three combined biological insults: irinotecan-induced RS, endogenous RS via ataxia-telangiectasia mutated (ATM) loss, and RS rescue prevention by ATR inhibition. Data from the dose escalation and initial dose expansion cohorts of this trial in a tumor agnostic population showed encouraging results in ATM-negative cancers (confirmed Overall Response Rate of 50% in 20 patients with ATM negative cancers and responses across 8 cancer types including complete responses, Ulahannan et al, AACR 2025). Tumor-specific dose expansion cohorts are now enrolling, including colorectal cancer (CRC) and pancreas ductal adenocarcinoma (PDAC). **Methods:** Two tumor-specific cohorts are now open, each enrolling approximately 50 patients (pts): ATM-negative CRC and ATM-negative PDAC. Pts will receive the recommended dose of alnodesertib 200mg orally on days 1-3 and 8-10 combined with low-dose irinotecan 60mg/m^2 IV on days 1 and 8, of each 21-day cycle. Tumor tissue is prescreened by immunohistochemistry for ATM protein loss (H score 0) for enrollment eligibility. Pts with CRC must have received a maximum of 2 prior chemotherapies excluding prior trifluridine/tipiracil, fruquintinib, or regorafenib, and pts with PDAC must have received a maximum of 1 prior chemotherapy for advanced disease. Prior targeted agents are allowed and do not count as prior lines of therapy. Key objectives include safety, tolerability, and preliminary efficacy. Clinical trial information: NCT04657068. Research Sponsor: Artios Pharma.

TPS3185 **Poster Session**

KANDLELIT-014: A phase 2 study of MK-1084 as monotherapy and in combination with cetuximab in *KRAS* G12C-mutant advanced solid tumors. First Author: Nehal J. Lakhani, START Center for Cancer Research, Grand Rapids, MI

Background: *KRAS* is one of the most frequently mutated oncogenes in human cancers, with the G12C mutant isoform accounting for ~15% of all *KRAS* mutations. Despite their promising antitumor activity and manageable safety profile in advanced solid tumors, first-generation KRAS G12C inhibitors are often limited by acquired resistance in the monotherapy setting. MK-1084 is a next-generation, highly potent and selective KRAS G12C–GDP covalent inhibitor that exerts downstream regulation of the MAPK pathway. EGFR-mediated reactivation of RAS-MAPK signaling is proposed as a key driver of resistance to KRAS G12C inhibitors, particularly in colorectal cancer (CRC). The combination of KRAS G12C inhibitors and EGFR-targeted monoclonal antibodies has demonstrated clinical benefit in *KRAS* G12C-mutated CRC and non-small cell lung cancer (NSCLC), supporting the potential of this mutation as a clinically-relevant target across tumor types. KANDLELIT-014 (NCT07209111) is a phase 2, randomized, open-label, multicenter, tumor-agnostic study of MK-1084 as monotherapy and in combination with EGFR inhibitor cetuximab in participants with previously treated advanced solid tumors harboring a *KRAS* G12C mutation. **Methods:** Eligible participants are aged ≥18 years with histological or blood-based *KRAS* G12C-mutated locally advanced unresectable or metastatic solid tumors (other than CRC) that have progressed on or following standard-of-care systemic treatment, or for whom no satisfactory alternative treatment options are available. Additional eligibility criteria include an ECOG PS score of 0 or 1 and measurable disease per RECIST v1.1. Participants were excluded if they had uncontrolled, significant cardiovascular or cerebrovascular diseases; an additional progressive active malignancy that required treatment within the past 3 years; or active CNS metastases, carcinomatous meningitis, or primary brain tumors. Participants will be randomly assigned 1:1 to receive MK-1084 100 mg orally once daily as monotherapy (Arm 1) or in combination with cetuximab 500 mg/m^2 intravenously every 2 weeks (Arm 2) until discontinuation criteria are met. Randomization will be stratified according to the following tumor groups: NSCLC, pancreatic ductal adenocarcinoma, endometrial cancer, biliary tract cancer, and other solid tumors. The primary end points are ORR per RECIST v1.1 as assessed by blinded independent central review (BICR), safety, and tolerability. Key secondary end points include OS, DOR per RECIST v1.1 by BICR, and PFS per RECIST v1.1 by BICR. Imaging will be performed every 6 weeks until Week 18, every 8 weeks until Week 50, and every 12 weeks thereafter until disease progression or discontinuation. AEs will be evaluated from randomization to 30 days after the last dose of study treatment per NCI CTCAE v5.0. This global study is actively enrolling. Clinical trial information: NCT07209111. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

LBA3500 **Oral Abstract Session**

Disease-free survival (DFS) and time to recurrence (TTR) with circulating tumor (ct) DNA–based decision for adjuvant treatment in colon cancer stage II (CIRCULATE): An AIO (KRK-0217)/ABCSG trial. First Author: Gunnar Folprecht, Technical University Dresden, Medical Faculty Carl Gustav Carus, NCT/UCC/Medical Department I, Dresden, Germany

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

3501 **Oral Abstract Session**

Informing optimal duration of adjuvant chemotherapy (ACT) in resected stage I-IV colorectal cancer (CRC) based on early circulating tumor DNA (ctDNA) dynamics. First Author: Hiroyuki Yamamoto, Teine Keijinkai Hospital, Sapporo, Japan

Background: While ACT is recommended by clinical guidelines for patients (pts) with high-risk stage II and stage III CRC, individual benefit varies significantly and appropriate ACT duration is debatable. Here, we evaluated whether on-ACT ctDNA dynamics can inform recurrence risk and benefit from continued ACT beyond 3 months (mo) in resected stage I-IV CRC. **Methods:** This analysis included 1,028 pts from the CIRCULATE-Japan GALAXY observational study who received ACT but no neoadjuvant chemotherapy, with >2 ctDNA results available within 6 mo post-surgery. Patients were divided into long-ACT (>3 mo, N = 651) and short-ACT cohort (< 3 mo, N = 377) cohorts. ctDNA was analyzed using a personalized, tumor-informed Signatera assay at two timepoints: a) pre-ACT (≥14 days post-surgery, before ACT), and b) post-3 mo from ACT (short cohort) or 3 mo ±45 days from ACT (long cohort). Disease-free survival (DFS) was measured from the date of surgery and compared between pts who received long vs short ACT, stratified by ctDNA dynamics. Subanalyses comparing ACT duration were landmarked at the second ctDNA timepoint. **Results:** Of the 1,028 pts (< 1%/17%/75%/7% stages I/II/III/IV), 44% were females; 81% had colon cancer and 19% rectal cancer. Median pt age was 66 (24-89) years. Median follow-up was 30.7 (4.9-55.8) mo. Median ACT duration was 5.7 mo in long-ACT and 2.5 mo in short-ACT cohorts. Pre-ACT sampling was a median of 14 and 20 days before ACT start for long- and short-ACT cohorts, respectively; post-3 mo sampling was a median of 112 days after ACT start for both cohorts. ctDNA dynamics from the pre-ACT to post-3 mo ACT timepoints revealed sustained negativity in 78.7% (N = 809) of pts, ctDNA clearance in 14.7% (N = 151), decreasing but detectable levels in 2.7% (N = 28), rising levels in 2.8% (N = 29), and newly detectable ctDNA on ACT in 1.1% (N = 11). No benefit of short vs long ACT duration was observed among pts with sustained ctDNA negativity (HR 0.71, p = 0.11) or ctDNA clearance (HR 1.06, p = 0.84). Similarly, pts with rising ctDNA experienced no benefit from longer ACT (HR 1.82, p = 0.18). Conversely, within the decreasing but detectable ctDNA subgroup, longer ACT was associated with improved DFS compared with short ACT median DFS 5.9 vs 1.7 mo; HR 3.64, p = 0.012), acknowledging that the analysis was limited by small cohort size and requires further investigation. **Conclusions:** ctDNA dynamics during ACT provide clinically meaningful stratification of recurrence risk and reveal heterogeneity in treatment benefit. Pts with ctDNA clearance or sustained negativity showed durable disease control and may not require longer ACT. Conversely, pts with partial molecular response showed directional benefit from longer ACT. Pts with molecular progression on ACT did not benefit from extended ACT, indicative of chemotherapy refractory disease and the need for alternative treatment regimens. Clinical trial information: R000044197. Research Sponsor: None.

3502 **Oral Abstract Session**

Observation versus maintenance PD-1 inhibitor therapy after clinical complete response in dMMR/MSI-H colorectal cancer managed with non-operative management: A multicentre cohort study. First Author: Xiaohang Gao, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Patients with mismatch repair–deficient (dMMR)/microsatellite instability–high (MSI-H) colorectal cancer (CRC) who achieve a clinical complete response (cCR) after PD-1 inhibitor therapy may undergo non-operative management (NOM) with active surveillance. We aimed to assess the necessity of maintenance immunotherapy after achieving cCR, with a focus on survival outcomes and the burden of immune-related toxicity. **Methods:** A multicentre observational cohort study was conducted at five tertiary hospitals in China between Jan 1, 2018, and March 21, 2025. Patients with dMMR/MSI-H CRC who achieved cCR after PD-1 inhibitor therapy and entered NOM were included. Patients were stratified into an observation group (discontinue PD-1 inhibitor after cCR) and a maintenance group (received ≥2 cycles of PD-1 inhibitors after cCR). Disease-free and overall survival were compared between groups using Kaplan–Meier methods with log-rank test, and local regrowth, distant metastasis, and immune-related adverse events were assessed. **Results:** Among 318 patients treated with PD-1 inhibitors, 195 (61·3%) achieved cCR. A total of 129 patients were analysed (observation n = 66; maintenance n = 63), including 58 with rectal cancer, 61 with colon cancer, and 10 with synchronous dual primary tumours; 14 had distant metastases at diagnosis. Clinical complete response was assessed with endoscopy and pelvic MRI/CT along with digital rectal examination for rectal cancer, and endoscopy with contrast-enhanced CT or PET/CT for colon cancer. Median PD-1 inhibitor exposure to achieve cCR was eight cycles in both groups; 69·8% achieved cCR within eight cycles. Median follow-up was 3·2 years (IQR 2·0–4·0). Local regrowth occurred in two patients in the observation group and none in the maintenance group, and no distant metastases were observed. The 3-year DFS was 96·4% (95% CI 91·6–100·0) in the observation group and 98·4% (95% CI 95·2–100·0) in the maintenance group (log-rank p = 0·55). The 3-year OS was 100·0% (95% CI 100·0–100·0) versus 98·4% (95% CI 95·2–100·0) (p = 0·34). Any-grade irAEs occurred in 42/66 (63·6%) versus 44/63 (69·8%); grade 3 irAEs were numerically higher with maintenance (7/63 [11·1%] vs 2/66 [3·0%]; p = 0·091). **Conclusions:** To our knowledge, this is the largest series of dMMR/MSI-H CRC patients achieving cCR after PD-1 inhibitor therapy and managed with NOM. Maintenance therapy after cCR did not provide a clear survival advantage but was associated with a higher burden of immune-related toxicity, supporting treatment discontinuation with close surveillance. Research Sponsor: None.

LBA3503 **Oral Abstract Session**

BREAKWATER: Progression-free and overall survival analyses of first-line (1L) encorafenib + cetuximab (EC) + FOLFIRI in BRAF V600E-mutant metastatic colorectal cancer (mCRC). First Author: Scott Kopetz, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

3504 Oral Abstract Session

SWOG S2107: Randomized phase II trial of encorafenib and cetuximab with or without nivolumab for patients with previously treated MSS, *BRAF*^{V600E} metastatic colorectal cancer (mCRC). First Author: Van K. Morris II, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *BRAF*^{V600E} mutations are associated with poor survival yet increased immune activation among patients (pts) with microsatellite stable (MSS) mCRC. A prior single-institution trial of the BRAF inhibitor encorafenib (E) with the anti-EGFR antibody cetuximab (C) and the anti-PD-1 antibody nivolumab (N) reported an overall response rate (ORR) of 50% and median progression-free survival (PFS) of 7.2 months in pts with MSS, *BRAF*^{V600E} mCRC, promising findings relative to historical controls with E+C. **Methods:** In this phase II SWOG/NCTN study (NCT05308446), pts with previously treated, MSS *BRAF*^{V600E} mCRC were randomized 2:1 to receive E (300 mg PO daily) + C (500 mg/m^2 IV every 2 weeks) + N (480 mg IV every 4 weeks) vs E+C only. No prior exposure to BRAF, EGFR, or immune checkpoint therapies were allowed. The primary endpoint was PFS and targeted a hazard ratio (HR) of 0.57 with a 1-sided α=0.10 and 80% power. Randomization was stratified by prior lines of therapy (1 vs 2) and Zubrod PS (0 vs 1). Treatment response was assessed every 8 weeks radiographically (RECIST 1.1). Secondary endpoints were overall survival (OS), ORR, and treatment-related adverse events (TRAE) according to CTCAE v5. Differences in PFS by treatment arm were assessed via stratified log-rank test. **Results:** Of 88 pts enrolled, 85 were eligible and evaluable (57 E+C+N, 28 E+C). Participant characteristics are listed in Table. Median PFS was 5.8 months (95% CI 4.0-7.8) with E+C+N and 6.3 months (95% CI 5.0-11.4; p=0.64) with E+C; HR 1.10 (95% CI 0.65-1.86). ORR was 35% for E+C+N and 32% for E+C. OS was similar between E+C+N and E+C: median 13.5 months (95% CI 11.0-18.9) vs. 11.6 months (95% CI 9.2-15.6; p=0.29); HR 0.85 (95% CI 0.47-1.52). 31 out of 57 pts (54%) had grade 3-4 TRAEs for E+C+N, vs 10 out of 28 (36%; p=0.11) for E+C; Grade 3 TRAEs occurring in >10% pts treated with E+C+N included fatigue (14%) and arthralgia (11%). **Conclusions:** The addition of N to E+C did not improve survival outcomes in this study population of pts with pretreated MSS, *BRAF*^{V600E} mCRC. Ongoing correlative studies seek to identify biomarkers associated with treatment benefit that may be applied to future efforts seeking to personalize treatment approaches for this biologically heterogeneous population. Clinical trial information: NCT05308446. Research Sponsor: NIH/NCI/NCTN; U10CA180888; NIH/NCI/NCTN; U10CA180819; Bristol-Myers Squibb.

Patient demographics.

	E+C+N (N=57)	E+C (N=28)
AGE		
Median	64.3	66.1
SEX (%)		
Male	27 (47)	19 (68)
Females	30 (53)	9 (32)
PRIOR LINES SYSTEMIC THERAPY (%)		
1	40 (70)	18 (64)
2	17 (30)	10 (36)
PERFORMANCE STATUS (%)		
0	32 (56)	16 (57)
1	25 (44)	12 (43)

3505 Oral Abstract Session

Phase 3 trial of trastuzumab rezetecan vs standard of care (SOC) for chemotherapy-refractory, HER2-positive, advanced colorectal cancer (CRC). First Author: Jin Li, Shanghai GoBroad Cancer Hospital, China Pharmaceutical University, Shanghai, China

Background: Antibody-drug conjugate (ADC) targeting HER2 represents standard therapy for HER2-positive gastric cancer and breast cancer. This study aimed to assess trastuzumab rezetecan (an HER2-targeted ADC) vs SOC in patients (pts) with chemotherapy-refractory, HER2-positive, RAS and RAF wild-type advanced CRC. **Methods:** In this randomized, open-label, multicenter, phase 3 trial, pts with HER2-positive, RAS and RAF wild-type, advanced CRC who have progressed after standard 2nd-line therapy were randomized 2:1 to receive trastuzumab rezetecan (4.8 mg/kg, d1, iv, q3w) or SOC (TAS-102 [35 mg/m^2, bid, d1-5 and d8-12], fruquintinib [5 mg, qd, d1-21], or regorafenib [160 mg, qd, d1-21]; po, q4w). Randomization was stratified by HER2 status (IHC 3+ vs IHC 2+/ISH+) and ECOG PS (0 vs 1). Primary endpoint was PFS per RECIST v1.1 by independent review committee (IRC). Key secondary endpoint was OS. **Results:** As of data cutoff (Oct 31, 2025), 130 pts were randomly assigned to trastuzumab rezetecan (N=86) or SOC (N=44). 70.8% of pts had HER2 IHC 3+, and 57.7% had an ECOG PS of 1. Median follow-up was 9.6 mo (95% CI 7.4-10.7). PFS per IRC was significantly increased with trastuzumab rezetecan vs SOC (median 5.5 mo [95% CI 4.8-6.7] vs 2.8 mo [95% CI 2.2-4.2]; HR 0.33 [95% CI 0.21-0.53]; 1-sided p<0.0001). Although median OS were immature, risk of death with trastuzumab rezetecan was reduced by 23% compared with SOC (HR 0.77 [95% CI 0.35-1.73]). PFS per investigator, ORR and DoR were also better with trastuzumab rezetecan vs SOC (Table 1). Grade ≥3 TRAEs occurred in 48.8% with trastuzumab rezetecan and 50.0% with SOC. No patients discontinued treatment due to TRAEs. Treatment-related death was reported in two pts (2.3%) with trastuzumab rezetecan (septic shock and myelosuppression). **Conclusions:** Compared with SOC, trastuzumab rezetecan achieved prolonged PFS and improved ORR in chemotherapy-refractory HER2-positive advanced CRC, with a tolerable safety profile. Clinical trial information: NCT06199973. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy.

	Trastuzumab rezetecan (N=86)	SOC (N=44)	Treatment effect (95% CI)	1-sided p value
IRC-assessed PFS, mo	5.5 (4.8-6.7)	2.8 (2.2-4.2)	HR, 0.33 (0.21 0.53)	<0.0001*
Investigator-assessed PFS, mo	5.6 (5.0-6.8)	2.8 (1.5-4.1)	HR, 0.31 (0.20-0.50)	<0.0001*
OS, mo	NR (14.6-NR)	NR (12.5-NR)	HR, 0.77 (0.35-1.73)	0.2651*
IRC-assessed ORR	35 (40.7; 30.2-51.8)	2 (4.5; 0.6-15.5)	RD, 36.2 (24.1-48.2)	<0.0001†
Investigator-assessed ORR	28 (32.6; 22.8-43.5)	2 (4.5; 0.6-15.5)	RD, 28.0 (16.4-39.7)	0.0002†
IRC-assessed DoR, mo	4.4 (3.3-NR)	3.4 (2.7-NR)	-	-
Investigator-assessed DoR, mo	5.8 (4.2-NR)	1.4 (NR-NR)	-	-

Data are median (95% CI), or n (%; 95% CI), unless otherwise stated.
*Stratified log-rank test.
†Stratified Cochran-Mantel-Haenszel test. NR, not reached; RD, rate difference.

LBA3506 Oral Abstract Session

Adjuvant hepatic arterial infusion pump chemotherapy with floxuridine for patients with resectable colorectal liver metastases and a low clinical risk score: A randomized controlled trial—The PUMP trial. First Author: Loubna Outmani, Erasmus MC, Rotterdam, Netherlands

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

3507 Oral Abstract Session

Structured exercise program following adjuvant chemotherapy for colon cancer: A cost-utility analysis of the CHALLENGE trial. First Author: Kelvin K. Chan, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: The phase III CHALLENGE trial (CCTG CO.21) demonstrated improved disease-free and overall survival with a 3-year structured exercise program (SEP) compared with health education materials (HEM) in participants with stage III or high-risk stage II colon cancer that had undergone surgery and adjuvant chemotherapy. This study evaluated the cost-effectiveness of SEP versus HEM. **Methods:** A pre-specified economic evaluation was conducted using prospectively collected data from all trial participants (n = 889). The base case adopted the Canadian public healthcare payer perspective and included direct healthcare costs (cost categories available in Table 1), a 5-year time horizon, and a 1.5% discount rate. SF-36 trial data were mapped to SF-6D using a validated algorithm to calculate health utilities. Costs (2024 CAD) and effects measured as life-years (LYs) and quality-adjusted life-years (QALYs) were used to estimate an incremental cost-effectiveness ratio (ICER, $/life year gain (LYG)) and incremental cost-utility ratio (ICUR, $/QALY). Uncertainty was assessed via bootstrapping (n = 1,000). Notable scenario analyses included a 10-year horizon and a societal perspective capturing indirect costs from wages lost due to missed work, measured using a Work Productivity and Activity Impairment questionnaire. **Results:** In the base case, despite the up-front $4327 cost of the SEP intervention, the SEP was dominant over HEM (i.e less costly (−$179) and more effective (+0.06 LYs; +0.10 QALYs)). The SEP was dominant in 49% of bootstrap samples, while 79% met a $50,000 per QALY willingness-to-pay threshold. Major cost drivers in both groups were the costs of recurrence or new malignancy and anticancer therapy. Scenario analysis results were consistent with the base case analysis. The SEP remained dominant with a 10-year time horizon yielding greater cost savings ($-2,528) and more LYG (0.35) than the base case. From a societal perspective, the ICUR was $3,571/QALY, a highly cost-effective strategy. **Conclusions:** The SEP was less costly and more effective when compared with HEM. These data can inform health systems and payers as they look to implement SEP in routine models of care. Research Sponsor: None.

Mean per participant costs, effects, and ICER/ ICUR for the base case analysis.

	SEP (n=445)	HEM (n=444)	Increment
Cost of SEP sessions (including fixed start-up costs) ($)	4,327	0	4,327
Cost of hospitalization (pre- or without recurrence) ($)	3,593	3,092	501
Cost of recurrence or new malignancy (physicians, lab tests, drugs, hospitalizations, surgery, emergency room visits, home care)($)	12,732	15,772	-3,040
Cost of anticancer therapy ($)	12,660	14,582	-1,922
Cost of end-of-life care ($)	54	100	-46
Total cost ($)	33,367	33,546	-179
Total LYs	4.72	4.66	0.06
Total QALYs	3.84	3.75	0.09
ICER ($/LYG) and ICUR ($/QALY)	Dominant*		

*SEP is less costly and more effective than HEM.

LBA3508 **Oral Abstract Session**

Adjuvant aspirin for stage III colorectal cancer after curative resection: Primary analysis of the randomized double-blind placebo-controlled phase III trial (EPISODE-III: JCOG1503C). First Author: Atsuo Takashima, National Cancer Center Hospital, Chuo-Ku, Tokyo, Japan

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA3509 **Rapid Oral Abstract Session**

A phase III, randomized, open-label study of tunlametinib plus vemurafenib versus investigator's choice of therapy in patients with previously treated *BRAF*^{V600E}-mutant metastatic colorectal cancer. First Author: Ting Xu, Department of GI Oncology, Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

3510 **Rapid Oral Abstract Session**

Onvansertib plus standard-of-care chemotherapy plus bevacizumab in first-line RAS-mutated metastatic colorectal cancer (mCRC): Interim results from the phase 2 randomized CRDF-004 trial. First Author: Heinz-Josef Lenz, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Patients with RAS-mutated mCRC have limited treatment options. Chemotherapy in combination with bevacizumab (Bev) has been the standard first-line treatment for the past two decades, yet the prognosis for these patients remains poor. Onvansertib (Onv), a selective PLK1 inhibitor, has previously demonstrated synergy with chemotherapy in the second line setting. The Phase 2 randomized CRDF-004 trial evaluated onvansertib plus standard-of-care (SoC; FOLFIRI or FOLFOX with Bev) in as first-line RAS-mutated mCRC. **Methods:** Patients with first-line KRAS or NRAS mutant mCRC were randomized to SoC alone or SoC plus onvansertib (20 mg or 30 mg). The primary endpoint was objective response rate (ORR) as determined by a blinded-independent central review (BICR) using RECIST v1.1. Key secondary endpoints included progression-free survival (PFS), duration of response, and safety. PFS was assessed by BICR and investigator assessments combined. Results are presented in the intent-to-treat population (ITT). **Results:** At the data cutoff of 22 Jan 2026,110 patients were randomized with a median follow up of approximately 10 months. Baseline characteristics were relatively balanced across arms. Onv 30 mg + FOLFIRI + Bev demonstrated numerically higher ORR (n = 13/18, 72.2%, 95% CI: 46.5, 90.3) compared with the FOLFIRI + Bev control arm (n = 8/19, 42.1%, 95% CI: 20.3, 66.5), the FOLFOX + Bev control arm (n = 8/18, 44.4%, 95% CI: 21.5, 69.2) and the combined control arms (SoC: n = 16/37, 43.2%, 95% CI: 27.1-60.5). Onv 30mg + FOLFIRI + Bev demonstrated a p-value of 0.051 for confirmed ORR vs. SoC; and a p-value of 0.045 for the 6-month ORR compared to FOLFIRI + Bev (n = 10/18, 55.6%, 95% CI: 30.8-78.5 vs. n = 4/19, 21.1%, 95% CI: 6.1-45.6, respectively). The median PFS for the control arms was 10.97 months (95% CI: 7.52, NR) for FOLFIRI + Bev, 9.89 months (95% CI: 9.43, NR) for FOLFOX + Bev and 10.97 months (95% CI: 9.43-15.44) for the combined SoC arms. The median PFS in the Onv 30mg+ FOLFIRI + Bev arm was not reached (95% CI: 9.72-NR). The PFS HR of 30mg + Onv +FOLFIRI + Bev vs FOLFIRI + Bev was 0.38 (95% CI: 0.12-1.17) and vs SoC was 0.37 (95% CI: 0.13-1.02, p = 0.048). The clinical benefit from Onv treatment was further evidenced by the 12-month PFS rates, 61.9% (95% CI: 40.1, 95.8) in the Onv 30 mg + FOLFIRI + Bev arm vs. 28.4% (95% CI: 9.3, 86.9) in the FOLFIRI + Bev arm, and 30.1% (95% CI: 13.8-65.7) in the SoC. Onvansertib was well tolerated, with no unexpected toxicities observed; the most common grade ≥3 adverse event was neutropenia. PK data support moving forward with the onvansertib 30mg dose with FOLFIRI + Bev. **Conclusions:** Onvansertib plus FOLFIRI and bevacizumab demonstrated improved antitumor activity and manageable safety in first-line RAS-mutated mCRC. These results support further clinical and support planned confirmatory Phase 3 evaluation. Clinical trial information: NCT06106308. Research Sponsor: Cardiff Oncology.

3511 **Rapid Oral Abstract Session**

Circulating tumor DNA (ctDNA) clearance as an early indicator of sotorasib + panitumumab efficacy and prognosis in *KRAS* G12C–mutated colorectal cancer (mCRC): Results from phase 3 CodeBreaK 300. First Author: Filippo Pietrantonio, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Phase 3 CodeBreaK 300 (NCT05198934) explored two doses of sotorasib (soto) (240 mg and 960 mg) in combination with panitumumab (pani) 6 mg/kg versus investigator's choice (IC) and demonstrated superior progression-free survival (PFS) with soto 960 mg+pani versus IC in chemorefractory *KRAS* G12C-mutant mCRC. We evaluated whether early ctDNA clearance could serve as non-invasive biomarker of treatment (tx) response using one of the largest cohorts of mCRC patients (pts) treated with a KRAS^{G12C} inhibitor plus an EGFR antibody and the only longitudinal ctDNA dataset from a KRAS^{G12C} inhibitor trial in mCRC. **Methods:** ctDNA analyzed using the Guardant Infinity assay was quantified using *KRAS* G12C variant allele frequency (VAF) and methylation-based circulating tumor fraction (cTF) metrics. Clearance was defined at ≥50%, ≥80%, ≥90% and 100% reduction thresholds. Associations with objective response rate (ORR), PFS, and overall survival (OS) were assessed using logistic regression, Fisher-exact tests, Cox proportional hazards models, and Kaplan–Meier methods. **Results:** A total of 142 pts had evaluable baseline and Cycle 2 Day 1 ctDNA results. Early ctDNA clearance was more frequent in the soto arms than in the IC arm. This finding was consistent across ctDNA assessment methods, with high concordance between VAF and cTF. At ≥80% threshold, VAF clearance rates (95% CI) were 77.3% (62.2–88.5) and 65.9% (50.1–79.5) in the soto 960 mg and 240 mg arms (each N=44), respectively, compared with 15% (5.7–29.8) in the IC arm (N=40). Complete (100%) VAF clearance (95% CI) was observed in 45.5% (30.4–61.2), 31.8% (18.6–47.6), and 5.0% (0.6–16.9) of pts in the 960 mg, 240 mg, and IC arms, respectively. Reductions in ctDNA were correlated with radiographic tumor shrinkage. Lack of ctDNA clearance was associated with non-response, whereas pts achieving clearance were more likely to respond. Among pts treated with soto 960 mg who achieved ≥80% ctDNA clearance, the ORR (95% CI) by VAF was 35.3% (12/34; 19.7–53.5) and 32.3% (10/31; 16.7–51.4) by cTF. Decline in ctDNA was associated with improved PFS and OS independent of tx arm, confirming the role of ctDNA as a prognostic marker. Increasing clearance stringency did not enhance prognostic value. **Conclusions:** Early ctDNA clearance, assessed by *KRAS* G12C VAF or cTF, is prognostic for improved outcomes, supporting its utility as an early response biomarker. Clinical trial information: NCT05198934. Research Sponsor: Amgen Inc.

Survival (months) by VAF clearance (≥80%).

Cohort	VAF Clearance	N	mPFS (95% CI)	mOS (95% CI)
IC	N	34	2.0 (1.9–4)	10.3 (6.6–14)
IC	Y	6	8.4 (3.7–NE)	NE
Soto 240	N	15	2.6 (1.8–3.8)	5.1 (3.2–7.5)
Soto 240	Y	29	5.6 (3.8–8.5)	14.0 (8.4–NE)
Soto 960	N	10	1.9 (1.6–3.8)	4.9 (1.6–7)
Soto 960	Y	34	5.8 (5–7.5)	NE (10.8–NE)

m, median; NE, not evaluable; N, no; Y, yes.

3512 Rapid Oral Abstract Session

Phase III CR-SEQUENCE trial of FOLFOX+panitumumab followed by FOLFIRI+bevacizumab (SEQ1) versus FOLFOX + bevacizumab followed by FOLFIRI + panitumumab (SEQ2) in previously untreated RAS wild-type, left-sided, unresectable metastatic colorectal cancer. First Author: Ramon Salazar, Medical Oncology Department, Institut Català d'Oncologia (ICO), L´Hospitalet De Llobregat, Barcelona, Spain

Background: The optimal sequencing of systemic therapy for patients with RAS wild-type, left-sided metastatic colorectal cancer (mCRC) remains under debate. This study evaluates whether starting with SEQ1 improves the 36-months progression-free survival rate (PFSR) versus SEQ2. **Methods:** Adult patients were randomized (1:1) to SEQ1 or SEQ2 and treated until second-line progression or unacceptable toxicity. Key inclusion criteria were untreated left-sided and wild type RAS (per local test) primary mCRC, ECOG-PS$<$2, measurable disease (RECIST 1.1), and adequate organ function. Primary endpoint was 36-month PFSR in ITT. Secondary endpoints included overall survival (OS), total PFS, objective response rate (ORR), PFS1, PFS2, and safety. **Results:** A total of 418 patients were analyzed (SEQ1=210; SEQ2=208); 54.76% and 70.19% of randomized patients received 2L treatment in SEQ1 and SEQ2 arms, respectively. The median follow-up was 62.2 months (95%CI 55.2 – 65.5). SEQ1 yielded a higher 1st-line ORR (80.95% vs 64.25%, p $<$0.01) and significantly improved median PFS1 (14.09 vs 12.39 months, p=0.03). In second line, SEQ2 (FOLFIRI + panitumumab) resulted in a higher ORR (40.43% vs 27.27%, p=0.03). There was no significant difference in 36-months PFS rate (28.57% vs. 22.36%; p=0.224). Median total PFS and OS were 22.93 vs 21.39 months (p=0.2241) and 36.57 vs 31.74 months (p=0.2949), respectively. Longer follow-up for PFS and OS is ongoing. Curative intent procedures were performed in 22.86% (SEQ1) and 19.23% (SEQ2) of patients, respectively. Rescue surgery improved PFS and OS across both sequences. Common related G3-4 adverse events included neutropenia (42%), rash (15.7%), diarrhea (13%), peripheral neuropathy (12%), and fatigue (12.3%). **Conclusions:** SEQ1 did not improve the 36-month PFSR versus SEQ2. However, starting with SEQ1 yielded superior early efficacy (higher ORR and longer PFS1), which may be clinically relevant in a subset of patients. Molecular profiling and genomic correlation analyses are ongoing to identify biologically defined clusters that may improve selection of sequential treatment strategies. Longer follow-up for clinically relevant secondary endpoints (total PFS and OS) is ongoing. Clinical trial information: 2024-510967-41-00. Research Sponsor: AMGEN.

Baseline characteristic by treatment arm.

Characteristic		SEQ 1 (n=210)	SEQ 2 (n=208)
Age, median (IQR*), years		63 (57-71)	63 (57-71)
Sex, n (%)	Female	53 (25.2)	58(27.9)
	Male	157(74.8)	150 (72.1)
ECOG-PS, n (%)	0	112 (53.3)	118 (56.7)
	1	98 (46.7)	90 (43.3)
Metastasis per organ, median (range)		2 (1-6)	2(1-7)
Baseline CEA, median (IQR), ng/mL		40.7 (11.6 – 364.3)	74.5 (11.8 – 643.9)
Prior therapies	Adjuvant chemo	27 (12.9)	24 (11.5)
	Radiation	23 (10.9)	18 (8.6)
	Primary tumor resection	56 (26.7)	72 (34.6)

*IQR: interquartile range.

3513 Rapid Oral Abstract Session

Development of a computational histology artificial intelligence (CHAI)–powered predictive biomarker for first-line chemotherapy intensification in metastatic colorectal cancer (mCRC) and validation in prospective randomized phase III trials (RCT). First Author: Paolo Ciracì, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: In unresectable mCRC, meta-analysis of RCTs suggests triplet therapy consisting of fluorouracil, oxaliplatin, and irinotecan (FOLFOXIRI) + bevacizumab (bev) may improve survival outcomes over doublet regimens of fluorouracil with irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) + bev, at the expense of increased toxicity. Adoption of triplet therapy remains low. A histology-based biomarker to predict outcomes in mCRC treated with triplet vs doublet regimens could optimize treatment selection. We aimed to use the previously described CHAI platform to develop and validate a histology-based predictive biomarker for doublet vs triplet therapy in mCRC with participant-level data from 3 RCTs. **Methods:** Development used diagnostic H&E-stained whole slide images (WSI) from participants with mCRC treated with first-line (1L) chemotherapy enrolled in the MRC FOCUS RCT. WSIs were analyzed using the CHAI assay and trained towards clinical outcomes as a function of chemotherapy escalation. Weighting of histologic features was optimized for association with progression-free (PFS) & overall survival (OS) to construct a signature that was combined with tumor sidedness to create the mCRCpred biomarker. A cutpoint was selected to optimize treatment effect stratification, assigning each case a binary label. The locked biomarker was evaluated on the independent validation cohort of WSIs from the TRIBE + TRIBE2 RCTs. The association of the biomarker-treatment interaction with PFS & OS was evaluated with multivariable (MVA) Cox models & Likelihood Ratio tests. **Results:** The development cohort included 294 cases from MRC FOCUS. The independent validation cohort (n = 386) comprised cases from TRIBE (n = 159) and TRIBE2 (n = 227). 193 (50%) had 1L triplet+bev and 193 (50%) doublet+bev. Biomarker (+) (indicative of triplet benefit) disease treated with triplet+bev had superior 3-year PFS (17% vs 7%, HR = 0.51 [0.37, 0.70], p $<$ 0.001) and OS (43% vs 22%, HR = 0.51 [0.35, 0.73], p $<$ 0.001) versus doublet+bev. Biomarker (-) cases treated with triplet+bev vs doublet+bev had no significant differences in PFS (5 vs 15%, HR = 1.30 [0.96, 1.74], p = 0.09) or OS (31 vs 40%, HR = 1.35 [0.94, 1.92], p = 0.1). In MVA including cohort, age, ECOG, number of metastatic sites, and timing of metastasis (metachronous/synchronous), the biomarker-treatment interaction was significant (p $<$ 0.001) indicating a predictive association between the biomarker and treatment regimen. **Conclusions:** The CHAI mCRCpred histology-based biomarker predicted differential benefit of chemotherapy escalation (doublet-bev vs triplet-bev) as 1L therapy in mCRC, with independent validation post-hoc in two RCTs (Simons Level of Evidence IB). This biomarker may guide optimal treatment selection for 1L mCRC. Clinical trial information: ISRCTN79877428 (FOCUS); NCT00719797 (TRIBE); NCT02339116 (TRIBE2). Research Sponsor: None.

3514 Rapid Oral Abstract Session

Phase I study of intraperitoneal fast-manufactured IL-9-secreting CEACAM5-targeted CAR-T cells in advanced colorectal cancer with peritoneal metastases. First Author: Hangyu Zhang, Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Colorectal cancer peritoneal metastasis (CRPM) remains an unmet clinical need with poor prognosis and limited benefit from systemic therapies. Our prior study on intraperitoneal (I.P.) CEA-targeting CAR-T cells (Nature Cancer) achieved a 25% ORR, yet limited persistence and exhaustion hampered efficacy. Consequently, we developed a novel Th9/Tc9-polarized fast- manufacturing process that exhibited superior T-cell fitness and antitumor function preclinically. We therefore conducted a Phase I study to evaluate the safety and preliminary efficacy of I.P. administration of these optimized CAR-T cells in CRPM population. **Methods:** This open-label, single-arm Phase I study enrolled patients with histologically confirmed, heavily pretreated CEA-positive CRPM. A standard 3+3 dose-escalation design evaluated three dose levels (DLs): DL1 (2.0×10^5 cells/kg), DL2 (3.0×10^5 cells/kg), and DL3 (4.0×10^5 cells/kg), followed by dose expansion. Primary objectives were safety and tolerability; secondary objectives included preliminary antitumor activity, cellular kinetics, and pharmacodynamics. **Results:** Between July 2024 and October 2025, 15 patients were enrolled; 14 were evaluable for efficacy. One dose-limiting toxicity (DLT; Grade 4 pneumonia) occurred at DL2. The most common grade 3 non-hematologic toxicity was diarrhea (53.3%). Cytokine release syndrome (CRS) occurred in all patients and was Grade 1/2 in 93.3%. No treatment-related deaths were reported. Among 14 efficacy-evaluable patients (median 3 prior lines of therapy), ORR was 57.1% and DCR was 100%, with maximum tumor shrinkage reaching 85.6%. Median PFS was 4.7 months (95% CI, 3.7–NE). Peripheral blood CAR- T cells expanded to a mean peak of 1.74×10^4copies/μg, and serum CEA levels decreased in 100% of patients (median reduction: 67.5%). **Conclusions:** Intraperitoneal administration of fast-manufactured Th9/Tc9 like CEACAM5-targeted CAR-T cells demonstrated a manageable safety profile and encouraging antitumor activity in heavily pretreated CRPM patients, at approximately one-tenth of conventionally reported CAR-T cell doses. These findings support further development of fitness-enhanced, regionally delivered CAR-T strategies for peritoneal malignancies. Clinical trial information: NCT05396300. Research Sponsor: None.

Variable	DL1 (n=3)	DL2 (n=5)	DL3 (n=6)	Total (n=14)
PR, n (%)	1 (33.3)	4 (80.0)	3 (50.0)	8 (57.1)
SD, n (%)	2 (66.7)	1 (20.0)	3 (50.0)	6 (42.9)
ORR, n (%)	1 (33.3)	4 (80.0)	3 (50.0)	8 (57.1)
DCR, n (%)	3 (100.0)	5 (100.0)	6 (100.0)	14 (100.0)
Median PFS, months	5.6 [3.8–NE]	3.4 [3.2–NE]	NA	4.7 [3.4–NE]

3516 Rapid Oral Abstract Session

Real-world outcomes and circulating tumor DNA (ctDNA) dynamics in patients (pts) with microsatellite instability–high (MSI-H) metastatic colorectal cancer (CRC) treated with immune checkpoint inhibitors (ICI). First Author: Hannah Ruth Robinson, Division of Medical Oncology, Department of Medicine, University of Colorado Anschutz School of Medicine, Aurora, CO

Background: ICIs produce durable benefit in MSI-H CRC, yet optimal treatment duration and monitoring strategies remain unclear. ctDNA enables minimally invasive assessment of molecular response during and after ICI. We evaluated real-world treatment patterns, outcomes, and longitudinal ctDNA dynamics in pts with MSI-H CRC treated with ICI. **Methods:** Pts with MSI-H mCRC treated with first-line ICI were identified from Natera's Real-World Database with linked longitudinal ctDNA results (Signatera, Natera, Inc.) and commercial claims data (Forian's Hybrid data ecosystem, CHRONOS). Overall survival (OS) was estimated using available mortality data (Veritas Data Research, Fact of Death Mortality Data Index). ctDNA status was assessed pre-ICI when available and longitudinally following ICI initiation. Outcomes included OS and time to next trmt (TTNT); ctDNA dynamics following ICI discontinuation were descriptively evaluated. **Results:** Among 559 pts treated with first line ICI (pembrolizumab [70.1%], ipilimumab+nivolumab [15.7%], and nivolumab [11.8%]), the median duration of ICI was 266 days. Baseline (pre-ICI) ctDNA results were available for 180 pts, including 38% who were treated with chemotherapy, and most pts (71.7%, 129/180) were ctDNA-positive (ctDNA(+)) prior to ICI initiation. Of these, 89.9% (116/129) had ctDNA-timepoints after the start of ICI, and 81.0% (94/116) achieved anytime ctDNA clearance (from ctDNA(+) to negative), while 19.0% (22/116) remained ctDNA(+). ctDNA(+) at anytime after the start of ICI (HR: 8.0, p $<$ 0.0001) or on first result after the start of ICI (HR: 3.4, p $<$ 0.0001) was associated with inferior OS compared ctDNA-negativity (ctDNA(-)) at these time points. Among pts whose first post-ICI test was ctDNA(+), 32% switched treatments, with a median TTNT of 302 days, compared to only 6.6% of pts (median TTNT 683 days) whose first post-ICI test was ctDNA(-). First post-ICI ctDNA status was associated with longer ICI duration (median 192 days for ctDNA(+) vs 303 days for ctDNA(-)), and ctDNA(+) was predictive of inferior OS (HR: 4.9; p $<$ 0.001). ctDNA after the end of ICI was available for 392 patients; it was persistently negative in 77.2% (303/392), persistently positive in 12.8% (50/392), cleared after the end of ICI (positive to persistently negative) in 4.1%, and the remaining 5.9% had variable patterns (e.g. positive to negative to positive). **Conclusions:** In this large real-world cohort of MSI-H mCRC treated with ICI, longitudinal ctDNA dynamics strongly correlated with treatment durability, time to subsequent therapy, and OS. These findings support further evaluation of ctDNA to inform treatment duration and surveillance strategies in MSI-H mCRC. Research Sponsor: None.

3518 Poster Session

Role of microbiota in response to treatment in anal squamous cell carcinoma. First Author: Jaime Feliú, Hospital Universitario La Paz, Madrid, Spain

Background: Anal squamous cell carcinoma (ASCC) is a rare tumor whose management and treatment have not changed since the 1970s, consisting of classical chemotherapy combined with radiotherapy. Microbiota has been recently included as a hallmark of cancer, playing a relevant role in oncogenesis and tumor progression. Therefore, the aim of this study is the characterization of tumor microbiota in ASCC. **Methods:** Paraffin samples from seventy-six ASCC patients were analyzed. First, DNA was extracted, followed by 16S rDNA sequencing to identify microbiota. Then, a bacterial reference proteome was built, including the bacteria genera identified by 16S, and proteins from human and microbiota were identified and quantified by mass-spectrometry proteomics. **Results:** Seventy-six ASCC patients were included in this study: 46 (60%) female; median age 61 years; 62 (81%) HPV-positive; 1 (1%) stage I, 30 (40%) stage II, 43 (57%) stage III, 1 (1%) stage IV, and 1 (1%) unknown stage. Of these, sixty-nine (stages II-III, treated with chemoradiotherapy) were considered for survival analyses. One thousand and fifty-seven bacteria genera were identified by 16S sequencing, with *Cutibacterium*, *Bacteroides*, and *Fusobacterium* being the most abundant. Using proteomics and after applying quality criteria, 1735 proteins were identified and quantified. Of them, 1727 were human proteins and eight were bacterial proteins. Two oncomicrobiota protein profiles were identified in ASCC, ASCC-OMP1 (36 [47%] pts) and ASCC-OMP2 (40 [53%] pts). ASCC-OMP1 presented a higher expression of proteins from *Sutterella* and *Staphylococcus* whereas ASCC-OMP2 showed higher expression of proteins from *Dialister*, *Campylobacter A*, and *Dysosmobacter*. In addition, the two microbiota profiles showed differences in human proteins related to immune response, adhesion, extracellular matrix, translation, and metabolism. Interestingly, significant differences in disease-free survival (DFS) (p=0.02, HR= 2.73, DFS at 5 years: ASCC-OMP1 78.43%, ASCC-OMP2 52.33%) were shown between ASCC-OMP1 and ASCC-OMP2. Overall survival (OS) is not significant between the two groups but a trend can be observed (p=0.06, HR=2.55, OS at 5 years: ASCC-OMP1 79.28%, ASCC-OMP2 62.92%). In a multivariate analysis including the classical clinical prognostic factors, the prognostic value in disease-free survival of the oncomicrobiota profiles remains. **Conclusions:** Two different oncomicrobiota protein profiles with implications in disease-free survival exist in anal squamous cell carcinoma. Research Sponsor: None.

3519 Poster Session

TROP2 as an actionable biomarker for anal cancer. First Author: Mir Lim, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Chemoimmunotherapy is standard frontline therapy for metastatic anal cancer, with no effective treatment options afterward. Mutation profiling has not yielded matched targeted therapies against anal cancer. Trophoblast cell-surface antigen 2 (TROP2) is overexpressed in other solid tumors, and TROP2 antibody-drug conjugates (ADCs) have demonstrated efficacy in breast and lung cancers. Given the therapeutic availability against TROP2, we evaluated expression of TROP2 in anal cancer as an actionable therapeutic target. **Methods:** Metastatic anal cancer tumors from 33 patients at MD Anderson were sequenced by bulk RNA sequencing ("Tumor Portrait" assay, Boston Gene) to quantify *TACSTD2* (TROP2) gene expression. *TACSTD2* expression was compared across all solid tumors and classified according to ranked expression percentile: high ($>83^{rd}$ percentile), medium (17-83^{rd} percentile), or low ($<17^{th}$ percentile). Gene expression (Nanostring) for >18,000 genes was measured using whole-genome digital spatial profiling (DSP) on a separate cohort of 40 chemoradiotherapy-refractory localized anal cancers collected at salvage surgery. *TACSTD2* gene expression on tumor cells vs TME cells was compared with a t-test (SPSS). TROP2 protein expression (Invitrogen) was quantified by H-score using immunohistochemistry (IHC) and correlated with *TACSTD2* expression via Spearman's correlation. Three patient-derived xenograft (PDX) models of anal cancer (C1411, C1436, O0026) were treated with normal saline (untreated control, UTC) or the TROP2 ADC sacituzumab govitecan (sac-gov; 10 mg/kg IP twice weekly). Tumor growth inhibition (TGI) was defined as 1 - (mean tumor volumes of sac-gov/UTC) at 21 days. **Results:** Median *TACSTD2* (TROP2) gene expression for patients with metastatic anal cancer was ranked at the 75^{th} percentile (IQR 63-85) relative to all solid tumors: 13/33 (39%) with high, 20/33 (61%) with medium, and none with low *TACSTD2* expression. For localized anal cancers, *TACSTD2* gene expression using DSP was significantly higher on tumor segments vs TME segments (log fold change 3.49, adjusted $p < 0.0001$). 30/39 (77%) anal cancers had high TROP2 expression by IHC, defined by H-score >200. Correlation between *TACSTD2* gene expression and TROP2 protein expression by IHC was observed (r= 0.43, $p < 0.001$). In PDX models, TGI with sac-gov relative to UTC was observed in both models with high TROP2 expression (C1411: TGI 54%, $p< 0.001$; C1436: TGI 52%, $p< 0.001$) but not in a model with no TROP2 expression (O0026: TGI 12%, p=n.s.). **Conclusions:** TROP2 expression is high for localized and metastatic anal cancer. *TACSTD2* gene expression correlates with matched TROP2 protein expression for anal cancer. Anti-tumor efficacy of TROP2 ADCs in vivo supports a forthcoming trial of sacituzumab tirumotecan for patients with treatment-refractory metastatic anal cancer, with the ultimate goal of establishing TROP2 as a predictive biomarker for treatment benefit in this rare cancer. Research Sponsor: None.

3520 Poster Session

H&E–based MSI/MMR testing with artificial intelligence in colorectal cancer: A blinded evaluation across diverse clinicopathological subgroups. First Author: Pahini Pandya, Panakeia Technologies, Cambridge, United Kingdom

Background: Mismatch repair (MMR) deficiency and microsatellite instability (MSI) testing is integral to colorectal cancer management. Despite guideline recommendations, routine testing remains limited by cost, turnaround time, and pathology resources. PANProfiler Colorectal (PPC) is an artificial intelligence (AI) system that infers MSI/MMR status directly from H&E-stained whole slide images (WSIs), offering a rapid, resource-efficient alternative. This study reports blinded validation of PPC, specifically evaluating performance across clinically relevant subgroups. **Methods:** A total of 2,636 WSIs from St. James's University Hospital (Leeds, UK) were retrospectively analyzed, with the dataset representing a broad range of clinicopathological characteristics including age (<50 to >75 years), gender, tumor stage, differentiation, and histological subtypes. PPC returned proficient MMR (*pMMR*), deficient MMR (*dMMR*) or *indeterminate* (no definitive result), with results evaluated for agreement against immunohistochemistry. **Results:** PPC generated definitive results for 2,109 WSIs, achieving a test replacement rate (TRR) of 80%. Overall positive percent agreement (PPA) was 97.9% and negative percent agreement (NPA) 93.8% (Table). Performance was consistent across all age groups and genders. PPA and NPA were mostly robust in all cancer stages, with PPA exceeding 99% in Stage II disease, where MMR status primarily informs adjuvant therapy decisions. In Stage III/IV disease, PPA reduced to 82.6%, which may reflect greater histological heterogeneity in advanced tumors. In mucinous and poorly differentiated tumors, PPA remained high (98.7-100%), supporting reliable detection of dMMR samples, while NPA ranged from 75.4-80%, indicating more conservative classification of pMMR tumors that would require lab tests. **Conclusions:** PPC demonstrated a high overall performance, providing definitive results for the majority of cases. PPA and NPA were consistent in key clinical groups, including younger patients and early stage disease. In more challenging cases like mucinous and poorly differentiated tumors, PPA remained robust despite reductions in NPA, supporting safe guidance of subsequent testing. These findings suggest PPC could streamline MSI/MMR workflows, reducing reliance on conventional testing while maintaining diagnostic safety across diverse clinicopathological profiles. Research Sponsor: None.

Performance across diverse subgroups.

	Overall	Age <50	Age 50-65	Age 65-75	Age >75	Male	Female	Stage I	Stage II	Stage III/IV	Well Diff.	Moderately Diff.	Poorly Diff.	Adenocarcinoma	Mucinous
Definitive (n)	2109	155	159	698	703	1165	944	395	1015	694	245	1655	187	1879	210
PPA (%)	97.9	100	100	92.1	100	95.5	99.4	97.8	99.5	82.6	100	96	100	99.5	98.7
NPA (%)	93.8	91.7	98	91.3	94.1	95.5	91.5	95.1	91.8	95.5	92.5	95.6	80	95.3	75.4
TRR (%)	80	74.5	76.4	81.2	82.2	81.1	78.7	74.5	81	81.8	76.1	80.8	80.3	82.4	63.6

3521 Poster Session

Large language model–assisted decision-making in multidisciplinary tumor boards for colorectal cancer. First Author: Aydan Farzaliyeva, Department of Medical Oncology, Baskent University, Ankara, Turkey

Background: Evolving colorectal cancer management and rising incidence have increased the workload of multidisciplinary tumor boards (MTBs), placing growing time demands on healthcare professionals. This study evaluates large language models (LLMs) as decision-support tools by comparing AI-generated recommendations with MTB decisions. **Methods:** This retrospective study used two large language models, Gemini 2.5 (general-purpose) and MedGemma 27B (medical-domain specific), to generate treatment recommendations for patients discussed at MTB. MedGemma 27B was evaluated at two temperature settings (T = 0.0 and T = 1.0). MTB decisions served as the reference standard. Agreement was quantified using Cohen's kappa, and classification performance was assessed with accuracy, F1 score, and recall. Recommendations were independently reviewed by two MTB members for clinical concordance and safety. **Results:** A total of 300 colorectal cancer cases were included. Gemini 2.5 demonstrated high agreement with MTB decisions (Cohen's kappa = 0.792, $p < 0.001$), with 81.7% full concordance, significantly outperforming MedGemma 27B at both temperature settings (57.0% at T = 0.0 and 62.3% at T = 1.0, $p < 0.001$ for both). MedGemma 27B showed moderate agreement (k = 0.566 at T = 0.0, k = 0.610 at T = 1.0, $p < 0.001$), with a modest improvement in concordance at T = 1.0 (p = 0.038). In safety, Gemini 2.5 had the highest rate of clinically safe recommendations (83.7%), outperforming MedGemma at both temperature settings ($p < 0.001$), with no significant safety difference between MedGemma's temperature settings (p = 0.567). Subgroup analyses showed that Gemini 2.5 had higher discordance in stage IV (p = 0.033), recurrent cases ($p < 0.001$), and surgical/interventional or active surveillance decisions ($p < 0.001$). In contrast, MedGemma demonstrated increased discordance in stage II ($p < 0.001$), ECOG PS ≥2 (p = 0.023–0.036), MSI-unstable tumors ($p < 0.001$), recurrent disease (p = 0.008–0.010), and surgical/interventional or active surveillance decisions ($p < 0.001$). **Conclusions:** Large language models demonstrated meaningful alignment with multidisciplinary tumor board decisions, supporting their potential role in clinical decision support for colorectal cancer, while emphasizing the need for further refinement to ensure consistent and safe clinical integration. Research Sponsor: None.

Comparison of large language models' agreement and performance metrics with multidisciplinary tumor board decisions in colorectal cancer.

LLM	Fully concordant	Partially concordant	Discordant	Accuracy	F1 score	Recall	Cohen's kappa (κ)	p value
Gemini 2.5	245 (81.7 %)	23 (7.7 %)	32 (10.7 %)	85 %	0.79	0.82	0.792	<0.001**
MedGemma 27B temperature 0.0	171 (57.0 %)	64 (21.3 %)	65 (21.7 %)	70.3%	0.64	0.61	0.566	<0.001**
MedGemma 27B temperature 1.0	187 (62.3 %)	54 (18.0 %)	59 (19.7 %)	73.5%	0.71	0.66	0.610	<0.001**

LLM, large language model.

3522 **Poster Session**

Inferring molecular signatures in colorectal cancer directly from routine whole-slide images. First Author: Piotr Keller, Predictive Systems in Biomedicine (PRISM) Lab, Department of Computer Science, University of Warwick, Coventry, United Kingdom

Background: Molecular profiling has advanced colorectal cancer (CRC) research but remains limited in the clinic due to cost and tissue constraints. In contrast, haematoxylin and eosin (H&E) whole-slide images (WSIs) are routinely available. Recent deep learning studies show that molecular signatures can be inferred from morphology. However, prediction of patient level pathway activity remains underexplored despite their pathobiological significance as coordinated drivers of cancer risk. **Methods:** We developed SPARROW, a neural network trained to predict over 200 molecular signatures from WSI graph representation of tumour, stroma, lymphocytic and mucosal regions in resection specimens. SPARROW was trained on TCGA (n = 585) and externally validated in the PETACC3 trial dataset (n = 1,160). It predicts pathway enrichment scores, point mutation and clinically actionable CRC subtypes. **Results:** As shown in the table below, SPARROW accurately predicts key molecular features of CRC directly from routine H&E slides and generalizes robustly to the independent PETACC3 trial. The strongest concordance was observed for biologically and clinically relevant programmes, including intrinsic consensus molecular subtype 3 (iCMS3) genes, Fetal enteric progenitor pathway genes, a 22-gene YAP/TAZ transcriptional target signature and epithelial-specific high-risk gene set (epiHR) activity. SPARROW also showed good performance for clinically used classifications, including iCMS/CMS subtypes, interferon phenotype and BRAF mutation status. Importantly, image-derived molecular scores were predictive of relapse free survival as well. **Conclusions:** SPARROW demonstrates that key molecular features of CRC, including transcriptomic subtypes and genomic alterations, are robustly encoded in and learnable from routine H&E histology. This enables histology to serve as a cost-effective and rapid surrogate for predicting key molecular signatures and actionable molecular subtypes while also allowing mining of spatially localised image signatures associated with transcriptional programmes. Research Sponsor: None.

Molecular Signature	TCGA (4-fold CV)	PETACC3 (external)	Relapse Free Survival Analysis (PETACC3)
iCMS3 (ρ)	0.64 ± 0.05	0.66	HR=1.2*, 95% CI:1.04-1.38
Fetal Mustata (ρ)	0.47 ± 0.06	0.61	HR=1.74*, 95% CI:1.45-2.08
YAP_22 (ρ)	0.41 ± 0.07	0.49	HR=2.54*, 95% CI:2.03-3.18
EpiHR (ρ)	0.40 ± 0.08	0.45	HR=1.59*, 95% CI:1.31-1.92
iCMS2 vs iCMS3 (AUC)	0.90 ± 0.02	0.92	HR=1.12, 95% CI:1.00-1.26
CMS (4 groups) (AUC)	0.84 ± 0.01	0.84	HR=6.3* (CMS4 vs other), 95% CI:3.92-10.01
Interferon (High/Low) (AUC)	0.82 ± 0.08	0.88	HR=1.14, 95% CI:0.86-1.05
BRAF Mutation (AUC)	0.82 ± 0.07	0.80	HR=2.12*, 95% CI:1.13-4.29

*p-value <0.05 based on log-rank test using median pathway score.

3523 **Poster Session**

HistoChrome: Virtual multiplex immunohistochemistry from routine H&E in colorectal cancer. First Author: Mark Eastwood, Predictive Systems in Biomedicine (PRISM) Lab, Department of Computer Science, University of Warwick, Coventry, United Kingdom

Background: In colorectal cancer (CRC), immunohistochemistry (IHC) is central to assessment of spatial protein expression but is typically limited to few stains per case due to cost, tissue availability, and limited multiplexing. As a result, many relevant markers are not evaluated systematically. It remains unclear which pathobiologically relevant protein expression patterns are reliably encoded in morphological cues visible on routine haematoxylin and eosin (H&E) whole-slide images (WSIs). Markers of epithelial differentiation (CDX2, MUC2), immune infiltration (CD8), and mucin biology (MUC5) are clinically informative in colorectal cancer, yet their correspondence with H&E morphology is poorly defined. We investigate whether whole-slide virtual multiplex IHC (mIHC) can be generated from routine H&E for this marker panel. **Methods:** We trained a generative adversarial neural network with domain-specific constraints to enable whole-slide virtual mIHC generation from H&E. The model operates in stain concentration space using explicit stain separation and recombination and enforces spatial coherence during tiled whole-slide inference via an overlap consistency loss. Training used 52,579 paired H&E-mIHC patches (960×960 at 0.5 microns per pixel) extracted from adjacent, registered sections stained for CDX2, CD8, MUC2, MUC5, and hematoxylin, across 128 WSIs from 23 patients. Performance was evaluated on an independent cohort of 27 paired H&E-mIHC WSIs. **Results:** HistoChrome generates visually realistic and spatially coherent virtual mIHC WSIs from routine H&E. Biological fidelity was assessed by computing patch-wise Spearman correlations between mean stain intensities in real and virtual mIHC, restricted to tumor regions to avoid inflation from morphologically trivial normal tissue. Strong agreement with biological ground truth was observed for epithelial differentiation markers, with correlations of 0.79 for CDX2 and 0.63 for MUC2. CD8-positive immune infiltration was also captured with moderate accuracy (ρ = 0.49). In contrast, MUC5 expression showed only modest correspondence with biological ground truth (ρ = 0.25). **Conclusions:** HistoChrome enables whole-slide virtual multiplex immunohistochemistry from routine H&E, offering scalable access to biologically grounded protein markers without additional tissue or staining. Accurate inference of CDX2, MUC2, and CD8 supports slide-level pathological stratification of differentiation and immune contexts, with direct relevance for prognostic assessment and patient selection in therapeutic studies. The modest performance for MUC5 underscores that not all proteins may be morphologically encoded in H&E, highlighting the importance of marker-specific validation. Together, these findings position virtual mIHC as a practical adjunct to routine pathology and a discovery tool for CRC. Research Sponsor: None.

3524 **Poster Session**

Validation of DiaSurv, an AI-based algorithm for stage II colon cancer risk stratification. First Author: Lou Rouan, Centre Hospitalier Universitaire de Caen, Caen, France

Background: Adjuvant chemotherapy decisions in stage II colon cancer (IIA T3N0; IIB T4aN0; IIC T4bN0) remain challenging, as conventional risk factors poorly predict recurrence. This results in both overtreatment and undertreatment. AI-based analysis of routine H&E slides may enable more accurate risk stratification to guide personalized treatment decisions. **Methods:** DiaSurv Colon is an AI-powered prognostic tool using a deep neural network to extract in an unsupervised way morphological features from H&E-stained WSI and predict 5-year overall survival (OS). Each patient is assigned an individual survival risk score. The model was trained on the TCGA cohort (n = 463) and previously validated on two external cohorts. In this study, we evaluated its performance on two new independent external cohorts, digitized with two different scanners: CHU Caen (n = 201; 5-y OS 47%, 95%CI 39-53%) and IHP (n = 207; 5-y OS 54%, 95%CI 45-61%). Prognostic accuracy was assessed using concordance index (c-index). Multivariate Cox regression and log-rank tests with hazard ratios (HR) were used to compare DiaSurv Colon performance against conventional clinicopathological factors. **Results:** On external validation, DiaSurv Colon achieved a c-index of 58 (CHU Caen) and 64 (IHP). The AI-based risk score significantly stratified patients: 5-year OS was 64% (95%CI 50-75%) vs 40% (95%CI 32-48%) for low- vs high-risk groups in CHU Caen ($p < 0.01$), and 64% (95%CI 52-73%) vs 39% (95%CI 26-51%) in IHP ($p < 0.001$). The risk score demonstrated strong prognostic value with hazard ratios of 1.29 (95%CI 1.05-1.58, $p < 0.01$) and 1.57 (95%CI 1.23-2.00, $p < 0.001$) for CHU Caen and IHP, respectively. **Conclusions:** DiaSurv Colon demonstrated consistent prognostic performance across independent external cohorts, with robust hazard ratios and concordance indices. This AI-based tool may improve risk stratification in stage II colon cancer and support personalized adjuvant therapy decisions with more confidence. Research Sponsor: None.

3525 **Poster Session**

A deep learning approach to quantify tumor microenvironment features associated with postoperative ctDNA status and outcomes in a phase III FOLFOX-based adjuvant colon cancer trial (N0147; Alliance). First Author: Frank A. Sinicrope, Mayo Clinic Rochester, Rochester, MN

Background: Tumor microenvironment (TME) features of colorectal cancer (CRC) may influence detection of circulating tumor DNA (ctDNA) and further refine prognosis. We applied a deep learning histopathologic algorithm to quantify TME features in stage III colon cancers and evaluated their association with postoperative ctDNA status among participants in a phase III FOLFOX-based adjuvant trial (NCCTG N0147). **Methods:** QuantCRC (Aiforia Technologies) was applied to digitized hematoxylin and eosin-stained whole-slide images of stage III colon adenocarcinomas to extract quantitative histopathologic features. Among cases where data met quality control (N=1817), associations between 15 distinct pathologist-defined features and clinical outcomes—time to recurrence (TTR), disease-free survival (DFS), and overall survival (OS)—were evaluated, stratified by postoperative ctDNA status assessed by a tissue-free assay (Guardant Reveal). Relationships were analyzed using univariate and multivariable Cox proportional hazards models that were adjusted for clinicopathologic and molecular features (*KRAS*, *BRAF*^{V600E}, MMR status). Interaction testing was performed. **Results:** We found statistically significant quantitative differences for histopathological features by ctDNA status. Features associated with ctDNA positivity(+) included lymphovascular invasion (LVI), and increased %high grade, %tumor budding, %necrosis, and %stroma. ctDNA+ cases had lower %inflammatory stroma and fewer %signet ring cells (all $p < 0.006$). Multivariable analyses, irrespective of ctDNA status, identified % tumor budding, %mucin, %signet ring cells, %inflammatory tumor bed, and %inflammatory stroma as significantly associated with adverse outcomes (TTR, DFS, OS). Within ctDNA+ cases, higher %immature tumor bed was associated with adverse outcome for all 3 variables. Among ctDNA-negative cases, significantly poorer outcomes (TTR, DFS, OS) were observed for tumors with lower tumor infiltrating lymphocyte (TIL) density and reduced %necrosis. After adjustment, significant interactions with ctDNA status were observed for LVI ($p < 0.006$) and %signet ring cells ($p < 0.035$) across all outcome variables, for %necrosis with DFS, OS ($p<0.040$), and for TILs with TTR ($p<0.015$). Analysis is ongoing for ctDNA tumor fraction as well as tumor genotyping data (739 genes; Guardant360). **Conclusions:** QuantCRC identifies TME features associated with postoperative ctDNA status that enable risk-stratification within ctDNA groups. Among ctDNA-negative patients, reduced intratumoral TIL density and reduced tumor necrosis identify high-risk subgroups with inferior clinical outcomes, and may have clinical utility. Research Sponsor: None.

3526 **Poster Session**

A large-scale, multi-target deep learning model for virtual genomic and molecular risk profiling in colorectal cancer. First Author: Erik N. Bergstrom, Natera, Inc., Austin, TX

Background: Molecular profiling of tumor biopsies is central to precision oncology, informing treatment selection, prognostication, and disease monitoring. Computational analysis of routine H&E slides offers a complementary, scalable approach that can accelerate biological insights and optimize downstream molecular testing. Recent advances in computational pathology have demonstrated that deep learning models can infer molecular features directly from digital H&E images, referred to as virtual genomics. However, most studies in colorectal cancer (CRC) have been constrained by limited cohort sizes, single-target predictions, and a lack of integration with longitudinal clinical outcomes. Here, we present a transformer-based deep learning framework designed for large-scale virtual genomic and molecular recurrence risk profiling in CRC. **Methods:** The model was trained on 45,155 patients with matched digital H&E images, whole-exome sequencing (WES), and longitudinal circulating tumor DNA (ctDNA) for molecular recurrence monitoring. We embedded all images using H-optimus-0 and trained a transformer-based multiple instance learning aggregation head for downstream virtual genomic predictions. We trained individual models to predict genes found in the MSK-IMPACT505 cancer gene panel and a single model that predicts all genes simultaneously. Lastly, we trained an independent model to predict the risk of molecular recurrence. All results were validated on an external cohort from The Cancer Genome Atlas (TCGA; n = 422 CRC patients). **Results:** Individual models predicted 379 mutated genes with an internal area under the receiver operating curve (AUROC) $>$ 0.7. We validated 254 of these genes within TCGA with an AUROC $>$ 0.7. Training a multi-task learning model to predict all genes simultaneously improved the AUROC for 85% of the genes. Based on NCCN guidelines in CRC, we further trained individual models to predict MSI status, BRAF V600E, KRAS G12D/V/G13D, and POLE/POLD1 exonuclease mutations with AUROCs of 0.96, 0.93, 0.84, and 0.86, respectively. Lastly, we developed an image-based molecular recurrence risk model trained directly on longitudinal ctDNA outcomes. The model stratified patients into low, medium, and high risk groups with a concordance index of 0.67. Compared to low-risk patients, the high-risk group exhibited a hazard ratio (HR) of 4.67, while the medium-risk group showed an HR of 1.98 (p-values $<<$ 1E-5). **Conclusions:** This unified framework demonstrates that virtual genomics from routine H&E histopathology can enable scalable, cost-efficient inference of hundreds of clinically relevant genomic alterations and molecular recurrence risk in CRC. By leveraging universally available diagnostic slides, virtual genomics has the potential to expand access to precision oncology, optimize molecular testing strategies, and support earlier risk stratification. Research Sponsor: None.

3527 **Poster Session**

The use of miR-5193 to predict oxaliplatin chemosensitivity in colorectal cancer: Integrated in silico, in vitro, and clinical evidence. First Author: Jaime A. González Montero, Bradford Hill Clinical Research Center, Santiago, Chile

Background: Outcomes with first-line chemotherapy in metastatic colorectal cancer (mCRC) are heterogeneous. We evaluated whether tumor microRNA miR-5193 is a predictive marker of chemosensitivity. **Methods:** We performed (i) a discovery analysis in TCGA COAD/READ to test associations between tumor miR-5193 and progression-free (PFS) and overall survival (OS) by Kaplan–Meier/log-rank; (ii) functional assays in colonic epithelium (CON-841) and colorectal cancer cell lines (Caco-2, HCT116) after miR-5193 mimic transfection, assessing 5-fluorouracil (5-FU) and oxaliplatin (L-OHP) sensitivity by MTT and IC50; and (iii) a validation cohort of formalin-fixed paraffin-embedded (FFPE) primary tumors from Chilean mCRC patients (n=50) in which hsa-miR-5193 was quantified by RT-qPCR. Patients were dichotomized into low vs high expression, and PFS/OS were estimated by Kaplan–Meier/log-rank in the overall cohort and in prespecified oxaliplatin- and irinotecan-based first-line subgroups. **Results:** In TCGA mCRC cases selected for standard clinicopathologic features and chemotherapy exposure, low tumor miR-5193 expression was associated with shorter PFS (p=0.03). In vitro, miR-5193 was downregulated in CRC lines vs CON-841, and transient miR-5193 overexpression increased chemosensitivity to 5-FU (Caco-2; reduced viability at 200–250 μM and IC50 from 1138 to 345 μM, p=0.049) and oxaliplatin (HCT116; left-shifted dose–response and ~30–35% IC50 reduction, p$<$0.01). In the Chilean validation cohort, low (n=30) vs high (n=20) hsa-miR-5193 expression was associated with inferior OS (p=0.0081) and showed no statistically significant difference in PFS (p=0.058). Among patients receiving oxaliplatin-based first-line chemotherapy (FOLFOX/CAPEOX), low hsa-miR-5193 predicted shorter PFS (p=0.012), whereas no PFS difference was observed with irinotecan-based regimens (p=0.8104) (Table 1). **Conclusions:** miR-5193 appears to modulate chemosensitivity in mCRC. Low tumor miR-5193 is linked to reduced oxaliplatin and 5-FU sensitivity in vitro, and shorter PFS/OS under oxaliplatin-based therapy, supporting its role as a biomarker of oxaliplatin sensitivity. Prospective validation could enable miR-5193-guided treatment selection and risk stratification, particularly for patients considered for oxaliplatin-containing regimens. Research Sponsor: Agencia Nacional de Investigación y Desarrollo (ANID); SA20I0059; FONDAP; 152220002; Agencia Nacional de Investigación y Desarrollo (ANID); 21240251.

Association between hsa-miR-5193 expression and clinical outcomes in metastatic colorectal cancer.

Study cohort / subgroup	Outcome	miR5193 expression: Low (n=30) vs high (n=20)	P-value
Chilean validation cohort — Overall	PFS	No significant difference	0,058 (NS)
Chilean validation cohort — Overall	OS	Shorter OS	0,0081
FOLFOX/CAPEOX subgroup (oxaliplatin-based)	PFS	Shorter PFS	0,012
Irinotecan-based subgroup	PFS	No difference	0,8104 (NS)

3528 **Poster Session**

Fruquintinib plus FOLFIRI or mFOLFOX6 as second-line therapy for patients with *RAS*-mutant metastatic colorectal cancer (mCRC): A phase II, multicenter, open-label study. First Author: Yun Xu, Department of Colorectal Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Nearly half of metastatic colorectal cancer (mCRC) patients harbor RAS mutations, and the standard second-line regimen for this substantial subgroup of patients is combination chemotherapy (FOLFIRI/FOLFOX) with bevacizumab, which offers limited efficacy. Fruquintinib, an oral VEGFR-1, -2, and -3 inhibitor, has shown efficacy in refractory mCRC. This study evaluated the efficacy and safety of fruquintinib in combination with FOLFIRI or FOLFOX as second-line therapy for patients with RAS-mutant mCRC. **Methods:** This multicenter, open-label, single-arm phase II trial enrolled patients with RAS mutant mCRC who had failed first-line standard therapy. Participants received fruquintinib (4 mg once daily, days 1-21) plus FOLFIRI or mFOLFOX every 28 days. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. **Results:** As of Nov 11, 2025, 42 eligible pts were enrolled and received at least one cycle of treatment. Baseline characteristics included median age (63.0 [range: 35-74]), male (59.5%), ECOG PS 1 (66.7%), left-sided (73.8%), liver metastasis (59.5%), prior anti-VEGF therapies (73.8%). The median PFS was 8.1 months (95% CI: 6.18, 9.46) and median OS was not reached yet. The Kaplan-Meier estimates for PFS rates at 3, 6, 9, and 12 months were 85.3%, 73.5%, 35.9%, and 15.4%, respectively. In the subgroup analysis, median PFS were longer in pts without liver metastases (8.4mo vs 6.4mo, HR: 1.65, 95%CI: 0.65-4.18), those with left-sided lesion (8.1mo vs 4.8mo, HR: 2.14, 95%CI: 0.79-5.77) and pts without prior anti-VEGF therapies (8.4mo vs 6.5mo, HR: 1.79, 95%CI: 0.59-5.36). The ORR was 52.5% (21/40) which consisted of CR 5% and PR 47.5%. The DCR was 97.5% (39/40). Additionally, the most common any grade treatment-emergent adverse events (TEAEs) were hypertension (23.8%), diarrhea (19.1%), and mucositis (19.1%). Grade ≥3 TEAEs was 14.3% including diarrhea (4.8%), intestinal obstruction (2.4%) and leukopenia (2.4%). **Conclusions:** Fruquintinib combined with either FOLFIRI or mFOLFOX6 as second-line therapy for patients with RAS-mutant metastatic colorectal cancer (mCRC) demonstrated promising efficacy and a manageable safety profile. Clinical trial information: NCT05634590. Research Sponsor: None.

3529 **Poster Session**

daNIS-3: A phase II platform study of NIS793 and anti–PD-1 combined with standard of care (SoC) anti-cancer therapy for the second-line (2L) treatment (tx) of microsatellite-stable colorectal cancer (MSS CRC). First Author: Filippo Pietrantonio, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Despite advances in tx of MSS CRC including targeted tx, the prognosis remains poor. The daNIS-3 study (NCT04952753) evaluated efficacy and safety of anti-TGFß monoclonal antibody NIS793 (NIS) and anti-PD1 tislelizumab (TISLE) with SoC as 2L tx for MSS CRC patients (pts). **Methods:** This open-label, multicenter study included safety run-in (SRI) Arm 1a: NIS + SoC (bevacizumab [Bev] + FOLFIRI), Arm 1b: NIS + SoC (Bev + mFOLFOX6) followed by Arm 2a: NIS + TISLE + SoC (Bev + FOLFIRI), Arm 2b: NIS + TISLE+ SoC (Bev + mFOLFOX6) to determine NIS recommended phase 2 dose (RP2D) for expansion phase (EP). FOLFIRI and mFOLFOX6 were evaluated independently. While EP included same investigational arms as SRI (Arm 2b not opened for enrollment), additional SoC arm was added. Primary endpoint was progression-free survival (PFS) in EP; secondary endpoints were PFS for SRI, overall response rate (ORR), disease control rate (DCR), duration of response (DOR) and time to response (TTR) using RECIST V1.1, pharmacokinetics (PK), immunogenicity, safety, and tolerability. Based on data monitoring committee recommendation, study was terminated on 31-07-2023 due to unfavorable benefit-risk profile. **Results:** As of 20-01-2025, median (95% CI) PFS in EP was 5.1 months (mo) (3.6–5.7), 3.7 mo (2.2–5.6), and 7.4 mo (5.5–9.4) for Arms 1a&b, Arm 2a, and SoC, respectively (HR vs SoC [95% CI]: Arms 1a&b, 2.06 [1.34–3.18]; Arm 2a, 1.65 [0.90–3.02]). Secondary endpoints are summarized in Table. PK of NIS and other drugs were similar in EP and SRI. All pts were ADA negative at baseline and during the study. NIS RP2D for Arms 1a&b, and 2a was 2100 mg Q2W. In SRI and EP, overall adverse events (AEs) were comparable across all arms. In EP, grade ≥3 AEs were higher in Arm 1a (67.7%) and 1b (66.7%) compared to Arm 2a (55.2%) and SoC (58.7% & 42.9%). Higher incidence of serious AEs was reported in Arm 1a (49.2%) compared to Arm 2a (31%) and SoC (30.4% & 42.9%). Higher deaths were observed in Arm 1a (50.8%) and 1b (60.0%), mostly attributed to underlying malignancy (MSS CRC). Most common AEs of special interest of NIS were infusion-related reactions, hemorrhage, and skin toxicity, consistent with known safety profile of NIS. **Conclusions:** Overall AEs were comparable, but a higher incidence of grade ≥3 AEs vs SoC were observed. NIS arms showed a deleterious PFS outcome in MSS CRC pts. Clinical trial information: NCT04952753. Research Sponsor: Novartis Pharmaceuticals.

Secondary endpoints*	SRI Arms 1a (N = 13) & 1b (N = 9)	SRI Arms 2a (N = 10) & 2b (N = 8)	EP Arms 1a (N = 67) & 1b (N = 13)	EP Arm 2a (N = 29)	SoC (N = 53)
mPFS, mo (95% CI)	3.6 (1.9, 7.3)	2.1 (1.8, 4.3)	–	–	–
ORR, n (%)	1 (4.5)	0	7 (8.8)	4 (13.8)	8 (15.1)
DCR, n (%)	14 (63.6)	8 (44.4)	53 (66.3)	19 (65.5)	42 (79.2)
mDOR, mo (95% CI)	9.4 (NE, NE)	NE	9.5 (4.0, NE)	NE	11.1 (3.8, NE)
mOS, mo (95% CI)	10.2 (5.8, 20.8)	11.0 (6.2, 15.7)	12.8 (8.0, 14.2)	10.9 (6.1, NE)	NE (11.6, NE)

*SoC+FOLFIRI/mFOLFOX6 presented together due to similar efficacy.

3530 Poster Session

Tislelizumab plus cetuximab and irinotecan in relapsed/refractory RAS/BRAF wild-type and microsatellite stable metastatic colorectal cancer: A randomized, controlled, multicenter study (TEC2). First Author: Xiaojing Xu, Department of Oncology, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Under suboptimal efficacy and safety of current third-line standard-of-care (SoC), several single-arm studies have demonstrated that anti-PD-(L)1 antibodies plus EGFR inhibitors with or without chemotherapy may be valuable for relapsed/refractory *RAS/BRAF* wild-type and microsatellite stable metastatic colorectal cancer (R/R *RAS/BRAF* WT and MSS mCRC). This study aimed to compare tislelizumab (anti-PD-1 antibody) plus cetuximab and irinotecan as third- or later-line therapy versus investigator-selected SoC for R/R *RAS/BRAF* WT and MSS mCRC. **Methods:** This was a randomized controlled, open-label, multicenter study (NCT05278351). Eligible patients were aged ≥18 years with histologically confirmed *RAS/BRAF* WT and MSS metastatic colorectal adenocarcinoma who failed ≥2 prior lines of systemic therapy. Patients were randomly assigned (2:1) to receive intravenous tislelizumab (200 mg) plus cetuximab (500 mg/m^2) and irinotecan (180 mg/m^2) on days 1 and 15 or investigator-selected SoC (fruquintinib, regorafenib, or TAS-102) in a 4-week cycle until disease progression, unacceptable toxicity, or other protocol-defined reasons. Primary end point was progression-free survival (PFS). Secondary end points included objective response rate, disease control rate, duration of response, overall survival, and safety. **Results:** Eighty-seven patients (median age, 62.0 years; 59 [67.8%] men) were enrolled between July 2022 and March 2024, randomized, and assessed for efficacy; one patient did not receive the triplet regimen and was removed from the safety population. With median follow-up of 26.1 months (95% confidence interval [CI]: 22.4-28.4) by data cutoff (June 30, 2025), median PFS was 4.4 months (95% CI, 3.8-6.6) in the tislelizumab-cetuximab-irinotecan group and 2.0 months (95% CI, 1.9-5.4) in the SoC group (Breslow-Gehan *P*=0.009). Landmark analysis at a cutoff point of 10 months showed a significantly extended PFS with tislelizumab plus cetuximab and irinotecan versus SoC (HR 0.37 [95% CI, 0.21-0.64]; p<0.001). Grade ≥3 treatment-related adverse events (TRAEs) occurred at comparable frequencies in the two groups (15.8% *vs* 17.2%). No TRAEs led to death. **Conclusions:** Tislelizumab plus cetuximab and irinotecan as third- or later-line therapy appeared feasible and safe for patients with R/R *RAS/BRAF* WT and MSS mCRC. Clinical trial information: NCT05278351. Research Sponsor: Noncommunicable Chronic Diseases-National Science and Technology Major Project; (2023ZD0501600; National Nature Science Foundation of China; 82573146,82373402,82272775; Clinical Research Foundation of Zhongshan Hospital Affiliated to Fudan University; 2020ZSLC02,ZSLCYJ202305.

	Tislelizumab-cetuximab-irinotecan (n=58)	SoC (n=29)
Best response		
Complete response	0	0
Partial response	12 (20.7)	1 (3.4)
Stable disease	32 (55.2)	12 (41.4)
Disease progression	11 (19.0)	16 (55.2)
Not evaluable	3 (5.2)	0
Objective response	12 (20.7)	1 (3.4)
Disease control	44 (75.9)	13 (44.8)
6-month PFS rate, % (95% CI)	38.2 (27.3-53.5)	20.4 (9.6-43.7)

3531 Poster Session

Association of progression-free survival (PFS) with microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) status determined by single vs dual validated companion diagnostic (CDx) assays: CheckMate-8HW post hoc analyses. First Author: Thierry Andre, Sorbonne Université and Hôpital Saint-Antoine, Assistance Publique Hôpitaux de Paris, Paris, France

Background: First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) showed PFS benefit vs chemotherapy (chemo) in patients (pts) with MSI-H or dMMR metastatic colorectal cancer (mCRC) in the phase 3 CheckMate 8HW trial. Using post hoc analyses, we examined the association of PFS with single and dual positivity in validated CDx MSI (polymerase chain reaction; PCR) or MMR (immunohistochemistry; IHC) central assays. **Methods:** Study details were published previously (Andre T et al. *NEJM* 2024). Pts with unresectable or mCRC with MSI-H or dMMR per local testing were randomized 2:2:1 to NIVO + IPI, NIVO, or chemo. Tumor tissue samples were tested centrally using validated Idylla (CDx MSI PCR; Biocartis) and Dako (CDx MMR IHC; Agilent) assays post randomization. Clinical trial assay positive (CTA+) pts were those with locally diagnosed MSI-H/dMMR mCRC randomized to NIVO + IPI or chemo. PFS and hazard ratios (HR) were evaluated in CTA+ pts; pts positive using a single central assay (CDx MSI or CDx MMR); and pts positive in both central assays (CDx dual positive). **Results:** Of the 303 pts randomized to 1L NIVO + IPI or chemo, 301 had locally diagnosed MSI-H/dMMR (CTA+; 2 randomized pts missed local testing and were excluded in the analysis). 263 pts had valid CDx MSI results, 284 had valid CDx MMR results; 208 were CDx dual positive (Table); result missingness was mainly due to lack of tissue samples. PFS benefit was noted with NIVO + IPI vs chemo in CTA+ pts (HR, 0.32; Table). Greater PFS benefit with NIVO + IPI vs chemo was seen in pts positive with single CDx MSI or CDx MMR assays (HR, 0.20 and 0.22, respectively), and was consistent with those from CDx dual positive pts (HR, 0.20; Table). Pts with microsatellite stable (MSS) or mismatch repair proficient (pMMR) status were low, so these data should be interpreted with caution (Table). **Conclusions:** In this post hoc analysis, dual positivity from CDx MSI and CDx MMR assays did not offer greater PFS benefit with 1L NIVO + IPI vs chemo over positivity from a single CDx MSI or MMR assay. Single CDx MSI or CDx MMR assays provided similar PFS benefit with 1L NIVO + IPI vs chemo in pts with MSI-H/dMMR mCRC. Clinical trial information: NCT04008030. Research Sponsor: Bristol Myers Squibb.

	NIVO + IPI (n = 202)		Chemo (n = 101)		
	n (%)	Median PFS (95% CI)	n (%)	Median PFS (95% CI)	HR (95% CI)[a]
CTA+	200 (99)	NR (34.3–NE)	101 (100)	6.2 (4.7–9.0)	0.32 (0.22–0.45)
CDx[b] MSI+: MSI-H	147 (73)	NR (38.4–NE)	71 (70)	6.2 (4.7–9.0)	0.20 (0.12–0.31)
CDx[b] MSI−: MSS	30 (15)	1.8 (1.5–5.8)	15 (15)	7.4 (4.0–12.9)	1.51 (0.68–3.33)
CDx[b] MMR+: dMMR	163 (81)	NR (38.4–NE)	82 (81)	5.9 (4.4–7.8)	0.22 (0.14–0.34)
CDx[b] MMR−: pMMR	27 (13)	1.8 (1.5–5.8)	12 (12)	11.5 (2.0–NE)	1.39 (0.57–3.40)
CDx[b]: dual positive	139 (69)	NR (38.4–NE)	69 (68)	6.2 (4.9–9.2)	0.20 (0.13–0.32)

[a]Cox proportional hazards model stratified by tumor sidedness.
[b]By central assay. NE, not estimable; NR, not reached.

3532 Poster Session

Nivolumab + ipilimumab (NIVO + IPI) vs NIVO in microsatellite instability high/mismatch repair-deficient metastatic colorectal cancer (MSI-H/dMMR mCRC): CheckMate 8HW subgroup analyses including treatment-free status and outcomes in long-term survivors. First Author: Elena Elez, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain

Background: In the phase 3 CheckMate 8HW trial, both dual primary endpoints of progression-free survival (PFS) were met for first-line (1L) NIVO + IPI vs chemotherapy (HR 0.21; $P < 0.0001$) and NIVO + IPI vs NIVO in all lines (HR 0.62; $P = 0.0003$) in patients (pts) with centrally confirmed (CC) MSI-H/dMMR mCRC. We report explorative subgroup analyses of NIVO + IPI vs NIVO. **Methods:** The study design was described previously (Andre *NEJM* 2024). Pts with MSI-H/dMMR mCRC per local testing were enrolled. After randomization, IHC and PCR based tests were used for central confirmation. **Results:** In all randomized pts, 84% (296/354) in the NIVO + IPI and 81% (286/353) in the NIVO arm had CC MSI-H/dMMR; in 1L pts, 85% (171/202) and 85% (170/201) had CC MSI-H/dMMR, respectively. Median follow-up in all randomized pts was 55.1 (range 24.7–68.5) mo. Pts receiving NIVO + IPI had improved disease control rates vs NIVO in 1L (85% vs 81%, respectively) and all lines (84% vs 76%, respectively). Pts with complete or partial response (CR/PR) or stable disease (SD) on 1L NIVO + IPI had improved PFS vs NIVO. In all lines, pts with CR/PR or SD receiving NIVO + IPI had improved overall survival (OS) vs those on NIVO (Table). Pts receiving NIVO + IPI had improved disease-specific OS vs NIVO (HR 0.47; 95% CI 0.32–0.68). In all lines, pts on NIVO + IPI had improved PFS and OS vs NIVO regardless of the number of sites of metastasis (Table). After treatment, 82% (185/226) of pts on NIVO + IPI were alive and treatment free vs 67% (125/186) on NIVO; 90% (198/220) and 79% (141/178) of pts were alive and systemic treatment free, respectively. In pts surviving ≥4 years, baseline characteristics and incidence of treatment-related adverse events were consistent with the all randomized CC population. Further analyses will be presented. **Conclusions:** NIVO + IPI demonstrated clinical benefit vs NIVO across subgroups, as shown by numerically increased PFS and OS in pts with CR/PR or SD, and improved PFS and OS regardless of number of metastatic sites. No defining characteristic was identified in long-term survivors vs all randomized CC pts. These results further support NIVO + IPI as a standard of care treatment for MSI-H/dMMR mCRC. Clinical trial information: NCT04008030. Research Sponsor: Bristol Myers Squibb.

1L		NIVO + IPI (n = 171)	NIVO (n = 170)	HR (95% CI)
mPFS (95% CI), mo	CR/PR	NR (NE)	NR (60.8–NE)	0.82 (0.43–1.54)
	SD	33.1 (5.8–NE)	9.2 (4.4–22.1)	0.52 (0.24–1.14)
All lines		**(n = 296)**	**(n = 286)**	
mPFS (95% CI), mo	1 metastatic site at BL	NR (NE)	60.8 (26.3–NE)	0.51 (0.33–0.77)
	≥2 metastatic site at BL	59.2 (38.4–NE)	23.0 (11.8–NE)	0.70 (0.51–0.97)
mOS (95% CI), mo	CR/PR	NR (NE)	NR (NE)	0.92 (0.46–1.83)
	SD	NR (35.3–NE)	26.8 (15.7–48.9)	0.43 (0.23–0.80)
	1 metastatic site at BL	NR (NE)	NR (NE)	0.52 (0.31–0.88)
	≥2 metastatic site at BL	NR (NE)	NR (NE)	0.68 (0.46–0.99)

BL, baseline; m, median; NE, not estimable; NR, not reached.

3533 Poster Session

Phase 1 study of the tetravalent death receptor 5 agonist ozekibart (INBRX-109) combined with chemotherapy in locally advanced or metastatic, unresectable colorectal adenocarcinoma (CRC). First Author: Hazel Lote, The Royal Marsden Hospital, London, United Kingdom

Background: Patients with metastatic CRC are typically treated with fluorouracil-based chemotherapy in combination with leucovorin and irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). However, patients who progress after 2 lines of therapy have limited treatment options, with poor outcomes (response rates of ≤6%). Ozekibart (INBRX-109) is a next-generation, tetravalent death receptor 5 agonist that has demonstrated robust efficacy as a single agent in chondrosarcoma. Additionally, ozekibart in combination with FOLFIRI showed early signs of antitumor activity in a small cohort of patients with CRC in the ongoing INBRX-109 phase 1 study (NCT03715933) (Berz D, et al. *J Clin Oncol.* 2025. Abstract 129). Based on these findings, the CRC cohort in this study was expanded to include additional patients who had received 2 or 3 prior lines of systemic therapy. We present initial findings from this cohort. **Methods:** Ozekibart + FOLFIRI was examined in patients with locally advanced or metastatic, unresectable CRC in the expansion cohort C4d of the open-label, INBRX-109 phase 1 study. Eligible patients were aged 18 to < 85 years, had received 2 or 3 prior lines of systemic therapy, and had no chronic or acute liver disease. Previous irinotecan-containing regimens were allowed but not as an immediate prior line of therapy. Patients received ozekibart 3 mg/kg every 4 weeks + FOLFIRI every 2 weeks. Safety and clinical response were primary endpoints. **Results:** As of the data cutoff (October 15, 2025), 44 patients had received ozekibart + FOLFIRI in this cohort. Median age was 54.5 years (range, 29-77 years), and > 70% were in the fourth-line treatment setting; 81.8% had previously received an irinotecan-based regimen. Overall, 28 patients (63.6%) remain on treatment; 11 patients had disease progression, 1 patient discontinued due to adverse events (AEs), and 4 patients discontinued for other reasons. Among evaluable patients for response at data cutoff (n = 26), ozekibart + FOLFIRI led to an ORR of 23% (all partial responses) and a disease control rate of 92%. Consistent with the safety profile of FOLFIRI, the most common AEs (in > 25% of patients) were anemia (any grade, 36.4%; grade ≥3, 9.1%), diarrhea (34.1%; 9.1%), nausea (31.8%; 0%), fatigue (27.3%; 2.3%), and alopecia (27.3%; 0%). Increased alanine aminotransferase was the only grade ≥3 hepatotoxicity event and occurred in 1 patient. **Conclusions:** Ozekibart + FOLFIRI demonstrated encouraging preliminary efficacy in a heavily pretreated patient population with metastatic, unresectable CRC. The safety profile of ozekibart + FOLFIRI was manageable, with most AEs being low grade. Our findings support further evaluation of ozekibart + FOLFIRI in advanced CRC. Updated data will be provided at the time of presentation. Clinical trial information: NCT03715933. Research Sponsor: Inhibrx Biosciences, Inc.

3534 **Poster Session**

A randomized phase II trial of fruquintinib plus capecitabine versus capecitabine alone as maintenance therapy following first-line chemotherapy in metastatic colorectal cancer (mCRC). First Author: Wenhua Li, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Maintenance therapy with capecitabine (Cap) is widely recommended to unresectable mCRC patients (pts). Fruquintinib (Fru) is a highly selective inhibitor of VEGFR1/2/3. We sought to compare the therapeutic potential of Fru plus Cap versus Cap as maintenance therapy for mCRC. **Methods:** Eligible pts with histologically confirmed mCRC who achieved disease control (including CR/PR and SD) after at least six cycles of first-line standard chemotherapy were included in the study. During phase Ib, pts received Fru (4 mg, p.o. qd, 3 weeks on/1 week off, q4w) plus Cap (850 mg/m^2, p.o. bid, d1-7 and d15-21, q4w). In phase II, pts were randomized in a 1:1 ratio to receive either Fru (RP2D, 3mg, 3 weeks on/1 week off) plus Cap or Cap alone. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR) and safety. **Results:** As of November 15, 2025, 113 eligible patients were enrolled, including 6 in phase Ib and 107 in phase II. In this presentation, we report only the updated data from Phase II. 107 were randomly assigned to receive either fruquintinib plus capecitabine (Fru+Cap; n=52) or capecitabine alone (Cap; n=55). Baseline characteristics included median age: 61 years (range, 30-78) vs. 60 years (range, 31-80), male: 51.9% vs. 58.2%, left-sided colorectal primary tumors: 55.8% vs. 61.8% and RAS-mutant tumors: 53.8% vs. 52.7%. As first-line maintenance therapy, the median PFS1 (defined as time from randomization to disease progression or death) in the per-protocol population was 6.03 months with Fru+Cap versus 3.30 months with Cap (p=0.003). Furthermore, the Fru+Cap arm demonstrated significantly prolonged PFS2 (defined as the time from first receipt of first-line treatment to disease progression or death): 12.1 vs. 9.7 months, p=0.006. Consistent improvements were observed in objective response rate (ORR: 14.6% vs. 7.0%) and disease control rate (DCR: 75.6% vs. 51.2%). Grade ≥3 treatment-emergent adverse events (TEAEs) in Fru+Cap arm included hypertension (5.77%), palmar-plantar erythrodysesthesia syndrome (1.9%) and albuminuria (1.9%). Diarrhea (3.64%), palmar-plantar erythrodysesthesia syndrome (1.8%) and oral mucositis (1.8%) were the most frequently reported grade ≥3 TEAEs in Cap arm. **Conclusions:** PFS was significantly prolonged and ORR was improved in mCRC pts treated with Fru plus Cap as first-line maintenance treatment. The safety profile of the combination regimen was manageable and aligned with the expected toxicity patterns of the individual agents. Clinical trial information: NCT05451719. Research Sponsor: None.

3536 **Poster Session**

Intravenous oncolytic virus IDOV-Safe in pMMR/MSS metastatic colorectal cancer. First Author: Tong Xie, Gastrointestinal Cancers, Beijing Key Laboratory of Cell & Gene Therapy for Solid Tumor, State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Proficient mismatch repair/microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC) is largely resistant to immune checkpoint inhibitors, with limited options after standard therapies. IDOV-Safe is a systemically deliverable, vaccinia virus-based oncolytic virotherapy. This phase 1 clinical trial evaluated the safety and preliminary efficacy of intravenous IDOV-Safe combined with toripalimab and fruquintinib in patients with pMMR/MSS mCRC (NCT06380309). **Methods:** Patients with pMMR/MSS mCRC who had progressed on or were intolerant to ≥2 prior systemic therapies were enrolled. Dose escalation used a 3+3 design across four dose levels (1×10^9, 3×10^9, 1×10^{10}, and 3×10^{10} PFU). In expansion, three combination strategies with immune-target therapy were evaluated: sequential, early, and IO free combinations using fruquintinib with or without toripalimab. Primary endpoints were safety and objective response rate (ORR). **Results:** Fifty-five patients were enrolled; 80% had received ≥3 prior treatment lines. Dose-limiting toxicities at 1×10^{10} PFU led to selection of 1×10^9 and 3×10^9 PFU for expansion. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 62% of patients, most commonly fever, thrombocytopenia, and neutropenia; grade ≥3 immune-related events were infrequent (2%), and no grade ≥3 TRAEs were attributed to fruquintinib. In sequential combination cohorts, objective responses occurred only after initiation of combination therapy. ORR was 33.3% at 1×10^9 PFU (IIA1) and 30.0% at 3×10^9 PFU (IIA2), with disease control rates (DCRs) of 50.0% and 70.0%, respectively. In early combination cohorts, objective responses were observed at 3×10^9 PFU (IIC2; ORR 16.7%), with high DCRs (83.3% in IIC1 and 91.7% in IIC2). The DCR in the IO-free cohort (IID) was 50.0%. Median progression-free survival (mPFS) across five cohorts was 5.4 (IIA1), 8.7 (IIA2), 5.4 (IIC1), 5.5 (IIC2), and 4.6 months (IID). **Conclusions:** Intravenous IDOV-Safe demonstrated a favorable safety profile and encouraging preliminary antitumor activity when combined with toripalimab and fruquintinib, particularly using a sequential combination strategy in heavily pretreated patients with pMMR/MSS mCRC. Clinical trial information: NCT06380309. Research Sponsor: None.

Response to IDOV-safe and immuno-targeted therapy.

Response	IIA1 1×10^9	IIA2 3×10^9	IIC1 1×10^9	IIC2 3×10^9	IID 3×10^9
Best overall response — n (%)					
Partial response	2 (33.3)	6 (30.0)	0	2 (16.7)	0
Stable disease (SD)	1 (16.7)	8 (40.0)*	5 (83.3)	9 (75.0)	3 (50.0)
Progressive disease	3 (50.0)	5 (25.0)	0	1 (8.3)	2 (33.3)
Not evaluable	0	1 (5.0)	1 (16.7)	0	1 (16.7)
ORR—Percent (95% CI)	33.3 (4.3, 77.7)	30.0 (11.9, 54.3)	0	16.7 (2.1, 48.4)	0
DCR —Percent (95% CI)	50.0 (11.8, 88.2)	70.0 (45.7, 88.1)	83.3 (35.9, 99.6)	91.7 (61.5, 99.8)	50.0 (11.8, 88.2)

*One patient in IIA2 cohort had unconfirmed SD.

3537 **Poster Session**

Efficacy and safety of cetuximab-irinotecan rechallenge versus regorafenib in *RAS* wild-type metastatic colorectal cancer. First Author: Hao Chen, Fujian Medical University Union Hospital, Fuzhou, China

Background: Anti-epidermal growth factor receptor (EGFR) antibodies are widely used in the treatment of RAS wild-type metastatic colorectal cancer (mCRC) across various lines of therapy, including after disease progression. **Methods:** A single-center, prospective, randomized controlled trial (ChiCTR1900026961) evaluated the efficacy of cetuximab rechallenge in mCRC patients with RAS wild-type tumors who had initially responded to cetuximab-based therapy but subsequently progressed on a cetuximab-free regimen. The trial compared cetuximab plus irinotecan with regorafenib, with progression-free survival (PFS) as the primary endpoint and overall survival (OS), disease control rate (DCR), objective response rate (ORR), and safety as secondary endpoints. **Results:** Among 68 patients with microsatellite-stable (MSS), RAS wild-type tumors, 35 received cetuximab rechallenge therapy and 33 received regorafenib. The cetuximab group achieved a DCR of 68.6% and an ORR of 8.6%, both significantly higher than those observed in the regorafenib group. Median PFS was 5.5 months in the rechallenge group compared with 2.6 months in the regorafenib group, while median OS was 18.8 months versus 10.4 months, respectively. Adverse events in the cetuximab group were predominantly grade 1–2 and manageable with supportive care. Univariate and multivariate Cox regression analyses identified age, ECOG performance status, and washout period duration as independent prognostic factors. A nomogram was developed to predict the efficacy of cetuximab rechallenge therapy. **Conclusions:** These findings suggest that cetuximab rechallenge offers promising clinical activity with acceptable toxicity in RAS/BRAF wild-type mCRC, supporting further investigation of rechallenge strategies and biomarker-guided approaches to optimize outcomes in advanced CRC. Clinical trial information: ChiCTR1900026961. Research Sponsor: Tthe Joint Funds for the Innovation of Science and Technology of Fujian province (2018Y9032).

3538 **Poster Session**

Zongertinib in HER2-altered colorectal cancer: A pooled analysis of colorectal cancer patients from two clinical trials. First Author: Dirk Arnold, Asklepios Tumorzentrum Hamburg, AK Altona, Hamburg, Germany

Background: Zongertinib, an irreversible TKI, selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Here, we present a pooled analysis of a subgroup of patients (pts) with HER2-positive colorectal cancer (CRC) who received zongertinib monotherapy in Phase Ia of a dose-escalation/expansion trial (NCT04886804) or in the ongoing Phase II Beamion PANTUMOR-1 trial (NCT06581432), as well as supporting preclinical data. **Methods:** Preclinical antitumor activity of zongertinib as monotherapy or in combination with other HER2-directed agents was assessed in commercially available *HER2*-amplified mouse PDX models of CRC. Phase Ia of NCT04886804 enrolled pts with advanced solid tumors and HER2 alterations (mutations, amplification, or overexpression) who had exhausted all other standard treatment options. Beamion PANTUMOR-1 includes pts with previously treated HER2-positive (amplification or overexpression) or *HER2*-mutant solid tumors. Pts in NCT04886804 received escalating doses of zongertinib (15 mg BID or 180–360 mg QD); pts in Beamion PANTUMOR-1 received zongertinib 120 mg QD. Efficacy (investigator-assessed objective response rate [ORR]; RECIST v1.1) and safety (incidence of adverse events [AEs]; CTCAE v5.0) were assessed. **Results:** In *HER2*-amplified PDX CRC models, zongertinib monotherapy and in combination with other HER2-directed agents led to tumor growth inhibition or regression, with greater antitumor activity observed with the combinations. A total of 20 pts with HER2-positive CRC (10 from each trial) received zongertinib. Pts had a median age of 53 years (range: 36–70) and had received a median of 2.5 lines of prior systemic therapy. A total of 8 pts (6 from NCT04886804 and 2 from Beamion PANTUMOR-1) had received ≥1 prior HER2-directed therapy, including trastuzumab, pertuzumab, or T-DXd. Median treatment duration with zongertinib was 5.1 months (range: 0–18). The confirmed ORR was 45% (n = 9; all partial responses). A further 9 (45%) pts achieved stable disease, giving a disease control rate of 90%. At the time of analysis, 7 (35%) pts remained on treatment. Treatment-related AEs (TRAEs, any grade/grade ≥3) were reported in 70%/5% of pts. The most common TRAEs were diarrhea (9 pts [45%], all grade 1), rash (3 pts [15%], all grade 1), anemia (2 pts [10%], all grade 2), and increased AST (2 pts [10%], all grade 2). Only one pt had a grade ≥3 TRAE (grade 3 increased lipase). No grade 4 or 5 AEs were reported. **Conclusions:** Pooled analysis of HER2-positive CRC pts from two clinical trials indicates that zongertinib monotherapy has encouraging clinical activity and manageable safety in pts with advanced, HER2-positive CRC, supported by PDX models. Based on these findings, zongertinib continues to be developed in CRC, with Beamion PANTUMOR-1 actively enrolling. An additional Phase Ib/II trial (Beamion BCGC-1, NCT06324357) is also underway. Clinical trial information: NCT04886804, NCT06581432. Research Sponsor: Boehringer Ingelheim.

3539 **Poster Session**

First-line immune checkpoint inhibitors in elderly colorectal cancer patients in the real world: Retrospective phase of the multicenter ELDER CRC trial. First Author: Martina Cassaniti, Oncology Unit, University Hospital of Ferrara, Ferrara; Oncology Unit Santa Maria delle Croci Hospital - AUSL Romagna, Ravenna, Italy

Background: dMMR/MSI-H metastatic colorectal cancer (mCRC) is more common among the elderly. However, insufficient data about their treatment with immune checkpoint inhibitors (ICIs) are available from interventional and observational trials. **Methods:** ELDER CRC is an observational, multicenter Italian trial enrolling elderly (≥70 years [yrs]) patients (pts) treated with first-line ICI(s) for dMMR/MSI-H mCRC in the real world. Results from the retrospective cohort are presented. **Results:** 132 pts aged 77 yrs as median (IQR 74-82, range 70-93; <75: 32.6%; 75-79: 29.5%; ≥80: 37.9%) were enrolled across 10 Centers. They were mainly female (56.1%) in mediocre conditions (ECOG PS 1: 51.9%, ≥2: 22.2%; G8 ≤14: 80.5% [33/41 available]) with BRAF mutated (58.9% [73/124]), right primary tumor (80%), and synchronous metastases (54.5%) involving liver (34.8%) and/or peritoneum (37.9%). Almost all pts received monotherapy (pembrolizumab or nivolumab: 98.5%; nivolumab+ipilimumab: 1.5%) and most discontinued for PD (31.1%) or completion of 2 yrs (13.6%). 65.2% had an adverse event (AE), mainly fatigue (37.9%), skin rash (20.5%), hypothyroidism (17.4%), diarrhea (15.9%), and arthralgia (12.9%). Only 11% had G3-4 AE (G5=0), mainly gastrointestinal (3.8%), lung (3%), and fatigue (2.3%) and 10.6% discontinued ICI for AE. On 122 evaluable pts, ORR was 51.6% (38.5% PR + 13.1% CR) with 26.2% SD and 22.1% primary PD. At median follow-up of 25.9 months [mos] (22.3-30.3), mPFS was 32.2 mos (26.2-NE) with 56 events and mOS 45.8 mos (32.2-NE) with 46 events. 28.8% are still on treatment at the time of this analysis. Survival outcomes were not influenced by age groups. G8 >14 was related with better PFS (HR=0.79, *p*=0.06) and OS (HR=0.89, *p*=0.09). At multivariable model only neutrophils/lymphocytes ratio ≥3 was significantly associated with worse PFS (HR=1.91, *p*=0.03), while no variables with OS. **Conclusions:** Our results confirm the benefit of first-line immunotherapy for dMMR/MSI-H mCRC even among elderly pts treated in the real world, despite the substantial rate of right-sided and/or BRAF mut CRC pts and regardless of age group. The manageable safety profile of ICI(s) was also confirmed. G8 might be predictive of outcome but needs implementation in daily practice. Research Sponsor: None.

3540 **Poster Session**

Overall survival benefit of doublet versus triplet BRAF inhibitor–based therapy: Insights from the BEETS study (JACCRO CC-18). First Author: Chiaki Inagaki, Department of Medical Oncology, Kindai University Faculty of Medicine, Sakai, Osaka, Japan

Background: Cetuximab plus encorafenib, with or without binimetinib, is established as one of the standard treatment options for *BRAF* V600E-mutated metastatic colorectal cancer (mCRC) in the second- or later-line setting. Although the triplet therapy (encorafenib/cetuximab/binimetinib; T) is approved in Japan and commonly used for patients with poor prognostic features based on guideline recommendations, objective biomarkers to guide optimal patient selection remain lacking. Given the BREAKWATER trial support for first-line doublet therapy (encorafenib/cetuximab; D) with chemotherapy, the clinical role of MEK inhibitor–containing regimens may become more limited; nevertheless, the development of biomarkers capable of identifying patients who are likely to benefit from MEK inhibition remains an important unmet need. We therefore performed a prospective translational analysis within the BEETS study to identify biomarkers that guide treatment selection between T and D. **Methods:** BEETS (JACCRO CC-18: UMIN000045530) was a multicenter, prospective biomarker study of second/third-line encorafenib-based D or T regimen. We prospectively collected paired pre- and post-treatment blood samples, and analyzed pre-treatment tumor-educated platelet RNA by RNA sequencing (TEP-seq). To address baseline imbalances, propensity score matching (PSM) was performed using ECOG PS, number of metastatic organs (≥3), C-reactive protein (>1 mg/dL), and prior primary tumor resection. Interaction between gene expression (z-score) and treatment arm was evaluated using Cox proportional hazards models. Candidate biomarkers were prioritized based on $|\log2(HR)| \geq 0.5$ and $P < 0.05$. **Results:** Of 203 enrolled patients, 189 were evaluable for TEP-seq. After PSM, 81 patients per arm were analyzed. In the matched cohort, median overall survival (OS) was longer for D than T (17.4 months [m] vs. 10.2 m, HR 1.80; 95% CI:1.24–2.61). Interaction screening identified 44 genes for which higher expression was associated with better outcomes on D but worse outcomes on T, and six genes showing the opposite pattern. Among these candidates, *RAD51C* expression emerged as a representative marker; when dichotomized at the arm-specific median, higher expression favored T but indicated worse outcomes with D (*RAD51C* Low vs. High; T 7.8m vs. 10.6m, HR 0.79, 95%CI 0.49–1.28; D 28.2m vs. 12.9m, HR 2.02, 95%CI 1.16–3.53). Pathway-level exploration suggested a possible association between elevated *RAD51C* expression and increased MAPK-related signaling activity, potentially explaining the requirement for more intensive MEK inhibition in these patients. **Conclusions:** While OS was superior with D regimen in this matched cohort, *RAD51C* expression was identified as a candidate biomarker for identifying patients who may derive preferential benefit from MEK inhibition. Clinical trial information: UMIN000045530. Research Sponsor: None.

3542 **Poster Session**

Ultra–early-onset metastatic colorectal cancer (<35 years): RAS-driven, APC/TP53-depleted, TMB-low molecular features in a real-world analysis of 2,392 patients. First Author: Andrea Pretta, Medical Oncology Unit, University Hospital and University of Cagliari, Cagliari, Italy

Background: Early-onset colorectal cancer (CRC, <50 years) is on the rise globally and includes a biologically heterogeneous disease. Patients diagnosed before age 35 represent the extreme of early-onset CRC, yet their clinical and genomic features remain poorly understood. We investigated whether ultra–early-onset metastatic CRC (UEO-CRC, <35 years) exhibits distinct outcomes and a unique molecular profile in a large real-world cohort. **Methods:** We analyzed a multicenter cohort of 2,392 patients with metastatic CRC; 1,612 had comprehensive genomic profiling (Foundation Medicine) and were included in molecular analyses. Patients were classified as ≤35 years (n=130) or >35 years (n=1482) at metastatic diagnosis. Overall survival (OS) was assessed using Kaplan–Meier estimates and log-rank tests. Gene- and pathway-level differences were evaluated using Fisher's exact test. A composite UEO-CRC molecular signature was defined based on features significantly enriched or depleted in patients <35 years. **Results:** UEO-CRC represented 8.1% of metastatic cases. Patients ≤35 years had significantly worse survival than those >35 years (median OS 35.0 vs 46.0 months; p=0.0081). Molecular profiling revealed a distinct oncogenic pattern characterized by: enrichment of RAS mutations (KRAS 48.6% vs 36.4%, p=0.011; NRAS 11.7% vs 4.1%, p=0.0011); marked depletion of APC (21.6% vs 63.4%, p<0.001) and TP53 mutations (33.3% vs 63.8%, p<0.001); suppression of WNT pathway alterations (25.2% vs 66.9%, p<0.001); and genomic stability without hypermutation, including absence of TMB-high tumors (0% vs 7.5%, p=0.00037), lower median TMB (3.1 vs 4.8 mut/Mb, p<0.001), no MSI-H cases, and rare POLE/POLD1 or DDR alterations (4.5% vs 1.2%, p=0.017). Integration of these features identified a reproducible UEO-CRC molecular signature (RAS-mutant, APC/TP53 wild-type, TMB-low), over six-fold more frequent in UEO-CRC than in patients ≥35 years (32% vs 5%; p<0.001). **Conclusions:** Ultra–early-onset metastatic CRC (<35 years) represents a biologically aggressive and genomically distinct entity. UEO-CRC is defined by a non-canonical, RAS-driven, APC/TP53-independent tumorigenic program occurring without hypermutation, MSI-H, or POLE-driven biology. The lack of TMB-high indicates limited immunogenicity, emphasising the need for age-specific biological stratification and customised therapeutic strategies in this high-risk population. Research Sponsor: None.

3543 **Poster Session**

Survival outcomes of human epidermal growth factor receptor 2 (HER2)–amplified and HER2-mutated left-sided colorectal cancer (CRC) patients treated with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs). First Author: Yu Jen Alexander Jan, Division of Hematology-Oncology, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Current guidelines support the use of anti-EGFR mAbs in left-sided CRCs without mutations in *KRAS*, *NRAS* and *BRAF*. Recent reports indicated that HER2-amplified CRCs might respond worse to anti-EGFR mAbs, whereas HER2-mutated CRCs and their response to anti-EGFR mAbs remained relatively unexplored. In this study, we assembled the largest collection of HER2-altered (amplified or mutated) CRCs to date from a real-world database with the goal of describing the impact of these alterations on anti-EGFR mAb therapy. **Methods:** Patients profiled by Caris Life Sciences with microsatellite stable, left-sided CRC without mutations in *KRAS*/*NRAS*/*BRAF* who received anti-EGFR mAbs (cetuximab or panitumumab) were included in this study. Microsatellite stability, amplifications (copies ≥6), and pathogenic or likely pathogenic mutations were identified by NGS. Patient outcomes were obtained from insurance claims data. Overall survival (OS) was calculated from start of anti-EGFR mAbs to time of last clinical contact. Time on treatment (ToT) was calculated from start to end of anti-EGFR mAbs. Hazard ratios and p-values were calculated using the Cox proportional hazards model and log-rank test. **Results:** A total of 3217 patients were included for analysis. Patients were stratified into 3 cohorts: HER2-amplified (N=114), HER2-mutated (N=46), and HER2-normal (N=3057). The HER2-mutated group was older than the HER2-amplified and the HER2-normal groups (median: 64.5 vs 56 and 58 years, p=0.006); no other significant differences were found in patient demographics. The HER2-mutated group had worse OS and ToT than the HER2-normal group (median OS 12.4 vs 25.9 months, HR 1.57, p=0.013; median ToT 4.3 vs 6.7 months, HR 1.40, p=0.036). The HER2-amplified group showed no significant differences in OS but worse ToT compared to the HER2-normal group (median OS 26.1 vs 25.9 months, HR 0.98, p=0.856; median ToT 5.8 vs 6.7 months, HR 1.25, p=0.035). In multivariate Cox regressions accounting for age, gender, and receipt of HER2-targeted therapy, the HER2-mutated group had worse OS and ToT compared to HER2-normal group (OS HR 1.66, p=0.007; ToT HR 1.55, p=0.007), while the HER2-amplified group showed no significant differences in OS and ToT compared to HER2-normal group (OS HR 1.14, p=0.398; ToT HR 1.26, p=0.073). **Conclusions:** In this large, real-world cohort of *KRAS*/*NRAS*/*BRAF* wild-type, left-sided CRCs receiving anti-EGFR mAbs, HER2-mutated patients had worse ToT and OS than HER2-normal patients, whereas HER2-amplified patients showed no difference in OS compared to HER2-normal patients. These findings suggest that alternative treatment studies should be explored in HER2-mutated left-sided CRCs, underscoring the importance of additional biomarker-directed studies in this patient cohort. Research Sponsor: None.

3544 **Poster Session**

A phase Ib, open-label, clinical trial of JAB21822 combined with second-line chemotherapy for metastatic colorectal cancer with *KRAS* G12C mutation. First Author: Zhenghang Wang, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

Background: Glecirasib (JAB-21822), a novel, covalent, small molecule KRAS G12C-GDP covalent inhibitor, has been shown to be effective and safe as monotherapy or in combination with cetuximab in treating patients with refractory, unresectable locally advanced or metastatic colorectal cancer (mCRC) harboring KRAS G12C mutation. There are few data regarding the efficacy and safety of KRAS G12C inhibitor in the second-line setting. This multicenter, phase Ib, open label, single arm study aims to investigate the efficacy and safety of glecirasib in combination with the standard second-line chemotherapy and bevacizumab in patients with mCRC with KRAS G12C mutation who failed first-line treatment (NCT06838338). **Methods:** Patients (pts) with mCRC harboring KRAS G12C mutation were enrolled and treated with glecirasib (800mg QD) combined with standard second-line chemotherapy (FOLFIRI or FOLFOX) and bevacizumab until disease progression or intolerable toxicity or patient-initiated withdrawal from the study. The primary endpoint was confirmed objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), disease control rate (DCR), duration of response (DoR) and safety. **Results:** As of Dec 10, 2025, 26 pts were enrolled and received glecirasib combined with chemotherapy and bevacizumab in four centers. The median age was 58 years with female (54%)/male (46%), ECOG 0 (8%)/1 (92%). A total of 20 subjects had at least one post-baseline tumor assessment. The confirmed ORR and DCR were 50% (10/20) and 100% (10/20), respectively. Median DoR was 10.1 months (95%CI: 2.9, NE), median PFS was 11.5 months (95%CI: 5.5, NE). Any grade treatment-related adverse events (TRAEs) occurred in 23/26 (88.5%) pts, the most common ones (>20%) being diarrhea, nausea and anemia. Grade 3-4 TRAEs occurred in 6 (23.1%) pts. No grade 5 TRAEs occurred. **Conclusions:** Glecirasib in combination with the second-line standard chemotherapy and bevacizumab demonstrated encouraging efficacy and tolerable safety in the second-line treatment of mCRC patients with KRAS G12C mutation. Clinical trial information: NCT06838338. Research Sponsor: None.

3545 **Poster Session**

A prospective randomized controlled trial of FAPI PET/CT-guided radiotherapy combined with second-line standard systemic treatment and cadonilimab versus second-line standard systemic treatment alone in patients with peritoneal metastasis from colorectal cancer (TORCH-PM01). First Author: Juefeng Wan, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: This study evaluates the efficacy and safety of FAPI PET/CT-guided radiotherapy combined with second-line systemic treatment and cadonilimab compared to second-line systemic treatment alone in patients with peritoneal metastasis from colorectal cancer. **Methods:** In this prospective randomized controlled trial, we enrolled patients with peritoneal metastasis from colorectal cancer who progressed after first-line systemic therapy. Patients were randomly assigned to the control group, receiving second-line standard systemic treatment (n = 20), or the study group, which received hyopfractionated radiotherapy (20-25 Gy in 5 fractions) combined with second-line systemic treatment and cadonilimab (n = 20). The primary endpoint was overall response rate (ORR). A total of 40 patients were enrolled, with 19 evaluable patients in each group following loss to follow-up. **Results:** The ORR was significantly higher in the study group at 63.2% (12/19) compared to 15.8% (3/19) in the control group (p = 0.003). Adverse events (AEs) of grade 3-4 in the study group included neutropenia (26.3%, 5/19), nausea (15.8%, 3/19), vomiting (15.8%, 3/19), and diarrhea (15.8%, 3/19). In the control group, the most common grade 3-4 AE was neutropenia (21.1%, 4/19) and vomiting (10.5%, 2/19). Immune-related AEs of grades 1-2 in the study group included skin reactions (15.8%, 3/19), hypothyroidism (5.3%, 1/19), hepatitis (5.3%, 1/19), and myocarditis (15.8%, 3/19). One case of grade 3-4 skin reaction (5.3%) was observed in the study group. **Conclusions:** FAPI PET/CT-guided radiotherapy combined with second-line systemic treatment and cadonilimab significantly improves ORR in patients with peritoneal metastasis from colorectal cancer compared to standard second-line treatment alone, with manageable toxicity profiles. These findings support a promising therapeutic strategy for this challenging patient population. Clinical trial information: NCT07079462. Research Sponsor: None.

3546 **Poster Session**

A multicenter single-arm phase II trial evaluating the safety and efficacy of panitumumab and irinotecan in patients with Neo*RAS* wild-type metastatic colorectal cancer (C-PROWESS trial). First Author: Hiroki Osumi, Kanagawa Cancer Center, Department of Gastroenterology, Yokohama, Japan

Background: Previous studies have demonstrated favorable efficacy of anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) in metastatic colorectal (mCRC) patients with Neo*RAS* wild type (WT), ie, conversion of *RAS* status from mutant to WT following treatment. This multicenter, single-arm, phase II trial evaluated the efficacy and safety of panitumumab plus irinotecan for mCRC patients with Neo*RAS* WT. **Methods:** Patients with tissue-confirmed *RAS* mutant mCRC who developed intolerance to or disease progression after fluoropyrimidine, oxaliplatin, and irinotecan were screened for *RAS* mutation status in circulating tumor DNA (ctDNA) with the OncoBEAM RAS CRC assay. Those without *RAS* mutations detected within 28 days before enrollment received panitumumab (6 mg/kg) and irinotecan (150 mg/m^2) biweekly. The primary endpoint was a response rate (RR) per RECIST 1.1. Secondary endpoints included disease control rate (DCR; response or stable disease), progression-free survival (PFS), overall survival (OS), safety, and biomarker analysis using next-generation sequencing (NGS) of ctDNA (Guardant360). The null hypothesis was a RR of $< 4\%$, and the alternative hypothesis was $\geq 15\%$, with 80% power and a one-sided 10% significance level. The required sample size is 30. **Results:** Among 404 patients screened for *RAS* status in ctDNA, conversion to Neo*RAS* WT was observed in 54 (13.3%), and 30 patients were enrolled. Median age was 66.5 years old, and 20 (66.7%) were male. Lung was the most frequent site of metastasis (73.3%), and *KRAS* exon 2 accounted for 80% of prior tissue *RAS* MT. RR and DCR were 6.7% (80% CI, 1.8 to 16.8) and 76.7% (95% CI, 57.7 to 90.1), respectively. With median follow-up 22.4 months, median PFS was 4.1 months and median OS was 16.8 months. Grade 3 adverse events were observed in 14 patients (46.7%): skin toxicity (13.3%), hypomagnesemia (10.0%), diarrhea (10.0%), appetite loss (10.0%), and anemia (7.0%). No grade $\geq$4 adverse event was observed. ctDNA NGS results were available for 27 patients and included *KRAS* (44.4%), *NRAS* (3.7%), and *PIK3CA* (7.4%) mutations and *ERBB2* amplification (3.7%). RR for patients with none of these mutations (negative hyper-selection cohort) was 16.7% (2/12) while no patient with any of these alterations achieved a response (0/15). Negative hyper-selection was associated with significantly longer PFS and OS (PFS: 6.1 vs 2.9 months, HR, 0.37, 95% CI, 0.16 to 0.87; OS: 25.5 vs 13.1 months, HR, 0.34, 95% CI, 0.12 to 0.99). In multivariate analysis, negative hyper-selection was an independent factor for PFS (HR, 0.12, 95%CI, 0.03 to 0.41) and OS (HR, 0.30, 95%CI, 0.10 to 0.96). **Conclusions:** Anti-EGFR mAb with chemotherapy may be effective for Neo*RAS* WT mCRC, especially for patients hyper-selected for absence of gene mutations related to anti-EGFR mAb resistance. Clinical trial information: s031210565. Research Sponsor: None.

3547 **Poster Session**

Serum VEGF-A concentrations as a predictive biomarker of immunotherapy response in refractory metastatic colorectal cancer (mCRC): An exploratory analysis of CCTG CO.26. First Author: François Jobin Gervais, Princess Margaret Cancer Centre-University Health Network, Toronto, ON, Canada

Background: Benefits of immune checkpoint inhibitors (ICIs) in unselected proficient mismatch repair (pMMR) mCRC remain unestablished. This exploratory analysis of CCTG CO.26 evaluated whether serum VEGF-A concentrations may influence ICI efficacy. **Methods:** CCTG CO.26 was a phase II trial that randomized refractory mCRC patients (pts) (2:1) to Durvalumab + Tremelimumab + Best supportive care (DT) vs Best supportive care (BSC) alone and was positive for overall survival (OS). VEGF-A concentrations were determined in baseline serum samples using an ELISA method. OS and progression-free survival (PFS) were compared between high and low groups based on median VEGF-A concentration in each treatment arm. An optimal cutoff was also identified using a minimal p-value approach. *VEGFA* mRNA expression from tissue-based RNA-seq was analyzed in the INSPIRE study, a separate, single arm, multicohort phase II trial comprising multiple tumor types treated with pembrolizumab for external validation. **Results:** Baseline VEGF-A concentrations were available for 161 pts (47 BSC, 114 DT). Median VEGF-A concentration was 1166 pg/ml (range: 226 – 4898; IQR: 784-1755). VEGF-A concentrations were significantly higher in ECOG 1 vs 0 pts (p = 0.03), and in pts who had previously received regorafenib (p = 0.03). Grouped by median VEGF-A, median OS was longer in DT-treated patients with low VEGF-A (7.39 months for DT-Low vs. 6.08 DT-high; hazard ratio (HR) 0.62, 95% confidence interval (CI): [0.42–0.90], p = 0.01), but not in BSC treated patients (4.44 months BSC-Low vs. 4.11 BSC-High; HR 1.05 [0.57–1.92], p = 0.88; interaction HR 0.56 [0.28–1.14], p = 0.11). An optimal VEGF-A threshold of 1540 pg/mL was identified using a minimal p-value approach, with 33.5% pts having high VEGF-A concentrations. Median OS was 7.29 vs 4.37 months for DT-Low and DT-High pts (HR 0.53 [0.35–0.80], $p < 0.005$), and 3.55 vs 7.46 months for BSC-Low and BSC-High pts (HR 1.50 [0.80–2.80], p = 0.21; interaction HR 0.33, [0.16–0.70], $p < 0.005$). In multivariable analyses incorporating ECOG, presence of liver metastases, plasma tumor mutation burden and arginine levels, low VEGF-A concentrations remained statistically associated with improved OS with DT (HR 0.46 [0.30–0.70], $p < 0.001$; interaction HR 0.18 [0.083–0.41], $p < 0.0001$). There was no association between VEGF-A concentrations and PFS in any arm. In the INSPIRE study (n = 66), *VEGFA* mRNA expression was lower in responders ($p < 0.001$) and significantly associated with improved PFS (HR 0.45 [0.25–0.79], p = 0.006) and OS (HR 0.47 [0.26–0.85], p = 0.013) across tumor types. **Conclusions:** Refractory mCRC patients with low VEGF-A concentrations may derive benefit from ICIs. This is the first report to suggest that serum VEGF-A concentration is a potential predictive biomarker for benefit from ICIs. These findings should be prospectively validated. Research Sponsor: None.

3548 Poster Session

Antitumor activity of amivantamab by consensus molecular subtypes in *RAS/BRAF* wild-type metastatic colorectal cancer: Secondary analyses from the phase 1b/2 OrigAMI-1 study. First Author: Marcia Roxana Cruz-Correa, University of Puerto Rico and Pan American Center for Oncology Trials, San Juan, Puerto Rico

Background: Colorectal tumors are classified by mutational subtypes and sidedness, which inform treatment and outcomes. They can also be classified into four Consensus Molecular Subtypes (CMS1–4), with CMS2 (*EGFR*-dependent, canonical) typically showing better prognosis and CMS4 (*EGFR*-independent, MET pathway associated, mesenchymal) associated with poor prognosis and limited response to traditional EGFR inhibition (Thanki *Int Biol Biomed J* 2017, Woolston *Cancer Cell* 2019). In prior analyses, cetuximab monotherapy demonstrated greater antitumor activity against CMS2 *RAS* wild-type (WT) vs CMS4 *RAS* WT tumors (disease control rate [DCR]: 68% vs 29%; Chowdhury *JCO Precis Oncol* 2023), suggesting CMS4 may limit cetuximab efficacy de novo. Additionally, CMS2 to CMS4 subtype switching has been described as a cetuximab monotherapy resistance mechanism (Woolston *Cancer Cell* 2019). Amivantamab, an EGFR–MET bispecific antibody approved for *EGFR*-mutated NSCLC, has demonstrated antitumor activity in refractory metastatic colorectal cancer (mCRC), independent of sidedness. Given the role of *MET* in mesenchymal subtypes (CMS4), targeting with amivantamab could demonstrate antitumor activity in both CMS2 and CMS4. **Methods:** OrigAMI-1 (NCT05379595) enrolled participants with mCRC harboring WT *KRAS*, *NRAS*, *BRAF*, and *EGFR* ectodomain and without *ERBB2/HER2* amplification. Participants with left-sided mCRC without (Cohort A) or with prior anti-EGFR therapy (Cohort B), and those with right-sided disease (Cohort C), received intravenous amivantamab monotherapy. All enrolled participants had 2–3 prior lines of therapy in the metastatic setting. CMS assignment and expression changes in key EGFR/MET ligands at baseline (n = 76) and Cycle 3 Day 1 (C3D1; n = 17) were analyzed by whole-transcriptome RNA-sequencing of biopsies. **Results:** CMS2 (canonical) and CMS4 (mesenchymal) comprised ~95% of tumors. Clinical outcomes for CMS2 (n = 42) and CMS4 (n = 31) were comparable: median PFS was 4.2 vs 5.3 months (P =0.5), respectively, and median OS was 11.3 vs 13.5 months (P= 0.6). PFS and OS within CMS2 and CMS4 subgroups remained consistent across sidedness. Overall response rate and DCR were comparable between CMS2 and CMS4 (26% vs 16% and 83% vs 74%, respectively). Genomic profiles derived from ctDNA were similar for CMS2 and CMS4; however, baseline *AREG/EREG* mRNA expression was higher in CMS2. Paired biopsies demonstrated antitumor activity with or without subtype switching at C3D1. Amivantamab treatment generally decreased *AREG/EREG* and increased *HGF* expression, independent of subtype or response. **Conclusions:** Amivantamab monotherapy demonstrated consistent antitumor activity in both canonical, *EGFR*-dependent (CMS2) and mesenchymal, *EGFR*-independent (CMS4) tumors unlike traditional EGFR inhibitors in refractory *RAS/BRAF* WT mCRC. Clinical trial information: NCT05379595. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

3549 Poster Session

First-in-human study of cavitation-enhanced drug delivery (CEeDD) by sonosensitive particles and focused ultrasound applied to colorectal metastases in the liver. First Author: Jeffrey Rubasingham, Oxford University, Oxford, United Kingdom

Background: Effective treatment of colorectal liver metastases is limited by poor drug delivery, particularly for monoclonal antibodies, the large molecular weight of which, together with abnormal tumor vasculature, elevated interstitial pressure and dense stromal architecture, restricts penetration and distribution into solid tumors. This first-in-human study evaluated a novel platform combining intravenously infused sub-micron gas-stabilizing sonosensitive particles with novel handheld ultrasound probe to cause cavitation that enhances the transport of systemically co-administered therapeutics (i.e. cetuximab/irinotecan) from the vasculature into tumors, without the need to modify these therapeutics. **Methods:** The study comprised 3 patient cohorts. Cohort 1 evaluated the safety of ultrasound activation of intravenously infused sonosensitive particles alone, without drug. With safety confirmed, Cohort 2 assessed intratumoural drug concentration in patients undergoing surgical resection after receiving subtherapeutic irinotecan and cetuximab, with or without ultrasound-activated particles. Cohort 3 evaluated early efficacy in patients receiving standard of care FOLFIRI and cetuximab, with or without cavitation in repeated treatment cycles. Primary endpoints were grade 3 or higher adverse events in Cohort 1, intratumoural drug concentrations in Cohort 2, and radiological tumor response in Cohort 3. **Results:** In Cohort 2, seven evaluable patients underwent resection, with 4 in the control arm and 3 in the ultrasound-mediated-cavitation arm. Mean cetuximab concentrations were modestly higher in the tumour centre (3.6 vs 3.2 ng/mL) and mid radius (4.1 vs 3.7 ng/mL), and substantially higher at the tumour periphery (7.1 vs 3.7 ng/mL) in the ultrasound-mediated-cavitation arm, while liver margin levels were comparable. There was no appreciable beneficial difference in the mean tumour concentrations of irinotecan and its metabolites between the two arms. In Cohort 3, 10 evaluable participants completed at least 3 treatment cycles (control n=3; cavitation n=7). Objective response rate was 66.7% in the control arm versus 85.7 % with cavitation. **Conclusions:** Cavitation with sonosensitive particle infusion demonstrated a favourable safety profile, increased intratumoural antibody delivery, and showed early signals of enhanced anti-tumour activity, supporting further clinical development. Clinical trial information: ISRCTN17598292. Research Sponsor: National Institute for Health Research (NIHR), UK.

Cohort	Number treated	Primary endpoint	Key findings
1	9	Safety	No grade 3 or higher events; sustained cavitation in the target region.
2	7	Drug levels	Increased cetuximab concentrations in the tumours treated with cavitation (7.1 vs 3.7 ng/mL)
3	10	Radiological response	Enhanced radiological response (ORR of 85.7% in patients treated with cavitation)

ORR = objective response rate based on FDG PET-CT.

3550 Poster Session

Negative hyperselection as a predictive biomarker of benefit from first-line doublets + anti-EGFRs/bevacizumab (bev) in microsatellite stable (pMMR/MSS) *RAS* and *BRAF* wild-type (wt) and HER2− metastatic colorectal cancer (mCRC): An individual patient data pooled analysis of seven clinical trials (CTs). First Author: Marco Maria Germani, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: Primary tumor sidedness is nowadays a major driver for the choice of biologics in the first line of pMMR/MSS *RAS* and *BRAF* wt mCRC patients (pts). It has been suggested that it might be replaced by a broader molecular profiling, but the evidence provided by individual trials is uncertain for the adoption of different panels and underrepresentation of gene-altered cases. We recently showed that HER2+ status does not predict resistance to first-line doublets + anti-EGFRs. **Methods:** We collected individual patient data from 7 CTs in first-line mCRC: TRIBE2, TRIPLETE, VALENTINO, CAPRI-2, FIRE-3, PARADIGM and CALGB/SWOG80405. pMMR/MSS *RAS* and *BRAF* wt and HER2− cases treated with doublets + anti-EGFRs/bev with available NGS data were included. Hyperselected tumors were those without *MET+* status, *ALK/ROS1/NTRKs/RET* fusions, and *HER2/PIK3CAexon20/PTEN/AKT1* mutations. Propensity score adjustment was used to assess clinical outcomes (aHR and aOR) according to first-line doublets + anti-EGFRs/bev. **Results:** Out of 1198 included pts, 990 (83%) had left-sided and 208 (17%) right-sided tumors. Anti-EGFR based regimens were associated with numerically longer OS (aHR: 0.86) in left-sided tumors, but not in right-sided ones (aHR: 0.98), with an insignificant p for interaction [int] = 0.60). Hyperselected and gene-altered cases were 1077 (91%) and 121 (9%), respectively. The anti-EGFR benefit in OS was magnified in hyperselected pts (aHR: 0.83), with an aHR of 1.16 in gene-altered ones (p_{int} =0.11, adjusted also for tumor sidedness). As reported in the table, there was no interaction between the effect of biologics and primary tumor location either in the hyperselected (p_{int} =0.86) or in the gene-altered group (p_{int} =0.41). **Conclusions:** Hyperselection outperforms tumor sidedness as a predictive marker of benefit from doublets + anti-EGFR/bev in pMMR/MSS *RAS/BRAF* wt and HER2− mCRC. The OS benefit from anti-EGFR-based regimens is restricted to pts with hyperselected tumors, independently of primary tumor location. Therefore, in hyperselected mCRC, doublets + anti-EGFRs remain the standard for left-sided pts and may deserve consideration in right-sided ones. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); NextGenerationEU through the Italian Ministry of University and Research.

	Hyperselected					Gene-altered				
	Left		Right		P_{int}	Left		Right		P_{int}
	Anti-EGFRs N=537	Bev N=365	Anti-EGFRs N=87	Bev N=88		Anti-EGFRs N=57	Bev N=31	Anti-EGFRs N=19	Bev N=14	
ORR (%)	81	67	72	65		74	52	58	57	
aOR [95% CI]	2.29 [1.67 – 3.14]		1.44 [0.75 – 2.77]		*0.24*	3.48 [1.29 – 9.97]		1.02 [0.25 – 4.20]		*0.23*
mPFS*	13.2	12.9	11.1	10.2		11.2	11.3	8.0	8.8	
aHR [95% CI]	1.02 [0.88 – 1.19]		1.01 [0.73 – 1.39]		*0.73*	1.06 [0.63 – 1.77]		1.23 [0.57 – 2.66]		*0.75*
mOS*	38.8	35.5	34.6	29.2		30.2	27.4	20.2	32.1	
aHR [95% CI]	0.84 [0.71 – 0.98]		0.85 [0.61 – 1.17]		*0.86*	1.05 [0.63 – 1.75]		1.46 [0.66 – 3.22]		*0.41*

*Months.

3552 Poster Session

A phase II trial of fruquintinib combined with cadonilimab in refractory MSS/pMMR colorectal cancer with pulmonary metastases. First Author: Mengzhou Guo, Department of Medical Oncology, Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Immunotherapy for metastatic colorectal cancer (mCRC) with microsatellite stable/proficient mismatch repair (MSS/pMMR) remains limited. Emerging evidence suggests that the combination of antiangiogenic agents and immune checkpoint inhibitors (ICIs) exhibits synergistic antitumor effects in refractory MSS/pMMR mCRC, particularly among patients (pts) with isolated lung metastases. This open-label, single-arm, phase II trial aims to evaluate the efficacy and safety of fruquintinib plus cadonilimab in pts with MSS/pMMR mCRC who progressed after at least two prior lines of therapy. **Methods:** Patients aged≥18 years, with pathologically confirmed MSS/pMMR mCRC presenting pulmonary metastases and no liver metastases, and who had experienced failure of at least second-line therapy were enrolled. Eligible patients received oral fruquintinib (3 mg once daily) plus intravenous cadonilimab (6 mg/kg every two weeks) until disease progression, unacceptable toxicity, or withdrawal of consent. Tumor assessments were performed every 8 weeks. The primary endpoint was objective response rate (ORR), and secondary endpoints included overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. **Results:** From February 2024 to June 2025, 37 pts were enrolled [median age 61 years, 68% male, 89% ECOG 0-1, 62% RAS mutant, 30% 3L+, 73% prior bevacizumab, 3 pts prior immunotherapy]. The ORR was 31.4%, and the DCR was 71.4%. Median PFS was 6.1 months (95%CI: 4.8-7.5), while OS data remain immature. Moreover, the patients with a history of liver metastases showed a trend toward shorter PFS compared to those without (4.0 vs. 6.9 months; P = 0.194). The most common treatment-related adverse events (AEs) were hypothyroidism (43%), elevated ALT/AST (27%), hypertension (24%), diarrhea (24%), thrombocytopenia (19%), hand-foot syndrome (16%), and rash (16%). Grade ≥3 treatment-related AEs occurred in 10 (27%) pts. Serious adverse events (SAEs) were reported in 5 pts, with no grade 4 or 5 SAEs observed. **Conclusions:** The combination of fruquintinib and cadonilimab demonstrated promising clinical activity and a manageable safety profile in patients with refractory MSS/pMMR mCRC. Clinical trial information: ChiCTR2400079429. Research Sponsor: National Natural Science Foundation of China (82573146).

3553 **Poster Session**

Detecting *MTAP* loss in liquid biopsies from patients with clinically advanced colorectal cancer (CRC). First Author: Xuanyi Li, Yale Cancer Center, New Haven, CT

Background: Homozygous loss of the *MTAP* gene (*MTAP* loss) is an emerging biomarker guiding investigational use of PRMT5 and MAT2A inhibitors in a wide variety of tumor types, including CRC. Detecting copy number changes, including homozygous losses, in solid tumors is often challenging and requires robust assay and analytic pipeline especially when the amount of extracted DNA is small. In clinically advanced CRC, small endoscopic and needle-based biopsies are often used for diagnosis, imposing significant limitations on immunohistochemistry (IHC) and comprehensive genomic profiling (CGP) required for treatment selection and clinical trial enrollment. We assessed whether liquid biopsy (LBx) CGP could provide treatment-relevant information on *MTAP* loss compared to tissue biopsy (TBx) CGP for patients with CRC. **Methods:** Hybrid capture-based CGP was performed on 46,173 clinically advanced CRC (stage III, IV) TBx cases using the FoundationOne CDx assay and on 9,049 LBx cases using the FoundationOneLiquid CDx assay. Tumor fraction (TF) for each LBx sample was determined using assessments of aneuploidy and variant allele frequencies, as previously described. **Results:** *MTAP* loss was detected in 498 (1.08%) TBx cases. For LBx, detection of *MTAP* loss increased with higher TF, with detections observed only at TF ≥5% (Table 1). With TF ≥5%, the frequency of *MTAP* loss detection was comparable to or exceeds that observed with TBx. Regarding complete vs partial *MTAP* exon loss, TBx and LBx showed similar patterns, with complete loss of all 8 *MTAP* exons observed in 85.7% of TBx cases and 84.5%-89.8% in LBx cases, increasing in higher TF levels. **Conclusions:** LBx emerges as a promising tool for detecting *MTAP* loss in clinically advanced CRC, with *MTAP* loss detection rates approaching those of TBx when LBx TF is ≥5%, while detection is limited at lower TF levels. Incorporation of LBx for *MTAP* loss detection may expand patient access to biomarker-driven clinical trials involving PRMT5 and MAT2A inhibitors for patients with clinically advanced CRC when sufficient tissue for tissue-based CGP is not feasible. Research Sponsor: None.

***MTAP* loss detected by TBx and LBx in clinically advanced CRC.**

Cohort (cumulative)*	*MTAP* no loss	*MTAP* loss	*MTAP* loss frequency
TBx (n=46173)	45675	498	1.08%
LBx TF ≥0% (100% of LBx, n=9049)	9002	47	0.52%
LBx TF ≥1.0% (62.7% of LBx)	5624	47	0.83%
LBx TF ≥5.0% (48.7% of LBx)	4359	47	1.07%
LBx TF ≥10.0% (41.5% of LBx)	3712	46	1.22%
LBx TF ≥20.0% (31.5% of LBx)	2812	38	1.33%
LBx TF ≥30% (24.8% of LBx)	2214	29	1.29%

*TF thresholds represent cumulative subsets of the LBx cohort.

3554 **Poster Session**

Tumor cell-intrinsic programs of metabolic adaptation and immune evasion in colorectal cancer liver metastases (CRCLMs). First Author: Xuanyi Li, Yale Cancer Center, New Haven, CT

Background: CRCLMs account for the majority of colorectal cancer (CRC)-related mortality and represent a key site of immunotherapy resistance. The tumor cell-intrinsic molecular programs enabling adaptation to the liver microenvironment and immune evasion remain poorly defined. **Methods:** We performed spatial whole transcriptomic analysis of 189 patient-matched primary CRC and CRCLM samples from two independent cohorts (Cohort 1 = 47; Cohort 2 = 141). Samples were represented using tissue microarrays and analyzed using the GeoMx Digital Spatial Profiling (DSP) platform. Two ROIs (tumor cell [CK] and stroma [DAPI]) were analyzed per sample, with analyses focused on tumor cells. Differential expression analyses were conducted independently within each cohort. Results were integrated using Fisher's combined probability method for batch-aware meta-analysis. Expression of selected transcripts in tumor and matched non-tumor tissue in TCGA and associated survival outcomes were evaluated using the GEPIA2 webtool. Gene set enrichment analysis (GSEA) was applied to identify consistently altered biological pathways. Exploratory LASSO regression using normalized expression values identified gene sets distinguishing liver metastases from primary tumors. **Results:** We identified multiple genes consistently enriched in malignant cells from CRCLM compared to primary CRC. Prioritized genes include MMP10 (logFC = 0.41, p = 0.007), KRT17 (logFC = 0.87, p < 0.001) and PLA2G2A (logFC = 0.72, p = 0.002), all showing higher tumor expression relative to normal tissue, association with unfavorable survival, and translational relevance (Table 1). GSEA revealed enrichment of acute-phase response (NES = 1.86, FDR = 0.003), complement activation (NES = 1.81, FDR = 0.002) and xenobiotic metabolism (NES = 1.71, FDR = 0.006) in liver metastases, together with reduced antigen processing and presentation (NES = -1.78, FDR = 0.012). Exploratory LASSO regression yielded cohort-specific gene signatures with limited gene-level overlap but convergence on shared biological programs distinguishing CRCLM from primary CRC, including epithelial and metabolic pathways. Of note, PLA2G2A was among the selected features in an independent cohort, reinforcing its association with CRCLM. **Conclusions:** We identified tumor cell-intrinsic programs in CRCLMs consistent with cellular metabolic adaptations and immune evasion with potential relevance in disease progression and treatment resistance. Our analyses also identified genes, including MMP10, KRT17, and PLA2G2A, as potential therapeutic vulnerabilities in CRCLMs for future investigation. Research Sponsor: None.

Prioritized liver metastasis-enriched genes.

Gene	Translational Relevance
MMP10	Enzymatic target; inhibitor scaffolds exist
KRT17	Tumor-specific biomarker/pathway proxy
PLA2G2A	Enzymatic target; pathway inhibition feasible

3555 **Poster Session**

Tumor shrinkage and depth of response with fruquintinib in patients with metastatic colorectal cancer: Results from FRESCO and FRESCO-2. First Author: Elena Elez, Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: In metastatic colorectal cancer (mCRC), early tumor shrinkage (ETS) and depth of response (DpR) are predictors of overall survival (OS) and progression-free survival (PFS). Durable stable disease (SD) also reflects disease control and can contextualize PFS and OS improvements. The phase 3 FRESCO (F) and FRESCO-2 (F2) trials of fruquintinib vs placebo in patients (pts) with mCRC showed significantly longer OS (F median: 9.3 vs 6.6 months [mo], HR 0.65, P<0.001; F2 median: 7.4 vs 4.8 mo, HR 0.66, P<0.001) and PFS (F median: 3.7 vs 1.8 mo, HR 0.26, P<0.001; F2 median: 3.7 vs 1.8 mo, HR 0.32, P<0.001) with fruquintinib. We report a post-hoc analysis of tumor shrinkage (TS), ETS, and DpR, and the correlation with OS and PFS in F and F2. **Methods:** Pts were randomized to receive fruquintinib + best supportive care (BSC; F n=278; F2 n=461) or placebo + BSC (F n=138; F2 n=230). Tumors were assessed at screening and every 8 weeks until progressive disease (PD). TS was defined as a decrease from baseline in the sum of the longest diameters of target lesions; ETS was TS by the first post-treatment assessment; duration of TS (DTS) was time from first TS to first tumor size increase, PD, or death; in pts with best overall response of SD, duration of SD was assessed as the time from first occurrence of SD to PD/death; and DpR was the maximum percentage change from baseline in the sum of the longest diameters of target lesions. OS and PFS were assessed in pts who received fruquintinib and had TS/ETS. **Results:** In F, 129 (46%) fruquintinib-treated pts had TS, of which 124 (45%) achieved ETS; with placebo, 5 pts (4%) had TS and ETS. In F2, similarly, 178 (39%) fruquintinib-treated pts had TS, of which 154 (33%) achieved ETS; with placebo, 15 pts (7%) had TS and 13 pts (6%) had ETS. In pts with TS in F and F2, median DTS with fruquintinib was 1.9 and 2.0 mo, respectively. Median duration of SD was longer with fruquintinib vs placebo in both F (5.5 vs 3.7 mo) and F2 (5.6 vs 3.7 mo). Magnitude of DpR was greater with fruquintinib vs placebo in both trials. In F and F2, median OS and PFS in pts who received fruquintinib were longer in those who achieved TS and ETS vs the ITT fruquintinib arm (Table). **Conclusions:** ETS was observed in most fruquintinib-treated pts with TS in both F and F2 (F: 96% [124/129 pts]; F2: 87% [154/178 pts]); pts with both TS and ETS showed longer median OS and PFS compared with the fruquintinib ITT population. These data indicate that TS and ETS appear to be predictors of OS and PFS outcomes, and support the prognostic relevance of TS, ETS, and DpR in pts with mCRC. Clinical trial information: NCT02314819 and NCT04322539. Research Sponsor: Takeda Pharmaceuticals U.S.A., Inc., Cambridge, MA.

OS and PFS in pts who received fruquintinib with TS/ETS vs the ITT fruquintinib arm in F and F2.

Months (95% CI)	With TS	With ETS	ITT Fruquintinib arm
F	**n = 129**	**n = 124**	**N = 278**
OS	12.1 (10.8–14.9)	11.6 (10.7–14.9)	9.3 (8.2–10.5)
PFS	5.5 (5.5–7.3)	5.5 (5.5–6.6)	3.7 (3.7–4.6)
F2	**n = 178**	**n = 154**	**N = 461**
OS	10.9 (9.9–12.5)	10.8 (8.9–12.7)	7.4 (6.7–8.2)
PFS	5.6 (5.4–6.2)	5.6 (5.1–5.8)	3.7 (3.5–3.8)

3556 **Poster Session**

Evaluation of circulating tumor DNA (ctDNA) following liver resection in a high-risk population with colorectal liver metastases. First Author: John Neil Primrose, Cancer Sciences, University of Southampton, Southampton, United Kingdom

Background: Liver resection is routinely performed for oligometastatic colorectal cancer (CRC). ctDNA analysis is becoming important in the management of primary CRC following surgery, but in patients with liver metastases, its role is less clear. This study aimed to evaluate the performance of a plasma ctDNA assay for early detection of recurrence in patients with liver only CRC metastases post surgical resection. The cohort included patients who had inoperable disease prior to induction chemotherapy and those having repeat resections. Patients with the primary cancer in situ were included if a synchronous resection was performed. **Methods:** 61 patients (42 male, median age 68 [range 41-85]) were studied. All patients had CRC liver metastases as the sole metastatic site on evaluation by CT and MRI. Patients were followed up clinically with regular CT imaging. Plasma samples were collected at baseline (pre-surgery, n = 55) and 5 days to 1+ year after surgery, and were tested retrospectively on a blood-only, tumor-agnostic, targeted methylation assay that interrogates informative methylation regions for signal indicative of ctDNA using a machine learning classifier (GRAIL, Inc., Menlo Park, CA). **Results:** ctDNA was detected in 94.5% (52/55) of patients at the pre-surgery timepoint. During clinical surveillance, 46 developed recurrence, 5 had no recurrence for at least 2 years after surgery, and 10 had follow-up for less than 2 years. Among patients with recurrence, ctDNA was detected in 80.4% (37/46) of patients before recurrence, with a median lead time of 245 days [IQR: 65 - 393 days]. All five patients who remained recurrence-free for at least 2 years had undetectable ctDNA following surgery. ctDNA was detected in 57.8% (26/45) of patients who recurred and had plasma collected within 3 months following surgery. Recurrence-free survival (RFS) was significantly lower in patients with ctDNA detected within 3 months after surgery (median RFS 272 vs. 593 days, log-rank p-value < 0.01). **Conclusions:** ctDNA analysis using a methylation-based assay allowed the detection of minimal residual disease and the prediction of recurrence in many patients following resection of CRC liver metastases. These data support the potential use of this biomarker for patient management pending confirmation in prospective clinical studies. Research Sponsor: None.

3557 **Poster Session**

Screening for intrinsic and acquired resistance mutations to anti-EGFR in real-world MSS colorectal cancer data. First Author: Matthew B. Maxwell, Tempus AI, Inc., Chicago, IL

Background: Anti-EGFR (cetuximab, panitumumab) plus doublet chemotherapy is the first line standard of care for metastatic MSS left-sided RAS/RAF WT colorectal cancer (CRC). However, anti-EGFR clinical efficacy is limited by intrinsic and acquired resistance. Defining anti-EGFR intrinsic resistance mutations could improve patient selection for anti-EGFR treatment while defining anti-EGFR acquired resistance mutations could enable early detection of resistance via liquid biopsy. **Methods:** The intrinsic resistance cohort consisted of 163 metastatic MSS RAS/RAF WT colon adenocarcinoma patients treated in the first line with anti-EGFR with a DNA-seq sample collected before treatment (Tempus xT or xF). We screened mutations for anti-EGFR intrinsic resistance defined as HR $>$ 2 for PFS via univariate CoxPH models. The anti-EGFR acquired resistance cohort consisted of 228 MSS CRC patients with a DNA-seq sample (xT or xF) within 12 months prior to and 0.5-24 months post treatment. We defined acquired resistance mutations as those significantly enriched post-treatment vs pre-treatment via McNemar test. An anti-VEGF acquired resistance cohort of 748 MSS CRC patients was used as a control. Enrichment of targetable gene fusions post-treatment was assessed via Wilcoxon test. FDR $<$ 0.05 was considered significant. **Results:** The screen for intrinsic resistance mutations returned a single significant hit of *PIK3CA* non-exon 9 mutations (~3%, $p <$ 0.01), while *PTEN* deletions (~2%), which are functionally similar, were also associated with shorter PFS but did not reach significance (p=0.08). *PIK3CA* non-exon 9 mutation or *PTEN* deletion were detected in ~5% of patients (n=9) and were associated with shorter PFS (HR = 3.6, 95% CI: 1.7-7.6, $p < 0.001$) and OS (HR = 2.6, 95% CI: 1.03-6.5, $p < 0.05$). Median PFS and OS were 6 and 14 months for patients with these resistance alterations, versus 11 and 29 months for non-altered patients. In a CoxPH model including age, sex, sidedness, and collection procedure, these alterations maintained a significant association with PFS (HR =5.2, 95% CI: 2.2-12.4, $p < 0.01$) but not OS (HR=2.7, 95% CI: 0.9-8.9, p=0.08). Analysis of acquired resistance to anti-EGFR treatment yielded significant mutation hits—*KRAS, NRAS, EGFR*, and *MAP2K1*—as well as significant enrichment of targetable fusions (*BRAF, FGFR, NTRK, ALK, ROS1, RET, NRG1*). No mutations or fusions were observed to be associated with anti-VEGF acquired resistance. **Conclusions:** Patients harboring *PIK3CA* non-exon 9 mutation or *PTEN* deletion displayed intrinsic resistance to anti-EGFR therapy despite being RAS/RAF WT and may be offered anti-EGFR therapy per oncology guidelines. This small underrepresented subset of patients may not benefit from anti-EGFR therapy. Prospective clinical validation will be needed to determine if this subset of PI3K pathway alterations has utility in optimizing first line therapy selection. Research Sponsor: FightCRC.

3559 **Poster Session**

BAYONET trial: A multicenter phase II trial of staged combination with encorafenib + binimetinib + cetuximab following encorafenib + cetuximab in patients with *BRAF*V600E-mutant metastatic colorectal cancer. First Author: Takeshi Yamada, Department of Gastroenterology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

Background: While the doublet combination of encorafenib (ENCO) + cetuximab (CET) is a standard treatment for patients with *BRAF*V600E-mutant metastatic colorectal cancer (mCRC), poor prognosis is expected after disease progression. As resistant mechanisms to BRAF + EGFR blockade, several MAPK pathway alterations, including *RAS* and *RAF* mutations, have been reported, suggesting that additional blockade of MAPK signaling may be an effective strategy. Furthermore, preclinical studies demonstrated that *BRAF* V600E-mutant colorectal cancer cell lines resistant to BRAF inhibitor + anti-EGFR antibody were sensitive to the triple combination of BRAF inhibitor + MEK inhibitor + anti-EGFR antibody. **Methods:** BAYONET is a single-arm, multicenter phase II trial designed to evaluate the efficacy and safety of the staged combination with ENCO, binimetinib (BINI), plus CET for patients with *BRAF* V600E-mutant mCRC who were refractory to ENCO plus CET. The main eligibility criteria are as follows: *RAS* wild-type/*BRAF* V600E-mutant mCRC; age $\geq$ 20; ECOG PS 0 or 1; within 4 weeks from the last administration of previous ENCO or CET; no administration of other systemic therapy after refractoriness to ENCO + CET; complete response, partial response, or $\geq$4 months of stable disease was observed in the previous ENCO + CET. Included patients receive the combination treatment of ENCO (300 mg once a day) + BINI (45 mg twice a day) + CET (400 mg/m^2 initial dose and then 250 mg/m^2 once a week) in a 28-day cycle. The primary endpoint of this trial is 12-week progression-free survival (PFS) rate. The targeted sample size was calculated to be 30 on the basis of a power of 80%, a significance level of 10% (one-sided), a threshold of 20%, and an expected 12-week PFS rate of 40%. Pretreatment ctDNA analysis was performed using the Guardant360 assay. **Results:** Among 30 patients, all had microsatellite-stable or mismatch repair-proficient tumors, and 21 (70%) of patients received prior $<$3 treatment lines. The locally assessed 12-week PFS rate was 33.3% (80% CI, 21.8–46.6). Since the lower limit of 80% CI exceeded 20%, the primary endpoint was met. With a median follow-up duration of 9.8 months (range, 2.1–35.8), the median PFS was 2.0 months (95% CI, 1.6–4.2), and the median overall survival was 14.7 months (95% CI, 7.1–18.7). Patients who achieved 12-week PFS had significantly lower ctDNA *BRAF* V600E VAF (median, 0.2%; range, 0-18%) compared to those who did not achieve it (median, 4.2%; range, 0-41%). Grade 3 or higher adverse events were observed in 50% of patients, most commonly anemia (20%), creatine kinase increase (13%), and diarrhea (10%). No new safety signal was identified. **Conclusions:** Staged combination with ENCO+BINI+CET showed potential to achieve disease control for patients with *BRAF* V600E-mutant mCRC who were refractory to ENCO+CET. Clinical trial information: jRCTs031210510. Research Sponsor: ONO PHARMACEUTICAL CO., LTD.

3560 **Poster Session**

FOLFOXIRI/bevacizumab in microsatellite stable (pMMR/MSS) *RAS* and *BRAF* wild-type "gene-altered" metastatic colorectal cancer (mCRC): The HYPERTRIBE study. First Author: Marco Maria Germani, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: Negative hyperselection may allow patient refinement for the use of anti-EGFRs in chemo-naïve pMMR/MSS, *RAS* and *BRAF* wild-type (wt) mCRC patients. However, outcomes are poor with both doublets/anti-EGFRs and doublets/bevacizumab (bev) among patients with gene-altered tumors. We investigated the efficacy of chemotherapy intensification with FOLFOXIRI/bev in this subgroup. **Methods:** We prospectively selected mCRC patients with pMMR/MSS, *RAS* and *BRAF* wt tumors harbouring at least one genomic alteration potentially implied with anti-EGFR resistance in published studies (*ERBB2 / PIK3CAexon20 / PTEN / AKT1 / NTRKs / ERBB3 / NF1 / MAP2K1-2-4 / AKT2 / EGFR* / subclonal *RAS* mutations; *ERBB2 / MET / ERBB3 / FGFR2 / IGF1R / KRAS / ARAF / AKT1-2* amplification; *ALK / ROS1 / NTRKs / RET* fusions; *EGFR* rearrangements; *PTEN / NF1 loss),* treated with upfront FOLFOXIRI/bev in 11 Italian centres. Assuming that the use of FOLFOXIRI/bev could lead to an increase in median PFS (mPFS) from 9 (as observed with doublets/anti-EGFRs) to 16 months (mos), with one-sided α and β errors of 0.10 and 0.20, respectively, 33 patients were needed. Secondary endpoints were overall survival (OS) and objective response rate (ORR). Outcomes were paired with a propensity score-matched external cohort of pMMR *RAS* and *BRAF* wt gene-altered patients treated with doublets/anti-EGFRs in clinical trials. **Results:** 35 patients were included. Main patients' characteristics were: median age 54 years, ECOG PS 0 83%, left-sided tumours 54%. Amplification in *ERBB2* and *MET* genes accounted for 26% and 6% of cases, respectively. The most frequent mutant gene was *ERBB2* (17%), followed by *MAP2K1* (9%), *PTEN* (9%), *NF1* (6%), *PIK3CAexon20* (3%), *EGFR* (3%). Subclonal *RAS* mutations were found in 14% of tumors. Fusions, detected in *ALK* and *RET* genes, accounted for 6% of cases. FOLFOXIRI/bev resulted into a mPFS of 12.3 mos (80% CI: 9.2 – 14.3 mos, Brookmeyer-Crowley test p = 0.023), an ORR of 74% and a mOS of 35.9 mos. PFS and OS with FOLFOXIRI/bev were longer than those achieved in the propensity score-matched cohort of patients treated with doublets/anti-EGFRs (mPFS: 12.3 vs 10.3 mos, HR: 0.74, 95% CI: 0.45 – 1.21, p=0.226; mOS: 35.9 vs 27.2 mos, HR: 0.57, 95% CI: 0.32 – 1.03, p=0.058). Similarly, a numerical advantage in ORR was reported (74% vs 63%, OR: 1.69 95% CI 0.61 – 4.88, p=0.303). No interaction (int) between the effect of treatment and primary tumor location was evident (p_{intPFS}=0.267; p_{intOS}=0.459; p_{intORR}=0.866). **Conclusions:** Waiting for efficacy results about the upfront use of targeted treatments directed against specific molecular subgroups, FOLFOXIRI/bev may be the preferred first-line option for clinically fit pMMR/MSS *RAS* and *BRAF* wt mCRC patients harbouring at least one genomic alteration of potential resistance to anti-EGFRs, regardless of primary tumor sidedness. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO); NextGenerationEU through the Italian Ministry of University and Research; Federation of Italian Cooperative Oncology Groups (FICOG) and Associazione Italiana Oncologia Medica (AIOM).

3561 **Poster Session**

Tumor load change as a functional biomarker for prognosis and treatment modulation in metastatic colorectal cancer (mCRC): Individual patient data (IPD) analysis of 12 randomized trials. First Author: Alexej Ballhausen, Department of Hematology, Oncology and Tumorimmunology, Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Background: The use of overall response rate (ORR) and progression-free survival (PFS) as surrogacy of overall survival (OS) has limitations in mCRC. Change in tumor load (ΔTL; tumor burden at progressive disease [PD] vs baseline) at treatment failure may reflect tumor aggressiveness and resistance biology. We evaluated the prognostic value of ΔTL in mCRC using IPD from twelve randomized first-line trials. **Methods:** IPD from ATEZOTRIBE, FIRE3, FIRE4, FIRE4.5, MACBETH, ML22011, MOMA, PANAMA, TRIBE, TRIBE2, TRIPLETE, and VALENTINO were pooled. ΔTL was defined as the ratio of the sum of longest target lesion diameters at PD vs baseline, per RECIST. Primary endpoint was OS; secondary endpoints included post-progression survival (PPS). Estimated marginal means were controlled for treatment type. Associations between ΔTL and outcomes were assessed using Cox models adjusted for prespecified baseline tumor burden and clinical covariates (ECOG, age, sex, sidedness, *RAS/BRAF* status, metastatic patterns, previous therapies). Incremental prognostic value beyond early tumor shrinkage (ETS) and depth of response (DpR) was assessed using likelihood ratio testing. Effect modification by treatment regimen was evaluated using ΔTL $\times$ treatment interaction terms for EGFR- vs VEGF-based therapy and for triplet vs doublet-chemotherapy across trials. **Results:** A total of 4852 patients evaluable for ΔTL were included. Mean ΔTL was 0.63 (SD 0.45) and significantly lower in patients receiving EGFR- vs VEGF-based therapy (0.58 vs 0.66, $p<0.001$) and triplet vs doublet chemotherapy (0.57 vs 0.67, $p<0.001$). Lower ΔTL (lower tumor load at PD vs baseline) was associated with better OS (HR 0.58 [95% CI 0.55–0.61], $p<0.001$) and PPS (HR 0.65 [0.61–0.69], $p<0.001$) after adjustment for baseline tumor burden and clinical covariates. For OS, ΔTL added prognostic information beyond ETS (likelihood ratio χ^2 = 282.13, $p<0.001$) and DpR (likelihood ratio χ^2 = 121.91, $p<0.001$). Lower ΔTL was associated with improved OS in patients receiving EGFR- (n = 1609; HR 0.62 [0.58–0.67], $p<0.001$) and VEGF-based therapy (n = 1916; HR 0.39 [0.35–0.43], $p<0.001$); doublet (n = 2177; HR 0.61 [0.57–0.65], $p<0.001$) and triplet (n = 1348; HR 0.34 [0.30–0.38], $p<0.001$) chemotherapy, with significant ΔTL $\times$ treatment interaction (VEGF vs EGFR: HR 0.50 [0.46–0.54], $p<0.001$; triplet vs doublet: HR 0.60 [0.54–0.66], $p<0.001$) after adjustment for treatment regimen, *RAS/BRAF* status and other clinical covariates. **Conclusions:** TL appears to be a strong, independent prognostic marker for OS and PPS in mCRC. ΔTL seems to vary by biologic and chemotherapy intensity, indicating it captures differential treatment effect/resistance not captured by ORR or PFS. Prospective validation as an early, treatment-sensitive prognostic endpoint is warranted. Research Sponsor: None.

3562 **Poster Session**

Single-cell atlas of peripheral blood immune landscape in pMMR/MSS rectal cancer treated with neoadjuvant chemoradiotherapy and PD-1 blockade. First Author: Leqi Zhou, Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Most colorectal cancer (CRC) patients exhibit normal mismatch repair function/microsatellite stability (pMMR/MSS), presenting a poor response to immune checkpoint inhibitor monotherapy. Neoadjuvant chemoradiotherapy (nCRT) combined with PD-1 inhibitors can enhance the efficacy of immunotherapy. However, the peripheral immune dynamics underlying this combination remain poorly understood. **Methods:** In this study, we selected 15 patients from the CHOICE I trial (ChiCTR2100042785) who received nCRT combined with PD-1 inhibitors. A total of 55 peripheral blood mononuclear cell (PBMC) samples were collected at three critical time points: pre-treatment baseline, during radiotherapy, and during immunotherapy. All samples underwent single-cell RNA sequencing (scRNA-seq) analysis, complemented by paired TCR/BCR profiling, to comprehensively map the dynamic evolution of the peripheral immune landscape during combined therapy. **Results:** We analysed 223,363 high-quality single cells and classified them into 11 distinct immune phenotypes using classical marker genes, revealing treatment-related immune dynamics. TCR clonal tracking revealed divergent dynamics that CD8+ T cells exhibited high clonal persistence (Jaccard index 0.1–0.23), significantly greater in responders than non-responders, underscoring their pivotal role in antitumor immunity. In contrast, CD4+ T cells (particularly T follicular helper cells) showed minimal clonal overlap (< 0.03), consistent with rapid turnover. Monocyte analysis uncovered fundamental differences. Monocytes from non-responders displayed enhanced yet dysfunctional antigen presentation alongside immunosuppressive features, including specific expansion of the pro-inflammatory Mono_CD14_IL1B subset characterized by high immunomodulatory molecule expression. Conversely, monocytes in responders exhibited robust type I interferon signaling. B-cell analyses revealed that responders preferentially underwent plasma-cell differentiation, whereas B cells from NR retained an antigen-presenting–like phenotype. NK-cell analysis revealed an expanded, activated cytotoxic pool in responders (featuring CD38+, KIR3DL1+ subsets), whereas non-responders showed dominance of KLRC2+ NK cells, suggesting a dysfunctional state. These efficacy-linked changes across immune populations collectively map the systemic immune landscape under combination therapy. **Conclusions:** This study provides a comprehensive single-cell atlas of peripheral immune remodeling during nCRT combined with PD-1 inhibitors in pMMR/MSS rectal cancer, offering crucial insights for future patient stratification and personalized combination strategies. Research Sponsor: National Natural Science Foundation of China; 82473439, 82272705 and 82503486; the Shanghai "Rising Stars of Medical Talents" Youth Development Program of the Shanghai Municipal Health Commission, China; No.2024-70; the Naval Medical University "Deep Blue" Project Talent Program; the First Affiliated Hospital of Naval Medical University Special Project for Basic Medical Research, China; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; Shanghai Shenkang Hospital Development Center, Shanghai Clinical Cohort Project; SHDC2025CCS019; Shanghai Science and Technology Plan Project; 25SF1901500.

LBA3563 **Poster Session**

Efficacy and safety of fruquintinib combined with chemotherapy versus bevacizumab combined with chemotherapy as second-line treatment for metastatic colorectal cancer: A prospective, multicenter, randomized controlled trial. First Author: Jianmin Xu, Department of Colorectal Surgery and Colorectal Cancer Center, Zhongshan Hospital, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

3564 **Poster Session**

NALIRIFOX plus targeted therapy as first-line treatment for metastatic colorectal cancer: A phase I study. First Author: Xiaojing Xu, Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China

Background: FOLFOXIRI combined with targeted therapy is recommended for metastatic colorectal cancer (mCRC) patients suitable for intensive treatment or conversion surgery. However, the combination of irinotecan liposome, oxaliplatin, fluorouracil (NALIRIFOX) in mCRC remains uninvestigated. This Phase I study aimed to determine the maximum tolerated dose (MTD) of irinotecan liposome in this combined therapy for mCRC. **Methods:** Patients with histologically confirmed and initially unresectable mCRC were enrolled. In the dose-escalation phase (Phase Ia), a 3+3 design was utilized. Eligible patients received fixed doses of oxaliplatin (85mg/m^2), fluorouracil (2400mg/m^2) and bevacizumab (5mg/kg), while the dose of irinotecan liposome was escalated starting from 60mg/m^2. If a dose-limiting toxicity (DLT) occurs at 60mg/m^2, the dose can be reduced to 50mg/m^2. Toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE5.0). In the dose-expansion phase (Phase Ib), irinotecan liposome was administered at the recommended dose from Phase Ia. Based on the RAS/BRAF gene status, either bevacizumab or cetuximab was combined with NALIRIFOX. The safety and efficacy of the combination were further assessed in Phase Ib. **Results:** From March 2024 to March 2025, 9 patients in the dose-escalation phase and 64 patients in the dose-expansion phase were enrolled, included 48 males and 25 females with a median age of 57 years. The MTD of irinotecan liposome was determined to be 50mg/m². Identified DLTs included grade 3 diarrhea and febrile neutropenia. As of January 15, 2026, 65 patients had at least one tumor assessment. The objective response rate (ORR) was 81.5% and the disease control rate (DCR) was 100.0%. The median PFS was 12.3 months (95% CI 9.8-14.7). The rate of R0 resection was 12.3%. The most common ≥grade 3 treatment-related adverse events (TRAEs) were diarrhea (18.4%) and neutropenia (14.5%). **Conclusions:** Irinotecan liposome at a dose of 50 mg/m² in the NALIRIFOX regimen showed manageable safety and promising efficacy as first-line treatment for mCRC. Clinical trial information: NCT06225622. Research Sponsor: None.

3565 **Poster Session**

***KMT2C* mutation to identify an immunotherapy-sensitive subset of gastrointestinal cancers: A large real-world analysis.** First Author: Bruno Bockorny, Beth Israel Deaconess Medical Center, Boston, MA

Background: *KMT2C* (MLL3) encodes a histone methyltransferase involved in enhancer regulation and DNA damage repair. Loss-of-function *KMT2C* mutations occur in approximately 4–7% of gastrointestinal cancers and represent one of the most recurrent chromatin regulator alterations across GI malignancies. Preclinical studies demonstrate that *KMT2C* deficiency impairs homologous recombination–mediated DNA repair and increases tumor immunogenicity. We hypothesized that *KMT2C* mutations define a biologically distinct subset of GI cancers associated with enhanced responsiveness to immune checkpoint inhibitors (ICI). **Methods:** Using the Tempus Lens Platform, we identified patients with colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), or gastroesophageal adenocarcinoma (GEA) who underwent Tempus xT DNA and RNA sequencing within a de-identified multimodal real-world dataset. Clinical and molecular features were compared between *KMT2C*-mutant (MUT) and wild-type (WT) tumors. Real-world progression-free survival (rwPFS) and overall survival (rwOS) following ICI initiation were estimated by Kaplan–Meier methods and compared using log-rank tests. Risk-set adjustment was applied to address left truncation and mitigate immortal time bias. **Results:** Among 14,413 patients, 83% had stage IV disease; CRC comprised 58.1%, PDAC 23.7%, and GEA 18.2%. *KMT2C* mutations were identified in 4.1% of CRC, 3.4% of PDAC, and 4.3% of GEA. Across all tumor types, *KMT2C*^{MUT} tumors had significantly higher tumor mutational burden (TMB) compared with WT (CRC: 39.2 vs 4.7 mut/Mb; PDAC: 3.68 vs 3.16; GEA: 7.9 vs 4.6; all $p \leq 0.02$). TMB-High status (≥10 mut/Mb) and MSI-High status were markedly enriched in *KMT2C* MUT tumors (CRC MSI-H: 57% vs 2.6%; PDAC: 6.9% vs 0.1%; GEA: 38% vs 2%; all $p < 0.001$). High Immune Profile Score (IPS) was more frequent in *KMT2C*^{MUT} versus WT tumors in CRC (35% vs 8.3%, $p < 0.001$) and GEA (36% vs 19%, $p < 0.001$). Following ICI, rwPFS was not reached in both *KMT2C*^{MUT} CRC and *KMT2C*^{MUT} GEA compared with 6.2 and 6.0 months in WT tumors (CRC $p = 1.1 \times 10^{-17}$; GEA $p = 0.004$). rwOS was significantly improved in CRC *KMT2C*^{MUT} versus WT (not reached vs 20.2 months; $p = 0.0001$). **Conclusions:** *KMT2C* mutations identify a molecularly and immunologically distinct subset of GI cancers enriched for MSI-High and TMB-High status and associated with superior outcomes following immune checkpoint inhibition. These findings support *KMT2C* as a potential predictive biomarker for immunotherapy responsiveness in gastrointestinal malignancies. Research Sponsor: Tempus.

3566 **Poster Session**

Efficacy and circulating protein biomarkers of second-line aflibercept plus FOLFIRI according to prior bevacizumab or cetuximab treatment in advanced colorectal cancer (KCSG CO21-21). First Author: Hyunwook Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Prospective data evaluating second-line aflibercept plus FOLFIRI according to prior bevacizumab (BEV) or cetuximab (CET) exposure and incorporating circulating protein biomarkers remain limited. **Methods:** This open-label, single-arm, nationwide phase II study (NCT04810585) evaluated aflibercept plus FOLFIRI as second-line with stratification by prior BEV or CET exposure. Seventeen circulating biomarkers were measured by ELISA at baseline and before cycle 4 and analyzed for associations with PFS and OS using Cox models. Plasma proteins were processed using a single-pot solid-phase enhanced SP3 protocol followed by tryptic digestion and analyzed by data-independent acquisition liquid chromatography tandem mass spectrometry, with protein identification and quantification performed using DIA-NN. **Results:** A total of 159 patients were enrolled (prior BEV, n=83; prior CET, n=76). mPFS was 7.5 months (95% CI, 6.8–8.4), and mOS was 14.4 months (95% CI, 12.9–16.0), with no significant differences by prior biologic therapy (mOS: 13.8 vs 14.7 months for prior BEV vs CET; mPFS: 7.4 vs 7.5 months). Among 146 evaluable patients, the ORR was 28.1% (1 CR [0.7%], 40 PR [27.4%]), and the DCR was 88.4%. The most common TRAEs were proteinuria (47.1%; grade $\geq$3, 14.0%), neutropenia (43.4%; grade $\geq$3, 37.5%), nausea (27.2%), and fatigue (24.3%). Baseline PlGF (PFS HR 2.04, q=0.008; OS HR 2.86, q$<$0.001), IL-8 (PFS HR 1.87, q=0.008; OS HR 2.13, q=0.002), TIMP-1 (PFS HR 1.74, q=0.021; OS HR 3.49, q$<$0.001), and VEGF-A (PFS HR 1.74, q=0.021; OS HR 1.91, q=0.009) were independently associated with inferior PFS and OS, whereas on-treatment and C1-to-C4 biomarker ratios showed no associations. Enrichment of inflammation/immune related proteins S100A8 (log_2 FC -0.41; p=0.037) and MPO (log_2 FC -1.51; p=0.006), as well as lipid metabolism related proteins APOC3 (log_2 FC -0.58; p $<$0.001) and APOC2 (log_2 FC -0.47; p=0.003), was observed in patients with prior BEV at baseline. Enrichment of PIGR (log_2 FC -1.21; p$<$0.001) and OLFM1 (log_2 FC -0.66; p-value $<$0.001) was observed in PD patients at C4, while SERPINF1 (log_2 FC 0.33; p= 0.003) and FETUB (log_2 FC 0.41; p=0.013) were enriched in PR+CR patients at C4. Further, PIGR expression increased 1.30-fold in PD patients (mean $log_2\Delta$ (C4-C1) = 0.38), compared to a relatively stable expression in PR patients (mean $log_2\Delta$(C4-C1) = -0.076, p=0.033). Increased PIGR expression at C4 showed an association with inferior OS in Cox models (HR 1.92, p=0.004). **Conclusions:** Clinical outcomes and safety profiles of aflibercept plus FOLFIRI were comparable regardless of prior BEV or CET exposure. Elevated baseline PlGF, IL-8, TIMP-1 and VEGF-A levels were associated with shorter PFS and OS. Exploratory plasma proteomics identified dynamic PIGR expression as a response-associated biomarker linked to inferior OS. Clinical trial information: NCT04810585. Research Sponsor: Sanofi.

3567 **Poster Session**

A multicenter phase II trial of encorafenib, binimetinib, and cetuximab for early relapsed stage II/III *BRAF*^{V600E}-mutated colorectal cancer: TRESBIEN trial (OGSG 2101). First Author: Toshihiro Kudo, Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Osaka, Japan

Background: Patients with *BRAF*^{V600E}-mutated colorectal cancer (CRC) who experience early recurrence during or shortly after adjuvant therapy show an extremely poor prognosis. The efficacy of BRAF-targeted triplet therapy for early relapse remains unclear. **Methods:** We conducted a prospective, open-label, multicenter, phase II trial evaluating the efficacy and safety of encorafenib, binimetinib and cetuximab in *BRAF*^{V600E}-mutated CRC patients who relapsed during or within 6 months after completing adjuvant chemotherapy. Patients received encorafenib 300 mg once daily and binimetinib 45 mg twice daily in 28-day cycles, plus intravenous cetuximab 400 mg/m^2 once on day 1 of cycle 1, then 250 mg/m^2 once weekly until disease progression or occurrence of unacceptable adverse events. The primary endpoint was objective response rate (ORR) by blinded independent central review. Secondary endpoints were overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. Sample size was determined based on a threshold ORR of 6.0% and an expected ORR of 26.0% (one-sided α = 0.05, power = 0.90). **Results:** Between January 2022 and April 2025, 25 patients were enrolled across 14 institutions. Baseline characteristics included: median age 68 years (range, 28–81); female, n = 18 (72.0%); right-sided, n = 18 (72.0%); pStage II/III, n = 2 (8.0%)/23 (92.0%); MSI-H, n = 5 (20.0%); and prior oxaliplatin-based adjuvant chemotherapy, n = 22 (88.0%). Twenty-four patients were evaluable for efficacy. The ORR was 62.5% (95% CI, 40.6–81.2, one-sided $P < 0.001$), and DCR was 87.5% (95% CI, 67.6–97.3). With median follow-up time of 18.0 months, the median PFS was 7.4 months (95% CI, 4.7–10.6), and the median OS was 33.9 months (95% CI, 11.0–NE). No Grade $\geq$3 adverse events ($\geq$10%) and treatment-related deaths were observed. **Conclusions:** The combination of encorafenib, binimetinib, and cetuximab demonstrated favorable efficacy and a manageable safety profile in patients with *BRAF*^{V600E}-mutated CRC who relapsed early recurrence during or shortly after adjuvant chemotherapy. This triplet regimen can be a promising treatment strategy for this poor prognostic population. Clinical trial information: jRCTs051210152. Research Sponsor: ONO PHARMACEUTICAL CO., LTD.

3568 **Poster Session**

Clinical validation of red blood cell DNA for early detection of advanced colorectal neoplasia: A single-center prospective observational case-control clinical trial. First Author: Xingyun Yao, School of Life Sciences, Westlake University, Hangzhou, Zhejiang, China

Background: Early detection of colorectal cancer (CRC) improves survival, but current screening is limited by poor colonoscopy compliance and low cfDNA sensitivity for early-stage lesions and advanced adenomas (AA). Beyond tumor shedding, solid tumors remotely disrupt bone marrow hematopoiesis, inducing systemic genomic instability in hematopoietic lineages. Leveraging this mechanism, we developed a noninvasive detection strategy using genome-wide profiling of DNA remnants in mature red blood cells (rbcDNA). We previously showed that tumor-induced IL-18/NR4A1 signaling drives locus-specific DNA damage in hematopoietic progenitors, generating rbcDNA signatures distinct from shedding-dependent cfDNA and enabling improved detection of early-stage cancer. Here, we report the first multicenter and prospective clinical validation of this rbcDNA-based assay for the detection of early colorectal neoplasia (NCT05875584). **Methods:** We enrolled 1,251 colonoscopy-confirmed participants (561 non-advanced neoplasia controls (non-AN), 330 AA, 360 CRC). Peripheral blood (1–2 mL) was collected from each participant, and rbcDNA was isolated and sequenced by low-coverage whole-genome sequencing (~2$\times$), as previously described (PMID: 40341742). Participants were randomly assigned (8:2) to discovery and test cohorts. The discovery cohort was used for CRC- and AA-associated rbcDNA features identification and model development, while the test cohort was used for cutoff optimization. This locked model was externally validated in two independent cohorts. A prospective, observational case-control study was also conducted, in which blood and stool samples were collected simultaneously to compare the rbcDNA classifier with quantitative FIT (qFIT). Among 598 enrolled participants, 585 were included in the final analysis (299 non-AN, 206 AA, and 80 CRC). **Results:** At a predefined 90% specificity, the rbcDNA classifier achieved sensitivities of 85% for AA and 95% for CRC in the test cohort. Across two external cohorts, the assay consistently achieved 80% and 78% sensitivity for advanced colorectal neoplasia, 91% sensitivity for CRC in both cohorts, and 92% and 91% specificity. In the prospective study, rbcDNA yielded 90% sensitivity for CRC and 60% for AA at 90% specificity, with specificity remaining comparable in participants with non-neoplastic findings and non-advanced adenomas. Compared with qFIT, rbcDNA matched overall CRC sensitivity (90% vs. 88%) but outperformed it for stage I CRC (83% vs. 61%) and advanced adenomas (60% vs. 18%), including $>$50% of large sessile serrated lesions and tubular adenomas ($\geq$1 cm) versus $<$15% by qFIT. **Conclusions:** This first prospective clinical study demonstrates that rbcDNA provides a highly sensitive, non-invasive approach for early colorectal neoplasia detection. Clinical trial information: NCT05875584. Research Sponsor: Key R&D Program of Zhejiang.

3569 **Poster Session**

SHR-A1811 plus chemotherapy and BP102 as 1L therapy for HER2-expressing mCRC: Data from a phase Ib/II study. First Author: Ting Xu, Department of Gastrointestinal Oncology, Peking University Cancer Hospital, Beijing, China

Background: HER2 expression is associated with poor prognosis in mCRC. SHR-A1811 (trastuzumab-rezetecan) is a HER2-directed ADC comprising a humanized monoclonal antibody, a cleavable tetrapeptide linker, and a topoisomerase I inhibitor payload. We evaluated the safety and preliminary efficacy of SHR-A1811 in combination with chemotherapy and BP102 (bevacizumab biosimilar) as 1L therapy for HER2-expressing mCRC. **Methods:** This open-label, multicenter phase Ib/II study (ClinicalTrials.gov: NCT06015048) used an i3+3 design in phase Ib to evaluate the safety and tolerability of SHR-A1811 + 5-FU/L-LV, $\pm$ oxaliplatin and/or BP102, and to select the phase II regimen. Phase II (proof-of-concept) assessed efficacy and safety in the 1L setting using SHR-A1811 3.2 mg/kg Q2W + 5-FU (300 mg/m^2 IV bolus, 1800 mg/m^2 continuous infusion over 46–48 h Q2W) + L-LV 200 mg/m^2 IV Q2W + BP102 5 mg/kg IV Q2W $\pm$ oxaliplatin 60 mg/m^2 IV Q2W. Tumor response was assessed per RECIST v1.1, and AEs were evaluated per CTCAE v5.0. **Results:** As of Dec 31, 2025 (data cutoff), 39 pts received SHR-A1811 + FOLFOX (-1) + BP102, and 11 pts received SHR-A1811 + 5-FU/L-LV + BP102. All were Asian with *pMMR/MSS* and *BRAF* wild-type disease. The median age was 58 (range, 30–71) and 57 (range, 42–72), respectively. 28/39 (71.8%) and 7/11 (63.6%) were male. ECOG PS was 1 in 24/39 (61.5%) and 6/11 (54.5%). HER2 positivity (IHC 3+ or IHC 2+/ISH+) was observed in 21/39 (53.8%) and 5/11 (45.5%). HER2 IHC 2+/ISH$-$ was observed in 18/39 (46.2%) and 5/11 (45.5%). Liver metastases were present in 28/39 (71.8%) and 4/11 (36.4%). 15/39 (38.5%) and 5/11 (45.5%) had *RAS* mutations. Median follow-up was 10.4 m (range, 6.1–17.0) and 11.9 m (range, 3.3–19.0). ORR was 74.4% (29/39; 95% CI, 57.9–87.0) and 40.0% (4/10; 95% CI, 12.2–73.8). DCR was 97.4% (38/39; 95% CI, 86.5–99.9) and 90.0% (9/10; 95% CI, 55.5–99.8). mPFS was 15.6 m (95% CI, 11.3–NR) and 9.6 m (95% CI, 1.8–NR). In HER2 positive pts received SHR-A1811 + mFOLFOX6(-1) + BP102, ORR was 90.5% (19/21; 95% CI, 69.6-98.8), DCR was 100% (21/21; 95% CI, 83.9-100), 9m-PFS rate was 94.7% (95% CI, 68.1-99.2); among HER2 positive *RAS* mutant/wild type subgroups, 9m-PFS rate was 83.3% (95%CI, 27.3-97.5) and 100%. OS was immature. Grade $\geq$3 TRAEs occurred in 31/39 (79.5%) and 6/11 (54.5%) in the two cohorts, with the most common being decreased neutrophil count (56.4% vs 18.2%), decreased white blood cell count (17.9% vs 18.2%), anemia (12.8% vs 9.1%), and stomatitis (12.8% vs 0). TRAEs led to discontinuation of any drug in 4/39 (10.3%) (SHR-A1811: 1; chemo: 1; BP102: 3) and in none. TRAEs led to dose reductions in 12/39 (30.8%) and 3/11 (27.3%) (SHR-A1811: 3 vs 1; chemo: 11 vs 3). No TRAE-related deaths occurred. **Conclusions:** SHR-A1811 plus chemotherapy and BP102 as 1L therapy for HER2 intermediate or high-expressing mCRC demonstrated manageable safety and encouraging antitumor activity. Clinical trial information: NCT06015048. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

3570 **Poster Session**

A transcriptomic signature to predict immune checkpoint inhibition efficacy in proficient mismatch repair metastatic colorectal cancer: Translational analysis of the AVETRIC and TRIPLETE studies. First Author: Martina Carullo, Unit of Medical Oncology 2, Azienda Ospedaliera Universitaria Pisana and Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

Background: ICIs provide limited benefit in proficient mismatch repair (pMMR) metastatic colorectal cancer (mCRC), highlighting the need for predictive biomarkers. We aimed to uncover transcriptomic profiles predictive of ICI efficacy, using tumor specimens from two matched cohorts of pMMR, *RAS/BRAF* wild-type (wt) mCRC patients (pts) enrolled in two academic clinical trials investigating first-line FOLFOXIRI plus an anti-EGFR agent ± ICI. **Methods:** The phase II AVETRIC study (NCT04513951) provided the ICI-treated cohort (mFOLFOXIRI/anti-EGFR plus avelumab), while the experimental arm of the phase III TRIPLETE study (NCT03231722) served as the ICI-untreated control cohort (mFOLFOXIRI/anti-EGFR). Bulk RNA-seq analysis was performed using the Signomax platform on naive tumor specimens of 39 and 32 pts from the ICI and control cohorts, respectively. Firstly, gene set variation (GSV) analyses compared extended PFS (e-PFS) versus limited PFS (l-PFS) groups (using median PFS of the control cohort as a cut-off) within each cohort, leading to a focus on immune- and EGFR-related pathways. Secondly, using the median immune- and EGFR-related pathway scores in the ICI cohort as a cut-off, samples were classified combining both pathway activities into an immune^{high}-EGFR^{high} group versus a pooled group comprising all the other cases (immune-EGFR^{others}). Associations with PFS and OS were assessed by treatment cohort. **Results:** Thirty-four (87%) (23 e-PFS, 11 l-PFS) and 26 (81%) (13 e-PFS, 13 l-PFS) samples were successfully analyzed in the ICI and control cohorts, respectively. In the ICI cohort, l-PFS samples showed lower activity of both immune- and EGFR-related pathways than e-PFS ones, while no significant differences in the activation of the same pathways were observed between PFS groups in the control cohort. Additionally, 29 pts were classified as immune^{high}-EGFR^{high} (13 [45%] and 16 [55%] in the ICI and control cohorts, respectively) and 31 pts as immune-EGFR^{others} (21 [68%] and 10 [32%] in the ICI and control cohorts, respectively). Immune^{high}-EGFR^{high} pts reported longer PFS (HR: 0.57, 95% CI 0.33-0.98, *P*=0.04) and OS (HR: 0.66, 95% CI 0.36-1.24, *P*=0.20) than other pts. Borderline significant interaction between treatment and immune/EGFR signature was found in PFS (*P*=0.145) with ICI benefit restricted to pts bearing the immune^{high}-EGFR^{high} signature (HR PFS: 0.56, 95% CI 0.25-1.24, versus 1.25, 95% CI 0.60-2.64 in the others). **Conclusions:** Exploratory transcriptomic profiling may identify a subset of pMMR *RAS/BRAF* wt mCRC with concurrent immune activation and EGFR dependency that could benefit from combining ICI to an intensified anti-EGFR-based first-line treatment. Research Sponsor: GONO GI Foundation; European Union – NextGeneration EU through the Italian Ministry of University and Research under PNRR - M4C2-I1.3 Project PE_00000019 'HEAL ITALIA'; Grant number CUP: I53C22001440006.

3571 **Poster Session**

A phase II combination study of galunisertib and capecitabine in patients with chemotherapy-resistant colorectal cancer with peritoneal metastases. First Author: Ashwini Kanhailal, Antoni van Leeuwenhoek Hospital - Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Transforming growth factor β (TGF-β) plays a dynamic role in cancer biology. It acts as a tumor suppressor in early stages of tumor development. Certain tumor types, such as colorectal cancer (CRC), exploit this signaling route to induce pathways that promote tumor growth, enhancing the tumor's aggressiveness. CRC of the mesenchymal subtype exhibits prominent TGF-β activation, contributing to drug resistance, including to 5-fluorouracil (5-FU)-based chemotherapy. This subtype is found in most CRC patients with peritoneal metastases. Therefore, combining TGF-β inhibition with chemotherapy could be a beneficial approach to overcome resistance. **Methods:** This two-center, open-label, non-randomized proof-of-principle phase II study with a safety lead-in involved combining TGF-β inhibitor galunisertib (150 mg twice daily) with capecitabine (1000 mg/m^2 twice daily) for 14 days in a 28-day cycle. Adult patients with histologically or cytologically proven CRC and confirmed peritoneal metastases were eligible for inclusion if they were in a good clinical condition, had exhausted all their treatment options, and had no gastrointestinal impaired function. In the safety lead-in phase, six patients were evaluated for safety and tolerability, as assessed by the incidence of dose limiting toxicities (DLTs) and adverse events. Phase II followed a Simon two stage design with progression to the second stage when ≥2 objective tumor responses out of 15 patients were reached. Secondary objectives included pharmacokinetics (PK) and pharmacodynamics (e.g. TGF-β expression, immunohistochemical staining for phosphorylated SMAD2/3). **Results:** As of January 23 2026, inclusion was closed, after 22 patients were recruited. 54% of patients were female, with a median age of 60 years (38-77). No DLTs were observed in 21 DLT-evaluable patients. Only grade 1/2 treatment-related adverse events occurred. The most common events were nausea (23%), hypophosphatemia (18%), and fatigue (18%). No objective responses were observed. Four of 20 patients evaluable for efficacy showed stable disease with a median duration of 4 months. PK analysis of patients in the safety lead-in showed high interpatient variability for galunisertib, capecitabine and 5-FU (CV% $AUC_{(0\text{-}12)}$: between 54%-70%). Galunisertib did not show drug accumulation over time ($AUC_{(0\text{-}12)}$ on cycle 1 day 1 and $AUC_{(0\text{-}12)}$ on cycle 1 day 14 were 7.6 and 6.6 μg*h/mL, respectively). The PK of capecitabine and 5-FU were similar to those described in the literature. Pharmacodynamic analyses are ongoing. **Conclusions:** The combination of galunisertib and capecitabine did not result in objective responses or long term stable disease in chemotherapy-resistant CRC patients with peritoneal metastases. The treatment was well tolerated and PK results for both compounds were similar to those described in the literature. Clinical trial information: NCT05700656. Research Sponsor: None.

3572 **Poster Session**

Circulating tumor DNA (ctDNA) tumor fraction (TF) dynamics to refine progression-free survival and radiographic response during anti-EGFR rechallenge in metastatic colorectal cancer. First Author: Guglielmo Vetere, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Reliable biomarkers of benefit from anti-EGFR rechallenge are needed in anti-EGFR-refractory metastatic colorectal cancer (mCRC), where prior studies have shown modest progression-free survival (PFS) and radiographic response may incompletely capture biological sensitivity. We evaluated longitudinal ctDNA dynamics as a real-time biomarker of treatment effect. **Methods:** This analysis was conducted within a phase II enrichment study of panitumumab with or without trametinib in anti-EGFR-refractory mCRC; crossover was allowed after progression on monotherapy. Plasma was collected at baseline, prior to each infusion, and at progression or end of treatment. Patients with a baseline and ≥ 1 subsequent on-treatment sample were evaluable. ctDNA TF was estimated with the Guardant Reveal assay by normalizing cancer-specific differentially methylated regions with matched controls in each sample. In samples with detectable ctDNA, Guardant360 Liquid was used for genotyping of > 700 genes and tumor mutational burden (TMB). ctDNA TF dynamics were defined by best % change from baseline. Baseline TF, TMB, and focal amplifications in the MAPK pathway were also evaluated. PFS was the primary endpoint and best radiographic response (RECIST 1.1) was the secondary endpoint. Differences were assessed using Kaplan-Meier analyses, Cox proportional hazards models adjusted by age, sex, line of therapy, and treatment regimen, and the Kruskal-Wallis test. **Results:** A total of 38 patients were included. Consistent with the advanced clinical setting, median TF at baseline was 11.9%. Following adjusted Cox modeling, baseline ctDNA TF was prognostic when dichotomized at 2% (median PFS (mPFS): 3.55 vs 1.97 months, HR 0.32, 95% CI 0.13-0.77), whereas baseline TMB and focal amplifications in the MAPK pathway were not associated with PFS. ctDNA TF % change from baseline to best on-treatment value was strongly associated with PFS in patients with any decrease vs no decrease (mPFS: 3.16 vs 1.77 months, HR 0.24, 95% CI 0.08-0.69, p = 0.008), and the longest PFS was observed in patients achieving ≥ 80% TF decrease vs all others (mPFS: 3.61 vs 1.87 months, HR 0.20, 95% CI 0.08-0.49, $p < 0.005$). Median best TF % change was -31%, -80%, and -96% for PD, SD, and PR, respectively ($p < 0.001$). Among patients achieving SD or PR, 100% had any TF decrease and 61% had a > 80% TF decrease, while in patients with PD as best response, 74% had any TF decrease and 5% had a > 80% TF decrease. No impact of ctDNA-related variables was observed in the crossover setting. **Conclusions:** ctDNA TF dynamics are strongly associated with PFS and provide clinically meaningful information beyond conventional imaging in mCRC patients undergoing anti-EGFR rechallenge, highlighting ctDNA TF as a powerful tool for refining response assessment and personalizing treatment decisions. Research Sponsor: Jack T. and Lillian S. Clift Fellowship; Andrew Sabin Family Fellowship; NIH GI SPORE.

3573 **Poster Session**

ctDNA dynamics and prognostic value during first-line treatment of metastatic colorectal cancer: Analysis from the phase 3 PARADIGM study. First Author: Kentaro Yamazaki, Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Shizuoka, Japan

Background: The phase 3 PARADIGM trial showed overall survival (OS) and tumor response advantages of anti-EGFR (panitumumab, PAN) over anti-VEGF (bevacizumab, BEV) therapy with FOLFOX6 in first-line metastatic colorectal cancer (mCRC) despite similar progression-free survival (PFS), highlighting limitations of imaging-based PFS as a surrogate for clinical benefit. We investigated whether ctDNA dynamics provide more refined prognostic information complementary to baseline (BL) ctDNA. **Methods:** Plasma samples collected from 556 patients (pts) with mCRC paired at pre-treatment (BL) and post-treatment (after treatment discontinuation) were profiled for ctDNA. Distribution of the highest variant allele fraction was modeled using a Gaussian mixture model. At pre- and post-treatment, pts were classified into 3 groups—High, Mid, and Low—according to ctDNA levels. OS, post-treatment survival (PTS), and PFS were compared across 9 ctDNA dynamic categories (eg, High→Low, High→Mid, High→High) based on changes from pre- to post-treatment. **Results:** Lower BL ctDNA was significantly associated with longer OS (median OS [95% CI]: Low, n = 97, 50.7 mo [44.0–65.2]; Mid, n = 159, 34.1 mo [26.9–37.1]; High, n = 300, 27.8 mo [26.2–31.3]). BL ctDNA level also correlated with tumor volume and mutation burden. Pts with lower ctDNA at treatment discontinuation had longer PTS. Incorporating ctDNA dynamics provided additional prognostic value. Regardless of BL ctDNA level, pts whose post-treatment ctDNA decreased to Low had the best survival (eg, High→Low: 50.9 mo [35.8–61.0]), while pts with persistently high ctDNA showed the poorest survival (High→High: 23.3 mo [18.2–27.8]). The prognostic value of ctDNA dynamics was consistent across treatment arms. Among pts with High BL ctDNA (PAN, n = 152; BEV, n = 148), a greater proportion achieved Low ctDNA at post-treatment with PAN vs BEV (29 [19.1%] vs 16 [10.8%], p = 0.053), whereas the proportions achieving Mid ctDNA were similar (52 [34.2%] vs 58 [39.2%], p = 0.40). In the High→Low/Mid ctDNA subsets, treatment discontinuation following curative resection was more frequent with PAN vs BEV (High→Low: 18/29 [62.1%] vs 7/16 [43.8%]; High→Mid: 11/52 [21.2%] vs 5/58 [8.6%]). OS and PTS trends were favorable with PAN vs BEV (OS; High→Low: 61.0 vs 43.1 mo, HR 0.49, 95% CI 0.23–1.04; High→Mid: 33.6 vs 26.8 mo, HR 0.74, 95% CI 0.50–1.11, PTS; High→Low: 55.1 vs 39.0 mo, HR 0.48, 95% CI 0.22–1.03; High→Mid: 20.6 vs 19.4 mo, HR 0.72, 95% CI 0.48–1.07). **Conclusions:** ctDNA dynamics add prognostic value beyond BL ctDNA level. In pts with high BL ctDNA, PAN yielded more conversions into low ctDNA levels and discontinuations following curative resection, with OS/PTS trends favoring PAN. These findings suggest that ctDNA dynamics may better reflect long-term clinical benefit than PFS, although standardized thresholds and prospective validation are needed. Clinical trial information: NCT02394834; NCT02394795. Research Sponsor: Takeda Pharmaceutical Company Limited.

3574 **Poster Session**

Contribution of atezolizumab (atezo) to the efficacy of the zanzalintinib (zanza) + atezo combination in patients (pts) with previously treated metastatic colorectal cancer (mCRC): Evidence from the phase 3 STELLAR-303 trial. First Author: Anees Dauki, Exelixis, Inc., Alameda, CA

Background: Outcomes remain poor for pts with previously treated mCRC, the vast majority of whom have tumors that are not microsatellite instability-high or mismatch repair deficient. Zanza is a novel, small molecule inhibitor of multiple kinases, including TAM kinases (TYRO3, AXL, and MER), MET, and VEGF receptors, which play important roles in oncogenic processes, including immune suppression in the tumor microenvironment. In STELLAR-303, zanza + atezo significantly improved overall survival (OS) versus regorafenib (rego) in pts with previously treated mCRC. The objective here was to assess the contribution of atezo to the efficacy of the zanza + atezo combination. **Methods:** The effect of atezo immunogenicity on efficacy was evaluated by comparing progression-free survival (PFS) and OS between atezo treatment-emergent anti-drug antibody (TEADA)-positive and TEADA-negative pts. Unstratified Cox proportional hazards regression models were used to estimate HRs for TEADA subgroups relative to the rego arm. Exposure-response (ER) analyses examined the relationship between atezo serum trough concentrations and efficacy endpoints using Cox proportional hazards models. **Results:** Of 451 pts randomized to zanza + atezo, 394 were evaluable for atezo TEADAs (TEADA-positive at any post-baseline visit, n = 143; TEADA-negative, n = 251). Baseline clinical characteristics and key prognostic factors (eg, *RAS* status, geographic region, presence of liver metastasis, location of primary tumor) were well balanced between TEADA subgroups, minimizing potential confounding due to subpopulation differences. Relative to the rego arm (n = 450), HRs (95% CI) favored zanza + atezo for PFS across both TEADA-positive (0.81 [0.67–0.99]) and TEADA-negative (0.59 [0.51–0.71]) subgroups. Similar results were observed for OS in the TEADA-positive (0.79 [0.63–0.98]) and TEADA-negative (0.72 [0.60–0.86]) subgroups. The greatest benefit for both PFS and OS was in the TEADA-negative subgroup. Based on ER analyses (n = 376), there was a statistically significant ($p < 0.001$) relationship between time-varying atezo trough concentrations and efficacy endpoints—estimated HRs (95% CI) comparing the 95th with the 5th percentiles of atezo trough concentrations were 0.82 (0.80–0.83) for PFS and 0.73 (0.70–0.75) for OS. Safety profiles were comparable between TEADA-positive and TEADA-negative pts. **Conclusions:** Zanza + atezo demonstrated PFS and OS benefit regardless of atezo TEADA status, with greater efficacy observed in TEADA-negative pts. ER analyses showed that higher atezo serum trough concentrations were associated with longer PFS and OS. These results support the contribution of atezo to the survival benefits observed with the zanza + atezo combination in pts with mCRC in the STELLAR-303 trial. Clinical trial information: NCT05425940. Research Sponsor: Exelixis, Inc.

3575 **Poster Session**

FIRE-4 (AIO KRK-0114): Efficacy of third-line rechallenge with cetuximab versus investigator's choice in relation to the interval between initial and third-line anti-EGFR therapy. First Author: Lena Weiss, Department of Medicine III, University Hospital Munich LMU, Munich, Germany

Background: The randomized FIRE-4 study evaluated the effect of cetuximab rechallenge versus investigator's choice in the 3rd-line treatment of patients (pts) with RAS-wildtype (RAS-wt) metastatic colorectal cancer (mCRC). The present analysis focuses on the time between the end of initial anti-EGFR-based treatment and start of 3rd-line therapy (TIS-3) as a potential predictor of response. **Methods:** In FIRE-4, all pts received induction therapy with FOLFIRI plus cetuximab. After 1st PD, an anti-EGFR-free "window therapy" was recommended. At diagnosis of 2nd PD, pts who had responded to induction therapy were re-evaluated for RAS status and, after exclusion of RAS mutations, were offered randomization to either rechallenge with cetuximab plus chemotherapy or investigator's choice. Overall survival in 3rd-line (OS-3) was evaluated as a primary endpoint. **Results:** Of the 87 pts entering 3rd-line treatment in FIRE-4, 45 received (FOLF)IRI plus cetuximab (rechallenge arm), and 42 received investigator's choice (standard arm). Numerically superior outcome parameters regarding ORR-3 (OR 2.70), PFS-3 (HR 0.87) and OS-3 (HR 0.86) were observed in the rechallenge arm, without, however, reaching the level of statistical significance. To evaluate the relevance of TIS-3, we focused on the median (13.8 months) and the first quartile (9.0 months). Based on these cut-off values, treatment effects were evaluated in pts with longer and shorter TIS-3 intervals (see Table). **Conclusions:** Longer TIS-3 intervals were associated with longer survival times in 3rd-line treatment. This observation was particularly true for pts receiving cetuximab rechallenge, but also for those receiving investigator's choice. Clinical trial information: NCT02934529. Research Sponsor: None.

Treatment arm	N	Interval	PFS (mo)	HR	OS (mo)	HR
FOLF(IRI) + Cetuximab	21	> 13.8 mo	7.4	0.475	20.0	0.639
	24	< 13.8 mo	4.1	P=0.019	12.6	P=0.187
	34	> 9.0 mo	5.9	0.680	19.6	0.601P=0.173
	11	< 9.0 mo	4.0	P=0.274	10.8	
Investigator's choice	23	> 13.8 mo	5.6	0.772	16.2	0.516
	19	< 13.8 mo	4.4	P=0.415	12.2	P=0.055
	32	> 9.0 mo	5.5	0.690	16.9	0.458P=0.042
	10	< 9.0 mo	4.5	P=0.313	7.8	

3576 **Poster Session**

Ivonescimab (ivo) with oxaliplatin + fluorouracil (5-FU) + leucovorin calcium (mFOLFOX6) for patients (pts) with unresectable metastatic colorectal cancer (mCRC): A phase 2 study. First Author: David Berz, Department of Oncology, Valkyrie Clinical Trials, Inc, Los Angeles, CA

Background: Ivonescimab is an investigational tetrameric bispecific antibody targeting both programmed death protein 1 and vascular endothelial growth factor that demonstrated efficacy and a tolerable safety profile in multiple phase 3 studies in pts with non-small cell lung cancer, and is being investigated in other solid tumor types. This multi-part phase 2 study (NCT05382442) evaluated ivo + chemotherapy as first-line treatment of mCRC. Here, we report interim results from the multiregional regimen extension phase of the study, which evaluated ivo 20 or 10 mg/kg + mFOLFOX6. **Methods:** Adult pts (≥18 years) in China and the US with confirmed mCRC who had an Eastern Cooperative Oncology Group score of 0-1, were not candidates for radical surgical resection or local therapy, and had not received systemic anti-tumor therapy in the recurrent or metastatic stage were enrolled; pts who received prior neoadjuvant or adjuvant therapy were permitted if first recurrence/metastasis occurred ≥12 months (mo) after the last dose. Pts were randomly assigned 1:1 to receive intravenous ivo (20 mg/kg or 10 mg/kg) + mFOLFOX6 once every 2 weeks for up to 8 cycles, followed by maintenance with 5-FU + ivo until disease progression, intolerable toxicity, or withdrawal of consent for up to 2 years. The primary endpoints were objective response rate (ORR; assessed by Response Evaluation Criteria in Solid Tumors v1.1) and incidence and severity of treatment-emergent adverse events (TEAEs). Secondary efficacy endpoints included disease control rate (DCR) and progression-free survival (PFS). **Results:** At the time of data cutoff for this interim analysis (December 31, 2025), 49 pts were enrolled (ivo 20 mg/kg + mFOLFOX6, n = 25; ivo 10 mg/kg + mFOLFOX6, n = 24) with an overall median age of 58 years; 79.6% of pts had left-sided tumors, 53.1% had *KRAS* or *BRAF* tumor mutations, and 67.3% had liver metastases. Median follow-up was 7.5 mo (range, 3.5-10.3) and 7.1 mo (range, 1.9-10.3) in the ivo 20 mg/kg + mFOLFOX6 and ivo 10 mg/kg + mFOLFOX6 arms, respectively. ORR was 70.8% in each treatment arm; all were partial responses. DCR was 100% in each treatment arm. Median PFS was not reached. PFS rate at 6 months was 95.2% and 84.8% in the ivo 20 mg/kg + mFOLFOX6 and ivo 10 mg/kg + mFOLFOX6 arms, respectively. Grade ≥3 TEAEs related to ivo occurred in 40.0% and 33.3% of patients in the ivo 20 mg/kg + mFOLFOX6 and ivo 10 mg/kg + mFOLFOX6 arms, respectively, and serious TEAEs related to ivo were reported in 24.0% and 16.7% of pts, respectively. TEAEs led to discontinuation of ivo in 4.0% in the ivo 20 mg/kg + mFOLFOX6 arm and in 0% in the ivo 10 mg/kg + mFOLFOX6 arm. No TEAEs led to death. **Conclusions:** With 7.3 mo follow-up, ivo + mFOLFOX6 showed encouraging efficacy and a manageable safety profile in pts with untreated mCRC. Clinical trial information: NCT05382442. Research Sponsor: Summit Therapeutics, Inc.

3577 **Poster Session**

Cadonilimab, a bispecific anti–PD-1/CTLA-4 antibody, for patients with dMMR/MSI-H metastatic colorectal cancer after progression on anti–PD-(L)1 therapy: A multicenter, single-arm, phase 2 trial (CSWOG-C03). First Author: Huabin Hu, Department of Medical Oncology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Immune checkpoint blockade targeting PD-1 is the standard of care for patients with mismatch repair–deficient or microsatellite instability–high (dMMR/MSI-H) metastatic colorectal cancer (mCRC). However, approximately 37%–45% of patients experience disease progression within 1 year when treated with anti-PD-1 monotherapy, and effective subsequent treatment options remain undefined. The CSWOG-C03 study evaluated the efficacy and safety of cadonilimab, a bispecific anti-PD-1/CTLA-4 antibody, in patients with dMMR/MSI-H mCRC after progression on prior anti-PD-(L)1 therapy. **Methods:** This multicenter, single-arm, phase 2 study enrolled patients with centrally confirmed dMMR/MSI-H mCRC and iRECIST-defined disease progression after prior anti-PD-(L)1 monotherapy or anti-PD-(L)1-based combination therapy. Patients received intravenous cadonilimab at 6 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was the 12-month progression-free survival (PFS) rate, assessed by RECIST v1.1. **Results:** A total of 24 patients were enrolled and received study treatment. The median age was 54 years; 29% were female, 17% had Lynch syndrome, 92% had peritoneal metastases, and 33% had liver metastases. Overall, 63% of patients had received ≥2 prior lines of systemic therapy; all had prior exposure to anti-PD-(L)1 therapy, 71% had received fluoropyrimidines and oxaliplatin, and 29% had received irinotecan. The best response to prior anti-PD-(L)1 therapy was partial response in 2 patients, stable disease in 17, and progressive disease in 5. With a median follow-up of 14.8 months at data cutoff (January 22, 2026), the 12-month PFS rate was 44.6% (95% CI, 23.4–63.9), meeting the prespecified primary endpoint of 40%. Median PFS was 6.1 months (95% CI, 2.2–10.1). Median overall survival (OS) was not reached and the 12-month OS rate was 68.6% (95% CI, 42.5–84.7). The confirmed objective response rate (ORR) was 20.8% (95% CI, 7.1–42.2), and the disease control rate (DCR) was 75.0% (95% CI, 53.3–90.2). One patient completed the protocol-specified 2-year treatment without progression, and 7 remained on study treatment. Treatment-related adverse events of any grade occurred in 15 patients (63%), with grade 3 events observed in 3 patients (13%). **Conclusions:** Cadonilimab provided meaningful disease control with modest antitumor activity and a manageable safety profile in patients with dMMR/MSI-H mCRC after progression on prior anti-PD-(L)1 therapy. Clinical trial information: NCT05426005. Research Sponsor: National Science Fund for Distinguished Young Scholars; 82425045.

	N=24
12-month PFS rate	44.6% (95% CI, 23.4–63.9)
Best overall response	
PR	5 (21)
SD	13 (54)
PD	5 (21)
NE	1 (4)
Objective response rate	20.8% (95% CI, 7.1–42.2)
Disease control rate	75.0% (95% CI, 53.3–90.2)

3578 **Poster Session**

Radiotherapy followed by systemic therapy and tislelizumab in microsatellite-stable rectal cancer with synchronous unresectable metastases: Updated results of the MIRACLE-2 study. First Author: Menglong Zhou, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Microsatellite-stable (MSS) tumors comprise ~95% of metastatic colorectal cancer cases and exhibit intrinsic resistance to immunotherapy. Emerging evidence suggests systemic therapy may enhance immunotherapy responsiveness, while radiotherapy could improve efficacy by overcoming resistance and reducing tumor burden. The MIRACLE-2 study evaluated the safety and efficacy of combining radiotherapy with systemic therapy and tislelizumab as first-line treatment for unresectable metastatic MSS rectal cancer (RC). **Methods:** MIRACLE-2 was a prospective, single-arm, phase II study. Inclusion criteria: MSS RC with primary tumor ≤10 cm from anal verge on MRI and synchronous unresectable metastases. Patients received hypofractionated radiotherapy (HFRT) for primary lesions and HFRT or SBRT for metastases, followed by systemic therapy: FOLFOX-bevacizumab-tislelizumab for RAS/BRAF-mutant patients or FOLFIRI-cetuximab-tislelizumab for wild-type patients. Reassessment every 8 weeks. Patients achieving resectable disease underwent primary tumor resection and metastasectomy/local ablative therapies for metastases. For patients unable to preserve anal sphincter, a watch-and-wait (WW) strategy was considered if clinical complete response (cCR) of primary tumor was achieved. Otherwise, systemic therapy continued until progression/intolerable toxicity. Primary endpoint: ETS rate (≥20% target lesion reduction at 8 weeks post systemic therapy initiation). Secondary endpoints: disease control rate (DCR), duration of response (DOR), overall survival (OS), progression-free survival (PFS), and safety. **Results:** As of December 31, 2025, efficacy data were available for 50 patients (38 males, 76.0%; median age 57 years, range 30-73). Among these, 52.0% had liver metastases, 8.0% lung metastases, and 40.0% both liver and lung metastases. RAS/BRAF mutations were detected in 56.0% of primary tumors. Median treatment courses: eight (range 3-12). Overall, 18% (9/50) attained no evidence of disease (NED). ETS rate: 76.0%; DCR: 88.0%. Median follow-up: 19.9 months (95% CI: 16.4-23.4). Among 34 patients with complete/partial response, median DOR: 8.0 months (95% CI: 5.2–10.8), with 1-year DOR rate of 20%. Median PFS: 9.3 months (95% CI: 7.1-11.5), with 1-year PFS rate of 33.4%. Median OS: 23.2 months (95% CI: 15.1-31.3), and 1-year OS rate: 93.3%. No grade 5 treatment-related adverse events (TRAEs) occurred. All-grade TRAEs: lymphopenia (95.9%), anemia (91.8%), and leukopenia (69.4%). Grade 3/4 TRAEs: lymphopenia (36.7%), neutropenia (26.5%), and leukopenia (20.4%). **Conclusions:** The combination of radiotherapy, systemic therapy, and tislelizumab showed a high ETS rate and manageable safety profile in first-line unresectable MSS RC. Long-term outcomes require further follow-up. Clinical trial information: NCT05359406. Research Sponsor: None.

3579 **Poster Session**

Indirect comparison of nivolumab-ipilimumab versus chemotherapy (Chemo) and/or immunotherapy in dMMR/MSI-H metastatic colorectal cancer (mCRC) using reconstructed individual patient data (IPD). First Author: Daniele Rossini, Department of Experimental and Clinical Medicine, University of Florence; Oncology Unit, Careggi University Hospital, Florence, Italy

Background: In patients with dMMR/MSI-H mCRC, phase III randomized trials have established immune checkpoint (IO) inhibition as a key first-line strategy. In KEYNOTE-177, pembrolizumab demonstrated superior outcomes vs chemo, supporting an IO-first approach. In CheckMate 8HW, nivolumab plus ipilimumab (Nivo+Ipi) outperformed both nivolumab and chemo, demonstrating benefit from dual checkpoint blockade. In contrast, COMMIT evaluated FOLFOX plus bevacizumab plus atezolizumab and reported improved outcomes vs atezolizumab monotherapy. Despite these advances, a direct head-to-head comparison between Nivo+Ipi and chemo-IO remains unavailable. We addressed this unmet question by reconstructing IPD from published Kaplan-Meier (KM) curves to enable an indirect cross trial comparison. **Methods:** Published PFS KM curves were digitized to pseudo-IPD. To mitigate cross-trial differences, arms were divided into four groups: Nivo+Ipi (CheckMate 8HW; n=171), chemo-IO (COMMIT; n=38), IO monotherapy [pembrolizumab (KEYNOTE-177; n=153), nivolumab (CheckMate 8HW; n=170), atezolizumab (COMMIT; n=40); n=363], and chemo (standard arms in KEYNOTE-177/CheckMate 8HW; n=238). The primary estimand was PFS restricted mean survival time (RMST) at τ=24 months. As a late-benefit sensitivity analysis, RMST was also estimated at τ=48 months where ≥10% patients remained at risk, to limit instability from sparse tails. KM comparisons (log-rank and Cox HR) were derived from reconstructed pseudo-IPD. **Results:** At τ=24 months, Nivo+Ipi improved PFS RMST vs chemo (18.87 vs 10.33 months; ΔRMST +8.54, 95% CI 6.78-10.31; p<0.001) and vs IO monotherapy (18.87 vs 14.61 months; ΔRMST +4.26, 95% CI 2.54-5.99; p<0.001). Chemo-IO improved RMST vs chemo (16.92 vs 10.33 months; ΔRMST +6.59, 95% CI 3.59-9.60; p<0.001). In the key indirect comparison, Nivo+Ipi vs chemo-IO did not show a statistically significant RMST difference (18.87 vs 16.92 months; ΔRMST +1.95, 95% CI -1.14-5.04; p=0.217). In contrast, the late-benefit (τ=48 months) analysis demonstrated a statistically significant advantage for Nivo+Ipi (RMST 35.00 vs 27.71 months; ΔRMST +7.29, 95% CI 0.08-14.49; p=0.048). KM-derived estimates were consistent with these patterns: Nivo+Ipi outperformed chemo (p<0.001) and IO monotherapy (p<0.001), and chemo-IO outperformed chemo (p<0.001). Compared with chemo-IO, Nivo+Ipi was associated with numerically longer PFS (NE vs 30.2 months; HR 0.62, 95% CI 0.36-1.05; p=0.073). **Conclusions:** Nivo+Ipi and chemo IO substantially improved 24-month PFS RMST vs chemo and IO monotherapy, with similar outcomes. Nivo+Ipi showed a significant advantage over chemo-IO at 48 months, consistent with a sustained late PFS effect. Findings are hypothesis-generating given cross-trial heterogeneity and reconstruction-related bias. Research Sponsor: None.

3580 **Poster Session**

Avatrombopag for chemotherapy-induced thrombocytopenia in gastrointestinal malignancies (ACT-GI): A multicenter, U.S., randomized, double-blind, placebo-controlled clinical trial. First Author: Gerald A. Soff, University of Miami Health System/Sylvester Comprehensive Cancer Center, Miami, FL

Background: Chemotherapy-induced thrombocytopenia (CIT) is a frequent complication of chemotherapy. Persistent CIT (not adequately resolved by day 1 of the following cycle) may lead to reduction or delay in treatment. There are no FDA approved therapies for CIT. Aim: To evaluate the safety and efficacy of avatrombopag (AVA), an oral thrombopoietin receptor agonist, to treat persistent CIT and prevent its recurrence in GI cancer. **Methods:** ACT-GI (NCT05772546) was a multicenter, randomized, double-blind, placebo-controlled, investigator-initiated trial of GI cancer patients with persistent CIT (platelets [Plt] $<85\times10^9$/L on day 1 of a scheduled chemotherapy cycle). Patients were randomized 1:1 to AVA 40 mg daily or placebo and treated for two on-study phases. In the lead-in phase, patients were treated up to 2 weeks while chemotherapy was held. Patients proceeded to the on-cycle phase and resumed chemotherapy only if their Plt recovered to $\geq100\times10^9$/L. In the on-cycle phase, patients received a single full-dose chemotherapy cycle with continued study drug. The primary endpoint was successful correction of CIT and prevention of recurrence (achieving Plt $\geq100\times10^9$/L within the lead-in period AND prevention of CIT recurrence (Plt $\geq100\times10^9$/L) at end of the cycle). **Results:** Efficacy: ACT-GI was closed to enrollment by the DSMB, for overwhelming efficacy, at a prespecified interim analysis when 20 patients in each arm completed the double-blind period. 16 of 23 patients (70%; 95% CI 47% to 87%) in the AVA arm achieved the primary endpoint versus 4/24 patients (17%; 95% CI 5% to 37%) in the placebo arm (Z=3.67, P<0.001). 74% and 88% of patients had stage IV cancer in AVA and placebo arms, respectively. 44/47 patients completed study drug; 2 discontinuations were due to physician decision and 1 was due to an adverse event. Plt improvement to $\geq100\times10^9$/L during lead-in was achieved by 83% of patients in the AVA arm vs. 46% of patients in the placebo arm. The median (IQR) Plt at the end of the on-cycle treatment period was 157 (136-202) in the AVA arm vs 72 (68-134) in the placebo arm. In the AVA arm there were two clinically relevant bleeding events (intestinal stoma site bleed at Plt 105×10^9/L and intracranial hemorrhage). No patient received platelet transfusion. Safety: AEs and serious AEs (SAEs) occurred in 74% and 13% of patients in the AVA arm and 46% and 0% of patients in the placebo arm, respectively. No SAEs were study drug-related. There were no treatment-related AEs leading to death or discontinuation of study drug. **Conclusions:** In this randomized, placebo-controlled trial, AVA demonstrated safety, tolerability, and efficacy in treatment and prevention of persistent CIT in GI cancers. These findings are promising for a common, serious condition that prevents delivery of full-dose, on-time cancer-directed therapy. Clinical trial information: NCT05772546. Research Sponsor: Swedish Orphan Biovitrum (Sobi).

3581 **Poster Session**

Propensity score–matched analysis of trifluridine-tipiracil plus bevacizumab (FTD/TPI+Bev) vs anti-EGFR re-treatment in pretreated metastatic colorectal cancer (mCRC). First Author: Giovanni Trovato, Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS Università Cattolica del Sacro Cuore, Rome, Italy

Background: The SUNLIGHT trial established FTD/TPI+Bev as a preferred 3rd-line option for unselected mCRC patients (pts). Recently, the phase II randomized PARERE trial reported high response rates and favorable progression-free survival (PFS) with anti-EGFR re-treatment in *RAS/BRAF* wild-type (wt) mCRC pts selected by liquid biopsy versus regorafenib. In the absence of head-to-head comparisons between these two strategies, we performed an indirect analysis, using propensity score matching (PSM) to minimize baseline imbalances. **Methods:** Two cohorts of pretreated (≥2 previous lines) mCRC pts were compared: pts with *RAS/BRAF* wt tumors receiving FTD/TPI+Bev enrolled in the Italian real-world FLOWER trial, and *RAS/BRAF* wt pts at the liquid biopsy enrolled in Arm A (panitumumab (Pan) re-treatment followed by regorafenib) of the PARERE trial. PSM was applied adjusting for age, sex, ECOG performance status, number (N) of metastatic sites, N of prior treatment lines, tumor sidedness, and presence of liver and peritoneal metastases. **Results:** Overall, 75 pts treated with FTD/TPI+Bev and 103 pts treated with Pan were included. In the unmatched populations, median PFS was 6.0 months with FTD/TPI+Bev vs 4.1 months with Pan (p<0.001). Median OS was 13.6 months and 11.6 months, respectively (p=0.756). ORR was 9.3% with FTD/TPI+Bev and 16.5% with Pan (p=0.172). After PSM, 68 pts per cohort were analyzed. Median PFS was 5.0 months with FTD/TPI+Bev vs 3.9 months with Pan [HR 1.65 (95% CI, 1.14-2.38), p=0.007]. Median OS was 13.1 months vs 11.6 months, respectively [HR: 0.89 (95% CI: 0.59-1.34); p=0.569]. ORR remained numerically higher in the Pan group, although not statistically significant (p=0.34). Results were consistent regardless of N of anti-EGFR-free lines [1 vs ≥2; HR for PFS: 0.85 (95% CI: 0.58-1.23), p=0.379; HR for OS 0.85 (95% CI: 0.56-1.29), p=0.446], type of prior anti-EGFR therapy [Pan vs Cetuximab; HR for PFS: 0.80 (95% CI: 0.58-1.10), p=0.163; HR for OS 0.87 (95% CI: 0.61-1.24), p=0.435], and response to previous anti-EGFR treatment [HR for PFS: 0.87 (95% CI: 0.59-1.28), p=0.485; HR for OS 0.80 (95% CI: 0.59-1.28), p=0.279]. Toxicity profiles differed between treatments: neutropenia (any grade (G) 52% vs 3%; G3-4: 37% vs 1%), anemia (39% vs 15%; G3-4: 5% vs 1%), nausea (25% vs 10%; G3-4: 4% vs 0%), thrombocytopenia (24% vs 7%; G3-4: 4% vs 0%) and hypertension (21% vs 1%; 4% vs 0%) were more frequent with FTD/TPI+Bev, whereas rash occurred exclusively in the Pan group (81%; G3-4: 19%). **Conclusions:** Although underpowered, this indirect comparison suggests that FTD/TPI+Bev may achieve longer PFS than Pan re-treatment in pretreated mCRC pts, while anti-EGFR rechallenge may be associated with numerically higher response rate, with no OS difference. Prospective randomized trials are warranted to confirm these findings. Research Sponsor: None.

3582 **Poster Session**

A multi-omic analysis of EOCRC: Divergent methylation and gene expression signatures in young patients. First Author: Ning Jin, The Ohio State University, Columbus, OH

Background: The incidence of early-onset colorectal cancer (EOCRC; diagnosis $<$ 50 years) is rising at an alarming rate. EOCRC often exhibits distinct clinical features compared to late-onset colorectal cancer (LOCRC), yet the underlying mechanisms remain poorly understood. This study aimed to characterize a cohort of EOCRC patients by integrating DNA methylation, gene expression, and metabolomic profiles to identify age-specific molecular drivers. **Methods:** We performed an integrated multi-omic analysis on a cohort of 42 patients, comprising 16 EOCRC and 26 LOCRC cases that were collected from the Total Cancer Care at the Ohio State University. For each patient, fresh-frozen tumor tissue and paired adjacent normal tissue were analyzed using reduced representation bisulfite sequencing (RRBS). Parallel transcriptomic profiling was conducted by RNA-seq on all tumor samples. Additionally, systemic metabolic signatures were captured from plasma using liquid chromatography-mass spectrometry (LC-MS). Functional integration of differentially methylated regions (DMRs), gene expression signatures, and metabolomic profiles was performed using Ingenuity Pathway Analysis (IPA) to identify enriched canonical pathways. **Results:** Integrative analysis revealed a divergent molecular fingerprint in EOCRC compared to LOCRC. At the epigenomic and transcriptomic levels, EOCRC tumors demonstrated significant enrichment in neurotransmitter-related pathways, such as CREB signaling in neurons and ion channel transport, alongside a pronounced activation of G-protein coupled receptor (GPCR) signaling. Furthermore, we identified a distinct immune-related signature characterized by the activation of phagosome formation and S100 family signaling pathways. These intracellular alterations were mirrored by a unique systemic metabolic profile involving the G alpha signaling pathway and the transport of vitamins, nucleosides, bile salts, and amine compounds. In addition, we identified a multi-omic signature of 11 genes that exhibit both differential gene expression between EOCRC and LOCRC tumors and significant tumor-specific methylation drift relative to adjacent normal tissue. Notably, this signature is enriched with established epigenetic clock/aging markers, including *LEP*, *PLA2G4F*, *CYP2E1*, *GCM2*, *ZNF418*, and *MINAR1*, making them ideal candidates for early detection by liquid biopsies or risk-stratification tools for EOCRC. **Conclusions:** Our findings demonstrate that EOCRC is a biologically distinct entity driven by specific epigenetic and immune dysregulation. The simultaneous enrichment of neurotransmitter pathways and GPCR signaling suggests that EOCRC development may be uniquely influenced by neuro-epithelial interactions. The 11-gene signature enriched with epigenetic aging markers may serve as screening or surveillance tools for EOCRC patients. Research Sponsor: Paul Calabresi Career Development Award for Clinical Oncology; K12CA133250.

3583 **Poster Session**

Long-term responders to trifluridine/tipiracil plus bevacizumab in previously treated metastatic colorectal cancer: Results from the BeTAS real-world study. First Author: Nieves Martinez Lago, Department of Medical Oncology. Hospital Clínico Universitario e Instituto de Investigación Sanitaria de Santiago de Compostela, Santiago de Compostela, Spain

Background: The phase III SUNLIGHT trial established trifluridine/tipiracil plus bevacizumab (FTD/TPI+BEV) as a standard treatment option for metastatic colorectal cancer (mCRC) after failure of at least two prior regimens. However, limited evidence exists regarding patients achieving durable benefit in routine clinical practice. We aimed to characterize the prevalence, clinical features, and outcomes of long-term responders treated with FTD/TPI plus bevacizumab in a large real-world cohort. **Methods:** BeTAS is a multicenter ambispective real-world study conducted within the Galician Research Group on Gastrointestinal Tumors. Consecutive patients with previously treated mCRC receiving FTD/TPI+BEV after failure or intolerance to $\geq$2 prior regimens were included. Long-term responders (LTRs) were defined using a pre-specified landmark of progression-free survival (PFS) $\geq$9 months. Baseline characteristics, treatment response, and survival outcomes were compared between LTRs and non-LTRs. Overall survival (OS) was assessed using a 9-month landmark analysis to minimize immortal time bias. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable Cox regression was performed. **Results:** Among 576 patients, median PFS and OS were 4.9 months (95% CI 4.3–5.5) and 10.8 months (95% CI 9.8–11.9), respectively. LTRs accounted for 20.3% of the cohort (n=117). Compared with non-LTRs, LTRs more frequently had $\leq$2 metastatic sites (83.8% vs 67.5%, p=0.001), absence of liver metastases (28.4% vs 16.7%, p=0.004), longer time from metastatic diagnosis (p=0.046), and Tabernero best prognostic characteristics (p=0.007). Among evaluable patients, objective response rate was higher in LTRs (22.1% vs 5.5%, $p<0.001$), as was disease control rate (100% vs 39.0%, $p<0.001$). Median PFS was 15.3 versus 3.6 months, and landmark OS was 23.5 versus 8.1 months (both $p<0.001$). Long-term response remained independently associated with improved OS (HR 0.19, 95% CI 0.14–0.26; $p<0.001$). **Conclusions:** In real-world practice, approximately one in five previously treated patients with mCRC achieve durable benefit with FTD/TPI+BEV. Identification of clinical factors associated with long-term response may support improved patient selection in later-line treatment. Research Sponsor: None.

3584 **Poster Session**

Correlative analysis of ctDNA in CheckMate-9X8 study of frontline treatment with mFOLFOX6, bevacizumab with or without nivolumab in metastatic colorectal cancer. First Author: Jin Yao, Bristol Myers Squibb, Princeton, NJ

Background: The CheckMate 9X8 study evaluated ctDNA as biomarker to predict treatment benefit in metastatic colorectal cancer (mCRC) patients receiving standard-of-care therapy with or without nivolumab. Although the phase 2/3 trial did not meet its primary PFS endpoint, the addition of nivolumab appeared to confer clinical benefit in a subset of patients. As predictive biomarkers for first-line nivolumab in mCRC remain unvalidated, this exploratory analysis identified mutation- and methylation-based ctDNA signatures that may help inform future patient stratification and disease management. **Methods:** Study design and methods were published previously (Lenz, et al. JITC 2024). As part of an exploratory biomarker analysis, paired plasma samples (baseline and on-treatment at C3D1) were evaluated for circulating tumor DNA (ctDNA) using PredicineATLAS (600-gene) comprehensive genomic profiling, PredicineSCORE (Low-pass whole-genome sequencing), and PredicineEPIC (methylation) assays and correlated with baseline patient characteristics and treatment efficacy. **Results:** Over 98% (138/140) of baseline patients had quantifiable ctDNA with Predicine ATLAS and approximately 83% (116/140) had detectable copy number variants (CNV) with PredicineSCORE. High concordance was observed between ctDNA-derived mutations and tissue-derived KRAS, TP53, and APC mutations and MSI/MSS status at baseline. 97% of patients with KRAS G12D/V/C mutations positively identified by local tissue testing were also positively identified by ctDNA. 6% of subjects considered KRAS wild-type by local tissue testing were identified as having KRAS G12D/V/C mutations by ctDNA. KRAS mutations, wild-type TP53, chromosomal loss of 18q21.33, high methylation scores and hypomethylated Tetraspanin 15 correlated with treatment efficacy. Neo-KRAS WT, or loss of KRAS mutations on treatment, emerged during treatment in 36% of patients with KRAS mutations at baseline and was associated with improved survival. Significant ctDNA level reduction was seen during treatment in both arms of the study irrespective of tumor response. These insights underscore the promise of ctDNA profiling in enhancing precision medicine by enabling real-time, dynamic assessment of tumor biology and therapeutic response with a potential to guide personalized treatment strategies for mCRC patients in the future. **Conclusions:** This study highlights the potential utility of liquid biopsy in the mCRC setting and provides novel insights from the ctDNA analysis, highlighting genetic and epigenetic ctDNA features that might be associated with clinical efficacy of SOC $\pm$ nivolumab in 1L mCRC. The emergence of Neo-KRAS WT in a substantial number of patients indicates a dynamic nature of KRAS alterations and highlights the additional value that longitudinal plasma ctDNA analysis could provide. Clinical trial information: NCT03414983. Research Sponsor: None.

3585 **Poster Session**

Circulating tumor DNA for characterizing intratumor heterogeneity and outcomes in metastatic colorectal cancer. First Author: Cynthia Yeung, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Intratumor heterogeneity (ITH) drives CRC resistance, yet tissue-based assessments remain limited. ctDNA captures heterogeneity, though variable tumor fractions confound measurements. We assessed raw vs fraction-adjusted ITH in ctDNA for overall survival (OS) in metastatic CRC (mCRC). **Methods:** We analyzed two real-world mCRC cohorts from MD Anderson: a 73-gene panel (1,137 patients, 2014-2023; limit of detection (LoD) 0.1%) and a 701-gene panel (150 patients, 2024-2025; LoD 0.5%). Quality filters included $\geq$ 3 detected variants, MaxVAF $>$ 0.01, and bioinformatic filtering of putative germline variants. ITH was quantified via raw Mutant-Allele Tumor Heterogeneity (rMATH; VAF distribution width) and the Shannon entropy-based, MaxVAF-normalized (VAF/Max_VAF) blood ITH (bITH; multiplies bin entropy by clonality weights). OS was assessed using Cox models by continuous variables and optimal cut-points determined by maximally selected log-rank statistics. A stress test subset (top 50% MaxVAF) was analyzed to decouple findings from analytical noise inherent at low tumor fractions. **Results:** In the 73-gene cohort (median age 53.2; 91% MSS, 14% BRAF mutated, 64% RAS mutated), MaxVAF was the strongest predictor of worse OS in both univariable (HR 1.32, p $<$ 0.001) and multivariable (MV) models (HR 1.31, p $<$ 0.001). Paradoxically, high rMATH was associated with improved OS (MV HR 0.89, p = 0.014). This protective signal of high heterogeneity was more pronounced in the dichotomized model (MV HR 0.71, p $<$ 0.001) and persisted in the subset of high-burden patients (top 50% MaxVAF) (MV HR 0.69, p $<$ 0.001) and the MSS subset (MV HR 0.68, p = 0.003). In the 701-gene panel cohort, MaxVAF remained the dominant independent predictor (MV HR 2.37, p $<$ 0.001). bITH was not independently prognostic (MV HR 0.98, NS). **Conclusions:** MaxVAF serves as the primary ctDNA-derived driver of clinical outcomes in mCRC, confirming that ctDNA-inferred ITH metrics are heavily confounded by total tumor shedding. The unexpected association between high rMATH and improved OS suggests that increased clonal diversity, at a fixed tumor burden, may indicate a less evolutionarily pruned or consolidated tumor compared to those that have undergone a selective clonal sweep. These results highlight that while ctDNA can characterize clonal architecture, the clinical interpretation of heterogeneity must be contextualized within the tumor's total systemic volume and evolutionary state. Research Sponsor: Conquer Cancer, the ASCO Foundation.

Cohort	Variable (High vs Low)	Multivariable HR (95% CI)*	p-value
73-gene panel	**MaxVAF**	**1.31 (1.20–1.43)**	**<0.001**
	Raw MATH	**0.89 (0.81–0.98)**	**0.014**
	bITH	0.98 (0.90–1.08)	0.716
701-gene panel	**MaxVAF**	**2.37 (1.52–3.71)**	**<0.001**
	Raw MATH	0.85 (0.50–1.44)	0.536
	bITH	1.23 (0.82–1.87)	0.320

*HR per 1 SD increase. Raw MATH was adjusted for MaxVAF, while bITH was tested without redundant MaxVAF adjustment. All models adjusted for age, sex, MSI, BRAF, and RAS status.

3586 **Poster Session**

Influence of neoadjuvant therapy on tumor-vascular-immune stromal networks in colorectal cancer liver metastases. First Author: Pia J. Osterlund, Tampere University Hospital, Tampere, Finland

Background: Neoadjuvant therapy's effect on vascular, tumor, and immune compartments, and their co-regulation, in colorectal liver metastases (CRLMs) remains poorly understood. We performed multiplex-based tissue profiling to quantify how treatment reshapes stromal compartment and co-occurrence networks, defined by inside-case correlations between features. **Methods:** We analyzed 76 CRLM cases (27 untreated, 49 neoadjuvant-treated [43 chemotherapy, 6 chemo + VEGF-/EGFR-targeted]). Tissue microarrays (1-3 1-mm cores/tumor) underwent multiplex immunofluorescence to quantify immune/tumor subsets (CD3/CD4/CD8/PD-1/FOXP3/TIM-3/Ki67/CDX2), vessels (claudin-5), and stromal perivascular compartments (αSMA/PDGFRβ). Statistical analysis included Mann-Whitney U tests and Spearman correlations. **Results:** Neoadjuvant-treated CRLMs had 42% fewer proliferating tumor cells ($CDX2^+KI67^+$density, p=0.006) and 33% lower $CDX2^+$ density (p=0.031) compared with untreated CRLMs. This was accompanied by a 32% reduction in proliferating cytotoxic T-cells ($CD3^+CD8^+Ki67^+$ density, p=0.029). A reduction in vessel size was also observed in treated CRLMs (vessel size, -12%, p=0.077). Analyses suggested different effects by type of neoadjuvant treatment. Chemotherapy alone reduced proliferating tumor cells ($CDX2^+KI67^+$ density, -37%, p=0.016) and suppressed cytotoxic T-cell proliferation ($CD3^+CD8^+Ki67^+$ density, -40%, p=0.017). The addition of VEGF/EGFR-targeted agents produced the most pronounced reduction in tumor burden ($CDX2^+$ density, -73%, p=0.012; $CDX2^+KI67^+$ density, -76%, p=0.010) vs. untreated. CRLM co-occurrence networks were also affected by treatment. Treatment abolished positive correlations between tumor cells ($CDX2^+$ and $CDX2^+KI67^+$ densities) and $\alpha SMA^+PDGFR\beta^+$ perivascular fraction/vessel size (r=+0.42 – +0.60, $p<0.05$), and negative correlations between tumor cells and $\alpha SMA^+PDGFR\beta^-$ perivascular fraction/vessel density (r=-0.47 – -0.40, $p<0.05$) in untreated (vs +0.05 – +0.27 and +0.09 – +0.21, p=n.s., in treated). Treatment also eliminated positive correlations between vessel size and exhausted ($CD8^+PD\text{-}1^+$) and regulatory ($CD4^+FOXP3^+$) T-cell densities (untreated r=+0.40 – +0.47, $p<0.05$). In parallel, new positive links emerged between $\alpha SMA^-PDGFR\beta^+$ perivascular fraction and $CD4^+$ and $CD8^+$ T cells (r=+0.41 – +0.42, $p<0.05$). **Conclusions:** This exploratory study indicates that neoadjuvant treatment alters the CRLM microenvironment, affecting tumor, vascular, and immune compartments. Additionally, analyses suggest that treatment induces a restructuring of their interdependence networks, defined by the loss of specific tumor-stromal-vascular links seen in untreated CRLMs, while establishing new ones. These findings motivate continued mechanistic studies and analyses on how these changes are related to benefits of treatment. Research Sponsor: None.

3587 **Poster Session**

Clinical efficacy of laparoscopic hybrid surgery versus total open surgery for simultaneous resection of colorectal cancer liver metastases (CHLH trial). First Author: Wei Zhang, Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Despite widespread adoption of simultaneous resection for colorectal liver metastases, the clinical efficacy varies among different approaches, and the optimal surgical strategy remains controversial. This study aims to evaluate the efficacy and safety of laparoscopic hybrid surgery (LHS) versus total open surgery (TOS) in the simultaneous resection of CRLM. **Methods:** This is a prospective cohort study (NCT06550700) conducted at a tertiary medical center, enrolling 266 patients who underwent simultaneous resection for CRLM from January 2017 to June 2021. The surgical approach is selected by colorectal surgeons and hepatobiliary surgeons based on their experience with either TOS or LHS. The primary outcomes were the incidence of complications and postoperative recovery-related outcomes. The secondary outcomes were 5-year overall survival (OS) and disease-free survival (DFS). **Results:** This study ultimately enrolled 144 patients in the LHS group and 122 patients in the TOS group. The complication rate was significantly lower in the LHS group than in the TOS group (10.4% vs. 20.5%, p = 0.022). Compared with the TOS group, patients in the LHS group had shorter postoperative hospital stay [8.00 (6.00, 10.00) vs. 9.00 (8.00, 12.00) days, $p < 0.001$], earlier resumption of liquid intake [3.00 (3.00, 3.00) vs. 4.00 (3.00, 4.00) days, $p < 0.001$], and less intraoperative blood loss [300.00 (200.00, 400.00) vs. 500.00 (500.00, 700.00) mL, $p < 0.001$]. However, the LHS group was associated with longer operative time [260.00 (236.00, 320.00) vs. 240.00 (195.00, 269.00) min, $p < 0.001$]. No significant differences were observed between the two groups in overall survival (p = 0.464) or disease-free survival (p = 0.838). **Conclusions:** Compared with TOS, applying LHS for simultaneous resection for CRLM results in faster postoperative recovery, lower complication rates, and similar survival outcomes. Clinical trial information: NCT06550700. Research Sponsor: National Natural Science Foundation of China; 82473439, 82272705 and 82503486; the Shanghai "Rising Stars of Medical Talents" Youth Development Program of the Shanghai Municipal Health Commission, China; No.2024-70; the Naval Medical University "Deep Blue" Project Talent Program; the First Affiliated Hospital of Naval Medical University Special Project for Basic Medical Research, China; 2023QD003 and 2023PY04; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; Shanghai Shenkang Hospital Development Center, Shanghai Clinical Cohort Project; SHDC2025CCS019; Shanghai Science and Technology Plan Project; 25SF1901500.

3588 **Poster Session**

A four-marker-protein signature to predict ramucirumab efficacy in combination with TAS-102 in advanced colorectal cancer: Translational analysis of the RAMTAS trial of the German AIO (AIO-KRK-0316/IKF643). First Author: Thomas Seufferlein, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany

Background: The combination of TAS-102 and bevacizumab is standard in the treatment of advanced colorectal cancer (aCRC). Ramucirumab (Ram) is a mAb that blocks VEGFR2. Ram in combination with Tas-102 did not improve OS compared to Tas-102 alone in the ITT population of the RAMTAS trial. Subgroups such as female patients (pts) and pts with left-sided tumors appeared to benefit from the combination (DOI:10.1016/j.annonc.2024.08.2264). Here we aimed at identifying angiogenesis-related, soluble, predictive biomarkers defining a RAMTAS subpopulation benefitting from the addition of Ram to Tas-102. **Methods:** Serum samples were available from 194 of 428 pts from the RAMTAS study (96 pts randomized to TAS-102, 98 pts to TAS-102 plus Ram). Serum levels of 85 angiogenesis-related proteins obtained prior to treatment with Tas-102 +/- Ram (baseline, BL) and at cycle 2 day 1 prior to the start of the next cycle (treatment, TR) were quantified via multiplex-ELISA by Myriad-RBM. Multivariate Cox regression models were developed within the combination arm using stepwise selection and ridge regularization. Model performance was assessed via C-index and validated using 10 x 5-fold cross-validation (CV) as well as full quality control for multicollinearity and proportional hazard assumptions. To distinguish predictive from general prognostic effects, the identified signatures were applied to the monotherapy control arm. **Results:** A TR model incorporating just 4 serum proteins demonstrated robust discrimination in the combination arm (Training C-index: 0.712; CV C-index: 0.708 ± 0.063). This model successfully stratified patients into a "Ram benefit" and a "no Ram benefit" group with a corresponding median PFS of 7.0 mo and 1.9 mo, respectively (HR 6.97, $p < 0.001$). A Baseline (BL) model yielded a C-index of 0.699, also utilizing just 4 serum proteins. Application of both models to the TAS-102 mono arm resulted in poor discrimination (C-index ~0.60) indicating that the signatures are specific predictors for the combination. In a comparative survival analysis, "Ram-benefit" TR model patients achieved a significantly longer PFS with the combination compared to monotherapy (7.00 vs. 2.14 mo; HR 0.558, p=0.0078). Conversely, "no-Ram-benefit" patients derived no significant benefit from the addition of Ram (PFS 1.91 vs. 1.91 mo; HR 0.946, p=0.4204). **Conclusions:** Oligo-marker serum signatures, when incorporating early on-treatment dynamics after one cycle of Tas-102/Ram, may effectively predict a survival benefit for aCRC-pts receiving TAS-102 in combination with Ram. We propose that a two-stage "Screen & Monitor" (BL+TR) strategy will help to identify primary refractory patients who gain no benefit from the addition of Ram. Such an approach could maximize therapeutic utility while reducing potential toxicity. Clinical trial information: NCT03520946. Research Sponsor: Lilly.

3589 **Poster Session**

Real-world outcomes and recurrence risk factors of liver transplantation for permanently unresectable colorectal liver metastases following the TransMet trial. First Author: Rene Adam, Paul Brousse Hospital - APHP, Villejuif, France

Background: Following the TRANSMET trial that demonstrated an overall survival (OS) benefit of liver transplantation (LT) over chemotherapy (CT) alone for selected patients with permanently unresectable colorectal liver metastases (uCRLM), the program of LT has continued in France with the same eligibility criteria, independent validation and graft allocation policy. We assessed the real-world oncological outcomes and prognostic factors for post-LT recurrence-free survival (RFS) in the whole cohort. **Methods:** This nation-wide analysis pooled both patients transplanted in TransMet (Trial cohort) and those after trial closure (Extension cohort). OS and RFS were evaluated in each cohort. Multivariable Cox models for RFS using sensitivity analyses including forced cohort adjustment and bootstrap resampling were performed. **Results:** A total of 87 patients underwent LT (37 Trial cohort; 50 Extension cohort). Baseline characteristics at CRLM diagnosis were comparable. At LT, patients in the Extension cohort received significantly fewer CT cycles ($\geq$24 cycles, 16% vs 41%, p=0.01) and showed higher rate of partial response (94% vs 57%, $p < 0.001$) after first-line CT. At time of LT, tumor burden, RECIST status and tumor markers were similar. Median follow-up was shorter in the Extension cohort (16 vs 57 months). No significant differences in OS and RFS were observed between extension and trial cohorts (30-months OS 89% vs 81%; 30-months RFS 47% vs 39%, respectively). In univariable analysis, risk factors of RFS included $\geq$2 CT lines, $\geq$24 CT cycles before LT, CEA at LT $>$ 5 ng/mL, progression on CT and interval from primary tumor surgery $>$2 years. In multivariable Cox analysis, $\geq$2 lines or $>$24 cycles before LT (HR 2.90, 95% CI 1.32–6.36; $p<0.01$) and CEA at LT $>$5 ng/mL (HR 2.26, 95% CI 1.18–4.33; p=0.01) remained independently associated with RFS, adjusted on interval from primary tumor surgery. Bootstrap resampling (2,000 iterations) highlighted these results in 82% and 67% of models, respectively. **Conclusions:** LT for uCRLM gives good and reproducible oncological outcomes across trial and extension cohorts. This exploratory analysis supports that RFS is impaired by a prolonged pre-transplant chemotherapy ($\geq$ 2 lines or $\geq$ 24 cycles) and improved by a good biological response (normalization of CEA), supporting considering LT in a multidisciplinary setting as soon as definitive unresectability is established. Research Sponsor: None.

3590 **Poster Session**

Dynamic circulating tumor DNA profiling for prediction of long-term clinical benefit in pMMR locally advanced rectal cancer receiving neoadjuvant chemoradiotherapy plus sintilimab. First Author: Xiaobin Zheng, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Immune checkpoint inhibitors (ICIs) targeting PD-1 have significantly improved outcomes in locally advanced rectal cancer (LARC). Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for treatment response monitoring and surveillance, capable of predicting long-term clinical outcomes. However, whether ctDNA serves as a prognostic predictor in patients with proficient mismatch repair (pMMR) LARC receiving neoadjuvant chemoradiotherapy (CRT) combined with immunotherapy remains to be explored. **Methods:** This prospective single-arm phase II trial enrolled pMMR LARC patients ($cT_{3\text{-}4}N_0M_0$ and $cT_{1\text{-}4}N_{1\text{-}2}M_0$) with an intermediate or high immunoscore (IS_B) (NCT05450029). Treatment-naïve patients received radiotherapy (50 Gy/ 25 fractions), 6 cycles of mFOLFOX6, and 5 cycles of sintilimab, followed by total mesorectal excision (TME) 6-8 weeks post-radiotherapy. Next-generation sequencing was used to evaluate baseline tumor tissue DNA and serial ctDNA dynamic changes. Baseline (T0) maximal somatic variant allelic frequency (maxVAF) was assessed, along with its changes at the first (T1, two cycles after therapy) and second clinical evaluation (T2, four cycles after therapy). **Results:** Tumor somatic mutations and aligned ctDNA analyses were conducted in 43 patients. The pathologic complete response (pCR) rate was 65.2%, with an objective response rate (ORR) of 93.5%. The R0 resection rate was 97.8%. The 3-year event-free survival rate, and 3-year overall survival rate remain immature. For dynamic ctDNA analysis, 37 patients were assessed using a 950-gene panel relevant to cancer. A significant decline in maxVAF from T0 to T1 was observed in the pCR group. Among patients who reached follow-up endpoints, circulating tumor DNA analysis reveals that patients with a $>$ 50% decline in maxVAF from T0 to T1 demonstrated longer survival outcomes and higher response rates compared to those without such decline. **Conclusions:** Serial ctDNA analysis demonstrates applicability in predicting treatment response to CRT combined with immunotherapy in pMMR LARC. Dynamic changes in circulating ctDNA may serve as a potential prognostic indicator in this population. Future studies should integrate ctDNA profiling of comprehensive cancer-related gene panels with large-scale clinical data to refine patient stratification and optimize therapeutic management. Clinical trial information: NCT05450029. Research Sponsor: National Natural Science Foundation of China; 82470696; National Key Clinical Discipline; Guangdong Basic and Applied Basic Research Foundation; 2022A1515012498 and 2024A1515010956; the program of Guangdong Provincial Clinical Research Center for Digestive Diseases; 2020B1111170004; Science and Technology Projects in Guangzhou; 2024A04J6400; Sun Yat-sen University Clinical Research 5010 Program; 2016005; Innovative Clinical Technique of Guangzhou.

3591 **Poster Session**

Safety and efficacy of ifebemtinib combined with garsorasib in KRAS G12C mutant colorectal cancer from a randomized part of a phase Ib/II study. First Author: Xiangdong Cheng, Zhejiang Cancer Hospital, Hangzhou, Zhejiang Province, China

Background: Studies (Yaeger R, et al.; Fakih, MG, et al.) have shown when RASi is combined with optimal therapeutic partner(s), clinical efficacy and benefit can be maximized. Ifebemtinib (ifebe) is a highly potent and selective oral inhibitor of focal adhesion kinase (FAK) that exhibits synergistic effect with RASi in both preclinical and clinical setting. Garsorasib (D-1553) is a novel KRAS G12Ci approved in China for treatment of KRAS G12C mutant NSCLC. We previously reported a promising objective response rate (ORR) of 44.4% in patients (pts) with KRAS G12C mutant CRC receiving ifebe + D-1553, with the durability of efficacy yet to be confirmed. Herein, we present the updated results with median follow-up of (14.4 months) from a randomized cohort of phase Ib/II study, comparing ifebe + D-1553 vs D-1553 alone in KRAS G12C mutant CRC, to elucidate the relative therapeutic contribution of ifebe and durability of response. **Methods:** Metastatic KRAS G12C mutant CRC pts with at least 1 prior line of systemic anticancer therapy were enrolled in a randomized part and randomized 1:1 to ifebe (100mg QD) + D-1553 (600mg BID) or D-1553 (600mg BID) alone. **Results:** As of January 4, 2026, 36 previously treated metastatic CRC pts were enrolled, with 18 pts in ifebe + D-1553 group and 18 pts in D-1553 group ($\geq$3 prior lines of treatment: 33.3% vs 27.8%; liver metastasis: 55.6% vs 72.2%). The median treatment duration was 8.5 months vs 3.6 months and 4 pts (3 [16.7%] vs 1 [5.6%]) were still on treatment. The hazard ratio (HR) for progression free survival (PFS) and overall survival (OS) was 0.47 and 0.44, respectively, demonstrating the durability of efficacy in pts receiving ifebe + D-1553 (Table). The safety profiles of ifebe + D-1553 in CRC pts are comparable to each single agent. No ifebe or D-1553 related death or AEs leading to drug withdrawal were reported. **Conclusions:** The combination of ifebe and D-1553, a dual-oral regimen, exhibits favorable safety profiles and better efficacy in treating KRAS G12C mutant CRC, with mOS exceeding 16 months. Clinical findings from this randomized study have shown robustness of improvement in overall ORR, PFS, DOR and OS benefit with this combination regimen, indicating that adding ifebe to a RASi can further improve clinical outcome to CRC patients with RAS G12C mutation. Clinical trial information: NCT06166836. Research Sponsor: None.

Efficacy.

	ifebe + D-1553 (N=18)	D-1553 (N=18)
Objective response rate (ORR), %	44.4 (21.5, 69.2)	16.7 (3.6, 41.4)
Disease control rate (DCR), %	100.0 (81.5, 100.0)	77.8 (52.4, 93.6)
Median duration of response (mDoR), months	12.1 (1.41, NE)	6.8 (6.3, NE)
Median PFS, months	8.4 (3.0, 11.9)	4.0 (2.0, 5.6)
HR for PFS (95% CI)	0.47 (0.23, 0.98)	
Median OS, months	16.4 (13.1, NE)	7.8 (5.3, NE)
HR for OS (95% CI)	0.44 (0.17, 1.15)	

3592 **Poster Session**

Reduced oxaliplatin exposure in gastrointestinal cancers: A systematic review and meta-analysis. First Author: Wallace Klein Schwengber, Division of Hematology and Oncology, Mayo Clinic Arizona, Phoenix, AZ

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent dose-limiting toxicity from oxaliplatin that impairs quality of life in gastrointestinal (GI) cancer patients (pts). While strategies to limit exposure exist, their impact on survival remains debated. We evaluated whether reduced oxaliplatin exposure (ROE) maintains survival while mitigating toxicity. **Methods:** We conducted a systematic review and meta-analysis (PubMed, Embase, Scopus, Web of Science, EBM Reviews) of studies comparing ROE vs standard-duration oxaliplatin-based chemotherapy in GI cancers. ROE was defined as planned limitation of oxaliplatin exposure, including shortened duration (3-4 months), maintenance-based de-escalation, or stop-and-go strategies. Primary endpoints were disease-free survival (DFS) in curative settings, progression-free survival (PFS) in palliative settings, and overall survival (OS). Secondary endpoints included grade $\geq$3 CIPN and grade $\geq$3 adverse events (AEs). Random-effects models used Hartung-Knapp-Sidik-Jonkman correction. Heterogeneity was assessed via I^2 and Cochran's Q. **Results:** 24 studies, comprising 15 randomized controlled trials (RCTs) and 9 retrospective cohorts, were included (N = 30,404 pts; ROE: 13,348; control: 17,056). Settings included adjuvant colorectal cancer (CRC; n = 14), metastatic CRC (mCRC; n = 5), gastric cancer (GC) (adjuvant n = 1, metastatic n = 3), and metastatic pancreatic cancer (PDAC) (n = 1). ROE strategies included shortened duration (n = 14), maintenance (n = 8), and stop-and-go (n = 2). In adjuvant CRC, ROE did not compromise DFS (HR 1.07; 95% CI, 0.98-1.16; p = 0.12; I^2 = 21.7%), including in high-risk subgroups (HR 1.14; 95% CI, 0.93-1.40; p = 0.14; I^2 = 38.9%); OS was also not different between groups (HR 1.00; 95% CI, 0.94-1.07; p = 0.89; I^2 = 0%), including high-risk pts (HR 1.01; 95% CI, 0.93-1.10; p = 0.68; I^2 = 0%). In mCRC, ROE showed no detriment to PFS (HR 1.11; 95% CI, 0.99-1.25; p = 0.07; I^2 = 0%) or OS (HR 1.06; 95% CI, 0.92-1.23; p = 0.33; I^2 = 0%). Similarly, in metastatic gastric cancer, PFS (HR 0.82; 95% CI, 0.34-1.99; p = 0.44; I^2 = 77.3%) and OS (HR 0.90; 95% CI, 0.67-1.21; p = 0.26; I^2 = 0%) were comparable. Findings remained concordant after restricting the analysis to only RCTs. Pooled analysis was not feasible for PDAC and adjuvant GC studies, but individual study findings were consistent with the above. ROE significantly reduced the risk of grade $\geq$3 CIPN (OR 0.32; 95% CI, 0.20-0.53; p $<$ 0.001; I^2 = 80.6%) and overall grade $\geq$3 AEs (OR 0.65; 95% CI, 0.50-0.86; p = 0.01; I^2 = 59.9%). **Conclusions:** Across GI malignancies, ROE was not associated with inferior DFS, PFS, or OS and was associated with lower rates of severe neurotoxicity and high-grade AEs. These findings support planned limitation of oxaliplatin exposure as a strategy to improve the therapeutic index of oxaliplatin-based chemotherapy across disease settings. Research Sponsor: None.

3593 **Poster Session**

Data from a real-world study: Association of CDCP1 expression level with survival outcomes in mCRC patients treated with bevacizumab or cetuximab plus chemotherapy. First Author: Yitzhar Efraim Goretsky, Division of Medical Oncology, Norris Comprehensive Cancer Center, Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: CUB domain-containing protein 1 (CDCP1) is a transmembrane protein shown to be over-expressed in colorectal cancer (CRC), with an important role in tumor initiation, growth and metastasis. Through interactions with EGFR, CDCP1 promotes nuclear translocation of the key regulators of Wnt signaling, β-catenin and E-cadherin. High CDCP1 expression has been associated with poor survival outcomes in multiple solid tumors but data in CRC remains limited. We investigated associations between CDCP1 level and survival outcomes in patients with metastatic CRC (mCRC) in the phase III clinical trial CALGB/SWOG 80405 (Alliance). **Methods:** Data from 433 mCRC patients in the CALGB/SWOG 80405 (Alliance) trial were analyzed. Patients received bevacizumab (n = 226) or cetuximab (n = 207) plus chemotherapy as 1st-line treatment. Tumor RNA was extracted from FFPE samples and processed through the HiSeq 2500 (Illumina) platform. Overall survival (OS) and progression free survival (PFS) curves were evaluated in all treatment subgroups and stratified according to high or low CDCP1 expression. Likelihood ratio tests, hazard ratios (HRs), and 95% confidence intervals (CIs) were calculated using Cox proportional hazards multivariate models, adjusting for age, sex, ECOG performance status, tumor location, number of metastatic sites, *KRAS* status, consensus molecular subtypes, and treatment arm. **Results:** Overall, low CDCP1 expression was associated with better OS compared to high expression (HR = 1.38; 95% CI 1.07-1.77; 35.8 vs 25.0 months, p = 0.045). Subgroup analysis re-demonstrated this pattern in males (HR = 1.64; 95% CI 1.64-2.28; 35.9 vs 23.6 months, p = 0.01), patients with MSS tumors (HR = 1.56; 95% CI 1.17-2.08; 36.7 vs 25.1 months, p = 0.0094), and patients treated with cetuximab+FOLFOX (HR = 1.79; 95% CI 1.16-2.77; 40.8 vs 24.0 months, p = 0.03). The effect of CDCP1 expression on PFS was less pronounced. Relative to high expression, low expression was associated with better PFS in males (HR = 1.49; 95% CI 1.10-2.03; 13.1 vs 9.8 months, p = 0.027) and left-sided tumors (HR = 1.50; 95% CI 1.10-2.04; 14.4 vs 10.1 months, p = 0.034). **Conclusions:** Our findings represent real-world data of the predictive role of CDCP1 in patients with mCRC undergoing anti-EGFR or anti-VEGF treatment. Consistent with studies of other cancers, we show that low CDCP1 expression is predictive of better survival outcomes, with subgroup analysis revealing associations in males, MSS tumors, and left-sided tumors. Among treatment groups, low CDCP1 expression is predictive of better OS in cetuximab+FOLFOX-treated patients, a key finding given CDCP1's close mechanistic ties to EGFR. Further studies should explore whether these associations are seen in other treatment modalities and whether CDCP1 blockade could represent a viable strategy in patients with high expression. Research Sponsor: National Cancer Institute.

3594 **Poster Session**

Multimodality neoadjuvant downstaging therapy before liver transplantation for colorectal liver metastasis: Real-world data from the Cleveland Clinic. First Author: Mazhar Khalil, Cleveland Clinic, Cleveland, OH

Background: Liver transplantation (LT) has a clear survival benefit in advanced, unresectable, liver-confined colorectal cancer liver metastasis (CRLM). However, pre-transplant management and optimal selection criteria remain understudied and previously reported data indicate recurrence-free survival $<$40% at 3- and 5-years post-LT. **Methods:** 23 patients entered the protocol; 22 patients underwent LT (12/2017-12/2025) utilizing the Cleveland Clinic protocol for down-staging prior to LT. The protocol involves intensive locoregional therapy (LRT) with systemic chemotherapy, aiming to reach minimal disease burden based on FDG PET-CT, ctDNA, and CEA. Patients with minimal or no detectable disease or irreversible treatment-induced liver injury undergo transplant. Patients must have disease control for at least 1 year after resection of the primary colorectal tumor. **Results:** Median age at LT was 45 years (IQR=39-50). Median largest tumor size on pre-LT imaging was 2.2 cm (1.6–7.35), and 18 patients (82%) had bilobar disease. Most patients received intensive systemic therapy (median=18 cycles, IQR=12-37), including 5-FU (n=18), oxaliplatin (n=18), irinotecan (n=13), and bevacizumab (n=17). Tumors were KRAS (n=6) and BRAF non-V600E (n=2) mutated. 20 patients (91%) received pre-LT LRT, including radioembolization (n=11), ablation (n=9), resection (n=10), and HAI pump (HAIP) (n=7). Only one patient dropped out of the pre-LT protocol for liver failure in 2017, suspected from combination of bilobar Y90 and SBRT. Pre-LT PET showed metabolic activity in 8 patients (36%). Median PET-Metabolic Tumor Volume (MTV) at protocol entry was 49.2cm^3 (18-162) and at LT was 0cm^3 (0-6.4) with a median MTV-reduction of 45.2cm^3 (18-156). Median MELD-Na at LT was 9 (IQR 6–13). Pre-LT tumor agnostic ctDNA was detected in 12/17 patients (71%). All patients with ctDNA(-) pre-LT had non-viable tumor on explant (n=5/5 vs. ctDNA(+)=5/12, p=0.028). At median follow-up of 1.6 years, 20 (91%) remain alive, and 18 (82%) are recurrence-free. Median RFS was 5.4 years (95%CI=3.52-7.36) and OS=6.72 years (95%CI=5.34-8.00). Recurrences were lung (n=2), liver (n=1), and liver+para-aortic (n=1) nodes. There was no post-LT recurrence when non-viable on PET scan and on histology (log-rank p$<$0.001). Pre-LT PET-MTV$>$70cm^3 correlated with histologically viable tumor (p=0.031). Pre-LT HAIP demonstrated a trend towards non-viable tumor on explant (n=5/7 non-viable, 71%). **Conclusions:** LT for CRLM shows clear survival benefit in randomized trials. Aggressive pre-LT locoregional and systemic therapies aimed at minimizing disease burden assessed by PET scan and ctDNA may demonstrate improved outcomes, as may HAIP. A clinical trial testing these hypotheses has been designed with expected enrollment in 2026 at three sites. Research Sponsor: None.

3595 **Poster Session**

Tumor-informed versus tumor-agnostic ctDNA assays for molecular residual disease detection in colorectal cancer: A systematic review and meta-analysis. First Author: Nain Tara, Guthrie Robert Packer Hospital, Sayre, PA

Background: Circulating tumor DNA (ctDNA) is increasingly used for detection of molecular residual disease (MRD) following curative-intent treatment for colorectal cancer (CRC). Two principal assay strategies exist: tumor-informed (TI) assays requiring prior tumor sequencing, and tumor-agnostic (TA) assays using fixed plasma-based panels. The relative prognostic and diagnostic performance of these approaches remain uncertain. Despite growing clinical adoption, no systematic comparison of their relative performance exists to guide assay selection. **Methods:** We performed a systematic review and meta-analysis in accordance with PRISMA 2020 guidelines. PubMed, Embase, Cochrane Library, and Web of Science were searched from inception to January 2025 for original studies evaluating ctDNA-based MRD detection after curative-intent treatment for CRC. Primary outcomes were hazard ratios (HRs) for recurrence-free survival (RFS) and diagnostic accuracy metrics (sensitivity and specificity). Random-effects models (DerSimonian-Laird estimator) were used to pool effect estimates; heterogeneity was assessed using I^2 statistics. Subgroup analyses were conducted by assay type (tumor-informed vs tumor-agnostic) and sampling strategy (landmark vs serial). Quality assessment was performed using QUADAS-2 for diagnostic studies and Newcastle-Ottawa Scale for prognostic studies. **Results:** Twenty-three studies comprising 9,847 patients met inclusion criteria. Eighteen studies evaluated tumor-informed assays (n=7,892) and eight evaluated tumor-agnostic assays (n=2,156), with three directly comparing both approaches. For tumor-informed assays, the pooled HR for recurrence in ctDNA-positive versus ctDNA-negative patients was 7.58 (95% CI, 6.21–9.25; I^2=24%). For tumor-agnostic assays, the pooled HR was 4.12 (95% CI, 3.18–5.34; I^2=18%). Subgroup analysis demonstrated significantly stronger prognostic discrimination for tumor-informed assays (ratio of HRs 1.84; 95% CI, 1.38–2.45; p$<$0.001). In serial sampling settings, tumor-informed assays achieved higher sensitivity for MRD detection than tumor-agnostic assays (88% vs 62%; p=0.002). At landmark timepoints, specificity was similar between approaches (97% vs 94%; p=0.08). Between study heterogeneity was low to moderate across analyses. **Conclusions:** Tumor-informed ctDNA assays demonstrate superior prognostic performance and higher sensitivity with serial sampling compared with tumor-agnostic approaches for MRD detection in colorectal cancer. TI assays may be preferred when longitudinal monitoring is feasible, while TA assays remain useful when tumor tissue is unavailable, or rapid results are needed. These findings support selection of ctDNA assay strategies based on clinical context. Research Sponsor: None.

3596 **Poster Session**

The efficacy and safety of sosimerasib monotherapy in pretreated colorectal cancer with KRAS G12C mutation: Results from a phase 1b study. First Author: Lihui Liu, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: KRAS G12C mutation is a key driver in approximately 3-4% of colorectal cancer (CRC) cases with poor prognosis. Sosimerasib is a novel, potent, and highly selective KRAS G12C inhibitor. This Phase 1b study evaluates the efficacy and safety of sosimerasib in patients with KRAS G12C-mutated locally advanced or metastatic CRC. **Methods:** Eligible patients who had received prior standard chemotherapy were enrolled in this study. Patients were administered sosimerasib at 500 mg orally once daily. The primary efficacy endpoint was the objective response rate (ORR) assessed by investigators according to RECIST 1.1. **Results:** As of May 3, 2025, a total of 56 patients were enrolled with a median age of 59 years (53.6% male). All patients had stage IV disease at baseline with an ECOG score of 0 (19.6%) or 1 (80.4%). Prior treatment lines ranged from 1 to 3, and most patients (38; 67.9%) had received oxaliplatin, irinotecan, and fluoropyrimidine as systemic therapy during the advanced disease period. With a median follow-up period of 9.9 months (range: 2.1-13.4), the confirmed ORR was 39.3% (95% CI: 26.5-53.3), the median time to response was 1.4 months (range: 1.3-4.2), and the disease control rate was 98.2% (95% CI: 90.5-100). The median duration of response was 8.6 months (95% CI: 4.2-NA). The median progression-free survival was 8.3 months (95% CI: 5.6-11.0). The median overall survival (OS) was not reached, with a 12-month OS rate of 71.5%. Among the patients who had previously received oxaliplatin, irinotecan, and fluoropyrimidine in the advanced setting, the confirmed ORR was 31.6% (95% CI: 17.5-48.7). Treatment-related adverse events (TRAEs) were reported in 53 (94.6%) patients, with grade 3-4 TRAEs occurring in 14 (25.0%) patients. No TRAE was fatal. The most common TRAEs were increased alanine aminotransferase (48.2%), increased aspartate aminotransferase (46.4%), anaemia (32.1%), and decreased white blood cell count (26.8%). TRAEs led to drug interruption in 9 (16.1%) patients, dose reduction in 3 (5.4%) patients, and permanent discontinuation in 1 (1.8%) patient. **Conclusions:** Sosimerasib monotherapy demonstrated clinically meaningful anti-tumor activity with an acceptable safety profile in patients with KRAS G12C-mutated locally advanced/metastatic CRC, supporting its potential for further development. Clinical trial information: ChiCTR2200059986. Research Sponsor: None.

3597 **Poster Session**

TAMS in appendiceal cancer: Association with metabolic remodeling, prognosis, and response to intra-tumoral therapy. First Author: Patrick Wagner, Allegheny Health Network Cancer Institute, Allegheny Health Network, Pittsburgh, PA

Background: Appendiceal cancer (AC) is a rare malignancy with a distinct immunobiology and propensity for peritoneal metastasis. Tumor-associated macrophages (TAMs) are recognized as influential immune cells in various cancers. In this study, we sought to define the role of TAMs in AC, given its unique immune landscape and peritoneal microenvironment. **Methods:** Immunohistochemistry-quantified M1-like (CD68+CD86+) and M2-like (CD68+CD206+) TAM densities in 112 archival AC specimens were compared against clinicopathologic features and overall survival (OS). In parallel, a comprehensive tissue proteomic analysis (LC-MS/MS) was performed. Gene set enrichment analysis identified proteomic signatures associated with M1 and M2 density. Independently prognostic proteins were identified via Cox regression. External validation was performed by correlating these proteomic signatures in independent tumor samples from the RIOT-1 clinical trial (NCT05751837), in which AC patients received intra-tumoral lipopolysaccharide (LPS), a TLR4 agonist. **Results:** M2-like TAMs outnumbered M1-like TAMs in AC (p = 0.0002), particularly in peritoneal metastases (p = 0.002), and were not associated with tumor grade or histology. Low M1 density ($<$ 18th percentile) correlated with worse OS (HR: 3.26, p = 0.03), while high M2 density ($>$ 52nd percentile) was associated with improved OS (HR: 0.1, p = 0.03). A combined high-M1/M2 percentile metric was highly prognostic of favorable OS (p $<$ 0.001), independent of age, grade, and disease extent. On proteomic analysis, M1-rich tumors exhibited high bioenergetic demands, extensive metabolic reprogramming (isoprenoid/amino acid metabolism), retinol/xenobiotic metabolism, while M2-rich tumors emphasized ECM remodeling, profound amino acid metabolism (immunosuppressive), oxidoreductase activity, and complement activation, with suppressed cell motility. The combined high-M1/M2 phenotype correlated with intense amino acid/lipid metabolism and redox homeostasis. Five TAM-related, independently prognostic proteins were identified: GATD1 (favorable, HR 1.53x10-16), and AGR2, ENOPH1, RHOA, SERPINB6 (adverse, HRs 5.51-10.39). In RIOT-1, intra-tumoral LPS increased M1/M2 TAM infiltration and induced proteomic changes significantly correlated with M1-related (p = 0.0016), M2-related (p = 0.008), and combined TAM signatures (p = 0.047), supporting therapeutic tractability. **Conclusions:** AC harbors a TAM-rich immune microenvironment in which M2-like TAMs and a combined M1/M2 phenotype paradoxically associate with favorable prognosis. Distinct TAM-linked metabolic programs and validated prognostic proteins suggest clinically relevant biologic underpinnings of these findings, while modulation of the AC microenvironment via regional innate immune activation may represent a promising therapeutic strategy. Research Sponsor: ACPMP.

3598 Poster Session

A multicenter randomized phase II trial assessing the efficacy and safety of mCapOX plus cetuximab with mFOLFOX6 plus cetuximab as first-line treatment for *RAS/BRAF* wild-type metastatic colorectal cancer: Updated results from the CAPCET study. First Author: Qiu Meng, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: The CAPCET study was designed to assess the efficacy and safety of modified capecitabine and oxaliplatin (mCapOX) plus cetuximab (CET) and modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus cetuximab (CET) for the first-line treatment of left-side unresectable RAS/BRAF wild-type (wt) metastatic colorectal cancer (mCRC). **Methods:** CAPCET was an open-label, randomized, multicenter, phase II non-comparative trial (NCT05022030). Patients with unresectable RAS/BRAF wt mCRC from 20 China centers were randomly assigned (1:1) to receive up to 12 cycles biweekly mCapOX (capecitabine 1000mg/m^2 twice daily on Day 1-7 and oxaliplatin 85 mg/m^2 on Day 1) plus CET (500mg/m^2) (arm A) or mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, fluorouracil 400mg/m^2 on day 1, and fluorouracil 2400 mg/m^2 over 46h) plus CET (500mg/m^2) (arm B) followed by maintenance (either capecitabine plus CET or capecitabine alone at the discretion of the investigators) or treatment-free intervals until progression on treatment, toxicity, or death. The primary endpoint was progression-free survival (PFS) rate at 9 months. This is an updated result with a median follow-up of 26.1 months and cost-effectiveness evaluation. **Results:** Between September 2021 and April 2024, 168 patients were enrolled in the intention-to-treat (ITT) population and 156 patients were included in the per-protocol (PP) population. In the ITT population, the 9 months-PFS rates were 67.9% (95% CI 58.6%-78.6%) in arm A and 61.9% (95% CI 52.3%-73.2%) in arm B, and the primary endpoint was met. The median PFS (arm A/B) was 11.6 months/10.8 months (P=0.183). The overall response rate (ORR) and disease control rate (DCR) in arm A were higher than those in arm B with 64.3% versus 56.0% and 90.5% versus 84.5%, respectively. The 2-year overall survival (OS) rate (arm A/B) was 75.8% vs 68.6%. The median OS was not reached in the arm A while it was 35.5 in the arm B. Grade≥3 adverse events (AEs) occurred in 26.1% of patients, with 15.0% in arm A and 37.0% in arm B. The most commonly Grade≥3 AEs was neutropenia, rash, and leukopenia and there were no grade 5 AEs reported. A cost-effectiveness analysis showed an incremental cost-effectiveness ratio of $19,067 per QALY for mCapOX + CET, below the Chinese willingness-to-pay threshold ($ 41,188/QALY). **Conclusions:** The CAPCET study met its primary endpoint. mCapOX + CET demonstrated higher ORR/DCR and 2-year OS, with reduced toxicity, compared to mFOLFOX6 + CET. These findings support mCapOX + cetuximab as a clinically effective, better-tolerated, and cost-effective first-line treatment for left-sided RAS/BRAF wild-type mCRC within the Chinese economic framework, providing rationale for ongoing phase III evaluation (NCT06616259). Clinical trial information: NCT05022030. Research Sponsor: National Science and Technology Major Special Project (2024ZD0521202), National Health Commission Center of Medical and Health Science Technology Development: Clinical Research Special Program (WKZX2023CX090001).

3599 Poster Session

Prediction of hematotoxicity using CT-derived body composition in rectal cancer patients receiving immunotherapy-based total neoadjuvant therapy. First Author: Ruone Xu, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Immunotherapy-based total neoadjuvant therapy (iTNT) is a promising strategy to enhance complete response rates and facilitate organ preservation in locally advanced rectal cancer (LARC). However, it is linked to a considerable incidence of severe hematotoxicity, while reliable predictive biomarkers are lacking. Body composition, reflecting nutritional status, has been linked to treatment-related toxicity, but its relationship with iTNT toxicity remains unclear. This study aimed to investigate the association between body composition and hematotoxicity of iTNT and to develop a predictive model. **Methods:** A cohort of 204 LARC patients treated with iTNT was included for model development, with internal training and validation via five-fold cross-validation. Additionally, 43 metastatic rectal cancer patients treated with the same regimen served as the external validation cohort. Body composition parameters were obtained from pretreatment CT images at L3. LASSO regression was applied to select variables and four machine learning (ML) algorithms including logistic regression, random forest (RF), support vector machine (SVM), and extreme gradient boosting (XGBoost) were developed. **Results:** 33.8% of the discovery cohort experienced grade 3-4 hematotoxicity. Among baseline characteristics, skeletal muscle index (SMI) showed the most significant correlation with toxicity. The cut-offs for SMI, determined by optimal stratification, were 50.0 cm²/m² for males and 39.6 cm²/m² for females. Patients with low SMI had a higher incidence of severe toxicities ($P < 0.001$). Seven features were included in the ML models: age, body mass index (BMI), SMI, subcutaneous adipose tissue index (SATI), subcutaneous adipose tissue attenuation (SAT_HU), visceral adipose tissue index (VATI), and skeletal muscle attenuation (SM_HU). The predictive performance of the models is summarized in the following table. Overall, the SVM model showed the highest discriminative performance and robust generalizability. **Conclusions:** SMI was significantly associated with hematotoxicity during iTNT. A CT-based machine learning model was developed and validated to predict hematotoxicity, with the SVM model showing the most robust performance (AUC > 0.85) to guide clinical decision-making. Research Sponsor: None.

Cohort	Model	Accuracy	Sensitivity	Specificity	AUC
Internal validation	SVM	0.850 ± 0.024	0.849 ± 0.021	0.833 ± 0.027	0.881 ± 0.019
	RF	0.755 ± 0.037	0.749 ± 0.037	0.777 ± 0.032	0.803 ± 0.033
	Logistic regression	0.704 ± 0.048	0.672 ± 0.055	0.720 ± 0.048	0.730 ± 0.033
	XGBoost	0.796 ± 0.024	0.769 ± 0.038	0.788 ± 0.036	0.814 ± 0.027
External validation	SVM	0.821 ± 0.034	0.829 ± 0.026	0.800 ± 0.019	0.858 ± 0.029
	RF	0.713 ± 0.030	0.723 ± 0.051	0.734 ± 0.043	0.750 ± 0.038
	Logistic regression	0.666 ± 0.034	0.652 ± 0.044	0.649 ± 0.027	0.671 ± 0.037
	XGBoost	0.751 ± 0.046	0.714 ± 0.038	0.744 ± 0.031	0.779 ± 0.044

3600 Poster Session

An early on-treatment "coordinated inflammatory niche" plasma signature as a predictor of response in the SYLT026 trial: Cadonilimab combined with FOLFIRINOX and bevacizumab as first-line treatment for microsatellite-stable/proficient mismatch repair (MSS/pMMR) metastatic colorectal cancer (mCRC). First Author: Yi Yin, Fujian Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, China

Background: The SYLT026 trial is a phase II study investigating the efficacy and safety of cadonilimab (an anti-CTLA-4/PD-1 bispecific agent) combined with FOLFIRINOX and bevacizumab as first-line treatment for microsatellite-stable/proficient mismatch repair (MSS/pMMR) metastatic colorectal cancer (mCRC). We previously reported the promising outcomes at ASCO GI 2026. Updated survival data are reported here. The determinants of effective immune responses in MSS/pMMR mCRC remain elusive; the "Coordinated Inflammatory Niche" plasma signature was analyzed to predict the immune checkpoint inhibitor (ICI) response. **Methods:** Plasma samples from eligible patients were collected before ICI treatment and profiled using three non-overlapping protein arrays comprising 120 human cytokines (QAH-CAA-2000). These cytokines were integrated into an Inflammatory Niche Index (INI) using machine learning (random forest algorithm). Its predictive value for durable PFS ($>$ 12 months) was evaluated and compared with single markers. **Results:** Between November 16, 2023, and July 26, 2024, 20 patients were enrolled. The ORR was 100% (all partial responses). As of the data cutoff (December 31, 2025), the median follow-up was 24.4 months (IQR 22.4–26.4), the median PFS (mPFS) was 17.2 months (IQR 13.6–20.7), and the OS maturity rate was 20%. Seventeen patients underwent cytokine array analysis. Cytokine profiling identified a 9-protein panel (IP-10, eotaxin, MCP-1, IGFBP-3, MCP-4, TARC, IL-17, CCL28, I-TAC) that was significantly upregulated in responders. Further random forest modeling revealed the importance ranking of each protein, with TARC and IP-10 as the two most significant predictors, consistent with their most pronounced differential expression in the heatmap. The INI demonstrated superior predictive accuracy (AUC = 0.944) compared with IP-10 alone (AUC = 0.71, p = 0.03). Patients with a high INI (n = 9) had promising outcomes: mPFS was not reached (12-month PFS rate 90%), compared with 6.5 months in the low INI group (n = 8) (HR = 0.16, p = 0.001). Gene set enrichment analysis linked a high INI to a baseline tumor microenvironment enriched for NK T cell-related signatures, suggesting a biological basis for the niche. **Conclusions:** CTLA-4/PD-1 immunochemotherapy induced deep and durable responses in MSS/pMMR mCRC. An early on-treatment plasma proteomic signature (INI) powerfully identifies patients destined for durable benefit, offering a transformative tool for ultra-early, biology-guided patient selection in MSS/pMMR mCRC. Clinical trial information: NCT05839470. Research Sponsor: None.

3601 Poster Session

Clinical implications of primary and metastatic tumor-informed clonal tracking for MRD assessment in oligometastatic colorectal cancer. First Author: Hyun Jin Bang, Chonnam National University Hwasun Hospital, Hwasun-Gun, South Korea

Background: While minimal residual disease (MRD) assays informed by primary tumor sequencing have demonstrated prognostic value in locally advanced colorectal cancer (CRC), the additive clinical benefit of combined tracking of metastatic-specific private variants in oligometastatic CRC (mCRC) remains unclear. We aimed to evaluate whether a combined primary and metastatic tumor-informed approach improves MRD detection sensitivity and prognostic accuracy following curative resection. **Methods:** We enrolled 24 patients who underwent curative resection for liver and/or lung oligometastases between 2023 and 2025. A comprehensive tumor-informed panel was designed based on variants identified through whole-exome sequencing (WES) of both primary and metastatic tissues. Serial plasma ctDNA was analyzed at three time points: post-metastasectomy (P1), post-adjuvant chemotherapy (P2), and at the time of recurrence (P3). The clinical performance of a primary tumor-only (PT-only) assay was compared with a combined primary and metastatic tumor-informed (PT+MT) assay. **Results:** The median age was 65 years (range 33–83), and 18 (75%) were male. Primary tumor locations included the colon (83%) and rectum (17%). Fourteen (58%) patients presented with synchronous metastases. Metastatic sites involved the liver (n = 13), lung (n = 10), or both (n = 1). At P1, P2, and P3, MRD positivity rates using the PT-only assay were 54%, 47%, and 100%, respectively. The PT+MT assay identified only one additional patient as MRD-positive at P1 compared to the PT-only assay. At a median follow-up of 29.2 months (IQR 22.6–32.7), 16 patients (67%) experienced recurrence. The PT-only assay showed significant prognostic impact (HR for ctDNA positivity: 4.53; 95% CI, 1.41–14.57; P = 0.006), which was comparable to the PT+MT assay (HR: 4.46; 95% CI, 1.38–14.38; P = 0.007). While PT+MT tracking did not significantly improve detection sensitivity at P1, it effectively captured clonal dynamics, showing a significant enrichment of metastatic-specific private variants in plasma at recurrence (26%, P3) compared to P1 (17%) and P2 (13%). **Conclusions:** Integrating metastatic-specific private variants into MRD tracking revealed distinct clonal dynamics but did not significantly enhance clinical sensitivity or prognostic performance compared to a primary tumor-informed assay in patients with oligometastatic CRC. These findings suggest that current MRD assay designs based on primary tumor sequencing remain a robust standard, even in the metastatic setting after curative resection. Research Sponsor: None.

3602 **Poster Session**

Multiplexed immunohistochemistry (mIHC) analysis and clinical outcomes of nelmastobart in combination with trifluridine/tipiracil and bevacizumab in patients with refractory colorectal cancer (phase 1b/2). First Author: Soohyeon Lee, Korea University Anam Hospital, Korea University College of Medicine, Seoul, South Korea

Background: Colorectal cancer (CRC) patients who are refractory or intolerant to oxaliplatin- and irinotecan-based regimens face limited treatment options and poor prognoses. BTN1A1, a novel immune checkpoint protein involved in tumor progression and immune evasion, presents a potential therapeutic target. Nelmastobart, a first-in-class anti-BTN1A1 monoclonal antibody, is being evaluated in combination with trifluridine/tipiracil and bevacizumab in the Phase 1b/2 STCUBE-003 trial (NCT06873763). This study employs multiplexed immunohistochemistry (mIHC) to characterize the tumor microenvironment (TME) and identify biomarkers predictive of therapeutic response in CRC patients. **Methods:** Tumor tissues from 120 CRC patients were prescreened for BTN1A1 expression via immunohistochemistry (IHC). A total of 61 patients with a tumor proportion score (TPS) $\geq$50 were enrolled in the Phase 2 study. Pathologists used the TPS to guide patient selection, with TPS $\geq$50 as the inclusion criterion. Selected samples were analyzed using mIHC (Opal and CellDIVE), utilizing a 20-protein panel relevant to cancer immunology. Protein co-expression and the spatial distribution of immune and malignant cells were evaluated to assess tumor-immune interactions. **Results:** Among 120 tumor samples analyzed by IHC, 78 (65%) exhibited TPS $\geq$50. Sixteen patients (13%) showed no expression (TPS 0), and 26 (21.6%) had low to medium expression (1 $\leq$ TPS $\leq$ 49). This expression profile aligns with previous CRC studies (STCUBE-001 and STCUBE-IIT-001). In the initial efficacy evaluation of 39 patients with TPS $\geq$50, 2 (4.8%) achieved a partial response (PR), 27 (69.2%) showed stable disease (SD), and 8 (20.5%) had progressive disease (PD). High BTN1A1 expression was significantly associated with a higher clinical response rate. mIHC analysis further revealed that BTN1A1 expression correlated with Ki-67, SLFN11, and YAP1, as well as distinct patterns of $CD8^+$ T-cell infiltration. **Conclusions:** BTN1A1 is consistently and highly expressed in refractory CRC (median TPS 50). mIHC analysis confirms that BTN1A1 is closely integrated with key immune checkpoints and tumor markers within the TME. Initial clinical results, which show disease control in the majority of patients, particularly within the TPS $\geq$50 population, support the utility of BTN1A1 as a predictive biomarker for Nelmastobart combination therapy. These findings justify the ongoing biomarker-driven Phase 2 portion of the STCUBE-003 trial. Clinical trial information: NCT06873763. Research Sponsor: None.

3603 **Poster Session**

Phase 1, FIH study of cabotamig, a TCE CDH17 X CD3, in CDH17-expressing GI malignancies. First Author: Roland Ching-Yu Leung, Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China

Background: Cadherin-17 (CDH17) is a specific cancer target; aberrant expression is up to >95% in GI tumors (stomach, pancreas, bile duct, rectum, small bowel and colon). Cabotamig (ARB202) is a humanized, IgG4, T-cell engaging antibody (TCE) that binds to CDH17 and CD3 T-cells forming synapse to aid activation. This study evaluated the safety, pharmacokinetics (PK), biomarkers, and anti-tumor activity of cabotamig in patients (pts) with CDH17+ gastrointestinal (GI) cancers. **Methods:** Pts $\geq$18 years with locally advanced or metastatic CDH17+ GI cancers refractory to therapies, measurable disease and ECOG 0/1 were enrolled. MABEL calculations per FDA TCE guidance were used (0.0003 mg/ml to 1.0 mg/ml by $^1/_2$ log increments). For safety given multi log difference in CDH17 density, an initial dose of 1/10 was given 3 days before the remaining 9/10. In the 4th cohort, patients with stable disease were given additional doses (7/10 cohort 4-6). Cohort was split into colorectal cancers (CRC) and non-CRC groups given the differences in CDH17 levels and symptoms. After the 7th cohort dosing proceeded to dose optimization. Data cutoff 02142025. **Results:** Pts (CRC 15/22 total) received cabotamig at 1/10 dose (0.00003-0.032 mg/kg) followed by 9/10 dose (0.0003 to 0.32 mg/kg) across 7 cohorts with the max. of 37.8(3.8/34) mg. The max. tolerated dose was not reached. Dose responsive cytokine release syndrome (CRS) symptoms were evident with more symptoms between the 1/10 and 9/10 dose and with increasing intensity with escalation. Treatment related AEs (CRS 17, fever 16, nausea 7, diarrhea 5, vomiting 5 fatigue 3 chills 2) were reported with 1st set or 2nd infusions and occurred in all patients without pre-corticosteroids in the 4th cohort and intensified even with premed up to the 7th cohort. PK data indicated dose proportionality and faster-than-typical IgG4 clearance. Anti-tumor biomarker activity, primarily CEA, but when present included other CA markers, showed a dose response (increase then a decrease to levels below baseline, consistent with target cell lysis) with a peak response between the 5th and 6th cohorts. **Conclusions:** This first-in-human (FIH) study (NCT05411133) targeting CDH17 in GI cancer pts showed a tolerable safety profile for cabotamig up to 0.32mg/kg. Step-up dosing appeared to mitigate dose responsive on-target tumor CRS and the lack of persistent GI toxicities indicated minimal on-target normal GI mucosal effects. Dose responsive biomarker anti-tumor activity of cabotamig was observed. Clinical trial information: NCT05411133. Research Sponsor: None.

3604 **Poster Session**

The CONVERGE study: A phase II, single-arm trial of adebelimab combined with targeted therapy and liposomal irinotecan-based chemotherapy for conversion surgery in unresectable MSS colorectal cancer liver metastases. First Author: Wenhui Yang, Department of Gastroenterology, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, China

Background: Liver metastasis is a key poor prognostic factor for colorectal cancer (CRC). Microsatellite stable (MSS) CRC predominates and is poorly responsive to single-agent immunotherapy. Only 10%–20% of patients with initially unresectable MSS colorectal cancer liver metastases (CRLM) are eligible for upfront curative resection, and conventional chemo-targeted therapy yields a conversion resection rate of merely 15%–30%. This phase II study evaluated the efficacy and safety of adebelimab (a PD-L1 inhibitor) plus molecularly stratified targeted therapy and liposomal irinotecan-based chemotherapy for unresectable MSS CRLM, focusing on hepatic metastatic lesion control (ChiCTR2600117031). **Methods:** This single-center, open-label phase II trial enrolled 45 patients with unresectable MSS CRLM (ECOG PS 0-1, no prior systemic anti-tumor therapy). Patients received adebelimab (1200mg IV, Q2W) + stratified targeted therapy (cetuximab for RAS/BRAF wild-type left-sided tumors; bevacizumab otherwise) + liposomal irinotecan-based chemotherapy (Q2W) for up to 12 cycles. Primary endpoint: conversion-to-resection rate. Secondary endpoints: ORR, DCR, R0 resection rate, hepatic metastasis pathological response, and safety (NCI-CTCAE v5.0). Efficacy was assessed per RECIST v1.1. **Results:** As of January 20, 2026, 42 patients were included in baseline analysis (median age 57.6$\pm$11.1 years, 64.3% male; mean hepatic metastasis diameter 37.21$\pm$19.00 mm, max 82.79 mm). Among 35 efficacy-evaluable patients, ORR was 45.7% (95% CI: 28.8%–63.4%) and DCR was 88.6% (95% CI: 73.3%–96.8%). Fourteen patients underwent surgery (conversion rate 45.2%, 95% CI: 27.3%–60.0%), all completing simultaneous resection of hepatic metastases and primary tumors. Of these 14 patients, 5 (35.7%) achieved hepatic TRG 0 (complete pathological regression) and 12 (85.7%) achieved R0 resection (95% CI: 49.2%–95.3%). For safety, 95.2% (40/42) of patients had AEs. Common ($\geq$10%) all-grade AEs were mainly hematological (leukopenia 23.8%, myelosuppression 21.4%). Grade 3 AEs were rare (predominantly leukopenia 14.3%), and no grade 4 AEs occurred. No any-grade immune-related AEs were reported. **Conclusions:** Adebelimab combined with molecularly stratified targeted therapy and liposomal irinotecan-based chemotherapy shows substantial efficacy and favorable safety for unresectable MSS CRLM, with excellent hepatic metastasis control. Its high conversion-to-resection rate and 35.7% hepatic TRG 0 rate confirm potential for deep pathological response. This regimen warrants further investigation as a promising conversion therapy for unresectable MSS CRLM. Genomic sequencing of successfully converted patients is ongoing to elucidate therapeutic mechanisms. Clinical trial information: ChiCTR2600117031. Research Sponsor: Hengrui Pharma.

3605 **Poster Session**

Association of concurrent GLP-1 receptor agonist use with survival outcomes in patients with metastatic colorectal cancer receiving immune checkpoint inhibitors. First Author: Shalin Rawal, NYMC at St. Mary's General Hospital and Saint Clare's Health, Denville, NJ

Background: Metabolic status and systemic inflammation are increasingly recognized as important modifiers of immune checkpoint inhibitor (ICI) response. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exhibit anti-inflammatory and immunomodulatory properties and are widely used in diabetes and obesity. However, their clinical impact on immunotherapy outcomes in metastatic colorectal cancer (mCRC) remains unclear. **Methods:** We conducted a retrospective observational cohort study using the TriNetX Global Collaborative Network, including electronic health records from 170 healthcare organizations between 2015 and 2025. Adults with mCRC who received at least one ICI were identified. Patients prescribed GLP-1 RAs within six months before or after ICI initiation were compared with non-exposed controls. Patients with prior bariatric surgery were excluded. Cohorts were balanced using 1:1 propensity score matching for demographics, metabolic conditions, and major comorbidities. Primary endpoint was all-cause mortality at 1, 3, and 5 years. Secondary outcomes included pneumonia, heart failure exacerbation, and major abdominal surgical procedures. Survival analyses were performed using Kaplan–Meier methods and Cox proportional hazards models. **Results:** Among 8,304 eligible patients, 148 received GLP-1 RAs. After propensity matching, 138 patients were included in each cohort with well-balanced baseline characteristics. At 1 year, mortality was lower in the GLP-1 cohort (27.5% vs 40.6%), corresponding to a 32% relative risk reduction (RR 0.68, 95% CI 0.49–0.95) and reduced hazard of death (HR 0.67, 95% CI 0.43–1.03). This association persisted at 3 years (27.5% vs 41.3%; RR 0.67, 95% CI 0.48–0.93; HR 0.68, 95% CI 0.45–1.05) and 5 years (28.3% vs 42.0%; RR 0.67, 95% CI 0.49–0.93), with higher 5-year survival probability (50.5% vs 41.5%). Secondary outcomes favored GLP-1 exposure, including lower incidence of pneumonia (10.9% vs 17.4%; HR 0.58) and fewer heart failure exacerbations (23.9% vs 31.9%; HR 0.75). Rates of major abdominal surgical procedures were numerically lower in the GLP-1 cohort. **Conclusions:** In this large real-world cohort, concurrent GLP-1 RA exposure was associated with clinically meaningful and durable survival benefit in mCRC patients receiving ICIs, without increased adverse clinical outcomes. These findings suggest a potential immunometabolic interaction and support prospective evaluation of GLP-1–based strategies as adjunctive modifiers of immunotherapy response. Research Sponsor: None.

3606 Poster Session

Dynamics of circulating monomeric C-reactive protein (mCRP) to predict outcomes with first-line alternating oxaliplatin-based chemotherapy and nivolumab in metastatic microsatellite-stable (MSS) colorectal cancer (CRC). First Author: Anniken Joerlo Fuglestad, Akershus University Hospital, Lorenskog, Norway

Background: Elevated CRP levels at CRC diagnosis are consistently associated with poor outcomes, suggesting a tumor-promoting and potentially immuno-suppressive inflammatory state. The clinically assessed CRP is a pentameric protein that can dissociate to mCRP, an isoform with pro-inflammatory effects on innate immune responses. The randomized METIMMOX trial (NCT03388190) evaluated potentially immunogenic short-course oxaliplatin-based chemotherapy (FLOX) alternating with nivolumab in previously untreated, unresectable metastatic MSS CRC. We investigated whether oxaliplatin-induced immunogenicity is measurable as an early change in circulating mCRP and may identify patients more likely to derive clinical benefit from sequential nivolumab. **Methods:** Patients were randomly assigned to the control group of FLOX (oxaliplatin, 5-fluorouracil, folinic acid) Q2W or the experimental group of alternating 2 cycles each of FLOX Q2W and nivolumab Q2W with prespecified break periods. The primary endpoint was progression-free survival (PFS). This *post hoc* analysis included 29 patients from the experimental group, of whom 28 had paired mCRP and clinical CRP measurements from baseline (Pre) and post second FLOX cycle (Post) timepoints. CRP was measured by standard immunoturbidimetry. Plasma mCRP was separated from CRP by 100-kDa filtration and quantified by targeted nano LC-timsTOF Pro mass spectrometry with AQUA standards. CRP at the reference limit 5.0 mg/L and mCRP at the median value 45 ng/mL were used as cutoff values. Changes from Pre to Post were denoted ΔmCRP and ΔCRP and categorized as ³0 (stable/increase) and < 0 (decrease). **Results:** Low Pre and low Post CRP were associated with prolonged PFS (log-rank p = 0.080 and p = 0. 002, respectively), while ΔCRP showed no association (log-rank p = 0.57). By contrast, a significant association was observed for ΔmCRP (log-rank p = 0.015), where median PFS was longer among the ΔmCRP ≥0 population (16.4 months [95% CI 8.8-23.9]; n = 15) *versus* the ΔmCRP < 0 population (9.2 months [95% CI 3.6-14.8]; n = 13). Notably, patients with the combination ΔCRP < 0 and ΔmCRP ≥0 (n = 8) had an undefined median PFS (≥41.6 months) at data cutoff, compared to median PFS 9.2 months (95% CI 1.4-16.9; n = 20) for all other patients (log-rank p = 0.022). **Conclusions:** Patients with metastatic MSS CRC who exhibited an increase in mCRP and decrease in clinical CRP following the initial 2 chemotherapy cycles of first-line oxaliplatin-based chemotherapy alternating with nivolumab had markedly prolonged PFS. Moreover, increased PFS was observed alongside increased circulating mCRP regardless of change in CRP. These data suggest an early increase in mCRP may be an indicator of immunotherapy-associated efficacy. Clinical trial information: NCT03388190. Research Sponsor: None.

3607 Poster Session

The SERPENTINE trial: A phase II clinical study decoding immune responses by scRNA-seq and TCR-seq analysis in patients with MSS metastatic colorectal cancer (mCRC) with and without liver metastases treated with durvalumab and tremelimumab. First Author: Iosune Baraibar, Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain

Background: Immune checkpoint inhibitor (ICI) therapy aims to instruct immune cells to efficiently recognize and eliminate cancer cells. It has shown efficacy in MSI colorectal (CRC), and, although there is no approval yet, a subset of patients with MSS CRC included in clinical trials respond to ICI, indicating a significant knowledge gap in our current understanding of immunological mechanisms in MSS CRCs. The relationship between the cellular and molecular responses to ICI in the tumor microenvironment (TME) and the clinical outcome remains poorly understood. We sought to address this gap in understanding through a series of high-throughput functional genomics analyses. **Methods:** Patients (pts) with refractory MSS CRC were treated with durvalumab (Dur) 1500mg plus tremelimumab (Trem) 300mg at Week 0, followed by Dur 1500 mg Q4W. We characterized the cellular makeup of the metastatic TME using single-cell RNA-seq, and cataloged T-cells clonotypes within metastases and in the blood using single-cell and deep TCR-seq. We collected data for each patient before and upon treatment initiation to explore the dynamic changes of the TME and blood in response to ICI. To facilitate direct comparisons between metastatic and primary TMEs, we integrated our dataset with an external single-cell RNA-seq dataset from primary CRC tumors. **Results:** 24 pts were included in the analysis (18 with no liver metastases (NLM), 6 with liver metastases (LM)). Around 200,000 single-cell profiles were collected from biopsies taken from 6 pts with LM and 10 pts with lung metastases. Disease Control Rate (DCR) was 39% for MSS CRC without LM (2 PR + 5 SD) and 0% for those with LM (p=0.13). Robust gene expression changes within the immune compartment of the TME were observed upon treatment, irrespective of overall treatment outcome, yet specific biological programs were differentially altered across patient response groups. Differences in the composition of TMEs in the lung and liver metastases were found with an enrichment of T regulatory and IFN-responder CD4 populations in the lung vs more CD8+ T cell subtypes in the liver. Tumor TCR analysis revealed that, following ICI treatment, liver metastases displayed a high diverse TCR repertoire, whereas lung metastases were less diverse and showed marked clonal expansion, suggesting greater T cell activity within the lung lesions (p=0.035). **Conclusions:** Prospective deep immune repertoire profiling detected profound differences in TME according to dissemination patterns, which might explain differences in treatment outcomes. Despite low overall efficacy with Dur and Trem in MSS patients, a trend to better response rate and DCR was observed in pts without LM. We propose immune cell tracking as powerful tool to quantify the efficacy of ICI in real time. Clinical trial information: NCT06680739. Research Sponsor: Astra Zeneca.

3608 Poster Session

Liver transplantation (LT) in liver limited metastatic colorectal cancer (CRC): Insights and opportunities. First Author: Jonathan W. Lee, Weill Cornell Medical College, New York, NY

Background: Liver transplantation (LT) for liver limited metastatic colorectal cancer (LL-mCRC) remains underutilized. Reasons for transplant ineligibility are not well described and the acceptance of this procedure for mCRC remains limited. Herein, we describe our initial experience with LT in patients with LL-mCRC. We characterize patient outcomes, characterize the pattern of failure for patients undergoing LT evaluation, and describe the prognostic implication of lymphadenectomy in LT evaluation. **Methods:** Patients with LL-mCRC potentially eligible for LT were identified, discussed in multidisciplinary tumor boards and liver transplantation clinics, and managed. The Weill Cornell Liver Transplant institutional database was queried to identify patients evaluated for LT, those who were transplanted, and those who were not. Demographic, surgical data, and clinical outcomes abstracted from medical record. **Results:** Between 7/2020 and 3/2025, 20 patients with LL-mCRC were evaluated for LT. Median age (range) 55 years (29-63); N=10 (50%) white; N=18 (90%) male. All had adenocarcinoma histology with N=14 (70%) left sided primary disease. At diagnosis, N=11 (55%) had ≥1 liver lesion >5.5cm and median CEA (range) was 200 (4.8-6945). The most common mutations were APC (60%), KRAS (55%), TP53 (45%), and PIK3CA (35%). N=6 (30%) had a LT with a median time from diagnosis to transplant of 23.7 months (mo) (range 16-42). The median overall survival (OS) from LT is 64.5 mo (range 22-87). N=5 (83%) are alive with a median follow up of 67 mo (range 22-87). N=3 patients had recurrent disease with a median time to recurrence of 3 mo (range 2-9), 2 in lungs, and 1 retrocrural lymph nodes. At this time, N=4 (67%) patients have no evidence of disease, and one with retrocrural lymph node disease is responding to treatment. The single patient who underwent LT and died was portal lymph node positive at the time of transplant and had an early recurrence (at 2 mo post-transplant). For the 14 patients who were evaluated for transplant, but did not undergo transplant, their mOS is 28 mo (range 13-44). Reasons why these patients did not undergo LT are shown in Table 1. The majority failed transplant evaluation due to progressive disease (lung 43%, liver 21%, abdomen 14%). Positive portal lymphadenectomy was a poor prognostic characteristic, with all 3 patients deceased. **Conclusions:** LT is a treatment option that confers durable remission and improved OS in LL-mCRC. Recurrent disease after transplant is generally controllable with local treatment modalities. Patient selection is critical in identifying appropriate LT candidates. Portal lymphadenectomy is prognostic and should be considered in all transplant evaluations. Research Sponsor: None.

	Not Transplanted N=14
New lung metastases	6 (43)
Progression in liver	3 (21)
Worsening liver function	2 (14)
Progression in lymph nodes	1 (7)
Peritoneal metastases at surgery	1 (7)
Patient preference	1 (7)

3609 Poster Session

Refining clinical trial eligibility for minimal residual disease in patients with colorectal cancer: The MD Anderson INTERCEPT experience. First Author: Soumya Shekhar, Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Detection of circulating tumor DNA (ctDNA) is prognostic for recurrence after completion of curative-intent therapy for patients (pts) with colorectal cancer (CRC). Our MD Anderson INTERCEPT platform enrolls ctDNA(+) CRC pts onto matched clinical trials, with the goal of eradicating minimal residual disease (MRD) and curing more pts with CRC. To gain insights on how to identify CRC pts most likely to have true MRD, we retrospectively reviewed the role of non-specific radiographic abnormalities in forecasting CRC recurrence. **Methods:** For this retrospective review of CRC pts included in ctDNA intervention trials (Table) from 1/2019-12/2025, MRD at baseline was defined as (1) having no radiographically evident disease at time of study enrollment and (2) detection of ctDNA on an MRD assay (Signatera). ctDNA levels were quantified as mean tumor molecules (MTM) per milliliter (mL) plasma. Radiographic sites of disease progression on clinical trials were compared with pre-treatment imaging. Median recurrence-free survival (RFS) was estimated using Kaplan Meier and compared with Cox regression. **Results:** 54 pts with definitively treated CRC prior to subsequent ctDNA(+) were enrolled across 4 trials (Table); 45 pts (83%) had stage IV disease. No pts had radiographically evident CRC at trial start. Median ctDNA levels were 0.45 MTM/mL (IQR 0.12 – 2.4). After a median follow up of 6.4 months (IQR, 3.5-9.5), 42 (78%) pts had recurred after treatment on a ctDNA intervention trial. Median RFS was 8.1 months (95% CI 4.4 - 9.4). Sites of recurrence were liver (N=20, 48%), lung (N=13, 31%), lymph nodes (N=10, 24%), and peritoneum (N=3, 7%). Upon retrospective review, minute but discernible lesions were identified at the sites of recurrence in 25 (60%) of the pts who had a recurrence on MRD trials. At eligibility evaluation these were characterized as "benign" in 14 (56%) or as "post-procedural" in 11 (44%) of the cases. The presence of indistinguishable CRC deposits at the start of the trial was associated with inferior RFS (4.2 vs 9.3 months; HR 1.96 (95% CI 1.04-3.70; p = 0.04). **Conclusions:** Subclinical radiographic findings may confound true identification of pts with CRC MRD for clinical trials. Optimizing definitions of radiographically detectable disease is warranted in order to ensure homogenous populations of CRC that are the most likely to benefit from novel MRD therapies. Research Sponsor: None.

Demographic characteristics across four trials.

		Number of Patients	Percentage (%)
Age at Enrollment	< 30	1	2.4
	30-39	3	7.3
	40-49	8	19.5
	50-59	12	29.3
	60-69	14	34.1
	70+	3	7.3
Gender	Male	34	63.0
	Female	20	37.0
Race/Ethnicity	White or Caucasian	34	63.0
	Black or African American	5	9.3
	Hispanic or Latino	11	20.4
	Asian	1	1.9
	Other	3	5.6
Stage at Enrollment	I	0	0.0
	II	0	0.0
	III	9	16.7
	IV	45	83.3
Trial	Bintrafusp alfa	4	7
	NK cells with cetuximab	15	27.8
	Lifestyle interventions	16	29.6
	Trifluridine/tipiracil	19	35.2

3610 Poster Session

Long-term survival and biomarker analysis of neoadjuvant chemoradiotherapy with or without PD-1 antibody sintilimab in pMMR locally advanced rectal cancer: A randomized clinical trial. First Author: Weiwei Xiao, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: We previously reported that adding sintilimab to neoadjuvant chemoradiotherapy (NACRT) significantly improved the complete response (CR) rate compared to NACRT in mismatch repair-proficient (pMMR) locally advanced rectal cancer (LARC) patients (44.8% vs. 26.9%; P = 0.031). Here, we present the long-term survival outcomes and exploratory biomarker analyses from this randomized trial. **Methods:** Between June 2020 and July 2022, a total of 134 patients with pMMR LARC were randomly assigned (1:1) to the experimental arm (NACRT plus sintilimab, n = 67) or the control arm (NACRT, n = 67). The primary endpoint was CR rate. Secondary endpoints included disease-free survival (DFS) and overall survival (OS). Survival analysis was estimated using the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HR) were calculated using the Cox proportional hazards model. Baseline tumor and blood samples were collected for whole exome sequencing. **Results:** With a median follow-up of 48.5 months, the experimental arm exhibited significantly superior 3-year DFS compared to the control arm (91.0% vs. 77.6%; HR = 0.37, 95% CI: 0.14-0.94, log-rank P = 0.030). Analysis of failure patterns showed lower rates of both local recurrence (1.5% [1/67] vs 3.0% [2/67] and distant metastases (9.0% [6/67] vs. 19.4%[13/67]) in the experimental arm. Notably, liver metastases were more frequent in the control arm (1.5% [1/67] vs. 9.0% [6/67]). Subgroup analyses identified a pronounced DFS benefit from combination therapy in patients aged $>$ 50 years (HR = 0.24, 95% CI: 0.07-0.86, P = 0.029) and those with extramural venous invasion (EMVI)-positive tumors (HR = 0.26, 95% CI: 0.09-0.81, P = 0.020). Notably, achieving a CR was consistently associated with a trend toward prolonged DFS in both the experimental (log-rank P = 0.129) and control arms (log-rank P = 0.145). In exploratory biomarker analysis, patients harboring MUC16 mutations in the experimental arm exhibited a trend toward improved DFS, although statistical significance was not reached (log-rank P = 0.318); conversely, no such trend was observed in the wild-type population (log-rank P = 0.496). The 3-year OS rates were 97.0% in both groups (log-rank P = 0.977). **Conclusions:** Adding PD-1 antibody to NACRT conferred a superior DFS benefit compared to NACRT in patients with pMMR LARC, particularly in older patients and those with EMVI-positive tumors, and potentially influenced the pattern of metastasis. MUC16 mutations warrant further investigation as a potential predictive biomarker for sensitivity to the combination therapy. Clinical trial information: NCT04304209. Research Sponsor: Non-communicable Chronic Diseases-National Science and Technology Major Project.

3611 Poster Session

Dual-microbial signature as a predictor of postoperative colorectal cancer recurrence. First Author: Pancheng Chen, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Current surveillance strategies for postoperative recurrence in colorectal cancer predominantly depend on tumor markers, imaging modalities, and endoscopic procedures; however, these approaches are challenged by suboptimal diagnostic accuracy. Consequently, the identification and validation of novel biomarkers represent an urgent clinical necessity. Sensitive microbiome-based approaches for postoperative risk stratification, surveillance optimization, and early recurrence detection may substantially influence clinical decision-making and resource allocation for colorectal cancer patients. **Methods:** This cohort study included CRC fecal and tumor samples from four independent cohorts (n = 615) in the Fudan University Shanghai Cancer Centre (Shanghai, China) between January 2017 and December 2020, with follow-up through December 2024. Fecal samples from the discovery (n = 250), training-validation cohorts (n = 153), as well as tumors with paired adjacent normal tissues from the investigation cohort (n = 244), were subjected to multi-omics analyses. We developed prediction models of disease-free survival by additionally incorporating dual-microbial signature including the abundance of Roseburia and Bifidobacterium. Both models were evaluated by internal validation cohort, and visual nomograms of prediction models were constructed accordingly. **Results:** We found that the combined high abundance of Roseburia and Bifidobacterium was associated with favorable outcomes (P = 0.039), especially in male (P = 0.018) and early-onset colorectal cancer (P = 0.047). Integration of clinical variables with a dual-microbial signature achieved a mean AUC $>$ 0.8 for recurrence prediction. A high combined abundance of Roseburia and Bifidobacterium was linked to reduced enrichment of primary bile acid biosynthesis pathways and increased enrichment of propanoate metabolism pathways. **Conclusions:** This study proposes a novel strategy for CRC recurrence risk assessment and highlights the potential of gut microbiota as a tertiary preventive approach in CRC management. However, the proposed model has not yet been implemented in clinical practice and requires validation in large, multicenter prospective cohorts before clinical translation. Research Sponsor: None.

3612 Poster Session

Targeting the Warburg effect: Mitochondrial metabolic modulation with intermittent fasting during neoadjuvant chemoradiation in rectal cancer compared with standard neoadjuvant chemoradiation and total neoadjuvant therapy. First Author: Krithikaa Sekar, Healthcare Global Enterprises limited, Bengaluru, India

Background: Cancer cells demonstrate metabolic inflexibility characterized by glycolytic dependence and dysfunctional mitochondrial oxidative phosphorylation [Warburg Effect]. Fasting and glucose restriction induce a metabolic shift toward mitochondrial fatty acid oxidation and ketone utilization in normal cells, while cancer cells are unable to adapt, resulting in increased oxidative stress and radio-sensitization. We evaluated whether inducing a fasting-mimicking metabolic state during neoadjuvant chemoradiation improves pathological complete response (pCR) rates in rectal cancer compared with total neoadjuvant therapy (TNT) and standard neoadjuvant chemoradiation (nCRT). **Methods:** 90 patients with locally advanced rectal adenocarcinoma were analyzed (30 per group). All patients had cT3N+ disease. Radiotherapy was delivered using IMRT/IGRT or adaptive techniques, receiving long-course radiotherapy (50.4 Gy in 28 fractions) with concurrent capecitabine. Group 1 received nCRT under a fasting-mimicking metabolic state using a structured low-carbohydrate diet [Non-Calorie Restricted] with $\geq$14 hours of daily fasting, titrated using continuous glucose monitoring [CGM] to achieve 16–17 hours per day with blood glucose levels $<$90 mg/dL. Group 2 received TNT consisting of nCRT followed by CAPEOX. Group 3 received standard nCRT without dietary intervention. The primary endpoint was pCR (ypT0N0) at surgery. pCR rates were compared between groups using the chi-square test or Fisher's exact test, as appropriate, with a two-sided p value $<$0.05 considered statistically significant. **Results:** Baseline characteristics were balanced across groups; all patients had cT3N+ disease. Median age was 55 years, with all adenocarcinoma histology. pCR rates were 93.3% (28/30) in the fasting-state nCRT group, 73.3% (22/30) in the TNT group, and 33.3% (10/30) in the standard nCRT group. Fasting-state nCRT was associated with significantly higher pCR rates compared with standard nCRT (χ^2=25.2, df=2; p$<$0.001). TNT was also superior to standard nCRT (p=0.004). The difference between fasting-state nCRT and TNT showed a strong numerical trend but did not reach statistical significance (p=0.08). **Conclusions:** Fasting-state metabolic modulation during neoadjuvant chemoradiation was associated with a striking increase in pCR rates. Mitochondrial stress induced by glucose restriction may enhance tumor radio-sensitivity through increased reactive oxygen species and impaired metabolic compensation. Precision-guided fasting represents a promising, low-cost therapeutic strategy warranting prospective larger cohort validation. Clinical trial information: CTRI/2024/10/075843. Research Sponsor: HCG Research Fund.

Comparison	pCR	p-value
Fasting-state nCRT	93.3% (28/30)	$<$ 0.001
TNT	73.3% (22/30)	0.004
Standard nCRT	33.3% (10/30)	0.08

3614 Poster Session

Predicting neoadjuvant chemoradiotherapy response and postoperative recurrence in locally advanced rectal cancer using a preoperative large language model. First Author: Xiaoxi Chen, Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China

Background: Neoadjuvant chemoradiotherapy (nCRT) is standard for locally advanced rectal cancer (LARC), yet responses are heterogenous and early identification of responders remains challenging. We developed a Transformer-based large language model that analyzes fragment-level patterns in circulating cell-free DNA (cfDNA) to predict pathological complete response (pCR) and postoperative recurrence risk independently of somatic mutation calling. **Methods:** A total of 510 plasma samples were collected from 102 LARC patients at five perioperative time points. The model was trained on post-nCRT cfDNA data from a training cohort (N = 62) to predict pCR, evaluated in an internal validation cohort (N = 40) and an external validation cohort (N = 96). Associations between model prediction scores, nCRT response, and recurrence-free survival (RFS) were assessed across time points. Fragment-level features contributing to model predictions were analyzed to provide biological interpretability. **Results:** The model demonstrated robust predictive performance, with AUCs of 0.909 (95% confidence interval [CI]: 0.812-1.000) in the training cohort, 0.903 (95% CI: 0.785-1.000) in the validation cohort, and 0.835 (95% CI: 0.754-0.916) in the external cohort. Patients achieving pCR had significantly higher prediction scores than non-pCR patients (Wilcoxon p $<$ 0.001), and scores inversely correlated with tumor regression grade (Jonckheere-Terpstra test p $<$ 0.001). At the predefined cutoff corresponding to 95% specificity in the training cohort, sensitivities were 0.73, 0.64, and 0.44 across datasets. High post-nCRT and post-surgical prediction scores were associated with improved RFS (log-rank p = 0.012 and p = 0.024, respectively), and all relapsed patients had consistently low post-nCRT scores. The top 1% of cfDNA fragments, ranked by model importance, were predominantly 50-100 bp with ~ 40% GC content, and the proportion of subnucleosomal particles was significantly higher in pCR versus non-pCR samples, providing biological insights into features driving the model. **Conclusions:** We developed a robust, mutation-independent framework for predicting nCRT response and postoperative recurrence risk in LARC, supporting individualized treatment decisions and post-surgical surveillance strategies. Research Sponsor: Natural Science Foundation of Hunan Province; 2024JJ5568.

3615 Poster Session

Association between circulating tumor DNA and local tumor regrowth and distant metastasis during nonoperative management in stage I–III rectal cancer. First Author: Kentaro Ochiai, Department of Colon and Rectal Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: During nonoperative management (NOM) for rectal cancer after a clinical complete response (cCR) or near-CR (nCR), 25–30% develop local regrowth and 5–10% develop distant metastasis, highlighting the need for improved risk stratification and surveillance. Circulating tumor DNA (ctDNA) has emerged as a prognostic biomarker, but its utility in NOM decision making remains undefined. **Methods:** We retrospectively studied 110 patients with stages I-III, microsatellite stable rectal adenocarcinoma achieving cCR/nCR after neoadjuvant therapy (2020-2024) managed with NOM and tumor-informed ctDNA testing in the INTERCEPT program (Signatera Exome). We assessed longitudinal ctDNA status during NOM and the first post-treatment ctDNA in relation to local regrowth and/or distant metastasis (Kaplan–Meier/log-rank; Fisher's exact). We also evaluated per-sample accuracy for events occurring within ±90 days of each blood draw. **Results:** Over a median follow-up of 25 months, 23 (20.9%) patients developed local regrowth and 12 (10.9%) developed distant metastases (Table 1). Patients with ever positive longitudinal ctDNA had an associated worse 2-year regrowth-free survival (41.7% vs 83.9%, P=0.0002) and metastasis-free survival (41.7% vs 94.9%, P<0.0001) than those with persistently negative ctDNA. Among patients with an evaluable first post-treatment ctDNA result (within 180 days post treatment; n=72), those with a positive result had an associated lower regrowth-free survival (P = 0.0006) and metastasis-free survival (P < 0.0001). In per-sample analysis (n=669), ctDNA showed low sensitivity and high specificity for local regrowth (41.4% and 94.3%) and higher sensitivity and specificity for distant metastasis (73.8% and 97.4%). Twenty-two of 23 patients with local regrowth underwent salvage surgery; ctDNA positivity at local regrowth was associated with more advanced pathological T stage (66.7% of ypT3–4 vs 15.4% of ypT0–2, P=0.01). **Conclusions:** During NOM for rectal cancer, ctDNA may be used to identify a small subgroup at high risk of local regrowth and/or distant metastasis. However, many local regrowth occurs despite persistently negative ctDNA, consistent with limited sensitivity. Negative ctDNA results should therefore not prompt de-escalation of endoscopic and radiologic surveillance when a NOM strategy is used. Research Sponsor: None.

Overall rates of local regrowth and distant metastasis.

	Local regrowth (n=23)[a]	P	Distant metastasis (n=12)	P
Longitudinal ctDNA		<.0001		<.0001
Persistently negative (n=95)	14/95 (14.7%)		3/95 (3.2%)	
Ever positive (n=15)	9/15 (60.0%)		9/15 (60.0%)	
First post-treatment ctDNA[b]		0.005		<.0001
Negative (n=67)	15/67 (22.4%)		5/67 (7.5%)	
Positive (n=5)	4/5 (80.0%)		4/5 (80.0%)	

[a]Two had synchronous and 5 had metachronous distant metastasis.
[b]Within 6 months post treatment, n = 72.

3616 Poster Session

Minimal residual disease (MRD) assessment by circulating tumor DNA (ctDNA) to stratify recurrence risk and adjuvant treatment benefit in a real-world colorectal cancer (CRC) cohort. First Author: Mariem Galuia, AdventHealth Cancer Institute, Orlando, FL

Background: ctDNA detection following curative surgery is known to predict recurrence in patients (pts) with stage II-III CRC. We investigate ctDNA dynamics in relation to clinical outcomes and their real-world impact on treatment decisions among pts with resected CRC. **Methods:** Based in a large community hospital system, we conducted a retrospective analysis of a prospectively maintained database inclusive of 407 pts with resected stage II-IV CRC. ctDNA was longitudinally quantified at MRD (2-12 weeks post-op) and surveillance timepoints (tp) using a clinically validated, personalized, tumor-informed 16-plex mPCR-NGS assay. Primary endpoint was the correlation between ctDNA status and disease-free survival (DFS) and overall survival (OS). Secondary objective was to evaluate its impact on treatment decisions. Survival distribution was analyzed by Kaplan-Meier Method. Multivariable Cox proportional hazards models were applied to adjust for clinicopathological covariates: age, gender, T, N, high risk features, obstruction, perforation, KRAS, BRAF, MMR. **Results:** Of 407 pts, 303 had complete evaluable data for analysis at cutoff 12/5/2025. After median follow-up of 29.6 months (mo), N=2342 ctDNA plasma levels were analyzed: 2 stage I, 119 stage II, 170 stage III, 12 stage IV. ctDNA at MRD tp was available for 259 pts (86%): 99 stage II, 144 stage III. ctDNA was negative at MRD tp in 211/259 (MRD-), positive in 48/259 (MRD+). Of 303 pts,180 (60%) received adjuvant chemotherapy (ACT): 38 MRD+, 118 MRD-. 123 (40%) were observed: 9MRD+, 93 MRD-. MRD positivity was significantly associated with inferior DFS in all stages combined (HR = 13.4, 95% CI: 7.64–23.64, p<0.0001) and in all stage-stratified subgroups. Multivariate analysis confirmed ctDNA-positivity to be the most significant prognostic factor associated with DFS when compared with clinicopathologic factors. In MRD+ subgroup, pts with transient ctDNA clearance had significantly worse DFS than those with sustained clearance (HR = 5.27, 95% CI: 2.49–11.14, p<0.0001). Among MRD- pts, ACT conferred no significant DFS benefit vs observation (HR=1.52, p<0.05). Among MRD+ pts, ACT did not reach statistical significance. ctDNA positivity predicted recurrence with a lead time up to 23.9 mo (median 3.8 mo) before imaging, including in low ctDNA shedding sites. 7% had metastatic disease diagnosed earlier because of a positive test, prompting timely therapy. ctDNA testing was associated with higher than historical rates of oligometastasis-directed therapy (17%). **Conclusions:** Our results highlight the value of post-surgical ctDNA monitoring as a prognostic biomarker in CRC and its potential value for treatment decision making. Clinical utility of ctDNA-guided AC will further be established by ongoing trials (CIRCULATE-NA). Research Sponsor: None.

3617 Poster Session

Safety, immunogenicity, and efficacy of Ad5.F35-GUCY2C-PADRE vaccine in patients with GI cancers at high risk of relapse: Results from a phase 2A trial. First Author: Babar Bashir, Sidney Kimmel Comprehensive Cancer Center at Thomas Jefferson University Hospital, Philadelphia, PA

Background: Guanylyl cyclase C (GUCY2C) is an intestinal tumor antigen ectopically expressed in some gastroesophageal and pancreatic cancers, highly expressed in nearly all colorectal cancers (CRC), and retained in metastases. Adenovirus serotype 5 (Ad5)-based cancer vaccines, including those targeting GUCY2C, are limited by pre-existing neutralizing antibodies (NAbs) targeting Ad5. Ad5.F35-GUCY2C-PADRE is a chimeric Ad5 vector (fiber of serotype 35) developed to overcome anti-Ad5 immunity and induce durable antitumor T-cell responses. We report initial immunogenicity, safety, and recurrence outcomes from a phase 2A dose-finding study in patients with resected GI malignancies. **Methods:** This open-label phase 2A study enrolled patients with resected, high-risk GI adenocarcinomas (CRC, pancreatic, gastric, and small bowel) with no evidence of disease 4-24 wks after standard adjuvant therapies. Oligometastatic stage IV CRC patients were also allowed (n=8). Patients were randomized to receive three i.m. administrations of Ad5.F35-GUCY2C-PADRE at 1×10^{11}, 1×10^{12}, or 5×10^{12} viral particles (vp) at 4-wk intervals. Primary endpoints were safety and GUCY2C-specific T-cell responses (IFNγ ELISpot). Exploratory endpoints included the impact of NAbs on T-cell responses and RFS, and the impact of dose on immunological and clinical outcomes. **Results:** Forty-six patients (29 CRC) completed treatment and were evaluable. Vaccination was well tolerated with no DLTs or TRSAEs; AEs were predominantly grade 1-2 flu-like symptoms. GUCY2C-specific T-cell responses increased in frequency and magnitude in a dose-dependent manner. Nearly all patients receiving higher doses produced T-cell responses regardless of NAb status (Table), supporting Ad5.F35 overcoming pre-existing NAbs. At the 2-year follow-up, there was a dose-dependent improvement in RFS among stage II-III CRC patients (Table), and RFS was significantly improved among immune responders vs non-responders ($P < 0.05$). **Conclusions:** Ad5.F35-GUCY2C-PADRE is safe, overcomes pre-existing Ad5 immunity, and induces robust, dose-dependent GUCY2C-specific T-cell responses. Vaccine-induced immunity is associated with improved RFS in CRC, supporting further development of the off-the-shelf Ad5.F35 platform for cancer vaccines and Ad5.F35-GUCY2C-PADRE for CRC recurrence prevention. Clinical trial information: NCT04111172. Research Sponsor: Targeted Diagnostics and Therapeutics, Inc.

Dose (vp)	Magnitude of GUCY2C-Specific T-cell Response[1]	% of Patients with a GUCY2C-Specific T-cell Response (N/N)[2]	CRC[3] Recurrences (%; N/N); Median RFS
1×10^{11}	9	33% (5/15)	50% (4/8); 512 days
1×10^{12}	92	94% (15/16)	17% (1/6); not reached
5×10^{12}	218	100% (15/15)	0% (0/7); not reached
	$P < 0.0001$	$P < 0.0001$	$P = 0.051$

[1]Median SFCs/5×10^5 PBMCs; [2]at 4 weeks after 1st vaccination; [3]excluding stage IV patients.

3618 Poster Session

SOCCER: A randomized phase II trial comparing complete clinical response after short course radiation or chemoradiation and consolidation chemotherapy in rectal cancer. First Author: Ramakrishnan Ayloor Seshadri, Integrated Cancer Care Group, Chennai, India

Background: The preferred total neoadjuvant treatment (TNT) regimen for an intentional watch-and-wait (W&W) approach in patients with rectal cancer is long course chemoradiation (LCRT) and consolidation chemotherapy (CNCT). The role of short course radiation (SCRT) and CNCT in this context is not well defined. The shorter treatment time of SCRT has advantages, especially in resource-constrained settings. This study aimed to select the more promising of the two TNT strategies for a W&W approach in patients with rectal cancer for further phase III evaluation. **Methods:** This dual-center, randomized phase II trial was conducted in Chennai and Vellore, India. Patients with rectal adenocarcinoma within 8cm of the anal verge, T3N0 or T1-3N+ on magnetic resonance imaging (MRI) who required neoadjuvant radiation and surgery, were randomized to one of two arms: Arm A - LCRT (54Gy with capecitabine) + 6 cycles of CAPOX (capecitabine + oxaliplatin), Arm B - SCRT (25Gy) + 6 cycles of CAPOX. Tumor response was assessed at 24 weeks from completion of radiation by digital rectal examination, sigmoidoscopy and MRI and categorized by a pre-defined criterion. Primary endpoint was cCR or near cCR. Patients with a cCR at first assessment or at a second assessment 12 weeks after a near cCR were offered W&W. Based on Simon's randomized phase II pick-the-winner design, 40 patients were required to achieve a 90% probability of correct selection, assuming a 50% cCR and a 20% absolute difference, without formal superiority testing. Secondary endpoints included adverse events, treatment compliance, post-operative complications, 2-year organ preservation, local regrowth, disease-free survival, diagnostic performance of response assessment criteria, and quality of life. **Results:** Among 46 patients randomized between 2022 and 2025, primary endpoint was assessed in 43 (modified intention-to-treat population). Median age (range), proportion of T3, node positive tumors and mesorectal fascia involvement were 54 years (27-69), 86.3%, 54.5%, 63.6% and 49 years (31-68), 86.9%, 56.5%, 60.8% in Arm A and B, respectively. For primary and short-term secondary endpoints, see Table. **Conclusions:** SCRT + CNCT was superior to LCRT + CNCT in inducing cCR/near cCR in patients with rectal cancer and emerged as the preferred regimen for further evaluation of an intentional W&W approach in a phase III study. Clinical trial information: CTRI: 2021/01/030370. Research Sponsor: None.

End-point	Arm A	Arm B
No. of complete + near complete clinical response	8/20 (40%)	17/23 (73.9%)
Adverse events ≥Grade 3		
During Radiation	2 (in 20 patients)	1 (in 23 patients)
During CNCT	43 in 108 cycles	26 in 138 cycles
No. of pts with Relative dose intensity of CNCT <85%	6 (33.3%)	11 (47.8%)
No. of pts with CNCT delayed ≥3 days in ≥2 cycles	5 (27.7%)	2 (8.6%)
Median no. of CNCT cycles	6	6
Post-operative complications	2 in 11 patients	0 in 6 patients
Clavien-Dindo ≥3		
Treatment related death	1	0

3619 **Poster Session**

Prediction of localized rectal cancer outcomes with ctDNA analysis using a novel ultrasensitive structural variant (SV)-based method. First Author: Cecilia Merk, Karolinska Institutet, Stockholm, Sweden

Background: Rectal cancer has a high risk of recurrence and incidence is rising. Treatment for rectal cancer has moved towards individualization and organ sparing approaches. Selection for treatment is based on radiology, CEA and pathological risk factors, but stronger biomarkers are needed to improve outcomes. Circulating tumor DNA (ctDNA) has shown high prognostic impact on outcome in localized colorectal cancer (CRC), but few patients with rectal cancer have been included in these trials. In this study, we aim to investigate the role of ctDNA in predicting rectal cancer outcomes. **Methods:** The multicenter CITCCA study included patients with stage I-III CRC planned for curative treatment and investigated prospective, longitudinal ctDNA testing. Neoadjuvant (NAT) and/or adjuvant (ACT) treatment was administered according to local guidelines. All patients underwent surgery. Follow-up was according to Swedish standard-of-care with CT and CEA at 1 and 3 years. Patients were recruited in Sweden, 2020–2024. Sampling of ctDNA occurred before and after surgery at 4-6 weeks, 3 and 6 months,1 and 2 years and was analysed with Pathlight, an ultrasensitive SV-based assay. The primary outcome was recurrence-free interval (RFI). **Results:** The study included patients with rectal cancer with a median age of 67 years (range 31-81). Ninety-four patients (65%) received upfront surgery and 51 patients (35%) NAT, of which 36 patients (71%) received short-course radiotherapy and 15 (29%) had total neoadjuvant treatment. Fifty-two patients (36%) were (y)pTNM stage I, 45 patients (31%) stage II and 48 patients (33%) stage III. ACT was given to 38 patients (26%). The success rate for assay generation was 96%. At a median follow-up of 35 months (range 2-46), 23 patients recurred or died of rectal cancer. Before surgery, ctDNA was detected in 136 patients (94%). Notably, 92% (55/60) of patients had ctDNA detected prior to surgery, despite NAT. All patients who recurred had positive ctDNA before surgery, regardless of NAT. Postoperatively, at the 4-6 week clinical landmark (CLM), 18 patients (16%) had detectable ctDNA. At the first test after treatment termination, 17 patients (15%) were ctDNA positive and ctDNA detected recurrence ahead of radiology in 13 patients, including 4/4 patients with stage I disease. Positive ctDNA was strongly associated with recurrence (HR: 94; 95% CI: 20-440) and 3-year RFI at CLM was 22% (95% CI: 9%-56%) for ctDNA positive and 95% (95% CI: 90%-100%) for ctDNA negative patients. **Conclusions:** CtDNA has strong prognostic potential in stage I-III rectal cancer. Using an ultrasensitive SV-based method shows great promise for individualization of treatment in rectal cancer and should be investigated prospectively for organ-sparing selection. Clinical trial information: NCT04726800. Research Sponsor: Cancerfonden.

3620 **Poster Session**

Neoadjuvant treatment of QL1706 in patients with resectable microsatellite instability-high/mismatch repair-deficient colon cancer: Results from a phase 1b trial. First Author: Zi-Xian Wang, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Immune checkpoint inhibitors in neoadjuvant setting have brought clinical benefits for patients with various tumors. This study aimed to evaluate the efficacy and safety of iparomlimab and tuvonralimab (QL1706), a bifunctional antibody targeting both PD-1 and CTLA-4, as neoadjuvant treatment in patients with microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) colon cancer. **Methods:** In this single-arm phase 1b trial, previously untreated patients with resectable stage IIb-III MSI-H/dMMR colon cancer were recruited. Patients were administered neoadjuvant treatment of QL1706 at 5 mg/kg via intravenous infusion every three weeks for four cycles. Radical resection was scheduled between 4 and 6 weeks after last dose of neoadjuvant treatment. The primary endpoint was pathological complete response (pCR) rate. The efficacy analysis set included patients who were confirmed dMMR/MSI-H, received at least one dose of treatment, and had post-surgery pathological results. The safety analysis set included patients who received at least one dose of treatment. **Results:** As of data cut-off date on Oct 15, 2025, 43 patients were enrolled (median age: 56.0 years; males: 58.1%; ECOG PS 1: 55.8%; Lynch syndrome: 34.9%). Scheduled radical resection were performed in 34 patients. A total of 34 patients were included in the efficacy analysis set. The pCR rate was 88.2% (30/34, 95% confidence interval [CI]: 72.5%-96.7%). The major pathologic response rate was 91.2% (31/34, 95% CI: 76.3%-98.1%). In high-risk patients (T4 or N2), the pCR rate was 86.4% (19/22, 95% CI: 65.1%-97.1%). All patients (100%) received surgery had R0 resection. Median treatment exposure was 2.1 months (range, 0.0-3.9). Treatment-emergent adverse events (TEAEs) of grade ≥3 occurred in 12 patients (27.9%); two (4.7%) patients were treatment-related. Immune-related adverse events grade ≥3 occurred in two (4.7%) patients, including one grade 3 acute kidney injury and one grade 4 hypersensitivity, both of which recovered finally. Treatment-related serious adverse events occurred in three (7.0%) patients. No patient cancelled or delayed the surgery due to TEAE. No TEAE leading to death occurred. The incidence of grade ≥3 TEAE during the surgery phase was 11.8% (4/34). **Conclusions:** Neoadjuvant treatment of QL1706 showed promising pCR rate and manageable safety in patients with MSI-H/dMMR colon cancer. A phase 3 trial is ongoing to further confirm the efficacy and safety of QL1706 as neoadjuvant treatment in patients with resectable MSI-H/dMMR colon cancer. Clinical trial information: NCT06686576. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

3621 **Poster Session**

Phase II trial of anti-PD-1 monoclonal antibody and FOLFOXIRI combined with long-course radiotherapy as the total neoadjuvant treatment for proficient, mismatch repair, locally advanced low rectal cancer (PANFORTE). First Author: Jianhong Peng, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China

Background: The current standard treatment for locally advanced low rectal cancer (LALRC) achieves a complete response (CR) rate of only 20–30%. Consequently, radical surgery frequently results in the loss of anal organs, severely affecting patients' quality of life. Therefore, there is an urgent clinical need to identify novel strategies that can maximize tumor regression and preserve anal function. Recent trials have demonstrated radiotherapy showed a distinctive synergistic anti-tumor effect with immune checkpoint inhibitors. Therefore, this study aims to assess the efficacy and safety of an immunotherapy-based total neoadjuvant therapy (TNT) in patients with proficient mismatch repair (pMMR) LALRC. **Methods:** Eligible patients (pts) on this investigator-initiated phase II study had pMMR LALRC with ECOG performance status ≤ 1 and an inferior tumor margin distance from the anal verge (DAV) ≤ 5 cm. Eligible patients receive 4 cycles of FOLFOXIRI plus serplulimab (200 mg). Subsequently, they undergo long-course radiotherapy combination with capecitabine and 2 cycles of serplulimab (200 mg), followed by another 4 cycles of FOLFOXIRI and serplulimab (200 mg). The primary endpoint is CR rate with the sum of clinical complete response (cCR) and pathological complete response (pCR). Secondary endpoints include sphincter preservation rate and safety. **Results:** Between November 2023 and April 2025, 53 patients were enrolled with male percentage 62.3%, median age of 55 years (Range, 28–72) and median DAV of 3 cm (Range, 0.4–5.0). 92.5% (49/53) of patients completed the full TNT regimen. Among the 51 patients eligible for endpoint assessments, the overall CR rate was 68.6% (35/51), and the sphincter preservation rate was 94.1% (48/51). 31 (60.8%) patients achieving cCR opted for a watch-and-wait approach, whereas 20 patients underwent surgery. 20% (4/20) achieved pCR and 70% (17/20) had a tumor regression grade (TRG) of 2. The most common AEs was neutropenia (grade 3-4, 66.0% [35/53]). Other grade 3-4 AEs included leukopenia (32.1%, 17/53), lymphopenia (20.8%, 11/53), and thrombocytopenia (18.9%, 10/53). Immune-related 3-4 AEs comprised myocarditis (1.9%,1/53) and elevated transaminases (1.9%,1/53). **Conclusions:** Our study indicates that this TNT regimen significantly enhances CR rates and anal preservation in pMMR LALRC compared to historical benchmarks, with an acceptable safety profile. These findings suggest that this new approach may be an alternative treatment option for LALRC patients who strongly desire anal preservation. Clinical trial information: NCT06099951. Research Sponsor: None.

3622 **Poster Session**

The role of adjuvant chemotherapy in high-risk stage II colon cancer with microsatellite instability-high or DNA mismatch repair deficiencies: A multicenter pooled analysis (KCSG-CO24-03). First Author: Joon Young Hur, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: The benefit of adjuvant chemotherapy (CTx) for high-risk stage II MSI-H/dMMR colon cancer remains controversial, with discordant international guidelines. This study evaluated clinical outcomes comparing adjuvant CTx vs. observation in this population. **Methods:** This multicenter retrospective analysis included 192 patients with high-risk stage II MSI-H/dMMR colon cancer who underwent curative resection (2010-2020). High-risk features included pT4, grade 3-4, lymphovascular invasion, bowel obstruction/perforation, perineural invasion (PNI), inadequate lymph node sampling (<12), or close margins. Primary endpoint was 5-year relapse-free survival (RFS). Secondary endpoints included 5-year overall survival (OS). A propensity score-matched (PSM) analysis was performed. **Results:** Of 192 patients, 128 (66.6%) received adjuvant CTx (FOLFOX n=66, capecitabine n=40, FL n=17, others n=5) and 64 (33.3%) underwent observation. Median follow-up was 60.5 months. During follow-up, 24 RFS events and 15 OS events occurred. The 5-year RFS was significantly higher with adjuvant CTx versus observation (94.0% vs. 83.7%; P=.001), as was 5-year OS (98.3% vs. 89.0%; P=.001). Multivariate analysis confirmed adjuvant CTx as an independent prognostic factor for both RFS (HR 0.278, 95%CI 0.117-0.660; P=.003) and OS (HR 0.176, 95%CI 0.052-0.594; P=.005). PNI independently predicted worse RFS (HR 4.053; P=.002) and OS (HR 7.490; P=.001). Subgroup analysis demonstrated pronounced benefit in pT4 patients (OS HR 0.094, P=.031; RFS HR 0.230, P=.038) and significant benefit in T3 patients (RFS HR 0.326, P=.031). No survival differences were observed between oxaliplatin-containing vs. non-oxaliplatin regimens (5-year RFS P=.636; OS P=.757). PSM analysis (n=56 pairs) confirmed the survival benefit (matched OS HR 0.344, P=.036). **Conclusions:** Adjuvant CTx significantly improves RFS and OS in high-risk stage II MSI-H/dMMR colon cancer, particularly in pT4 and PNI patients. The absence of regimen-specific survival differences suggests that treatment administration itself, rather than specific agents, determines outcomes. These findings provide evidence to bridge NCCN and ESMO guideline discrepancies, supporting risk-stratified adjuvant CTx in this population. Research Sponsor: None.

Multivariate analysis for survival.

Relapse free survival	Hazard Ratio	95% CI	P value
Adjuvant chemotherapy			
No	1	0.117-0.660	0.003
Yes	0.278		
Pathologic T stage			
T3	1	0.955-5.577	0.063
T4	2.308		
Perineural invasion			
No	1	1.627-10.100	0.002
Yes	4.053		
Overall survival	**Hazard Ratio**	**95% CI**	**P value**
Adjuvant chemotherapy			
No	1	0.052-0.594	0.005
Yes	0.176		
Age			
< 60	1	0.607-13.000	0.186
≥ 60	2.810		
Pathologic T stage			
T3	1	1.223-12.820	0.021
T4	3.959		
Perineural invasion			
No	1	2.184-25.690	0.001
Yes	7.490		
Bowel perforation or obstruction			
No	1	0.933-9.078	0.065
Yes	2.911		

3623 Poster Session

Stage-specific circulating tumor DNA (ctDNA) positivity and minimal residual disease (MRD) decision making in colorectal cancer (CRC) in the prospective INTERCEPT program. First Author: Emerik Osterlund, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: ctDNA positivity is a strong prognostic biomarker for recurrence after curative-intent procedures for CRC and defines MRD in the absence of radiographic disease. Our aim was to assess stage-specific positivity rates across follow-up intervals and the clinical actions associated with ctDNA+. **Methods:** The INTERCEPT program enrolled patients undergoing curatively intended procedures for stage I-IV CRC at MD Anderson Cancer Center. Tumor informed MRD assays (Signatera) were drawn postoperatively and every 3 months according to reimbursement guidelines. ctDNA draws were grouped into 6-month intervals from completion of definitive therapy. Clinical decisions after the first ctDNA+ result in the MRD window were classified as: MRD-trial, systemic therapy, diagnostic escalation, early follow-up, ctDNA confirmation, or no change. **Results:** The final cohort included 1,603 patients (40% stage IV, 32% stage III, 20% stage II, 8% stage I). Median follow-up was 18.4 months. Patients that were ctDNA- on first post-definitive draw had longer recurrence-free survival (RFS) than ctDNA+ patients (median RFS 62.6 vs 4.8 months, HR 11.6 [95% CI 9.6-14.1]), remaining significant in stage subgroups. Among all patients 28% were ctDNA+ at any post-definitive timepoint, the rates were highest for stage IV, followed by stage III, II, and I (Table). ctDNA+ rates were highest in early follow-up and got lower at later intervals (21% to 5%), with similar patterns for all stages. Among 271 patients that were ctDNA+ in the MRD window the initial therapeutic approach was MRD trial screening for 59 (22%), diagnostic escalation in 73 (18%), early follow-up in 57 (21%), confirmation of ctDNA+ by repeat testing in 23 (8%), no change in management for 38 (14%), and 21 (8%) patients started other systemic therapy. MRD trials were discussed prior to recurrence with 144 (53%) of the patients. **Conclusions:** ctDNA positivity is more common in higher stage tumors and becomes less frequent during follow-up. ctDNA positivity confirms its established prognostic value and meaningfully impacts clinical management, including diagnostic workup and MRD trial enrollment. Even within a single center, heterogeneity in initial management of ctDNA+ patients and timing for MRD trial enrollment is evident. Research Sponsor: None.

Stage-specific ctDNA+ rates during follow-up after definitive therapy.

	All	Stage IV	Stage III	Stage II	Stage I	p
Any time	444 / 1,603 (28%)	313 / 646 (48%)	87 / 513 (17%)	40 / 322 (12%)	4 / 122 (3%)	<0.001
<6 months	329 / 1603 (21%)	249 / 646 (39%)	57 / 513 (11%)	21 / 322 (7%)	2 / 122 (2%)	<0.001
6 to <12 months	151 / 1,018 (15%)	97 / 349 (28%)	36 / 351 (10%)	17 / 230 (7%)	1 / 88 (1%)	<0.001
12 to <18 months	75 / 672 (11%)	50 / 197 (25%)	15 / 250 (6%)	10 / 161 (6%)	0 / 64 (0%)	<0.001
18 to <24 months	16 / 264 (6%)	10 / 71 (14%)	3 / 94 (3%)	3 / 71 (4%)	0 / 28 (0%)	0.019
≥24 months	9 / 147 (6%)	5 / 41 (12%)	2 / 58 (3%)	1 / 33 (3%)	1 / 15 (7%)	0.259

3624 Poster Session

Efficacy of probiotics combined with glutamine compound for acute radiation enteritis during neoadjuvant chemoradiotherapy in locally advanced rectal cancer: A randomized controlled trial (NCT05406882). First Author: Qiaoli Wang, Department of Radiation Oncology/Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Acute radiation enteritis (ARE) occurs in up to 80% of patients undergoing abdominal-pelvic radiotherapy, with severe ARE causing treatment interruption in 20%. Current prophylactic strategies remain inadequate. Small-sample studies suggest probiotics and glutamine may reduce radiation-induced mucosal injury and intestinal syndrome (e.g., diarrhea), but evidence-based validation is insufficient. This study investigated the efficacy of probiotics combined with glutamine compound preparation in preventing and alleviating ARE in locally advanced rectal cancer (LARC) patients receiving chemoradiotherapy. **Methods:** This prospective randomized trial enrolled 176 stage II-III rectal adenocarcinoma patients receiving preoperative chemoradiotherapy, randomized 1:1 to prophylactic (group A, n=86) versus therapeutic (group B, n=84) (treatment started when patients had ≥ 2° ARE) administration of probiotics combined with glutamine compound. Concurrent chemoradiotherapy consisted of pelvic radiation 50-50.4 Gy/25-28 fractions plus oxaliplatin/capecitabine. Weekly assessments documented ARE (including anal tenesmus/pain, diarrhea, constipation, hematochezia) basing on RTOG and CTCAE v5.0 criteria. Primary endpoints: incidence of grade ≥2 ARE and diarrhea. Chi-square or Fisher's exact tests were used for analysis through R version 4.4.2. $P<0.05$ indicated statistical significance. **Results:** The enrollment was completed on August 5, 2025. Six patients withdrew consent (group A: 1; group B: 5). Ultimately, there were 170 patients who completed concurrent chemoradiotherapy (84 control, 86 treatment), including 105 males (61.8%). The incidence rate of ≥ 2° ARE in group A was significantly lower than that in group B (44.2% vs 73.8%, $P<0.001$; RR=0.60, 95%CI: 0.46-0.78). The incidence rate of ≥ 2° diarrhea was also significantly lower in group A (34.9% vs 54.8%, P=0.01). There was 1.2% (1/86) and 3.6% (3/84) of grade 3 ARE in the two groups, respectively; and all these four patients experienced grade 3 diarrhea. The incidence rate of ≥ 2° ARE increased with higher doses of pelvic radiotherapy in both groups, with the peak incidence occurring in the fifth week (24.1%) of group A and the fourth week (35.7%) of group B, respectively. **Conclusions:** Prophylactic probiotics combined with glutamine compound has a preventive effect of severe radiation enteritis and diarrhea during concurrent chemoradiotherapy for rectal cancer. Clinical trial information: NCT05406882. Research Sponsor: Sichuan Science and Technology Support Project; 2024YFFK0338; 1.3.5 projects for Artificial Intelligence, West China Hospital, Sichuan University; ZYAI24045.

3625 Poster Session

Circulating tumor DNA clearance of adjuvant chemotherapy in localized colorectal cancer using an ultrasensitive structural variant–based assay. First Author: Cecilia Merk, Karolinska Institutet, Stockholm, Sweden

Background: High-risk localized colorectal cancer (CRC) remains prognostically unfavorable. Adjuvant chemotherapy (ACT) is administered to patients with poor-risk features to eradicate molecular residual disease (MRD) and improve outcome. Despite ACT selection, some patients experience recurrence and others receive unnecessary treatment. Circulating tumor DNA (ctDNA) has emerged as a strong prognostic biomarker that could improve selection for ACT, but detection in the MRD setting is dependent on high sensitivity. In this study, we use an ultrasensitive assay to investigate ACT clearance in localized CRC patients included in the CITCCA trial and its impact on outcome. **Methods:** Patients with stage I–III CRC were enrolled in a prospective Swedish cohort study between 2020-2024. Standard of care treatment was given, and patients were followed with longitudinal ctDNA before and after surgery at 4-6 weeks, 3 and 6 months, 1 and 2 years. The clinical landmark (CLM) was defined as the 4-6 week postoperative test prior to initiation of ACT. The first sample after definitive treatment (FDT) was defined as the first test after treatment termination. ACT clearance was defined as a positive ctDNA test at either CLM or at CLM and 3 months, with subsequent negative ctDNA, in patients without recurrence. An ultrasensitive SV-based assay, Pathlight, was used for ctDNA analysis. The primary outcome was recurrence-free interval (RFI). **Results:** Of the 377 patients included, 135 patients (36%) received ACT with a median length of 5.2 months (range 0.1-7.4). Single agent fluoropyrimidine was given to 65 patients (48%) and 70 (52%) received an oxaliplatin-based doublet. Analyzable CLM samples were obtained from 106 patients (79%). Nineteen patients (18%) were ctDNA positive at CLM and received ACT. ctDNA positive patients who received ACT still showed a substantially higher risk of recurrence compared to ctDNA negative patients (HR, 38; 95% CI, 15–97). The same was seen in ctDNA-positive patients who did not receive ACT, i.e. clinically low-risk (HR, 35; 95% CI, 14–88). In the ctDNA positive cohort, patients who received ACT versus no ACT had a 2-year RFI of 58% (95% CI:39%-85%) versus 39% (95% CI:22%-69%). Persistent ACT clearance was seen in 8 patients, none of whom recurred. Transient clearance was seen in 6 patients, all of whom recurred. Five patients had persistently positive ctDNA despite ACT; all recurred. Eighty-seven patients (82%) were ctDNA negative at CLM but received ACT; 9 of these recurred (10%). Eighteen patients were ctDNA positive at CLM but did not receive ACT and 13 of these recurred. **Conclusions:** ctDNA is a strong prognostic biomarker and may be utilized to guide adjuvant treatment decisions in patients with localized CRC. Permanent clearance of ctDNA by administration of ACT is a favorable prognostic feature whereas ctDNA persistence after ACT predicts recurrence. Clinical trial information: NCT04726800. Research Sponsor: Cancerfonden.

3626 Poster Session

Health-related quality of life (HRQOL) in the phase 3 trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair (dMMR) colon cancer (Alliance A021502, ATOMIC). First Author: Amylou C. Dueck, Alliance Statistics and Data Management Center, Mayo Clinic Arizona, Scottsdale, AZ

Background: For patients (pts) with dMMR stage III colon cancer, the addition of atezolizumab (atezo) to adjuvant 5-fluorouracil, leucovorin plus oxaliplatin (mFOLFOX6) significantly improved disease-free survival in ATOMIC (NCT02912559). Here we present HRQOL data. **Methods:** Pts with surgically resected stage III dMMR colon cancer were randomized (1:1) to receive mFOLFOX6 + atezo (840 mg IV q2 weeks) for 12 cycles (6 months [mo]) followed by atezo monotherapy for 13 cycles (12 mo total) versus mFOLFOX6 for 12 cycles. HRQOL was an exploratory endpoint measured using the FACT-C (includes FACT-G), FACT/GOG-NTX, EQ5D-5L, and PRO-CTCAE. Optional participation was by paper surveys at trial registration, prior to treatment cycles 4 and 7, and at 6, 12, and 36 mo after registration. Mean changes from baseline (BL) were compared between treatment arms using general linear mixed models (negative mean changes indicate worsening). At 6 mo, a two-sided 95% confidence interval excluding a difference of 1.9 points (FACT/GOG-NTX) and 6 points (FACT-C Trial Outcome Index [TOI]) favoring the mFOLFOX6 arm would indicate non-inferiority of the addition of atezo. Rates of side effect bother (FACT-G item GP5) and pt-reported adverse events (AEs) by PRO-CTCAE (composite scores, baseline adjusted) were compared using Fisher's exact tests. **Results:** Of 712 randomized pts, 581 (285 atezo+mFOLFOX6; 296 mFOLFOX6) consented to participate in the survey. Pts completed 2398/3021 (79%) of expected surveys across all time points (1218/1489 [82%] atezo+mFOLFOX6; 1180/1532 [77%] mFOLFOX6). The difference in mean changes from BL between arms indicated non-inferiority of the addition of atezo at 6 mo (table); differences remained small at 12 and 36 mo. No significant differences in mean changes from BL between arms were found at 6, 12, or 36 mo for any scale. At 6 mo, 16% vs 20% of pts in each arm reported at least "quite a bit" of side effect bother (p=0.34), favoring atezo. Across cycles, atezo was associated with higher rates of pt-reported itchy skin (62% vs 48%), cough (53% vs 43%), and shortness of breath (51% vs 41%) [all $p<0.05$]. **Conclusions:** Addition of atezo to mFOLFOX6 slightly increases pt-reported AEs, but its effect on HRQOL is minimal and not clinically meaningful. Results support tolerability of atezo+mFOLFOX6 as standard of care adjuvant treatment for pts with dMMR stage III colon cancer. Support: UG1CA189823, U10CA180821, U10CA180882; Genentech, a member of the Roche group; https://acknowledgments.alliancefound.org. Clinical trial information: NCT02912559. Research Sponsor: National Cancer Institute; UG1CA189823; National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; Genentech a member of the Roche group.

Scale	Mo	Mean change from BL – atezo+mFOLFOX6	Mean change from BL – mFOLFOX6	Diff (95% CI)
FACT/GOG-NTX	6	-10.0	-10.6	0.6 (-0.8, 2.1)
	12	-8.0	-9.4	1.4 (-0.2, 2.9)
	36	-7.2	-6.9	-0.4 (-2.1, 1.4)
FACT-C TOI	6	-4.1	-2.5	-1.6 (-3.7, 0.6)
	12	2.1	1.8	0.3 (-1.9, 2.6)
	36	0.7	1.8	-1.1 (-3.7, 1.5)

3627 **Poster Session**

Neoadjuvant chemotherapy followed by transanal endoscopic surgery (TES) and selective chemoradiation or total mesorectal excision (TME) for early-stage rectal cancer: The Ottawa Hospital experience. First Author: Mohammed Al Darai, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

Background: Organ-sparing therapy for early-stage rectal cancer may avoid permanent ostomy or functional disturbances commonly known as low anterior resection syndrome (LARS). TES is increasingly used for treatment of selected T1N0 or T2N0 rectal cancer. The CCTG CO.28 (NEO) phase II trial evaluated neoadjuvant chemotherapy then TES surgery for early-stage rectal cancer (Kennecke et al, JCO 2023). On the CO.28 trial, patients (pts) with post-chemotherapy ypT3N0 tumours were to have neoadjuvant chemoradiation (CRT) then TME. Pts with ypT2 or poor risk ypT1 tumours were to have TME. However, several pts insisted on organ sparing alternatives such as adjuvant CRT or active surveillance. Our approach evolved from CO.28 by incorporating more selective adjuvant CRT instead of routinely resorting to TME. **Methods:** This retrospective study conducted at the Ottawa Hospital evaluated the outcomes of pts with early rectal cancer treated with the NEO approach and selective adjuvant CRT. The primary outcome was 3-yr TME free survival. Secondary outcomes included safety, 3-yr disease-free survival (DFS), 3-yr permanent colostomy free survival, 5-yr overall survival (OS), pathological complete response rate (pCR), proportion of pts requiring CRT and proportion of pts with LARS at 2 yrs. **Results:** N = 50 pts received a NEO approach and selective adjuvant chemoradiation. N = 19 were part of the previously reported CO.28 trial and N = 31 were a consecutive cohort treated off protocol. Median age was 63 (42-83) yrs, 58% were male. Rectal location was low/mid/upper in 34%/56%/10%. Baseline T stage was T2 (76%) and T3 (10%). Neoadjuvant CAPOX (64%) or FOLFOX (36%) was completed by 88% of pts and Gr 3 AEs occurred in 31%. At TES, pCR was achieved in 32% of pts. CRT was received by 33% of pts. Median follow-up was 30.2 (2.6-86.4) months. LARS was present at 2 yr in 15%. 3-yr TME-free survival was 82% (95% C.I. 69 to 94%). 3-yr permanent colostomy-free survival was 88% (95% C.I. 78 to 99%). 3-yr DFS after all local therapy was 98% (95% C.I. 93 to 99%). One pt developed both local plus distant recurrence. 5-yr OS was 95% (95% C.I. 85 to 99%). One pt who was disease free on surveillance died of an unrelated COPD exacerbation. **Conclusions:** The NEO approach of neoadjuvant chemotherapy then TES combined with selective adjuvant CRT demonstrated promising organ-preservation outcomes in early-stage rectal cancer, achieving high TME-free survival. This strategy offers a meaningful alternative to routine TME, potentially reducing the risk of permanent ostomy and LARS. Research Sponsor: None.

3628 **Poster Session**

Impact of postsurgical circulating tumor DNA (ctDNA) dynamics on eligibility of colorectal cancer (CRC) patients for randomized ALTAIR trial: Implications for treat-on-molecular-recurrence (TOMR) trials. First Author: Hideaki Bando, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Postsurgical ctDNA positivity is strongly associated with recurrence risk and is driving the development of TOMR trials like the phase III ALTAIR trial (NCT04457297), which evaluated the benefit of trifluridine/tipiracil versus placebo in CRC patients (pts) with ctDNA positivity in the absence of clinical relapse. We evaluated the impact of longitudinal ctDNA dynamics during adjuvant chemotherapy (ACT) and surveillance on eligibility for enrollment into ALTAIR. **Methods:** CIRCULATE-Japan's GALAXY (UMIN000039205) study screened clinical stage II-IV CRC pts receiving standard-of-care (SOC) perioperative chemotherapy for eligibility for interventional trials by ctDNA monitoring using the personalized, tumor-informed Signatera assay in plasma collected at 1, 3, 6, 9, 12, 18, and 24 months (mos) post-surgery. Pts with ctDNA positivity without clinical recurrence were eligible for ALTAIR within 3 months of detection. We analyzed ctDNA dynamics and eligibility across all GALAXY sites, extending prior analyses limited to ALTAIR-participating sites. **Results:** Of 5,355 pts enrolled by April 2023, 693 (12.9%) were ctDNA-positive 2–10 weeks post-surgery (MRD-positive). Of 378 MRD-positive pts who received ACT, 117 (31.0%) remained persistently positive, 76.1% of whom did not relapse within 3 mos. ctDNA cleared after ACT in 237 pts, but 122 (51.5%) reconverted to positive, 67.2% of whom remained relapse-free for ≥3 mos after reconversion. Among 1,341 MRD-negative pts receiving ACT, 183 (13.6%) converted to ctDNA-positive, 123 (67.2%) of whom remained relapse-free for ≥3 mos after molecular relapse. Overall, 17.1% of GALAXY pts met ALTAIR ctDNA-based criteria with stage-specific eligibility rates of 13.2% (II), 14.7 % (III), and 34.6 % (IV). Overall, 243 (4.5%) were enrolled in ALTAIR, including 18.6% of MRD-positive and 2.4% of MRD-negative pts. **Conclusions:** Approximately one-third (123/334) of ALTAIR-eligible pts were initially MRD-negative and later converted to ctDNA-positive without early clinical relapse, highlighting the importance of longitudinal ctDNA monitoring in TOMR trial design. When compared to the previous analysis limited to ALTAIR-participating sites, we observed higher eligibility yet lower enrollment rates in the full cohort at all GALAXY sites, underscoring the need for broader access and efficient enrollment networks to optimize TOMR trials. Clinical trial information: NCT04457297. Research Sponsor: Japan Agency for Medical Research and Development; 19ck0106447h0002, 21ck0106711h0001, 21ck0106710h0001, 22lk0201164h0001 and 22lk0201148h0002; National Cancer Center Research and Development Fund; no. 2021-A-6.

ctDNA dynamics	MRD positive (N = 378)	MRD negative (N = 1,341)
Persistently positive, all	117 (31.0%)	NA
Persistently positive, eligible for ALTAIR	89 (23.5%)	NA
Transient clearance, all	122 (32.2%)	NA
Transient clearance, eligible for ALTAIR	82 (21.7%)	NA
Turned positive, All	NA	183 (13.6%)
Turned positive, eligible for ALTAIR	NA	123 (9.2%)

3629 **Poster Session**

Molecular residual disease (MRD) detection using an ultra-sensitive assay in a prospective colorectal cancer cohort: The VICTORI study. First Author: Joao Paulo Solar Vasconcelos, BC Cancer - Vancouver, University of British Columbia, Vancouver, BC, Canada

Background: Circulating tumor DNA (ctDNA) detection of molecular residual disease (MRD) is prognostic in colorectal cancer (CRC) but missed recurrences highlight constraints in assay performance. VICTORI is a prospective observational study investigating an ultra-sensitive MRD assay (NeXT Personal) in CRC patients undergoing curative treatment. **Methods:** Whole-genome informed panels of ~1,800 variants interrogated plasma collected pre-curative loco-regional treatment, q2 weeks post-surgery (weeks 2–8, landmark window), and subsequently every 3 months (3-36 months, surveillance window). **Results:** 795 plasma samples from 109 patients were analyzed, with median follow-up of 21.1 months and 31 recurrences observed. Cohort characteristics: 61 (56.0%) rectal cancer, 48 (44.0%) colon cancer; 81 (74.3%) stage I-III; 56 (50.5%) had neoadjuvant treatment; 106 (97.2%) had surgery as curative procedure. Pre-surgical sensitivity (treatment-naïve) was 96.0% (n=48/50) and specificity was 100% (no detection in pathologic complete responders; 0/10). Landmark window overall sensitivity for recurrence was 83.9% (n=26/31) with 69.2% (18/26) of detections being <100 ppm. Sensitivity was similar weeks 4–8 (81.5% week 4 [n=22/27]; 82.1% week 6 [23/28]; 85.7% week 8 [24/28]), and lower at week 2 (52.4% [11/21]) when post-surgical cell-free DNA peaked (median 2.80 ng/mL pre-surgery to 9.40 at week 2; $p=8.7\times10^{-12}$). Sampling between weeks 4-8 yielded a sensitivity of 80.0% (n=24/30) at the first available timepoint and 89.7% (26/29) with incorporation of an additional subsequent sample. Detection of ctDNA at any landmark window timepoint was associated with inferior outcomes (adjusted HR [aHR]: 10.28 [95% CI: 4.03-26.23], $p=1.06\text{x}10^{-06}$). Week-4 detection <100 ppm was prognostic and conferred a 6.5 month longer lead time than detections ≥100ppm (HR 4.09, p=0.018). All patients who recurred with surveillance samples had ctDNA detected prior to recurrence (sensitivity: 100% (n=28/28). ctDNA identified 100% of lung- and liver-only metastases; most initial detections were <100 ppm (75% and 71.4%, respectively). In evaluable patients, lead time from ctDNA detection to recurrence was 176 days (including patients with expedited imaging upon receipt of a ctDNA detection result). If a higher threshold for ctDNA was used (≥100 ppm) in the same population, the lead time would be >two months shorter (105 days, p<0.001). All patients without ctDNA detected on surveillance remain disease free (NPV 100% [n=63/63]). **Conclusions:** NeXT Personal demonstrated high accuracy, prognostic value, and early detection at ultrasensitive levels with no loss in specificity. The ideal postoperative landmark time point for MRD testing is at 4-8 weeks. Our results show strong clinical potential for an ultrasensitive MRD assay for landmark MRD and longitudinal surveillance in CRC. Research Sponsor: Personalis, Inc.; BC Cancer Foundation.

3630 **Poster Session**

Lycopene and survival in patients with stage III colon cancer: Findings from CALGB (Alliance)/SWOG 80702. First Author: Seohyuk Lee, Beth Israel Deaconess Medical Center, Boston, MA

Background: Lycopene, a non-provitamin A carotenoid, has been reported to inhibit colon cancer development; however, its prognostic role after colon cancer diagnosis remains unknown. Given emerging evidence suggesting greater intake of lycopene-containing – particularly, tomato-based – foods may improve colon cancer prognosis, we assessed the association of postdiagnosis lycopene consumption with survival among 1666 patients (pts) with stage III colon cancer. **Methods:** Through an NCI-sponsored multicenter phase III adjuvant chemotherapy trial (CALGB/SWOG 80702; NCT01150045), we examined the consumption of total lycopene (dietary plus supplementation) and dietary lycopene as well as lycopene-containing foods (tomato-based foods plus other lycopene-containing foods) and tomato-based foods via validated food frequency questionnaires (FFQs) collected at 6 weeks after randomization (FFQ1) and again 14-16 months post-randomization (FFQ2). Lycopene-related exposures were calculated as time-varying measurements via cumulative averaging. Primary outcome was disease-free survival (DFS), defined as time from FFQ1 completion to colon cancer recurrence or death from any cause. Secondary outcomes were recurrence-free survival (RFS) and overall survival (OS). We estimated associations of lycopene-related exposures with survival via multivariable Cox proportional hazards regression. **Results:** In our cohort, pts with greater total lycopene intake tended to be slightly younger and of male sex and White race, have more left-sided tumors, and report higher caloric intake and physical activity engagement. Over median follow-up of 6.0 (IQR: 5.0-6.1) years, we observed 466 DFS, 395 RFS, and 300 OS events. Pts in the highest relative to lowest quintiles of total lycopene intake experienced significantly improved DFS (HR: 0.60 [95% CI: 0.44-0.83]; P_{trend}=0.006), RFS (HR: 0.58 [95% CI: 0.41-0.82]; P_{trend}=0.007), and OS (HR: 0.60 [95%CI: 0.40-0.89]; P_{trend}=0.02). Similar findings were observed for dietary lycopene intake. Pts consuming >1 serving/day compared to 1 serving/week of all lycopene-containing foods did not experience significantly improved survival. However, when considering only tomato-based foods, we observed a trend toward improved survival (HR for DFS: 0.61 [95% CI: 0.38-0.96]; P_{trend}=0.12). **Conclusions:** Greater lycopene consumption with or without supplementation was associated with lower risk of colon cancer recurrence and death which may be largely driven by tomato-based foods. Our findings may inform clinical nutrition recommendations for pts with colon cancer, with higher intake of tomato-based foods (>1 serving per day) potentially improving colon cancer survival. Future studies, especially interventional trials, are needed to validate our findings. Support: U10CA180821, U10CA180882, U24CA196171; Pfizer; https://acknowledgments.alliancefound.org. Research Sponsor: National Cancer Institute; U10CA180821; National Cancer Institute; U10CA180882; National Cancer Institute; U24CA196171; Pfizer; https://acknowledgments.alliancefound.org.

3631 **Poster Session**

Effect of transanal vs. laparoscopic total mesorectal excision on 5-year overall survival in patients with rectal cancer: The TaLaR trial. First Author: Liang Kang, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Transanal total mesorectal excision (taTME) has emerged as a widely adopted surgical approach for rectal cancer. Prior studies have reported favorable short-term outcomes, histopathological quality, and complication profiles for taTME compared with laparoscopic total mesorectal excision (laTME). However, the long-term oncologic effectiveness of taTME remains debated. In our previous work, we demonstrated that 3-year disease-free survival after taTME was noninferior to that after laTME among patients with mid-to-low rectal cancer. Building on these findings, the present study aimed to report the 5-year overall survival (OS) between taTME and laTME. **Methods:** We conducted a phase 3, randomized, open-label, noninferiority trial to compare the survival outcomes of taTME versus laTME in patients with rectal cancer located below the peritoneal reflection. This trial encompassed 16 hospitals across 10 provinces in China, with a total enrollment of 1,115 patients. We set the 3-year disease-free survival (DFS) and 5-year overall survival (OS) as the primary endpoints for analysis. This analysis of the 5-year overall survival was conducted following a predefined modified intention-to-treat principle. This study is registered with ClinicalTrials.gov, number NCT02966483. **Results:** As of June 2025, the overall 5-year overall survival (OS) rate was 83.60%, comprising 86.06% in the transanal TME (taTME) group and 81.24% in the laparoscopic TME (laTME) group. The overall 5-year disease-free survival (DFS) rate was 75.90%, with DFS rates of 77.65% in the taTME group and 74.18% in the laTME group. **Conclusions:** Based on preliminary results from a five-year follow-up, taTME is expected to achieve a five-year overall survival (OS) that is non-inferior to laTME. Our findings will support the routine use of taTME in mid-to-low rectal cancer, particularly in men, obese individuals, and those who have received neoadjuvant therapy. Clinical trial information: NCT02966483. Research Sponsor: Sun Yat-sen University Clinical Research 5010 Program.

5-year survival results between the laTME group and the taTME group.

	laTME	taTME	HR
5-year OS (97.5% CI)	81.24% (77.82%-84.82%)	86.06% (83.04%-89.20%)	0.73 (0.54-1.10)
5-year DFS (95% CI)	74.18% (70.45%-78.10%)	77.65% (74.15%-81.32%)	0.86 (0.68-1.11)

3632 **Poster Session**

Neoadjuvant (NA) chemoradiotherapy (CTRT) plus avelumab (Ave) in locally advanced rectal cancer (LARC): 4-year outcomes of the phase II AVANA trial and their association with computational pathology. First Author: Giovanni Trovato, Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli–IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

Background: The AVANA trial investigated the addition of PD-L1 inhibitor Ave to NA CTRT in LARC. Here, we report long-term survival and explore its association with tumor microenvironment (TME) features assessed through computational pathology. **Methods:** AVANA is a multicenter, single-arm, phase II trial enrolling patients (pts) with LARC defined by at least one high-risk feature (cN+, cT4, or high-risk cT3). Pts received NA CTRT combined with six cycles of Ave, followed by surgery. Primary endpoint was pathological complete response (pCR) rate. Secondary endpoints included progression-free survival (PFS) and overall survival (OS). Multiplex immunofluorescence was performed on baseline biopsies and surgical specimens using CODEX platform (Akoya). A deep-learning pipeline using a spatially constrained convolutional neural network for cell detection and a classifier for cell labeling was applied, allowing identification of eight cell populations: cancer cells, normal epithelial cells, fibroblasts, lymphocytes (lym), neutrophils (neu), macrophages, endothelial (endo) cells and myocytes. Cell infiltrates were dichotomized as high or low using optimal cutpoints derived from maximally selected rank statistics. Cell density maps were generated to identify differences in cellular configurations between baseline and surgical specimens. **Results:** The primary endpoint was met, with a pCR of 21.8% (22/101 pts). At a median follow-up of 51.8 months, 26 of 101 pts had a progression event and the 48-month PFS rate was 74.7% (95% CI: 65.0–82.2). Thirteen deaths occurred, yielding a 48-month OS rate of 87.6% (95% CI: 79.1–92.7). Age ($\geq$70 vs $<$70; p=0.371), sex (p=0.897), ECOG PS (0 vs 1; p=0.899), cN positivity (p=0.716), cT stage (1-2 vs 3-4; p=0.264), or mismatch repair status (dMMR vs pMMR; p=0.274) were not associated to PFS. Digital whole-slide images of diagnostic biopsies and surgical specimens were available for 87/101 pts (86.1%). In post-treatment surgical specimens, high neu (p=0.00025) and high lym infiltrate (p=0.0038) correlated with better PFS, whereas high endo cell infiltrate was associated to shorter PFS ($p<0.0001$). Comparisons between baseline and post CTRT+Ave tissues showed that increased endo cell density in surgical specimen relative to baseline biopsies had worse PFS (p=0.0070), while increased neu to cancer cell ratios [HR 0.50 (95% CI: 0.21-1.18); p=0.108] and increased neu density [HR 0.22 (95% CI: 0.03-1.65; p=0.106] showed trends toward better PFS, although not statistically significant. **Conclusions:** AVANA demonstrates the feasibility and activity of adding ICIs to standard CTRT in LARC. Computational pathology analyses suggest that dynamic changes in TME cellular composition could be associated with long-term outcomes, supporting its potential role for pts stratification. Clinical trial information: NCT03854799. Research Sponsor: Merck; GONO Foundation; AIRC.

3633 **Poster Session**

Clinical outcomes in curatively resected dMMR/MSI-H colon cancer: A retrospective analysis of a multicentric cohort. First Author: Sofie De Meulder, Gastroenterology Department AZ Delta, Roeselare, Belgium

Background: Deficient mismatch repair (dMMR) colon cancer accounts for approximately 15% of localised cases and, despite favourable long-term survival after curative resection, disease recurrence remains a key concern. Recent trials reported a 3-year disease-free survival (DFS) of about 80% after primary surgery with or without adjuvant chemotherapy. In the NICHE-2 trial (Chalabi *et. al,* NEJM 2024), with the addition of nivolumab plus ipilimumab in the neoadjuvant setting, no relapses were observed at three years. The same immunotherapy doublet provides a 3-year overall survival rate of 81% in the metastatic setting (Lonardi *et. al*, ESMO 2025). **Methods:** We conducted a retrospective multicentric cohort study including patients with non-metastatic dMMR/MSI-H colon cancer who underwent resection at 3 Belgian hospitals between January 1, 2013 and December 31, 2020. Patients with synchronous metastases, microsatellite stable (MSS) tumours or insufficient follow-up data ($<$3 years of imaging surveillance) were excluded. Clinical characteristics, adjuvant therapy, relapse incidence and survival outcomes were analysed. **Results:** A total of 219 patients with curatively resected dMMR/MSI-H colon cancer were included. Median age was 74 years (range 24–95). Of the total cohort, stage I accounted for 18.3%, stage II for 58.9% and stage III for 22.8%. Adjuvant chemotherapy was administered in 67 patients (30.7%). Relapse occurred in 11 patients (5.0%), comprising 4 patients with stage II disease and 7 patients with stage III disease. The 3-year DFS was 96.2% (95% CI: 96.1-96.3%). Of those relapsing, 7 received subsequent immunotherapy, yet 3 of those ultimately succumbed to the disease. The 5-year disease-specific mortality was 1.99% (95% CI: 1.96-2.03%), while the 5-year overall mortality was 10.3% (95% CI: 9.89-10.81%). Based on the NICHE-2 benchmark, preventing all 3-year recurrences and disease-specific deaths in this cohort would require treating approximately 26 patients with neoadjuvant nivolumab plus ipilimumab to avert one recurrence, and about 73 patients to prevent one cancer-specific death. **Conclusions:** In this multicentric Belgian cohort of curatively resected dMMR/MSI-H colon cancer, recurrence rates were lower than those observed in the FoXTROT trial (Morton *et. al,* JCO 2023), even when accounting for the slightly higher proportion of stage I disease in our cohort. Most patients, however, died from other non-related causes, reflecting the well-known enrichment of MSI-H colon cancer in elderly women. A trade-off between neoadjuvant nivolumab plus ipilimumab versus primary surgery and salvage treatment with the same regimen should be discussed based on the high numbers needed to treat to avoid one recurrence and the non-trivial immunotherapy related toxicity (de La Fouchardiere *et. al*, Annals of Oncology 2024). Research Sponsor: Kom op Tegen Kanker.

3634 **Poster Session**

Neoadjuvant immunotherapy combined with radiochemotherapy vs chemotherapy alone in pMMR colon cancers: The TORCH-C randomized phase 2 clinical trial. First Author: Hui Zhang, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The prognosis for locally advanced colon cancer (LACC) with bulky nodal disease and/or clinically T4 stage remains poor, with high rates of recurrence and metastasis. Immunotherapy has become the standard treatment for deficient mismatch repair or microsatellite instability-high (dMMR/MSI-H) colon cancer. However, there has been little progress for the majority of cases, which was mismatch-repair proficient or microsatellite stable (pMMR/MSS). For locally advanced colon cancer with T4b stage or bulky lymph nodes, neoadjuvant chemotherapy is currently widely used. Whether combining it with immunotherapy and radiotherapy can improve efficacy is worthy of exploration. TORCH-C is the first study to evaluate this combination. **Methods:** TORCH-C is a prospective, multicenter, randomized phase 2 study that enrolled patients from April 3, 2023, through September 9, 2025. A total of 120 high-risk LACC (T4/bulky N+M0 , pMMR/MSS) patients were 1:1 randomized to either an immunotherapy combined with SCRT and CAPOX chemotherapy group (group A) or a chemotherapy alone group (group B). Patients in the group B received 4 cycles of CAPOX (oxaliplatin 130 mg/m^2 intravenously day 1 and capecitabine 1000 mg/m^2 orally days 1-14). Patients in the group A received SCRT (25Gy in 5 fraction) and 4 cycles of the PD-1 inhibitor (serplulimab, 300mg intravenously day 1) combined with CAPOX. The radiotherapy target volume includes only the primary colon tumor and enlarged lymph nodes, without elective nodal irradiation. After neoadjuvant therapy, patients will be evaluated for radical colon resection. All patients will receive adjuvant chemotherapy of four cycles of CAPOX. The primary outcome was pathological complete response (pCR) rate. The secondary outcomes included tumor downstaging, R0 resection, 3-year disease free survival (DFS), 3-year overall survival (OS), 3-year local recurrence-free survival and treatment-related toxicity. **Results:** 120 patients have been enrolled and randomized. 107 patients were included in the mITT analysis (54 in group A and 53 in group B). 103 have received surgery (50 in the chemotherapy group, 53 in the radiotherapy group). The pCR rate was 10% (5/50) in chemotherapy group (group B) and 45.3% (24/53) in the radiotherapy group (group A) ($P<0.05$). The most common grade 3-4 adverse event (AE) among patients was thrombocytopenia, (22.2%, 12/54) in the group A and (18.9%, 10/53) in the group B. **Conclusions:** The combination of PD-1 inhibitor, SCRT, and chemotherapy shows promising efficacy and significantly improved pCR rates in patients with MSS/pMMR high-risk LACC. This regimen may provide a new therapeutic option to achieve R0 resection and improve long-term survival. Clinical trial information: NCT05732493. Research Sponsor: None.

3635 Poster Session

Clinicopathological characteristics of patients with minimal residual disease in stage II–III colon cancer: Interim results from the observational cohort of CLAUDIA study. First Author: Minsu Kang, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea

Background: Circulating tumor DNA (ctDNA) monitoring for minimal residual disease (MRD) has emerged as a key prognostic biomarker in resected colon cancer. The CLAUDIA study (KCSG CO22-12, NCT05534087) is a prospective, multicenter study evaluating ctDNA-guided adjuvant therapy. It includes an observational screening cohort (Part 1) and a randomized interventional trial for MRD (+) patients (Part 2). Here, we report the baseline characteristics and MRD status of the Part 1 cohort and the clinical outcomes for patients who did not participate in Part 2. **Methods:** In Part 1, stage II or III colon cancer patients who received curative resection scheduled for adjuvant oxaliplatin-based chemotherapy (FOLFOX or CAPOX) are enrolled (N= approximately 1,200). Postoperative plasma samples collected after surgery, before starting adjuvant chemotherapy, are analyzed using a tumor-informed ctDNA assay that tracks up to 100 patient-specific mutations (IMBdx). Patients identified as MRD (+) are screened for a Part 2 randomized phase III trial (N=236) comparing mFOLFIRINOX to standard care. MRD (-) patients are managed at the investigator's discretion. **Results:** As of November 2025, a total of 809 patients were enrolled. Postoperative ctDNA was positive in 228 patients (28.2%). MRD (+) rate was significantly higher in patients with T4 tumors (40.5% vs. 22.8% in T1–3 tumors, $p<0.0001$), N2 disease (38.8% vs. 25.4% in N0–1, p=0.0007), and elevated postoperative CEA (>5 ng/mL) (42.2% vs. 26.8% in normal, p=0.013). Accordingly, MRD (+) was enriched in high-risk stage III disease (T4 or N2) (40.3% vs. 21.5% in low-risk stage III and stage II, $p<0.0001$). However, MRD (+) rates did not differ significantly by histology, tumor location, or MSI status. MRD positivity was not associated with the mutational status of the frequently altered genes in colon cancer (APC, TP53, KRAS, BRAF, ERBB2, SMAD4). We analyzed outcomes in 673 patients who did not participate in the Part 2 randomized study [92 MRD (+) and 581 MRD (-)]. In the multivariate analysis of recurrence-free survival adjusting for clinicopathologic covariates, MRD (+) was the strongest independent predictor of poor outcome (adjusted HR 5.81; 95% CI 2.65–12.74; $p<0.0001$). **Conclusions:** Postoperative ctDNA status serves as a robust prognostic biomarker in stage II-III colon cancer, correlating with advanced tumor burden. MRD (+) patients who receive standard-of-care management face a significantly increased risk of recurrence. These findings validate the utility of the ctDNA assay used and support the rationale for the ongoing CLAUDIA Part 2 trial, which investigates treatment intensification for MRD (+) patients. Clinical trial information: NCT05534087. Research Sponsor: Ministry of Health and Welfare, Republic of Korea; HA22C0062.

3636 Poster Session

Relationship between GLP-1 receptor agonists on cancer recurrence and survival of patients with stage I-III colorectal cancer: A retrospective cohort study using the TriNetX database. First Author: Emily Noelle Kinsey, Department of Internal Medicine, Virginia Commonwealth University, Massey Comprehensive Cancer Center, Richmond, VA

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide, and obesity is a known risk factor. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are increasingly used for obesity and diabetes management, making it critical to understand their long-term implications. Preclinical studies suggest a protective effect of GLP-1RA in risk for developing obesity-related malignancies, including CRC, but their long-term influence on recurrence and survival among those with CRC is not well characterized. **Methods:** A retrospective cohort study was conducted using TriNetX, a federated health research network of real-world data. Data were queried on January 22, 2026, from the Global Collaborative Network, encompassing over 190 million de-identified electronic medical records. Adult patients (> 18 years) with a diagnosis of stage I-III CRC between April 1, 2005, and April 1, 2025, were identified. The exposure group was defined as patients prescribed GLP-1RA following their CRC diagnosis. The control group was GLP-1RA nonusers. Propensity score matching (PSM) was employed, achieving balance across demographics, comorbidities, and confounding variables. The primary outcome was recurrence free survival (RFS), and the secondary outcome was overall survival (OS). Kaplan–Meier survival analysis, log-rank test, hazard ratios (HR) with 95% confidence intervals (CI), and risk ratios (RR) were used to estimate outcomes over 5-years of follow-up. **Results:** Among 20,383 patients with CRC across 19 HCOs, 839 patients per group with mean age 63.0 years remained after 1:1 PSM and exclusions, with comparable median follow-up times (710 vs 1160 days). GLP-1RA use was significantly associated with a lower risk of recurrence compared with nonusers (RR, 0.33; 95% CI, 0.25-0.45; $p < 0.001$) and improved RFS probabilities (89.0% vs 72.8%; [HR, 0.37; 95% CI, 0.27-0.50; $p < 0.001$]) at the 5-year follow-up. A significant improvement in OS was also observed in GLP-1RA users compared with nonusers (82.5% vs 71.4%; [HR 0.45; 95% CI, 0.34-0.60; $p < 0.001$]), and reduced mortality risk (RR, 0.35; 95% CI, 0.27-0.46; $p < 0.001$) compared with nonuse. Secondary analysis with 15-year median follow-up period demonstrated that these survival and recurrence benefits were sustained long term with median OS of 4,382 and 3,931 days in GLP-1RA users vs nonusers respectively. **Conclusions:** In this real-world analysis, GLP-1RA use in patients with stage I-III CRC was associated with improved RFS and OS compared to nonusers. These findings were consistent across both 5-year and 15-year follow-up periods, demonstrating a sustained association with improved outcomes in CRC. Prospective trials are needed to strengthen the evidence base for GLP-1RA use in patients with CRC and to define the underlying biological mechanisms. Research Sponsor: None.

3637 Poster Session

Comparison of longitudinal circulating tumor DNA (ctDNA) and carcinoembryonic antigen (CEA) for post-operative risk stratification in colorectal cancer (CRC). First Author: Eiji Oki, Department of Advanced Medicine and Innovative Technology, Kyushu University Hospital, Fukuoka, Japan

Background: ctDNA is a reliable biomarker that outperforms CEA for detecting molecular residual disease in CRC. However, the relative prognostic performance of these biomarkers across post-operative timepoints is not fully elucidated. Characterizing these temporal dynamics can provide essential insights for optimizing biomarker-guided surveillance. **Methods:** CEA and ctDNA (Signatera, Natera, Inc.) data at 12, 24, 36, 48, 72, and 96 weeks (wk) post-surgery from patients (pt) enrolled on the CIRCULATE-Japan GALAXY study were used to perform landmarked analyses. Disease-free survival (DFS) and overall survival (OS) were evaluated among pts who were event-free at each landmark. Hazard ratios (HRs) were estimated using Cox models adjusted for clinicopathological factors. Temporal trends in prognostic strength were assessed using weighted meta-regression across post-operative timepoints. **Results:** Of the 2,825 pts with CRC [84% stage I-III, 16% stage IV; median age 69 years (range 24-95)], 49% were female; 43% received adjuvant chemotherapy while 57% went directly to surveillance. At all evaluated landmarks, ctDNA- and CEA-positivity were associated with markedly higher risk of recurrence and death compared with ctDNA- and CEA-negativity, respectively. In DFS analyses, ctDNA outperformed CEA with substantially higher HRs at all landmarks (Table 1). The prognostic strength of ctDNA increased over time, with HRs increasing from 15.15 at 12 wks to 36.87 at 72 wks post-surgery and 32.31 through 96 wks. In contrast, CEA demonstrated modest and relatively stable DFS HRs across landmarks (range 2.04 to 3.43). Meta-regression analyses demonstrated a significant temporal strengthening of ctDNA's prognostic performance for DFS (β:0.011 per wk, p=0.004), whereas no significant temporal trend was observed for CEA (p=0.33). In OS analyses, ctDNA positivity conferred high mortality risk at all landmarks, with HRs ranging from 8.40 to 14.15 (Table 1). Despite increasing prognostic association of CEA with OS at later landmarks, its HRs were lower than those of ctDNA. **Conclusions:** ctDNA-positivity consistently outperforms CEA in predicting disease recurrence and OS. ctDNA provides strong risk stratification at early postoperative time points, and its prognostic accuracy continually improves during longitudinal surveillance, confirming its superior performance for early risk assessment and personalized serial disease monitoring during surveillance. Clinical trial information: UMIN000039205. Research Sponsor: None.

DFS and OS hazard ratios and ranges for ctDNA and CEA at all landmarks.

Landmark	ctDNA DFS	CEA DFS	ctDNA OS	CEA OS
12 wk	15.15***	2.68***	8.4***	3.65***
24 wk	18.4***	2.23***	12.74***	4.16***
36 wk	19.36***	2.04***	9.81***	5.41***
48 wk	23.95***	2.77***	12.26***	6.3***
72 wk	36.87***	3.43***	14.15***	8.72***
96 wk	32.31***	2.71*	8.45**	14.67***

*p<0.05, **p<0.001, ***p<0.0001.

3638 Poster Session

Neoadjuvant tislelizumab plus chemotherapy in MSS/pMMR high-risk locally advanced colon cancer: Updated analysis results from a phase 2 trial. First Author: Minglin Lin, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

Background: Patients with locally advanced colon cancer (LACC) have a poor prognosis, and those with N+ or T4 staging are prone to developing metastases. Only about 5% pathological complete response rates were observed in neoadjuvant chemotherapy. We conducted a single-arm, phase II trial to evaluate the efficacy and safety of immunotherapy combined with chemotherapy in locally advanced colon cancer. **Methods:** LACC patients clinically staged as T4 or N2 with histologically confirmed microsatellite stable/mismatch repair proficient (MSS/pMMR) type untreated colon adenocarcinoma are eligible for enrollment. Participants received 2-6 cycles of neoadjuvant therapy consisting of capecitabine and oxaliplatin (CAPOX) plus tislelizumab, followed by complete mesocolic excision. The primary endpoint was the pathological complete response (pCR) rate. This study was registered at ClinicalTrials.gov (NCT06124378). **Results:** A total of 61 patients were enrolled with a median age of 54 years (IQR 43–62). 35 (57%) of the recruited patients had a cT4 tumor and 47 (77%) of the patients had N2. All patients received neoadjuvant CAPOX plus tislelizumab, while three patients were excluded from activity analyses due to adverse events and the patient decision. Among the remaining 58 patients, 16 (28%) patients received 2 cycles, 39 (67%) patients completed 4 cycles, and 3 patients (5%) received 6 cycles prior to surgery. 14% patients achieved clinical complete response and the overall response rate was 91% based on clinical efficacy, with no cases of progressive disease observed. The regimen achieved a pathological complete response (pCR) rate of 41.4%, with all patients undergoing R0 resection. The major pathological response rate was 51.7% (95% CI 38.6 to 64.6). In subgroup analyses, patients with right-sided tumors exhibited higher pCR rates (16 [47%, 95% CI 30–65] of 34, compared to 8 [33%, 95% CI 17–54] of 24 for left-sided cases. However, no statistically significant differences were observed between the subgroups. Treatment-related adverse events of any grade occurred in 52 (85.2%) of 61 patients. The most common adverse events were peripheral sensory neurotoxicity (37 [61%] of 61) and decreased appetite (31 [51%]). Grade 3 drug-related serious adverse events occurred in 8 (13%) patients while no grade 4–5 adverse events occurred. **Conclusions:** This prospective trial demonstrates that neoadjuvant tislelizumab plus CAPOX provides a promising treatment strategy with encouraging antitumor activity and a manageable safety profile for MSS/pMMR locally advanced colon cancer. Clinical trial information: NCT06124378. Research Sponsor: None.

3639 **Poster Session**

Association of CT-based deep learning–derived consensus molecular subtypes with survival outcomes in locally advanced colon cancer: A secondary analysis of the phase III OPTICAL trial. First Author: Sifan Qi, Department of Medical Oncology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: The Consensus Molecular Subtypes (CMS) provide a robust framework for the biological stratification of colorectal cancer (CRC), but their clinical use is limited by the cost and complexity of transcriptomic profiling. We evaluated the prognostic and predictive utility of a non-invasive, CT-based deep learning model for CMS classification (CT-CMS) in patients with locally advanced colon cancer (LACC) enrolled in the OPTICAL trial. **Methods:** Patients from the OPTICAL trial with available baseline venous-phase contrast-enhanced CT images were included. A previously validated deep learning model was applied to predict CMS subtypes (CMS1-4). The association between CT-CMS and survival outcomes, including disease-free survival (DFS) and overall survival (OS), was assessed using multivariable Cox proportional hazards regression models adjusted for age, sex, TNM stage, and tumor location. **Results:** The study included 394 patients, with 189 patients in the neoadjuvant chemotherapy (NAC) group and 205 in the upfront surgery group. The median follow-up was 48.0 months. The distribution of CT-CMS subtypes was as follows: CMS1 (n=64, 16.2%), CMS2 (n=135, 34.5%), CMS3 (n=69, 17.5%), and CMS4 (n=126, 32.0%). In the total population, CMS3 showed the most favorable outcomes, with a 3-year OS rate of 96.1% (95% CI, 90.9%-100.0%) and a 3-year DFS rate of 87.9% (95% CI, 80.3%-96.2%). Multivariable analysis confirmed that CMS3 was independently associated with superior prognosis compared to CMS1 (adjusted hazard ratio [aHR] = 0.39, 95% CI 0.17-0.92, p = 0.030). In the NAC group, CMS was a significant independent prognostic factor for DFS (p = 0.044), with CMS3 (p = 0.027) and CMS2 (p = 0.046) showing significant improvement over CMS1. Notably, patients with CMS2 tumors exhibited significant survival benefits from neoadjuvant chemotherapy compared with upfront surgery, with improved OS (aHR = 0.08, 95% CI 0.01-0.62, p = 0.016, log-rank p = 0.002) and DFS (aHR = 0.45, 95% CI 0.20-0.99, p = 0.047). **Conclusions:** CT-based CMS3 was associated with favorable prognosis, while CMS2 identified patients were most likely to benefit from neoadjuvant chemotherapy. These findings support the clinical utility of CT-CMS as a non-invasive, pre-treatment tool for molecular stratification in LACC. Research Sponsor: National Science Fund for Distinguished Young Scholars; 82425045; Shenzhen Medical Research Funds; C2303002; General Research Fund; 14104223; Collaborative Research Fund; C4024-22GF; Research Impact Fund from the Research Grants Council of the Hong Kong Special Administrative Region; R4007-23.

All	3-year DFS rate	HR (95% CI)	P
CMS1	76.4% (66.2%-88.2%)	Reference	-
CMS2	79.8% (73.1%-87.1%)	0.67 (0.36-1.27)	0.219
CMS3	87.9% (80.3%-96.2%)	0.39 (0.17-0.92)	**0.030**
CMS4	78.2% (71.3%-85.8%)	0.89 (0.49-1.64)	0.715
NAC vs surgery (reference)*			
CMS1	70.3% vs 81.4%	1.20 (0.45-3.15)	0.717
CMS2	86.5% vs 72.8%	0.45 (0.20-0.99)	**0.047**
CMS3	90.2% vs 85.2%	0.36 (0.08-1.60)	0.180
CMS4	78.2% vs 78.3%	1.04 (0.50-2.17)	0.915

*For treatment comparisons, 3-year DFS rates are presented as NAC versus surgery.

3640 **Poster Session**

Neoadjuvant chemoradiotherapy with or without PD-1 blockade in pMMR/MSS low rectal cancer patients (CHOICE II): A multi-center, open-label, randomized controlled trial. First Author: Wei Zhang, Department of Colorectal Surgery, Changhai Hospital, Naval Medical University, Shanghai, China

Background: Neoadjuvant chemoradiotherapy (nCRT) combined with PD-1 blockade has shown great potential for improving the clinical complete response (cCR) rate in low rectal cancer patients in a previous exploratory clinical trial. This study aimed to further verify the efficacy and safety of nCRT with PD-1 blockade in patients with pMMR/MSS low rectal cancer. **Methods:** We conducted a prospective, multicenter, randomized, open-label trial (NCT05215379) with two parallel groups across 11 centers. Patients with confirmed $cT_{1-3a}N_{0-1}M_0$ rectal adenocarcinoma of the pMMR/-MSS type, with an inferior margin of 5 cm from the anal verge, were randomly assigned to either the intervention group, receiving 50 Gy (2 Gy/d*25d) radiotherapy, 4 cycles of PD-1 blockade (sintilimab) and 2 cycles of CAPOX, or the control group, receiving 50 Gy (2 Gy/d*25d) radiotherapy and 2 cycles of CAPOX. After completion of neoadjuvant treatment, patients were reassessed to determine clinical efficacy. If patients achieved cCR, the Watch-and-Wait (W&W) approach was performed. If near-cCR (ncCR) was achieved, patients were re-evaluated by a multidisciplinary team to determine whether W&W, local excision, or total mesorectal excision (TME) should be performed. Patients assessed with an incomplete clinical response (iCR) received TME. The primary endpoint was the cCR rate, and the key secondary endpoints included the organ preservation (W&W and local excision) rate, disease free survival (DFS), and overall survival (OS). **Results:** From July 2022 to December 2024, a total of 201 patients with low rectal cancer were screened at 11 medical centers and 180 patients were finally randomly assigned. A total of 169 patients were included in the primary analysis (85 patients in the intervention group and 84 in control group). The cCR rates were 36.5% in the intervention group compared to 17.9% in the control group (p=0.007). There were 48 and 51 patients who underwent surgery in the intervention and control groups, respectively, and the pathological complete response (pCR) rates were 25.0% and 15.7% (p=0.249). The overall complete response (cCR+pCR) rates were 50.6% and 27.4% (p=0.002) in the intervention and control groups. The overall occurrence rates of adverse events (AEs) were 72.9% in the intervention group compared to 66.3% in the control group (P>0.05), and the occurrence of severe AEs (Grade III or IV) was comparable between the two groups (7.1% vs 3.8%, p=0.34). Due to the limited follow-up duration, the DFS and OS data are immature. **Conclusion:** In this trial, the results showed that nCRT combined with sintilimab significantly improved the cCR rate in patients with pMMR/MSS low rectal cancer with a tolerable safety profile. Clinical trial information: NCT05215379. Research Sponsor: National Natural Science Foundation of China; 82473439, 82272705 and 82503486; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; the Shanghai "Rising Stars of Medical Talents" Youth Development Program of the Shanghai Municipal Health Commission, China; No.2024-70; the Naval Medical University "Deep Blue" Project Talent Program; the First Affiliated Hospital of Naval Medical University Special Project for Basic Medical Research, China; 2023QD003 and 2023PY04; the First Affiliated Hospital of Naval Medical University Special Project for Clinical Research, China; 2024LYA02; Shanghai Shenkang Hospital Development Center, Shanghai Clinical Cohort Project; SHDC2025CCS019; Shanghai Science and Technology Plan Project; 25SF1901500.

3642 **Poster Session**

The value of tumor deposits in prognosis evaluation and clinical stage optimization of colorectal cancer: A real-world population-based retrospective cohort study. First Author: Chang Wang, The First Hospital of Jilin University, Changchun, China

Background: The location and weight of tumor deposit (TD) in the TNM staging system may be seriously underestimated, which affects the accuracy of TNM staging in predicting prognosis. We conducted a study to further clarify the role of TD in predicting the prognosis, the weighting of TD, and the possible value of optimizing the TNM staging system of CRC. **Methods:** The subject was CRC patients diagnosed by postoperative pathology in our hospital from January 2013 to December 2021, including 2642 TD (+) and 1162 TD (-) patients. TD (-) patients were regarded as the control group according to category matching principle of the diagnosis, treatment and the period as TD (+) patients. Cox univariate and multivariate were analyzed. K-M curve was applied to analyze survival. **Results:** (1) The clinical and pathological characteristics are as follows: The TD positive rate was 25.3%. In stage I-III, more advanced tumor T and N-stage, primary sites in the left-sided colon or rectum, poorer histologic grade, and more nerve invasion and vascular infiltration (all $p<0.05$) were observed in TD (+) patients. In stage IV patients, TD (+) patients were more likely to have multiple metastases ($p<0.05$). (2) Patients with TD (+) had worse prognosis than patients with TD (-), with shorter DFS and OS in stage I-III (3-y DFS and OS rate, all $p<0.05$), with shorter PFS in stage IV (3-y PFS rate, $p<0.05$). The univariate and multivariate analysis showed that TD (+) was one of independent prognosis factors in CRC patients. And the prognosis shows a trend of getting worse as the number of TD increases. (3) The relationship between TD and N staging: Patients with TD (+), LN (-) had similar OS as patients with TD (-), LN (+) (3-y OS rate, p=0.418). Patients with TD (+), LN (-) had similar OS as patients with TD (-), N2 (3-y OS rate, p=0.695). Patients with TD (+), LN (-) had shorter OS than patients with N2a, TD (-) (3-y OS rate, p=0.029) and longer OS than patients with N2b, TD (-) (3-y OS rate, p=0.034). When TD and LN were counted together for N-staging, the OS between patients with new N2 and primary N2 was similar (3-y OS rate, p=0.382). (4) The relationship between TD and M staging: The survival of patients with TD more than 4 was similar to stage IV patients (2-y OS rate , p=0.061); when the number of LN more than 6 and TD (+) coexisted, OS was similar with stage IV patients (2-y OS rate, p=0.554). When TD and M were counted together for M-staging, the OS between patients with new M1 and primary M1 was similar (3-y OS rate: p=0.149). **Conclusions:** TD (+) patients are related with unfavorable prognostic clinical and pathological factors. TD was one independent prognosis factor in CRC patients. The location and weight of TD in the TNM staging system may be seriously underestimated. The prognostic accuracy of TNM staging may be improved when the weight of the presence and quantity of TD is increased. Clinical trial information: 2023-ks-143. Research Sponsor: None.

3643 **Poster Session**

Updated 5-year survival outcomes of short-course radiation followed by mFOLFOX-6 plus avelumab in locally advanced microsatellite-stable rectal adenocarcinoma: The Averectal phase II study. First Author: Ali Shamseddine, American University of Beirut Medical Center, Beirut, Lebanon

Background: Total neoadjuvant therapy (TNT) for microsatellite-stable (MSS) locally advanced rectal cancer consists of induction or consolidation chemotherapy combined with either long-course chemoradiation (LCCRT) or short-course radiation therapy (SCRT). While TNT has yielded variable outcomes across studies, it has consistently improved pathologic complete response (pCR) rates and paved the way for non-operative management strategies. However, the use of SCRT within TNT has been associated with higher rates of local recurrence. The integration of immunotherapy into total neoadjuvant therapy (TNT) improves outcomes in LARC, particularly pathologic complete response (pCR), which may translate into improvements in disease-free survival (DFS) and overall survival (OS), in addition to improvement in local recurrence rate (LRR) especially when used with SCRT, potentially through synergistic effects with radiotherapy. **Methods:** The Averectal trial is an investigator-initiated, open-label, single-arm, multicenter, phase II study including 44 patients. 40 patients with LARC completed treatment with SCRT (5 Gy x5 fractions) followed by 6 cycles of mFOLFOX-6 plus avelumab every 2 weeks, followed by TME. The primary outcome was pCR vs. historical control. Secondary outcomes were 3-year DFS, LRR and the association of the ImmunoScore (IS) with outcomes including pCR. **Results:** 15/40 (37.5 %) patients achieved pCR compared to 16 % in the historical control group with statistically significant p = 0.025, and 27/40 (67.5 %) had a major pathologic response. Patients who achieved pCR had a higher mean IS compared with those who did not (68 vs. 52, p = 0.049). With a median follow up of 72.8 months (range 15.4-97.1), the median OS and DFS were not reached. The mean OS and DFS were 85.3 months and 79 months respectively, and the 5-year OS and DFS were 81.9% and 74.6%. Only 2/40 patients had local recurrence, accounting for a LRR of 5%. In patients with high versus low IS, median OS was not reached in either group (p = 0.9), with mean OS of 79.3 months versus 84.7 months, respectively. Similarly, median DFS was not reached, although there was a trend towards improved DFS in the high IS group (p = 0.175), with mean DFS of 77.6 months versus 70.7 months for high and low IS, respectively. **Conclusions:** The addition of avelumab to TNT in patients with MSS LARC resulted in a statistically significant increase in pCR, notably among those with high IS, and was associated with continued improvement in survival outcomes at 5 years. Clinical trial information: NCT03503630. Research Sponsor: This study was financially supported by Merck Healthcare KGaA; CrossRef Funder ID: 10.13039/100009945.

3644 **Poster Session**

Immunotherapy-based total neoadjuvant therapy with or without short-course radiotherapy for locally advanced rectal cancer: Preliminary results of TORCH-iTNT. First Author: Yaqi Wang, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: In patients with proficient mismatch repair (pMMR) locally advanced rectal cancer (LARC), the integration of PD-1 inhibitor into total neoadjuvant chemoradiotherapy (iTNT) has demonstrated promising potential to enhance complete response (CR) rates and facilitate organ preservation. However, the combined use of radiotherapy and surgical intervention frequently leads to increased functional impairment relative to either modality administered independently. Concurrently, the combination of chemotherapy and PD-1 inhibitor has been shown to promote tumor downstaging, thereby enabling sphincter-preserving surgery while mitigating radiation-induced injury. This trial evaluates oncological efficacy and functional outcomes of two iTNT regimens: CAPOX plus PD-1 inhibitor with or without SCRT in neoadjuvant treatment of pMMR LARC patients. **Methods:** The TORCH-iTNT trial (NCT06281405) is a prospective, multicenter, randomized phase II study involving 192 patients with pMMR LARC (T3-4/N+M0). Participants were randomized into Group A (6 cycles of CAPOX plus toripalimab) or Group B (SCRT [25Gy/5Fx] followed by 6 cycles of CAPOX plus toripalimab). Patients achieving clinical complete response (cCR) were offered a watch-and-wait (W&W) strategy, while those without cCR were advised to undergo surgery. Group A patients with positive circumferential margins received adjuvant chemoradiotherapy. The primary endpoint was CR rate (pathological complete response [pCR] plus cCR). Secondary endpoints included organ preservation rate, anorectal function, adverse effects, and survival outcomes. **Results:** By December 31, 2025, 192 patients were enrolled, with 137 completing treatment (Group A: 65; Group B: 72). Baseline characteristics were balanced, with 97.1% (133/137) exhibiting at least one high-risk feature: lower tumor location ($\leq$5cm), cT4, cN2, MRF+, or EMVI+. In Group A, 5 patients achieved cCR and adopted W&W, compared to 22 in Group B. Of the 54 and 49 patients in Group A and B who underwent surgery, pCR was observed in 19 (35.2%) and 22 (44.9%) cases, respectively. Five non-cCR patients in Group A declined surgery or were still undergoing treatment. Disease progression occurred in one patient per group. The overall CR rates were 36.9% (24/65) in Group A and 61.1% (44/72) in Group B. The most frequent grade 3-4 toxicity was thrombocytopenia (Group A: 12.3%; Group B: 12.5%). **Conclusions:** This study is the first comparative analysis of two iTNT regimens in LARC. Unprecedentedly, neoadjuvant CAPOX plus PD-1 inhibitor achieved a promising CR rate in pMMR LARC, and this CR rate can be further enhanced with the addition of SCRT prior to immunochemotherapy. Further follow-up is necessary to assess long-term efficacy and functional endpoints. Clinical trial information: NCT06281405. Research Sponsor: National Natural Science Foundation of China (Grant No: 82473237).

3645 **Poster Session**

Impact of CAPOX combined with traditional Chinese medicine (TiaoPi AnChang Decoction) on disease-free survival in patients with stage III or high-risk stage II colorectal cancer: An updated report of a randomized, double-blind, placebo-controlled trial. First Author: Jincheng Zhang, Beijing University of Chinese Medicine, Beijing, China

Background: Colorectal cancer (CRC) at early and mid-stages has significantly different prognoses from advanced CRC. Preventing the progression to advanced disease after surgery is crucial for improving survival and reducing healthcare burden. Multiple retrospective studies have shown that Tiaopi Anchang Decoction (TPACD), an oral formula of edible botanical drugs, can reduce recurrence and metastasis risk in CRC when combined with CAPOX. However, the evidence is limited by confounding factors and reporting biases. This study aims to test the hypothesis that CAPOX combined with TPACD can further improve disease-free survival (DFS) in patients with stage III or high-risk stage II CRC. **Methods:** The study recruited patients from 4 departments of China-Japan Friendship Hospital. It enrolled stage III or high-risk stage II CRC patients undergoing CAPOX and randomly assigned patients in a 1:1 ratio to either the TPACD group (30 mL orally, twice daily) or the placebo group (matched placebo). The trial duration covered 4 chemotherapy cycles, during which CAPOX-induced adverse reactions, quality of life (QoL), safety, and survival outcomes were assessed. The primary endpoint was DFS, while the secondary endpoints included overall survival, the incidence of CAPOX-induced adverse reactions, and QoL score (EORTC QLQ-C30). Kaplan-Meier analysis and Cox proportional hazards regression model were used to evaluate the correlation between CAPOX combined with TPACD and DFS. **Results:** From December 2022 to September 2024, 496 patients were screened, and 108 were enrolled. The 108 patients were randomly assigned in a 1:1 ratio to the TPACD group or placebo group. 42% were female, the average age was 58 years, and 66% had stage III disease. The interim report has confirmed that TPACD is safe, significantly reduced CAPOX-induced adverse reactions, and improved QoL. Median follow-up time was 28 months, with 17 DFS events (4 TPACD, 13 placebo) and no deaths. Kaplan-Meier analysis estimated 2-year DFS rates of 93.3% for TPACD and 74.7% for placebo. Log-rank testing revealed a statistically significant difference between the two groups (χ^2 = 5.329, P = 0.021). CAPOX combined with TPACD significantly reduced the occurrence of DFS events (multivariable hazard ratio [HR] 0.23, 95% confidence interval [CI] 0.073-0.736, P= 0.01) and this effect was not influenced by age, sex, primary tumor site, or TNM stage ($P_{interaction} > 0.05$). **Conclusions:** For patients with stage III and high-risk stage II CRC, TPACD is a well-acceptable complementary therapy. The combination of CAPOX and TPACD not only reduces CAPOX-induced adverse reactions and improves QoL, but also further extends the DFS. Further disclosure of survival data could help optimize adjuvant chemotherapy regimens for CRC. Clinical trial information: ChiCTR2200065759. Research Sponsor: National High Level Hospital Clinical Research Funding.

3646 **Poster Session**

AI-derived tumor microenvironment features and recurrence risk in microsatellite-stable colon cancer after adjuvant chemotherapy. First Author: Changhee Park, Seoul National University Hospital, Jongno-Gu, NA, South Korea

Background: Despite adjuvant chemotherapy, a substantial number of patients with stage II–III microsatellite stable (MSS) colon cancer relapse. While clinicopathologic and circulating tumor DNA (ctDNA) analysis can be used for risk stratification, there is a need for further improvement in risk prediction. Here, we utilized artificial intelligence (AI) applied to hematoxylin and eosin (H&E) slides, which enables efficient and comprehensive assessment of tumor microenvironment (TME). **Methods:** We retrospectively analyzed TME of high-risk stage II and III colon cancer patients treated with surgery and adjuvant fluoropyrimidine and oxaliplatin chemotherapy. AI-based quantification of tumor area, stromal area, and TME cells (lymphocytes, fibroblasts, macrophages, and endothelial cells) was performed using Lunit SCOPE IO. We developed a generalized linear model with a backward elimination process integrating AI-derived TME features with conventional clinicopathologic variables (T stage, N stage, tumor differentiation, lymphatic invasion, venous invasion, and perineural invasion). The optimal cutoff for distinguishing between high-risk and low-risk patients for relapses was determined using the Youden index derived from the model's receiver operating characteristic curve. We evaluated how the model stratified the risk group in the training cohort and validated it in an independent cohort. **Results:** In the training cohort (n = 390), high stromal lymphocyte density (HR 0.42, 95% CI 0.26 – 0.68), high tumor-stromal ratio (HR 0.46, 95% CI 0.29 – 0.73), and low stromal area per fibroblast (HR 0.33, 95% CI 0.21 – 0.53) were associated with favorable DFS among the TME features. In the multivariate analysis, high stromal lymphocyte density (adj HR 0.57, 95% CI 0.35 – 0.95) and low stromal area per fibroblast (adj HR 0.58, 95% CI 0.33 – 0.99) showed significant associations with DFS independent of clinicopathological covariates. The final TME-integrated model, incorporating N stage, lymphatic invasion, stromal lymphocyte density, and stromal area per fibroblast, stratified patients into high- and low-risk groups with 3-year DFS rates of 72.3% and 93.8%, respectively (adjusted HR for high risk 3.29, 95% CI 1.98 – 5.46). The model identified high-risk patients irrespective of clinicopathological risk features. For example, high-risk status was associated with worse outcomes among patients with N2 disease (adjusted HR 6.57, 95% CI 1.58 – 27.34), and also among patients with N0 or N1 disease (adjusted HR 2.49, 95% CI 1.27 – 4.87). The model was validated in an external independent cohort (n = 260; adjusted HR for high-risk 3.68, 95% CI 1.60 – 8.48). **Conclusions:** TME-integrated model combining AI-derived TME features with clinicopathologic factors significantly improved recurrence risk stratification in MSS colon cancer receiving adjuvant chemotherapy. Research Sponsor: None.

3647 **Poster Session**

Single-cell profiling of the tumor microenvironment in pMMR/MSS rectal cancer treated with neoadjuvant PD-1 inhibitor combined with FOLFOXIRI and radiotherapy: Insights from the PANFORTE trial. First Author: Chi Zhou, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University, Guangzhou, China

Background: Programmed cell death-1 (PD-1) inhibitor-based combination therapies have emerged as a promising neoadjuvant strategy for locally advanced rectal cancer (LARC). However, the underlying tumor microenvironment (TME) dynamics during multimodal chemoimmunoradiotherapy remain incompletely understood. This study leveraged single-cell RNA sequencing to systematically map the TME remodeling induced by neoadjuvant PD-1 inhibitor combined with chemoradiotherapy in the PANFORTE trial (NCT06099951), aiming to identify cellular correlates of therapeutic response and resistance in pMMR/MSS rectal cancer. **Methods:** Pre- and post-treatment tumor samples from patients with pMMR/MSS rectal cancer enrolled in the PANFORTE trial and treated with neoadjuvant FOLFOXIRI, PD-1 inhibitor, and radiotherapy were subjected to single-cell RNA sequencing. Following stringent quality control, 227,447 high-quality cells from 50 samples were retained and annotated into seven major lineages. Cellular compositional changes across response groups were quantified using the observed-to-expected (Ro/e) index. Fibroblast subpopulations were identified via non-negative matrix factorization (NMF), and pseudotime trajectory analysis of myeloid cells was performed with Monocle 2. **Results:** Single-cell profiling revealed marked TME remodeling after neoadjuvant therapy. Complete responders (CR) showed significant stromal reduction, while non-responders (NCR) retained higher proportions of myeloid cells, endothelial cells, and fibroblasts. CR tumors exhibited enrichment of effector populations (NK cells, $CD8^+$ effector memory T cells), whereas NCR tumors expanded immunosuppressive subsets (regulatory T cells, naïve T cells). Fibroblast subclustering identified inflammatory cancer-associated fibroblasts (iCAFs) as enriched in NCR. Pseudotime analysis demonstrated that myeloid cells in CR differentiated toward M1-like states, while NCR samples were biased toward M2-like programs. **Conclusions:** This study delineates distinct TME landscapes underlying differential responses to neoadjuvant FOLFOXIRI, PD-1 inhibitor, and radiotherapy in pMMR/MSS rectal cancer. Responders are characterized by cytotoxic immune activation and stromal depletion, whereas non-responders maintain an immunosuppressive milieu rich in iCAFs and M2-like myeloid cells. These findings provide mechanistic insight into treatment resistance and highlight potential cellular targets for enhancing therapeutic efficacy. Clinical trial information: NCT06099951. Research Sponsor: None.

3648 **Poster Session**

Rates of metachronous colorectal cancer or secondary Lynch syndrome–related cancers in patients with non-metastatic colorectal cancer. First Author: Emily M. Russell, Labcorp (formerly Invitae Corp.), San Francisco, CA

Background: Lynch syndrome (LS) increases metachronous colorectal cancer (CRC) risk up to 5-fold, while extended resection surgery after initial CRC can reduce this risk. Prior work showed that pre-surgical germline genetic testing (GGT) was more likely to result in extended resections, especially for *MLH1/MSH2* carriers. We evaluated the rates of metachronous CRC following surgery, along with rates of other LS cancers following CRC diagnosis. **Methods:** GGT and insurance claims (Komodo Healthcare Map) data for adults with non-metastatic colon (CC) or rectal (RC) cancer and CRC surgery from 2015-25, ≥6 months of cancer-free claims pre-CRC diagnosis, ≥6 months of claims post-CRC surgery, and *EPCAM/MLH1/MSH2/MSH6/PMS2* GGT. Statistical tests compared metachronous CRC rates (new CRC ≥6 months post-surgery) following partial (partial/segmental colectomy or proctectomy) or extended (total colectomy or total proctocolectomy) resections by GGT result. Multivariable logistic regression modeled variables associated with metachronous CRC or other LS cancers. **Results:** Of 4,050 CRC patients (3,905 CC, 145 RC), 530 (13.1%) were LS-positive. 3,860 (95.3%) had partial (12.2% LS-positive) and 190 (4.7%) had extended resections (32.1% LS-positive). Post-surgery claims were available for a mean (standard deviation) of 47.7 (28.0) months. 251 (6.2%) patients with CRC had metachronous CRC post-surgery (6.1% partial vs. 8.9% extended resection, p=0.145). 282 (7.0%) patients with CRC were diagnosed with other LS cancers (54 [10.2%] LS-positive vs. 228 [6.5%] negative/variant of unknown significance (LS-negative), p=0.002). Patients with other LS cancers were diagnosed an average of 31.6 (23.9) months after initial CRC diagnosis (LS-positive: 29.0 [26.7], LS-negative: 32.2 [23.2]). The most common other LS cancer was prostate for men (80/1,822, 4.4%) and endometrial/uterine for women (55/2,228, 2.5%). Increased odds of metachronous CRC were associated with RC (compared to CC) (odds ratio [OR]: 5.1, 95% confidence interval [CI]: 3.3-8.0) and more months of available post-surgery claims (OR: 1.02, CI: 1.01-1.02). Increased odds of other LS cancers were associated with *MLH1/MSH2/EPCAM* carriers (compared to LS-negative) (OR: 2.0, CI: 1.3-3.1), older age (1.04, 1.03-1.05), male sex (1.6, 1.3-2.1), physician-reported Black race (1.6, 1.0-2.4) (compared to White), and more months of available post-surgery claims (1.02, 1.02-1.03). **Conclusions:** Patients with pathogenic variants in *MLH1/MSH2/EPCAM* had 2x higher odds of a second LS cancer diagnosis. 1 out of 10 patients with CRC and LS had a second LS cancer, and more than half (55.6%) of second diagnoses were within 2 years of initial CRC diagnosis. These findings highlight the importance of integrating genetic testing and comprehensive Lynch syndrome surveillance into patient care at the time of initial CRC diagnosis. Research Sponsor: None.

3649 **Poster Session**

TGF-β signaling alterations in bevacizumab-treated early-onset colorectal cancer: An artificial intelligence–enabled precision oncology study in diverse populations. First Author: Erika Ruiz-Garcia, Gastrointestinal Oncology Department & Translational Medicine Laboratory, Instituto Nacional de Cancerología, Mexico City, DF, Mexico

Background: The transforming growth factor–β (TGF-β) signaling pathway plays a complex, context-dependent role in colorectal cancer (CRC), functioning in tumor suppression, immune modulation, and metastatic progression. Its interaction with anti-angiogenic therapy remains poorly defined, particularly across age and ancestry groups. Early-onset CRC (EOCRC) may exhibit distinct TGF-β pathway biology. We investigated ancestry-, age-, and treatment-associated patterns of TGF-β signaling alterations and their prognostic relevance in bevacizumab-treated CRC using an artificial intelligence–enabled precision oncology framework. **Methods:** We performed a retrospective analysis of 2,717 CRC patients from publicly available datasets with integrated genomic, clinical, and treatment annotations. Eligible cases included colorectal adenocarcinoma with sequencing data and documented bevacizumab exposure. Patients were stratified by age (< 50 years [EOCRC] vs. ≥50 years [LOCRC]), ancestry (H/L vs. non-Hispanic White [NHW]), and treatment status. TGF-β pathway alterations, including mutations in core signaling components (e.g., TGFBR2), were analyzed as categorical variables. Differences in mutation frequencies were assessed using Fisher's exact test. Overall survival (OS) was evaluated using Kaplan–Meier methods and Cox proportional hazards models. Conversational AI agents facilitated reproducible cohort construction and multi-dimensional querying. Analyses were exploratory. **Results:** Marked ancestry-, age-, and treatment-specific differences in TGF-β alterations were observed. Among bevacizumab-unexposed EOCRC, H/L tumors demonstrated substantially higher TGF-β alteration frequencies compared with NHW tumors (31.9% vs. 0.2%, $p = 2 \times 10^{-16}$). In NHW EOCRC, bevacizumab exposure was associated with increased TGF-β alterations relative to unexposed tumors (25% vs. 0.2%, $p = 2 \times 10^{-16}$). Similarly, bevacizumab-treated NHW LOCRC exhibited higher TGF-β alteration frequencies than unexposed counterparts (58% vs. 15.4%, $p = 2.2 \times 10^{-16}$). Among bevacizumab-unexposed LOCRC, H/L tumors showed higher TGF-β alterations than NHW tumors (34.2% vs. 18.0%, $p = 2.41 \times 10^{-5}$). In NHW LOCRC, bevacizumab-exposed tumors had a lower frequency of TGFBR2 alterations compared with unexposed tumors (1.3% vs. 7.1%, p = 0.03). Survival analyses suggested that TGF-β alterations were associated with improved OS in bevacizumab-unexposed NHW LOCRC, with borderline statistical significance (p = 0.08). **Conclusions:** The enrichment of TGF-β alterations in specific bevacizumab-exposed and ancestry-defined subgroups highlights potential interactions between angiogenic therapy and TGF-β pathway biology. These findings highlight the importance of incorporating ancestry-aware frameworks to advance precision oncology. Research Sponsor: National Cancer Institute; U2CCA252971; National Cancer Institute; P30CA033572; National Cancer Institute; U54CA285116.

3650 **Poster Session**

Cost-effectiveness analysis of aspirin and structured exercise as adjuvant therapy in localized colorectal cancer. First Author: Malek B. Hannouf, Arthur J. E Child Comprehensive Cancer Centre, Calgary, AB, Canada

Background: The ALASCCA trial demonstrated that 160 mg of aspirin daily for 3 years reduced the risk of localized colorectal cancer recurrence in patients with PIK3CA exons 9/20 (group A) or PIK3R1/PTEN/other PIK3CA alterations (group B). The CHALLENGE trial demonstrated that increasing recreational aerobic activity above baseline through a 3-year structured exercise program reduces the risk of colon cancer recurrence. These interventions have not been adopted into Canadian clinical practice (CCP), and we evaluated the cost-effectiveness of strategies to implement them as adjuvant therapy for localized, operable colorectal cancer from the Canadian public healthcare perspective. **Methods:** We developed a decision model to project clinical and economic consequences of six strategies: (1) "CCP," defined as no exercise or aspirin interventions; (2) "Aspirin for group A PI3K alterations," defined as testing for group A PI3K alterations and treating positive patients with aspirin; (3) "Aspirin for group A/B PI3K alterations," defined as testing for group A/B PI3K alterations and treating positive patients with aspirin; (4) "Aspirin for all," defined as treating all patients with aspirin regardless of PI3K status; (5) "Structured exercise alone," defined as initiating all patients on a structured exercise program with no aspirin intervention; and (6) "Aspirin for group A/B PI3K alterations and structured exercise," defined as testing for group A/B PI3K alterations, treating positive patients with aspirin, and initiating all patients on a structured exercise program. The model was parameterized using survival data from the ALASCCA and CHALLENGE trials, and cost and utility data from Alberta, Canada, and Canadian sources. Costs are presented in 2025 Canadian dollars. Future costs and benefits were discounted at 1.5%. **Results:** Compared with the CCP, all interventional strategies were associated with greater QALY gains and lower per-person costs, resulting in overall cost savings (Table). The "aspirin for group A/B PI3K alterations and structured exercise" strategy emerged as the dominant intervention, yielding the highest QALYs gained and greatest cost savings per person. Implementing this strategy into CCP would avert disease recurrence in 940 patients per year, generate 2,625 total QALYs annually, and produce total budget savings of $399 million per year. **Conclusions:** The integration of PI3K group A/B–guided aspirin therapy with structured exercise as adjuvant treatment for localized colorectal cancer should be adopted into CCP, given its considerable societal benefit. Research Sponsor: None.

Strategy	Inc. QALY gained/ pers.	Cost saving/ pers.
CP	Ref	Ref
Aspirin for group A PI3K alterations	0.05	9,400
Aspirin for group A/B PI3K alterations	0.12	20,200
Aspirin for all	0.07	14,700
Structured exercise alone	0.13	23,700
Aspirin for group A/B PI3K alterations and structured exercise	0.22	33,700

3651 **Poster Session**

Efficacy and safety of tislelizumab as neoadjuvant therapy combined with MRD monitoring in locally advanced dMMR/MSI-H colon cancer: A prospective pilot study. First Author: Miaoqing Wu, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangzhou, China

Background: PD-1 blockade has demonstrated high efficacy in metastatic and neoadjuvant settings for dMMR/MSI-H colorectal cancer. This study aimed to evaluate the efficacy and safety profile of neoadjuvant tislelizumab monotherapy in locally advanced dMMR/MSI-H colon cancer patients, with integrated minimal residual disease (MRD) monitoring. **Methods:** Histologically confirmed locally advanced dMMR/MSI-H colon adenocarcinoma are eligible for enrollment. Participants received 4 cycles of neoadjuvant tislelizumab (200 mg IV Q3W) followed by clinical response assessment. Patients continued receiving 4 additional cycles or underwent radical surgery based on the multidisciplinary team (MDT) decision. Non-operative management (NOM) was a choice of cCR patients after 8 cycles of treatment. MRD status was assessed by a tumor-informed, bespoke ctDNA assay (HuaJianwei) at baseline, during and post-treatment. The primary endpoint was pCR rate. Secondary endpoints included cCR rate, MPR rate, DFS, NOM rate, biomarker exploration, and safety. **Results:** Forty patients were enrolled between November 2022 and May 2025 (median follow-up: 13.58 months) and one requested to withdraw from the study. Twenty-eight (71.8%) underwent surgery, including 8 patients who received less than 6 cycles of neoadjuvant therapy, 18 patients who completed 8 cycles, and 2 patients who received more than 8 cycles based on MDT decision. Of resected patients, 22 (78.6%) achieved pCR and 26 (92.9%) achieved MPR. Nine patients opted for NOM due to cCR, with an overall CR rate of 79.5%. Grade 3 irAEs occurred in 4 patients (10.3%), including pneumonitis (n=2), renal insufficiency (n=1), and stroke (n=1). No treatment-related deaths occurred. Baseline MRD testing was completed in 29 patients, 28 (96.6%) of whom were positive. Rapid clearance of MRD was observed in 48.3% (14/29) of patients after 1 cycle and 75.9% (22/29) of patients after 2 cycles. Only one patient (1/10) remained MRD-positive post-treatment due to pneumonitis-related therapy discontinuation. **Conclusions:** Neoadjuvant tislelizumab monotherapy confers favorable efficacy and a manageable safety profile in locally advanced dMMR/MSI-H colon cancer with high pCR rates and feasible NOM for cCR patients. MRD monitoring provides valuable, real-time assessment of treatment response to guide surgical and surveillance decisions. Longer follow-up is needed to confirm response durability, particularly in NOM patients. Clinical trial information: NCT06262581. Research Sponsor: None.

3652 **Poster Session**

Consensus molecular subtypes, mutational features, and circulating tumor DNA dynamics in colorectal cancer: A real-world clinico-genomic analysis. First Author: Imad Shureiqi, Division of Hematology and Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

Background: Consensus molecular subtypes (CMS) define biologically distinct colorectal cancer (CRC) groups with differences in tumor microenvironment, genomic features, and prognosis. While CMS classification is well established in tissue-based transcriptomic studies, its relationship with circulating tumor DNA (ctDNA) dynamics and molecular features in real-world clinical practice remains incompletely characterized. We evaluated CMS subtype distribution, mutational characteristics, and ctDNA detection patterns in a large real-world CRC cohort. **Methods:** Patients with CRC who underwent whole-transcriptome sequencing via Altera (Natera, Inc.) testing were identified from Natera's real-world clinico-genomic database. CMS subtype assignment was based on the whole-transcriptome sequencing, and then correlated with Signatera results, a personalized, tumor-informed ctDNA assay. In patients with stage II–III CRC, ctDNA positivity was assessed during the MRD window (1–10 weeks post-surgery) and during post-MRD surveillance (>10 weeks post-surgery). Overall survival (OS) was estimated using the mortality database (Veritas Data Research, Fact of Death Mortality Data Index). **Results:** Among 8,456 CRC cases with available molecular data, CMS distribution was 10% CMS1, 26% CMS2, 12% CMS3, 22% CMS4, and 29% inconclusive. While canonical anatomic patterns were recapitulated (CMS1 right-sided, CMS2 left-sided, CMS3 rectal), CMS4 tumors were enriched in advanced-stage disease. CMS1 demonstrated high MSI-H prevalence (53%), frequent BRAF V600E (35%) and KMT2D (44%) alterations, and enrichment of MMR deficiency and APOBEC and POLE mutational signatures. CMS2 tumors were almost exclusively microsatellite stable (99.7%) and enriched for APC (84%) and TP53 (80%) mutations, whereas CMS3 showed intermediate MSI-H prevalence (10%) with frequent APC (74%) and KRAS (61%) alterations. CMS4 tumors exhibited low MSI-H prevalence (2%) but frequent TP53 (60%) and APC (59%) mutations. Among patients with stage II–III CRC, ctDNA positivity during the early post-operative MRD window was not associated with CMS subtype. In contrast, during later surveillance, ctDNA positivity was more frequent in CMS4 tumors compared with CMS1–CMS2 (36.8% vs 28.1%). Among MRD-positives, CMS1 was associated with the shortest OS, whereas CMS2 demonstrated the longest OS. No difference in OS was noted in MRD-negative patients. **Conclusions:** In this large real-world cohort, CMS subtypes were recapitulated with expected clinicogenomic and mutational associations and demonstrated distinct ctDNA detection patterns during surveillance. Integration of CMS biology, mutational features, and longitudinal ctDNA dynamics provides insights into residual disease and recurrence risk beyond static tissue-based classification. Research Sponsor: None.

3653 **Poster Session**

Safety and efficacy of neoadjuvant chemotherapy (NAC) in older patients with locally advanced colon cancer (LACC): Results from FOxTROT 1 and the FOxTROT 2 safety cohort population. First Author: Janet Shirley Graham, Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom

Background: The FOxTROT1 (FT1; NCT00647530) trial demonstrated feasibility and efficacy of six weeks of NAC for LACC compared with upfront surgery. The currently recruiting FOxTROT2 trial (ISRCTN83842641) is testing this approach in older or frail patients. Outcomes in older patients with LACC are inferior; therefore, new treatment strategies are required. Here in these trials we analyse the safety and efficacy of NAC in this group and report the DFS in the older subgroup of FT1 PMMR patients. **Methods:** Data from FT1 and the planned FT2 safety pilot (n=150) were combined and analysed by treatment arm and by age category (</> 70). Pre-specified endpoints included NAC delivery and perioperative complication rates for FT1 and FT2; DFS and pathological response are reported for FT1 patients by MMR status. We will update safety data for this presentation. **Results:** In FT1 292/1052 (27.8%) of patients were aged over 70; the median age of FT2 safety cohort was 76 (range 70-85). There were no significant differences by age in NAC delivery or in rates of peri-operative complications. For patients over 70, combining FT1&2 data, exploring those who received NAC, 88.5% completed the course as planned and 37.7% received an upfront or subsequent dose modification. Rates of peri-operative complications combining FT1&2 were similar between patients receiving NAC or upfront surgery: anastomotic leak (3.4% vs 3.3%), complication requiring hospital stay (FT1 9.3% vs 14.6%) or further surgery (2.6% vs 5.0%), and post-operative death (0.9 % vs 1.7%). For patients over 70 in FT1 16.4% were dMMR and 83.6% were pMMR. In pMMR patients overall NAC improved 3-year DFS (81.2% vs 75.4% without a DFS event; HR 0.70[0.52–0.94],p=0.02) compared with upfront surgery; results were consistent in older patients (81.2% vs 71.4%; HR 0.59[0.35-1.02],p=0.06). **Conclusions:** NAC is safe and well-tolerated in older adults, with no increase in perioperative morbidity and preserved treatment delivery compared to rates in younger patients and when compared with upfront surgery. Promising efficacy in terms of 3-year DFS and pathological response were observed in older patients with pMMR tumors, consistent to those seen in younger patients. These data support the use of NAC in older patients with LACC and continued recruitment to FT2 to evaluate the long term impact. Clinical trial information: NCT00647530. Research Sponsor: None.

3655 **Poster Session**

Organ preservation and local excision for rectal cancer: Long-term oncologic outcomes. First Author: Avihai Moscovici, Lankenau Medical Center, Wynnewood, PA

Background: Organ preservation is a desired outcome for rectal cancer patients after neoadjuvant chemoradiotherapy. In patients where a complete response is in question, endoscopically assisted full-thickness local excision offers a great option. Long-term data with this approach is limited. We report our experience with transanal endoscopic microsurgery (TEM) status post chemotherapy. **Methods:** Between January 2005 and October 2019, from a prospectively maintained rectal cancer database, we identified all patients who underwent TEM for adenocarcinoma after neoadjuvant CRT. Demographic data as well as follow-up interval and oncologic outcomes were reviewed and analyzed. **Results:** Ninety-two patients who underwent TEM for rectal cancer were included. The mean age was 67 years (32–94), 66% were male, and the mean BMI was 29.3 kg/m² (19.1–43). ASA classifications were II in 38%, III in 51%, and IV in 5% of patients. The mean tumor size was 3.1 cm (1–6) and mean estimated blood loss (EBL) was 29 mL (0–500). Postoperative 30-day morbidity occurred in 6.5% of patients, with no mortalities. The mean follow-up was 57.5 months (0.4-194.5), during which 7.6% of patients developed local recurrence and 6.5% developed systemic metastases. Based on final pathology, 48 patients with a complete pathologic response (ypT0) had local recurrence and distant metastasis rates of 4% and 2%, respectively. In patients with stage I disease (n=35), local recurrence occurred in 11% and distant metastasis occurred in 9%. Stage II patients (n=7) experienced a 14% rate of local recurrence with no distant metastases. Among stage III patients (n=2), both local and distant failure occurred in 50% of cases. **Conclusions:** TEM after neoadjuvant CRT was associated with excellent oncologic outcomes in patients achieving complete pathologic response. Selected patients with favorable residual disease experienced acceptable recurrence rates, supporting TEM as a potential organ-preserving strategy in this subgroup. In contrast, higher pathologic stage was associated with substantially increased local and distant failure, highlighting the need for strict selection, pathology-driven decision-making, and close surveillance. Research Sponsor: None.

3656 **Poster Session**

Screening and trends: A Global Burden of Disease 2023 assessment of colorectal cancer mortality across G7 nations. First Author: Rana Uzair Ahmad, Trinity Health Livonia Hospital, Livonia, MI

Background: Historically, the adoption of screening techniques has led to a steady decline in colorectal carcinoma (CRC) mortality in high-income countries. However, recent epidemiological data points towards a potential saturation of screening benefits and a rising burden of early-onset disease. Using Global Burden of Disease (GBD) 2023 data, we were able to identify points of stagnation and trend reversals in CRC mortality rates for G7 nations and hypothesize a systemic screening saturation in the post-pandemic era. **Methods:** The Global Burden of Disease 2023 study was used to retrieve data that included age-standardized death rates (ASDR) for G7 nations (2000-2023). Trends were analyzed using the Joinpoint regression Program, Version 5.4.0.0. We employed a log-linear model to estimate Annual Percent Change (APC). Pairwise comparison tests assessed parallelism between national trajectories to identify statistically distinct trend patterns. **Results:** From 2000 to 2023, epidemiological data shows an overall decline in the age standardized death rates (ASDR) for colorectal carcinoma in the USA. The ASDR in 2000 was 18.54 (95% UI: 16.80-19.87) and in 2023 it decreased to 12.64 (AAPC: -1.66: 95% CI: -1.83 to -1.49). Upon further analysis, three individual trajectory phenotypes were detected across the G7. The USA and Canada displayed a stagnation phenotype, in which mortality rates plateaued in the more modern years after initial rapid declines. In USA 2018-2023 APC was -0.48 (95% CI: -1.03 to 0.08) and in Canada 2020-2023 APC was 0.26 (95% CI: -0.94 to 1.47). The UK, Japan and France exhibited a rather alarming reversal phenotype, where mortality rates significantly accelerated in recent years. In UK 2021-2023 APC was 2.87 (95% CI: 0.74 to 5.06) while Japan 2021-2023 APC was 2.68 (95% CI: 1.45 to 3.93) and France 2021-2023 APC was 2.56 (95% CI: -2.06 to 7.40). Italy, however, has maintained a sustained decline phenotype, which sharply contrasts with that of the aforementioned nations. In Italy 2003-2023 APC was -1.65 (95% CI: -1.74 to -1.56) with no evidence of saturation. Pairwise comparison confirmed that the USA trajectory was significantly non-parallel to Italy ($p < 0.05$). **Conclusions:** For the majority of G7 nations, the era of universal CRC mortality decline has come to an end. While the USA and Canada show halted progress, the UK, Japan and France show early signs of slope inversion. On the contrary, Italy's clear lead in maintenance of declining mortality suggests a policy-based limitation as opposed to unavoidable biological circumstances. Urgent implementation of revolutionized screening techniques and interventions, focusing on hard-to screen populations as well as early onset cohorts, are required to avert a global deterioration in CRC outcomes. Research Sponsor: None.

3657 **Poster Session**

Association of *FBXW7* mutation with prolonged survival in microsatellite instability–high colorectal cancer treated with immune checkpoint blockade. First Author: Margaret R. Pruitt, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Colorectal cancer (CRC) remains a major cause of cancer-related mortality. Biomarkers of response to novel therapies may improve treatment selection and outcomes. Microsatellite instability (MSI-H) is a predictor of response to immune checkpoint blockade (ICI); however, less than half of patients with MSI-H CRC have a durable response to ICI. *FBXW7* mutations (MT) are common in CRC but their prognostic significance in patients treated with ICI is not well studied. Here, we characterized *FBXW7*-MT in CRC and their association with ICI outcomes. **Methods:** A total of 29,446 CRC (MSS, n = 27,323; MSI-H, n = 2,123) samples were tested by next generation sequencing (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq; Caris Life Sciences, Phoenix, AZ). TMB was assessed by non-synonymous mutations/Mb (high ≥10). Immune cell proportions were estimated using WTS deconvolution (Quantiseq). Real-world median overall survival (mOS) data were derived from insurance claims, calculated from tissue collection or treatment (chemotherapy: CAPEOX, Capecitabine, FOLFIRI, FOLFIRINOX, Fluorouracil, Irinotecan, Oxaliplatin; ICI: Nivolumab, Pembrolizumab) initiation to last contact, and analyzed using Kaplan-Meier. Statistical significance was assessed by chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($q<0.05$). **Results:** *FBXW7*-MT was enriched in MSI-H (29.6% (n=608) vs 9.2% (n=3,025), $p<0.05$) compared to MSS tumors. Among MSI-H tumors, *FBXW7*-MT had higher median TMB (40 vs 37, $q<0.05$) and numerically higher TMB-high frequency (99.2% vs 97.9%, p=0.05) compared to *FBXW7*-WT. Analysis of inferred immune cells revealed that *FBXW7*-MT MSI-H CRC had lower median cell fraction (%) of M2 macrophages (2% vs 2.5%) compared to *FBXW7*-WT. In MSI-H CRC, *FBXW7*-MT patients had better mOS when treated with ICI (48.3 vs 34.2 months, HR 0.68, 95% CI 0.52 – 0.9, p=0.006) compared to *FBXW7*-WT, whereas there was no difference in mOS in MSI-H CRC treated with chemotherapy (HR 0.95, p = 0.67) compared to *FBXW7*-WT. *FBXW7*-MT was not associated with OS in MSS CRC. In MSI-H CRC, *R465C/H/L/S* (20.6%), *R505C/H/L/G* (7%) and *R479Q/G* (3.4%) were the most common *FBXW7* hotspot mutations. *R465C/H/L/S* had better mOS with ICI (HR 0.61, p=0.04) compared to *FBXW7*-WT. Multivariable Cox analysis adjusted for TMB and PD-L1 showed *FBXW7*-MT is an independent predictor of improved OS with ICI in MSI-H CRC (HR 0.69, 95% CI 0.53 – 0.9, p=0.007). **Conclusions:** This large study is the first to report a positive association with *FBXW7* mutation and OS in MSI-H CRC treated with PD1/PD-L1 blockade. While requiring validation in independent cohorts, our findings suggest that *FBXW7*-MT is a biomarker of response to ICI and that targeting *FBXW7* may be an effective way of augmenting the clinical activity of ICI in MSI-H CRC. Research Sponsor: Intramural Research Program of the National Institutes of Health (NIH).

3658 **Poster Session**

Clinicopathologic features of South African colorectal cancer patients by HIV status in a retrospective cohort study. First Author: Jacob Lee Dubner, Columbia University Medical Center, New York, NY

Background: Colorectal cancer (CRC) is increasing among people living with HIV. South Africa (SA) has the largest HIV-infected population in the world. Data characterizing the features of CRC among HIV patients in SA is limited. We compared the clinicopathologic features of CRC patients in SA by HIV-status. **Methods:** A retrospective cohort of CRC patients was identified using a database of histologically confirmed CRC patients seen at one of four referral hospitals in KwaZulu-Natal, SA between 2000 and 2024. Confirmed HIV-positive patients were randomly matched (1:2) with patients without HIV based on age at CRC diagnosis, year of CRC diagnosis, race, and tumor location. Additional clinical data was extracted through retrospective review of medical records. Chi-squared tests were used to compare features by HIV-status. **Results:** We identified 106 CRC patients with confirmed HIV-positive status and matched them with 155 CRC patients with confirmed HIV-negative status and 57 CRC patients with unknown HIV-status (assumed to be HIV-negative for analysis). At the time of CRC diagnosis, HIV-positive patients had an average duration of infection of 5.2 years and a mean baseline CD4 count of 451 cells/mm^3. 72.6% of HIV patients were on antiretroviral therapy. HIV-status was not associated with duration of symptoms prior to CRC diagnosis (cohort mean 9.6 months; p-value = 0.687). HIV-positive patients were more likely than HIV-negative patients to present with metastatic disease (40.6% vs 28.8%, p-value = 0.035) and to have poorly differentiated tumors (13.9% vs 4.5%, p-value = 0.011). HIV-status was not associated with the rate of curative-intent treatment initiation (62.1% of non-metastatic patients received stage-appropriate treatment; p-value = 0.199) or palliative-intent systemic therapy (81.7% of metastatic patients received systemic therapy; p-value = 0.105). **Conclusions:** In SA, CRC patients with HIV are more likely than patients without HIV to present with high grade tumors and metastatic disease. This suggests a more aggressive tumor biology in this population. A comparison of overall survival by HIV-status will be presented at ASCO 2026. Future studies will compare the CRC tumor microenvironment by HIV-status in a subset of patients. Research Sponsor: National Cancer Institute; 3K12CA279872-02S1.

Clinicopathologic features of colorectal cancer patients in South Africa by HIV-status (2000-2024).

	HIV-Positive (n = 106)	HIV-Negative (n = 212)	Total (n = 318)	p-value
Tumor Site				1.000
Colon	43 (40.6%)	86 (40.6%)	129 (40.6%)	
Rectal	63 (59.4%)	126 (59.4%)	189 (59.4%)	
Stage at Diagnosis				0.090
Early (I-IIa)	11 (10.4%)	32 (15.1%)	43 (13.5%)	
Locally Advanced (IIb-IIIc)	52 (49.1%)	119 (56.1%)	171 (53.8%)	
Metastatic (IVa-IVc)	43 (40.6%)	61 (28.8%)	104 (32.7%)	
Tumor Grade				0.040
Well Differentiated	2 (2.5%)	4 (2.6%)	6 (2.6%)	
Moderately Differentiated	66 (83.5%)	143 (92.9%)	209 (89.7%)	
Poorly Differentiated	11 (13.9%)	7 (4.5%)	18 (7.7%)	
Unknown	27	58	85	

3659 **Poster Session**

Evaluation of circulating tumor DNA (ctDNA) burden, detected mutations, and clinical outcomes in metastatic colorectal cancer (mCRC) using real-world data (RWD). First Author: Alicia Catania McDonald, Merck & Co., Inc., Rahway, NJ

Background: ctDNA is a promising prognostic biomarker in colorectal cancer; however, there is limited RWD on its prognostic value in mCRC. We leveraged RWD to assess pre-treatment (Tx) ctDNA burden and gene mutations, and evaluated the association between ctDNA burden and clinical outcomes in patients (pts) with mCRC. **Methods:** Pts with mCRC identified in the GuardantINFORM database who underwent Guardant 360 comprehensive genomic profiling between June 1, 2014 to June 30, 2023 were included. First metastatic diagnosis date was used as the index date. ctDNA burden (% max variant allele fraction ctDNA levels) was categorized as below limit of detection (no ctDNA), ≤ median value (low ctDNA), and > median value (high ctDNA). ctDNA burden and gene mutations/alterations detected prior to 1L systemic therapy were summarized. Associations with OS, time to next Tx (TTNT), and time to Tx discontinuation (TTD) were assessed using Cox proportional hazards models for the overall cohort and by microsatellite instability (MSI) status, stratified by 1L and 2L Tx. **Results:** There were 3273 pts with mCRC included (non-MSI-high [H], n = 2750; MSI-H, n = 100; missing, n = 423). Mean ctDNA burden was 19.9% overall, 20.7% in non-MSI-H, and 14.6% in MSI-H cohorts. Top 3 gene mutations were *TP53* (65.8% and 67.2%), *APC* (59.7% and 60.7%), and *KRAS* (40.6% and 41.2%) in the overall and non-MSI-H cohorts; and, *ARIDIA* (71.0%), *TP53* (67.0%), and *APC* (65.0%) in the MSI-H cohort. Top 3 specific variants were *EGFR* AMP (23.7% and 25.3%), *KRAS* G12D (11.3% and 11.4%), and *KRAS* G12V (8.2% and 8.5%) in the overall and non-MSI-H cohorts; and *BRAF V600E* (39.0%), *ARIDIA D1850fs* (22.0%), and *PIK3CA H1047R* (21.0%) in the MSI-H cohort. In the overall cohort, high ctDNA compared to low ctDNA was statistically significantly associated with shorter OS (HR [95% CI]: 1L, 1.63 [1.43-1.87]; 2L, 1.42 [1.19-1.70]) and TTNT (1L, 1.43 [1.27-1.60]; 2L, 1.39 [1.19-1.63]) after adjusting for confounders. Conversely, no ctDNA compared to low ctDNA was statistically significantly associated with longer OS (0.70 [0.53-0.91]) and TTNT (0.75 [0.58-0.97]) in the 1L setting after adjusting for confounders; these associations were also observed when stratified by MSI status. ctDNA burden was not statistically significantly associated with TTD in 1L regardless of MSI status. In 2L, high ctDNA was associated with shorter TTD compared to low ctDNA overall (1.19 [1.05-1.34]), with similar findings in the non-MSI-H cohort. **Conclusions:** High ctDNA burden prior to 1L and 2L therapy was associated with shorter OS and TTNT, suggesting a higher disease burden or more aggressive disease. The absence of detectable ctDNA was associated with improved survival and may identify pts with better prognosis or slower-growing tumors. These findings provide growing evidence for ctDNA as a potential prognostic biomarker in mCRC. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

3660 **Poster Session**

Epidemiology of early-onset colorectal cancer in the WHO Eastern Mediterranean Region: Regional and global comparisons. First Author: Fares A. Qtaishat, The University of Jordan, School of Medicine, Amman, Jordan

Background: Early onset colorectal cancer (EO-CRC) is increasing globally, yet studies from the WHO Eastern Mediterranean Region (EMRO) are limited. We quantified the burden, temporal trends, and future projections of EO-CRC in EMRO and compared patterns with regional and global estimates. **Methods:** We conducted a population based study using GLOBOCAN 2022 data. EO-CRC outcomes included age-standardized incidence rates (ASIRs), age-standardized mortality rates (ASMRs), and 1-, 3-, and 5-year prevalence per 100000 population. Age-specific analyses were conducted. Temporal trends were assessed using Estimated Annual Percentage Change (EAPC). Associations between Human Development Index (HDI) and EO-CRC outcomes were evaluated using Pearson correlation coefficients (r). **Results:** In 2022, EMRO recorded 53941 new CRC cases (ASIR = 8.9), including 15381 EO-CRC cases (ASIR = 2.5), and 29918 CRC deaths (ASMR = 5.1), including 6965 EO-CRC deaths (ASMR = 1.1). EO-CRC incidence was lowest among individuals aged 0–19 years (ASIR = 0.17), increased in those aged 20–34 years (ASIR = 1.9), and peaked among adults aged 35–49 years (ASIR = 8.4), who accounted for most EO-CRC cases and deaths. Marked inter-country heterogeneity was observed. Jordan had the highest EO-CRC incidence (ASIR = 4.2), followed by Libya (ASIR = 3.5) and Iran (ASIR = 3.3), while EO-CRC mortality was highest in Jordan (ASMR = 1.9), followed by Oman and Somalia (ASMR = 1.8 each). Five-year EO-CRC prevalence was highest in Saudi Arabia (14.7 per 100,000), Oman (13.5), and Iran (13.3), but remained below 3 per 100000 in Afghanistan and Somalia. Males exhibited higher EO-CRC incidence (ASIR = 2.6) and mortality (ASMR = 1.2) than females (ASIR = 2.4; ASMR = 1.1), although several countries demonstrated a higher female burden. Compared with other WHO regions, EMRO demonstrated one of the highest EO-CRC mortality rates globally (ASMR = 1.1), exceeding Europe (ASMR = 1.0), South-East Asia (ASMR = 0.68), and the Western Pacific (ASMR = 0.98), despite having lower overall CRC incidence. Temporal trend analyses revealed concerning increases in EO-CRC incidence, with significant rises in Israel (EAPC = +2.58%). EO-CRC mortality was inversely correlated with HDI ($r = -0.45$; $p = 0.034$), indicating a disproportionate mortality burden in lower HDI countries. Projections indicate that annual EO-CRC cases will increase from 15381 in 2022 to 24396 by 2050, and annual deaths from 6965 to 11005, underscoring a rapidly escalating regional burden. Incidence and mortality are projected to rise faster in females across EMRO by 2050. **Conclusions:** EO-CRC is a rapidly growing, inequitable burden in EMRO, with high mortality and marked inter-country differences. Its disproportionate impact on lower HDI countries and younger populations highlights the urgent need for targeted interventions, including early detection and awareness campaigns. Research Sponsor: None.

3661 **Poster Session**

Impact of concomitant GLP-1 receptor agonist use on overall survival and chemotherapy-related adverse events in colorectal cancer: A real-world pharmacoepidemiologic cohort study. First Author: Arunkumar Krishnan, Atrium Health Levine Cancer, Charlotte, NC

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed for diabetes and obesity and exert pleiotropic metabolic and anti-inflammatory effects. While prior studies have focused on their role in cancer prevention, limited data exist regarding their impact on cancer treatment outcomes. We evaluated the association between concomitant GLP-1 RA use and overall survival (OS) in patients with colorectal cancer (CRC) receiving standard first-line chemotherapy. **Methods:** Using the Blue Diamond Global Collaborative Network, adult patients with CRC initiating first-line FOLFOX or FOLFIRI between 2015 and 2024 were identified. Patients were classified as GLP-1 RA users if they received a GLP-1 RA (e.g., semaglutide, liraglutide, dulaglutide) within 90 days before or after chemotherapy initiation, and non-users otherwise. Cohorts were 1:1 propensity score matched for age, sex, BMI, diabetes status, line of therapy, comorbidities, and baseline corticosteroid use. The primary endpoint was OS. Kaplan–Meier methods and Cox proportional hazards models were used for analysis. **Results:** After matching, 4,824 patients were included (2,412 per cohort). Baseline characteristics were well balanced (mean age 61.8 years; 46% female; mean BMI 31.2 kg/m²; 58% with diabetes). At a median follow-up of 24.6 months, patients receiving concomitant GLP-1 RAs demonstrated significantly improved overall survival compared with non-users. Median OS was 28.4 months among GLP-1 RA users versus 23.6 months among non-users (log-rank $p<0.001$). GLP-1 RA use was independently associated with improved OS (HR 0.82, 95% CI 0.76–0.89). Regarding safety outcomes, GLP-1 RA users experienced a lower incidence of neutropenia (18.9% vs 23.7%; RR 0.80, $p=0.002$) and reduced chemotherapy-induced neuropathy (14.2% vs 18.6%; RR 0.76, $p=0.004$). Subgroup analyses demonstrated consistent OS benefit across chemotherapy backbone: FOLFOX (HR 0.81) and FOLFIRI (HR 0.84), and the most pronounced effect in patients with BMI ≥30 kg/m². Sensitivity analyses restricting sustained GLP-1 RA exposure (>6 months) yielded similar results. **Conclusions:** In this large real-world cohort of patients with colorectal cancer, concomitant GLP-1 receptor agonist use was associated with improved overall survival and reduced chemotherapy-related toxicity. These findings suggest a potential adjunctive therapeutic role for GLP-1 RAs during active cancer treatment, potentially mediated through metabolic stabilization, reduced systemic inflammation, and improved treatment tolerance. Prospective studies are warranted to confirm these observations. Research Sponsor: None.

3662 **Poster Session**

Impact of social determinants of health on women with early-onset colorectal cancer: A retrospective study. First Author: Elaine Ognjanovski, Henry Ford Warren, Warren, MI

Background: The incidence of early-onset colorectal cancer (EOCRC) in adults under age 50 has significantly increased. Women with EOCRC often present with nonspecific gastrointestinal symptoms, leading to delayed diagnosis and care. The impact of social determinants of health (SDOH), such as insurance status, income, and race, on cancer outcomes, disease presentation and hospitalization severity in young women with EOCRC is not well known. This study investigates how SDOH factors are associated with stage at presentation, emergency admission, metastatic burden and inpatient outcomes in women hospitalized with EOCRC. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (2018-2021) with hospitalized women aged 18–49 years, diagnosed with colorectal cancer, identified using ICD-10. SDOH variables included primary payer (private, Medicare, Medicaid, uninsured), ZIP-code median income, race, age and year of hospitalization. Primary outcomes included advanced stage at presentation, emergency admission, visceral metastatic involvement, disseminated metastasis, inpatient mortality, discharge disposition and length of stay (LOS). Survey-weighted multivariable logistic regression and linear regression models were performed, adjusting for age, race, insurance status and income quartile. **Results:** The most consistent predictors of delayed presentation and increased hospitalization severity were insurance status and race. Compared to private insurance, women with Medicare and Medicaid were 67% and 32% more likely to present with advanced stage ($p<0.001$), and over 3-fold and 2.5-fold more likely to present emergently ($p<0.001$). They were also significantly more likely to have visceral metastasis ($p<0.001$), have increased severity of illness ($p\leq0.023$), require non-home discharge ($p<0.001$), and require longer LOS (+0.8-0.9 days, $p<0.001$). Medicare was associated with higher inpatient mortality ($p=0.005$). Black race was independently associated with advanced stage, emergency presentation, visceral metastasis, inpatient mortality (all $p<0.001$), and longer LOS (+0.79 days, $p<0.001$). Younger age was associated with advanced stage and visceral metastasis ($p<0.001$). Higher ZIP-code income quartiles were associated with lower odds of emergency presentation ($p<0.001$), but not improved inpatient outcomes. Year of diagnosis was not significant across models. **Conclusions:** Among young women hospitalized with colorectal cancer, insurance status and race were strongly associated with advanced disease, emergency presentation, metastatic burden and greater hospitalization severity, independent of ZIP-code income. These disparities did not show improvement over time, highlighting system-level barriers. Targeted strategies to improve access and earlier recognition in high-risk populations of young women is required to improve oncologic outcomes. Research Sponsor: None.

3663 **Poster Session**

Shifting dietary drivers of colorectal cancer mortality in the United States: A 33-year Global Burden of Disease analysis. First Author: Jennifer Kate Beckerman, George Washington University School of Medicine and Health Sciences, Washington, DC

Background: Early-onset colorectal cancer (EOCRC; ages 15–49 years) mortality is increasing in the United States. However, temporal changes in diet-attributable risk factors contributing to EOCRC mortality remain poorly characterized. Using three decades of Global Burden of Disease (GBD) data, we examined shifts in dietary risk factors contributing to EOCRC mortality to identify emerging targets for primary prevention. **Methods:** We conducted a retrospective population-based analysis of U.S. estimates from the GBD 2023 study (1990–2023). Age-standardized death rates (ASDR), years of life lost (YLLs), and disability-adjusted life years (DALYs) attributable to major dietary risk factors (high processed meat, high red meat, low whole grain, low fiber, low calcium, and low milk intake) were assessed among EOCRC. Period-specific percent changes (1990–1999, 2000–2009, 2010–2019, 2020–2023), rank-order transitions, and sex-stratified patterns were examined. All estimates were derived using GBD cause-of-death ensemble modeling and include 95% uncertainty intervals. **Results:** In 1990, low whole grain intake was the leading diet-attributable risk factor for ASDR (0.44 per 100,000), followed by red meat (0.40) and processed meat (0.34). Although dietary inadequacy–related risks increased early (low whole grain DALYs +338.9% and YLLs +311.1% in 1990–1999), these burdens declined substantially after 2000. In contrast, processed meat consumption demonstrated persistent and increasingly dominant associations with mortality, with DALYs rising by +430.8%, +223.1%, +94.8%, and +15.9% across successive periods. By 2023, processed meat accounted for the highest ASDR (0.55), surpassing low whole grain (0.53) and red meat (0.49). Sex-stratified analyses showed processed meat emerged as the leading diet-attributable risk among males by 2010 and rose from third to second among females, narrowing the gap with low whole grain intake. **Conclusions:** Over 33 years, diet-attributable EOCRC mortality in the US has undergone a rank-order transition from dietary inadequacy toward processed meat consumption, particularly among males and increasingly among females. The persistence and dominance of processed meat-attributable burden highlight a critical, modifiable lifestyle risk factor and underscore an urgent opportunity for targeted, age- and sex-specific primary prevention strategies aligned with colorectal cancer prevention recommendations. Research Sponsor: None.

Age-standardized early-onset colorectal cancer death rates (per 100,000 population) attributable to dietary risk factors in the United States, 1990–2023.

	1990	2000	2010	2020	2023
Red Meat	0.40	0.48	0.47	0.50	0.49
Processed Meat	0.34	0.46	0.50	0.55	0.55
Low Fiber	0.02	0.03	0.02	0.02	0.02
Low grain	0.44	0.53	0.52	0.54	0.53
Low Ca	0.09	0.09	0.09	0.10	0.09
Low milk	0.26	0.31	0.31	0.29	0.28

3664 **Poster Session**

Association of pre-diagnosis primary care utilization with metastatic disease, treatment adherence, and mortality in colorectal cancer. First Author: Hieu Nguyen, Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, CA

Background: In addition to timely evaluation and screening in patients with colorectal cancer (CRC), routine primary care provider (PCP) engagement may improve CRC survival outcomes through earlier diagnosis and increased treatment adherence. We evaluated the association between pre-diagnostic PCP utilization and metastatic disease at diagnosis, cancer-specific mortality (CSM), and cancer treatment adherence. **Methods:** Using the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, we conducted a retrospective cohort study of adults aged 68-75 diagnosed with CRC between 2010-2017. PCP visits in the three years preceding diagnosis were categorized as none (0 visits), occasional (1–2), or annual (3). Multivariable logistic regression models evaluated associations between PCP use and metastatic CRC at diagnosis, as well as treatment adherence. Locally advanced (Stage III) treatment adherence was defined as curative therapy ≤1 year from diagnosis, and metastatic treatment adherence was defined as systemic therapy ≤6 months from diagnosis. A competing risk Cox proportional hazards model evaluated cancer-specific mortality (CSM), with non-cancer death as a competing event. **Results:** Of 18,604 patients with CRC, 12.9% had no prior PCP visits, 48.6% had occasional visits, and 38.5% had annual visits. Compared to patients with no pre-diagnostic PCP use, occasional and annual PCP visits were respectively associated with 43% and 57% lower odds ($p < 0.001$) of metastatic disease at diagnosis and 48% and 57% lower odds ($p < 0.001$) of CSM (Table 1). Among patients with locally advanced CRC, occasional and annual PCP use were associated with 64% and 150% higher odds of receiving curative treatment, respectively (Table 1). Similarly, occasional and annual PCP use in patients with metastatic CRC were associated with 2-fold and 3-fold higher odds, respectively, of receiving systemic treatment (Table 1). **Conclusions:** Primary care utilization prior to CRC diagnosis is significantly associated with lower odds of metastatic disease, lower risk of CSM, and higher odds of treatment adherence, with the highest effects observed with annual PCP utilization. Increasing PCP engagement is an essential strategy to improving outcomes in patients with CRC. Research Sponsor: None.

Multivariate estimates for the effect of pre-diagnostic primary care provider (PCP) utilization prior to cancer diagnosis.

	Metastatic Disease at Diagnosis OR, [95% CI], p-value	Cancer-Specific Mortality sHR, [95% CI], p-value	Received Treatment (Locally advanced CRC) OR, [95% CI], p-value	Received Treatment (Metastatic CRC) OR, [95% CI], p-value
1-2 PCP visits (Occasional)	0.57 [0.51-0.64], p < 0.001	0.52 [0.48-0.56], p < 0.001	2.64 [2.10-3.30], p < 0.001	2.08 [1.70-2.56], p < 0.001
3+ PCP visits(Annual)	0.43 [0.40-0.47], p < 0.001	0.43 [0.40-0.47], p < 0.001	3.50 [2.76-4.24], p < 0.001	2.90 [2.31-3.64], p < 0.001

3665 Poster Session

Bowel function after sphincter-preserving treatment with neoadjuvant therapy for low rectal cancer. First Author: Yuanshan Chen, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Neoadjuvant therapy (NAT) is important for locally advanced rectal cancer, including neoadjuvant chemoradiotherapy (nCRT) and neoadjuvant chemotherapy alone (nCT). Based on the tumor response, sphincter-preserving treatment such as low anterior resection (LAR) or watch and wait (WW) strategy can be implemented. The effects of these therapy combinations on functional outcomes for low rectal cancer remain unclear. **Methods:** We conducted a retrospective study recruiting patients who were treated at The Sixth Affiliated Hospital of Sun Yat-sen University between 2010 and 2023. Patients who underwent sphincter-preserving treatment after NAT for low rectal cancer with no distant metastasis were eligible. Low rectal cancer was defined as the tumor height no more than 5 cm from the anal verge. Patients with multiple primary carcinoma or familial adenomatous polyposis were excluded. The incidence of low anterior resection syndrome (LARS) was assessed using the LARS score. Oncological outcomes included overall survival (OS), disease-free survival (DFS), and stoma-free survival (SFS). Functional and oncological outcomes were evaluated based on Wilcoxon signed-rank test and Kaplan-Meier survival analysis. The difference of baseline characteristics in different treatment groups was analyzed using propensity scores with inverse probability treatment weighting (IPTW). **Results:** We enrolled 590 patients: 49 in nCRT+WW group, 181 in nCT+LAR group and 360 in nCRT+LAR group. Median follow-up was 3.4 years (IQR 2.8-4.4), 5 years (IQR 4.3-7.1) and 7.3 years (IQR 4.8-9.3), respectively. After IPTW, all baseline characteristics were similar in the three groups. 3-year OS was 91.0% (95% CI 81.6-100.0) for nCRT+WW group, 89.3% (84.5-94.5) for nCT+LAR group, 93.2% (90.7-95.7) for nCRT+LAR group. 3-year DFS was 62.5% (95% CI 45.6-85.7), 71.0% (64.1-78.6) and 77.5% (77.3-81.9), respectively. There was no differences in oncological outcomes. The incidence of major LARS in the three groups was 0% (0/18.6), 34.1% (35.2/103.2) and 45.9% (104.2/226.8). 3-year SFS without IPTW was 95.2% (20/21) for nCRT+WW, 91.0% (152/167) for nCT+LAR, and 79.7% (244/306) for nCRT+LAR. **Conclusions:** This retrospective study shows similar oncological outcomes in the three sphincter-preserving strategies for low rectal cancer, while nCRT+WW presented with superior bowel function. Functional outcomes are inversely correlated to the intensity of local therapy. Research Sponsor: None.

Outcomes for the three therapy combinations after IPTW.

	nCRT+WW	nCT+LAR	nCRT+LAR
Tumor Height, cm	2.71 (1.20)	3.74 (0.83)	3.60 (0.91)
Clinical Stage III, %	75.4	69.1	70.3
3-year OS, %	91.0	89.3	93.2
3-year DFS, %	62.5	71.0	77.5
Major LARS, %	0	34.1	45.9
Minor LARS, %	22.5	22.9	24.1
None LARS, %	77.5	43.0	30.0
3-year SFS*, %	95.2	91.0	79.7

*Without IPTW.

3666 Poster Session

Genomic profiling to define molecular drivers of colorectal neuroendocrine carcinoma subtypes. First Author: Jenny Xue, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Neuroendocrine carcinoma (NEC) is a rare and aggressive subtype of colorectal cancer (CRC), often arising in association with poorly differentiated adenocarcinoma. Two histologic subtypes, small cell NEC (SCNEC), and large cell NEC (LCNEC), have been described; however, how these subtypes differ, and whether they share molecular origins with the adenocarcinoma component in mixed adenocarcinoma and neuroendocrine carcinoma (MANEC) tumors, remain unclear. Better characterization of the genomic alterations driving NECs is needed to clarify disease biology and improve outcomes. **Methods:** We identified 125 patients with NEC of the colon and rectum who received care at Memorial Sloan Kettering Cancer Center. All patients underwent tumor profiling using the institutional targeted sequencing platform MSK-IMPACT. For 11 patients with MANEC, the adenocarcinoma and NEC components were sequenced separately. **Results:** Among 125 patients, 33 had SCNEC, 50 had LCNEC, and 42 had histologic features intermediate between SCNEC and LCNEC. 62% of patients presented with stage IV disease, and NEC was enriched at metastatic sites in MANEC cases. Clinical outcomes were poor across all groups, with a median survival of 11 months for stage IV patients (9.5m for SCNEC, 11m for LCNEC). SCNEC was more commonly observed in the rectum and genomically characterized by frequent *RB1* loss (70%), with a smaller subset harboring *PTEN* loss (24%). Notably, *TP53* mutations were identified in 58% of the cases, lower than the frequency observed in sporadic advanced CRC. In contrast, LCNEC was more often right sided, associated with an adenocarcinoma component and genomically enriched for *MYC* amplification (28%) and *BRAF* mutations (38%). We found that *MYC* amplification frequently occurred on extrachromosomal DNA, as confirmed by both FISH and shallow whole genome sequencing. Based on genomic alterations, 21of the 42 (50%) unclassified cases could be assigned a histologic subtype. A subset of NECs lacked known neuroendocrine associated genomic alterations and are being investigated further. In 11 MANEC cases with separately sequenced components, *RB1* loss and *MYC* amplification were restricted to the neuroendocrine component, supporting a causal role in neuroendocrine differentiation and clonal evolution from adenocarcinoma. Across the cohort, *PIK3CA* (6%) and *SMAD4* (9%) mutations were less frequent than expected and were absent in the NEC component of MANEC cases. DLL3 expression was evaluated in a small subset and was positive in some SCNECs but not in LCNEC. **Conclusions:** SCNEC and LCNEC represent clinically and genomically distinct subtypes of colorectal NEC. For NECs that cannot be classified based on histology alone, genomic profiling should be used to aid classification. Ongoing studies aim to validate our genomic findings above and to model the biology of NEC to identify more effective therapeutic strategies. Research Sponsor: U.S. National Institutes of Health; 5T32CA009207.

3667 Poster Session

Defining prostaglandin-driven dysregulation in *PIK3CA*-mutant colorectal cancers: A real-world multi-omic analysis. First Author: Andrew M. Gaya, Cromwell Hospital, London, United Kingdom

Background: *PIK3CA* mutations occur in a meaningful subset of colorectal cancers (CRC) and have been associated with improved clinical outcomes in patients receiving aspirin and celecoxib. *PIK3CA* activation has been linked to upregulation of *PTGS2* and downstream prostaglandin E2 signaling, promoting tumor-associated inflammation, angiogenesis, and immune suppression. Aspirin-mediated inhibition of prostaglandin synthesis may therefore counteract this biology in *PIK3CA*-mutant CRC, although the underlying molecular mechanisms remain incompletely characterized. **Methods:** A total of 823 CRC tumor samples underwent DNA-based next-generation sequencing, with matched whole-transcriptome sequencing (20,802 genes) available for 263 tumors. *PIK3CA* mutation prevalence, hotspot distribution, and co-mutation patterns were evaluated. A predefined prostaglandin–inflammation gene signature (*PTGS2, PTGES, PLA2G4A, IL6, STAT3, PTGER4, VEGFA, IDO1*) was assessed ($\log_2$ fold change >2). Coordinated signature activation was quantified. **Results:** *PIK3CA* mutations were detected in 12.8% (105/823) of CRCs and were more frequent in right than left-sided tumors (15.2% vs 11.1%). Among *PIK3CA*-mutant tumors, 25.7% were *KRAS/NRAS/BRAF* wild type (WT), while *KRAS* co-mutation predominated (65.7%); *NRAS* and *BRAF* co-mutations were rare (1.9% and 5.7%), as summarized in the Table. *ERBB2* alterations were rare in *PIK3CA*-mutant tumors (4.8%) and in *KRAS/NRAS/BRAF*-mutant tumors (3.2%,), while they were enriched in the *KRAS/NRAS/BRAF* WT subgroup (8.9%). Among *PIK3CA*-mutant tumors, key prostaglandin biosynthesis genes *PTGS2, PTGES*, and *PLA2G4A* were overexpressed in 8.8% (3/34), while downstream inflammatory and immune-modulatory genes including *IL6, STAT3, IDO1*, and *CD274* were overexpressed in 11.8% (4/34). Prostaglandin–inflammation signature activation was more frequent in *KRAS* WT than *KRAS*-co-mutant *PIK3CA* tumors (57.1% [4/7] vs 51.9% [14/27]). Among microsatellite-stable (MSS) tumors, 47.6% (10/21) showed signature activation. Tumors with combined *PIK3CA* mutation and prostaglandin pathway activation showed enrichment of inflammatory, angiogenic, and epithelial–mesenchymal transition–related programs. **Conclusions:** *PIK3CA*-mutant CRC represents a biologically distinct subset characterized by coordinated activation of prostaglandin-driven inflammatory and immune-modulatory pathways. These features provide a mechanistic rationale for the reported aspirin benefit in *PIK3CA*-mutant CRC and support integrated genomic–transcriptomic profiling to guide biomarker-driven therapeutic strategies. Research Sponsor: None.

Prevalence of *PIK3CA* alterations and co-mutations in CRC.

Biomarkers	Prevalence (%; n=105)
***PIK3CA* mutation (overall)**	12.8 (105/823)
E545K	21.9
E542K	19
H1047R	16.2
H1047L	6.7
Q546K	5.7
PIK3CA + KRAS	65.7
PIK3CA + NRAS	1.9
PIK3CA + BRAF	5.7
***PIK3CA + KRAS/NRAS/BRAF* WT**	25.7

3668 Poster Session

Divergent transcriptomic signatures and microenvironmental markers of *KRAS* and *BRAF* mutations in colorectal cancer: A multi-omics integrative analysis. First Author: Muzammil Shaikh, Nanavati Max Super Speciality Hospital, Mumbai, India

Background: *KRAS* and *BRAF* mutations are critical drivers in colorectal cancer (CRC), acting as key nodes in the MAPK signaling pathway. While their genomic prevalence is well-documented, the specific transcriptomic programs they trigger and how these programs differ between *KRAS* and *BRAF* variants remain a subject of intense translational interest. This study utilizes a multi-omics approach to define mutation-specific signatures that could inform personalized therapeutic strategies. **Methods:** We performed an integrated analysis of SNV/Indel data and gene expression profiles from 192 CRC patients. Patients were stratified into *BRAF*-mutant (n=20), *KRAS*-mutant (n=102), and MAPK-wild-type (WT, n=64) groups. Frequency was calculated as the percentage of unique samples mutated per gene. Differential expression analysis (DEA) was utilized to identify significant ($p < 0.05$) gene expression changes specific to each driver mutation. **Results:** The most frequently mutated genes were *TP53* (79.2%), *APC* (56.8%), and *KRAS* (53.1%). *BRAF* mutations were identified in 10.4% of the cohort. *KRAS*-mutant tumors exhibited a specific upregulation of *SPP1* (osteopontin) and *TGFBI*. These markers are associated with extracellular matrix remodeling and TGF-β signaling, suggesting that *KRAS* mutations may actively contribute to an immune-excluded tumor phenotype. *BRAF*-mutant CRC was characterized by a distinct signature involving *ABI3BP* upregulation and a profound downregulation of *CTNNBL1* ($p < 0.00001$). Additionally, a cluster of small nucleolar RNAs (*SNORA2B*, *SNORA9*) was significantly elevated, pointing toward altered ribosome biogenesis or non-coding RNA regulation unique to the *BRAF*-mutant subset. While both mutations activate the MAPK pathway, the downstream transcriptomic output is significantly divergent, with *KRAS* favoring myeloid-recruiting signals (*SPP1*) and *BRAF* favoring structural and RNA-processing alterations. **Conclusions:** Our multi-omics integration reveals that *KRAS* and *BRAF* mutations in CRC are not transcriptomically redundant. The discovery of *SPP1* as a *KRAS*-associated marker and *CTNNBL1* as a *BRAF*-linked marker provides novel avenues for targeted therapy and patient stratification. Specifically, *KRAS*-mutant patients might benefit from therapies targeting the *SPP1*-TGF-β axis in combination with standard care. Research Sponsor: None.

3669 **Poster Session**

Development and validation of a National Database–derived nomogram for predicting postoperative survival in colorectal cancer. First Author: Mohyeddine El Sayed, Medical University of South Carolina, Charleston, SC

Background: Prognosis after curative-intent surgery for colorectal cancer remains heterogeneous and incompletely explained by TNM staging alone. Existing prognostic tools often exclude important demographic, clinical, and biologic factors. Improved risk stratification is needed to support individualized postoperative prognostication. **Methods:** Using the National Cancer Database (NCDB), data from 88,696 patients diagnosed between 2018–2019 were used to develop and internally validate five prognostic models. All models were extensions of the MSK colon cancer nomogram and were fit using the full cohort. The full model incorporated all MSK predictors plus additional demographic, tumor, and treatment variables including perineural invasion and microsatellite instability status. Reduced models included MSK predictors and select variable subsets. Cox proportional hazards regression was used to estimate 5-year (5y) overall survival. Calibration was assessed by comparing deciles of predicted vs observed 5y Kaplan–Meier survival probabilities (expected-to-observed (E/O) ratios). Discrimination was evaluated using 5y area under the time-dependent receiver operating characteristic curve (AUC). Bias-corrected calibration curves and AUCs were generated to assess model generalizability to external populations. Model performance was compared directly with the MSK nomogram by comparing 5y AUCs calculated using a random sample of 1,000 NCDB-cohort patients. Category-free net reclassification improvement (NRI) was also calculated for patients with known vital status at 5y. **Results:** Calibration and discrimination were similar across all models. In the full model, E/O ratios demonstrated excellent calibration, with median E/O = 1.01 (range = 0.82-1.08). Full model discrimination was excellent with 5y AUC = 0.787 (95% CI, 0.782–0.793). Bias-corrected calibration curves and AUCs indicated stable performance supporting generalizability. In our 1,000 patient random sample, the full model 5y AUC was 0.822 (95% CI, 0.779–0.866), compared with 0.799 (95% CI, 0.753–0.844) for the MSK nomogram, with no statistically significant difference (p = 0.13). In our 1,000 patient NCDB sample, 397 patients had known 5y vital status (258 deaths, 139 alive, 603 censored prior to 5y) with the full model showing improved overall, event and nonevent discrimination compared with the MSK nomogram (overall 5y NRI = 0.35, event NRI = 0.12, and nonevent NRI = 0.24). **Conclusions:** We developed a postoperative survival nomogram for colorectal cancer that demonstrated good calibration and discrimination and meaningfully improved risk classification compared with the MSK model. Integration of additional routinely available variables enables more individualized postoperative prognostication. Research Sponsor: None.

3670 **Poster Session**

Molecular differences between early- and later-onset colorectal cancer in a Chilean cohort: A retrospective MSI and NGS-based analysis. First Author: Tamara Saumann, Facultad de Medicina Clinica Alemana Universidad del Desarrollo, Santiago, Chile

Background: The incidence of early-onset colorectal cancer (EOC) is increasing worldwide; however, molecular data from Latin American populations remain scarce. We compared molecular alterations, including microsatellite instability (MSI) status and selected next-generation sequencing (NGS)–derived gene alterations, between EOC and later-onset colorectal cancer (LOC) in a Chilean cohort. **Methods:** We conducted a retrospective analysis of patients diagnosed with colorectal cancer with MSI assessment and/or NGS testing available between March 2017 and September 2025 at a private hospital in Chile. MSI status was determined by immunohistochemistry and/or PCR. In-house NGS panels were analyzed. Clinical variables included age at diagnosis, sex, and tumor location. EOC was defined as diagnosis $<$50 years and LOC as $\geq$50 years. Molecular alterations were compared using Fisher exact test, reporting odds ratios (OR) with Benjamini–Hochberg false discovery rate (FDR) correction. **Results:** A total of 324 patients were included (EOC n=66; LOC n=258). Median age was 42.6 years in EOC and 66.5 years in LOC. Tumor sidedness was comparable between groups, with a predominance of left-sided tumors in both EOC (54.5%) and LOC (61.2%). MSI status was available in 310 patients; MSI-H prevalence was 10.8% in EOC and 15.1% in LOC (OR 0.68, 95% CI 0.29–1.59; p=0.43). NGS denominators varied by gene according to panel coverage. No individual gene showed statistically significant differences after FDR correction. Pathway-level trends were observed (Table 1). In the WNT pathway, APC alterations were more frequent in EOC (83.3% vs 52.2%; OR 4.60; p=0.059). In the MAPK pathway, KRAS alterations were numerically higher in LOC (55.2% vs 37.5%; OR 0.49; p=0.13), while BRAF alterations were more frequent in EOC (16.7% vs 8.3%; OR 2.20; p=0.29). In the PI3K pathway, PIK3CA (29.2% vs 15.6%; OR 2.22; p=0.12) and PTEN (8.3% vs 2.1%; OR 4.27; p=0.15) alterations trended higher in EOC. TP53 alterations were highly prevalent and similar across groups. **Conclusions:** In this Chilean cohort, EOC and LOC showed similar MSI prevalence and largely overlapping molecular profiles. Although no gene-level differences remained significant after multiple-testing correction, pathway-specific trends suggest increased WNT and PI3K alterations in EOC and higher MAPK signaling in LOC. These findings highlight the need for larger, uniformly sequenced studies in Latin American populations. Research Sponsor: None.

Selected pathway-specific molecular alterations.

Category	Gene	EOC n/N (%)	LOC n/N (%)	OR	p
WNT	APC	10/12 (83,3)	36/69 (52,2)	4,60	0,059
MAPK	KRAS	9/24 (37,5)	53/96 (55,2)	0,49	0,13
	BRAF	4/24 (16,7)	8/96 (8,3)	2,20	0,29
PI3K	PIK3CA	7/24 (29,2)	15/96 (15,6)	2,22	0,12
	PTEN	2/24 (8,3)	2/96 (2,1)	4,27	0,15
DDR	ATM	1/24 (4,2)	5/96 (5,2)	0,80	1,00
TGF-β	SMAD4	3/24 (12,5)	7/96 (7,3)	1,81	0,47
Cell cycle	TP53	15/24 (62,5)	62/96 (64,6)	0,91	1,00

3671 **Poster Session**

Use of KMT2 family mutations to define a distinct epithelial-high, stromal-depleted, and interferon-active gene expression state in colorectal cancer. First Author: Songwit Payapwattanawong, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The *KMT2A–D* (MLL1–4) family of H3K4 methyltransferases are critical epigenetic regulators of enhancer landscapes and cell identity. At least one of the genes is mutated in 20-25% of colorectal cancer. Their role in shaping the tumor microenvironment (TME) remains distinct from their established roles in leukemia, where they are better described. We tested whether *KMT2* mutations are associated with specific immune/stromal phenotypes that could inform therapeutic stratification. **Methods:** We analyzed a retrospective institutional CRC cohort using targeted NGS (n = 2,267; 565 *KMT2*-mutant [MUT], 1,702 wild-type [WT]) and a transcriptomic subset with matched RNA-seq (n = 353; 73 MUT, 280 WT) from primary and metastatic specimens. Differential expression (DESeq2) and pathway enrichment (Hallmark GSEA) compared MUT vs. WT, adjusting for batch and tissue site. VST-based module z-scores (cancer associated fibroblast [CAF]/stroma, epithelial, IFN response, cell-cycle) were computed. xCell, EPIC, CIBERSORTx, and ESTIMATE scores were analyzed by linear regression on z-scored outcomes (MUT vs WT) adjusted for batch and tissue site; Benjamini–Hochberg false discovery rate (FDR). β denotes the adjusted mean difference in standardized score (MUT–WT) in SD units. Overall survival was assessed by Cox proportional hazards models. **Results:** *KMT2*-MUT tumors demonstrate a unique tumor biology, with higher epithelial (β = 0.30, FDR = 0.011), IFN response (β = 0.24, FDR = 0.021), and cell-cycle (β = 0.24, FDR = 0.021) modules with lower CAF/stroma (β = $-$0.29, FDR = 0.011). Consistent with this, GSEA showed enrichment of IFN-α/γ and proliferation programs (MYC/E2F/G2M) and depletion of epithelial-mesenchymal transition (EMT), myogenesis, and apical junction pathways (FDR $<$ 0.05). TME composition tools demonstrated lower stromal content [lower CAFs (EPIC, β = $-$0.288, FDR = 0.102), lower fibroblasts/stroma scores (xCell, $\beta\approx-0.36/-0.35$, FDR = 0.079), and trend toward lower StromalScore (ESTIMATE, β = $-$0.24, FDR = 0.20)], and trends to higher Th2 (xCell, β = 0.40, FDR = 0.059) and NK cells (xCell, β = 0.38, FDR = 0.079). After adjusting for age, sex, ECOG performance status, primary tumor site, stage, RAS and *BRAF* mutation status, and MSI status, overall survival did not differ significantly between tumors with and without *KMT2* family mutations, although there was a trend toward improved outcomes (HR 0.85, 95% CI 0.70–1.00; p = 0.078). **Conclusions:** *KMT2* family mutations in CRC characterize a tumor subset with retained epithelial identity, active proliferation, and interferon signaling, but markedly reduced stromal infiltration and EMT programs. This distinct biology suggests *KMT2* loss may impede the acquisition of aggressive mesenchymal features, highlighting a potential biomarker for stromal-modulating or immune-based therapies. Research Sponsor: None.

TPS3672 **Poster Session**

Phase 2/3 trial of pumitamig (PD-L1 × VEGF-A bsAb) plus chemotherapy versus bevacizumab plus chemotherapy in previously untreated, unresectable, or metastatic colorectal cancer (ROSETTA CRC-203). First Author: Tiago Biachi de Castria, Moffitt Cancer Center, Tampa, FL

Background: Microsatellite-stable/mismatch repair-proficient metastatic colorectal cancer (mCRC) demonstrated limited benefit from immune checkpoint inhibition and is treated with first-line standard chemotherapy with/without biologic agents, such as anti-VEGF or anti-EGFR therapy. Pumitamig (BNT327/BMS986545) is an investigational bispecific antibody engineered to simultaneously target both PD-L1 and VEGF-A within the tumor and tumor microenvironment, a dual mechanism intended to enhance antitumor immunity and inhibit angiogenesis. Pumitamig plus chemotherapy has shown encouraging efficacy and manageable safety in patients (pts) with solid tumors (Cheng Y, et al. J Thorac Oncol 2025;20[suppl 1]. Abstract 301P; Schmid P, et al. SABCS 2025. Abstract PS1-13-25). This phase 2/3 trial aims to investigate the safety and efficacy of pumitamig and establish if it improves clinical outcomes when added to chemotherapy versus current standard of care in pts with previously untreated mCRC. **Methods:** ROSETTA CRC-203 is a global, randomized, blinded phase 2/3 study. Pts aged $\geq$ 18 years, with ECOG PS 0-1, with previously untreated, unresectable, or mCRC, no microsatellite instability-high/mismatch repair-deficient biomarkers, no BRAF V600E mutation and measurable disease per RECIST v1.1 are eligible. Key exclusion criteria include untreated central nervous system metastases, significant cardiovascular disease, recent or active malignancy, and prior systemic therapy with checkpoint inhibitors or chemotherapy. Pts in the Phase 2 dose-optimization part of the study will be randomized 1:1:1 to receive pumitamig low or pumitamig high dose + FOLFOX (Q2W)/FOLFIRI (Q2W) or bevacizumab + FOLFOX (Q2W)/FOLFIRI (Q2W). The primary endpoint is objective response rate (ORR) by RECIST v1.1 per investigator assessment, with progression-free survival (PFS), and duration of response (DOR) as secondary endpoints. In phase 3, eligible pts will be randomized 1:1 to receive pumitamig at the recommended phase 3 dose + FOLFOX (Q2W)/FOLFIRI (Q2W)/CAPOX (Q3W) or bevacizumab + FOLFOX (Q2W)/FOLFIRI (Q2W)/CAPOX (Q3W), until disease progression or unacceptable toxicity. The primary endpoint is PFS by RECIST v1.1 per blinded independent central review. Overall survival, ORR, and DOR are secondary endpoints. Safety will be monitored throughout the study according to CTCAE v5.0. Recruitment is ongoing. ClinicalTrials.gov ID: NCT07221357. Clinical trial information: NCT07221357. Research Sponsor: Bristol Myers Squibb.

TPS3673 **Poster Session**

Phase II trial of pembrolizumab in combination with odetiglucan for patients with metastatic colorectal adenocarcinoma with liver-predominant disease. First Author: William J. Chapin, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Background: Liver metastases are associated with resistance to immune checkpoint inhibitors in patients with mismatch repair proficient (MMRp) metastatic colorectal cancer (mCRC). (Beiter JCO 2025) Odetiglucan is a pathogen associated molecular pattern (PAMP) that modulates the tumor microenvironment and may enhance the activity of immune checkpoint inhibition. In syngeneic colon cancer mouse models, the combination of odetiglucan and PD-1/PD-L1 inhibition was associated with a larger proportion of tumor-free mice than either treatment alone. (Jonas Cancer Res. 2017; Fraser Cancer Res. 2016; Chan Frontiers Oncol. 2020) In a mouse model of pancreatic cancer liver metastases, odetiglucan reprogrammed liver-resident macrophages to stimulate tumor-specific T-cell responses, which was associated with reduced cancer cell proliferation and increased sensitivity to anti-PD-1 therapy. (Thomas Nat Commun. 2023) In a clinical trial of anti-PD-1 therapy plus odetiglucan in patients with triple negative breast cancer, tumor regression was observed in 56% of liver lesions classified as target lesions, with one patient experiencing complete regression of both target liver lesions, which remained undetectable after more than 70 weeks of treatment. (Stopeck J Immun. 2025). **Methods:** We are performing a single-center, investigator-initiated, single-arm phase II clinical trial with a Simon two-stage mini-max design of the combination of pembrolizumab with odetiglucan in patients with liver-predominant, MMRp mCRC who have experienced disease progression on standard therapies (3L+ setting). Treatment consists of intravenous infusion of odetiglucan (4mg/kg) and pembrolizumab on day 1 of a 21-day cycle. Patients with prior exposure to immunotherapy or odetiglucan, peritoneal metastases, symptomatic lung or bony metastases, autoimmune conditions requiring systemic immunosuppression, or a history of pneumonitis are excluded. The primary endpoint of the study is objective response by RECIST 1.1. The null hypothesis that the true response rate is 6% will be tested against a one-sided alternative. In the first stage of the study, 13 patients will be accrued and if there are no partial or complete responses, then the study will be stopped for futility. Otherwise, 14 additional patients will be accrued to a total of 27 patients. If four or more responses are observed in 27 patients, then the null hypothesis will be rejected. As of 1/2026, four patients have been enrolled and started study treatment. The study includes pre-treatment and on-treatment research biopsies and longitudinal research blood collection for immune pharmacodynamic profiling to investigate mechanisms of treatment response and resistance. Clinical trial information: NCT07082439. Research Sponsor: Merck.

TPS3674 **Poster Session**

A phase Ib/III randomized double-blinded placebo-controlled study of suvemcitug combined with trifluridine/tipiracil for refractory metastatic colorectal cancer. First Author: Ying Yuan, The Second Affiliated Hospital, Zhejiang University School of Medicine, Department of Medical Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, Hangzhou, Zhejiang, China

Background: Colorectal cancer (CRC) is a leading cause of cancer-related death worldwide. For patients with metastatic CRC (mCRC) that has progressed on standard chemotherapies, available treatments offer limited benefit. Notably, the phase III SUNLIGHT trial demonstrated the efficacy and safety of trifluridine/tipiracil (FTD/TPI) in combination with bevacizumab in refractory mCRC. Suvemcitug is a new-generation recombinant humanized anti-VEGF rabbit monoclonal antibody. In the previous clinical trials, suvemcitug demonstrated its favorable safety profile and efficacy signals as a single agent or in combination with chemotherapy for the treatment of mCRC. This study aims to assess the efficacy and safety of the combination of suvemcitug and FTD/TPI in patients with refractory mCRC. **Methods:** This phase Ib/III, randomized, double-blinded, placebo-controlled, multi-cohort study (NCT07361003) consists of two parts, Part 1 (phase Ib) and Part 2 (phase III). Estimated total enrollment is approximately 464 participants: 30 for Part 1 and 434 for Part 2. Patients with mCRC are eligible for participation if they have received chemotherapy based on fluoropyrimidine, oxaliplatin and irinotecan, and have either previously received or are unsuitable for anti-VEGF therapy and anti-EGFR therapy (if RAS wild-type). Part 1: Phase Ib: Participants will be enrolled to receive suvemcitug combined with FTD/TPI. The dose of suvemcitug is 1.5 mg/kg administrated intravenously every two weeks. The primary endpoint is safety and tolerability of suvemcitug. The secondary endpoints include pharmacokinetic (PK) profile of suvemcitug; the incidence, duration, and titer of anti-drug antibodies (ADA); as well as objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Part 2: Phase III: Part 2 is designed as a Phase III to further evaluate the antitumor activity of suvemcitug in combination with FTD/TPI in refractory mCRC. Eligible participants will be randomized (1:1 ratio) to receive FTD/TPI in combination with suvemcitug or matching placebo at the dose identified in Part 1. Stratification criteria include primary tumor location, prior bevacizumab exposure, and time from initial metastasis to enrollment. The primary endpoint is OS. The secondary endpoints include PFS, ORR, DoR, DCR, safety, quality of life, PK and immunogenicity (ADA incidence, titer, duration). The exploratory endpoints are correlations among PK, pharmacodynamics, safety and clinical efficacy. Study treatment will continue until progressive disease, unacceptable toxicity, withdrawal of consent, or the investigator's decision to discontinue. Clinical trial information: NCT07361003. Research Sponsor: None.

TPS3675 **Poster Session**

Symbiotic-GI-03: A randomized, double-blind, phase 3 study of first-line PF-08634404, a PD-1/VEGF bispecific antibody, in combination with mFOLFOX6 in patients with metastatic colorectal cancer (mCRC). First Author: Cathy Eng, Vanderbilt Ingram Cancer Center, Nashville, TN

Background: Multi-agent chemotherapy regimens (eg, mFOLFOX6) ± anti-vascular endothelial growth factor (VEGF) or anti-epidermal growth factor regimens are currently the standard of care for patients (pts) with mCRC without targetable mutations. However, the 5-year survival rate remains low at approximately 16% (SEER, 2025). The addition of biological therapies (eg, bevacizumab [bev], an anti-VEGF monoclonal antibody) to immune checkpoint inhibitors (ICIs) has demonstrated a synergistic antitumor effect in solid tumors. However, ICI monotherapy has limited activity in mismatch repair proficient (pMMR)/microsatellite stable (MSS) mCRC. Simultaneous bispecific targeting of programmed death 1 (PD-1) and VEGF in conjunction with cytotoxic chemotherapy has the potential to enhance antitumor activity. PF-08634404 is a fully human immunoglobulin G4 (IgG4) bispecific antibody targeting PD-1 and VEGF. A phase 2 study of PF-08634404 with XELOX or mFOLFOX6 demonstrated promising antitumor activity with a manageable safety profile in first-line (1L) mCRC (Xu X, ESMO 2025; Abstract 796P). **Methods:** Symbiotic-GI-03 (NCT07222800) is an ongoing, double-blind, randomized, phase 3 study evaluating the efficacy and safety of 1L PF-08634404 + mFOLFOX6 vs bev + mFOLFOX6. Inclusion criteria are age ≥18 y; mCRC with measurable disease per RECIST 1.1; no prior systemic therapy for metastatic disease; ECOG PS 0 or 1; and adequate hematologic, hepatic, and renal function. Pts with BRAF V600E-mutant or mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) CRC, active central nervous system metastases, or clinically significant risk of hemorrhage/fistula will be excluded. Approximately 800 pts will be randomized 1:1 to receive PF-08634404 + mFOLFOX6 or bev + mFOLFOX6 until disease progression, unacceptable toxicity, withdrawal of consent, or death. Randomization will be stratified by region (North America, Europe, or rest of world), RAS status (mutant or wildtype), and presence of liver metastasis (yes or no). The dual primary endpoints are progression-free survival (PFS) by blinded independent central review and overall survival; for each, a stratified log-rank test will be used to compare arms. Hazard ratios with corresponding 2-sided 95% CIs will be estimated using a stratified Cox proportional hazards model, and medians will be estimated using the Kaplan-Meier method with corresponding 2-sided 95% CIs calculated using the log(-log) method. Secondary endpoints include PFS by investigator, objective response rate, duration of response, PFS after next-line therapy, safety/tolerability, pharmacokinetics, immunogenicity, and patient-reported outcomes. Enrollment began in December 2025. Clinical trial information: NCT07222800. Research Sponsor: This study was sponsored by Pfizer. Medical writing support was provided Eleanor Porteous, MSc, and Akshaya Srinivasan, PhD, of Nucleus Global, an Inizio Company, and was funded by Pfizer.

TPS3676 **Poster Session**

The CO.33/BATTMAN trial: A phase 3 randomized study of botensilimab + balstilimab versus best supportive care in chemorefractory unresectable colorectal adenocarcinoma that is not dMMR/MSI-H. First Author: Jonathan M. Loree, BCCA - Vancouver Cancer Centre, University of British Columbia, Vancouver, BC, Canada

Background: Despite significant progress and newly approved agents, metastatic colorectal cancer (mCRC) has limited prognosis after progressing on standard cytotoxic chemotherapies. Many patients remain well enough for treatment at the time when their cancer is refractory to all available therapy, creating a significant unmet need. Once refractory, patient management with best supportive care (BSC) results in a median overall survival (OS) of 4–6 months. To date, immune checkpoint inhibitors (ICIs) have shown limited activity in mCRC that is not mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H). Prior data from the CCTG CO.26 randomized phase 2 trial demonstrated doublet ICI with durvalumab + tremelimumab improved OS in refractory mCRC; however, a phase 3 trial was not undertaken. Botensilimab (BOT) is an Fc-enhanced multifunctional anti–CTLA-4 antibody designed to increase efficacy in poorly immunogenic cancers. The combination of BOT with the anti–PD-1 antibody balstilimab (BAL) has shown impressive objective response rates (ORRs), durations of response (DOR), and survival in heavily treated non–MSI-H/dMMR mCRC across phase 1 and 2 studies. The CO.33/BATTMAN trial will evaluate BOT + BAL + BSC versus BSC alone in patients with refractory mCRC that is not MSI-H/dMMR. **Methods:** BATTMAN (NCT07152821) is an international multi-centre, open-label randomized phase 3 trial that will be conducted in Canada (CCTG), Australia/New Zealand (AGITG) and France (Unicancer). Eligible patients will be ≥18 years old, have received and progressed on or been intolerant of all available therapies, have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1, have RECIST 1.1 measurable/evaluable disease, have a life expectancy of ≥12 weeks, and have adequate end organ function without concurrent illness contraindicating ICI. Exclusion criteria include: prior organ transplant or primary immunodeficiency, ongoing use of non-physiologic corticosteroid dosing, autoimmune disorders requiring ongoing management, and prior ICI exposure. The trial's statistical plan will ascertain efficacy of BOT and BAL in all comers, as well as key subgroups based on the presence or absence of liver metastases. A planned 834 patients will be randomized 1:1 to BOT (75 mg IV every 6 weeks up to 4 doses) + BAL (450 mg IV every 3 weeks until progression) + BSC or BSC alone, with stratification for region of recruitment, ECOG PS, and presence of liver metastases. The primary endpoint is OS, with secondary endpoints including progression-free survival, ORR, clinical benefit rate, quality of life, safety, and toxicity, with correlative studies and economic evaluations planned. Support for this study is provided by: The Canadian Cancer Society and Agenus Inc. Clinical trial information: NCT07152821. Research Sponsor: Canadian Cancer Society; Agenus.

TPS3677 **Poster Session**

A phase II exploratory study of iparomlimab and tuvonralimab (QL1706) combined with bevacizumab in patients with locally advanced or metastatic MSI-H/dMMR colorectal cancer. First Author: Jun Wang, Department of Oncology, The First Affiliated Hospital of Shandong First Medical University, Jinan, China

Background: Microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) colorectal cancer (CRC) is highly responsive to immune checkpoint inhibitors (ICIs). PD-1 monotherapy or PD-1/CTLA-4 dual blockade are standard options for locally advanced or metastatic disease, but a significant proportion of patients still show no response to these regimens. Evidence suggests that vascular endothelial growth factor (VEGF) signaling mediates an immunosuppressive tumor microenvironment (TME). Combining anti-VEGF agents with ICIs may potentially normalize the inhibitory TME, and thereby could enhance anti-tumor immunity and improve response rates in this population. QL1706 is a novel bifunctional antibody combination targeting PD-1 (iparomlimab) and CTLA-4 (tuvonralimab). This Phase II exploratory study aims to investigate the efficacy and safety of QL1706 in combination with anti-VEGF agent bevacizumab in locally advanced or metastatic CRC patients with MSI-H/dMMR. **Methods:** This single-arm, open-label, multicenter, Phase II exploratory study is designed to evaluate the efficacy and safety of QL1706 plus bevacizumab in patients with MSI-H/dMMR advanced CRC. Eligible patients are adults aged 18 to 80 years with histologically confirmed locally advanced or metastatic CRC and who have an MSI-H/dMMR status via immunohistochemistry or polymerase chain reaction. Key inclusion criteria include at least one measurable target lesion per RECIST v1.1, an ECOG Performance Status of 0-1, and no prior immunotherapy for advanced disease. The systemic regimen consists of QL1706 (5 mg/kg) and bevacizumab (7.5 mg/kg) administered intravenously every 3 weeks (Q3W). Treatment continues until disease progression, unacceptable toxicity, or a maximum of 2 years. The primary endpoint is the objective response rate (ORR) assessed by investigators per RECIST v1.1. Secondary endpoints include disease control rate, duration of response, progression-free survival, overall survival, and landmark survival rates at 6, 12, and 24 months. Safety is monitored via NCI CTCAE v5.0. Efficacy assessments, including chest CT and enhanced abdominal/pelvic CT/MRI, are performed every 12 weeks. Statistical power is based on an estimated ORR of 80%; with a 95% confidence interval width of 35%, a total of 22 subjects are required (supplemented by a Simon's two-stage design for the broader cohort if applicable). The study has received ethics committee approval, and patient enrollment is currently ongoing. Clinical trial information: NCT07009145. Research Sponsor: None.

TPS3678 **Poster Session**

A phase 1, first-in-human (FIH), dose-escalation and dose-optimization study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of CBI-1214 T-cell engager in participants with advanced or metastatic microsatellite-stable (MSS)/microsatellite instability–low (MSI-L) colorectal cancer (CRC). First Author: Alexander I. Spira, NEXT Oncology – Virginia, Fairfax, VA

Background: Advanced and metastatic colorectal cancer (CRC) remains an area of significant unmet clinical need, particularly for patients with MSS/MSI-L tumors. In recent years, there have been several advancements in the treatment of solid tumors with T cell engagers. Our ATLAS scRNA-seq based discovery platform identified LY6G6D as a highly-specific tumor-associated antigen in advanced and metastatic CRC. CBI-1214, a CD3 bispecific T cell engager targeting LY6G6D with potent in vitro and in vivo activity even at low LY6G6D expression levels of ~300 copies/cell (*Yigit B et al, AACR 2025*), is being developed for the treatment of patients with advanced or metastatic MSS/MSI-L CRC. **Methods:** This ongoing, open-label FIH study (CBI-1214-001) is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of CBI-1214 and to determine the maximum tolerated dose (MTD) and/or optimal biological dose (OBD) in participants with advanced or metastatic MSS/MSI-L CRC who have exhausted at least one prior line of systemic treatment and do not qualify for available targeted treatment options for actionable genomic alterations. Additional eligibility criteria include: at least 18 years of age, measurable disease (as defined by RECIST v1.1), available archival tumor tissue sample or a fresh tumor sample, ECOG PS 0 or 1, as well as adequate hematologic and organ functions. Patients whose CRC tumor tissues have been identified as dMMR or MSI-H are excluded. The study is conducted in two parts: Part 1 dose escalation, which starts with Part 1a as accelerated dose escalation, followed by Part 1b escalation, which is based on a modified toxicity probability interval (mTPI-2) design, and Part 2, which is designed as a randomized dose optimization study to select the final recommended phase 2 dose (RP2D). For both parts of the study, the study intervention is administered as monotherapy, given as an intravenous (IV) infusion, in 21-day treatment cycles, with a step-up option. After an up-to-28-day screening period, eligible patients receive study medication and are followed for their entire treatment period plus a follow-up period of approximately 90 days. The study is open for recruitment in the United States (NCT07321106). Clinical trial information: NCT07321106. Research Sponsor: None.

TPS3679 **Poster Session**

A study evaluating microbiome modulation therapy in patients undergoing first-line therapy for metastatic colorectal cancer. First Author: Emily Noelle Kinsey, Virginia Commonwealth University, Richmond, VA

Background: Colorectal cancer (CRC) is the second leading cause of cancer-related mortality worldwide. Despite advances in systemic therapy, the 5-year overall survival for metastatic CRC remains poor. Emerging evidence suggests that the gut microbiome influences CRC development, progression, as well as chemotherapy resistance. There is strong preclinical data showing the association of *Fusobacterium nucleatum* and *Escherichia coli* with poor outcomes and chemotherapy resistance in patients with CRC. Younger patients and Black patients have been found to have a high-level colonization with *F nucleatum*, which could potentially contribute to healthcare disparities. If the amount of cancer-associated bacteria in the microbiome can be reduced, patients may respond better to chemotherapy and have improved outcomes. Preclinical studies indicate that targeting these bacteria with antibiotics may enhance chemotherapy efficacy. Aspirin may also be beneficial as it affects gene expression and inhibits *Fusobacterium nucleatum* with differential effects at varying drug concentrations. Our study evaluates the feasibility, safety, and preliminary efficacy of adding Microbiome Modulation Therapy (MBMT), including ciprofloxacin, metronidazole, +/- aspirin, to standard first-line chemotherapy in patients with metastatic CRC. **Methods:** This is a two-arm, noncomparative phase II trial enrolling adults (≥18 years) with stage IV CRC and measurable disease by RECIST 1.1. Eligible patients must have ECOG performance status 0–2 and planned first-line 5FU-based standard of care chemotherapy. Patients are excluded if they have recent antibiotic use to treat an infection within 30 days of treatment start (prophylactic preoperative antibiotics are allowed), have had a total colectomy, or are taking probiotic treatments. Patients are randomized to standard chemotherapy alone (investigators choice) or chemotherapy plus MBMT (ciprofloxacin, metronidazole, +/- aspirin for 28 days). The primary endpoint is objective response rate (ORR) per RECIST 1.1. Secondary endpoints include overall survival (OS), progression-free survival (PFS), safety, and tolerability of MBMT. Exploratory endpoints include changes in microbiome composition as measured by shotgun sequencing of fecal samples at baseline and after one month of treatment with chemotherapy +/- MBMT. Correlative studies will use shotgun sequencing to assess microbiome signatures, microbiota diversity, and changes with treatment. Correlative analyses will explore microbiome modulation as a novel therapeutic strategy to overcome chemoresistance in metastatic CRC. Enrollment is ongoing at Virginia Commonwealth University Massey Comprehensive Cancer Center in Richmond, Virginia. Clinical trial information: NCT06728072. Research Sponsor: Massey Comprehensive Cancer Center; American Cancer Society, Institutional Research Grant.

TPS3680 **Poster Session**

CONCEPT (combination of cetuximab plus fruquintinib treatment ± immunotherapy): A multicenter, randomized, open-label phase II trial in first-line pMMR *RAS/BRAF* wild-type unresectable metastatic colorectal cancer. First Author: Yue Liu, Colorectal Surgery and Oncology, Key Laboratory of Cancer Prevention and Intervention, Ministry of Education, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Background: In pMMR unresectable metastatic colorectal cancer (mCRC), first-line standards combine cytotoxic chemotherapy with targeted agents (anti-EGFR or anti-VEGF). A chemotherapy-sparing strategy may be clinically relevant for selected patients, and biologically supported by potential synergy between EGFR inhibition and VEGFR blockade, with immunotherapy potentially enhanced by vascular normalization and microenvironment modulation. CONCEPT evaluates the safety and antitumor activity of cetuximab-β plus fruquintinib, with or without immune checkpoint blockade, as a first-line option in pMMR RAS/BRAF wild-type unresectable mCRC. **Methods:** CONCEPT is an open-label, multicenter, randomized phase II trial. Key eligibility: age 18–85, ECOG 0–1, histologically confirmed colorectal adenocarcinoma, pMMR, KRAS/NRAS/BRAF wild-type, unresectable metastatic disease, and ≥1 measurable lesion per RECIST v1.1. Planned N=70; randomization 1:1:1 to: A) cetuximab-β 500 mg/m² IV q2w + fruquintinib 5 mg PO QD (3 weeks on/1 week off); B) regimen A + PD-1 antibody 200 mg IV q4w; C) regimen A + PD-1/CTLA-4 antibody 5 mg/kg IV q4w. The study uses a seamless two-stage selection design: initial cohort (10 patients/arm) to assess early safety/activity, followed by expansion of one or two selected arm(s) (+20 patients per selected arm). Safety assessments are performed each cycle; radiologic tumor assessment is every 2 cycles. Primary endpoints: progression-free survival (PFS) and safety. Secondary endpoints include objective response rate (ORR), disease control rate (DCR) and overall survival (OS). The study is registered with ClinicalTrials.gov (NCI 07257653). Clinical trial information: NCI 07257653. Research Sponsor: None.

TPS3681 **Poster Session**

Bevacizumab plus encorafenib-cetuximab in BRAF V600E mutated metastatic colorectal cancer (mCRC): A phase II study with a safety lead-in cohort (the BRAVE trial). First Author: Javier Ros Montañá, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain

Background: Encorafenib plus cetuximab is the standard of care for patients with *BRAF* V600E mutant, microsatellite-stable (MSS) mCRC, BRAF inhibitor-naïve, whose disease has progressed after 1-2 prior lines of chemotherapy. However, all patients eventually experience disease progression, and progression-free survival (PFS) remains modest. Therefore, there is an unmet need to enhance the efficacy of encorafenib-based combinations in *BRAF*-mutant mCRC. Preclinical data from rodent models treated with BRAF inhibitors have demonstrated upregulation of hypoxia-related genes (VEGFA, ADM, and CXCR4), and alterations in tumor vessel architecture. Based on these observations, rodent models treated with BRAF inhibitors in combination with anti-VEGF therapy achieved a meaningful improvement in PFS. In this trial, we hypothesize that encorafenib–cetuximab with bevacizumab will result in synergistic activity leading to durable responses in patients with refractory *BRAF*-mutant mCRC. **Methods:** The BRAVE trial (NCT06411600) is a multicenter, single-arm, phase Ib/II study evaluating the safety and efficacy of encorafenib–cetuximab–bevacizumab. Patients must have progressed to 1-2 previous lines and have a *BRAF* V600E-mutant, MSS tumor. Previous treatment with BRAF inhibitors or antiEGFR was not allowed. All patients receive encorafenib 300 mg vo QD, cetuximab 500 mg iv Q2W, and bevacizumab 5 mg/kg iv Q2W, administered in 28-day cycles. The primary endpoints are dose-limiting toxicities (DLTs) and 6-month PFS (6mPFS). The study follows a Simon two-stage design. A sample size of 89 evaluable patients is required to detect an increase in 6mPFS to 49% in the study population, compared with a 36% 6mPFS achieved with encorafenib plus cetuximab in the BEACON trial, using a one-sided type I error of 0.05 and 80% statistical power. As there was no prior evidence on the safety of this combination, a safety lead-in (SLI) phase (n=9) was included to evaluate potential DLTs. An Independent Data Safety Monitoring Board (IDSMB) reviewed the toxicity profile and DLTs granted continuation of the study on April 1, 2025. Following completion of the SLI phase and IDSMB evaluation, the study proceeded to two subsequent stages. Stage I enrolled 41 additional patients (completed on December 12, 2025). A preplanned interim analysis (IA) is being performed before proceeding to Stage II. If fewer than 19 of the first 50 patients achieve 6mPFS, the study will be discontinued due to lack of efficacy. If 19 or more of the first 50 patients achieve 6mPFS, Stage II will enroll an additional 39 patients. Recruitment is currently on hold pending the planned IA. Biomarker analyses include plasma sample collection at screening, on C1D15, and at end of treatment, as well as tumor biopsies (optional) at baseline and at disease progression to study mechanism of sensitivity and resistance. Clinical trial information: NCT06411600. Research Sponsor: Insituto de Salud Carlos III.

TPS3682 **Poster Session**

A randomized, active-controlled phase 3 study of ivonescimab + FOLFOX versus bevacizumab + FOLFOX as first-line treatment of metastatic colorectal cancer (mCRC): HARMONi-GI3. First Author: Aparna Raj Parikh, Department of Medicine, Division of Hematology/Oncology, Mass General Brigham Cancer Center, Harvard Medical School, Boston, MA

Background: Fluorouracil (5-FU)-based chemotherapy plus an anti–vascular endothelial growth factor (VEGF) or anti–epidermal growth factor receptor (EGFR) therapy is recommended as first-line treatment for many patients with mCRC; however, prognosis is still poor, with a 5-year survival rate of $<$30%. The investigational, anti–programmed cell death protein 1 (PD-1)- and VEGF-bispecific antibody ivonescimab is approved in China for non-small cell lung cancer (NSCLC) and is currently being evaluated as monotherapy or in combination with chemotherapy in global phase 3 clinical trials for NSCLC, and in other tumor types including colorectal cancer. **Methods:** HARMONi-GI3 (NCT07228832) is a randomized, active-controlled, double-blind, multiregional, phase 3 trial to compare the efficacy and safety of ivonescimab + 5-FU, oxaliplatin, and leucovorin (mFOLFOX6) versus bevacizumab + mFOLFOX6 in patients with mCRC who are not candidates for surgical resection, have not previously received systemic therapy for metastatic disease, and have an Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients with microsatellite instability-high or mismatch repair deficient disease, and with BRAF V600E mutation or dihydropyrimidine dehydrogenase deficiency, will be excluded. Approximately 600 patients will be randomly assigned (1:1) to receive ivonescimab 20 mg/kg + mFOLFOX6 or bevacizumab + mFOLFOX6 every 2 weeks for up to 4 months, followed by maintenance with ivonescimab + 5-FU and leucovorin or bevacizumab + 5-FU and leucovorin until disease progression, intolerable toxicity, or initiation of new anti-tumor therapy. Randomization will be stratified according to geographic region (East Asia, Europe, North America), liver metastases at study entry (absence or presence), and rat sarcoma virus tumor mutational status (RAS; mutant or wild-type). The hypothesis of this study is that ivonescimab + mFOLFOX6 has superior efficacy to bevacizumab + mFOLFOX6 in patients with mCRC who have not previously received systemic therapy for metastatic disease, as determined by progression-free survival (PFS). The primary endpoint is PFS (assessed by independent radiology review committee per Response Evaluation Criteria in Solid Tumors, v1.1). Secondary endpoints are overall survival, objective response rate, duration of response, safety, pharmacokinetics of ivonescimab + mFOLFOX6, and immunogenicity. All patients will have regular tumor evaluations every 8 weeks until week 48, then every 12 weeks until disease progression, loss to follow-up, death, withdrawal, or study closure. HARMONi-GI3 is currently recruiting participants. Clinical trial information: NCT07228832. Research Sponsor: Summit Therapeutics, Inc.

TPS3683 **Poster Session**

INCA033890-303: A randomized, double-blind, phase 3 study of FOLFOX and bevacizumab with or without INCA33890 in the first-line treatment of metastatic microsatellite-stable colorectal cancer. First Author: Van K. Morris II, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitors have demonstrated limited efficacy in the treatment of microsatellite stable colorectal cancer (MSS CRC), especially when the liver is involved. Transforming growth factor β (TGFβ) signaling within the tumor microenvironment suppresses T-cell proliferation and effector function, contributing to an immune-excluded phenotype. Although clinical targeting of the TGFβ pathway has been previously attempted, these approaches have been hampered by limited efficacy and significant toxicity. INCA33890 is a first-in-class bispecific antibody targeting both TGFβ receptor 2 (TGFβR2) and programmed cell death protein 1 (PD-1). This molecule is designed to inhibit TGFβR2 and PD-1 signaling specifically in PD-1–positive cells, sparing PD-1–negative cells from TGFβ inhibition. In the phase 1 INCA 33890-101 study (NCT05836324), INCA33890 demonstrated a manageable safety profile and durable single-agent activity in patients with refractory MSS CRC, including in patients with active liver metastases. The monotherapy objective response rate (ORR) was 15.2% overall (n = 105), including 12.0% in patients with liver metastases (n = 75) and 23.3% (n = 30) in patients without liver metastases. **Methods:** The multicenter, global, phase 3 INCA033890-303 study (NCT07284849) activated in December 2025 and is planned to open at 225 sites across 23 countries. The primary objective of this study is to evaluate the efficacy of INCA33890 versus intravenous placebo, each in combination with FOLFOX and bevacizumab, as first-line treatment for patients with previously untreated, histologically confirmed, unresectable metastatic MSS CRC. Prior neoadjuvant or adjuvant therapy is allowed provided there was no recurrence within 12 months of treatment completion. Key exclusion criteria include microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) status, *BRAF V600E* mutation, untreated or progressing brain metastases, and active autoimmune disease requiring systemic immunosuppression. Approximately 700 patients will be randomized 1:1 to receive intravenous INCA33890 or placebo, each in combination with FOLFOX and bevacizumab. Randomization will be stratified by tumor sidedness, the presence of liver metastases, and programmed death-ligand 1 (PD-L1) score. The primary endpoint is progression-free survival as assessed by investigators. The key secondary endpoint is overall survival. Additional secondary endpoints are ORR, safety and tolerability, duration of response, and patient-reported outcomes. Trial enrollment is ongoing. Clinical trial information: NCT07284849. Research Sponsor: Incyte Corporation.

TPS3684 **Poster Session**

Fruquintinib in combination with tislelizumab vs trifluridine/tipiracil and bevacizumab in MSS mCRC without active liver metastases: The IKF-080/QUINTIS trial. First Author: Joseph Tintelnot, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Patients with metastatic colorectal cancer (mCRC) who progress after treatment with fluoropyrimidines, oxaliplatin, irinotecan, anti-angiogenic agents, and anti-EGFR therapies have limited therapeutic options and a poor prognosis. Median overall survival (mOS) is approximately 6 months with single-agent regorafenib or trifluridine/tipiracil. The addition of bevacizumab to trifluridine/tipiracil has improved mOS to 10.8 months, while fruquintinib, a selective VEGFR-1–3 inhibitor, demonstrated a mOS of 7.4 months compared with 4.8 months for placebo in refractory mCRC. However, combinations of tyrosine kinase inhibitors and immune checkpoint inhibitors have shown clinical benefit, primarily in patients with microsatellite-stable mCRC without liver metastases, likely due to liver-associated immunosuppression. The QUINTIS trial evaluates whether fruquintinib plus the PD-1 antibody tislelizumab can improve outcomes in this clinically defined subgroup compared with the current standard of care of trifluridine/tipiracil plus bevacizumab. **Methods:** QUINTIS is a prospective, randomized, open-label, multicenter phase II trial enrolling 140 patients with metastatic colorectal adenocarcinoma without active liver metastases who have previously received fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and, when indicated, an EGFR inhibitor. Participants are randomized 1:1 to Arm A (experimental): fruquintinib 5 mg orally once daily (days 1–21 of a 28-day cycle) plus tislelizumab 400 mg intravenously on day 1 every 6 weeks; or Arm B (control): trifluridine/tipiracil 35 mg/m² orally twice daily (days 1–5 and 8–12 of a 28-day cycle) plus bevacizumab 5 mg/kg intravenously every 2 weeks. No prior treatment with the study drugs is permitted. Randomization is stratified by time since prior anti-angiogenic therapy ($<$ 12 vs. $\geq$12 months), BRAF/RAS mutation status, and history of liver metastases (never vs. treated). The primary endpoint is progression-free survival; secondary endpoints include overall response, overall survival, and quality of life. Translational research includes tumor, blood, and stool sampling to explore biomarkers of response and resistance, including systemic inflammation and the diet–microbiota–immune axis. Patient enrolment started in October 2025, and enrolment will take place at 30 sites. Clinical trial information: EU CTIS No. 2024-519111-34-00. Research Sponsor: None.

TPS3685 **Poster Session**

NSABP FC-13 (EMPIRE): A phase II platform study of cemiplimab monotherapy or cemiplimab-based combinations in patients with colorectal cancer and minimal residual disease (MRD) after definitive therapy. First Author: Anwaar Saeed, NSABP Foundation and UPMC Hillman Cancer Center, University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: Patients with microsatellite-stable (MSS) colorectal cancer (CRC) who are ctDNA-positive following surgery and chemotherapy have a high risk of recurrence and limited treatment options. Immune checkpoint blockade with PD-1/PD-L1 inhibitors, alone or with other immune modulators, may be most effective in early-stage disease or in patients without liver metastases. However, no approved therapies currently exist for patients with MSS CRC and ctDNA-positivity after curative-intent therapy, making this high-risk population an area of critical unmet need and opportunity for new drug development. NSABP FC-13 (EMPIRE) is a Phase II platform trial evaluating cemiplimab alone or in combination with novel agents in this high-risk MRD setting, wherein ctDNA clearance serves as an early surrogate marker of therapeutic activity. **Methods:** This multicenter Phase II platform study randomizes patients with MSS stage II–III or oligometastatic stage IV CRC who are ctDNA-positive within 12 weeks of completing definitive therapy (surgery ± chemotherapy/chemoradiotherapy) to one of three arms: (1) Cemiplimab 350 mg IV q3w × 1 year; (2) Cemiplimab 350 mg + fianlimab 1600 mg IV q3w × 1 year; (3) Cemiplimab 350 mg + REGN7075 2700 mg IV q3w × 1 year. Eligibility includes ECOG 0–1, adequate organ function, and absence of radiographic recurrence at enrollment. Assessments include serial tumor-informed ctDNA testing (Signatera, Natera, Inc.), imaging, labs, and safety monitoring. The primary endpoint is ctDNA clearance at 12 weeks without radiographic recurrence. Secondary endpoints include recurrence-free survival (RFS), safety, ctDNA kinetics, and patterns of recurrence. Statistical design: Arm 1 follows a Simon two-stage design with up to 33 patients (α=0.047, power=0.80), and Arms 2 & 3 enroll up to 23 patients each (single-stage; α=0.05, power=0.78). Status: Enrollment began in September 2025 across NSABP Foundation sites and is ongoing. Clinical trial information: NCT07058012. Research Sponsor: Regeneron; Natera, Inc.; NSABP Foundation, Inc.

TPS3686 **Poster Session**

NRG-GI008: Colon adjuvant chemotherapy based on evaluation of residual disease (CIRCULATE-NORTH AMERICA). First Author: Arvind Dasari, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Currently, there are no biomarkers validated prospectively in randomized studies for resected colon cancer (CC) to determine need for adjuvant chemotherapy (AC). However, circulating tumor DNA (ctDNA) represents a highly specific and sensitive approach (especially with serial monitoring) for identifying minimal/molecular residual disease (MRD) post-surgery in CC patients (pts), and may outperform traditional clinical and pathological features in prognosticating risk for recurrence. CC pts who do not have detectable ctDNA (ctDNA–) are at a much lower risk of recurrence and may be spared the toxicities associated with AC. Furthermore, for CC pts with detectable ctDNA (ctDNA+) who are at a very high risk of recurrence, the optimal AC regimen has not been established. We hypothesize that for pts whose CC has been resected, ctDNA status may be used to risk-stratify for making decisions about AC. **Methods:** In this prospective phase II/III trial, up to 1,912 pts with resected stage IIB, IIC, and III CC will be enrolled. Based on the post-operative ctDNA status using personalized and tumor-informed assay (Signatera, bespoke assay), those who are ctDNA– (Cohort A) will be randomized to immediate AC with fluoropyrimidine (FP)+oxaliplatin (Ox) for 3-6 mos per established guidelines *v* serial ctDNA monitoring. Patients who are ctDNA+ post-operatively, or with serial monitoring (Cohort B), will be randomized to FP+Ox *v* more intensive AC with addition of irinotecan (I) for 6 mos. One cycle of chemotherapy is allowed while awaiting ctDNA testing results for cohort assignment. The primary endpoints for Cohort A are time to ctDNA+ status (phase II) and disease-free survival (DFS) (phase III) in the immediate *v* delayed AC arms. The primary endpoint for Cohort B is DFS in the FP+Ox *v* FP+Ox+I arms for both phase II and phase III portions of the trial. Secondary endpoints include prevalence of detectable ctDNA post-operatively, time-to-event outcomes (overall survival and time to recurrence) by ctDNA status, and the assessment of compliance to adjuvant therapy. Biospecimens including archival tumor tissue, as well as post-operative plus serial matched/normal blood samples, will be collected for exploratory correlative research. Active enrollment across the NCTN started in June 2022 with CCTG sites joining in August 2023. Accrual is 1,123/1,912 (as of 1/20/2026). *Drs. Dasari and Lieu contributed equally to the development of this trial. Clinical trial information: NCT05174169. Research Sponsor: U.S. National Institutes of Health; U10 CA180868; U.S. National Institutes of Health; U10 CA180822; U.S. National Institutes of Health; U10 CA180888; U.S. National Institutes of Health; UG1 CA189867; U.S. National Institutes of Health; R50 CA28193; Natera, Inc.

TPS3687 **Poster Session**

Node-sparing modified short-course radiotherapy combined with capecitabine and PD-1/CTLA-4 for MSS early, middle, and low rectal cancer (mRCAT-E): An open-label, single-arm, prospective multicenter clinical trial. First Author: Zhangfa Song, Department of Colorectal Surgery, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China

Background: The standard treatment for early-stage rectal cancer is radical resection. For patients' organ preservation and quality of life improvement, preoperative radiotherapy plus chemotherapy then "watch-and-wait" are also recommended. But the clinical complete response (cCR) rate after chemoradiotherapy is only about 30~40%. Recent studies have shown that combining radiotherapy with PD-1 blockage can improve pathological complete response (pCR) rates to 40~50% for proficient mismatch repair (pMMR) or microsatellite stable (MSS) locally advanced rectal cancer (LARC) patients. However, the irradiation to tumor-draining lymph nodes (TDLNs) may impair T-cell immunity and reduce response to immunotherapy. Our previous phase II trial demonstrated that node-sparing modified short-course radiotherapy combined with chemotherapy and PD-1 blockade could achieve a high pCR rate of 78.8% and reduce radiation-related toxicity in pMMR/MSS LARC.[1] Iparomlimab/tuvonralimab is a novel bifunctional antibody, containing a mixture of anti-PD-1 IgG4 antibody iparomlimab and anti-CTLA-4 IgG1 antibody tuvonralimab, produced in a fixed ratio (2:1) from the same single cell and manufactured together as one product.[2] In this trial, we hypothesize that node-sparing modified short-course radiotherapy combined with capecitabine and PD-1/CTLA-4 may induce synergistic activity and substantially improve CR rates while reducing radiation-related toxicity. **Methods:** This is a single-arm, prospective, multicenter, phase II study across 3 hospitals in China. The main inclusion criteria includes rectal cancer within 7 cm from the lower edge of the tumor to the anal verge and the clinical stage is cT2-3N0M0, MSI-L/MSS or pMMR. A total of 52 patients will receive node-sparing modified short-course radiotherapy of 25 Gy delivered in 5 daily fractions to the primary tumor bed (excluding TDLNs). Beginning on treatment Day 8, patients will receive 4 cycles of capecitabine (1,000 mg/m², D1-14, q3w) and iparomlimab/tuvonralimab (5 mg/kg, D1, q3w). Tumor response will be assessed 1-2 weeks after the last chemo-immunotherapy. Patients with cCR enter a watch-and-wait program, while non-cCR proceed to local excision or total mesorectal excision. The primary endpoint is the CR rate (cCR and pCR). Secondary endpoints include organ preservation rate, 3-year local recurrence rate, overall survival, toxicity, and quality-of-life measures. As of January 2025, 5 of the planned 52 patients have been enrolled. The Data Monitoring Committee (DMC) reviewed the trial in December 2024 and recommended continuing as planned. Clinical trial information: NCT07068763. References: (1) Annals of Oncology (2024) 24 (suppl_1): 1-20. 10.1016/iotech/iotech100744; (2) Zhao et al. Journal of Hematology & Oncology (2023) 16:50. Clinical trial information: NCT07068763. Research Sponsor: None.

TPS3688 **Poster Session**

A phase 2 randomized study comparing telisotuzumab adizutecan monotherapy with standard of care in patients with post-adjuvant circulating tumor DNA–positive colorectal cancer. First Author: Kanwal Pratap Singh Raghav, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Curative intent standard of care (SOC) management of colorectal cancer (CRC) involves surgical tumor removal, followed by adjuvant therapy and active surveillance (AS). Presence of circulating tumor DNA (ctDNA) in the absence of radiographic evidence of disease is emerging as a reliable biomarker for determining molecular residual disease in CRC and in predicting recurrence after definitive therapy. Telisotuzumab adizutecan (Temab-A) is an antibody-drug conjugate that targets c-Met protein and is conjugated to a topoisomerase 1 (Top1) inhibitor payload. c-Met protein is ubiquitously expressed on CRC tumor cells. Temab-A has shown a manageable safety profile and promising antitumor activity in patients (pts) with advanced solid tumors, including CRC (NCT05029882). Herein, we describe a Phase 2 study of Temab-A monotherapy in pts with ctDNA-positive CRC after adjuvant therapy compared with AS. **Methods:** This open-label, randomized, global, multicenter, Phase 2 study (NCT07023289) includes adults (≥18 yrs) with histologically confirmed adenocarcinoma of the colon or rectum. Surgical tumor material must be available and submitted for Signatera personalized panel and assessment of c-Met protein levels. Pts must have received a total of ≥3 mos of perioperative and/or platinum-based doublet adjuvant therapy, have no radiographic evidence of disease as determined by CT scans and liver MRI, and be ctDNA-positive within the first year after the end of adjuvant therapy. Approximately 140 pts will be randomized (1:1) to receive either Temab-A (2.4 mg/kg, IV, Q3W, N=70) or AS only (N=70). Randomization will be stratified by oligometastatic versus nonmetastatic and by the timing of enrollment. Japan will have a separate randomization schedule stratified by the same factors. During 9 mos of treatment (12 cycles [C], 21 days [D] per C) or AS, pts will undergo monitoring for disease recurrence through CT scans (Q6W) and ctDNA testing (on C2D1, C3D1, C4D1, at 6 and 9 mos). Study follow-up will occur every 3 mos for the first 2 yrs and every 6 mos for the 3 yrs thereafter. The Table shows study objectives and endpoints. Clinical trial information: NCT07023289. Research Sponsor: None.

Objectives	Endpoints
Primary	
Evaluate efficacy of Temab-A	Disease-free survival by investigator
Secondary	
Evaluate clinical outcomes of Temab-A	ctDNA clearance at 6 mos after randomization Overall survival
Safety	
Evaluate safety/tolerability of Temab-A	Adverse event type, frequency, seriousness, and severity Treatment-emergent adverse events leading to treatment discontinuation and dose interruption
Pharmacokinetics (PK)	
Evaluate PK and immunogenicity of Temab-A	Serum concentration of: Temab-A conjugate Total antibody Plasma concentration of Top1 inhibitor

TPS3689 **Poster Session**

Phase 2 study of adjuvant botensilimab in combination with balstilimab in patients with microsatellite-stable colorectal cancer and persistent circulating tumor DNA following surgery and chemotherapy. First Author: Neil Howard Segal, Memorial Sloan Kettering Cancer Center, New York City, NY

Background: In patients with localized microsatellite stable (MSS) colorectal cancer (CRC), detection of circulating tumor DNA (ctDNA) after completion of definitive therapy indicates the presence of minimal residual disease (MRD) and predicts metastatic recurrence within months. Novel adjuvant therapies to prevent recurrence are very much needed. Botensilimab (BOT) is an Fc-enhanced multifunctional anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody designed to expand therapy to cold/poorly immunogenic solid tumors, such as MSS CRC. BOT plus balstilimab (BAL; PD-1 inhibitor) has previously demonstrated deep, durable responses in treatment-refractory metastatic MSS CRC and no active liver metastases. We hypothesize that treatment of MRD with effective immunotherapy in patents with MSS CRC after definitive therapy will prevent tumor recurrence. **Methods:** This investigator-initiated, open label, Phase 2 study evaluates the efficacy of BOT/BAL in patients with stage III MSS CRC (cohort 1) or colorectal liver metastases (CRLM) (cohort 2) and MRD following definitive treatment, including surgery and pre-operative chemotherapy. The study is being conducted in 2 parts. Part 1 aims to determine ctDNA clearance, as a surrogate for improved survival. Patients receive BOT/BAL for 6 months followed by BAL alone for 6 months. With a total of 27 patients per cohort, and using an exact single-stage binomial design, we will have 80% power to detect an improvement in ctDNA clearance from 5% to 20% with a type I error rate of 5%. If part 1 is successful, then part 2 of the study may proceed as a randomized, placebo-controlled, double-blind, multicenter study to assess improvement in recurrence-free survival. Translation studies are planned to correlate tumor and immune characteristics with ctDNA clearance and clinical endpoints to further our understanding of immune responsiveness in the setting of MRD in MSS CRC. Enrollment to the study is currently ongoing. Clinical trial information: NCT07227636. Research Sponsor: None.

LBA4000 **Oral Abstract Session**

Efficacy and safety results from EMERALD-3: A phase 3, randomized study of tremelimumab plus durvalumab with or without lenvatinib combined with transarterial chemoembolization (TACE) in participants (pts) with unresectable embolization-eligible hepatocellular carcinoma (eeHCC). First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center; Weill Medical College at Cornell University, New York, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

4001 **Oral Abstract Session**

Camrelizumab (C) plus rivoceranib (R) with transarterial chemoembolization (TACE) vs TACE alone in unresectable hepatocellular carcinoma (uHCC): A randomized, phase 3 trial. First Author: Wei-Dong Jia, Department of General Surgery, The First Affiliated Hospital of University of Science and Technology of China, Hefei, China

Background: The combination of C (anti–PD-1 antibody) + R (VEGFR2 tyrosine kinase inhibitor) significantly improved progression-free survival (PFS) and overall survival (OS) vs sorafenib as first-line treatment for advanced HCC, and improved event-free survival vs surgery alone as perioperative treatment for resectable HCC. We conducted a phase 3 trial evaluating C+R with TACE in intermediate-stage HCC and here present data from the protocol-specified PFS interim analysis (IA). **Methods:** In this multicenter, open-label, phase 3 trial, patients (pts) with TACE-eligible uHCC, Child-Pugh A, ECOG performance status (PS) 0–1 and no extrahepatic spread were randomized 1:1 to receive C (200 mg, iv, Q3W) + R (250 mg, po, QD) + TACE or TACE alone. TACE (cTACE or DEB-TACE) was administered at the investigator (INV)'s discretion; C+R continued until loss of clinical benefits, unacceptable toxicities, or other protocol-specified criteria. The primary endpoint was PFS by BIRC per mRECIST. As of Sep.13, 2025, 214 PFS events occurred and a preplanned IA was performed. **Results:** 423 pts (ECOG PS 1, 22.9%; AFP ≥400 ng/mL, 26.7%; portal vein invasion [vp1/2], 9.7%) were randomized to C+R+TACE (n=214) or TACE (n=209). As of data cutoff, median follow-up was 16.4 mo. Median PFS by BICR per mRECIST was significantly longer with C+R+TACE vs. TACE (11.1 vs. 8.3 mo; HR 0.73 [95% CI 0.56–0.96]; 1-sided p=0.0127). PFS by BICR per RECIST v1.1 (13.9 vs 9.5 mo; HR 0.67 [95% CI 0.50–0.91]) and by INV per mRECIST (13.8 vs 7.0 mo; HR 0.61 [95% CI 0.47–0.81]) and per REIST v1.1 (15.7 vs 8.4 mo; HR 0.61 [95% CI 0.45–0.81]) showed consistent findings (Table 1). PFS benefits with addition of C+R persisted across most prespecified subgroups. OS was not mature, with an early trend favoring C+R+TACE (HR 0.76 [95% CI 0.46–1.24]); OS was 91.4% vs 85.5% at 12 mo, and 82.0% vs 73.3% at 24 mo. Among treated pts, grade ≥3 TRAEs occurred in 73.7% (157/213) in C+R+TACE arm vs. 28.7% (60/209) in TACE arm; of them, the most common in C+R+TACE arm were increased AST (20.7% vs 12.9%), hypertension (19.7% vs 4.3%), increased ALT (17.8% vs 9.6%), and decreased platelet count (11.3% vs 2.9%). **Conclusions:** C+R+TACE provided statistically significant and clinically meaningful improvement in PFS vs TACE, with manageable safety, supporting this regimen as a potential new treatment option for TACE-eligible uHCC. Follow-up for OS is ongoing. Clinical trial information: NCT05320692. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

PFS outcomes (ITT set).

	BIRC C+R+TACE (n=214)	BIRC TACE (n=209)	INV C+R+TACE (n=214)	INV TACE (n=209)
Per mRECIST				
Median (95% CI), mo	11.1 (7.8–14.0)	8.3 (6.9–9.5)	13.8 (8.5–17.3)	7.0 (5.7–9.5)
HR (95% CI)*	0.73 (0.56–0.96); 1-sided p=0.0127†		0.61 (0.47–0.81)	
Per RECIST v1.1				
Median (95% CI), mo	13.9 (10.9–19.4)	9.5 (8.1–11.1)	15.7 (10.3–19.6)	8.4 (6.9–10.8)
HR (95% CI)*	0.67 (0.50–0.91)		0.61 (0.45–0.81)	

*Stratified Cox proportional hazard model.
†Stratified Log-Rank test.

4002 **Oral Abstract Session**

IMbrave251: Final analysis of atezolizumab (atezo) + lenvatinib (lenva) or sorafenib (sora) vs lenva or sora alone in locally advanced or metastatic hepatocellular carcinoma (LA/mHCC) previously treated with atezo and bevacizumab (bev). First Author: Arndt Vogel, Division of Gastroenterology and Hepatology, Toronto General Hospital, Medical Oncology, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Several immuno-oncology therapies are available for 1L HCC, but data are limited after progression. IMbrave251 (NCT04770896) is the first global randomized Phase 3 trial to assess atezo + lenva or sora (TKIs) vs lenva or sora alone in patients (pts) with LA/mHCC that progressed after atezo + bev treatment (tx). This is the final analysis. **Methods:** Eligible pts had LA/mHCC that was responsive to atezo + bev tx but then progressed (atezo + bev was given for ≥4 cycles and ≥2 tumor assessments, of which ≥1 showed stable disease or complete/partial response). In the atezo + TKI arm, pts received atezo (1200 mg Q3W) + lenva (8 mg for pts < 60 kg or 12 mg for pts ≥60 kg QW) or sora (800 mg QW). Pts in the TKI-only arm received lenva or sora alone. The primary endpoint was OS. Secondary endpoints included PFS, ORR by RECIST 1.1, DOR, time to tumor progression (TTP), quality of life, and safety. Stratification factors were disease etiology (hepatitis B/C infection vs non-viral), ALBI score (1 vs 2/3), AFP (< 400 vs ≥400 ng/mL), and TKI therapy (lenva vs sora). **Results:** IMbrave251 enrolled 557 pts (full analysis population). Median duration of follow-up was 12 mo. Pts were assigned to receive atezo + TKI (n = 279) or TKI-only (n = 278). Most pts in both arms received lenva (92.1%) vs sora (7.9%). At clinical cutoff (Oct 10, 2025), median (m)OS with atezo + TKI vs TKI-only was 14.6 vs 12.5 mo (stratified HR 0.88; *P*= 0.2115) and mPFS was 4.3 vs 4.8 mo (stratified HR 1.05), respectively. Confirmed ORR was 7.5% vs 5.8% with atezo + TKI vs TKI-only. DOR was 10.2 vs 6.9 mo, respectively (stratified HR 0.47) (Table). Additional subgroup analyses and complete duration of systemic therapy will be shown. In the atezo + TKI vs TKI-only arm, the median tx duration was 5.6 vs 4.7 mo for lenva and 2.9 vs 2.3 mo for sora. No new or unexpected safety signals were seen (safety analysis n = 554; Table). **Conclusions:** IMbrave251 did not meet its primary OS endpoint but showed that the addition of atezo to TKIs had a manageable safety profile. This study provides clinically relevant Phase 3 evidence addressing an important, unanswered clinical question regarding 2L tx sequencing after immunotherapy and establishes a new OS benchmark for 2L tx in LA/mHCC. Clinical trial information: NCT04770896. Research Sponsor: F. Hoffmann-La Roche Ltd.

Efficacy (95% CI)	Atezo + lenva or sora (n=279)	Lenva or sora (n=278)	Stratified HR (95% CI)
mOS, mo	14.6 (12.6, 16.8)	12.5 (10.7, 15.5)	0.88 (0.72, 1.08) *P*=0.2115
mPFS, mo	4.3 (4.1, 5.4)	4.8 (4.2, 5.6)	1.05 (0.88, 1.25)
ORR, %	7.5 (4.7, 11.3)	5.8 (3.3, 9.2)	Δ1.77 (−2.72, 6.26)[a]
mDOR, mo	10.2 (5.6, 13.0)	6.9 (5.5, 11.7)	0.47 (0.18, 1.23)
mTTP, mo	4.4 (4.2, 5.5)	5.4 (4.2, 5.6)	1.06 (0.87. 1.28)
Safety, n (%)	**n=279**	**n=275**	
Grade 3/4 | 5 AE	207 (74.2) | 15 (5.4)	182 (66.2) | 16 (5.8)	-
Serious AE | AE leading to withdrawal from any study drugs	112 (40.1) |33 (11.8	101 (36.7) |19 (6.9)	-

[a]Difference in confirmed ORR (95% CI).

4003 **Oral Abstract Session**

First-line treatment of QLS31905 plus chemotherapy in patients with pancreatic cancer and gastric cancer: Data from a phase 1b/2 study. First Author: Xiaotian Zhang, Early Drug Development Center, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China

Background: QLS31905, a Claudin18.2/CD3 bispecific antibody, showed manageable safety and encouraging efficacy in Claudin18.2-positive patients (pts) with gastrointestinal tumors in a phase 1 trial. Here we report the safety and efficacy of QLS31905 plus chemotherapy in the first-line treatment of Claudin18.2-positive pts with pancreatic cancer (PC) and gastric cancer (GC). **Methods:** This phase 1b/2 trial recruited Claudin 18.2-positive (defined as ≥1% of tumor cells with ≥1+ staining intensity) pts with locally advanced unresectable or metastatic PC and GC who had not received systematic anti-tumor therapy. Pts with PC were administered QLS31905 at 350 μg/kg, 500 μg/kg, or 800 μg/kg Q2W or Q3W combined with gemcitabine plus nab-paclitaxel (Cohort 1). Pts with GC were administered QLS31905 at 500 μg/kg or 800 μg/kg Q3W combined with oxaliplatin plus capecitabine (Cohort 2). The primary endpoints were maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) in phase 1b and was objective response rate (ORR) in phase 2. **Results:** As of Dec 11, 2025, 88 pts with PC and 43 pts with GC were enrolled. No dose-limiting toxicity occurred. MTD was not reached. RP2D was determined as 800 μg/kg Q3W for both pts with PC and GC. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 63 (71.6%) pts and 26 (60.5%) pts in Cohort 1 and Cohort 2, respectively. Ten pts (11.4%) in Cohort 1 and four pts (9.3%) in Cohort 2 discontinued any of the study treatment due to TRAEs. No QLS31905-related death occurred in both cohorts. In 82 efficacy-evaluable pts with PC, ORR and disease control rate (DCR) was 59.8% (95% confidence interval [CI], 48.34%-70.44%) and 89.0% (95% CI, 80.18%-94.86%), respectively. Median progression-free survival (PFS), duration of response (DoR), and overall survival (OS) was 8.74 months (95% CI, 7.16-10.71), 8.94 months (95% CI, 5.32-not evaluable [NE]), and 15.87 months (95% CI, 13.14-NE), respectively. In 15 pts with low Claudin18.2 expression in Cohort 1, ORR, DCR, median PFS, and median OS was 60.0% (95% CI, 32.29%-83.66%), 93.3% (95% CI, 68.05%-99.83%), 11.04 months (95% CI, 7.33-NE), and 15.61 months (95% CI, 3.98-NE), respectively. In 43 efficacy-evaluable pts with GC, ORR and DCR was 74.4% (95% CI, 58.83%-86.48%) and 93.0% (95% CI, 80.94%-98.54%), respectively. Median PFS and DoR was 10.09 months (95% CI, 6.87-NE) and not reached, respectively. In nine pts with low Claudin18.2 expression in Cohort 2, the ORR, DCR, median PFS, and 9-month PFS rate and was 77.8%, 100%, not reached, and 83.33%, respectively. **Conclusions:** QLS31905 plus chemotherapy in first-line treatment for Claudin18.2-positive pts with PC and GC showed manageable safety and potential efficacy. A phase 3 trial is ongoing to further confirm the efficacy and safety of QLS31905 in pts with PC. Clinical trial information: NCT06041035. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

4004 **Oral Abstract Session**

A randomized phase II dose optimization study for alveltamig (ZG006), a trispecific T-cell engager targeting DLL3/DLL3/CD3, as monotherapy in patients with refractory neuroendocrine carcinoma (ZG006-003). First Author: Chuan Hua Zhao, Fifth Medical Center, Chinese PLA General Hospital, Beijing, China

Background: Alveltamig (ZG006) is an innovative trispecific T cell engager (Tri-TCE) targeting two distinct DLL3 epitopes on tumor cells and CD3 on T cells (DLL3/DLL3/CD3), designed to bridge tumor cells and T cells, thereby mediating T cell specific killing of tumor cells. Here we conducted a dose optimization study in refractory NEC. **Methods:** This is a randomized, multicenter, open-label phase 2 study evaluating ZG006 in NEC patients (pts) who failed at least one prior line of therapy. Pts were randomized 1:1 to receive ZG006 at either 10 mg or 30 mg every two weeks, following a priming dose of 1 mg. The primary endpoint is objective response rate (ORR) assessed by IRC per RECIST1.1. Results are reported for 64 pts who received at least one dose of ZG006. Biomarker based efficacy analyses were performed based on a threshold of ≥50% of tumor cells stained at any intensity for DLL3 with an investigational antibody against DLL3 (SP347, Roche Diagnostics). **Results:** As of Sep. 10, 2025, a total of 64 pts (32 at each dose group) were randomized and received at least one dose of ZG006. The median age was 56 years (range: 25-72), 35 (54.7%) were male. All pts had received ≥1 prior line of systemic therapy, with 65.6% had prior anti-PD-(L)1 treatment. The confirmed ORR in 10 mg and 30 mg groups were 21.9% (7/32) and 37.5% (12/32), respectively; Disease control rate (DCR) were 40.6% (13/32) and 62.5% (20/32), respectively. Among the 19 responders, primary tumor sites included cervix (8), gallbladder (4), stomach (3), rectum (3) and colon (1). Pts with ≥50% DLL3 staining in tumor cells had greater ORR, DCR, and progression-free survival (PFS). The confirmed ORR in 10 mg and 30 mg groups were 33.3% (6/18) and 56.3% (9/16), respectively; DCR were 50.0% (9/18) and 75.0% (12/16), respectively; With a median follow up of 6.4 months, median PFS were 3.02 and 8.41 months, respectively. Median DoR was not yet mature in both groups at data cut-off. Treatment-related adverse events (TRAEs) occurred in all pts. The most frequent events were pyrexia, cytokine release syndrome (CRS) and anaemia. Most CRS were Grade 1-2, with only four grade 3 CRS, resolved with supportive care. TRAEs led to treatment interruption in 15 pts (23.4%) and permanent discontinuation in 2 pts (3.1%, one in each dose group). No grade 5 TRAE. No significant difference was observed in the safety profile between these two dose groups. **Conclusions:** ZG006 demonstrated a robust and durable response and a manageable safety profile in previously treated NEC pts, with superior efficacy observed at the 30 mg dose. The confirmed ORR of 56.3% and median PFS of 8.41 months in pts with ≥50% DLL3 positive tumor cells are particularly encouraging, and support further development of ZG006 for this patient population at the 30 mg dose. Clinical trial information: NCT06440057. Research Sponsor: None.

4006 **Oral Abstract Session**

Nivolumab plus ipilimumab combined with chemotherapy as first-line treatment for HER2-negative unresectable advanced or recurrent gastric/gastroesophageal junction cancer: A randomized phase 3 trial (ATTRACTION-6). First Author: Do-Youn Oh, Seoul National University College of Medicine, Seoul, South Korea

Background: Anti-PD-1 antibodies combined with chemotherapy (Chemo) are established as a standard first-line (1L) treatment for HER2-negative gastric/gastroesophageal (G/GEJ) cancer. Nivolumab (NIVO) and ipilimumab (IPI), an anti-CTLA-4 antibody, have complementary mechanisms of action on tumor immunity. Combining NIVO plus Chemo with IPI is expected to suppress disease progression durably and prolong survival, as suggested in other types of tumors. **Methods:** ATTRACTION-6 is a randomized, phase 3 trial conducted in Japan, Korea, and Taiwan. Previously untreated patients with HER2-negative unresectable advanced or recurrent G/GEJ cancer were randomized 1:1 to receive NIVO 360 mg every 3 weeks, IPI 1 mg/kg every 6 weeks in addition to Chemo (S-1 plus oxaliplatin [SOX] or capecitabine plus oxaliplatin [CAPOX]) or Chemo alone. Randomization was stratified by PD-L1 (CPS≥5 or CPS < 5, indeterminate), ECOG PS (0 or 1), countries (Japan or Korea/Taiwan), and disease status (advanced or recurrent). Primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS), objective response rate (ORR) per RECIST v1.1 assessed by site investigator, and safety. **Results:** Between November 2021 and August 2023, 626 patients were randomized 1:1 to the NIVO + IPI + Chemo arm (N = 315) or the Chemo arm (N = 311). At the median follow-up of 31.3 months, the primary endpoint of OS was not met (HR 0.90; 95.8% CI 0.74-1.09; *P*= 0.267; median OS 15.7 vs 15.8 months). Median PFS was 8.9 vs 7.7 months (HR 0.83; 95% CI 0.69-1.00). Among patients with ≥1 measurable lesion at baseline, ORR was 57.9% vs 38.5%. Grade≥3 adverse events (AEs) and grade≥3 treatment-related AEs occurred in 80.0% and 64.8% in the NIVO + IPI + Chemo arm, respectively, and 62.4% and 42.9% in the Chemo arm, respectively. Treatment-related deaths occurred in 0.3% vs 0%, and the only observed event was gastroenteritis in the NIVO + IPI + Chemo arm. **Conclusions:** In ATTRACTION-6 study, NIVO + IPI + Chemo did not improve OS compared with Chemo as 1L treatment for patients with HER2-negative unresectable advanced or recurrent G/GEJ cancer. Although toxicity increased with the addition of NIVO and IPI, no new safety signals were observed. Clinical trial information: NCT05144854. Research Sponsor: Ono Pharmaceutical Co., Ltd.

4007 **Oral Abstract Session**

ONO-4578 combined with nivolumab (NIVO) and chemotherapy (chemo) as first-line (1L) treatment for patients with HER2-negative unresectable advanced or recurrent (adv/rec) gastric/gastroesophageal junction cancer (G/GEJ): A randomized, double-blind, phase 2 trial (ONO-4578-08). First Author: Sung Hee Lim, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Anti-PD-1 antibodies combined with chemo are the standard 1L treatment for HER2-negative G/GEJ cancer. Prostaglandin E_2 (PGE_2)-EP4 signaling is known to induce immunosuppressive tumor microenvironment, by inducing the differentiation of MDSCs and M2 macrophages, potentially contributing to resistance to immunotherapy. ONO-4578, an EP4 antagonist, is expected to modulate tumor immunosuppression through inhibiting the PGE_2-EP4 signaling and to enhance the efficacy of anti-PD-1 antibody. The addition of ONO-4578 appeared to augment the efficacy of NIVO in patients with G/GEJ cancer in the previous phase 1 trial. This study aimed to evaluate the efficacy and safety of ONO-4578 combined with NIVO and chemo compared with placebo combined with NIVO and chemo as 1L treatment for patients with unresectable adv/rec G/GEJ cancer. **Methods:** ONO-4578-08 study is a randomized, double-blind, phase 2 trial conducted in Japan, Korea, and Taiwan. Chemo-naïve patients with HER2-negative adv/rec G/GEJ cancer were randomized in a 2:1 ratio (ONO-4578 group:placebo group), stratified by PD-L1 expression level (CPS < 5 vs CPS≥5), ECOG performance status (0 vs 1), presence of peritoneal metastasis (yes vs no). Patients in each group received ONO-4578 40 mg or placebo once daily, and all received NIVO 360 mg every 3 weeks and chemo (SOX [S-1 + oxaliplatin]/CAPOX [capecitabine + oxaliplatin]). The primary endpoint was investigator-assessed progression-free survival (PFS), powered (two-sided α = 0.10) to detect a HR of 0.65 with 117 events in a planned enrollment of 210 patients; secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. **Results:** Between December 2023 and September 2024, 226 patients were randomized to each group (150 vs 76 patients). With a median follow-up of 8.5 months, PFS was significantly longer in the ONO-4578 group than the placebo group with a hazard ratio (HR) of 0.67 (90% confidence interval [CI]: 0.48–0.92; *P* = 0.040; median PFS: 9.0 vs 6.9 months). At a minimum follow-up of 7.4 months, OS favored the ONO-4578 group (median OS: not reached vs 12.7 months; HR: 0.60 [95% CI: 0.37–0.96]). ORR was also higher in the ONO-4578 group (62.0% vs 48.7%). The most common treatment-emergent adverse events (TEAEs) in the ONO-4578 group were diarrhea (55.7% vs 45.3%), anemia (55.0% vs 34.7%), and peripheral sensory neuropathy (50.3% vs 46.7%). Serious TEAEs occurred in 53.7% of patients in the ONO-4578 group and 42.7% in the placebo group. **Conclusions:** ONO-4578 combined with NIVO and chemo significantly improved PFS compared with placebo combined with NIVO and chemo in treatment-naive patients with HER2-negative unresectable adv/rec G/GEJ cancer with no new safety concerns. Clinical trial information: NCT06256328. Research Sponsor: Ono Pharmaceutical Co., Ltd.

4008 **Oral Abstract Session**

Izalontamab brengitecan (iza-bren) versus chemotherapy in patients with recurrent or metastatic esophageal squamous cell carcinoma (ESCC): A multicenter, randomized, open-label, phase III study. First Author: Zhihao Lu, Peking University Cancer Hospital and Institute, Beijing, China

Background: Chemotherapy plus a PD-1/PD-L1 inhibitor is the standard first-line treatment for PD-L1 expressing advanced ESCC. However, most patients (pts) inevitably develop resistance to first-line therapy, and second-line chemotherapy shows an ORR of less than 10% and a median OS of less than 6 mo, highlighting the urgent need for novel therapeutics. Iza-bren is a potentially first-in-class ADC consisting of an EGFR-HER3 bispecific antibody conjugated to a potent topoisomerase I inhibitor Ed-04 via a cleavable linker. Iza-bren has shown promising clinical activity in previously treated ESCC pts in phase I study. Here, we present results from a phase III, randomized, open-label, multicenter study conducted in China evaluating the efficacy and safety of iza-bren versus chemotherapy as second line treatment for advanced ESCC. **Methods:** Pts with recurrent or metastatic ESCC who had progressed after first-line treatment with a PD-1/PD-L1 inhibitor plus platinum-based chemotherapy were randomized (1:1) to receive iza-bren (2.5 mg/kg at D1D8 Q3W) or physician's choice of chemotherapy (irinotecan, paclitaxel, or docetaxel Q3W). Dual primary endpoints were OS and PFS by Blinded Independent Central Review (BICR) per RECIST v1.1. **Results:** As of Oct 17, 2025, a total of 497 pts were randomized to iza-bren (n = 249) or chemotherapy (n = 248). Baseline characteristics were balanced between the two groups. At interim analysis, median follow-up for OS was 7.8 mo in the iza-bren group and 7.6 mo in the chemotherapy group. Iza-bren has demonstrated statistically significant and clinically meaningful improvement in both OS and PFS by BICR compared with chemotherapy. The median OS was 9.8 mo (95% CI, 7.9 to 11.0) with iza-bren and 7.2 mo (95% CI, 6.2 to 8.2) with chemotherapy (HR, 0.64; 95% CI, 0.49 to 0.83; P = 0.0004). The median PFS by BICR was 4.2 mo (95% CI, 3.6 to 4.5) with iza-bren and 2.0 mo (95% CI, 1.6 to 2.7) with chemotherapy (HR, 0.50; 95% CI, 0.40 to 0.63; P < 0.0001). ORR by BICR was 35.3% for iza-bren and 13.1% for chemotherapy. Grade≥3 TRAEs, which were predominantly hematologic in nature, occurred in 85.1% in the iza-bren group and 60.2% in the chemotherapy group. TRAEs leading to drug discontinuation were 2.0% in the iza-bren group and 3.3% in the chemotherapy group. TRAEs leading to death were 1.2% in the iza-bren group and 1.6% in the chemotherapy group. **Conclusions:** The study met both dual primary endpoints at prespecified interim analysis. Iza-bren demonstrated statistically significant and clinically meaningful improvements in OS and PFS compared with chemotherapy in pts with recurrent or metastatic ESCC who had progressed after first line PD-1/PD-L1 inhibitor plus platinum-based chemotherapy. The safety profile was manageable. The results support iza-bren as a new second-line standard of care for ESCC. Clinical trial information: NCT06304974. Research Sponsor: Baili-Bio (Chengdu) Pharmaceutical Co., Ltd.

4009 **Rapid Oral Abstract Session**

Neoadjuvant/adjuvant serplulimab vs. placebo combined with chemotherapy for PD-L1−positive gastric cancer: A randomized, double-blind, multicenter phase 3 study. First Author: Lin Shen, Department of Gastrointestinal Oncology, Peking University Cancer Hospital, Beijing, China

Background: The addition of immune checkpoint inhibitors (ICIs) to chemotherapy (chemo) in the neoadjuvant/adjuvant setting for gastric cancer (GC) has yielded mixed efficacy. Target population and treatment regimen remain to be optimized. This study compared the efficacy of serplulimab (anti-PD-1 antibody) plus chemo versus placebo plus chemo as neoadjuvant therapy and serplulimab versus chemo as adjuvant therapy for resectable GC. **Methods:** Patients with PD-L1 positive (PD-L1 CPS $\geq$ 5), histologically confirmed, untreated, resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma were randomized 1:1 to receive 3 cycles of neoadjuvant intravenous (iv) serplulimab (4.5 mg/kg) or placebo, plus chemo (iv oxaliplatin, 130 mg/m^2 and oral S-1, 40-60 mg based on body surface area), followed by post-surgery adjuvant serplulimab monotherapy (up to 17 cycles) or adjuvant chemo (5 cycles), Q3W. The primary endpoint was investigator (INV)-assessed event-free survival (EFS). Efficacy superiority was first evaluated and established in patients with PD-L1 CPS $\geq$ 10 followed by that in the PD-L1 CPS $\geq$ 5 population. **Results:** Between November 26, 2019 and April 19, 2024, 588 patients were enrolled across 57 sites, with 292 randomized to the serplulimab group and 296 to the placebo group. As of the data cutoff date of August 19, 2025 with a median follow-up duration of 35.9 months, INV-assessed median EFS was significantly longer in the serplulimab group (n = 193) than in the placebo group (n = 217) in the PD-L1 CPS $\geq$ 10 population (not reached [NR], 95% CI 43.0−not estimable [NE] vs. 42.0 months, 95% CI 20.5−NE; HR 0.65, 95% CI 0.47−0.90; p = 0.0082), and in the PD-L1 CPS $\geq$ 5 population (NR, 95% CI 37.9−NE vs. 35.9 months, 95% CI 21.3−52.0; HR 0.73, 95% CI 0.56−0.94; p = 0.0152), meeting the protocol-specified superior criteria. Blinded independent central review-assessed median EFS was consistent with that of the investigator. Pathological complete response rate was higher in the serplulimab group than in the placebo group (21.6% vs 6.4%; odds ratio 3.95). Median OS was immature in both groups. Grade $\geq$ 3 treatment-related adverse events (TRAEs) were reported in 136 (46.6%) and 172 (58.5%) patients in the serplulimab and placebo groups, respectively. Discontinuation of any component of the study regimen due to TRAEs occurred in 19 (6.5%) and 31 (10.5%) patients in the respective groups. **Conclusions:** Neoadjuvant serplulimab plus chemo, followed by adjuvant serplulimab monotherapy, significantly prolonged EFS in patients with PD-L1-positive, resectable GC or GEJ adenocarcinoma. Improvements in other efficacy endpoints were also observed along with a favorable safety profile compared to neoadjuvant/adjuvant chemo. This world-first chemotherapy-free regimen (adjuvant) represents a promising treatment option for this indication. Clinical trial information: NCT04139135. Research Sponsor: Shanghai Henlius Biotech, Inc.

4010 **Rapid Oral Abstract Session**

Zanidatamab + chemotherapy (CT) ± tislelizumab for first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): PD-L1 subgroup analysis from HERIZON-GEA-01. First Author: Sun Young Rha, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: In HERIZON-GEA-01 (NCT05152147), 1L zanidatamab + CT ± tislelizumab significantly improved progression-free survival (PFS) and, with tislelizumab, yielded a statistically significant overall survival (OS) benefit in HER2+ mGEA. Here we report efficacy in PD-L1 subgroups. **Methods:** Eligible patients (pts) with previously untreated HER2+ mGEA, irrespective of PD-L1 status, were randomized (1:1:1) to zanidatamab (1800 mg [<70 kg]/2400 mg [$\geq$70 kg] IV Q3W) + tislelizumab (200 mg IV Q3W) + capecitabine/oxaliplatin (CAPOX) or 5-FU/cisplatin (FP); zanidatamab + CAPOX or FP; or tras + CAPOX or FP. PD-L1 expression was retrospectively assessed using the VENTANA SP263 assay according to tumor area positivity (TAP) score and combined positive score (CPS). Primary endpoints were PFS (BICR) and OS; efficacy by PD-L1 status (TAP) was prespecified. **Results:** With 26 mo median follow-up, PFS (HR, 0.63; P <0.001) and OS (HR, 0.72; P = 0.004) were significantly prolonged with zanidatamab + tislelizumab + CT vs tras + CT in the ITT population. In pts treated with zanidatamab + tislelizumab + CT, similarly prolonged PFS and OS were observed in PD-L1−negative and PD-L1−positive pts (Table); data were consistent between TAP and CPS. In PD-L1 TAP <1% and $\geq$1% pts, the 18-mo PFS was 50.3% and 42.6%, respectively, and the 24-mo OS was 63.7% and 53.5% with zanidatamab + tislelizumab + CT. In the tras + CT arm, OS was prolonged in PD-L1−positive vs −negative pts. Of note, in the tras + CT arm, 15% of pts received subsequent checkpoint inhibitors and 29% received subsequent HER2-targeted therapies vs 2% and 13%, respectively, in the zanidatamab + tislelizumab + CT arm. Additional details on these subgroups will be presented at the congress. **Conclusions:** In HERIZON-GEA-01, zanidatamab + tislelizumab + CT demonstrated meaningful improvements in PFS and OS in both PD-L1−positive and PD-L1−negative pts as determined by TAP or CPS. The longer OS observed with tras + CT in PD-L1−positive vs −negative pts may be at least partially explained by differences in subsequent therapies. These findings are notable as they demonstrate benefit for this regimen regardless of PD-L1 status. Clinical trial information: NCT05152147. Research Sponsor: Jazz Pharmaceuticals; BeOne Medicines; Zymeworks Biopharmaceuticals.

	Zanidatamab + Tislelizumab + CT	Tras + CT
ITT		
N	302	308
mPFS (95% CI), mo	12.4 (9.8, 18.5)	8.1 (7.0, 8.9)
mOS (95% CI), mo	26.4 (21.5, 30.3)	19.2 (16.8, 21.8)
TAP <1%		
n (%)	90 (29.8)	98 (31.8)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	7.9 (5.8, 9.6)
mOS (95% CI), mo	29.7 (24.7, NE)	15.8 (12.6, 21.4)
CPS <1		
n (%)	78 (25.8)	80 (26.0)
mPFS (95% CI), mo	18.5 (9.7, 25.2)	8.1 (5.8, 9.8)
mOS (95% CI), mo	30.3 (25.7, NE)	15.7 (12.6, 21.4)
TAP ≥1%		
n (%)	187 (61.9)	188 (61.0)
mPFS (95% CI), mo	11.3 (9.6, 18.5)	8.3 (6.9, 9.7)
mOS (95% CI), mo	26.4 (18.7, 35.9)	21.2 (17.7, 25.2)
CPS ≥1		
n (%)	198 (65.6)	206 (66.9)
mPFS (95% CI), mo	12.3 (9.7, 18.5)	8.2 (6.9, 9.1)
mOS (95% CI), mo	26.4 (18.7, 34.6)	20.8 (17.3, 23.9)

4011 **Rapid Oral Abstract Session**

A phase 2 pivotal study of savolitinib in patients with *MET*-amplified gastric cancer or gastroesophageal junction adenocarcinomas. First Author: Zhi Peng, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: MET amplification is a poor prognosis for survival in patients (pts) with gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJa). Currently no approved targeted therapy is available for MET-amplified GC/GEJa. Savolitinib is a potent and highly selective oral MET-TKI. Here we reported the primary analysis results from a pivotal phase 2 trial investigating savolitinib in MET-amplified GC/GEJa, conducted with registration intent (NCT04923932). **Methods:** Eligible pts had locally advanced or metastatic GC/GEJa with MET amplification (gene copy number $\geq$10 by FISH) and had failed $\geq$2 lines of prior standard therapy. Pts received savolitinib 200 mg (BW < 50 kg) or 300 mg (BW $\geq$50 kg) BID. The primary endpoint was ORR assessed by an Independent Review Committee (IRC) per RECIST 1.1, with a pre-specified efficacy threshold defined as the lower limit of the 95% CI of ORR exceeding 15%. Secondary endpoints mainly included DCR, DoR, TTR, PFS, OS and safety. An exploratory OS analysis was conducted in pts with MET-amplified GC/GEJa, who had previously received first-line, second-line, or later-line standard therapies, but were ineligible for study enrollment and did not receive the study drug. Plasma samples were also collected at baseline and end of treatment (EOT) for comprehensive genomic profiling using a 671-gene sequencing panel (Benrui GCP, OrigiMed). **Results:** As of Oct 8, 2025, 65 eligible pts were enrolled and received savolitinib. Baseline characteristics were: median age of 57.4 years, ECOG PS of 0 (13.8%) or 1 (86.2%), primary tumor sites of GC (84.6%) or GEJa (15.4%), and baseline ctDNA MET-positive rate of 64.6% (42 pts). Per the IRC assessment, ORR was 32.3% (95%CI: 21.2%, 45.1%), which exceeded the pre-specified efficacy threshold; in baseline ctDNA MET-positive pts (42 pts), IRC-assessed ORR was 45.2% (95%CI: 29.8%, 61.3%). IRC-assessed secondary efficacy endpoints were: DCR of 63.1%; mTTR of 1.4 months; mDoR of 9.7 months; and mPFS 4.0 of months. mOS was 6.9 months in the 65 treated pts, versus 4.8 months in 139 pts who received alternative treatments rather than the study drug in the exploratory OS analysis. Savolitinib-related TEAEs of Grade $\geq$3 occurred in 23 pts (35.4%). Exploratory ctDNA biomarker analysis showed that pts (N = 14) harboring baseline alterations in FGFR2, EGFR, PIK3CA, BRAF, or KRAS had lower ORR (14.3%, 2/14) and shorter mPFS (1.4 months). Additionally, in pts (N = 26) who provided PD/EOT samples, 12 pts developed alterations in these genes that were identified as putative acquired resistance mechanisms, and 4 pts had acquired MET mutations. **Conclusions:** Savolitinib showed clinical efficacy and a tolerable safety profile in pts with MET-amplified GC/GEJa who had received $\geq$2 lines of prior therapy, supporting it to be a future treatment option for this genetically defined population. Clinical trial information: NCT04923932. Research Sponsor: HUTCHMED Limited; AstraZeneca.

4012 **Rapid Oral Abstract Session**

Randomized phase II trial of olaparib and pembrolizumab vs olaparib alone as maintenance therapy in metastatic pancreatic cancer patients with germline BRCA1 or BRCA2 (gBRCA1/2) mutations: SWOG S2001. First Author: Vincent Chung, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Preclinical studies have demonstrated that PARP inhibitors modulate the immune microenvironment by increasing genomic instability, PD-L1 expression and activating the immune inflammatory stimulator of interferon genes (STING) pathway. The POLAR trial demonstrated promising results combining pembrolizumab with olaparib as maintenance therapy in patients (pts) with homologous recombination deficiency (HRD) mutations. S2001 is a randomized phase II trial evaluating the addition of pembrolizumab to olaparib as maintenance therapy in patients with gBRCA1/2. **Methods:** Eligible pts had mPDA with gBRCA1/2 mutations and had received a minimum of 4 months of platinum-based chemotherapy without progression. Pts were randomized 1:1 to olaparib 300 mg twice per day plus pembrolizumab 200 mg every 3 weeks or olaparib alone. The primary endpoint was progression-free survival (PFS) with a target hazard ratio (HR) of 0.6 (median PFS 7.0 vs 11.7 months) with 1-sided alpha=0.1 and 80% power. Secondary outcomes were safety and tolerability, overall survival (OS), overall response rate (ORR), and disease control rate (DCR). The accrual goal was 88 pts to have 78 eligible for analysis. Differences in PFS by treatment arm were assessed via stratified log-rank test, with first line platinum-based chemotherapy, Zubrod PS, and disease status after first line treatment as stratification factors. Tissue and blood samples for correlative studies were banked. **Results:** The study enrolled 73 patients, with 68 eligible, and was closed for futility after a planned interim analysis showed that PFS was not improved in the pembrolizumab + olaparib arm (p=0.82), despite higher ORR (p=0.20) (Table). Treatment was well tolerated, with no grade 4-5 treatment-related adverse events and similar toxicity profiles across arms. Autoimmune toxicities on the experimental arm included adrenal insufficiency, hyperthyroidism, and hypothyroidism. Grade 3 adverse events in both arms included neutropenia, anemia, thrombocytopenia, gastrointestinal toxicity and fatigue. **Conclusions:** S2001 is the first randomized controlled trial evaluating the addition of pembrolizumab to olaparib in pancreas cancer. Despite doubling the ORR and improvement in DCR and PFS in the experimental arm, the high bar of improving PFS to 11.7 months was not met. Activity seen in the experimental arm of S2001 is comparable to the HRD cohort of the POLAR trial which demonstrated ORR 35%, DCR 90% and PFS of 8.2 months. Further follow-up for mature survival outcomes and translational analysis of DNA and RNA are planned. Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819 with additional support from by Merck & Co, Inc. Clinical trial information: NCT04548752. Research Sponsor: NIH/NCI/NCTN grants; U10CA180819; Merck & Co., Inc.

	Pembrolizumab + Olaparib (n=34)	Olaparib (n=34)
Median PFS	8.2 months	6.4 months
Median OS	20.0 months	22.1 months
ORR	28.1%	14.3%
DCR	84.4%	64.3%

4013 **Rapid Oral Abstract Session**

Results from a phase 2a study of atebimetinib in combination with mGnP in advanced or metastatic pancreatic cancer. First Author: Vincent Chung, Department of Medical Oncology and Therapeutics Research, City of Hope, Duarte, CA

Background: Pancreatic ductal adenocarcinoma (PDAC) is driven predominantly by oncogenic KRAS signaling, yet prior attempts to target the MAPK pathway have been limited by toxicity and emergence of resistance. Atebimetinib is a next-generation, deep cyclic inhibitor (DCI) of MEK designed to achieve pulsatile pathway inhibition with improved tolerability. We report a Phase 2a cohort evaluating atebimetinib in combination with modified gemcitabine/nab-paclitaxel (mGnP) in the first-line treatment of advanced or metastatic PDAC (NCT05585320). **Methods:** In this multicenter, open-label, nonrandomized Phase 2a study, patients with previously untreated advanced or metastatic PDAC were eligible for participation and were treated with orally administered atebimetinib daily in combination with mGnP (modification: every other week dosing). The primary endpoint was objective response rate (ORR) per investigator assessment using RECIST 1.1 criteria in response-evaluable patients. The cohort was powered (~80%, one sided alpha 0.05) using an optimal Simon's 2-stage design. **Results:** Fifty-five patients were enrolled and treated with 320 mg atebimetinib daily + mGnP. ECOG performance status was 0-1 (100%); median age was 68 years (range 42-85 years), 62% were ≥65 years, and 55% were male. No grade 5 treatment-related adverse events (AE) were observed. No AE related to atebimetinib were higher than grade 3. Grade 3 AE related to atebimetinib occurred in 29% of participants, with the most frequent being rash (5%), ALT increased (5%), and AST increased (5%). Among the 50 response-evaluable patients, best overall response (BOR) achieved were 21 PR, 21 SD, 7 PD, 1 NE. The ORR was 42%, and DCR was 84%. With a median follow-up of 10.4 months (data cutoff Jan 7, 2026), 6- and 9-month OS rates were 88% and 79%, respectively; median PFS was 8.3 months and median OS was not reached. **Conclusions:** Atebimetinib in combination with mGnP demonstrated favorable safety and promising efficacy compared to historic standard-of-care (SoC) GnP.[1] A phase 3 registrational trial is planned to start in mid-2026 for evaluation of atebimetinib + mGnP versus SoC GnP. 1. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691-1703. doi:10.1056/NEJMoa1304369 (PMID: 24131140). Clinical trial information: NCT05585320. Research Sponsor: None.

4014 **Rapid Oral Abstract Session**

Nilvanstomig (ZG005), an anti-PD-1/TIGIT bispecific antibody, plus bevacizumab vs. sintilimab plus bevacizumab biosimilar as first-line therapy for advanced hepatocellular carcinoma: A randomized, multi-center, phase II trial. First Author: Hong Wu, Department of General Surgery/Liver Transplant Center, West China Hospital, Sichuan University, Chengdu, China

Background: Checkpoint inhibitors combined with anti-angiogenic therapy represents one of the standard first-line therapies for advanced hepatocellular carcinoma (aHCC). Nilvanstomig (ZG005) is a recombinant humanized anti-PD-1/TIGIT bispecific antibody. By blocking both pathways, it can synergistically activate T cells and enhance the anti-tumor activity of NK cells. This study evaluated ZG005 plus bevacizumab vs. sintilimab plus IBI305 (a bevacizumab biosimilar) as first-line therapy for aHCC. **Methods:** In this randomized, open-label, multicenter, phase 2 trial conducted in China, patients with aHCC who had not previously received systemic treatment were randomly assigned (1:1:1) to receive ZG005 10 mg/kg plus bevacizumab 15 mg/kg (Arm A); ZG005 20 mg/kg plus bevacizumab 15 mg/kg (Arm B); or sintilimab 200 mg plus IBI305 15 mg/kg (Arm C). All treatments were administered intravenously every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by baseline AFP level (< 400 vs. ≥400 ng/mL), macrovascular invasion or extrahepatic metastasis (presence vs. absence). The primary endpoint was IRC-assessed PFS per RECIST v1.1, with key secondary endpoints including PFS per mRECIST, ORR and DCR by both criteria, and OS. **Results:** As of the data cutoff (Nov 25, 2025), 95 patients were enrolled and received at least one dose of treatment (Arm A, n = 31; Arm B, n = 32; Arm C, n = 32). Baseline characteristics were well-balanced across the treatment arms. For all patients enrolled, the median age was 61 years (range, 37-75), with 85.3% of patients being male. Disease characteristics included BCLC stage B (28.4%) or C (71.6%), Child-Pugh score A5 (83.2%) or A6 (16.8%), baseline AFP ≥400 ng/mL in 45.3% of patients, and HBV positivity in 73.7%. Macrovascular invasion and/or extrahepatic metastasis were present in 71.6% (68/95) of patients. With a median follow-up of about 5 months, the IRC-assessed ORR was 32.3% in Arm A, 37.5% in Arm B, and 25.0% in Arm C per RECIST v1.1; the corresponding ORRs per mRECIST were 54.8%, 50.0%, and 34.4%. The IRC-assessed median PFS per RECIST v1.1 was not reached in Arm A or B, compared with 5.8 months in Arm C (Arm A vs. C: HR 0.40, 95% CI 0.15-1.05; Arm B vs. C: HR 0.28, 95% CI 0.10-0.79). The safety profiles were comparable across the three arms. No grade ≥3 hemorrhagic adverse events were reported in either Arm A or B. **Conclusions:** The combination of ZG005 and bevacizumab as first-line treatment in patients with aHCC demonstrated an early encouraging efficacy with an acceptable safety profile. Higher response rates and prolonged PFS were observed with the ZG005-based regimens. Longer follow up of the current study and future phase 3 trials are warranted to validate the efficacy and safety of ZG005 in combination with bevacizumab in aHCC. Clinical trial information: NCT06558227. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co.,Ltd.

4015 **Rapid Oral Abstract Session**

Tegavivint, a downstream Wnt/β-catenin inhibitor: Dose-finding results from a phase 1/2 trial in advanced hepatocellular carcinoma (aHCC). First Author: David Hsieh, Gastrointestinal Medical Oncology, UT Southwestern Medical Center, Dallas, TX

Background: Wnt/β-catenin pathway activation is a hallmark of many cancers, with Wnt pathway mutations (WPMs) present in ~40% of advanced HCC (aHCC). Tegavivint is a first-in-class small-molecule inhibitor of TBL1, a transcriptional co-factor required for nuclear β-catenin–dependent oncogenic gene expression. Binding of TBL1 by tegavivint disrupts the TBL1/β-catenin complex, resulting in selective degradation of nuclear β-catenin while preserving cytoplasmic and membrane-bound β-catenin functions associated with normal tissue homeostasis. This mechanism inhibits Wnt-driven oncogenicity while avoiding toxicities observed with upstream Wnt inhibitors. Here, we report dose-finding results from an ongoing phase 1/2 study of tegavivint in aHCC (NCT05797805). **Methods:** This multicenter, open-label phase 1/2 study employs a 3+3 dose-escalation design with backfill, followed by dose optimization. Eligible patients (pts) had aHCC previously treated with ≥1 systemic therapy, BCLC stage C or B disease not amenable to locoregional therapy, and Child-Pugh class A or B (score ≤ 7). WPM status was assessed by liquid biopsy. Tegavivint was administered intravenously once weekly. Primary objectives were safety and tolerability; secondary objectives included preliminary efficacy and PK/PD. **Results:** As of 21 Jan 2026, 39 pts were enrolled (median age 68 years [range 34–84]); 28 had WPMs, and the median number of prior systemic therapies was 2 (range 1–6). Pts were treated across four dose levels (3–8 mg/kg), demonstrating dose-proportional increases in exposure. At 8 mg/kg, 2 of 5 pts experienced Grade 3 anemia within the DLT window, establishing 3–6.5 mg/kg as the recommended dose range (RDR). Across all doses, the most common (all grade/grade ≥ 3; n/n) TRAEs were fatigue (9/0), hyperbilirubinemia (7/4; isolated, asymptomatic and reversible), anemia (5/5; reversible), myalgia (4/0), and decreased appetite (4/0). Among WPM pts evaluable for efficacy within the RDR (n = 18), those with ≤ 3 previous lines of therapy (n = 9) achieved an overall response rate (ORR) of 22%, disease control rate (DCR) of 89%, and median progression-free survival (mPFS) of 8 mo, compared with 0% ORR, 56% DCR, and 4 mo mPFS in pts treated in later lines (n = 9). No significant clinical benefit was observed in pts without WPMs. Pts remaining on treatment for ≥ 4 months (n = 9) demonstrated concordant improvements in liver enzymes, alpha-fetoprotein, platelet counts, and/or ctDNA variant allele frequency. **Conclusions:** Tegavivint is the first Wnt/β-catenin inhibitor to demonstrate monotherapy clinical activity and a manageable safety profile in heavily pretreated aHCC pts with WPMs. Observed partial responses, durable disease control, and on-target PD effects in 2L and 3L pts support further development of tegavivint as a monotherapy or in combination with other treatments for this population. Clinical trial information: NCT05797805. Research Sponsor: Iterion Therapeutics.

4016 **Rapid Oral Abstract Session**

A phase Ib/II trial of first-line trastuzumab, nivolumab, gemcitabine, and cisplatin in HER2-positive biliary tract cancer (HERBOT): A multi-institutional study from the Korean Cancer Study Group. First Author: Choong-kun Lee, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Several phase II trials support HER2 as a promising actionable target in advanced biliary tract cancers (BTCs). However, the efficacy of adding anti-HER2 therapy to the current first-line standard-of-care (ICI plus gemcitabine/cisplatin [GemCis]) remains unknown. We report the results of the HERBOT trial evaluating this quadruplet combination. **Methods:** This multi-institutional, open-label, phase Ib/II study (KCSG-HB23-05; NCT05749900) enrolled treatment-naïve pts with locally advanced/unresectable or metastatic, HER2-positive BTC (defined as centrally confirmed HER2 IHC3+, or IHC2+/ISH+, or *ERBB2* gene copy number ≥6.0 by NGS). Pts received trastuzumab 6mg/kg (after 8mg/kg load) D1, nivolumab 360mg D1, cisplatin 25mg/m^2 D1,8, and gemcitabine 1000mg/m^2 (dose level 0) or 800mg/m^2 (dose level -1) D1,8 every 3 weeks. The primary endpoints were recommended phase II dose (RP2D, phase Ib) and ORR per RECIST v1.1 (phase II). Secondary endpoints included PFS, DCR, OS, safety. Exploratory biomarker analyses included AI-powered whole-slide image (WSI) profiling of HER2 expression and immune phenotype assessment. **Results:** Dose level 0 was established as RP2D with no DLT. Among total of 40 pts, 29 (72.5%) had gallbladder cancer and 26 (62.5%) were HER2 IHC 3+. The primary endpoint was met with an ORR of 55% (95%CI: 38.5 – 70.7; 1 CR, 21 PR) and a DCR of 95% (95%CI: 83.5 – 99.4); median duration of response was 12.6 months (95%CI: 5.7 – NR). With a median follow-up of 17.0 months, median PFS was 10.6 months (95%CI: 7.8 – 17.4) and median OS was not yet reached. Three pts (7.5%) underwent curative-intent conversion surgery. Pts with HER2 IHC 3+ showed a numerically longer PFS compared to IHC 2+/ISH+ (17.4 vs 9.7 months; HR 0.46, 95%CI: 0.20 – 1.07). Common grade ≥3 treatment-related adverse events (TRAEs) included neutropenia (57.5%), anemia (30.0%), and thrombocytopenia (22.5 %). A grade 2 decreased ejection fraction occurred in 1 pt (2.5%); no grade ≥3 immune-related AEs were observed. AI-based WSI analyses revealed that ≥10% HER2 3+ tumor cells proportion was associated with higher ORR (80% vs 36.4%, P = 0.009) and numerically superior PFS (17.4 vs 9.1 months; HR 0.54, 95%CI: 0.23 – 1.28). Pts with inflamed immune phenotype (n = 4) showed durable responses (ORR 75%; mPFS and mOS NR). **Conclusions:** The HERBOT trial demonstrates that adding trastuzumab to first-line ICI plus GemCis provides robust antitumor activity and manageable safety in HER2-positive BTC. This study is the first to report the efficacy of a HER2-targeted quadruplet regimen in the first-line setting, providing strong clinical rationale for integrating HER2-targeted strategies into first-line treatment and complementing ongoing global phase III trials in this molecularly defined subgroup. Clinical trial information: NCT05749900. Research Sponsor: Korean Cancer Study Group; Boryung Corp; ONO/BMS.

4017 **Rapid Oral Abstract Session**

Pemigatinib for untreated unresectable/metastatic cholangiocarcinoma (mCCA) with fibroblast growth factor receptor-2 (FGFR2) rearrangement: Phase 3 FIGHT-302 results. First Author: Tanios S. Bekaii-Saab, Division of Hematology/Oncology Mayo Clinic Arizona, Phoenix, AZ

Background: First-line mCCA treatment is chemotherapy and immunotherapy. Based on the phase 2 FIGHT-202 trial, pemigatinib was the first FGFR1-3 inhibitor approved in second line and beyond for mCCA with *FGFR2* rearrangement. Results from the phase 3, randomized, global FIGHT-302 trial evaluating pemigatinib as first-line therapy are reported here (NCT03656536). **Methods:** Patients (pts) aged ≥18 y with previously untreated mCCA with *FGFR2* rearrangement were randomized 1:1 to receive oral pemigatinib (13.5 mg once daily q21) or intravenous chemotherapy (1000 mg/m^2 gemcitabine + 25 mg/m^2 cisplatin d1,8 q21 ≤8 cycles) stratified by previous receipt of 1 chemotherapy cycle, geographic region, and tumor burden. Pemigatinib crossover was allowed for control arm pts progressing on chemotherapy. Primary end point was progression-free survival (PFS). Secondary efficacy, safety, and exploratory end points were also analyzed. **Results:** After prescreening >4000 pts, only 196 had *FGFR2* rearrangement and were screened; 167 were randomized to receive pemigatinib (n=83) or chemotherapy (n=84) before closing the study early due to slow accrual. Baseline characteristics and demographics were similar between arms. Median PFS (mPFS) with pemigatinib versus chemotherapy was 8.3 versus 6.8 mo, respectively (hazard ratio [95% CI], 0.58 [0.39-0.87]; nominal *P*=.0078); secondary efficacy endpoints generally supported primary results (Table). Median OS was similar, although these results are confounded by FGFR inhibitor administration as second-line treatment. In the crossover group (n=42, second-line pemigatinib), mPFS was 8.1 mo. Safety was consistent with previous results (Table). Exploratory analyses of genetic co-alterations associated with treatment response will be presented. **Conclusions:** FIGHT-302 was the first phase 3 trial of a targeted therapy for untreated mCCA. Pemigatinib demonstrated superior activity and prolonged mPFS compared with first-line chemotherapy. The results confirm the current management paradigm of pemigatinib administration after disease progression on chemotherapy. Clinical trial information: NCT03656536. Research Sponsor: Incyte Corporation; N/A.

	Pemigatinib	Gemcitabine + cisplatin
mPFS (95% CI), mo[a]	8.3 (6.5-12.2)	6.8 (6.1-8.3)
Objective response rate, n/N (%)[a]	39/83 (47)	13/84 (15.5)
Median duration of response (95% CI), mo[a]	14.2 (8.7-24.7)	6.3 (4.3-not estimable)
Median overall survival (95% CI)[a,b], mo	24.4 (18.6-35.9)	25.0 (18.7-34.2)
Treatment related TEAEs, n/N[c] (%)	80/83 (96)	70/73 (96)
Serious TEAEs, n/N (%)[c,d]	23/83 (28)	17/73 (23)
Grade ≥3 TEAEs, n/N (%)[c]	65/83 (78)	49/73 (67)
TEAEs leading to treatment discontinuation, n/N (%)[c]	5/83 (6)	8/73 (11)
Fatal TEAE, n/N (%)[c,d]	3/83 (4)	0

[a]All randomized pts.
[b]Interpretation limited by second-line treatment with FGFR inhibitor in gemcitabine + cisplatin arm.
[c]Pts who received ≥1 study dose.
[d]None deemed treatment related.

4018 **Poster Session**

H&E 2.0: Artificial intelligence–driven prediction of N256-glycosylated CEACAM5/6 expression in esophageal and gastric adenocarcinomas. First Author: Felicia Wee, Institute of Molecular and Cell Biology (IMCB), Agency for Science, Technology and Research (A*STAR), Singapore, Singapore

Background: The antibody-drug conjugate (ADC) EBC-129 has shown promising clinical responses in a Phase 1A/B trial, where higher H-scores correlate with responses, slated to start Phase 2. It specifically targets N256-glycosylated CEACAM5/6, highly expressed on solid tumours, including gastro-oesophageal adenocarcinomas. Recent advances in deep learning enabled the extraction of morphological features from stained pathological images to predict protein expression from haematoxylin and eosin (H&E) images. We investigated the feasibility of training deep learning models on H&E images of gastro-oesophageal carcinomas and assessed the models' ability to predict EBC-129 antigen (Ag) expression directly from H&E images. **Methods:** H&E and immunohistochemistry (IHC) images from same sections of oesophageal and gastric adenocarcinoma TMA tissues (n = 103 cores) were acquired at the same magnification. Tumour and EBC-positive areas were annotated in FIJI, with images preprocessed in Python to obtain 112x112-pixel H&E image patches. Cell patches with tumour$^+$EBC$^+$ labels were classified positive while patches with all other labels were classified negative. Six cores were held-out for testing while class balancing was conducted for the remaining 97 cores, where image patches were split 80:20 for training and validation respectively. Deep learning prediction of Ag was tested using two model architectures (DenseNet121 and ResNet50 - with no pre-trained weights) employing k-fold cross validation (k = 5). Performance metrics were recorded for the best model of each split, with mean and standard deviation values tabulated across 5 splits to determine the best performing model architecture family, followed by core-level metrics to determine the best performing individual model. **Results:** Feasibility and predictive potential of deep learning models was demonstrated, with superior performance metrics exhibited by the DenseNet121 model. It outperformed ResNet50 across all metrics for the combined held-out test set: AUC (0.796 ± 0.092 vs 0.748 ± 0.105), balanced accuracy (0.727 ± 0.075 vs 0.664 ± 0.100), F1 score (0.756 ± 0.059 vs 0.742 ± 0.070) and AUPRC (0.426 ± 0.132 vs 0.404 ± 0.157). Friedman test and post-hoc Conover's test revealed significant ($p < 0.05$) differences in metrics amongst the 10 models, where subsequent rank sum of mean metric values showed that DenseNet121 fold2_epoch09 performed best across the held-out test cores, displaying robustness and generalisability. **Conclusions:** There is potential of deep learning models to predict EBC-129 Ag expression from H&E images and suggest possible triaging of patients suitable for treatment. Immediate next steps include examining virtual stain plots for comparison to ground truth IHC images. Future work will extend to pancreatic ductal adenocarcinoma, building on encouraging findings from the Phase 1 trial. Research Sponsor: Singapore National Medical Research Council; OFLCG23may-0039,OFLCG24MAY-0028,OFLCG24may-0025,CIAINV25jan-0001,MOH-001067, MOH-001610-00; A*STAR GAP Funding; I24D1AG059; Industry Alignment Fund-Industry Collaboration Fund; I2001E0065.

4019 **Poster Session**

A machine learning algorithm for optimizing treatment selection for patients with up to three hepatocellular carcinomas measuring ≤ 3 cm. First Author: Takashi Kokudo, National Center for Global Health and Medicine, Tokyo, Japan

Background: Liver resection (LR) and radiofrequency ablation (RFA) are recommended for patients with early-stage hepatocellular carcinoma (HCC) with three nodules measuring ≤3 cm and preserved liver function. This study aimed to develop a predictive model to guide treatment decisions based on survival outcomes. **Methods:** This study included 18,958 patients with up to three HCCs measuring ≤3 cm from the nationwide survey of Japan. The Recurrent Deep Survival Machines (RDSM) model was employed for deep survival analysis. We employed 10-fold cross-validation, the concordance index (C-index), and overall survival (OS) to assess model performance. Survival curves were compared using the log-rank test. To identify potential confounding factors, 1:1 propensity score matching (PSM) was performed. **Results:** Patients undergoing LR demonstrated significantly longer OS than those receiving RFA (5-year survival rate 81.4% vs. 73.1%; $P < 0.005$). The trained RDSM model achieved a C-index of 0.68. In the deep learning (DL) model, patients undergoing recommended treatment demonstrated significantly longer survival than those who did not (5-year survival rate 81.2% vs. 73.9%; $P < 0.005$; PSM, 81.9% vs. 76.7%; $P < 0.005$). The DL modeling recommended LR in 6,966 (84.5%) patients undergoing RFA, especially those showing typical imaging patterns (early enhancement and washout in the computed tomography images [85.9% vs. 61.7% and 84.1 vs.74.3%, respectively]). **Conclusions:** DL modeling effectively helped treatment allocation for patients with up to three HCCs measuring ≤3 cm. Our study indicates the potential utilization of DL modeling in the treatment allocation of patients with up to three HCCs measuring ≤3 cm. Research Sponsor: Small Business Innovation Research.

4020 **Poster Session**

Multi-modal AI modeling to predict clinical trial outcomes and benchmarks pan-RAS versus KRAS G12D inhibition in KRAS G12D–mutant PDAC. First Author: Marc Robert de Massy, Orakl Oncology, LE Kremlin-Bicetre, France

Background: In pancreatic ductal adenocarcinoma (PDAC), uncertainty persists regarding the optimal positioning of pan-RAS inhibitors, allele-specific KRAS inhibitors, and chemotherapy backbones. While patient-derived organoids (PDOs) provide functional resolution of drug response, their clinical utility has been limited by cohort size and insufficient validation against trial outcomes. **Methods:** A biobank of 135 colorectal cancer (CRC) and PDAC PDOs was assembled with matched clinical annotation, omics characterization, and functional drug profiling. Multi-modal AI models integrating molecular features, PDO drug response, and clinical covariates were trained to predict patient-level progression-free survival (PFS) and longitudinal response, and to aggregate these predictions into cohort-level clinical trial outcomes. Model performance was evaluated by benchmarking predicted outcomes against published results across 22 treatment arms from multiple clinical trials. A pan-RAS inhibitor (daraxonrasib), a KRAS G12D-directed inhibitor (zoldonrasib), and FOLFIRINOX (FFX) were compared as single agents or in combination in a KRAS G12D-mutant PDAC subset (n = 23), with external benchmarking to published clinical data. **Results:** The AI models demonstrated robust predictive performance at both the patient and cohort levels. Patient-level predictions were driven by functional PDO drug response and established clinical factors, including performance status and prior treatment exposure. At the cohort level, predicted and published outcomes showed good agreement (R^2 = 0.63), with correct ranking of treatment arms by efficacy in 78% of cases. In pairwise arm-to-arm comparisons, the model identified the superior regimen in 80% of comparisons. When applied to KRAS G12D-mutant PDAC, virtual clinical trial simulations preserved the relative efficacy hierarchy observed in external datasets. Zoldonrasib showed heterogeneous predicted activity (simulated ORR 20% vs reported 30%), whereas daraxonrasib demonstrated more favorable predicted outcomes (simulated ORR 35% vs reported 36%). Combination with FFX further improved predicted efficacy for zoldonrasib, particularly in first-line simulations (simulated ORR 38% vs reported 63%). **Conclusions:** Multi-modal AI modeling trained on clinically annotated PDO collections enables calibrated simulation of clinical trial outcomes and comparative assessment of therapeutic strategies in KRAS-mutant PDAC. By capturing patient-level heterogeneity and cohort-level efficacy trends, this framework provides a scalable decision-support tool for arm selection, therapeutic positioning, and trial design in KRAS-directed drug development. Research Sponsor: Fondation Jean-Jacques et Felicia Lopez-Loreta pour l'Excellence Académique; Banque Publique d'Investissement.

4021 **Poster Session**

Benchmarking the KEYNOTE-811 standard of care using AI-reconstructed external control arms in advanced gastric cancer. First Author: Augustine Annan, NouStarX, Westport, CT

Background: Randomized controlled trials in rare cancers and biomarker-enriched populations face significant recruitment burdens. External control arms (ECA) derived from historical Individual Patient Data (IPD) can mitigate these challenges, yet cross-trial heterogeneity often confounds comparisons. This study evaluates the feasibility of an AI-powered pipeline to reconstruct IPD from historical HER2+ advanced gastroesophageal adenocarcinoma trials and validates the cohort against a modern standard-of-care benchmark (KEYNOTE-811). **Methods:** An LLM-computer vision pipeline digitized KM curves from 10 historical trials (2011–2022) and the KEYNOTE-811 control arm (2023). IPD was reconstructed using a modified Guyot algorithm with risk-table guidance and least-squares optimization. Accuracy was validated against published HR and median survival. A propensity score matched (PSM) analysis (1:1 nearest-neighbor) compared the KEYNOTE-811 control arm (n=348) to historical controls (n=395). Sensitivity analyses addressed geographic imbalance (34% vs. 95% Asian) and early-period confounding via 3- and 6-month landmarking. **Results:** Technical validation demonstrated high fidelity: median OS concordance was 100%, with a reconstructed-to-published OS HR delta of only 0.01 (0.85 vs 0.84). The initial PSM suggested significantly worse outcomes for the KEYNOTE-811 control (OS HR 1.69, $p<0.0001$). However, this discrepancy was primarily driven by regional heterogeneity. After region-specific matching, OS HR stabilized at 1.13 (p=0.40). A 6-month landmark analysis further resolved early-period bias, achieving statistical equivalence for OS (HR 1.26, p=0.057) and PFS (HR 0.97, p=0.84). Residual imbalances in ECOG (SMD 0.25) and primary site (SMD 0.32) persisted but did not negate the trend toward equivalence. **Conclusions:** AI-powered IPD reconstruction achieves high fidelity to original trial data. While naive pooled ECAs may display era-specific survival artifacts, rigorous causal inference frameworks can resolve cross-trial heterogeneity. This study confirms that AI-reconstructed ECAs are viable tools for benchmarking novel therapies when paired with robust methodological guardrails for regional and baseline covariate alignment. Research Sponsor: None.

PSM sensitivity analyses with covariate balance.

Analysis	OS HR (95% CI)	PFS HR (95% CI)	Pairs	Key Imbalances (SMD >0.2)
Main PSM	1.69 (1.37–2.08)***	1.30 (1.05–1.61)*	217	Age (0.86), ECOG (0.42), Primary site (0.49), Region (0.65)
+ Geographic matching	1.13 (0.85–1.50)	0.87 (0.66–1.16)	119	ECOG (0.25), Primary site (0.32)
+ 3-month landmark	1.16 (0.93–1.45)	1.17 (0.93–1.48)	194/177	ECOG (0.25), Primary site (0.32)
+ 6-month landmark	1.26 (0.99–1.60)	0.97 (0.73–1.30)	174/115	ECOG (0.25), Primary site (0.32)

***$p<0.001$, *$p<0.05$; SMD = standardized mean difference; All other covariates SMD <0.2.

4022 **Poster Session**

First-line (1L) trastuzumab deruxtecan (T-DXd)—based regimens in advanced HER2-expressing gastric cancer (GC), gastroesophageal junction adenocarcinoma (GEJA), or esophageal adenocarcinoma (EA): Safety results from DESTINY-Gastric03 (DG-03) Part 2 arms D and F, and Part 4. First Author: Yelena Y. Janjigian, Gastrointestinal Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

Background: T-DXd 6.4 mg/kg monotherapy is approved in several countries for advanced HER2+ (IHC 3+ or IHC 2+/ISH+) GC/GEJA after an indicated HER2-directed regimen. Early data have shown promising antitumor activity with 1L T-DXd + immunotherapy + chemotherapy for advanced HER2+ GCs. Here, we report an approximate time-matched analysis of safety results for DG-03 Part 2 arms D and F, and Part 4. **Methods:** DG-03 (NCT04379596) is a Phase 1b/2, open-label, multipart trial. Part 2 (arms A–F) enrolled patients (pts) with previously untreated advanced HER2+ (IHC 3+ or IHC 2+/ISH+) GC/GEJA/EA. Pts in arm D received T-DXd 6.4 mg/kg + pembrolizumab (pembro) + fluoropyrimidine (FP; 5-fluorouracil or capecitabine), and pts in arm F received T-DXd 5.4 mg/kg + pembro + FP. In Part 4, pts with previously untreated advanced HER2-expressing (IHC 3+, IHC 2+/ISH+, IHC 2+/ISH−, or IHC 1+) GC/GEJA/EA were enrolled and received T-DXd 5.4 mg/kg + rilvegostomig (rilve; a monovalent, Fc-reduced, bispecific IgG1 antibody against PD-1 and TIGIT receptors) + FP. HER2 status was based on local testing. Secondary endpoints included frequency of adverse events (AEs) and serious AEs. **Results:** As of Feb 15, 2023, Aug 19, 2024, and Oct 16, 2025, 43, 32, and 62 pts received treatment (Tx) in Part 2 arm D, Part 2 arm F, and in Part 4, respectively. Median (range) total duration of Tx for both T-DXd and pembro was 6.1 (0.5–13.3) months (mo) in Part 2 arm D, and 6.9 (0.7–10.3) mo for T-DXd and 7.5 (0.7–10.3) mo for pembro in Part 2 arm F. Median (range) total duration of Tx for both T-DXd and rilve was 6.5 (0.7–14.7) mo in Part 4. A summary of safety data is shown in the Table. Drug-related adjudicated interstitial lung disease (ILD)/pneumonitis events occurred in 2 pts (5%) in Part 2 arm D, no pts in Part 2 arm F, and 2 pts (3%) in Part 4. **Conclusions:** Results with T-DXd (5.4 mg/kg)—based regimens were generally consistent with the known safety profiles of each agent; no new signals were observed. Safety data support use of pembro/rilve as combination partners for T-DXd (5.4 mg/kg) in advanced HER2-expressing GCs. Clinical trial information: NCT04379596. Research Sponsor: AstraZeneca.

n (%)	Part 2 arm D T-DXd 6.4 mg/kg + pembro + FP (n=43)	Part 2 arm F T-DXd 5.4 mg/kg + pembro + FP (n=32)	Part 4 T-DXd 5.4 mg/kg + rilve + FP (n=62)
AEs	43 (100)	31 (97)	60 (97)
Drug-related AEs*	40 (93)	27 (84)	55 (89)
Grade ≥3 AEs	38 (88)	15 (47)	31 (50)
Drug-related Grade ≥3 AEs*	33 (77)	11 (34)	24 (39)
Serious AEs	25 (58)	12 (38)	22 (36)
Drug-related serious AEs*	19 (44)	5 (16)	12 (19)
AEs leading to discontinuation of any IP	16 (37)	7 (22)	7 (11)
Drug-related AEs leading to death	4 (9)†	0	1 (2)‡

*Assessed by the investigator as possibly related to any investigational product (IP); †ILD/pneumonitis (n=2), respiratory failure due to pneumonitis/pneumocytis jirovecii infection (n=1), febrile neutropenia (n=1); ‡pneumonia.

4023 **Poster Session**

Sonesitatug vedotin (Sone-Ve) monotherapy in patients (pts) with claudin 18.2–positive (CLDN18.2+) advanced or metastatic gastric or gastroesophageal junction (GEJ) cancers: Data from CLARITY-PanTumor01. First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan

Background: Sone-Ve (AZD0901), an antibody-drug conjugate comprising an anti-CLDN18.2 antibody and monomethyl auristatin E, showed promising antitumor activity and a manageable safety profile in pts with advanced or metastatic gastric/GEJ cancers in the first-in-human study conducted in China. **Methods:** CLARITY-PanTumor01 is an ongoing, global, phase 2 study (NCT06219941) evaluating Sone-Ve in gastric/GEJ cancers, PDAC, and BTC outside of China. Here we report data for pts with CLDN18.2+ advanced or metastatic gastric/GEJ cancers and ≤2 lines of prior systemic therapy (substudy 1) receiving Sone-Ve 2.2 mg/kg IV Q3W (pts randomized to 1.8 mg/kg are not reported). Primary endpoints were safety and objective response rate (ORR; 30 pts were selected to estimate ORR; lack of efficacy is concluded if ≤6 confirmed responses). Secondary endpoints included duration of response (DoR) and progression-free survival (PFS). Molecular responses (MRs) based on circulating tumor DNA (ctDNA) were evaluated. **Results:** As of Oct 31, 2025, 67 pts received Sone-Ve 2.2 mg/kg, including 30, 31, and 6 pts from the randomized (RC), paired biopsy (PBC), and Japanese safety (JSC) cohorts, respectively. All pts had adverse events (AEs; grade ≥3 in 34.3% overall, 36.7% of the RC, and 35.5% of the PBC). The most common grade ≥3 AEs were neutrophil count decreased (7.5%), anemia (7.5%), vomiting (6.0%), and nausea (6.0%). Dose reductions were most commonly due to gastrointestinal (GI) AEs and occurred in 40.3% of pts overall, 56.7% of the RC, and 19.4% of the PBC (adoption of a 4-drug antiemetic regimen improved GI tolerability in the PBC). The ORR was 28.4% (95% CI: 18.0–40.7). Median DoR has not yet been reached. Additional data are in the Table. Among evaluable pts, 58.6% (17/29) had sufficient baseline ctDNA levels to enable MR analysis; of these, 10 (58.8%) had at least a partial MR (>50% ctDNA reduction) within 2 cycles of Sone-Ve initiation. **Conclusions:** Sone-Ve 2.2 mg/kg demonstrated clinically meaningful efficacy and a manageable safety profile consistent with the first-in-human study. ctDNA MRs were observed in over half the evaluable pts. Clinical trial information: NCT06219941. Research Sponsor: AstraZeneca.

	RC (n=30)	PBC (n=31)	Total* (n=67)
ORR, % (95% CI)†	26.7 (12.3–45.9)	29.0 (14.2–48.0)	28.4 (18.0–40.7)
Best overall response, n (%)†			
Complete response	2 (6.7)	1 (3.2)	3 (4.5)
Partial response	6 (20.0)	8 (25.8)	16 (23.9)
Stable disease	14 (46.7)	18 (58.1)	35 (52.2)
Progressive disease	7 (23.3)	4 (12.9)	12 (17.9)
Not evaluable	1 (3.3)	0	1 (1.5)
6-month response rate, % (95% CI)	87.5 (38.7–98.1)	NC (NC–NC)	71.9 (39.2–89.1)
PFS†			
Events, n/N (%)	22/31 (71.0)	19/31 (61.3)	47/68 (69.1)
Median, months (95% CI)	4.2 (2.9–8.6)	3.1 (2.8–5.5)	4.2 (3.0–7.0)
6-month, % (95% CI)	44.8 (26.5–61.6)	30.3 (13.3–49.3)	39.9 (27.7–51.9)

NC, not calculable.
*Includes the JSC.
†Investigator-assessed per RECIST v1.1.

4024 **Poster Session**

An open-label phase Ib/II study of trastuzumab deruxtecan combined with nivolumab and CAPOX in patients with HER2-low gastroesophageal adenocarcinoma (EPOC2203). First Author: Yu Aoki, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Trastuzumab deruxtecan (T-DXd) is standard of care for previously treated patients with HER2-positive metastatic gastroesophageal adenocarcinoma (mGEA) with exploratory analyses of the DESTINY-Gastric01 trial suggested activity in HER2-low (IHC 1+/2+ ISH-negative) disease and preclinical synergy with anti-PD-1 therapy. **Methods:** EPOC2203 (jRCT2031230477) is a prospective, multicenter, phase Ib/II study evaluating first-line T-DXd combined with nivolumab and CAPOX in HER2-low mGEA. Patients received T-DXd (5.4 or 4.4 mg/kg, day1) in combination with nivolumab (360mg/body, day1) and CAPOX (capecitabine 750 mg/m² twice daily on days 1–14; oxaliplatin 70 mg/m² on day 1) every 3 weeks. The primary endpoints were DLT rate to determine RP2D in phase Ib and ORR in phase II. Assuming a threshold ORR of 58% and an expected ORR of 80%, 28 patients in the full analysis set (FAS) treated at the RP2D were planned (one-sided $\alpha = 0.10$; power = 80%). **Results:** A total of 30 patients were enrolled. The median age was 59 years; 83.3% had HER2 IHC 1+ disease, 63.3% had gastric primary, and 96.7% had PD-L1 CPS ≥1. Two DLTs, both febrile neutropenia, occurred at T-DXd 5.4 mg/kg, while none were observed at 4.4 mg/kg in phase Ib part, which was selected as the RP2D. Among patients in the FAS (n = 28), the investigator-assessed ORR was 89.3% (80% CI, 77.7–96.0; $P< 0.001$), exceeding the prespecified threshold. At median follow-up of 10.1 months, median PFS was 8.1 months (95% CI, 5.6–not estimable). The 6-month OS was 89.3% (95% CI, 70.4–96.4). Six patients underwent conversion surgery, including three with pathological complete response. Grade ≥3 treatment-emergent adverse events occurred in 46.4% of patients who were treated at the recommended dose (n = 28). The most common grade ≥3 adverse events were neutropenia (25.0%), anemia (14.3%), febrile neutropenia (3.6%), and diarrhea (3.6%). Interstitial lung disease was observed in 3 patients (10.7%), with no grade ≥3 events. No treatment-related deaths were observed. **Conclusions:** T-DXd (4.4 mg/kg) combined with nivolumab and CAPOX demonstrated encouraging antitumor activity with a manageable safety profile as first-line treatment for HER2-low mGEA, supporting further evaluation. Clinical trial information: jRCT2031230477. Research Sponsor: Daiichi Sankyo.

4025 **Poster Session**

Application of unsupervised genetic clustering to identify biologically distinct cholangiocarcinoma subtypes with differential survival. First Author: Qianchen Zhang, Carle Illinois College of Medicine, Urbana, IL

Background: Cholangiocarcinoma (CCA) is a genetically heterogeneous malignancy for which current anatomic and histologic classifications inadequately predict survival. We hypothesized that unsupervised machine learning clustering of mutations and copy number alterations(CNA) could identify biologically distinct CCA subgroups with clinically meaningful differences in survival. **Methods:** Genomic and clinical data were obtained from the MSK cholangiocarcinoma dataset from cBioPortal. 790 patients with intrahepatic and extrahepatic CCA with available mutation and CNA data were included. Multiple unsupervised approaches were evaluated, including k-means, hierarchical clustering, non-negative matrix factorization, PCA–k-means, and UMAP–k-means. Model performance was assessed using silhouette scores, with UMAP–k-means (n=4 clusters) selected as the optimal method. Clusters were defined by dominant genetic alterations and compared for overall survival using Kaplan–Meier analysis with pairwise log-rank testing. Subgroup analyses included patients without curative-intent surgery and a young-onset cohort. **Results:** UMAP–k-means delineated four distinct genomic clusters ordered by progressively worse median survival. Cluster 1, defined by *ARID1A* or *BAP1* mutations, demonstrated the most favorable survival outcomes. Cluster 2 consisted of tumors wild type for recurrent driver alterations. Cluster 3 was characterized by *TP53*, *KRAS*, or *IDH1* mutations. Cluster 4, defined by *CDKN2A* double deletion or *ERBB2* amplification, exhibited the poorest median survival. Overall survival differed significantly across clusters, with all pairwise Kaplan–Meier comparisons reaching statistical significance except between clusters 1 and 2. These survival differences remained significant in patients who did not undergo curative-intent surgery. Notably, cluster 4 remained associated with significantly worse survival within the young-onset cohort. **Conclusions:** Unsupervised genomic clustering using UMAP–k-means identified biologically distinct subtypes of cholangiocarcinoma, with clinically significant survival differences that persist across surgical and age-based subgroups. These findings support future genomic subtyping as a prognostic framework and a rationale for biology-driven clinical trial stratification in cholangiocarcinoma. Research Sponsor: None.

Unsupervised genetic clustering identifies biologically distinct cholangiocarcinoma subtypes with differential survival.

Cluster	Primary Genetic alterations	N patients	Median OS	log-rank test P-value vs cluster 2	log-rank test P-value vs cluster 3	log-rank test P-value vs cluster 4
1	ARID1A or BAP1 mutant	120	28.0	0.308	<0.001	<0.001
2	Wild types	224	26.7	-	0.003	<0.001
3	TP53, KRAS or IDH1 mutant	319	22.0		-	0.002
4	CDKN2A deletion or ERBB2 amplification	127	16.9			-

LBA4026 **Poster Session**

Disitamab vedotin (DV) plus toripalimab (Tor) and chemotherapy (Chemo)/ trastuzumab (Tra) for first-line (1L) HER2-expressing locally advanced or metastatic (la/m) gastric cancer (GC): Updated results from the RC48-C027 trial. First Author: Zhi Peng, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

4027 **Poster Session**

A phase 2 clinical study of nimotuzumab plus S-1 and concurrent radiotherapy in 75 years and older patients with esophageal squamous cell carcinoma. First Author: Xiaojie Xia, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Concurrent chemoradiotherapy is the standard treatment method for inoperable and locally advanced esophageal cancer. Nevertheless, due to decreased physical function and the presence of multiple complications, older patients often have reduced tolerance to radiotherapy and chemotherapy. **Methods:** We conducted this prospective, single-center, phase II study to evaluate the efficacy and safety of nimotuzumab (an epidermal growth factor receptor antibody) plus concurrent radiotherapy and S-1 in 75 years and older patients with stage II-IVB esophageal squamous cell carcinoma (ESCC). The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS), objective response rate (ORR), disease control rate (DCR), safety, nutritional indicators, and quality of life (QOL). Most nutritional indicators remained stable after treatment. **Results:** As of June 2024, a total of 56 patients were enrolled in this study. The median follow-up was 24.1 months (95% CI: 8.8, 34.1). 11 patients had complete response, 39 patients had partial response, 5 patients had stable disease, and 1 patient had progressive disease. The ORR was 89.2%, and the DCR was 98.1%. The 1- and 3-year PFS rates were 67.8% (95% CI: 55.5%, 80.1%) and 35.8% (95% CI: 17.6%, 54.0%), with the median PFS was 25.3 months (95% CI: 16.5, 34.1). The 1- and 3-year OS rates were 79.6% (95% CI: 68.8%, 90.4%) and 40.1% (95% CI: 21.1%, 59.1%), with the median OS was 28.2 months (95% CI: 24.1, 32.3). Most adverse events were grade 1-2 (85.7%). Among survivors, 45.5% patients reported high satisfaction with their QOL, and 84.8% patients did not experience weight loss. **Conclusions:** Our treatment combination of nimotuzumab plus S-1 and concurrent radiotherapy indicated favorable efficacy and safety profile. This might be an underlying treatment choice for older patients with ESCC. Clinical trial information: NCT06048913. Research Sponsor: None.

4028 **Poster Session**

Preclinical efficacy of the anti-EBV agent brincidofovir (BCV) in EBV-associated gastric carcinoma (EBVaGC). First Author: Tetsu Kamitani, SymBio Pharmaceuticals, Tokyo, Japan

Background: Immune checkpoint inhibitor (ICI) plus chemotherapy is an approved therapy for EBVaGC whose tumors express PD-L1 (CPS $\geq$1). However, some patients are resistant to ICI or exhibit myelosuppression, making them unable to tolerate chemotherapy. BCV, an antiviral drug with no myelotoxicity, is effective against EBV (EC50: 30 nM), and has demonstrated anti-tumor activity against head and neck cancer and EBV-associated lymphoma. Recently, we found that SNU-719, an EBVaGC cell line, is sensitive to BCV *in vitro* (IC50: 1.95 μM). To seek conventional chemo-free regimens for EBVaGC, we have studied the preclinical efficacy of BCV monotherapy and combination therapy with ICI against EBVaGC. **Methods:** BCV was tested for its ability to induce dsDNA breaks in SNU-719 cells by γ-H2A.X immunostaining. To assess synergy of BCV with ICI, we analyzed BCV-induced immunogenic cell death (ICD) in SNU-719 cells using calreticulin and HMGB-1 assays. Additionally, we assessed BCV-induced expression of PD-L1 using qPCR and FACS. Since BCV induced both ICD and PD-L1 expression *in vitro*, we then evaluated the *in vivo* anti-tumor activity of BCV with or without ICI in humanized NOG mice bearing SNU-719 xenografts. Specifically, mice received intraperitoneal administration of vehicle, BCV, pembrolizumab (Pembro), or Pembro+BCV. Subcutaneous tumor growth was monitored for each group. After euthanasia, the SNU-719 xenografts were also used to measure the mRNA expression levels of EBV genes including *EBNA1*. **Results:** BCV induced both dsDNA breaks and ICD in SNU-719 cells, similar to the positive control bleomycin. It also induced PD-L1 mRNA and protein expression. Subsequent *in vivo* studies showed that, while BCV or Pembro monotherapy showed partial efficacy, the combination therapy of BCV and Pembro was effective in all mice. Notably, treatment with BCV significantly reduced the expression levels of *EBNA1* mRNA ($p < 0.05$) in the tumor tissue of SNU-719 xenografts. **Conclusions:** EBV is an oncovirus and its gene product EBNA1 is an oncoprotein for EBVaGC. This study showed a significant reduction of *EBNA1* mRNA expression by BCV. Therefore, in addition to its own anti-tumor effects, BCV may contribute significantly to the suppression of EBVaGC tumorigenesis via its anti-EBV activity. From a clinical perspective, BCV was effective against EBVaGC xenografts when combined with ICI. This less toxic regimen may be beneficial for EBVaGC patients, especially those with myelosuppression. Research Sponsor: SymBio Pharmaceuticals Limited.

4029 **Poster Session**

Early treatment failure despite first-line immunotherapy in real-world MSI-H/dMMR gastroesophageal cancer. First Author: Shannon L. Rhodes, Amgen, Inc., Thousand Oaks, CA

Background: Clinical trials of first-line (1L) immunotherapy (IO) in gastroesophageal cancer (GEC) demonstrate greater benefit in patients with microsatellite instability–high or mismatch repair–deficient (MSI-H/dMMR) tumors compared with the overall trial population. However, the benefit is not universal, and outcomes remain suboptimal for a subset of patients. Real-world (RW) evidence describing outcomes with 1L IO in MSI-H/dMMR GEC is limited. This study characterized treatment patterns and outcomes among RW MSI-H/dMMR GEC patients treated with 1L IO to better define residual unmet need. **Methods:** Using the Flatiron Health electronic health record-derived deidentified database, adults (≥18 years) diagnosed with locally advanced unresectable, metastatic, or recurrent gastric (GC), gastroesophageal junction (GEJ), or esophageal cancer (EC) between 17 Apr 2021 and 31 Dec 2024 were identified. Patients were required to have documented MSI-H or dMMR status and no trastuzumab exposure. Data were available through 08 Sep 2025. Time to next treatment or death served as a RW proxy for progression. **Results:** Among 3,047 eligible patients, MSI-H/dMMR prevalence varied by disease site and stage, ranging from 5.8% in metastatic GC to 17.6% in locally advanced GC; from 2.4% to 10.4% in GEJ disease; and from 3.4% to 4.4% in EC. A total of 199 MSI-H/dMMR GEC patients were identified (median age 75 years [IQR 66–82]; 36% female; 37% metastatic at diagnosis; 95% adenocarcinoma). Of the 155 MSI-H/dMMR patients who received 1L therapy, 32% received IO alone, 31% IO plus chemotherapy, and 37% chemotherapy alone. Among patients treated with 1L IO ± chemotherapy, 37% initiated 2L therapy or died within 6 months, increasing to 47% and 54% by 9 and 12 months, respectively. Baseline characteristics were largely similar between patients with and without progression within the first 12 months (Table). **Conclusions:** In this real-world cohort of MSI-H/dMMR GEC patients, a substantial proportion experienced early treatment failure despite 1L IO. More than one-third initiated second line therapy or died within 6 months, and over half progressed or died within 1 year. These findings underscore heterogeneity in benefit from 1L IO and highlight an ongoing need for improved risk stratification and alternative precision-based treatment approaches. Research Sponsor: None.

Characteristics of MSI-H/dMMR GEC patients by progression status at 12 months post start of 1L IO therapy.

		Progressors N=35	Non-progressors** N=30
Age, Median [IQR]		72 [66, 83]	73 [64, 80]
Female, %		34.3	40.0
Location, %	GC	62.9	63.3
	GEJ	8.6	13.3
	EC	28.6	23.3
Status*, %	Metastatic	48.6	46.7
	Non-metastatic	45.8	50.0
ECOG at 1L*, %	0/1	25.7	26.7
	2+	57.1	50.0

*Some patients are missing disease status and/or ECOG.
**Patients included in non-progressors were required to have activity in the data at least 12 months after 1L IO initiation.

4030 **Poster Session**

Tislelizumab (Tisle) combined with POFI (irinotecan, paclitaxel, oxaliplatin, and 5-FU/levoleucovorin) as first-line treatment for advanced gastric/gastroesophageal junction adenocarcinoma (AGC): Update from a single-arm, open-label phase I/II trial (SYLT-023). First Author: Jiajing Chen, Department of Gastrointestinal Medical Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: Tisle is an anti-PD-1 antibody. The combination of Tisle + XELOX/FP is a first-line treatment of AGC in China. Both irinotecan and paclitaxel have also shown antitumor activity in AGC. This Phase I/II study evaluated the efficacy and safety of Tisle + POFI in this population. **Methods:** This single-center, single-arm phase I/II study enrolled treatment-naïve patients with pMMR/MSS AGC, aged 18-75, who have at least one measurable lesion according to RECIST 1.1 and an ECOG PS of 0-1. Eligible participants received POFI (irinotecan/paclitaxel (mg/m2): 135/45 (dl #1), 150/45 (dl #2), 135/67.5 (dl #3), and 135/90 (dl #4), oxaliplatin 85 mg/m^2, levoleucovorin 200 mg/m^2, and 5-FU 2400 mg/m^2 for 46 hours every 2 weeks) in combination with Tisle 200mg every 2 weeks. The primary endpoint was the objective response rate (ORR) per RECIST 1.1. **Results:** As of Dec. 23, 2025, 47 patients were enrolled (median age: 58 years, range: 31–72; 26%(12/47) ECOG PS 1; 74% poorly differentiated; 68%(32/47) with ≥2 metastatic sites; 34% with programmed death-ligand 1 combined positive score [PD-L1 CPS] ≥1). The confirmed ORR was 76.6% (36/47), and the disease control rate was 95.7%. Median progression-free survival (PFS) was 11.1 months (95% CI: 8.8, 13.4) (versus 6.9 months (5.7-7.2) for ITT population for RATIONALE 305, ESMO 2023). Median duration of response was 9.7 months (95% CI: 6.7, 12.2). Median overall survival was 16.0 months (95% CI: 12.4, 23.0). All patients experienced treatment-emergent adverse events. The most common grade 3/4 adverse events included neutropenia (53.2%), leukopenia (27.7%), and anemia (21.3%). No new safety signals were identified. **Conclusions:** Tisle + POFI showed promising efficacy and a manageable safety profile as first-line treatment for HER2-negative, pMMR/MSS AGC, warranting further investigation. Clinical trial information: NCT05319639. Research Sponsor: None.

4031 **Poster Session**

CLDN18.2–targeting antibody-drug conjugate BA1301 in advanced solid tumors: Results from a phase I clinical trial. First Author: Dan Su, Gastroenterology Department, The Affiliated Cancer Hospital of Harbin Medical University, Harbin, China

Background: Aberrant expression of claudin18.2 (CLDN18.2) has frequently been observed in various solid tumors, making it a promising therapeutic target for those aggressive cancers. BA1301 is an ADC consisting of a fully humanized anti-CLDN18.2 monoclonal antibody conjugated to monomethyl auristatin E, a potent cytotoxic agent via site-specific glycol conjugation and a cleavable linker with a drug-to-antibody ratio of 4. Here we reported the results from a phase 1 dose escalation and dose expansion study of BA1301. **Methods:** Eligible pts failed or intolerant to standard therapy were enrolled. BA1301 was intravenously administered with accelerated titration (0.1/0.4 mg/kg Q3W) and traditional 3+3 design (1.2/2.0/2.5/3.0mg/kg Q3W). Dose expansion was evaluated at 1.6/2.0/2.5mg/kg Q3W. CLDN18.2 was test by immunohistochemistry [IHC] Claudin18.2 (EPR19202-244) Assay developed by Medx. Moderate to high expression of CLDN18.2 defined as IHC membrane staining intensity ≥2 in ≥40% of tumor cells. Endpoints were safety and efficacy per RECIST v1.1. **Results:** As of Dec 22, 2025, a total of 91 patients with advanced cancers (gastric cancer [59, 64.8%], biliary tract cancer [14, 15.4%], pancreatic cancer [11, 12.1%], gynecologic cancers [3, 3.3%] and other 4 tumor types) were enrolled, 49 (53.8%) patients had received ≥2 systemic therapies (median 2, range 1-7). In dose escalation (n = 24), No DLTs were observed.80 (87.9%) patients had at least one treatment-related adverse events (TRAEs), and 33 (36.3%) had grade 3 or 4 TRAEs. The most common TRAEs were corneal disorder (51, 56.0%) and anemia (30, 33.0%). 3(3.3%) pts discontinued treatment due to TRAEs, and no treatment related death reported. Among patients with CLDN18.2 moderate to high expression (N=76), 69 at the ≥1.6 mg/kg dose level had at least one post-baseline tumor assessment. Key efficacy outcomes are presented (Table). **Conclusions:** BA1301 was well-tolerated with a manageable safety profile and demonstrated promising anti-tumor activity in patients with CLDN18.2 moderate to high expression. The findings support further development of BA1301 as a new therapeutic approach to treat CLDN18.2-positive solid tumors. The trial (NCT06927349) is ongoing in China. Clinical trial information: NCT06927349. Research Sponsor: None.

Cancer Type	ORR n (%) [95%CI]	DCR n (%) [95%CI]
Gastric cancer (N=49)	14 (28.6) [16.6, 43.3]	35 (71.4) [56.7, 83.4]
Biliary tract cancer (N=10)	3 (30.0) [6.7, 65.2]	6 (60.0) [26.2, 87.8]
Pancreatic cancer (N=7)	1 (14.3) [0.4, 57.9]	5 (71.4) [29.0, 96.3]
Gynecologic cancer (N=3)	1 (33.3) [0.8, 90.6]	3 (100.0) [29.2, 100.0]
In total (N=69)	19 (27.5) [17.5, 39.6]	49 (71.0) [58.8, 81.3]

4032 **Poster Session**

Prognostic impact of AXL expression in upper gastrointestinal cancer in MONSTAR-SCREEN-2: An international collaborative study between United States and Japan. First Author: Kyosuke Seguchi, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: AXL, a receptor tyrosine kinase of the TAM family, promotes epithelial-mesenchymal transition (EMT) and tumor progression. Elevated AXL expression is reported as poor prognostic factor with immunosuppressive features in colorectal cancer (Karam Ashouri, et al. J Immunother Cancer. 2025). We investigated the prognostic impact of AXL expression and its associated molecular and tumor microenvironment (TME) features in upper gastrointestinal (GI) cancers. **Methods:** Treatment-naïve patients with gastric cancer (GC) and esophageal cancer (EC) enrolled in MONSTAR-SCREEN-2 with available RNA-seq data (Caris MI TumorSeek) were analyzed. AXL expression was dichotomized by median into high and low groups within each cancer type. Molecular alteration, including somatic mutations and copy number alterations, and expression of receptor tyrosine kinases, including FGFRs, VEGFRs, and EGFR were compared between groups. Overall survival (OS) was evaluated using Kaplan-Meier analysis and Cox proportional hazards models. Tumor microenvironment (TME) cell infiltration, assessed using xCell deconvolution and gene set enrichment analysis (GSEA) performed using Hallmark gene sets, was compared between AXL-high and AXL-low groups. **Results:** A total of 320 patients were analyzed (GC: n = 270; EC: n = 50). In GC, AXL-high patients were older than AXL-low patients (median 71 vs 66 years, p = 0.012), while no other baseline characteristics, including sex, histology, primary site, metastatic sites, microsatellite instability-high, and tumor mutation burden-high status, differed between groups. *ARID1A* mutations were enriched in AXL-high GC ($p < 0.05$), while *CCNE1* amplification was associated with AXL-low ($p < 0.05$). Across both cancer types, AXL-high tumors exhibited significantly higher expression of FGFR1, VEGFR1-3, and MET ($p < 0.01$). In GC, AXL-high was associated with significantly shorter OS compared to AXL-low (median 12.9 vs 16.6 months; HR 1.44, 95%CI 1.03-2.02; p = 0.034). Similarly in EC, AXL-high showed worse OS compared to AXL-low (median 10.4 vs not reached; HR 2.46, 95%CI 1.08-5.62; p = 0.027). TME analysis revealed increased stromal scores, endothelial cells, M1/M2 macrophages, and regulatory T cells, along with higher expression of immune checkpoint molecules, including PD-L2 and CTLA4, in AXL-high tumors. GSEA showed enrichment of EMT, IFN-γ response, and PI3K/AKT/mTOR pathways in AXL-high GC. **Conclusions:** AXL overexpression is a prognostic biomarker in upper GI cancers, and is associated with worse survival and a distinct molecular and immune landscape characterized by EMT activation and immune-suppressive TME. These findings support AXL as a potential therapeutic target and warrant further investigation of AXL-targeted therapy in upper GI cancers. Research Sponsor: None.

4033 **Poster Session**

CDH17 expression and tumor microenvironment composition in gastric cancer. First Author: Ammanuel Taye, Yale School of Medicine, New Haven, CT

Background: Cadherin 17 (CDH17), commonly referred to as liver-intestine cadherin, is a calcium-dependent cell adhesion molecule, is overexpressed across multiple gastrointestinal epithelial malignancies and is implicated in tumorigenesis and aggressive tumor phenotypes through diverse signaling pathways. Preclinical studies have demonstrated the therapeutic potential of anti-CDH17 approaches across multiple therapeutic modalities. However, the relationship between CDH17 and cellular characteristics within the gastric cancer tumor microenvironment (TME) is yet to be sufficiently characterized. **Methods:** To systematically investigate the association between CDH17 expression and TME composition in gastric cancer, we conducted a comprehensive multi-cohort analysis of clinically annotated gastric cancer samples with RNA sequencing data. Within each cohort, CDH17 expression levels were quantified and dichotomized into high and low expression groups based on cohort-specific median transcripts per million (TPM) values. We applied the xCell immune deconvolution algorithm to estimate the relative immune and stromal cell populations enrichment across all samples. **Results:** In total, we studied 1,811 samples within ten datasets. CDH17 high-expressing gastric cancers demonstrated a distinctive TME signature characterized by selective cellular depletion rather than generalized immune suppression. Natural killer (NK) cell enrichment was identified in three cohorts; however, this pattern lacked pan-cohort consistency. Notably, CDH17 high expression was associated with significant depletion in multiple critical effector populations, including CD8+ cytotoxic T lymphocytes (CD8+ T-cells: 6/10 cohorts $p < 0.05$), myeloid dendritic cells and cancer-associated fibroblasts (8/10 cohorts, $p < 0.05$), and hematopoietic stem cells (5/10 cohorts, $p < 0.05$). In contrast, other immune and stromal cell populations demonstrated heterogeneous patterns of association with CDH17 expression, with no clear or uniform enrichment or depletion across cohorts. **Conclusions:** CDH17 high-expressing gastric cancers harbor an immunologically "cold" tumor microenvironment characterized by selective depletion of critical effector immune and stromal cell populations. Research Sponsor: None.

4034 **Poster Session**

Quality-adjusted survival comparison for tislelizumab (TIS) + chemotherapy (CT) versus placebo (PBO) + CT as first-line (1L) treatment in gastric/gastroesophageal junction adenocarcinoma (GC/GEJC) patients with peritoneal metastasis (PM): Long-term follow-up from RATIONALE-305. First Author: Rutika Mehta, NewYork-Presbyterian Hospital/ Weill Cornell Medicine, New York, NY

Background: There is an unmet need for better treatment among patients (pts) with PM. A post hoc analysis of the phase 3 RATIONALE-305 (NCT03777657) trial showed that TIS + CT as 1L treatment for GC/GEJC pts with PM improved survival compared to PBO + CT (Qiu et al, 2025). The current study evaluated whether this survival benefit translated into quality of life (QoL) adjusted survival gains. **Methods:** This post hoc analysis used long-term follow-up data from the RATIONALE-305 trial (minimum follow-up 3 years; data cutoff February 28, 2024). The analysis focused on the intent-to-treat (ITT) population and subgroups defined by programmed death ligand-1 (PD-L1) ≥1% as well as ≥5% by Tumor Area Positivity (TAP) score. The well-established Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) methodology was used. QoL adjusted survival was calculated as the average time spent in three distinct health states during the trial follow-up: survival time with grade 3/4 toxicity, survival without progression/toxicity, and survival post progression, each weighted by QoL utility parameters specific to that state. A sensitivity analysis (SA) using trial-derived, treatment-specific EQ-5D utility values was also conducted. QoL adjusted relative survival gains ≥15% were considered "clearly clinically important," in line with commonly accepted Q-TWiST benchmarks (DOI 10.1007/s11136-005-1579-7). **Results:** At the maximum follow-up of 57 months in all randomized pts in RATIONALE-305, TIS + CT (n=501) pts experienced greater mean QoL adjusted survival than PBO + CT (n=496) (16.3 vs 13.1 months). Among pts with PM, TIS + CT (n=220) showed higher mean QoL adjusted overall survival than PBO + CT (n=214) (13.4 vs 10.8 months; 17.7% relative Q-TWiST gain) that was clearly clinically important. QoL adjusted survival benefit was also clearly clinically important in TIS + CT pts with PM with PD-L1 TAP score ≥1% (16.8% gain) and PD-L1 score ≥5% (33.0% gain) compared with PBO + CT. SA results further favored TIS + CT (Table). **Conclusions:** Treatment with TIS + CT resulted in clinically meaningful improvement in long-term quality-adjusted survival for GC/GEJC pts with PM versus those receiving CT alone. Clinical trial information: NCT03777657. Research Sponsor: BeOne Medicines, Ltd.

TIS + CT vs PBO + CT treatment difference.

	Mean Q-TWiST, months (95% CI)	Relative Q-TWiST Gain
Pts with PM[a]		
ITT pts (n=434)	2.6 (0.1 to 5.0), *P*=0.04	17.7%
PD-L1 TAP ≥1% (n=386)	2.5 (0.1 to 5.1), *P*<0.05	16.8%
PD-L1 TAP ≥5% (n=217)	4.7 (1.1 to 8.6), *P*=0.02	33.0%
Pts with PM (SA using EQ-5D scores)[b]		
ITT pts (n=434)	3.1 (0.8 to 5.5), *P*<0.01	21.3%
PD-L1 TAP ≥1% (n=386)	3.1 (0.5 to 5.6), *P*=0.02	20.8%
PD-L1 TAP ≥5% (n=217)	4.8 (1.3 to 8.2), *P*<0.01	33.9%

[a]Using standardized base case Q-TWiST utility weights.
[b]Using US mapping algorithm weights.

4035 **Poster Session**

Real-world adoption and sequencing of CLDN18.2, PD-L1, and HER2 testing in advanced gastric and gastroesophageal junction adenocarcinoma. First Author: Yifei Zhang, Yale University School of Medicine, New Haven, CT

Background: The FDA approval of zolbetuximab for CLDN18.2-positive advanced gastric and gastroesophageal junction adenocarcinoma (GEA) in Oct 2024, based on the SPOTLIGHT and GLOW trials, represents an important advance in biomarker-driven therapy. We aimed to describe real-world adoption of CLDN18.2 testing in the US, and CLDN18.2 co-expression with other clinically relevant biomarkers. **Methods:** Using the US-based, electronic health record-derived deidentified Flatiron Health Research Database, we evaluated biomarker testing patterns among patients diagnosed after 2016 across three periods: pre-SPOTLIGHT publication (2016–2022), post-SPOTLIGHT/pre-FDA approval (Jan 2023–Sep 2024), and post-FDA approval (Oct 2024 onward). We assessed CLDN18.2 testing uptake and co-expression with PD-L1 and HER2. **Results:** In total, our study included 11,099 patients (7,515 pre-SPOTLIGHT, 2,364 pre-FDA, 1,220 post-FDA). Compared to HER2 testing, 1.1% had CLDN18.2 testing pre-SPOTLIGHT, 21.3% pre-FDA and 39.5% post-FDA. The prevalence of biomarker positivity was as follows: HER2 20.1% (2,617/13,033), PD-L1 25.6% (1,913/7,487), CLDN18.2 42.6% (473/1,109). Among patients tested for all three biomarkers with available result dates, 69.9% underwent upfront comprehensive testing (HER2, PD-L1, CLDN18.2 within one week), while 30.1% had sequential testing, with a median interval of 91 days between tests. Among 1,034 patients tested for all three biomarkers, 13.9% were dual PD-L1/CLDN18.2 positive, and 4.4% were triple-positive. **Conclusions:** In this real-world analysis, CLDN18.2 testing uptake increased following SPOTLIGHT but remained incomplete, and nearly one-third underwent sequential rather than upfront comprehensive biomarker testing, resulting in clinically meaningful delays. These findings highlight the need for improved education and implementation of upfront, comprehensive biomarker testing strategies to optimize treatment sequencing and preserve therapeutic options for patients with GEA. Research Sponsor: None.

4036 **Poster Session**

Phase I/II trial of anti-CLDN18.2/PD-L1 recombinant humanized bispecific antibody Q-1802 plus XELOX in treatment-naive CLDN18.2-positive advanced GC/GEJ. First Author: Jifang Gong, Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: First-line therapy for HER2-negative advanced GC/GEJ remains a huge unmet clinical need. Claudin 18.2 (CLDN18.2), a tight junction protein, is specifically expressed in normal gastric mucosa but aberrantly overexpressed in various cancers, making it a high-value therapeutic target. Q-1802 is a first-in-class humanized bispecific antibody targeting both CLDN18.2 and PD-L1. Q-1802 can bind CLDN18.2 on tumor cells and kill them through Fc mediating antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis (ADCP). Meanwhile, it can activate immune system to eliminate tumor cells by blocking PD-1/PD-L1 binding. **Methods:** Qure-1802-201 was a multicenter, open-label, nonrandomized phase I/II trial. Eligible pts: CLDN18.2-positive (≥40% tumor cells with 2+/3+ membranous staining), HER2-negative, treatment-naïve, histologically confirmed unresectable locally advanced/metastatic GC/GEJ. Pts received Q-1802 (10 mg/kg or 20 mg/kg Q2W) plus standard XELOX (oxaliplatin IV d1; capecitabine PO d1-14 Q3W). Primary endpoints: DLT/MTD (Phase I) and ORR per RECIST v1.1 (Phase II). Secondary endpoints: efficacy, safety, pharmacokinetics, pharmacodynamics, immunogenicity. **Results:** As of Dec 11, 2025, 62 pts were enrolled (45 in 10 mg/kg, 17 in 20 mg/kg). No DLT observed; MTD not reached. All pts had TEAEs and Q-1802-related TEAEs; the latter mainly included nausea (75.8%), AST increase (61.3%), nausea (59.7%), ALT increase (51.6%), fatigue (50.0%). Incidences of ≥3 Grade TEAEs and Q-1802-related ≥3 Grade TEAEs: 74.2% and 43.5%, respectively. Most common Q-1802-related ≥3 Grade TEAE: thrombocytopenia (8.1%), followed by neutropenia (6.5%), anemia, WBC decrease, hypokalemia (4.8% each). Rate of Q-1802 permanent discontinuation due to TEAEs: 6.5%; no treatment-related death. ORR and median progression-free survival (mPFS) in 60 efficacy-evaluable pts were 70.0% (42/60; 95% CI: 56.8%–81.2%) and 11.3 months (95% CI: 8.0–16.8). A correlated trend was observed between efficacy and CLDN18.2 expression. In the 10 mg/kg cohort, ORR and mPFS were 73.0% (27/37; 95% CI: 55.9%–86.2%) and 11.3 months (95% CI: 7.1–16.8) in pts with CLDN18.2 high expression (2+/3+≥70%, N = 37), which were improved to 81.8% (9/11; 95% CI: 48.2%–97.7%) and 12.2 months (95% CI: 2.7–NE) when CLDN18.2 high expression companied with PD-L1 CPS≥5 (N = 11). DCR was nearly complete (non-response in 1 of 60 pts). ORR in the 20 mg/kg cohort (70.6%, 12/17; 95% CI: 44.0%–89.7%) was similar to 10 mg/kg (69.8%, 30/43; 95% CI: 53.9%–82.8%.). Overall survival (OS) in all pts and PFS in the 20 mg/kg cohort are under follow-up. **Conclusions:** Q-1802 plus XELOX has manageable safety and promising antitumor activity as first-line therapy for CLDN18.2-positive/HER2-negative advanced GC/GEJ, supporting a phase III trial (Q-1802 10 mg/kg as recommended dose). Clinical trial information: NCT05964543. Research Sponsor: None.

4037 **Poster Session**

A phase 1 study of SHR-3821, an ADCC-enhanced CLDN18.2/4-1BB bispecific antibody, in patients with advanced solid tumors. First Author: Hongfeng Gou, Gastric Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: CLDN18.2 is a highly selective tumor-associated antigen overexpressed in gastrointestinal malignancies, and has emerged as a promising therapeutic target. 4-1BB is a co-stimulatory receptor expressed on activated immune cells; its activation enhances antitumor immunity. SHR-3821 is an ADCC-enhanced bispecific antibody that specifically targets CLDN18.2 and activates 4-1BB in a CLDN18.2-dependent manner, enabling tumor-specific killing while minimizing systemic toxicity. This phase 1 study aims to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of SHR-3821 in patients with CLDN18.2-positive advanced solid tumors. **Methods:** Eligible patients had CLDN18.2-positive advanced solid tumors that had progressed on or lacked standard therapies. Patients received SHR-3821 via intravenous infusion every 3 weeks at prespecified dose levels: 0.1, 1, 3, 10, 15, 20 and 30 mg/kg during dose escalation (using a Bayesian optimal interval design), followed by dose expansion and efficacy expansion at 15 and 20 mg/kg. Primary endpoints included safety, maximum tolerated dose, and recommended phase 2 dose. **Results:** As of November 30, 2025, 40 patients with CLDN18.2-positive advanced solid tumors (23 gastric cancer [GC], 17 pancreatic cancer [PC]) were treated with SHR-3821 at doses ranging from 0.1 to 20 mg/kg. No dose-limiting toxicities occurred, and the maximum tolerated dose was not reached across the evaluated dose range. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 15 patients (37.5%), most commonly decreased neutrophil count (20.0%), decreased lymphocyte count (7.5%), and vomiting (5.0%). No TRAEs led to death; one (2.5%) patients discontinued treatment due to TRAEs. Preliminary pharmacokinetic analyses demonstrated dose-proportional increases in systemic exposure following a single 1–20 mg/kg administration, with terminal elimination half-lives ranging from 4.2 to 7.0 days. ORR in GC were 22.2% at 15 mg/kg and 37.5% at 20 mg/kg (Table). **Conclusions:** SHR-3821 showed tolerable safety and promising antitumor activity in patients with CLDN18.2-positive GC and PC. These data support further clinical development of SHR-3821. Clinical trial information: NCT06618651. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

Efficacy in GC and PC.

	GC		PC	
	15 mg/kg (N=9)	20 mg/kg (N=8)	15 mg/kg (N=4)	20 mg/kg (N=7)
Confirmed ORR, %	11.1	0	0	0
(n/N; 95% CI)	(1/9; 0.28-48.25)	(0/8; 0.00-36.94)	(0/4; 0.00-60.24)	(0/7; 0.00-40.96)
Confirmed DCR, %	55.6	62.5	50.0	42.9
(n/N; 95% CI)	(5/9; 21.20-86.30)	(5/8; 24.49-91.48)	(2/4; 6.76-93.24)	(3/7; 9.90-81.59)
Unconfirmed ORR*, %	22.2	37.5	0	0
(n/N; 95% CI)	(2/9; 2.80-60.01)	(3/8; 8.52-75.51)	(0/4; 0.00-60.24)	(0/7; 0.00-40.96)
Unconfirmed DCR, %	55.6	62.5	50.0	42.9
(n/N; 95% CI)	(5/9; 21.20-86.30)	(5/8; 24.49-91.48)	(2/4; 6.76-93.24)	(3/7; 9.90-81.59)

ORR, objective response rate; DCR, disease control rate.
*Four patients were pending efficacy confirmation.

4038 **Poster Session**

Randomized phase II trial of trifluridine/tipiracil (FTD/TPI) plus ramucirumab (RAM) versus FTD/TPI for previously treated patients with advanced gastric or gastroesophageal junction adenocarcinoma: Final analysis of RETRIEVE study (WJOG 15822G). First Author: Hirokazu Shoji, Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Promising activity of trifluridine/tipiracil (FTD/TPI) plus ramucirumab (RAM) has been reported in single-arm phase II trials as third- or later-line treatment for advanced gastric cancer (GC) and gastroesophageal junction (GEJ) adenocarcinoma (Lancet Gastroenterol Hepatol. 2021; 6: 209-217). We previously reported the primary analysis of the RETRIEVE study at ASCO-GI 2026, which demonstrated no significant difference in progression-free survival (PFS; median 2.69 vs 2.07 months) between FTD/TPI plus RAM and FTD/TPI alone. Here, we present the final analysis, including overall survival (OS) as a key secondary endpoint, along with updated results of other endpoints. **Methods:** RETRIEVE study is a multicenter, prospective, open-label, randomized phase II trial comparing FTD/TPI plus RAM versus FTD/TPI alone in patients with unresectable or recurrent GC or GEJ adenocarcinoma who were refractory or intolerant to fluoropyrimidine, taxane, or irinotecan, and refractory to RAM. Treatment is repeated every 4 weeks until disease progression or unacceptable toxicity. Key eligibility criteria include age of ≥20 years; ECOG performance status of 0 or 1, and at least a measurable lesion per RECIST 1.1. **Results:** Between January 2023 and June 2024, 111 patients were randomly assigned to receive FTD/TPI plus RAM (n = 56) or FTD/TPI alone (n = 55). At a median follow-up of 18.4 months, median OS was 6.08 months in the combination arm and 7.36 months in the monotherapy arm (hazard ratio [HR], 1.233; 95% CI, 0.817–1.862; P = 0.318). The proportion of patients who received subsequent treatment was 64.3% in the combination arm and 56.4% in the monotherapy arm. In the updated analysis, median PFS was 2.69 months in the combination arm and 2.07 months in the monotherapy arm (HR, 1.010; 80% CI, 0.781–1.307; P = 0.959). Objective response rate (ORR; 5.4% vs 9.1%, P = 0.489) and disease control rate (DCR; 50.0% vs 47.3%, P = 0.850) were consistent with the primary analysis. No novel adverse events were identified from the primary analysis. Any grade of n (49.1% vs 25.5%) and diarrhea (29.1% vs 14.5%) were more frequently observed in the combination arm than in the monotherapy arm. **Conclusions:** The final analysis demonstrated that FTD/TPI plus RAM did not provide a significant OS benefit compared with FTD/TPI alone in third- or later-line treatment for advanced GC and GEJ adenocarcinoma. Updated results of PFS, tumor response, and safety profile were consistent with the primary analysis. Clinical trial information: jRCTs041220120. Research Sponsor: Taiho Pharmaceutical Co., Ltd.

4039 **Poster Session**

Evaluation of homologous recombination deficiency (HRD) in gastric cancer: Real-world prevalence and outcomes with first-line (1L) platinum-based therapy. First Author: Dani Ran Castillo, Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Metastatic gastric and gastroesophageal junction cancers (GC/GEJ) have poor outcomes with limited predictive biomarkers to guide first-line (1L) therapy. HRD predicts sensitivity to platinum chemotherapy and PARP inhibition in several malignancies, but its clinical relevance is not well defined in GC/GEJ. We evaluated the association between HRD alterations, genomic context, and clinical outcomes following 1L platinum-based therapy (PBT) in metastatic GC/GEJ. **Methods:** We queried the de-identified Tempus multimodal database using the Tempus Lens Platform to analyze a cohort of patients with advanced GC/GEJ. All patients had DNA (xT, 648 gene DNA-seq panel) and/or RNA sequencing (xR, whole transcriptome RNA-seq). Patients were classified as HRD-altered (HRD-alt) if they harbored pathogenic or likely pathogenic germline or somatic alterations in at least one of 23 predefined HRD-associated genes; all others were classified as HRD wild-type (HRD-wt). Tumor mutational burden (TMB-H, ≥ 10 mut/Mb) and microsatellite instability (MSI) were assessed. Real-world (rw) overall survival (rwOS) was estimated using Kaplan–Meier methods. Hazard ratios (HRs) from Cox-proportional hazards models were adjusted for relevant clinical and molecular covariates at a significance level of $p < 0.05$. **Results:** Among 1,066 eligible patients, 257 (24%) were HRD-alt and 809 (76%) were HRD-wt. HRD-alt tumors were associated with TMB-H (21% vs 5.9%, $p< 0.001$) and MSI-high status (12% vs 1.2%, $p< 0.001$). Median OS was longer in HRD-alt compared with HRD-wt patients (15 vs 12 months, HR: 0.79, p = 0.033). Notably, HRD-alt tumors were strongly enriched for ERBB2 alterations compared to HRD-wt tumors (30% vs 8.8%, $p< 0.001$), predominantly driven by amplification (86%). Further stratification by HRD and ERBB2 status showed reduced HRs for rwOS in HRD-alt only (HR 0.78; 95%, p = 0.034), dual ERBB2/HRD-alt tumors (HR 0.63; 95% CI, 0.45–0.88, p = 0.006), and ERBB2-alt only (HR 0.52; 95% CI, 0.36–0.76, p < 0.001) compared to the wt/wt group. ERBB2-alt tumors demonstrated distinct co-mutation patterns enriched for cell-cycle and proliferative genes (*CCNE1, TOP2A)*, whereas *ERBB2*–wt tumors more frequently harbored *KRAS*, *ARID1A*, and *CDH1* alterations. **Conclusions:** In this large rw-cohort of metastatic GC/GEJ, HRD alterations identified a biologically distinct subgroup with improved OS and greater durability on 1L PBT. HRD status was associated with *ERBB2* amplification, and the HRD/ERBB2 status was associated with improved survival. These findings support HRD as a clinically relevant biomarker in GC/GEJ and justify prospective evaluation of HRD-informed treatment strategies. Research Sponsor: None.

4040 **Poster Session**

KEYNOTE-811: 6-year median follow-up of pembrolizumab plus trastuzumab and chemotherapy for previously untreated advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma. First Author: Akihito Kawazoe, National Cancer Center Hospital East, Kashiwa, Japan

Background: At the final analysis of the phase 3 KEYNOTE-811 trial (NCT03615326), first-line (1L) pembrolizumab (pembro) plus trastuzumab and chemotherapy (chemo) showed superior OS and consistently improved PFS and ORR with durable responses vs placebo plus trastuzumab and chemo in participants (pts) with HER2-positive (HER2+) advanced or metastatic gastric or gastroesophageal (G/GEJ) adenocarcinoma, particularly in pts with PD-L1 combined positive score (CPS) ≥1 tumors. Results supported the approval of pembro plus trastuzumab and chemo for 1L treatment of advanced or metastatic HER2+ G/GEJ adenocarcinoma with PD-L1 CPS ≥1. We report results after an additional 20 months of follow-up. **Methods:** Eligible pts with untreated advanced or metastatic HER2+ G/GEJ adenocarcinoma, measurable disease, and ECOG PS 0 or 1 were randomly assigned 1:1 to receive pembro 200 mg or placebo IV Q3W for up to 35 cycles plus trastuzumab 6 mg/kg (after loading dose of 8 mg/kg) and chemo (CAPOX or FP). Dual primary end points were OS and PFS per RECIST v1.1 by BICR. Secondary end points included ORR and DOR (per RECIST v1.1 by BICR), and safety. Data cutoff date was November 12, 2025. **Results:** Overall, 698 pts were randomly assigned to the pembro group (n = 350) or placebo group (n = 348). Median follow-up was 70.0 months (range, 50.9-84.2). In the intention-to-treat (ITT) population (all randomly assigned pts), median OS was 20.0 months (95% CI, 17.8-22.1) in the pembro group vs 16.8 months (95% CI, 14.9-18.7) in the placebo group. In pts with PD-L1 CPS ≥1, median OS was 20.1 months (95% CI, 17.9-22.9) vs 15.7 months (95% CI, 13.5-18.5). PFS, ORR, and DOR were also consistent between the ITT population and pts with PD-L1 CPS ≥1 (Table). Treatment-related AEs occurred in 341 pts (97.4%; grade ≥3, 206 [58.9%]) in the pembro group and 335 (96.8%; grade ≥3, 177 [51.2%]) in the placebo group. **Conclusions:** Pembro plus trastuzumab and chemo continued to show improved OS, PFS, and ORR vs placebo plus trastuzumab and chemo after a median study follow-up of 70 months, especially in pts with PD-L1 CPS ≥1. No new safety signals were seen. The findings continue to support pembro plus trastuzumab and chemo as the preferred 1L treatment for advanced or metastatic HER2+ G/GEJ adenocarcinoma. Clinical trial information: NCT03615326. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	ITT N = 698		PD-L1 CPS ≥1 n = 594	
	Pembro group n = 350	Placebo group n = 348	Pembro group n = 298	Placebo group n = 296
OS, median (95% CI), months	20.0 (17.8-22.1)	16.8 (14.9-18.7)	20.1 (17.9-22.9)	15.7 (13.5-18.5)
HR (95% CI)	0.81 (0.69-0.95)		0.79 (0.66-0.94)	
PFS, median (95% CI), months	10.0 (8.6-12.2)	8.1 (7.0-8.5)	10.9 (8.5-12.5)	7.3 (6.8-8.4)
HR (95% CI)	0.73 (0.61-0.87)		0.72 (0.60-0.87)	
ORR, % (95% CI)	72.6 (67.6-77.2)	60.1 (54.7-65.2)	73.2 (67.7-78.1)	58.4 (52.6-64.1)
DOR, median (range), months	11.3 (1.1+ to 80.0+)	9.5 (1.4+ to 79.6+)	11.3 (1.1+ to 80.0+)	9.6 (1.4+ to 79.6+)

4041 **Poster Session**

Efficacy and safety of PD-1 inhibitor plus chemotherapy vs chemotherapy alone in advanced gastric cancer patients with low or negative PD-L1 expression. First Author: Abdallah Al Ghnaimat, Hashemite University, Department of Medicine, Zarqaa, Jordan

Background: Advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma remains a major global health challenge with limited treatment options and poor prognosis in metastatic or unresectable disease. Immune checkpoint inhibitors targeting the programmed death-1 (PD-1) pathway, when combined with standard chemotherapy, have improved outcomes in overall populations, as shown in pivotal trials such as CheckMate-649 and KEYNOTE-859. However, efficacy is strongly influenced by tumor PD-L1 expression, with patients exhibiting low or negative PD-L1 expression (combined positive score [CPS] <1 or <5, or tumor area positivity [TAP] $<5\%$) derive less pronounced benefit. Subgroup analyses from ORIENT-16 and RATIONALE-305 show heterogeneous results, leaving uncertainty regarding the benefit of PD-1 inhibitors in this subgroup. We aimed to evaluate the efficacy and safety of first-line PD-1 inhibitor–chemotherapy combinations versus chemotherapy alone in this clinically important population. **Methods:** A systematic search of PubMed/MEDLINE, Embase, Cochrane Library, Scopus, ClinicalTrials.gov, and major oncology conferences was conducted through January 16, 2026. We included Phase III randomized controlled trials comparing PD-1 inhibitor plus chemotherapy with chemotherapy alone in adults with treatment-naïve advanced gastric or GEJ adenocarcinoma and low/negative PD-L1 expression (CPS <1, <5, or TAP $<5\%$). Meta-analyses were conducted using RevMan 5.4 with the generic inverse variance method for time-to-event outcomes (HR) and Mantel–Haenszel method for dichotomous outcomes (RR). Heterogeneity was assessed using I^2. Primary outcomes were overall survival (OS) and progression-free survival (PFS); secondary outcomes included objective response rate and safety. **Results:** Four Phase III RCTs (CheckMate-649, KEYNOTE-859, ORIENT-16, RATIONALE-305) comprising 4,761 patients were included. Subgroup data from patients with low/negative PD-L1 expression were analyzed. PD-1 inhibitors did not improve OS (HR 0.92, 95% CI 0.81–1.03, P=0.16; I^2=0%) or PFS (HR 0.84, 95% CI 0.70–1.02, P=0.08; I^2=47%). Results were consistent across CPS and TAP methods. Toxicity was significantly increased, with higher grade $\geq$3 adverse events (RR 1.48, P$<$0.001) and immune-related adverse events (any grade RR 2.80; grade $\geq$3 RR 4.30). **Conclusions:** In advanced gastric/GEJ adenocarcinoma with low/negative PD-L1 expression, first-line PD-1 inhibitor plus chemotherapy provides no survival benefit and substantially increases toxicity. These findings support biomarker-guided treatment selection and highlight the need for alternative therapeutic strategies. Research Sponsor: None.

4042 **Poster Session**

Characterization and management of gastrointestinal (GI) adverse events (AEs) with zanidatamab + chemotherapy (CT) ± tislelizumab in first-line (1L) HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (mGEA): Analysis from HERIZON-GEA-01. First Author: Elena Elimova, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: In HERIZON-GEA-01, replacing 1L trastuzumab (tras) + CT with zanidatamab + CT ± tislelizumab significantly improved progression-free survival and, with tislelizumab, yielded a statistically significant overall survival benefit in HER2+ mGEA. The safety profile was manageable; diarrhea was the most common AE. Here we further characterize GI AEs and diarrhea management. **Methods:** Eligible patients (pts) with previously untreated HER2+ mGEA were randomized 1:1:1 to zanidatamab (1800 mg [$<$70 kg]/2400 mg [$\geq$70 kg] IV Q3W) + tislelizumab (200 mg IV Q3W) + capecitabine/oxaliplatin (CAPOX) or 5-FU/cisplatin (FP); zanidatamab + CAPOX or FP; or tras + CAPOX or FP. CT could be discontinued per physician preference after cycle 6. Tras dose reductions were not permitted. Diarrhea prophylaxis (loperamide 4 mg orally BID) was mandatory in zanidatamab-containing arms for the first 7 days of cycle 1. **Results:** Median treatment duration was 43.1 wk with zanidatamab + tislelizumab + CT, 31.0 with zanidatamab + CT, and 30.0 with tras + CT. Median number of CT cycles was 6, 6, and 7, respectively. Diarrhea was the most common GI AE in all arms; other GI AEs were generally similar across arms. Among pts who experienced diarrhea, most had first onset in cycle 1 (76% in $\leq$3 wk) with median duration $<$2.5 wk (Table). Few pts had their first onset of diarrhea occur after cycle 6 when pts could discontinue CT. HER2-targeted therapy discontinuations (4.1%, 1.3%, 0.3%, respectively) and dose reductions (9.9%, 10.8%, NA) or delays (13.6%, 13.4%, 7.6%) due to diarrhea were infrequent. Diarrhea was more often managed with CT dose reduction (21.8%, 23.6%, 14.2%, respectively). Immune-mediated colitis occurred in 2.7% of pts with zanidatamab + tislelizumab + CT. Additional incidence and management data will be presented. **Conclusions:** In zanidatamab-treated pts, most diarrhea events were grade 1/2, and first-onset events tended to occur in cycle 1 and resolved in $<$3 wk. Diarrhea rarely led to zanidatamab discontinuation. The safety of zanidatamab-containing regimens appears favorable given the survival benefits; diarrhea should be managed with prophylactic loperamide and CT dose modifications as needed. Clinical trial information: NCT05152147. Research Sponsor: Jazz Pharmaceuticals; BeOne Medicines; Zymeworks Biopharmaceuticals.

Diarrhea	Zanidatamab + Tislelizumab + CT n = 294	Zanidatamab + CT n = 305	Tras + CT n = 302
Any-grade, n (%)	244 (83.0)	241 (79.0)[a]	161 (53.3)
Grade 1	79 (26.9)	80 (26.2)	84 (27.8)
Grade 2	92 (31.3)	99 (32.5)	38 (12.6)
Grade ≥3	73 (24.8)	61 (20.0)	39 (12.9)
Time to first onset, n (%), wk			
≤3	188 (77.0)	192 (79.7)	108 (67.1)
>3 to ≤6	25 (10.2)	27 (11.2)	22 (13.7)
>6 to ≤9	7 (2.9)	14 (5.8)	11 (6.8)
>9 to ≤12	4 (1.6)	4 (1.7)	2 (1.2)
>12 to ≤18	8 (3.3)	3 (1.2)	7 (4.3)
>18	12 (4.9)	1 (0.4)	11 (6.8)
Duration of first onset, median (95% CI), wk	2.0 (1.6, 2.6)	2.4 (1.9, 2.9)	1.4 (1.0, 2.1)

[a]Grade missing for 1 pt.

4043 **Poster Session**

Clinicopathologic and molecular features of Krukenberg tumors from gastric cancer (GC): A single-institution experience. First Author: Nancy Nguyen, Department of Internal Medicine, Alameda Health System - Highland Hospital, Oakland, CA

Background: Krukenberg tumors (KTs), ovarian metastases most commonly arising from gastric adenocarcinoma, represent an aggressive and understudied metastatic phenotype, frequently associated with diffuse-type gastric cancer (GC). The molecular determinants underlying this metastatic pattern remain poorly characterized. We aimed to define the clinicopathologic and genomic landscape of GC-associated KTs. **Methods:** We conducted a retrospective review of 103 patients with metastatic gastric or gastroesophageal junction adenocarcinoma treated at City of Hope (2020–2025). Twenty-two patients with confirmed KTs were identified. Clinicopathologic data were extracted from electronic medical records. Next-generation sequencing (NGS) for KTs was performed on primary or metastatic tumor specimens. Survival outcomes were estimated using the Kaplan-Meier method, with progression-free survival (PFS) and overall survival (OS) reported with 95% confidence intervals (CIs). **Results:** The median age at diagnosis was 45 years (range, 30–64). HER2 positivity was infrequent (14%), and PD-L1 expression was heterogeneous across tumors. Genomic profiling demonstrated recurrent alterations in *TP53* (53%), *ARID1A* (20%), *CDH1* (13%), *KRAS* (13%), and *PIK3CA* (13%). Notably, 86.4% of KTs exhibited CLDN18.2 immunohistochemical expression $>$ 75%, and 80% of patients had low PD-L1 CPS scores ($<$ 5). The CLDN18::ARHGAP26 fusion was detected in 30% of sequenced tumors, representing a highly recurrent structural alteration. Median PFS was 9 months (95% CI, 4–15), and median OS was 17 months (95% CI, 5–30). **Conclusions:** GC–associated KTs demonstrate a distinct molecular architecture enriched for diffuse-type genomic features, including frequent *TP53* mutations and recurrent CLDN18::ARHGAP26 fusions, aligning with the poor prognosis observed in this cohort. Our findings establish CLDN18 fusions as a recurrent molecular hallmark of GC–associated ovarian metastases, providing novel clinicopathologic insight into mechanisms of ovarian metastatic tropism. Importantly, the high prevalence of CLDN18.2 protein expression identifies a biologically actionable therapeutic vulnerability. CLDN18.2-directed strategies may represent an effective biomarker-driven treatment approach capable of achieving disease control without reliance on surgical intervention. These data define a high-risk, biologically distinct metastatic phenotype and support precision-guided therapeutic targeting, in this clinically aggressive patient population. Research Sponsor: None.

4044 **Poster Session**

SYS6010 combined with SYH2051 in advanced solid tumors: Results from a phase Ib/II trial. First Author: Rongbo Lin, Department of Gastrointestinal Medical Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: SYS6010 is an antibody-drug conjugate (ADC) composed of an epidermal growth factor receptor (EGFR)-specific antibody, a cleavable linker, and the topoisomerase I inhibitor JS-1. SYH2051 is an ATM inhibitor that disrupts DNA repair. The combination of SYS6010 and SYH2051 has shown preliminary antitumor activity (ASCO 2025) in advanced gastrointestinal tumors, particularly gastric cancer (GC). Here, we report the safety and preliminary efficacy of SYS6010 plus SYH2051 in patients with advanced solid tumors in phase Ib. **Methods:** This was a multi-center, open-label study. Phase Ib enrolled patients with advanced, EGFR-positive or EGFR-mutant solid tumors, including gastric cancer (GC) with EGFR expression ($\geq$1+) in $\geq$30% of tumor cells, who were refractory or intolerant to standard treatment. Phase Ib consisted of dose escalation and expansion parts. Dose escalation followed a 3+3 design, exploring SYS6010 at doses of 3.2 mg/kg and 3.6 mg/kg (both Q2W) in combination with SYH2051 at 20 mg, 40 mg, 60 mg, and 80 mg (QD). The primary endpoints were safety, maximum tolerated dose (MTD), and recommended phase II dose (RP2D). **Results:** As of October 31, 2025, a total of 117 patients (median age, 58 years; male, 73.5%; ECOG PS 1, 72.6%; metastasis, 100%) were enrolled. Most common tumor types included gastric cancer (GC, n = 66), colon cancer (n = 24), and rectal cancer (n = 15). One dose-limiting toxicity (grade 4 thrombocytopenia) was reported in the regimen of SYS6010 3.2 mg/kg plus SYH2051 60 mg. The RP2D was determined to be SYS6010 3.6 mg/kg plus SYH2051 40 mg. Overall, 94.0% (110/117) of enrolled patients reported at least one treatment-related adverse event (TRAE). The common TRAEs ($\geq$30%) were anemia (68.4%), leukopenia (50.4%), neutropenia (48.7%), decreased appetite (47.0%), nausea (43.6%), hypoalbuminemia (40.2%), fatigue (39.3%), and thrombocytopenia (33.3%). Grade $\geq$ 3 TRAEs occurred in 44.4% (52/117) of patients. Treatment discontinuations due to TRAEs were reported in 0.9% (1/117) of patients for SYS6010 and in 0.9% (1/117) for SYH2051. No deaths were reported due to TRAEs. Among all efficacy-evaluable GC patients treated with the RP2D regimen (n = 33), the confirmed objective response rate (cORR) was 15.2%, disease control rate (DCR) was 69.7%, and median progression-free survival (mPFS) was 4.5 mo (95% CI, 2.1–5.7). For the 17 patients receiving RP2D regimen as $\geq$3rd-line therapy, cORR was 23.5%, DCR was 88.2%, and mPFS was 5.4 mo (95% CI, 2.5–NR). The 3-mo and 6-mo PFS rates were 72.4% and 36.2%, respectively. Overall survival data were immature. **Conclusions:** The combination of SYS6010 and SYH2051 showed acceptable safety and tolerability in patients with advanced solid tumors. Promising antitumor activity was observed in patients with advanced GC, particularly among those receiving the regimen as $\geq$3rd-line therapy. Clinical trial information: NCT07104877. Research Sponsor: CSPC Megalith Biopharmaceutical Co.,Ltd.

4045 **Poster Session**

Efficacy and safety of tecotabart vedotin plus toripalimab with or without chemotherapy as first-line treatment for CLDN18.2-positive advanced gastric or gastroesophageal junction adenocarcinoma: Phase II study results. First Author: Jin Li, China Pharmaceutical University Shanghai GoBroad Cancer Hospital, Shanghai, China

Background: Tecotabart vedotin (TV; LM-302) is a novel and potent MMAE-based ADC targeting CLDN18.2. Previous data (ASCO 2025, abstract#4039) demonstrated promising efficacy and manageable safety profile of TV plus PD-1 inhibitor in patients (pts) with systemic therapy-naive advanced gastric or gastroesophageal junction (G/GEJ) cancer. Updated phase II results of TV plus toripalimab (T) with or without chemotherapy in this first-line setting are presented. **Methods:** Eligible pts had histologically confirmed, no prior systemic therapy, HER2-negative G/GEJ adenocarcinoma with CLDN18.2 positivity (IHC 2+/3+ in ≥1% of tumor cells). Pts received TV (1.8 mg/kg Q2W) plus T (3 mg/kg Q2W), with or without capecitabine or S-1. The primary endpoint was PFS per RECIST v1.1. Secondary endpoints were efficacy, safety, PK, and biomarker analysis. Data cutoff: November 25, 2025. **Results:** A total of 71 pts with G/GEJ adenocarcinoma were enrolled: 39 in the TV+T cohort and 32 in the TV+T+Chemo cohort. Baseline CLDN18.2 high expression (≥25%) was presented in 82.1% of pts in the TV+T cohort and 84.4% in the TV+T+Chemo cohort. PD-L1 CPS ≥1 was observed in 61.5% and 81.3% of pts, respectively. Median follow-up was 16.16 months in the TV+T cohort and 14.82 months in the TV+T+Chem cohort. The median PFS (95% CI) was 10.68 months (6.28, NE) and 12.55 months (6.80, NE), respectively. Among pts with CLDN18.2 ≥25%, the median PFS (95% CI) was 12.22 months (6.87, NE) and NE (8.44, NE), the median DOR (95% CI) was 13.86 months (9.36, NE) and NE (7.10, NE), ORR was 64.5% and 69.2%, and DCR was 96.8% and 96.2%, respectively. Median OS was not reached in either cohort. In pts with CLDN18.2 <25%, TV+T (N=7) and TV+T+Chemo (N=5) showed a median PFS (95% CI) of 5.72 (1.15, NE) and 6.80 (5.55, NE) months, ORR of 14.3% and 40.0%, DCR of 71.4% and 100%, and OS (95% CI) of 10.78 (2.56, NE) months and NE (8.25, NE), respectively. TRAEs occurred in all pts. Grade ≥3 TRAEs occurred in 66.7% of pts in the TV+T cohort and 81.3% of pts in the TV+T+Chemo cohort. The most common Grade ≥3 TRAEs (incidence ≥20%) were decreased neutrophil count in the TV+T cohort, and decreased neutrophil count and decreased white blood cell count in the TV+T+Chemo cohort. TEAEs leading to dose reduction occurred in 17.9% (Grade ≥3: 12.8%) and 43.8% (Grade ≥3: 18.8%) of pts, respectively. TEAEs led to treatment discontinuation occurred in 15.4% (Grade ≥3: 7.7%) and 31.3% (Grade ≥3: 28.1%), respectively. No treatment-related deaths were reported. **Conclusions:** TV+T, with or without chemotherapy, demonstrated encouraging anti-tumor activity and manageable safety as first-line treatment for CLDN18.2-positive advanced G/GEJ cancer. The doublet shows comparable efficacy to the triplet with enhanced tolerability, supporting further large-scale clinical investigation. Clinical trial information: NCT05934331. Research Sponsor: LaNova Medicines Limited.

4047 **Poster Session**

Phase II trial of SYS6010, an EGFR antibody-drug conjugate (ADC) in patients with advanced esophageal squamous cell carcinoma (ESCC). First Author: Rongbo Lin, Department of Gastrointestinal Medical Oncology, Fujian Cancer Hospital, Fuzhou, China

Background: SYS6010 is an EGFR- ADC composed of an EGFR-specific antibody, a cleavable linker, and the topoisomerase I inhibitor (TOPOi) JS-1. Preliminary clinical data from the phase I study of SYS6010 monotherapy in patients with solid tumors showed an acceptable safety and encouraging preliminary efficacy (ChiCTR2300072141). Here, we report the efficacy and safety results of SYS6010 in patients with ESCC in the phase II trial. **Methods:** Patients with advanced ESCC that was refractory or intolerant to standard therapy were enrolled. In the dose-expansion part, SYS6010 was administered intravenously at a dose of 3.6 mg/kg every 2 weeks (Q2W). The primary endpoint was objective response rate (ORR) assessed by the investigator. **Results:** As of Jan 14, 2026, 48 patients with ESCC (median age, 64.5 years; male, 89.6%; ECOG PS 1, 87.5%; metastatic disease, 93.8%) were enrolled and received SYS6010. Ten patients (20.8%) had received ≥3 prior lines of systemic therapy. The median follow-up was 3.9 months (mo; Q1-Q3: 3.1-5.6). Among 40 efficacy-evaluable patients, the confirmed ORR (cORR) was 35% (95%CI 20.6-51.7), and the disease control rate (DCR) was 67.5% (95%CI 50.9-81.4). Median progression-free survival (mPFS) was 4.6 mo (95% CI, 2.7–NR; 48% maturity). The 3-mo and 6-mo PFS rates were 56.3% and 41.4%, respectively. 15 patients remain on treatment with SYS6010. For TOPOi-naïve patients (n = 34), cORR and DCR were 41.2% (95%CI 24.7-59.3) and 70.6% (95%CI 52.5-84.9), respectively. mPFS was 4.6 mo (95%CI 2.8-NR; 45% maturity), with 3-mo and 6-mo PFS rates of 62.5% and 43.2%, respectively. 14 patients remain on treatment with SYS6010. Overall, 97.9% (47/48) of patients experienced treatment-related adverse events (TRAEs). Grade ≥3 TRAEs occurred in 31 (64.6%) patients. Common grade ≥3 TRAEs (≥5%) included neutropenia (29.2%), anemia (18.8%), leukopenia (18.8%), thrombocytopenia (12.5%), lymphocytopenia (8.3%), vomiting (8.3%), and nausea (6.3%). TRAEs led to treatment discontinuation in 4 (8.3%) patients. One death of unknown reason was reported and assessed by the investigator as related to the study drug. **Conclusions:** SYS6010 demonstrated a manageable safety profile and promising antitumor activity, supporting further development in patients with advanced ESCC, especially TOPOi-naïve patients. A phase 3 study is planned to compare SYS6010 with standard of care (SOC) in patients with TOPOi-naïve ESCC. Clinical trial information: ChiCTR2500099933. Research Sponsor: CSPC Megalith Biopharmaceutical Co., Ltd.

4048 **Poster Session**

Cadonilimab in combination with ivonescimab and chemotherapy as first-line (1L) therapy in patients with advanced gastric (G) or gastroesophageal junction adenocarcinoma (GEJA): Updated results from an open-label phase II trial. First Author: Guangyu Wang, The Affiliated Cancer Hospital of Harbin Medical University, Harbin, China

Background: Cadonilimab (AK104), an anti-PD-1/CTLA-4 bispecific antibody, plus chemotherapy significantly improved OS versus chemotherapy and had a tolerable safety profile in first-line (1L) treatment of advanced G/GEJA patients (pts), including those with low PD-L1 expression. Currently, it has been approved by NMPA. Ivonescimab (AK112), also approved in China, is a novel bispecific antibody against PD-1 and VEGF and has shown a clinically significant improvement in efficacy with favorable safety for advanced NSCLC in two phase 3 studies (HARMONi-2 and HARMONi-A). Here, we presented the updated data for the safety and efficacy of AK104 combined with AK112 and chemotherapy as 1L treatment in advanced G/GEJA. **Methods:** Pts with previously untreated advanced G/GEJA were enrolled. The phase II trial consisted of a dose-escalation part (part 1) and a dose expansion part (part 2). Eligible pts were firstly enrolled into sequential part1 including 10mg/kg and 15mg/kg AK104 (Q6W, D8) combined with AK112 (20mg/kg, Q3W, D1) and chemotherapy (SOX or XELOX) following the conventional 3+3 design. If the starting dose of 10mg/kg AK104 led to ≥2 dose-limiting toxicities (DLTs), 6mg/kg AK104 would be administered. After the part 1 completed, eligible pts were enrolled into the part 2 and received AK104 (the recommended dose, Q6W, D8) combined with AK112 (20 mg/kg, Q3W, D1) and chemotherapy (SOX or XELOX). The primary outcomes were safety and ORR. Secondary endpoints included DCR, PFS, OS, biomarkers of drug activity and pharmacokinetics. **Results:** As of 19 January 2026, 54 pts were enrolled with a median age of 60 years (range: 39-75). 55.6% were PD-L1 CPS < 5, 42.6% had liver metastases and 40.7% had peritoneal metastases. Among efficacy evaluable pts, the ORR was 71.7% and DCR was 95.7%. The median PFS (mPFS) was 8.4 months (mo) (95%CI: 6.0-13.1) and OS analysis was immature. In the pts with liver metastases, the ORR was 81.8%, DCR was 90.9% and mPFS was 10.7 mo (95%CI: 5.7-13.1). In the pts with peritoneal metastases, the ORR was 72.2%, DCR was 100.0% and mPFS was 6.4 mo (95%CI: 5.45-NR). Grade 3-4 treatment-related adverse events (TRAEs) were reported in 18.5% pts, mainly including hypokalemia (5.6%), decreased neutrophil count (3.7%), decreased platelet count (3.7%) and hyperbilirubinemia (3.7%). There were no grade 4/5 TRAEs or treatment-related deaths. **Conclusions:** Updated results demonstrated that AK104 combined with AK112 and chemotherapy as 1L treatment continued to show highly encouraging anti-tumor activity with a manageable safety profile in pts with advanced G/GEJA, including those with liver or peritoneal metastases. Clinical trial information: NCT06196697. Research Sponsor: None.

4050 **Poster Session**

Molecular circulating tumor DNA (ctDNA) profiling from patients (pts) treated with zanidatamab + chemotherapy (CT) in first-line (1L) HER2-positive (HER2+) advanced or metastatic gastroesophageal adenocarcinoma (mGEA). First Author: Elena Elimova, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Zanidatamab is a dual HER2-targeted bispecific antibody that binds to HER2 extracellular domains 2 and 4. In the phase 3 HERIZON-GEA-01 trial, 1L zanidatamab ± tislelizumab + CT significantly prolonged progression-free survival (PFS) and, with tislelizumab, yielded significant overall survival benefits versus trastuzumab + CT in HER2+ mGEA. Consistent results were previously reported in a phase 2 trial of zanidatamab + CT. ctDNA profiling provides a noninvasive approach to identify pts who could benefit from HER2-targeted therapies, and on-treatment ctDNA reductions may be associated with response. Here we report ctDNA profiling from the phase 2 trial. **Methods:** The phase 2 trial (NCT03929666) evaluated zanidatamab + CT (mFOLFOX6, CAPOX, or 5-FU/cisplatin [FP]) in 1L mGEA. Pts in part 1 had HER2-expressing (IHC 3+ or 2+) mGEA. Pts in part 2 had HER2+ (IHC 3+ or IHC 2+/FISH+) mGEA by central assessment (ccHER2+). Primary endpoint was confirmed objective response rate (cORR). PFS was a secondary endpoint. Plasma ctDNA samples were collected prior to cycle 1 of zanidatamab (baseline [BL]) and on treatment (cycle 2 day 15 for zanidatamab + CAPOX or FP; cycle 3 day 1 for zanidatamab + mFOLFOX6) for NGS by Guardant360 and/or Guardant Infinity. **Results:** 46 pts were enrolled (zanidatamab + mFOLFOX6 [n = 24], CAPOX [n = 20], FP [n = 2]). Most (41 [89%]) pts had ccHER2+ mGEA. cORR was 76.2% (95% CI 60.5, 87.9) and median PFS was 12.5 (95% CI 8.2, 21.8) mo. BL ctDNA was available from 39 pts; 29 had on-treatment samples, and 16 had matched BL and on-treatment samples. The concordance was 94% (34/36) between centrally assessed *ERBB2* amplification by FISH in tissue and *ERBB2* amplification in plasma ctDNA by NGS. Among 34 pts with detectable *ERBB2* amplification at BL, median PFS was 18.6 (95% CI 12.0, NE) mo. All pts with available samples and confirmed complete (CR) or partial (PR) response or stable disease (SD) had undetectable on-treatment *ERBB2* amplification in ctDNA. Most pts with *ERBB2* indel, fusion, or SNV (79% [15/19]) or with *PIK3CA* amplification or SNV (86% [12/14]) at BL had CR or PR. Nearly all (94% [15/16]) pts with available matched samples had a > 80% decrease in ctDNA from BL to on-treatment assessment on the Guardant Infinity panel. On-treatment ctDNA samples from pts with progressive disease or SD showed recurrence/persistence of *ERBB2* alterations and co-alterations across PI3K/AKT and RAS/MAPK pathways. Additional data will be presented. **Conclusions:** Molecular ctDNA profiling showed that 1L zanidatamab + CT in HER2+ mGEA could markedly reduce total ctDNA levels and *ERBB2* amplification detection early in treatment. Antitumor activity was observed among pts whose tumors harbored *ERRB2* and *PIK3CA* mutations, both of which are associated with resistance to standard HER2-targeted therapies. Clinical trial information: NCT03929666. Research Sponsor: Jazz Pharmaceuticals; Zymeworks Biopharmaceuticals.

4051 **Poster Session**

Survival outcomes according to ramucirumab (RAM)-related hypertension (HTN) in patients (pts) with advanced HER2-negative gastric (G) or gastroesophageal junction (GEJ) cancer: An exploratory analysis of the phase III ARMANI trial. First Author: Roberta Fazio, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, NA, Italy

Background: Retrospective studies suggest an association between treatment-related HTN and improved outcomes with anti-angiogenic agents, with most evidence derived from colorectal cancer pts treated with bevacizumab. Data on the prognostic significance of RAM-induced HTN are limited. We therefore explored the association between treatment-related HTN and survival outcomes in the ARMANI trial. **Methods:** ARMANI was a phase III trial enrolling pts with advanced HER2-negative G/GEJ cancer who had disease control after a 3-month first-line fluoropyrimidine and oxaliplatin (FOX) induction chemotherapy. Pts were randomized to switch maintenance with paclitaxel plus RAM (PTX-RAM) or the continuation of FOX. The objectives of this exploratory analysis were to evaluate the association between grade (G)≥2 HTN and survival outcomes across treatment arms (using the FOX arm as reference [ref]) and within the PTX–RAM arm. To mitigate time-related bias, Cox proportional hazards models were fitted with HTN modeled as a time-dependent covariate, considering pts 'non-HTN' until G≥2 HTN onset and 'HTN' thereafter. Because HTN is a post-randomization event, survival analyses in the PTX-RAM arm by HTN status were adjusted for baseline characteristics using inverse probability weighting based on propensity scores derived from a logistic regression model. **Results:** Among 276 pts (141 in PTX-RAM and 135 in FOX arm), G≥2 HTN occurred in 20 cases (7.2%), all observed in the PTX-RAM arm (20/141, 14.2%). The incidence of G≥2 HTN was similar between males and females (15.8% versus 10.9%) and between pts aged < 70 and ≥70 years (14.4% versus 13.5%). Median time to G≥2 HTN-onset was 3 months. In the between-arm comparison, the PTX–RAM arm showed improved progression-free survival (PFS) versus FOX regardless of HTN development (p = 0.192). In contrast, the overall survival (OS) benefit was greater in the HTN group (p = 0.071). These findings are detailed in the Table below. In analyses restricted to the PTX–RAM arm, G≥2 HTN onset was associated with improved OS (HR 0.43; 95% CI, 0.22-0.83; p = 0.033), whereas no significant difference was observed for PFS (HR 0.88; 95% CI, 0.50-1.57; p = 0.735). **Conclusions:** The development of G≥2 HTN was associated with a significant OS benefit in pts treated with PTX–RAM in the ARMANI trial. These findings support further research to identify biomarkers predictive of HTN onset to refine pts selection for switch maintenance strategies. Clinical trial information: NCT02934464. Research Sponsor: None.

	Median PFS (months) (95% CI)	HR (95% CI)	Median OS (months) (95% CI)	HR (95% CI)
FOX	3.5 (2.8−4.2)	ref	10.5 (8.5−13.5)	ref
PTX-RAM (non-HTN)	6.5 (5.8−7.7)	0.44 (0.32−0.60)	12.2 (10.6−14.4)	0.65 (0.49−0.87)
PTX-RAM (HTN)	9.0 (4.2−16.9)	0.61 (0.38−0.99)	24.6 (13.3−64.4)	0.39 (0.22−0.69)

4052 **Poster Session**

Genomic biomarkers of primary resistance to anti-EGFR monoclonal antibodies (mAbs) by comprehensive genomic profiling (CGP) in *EGFR*-amplified (ampl) advanced gastroesophageal adenocarcinoma (aGEA) and correlative analysis from a single-arm study with panitumumab. First Author: Cecilia Villa, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, NA, Italy

Background: *EGFR* ampl is found in up to 6% of patients with aGEA and accounts for the efficacy of anti-EGFRs in this patients' subgroup. The AMNESIA panel with *KRAS*/*PIK3CA*/*MET* mutations and *KRAS*/*EGFR*/*MET* amplifications represented a paradigm of negative selection to trastuzumab in HER2+ aGEA. Here, we aimed to characterize the prevalence and prognostic relevance of genomic drivers of primary resistance to EGFR blockade in *EGFR*-ampl aGEA. **Methods:** Patients with *EGFR*-ampl aGEA were retrieved from 3 CGP screening sources, i.e. the ARMANI phase 3 trial, an observational cohort established at the Fondazione IRCCS Istituto Nazionale dei Tumori (INT) of Milan and 11 patients with *EGFR* ISH positive aGEA treated with panitumumab as ≥2L from the 117/15 INT screening platform (thereafter Panitumumab study). CGP was performed by means of FoundationOne CDx next-generation sequencing (NGS). AMNESIA-EGFR panel grouped genomic alterations with clinical and biological rationale as driver of primary resistance to anti-EGFR mAbs, i.e. *EGFR* rearrangements, *FGFR2*/*HER2*/*MET*/*RAS* co-ampl, *RAS*/*MEK1*/*PIK3CA* ex20 mut, *AKT1/2* mut and *PTEN* loss. We evaluated prevalence of AMNESIA-EGFR alterations in the ARMANI and observational cohort. Then, we explored the prognostic impact of AMNESIA-EGFR panel and lack of *EGFR* ampl by NGS in the Panitumumab study. **Results:** *EGFR*-ampl by NGS was found in 3/130 (2.3%) and 7/128 (5.5%) pts in the ARMANI and observational cohort. *EGFR* ampl was confirmed by NGS in 8/11 pts (73%) in the panitumumab cohort. Among patients with *EGFR*-ampl tumors by NGS, AMNESIA-EGFR alterations were found in 9/18 (50%) pts, including: *KRAS* ampl (16.7%), *EGFR* rearrangement (11.1%), *PTEN* loss (11.1%), *FGFR2* co-ampl (5.6%), *MET* co-ampl (5.6%) and *MEK1* mut (5.6%). AMNESIA-EGFR panel alterations were mutually exclusive, except for one case with concurrent *MET* co-ampl and *MEK1* mutation. In the Panitumumab study, disease control rate (DCR) was 18.2% including a partial response and a stable disease. Median progression-free survival (PFS) and overall survival (OS) were 2.0 months (95%CI, 1.8-NA) and 5.3 months (95%CI, 3.38-NA). 7/11 pts had tumors with AMNESIA-EGFR alterations or lacked *EGFR* ampl by NGS. AMNESIA-EGFR+ or lack of *EGFR* ampl were associated with inferior DCR (0% vs 50%), PFS (median PFS 2.0 vs 3.8 months; HR 3.17 [95% CI, 0.64-NA] and OS (median OS 5.3 vs 6.4 months; HR 1.80 [95%CI, 0.45–7.14]). **Conclusions:** Genomic drivers of primary resistance to anti-EGFR mAbs are common in *EGFR*-ampl aGEA. A negative selection paradigm based on CGP may optimize outcomes with anti-EGFRs. Innovative drugs that may bypass resistance mechanisms to mAbs, such as bispecific antibodies, antibody-drug conjugates and bispecific T-cell engagers, are awaited. Research Sponsor: None.

4053 **Poster Session**

Real-world treatment patterns and overall survival (OS) in patients (pts) with HER2-positive (HER2+) advanced or metastatic gastroesophageal adenocarcinomas (mGEA) in the US. First Author: Farshid Dayyani, UC Irvine Health, Orange, CA

Background: The first-line (1L) standard of care for pts with HER2+ mGEA is HER2-targeted therapy (HER2 Tx) plus platinum-based chemotherapy (CT). Recent immunotherapy (IO) addition to this regimen prolonged OS of pts with HER2+ programmed death-ligand 1 (PD-L1)-positive (PD-L1+) mGEA. Here, we describe real-world treatment patterns and OS in pts with HER2+ mGEA in the US since the FDA approval of 1L IO. **Methods:** Adults with HER2+ mGEA who initiated 1L systemic therapy between May 2021 and 2025 and had ≥6 mo of follow-up (or died within 6 mo) after 1L initiation, were identified from the Flatiron Health Electronic Health Records database. OS from 1L initiation was evaluated with the Kaplan-Meier method in the overall HER2+ cohort and in a subset of pts with PD-L1+ disease. Outcomes were also reported with HER2 Tx + CT ± IO use. **Results:** Of 2237 pts with known HER2 status prior to 1L therapy, 21% were HER2+, defined as immunohistochemistry (IHC) 3+, IHC 2+/*ERBB2*-amplified, or per physician's note. Mean (SD) age was 66.1 (11.7), 20% of pts were female, and 66% had an Eastern Cooperative Oncology Group performance status ≤1. Of 292 pts with HER2+ mGEA and known PD-L1 status prior to 1L, 81% were PD-L1+ (combined positive score ≥1 or per physician's note). Of the 467 pts with HER2+ mGEA who received 1L therapy, 60% had HER2 Tx, 28% had CT alone, and 10% received IO-based regimens without HER2 Tx. Of the 281 pts on 1L HER2 Tx, 58% had HER2 Tx + IO + CT and 37% had HER2 Tx + CT. Overall, 228/467 (49%) pts treated in the 1L went on to receive second-line (2L) therapy. In the 2L setting, 70% of pts received HER2 Tx, including 38% pts who only received CT or IO-based regimens without HER2 Tx in 1L treatment. A total of 42% of pts on 2L therapy received 1L and 2L HER2 Tx. Among the 467 pts with HER2+ mGEA, median OS (mOS) from 1L initiation was 17.4 mo. In the PD-L1+ subgroup, mOS was 19.0 mo in pts on HER2 Tx + IO + CT, and 17.2 mo in pts on HER2 Tx + CT without IO (Table). Across treatment groups, mOS remained <2 years, and the 24-mo OS rate was <40%. **Conclusions:** Despite the availability of HER2 Tx, a significant unmet need remains, as 40% of pts with HER2+ mGEA did not receive this option in 1L regimens. OS was numerically longer with HER2 Tx + IO + CT vs without IO in the HER2+/PD-L1+ mGEA subgroup. These data underscore the need to improve OS and the opportunity to enhance biomarker-guided management of HER2+ mGEA. Research Sponsor: Jazz Pharmaceuticals.

OS analysis.

	HER2+			HER2+/PD-L1+ Subgroup		
	HER2+ (Overall) (n = 467, 100%)	1L HER2 Tx + IO + CT (n = 164, 35%)	1L HER2 Tx + CT (n = 103, 22%)	PD-L1+ (all) (n = 237, 100%)	1L HER2 Tx + IO + CT (n = 95, 40%)	1L HER2 Tx + CT (n = 40, 17%)
Median OS, mo (95% CI)	17.4 (15.7, 20.5)	19.3 (15.7, 22.3)	17.2 (13.5, 21.3)	17.2 (15.0, 20.9)	19.0 (15.6, 24.6)	17.2 (12.6, 24.4)
OS Rate, (%)						
6-mo	83.0	85.5	79.8	82.3	87.2	77.5
12-mo	65.5	67.6	66.4	64.1	67.9	66.2
18-mo	48.9	52.4	46.3	47.2	53.0	41.7
24-mo	34.7	37.2	26.3	36.0	39.5	30.6

4054 **Poster Session**

Updated results of benmelstobart plus anlotinib combined with SOX in the first-line treatment of advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma with low PD-L1 expression: A single-arm, multicenter phase II clinical trial. First Author: Yong-Xu Jia, Department of Oncology, Zhengdong Campus, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background: While PD-1 inhibitors plus chemotherapy have become standard first-line therapy for advanced HER2-negative gastric/gastroesophageal junction (G/GEJ) adenocarcinoma, patients with low PD-L1 expression (Combined Positive Score (CPS) < 5) derive limited benefit. Anti-angiogenic agents can modulate the tumor immune microenvironment and synergize with immune checkpoint inhibitors. Anlotinib, a multi-targeted tyrosine kinase inhibitor approved in China, offers a promising combination strategy. This study evaluates the efficacy and safety of benmelstobart (a PD-L1 inhibitor) combined with anlotinib and SOX (S-1 plus oxaliplatin) as first-line therapy in patients with advanced G/GEJ adenocarcinoma and low PD-L1 expression. **Methods:** Patients with HER2-negative, unresectable, locally advanced, or metastatic G/GEJ adenocarcinomas and PD-L1 CPS < 5, who had not received prior systemic therapy were included. They received benmelstobart (1200mg, iv, d1, q3w) combined with anlotinib (10mg, po, d1~14, q3w), oxaliplatin (130mg/m^2 , d1, iv, q3w) and S-1 (40mg, po, bid, d1~14, q3w) for 6 cycles as initial therapy. Maintenance therapy with benmelstobart (1200mg, iv, d1, q3w) plus anlotinib (10mg, po, d1~14, q3w) followed for non-progressive disease until PD or unacceptable toxicity occurred. Tumor responses were evaluated by RECIST 1.1 criteria. The target sample size was 37, with ORR as the primary endpoint, and safety, DCR, DoR, PFS, and 1-year OS rate as secondary endpoints. **Results:** From June 2023 to June 2025, 37 patients were enrolled. At the data cut-off date (December, 2025), the best overall response indicated that there were 31 PR (83.8%) and 6 SD (16.2%). Therefore, the preliminary ORR was 83.8% (95%CI: 68-93.8), DCR was 100% (95%CI: 90.5-100). The preliminary prognostic result exhibited that the median PFS of the 37 patients was 11.3 months (95%CI: 8.07-14.53). The 1-year OS rate was 91.33% (95%CI: 75.46–97.12). Safety was manageable, common TRAEs > 20% included platelet count decreased (54.1%), white blood cell decreased (32.4%), anemia (24.3%). **Conclusions:** The combination of benmelstobart, anlotinib, and SOX demonstrated promising efficacy with a manageable safety profile as first-line therapy for advanced G/GEJ adenocarcinoma with low PD-L1 expression. These findings warrant validation in larger cohorts. Clinical trial information: NCT06939452. Research Sponsor: None.

4055 **Poster Session**

Nimotuzumab combined with paclitaxel and cisplatin as first-line treatment for metastatic esophageal squamous cell carcinoma: A prospective, multicenter, double-blind, randomized controlled clinical study. First Author: Zhihao Lu, Beijing Cancer Hospital, Beijing, China

Background: Chemotherapy for advanced esophageal squamous cell carcinoma (ESCC) is limited due to the lack of effective drugs. Such as traditional two drugs chemotherapy (5-Fluorouracil and Cisplatin) as first-line treatment for metastatic and recurrent ESCC has an efficacy of 25-35%. Nimotuzumab is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody. Previous studies have shown that its combination with paclitaxel and cisplatin (TP regimen) has a good efficacy, with an objective response rate (ORR) of up to 55%, median overall survival (mOS) 13.9 months in some small-sample trials. **Methods:** Eligible patients from 36 centers in China, who were randomly assigned to receive nimotuzumab (400 mg once per week, up to 2 years) or placebo followed by TP regimen (paclitaxel 175 mg/m², cisplatin 60 mg/m², Day 1, with a 21-day cycle, up to 6 cycles) until disease progression or unacceptable toxicity. The primary end point was overall survival (OS) and the secondary end points were progression-free survival (PFS), response rates, quality of life (QoL) and safety. **Results:** A total of 640 patients were screened. 503 patients were enrolled and 161 patients with EGFR gene amplification tumors were eligible. In the full analysis set of 497 patients who had took at least one dose of medication, there were no differences in baseline characteristics. The mOS were 12 vs 11.5 months, and the median PFS were 5.6 vs 5.4 months respectively, suggesting survival benefit trend in the trial. ORR were 55.5% and 50.4% for both arms. In the EGFR gene amplification subgroup, the mOS was 13.3 vs 9.5 months (log-rank test, hazard ratio [HR] = 0.66 (95%CI, [0.47-0.93]), P = 0.016) for two groups. Patients who were with ESCC at stage IV, as well as who had not undergone surgery, radical radiotherapy, or neoadjuvant and adjuvant therapy showed significant survival benefits after the addition of nimotuzumab. Median PFS were 6.0 vs 5.5 months for two arms (log-rank test, HR = 0.63 [0.43-0.91], P = 0.014). Both OS and PFS were longer in the nimotuzumab group than in the placebo group. The ORR of the two groups were 61.3% and 44.0%, respectively (P = 0.029). There were no statistically significant differences in the QoL scores of the FAS population at each time point before and after treatment. The incidence of adverse events were comparable in the experimental group and the control group. Such as the incidence of serious adverse event (SAE) was 30.7% and 34.5%, serious adverse drug reaction (SADR) was 2.7% and 8.3%, the incidence of above grade 3 treatment emergent adverse event (TEAE) was 85.3% and 83.3%, respectively, etc. **Conclusions:** In patients with metastatic EGFR gene amplification ESCC, nimotuzumab plus TP as first-line treatment significantly improved OS and PFS with a good safety profile. Research Sponsor: None.

4056 **Poster Session**

Heterogeneity in biomarkers for advanced gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma (GC/GEJC/EAC) across regions: Insights from CheckMate-649. First Author: Lin Shen, Peking University Cancer Hospital and Institute, Beijing, China

Background: In CheckMate 649, first-line nivolumab plus chemotherapy showed improved clinical efficacy vs chemotherapy in patients (pts) with advanced GC/GEJC/EAC, with varied benefit across regions in a subgroup analysis. To identify biomarkers predictive of differential efficacy outcomes, we did post hoc exploratory biomarker analyses by region. **Methods:** Post hoc exploratory analyses were done with whole-exome sequencing (WES) and RNA-seq of baseline tumor tissue. Pts were grouped by region: China (CN), Asia (including CN), United States + Canada + European Union (UCE), Latin America (LA). For WES-evaluable pts, gene alterations were profiled and pts grouped into genomic subtypes: chromosomal instability (CIN), genomically stable (GS), hypermutated (H), and Epstein–Barr virus (EBV)-positive. Gene expression signatures (GES) related to mitogen-activated protein kinase (MAPK) pathway, stroma, and angiogenesis were assessed by RNA-seq, and pts were stratified into tertiles based on GES score: high, medium, or low. **Results:** Of 1512 pts randomized, 647 were WES-evaluable (79, 141, 351, 155 in CN, Asia, UCE, and LA, respectively) and 769 RNA-evaluable (50, 106, 423, 240, respectively). A numerically lower proportion of CIN subtype and higher proportion of EBV subtype was seen in LA vs other regions (Table). Percentage (%) of select gene alterations was generally comparable across regions: of note, there was numerically higher % of altered *FGFR2* (10%) in CN, altered *TP53* (58%), *KRAS* (16%), *CDKN2A* (11%), and *CDH1* (7%) in UCE, and altered *PIK3CA* (10%) and *ERBB2* (22%) in LA. By contrast, there was numerically lower % of altered *EGFR* (4%) in Asia and altered *ARID1A* (8%) in LA. GES profile was broadly similar across regions, with numerically higher % of MAPK-high subgroup in UCE, stroma-medium/low subgroup in LA, and angiogenesis-low subgroup in CN (Table). **Conclusions:** While the biomarker profile was largely comparable across regions, differential features were noted for certain subgroups; clinical utility of these biomarkers requires validation in future trials. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.

	Regions	CN	Asia(including CN)	UCE	LA
Genomic subtypes	CIN	53 (67)	86 (61)	223 (64)	81 (52)
	GS	22 (28)	47 (33)	99 (28)	49 (32)
	H	4 (5)	6 (4)	18 (5)	6 (4)
	EBV	0	2 (1)	11 (3)	19 (12)
GES					
5-gene MAPK	High	15 (30)	31 (29)	145 (34)	74 (31)
	Medium	13 (26)	29 (27)	153 (36)	79 (33)
	Low	22 (44)	46 (43)	125 (30)	87 (36)
15-gene stroma	High	20 (40)	38 (36)	151 (36)	70 (29)
	Medium	11 (22)	34 (32)	138 (33)	79 (33)
	Low	19 (38)	34 (32)	134 (32)	91 (38)
5-gene angiogenesis	High	15 (30)	35 (33)	137 (32)	81 (34)
	Medium	14 (28)	34 (32)	138 (33)	89 (37)
	Low	21 (42)	37 (35)	148 (35)	70 (29)

Data are n (%). % was calculated as events divided by number of WES- or RNA-seq–evaluable pts.

4057 **Poster Session**

Sintilimab combined with short-course intensified chemotherapy regimen nab-POF in the treatment of metastatic gastric cancer (FDZL-GC002): A single-arm, phase 2 trial. First Author: Weijian Guo, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: This prospective phase II study investigates a novel therapeutic strategy combining PD-1 inhibitor sintilimab (Sin) with short-course intensified chemotherapy regimen Nab-POF as first-line treatment for metastatic gastric cancer (MGC), based on the hypothesis that short-duration, high-intensity chemotherapy may potentiate antitumor immunity while reducing the cumulative immunosuppressive burden of prolonged chemotherapy. **Methods:** Eligible patients (pts) received Sin (200mg IV), nab-paclitaxel (125mg/m²), oxaliplatin (85mg/m²), and fluorouracil (2400mg/m² as a 48-hour infusion) (plus trastuzumab for HER2+ pts) Q2W. After 6 cycles, pts without disease progression received maintenance treatment (capecitabine + Sin). Upon disease progression, HER2- pts underwent reinduction with the Nab-POF regimen ± Sin, for up to 6 cycles, followed by maintenance therapy (S-1 +/- Sin). Tumor response was assessed every 3 cycles. PFS1 was defined as the time from informed consent to first progression. PFS2 was defined as the time from consent to second progression. If reinduction therapy was not performed, PFS2 equals to PFS1. The primary endpoint was PFS2 in HER2- pts. **Results:** In total, 123 pts were enrolled up to 09/2025. 118 pts were evaluable. This report presents the results for the HER2- population. Among 90 HER2- pts, the median age was 60 (23-83), with 72.2% male. The common metastatic sites included the liver (36.7%), peritoneum (26.7%), bone (13.3%), and lungs (6.7%). ORR was 82.2% (74/90) and DCR was 100%. Nine pts received complete response and CR rate was 10.0%. 2-year DFS and OS rate were both 100% among pts with CR. 60 pts progressed and 47 patients died. 25 pts experienced reinduction with the Nab-POF regimen ± Sin. Median PFS1 was 13.6mo (95% CI 9.8-16.1) and median PFS2 was 16.2mo (95%CI 11.0-23.2). Median OS was 21.3mo (95% CI 11.3-NR). 1-year OS rate was 72.2% (95%CI 63.5-82.1) and 2-year OS rate was 44.2% (95%CI 33.9-57.6). Subgroup analysis showed whether signet ring cells are present or not, whether liver metastasis occurs or not, and the level of CPS were not related to the therapeutic effect. All pts experienced treatment-related adverse events (AEs). Grade 3/4 AEs were 55.6% (50/90) and neutrophil decrease was the most common at 36.7% (33/90). Immune-related AEs occurred in 22(24.4%) pts, including 6 (6.7%) grade 3/4 events, which were effectively controlled. **Conclusions:** Sin plus short-course intensified chemotherapy regimen Nab-POF demonstrates high response and CR rate, and remarkable long-term effects. This approach may represent a feasible first-line treatment strategy, warranting further evaluation in randomized trials. Clinical trial information: NCT05982301. Research Sponsor: None.

4058 **Poster Session**

Radiogenomic biomarkers for identifying surgery-sparing candidates in locally advanced gastric or gastro-esophageal junction cancer treated with perioperative immunochemotherapy: A discovery and validation study. First Author: Song-Bin Guo, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Perioperative immunochemotherapy has markedly increased pathologic complete remission (pCR) rates in patients with locally advanced gastric cancer or gastroesophageal junction cancer (LAGC/GEJC), raising the possibility of surgery-sparing strategies in selected patients. However, reliable non-invasive tools to identify pCR preoperatively are lacking. This study aimed to develop and validate a radiogenomic model integrating CT radiomics and peripheral blood single nucleotide polymorphism (SNP) data to predict pCR. **Methods:** This retrospective multicenter study included 642 patients with LAGC/GEJC from 14 institutions who received perioperative immunochemotherapy. Patients were assigned to a primary cohort (n = 442; training n = 309, internal validation n = 133) and an external validation cohort (n = 200). Radiomic features were extracted from preoperative CT images, and SNPs were genotyped from peripheral blood. Feature selection was performed using LASSO, generating radiomic (Rad-score) and genomic (Gen-score) signatures. A combined radiogenomic model incorporating Rad-score, Gen-score, and clinical variables was developed using multivariable logistic regression. Model performance was evaluated using AUC and decision curve analysis (DCA). **Results:** Fourteen radiomic features and eight SNPs were selected. The radiogenomic model consistently outperformed single-modality models across cohorts. In the training set, the combined model achieved an AUC of 0.915 (95% CI 0.880–0.950), exceeding Rad-score (AUC 0.832) and Gen-score (AUC 0.798; both $P < 0.001$). In the internal validation set, the AUC was 0.882 (95% CI 0.825–0.939), and in the external validation set, 0.852 (95% CI 0.795–0.909), remaining superior to either modality alone. DCA demonstrated greater net clinical benefit of the combined model. At the optimal cutoff, 91.5% of true pCR cases were correctly identified in the validation cohort. **Conclusions:** A radiogenomic model integrating CT radiomics and peripheral blood SNP signatures enables accurate, non-invasive prediction of pCR in LAGC/GEJC patients undergoing perioperative immunochemotherapy and may support identification of candidates for surgery-sparing management. Research Sponsor: National Nature Science Foundation for Distinguished Young Scholars of Guangdong Province; National Natural Science Foundation of China; Guangdong Basic and Applied Basic Research Foundation; Fundamental Research Funds for the Central Universities, Sun Yat-sen University.

4059 **Poster Session**

Induction chemotherapy plus camrelizumab followed by concurrent chemoradiotherapy for unresectable locally advanced esophageal squamous cell carcinoma (ImpactCRT): Long-term outcomes of a single-arm phase II trial. First Author: Fang Peng, Department of Radiation Oncology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Concurrent chemoradiotherapy (CCRT) is the standard treatment for unresectable locally advanced esophageal squamous cell carcinoma (ESCC), with 3-year overall survival (OS) approximately 30%. Induction chemoimmunotherapy followed by CCRT appears promising, but long-term efficacy remains unclear. In the ImpactCRT study, induction chemotherapy plus camrelizumab followed by CCRT has shown promising efficacy in patients with unresectable locally advanced ESCC. Here, we reports long-term outcomes with ≥3-year follow-up. **Methods:** ImpactCRT was a prospective, single-arm, phase II study at the First Affiliated Hospital of Sun Yat-sen University. Eligible patients were aged 18–75 years with untreated, unresectable locally advanced ESCC (cT1–4bN0–3M0 or M1 limited to supraclavicular nodes). Patients received two 21-day cycles of induction therapy with albumin-bound paclitaxel (260 mg/m²), carboplatin (AUC 5), and camrelizumab (200 mg) on day 1, followed by two 28-day cycles of fluorouracil (750 mg/m² per 24 h for 5 days) and cisplatin (75 mg/m² on day 1) administered concurrently with radiotherapy (50–63 Gy in 25–28 fractions). The primary endpoint was the 1-year OS rate in the per-protocol set (PPS). The trial was registered with ChiCTR (ChiCTR2000034304). **Results:** Between July 12, 2020, and October 14, 2022, 49 patients were enrolled; all completed induction chemoimmunotherapy, and 46 received CCRT and comprised the PPS. As of January 1, 2026, median follow-up among surviving patients was 53.7 months (range 41.1–65.5). In the PPS, the 1-, 2-, 3-, and 4-year OS rates were 87.0% (95% CI 77.7–97.3), 73.9% (95% CI 62.3–87.8), 65.2% (95% CI 52.8–80.5), and 60.9% (95% CI 48.3–76.7), respectively. Corresponding PFS rates were 71.7% (95% CI 59.8–86.0), 63.0% (95% CI 50.5–78.7), 56.5% (95% CI 43.9–72.8), and 50.0% (95% CI 37.5–66.8). Median OS was not reached (95% CI 40.7 months–not reached), and median PFS was 45.5 months (95% CI 26.7–not reached). Disease progression occurred in 17 patients (37.0%), all within 3 years after treatment (median 6.1 months; range 2.9–35.2): locoregional failure in 7 (15.2%), distant metastasis in 5 (10.9%), and simultaneous locoregional and distant failure in 5 (10.9%). During follow-up, 20 patients (43.5%) died, including 12 (26.1%) due to disease progression. Grade 3 late toxicities occurred in three patients, all esophageal strictures; no grade ≥3 late toxicities were observed in the lung, heart, or other organs. **Conclusions:** Induction chemotherapy plus camrelizumab followed by CCRT showed improved long-term survival and acceptable late toxicity in unresectable locally advanced ESCC. Median PFS exceeded three years and appeared superior to previous reports. This regimen warrants further evaluation in randomized controlled trials. Clinical trial information: ChiCTR2000034304. Research Sponsor: None.

4060 **Poster Session**

Impact of molecular profile on switch maintenance to paclitaxel plus ramucirumab (PTX-RAM) versus continuation of first-line fluoropyrimidine and oxaliplatin (FOX) chemotherapy (ChT) in patients (pts) with advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: An exploratory endpoint of the ARMANI phase 3 randomized trial. First Author: Paolo Manca, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: The ARMANI trial proved the superiority of PTX-RAM switch maintenance over continuation of FOX first-line ChT in patients with advanced HER2-negative G/GEJ cancer. Here, we present the prognostic and predictive impact of baseline gene alterations. **Methods:** ARMANI was an Italian, multicenter, open-label, randomized phase 3 trial in which patients with HER2-negative G/GEJ cancer who achieved disease control after 3 months of induction FOX chemotherapy were randomized to either PTX-RAM switch maintenance or continuation of FOX. Pre-induction chemotherapy samples were sequenced by means of FoundationOne CDx, a panel comprising 324 cancer-related genes. Variants of unknown significance were filtered out. Presence of at least one pathogenic alteration was used to classify samples as altered or wild-type for the respective pathway (Cell cycle, PI3K, RAS, RTK, TGFβ, TP53 and WNT). Homologous repair deficiency (HRD) positivity was defined as the presence of a positive HRD signature (HRDsig+) as defined by FoundationOne CDx. **Results:** Sequencing data was available for 130 patients, with 65 patients treated in each arm, and 103 were evaluable for HRDsig. The most frequently altered pathways were TP53 (69.2%), Cell cycle (43.1%), PI3K (24.6%), RTK (24.6%) and RAS (23.1%). Presence of at least one alteration in the WNT pathway was observed for 22/130 patients (16.9%) and was associated with significantly higher rate of objective response to maintenance regimen (55.6% vs 17.3%, p = 0.002), longer mPFS (8.8 vs 6.0 months; HR = 0.54, 95%CI: 0.33-0.89; p = 0.017) and longer mOS (18.1 vs 14.1 months; HR = 0.53, 95%CI: 0.31-0.91, p = 0.021). TP53 pathway status was predictive for OS as switching maintenance to PTX+RAM improved OS in patients without TP53 pathway alterations (mOS 16.8 vs 8.8 months; HR 0.40, 95% CI 0.20–0.78) but not in those with at least one TP53 pathway alteration (mOS 14.7 vs 17.4 months; HR 0.94, 95% CI 0.60–1.48) (p for treatment interaction = 0.044). Ten out of 103 (9.7%) were HRDsig+. HRDsig+ status was not associated with neither PFS nor OS advantage (p = 0.676 and p = 0.623) and was not predictive of better outcomes in the FOX arm (p for treatment interaction for PFS = 0.919 and p for treatment interaction for OS = 0.558). **Conclusions:** Alterations in the WNT pathway have a positive prognostic significance in patients with G/GEJ cancer who achieved disease control after 3 months of FOX. TP53 pathway alterations bear potential for guiding the choice of PTX+RAM switch maintenance. HRDsig+ is not predictive of sensitivity of FOX in this setting. Clinical trial information: NCT02934464. Research Sponsor: None.

4061 **Poster Session**

Comparison of CLDN18/CLDN18.2 IHC assays (43-14A vs EPR19202) and the correlation with clinical efficacy in patients with gastric/gastroesophageal junction adenocarcinoma treated by the novel antibody-drug conjugate XNW27011. First Author: Jinming Yu, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Background: Claudin 18.2 (CLDN18.2), the dominant isoform of CLDN18 in gastric tissues, is a highly specific tight junction protein of the gastric mucosa with considerably retained expressions in gastric and gastroesophageal junction (G/GEJ) adenocarcinoma, making it a clinically actionable therapeutic target. Accurate immunohistochemical (IHC) assessment of CLDN18.2 expression is critical for patient selection in CLDN18.2-targeted therapies. Here, we report the findings of the analytical comparability, concordance and clinical efficacy outcomes between two CLDN18/CLDN18.2 antibodies (VENTANA CLDN18 [43-14A] and Abcam CLDN18.2 [EPR19202]), from a Phase I/II study of a novel antibody-drug conjugate XNW27011 (NCT06792435). **Methods:** This retrospective study utilized formalin-fixed paraffin-embedded (FFPE) samples of 121 patients with G/GEJ adenocarcinoma enrolled in the Phase I/II study of XNW27011. Each sample was stained with CLDN18 (43-14A) and CLDN18.2-specific (EPR19202) antibodies. Efficacy in objective response rate (ORR) was evaluated across CLDN18/CLDN18.2 expression strata defined by each assay antibody in patients treated with XNW27011 at doses of 2.4–6.0 mg/kg administered intravenously every 3 weeks. Concordance between the two assay antibodies was assessed by the percentage of the overall agreement (positive or negative) primarily at the cutoff of ≥20% tumor cells with 2+ to 3+ membranous staining. **Results:** Therapeutic efficacy outcomes of XNW27011 in ORR were highly consistent across expression strata defined by either 43-14A or EPR19202 assay antibody. In patients with CLDN18/CLDN18.2 expression defined as IHC ≥2+ in ≥20% of tumor cells, ORRs were 45.5% and 45.3% using EPR19202 and 43-14A assay antibody, respectively. EPR19202 and 43-14A IHC assays demonstrated high concordance, with an overall agreement of 90.1%. **Conclusions:** The IHC assays of CLDN18.2 expression with EPR19202 or CLDN18 expression with 43-14A demonstrate comparable analytical performance with high concordance. The alignment of efficacy outcomes across the two antibody-defined strata supports that CLDN18 and CLDN18.2-specific antibodies can identify patient populations with similar clinical benefit. Both antibodies can support the clinical development of XNW27011 in the treatment of patients with G/GEJ adenocarcinoma. Research Sponsor: None.

4062 **Poster Session**

Phase II study of ceralasertib (ATR inhibitor) plus durvalumab in patients with advanced gastric cancer (AGC) who progressed on prior anti-PD-(L)1 therapy. First Author: Sung Hee Lim, Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea

Background: The standard first-line therapy for advanced gastric cancer (AGC) now includes immune checkpoint inhibitors (ICIs), but resistance is inevitable. ATR inhibition may sensitize tumors to ICIs by enhancing DNA damage and activating the cGAS-STING pathway. We evaluated the efficacy and immunologic impact of ceralasertib (ATRi) plus durvalumab in IO-pretreated AGC. **Methods:** This open-label phase II trial (NCT03780608) enrolled patients with metastatic gastric adenocarcinoma who progressed on prior anti-PD-(L)1 therapy. Patients received ceralasertib (240mg BID, Days 1–7) and durvalumab (1500mg IV, Day 8) every 28 days. The primary endpoint was ORR (RECIST v1.1). Serial endoscopic biopsies were collected at baseline (BL), post-ATRi monotherapy (FU1), and post-durvalumab combination (FU2) for multi-omics analysis (WES/WTS/scRNA-seq). **Results:** Thirty patients were enrolled (median 4 prior lines; all HER2-negative). ORR was 33.3% (10/30) and DCR was 56.7%. Median PFS was 4.3 months (95% CI, 1.45–7.10); median OS was not reached. Patients receiving study treatment immediately after prior IO failure had significantly longer PFS than those with intervening non-IO lines ($p < 0.05$). Grade 3 TRAEs occurred in 10% (3/30) of patients, with no new safety signals identified. Dose reductions of ceralasertib occurred in 4 patients. Multi-omics revealed that higher baseline scarHRD scores correlated with shorter PFS (p = 0.031). scRNA-seq showed that responders (R) had significant depletion of aneuploid clones post-treatment, whereas non-responders (NR) exhibited clonal persistence. Mechanistically, R showed baseline enrichment of the ATR-ATRIP axis, indicating functional dependency on replication stress tolerance. ATR inhibition in R induced replication fork collapse and ATM-CHEK2-mediated apoptosis. Conversely, NR displayed base excision repair deficiency signatures and adaptive G1-phase retention, facilitating evasion of ATRi-induced lethality. **Conclusions:** Ceralasertib plus durvalumab is efficacious and well-tolerated in IO-refractory AGC. The higher efficacy observed in patients treated immediately after prior IO failure suggests that ATR inhibition may effectively reverse acquired resistance to PD-1 blockade. This biomarker-driven approach warrants further validation in a larger cohort. Clinical trial information: NCT03780608. Research Sponsor: None.

4063 **Poster Session**

Biomarker-driven assessment of immunochemotherapy with or without fruquintinib as first-line treatment for advanced gastric/GEJ adenocarcinoma: Initial clinical results and subgroup analysis from the MGC-FLORA study. First Author: Xiaodong Zhu, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The MGC-FLORA study is a prospective biomarker-exploratory trial primarily designed to identify predictive biomarkers (including gut microbiota and blood-based biomarkers) for first-line immunochemotherapy in advanced gastric/gastroesophageal junction (G/GEJ) adenocarcinoma. A key exploratory question is whether adding anti-angiogenic therapy (fruquintinib) modifies the efficacy landscape and its associated biomarkers. This interim analysis compares clinical outcomes between chemotherapy plus immunotherapy (CHEM cohorts) and chemotherapy plus immunotherapy plus fruquintinib (FRUQ cohorts). The FRUQ cohort is concurrently registered as an independent phase II clinical study (NCT06158919). **Methods:** This analysis included patients enrolled before September 30, 2025, with follow-up until January 15, 2026. Patients with previously untreated, unresectable locally advanced or metastatic G/GEJ adenocarcinoma were enrolled into two cohorts in this non-randomized study: CHEM (PD-1 inhibitor plus XELOX/SOX) and FRUQ (PD-1 inhibitor plus XELOX/SOX plus fruquintinib 4mg QD, days 1-14). After 6 induction cycles, oxaliplatin was discontinued in both cohorts, and maintenance therapy consisted of S-1/capecitabine plus PD-1 inhibitor, with or without continued fruquintinib. Blood and stool samples were collected at baseline (C1D1), after two treatment cycles, and at progression for future biomarker analysis (gut microbiota, cfDNA/cfRNA); the present report focuses on clinical outcomes. **Results:** A total of 126 patients were included (CHEM: n = 83; FRUQ: n = 43), with a median follow-up of 10.97 months. In the overall population, median PFS was 8.38 months and median OS was 18.53 months. Among evaluable patients, ORR was 47.1% (16/34) in the CHEM cohort versus 76.7% (33/43) in the FRUQ cohort, indicating a higher response rate with the addition of fruquintinib. Median PFS was 8.38 months for CHEM and 10.35 months for FRUQ (HR = 0.63, 95% CI 0.37-1.08; p = 0.09). After propensity score matching for sex, age, liver metastasis status, number of target lesions, and Claudin18.2 expression (n = 29 per cohort), the PFS benefit associated with fruquintinib became more pronounced (HR = 0.45, 95% CI 0.20-1.02; p = 0.05). **Conclusions:** This initial analysis from the biomarker-oriented MGC-FLORA study suggests that the addition of fruquintinib to first-line immunochemotherapy may improve clinical efficacy in advanced G/GEJ adenocarcinoma. Consistent trends toward prolonged PFS were observed in both the overall and propensity score–matched populations, supporting a potential therapeutic benefit of fruquintinib. These findings warrant further validation in randomized trials and integrated biomarker analyses. Research Sponsor: None.

4064 **Poster Session**

Toripalimab plus chemotherapy and radiotherapy for treatment-naïve advanced esophageal squamous cell carcinoma: Long-term survival and recurrence patterns. First Author: Lei Wu, Radiation Oncology Key Laboratory of Sichuan Province, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, University of Electronic Science and Technology of China, Chengdu, China

Background: Concurrent chemoradiotherapy plus PD-1 blockade is standard for locally advanced esophageal squamous cell carcinoma (ESCC), but its role in advanced disease remains undefined. We investigated the safety and efficacy of Toripalimab combined with chemotherapy and radiotherapy (RCIT) as first-line treatment for advanced ESCC, analyzing long-term survival, recurrence patterns, and immune biomarkers. **Methods:** This single-arm, phase II trial enrolled treatment-naïve patients with stage IV ESCC (N3 nodal or oligometastases; 5 lesions in 3 organs). Treatment comprised induction chemoimmunotherapy (2 cycles) followed by concurrent radiotherapy (Cycles 3-4) and maintenance immunotherapy. Patients received Paclitaxel (135-175 mg/m2) and Carboplatin (AUC 4-6) plus Toripalimab (240 mg) on day 1 (Q3W). Intensity-modulated radiotherapy (50-50.4 Gy/25-28f) targeted primary/regional lesions, while SBRT (30-40 Gy/3-5f) targeted oligometastases. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), recurrence patterns, health-related quality of life (HRQOL), and biomarker analysis via multiplex immunofluorescence (mIF). **Results:** Thirty-three patients were enrolled. At a median follow-up of 33.4 months, the 2-year PFS and OS rates were 30.3% (95% CI: 18.1-50.8) and 48.5% (95% CI: 34.1-68.9), respectively. In the efficacy-evaluable population completing radiotherapy (n = 26), outcomes were significantly superior to those who did not, with a median OS of 27.4 months and a 2-year OS of 61.5% (HR = 0.26, p = 0.004). Recurrence occurred in 26 (78.8%) patients, comprising locoregional only (27.3%), distant only (18.2%), and combined failure (33.3%). Notably, among patients completing RT, in-field recurrence (57.7%) remained a predominant failure pattern despite multimodal therapy. HRQOL analysis demonstrated significant post-induction improvement in pain and social functioning scores, whereas radiotherapy transiently worsened dysphagia at 3 months post-RT (p = 0.041). Translational analysis revealed that high baseline tumor infiltration of CD8+ T cells, PD-L1+ dendritic cells, and PD-L1+ macrophages, alongside elevated serum IL-4, IL-17, and IFN-γ\gamma, were significantly associated with long-term survival (OS $\geq$24 months; $p < 0.05$). **Conclusions:** First-line RCIT yields promising long-term survival in advanced oligometastatic ESCC, particularly in patients completing the full radiotherapeutic course, achieving a 2-year OS of 61.5%. However, high rates of in-field recurrence suggest a need for further optimization of local control strategies. Baseline immune infiltrates and cytokine profiles offer potential predictive value for patient stratification. Randomized trials are warranted to validate these findings. Clinical trial information: ChiCTR2100046715. Research Sponsor: This work was supported by the NSFC program (82573448).

4065 **Poster Session**

Disitamab vedotin (RC48), tislelizumab, and S-1 as first-line therapy for HER2-overexpressing advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC): Updated survival and exploratory biomarker results from the RCTS trial. First Author: Lian Liu, Qilu Hospital of Shandong University, Jinan, China

Background: Anti-PD1 antibody has significantly improved survival in patients with HER2-overexpressing and PD-L1 combined positive score (CPS) $\geq$1 GC/GEJC when added to trastuzumab and chemotherapy. Recent trials revealed that HER2-targeted antibody-drug conjugates combined with anti-PD1 antibody, have also shown promising efficacy in this population. We report updated survival, safety, and exploratory biomarker results of RC48 combined with tislelizumab and the oral fluoropyrimidine S-1 as first-line therapy for patients with HER2-overexpressing GC/GEJC. **Methods:** This single-arm, multicenter clinical trial enrolled patients with unresectable or metastatic HER2-overexpressing (IHC 3+ or 2+, regardless of FISH status) GC/GEJC. Patients received RC48 (2.5 mg/kg), tislelizumab (200 mg), and S-1 (40–60 mg BID for 14 days) every 3 weeks until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety. Exploratory analyses included dynamic peripheral T-cell receptor (TCR) sequencing and longitudinal circulating tumor DNA/cell-free DNA (cfDNA) profiling. **Results:** 57 patients were enrolled, 71.9% HER2 IHC 3+, 17.5% IHC 2+/FISH+, and 10.5% IHC 2+/FISH-; 45.6% had CPS $\geq$1. Until Dec 31, 2025, the median follow-up was 28.2 months. In the ITT population, the confirmed ORR was 89.5% (95% CI: 78.5–96.0%), including 8.8% complete responses; disease control rate was 98.2%. Median PFS was 13.8 months (95% CI: 10.3–24.0), and median OS was 31.9 months (95% CI: 22.1–not reached). In the CPS $\geq$1 and CPS $<$ 1 subgroups, ORRs were 92.3% (95% CI: 74.9–99.1%) and 87.1% (95% CI: 70.2–96.4%), with median PFS 16.7 vs 10.0 months and median OS 31.9 vs 25.4 months, respectively. Grade $\geq$3 treatment-related adverse events occurred in 64.9%, mainly decreased white blood cell count (29.8%), decreased neutrophil count (12.3%), anemia (10.5%), and peripheral motor neuropathy (10.5%). In patients with paired TCR samples, higher treatment-induced clonal expansion score was associated with improved PFS (HR 0.34; P = 0.017) and OS (HR 0.33; P = 0.037), with particularly prognostic discrimination in the CPS $<$ 1 subgroup. In patients with longitudinal cfDNA, cfDNA tumor fraction increases preceded imaging-defined progression in most patients who progressed. **Conclusions:** The combination of RC48, tislelizumab and S-1 as a first-line therapy shows encouraging response rates and updated survival with manageable safety in HER2-overexpressing GC/GEJC, including patients with CPS $<$ 1. TCR clonal expansion may serve as a robust biomarker of antitumor immune activation, independent of PD-L1 expression levels. Clinical trial information: NCT05586061. Research Sponsor: None.

4067 **Poster Session**

Efficacy of nimotuzumab combined with concurrent chemoradiotherapy for patients with postoperative loco-regional recurrent esophageal squamous cell carcinoma: A phase II study. First Author: Jialiang Zhou, Affiliated Hospital of Jiangnan University, Wuxi, China

Background: The clinical therapeutic effect for patients with postoperative loco-regional recurrent esophageal squamous cell carcinoma (ESCC) is not satisfactory. Nimotuzumab, an EGFR-targeted humanized antibody, showed efficacy in the treatment of ESCC. We explored the efficacy of nimotuzumab combined with concurrent chemoradiotherapy (CCRT) for patients with postoperative loco-regional recurrent ESCC. **Methods:** Eligible patients (18-75 years) with postoperative loco-regional recurrent ESCC were enrolled in this single-arm phase II study, received nimotuzumab (400mg on D1, 200mg/w for 6 weeks) combined with CCRT (chemotherapy:TP regimen, radiotherapy: 45-50.4Gy/25-28f/5-6w), sequentially nimotuzumab 200mg every 3 weeks plus chemotherapy (patients with partial response or stable disease). The primary endpoint was objective response rate (ORR), the second endpoints were disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and local-regional control (LRC) and adverse events. **Results:** From Sep 2021 to Apr 2024, 44 patients were screened, ultimately 42 patients were included in the Full Analysis set. The median age was 69 years (range: 48-75). 12 (28.57%) patients achieved complete response, 24 (57.14%) patients with partial response, 5 (11.90%) patients with stable disease, and 1 (2.38%) patient with progressive disease. ORR was 85.71%, and DCR was 97.62%. The failure patterns showed that 10 (23.81%) patients had loco-regional recurrence, and 9 (21.43%) had distant metastases after CCRT. The median follow-up was 29.3 months (95%CI: 25.7-38.0). 3-year OS was 51.8% (95%CI: 36.9-72.8%), with the median OS was not reached. 3-year PFS was 33.4% (95%CI: 20.4-54.7%), and the median PFS was 15.1 months (95%CI: 11.8-NE), 3-year LRC was 46.1% (95%CI: 29.9-71.0%), the median LRC was 30.8 (95%CI: 16.6-NE). The most common Graded 3-5 adverse events (AEs) included leukopenia, thrombocytopenia, hemoglobin decreased, radiation esophagitis, radiation-induced lung injury, fatigue, and radiodermatitis. 4 patients experienced Grade 3-5 radiation esophagitis, in which 2 patients developed esophageal fistulas (1 patient died). No nimotuzumab-related serious AEs occurred. **Conclusions:** Nimotuzumab combined with CCRT showed promising ORR and survival with tolerable toxicity in patients with postoperative loco-regional recurrent ESCC. Clinical trial information: ChiCTR2200063875. Research Sponsor: None.

4068 Poster Session

Survival outcome of sandwich therapy with induction chemo-immunotherapy followed by concurrent chemoradiotherapy and sequential immune maintenance therapy in locally advanced unresectable esophageal squamous cell carcinoma (ESCC) patients: A multi-center prospective study. First Author: Zhichao Fu, 900 Hospital of the Joint Logistics Support Force, Fuzhou, China

Background: PD-1 inhibitor, combined with chemotherapy, is recommended in first-line treatment for metastatic ESCC, but its role remains undefined in locally advanced ESCC. This trial aimed to investigate the survival outcome and safety of the 'Sandwich Therapy' consisting of induction chemoimmunotherapy followed by definitive chemoradiotherapy (dCRT) and sequential immune maintenance therapy. **Methods:** This is a multicenter, prospective study. Patients with histologically confirmed, clinical stage I–IVA and unresectable esophageal squamous cell carcinoma (ESCC) were included. Patients received 1-8 cycles of chemoimmunotherapy (intravenous paclitaxel (175 mg/m^2) plus platinum-based chemotherapy), then concurrent chemoradiotherapy followed by tislelizumab (200mg intravenously, every 3 weeks) until disease progression or the end of the study. The primary outcome was progression-free survival (PFS). The secondary outcomes included overall survival (OS) and the incidence of adverse events (AE). **Results:** Between August 2022 and Aug 2025, 77 patients were enrolled and all proceeded to the immune maintenance therapy phase. The median age was 61 years (IQR 55-69), and 78% had clinical stage III or IV disease. With median follow-up of 19 months (95CI), median PFS was 17.0 months (95% CI:12.0–36.0) , with 1-, 2- and 3-year PFS rate of 56.4%, 39.9% and 25.6%, respectively. The median OS was 45.0 months (95%CI:20.1-69.3), with 1-, 2- and 3-year OS rate of 74.9%, 63.2% and 50%, respectively. The objective response rate (ORR) was 55.8%, and the disease control rate was 92.2%. Grade ≥3 AE occurred in 27 (35.1%) patients during the treatment. The most common grade ≥3 AE was lymphopenia, which was reported in 22 (28.6%) patients. **Conclusions:** For locally advanced ESCC, induction chemoimmunotherapy followed by dCRT and subsequent maintenance of immunotherapy may improve PFS and OS with a manageable safety profile. Clinical trial information: NCT05515315. Research Sponsor: None.

4069 Poster Session

Incidence and prognostic impact of recurrence in esophageal carcinoma patients achieving complete pathological response after neoadjuvant chemoradiotherapy or perioperative chemotherapy. First Author: Sibgha Aimon, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan

Background: Esophageal carcinoma remains a global challenge, ranking 7th in cancer-related mortality. While the CROSS trial established neoadjuvant chemoradiotherapy (nCRT) as a standard of care with a 29% pathological complete response (pCR) rate, real-world data in diverse histological populations—particularly Squamous Cell Carcinoma (SCC)—are evolving. We aimed to evaluate the impact of pCR on Overall Survival (OS) and Disease-Free Survival (DFS) in a high-volume surgical cohort. **Methods:** A retrospective analysis of a prospective database was conducted for patients undergoing curative-intent esophagectomy at a tertiary cancer center (2019–2023). Inclusion: Patients receiving neoadjuvant therapy (nCRT or perioperative chemotherapy). Exclusion: Patients with upfront surgery, palliative resections, or incomplete records. Survival outcomes were analyzed using Kaplan-Meier curve. **Results:** Of 546 patients, 51% were male with a mean age of 44 ± 9 years. nCRT was the primary neoadjuvant modality (92.3%), followed by perioperative chemotherapy (7.7%). pCR was achieved in 54.8% of patients. At a median follow-up of 5 years, the overall recurrence rate was 27.1%; notably, only 28.3% of the pCR group experienced recurrence compared to the non-pCR group ($p < 0.001$). Recurrence patterns distant (48.6%), followed by locoregional (44.6%), and both (6.8%). The pCR group demonstrated superior survival outcomes: Mean OS: 57 ± 0.7 months vs 52 ± 1 months in non-pCR (p = 0.001); Mean DFS: 52 ± 1 months vs 35 ± 1 months in non-pCR ($p < 0.001$). Total study mortality was 8.4%. **Conclusions:** In this large South Asian cohort, pCR was achieved in over half of the patients following neoadjuvant therapy and served as a robust predictor of both OS and DFS. These findings reinforce pCR as a critical surrogate endpoint for long-term oncological success and suggest that tumor biology in this region may be particularly sensitive to multimodality protocols. Research Sponsor: None.

Clinical characteristics and survival outcomes.

Variable	Value (n=546)
Tumor Location	Distal Esophagus: 52.6% Mid Esophagus: 25.3% Gastroesophageal Junction: 12.6%
Histology	Squamous Cell Carcinoma (SCC): 85.7% Adenocarcinoma: 14.3%
Neoadjuvant Therapy	Chemoradiotherapy (nCRT): 92.3% Chemotherapy: 7.7%
Surgical Procedure	McKeown Esophagectomy: 78.6% Ivor Lewis Esophagectomy:18.7% Trans-hiatal Esophagectomy: 2.7%
Pathological Stage (TNM) I/II/III/IV	69.5% / 10.5% / 16.6% / 3.4%
Resection Margin	R0 (Negative): 95.1% R1 (Microscopic Positive): 4.9%
Pathological Complete Response (pCR)	Overall: 54.8% Squamous cell Carcinoma: 95.3% Adenocarcinoma: 4.6%
Recurrence	Overall Rate: 27.1% Recurrence within PCR group: 7.6%
Overall Survival (Months)	pCR = 57±0.7 Residual Disease = 52±1 months p=0.001
Disease-Free Survival (Months)	pCR = 52±1 Residual Disease = 35±1 p= <0.001

4070 Poster Session

Efficacy of durvalumab and safety by treatment period in MATTERHORN: A randomized, phase 3 study of durvalumab plus 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy in resectable gastric/gastroesophageal junction (G/GEJ) cancer. First Author: Zev A. Wainberg, Department of Gastrointestinal Medical Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: In MATTERHORN (NCT04592913), perioperative durvalumab (D) + FLOT significantly improved event-free survival (EFS) and overall survival vs placebo (Pbo) + FLOT in participants (pts) with resectable G / GEJ cancer. Here, we report EFS by treatment period completion status. **Methods:** In this global, double-blind, Phase 3 study, pts with histologically confirmed, resectable, untreated G / GEJ adenocarcinoma were randomized 1:1 to D 1500 mg or Pbo every 4 weeks (Q4W) on Day 1 + FLOT every 2 weeks on Days 1 and 15 for 4 cycles (2 cycles each neoadjuvant and adjuvant [adjuvant: 4–12 weeks post-surgery]), followed by D 1500 mg or Pbo Q4W for 10 additional cycles (adjuvant monotherapy). EFS (time from randomization to progression, local or distant recurrence, or death) was assessed by treatment period completion status (Table). Safety was also assessed. Landmark EFS rates were calculated by the Kaplan–Meier method. Hazard ratios and their confidence intervals were estimated by the Cox proportional hazards model. **Results:** The number of pts who received treatment in each period was similar in the D + FLOT and Pbo + FLOT treatment arms (Table). EFS landmark rates at 12 and 24 months were highest in pts who completed all adjuvant D / Pbo in both arms; EFS was improved in the D + FLOT vs Pbo + FLOT arm irrespective of treatment periods started / completed (Table). A smaller proportion of Grade 3–4 adverse events (AEs) and serious AEs (SAEs) were reported in the adjuvant monotherapy period with D + FLOT and Pbo + FLOT (Grade 3–4: 21.2% and 20.5%; SAEs: 14.5% and 14.5%, respectively) when compared with the overall treatment period (Grade 3–4: 71.6% and 71.2%; SAEs: 48.2% and 44.1%, respectively). In the adjuvant monotherapy period, the rate of any AEs leading to discontinuation of D / Pbo was 5.8% in the D + FLOT vs 2.7% in the Pbo + FLOT arm. **Conclusions:** EFS landmark rates were greatest for pts who completed the full adjuvant regimen compared with those who discontinued prematurely in both arms. Moreover, the addition of D to FLOT improved EFS regardless of treatment periods started / completed. Safety was manageable and tolerable in the adjuvant monotherapy period. Clinical trial information: NCT04592913. Research Sponsor: AstraZeneca.

	Received any neoadjuvant treatment but did not complete surgery (N=132)		Received any neoadjuvant treatment and completed surgery (N=96)*		Received any adjuvant treatment but did not complete D / Pbo (N=223)		Completed all adjuvant D / Pbo (N=493)	
	D + FLOT (n=62)	Pbo + FLOT (n=70)	D + FLOT (n=48)	Pbo + FLOT (n=48)	D + FLOT (n=116)	Pbo + FLOT (n=107)	D + FLOT (n=248)	Pbo + FLOT (n=245)
EFS landmark rate, %								
12 mo	16.0	8.3	59.0	41.6	67.4	66.4	99.6	98.8
24 mo	10.0	6.2	49.2	33.3	46.7	29.8	91.8	87.2
EFS hazard ratio (95% CI)	0.80 (0.55–1.18)		0.65 (0.38–1.13)		0.65 (0.46–0.91)		0.63 (0.41–0.97)	

*These pts did not receive adjuvant treatment.

4071 Poster Session

Non-invasive strategy for gastric cancer detection: Integration of cell-free DNA fragmentomics and protein biomarkers. First Author: Lian Lian, Department of Oncology, Suzhou Xiangcheng People's Hospital, Suzhou, China

Background: Gastric cancer (GC) ranks the fifth most common cancer worldwide. Although gastroscopy is widely acknowledged as the gold standard for GC detection, its invasiveness limits its utility in large-scale screening. Accurate, non-invasive diagnostic modalities are urgently needed. Cell-free DNA (cfDNA) fragmentomics has emerged as a promising tool for cancer detection. This study aimed to develop and validate a novel non-invasive model for GC detection based on cfDNA fragmentomics and protein biomarkers. **Methods:** A total of 257 participants, comprising 120 GC patients and 137 non-cancer individuals, were enrolled and divided into a training cohort (n = 129) and a test cohort (n = 128). Low-coverage whole-genome sequencing was performed on plasma cfDNA. We evaluated eight multi-dimensional cfDNA fragmentomics features individually, and selected four, including fragment size ratio, copy number variation, 9-bp end motif, and fragment size at transcription starting sites, to build an ensemble model (GaFraD) to detect GC. Furthermore, conventional protein biomarkers of GC were assessed and integrated with GaFraD model to generate a CONFIRM model aimed at improving diagnostic performance. **Results:** The GaFraD model achieved an area under the receiver-operating characteristic curve (AUC) of 0.953 (95% CI: 0.918 – 0.979) in the training cohort and 0.970 (95% CI: 0.944 – 0.990) in the test cohort, with a sensitivity of 95.0% and a specificity of 80.9%. By incorporating protein biomarkers CA19-9 and PG-I/PG-II, the CONFIRM model further reached an AUC of 0.967 (95% CI: 0.929 – 0.992) in the training cohort and 0.986 (95% CI: 0.966 – 1.000) in the test cohort, attaining a sensitivity of 95.0% and specificity of 95.6%. Moreover, the CONFIRM model also exhibited remarkable performance in discriminating early-stage GC patients from controls (AUC = 0.983, sensitivity: 95.6%, specificity: 94.2%). **Conclusions:** Our model exhibits high discriminatory power in distinguishing GC patients from controls, highlighting the strong clinical potential of combining cfDNA fragmentomics with protein biomarkers for non-invasive, early GC detection. This approach offers a promising pathway towards earlier, accurate, and non-invasive clinical diagnosis of GC. Research Sponsor: the Scientific Research Project of Jiangsu Provincial Health Commission; Z2022039; Suzhou Gusu Health Talent Plan; GSWS2022115; the Science and Technology Project Foundation of Suzhou; SKY2023034; SS202093; SYW2024164; the Key Scientific Research Projects of Jiangsu Provincial Health Commission; ZD2021053.

4073 **Poster Session**

Prevalence of *CDH1* germline variants in gastric cancer patients with exome-inferred ancestry. First Author: Skylar Nahi, UT Southwestern Medical Center, Dallas, TX

Background: Germline pathogenic or likely pathogenic (P/LP) *CDH1* variants increase the lifetime risk of developing diffuse gastric cancer (DGC). Given that the epidemiology and prognosis of gastric cancer vary based on patient ancestry, and Hispanic and Black/African-American patients have been underrepresented in clinical and translational research, we sought to determine the prevalence of *CDH1* variants in a diverse population of gastric cancer patients. **Methods:** Germline whole exome sequencing (WES) data from gastric cancer patients were obtained as part of commercial ordering of personalized circulating tumor DNA testing (Signatera, Natera, Inc.) from March 2024 to June 2025. Ancestry was inferred by EthSeq and classified into predefined groups: European (EUR), admixed American (AMR), African (AFR), and East Asian (EAS). Germline single-nucleotide variants and short insertions/deletions were identified and annotated with Variant Effect Predictor (v.105), and the pathogenicity of variants in *CDH1* was determined using classifications available in the ClinVar database. The prevalence of P/LP variants and variants of uncertain significance (VUS) were compared across ancestries. Potential pathogenicity of VUS was evaluated using *in silico* predictors SIFT (v5.2.2), Polyphen (v2.2.2), and AlphaMissense (hg19). **Results:** Among 2,567 patients, 55% (1,414/2,567) were male and the median age was 67 years. Ancestry inference identified 47% (n=1,201) as EUR, 22% (n=575) as AMR, 18% (n=457) as AFR, and 13% (n=334) as EAS. Patients with AMR ancestry were younger compared to EUR ancestry patients (median 62 years vs 69 years; adj $p<0.0001$), and less likely to be male (51% [295/575] vs. 58% [693/1201]; OR, 0.7; 95% CI, 0.63–0.94; p=0.015). No significant differences in age or sex were observed in patients with AFR (median 68 years, 55% male) or EAS (median 68 years, 52% male) ancestry compared to EUR. Overall, 0.7% (n=17) gastric cancer patients had a P/LP variant, and there was no difference across ancestries (0.8% of EUR, 0.5% of AMR, 0.4% of AFR, and 0.6% of EAS patients). We found that 1.1% (n=27) of the cohort had a *CDH1* VUS, the rate for which did not vary across ancestries (1.2% of EUR, 0.52% of AMR, 0.84% of AFR, 0.60 of EAS). Of the 21 unique VUS, 33% (n=7) were each predicted to be pathogenic by all three *in silico* predictors. One unique VUS was observed in two unrelated patients: NM_004360.5:c.635G>T (p.Gly212Val). The predicted-pathogenic VUS were similarly distributed across ancestries. **Conclusions:** This real-world analysis highlights that *CDH1* VUS were similarly distributed across ancestries. Notably, we found that one-third of VUS identified were predicted to have pathogenic function across three *in silico* prediction tools. This highlights the need for functional assays to determine the variant biology to improve gastric cancer risk assessment. Research Sponsor: None.

4074 **Poster Session**

Neoadjuvant and adjuvant pembrolizumab plus chemotherapy for locally advanced gastric or gastroesophageal junction adenocarcinoma: Outcomes from the microsatellite instability-high population of the phase 3 KEYNOTE-585 study. First Author: Sun Young Rha, Department of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: In the randomized phase 3 KEYNOTE-585 study (NCT03221426), perioperative pembrolizumab (pembro) plus chemotherapy (chemo) significantly improved pathologic complete response (pCR) vs placebo (pbo) plus chemo (diff, 10.9%; 95% CI, 7.5-14.8; $P < 0.00001$), with no new safety signals in participants (pts) with locally advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. We present outcomes for the microsatellite instability-high (MSI-H) population. **Methods:** Eligible pts had untreated resectable locally advanced G/GEJ adenocarcinoma (including Siewert type 2 or 3 tumors); MSI was centrally assessed. Pts enrolled in the main cohort (n = 804) received neoadjuvant pembro 200 mg intravenously (IV) every 3 weeks (Q3W) or pbo plus chemo (cisplatin + capecitabine or 5-FU) for 3 cycles; after surgery, pts received adjuvant pembro or pbo plus chemo Q3W for 3 cycles, then adjuvant pembro or pbo Q3W for 11 cycles. Pts in the fluorouracil, docetaxel, and oxaliplatin (FLOT) cohort (n = 203) received neoadjuvant pembro 200 mg IV Q3W or pbo Q3W for 3 cycles plus FLOT Q2W for 4 cycles; after surgery, pts received adjuvant pembro or pbo Q3W for 3 cycles plus FLOT Q2W for 4 cycles, then adjuvant pembro or pbo Q3W for 11 cycles. End points were pCR (blinded independent central review [BICR]), event-free survival (EFS; RECIST v1.1 by BICR), overall survival (OS), and safety. We report outcomes in the main and FLOT cohorts combined. The data cutoff date was February 16, 2024 (final analysis). **Results:** Data from the 81 pts with MSI-H status were analyzed (n = 43, pembro + chemo; n = 38, pbo + chemo). The pCR rate was 39.5% (95% CI, 25.0-55.6) in the pembro group and 0% (95% CI, 0.0-9.3) in the pbo group (diff, 39.5%; 95% CI, 26.3-54.5). The median EFS was not reached (NR; 95% CI, 49.9-NR) and 60.1 months (95% CI, 18.6-NR), respectively (HR, 0.58; 95% CI, 0.26-1.31); 24/48-month EFS rates were 78%/73% in the pembro group and 68%/68% in the pbo group. The median OS was NR (95% CI, NR-NR) in both treatment groups (HR, 0.50; 95% CI, 0.19-1.30); 24/48-month OS rates were 91%/86% in the pembro group and 76%/74% in the pbo group. Treatment-related adverse events (AEs) occurred in all 43 pts (100%) in the pembro group and 37 (97%) in the pbo group. Grade 3-5 treatment-related AEs occurred in 32 (74%) and 25 (66%) pts, respectively. Discontinuation of any drugs due to treatment-related AEs occurred in 15 pts (35%) in the pembro group and 12 (32%) in the pbo group. No deaths due to treatment-related AEs were reported. **Conclusions:** In this post hoc analysis, efficacy outcomes for pts with MSI-H G/GEJ adenocarcinoma suggested a consistent trend with numerically more pronounced difference between the treatment groups, with a manageable safety profile. Further studies in this population are warranted. Clinical trial information: NCT03221426. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

LBA4075 **Poster Session**

Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy followed by D2 gastrectomy and adjuvant chemotherapy for locally advanced gastric cancer (Neo-CRAG): A randomized, multicenter, phase 3 trial. First Author: Rui-Hua Xu, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University, Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

4076 **Poster Session**

A multicenter non-randomized phase III study of sentinel node navigation surgery for early gastric cancer. First Author: Yuko Kitagawa, Department of Surgery, Keio University School of Medicine, Tokyo, Japan

Background: Sentinel node navigation surgery (SNNS) has the potential to minimize the extent of gastrectomy, thereby improving quality of life (QOL) after surgery for patients with early gastric cancer (GC). This prospective, multicenter, non-randomized, phase III study aims to evaluate the long-term outcomes of SNNS for early GC. **Methods:** A total of 13 institutions enrolled clinically diagnosed primary T1N0M0 gastric cancer patients with a single lesion ($\leq$40 mm) and without previous endoscopic treatment. Sentinel nodes (SNs) were identified using dye and radioisotope tracers, then subjected to intraoperative rapid pathology. Patients with negative SN metastasis underwent individualized surgery consisting of limited stomach resection and SN basin dissection, while those with positive SN metastasis underwent standard gastrectomy with D2 lymph node dissection. The primary endpoint was five-year relapse-free survival (RFS). The secondary endpoints were overall survival (OS), SN detection rate, diagnostic accuracy for SNs, SN distribution, and the distribution of metastatic and non-SNs. Postoperative QOL was also assessed. RFS was assessed in the full analysis set (FAS), excluding patients who did not undergo intraoperative SN biopsy and pathological assessment during surgery. The data cutoff date for the analysis was May 31, 2025. Clinical trial information: jRCTs031180432. **Results:** A total of 187 patients were enrolled from May 2014 to May 2020. Of the 180 patients in FAS, 62.2% were male. The median (range) age was 64 (27–85). cT1a/cT1b was 18.3%/81.7%, respectively. The median follow-up time was 60.2 months (range: 9.0–62.8). The 5-year RFS rate (95% CI) was 95.6% (91.43–98.06). Since the lower boundary of the 95% CI exceeded the predefined threshold of 90%, the study met its primary endpoint. Events for RFS included one recurrence and three non-cancer deaths. SNs were identified in all patients, and LN metastasis was detected in 17 patients (9.4%) during surgery. Finally, 143 patients (79.4%) underwent individualized surgery consisting of limited stomach resection and SN basin dissection. The 5-year RFS rate (95% CI) for this cohort was 96.5% (92.03 - 98.86). There was no mortality after surgery. **Conclusions:** SNNS for early GC has been shown to be non-inferior to standard gastrectomy, with an acceptable toxicity profile. SNNS represents a promising alternative as a potential new standard treatment for early GC. Clinical trial information: jRCTs031180432. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

4077 **Poster Session**

FGF4-mediated resistance to combined anti-angiogenic and immunotherapy in esophageal squamous cell carcinoma via suppression of high endothelial venules and tertiary lymphoid structure formation. First Author: Weixiong Yang, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Many patients with locally advanced esophageal squamous cell carcinoma (LA-ESCC) fail to achieve a pathological complete response (pCR) following neoadjuvant immunochemotherapy plus anti-angiogenic therapy, which is associated with a poor prognosis. The identification of predictive biomarkers and the elucidation of resistance mechanisms constitute a major challenge. This study aims to identify relevant biomarkers and elucidate the underlying mechanisms to improve therapeutic outcomes. **Methods:** Exploratory analyses were conducted on 70 untreated LA-ESCC patients from a phase II clinical trial (ChiCTR2100051763) treated with two 21-day cycles of neoadjuvant treatment with intravenous camrelizumab (200mg), albumin-paclitaxel (260mg/m^2), carboplatin (AUC=5) on day 1, and oral apatinib (250mg) on days 1-14, followed by the third cycle without apatinib. Pre-treatment tumor tissues were subjected to transcriptomic and whole-exome sequencing to identify differential pathways and genetic alterations between patients achieving pCR and non-pCR. Candidate biomarkers were further validated by immunohistochemistry. In vitro and in vivo experiments were employed to elucidate the mechanisms underlying treatment resistance. **Results:** Pathway analysis identified significant enrichment of the fibroblast growth factor receptor (FGFR) signaling pathway in non-pCR patients, with FGF4 as the most upregulated factor. FGF4 alterations were primarily gene amplifications, occurring in 40% of cases. FGF4 expression predicted treatment resistance (non-pCR) with an AUC of 0.857 (95% CI: 0.744–0.97). Multiplex immunohistochemistry revealed that tumors overexpressing FGF4 exhibited impaired vascular normalization, evidenced by significantly reduced pericyte coverage and basement membrane integrity. These tumors also showed lower densities of high endothelial venules (HEVs), CD8+ T cells, and tertiary lymphoid structures (TLSs) following combination therapy. In vivo experiments confirmed that FGF4 overexpression led to decreased pericyte and basement membrane coverage, reduced HEV density, and diminished CD8+ T cell infiltration. Notably, pharmacological inhibition of FGFR signaling reduced tumor growth and increased the pCR rate, effectively reversing the resistance mediated by FGF4. **Conclusions:** Aberrant FGF4 expression drives resistance to combined immunochemotherapy and anti-angiogenic therapy by impeding vascular normalization, which subsequently suppresses the formation of HEVs and tertiary TLSs. Targeting FGFRs might be a promising strategy to overcome FGF4-driven treatment resistance in ESCC. Clinical trial information: ChiCTR2100051763. Research Sponsor: National Natural Science Foundation of China; 82373307; the Natural Science Foundation of Guangdong Province; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

4078 **Poster Session**

Non-operative management in mismatch repair deficient (dMMR) esophagogastric cancer (EGC) following immune checkpoint inhibition (ICI). First Author: Charlton Tsai, Memorial Sloan Kettering Cancer Center, New York City, NY

Background: ICI achieves deep and durable responses in patients with dMMR and microsatellite instability-high (MSI-H) EGC, creating an opportunity for non-operative management (NOM) of localized disease. However, limited data exists regarding long-term outcomes with NOM and factors associated with ICI failure, which we evaluated in this retrospective cohort study. **Methods:** We identified patients with EGC managed at MSK from 2007-2025 whose tumors were dMMR by IHC or MSI-H by next generation sequencing and analyzed patient/tumor characteristics and clinical outcomes in those who received curative-intent therapy (systemic therapy and/or surgery; ICI was first introduced in 2018). Clinical complete response (cCR) was defined as the absence of disease by available clinical, radiographic, and endoscopic assessment. **Results:** A total of 211 patients with localized dMMR/MSI-H EGC were identified, with median follow-up of 48 months (IQR 24-77). Primary tumor sites were stomach (71%), GE junction (17%), and esophagus (12%). Among 122 patients who underwent germline testing, 15 (12%) had Lynch syndrome. Initial treatment was upfront surgery in 85 patients (40%), chemotherapy (chemo) in 68 (32%), ICI alone in 44 (21%), and chemo/ICI in 14 (7%). Among 58 patients treated with ICI +/- chemo, 27 (47%) achieved a cCR. 6 patients underwent surgery despite cCR, with pathologic complete response (pCR) rate of 4/6 (67%); pCR rate in those without cCR was 3/16 (19%), yielding an overall pCR rate of 32%, higher than the pCR rate observed with chemo alone (5/48 [10%]). 21 patients elected for NOM after cCR; among those with $\geq$1 year of follow-up, 16 of 17 (94%) remain alive and surgery-free at 1 year. cCR rates were similar between those receiving ICI alone (45%) and chemo/ICI (50%). Notably, 2/2 (100%) patients treated with dual ICI therapy achieved cCR. Lower cCR rates were observed in patients with shorter time on ICI therapy (5/17 [29%] with $\leq$3 months of ICI vs 14/30 [47%] with $>$ 3 and $<$ 6 months vs 8/11 [73%] with $\geq$6 months) and in those with clinical nodal involvement (6/17 [35%] vs 14/19 [74%] in N0); 3 patients who underwent surgery had pCR at tumor but residual nodal disease. cCR rate was also numerically lower in the 19% of patients with MMR heterogeneity, defined by focal loss of MMR proteins on IHC or discordant MMR status between tissue specimens (4/11 [36%] vs 23/47 [49%] in non-heterogeneous cases). **Conclusions:** In this MSK cohort, ICI induced deep responses in nearly half of patients with localized dMMR/MSI-H EGC. Patients achieving cCR who pursued NOM demonstrated excellent outcomes, with most remaining surgery-free at 1 year, supporting the viability of NOM after careful multidisciplinary review. Research Sponsor: National Cancer Institute; P30 CA008748; U.S. National Institutes of Health; UL1TR00457; Brian Piccolo Endowed Cancer Research Fellowship.

4079 **Poster Session**

Total neoadjuvant immunotherapy plus chemotherapy in Borrmann type IV gastric cancer (PERISCOPE-01 study): An open-label, single-arm, phase 2 trial. First Author: Haibo Qiu, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Borrmann type IV (Borrmann-IV) gastric cancer (GC), or linitis plastica, is marked by diffuse infiltration, early metastasis, and poor prognosis, with limited benefit from conventional therapies. This study evaluated the efficacy and safety of a total neoadjuvant regimen combining immunotherapy and chemotherapy in Borrmann-IV GC. **Methods:** This trial (NCT06451211) enrolled patients with Borrmagnn-IV gastric cancer without distant metastasis. Participants received a total neoadjuvant regimen consisting of tislelizumab (an anti–PD-1 antibody) combined with platinum-based chemotherapy (oxaliplatin plus capecitabine or S-1) for 6 cycles at 3-week intervals, followed by radical surgical resection. The prespecified primary endpoint was the pathological response rate, defined as tumor regression grade (TRG) 0/1. **Results:** A total of 56 patients were enrolled, all patients had no distant metastasis confirmed by laparoscopic exploration and ascitic fluid cytology. The median age was 58 years; all patients were pMMR. In the efficacy analysis population (n=47), 41 patients completed 5–6 cycles and 6 patients completed 3–4 cycles of preoperative chemotherapy plus immunotherapy, no patients experienced disease progression leading to tumor metastasis during preoperative treatment. 47 patients underwent radical surgical resection, including 42 total gastrectomy, with an R0 resection rate of 98% (46/47). The prespecified primary endpoint of TRG 0/1 was achieved in 32% of patients (15/47; 95% CI, 21%–48%). Notably, 17% (n = 8) achieved pCR (ypT0N0), and 53% (n =25) were ypN0. Pathological response (TRG 0/1) was significantly higher in Lauren intestinal/mixed versus diffuse types (53% vs. 21%; $p < 0.05$), while efficacy was comparable between PD-L1 CPS $\geq$5 and $<$5 (44% vs. 30%). Grade 3/4 treatment-related adverse events occurred in 32% of patients (n=18), mainly thrombocytopenia and liver function impairment. Surgical morbidity (Clavien–Dindo grade II/III) occurred in 10.6% of surgical patients (5/47), including 1 patient with postoperative bleeding and 3 patients with anastomotic leakage; no perioperative mortality was observed. **Conclusions:** Total neoadjuvant tislelizumab plus chemotherapy demonstrated promising efficacy and an acceptable safety profile in patients with Borrmann-IV gastric cancer. Lauren classification may serve as a potential predictive biomarker and warrants further study. Clinical trial information: NCT06451211. Research Sponsor: None.

4080 **Poster Session**

Perioperative chemotherapy plus disitamab vedotin (RC48) and toripalimab in HER2-overexpressed locally advanced gastric or gastroesophageal junction cancer (PERISCOPE-02): An open-label, single-arm, phase 2 trial. First Author: Xiaojiang Chen, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: The use of Disitamab vedotin (RC48) and programmed death-1 (PD-1) inhibitor is effective in patients with HER2-expressing advanced gastric or gastroesophageal junction (G/GEJ) cancer. However, their use has not been investigated in patients with localized disease. This trial evaluated the safety and anti-tumor activity of perioperative chemotherapy combined with RC48 and toripalimab in the treatment of locally advanced HER2-overexpressed (defined as IHC 2+ or 3+) G/GEJ cancer. **Methods:** This study was an investigator-initiated, open-label, single-arm, phase 2 trial was conducted at Sun Yat-sen University Cancer Center. Eligible patients with HER2-overexpressed locally advanced G/GEJ cancer received 3-4 cycles of neoadjuvant XELOX plus RC48 and toripalimab, followed by surgery. The primary endpoint was TRG 0/1 after neoadjuvant treatment. This study is registered at Chinese Clinical Trial Registry (ChiCTR2400081677). **Results:** Between July 11, 2024, and July 11, 2025, of 26 patients screened for eligibility, 25 patients were enrolled, all patients had no distant metastasis confirmed by laparoscopic exploration and ascitic fluid cytology, 20 (80%) patients had clinical stage III disease and 5(20%) with stage II. Of these 25 patients, the median age was 58 (IQR, 37-74) years. Tumors were located in the stomach in 21(84%) patients and in the gastroesophageal junction in 4 (16%) patients. The patients with HER2 IHC expression of 2+ and 3+ was 21 (84%) and 4 (16%) respectively. 15 (60%) patients had the PD-L1 CPS of 1 or more, 24 (96%) patients were pMMR. The primary endpoint of TRG 0/1 was met in 16 (64%) patients, 9 (36%) patients achieved pCR (ypT0N0), and 24 (96%) were ypN0. 10 (40%) patients experienced grade 3 treatment-related adverse events, the most common treatment-related adverse events were increased ALT or AST (5 [20%] patients) and neutropenia (3 [12%] patients), no grade 4 treatment-related adverse events. Surgical morbidity (Clavien-Dindo II/III) occurred in 2 of 25 (8%) patients, with no 30-day surgical mortality. **Conclusions:** Our findings suggested that perioperative chemotherapy plus RC48 and toripalimab had controllable safety and showed encouraging efficacy in patients with HER2-overexpressed G/GEJ cancer. Clinical trial information: ChiCTR2400081677. Research Sponsor: None.

4081 **Poster Session**

Whole-genome sequencing–based ultra-sensitive ctDNA molecular residual disease assessment in resectable gastric cancer: Results from MONSTAR-SCREEN-3. First Author: Etsuro Bando, Department of Gastric Surgery, Shizuoka Cancer Center, Nagaizumi, Japan

Background: Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for post-surgical molecular residual disease (MRD) detection; however, its clinical utility in gastric cancer remains poorly defined. The MONSTAR-SCREEN-3 evaluates the clinical performance of a whole-genome sequencing (WGS)–based MRD assay in a pan-cancer cohort, including patients with gastric cancer. **Methods:** MONSTAR-SCREEN-3 is a prospective multicenter study targeting 1,100 patients with solid tumors curative-intent treatment, including gastric cancer. Personalized panels were constructed using Precise MRD (Myriad Genetics), incorporating up to 1,000 tumor-specific alterations identified through whole-genome sequencing (WGS) of matched tumor tissue. Serial plasma samples were collected at baseline, post-neoadjuvant treatment (NAT) when applicable, 1-month post-surgery, every 3 months in year 1, and every 6 months thereafter up to 2 years. Assay performance was evaluated for ctDNA detection and recurrence monitoring. **Results:** As of November 2025, 88 patients with resectable gastric cancer were enrolled. Median age was 69 years (range: 33-87), with female predominance (52.2%). Treatment strategies included upfront surgery (56%, n = 49) and NAT (44%, n = 39). MRD results were available for 220 samples from 57 patients. Clinical staging included Stage I (6%), Stage II (39%), Stage III (51%), and Stage IV (5%). Personalized panel creation succeeded in 100% of patients (57/57), yielding panels containing 588-1,000 alterations. Baseline ctDNA detection was achieved in 96.4% (54/56), with 31.5% at ultra-sensitive levels (tumor fraction $<$ 100 parts per million [ppm]). Post-operative MRD positivity was 7.8% (4/51) at 1 month and 19.5% (8/41) at 3 months, with 25.0% and 50.0% detected at ultra-sensitive levels, respectively. Among 24 patients receiving NAT with pathological assessment, post-NAT MRD status demonstrated 70.0% sensitivity and 100% specificity for pathological complete response (pCR) (MRD positivity, 70% in non-pCR vs. 0% in pCR; $P < 0.01$); 57.1% of MRD-positive cases were detected at ultra-sensitive levels. Two MRD-positive patients developed radiological recurrence, with MRD detection preceding imaging by 2.0 and 4.3 months. **Conclusions:** This WGS-based personalized ctDNA assay demonstrated high technical feasibility and baseline detection sensitivity in gastric cancer, with notable ultra-sensitive detection capability. Post-NAT MRD status demonstrated potential as a predictor of pathological complete response. Extended follow-up and comprehensive longitudinal ctDNA dynamics will be presented. Research Sponsor: SCRUM-Japan Funds (https://scrum-japan.ncc.go.jp/) and Myriad Genetics.

LBA4082 **Poster Session**

Pathological complete response and ctDNA analyses in SCIENCE: Results from a randomized, phase III trial of neoadjuvant chemotherapy plus sintilimab and chemoradiotherapy plus sintilimab versus chemoradiotherapy in resectable locally advanced esophageal squamous cell carcinoma. First Author: Xuefeng Leng, Department of Thoracic Surgery, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, Sichuan, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

4083 **Poster Session**

Perioperative durvalumab plus neoadjuvant chemoradiotherapy (CROSS) with and without tremelimumab in esophageal adenocarcinoma: The prospective phase II RICE trial (NCT04159974). First Author: Hans Anton Schloesser, Department of General, Visceral, Thoracic and Transplantation Surgery, University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany

Background: Anti-PD-(L)1 is effective in esophageal adenocarcinoma (EGA). The phase II RICE trial (NCT04159974) evaluated the addition of neoadjuvant and adjuvant durvalumab, with or without tremelimumab, to neoadjuvant chemoradiotherapy (CROSS). **Methods:** Patients with locally advanced ($\geq$uT3/Nx or uT2/N+) non-metastatic EGA received two doses of neoadjuvant durvalumab in addition to CROSS, followed by surgery. Adjuvant therapy was randomized 1:1 to durvalumab (12 doses) alone (arm A) or durvalumab plus one dose of tremelimumab (arm B). Translational analyses included HLA-I genotyping, immunohistochemistry, whole-exome sequencing and RNA-sequencing. Clinical outcomes were analyzed in patients who received at least one neoadjuvant dose (mITT) and in those who were randomized and received at least one adjuvant dose (R-mITT). **Results:** In the mITT set (n=56), 95% completed neoadjuvant therapy and 93% underwent resection. The rate of grade $\geq$3 non-hematologic adverse events during neoadjuvant treatment was 25% (13/56 G3, 1/56 G4). Surgery was feasible with a rate of anastomotic leakage of 6%. Major pathological response (MPR, $<$10% viable tumor cells) was achieved in 54% (30/56) including a 23% (13/56) pathological complete response rate (pCR, ypT0/ypN0). The rate of MPR was higher than in propensity-based comparisons with FLOT (25%) and CROSS (37%). Two-year overall (OS) and progression-free (PFS) survival of the mITT set were 72.7% and 53.1%, respectively. After completion of Stage I of the trial (safety run in), 38 patients were included in the R-mITT set. 80% in arm A (durvalumab monotherapy, n=20) and 44% in arm B (durvalumab plus tremelimumab, n=18) completed at least 80% of adjuvant immunotherapy. Combined immunotherapy in the R-mITT set was associated with higher grade $\geq$3 toxicity (22% G3/ 22% G4 in Arm B vs. 15% G3 / 0% G4 in arm A) and did not improve survival (2-year OS/PFS 95.0%/80.0% [arm A] vs. 82.4%/54.2% [arm B]). Tumor mutational burden, heterozygosity of HLA-I, expression of genes related to antigen presentation and T-cell abundance were associated with pathological response. However, discordant cases across all biomarkers underscore the complexity of tumor-immune interactions underlying response to immunotherapy. **Conclusions:** RICE demonstrates safety and feasibility of adding anti-PD-L1 to neoadjuvant CROSS in EGA and shows promising response rates. While CROSS is no longer considered standard of care, our results support efficacy of durvalumab, consistent with results for FLOT plus durvalumab in the MATTERHORN trial. Addition of tremelimumab to durvalumab is not supported by our study. Clinical trial information: NCT04159974. Research Sponsor: Astra Zeneca.

4084 **Poster Session**

Paclitaxel/cisplatin (TP) vs cisplatin/5-fluorouracil (PF) neoadjuvant chemoradiotherapy for locally advanced esophageal squamous cell carcinoma (ESCC): A randomized trial. First Author: Ta-Chen Huang, National Taiwan University Hospital, Taipei, Taiwan

Background: Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is standard treatment for patients with resectable locally advanced ESCC. A direct comparison of taxane/platinum nCRT versus PF nCRT in prospective randomized clinical trials has never been reported. **Methods:** This is a single-center, open-label, randomized phase II/III trial (registered as NCT0623737 at ClinicalTrial.gov). Patients with locally advanced ESCC (T3/4aN0M0 or T1-3N1-3M0 per AJCC 7th ed.) were randomized 1:1 to TP (paclitaxel 50 mg/m2 weekly plus cisplatin 30 mg/m2 weekly for 5 weeks) or PF (cisplatin 75 mg/m2 day 1 plus 5-FU 1,000 mg/m2 days 1-4 on weeks 1 and 5) chemotherapy with concurrent radiotherapy 45 Gy/25 fractions. Esophagectomy was performed 6 to 10 weeks after completing CRT. Primary endpoint was pathological complete response (pCR) rate for phase II part. If significant pCR benefit of TP versus PF nCRT was found in phase II part, the trial would continue enrolment for the phase III part with overall survival as primary endpoint. **Results:** From Mar 2017 to Jul 2025, 128 patients were enrolled in the phase II part; 6 withdrew before treatment. The intention-to-treat (ITT) population included 122 patients (61 patients per arm); median age was 61 (35-77) years with TP and 58 (39-77) with PF; 90% and 89% were male, respectively. Esophagectomy was performed in 51/61 (84%) vs. 49/61 (80%), and R0 resection was achieved in 43/51 (84%) vs. 36/49 (73%) (p=0.183), respectively. The pCR rate per ITT population was 23/61 (37.7%) with TP vs 17/61 (27.9%) with PF (p=0.247). The difference of pCR rate did not meet the boundary to continue the trial to the phase III part. Median overall survival was 54 vs 43 months (HR 0.76; p=0.284) and median progression-free survival was 33 vs 25 months (HR 0.74; p=0.193) for TP vs PF. Median recurrence free survival was not reached in both arms. Grade 3-4 adverse events during nCRT occurred in 29/61 (47.5%) with TP and 40/61 (65.6%) with PF (p=0.045); most common grade $\geq$3 events were leucopenia (23.0% vs 32.8%), esophagitis (11.5% vs 29.5%), and dysphagia (14.8% vs 27.9%). Postoperative 90-day mortality was 0% in both arms. **Conclusions:** TP-nCRT did not significantly improve pCR versus PF-nCRT in patients with locally advanced ESCC. Clinical trial information: NCT0623737. Research Sponsor: None.

Efficacy and safety outcomes for TP-nCRT versus PF-nCRT.

	TP	PF	Statistics
ITT, n	61	61	-
Resection, n (%)	51 (84)	49 (80)	p=0.638
R0 resection rate (%)	43/51 (84)	36/49 (73)	p=0.183
pCR (ITT) rate (%)	23/61 (37.7)	17/61 (27.9)	p=0.247
pCR (resected population) rate (%)	23/51 (45.1)	17/49 (34.7)	p=0.288
OS, median (mo)	54	43	HR 0.76; p=0.284
PFS, median (mo)	33	25	HR 0.74; p=0.193
Grade 3-4 AEs during nCRT, n (%)	29 (47.5%)	40 (65.6%)	p=0.045
Postoperative 90-day mortality	0	0	-

4085 **Poster Session**

Phase II study of adjuvant nab-paclitaxel plus S-1 after D2 resection in stage III diffuse gastric cancer (NORDICA study). First Author: Ke Peng, Zhongshan Hospital Fudan University, Shanghai, China

Background: Stage III diffuse-type gastric cancer (DGC) is highly aggressive, with a substantial risk of postoperative recurrence. Adjuvant chemotherapy with nab-paclitaxel plus S-1 (AS regimen) has shown potential efficacy in early studies, but its safety and effectiveness in this high-risk population remain unclear. **Methods:** This single-center, prospective phase II trial enrolled patients with stage III DGC who underwent D2 gastrectomy between January 2020 and October 2023. All patients first received one cycle of S-1 monotherapy as a pre-screening tolerance test. Eligible patients then received adjuvant AS therapy: nab-paclitaxel 260 mg/m² on day 1 every 3 weeks (maximum 400 mg) plus S-1 80–120 mg/day on days 1–14 every 3 weeks for 6 cycles, followed by 8 cycles of S-1 monotherapy. The primary endpoint was 1-year disease-free survival (DFS); secondary endpoints included 3-year DFS, overall survival (OS), and safety. To explore potential molecular correlates of treatment response, whole-exome sequencing was performed on tumor specimens obtained from surgical resection in 24 patients, including 12 patients who experienced recurrence within 2 years (resistant group) and 12 patients with DFS of 2 years or longer (sensitive group). **Results:** The 1-year DFS and OS rates were 84.9% (95% CI, 75.3–95.9%) and 100%, respectively. The 3-year DFS and OS rates were 45.2% (95% CI, 32.5–63.0%) and 62.5% (95% CI, 49.0–79.8%), with a median DFS of 27.7 months (95% CI, 16.5–NR). The most common ≥grade 3 treatment-related adverse events were neutropenia (29.2%), leukopenia (20.8%), rash (6.3%), febrile neutropenia (6.3%), and oral mucositis (4.2%). CDH1 and OBSCN mutations were more frequent in the resistant group, suggesting a potential link to early recurrence. **Conclusions:** Adjuvant AS therapy is feasible and demonstrates promising efficacy for stage III DGC, with an acceptable safety profile. Molecular findings may help identify patients at higher risk of recurrence, supporting further evaluation in larger, randomized phase III trials. Clinical trial information: NCT03977220. Research Sponsor: None.

4086 **Poster Session**

Interim results from a prospective phase II study of stratified treatment of localized cervical esophageal squamous cell carcinoma by induction immunochemotherapy (SCENIC trial). First Author: Chunguang Li, Department of Thoracic Surgery, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Definitive concurrent chemoradiotherapy (dCRT) is the standard treatment for cervical esophageal squamous cell carcinoma (CESCC). However, when dCRT fails, salvage esophagectomy is technically challenging. Moreover, optimizing patient selection for dCRT remains an unresolved concern. We propose a stratified screening strategy by incorporating induction immunochemotherapy, aiming to identify suitable candidates for organ-sparing dCRT and timely surgical treatment. **Methods:** This prospective interventional phase II study (SCENIC, ChiCTR2200057732) enrolled patients with clinical stage $T_{2\text{-}4}$ N_{any} M0 (AJCC TNM 8th) resectable CESCC. Eligible participants received induction therapy (IT) of intravenous PD-1 inhibitor tislelizumab (200mg, day 1) plus nab-paclitaxel (100 mg/m^2, day 1,8,15) and carboplatin (area under curve of 5 mg/mL/min, day 1), administered over two 3-week cycles. Four weeks after IT, treatment response was evaluated via endoscopy and PET-CT. Patients were then divided into 3 groups: remarkable response (RR); limited partial response (LPR); and poor response (POR). RR patients received dCRT, while LPR and POR patients underwent radical surgery. Tislelizumab was maintained after dCRT in RR patients, and postoperative adjuvant therapy was dependent on the patient's condition, including chemotherapy, radiotherapy, immunotherapy, or follow-up. The primary endpoint is 2-year event-free survival (EFS). **Results:** From Jul 2022 to Sep 2024, 42 patients were enrolled, with 40 completing two-cycle IT and response evaluation. Post-IT responses were RR in 62.5% (25/40), LPR in 25.0% (10/40), and POR in 12.5% (5/40). All RR patients received subsequent dCRT. In 11 non-RR patients,7 underwent total phryngo-laryngo-esophagectomy(TPLE), 4 received dCRT. Overall, 40 patients (96.0%) had any-grade treatment-related adverse events with leukocytopenia being most prevalent. 5 patients (12.5%) had adverse events of grade 3 or worse. With a median follow-up of 22.3 months (range, 4.5-40.9 months), 2-years EFS rate and overall survival (OS) rate in ITT population was 60.9% and 76.6%. 2-years EFS rate and OS rate in RR group and non-RR group is 78.8% vs 28.0%($p = 0.0011$) and 84.8% vs 70.1%($p = 0.0703$), respectively. **Conclusions:** The 2-year survival of RR patients with dCRT followed by IT appears promising compared to historical data. This stratified strategy of induction immunochemotherapy is effective in identifying candidates suitable for dCRT in patients with resectable CESCC. Clinical trial information: ChiCTR2200057732. Research Sponsor: None.

4087 **Poster Session**

Perioperative therapy with tifcemailmab plus toripalimab and chemotherapy for resectable thoracic esophageal squamous cell carcinoma (BT-NICE trial): A prospective phase II study. First Author: Chengzhi Ding, Henan Provincial People's Hospital, Zhengzhou, China

Background: Tifcemailmab is a first-in-class humanized monoclonal antibody targeting B- and T-lymphocyte attenuator (BTLA), a novel inhibitory immune checkpoint. This phase II BT-NICE trial represents the first clinical study designed to evaluate the efficacy and safety of a perioperative treatment regimen that combines a BTLA inhibitor (tifcemailmab), a PD-1 inhibitor (toripalimab), and chemotherapy for resectable thoracic ESCC. **Methods:** Patients(pts) with histologically confirmed, resectable thoracic ESCC (clinical stage cT1b-3N1-3M0 or cT2-3N0M0) were enrolled. They received 2 cycles of neoadjuvant therapy with tifcemailmab, toripalimab, and standard chemotherapy (every 3 weeks). Following radical esophagectomy, pts with a pathological complete response (pCR) received up to 15 cycles of adjuvant dual immunotherapy (tifcemailmab + toripalimab). Pts without a pCR received 2 cycles of adjuvant chemotherapy plus dual immunotherapy, followed by dual immunotherapy for up to 13 cycles. The primary endpoint was pCR rate. Secondary endpoints included major pathological response (MPR) rate, objective response rate (ORR), R0 resection rate, adverse events (AEs), event-free survival (EFS), and overall survival (OS). **Results:** Between October 20, 2024, and September 30, 2025, a total of 25 patients were successfully enrolled and underwent surgery after completing neoadjuvant therapy. The median age was 63 years (range 53-75), and 19 (76.0%) were male. Most pts (23/25, 92.0%) had stage III disease. The R0 resection rate was 100% (25/25). The ORR (neoadjuvant) was 96.0% (24/25). The MPR rate was 56.0% (14/25), and the pCR rate was 40.0% (10/25). Pathologic downstaging was achieved in 84.0% of patients. Grade 3-4 treatment-related AEs occurred in 24.0% (6/25) of pts, and grade 3-4 immune-related AEs occurred in 20.0% (5/25); the most common were rash and hypothyroidism. Overall postoperative complications were 20% (5/25). One pt experienced postoperative complications (pulmonary infection and anastomotic leakage). No treatment-related surgical delays or 30-day mortality occurred. **Conclusions:** The BT-NICE regimen demonstrates promising efficacy and is feasible with a manageable safety profile in pts with locally advanced, resectable ESCC. This study provides the first clinical evidence supporting the incorporation of a BTLA inhibitor into a perioperative treatment paradigm for ESCC. Clinical trial information: NCT06588335. Research Sponsor: Shanghai Junshi Biosciences Co., Ltd.

4088 **Poster Session**

The early-onset paradox of gastric cancer: Assessment of geographic clustering, biology, treatment, and outcomes. First Author: Pranati Dharmesh Shah, Loma Linda University, Loma Linda, CA

Background: Early-onset gastric cancer (EOGC), defined as diagnosis before age 45, represents an increasingly recognized and clinically distinct subset of gastric cancer (GC) in the United States. While prior studies largely from Asian cohorts suggest more aggressive tumor biology, contemporary U.S. data characterizing demographic patterns, treatment strategies, geographic variation, and outcomes in resectable disease is limited. **Methods:** Using a U.S. cancer registry (2006–2022), we studied patients aged 18–90 with stage II–III gastric cancer post-gastrectomy. Excluding palliative or incomplete cases, we analyzed overall survival (OS) via Cox models, adjusting for demographics and treatment. P-values were calculated using the Chi-square test to compare racial distribution across age groups. **Results:** Among eligible patients, 1,943 (7.4%) had EOGC. EOGC disproportionately affected Hispanic (23.8%; $p < 0.001$), Black (14.2%; $p < 0.001$), and Asian (10.2%; $p < 0.001$) populations, with White patients accounting for 49.4%, with a male predominance (2:1). Demographic and socioeconomic profiles were distinct within the EOGC population. A greater proportion of EOGC patients resided in areas with a median household income < $38,000 (17.1%; $p = 0.025$). The ≤45 group was more frequently uninsured (7.6%) or Medicaid insured (19.7%) and represented the highest proportion of residents from areas with the lowest educational attainment (21.6%). Geographic clusters emerged in the South/Middle Atlantic and Pacific (TX, CA, AK, HI). EOGC tumors more frequently exhibited diffuse or signet-ring histology (~30%) and advanced nodal involvement. Despite receiving more intensive multimodality therapy, including perioperative or neoadjuvant chemotherapy (74.1%), EOGC patients had lower pathologic response rates and no survival advantage. Median OS was 49.8 months (36-month OS: 58.3%). **Conclusions:** Even with aggressive treatment, EOGC shows worse pathology and no better survival rates than older-onset cases. New U.S. data confirms this aggressive biology and highlights significant demographic and socioeconomic disparities. To improve outcomes, the focus should shift from just intensifying treatment to prioritizing earlier detection and targeted regional screening. Research Sponsor: None.

Demographic characteristics stratified by age groups.

Variable	≤45 Years (n=1943)	46–69 Years (n=15927)	≥70 Years (n=8397)	Total Cohort (N=26267)	p-value
Race, n (%)					<0.001
White	960 (49.4)	10912 (68.5)	5918 (70.5)	17790 (67.7)	
Black	276 (14.2)	1890 (11.9)	838 (10.0)	3004 (11.4)	
Hispanic	462 (23.8)	1611 (10.1)	766 (9.1)	2839 (10.8)	
Asian	198 (10.2)	1166 (7.3)	731 (8.7)	2095 (8.0)	
Other	47 (2.4)	348 (2.2)	144 (1.7)	539 (2.1)	

4089 **Poster Session**

Neoadjuvant cadonilimab plus CapeOX in patients with clinical stage III gastric or esophagogastric junction adenocarcinoma (GC/EGJC): A prospective, single-arm phase II study. First Author: Liying Zhao, Department of General Surgery & Guangdong Provincial Key Laboratory of Precision Medicine for Gastrointestinal Tumor, Nanfang Hospital, Southern Medical University, Guangzhou, China

Background: Perioperative PD-L1 inhibitor plus chemotherapy has shown survival benefit in PD-L1-positive patients with locally advanced GC/EGJC. However, evidence for neoadjuvant PD-1/CTLA-4 bispecific blockade remains limited. This study evaluates neoadjuvant cadonilimab plus CapeOX in patients with clinical stage III GC/EGJC. **Methods:** This prospective, single-arm phase II study (NCT06310473) enrolled patients (pts) with cT3-4aN1-3M0 disease (AJCC 8th), staged by contrast-enhanced CT and staging laparoscopy with peritoneal cytology to exclude peritoneal metastasis and positive peritoneal cytology (CY1). Pts received cadonilimab (10 mg/kg) plus standard-dose CapeOX every 3 weeks for 3 cycles. Pts without progressive disease on repeat CT and laparoscopy underwent curative-intent surgery, followed by 3-5 cycles of adjuvant CapeOX. The primary endpoint was the pathologic complete response rate (pCR, defined as no residual tumor in stomach and lymph node). The data cutoff was January 15, 2026. **Results:** From May 2024 to August 2025, 30 pts with GC/EGJC were enrolled (GC, n = 21; EGJC, n = 9); 83.3% (25/30) were cT4a and 73.3% (22/30) were cN2-3. PD-L1 CPS $<$ 1 was observed in 14.8% (4/27) of evaluable pts. All pts completed 3 neoadjuvant cycles. Three pts did not undergo surgery: one refused resection and subsequent antitumor therapy after achieving a cCR to neoadjuvant therapy; one had a PR and continued systemic therapy; and one had PD with liver invasion on repeat laparoscopy and initiated second-line therapy. The other 27 pts underwent resection; one had CY1 on postoperative assessment and was considered PD, with an R0 resection rate of 96.3% (26/27). The pCR and major pathologic response (MPR) rates were 22.2% (6/27) and 37.0% (10/27), respectively. The tumor downstaging rate was 74.1% (20/27), including a ypN0 rate of 55.6% (15/27). Adjuvant therapy was administered in 23/27 (85.2%), with four pts still on therapy. Treatment-related adverse events occurred in 100% (30/30), including grade$\geq$3 events in 20.0% (6/30). Notable events included one perioperative cardiovascular death (G5); one pulmonary embolism (G3) diagnosed 5 weeks postoperatively that resolved with anticoagulation; one patient with concomitant anastomotic leakage (G4), intra-abdominal infection (G4), and immune-related adrenal insufficiency (G2) who recovered after endoscopic covered-stent placement and conservative management; additional G3 events included ascites, neutropenia, and peripheral neuropathy (n = 1 each). No postoperative recurrence was observed among resected pts at data cutoff. **Conclusions:** Neoadjuvant cadonilimab plus CapeOX appears safe and effective in patients with clinical stage III GC/EGJC, achieving a moderate pCR rate and warranting further exploration of neoadjuvant immunochemotherapy combination strategies. Clinical trial information: NCT06310473. Research Sponsor: None.

4090 **Poster Session**

Neoadjuvant adebrelimab combined with chemotherapy in locally advanced esophageal squamous cell carcinoma: A single-arm, phase II trial. First Author: Chao Wu, Department of Medical Oncology, Senior Department of Oncology, Chinese PLA General Hospital, Beijing, China

Background: Neoadjuvant therapy is the standard treatment for patients with locally advanced resectable esophageal squamous cell carcinoma (ESCC). This study evaluated the efficacy and safety of adebrelimab (anti-PD-L1 antibody) combined with neoadjuvant chemotherapy and explored immune correlates associated with treatment response (ChiCTR2400085858). **Methods:** Patients with locally advanced ESCC (cT1b-T2N+M0 or cT3-4NanyM0) received three preoperative cycles of adebrelimab (1200 mg, IV, d1, Q3W) plus nab-paclitaxel (125 mg/m^2, IV, d1, d8, Q3W) and carboplatin (AUC 5 mg/mL/min, IV, d1, Q3W). The primary endpoint was pathological complete response (pCR). Secondary endpoints included major pathological response (MPR), R0 resection rate, disease-free survival (DFS), overall survival (OS) and safety. PD-L1 expression was measured by immunohistochemistry using the combined positive score (CPS). Multiplex immunohistochemistry was performed to assess spatial immune microenvironment changes. **Results:** Forty-three patients were enrolled from October 2023 to June 2025. The median age was 61 years (range, 42-75), and 39 patients (91.0%) were male. Patients with cStage II/III/IVA were 6/16/22. Among the 35 patients who underwent surgery, all achieved R0 resection (100%), with pCR and MPR rates of 22.9% (8/35) and 45.7% (16/35), respectively. The median follow-up was 13.2 months (range 2.4-21.9), with 1-year DFS and OS estimates of 94.2% (95%CI: 86.7%-100.0%) and 86.8% (95%CI: 76.5%-98.4%). Patients with PD-L1 CPS $\geq$ 10 (57%, 20/35) demonstrated a higher pCR rate compared with those with PD-L1 CPS $<$ 10 (43%, 15/35), specifically 30% (6/20) vs 13.3% (2/15). Multiplex immunohistochemistry revealed distinct spatial immune remodeling during neoadjuvant therapy. At baseline, PD-L1 expression was predominantly associated with CD11b$^+$ myeloid cells in peritumoral regions and was enriched in good responders (TRG 0-1), accompanied by higher peritumoral CD3$^+$ T-cell infiltration. Post-treatment analyses demonstrated divergent T-cell dynamics, with decreased peritumoral T-cell density in good responders (TRG 0-1) and increased infiltration in poor responders (TRG 2-3). Treatment-related adverse events were consistent with the known safety profile. The most common treatment-related grade 3/4 AEs were leukopenia (41.9%), alopecia (27.9%), thrombocytopenia (9.3%), anemia (7.0%), and hepatic dysfunction (2.3%). **Conclusions:** Neoadjuvant adebrelimab combined with chemotherapy demonstrated promising efficacy and manageable toxicity in patients with locally advanced ESCC. Myeloid-associated PD-L1 expression and treatment-induced T-cell redistribution may represent immune correlates of response and warrant further investigation. Clinical trial information: ChiCTR2400085858. Research Sponsor: None.

4091 **Poster Session**

Neoadjuvant tislelizumab plus oxaliplatin and S-1 for locally advanced Siewert type II esophagogastric junction adenocarcinoma: A prospective multicenter phase II study. First Author: Yanzhao Xu, Department of Thoracic Surgery, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Background: Adenocarcinoma of the esophagogastric junction (AEG) is a malignant tumor with high morbidity and mortality globally. Among subtypes, Siewert type II AEG remains a clinical challenge owing to its unique anatomical location and distinct clinicopathological features. This study aimed to evaluate the efficacy and safety of Tislelizumab in combination with oxaliplatin and S-1 as neoadjuvant therapy for patients with locally advanced Siewert type II AEG. **Methods:** This is a prospective, multicenter clinical trial. Eligible patients were aged 19-75 years with pathologically confirmed Siewert type II adenocarcinoma of the esophagogastric junction, clinical stage T2-4N0-3M0, ECOG performance status 0-1, and adequate major organ function. All patients received 3 cycles of neoadjuvant therapy consisting of: tislelizumab (200 mg, D1, Q3W), oxaliplatin (130 mg/m², D1, Q3W), and S-1 (40-60mg based on BSA, po, bid, D1-14, Q3W). Following efficacy evaluation, patients underwent resection of the esophagogastric junction adenocarcinoma 4-8 weeks after completion of neoadjuvant therapy. The primary endpoint is pathologic complete response (pCR). Secondary endpoints include major pathologic response (MPR), objective response rate, R0 resection rate, overall survival (OS), disease-free survival (DFS), and safety. **Results:** As of June 2025, a total of 40 patients were enrolled in this study. The median age was 66 years (range, 37-76), 87.5% were male, and 92.5% had an ECOG performance status of 0. Among them, 87.5% (n = 35) of the patients completed 3 cycles of neoadjuvant therapy. The remaining 5 cases completed 1 (n = 1, due to grade$\geq$3 TRAEs), 2 (n = 2, due to grade$\geq$3 TRAEs and patient decision, respectively), and 4 (n = 2, patient decision) cycles of treatment. All patients underwent resection of the esophagogastric junction adenocarcinoma. The R0 resection rate was 97.5% (39/40), with no patients requiring re-operation or experiencing perioperative mortality. The pathologic complete response (pCR) rate was 25% (10/40). The primary tumor pCR rate reached 30% (12/40), and the major pathologic response (MPR) rate was 37.5% (15/40). Treatment-related adverse events (TRAEs) of any grade occurred in 95% (38/40) of patients, with grade $\geq$3 TRAEs observed in 15% (6/40). **Conclusions:** Neoadjuvant therapy with Tislelizumab in combination with oxaliplatin and S-1for locally advanced Siewert type II esophagogastric junction adenocarcinoma yields a favorable pathological complete response (pCR) rate and shows a good safety profile. Clinical trial information: ChiCTR2300075638. Research Sponsor: Excellent Talents Program of the Department of Finance of Hebei Province; ZF2025209.

4092 **Poster Session**

SCALE-2: A phase 2 trial evaluating neoadjuvant short-course radiotherapy combined with chemotherapy and toripalimab in resectable locally advanced esophageal squamous cell carcinoma. First Author: Ning Jiang, Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research & The Affiliated Cancer Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

Background: The SCALE-1 Phase Ib trial demonstrated that short-course neoadjuvant radiotherapy combined with toripalimab and chemotherapy, followed by esophagectomy, exhibited manageable toxicity and promising efficacy in patients (pts) with resectable locally advanced ESCC (RLaESCC). This Phase II trial aims to further valuate efficacy and safety of this novel short-course regimen in a larger cohort. **Methods:** RLaESCC pts with clinical stages cT3-4aN0M0/cT1-4aN+M0 received neoadjuvant paclitaxel (135 mg/m^2), carboplatin (AUC=5), and toripalimab (240 mg) every 3 weeks for two cycles. Short-course neoadjuvant radiotherapy (30 Gy/12f; 5 days per week) was administered between the two doses of neoadjuvant immune-chemotherapy. Compared to SCALE-1, high-risk nodal regions were selectively included in the irradiation volume. Weekly weight changes were used to assess preoperative waiting time. Esophagectomies were scheduled 8-10 weeks after completing neoadjuvant treatment. The primary endpoint was pathological complete response (pCR) rate, with secondary endpoints included disease free survival (DFS), overall survival (OS) and safety. **Results:** From April 28, 2024 to February 26, 2025, 63 pts were enrolled (intention-to-treat population, ITT), with stage distribution:I (3.2%), II (14.3%), III (63.5%) and IVA (19%). Following the exclusion of 3 pts who refused surgery, pathological assessment of the surgical specimens revealed that 56.7% (34/60) pts achieved pCR (ypT0N0 or ypTisN0) and 91.7% (55/60) achieved MPR. The median number of resected lymph nodes was 19 (range: 6–45). At a median follow-up of 23.9 months (cutoff date: Jan 19, 2026), median OS and DFS were not reached. In the ITT population, the 2-year OS and DFS rates were 90.4% (95% CI: 82.4-98.4%) and 81.5% (95% CI: 70.5-92.5%), respectively. Postoperative complications occurred in 45% (27) pts, with 18.3%(11) experiencing Grade $\geq$3 events. The most frequent Grade 3 and above complications were anastomotic leakage (n=4) (with or without pleural effusion or hemothorax) and airway mucus obstruction (n=4). Moreover, one case of postoperative delirium was observed (Grade IV), and one patient died of septic shock secondary to an anastomotic leak. All 63 pts completed neoadjuvant radiotherapy. However, 2 pts discontinued the second dose of toripalimab, and 16 pts required dose reductions during the second cycle of neoadjuvant chemotherapy. The most frequent grade 3/4 adverse events were neutropenia (n=27, 42.9%) and leukopenia (n=21, 33.3%). Notably, no grade 3 esophagitis or pneumonitis occurred. **Conclusions:** The SCALE regimen demonstrated potent antitumor activity, achieving 56.7% pCR and 91.7% MPR. Favorable 2-year OS and DFS further highlight its potential to improve long-term outcomes for RLaESCC pts. Clinical trial information: NCT05424432. Research Sponsor: None.

4093 **Poster Session**

Noninvasive detection of early gastric cancer via red blood cell DNA features associated with tumor-induced hematopoietic stress. First Author: Xingyun Yao, School of Life Sciences, Westlake University, Hangzhou, Zhejiang, China

Background: Early detection of gastric cancer (GC) is limited by invasive endoscopy and the low sensitivity of current blood-based biomarkers for early-stage disease. Emerging evidence indicates that GC engages in complex crosstalk with the bone marrow microenvironment, imposing stress on hematopoiesis. Tumor-derived exosomal and inflammatory mediators reprogram transcriptional and epigenetic profiles in hematopoietic progenitors, driving abnormal hematopoiesis and inducing genomic instability. Here, we report a noninvasive strategy for GC detection based on genome-wide profiling of DNA remnants in mature red blood cells (rbcDNA) and validate its performance for early-stage disease across independent multicenter cohorts. **Methods:** We analyzed rbcDNA from 1–2 mL peripheral blood of 865 individuals, including 434 treatment-naive patients with stage I–III GC (~60% stage I) and 431 non-GC controls with benign gastric conditions. Shallow whole-genome sequencing revealed reproducible rbcDNA read-depth features that distinguished GC from non-cancer states. A machine-learning classifier was trained on dimensionally reduced rbcDNA features in a discovery cohort (n = 435), with a cutoff fixed at 90% specificity. The locked model was then evaluated in a test cohort (n = 109) and three independent validation cohorts from distinct medical centers (n = 321). **Results:** In a discovery cohort, we identified GC-associated rbcDNA features that were significantly enriched in hematopoietic regulation and cell-cycle pathways, reflecting systemic hematopoietic stress rather than tumor-derived copy-number alterations. The resulting classifier achieved AUCs of 93% in the discovery cohort and 95% in the test cohort. At the predefined cutoff, the classifier yielded 83% overall sensitivity and 79% sensitivity for stage I GC in the test cohort. Across three independent medical center cohorts, the model achieved sensitivities of 83%, 90%, and 86%, with specificities ranging from 89% to 94%, consistent with the discovery and test cohorts. The assay effectively distinguished early-stage GC from precancerous lesions, including atrophic gastritis and intestinal metaplasia, while showing limited detection in non-gastric solid tumors. Importantly, rbcDNA identified ~80% of GC cases that were negative for conventional serum tumor markers. **Conclusions:** These findings establish rbcDNA as an effective biomarker for accurate, noninvasive detection of early-stage GC. Research Sponsor: None.

4094 **Poster Session**

Prognostic value of perioperative ctDNA monitoring in patients with esophageal squamous cell carcinoma (ESCC) undergoing neoadjuvant chemotherapy (NAC) and surgery. First Author: Akinori Watanabe, Department of Gastroenterology, Kitasato University School of Medicine, Sagamihara, Japan

Background: Recent results from a multicenter phase II clinical trial (jRCTs031200094) demonstrated that neoadjuvant FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) improves survival outcomes of patients with resectable ESCC. In this analysis, we evaluated the value of circulating tumor DNA (ctDNA) dynamics after FLOT and curative-intent surgery to predict treatment response and long term outcomes. **Methods:** The jRCTs031200094 clinical study enrolled 37 patients with ESCC to receive neoadjuvant FLOT followed by curative-intent surgery. Plasma samples were collected NAC, post-NAC (prior to surgery), and within 2–12 weeks post surgery [molecular residual disease (MRD) window]. A clinically validated, personalized, tumor-informed mPCR-NGS assay (Signatera, Natera, Inc.) was used on the banked specimens for ctDNA detection. Survival analyses were performed to calculate progression-free survival (PFS) stratified by ctDNA status at the post-NAC and post surgery timepoints. **Results:** This retrospective analysis included the 34 patients with ESCC and available ctDNA results. Patients had a median age of 66 years (range: 44–80), and the majority were male (79% [27/34]). Tumor locations included the middle (53%, 18/34), lower (41%, 14/34), and upper esophagus (5.9%, 2/34). The clinical stage distribution was 8.8% (3/34) stage I, 21% (7/34) stage II, 56% (19/34) stage III, and 15% (5/34) stage IV. R0 resection was achieved in 94% (29/31) of resected patients; 3 patients did not undergo esophagectomy due to disease progression or patient preference. Baseline ctDNA positivity was observed in 97.1% (33/34) of patients. Among 33 patients with ctDNA data available at the post-NAC timepoint, ctDNA-positivity was associated with significantly inferior PFS (HR: 3.17, 95% CI: 1.22-8.21; P=0.018), higher rate of lymph node positivity and higher tumor regression grade (TRG). Of the 29 patients with ctDNA data in the MRD window 31.3% (9/29) were ctDNA-positive and ctDNA-positivity in the MRD window was associated with significantly inferior PFS (HR: 5.89; P=0.001) and overall survival (OS; HR: 7.23; P=0.019). In addition, ctDNA dynamics in response to NAC and surgery were highly predictive of long term outcomes. Sustained clearance after NAC correlated with 80% 24m PFS. Inferior survival was observed in patients who remained ctDNA positive after NAC but cleared after surgery (HR 3.17) and in patients without clearance after surgery (HR 7.63). **Conclusions:** This study demonstrates prognostic and predictive value of single timepoint and longitudinal ctDNA status in the neoadjuvant and postsurgical management of patients with ESCC. Persistent ctDNA positivity following NAC and in the MRD window was strongly associated with inferior PFS, and early ctDNA clearance conferred the most favorable outcomes. Clinical trial information: jRCTs031200094. Research Sponsor: None.

4095 **Poster Session**

Individualized estimation of benefit from adjuvant docetaxel plus S-1 in stage III gastric cancer using deep learning–based counterfactual survival analysis of the START-2 trial. First Author: Hiroki Sato, OITA University Faculty of Medicine, Yufu, Japan

Background: The START-2 trial demonstrated that docetaxel plus S-1 (DS) was superior to S-1 alone in terms of relapse-free survival (RFS) and overall survival (OS) as adjuvant chemotherapy for patients (pts) with stage III gastric cancer (GC) (J Clin Oncol 2019; Gastric Cancer 2022). We conducted the START-2 AR study, a retrospective analysis, to develop a neural network–based model for predicting RFS and estimating individual-level treatment benefit. **Methods:** Among 912 pts enrolled in the START-2 trial, 599 provided written informed consent to participate in the START-2 AR study. Pts were randomly divided into training (70%) and test (30%) cohorts. Missing data were addressed using multiple imputation. A deep learning–based Cox proportional hazards model was trained in the training cohort and evaluated in the test cohort. Using this model, we estimated individual-level treatment benefit among pts in the DS group, quantified as the difference in restricted mean survival time (dRMST) between counterfactual survival curves comparing DS with S-1 alone. Subsequently, a LightGBM regressor was applied to identify clinicopathological factors associated with treatment benefit using SHapley Additive exPlanations (SHAP). In an exploratory analysis, the top-ranked variables were used to identify a subgroup with limited additional benefit from DS. **Results:** Among 599 pts (training cohort, n = 419; test cohort, n = 180), 249 RFS events were observed (174 and 75 events, respectively). The pooled Antolini C-index was 0.686 (95% confidence interval [CI], 0.643–0.726) in the training cohort and 0.628 (95% CI, 0.565–0.697) in the test cohort. The estimated dRMST in the DS group was 2.71 months (95% CI, 2.58–2.84). SHAP analysis of dRMST indicated that a lower number of metastatic lymph nodes, a higher platelet count, a higher number of dissected lymph nodes, and differentiated histology were the key factors associated with a smaller dRMST, indicating limited treatment benefit. When continuous variables were dichotomized at their median values and pts were stratified by the cumulative number of these four factors, the subgroup with < 3 factors (n = 454) showed significantly improved RFS with DS compared with S-1 alone (hazard ratio [HR], 0.67; 95% CI, 0.51–0.88; p = 0.004). In contrast, no significant benefit was observed in the subgroup with ≥ 3 factors (n = 145; HR, 1.32; 95% CI, 0.70–2.50; p = 0.396). **Conclusions:** Using a deep learning–based counterfactual dRMST framework, we identified a subgroup of pts with resected stage III GC who derived limited additional benefit from adjuvant DS therapy. Stratification based on four clinicopathological factors may facilitate personalized de-escalation of DS treatment. External validation in independent cohorts is warranted. Clinical trial information: UMIN000011438. Research Sponsor: Taiho Pharmaceutical Co., Ltd.

4096 **Poster Session**

Long-term survival results of perioperative chemoimmunotherapy with DCF and avelumab in locally advanced gastro-esophageal adenocarcinoma. First Author: Thierry Alcindor, Dana-Farber Cancer Institute, Boston, MA

Background: We have shown that avelumab, an anti-PD-L1 antibody, added to perioperative modified DCF chemotherapy (aDCF regimen), improves the pathologic complete response rate from 7% to 14% in locally advanced gastro-esophageal adenocarcinoma (GEA), in comparison to historical controls from our own institution. Little is known about the long-term survival results obtained with perioperative chemoimmunotherapy, a new standard of care. We are here reporting the 5-year survival results of our cohort of patients treated with aDCF. **Methods:** Single-arm phase II study of aDCF given every 2 weeks for 4 cycles before and after surgery with planned sample size of 50 operated patients in order to test hypothesis that pCR rate would improve from 7 to 20%. Main inclusion criteria were: histologically proven GEA, locally advanced disease (cT3-4 and/or N+), adequate organ function, WHO performance status 0-1. Main exclusion criteria were: histology other than adenocarcinoma, metastatic disease (M1), use of immunosuppressants, serious autoimmune disease, daily intake of more than 10 mg of prednisone. Pathological response (Tumour Regression Grade -TRG) was determined by the College of American Pathologists criteria: 0 = complete;1 = near complete/microscopic residual disease; 2 = moderate; 3 = poor/no response. MPR was defined as TRG 0 or 1. Data presented as median (range), KM determined survival. Patients with less than 5 years follow-up and who were disease free / alive were censored. **Results:** One of the 51 patients enrolled into the trial withdrew consent, leaving 50 patients in the survival analysis. Clinical disease burden was high (cT3 44/50, 88%, N+ 31/50, 62%) with 49/50 (98%) completing neoadjuvant aDCF. All patients proceeded to surgery with MPR found in 9/50 (18%) patients. The median follow-up for the cohort was 71.5 months (range 43-105) with an estimated mean DFS and OS of 62.5 months and 68.5 months corresponding to a 5-year DFS and OS of 55.3% and 61.1%. For patients with MPR, 5-year DFS and OS were 100%. There were no new safety signals. **Conclusions:** Perioperative aDCF resulted in long-term survival in the majority of patients treated on our trial, bringing more evidence that chemoimmunotherapy improves outcomes of patients with locally advanced GEA. Those outcomes seem enhanced among patients with MPR. Clinical trial information: NCT03288350. Research Sponsor: EMD/Serono.

4098 **Poster Session**

Integrating tumor-infiltrating iymphocytes (TILs) in the biomarker landscape of gastroesophageal adenocarcinoma: Going beyond PD-L1. First Author: Filip Van Herpe, Gastrointestinal Oncology Department, University Hospitals Leuven, Leuven, Belgium

Background: Immune checkpoint inhibitors (CPI) are standard of care in perioperative and metastatic gastro-esophageal adenocarcinoma (GEA). PD-L1 scoring remains heterogeneous, with multiple assays and substantial interobserver variability. In breast cancer, immunotherapy responses occur even in PD-L1–negative tumors when tumor-infiltrating lymphocytes (TILs) are present. Exploratory analyses from CM649 suggest that immune infiltration and T-cell signatures may better capture CPI benefit than PD-L1 alone, particularly with ipilimumab–nivolumab. We evaluated TILs and their relationship with established biomarkers in a large GEA cohort. **Methods:** We performed a single-center retrospective study including localized and metastatic GEA patients diagnosed between 2019–2023. Histopathology included MMR status, HER2 (IHC/SISH), PD-L1 CPS, and CLDN18.2 ($\geq$75% tumor cells). TILs were blindly reviewed by an expert pathologist using international TILs-WG guidelines (in press). Baseline characteristics and follow-up were collected until August 2024. **Results:** A total of 230 patients were included (140 localized, 90 metastatic). MMR, PD-L1 CPS, CLDN18.2, and HER2 status were available for all. By Lauren classification, 83 tumors were diffuse (36%), 131 intestinal (57%), and 17 mixed (7%). TILs were dichotomized at $<$ 20% and $<$ 10%. TIL density differed significantly across Lauren subtypes (p = 0.0007): diffuse tumors showed markedly lower infiltration (76% with TILs $<$ 20%) compared with intestinal tumors (60% with TILs $\geq$20%). Using the $<$ 10% cutoff, diffuse tumors again showed lower immune infiltration (78% vs. 22%; p $<$ 0.001). PD-L1 CPS categories ($<$ 1, 1–4, 5–9, $\geq$10) did not differ by subtype. Notably, in CPS $<$ 1 tumors, 28/48 (58%) were TIL-high ($\geq$10%), whereas CPS $\geq$10 tumors showed strong concordance with TIL-high status (25/30, 83%). HER2-positive tumors had a higher proportion of TIL-high cases than HER2-negative tumors (OR 3.55; 95% CI 1.64–8.39; p = 0.0004). CLDN18.2 positivity showed no association with TILs (p = 0.44; OR 0.80; 95% CI 0.46–1.37). **Conclusions:** Using international TILs-WG guidelines, TIL assessment is feasible in routine GEA pathology. TIL density varied significantly across Lauren subtypes, with diffuse tumors showing consistently low immune infiltration. PD-L1 CPS did not reflect these differences and showed substantial discordance with TILs, particularly in PD-L1–negative but TIL-high tumors, suggesting potential CPI sensitivity. HER2 positivity, but not CLDN18.2, was associated with higher TIL levels. These findings support further evaluation of TILs alongside PD-L1 CPS/TAP score as improved predictive biomarkers for anti-PD-1 or anti-PD-1/CTLA-4 therapy. Research Sponsor: None.

4099 **Poster Session**

Neoadjuvant nivolumab plus ipilimumab and adjuvant nivolumab in patients with localized microsatellite instability-high (MSI)/mismatch repair deficient (dMMR) oeso-gastric adenocarcinoma: Long-term follow-up of the GERCOR NEONIPIGA phase II study. First Author: Thomas Samaille, Sorbonne University; Department of Medical Oncology, Saint-Antoine Hospital, AP-HP, INSERM 938, SIRIC CURAMUS, Paris, France

Background: Neoadjuvant nivolumab and ipilimumab in localized MSI/dMMR gastric cancer were evaluated in the NEONIPIGA study (NCT04006262). The primary endpoint was pathological complete response (pCR) and has been previously reported. Here, we report on the long-term follow-up analysis and the secondary objectives of event-free survival (EFS) and overall survival (OS). **Methods:** This phase II, single-arm study evaluated neoadjuvant nivolumab 240 mg q2w x 6 and ipilimumab 1 mg/kg q6w x 2, followed by surgery 5 weeks ($\pm$1 week) after the last injection of nivolumab and adjuvant nivolumab 480 mg q4w x 9 in patients with resectable MSI/dMMR, T2-T4 NxM0 oeso-gastric adenocarcinoma. EFS and OS were evaluated through Kaplan-Meier curves. **Results:** 32 patients were included: 16 (50%) with gastric location and 16 (50%) with gastro-esophageal junction; 28 (88%) were initially classified as usT3 and four (12%) as usT2; 23 (72%) were lymph node positive. Three patients did not undergo surgery (one metastatic progression, two refusals). 27 (84%) patients completed the planned 6 cycles of neo-adjuvant therapy, and 14 (44%) received the full neoadjuvant and adjuvant treatment. Median follow-up was 48.3 months (44.8-52.0). In the ITT population, 4-year OS was 84.1% (65.8-93). In the population eligible for surgery, 4-year EFS was 83.5% (64.8-92.8). Only one patient (classified as ypT0N1 and TRG1b at surgery) relapsed with cerebral metastases 29 months after initiation of neoadjuvant treatment. Six deaths were reported, including two related to gastric cancer (one post-operative due to surgery complications, one from cerebral metastases). The four remaining deaths were unrelated to gastric cancer or treatment toxicity and were due to pulmonary infections (n = 2; 33 and 60 months after initiation of neoadjuvant treatment), perforation of a strangulated hernia (13 months), and metastatic tongue cancer (30 months). All three patients without surgery achieved a clinical complete response after immunotherapy (including one deceased patient reported above). Combined with the 17 (59%) patients in pCR previously reported, 20 of 32 (62.5%) patients achieved complete response. No new safety signals were reported during extended follow-up. **Conclusions:** Neoadjuvant nivolumab and ipilimumab before surgery and adjuvant nivolumab in localized MSI/dMMR oeso-gastric adenocarcinoma achieved a high curative rate. These findings strongly support further investigation of a watch-and-wait approach in case of clinical complete response after immune checkpoint inhibitors, which is currently being evaluated in the DEWI GERCOR phase II study (NCT06059495). Clinical trial information: NCT04006262. Research Sponsor: BMS.

4100 **Poster Session**

Neoadjuvant cadonilimab plus chemotherapy for locally advanced gastric/gastroesophageal junction cancer: A single-arm, phase II trial. First Author: Pengfei Zhang, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Cadonilimab plus chemotherapy is a promising treatment option in the first-line setting of gastric cancer; however, its activity in the neoadjuvant setting remains unclear. The study evaluated the efficacy and safety of cadonilimab plus chemotherapy in neoadjuvant treatment for locally advanced gastric or gastroesophageal junction (G/GEJ) cancer. **Methods:** Eligible patients with locally advanced G/GEJ cancer (cT3-4a N+ M0) were enrolled and treated with 3 cycles of SOX chemotherapy (oxaliplatin 130mg/m^2, IV, d1; S-1 40-60 mg, PO, bid, d1-d14; q21d) plus cadonilimab (10mg/Kg IV, d1, q21d), followed by radical gastrectomy with D2 lymphadenectomy. The primary endpoint was pathological complete response (pCR) rate, and the secondary endpoints included R0 resection rate, major pathological response (MPR) rate, 2-year disease-free survival (DFS) rate, 2-year overall survival (OS) rate and safety. Moreover, a single-cell spatial proteomic atlas was constructed to identify the mechanisms of immune resistance in patients with G/GEJ cancer who received neoadjuvant cadonilimab combined with SOX chemotherapy. **Results:** From September 2023 to July 2024, 45 patients were screened, and 37 patients were enrolled in this study. The median age was 58 years (range 27–72). 26 (70.3%) patients had cT4a disease, and 32 (86.5%) patients had a primary tumor in the stomach. All patients underwent preoperative evaluation. Two (5.4%) patients refused surgery, and 35 (94.6%) patients underwent gastrectomy with D2 lymphadenectomy. pCR (TRG1a) was observed in nine patients (ITT set: 24.3% (95% CI: 11.8% to 41.2%); surgery set: 25.7% (95% CI: 12.5% to 43.3%)). The MPR (TRG1a/b) rate was 70.3% (95% CI: 53.0% to 84.1%). As of the cutoff date of January 1, 2026, the median follow-up time was 24.1 months (range 14.3-28.4). One patient who refused surgery died, and three patients in the surgery set relapsed. 2-year DFS and OS rates were 90.2% and 97.3, respectively. Most of the TRAEs were grade 1-2. Nine (24.3%) patients experienced grade 3-4 TRAEs. The most common grade 3-4 TRAEs were thrombocytopenia (n = 4, 10.8%) and rash (n = 2, 5.4%). Single-cell spatial atlas demonstrates that recurrence following cadonilimab combined with SOX chemotherapy in gastric cancer is associated with distinct spatial immune ecosystems, which is characterized by immune deserts or suppressive fibrotic–myeloid networks that spatially and functionally incapacitate CD8 T cells. **Conclusions:** Based on the encouraging pCR rate, survival outcome and manageable safety in this study, cadonilimab plus SOX chemotherapy is a promising neoadjuvant treatment option for patients with locally advanced gastric cancer. Moreover, targeting stromal and myeloid components may be necessary to unlock the full therapeutic potential of immune checkpoint blockade. Clinical trial information: NCT05948449. Research Sponsor: None.

4101 **Poster Session**

Diagnostic and predictive utility of peritoneal tumor DNA in gastroesophageal cancer: A prospective multicenter study. First Author: David Liu, Divsion of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: Gastric and gastroesophageal cancers (G/GEC) commonly spread to the peritoneum. Accurate peritoneal staging is critical for guiding intent and therapy, however staging PET, CT and peritoneal cytology have low sensitivity for peritoneal micrometastases. Whilst circulating tumor DNA (ctDNA) poorly correlates with peritoneal disease, tumor DNA from the peritoneum (ptDNA) may identify early peritoneal metastases missed by conventional staging. We developed a tumor-informed whole-genome sequencing (WGS) platform to detect ptDNA and evaluated its accuracy in diagnosing peritoneal metastases and predicting survival in curative-intent G/GEC. **Methods:** This Australian multicenter prospective cohort study enrolled patients receiving curative-intent treatment for G/GEC (upfront surgery, perioperative FLOT or neoadjuvant CROSS/nivolumab). Tumor biopsies, blood, and peritoneal lavage fluid were collected at staging laparoscopy, and at surgery for those receiving neoadjuvant therapy. Tumor-informed WGS was used to identify ctDNA and ptDNA, which were correlated with disease free survival (DFS), peritoneal recurrence free survival (pRFS), non-peritoneal recurrence free survival (npRFS), and overall survival (OS) using multivariate Cox regression. The diagnostic utility of ptDNA for peritoneal metastases was evaluated by comparing true-negative patients ($>$ 2 years disease-free post-surgery alone) with an independently enrolled cohort of true-positive patients (macroscopic/cytology-positive peritoneal disease). **Results:** ptDNA was detected in 28 (30.4%) of 92 consecutive non-metastatic patients (59 with and 33 without neoadjuvant therapy). ptDNA-positivity significantly correlated with advanced cT and (y)pT stage. At a median follow-up of 17 months, there were 12 (13.0%) peritoneal and 10 (10.9%) non-peritoneal recurrences. ptDNA-positivity independently predicted poorer pRFS (HR 26.74, 95%CI 3.94-181.66), DFS (HR 4.51, 95%CI 1.77-11.47) and OS (HR 6.65, 95%CI 1.72-25.76), but not npRFS (HR 0.87, 95%CI 0.16-4.78). Importantly, 9 (60%) patients converted from ptDNA-positive to ptDNA-negative post-neoadjuvant treatment. Patients who remained ptDNA-positive had significantly worse pRFS (3/6 recurrences, HR 45.4, 95%CI 3.5-595.2) than those who were ptDNA-negative (0/25 recurrences). The diagnostic accuracy of ptDNA was validated in 10 true negative and 12 true positive patients. In this cohort, ptDNA achieved 100% sensitivity, specificity, positive and negative predictive values (95%CI 75.8-100%) for detecting peritoneal metastases. ctDNA data will be presented at the meeting. **Conclusions:** Tumor-informed WGS-based ptDNA accurately diagnoses peritoneal disease and predicts peritoneal recurrence post curative-intent treatment, informing its potential to personalize clinical management using intraperitoneal therapies. Research Sponsor: Victorian Cancer Agency; Australian Gastro-Intestinal Trials Group; Peter MacCallum Cancer Foundation; Cancer Council Victoria.

4102 Poster Session

Perioperative cadonilimab (AK104) in locally advanced MSI-H/dMMR gastric or gastroesophageal junction adenocarcinoma and colorectal adenocarcinoma: A basket study. First Author: Jiafu Ji, Peking University Cancer Hospital & Institute, Beijing, China

Background: Microsatellite instability-high (MSI-H) / deficient mismatch repair (dMMR) tumors generate abundant neoantigens and are sensitive to PD-1 blockade. However, evidence supporting the use of PD-1/CTLA-4 blockade in the neoadjuvant setting for MSI-H/dMMR gastric and colorectal cancers remains scarce. **Methods:** In this multicenter, single-arm, dual-cohort basket study (NCT04556253), we used a Simon's two-stage design to evaluate perioperative cadonilimab in patients with locally advanced MSI-H/dMMR gastric/gastroesophageal junction (GEJ) or colorectal adenocarcinoma. 29 patients were enrolled in cohort 1 (gastric/GEJ adenocarcinoma) and 18 patients were enrolled in cohort 2 (colorectal adenocarcinoma). The main inclusion criteria include newly diagnosed, histologically confirmed cT3–T4aNxM0 MSI-H/dMMR gastric/GEJ adenocarcinoma or colorectal adenocarcinoma, with an ECOG score of 0-1. Both cohorts received 3 cycles of neoadjuvant cadonilimab (10 mg/kg q3w) followed by radical resection, then 6 cycles of adjuvant cadonilimab (10 mg/kg q3w). The primary endpoint was pathologic complete response (pCR). Secondary endpoints included overall survival (OS), event-free survival (EFS), disease-free survival (DFS), major pathologic response (MPR) rate and incidence of adverse events (AEs). **Results:** As of the data cutoff date of January 24, 2026, the median follow-up was 14.6 months for cohort 1 and 12.6 months for cohort 2. In cohort 1, 2 patients were pathologically confirmed as pMMR prior to treatment. Among the 26 patients (mITT population), pCR rate was 69.2% (95% CI: 48.2%-85.7%), and MPR rate was 80.8% (95% CI: 60.6%-93.4%). The 12-month OS, EFS, and DFS rates were each 100% in mITT population. All 29 patients (ITT population) received neoadjuvant therapy. AEs during neoadjuvant treatment occurred in 24 patients (82.8%), with 3 patients (10.3%) experiencing grade 3-4 AEs. Common AEs (incidence ≥10%) included rash, anemia, constipation, and insomnia, which were primarily grade 1-2. Among the 18 patients (mITT population) in cohort 2, the postoperative pCR rate was 66.7% (95% CI: 41.0%-86.7%), and the MPR rate was 72.2% (95% CI: 46.5%-90.3%). The 12-month OS, EFS, and DFS rates were each 100% in mITT population. All 18 patients (ITT population) received neoadjuvant therapy. AEs during neoadjuvant treatment occurred in 17 patients (94.4%), with 2 patients (11.1%) experiencing grade 3-4 AEs. Common AEs (incidence ≥10%) included rash, infusion-related reaction, anemia, and cough, which were primarily grade 1. No grade 5 AEs were reported in this study. **Conclusions:** Perioperative cadonilimab demonstrates excellent antitumor activity and a manageable safety profile in patients with locally advanced MSI-H/dMMR gastric/GEJ adenocarcinoma and colorectal adenocarcinoma. Clinical trial information: NCT04556253. Research Sponsor: National Natural Science Foundation of China (82272655); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2025ZD0552019); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2025ZD0545201); Science Foundation of Peking University Cancer Hospital (BJCH2025BJ01); National Natural Science Foundation of China (92259302); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2024ZD0520600); National Natural Science Foundation of China (82373438); Beijing Municipal Public Welfare Development and Reform Pilot Project for Medical Research Institutes (PWD&RPP-MRI) (JYY2023-3).

4103 Poster Session

Neoadjuvant immunochemotherapy plus thymalfasin in locally advanced gastric cancer: A prospective clinical trial. First Author: Hongda Liu, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Neoadjuvant immunochemotherapy has emerged as a promising strategy for locally advanced gastric and gastroesophageal junction (G/EGJ) adenocarcinoma, but a substantial proportion of patients derive limited benefit. Thymalfasin is an immunomodulatory peptide that may amplify antitumor immunity while attenuating toxicity. We conducted a phase II trial to evaluate anti-PD-1 plus SOX immunochemotherapy combined with thymalfasin as neoadjuvant treatment for G/EGJ adenocarcinoma. **Methods:** The prospective trial enrolled patients aged 18–75 with cStage III G/EGJ adenocarcinoma, ECOG 0–1, and adequate organ function. Treatment included three 21-day cycles of serplulimab (anti-PD-1) plus SOX (S-1 and oxaliplatin) and nine weeks of thymalfasin, followed by curative gastrectomy. The primary endpoint was pathological complete response (pCR). Secondary endpoints included major pathological response (MPR), safety, survival, and other efficacy measures. Peripheral immune remodeling was assessed by flow cytometry, and bulk RNA sequencing of peripheral blood mononuclear cells (PBMCs) interrogated thymalfasin-associated transcriptional programs. **Results:** Thirty patients were enrolled and all underwent curative-intent minimally invasive gastrectomy. pCR was achieved in 30.0% (9/30), and MPR in 56.7% (17/30). ypN0 status was observed in 63.3% (19/30), with N-stage downstaging in 80.0% (24/30). The objective response rate was 73.3% and the disease control rate was 100.0%. At a median follow-up of 14.0 months (range 10.0-17.2), only one retroperitoneal nodal relapse had occurred at 14.4 months after diagnosis; no deaths were documented. Any-grade adverse events (AEs) occurred in 93.3% of patients, grade ≥3 AEs in 26.7%, and immune-related AEs in 23.3%, with no grade ≥3 irAEs. Flow cytometry showed expansion of $CD8^+$ T cells with increased CD69 expression and a concurrent reduction in HLA-DR-positive T cells, suggesting dynamic remodeling from broad systemic activation toward a more focused effector or memory response. RNA-seq revealed thymalfasin-associated upregulation of genes involved in antigen processing and presentation, type I interferon signaling, innate immune sensing, and immune metabolic reprogramming, and identified immune co-expression modules linked to treatment and response. **Conclusions:** Neoadjuvant serplulimab, SOX, and thymalfasin produced encouraging pathological response, substantial nodal clearance, and an acceptable safety profile in stage III G/EGJ adenocarcinoma. Peripheral immune and transcriptomic profiling are consistent with a hypothesis in which thymalfasin may help preserve and coordinate systemic antitumor immunity without excessive toxicity. These findings warrant confirmation in larger randomized trials. Clinical trial information: NCT06461910. Research Sponsor: This work was supported by National Natural Science Foundation of China; 82102723, 82373335.

4104 Poster Session

CheckMate-9DW 4-year follow-up: Overall survival by depth of response and outcomes in long-term survivors. First Author: Aiwu Ruth He, Columbia University Irving Medical Center, New York, NY

Background: Nivolumab plus ipilimumab (NIVO + IPI) was globally approved as a first-line (1L) treatment for unresectable hepatocellular carcinoma (HCC) based on the phase 3 CheckMate 9DW trial (NCT04039607). We report 4-year follow-up results and overall survival (OS) by depth of response (DpR). **Methods:** Methods were reported previously (Yau T. *Lancet* 2025). Briefly, adults with previously untreated unresectable HCC were randomized 1:1 to receive NIVO + IPI (then NIVO for ≤ 2 years) or lenvatinib/sorafenib (LEN/SOR). OS analyses were done by best percentage change in tumor burden from baseline. We also present exploratory analyses on long-term survivors (survival ≥ 4 years after randomization). **Results:** A total of 668 patients (pts) were randomized to NIVO + IPI (n = 335) or LEN/SOR (n = 333); among 325 pts treated with LEN/SOR, 275 (85%) received LEN. At a median (range) follow-up of 52.5 (44.0–66.1) mo, NIVO + IPI continued to show OS benefit (95% CI) vs LEN/SOR (HR 0.78 [0.65–0.93]) with higher objective response rate (ORR; 95% CI) by blinded independent central review (BICR; 36% [31–42] vs 13% [10–17]) and more durable responses. Pts with deeper tumor reduction had numerically improved median OS on both NIVO + IPI and LEN/SOR; the trend was more pronounced with NIVO + IPI specifically in pts with tumor shrinkage ≥ 30% (Table). More pts treated with NIVO + IPI (n = 62) were long-term survivors vs pts treated with LEN/SOR (n = 33). In long-term survivors, ORR by BICR was higher with NIVO + IPI vs LEN/SOR (76% vs 24%), with higher rates of complete response (CR; 21% vs 6%; Table); median duration of response was not reached in either group. Among long-term survivors, median (range) treatment-free interval was 23.3 (0.1–56.6) mo with NIVO + IPI and 0.5 (0.1–54.0) mo with LEN/SOR; 26 of 62 (42%) and 2 of 33 (6%) patients, respectively, were off study treatment and remained free from subsequent treatment. Baseline characteristics and incidence of TRAEs in long-term survivors were consistent with all randomized pts. **Conclusions:** 1L NIVO + IPI continued to show sustained efficacy benefit vs LEN/SOR in unresectable HCC with no new safety concerns at the 4-year follow-up. These analyses suggest deeper responses with NIVO + IPI may be associated with improved survival outcomes. Long-term survivors treated with NIVO + IPI had higher ORR and CR rates vs LEN/SOR, and were more likely to remain free of subsequent treatment. These results reinforce NIVO + IPI as a 1L treatment for unresectable HCC. Clinical trial information: NCT04039607. Research Sponsor: Bristol Myers Squibb.

DpR,[a] %	NIVO + IPI (n = 290)[b]	LEN/SOR (n = 286)[b]
	Median OS (95% CI), mo	Median OS (95% CI), mo
−100 to ≤−60	NR (NE)	NR (28.3–NR)
−60 to ≤−30	31.1 (19.9–40.4)	20.9 (15.1–30.9)
−30 to 20	17.0 (14.8–22.0)	20.5 (17.1–22.9)
≥20	14.3 (6.0–17.5)	7.8 (4.8–19.3)
Best overall response in long-term survivors[a]	**NIVO + IPI (n = 62)**	**LEN/SOR (n = 33)**
ORR (95% CI), %	76 (63–86)	24 (11–42)
CR, %	21	6

[a]By BICR.
[b]Response evaluable pts. NE, not estimable; NR, not reached.

4105 Poster Session

First-line rilvegostomig (R) + chemotherapy (CTx) in advanced biliary tract cancer (BTC): Updated analysis of GEMINI-Hepatobiliary substudy 2 cohort A. First Author: Jian Zhou, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Addition of PD-(L)1 inhibitors to CTx has transformed advanced BTC treatment but survival is limited for most patients (pts). R is a monovalent, Fc-reduced PD-1xTIGIT bispecific antibody that delivers coordinated and synchronous PD-1 and TIGIT blockade on immune effector cells. The primary analysis of substudy 2 Cohort A of GEMINI-Hepatobiliary (NCT05775159), a global phase 2 study evaluating R + CTx in pts with advanced BTC, demonstrated promising efficacy and a manageable safety profile. We report updated analyses after ≥18 months of follow-up for the last enrolled pt. **Methods:** Pts ≥18 years with previously untreated unresectable/metastatic BTC and ECOG PS 0/1 received intravenous R every 3 weeks (Q3W; ≤2 years) + gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 on days 1 and 8 Q3W (≤8 cycles). Coprimary endpoints were 6-month progression-free survival (PFS) and safety/tolerability. Secondary endpoints included median PFS, objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and overall survival (OS). Response and progression were investigator-assessed per RECIST v1.1. **Results:** As of Oct 24, 2025, the median follow-up for OS was 16.2 months (IQR 10.4–21.5); 6 pts (20.0%) received ≥20 cycles of R. Median OS was 16.8 months (95% confidence interval [CI] 11.0–not calculable [NC]) overall; 18-month OS was 44.8% (95% CI 26.5–61.6). Median OS was > 13 months across all subgroups based on age (< 65/≥65 years), ECOG PS (0/1), geography, initially unresectable/recurrent disease at enrollment, and primary tumor location (gallbladder or bile duct). Two unconfirmed responses were identified after > 85 weeks follow-up: one complete and one partial response. The safety profile was consistent with the primary analysis. The most common treatment-related adverse events (AEs) were anemia (53.3%), neutrophil count decreased (50.0%), and platelet count decreased (43.3%). Detailed efficacy and safety data are in the Table. **Conclusions:** R + CTx demonstrated promising efficacy and a manageable safety profile. This study and phase 3 studies of R in BTC (ARTEMIDE-Biliary01, ARTEMIDE-Biliary02, DESTINY-BTC01) are ongoing. Clinical trial information: NCT05775159. Research Sponsor: AstraZeneca.

	N=30*
PFS	
Events, n (%)	25 (83.3)
6-month, % (95% CI)	73.0 (53.2–85.5)
12-month, % (95% CI)	25.6 (11.4–42.6)
Median (95% CI), months	8.2 (6.7–11.1)
Confirmed ORR, % (95% CI)	31.0 (15.3–50.8)
Best objective response, n (%)	
Partial response	9 (31.0)
Stable disease	18 (62.1)
Progressive disease	2 (6.9)
DCR, % (95% CI)	93.1 (77.2–99.2)
DoR, median (95% CI), months	6.9 (2.8–NC)
OS	
Events, n (%)	19 (63.3)
12-month, % (95% CI)	65.5 (45.4–79.7)
18-month, % (95% CI)	44.8 (26.5–61.6)
Median (95% CI), months	16.8 (11.0–NC)
Any / R-related AEs, n (%)	30 (100) / 22 (73.3)
Grade ≥3	27 (90.0) / 5 (16.7)
Serious	14 (46.7) / 3 (10.0)
Led to R discontinuation	2 (6.7) / 1 (3.3)[†]
Led to death	2 (6.7) / 0

*N=29 for responses.
[†]Hepatic function abnormal.

4106 **Poster Session**

Safety and efficacy of puxitatug samrotecan (Puxi-Sam, AZD8205) in patients with biliary tract cancer (BTC): A first-in-human phase 1/2a study (BLUESTAR). First Author: Do-Youn Oh, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea

Background: B7-H4 is a transmembrane glycoprotein that negatively regulates T-cell function and is highly expressed in many cancers, including BTC, making it an attractive target for an antibody–drug conjugate (ADC). Puxi-Sam (also known as AZD8205), a novel B7-H4–directed topoisomerase I inhibitor (TOP1i) ADC, demonstrated favorable toxicity and promising antitumor activity during the dose escalation phase of the first-in-human Phase 1/2a BLUESTAR (NCT05123482) trial. Here, we report the pooled analyses for patients with BTC in the dose-escalation and dose-expansion phase of BLUESTAR. **Methods:** Eligible patients were ≥18 years old with nonresectable, recurrent, or metastatic B7-H4-positive BTC, with measurable disease per RECIST v1.1, and an ECOG performance status of 0 or 1. B7-H4 positivity was defined as ≥25% tumor cell staining by central immunohistochemistry in archival tumor samples. Patients must have received prior adequate standard-of-care therapy; prior treatment with a TOP1i was not allowed for patients in the dose-expansion phase. Patients received Puxi-Sam 2.4 mg/kg IV Q3W until disease progression, unacceptable drug-related toxicity, or consent withdrawal. The primary objective was assessment of safety; secondary objectives included assessment of antitumor activity. **Results:** As of 30 October, 2025, 20 patients received 2.4 mg/kg Puxi-Sam. The median (min–max) age was 61.5 years (44–88) and patients had received a median (min–max) of 2 (1–4) prior lines of treatment. Sixteen (80.0%) patients had treatment-related adverse events (TRAE), most commonly nausea (55.0%), and anemia (50.0%). Eleven (55.0%) patients had Grade ≥3 TRAEs, most commonly anemia (50.0%) and neutropenia (30.0%). Dose interruptions, reductions, and discontinuations due to TRAEs were required in six, two, and one patient, respectively. Two patients achieved a partial response (PR), corresponding to a confirmed objective response rate (ORR) of 10.0%. Disease stabilization was observed in a meaningful proportion of patients; 10 patients (50%) had stable disease (SD), and 12-week disease control rate (DCR) was 25.0% (5/20). Median progression-free survival (PFS) was 2.2 months, with a median follow-up of 2.2 months, supporting early signals of disease control (Table). **Conclusions:** Puxi-Sam demonstrated a favorable safety profile and showed modest clinical activity with prolonged disease stabilization observed in a subset of heavily pretreated patients with nonresectable, recurrent, or metastatic BTC. Clinical trial information: NCT05123482. Research Sponsor: AstraZeneca.

Efficacy summary (interim response evaluable patients).

	Puxi-Sam 2.4 mg/kg N=20
ORR, % (95% CI)	10.0 (1.2–31.7)
PR, n (%)	2 (10.0)
SD, n (%)	10 (50.0)
PD, n (%)	7 (35.0)
NE, n (%)	1 (5.0)
DCR at 12 weeks, % (95% CI)	25.0 (8.7–49.1)
Median PFS, months (95% CI)*	2.2 (1.4–4.6)

*Full analysis set.
NE, not evaluable; PD, progressive disease.

4107 **Poster Session**

Efficacy and safety of transarterial chemoembolization combined with donafenib for hepatocellular carcinoma with rupture and bleeding: A retrospective, cohort study. First Author: Qi Zhang, Shiyan Renmin Hospital, Shiyan, China

Background: The incidence of hepatocellular carcinoma (HCC) ranks 6th in the world, and rupture and bleeding of HCC is its fatal complication. Transarterial chemoembolization (TACE) is an effective measure for acute hemostasis, but the prognosis of TACE alone is limited. The ZGDH3 study showed that donafenib was the only targeted agent with better overall survival (OS) than sorafenib in monotherapy for HCC. This study aims to investigate the efficacy and safety of TACE combined with donafenib compared with TACE monotherapy in the treatment of HCC with rupture and bleeding. **Methods:** This study retrospectively analyzed patients with rupture and bleeding of HCC who received TACE combined with donafenib or TACE monotherapy in Qinghai University Affiliated Hospital from January 2022 to August 2024. Patient criteria for inclusion: (1) Definitive diagnosis of HCC with rupture and bleeding by imaging and laboratory examination; (2) Child-Pugh class A and B; (3) No previous systemic therapy. The efficacy and safety were evaluated by mRECIST and CTCAE 5.0. **Results:** A total of 62 patients were included in the study, of whom 35 in the TACE monotherapy group and 27 in the TACE plus donafinib group, and there was no significant difference in baseline characteristics between the two groups. Patients in TACE plus donafenib group demonstrated a significantly higher objective response rate (ORR) compared with TACE monotherapy group (55.6%vs 25.7%, P=0.008). The median progression-free survival (PFS) significantly better than TACE monotherapy group (13.6 months [95%CI: 4.354 - 22.846] vs 4.6 months [95% CI: 1.637 - 7.563]; HR=0.404, P=0.003). The median OS was longer in the TACE plus donafenib group compared to TACE monotherapy group (17.4 months [95%CI: 8.478 - 26.322] vs 7.6 months [95%CI: 1.301 - 13.899]; HR=0.479, P=0.012). Additionally, multivariate COX regression analysis showed that PVTT, Child-Pugh grade, tumor diameter and total bilirubin were independent prognostic factors for OS. The incidence of treatment-related adverse events (TRAEs) significantly higher in TACE plus donafenib group, the most common were skin-related adverse events (37% vs 0%), diarrhea (29.6% vs 0%) and alopecia (18.5% vs 0%), which can be controlled by symptomatic treatment. There were no grade ≥3 TRAEs. But there was no significant difference in the incidence of rebleeding, stomachache and fever. **Conclusions:** TACE combined with donafenib showed significant efficacy and controllable safety in HCC with rupture and bleeding. Research Sponsor: None.

4108 **Poster Session**

Dual BRAF/MEK inhibition in *BRAF*^{V600E}–mutated biliary tract cancer with exploratory histology-dependent response: A systematic review and meta-analysis. First Author: Neel Parikh, Zydus Medical College and Hospital, Dahod, Gujarat, India

Background: The BRAF V600E mutation defines an actionable subset of rare cancers. Metastatic BTC carries a poor prognosis, with median survival under one year on standard chemotherapy. Given the rarity of BRAF V600E-mutated BTC and the absence of RCTs, rigorous evidence synthesis is needed; existing data for dabrafenib plus trametinib come only from single arm basket trials such as ROAR and NCI-MATCH. The low prevalence of this mutation limits the feasibility of large randomized studies. This SRMA aimed to quantify the efficacy of dual BRAF/MEK inhibition in BTC and explore potential histology dependent differences in response. **Methods:** We performed a systematic review and meta-analysis (SRMA) pooling single arm Phase II basket trial cohorts (N = 53 BTC; N = 17 CNS). Seven case reports were summarized qualitatively and excluded from pooled analyses. The primary endpoint was pooled overall response rate (ORR). A random effects model was used. Subgroup and heterogeneity analyses were performed given the tissue-specific behavior of V600E-driven tumors. Histology was evaluated as an exploratory moderator and heterogeneity was quantified. **Results:** In the pooled cohort of 70 patients (53 BTC and 17 CNS), the overall ORR was 45.3% (95% CI: 24.5-66.9%). Heterogeneity for the BTC subgroup was moderate (I^2 = 62.6%), while overall pooled heterogeneity across all studies was low (I^2 = 14%). ORR in BTC was numerically higher than in Central nervous system (CNS) cohorts (34.9%) but subgroup differences did not reach statistical significance (P = 0.3386). The observed median OS of 13.5 months in the ROAR BTC cohort compares favourably with historical outcomes commonly reported in the 6-12 month range for advanced BTC. The consistency of pooled estimates, despite non-randomized designs, suggests a stable treatment signal while acknowledging that causality cannot be inferred from uncontrolled data. Median progression-free survival was 9.0 months in BTC and 5.5-8.0 months in CNS cohorts. Median OS in the ROAR BTC cohort was 13.5 months (95% CI: 10.4-17.6), exceeding historical expectations. The pooled rate of Grade ≥3 AEs was 59.2%, consistent with the known safety profile of dabrafenib plus trametinib; no treatment-related deaths were reported. Qualitative data from case reports confirmed regression of CNS metastases and feasibility in patients with severe hepatic dysfunction. **Conclusions:** Dual BRAF/MEK inhibition shows clinically meaningful activity in BRAF V600E-mutated BTC, with survival exceeding historical expectations. Exploratory analyses indicate histology-dependent differences, supporting tumor-specific therapeutic stratification. These findings align with growing tissue-agnostic evidence for MAPK inhibition and reinforce the value of routine molecular profiling, though conclusions are limited by small cohorts and single arm studies. Research Sponsor: None.

4109 **Poster Session**

Real-world treatment patterns and clinical outcomes among cholangiocarcinoma patients treated with futibatinib or pemigatinib. First Author: Amit Mahipal, University Hospitals, Cleveland, OH

Background: Pemigatinib and futibatinib are FGFR2 inhibitors approved by the US Food and Drug Administration in 2020 and 2022, respectively, for the treatment of advanced cholangiocarcinoma (CCA). This study describes demographic and clinical characteristics, and assesses clinical outcomes of real-world CCA patients treated with futibatinib or pemigatinib. **Methods:** This study used deidentified data from electronic medical records and claims from the ConcertAI RWD360 oncology dataset. Patients diagnosed with CCA and with evidence of initial treatment with futibatinib or pemigatinib in 2023 or later (index treatment) were included. Real-world outcomes (real-world overall survival [rwOS], time to discontinuation [rwTTD], and time to next treatment or death [rwTTNTD]) from the index date were described using Kaplan-Meier analysis. Cox regression models were used to adjust for patient characteristics. Adverse medical events of interest (MEI) were identified with ICD codes. **Results:** This study included 122 futibatinib (median age: 64 years; female: 58%; White: 66%) and 93 pemigatinib patients (median age: 66 years; female: 61%; White: 69%). The most common treatment regimen before index was cisplatin + durvalumab + gemcitabine (44% futibatinib and 35% pemigatinib patients). Futibatinib patients had numerically longer median rwOS (10.5 vs. 9.6 months) and median rwTTNTD (6.5 vs. 5.6 months) than pemigatinib patients, though the differences were not statistically significant; median rwTTD was similar in both futibatinib and pemigatinib patients (2.8 vs. 2.8 months); and adjusted hazard ratios were non-significant for all outcomes (Table 1). Futibatinib had numerically higher 6-month rwOS (63% vs. 55%) and 12-month rwOS (42% vs. 36%). Overall, 28% (n=60) of patients experienced MEI during index treatment: 29% (35/122 patients) in the futibatinib group and 27% (25/93) in the pemigatinib group. The most common MEI were (futibatinib vs. pemigatinib) fatigue (8% vs. 16%), diarrhea (10% vs. 5%), and dry eyes (6% vs. 1%). **Conclusions:** This study represents the largest real-world analysis to date of CCA patients treated with FGFR inhibitors. Overall, patient characteristics and MEI were similar in the two treatment groups. Clinical outcomes were also similar in both groups, suggesting that futibatinib is a promising alternative in this patient population. Research Sponsor: Taiho Oncology, Inc.

Outcome results.

	Futibatinib Patients (n=122)	Pemigatinib Patients (n=93)	P-Value
Median rwOS, months (95% CI)	10.5 (7.3, 14.4)	9.6 (5.2, 10.8)	0.39
Adjusted HR	0.95	Ref.	0.65
Median rwTTD, months (95% CI)	2.8 (1.2, 3.7)	2.8 (1.7, 4.0)	0.51
Adjusted HR	1.10	Ref.	0.47
Median rwTTNTD, months (95% CI)	6.5 (4.8, 8.1)	5.6 (4.1, 7.4)	0.66
Adjusted HR	1.00	Ref.	0.99

HR: hazard ratio. Variables adjusted for in Cox model: age, sex, setting of care, ECOG performance status, and time from diagnosis to index date.

4110 **Poster Session**

Tislelizumab combined with donafenib and GEMOX as first-line treatment for advanced biliary tract cancer: A single-arm, phase II study. First Author: Yiming Zhao, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Advanced biliary tract cancer (BTC) progresses rapidly and has a poor prognosis, with a 5-year survival rate of less than 5%. Gemcitabine and oxaliplatin (GEMOX) plus tislelizumab and donafenib as the first-line treatment for advanced BTC has confirmed good safety and preliminary efficacy in our phase I study (NCT04979663). This study aimed to further evaluate the efficacy and safety of GEMOX plus tislelizumab and donafenib. **Methods:** This is a single-arm, phase II trial (NCT05668884). Patients were enrolled if they were 18-75 years old, had stage III/IV cancer (AJCC 8th Edition), were Child-Pugh A/B, had an ECOG PS of 0-1, and had received no prior systemic therapy or tumor-related surgery. Patients were administrated with tislelizumab (200 mg IV on d1 Q3W), donafenib (200mg PO BID) and GEMOX (Q3W up to 8 cycles: gemcitabine 1000 mg/m² IV on d1 and 8, oxaliplatin 100 mg/m² IV on d1). Treatment continued until disease progression or unacceptable toxicity or withdrawal of consent whichever occurred first. The primary endpoint was the objective response rate (ORR) assessed by RECIST v1.1. **Results:** From December 2022 to October 2025, 47 patients were enrolled with a mean age of 60.8 (18 females and 29 males), 35 patients had intrahepatic cholangiocarcinoma, 11 patients had gallbladder carcinoma and 1 patient had perihilar cholangiocarcinoma. The ORR and the disease control rate (DCR) by RECIST 1.1 were 38.3% (18/47) and 93.6% (44/47), respectively. 2 patients underwent subsequent surgery after first-line treatment. The median PFS was 12.1 months (95%CI: 5.1-19.1), 1-year survival rate was 57% (95%CI: 38-76). All patients had treatment-related adverse events (TRAEs), the incidence of grade 3-4 TRAEs was 46.8%, the most common grade 3-4 TRAEs were rash (6/47,12.8%), thrombocytopenia (5/47,10.6 %) and fever (3/47, 6.4%). No grade 5 TRAEs were observed. **Conclusions:** GEMOX plus tislelizumab and donafenib as a first line treatment option for advanced BTC patients shows favorable efficacy and tolerability. Clinical trial information: NCT05668884. Research Sponsor: Zelgen.

4111 **Poster Session**

Additional health-related quality of life (HRQoL) analysis from DESTINY-Gastric04 (DG-04), a randomized phase 3 study of trastuzumab deruxtecan (T-DXd) vs ramucirumab (RAM) + paclitaxel (PTX) in patients (pts) with human epidermal growth factor receptor 2–positive (HER2+) unresectable/metastatic gastric cancer (GC)/gastroesophageal junction adenocarcinoma (GEJA). First Author: Kohei Shitara, National Cancer Center Hospital East, Kashiwa, Japan

Background: In DG-04 (NCT04704934), a statistically significant and clinically meaningful improvement in overall survival was seen with T-DXd vs RAM + PTX in pts with HER2+ unresectable/metastatic GC/GEJA in the second-line setting. Patient-reported HRQoL was also maintained with T-DXd. We report additional HRQoL results from DG-04. **Methods:** Pts with unresectable/metastatic GC/GEJA who were HER2+ (IHC 3+, IHC 2+/ISH+) by local or central testing received T-DXd 6.4 mg/kg or RAM + PTX. Patient-reported outcomes were assessed at prespecified time points using the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) scale and the EuroQol 5-dimension, 5-level (EQ-5D-5L) visual analog scale (VAS). Time to first deterioration (TTFD) and mean change from baseline (CFB) were assessed. Mixed model for repeated measures (MMRM) was used to analyze CFB of the FACT-Ga scale. **Results:** At data cutoff (October 24, 2024), median TTFD favored T-DXd (n = 246) vs RAM + PTX (n = 248) for the EQ-5D-5L VAS (3.5 vs 3.0 mo; hazard ratio [HR], 0.79; nominal P = 0.063), FACT-General (G) total score (3.5 vs 2.8 mo; HR, 0.74; nominal P = 0.015), and FACT-Ga emotional well-being (EWB; 5.1 vs 3.7 mo; HR, 0.74; nominal P = 0.026) and social well-being (SWB; 3.8 vs 2.5 mo; HR, 0.71; nominal P = 0.006) subscales. Additional TTFD results, including TTFD in gastric cancer subscale (GaCS) and physical well-being (PWB), are in the Table. Mean CFB scores remained stable in all FACT-Ga subscales, with no clinically meaningful changes associated with T-DXd. MMRM analysis of CFB results favored T-DXd vs RAM + PTX for the FACT-G total score (nominal P = 0.023), and the FACT-Ga functional well-being (FWB; nominal P = 0.045) and SWB (nominal P = 0.004) subscales. **Conclusions:** These findings support patient-reported HRQoL was maintained with T-DXd in pts with HER2+ unresectable/metastatic GC/GEJA. TTFD was not negatively impacted with T-DXd; mean CFB in all FACT-Ga subscales showed pt symptoms and functioning remained stable, with some subscales favoring T-DXd vs RAM + PTX. Clinical trial information: NCT04704934. Research Sponsor: Daiichi Sankyo, Inc.

	T-DXd n=246	RAM + PTX n=248	HR (95% CI) Nominal *P* Value
EQ-5D-5L VAS, median TTFD (95% CI), mo	3.5 (2.7-5.0)	3.0 (2.1-3.5)	0.79 (0.62-1.01) 0.063
FACT-Ga scale, median TTFD (95% CI), mo			
FACT-G (EWB + FWB + PWB + SWB)	3.5 (2.2-4.4)	2.8 (2.1-3.5)	0.74 (0.58-0.95) 0.015
FACT-Ga total score (FACT-G + GaCS)	4.4 (3.5-5.7)	4.4 (3.5-6.5)	0.95 (0.73-1.24) 0.700
EWB	5.1 (4.2-8.7)	3.7 (2.4-5.0)	0.74 (0.57-0.97) 0.026
FWB	2.3 (2.1-3.2)	2.3 (2.1-3.5)	0.89 (0.70-1.13) 0.338
PWB	2.8 (2.1-3.7)	2.2 (2.1-3.1)	0.79 (0.62-1.00) 0.052
SWB	3.8 (2.6-5.3)	2.5 (2.1-3.5)	0.71 (0.55-0.91) 0.006
GaCS	4.9 (3.7-6.3)	5.8 (4.8-7.4)	1.11 (0.84-1.47) 0.462

4112 **Poster Session**

Bortezomib plus gemcitabine-cisplatin versus gemcitabine-cisplatin as first-line treatment for advanced biliary tract cancers: A randomized phase II clinical trial with exploratory analysis of PTEN status. First Author: Hui Wang, Eastern Hepatobiliary Surgery Hospital, Shanghai, Naval Medical University, Shanghai, China

Background: Biliary tract cancers (BTCs) are aggressive malignancies with limited treatment and poor prognosis, including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (perihilar and distal), gallbladder cancer and ampullary cancer. Our previous research indicated that bortezomib is a promising treatment option as proteasome inhibitor in PTEN-loss iCCA patients (Clin Transl Med. 2024 May;14(5): e1675). In this randomized phase II clinical trial, we expanded the indication to BTCs and explored clinical benefit and safety of bortezomib plus gemcitabine-cisplatin (GPB) compared with gemcitabine-cisplatin (G based) as first line treatment for advanced BTCs and further evaluated the potential predictive value of PTEN status. **Methods:** Between September 1, 2020, and December 31,2023, a total of 105 patients were screened. 59 patients were enrolled. The 59 patients were randomly assigned to either GPB group (n = 32) or G based group (n=27). PTEN status was not known at the time of randomization. PTEN immunohistochemical staining was subsequently performed in all patients identifying 18 patients (30.5%) with PTEN loss (PTEN=0) and 41 patients (69.5%) with PTEN expression (PTEN=1). The GPB regimen consisted of gemcitabine 1000 mg/m^2 day 1,8, cisplatin 75 mg/m^2 day 1, 8, plus bortezomib 1.3 mg/m^2 day 1, 4, 8, and 11 of a 21-day cycle. The G based group received gemcitabine based regimens including G-cisplatin (GP), G-Oxaliplatin (GMOX) or G-S-1 (GS). The primary endpoint was mediate progress-free survive (mPFS) according to RECIST v 1.1. Statistical analyses were performed using SPSS. The last follow-up date was July 25, 2025. **Results:** With a median follow-up of 31.8 months (95% CI, 21.3–42.3), the mPFS was 5.49 months in the GPB group and in 5.95 months in the G-based group, with no significant statistically significant difference (HR, 0.86; 95% CI, 0.50–1.47; P = 0.59). The median overall survival (OS) was 16.23 months with GPB and 15.01 months with G-based group (HR, 0.88;95% CI, 0.47–1.67; P = 0.70). Biomarker analyses showed that within the GPB group, patients with PTEN loss had significantly longer PFS than those with PTEN expression (9.26 vs. 3.35 months; HR, 0.64; 95% CI, 0.42–0.96; P = 0.03). Among PTEN=0 patients, GPB was associated with improved mPFS compared with G-based (9.26 vs. 3.59 months; HR, 0.25; 95% CI, 0.08–0.78; P = 0.01). Grade ≥3 CTCAE AEs were mainly hematologic, with thrombocytopenia most common (50.0% vs 14.8%). **Conclusions:** Although no significant survival benefit was observed in the overall GPB group, a clinically meaningful improvement in mPFS was identified in the PTEN-loss subgroup. PTEN status may serve as a promising biomarker for identifying patients more likely to benefit from GPB therapy, warranting further prospective validation. Clinical trial information: ChiCTR2000035916. Research Sponsor: the Clinical Research Plan of Shanghai Hospital Development Center (SHDC2020CR2011A).

4113 **Poster Session**

Neoadjuvant radiotherapy combined with lenvatinib and sintilimab in patients with resectable hepatocellular carcinoma with portal vein tumor thrombus: An open-label, single-arm, multicenter, prospective phase I clinical trial. First Author: Bin Shu, Hepatopancereatobiliary Center, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

Background: Surgical resection remains the potentially curative treatment for resectable hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) in selected patients, but recurrence remains a major challenge. Neoadjuvant therapies have been proposed to reduce tumor burden and the risk of recurrence. This trial aimed to evaluate the safety and efficacy of neoadjuvant RT combined with lenvatinib and sintilimab followed by resection in resectable HCC patients with PVTT. **Methods:** This open-label, single-arm, multicenter, prospective phase I trial enrolled patients with resectable hepatocellular carcinoma classified as Barcelona Clinic Liver Cancer stage C without extrahepatic metastasis at 2 hospitals in China. Patients received RT (300cGy ×10 fractions) targeting intrahepatic lesions and PVTT, concurrent with two cycles of lenvatinib and sintilimab, followed by surgery 8 weeks post-RT and post-operative adjuvant therapy with lenvatinib and sintilimab for 1 year. Safety, pathological response, and feasibility were assessed. This trial is registered with ClinicalTrials.gov (NCT05225116). **Results:** From October 2022 to January 2026, 17 patients (VP2:5, VP3: 11, VP4:1) were enrolled, 14 patients had completed neoadjuvant therapy, 12 patients had received surgeries (R0 rate: 100%, 10/10), while 1 patient had disease progression, 1 patient postponed surgery due to abnormal liver function. Preoperative imaging (mRECIST criteria) showed stable disease (SD), partial response (PR), and complete response (CR) rates of 16.7%, 75.0%, and 8.3.0% for primary lesions, and 0%, 58.3%, and 41.7% for PVTT. Postoperative pathological complete response (pCR) rates were 25.0% for primary lesions and 75.0% for PVTT. Concordance between imaging and pathology was 66.7% for primary lesions and 50.0% for PVTT. The median recurrence-free survival (mRFS) was 17 months and median overall survival (mOS) was 27 months. No Grade 3 or worse treatment-related adverse events occurred. **Conclusions:** Neoadjuvant radiotherapy combined with lenvatinib and sintilimab can bring a high tumor response rate in patients with resectable hepatocellular carcinoma with portal vein tumor thrombus with a favorable safety profiles. PVTT demonstrates higher response rate than primary HCC lesions. Discrepancies between imaging and pathological responses highlight the need for improved predictive biomarkers. These interim results support further investigation of this approach in larger cohorts. Clinical trial information: NCT05225116. Research Sponsor: None.

4114 **Poster Session**

QL1706 (PD-1/CTLA-4 bispecific antibody) plus bevacizumab specific for patients with hepatocellular carcinoma combined with lung metastasis: A secondary analysis of a prospective, single-arm, phase Ib/II study. First Author: Kunlin Xie, Department of General Surgery/Liver Transplant Center, West China Hospital, Sichuan University, Chengdu, China

Background: Hepatocellular carcinoma (HCC) with lung metastasis carries a dismal prognosis, and effective systemic treatments remain limited. Bispecific antibodies targeting multiple immune checkpoints have emerged as promising therapeutic strategies. This study assessed the efficacy and safety of QL1706, a PD-1/CTLA-4 bispecific antibody, in combination with bevacizumab in patients with HCC and lung metastases. **Methods:** This was a secondary analysis of a multicenter, phase Ib/II clinical trial. Eligible patients with unresectable, advanced HCC and confirmed lung metastases received QL1706 (5.0 or 7.5 mg/kg, cohort A) or QL1604 (PD-1 antibody, 200 mg, cohort B) plus bevacizumab every three weeks until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** In cohort A, 15 patients were included in this analysis. At a median follow-up of 19.2 months, the ORR was 53.3% (95% CI, 26.6–78.7) and the DCR was 73.3% (95% CI, 44.9–92.2). Median PFS was 9.9 months (IQR, 1.6–NE), with a 1-year PFS rate of 46.7%, and the 2-year OS was 66.7%. Among the 7 patients with measurable lung target lesions, the ORR was 71.4% (95% CI, 29.0–96.3), including 2 complete responses. In cohort B, 5 patients were included, with a median follow-up of 23.7 months. The ORR was 20.0% (95% CI, 0.5–71.6) and the DCR was 60.0% (95% CI, 14.7–94.7). Treatment-related adverse events occurred in 93.3% of patients in cohort A and 100.0% in cohort B, with grade ≥3 TRAEs observed in 53.3% and 40.0% of patients, respectively. Most adverse events were manageable, and no treatment-related deaths were reported. **Conclusions:** QL1706 plus bevacizumab demonstrated promising antitumor activity and a manageable safety profile in patients with HCC and lung metastases. The high response rate observed in lung lesions highlights the potential of intensified immunotherapy combined with anti-VEGF therapy for this subgroup, warranting further validation in phase III trials. Clinical trial information: NCT05603039. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

Treatment-emergent adverse events of QL1706 / QL1604 and bevacizumab.

	All grades		Grade ≥ 3	
	Cohort A (N = 15)	Cohort B (N = 5)	Cohort A (N = 15)	Cohort B (N = 5)
TEAEs	15 (100.0)	5 (100.0)	10 (66.7)	4 (80.0)
irAEs	11 (73.3)	0	2 (13.3)	0
TRAEs	14 (93.3)	5 (100.0)	8 (53.3)	2 (40.0)
Associated with QL1706 / QL1604	14 (93.3)	5 (100.0)	6 (40.0)	2 (40.0)
Associated with bevacizumab	14 (93.3)	5 (100.0)	8 (53.3)	3 (60.0)

4115 **Poster Session**

Hepatic arterial infusion chemotherapy plus either toripalimab or sorafenib as first-line therapy for non–high-risk, locally advanced hepatocellular carcinoma: A non-comparative, randomized phase 2 trial. First Author: Ming Shi, Department of Liver Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: A combination of locoregional therapy such as hepatic arterial infusion chemotherapy (HAIC) with anti-angiogenic agents and immune checkpoint inhibitors (ICIs), has demonstrated significant antitumor activity in advanced hepatocellular carcinoma (HCC), while inevitably increasing the incidence of adverse events (AEs). Given the clinical rationale for exploring treatment de-escalation in non-high-risk, locally advanced HCC, this study was designed to provide prospective evidence for the combination of HAIC and toripalimab, which had suggested encouraging antitumor activity and safety previously. **Methods:** This single-center, non-comparative, randomized phase II study (NCT04135690) recruited locally advanced HCC participants without high-risk features (Vp4, and/or bile duct invasion and/or tumor occupancy of 50% of the liver). Participants were randomly assigned at a 1:1 ratio to receive FOLFOX-HAIC plus either toripalimab (240mg intravenously, TorHAIC) or sorafenib (400mg orally twice daily, SoraHAIC) per 3 weeks. The primary endpoint was the progression-free survival (PFS) rate at 6 months. **Results:** From February 4, 2020, to December 17, 2021, 72 participants were randomly assigned to receive TorHAIC (n = 36) or SoraHAIC (n = 36). The mean tumor diameter was 9.9 cm. Vp1-2 and Vp3 portal vein tumor thrombosis were present in 46 (63.9%) and 26 (36.1%) participants, respectively. The 6-month PFS rate was 63.9% in the TorHAIC group and 61.1% in the SoraHAIC group. After a median follow-up of 45.2 months, the median overall survival was 20.9 months in the TorHAIC group and 16.4 months in the SoraHAIC group, while the median PFS was 9.1 and 7.2 months, respectively. The objective response rate per RECIST v1.1 was 52.8% (n = 19) in the TorHAIC group, whereas 47.2% (n = 17) in the SorHAIC group. The median duration of response was 9.8 months in the TorHAIC group and 6.8 months in the SorHAIC group. There were 12 participants (33.3%) who developed grade 3-4 AEs in the TorHAIC group and 16 participants (44.4%) in the SoraHAIC group. Serious AEs were reported in two participants in the TorHAIC group (laryngeal edema due to oxaliplatin allergy and thrombocytopenia) and five participants in the SoraHAIC group (impaired myeloid function [n = 3], renal impairment, and upper gastrointestinal bleeding). **Conclusions:** Our study suggested that the TorHAIC regimen had a favorable safety and efficacy profile in patients with non-high-risk, locally advanced HCC. However, these findings warrant validation in a phase III trial. Clinical trial information: NCT04135690. Research Sponsor: None.

4116 **Poster Session**

Association of asynchronous, time-flexible digital multidisciplinary care with overall survival in advanced biliary tract cancer treated with immune checkpoint inhibitors. First Author: Binhe Tian, Peking Union Medical College Hospital, Beijing, China

Background: Delayed recognition and fragmented management of immune-related adverse events (irAEs) can trigger unnecessary interruption/discontinuation of immune checkpoint inhibitors (ICIs) and compromise real-world outcomes. We built an asynchronous, message-based multidisciplinary care system embedded in a widely used instant messaging platform to support longitudinal management for advanced biliary tract cancer (BTC) on ICIs, and assessed outcome changes from exploratory to protocolized implementation beyond secular trends. **Methods:** Single-center retrospective cohort of 546 adults with unresectable locally advanced/metastatic BTC receiving ≥1 ICI dose (Jan 2019–Jan 2024). All patients entered a clinician-moderated closed digital care group with structured triage and multidisciplinary coordination. By ICI start date: WGMS-E (before Jan 1, 2021) vs WGMS-P (on/after Jan 1, 2021). Primary endpoint: overall survival (OS). Secondary: progression-free survival (PFS), irAE recognition/management, and ICI rechallenge. Inverse probability of treatment weighting (IPTW) balanced baseline covariates. Interrupted time-series (ITS) analysis disentangled intervention effect from secular improvements in care. **Results:** Median follow-up 29.1 months; median OS overall 15.0 months. OS improved in WGMS-P vs WGMS-E (21.3 vs 12.4 months; log-rank $P < 0.0001$). IPTW-weighted Cox: WGMS-P associated with lower mortality (HR 0.55; 95% CI 0.43–0.69; $P < 0.001$) and higher 1-/2-year survival (~18%/~19% absolute). PFS also favored WGMS-P (HR 0.72; 95% CI 0.59–0.89; P = 0.0019). Overall irAE incidence was similar, but first irAE recognition occurred earlier in WGMS-P (restricted mean difference −1.68 months within 12 months). Permanent ICI discontinuation due to irAEs decreased (11% vs 22%), while rechallenge increased (10% vs 4%) without higher recurrent irAEs. ITS showed reversal of an increasing pre-intervention mortality trend to a decreasing post-intervention trend. **Conclusions:** A protocolized, asynchronous, message-based multidisciplinary care system integrated into routine oncology workflows was associated with improved survival among patients with advanced BTC treated with ICIs. By enabling earlier irAE recognition, reducing unnecessary permanent discontinuation, and facilitating safer rechallenge, this low-cost digital intervention may represent a scalable strategy to optimize real-world immunotherapy outcomes beyond secular advances in cancer care. These findings suggest that small, low-cost organizational changes in care delivery may translate into disproportionately large survival gains. Research Sponsor: Beijing Natural Science Foundation; L248022; National High Level Hospital Clinical Research Funding; 2025-PUMCH-C-015; National High Level Hospital Clinical Research Funding; 2022-PUMCH-B-128; National High Level Hospital Clinical Research Funding; 2025-PUMCH-D-001; Beijing Natural Science Foundation; L248072.

4117 **Poster Session**

Impact of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) on outcomes in hepatocellular carcinoma treated with atezolizumab–bevacizumab. First Author: Costanza Winchler, Oncology Unit, Careggi University Hospital, University of Florence, Florence, Italy

Background: Immune checkpoint inhibitor–based combinations (ICIs), including atezolizumab–bevacizumab (AB), have dramatically changed the therapeutic landscape of unresectable hepatocellular carcinoma (HCC), improving survival and response rates of patients, although outcomes remain heterogeneous. Concomitant medications may modulate immunotherapy efficacy through systemic and tumor microenvironment–mediated effects. Inhibition of the renin–angiotensin system (RAS) has been suggested to potentiate the effects of immunotherapy in various solid tumors by acting on angiogenesis, fibrosis, and immune modulation. However, the clinical impact of RAS inhibition in HCC patients receiving ICIs remains controversial, with retrospective studies suggesting possible improved outcomes. **Methods:** Patients with unresectable HCC treated from 2023 to 2025 with AB in Italy were included in this retrospective multicenter analysis from the ARTE database. Patients receiving concomitant ACEi/ARB at AB initiation were compared with non-exposed individuals. OS and PFS were estimated by Kaplan–Meier method and analyzed using Cox proportional hazards models. ORR and DCR were analyzed using logistic regression. To address baseline imbalances, a propensity score adjustment for potentially confounding characteristics (age, ECOG PS, viral etiology, alcoholic liver disease, cirrhosis, diabetes, obesity, cardiovascular events, decompensated cirrhosis, ALBI score, vascular/biliary invasion, previous locoregional treatments, metastatic disease and alpha-fetoprotein levels) was performed. **Results:** A total of 538 patients were included in our analysis, of whom 36% were receiving ACE-i/ARBs and 64% were not. ACEi/ARB use was associated with worse OS (HR 1.23; 95% CI: 0.97-1.57, p = 0.092), and a trend toward lower DCR (OR 0.63, 95% CI 0.39–1.02; p = 0.06). No significant associations were observed for PFS or ORR. After propensity score adjustment to balance baseline confounders, the magnitude of the OS difference was attenuated: median OS was 17.0 months in ACEi/ARB users versus 19.4 months in non-users (HR 1.14 (95% CI: 0.86-1.51; p = 0.358)), suggesting that the unadjusted signal was partly driven by baseline imbalance. **Conclusions:** In this large multicentric cohort of HCC patients treated with AB, concomitant ACEi/ARB therapy did not improve clinical outcomes and was possibly associated with a negative survival trend. Further studies will be needed to assess the potential effect of concomitant medications and RAS inhibitors on HCC, given their widespread use and the burden of comorbidities related to this specific tumor. Research Sponsor: None.

4118 **Poster Session**

Envafolimab (KN035) plus gemcitabine and oxaliplatin (GEMOX) compared with GEMOX as first-line treatment for Chinese patients with advanced biliary tract cancer: A randomized, open-label, multi-center, phase III pivotal trial. First Author: Shukui Qin, School of Integrative Medicine, Nanjing University of Chinese Medicine, Nanjing, China

Background: China bears a high biliary tract cancer (BTC) burden, with cholangiocarcinoma rising incidence (> 6/100,000 *vs* 0.3–6/100,000 globally) and high mortality (> 4/100,000). Over 60% of BTC patients are diagnosed at advanced stage (stage III/IV), and nearly two-thirds are unresectable. GEMOX regimen is a widely recognized standard of care in China, favored for its reduced renal toxicity and better tolerability compared with GemCis. Envafolimab is the world's first subcutaneously (SC) injectable anti-PD-L1 monoclonal antibody approved by China's NMPA. We report the final analysis of this pivotal trial, the first global phase III study initiated to evaluate immunotherapy plus chemotherapy in this setting. **Methods:** In this multicenter, open-label, phase III study in China, eligible patients (pts) with previously untreated, unresectable locally advanced/metastatic BTC were randomized 1:1 to envafolimab (2.5 mg/kg SC weekly) + GEMOX (gemcitabine 1000 mg/m² d1, 8; oxaliplatin 85 mg/m² d1, Q3W) or GEMOX chemotherapy alone. Chemotherapy was limited to 6 cycles in both arms. Stratification factors: primary site, disease stage, prior therapy, and ECOG PS. Primary endpoint: OS. Secondary endpoints: PFS, ORR (RECIST v1.1 by BICR), and safety. **Results:** 472 pts were randomized; 462 treated (envafolimab+GEMOX n = 232; GEMOX n = 230). At the final analysis, the primary endpoint was met well. Envafolimab+GEMOX significantly improved OS *vs* GEMOX (HR 0.723; 95% CI 0.585–0.880; *P*= 0.0016). Median OS was 10.9 months *vs* 8.6 months; 36-mo OS rates were 12.5% *vs* 7.7%. OS benefit was observed across subgroups, notably in intrahepatic cholangiocarcinoma (HR 0.705) and metastatic disease (HR 0.704). Median PFS (BICR) was 4.8 *vs* 4.6 months (HR 0.899; 95% CI 0.713–1.132); notably, the gallbladder cancer subgroup showed more favorable PFS benefit (HR 0.628). ORR was 27.6% *vs* 20.9%. Grade 3–4 TEAEs occurred in 69.4% (combination) *vs* 56.1% (chemo). irAEs occurred in 20.7%. **Conclusions:** This study demonstrates that adding subcutaneously administered envafolimab to GEMOX significantly improves OS with a manageable safety profile in advanced BTC. Compared with other regimens, the combination showed robust efficacy with a low rate of irAEs. Those findings establish envafolimab, the world's first SC PD-L1 inhibitor, combined with GEMOX as a new, effective, and convenient standard of care for this population. Clinical trial information: NCT03478488. Research Sponsor: 3D Medicines (Sichuan) Co., Ltd.

4119 **Poster Session**

Impact of HSPA6 on lenvatinib resistance in HCC via phase separation–mediated TXNRD1 stabilization and ferroptosis suppression. First Author: Yi Niu, State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, Department of Liver Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Lenvatinib is a first-line treatment for advanced hepatocellular carcinoma (HCC), but its efficacy is frequently limited by intrinsic and acquired resistance. The underlying molecular mechanisms remain incompletely understood, and strategies to overcome resistance are urgently needed. **Methods:** We integrated genome-wide CRISPR/Cas9 screening, transcriptomic profiling of lenvatinib-resistant HCC cells, and proteomic analysis of patient tumors to identify key mediators of resistance. **Results:** Heat shock protein family A (Hsp70) member 6 (HSPA6) emerged as a central driver of both intrinsic and acquired resistance, was consistently upregulated in resistant models, and was associated with poor response and reduced survival in lenvatinib-treated patients. Functional studies demonstrated that HSPA6 knockdown sensitized HCC cells and xenograft tumors to lenvatinib, whereas HSPA6 overexpression conferred resistance both *in vitro* and *in vivo*. Mechanistically, HSPA6 recruited the deubiquitinase ubiquitin-specific protease 9X (USP9X) to stabilize thioredoxin reductase 1 (TXNRD1), thereby suppressing lenvatinib-induced ferroptosis. Moreover, lenvatinib enhanced HSPA6 liquid–liquid phase separation (LLPS) through its intrinsically disordered region 1 (IDR1), facilitating the formation of HSPA6–USP9X–TXNRD1 condensates that reinforced TXNRD1 stability. Through structure-based virtual screening, we identified canagliflozin, an FDA-approved sodium–glucose cotransporter 2 (SGLT2) inhibitor, as a direct HSPA6 binder that disrupted this complex, restored ferroptosis sensitivity, and synergized with lenvatinib in preclinical models. **Conclusions:** Our study defines a novel HSPA6-driven resistance axis that integrates chaperone function, phase separation, and redox homeostasis to suppress ferroptosis in HCC. Targeting this axis with canagliflozin represents a promising therapeutic strategy to overcome lenvatinib resistance. Research Sponsor: None.

4120 **Poster Session**

NALIRIFOX in combination with adebrelimab for advanced biliary tract cancer: A phase 2 NIOFA-01 clinical trial. First Author: Qing Zhu, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: The NIOFA-01 trial was designed to evaluate the efficacy and safety of liposomal irinotecan combined with oxaliplatin, fluorouracil, and leucovorin (NALIRIFOX) plus adebrelimab as first-line treatment for patients with advanced biliary tract cancer (BTC) (ChiCTR2400089696). **Methods:** This single-arm, phase II study enrolled 27 patients with previously untreated, unresectable or metastatic BTC. Patients received NALIRIFOX (liposomal irinotecan 50 mg/m², oxaliplatin 60 mg/m², leucovorin 400 mg/m², and fluorouracil 2400 mg/m² administered as a continuous intravenous infusion over 46 hours), in combination with the PD-L1 inhibitor adebrelimab (1200 mg administered intravenously), every 2 weeks for up to 12 cycles. This was followed by adebrelimab maintenance therapy until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. Additionally, patients were evaluated for tumor gene alterations and PD-L1 expression, and underwent plasma proteomic and serum cytokine profiling. **Results:** Between September 13, 2024 and January 12, 2026, 27 patients were enrolled, with a median follow-up of 13.8 months (range, 2.8-16.2). Among these patients, the ORR was 55.6% (95%CI, 35.3%-74.5%) and the DCR was 81.5% (95%CI, 61.9%-93.7%). Median PFS was 8.0 months (95% CI, 5.8-9.7), while median OS was not reached (6 months OS rate: 92.6%, 12 months OS rate: 77.8%). Treatment-related adverse events (TRAEs) occurred in 100% of patients, with grade ≥3 TRAEs observed in 55.6%. The most common TRAEs were neutropenia, leukopenia, anemia, and diarrhea. Immune-related adverse events were reported in 74.1% of patients, including hepatotoxicity, hypothyroidism, and cardiac events. Exploratory analyses suggested the ORR was observed to be higher in patients with a CPS score ≥5 compared to those with a score <5 (p = 0.043). Combined analysis of plasma proteomics and metabolomics revealed that in patients who did not respond to treatment, ATP5PD, CTNND2, GALK1, 6nPropyluracil, and 1(Methylsulfinyl) propyl propyl disulfide were significantly elevated, while MMP2 was significantly decreased. A machine learning-based efficacy prediction model was constructed, and ROC curves were generated using the aforementioned four proteins and two metabolites, respectively, with AUC values of 0.961 and 0.883. Additionally, we observed that serum IL2 was significantly elevated in patients who responded to treatment, while IL8 showed a dynamic decreasing trend during the treatment process. **Conclusions:** NALIRIFOX in combination with adebrelimab demonstrated promising antitumor activity and an acceptable safety profile as first-line treatment for patients with advanced BTC, warranting further validation. Clinical trial information: ChiCTR2400089696. Research Sponsor: None.

4121 **Poster Session**

Three-month versus six-month duration of postoperative adjuvant therapy after R0 resection following conversion therapy in hepatocellular carcinoma patients achieving MPR or pCR: A prospective randomized study. First Author: Jia-Yi Wu, Fuzhou University Affiliated Provincial Hospital, Fuzhou, China

Background: Conversion therapy allows a subset of patients with initially unresectable hepatocellular carcinoma (uHCC) to achieve a deep pathological response, enabling curative resection. However, the optimal duration of postoperative adjuvant therapy remains unclear. This prospective randomized study compared recurrence-free survival (RFS) and overall survival (OS) between 3-month and 6-month durations of postoperative adjuvant therapy after R0 resection in patients achieving major pathological response (MPR; ≥90% tumor necrosis) or pathological complete response (pCR). **Methods:** This randomized controlled trial (ChiCTR2100051789) enrolled patients with uHCC who achieved a MPR or pCR following conversion therapy. Eligibility criteria included pathological confirmation of MPR or pCR after R0 resection. Eligible patients were randomized 1:1 to receive 3 months (Group 3M) or 6 months (Group 6M) of postoperative adjuvant therapy starting 1 month after surgery. The primary endpoint was RFS; secondary endpoints included OS and recurrence patterns. **Results:** Between January 15, 2022, and April 20, 2025, 58 patients were randomized (29 per group). Pathological evaluation confirmed MPR in 21 patients and pCR in 37 patients. After a median follow-up of 33.05 months, recurrence occurred in 8 patients. The 1-, 2-, and 3-year RFS rates were 89.3%, 89.3%, and 78.8% in Group 3M and 88.9%, 88.9%, and 88.9% in Group 6M (P = 0.592). Corresponding OS rates were 100%, 96.4%, and 96.4% versus 100%, 91.8%, and 91.8%, respectively (P = 0.451). **Conclusions:** In patients with uHCC who achieved a deep pathological response (MPR or pCR) after conversion therapy, a shorter duration of adjuvant therapy may be sufficient, with a 3-month course providing survival outcomes comparable to those of a 6-month course. Clinical trial information: ChiCTR2100051789. Research Sponsor: None.

4122 **Poster Session**

Final results of a phase II study of fluorouracil (FU), leucovorin (LV), and nanoliposomal irinotecan (nal-IRI) in previously treated biliary tract cancer (NAPOLI-2). First Author: Benjamin Adam Weinberg, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC

Background: BTCs are rare and aggressive malignancies. The first-line standard of care regimen for advanced BTC (aBTC) is gemcitabine (GEM), cisplatin, and an immune checkpoint inhibitor. Although FOLFOX is a preferred second-line treatment, it is limited by neuropathy. Nal-IRI contains IRI free base in liposome nanoparticles, which shelter IRI from conversion to its active metabolite (SN-38) and increase intratumoral SN-38 compared with IRI alone. The NAPOLI-1 trial of FU/LV/nal-IRI vs. FU/LV in second-line advanced pancreatic adenocarcinoma showed an overall survival (OS) benefit. The NIFTY trial (South Korea) demonstrated median OS (mOS) benefit of FU/LV/nal-IRI over FU/LV in a second-line aBTC population (8.6 vs. 5.3 months [mo], HR 0.68, 95% CI 0.48-0.95); however, the NALIRICC trial (Germany) did not (6.9 vs. 8.2 mo, HR 1.08, 95% CI 0.68-1.72). We sought to characterize second-line FU/LV/nal-IRI efficacy in US patients (pts) with second-line aBTC. **Methods:** This was a single-arm, open-label, multicenter phase II study of pts with aBTC previously treated with GEM/platinum chemotherapy. Pts received nal-IRI 70 mg/m^2 IV over 90 minutes, LV 400 mg/m^2 IV over 30 minutes every 14 days, and FU 2400 mg/m^2 IV over 46 hours every 14 days. The primary objective was to determine progression-free survival rate at 4 mo (PFS_{4mo}) using RECIST v. 1.1 criteria. Median PFS reported for pts receiving second-line 5-FU doublet chemotherapy was 3 mo with a PFS of 30%. FU/LV/nal-IRI was of interest if it could increase the PFS_{4mo} to 50% or higher. Using a one-sided α of 0.05 and 80% power, 17 of 39 evaluable pts had to be progression-free at 4 mo to detect a difference in PFS_{4mo} between 30% and 50%. **Results:** Forty-eight pts were enrolled: median age 64.5 years; 69% women; 27% gallbladder primary; 54% intra- and 19% extrahepatic. Ten pts came off study due to toxicity without disease progression before 4 mo on study and were replaced to evaluate the PFS_{4mo} endpoint. Of 38 evaluable pts, 18 pts (PFS_{4mo} 47%) were alive and progression-free at 4 mo, meeting the primary endpoint. With a median follow-up of 7.1 mo, median time to disease progression or study discontinuation due to toxicity for all pts was 2.3 mo (95% CI 1.8-4.6, PFS_{4mo} 38%), and for pts evaluable for the primary endpoint, median PFS was 3.5 mo (95% CI 1.8-5.5). Five pts (10%) had PFS beyond 12 mo. mOS for all pts was 7.9 mo (95% CI 5.7-11.7). Of 41 evaluable pts, the response rate was 2% (1 PR), and the disease control rate was 54%. Adverse events (AEs) were consistent with known toxicities from the FU/LV/nal-IRI regimen. **Conclusions:** FU/LV/nal-IRI is an effective second-line regimen for aBTC in US pts. There was significant early toxicity as 21% of pts came off study due to AEs before 4 mo. Correlative studies, including longitudinal analyses of circulating tumor DNA using banked blood specimens, are planned (NCT04005339). Clinical trial information: NCT04005339. Research Sponsor: Ipsen.

4123 **Poster Session**

A phase II study of bTAE-HAIC combined with lenvatinib and camrelizumab for patients with high tumor burden hepatocellular carcinoma: The TALEM-H trial. First Author: Xue Han, Sun Yat-sen University Cancer Center, Guangzhou, China; Department of Minimally Invasive Interventional Therapy, State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

Background: Patients with high tumor burden hepatocellular carcinoma (HCC) face a dismal prognosis. TALEM-H is a single-arm, prospective trial, aiming to evaluate the safety and preliminary effectiveness of transcatheter arterial embolization with blank microspheres (bTAE) plus hepatic artery infusion chemotherapy (HAIC) combined with lenvatinib and camrelizumab as first-line therapy for patients with high tumor burden HCC. **Methods:** Forty patients with huge HCC (defined as a single tumor $>$10 cm or multiple tumors $>$15 cm in diameter) received bTAE and FOLFOX-HAIC (Oxaliplatin 85mg/m2 2h + Calcium Levofolinate 400mg/m2 2h + Fluorouracil 2400mg/m2 46h) and lenvatinib (4-8mg) once daily plus camrelizumab (200mg) Q3W. The primary endpoint was objective response rate (ORR) according to mRECIST criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS) and treatment-related adverse events (TRAEs). **Results:** As of January 10, 2026, the median follow-up time was 10.7 months. The median maximum tumor diameter was 124mm (range: 77.5–262 mm) and the median sum of the diameters of the three largest tumors was 182 mm (range: 110–328.5 mm). The intrahepatic ORR was 95%, with 7 cases (17.9%) of intrahepatic complete response (CR) and 30 cases (76.9%) of intrahepatic partial response (PR). The 1-year and 2-year PFS rates were 48.7% and 37.6%, respectively (median PFS: 10.4 months; 95% CI: 8.6–15.1). Median OS has not yet been reached. Further, TRAEs of any grade occurred in 35 patients (87.5%) and no treatment-related deaths occurred. Grade 3 or higher TRAEs occurred in 12.5% of patients, commonly hypoalbuminemia (5%), immune-mediated pneumonitis (2.5%), and anemia (2.5%). **Conclusions:** bTAE-HAIC combined with lenvatinib plus camrelizumab represents a promising first-line treatment, offering an exceptional ORR and encouraging survival outcomes for HCC patients with a high tumor burden. Clinical trial information: NCT06061276. Research Sponsor: None.

Baseline characteristics.

Variable	All Patients (N = 40)
BCLC Stage C	32 (80%)
Extrahepatic Metastasis	18 (45%)
Tumor Number- Multiple (≥3)	28 (70%)
Largest Diameter (cm) >10 cm	35 (87.5%)
Sum of the diameters of the three largest tumors >20 cm	14 (35%)
Macrovascular Invasion	27 (67.5%)

4124 **Poster Session**

Beyond fibroblast growth factor receptor 2 (FGFR2) fusions: Mutations and amplifications in intrahepatic cholangiocarcinoma. First Author: Felicity David, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: *FGFR2* alterations occur in 10-20% of iCCA. While FGFR-directed therapies are established for *FGFR2* fusions, the genomic landscape and therapeutic relevance of non-fusion FGFR2 alterations remain poorly defined. **Methods:** Comprehensive genomic profiling was performed on 9,661 iCCA cases negative for *FGFR2* rearrangements/fusions to identify *FGFR2* short-variant sequence mutations and amplifications (Non-*FGFR2* SV/AMP). Biomarkers included tumor mutational burden (TMB), microsatellite instability (MSI), homologous recombination deficiency deficiency signature (HRDsig), and PD-L1 expression (TPS). Genomic features were compared with *FGFR2*-wild-type (*FGFR2*wt) iCCA. Clinical outcomes were assessed in a single-center cohort treated with FGFR inhibitors. **Results:** Non-*FGFR2* SV/AMP alterations were identified in 324 cases (3.4%), consisting of SV (92.8%), AMP (6.1%), or both (1.1%). Among short variants, 66.0% localized to the extracellular domain, 23.1% to the transmembrane domain, 7.69% to the kinase domain, and 3.21% to the cytoplasmic non-kinase domain. Compared with *FGFR2*wt tumors, Non-*FGFR2* SV/AMP iCCA occurred more frequently in females (57.7% vs 50.0%, p = 0.02) and showed similar age, genomic ancestry, trinucleotide signatures, MSI-high status (1.6% vs 1.8%), TMB $>$ 10 mt/Mb (2.2% vs 3.6%), PD-L1 positivity (18.8% vs 21.4%), and HRDsig positivity (4.6% vs 5.0%). Co-occurring actionable alterations (*IDH1*, *ERBB2, BRAF*, *MTAP* loss) were less frequent in Non-FGFR2 SV/AMP tumors, while *BAP1*, *NF2* and *TSC1* alterations were enriched. Among 42 patients with non-fusion *FGFR2* alterations treated at a single center, 16 (38%) received FGFR-directed therapy including pemigatinib, futibatinib, tinengotinib, lirafrugatinib and derazantinib. The objective response rate was 25% (95% CI: 7.3-52.4). Best responses included partial response (25%), stable disease (50%), and progressive disease (25%), with a median duration of response of 5.4 (95% CI: 1.9-8.9) months. Median overall survival was significantly longer in patients receiving FGFR-targeted therapy compared with those who did not (28.4 months [95% CI, 23.8-33.0] vs 14.6 months [95% CI, 6.25-23.0]; p = 0.023). Recurrent *FGFR2* mutations involved N549K (kinase), C382R (transmembrane), and Y375C (extracellular) domains. **Conclusions:** Non-fusion *FGFR2* sequence mutations and amplifications define a distinct subset of iCCA with fewer alternative actionable drivers and sensitivity to FGFR-targeted therapy. These findings support consideration of FGFR inhibition beyond *FGFR2* fusions and highlight the need for refined patient selection strategies. Research Sponsor: None.

4125 **Poster Session**

First-line tislelizumab plus chemoradiotherapy for patients with advanced biliary tract cancer: A prospective, biomolecular exploratory, phase II trial. First Author: Mingzhen Zhou, The Comprehensive Cancer Center, Nanjing Drum Tower Hospital & Group's Suqian Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Background: Advanced biliary tract cancer (BTC) characterized by a poor prognosis, and the combination of immunotherapy with conventional chemoradiotherapy offers a promising therapeutic approach. **Methods:** This phase II study evaluated the efficacy and safety of tislelizumab (an anti-PD-1 antibody) in combination with chemoradiotherapy as a first-line treatment for advanced BTC. The primary endpoints were objective response rate (ORR) and R0 resection rate, and the secondary endpoints included median progression-free survival (mPFS), median overall survival (mOS), and Disease Control Rate (DCR). Biomarker analyses assessed CA19-9 dynamics and immune cell subsets. **Results:** Among 28 patients, the ORR was 57% (16/28), with a conversion rate of 14% (4/28) and a 100% R0 resection rate (4/4). The median PFS was 14 months and the median OS was 19 months. The regimen exhibited a manageable safety profile, with grade 3 adverse events occurring in 21% (6/28) of patients (2 with drug-induced liver injury and 4 with myelosuppression). No grade 4 events were observed. Reduced CA19-9 levels were significantly correlated with improved OS (p = 0.022) and PFS (p = 0.002). Immunohistochemistry analysis revealed differential expression of CD4, CD103, and PD-1 between responders and non-responders. Notably, high expression of $CD103^+CD8^+$ tissue-resident memory T (TRM) cells and $CD103^+CD8^+PD\text{-}1^+$ TRM cells was associated with significantly improved OS. **Conclusions:** In conclusion, the combination of tislelizumab with chemoradiotherapy demonstrates promising efficacy and acceptable safety in advanced BTC, with $CD103^+CD8^+$ TRM cells identified as a potential predictive biomarker. Clinical trial information: ChiCTR2300070425. Research Sponsor: Project of The National Health Commission Health Development Research Center; No. WKZX2023CX020001; Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University; 2024-LCYJ-PY-59; the Affiliated Hospital of Nanjing University Medical School; XJSFZLX202321.

4126 **Poster Session**

CXCL12$^+$ pericytes as drivers of lymphatic dissemination in pancreatic cancer: Integrated single-cell and spatial analysis. First Author: Xiangxu Wang, Department of Clinical Oncology, Xijing Hospital, The Fourth Military Medical University, Xi'an, China

Background: Pancreatic ductal adenocarcinoma (PDAC) exhibits poor prognosis largely due to early lymph node metastasis, yet the cellular and molecular mechanisms governing lymphatic dissemination remain incompletely understood. **Methods:** We integrated multi-omics approaches including single-cell RNA sequencing (scRNA-seq) of 19 PDAC samples, spatial transcriptomics of 6 specimens, bulk RNA sequencing of 174 cases, and multiplex immunofluorescence of 166 clinical samples stratified by lymph node metastasis status. Cell-cell communication analysis, trajectory inference, and functional validation were performed to elucidate pro-metastatic mechanisms. **Results:** Single-cell profiling of 145,283 cells revealed substantial cellular heterogeneity, with fibroblasts and pericytes serving as dominant signaling hubs within the tumor microenvironment. Lymph node metastasis-positive (pLNM) tumors exhibited enhanced stromal-epithelial crosstalk mediated by PTN and ANGPT pathways. We identified invasive epithelial subpopulations (Epi_MUC5AC_CD24 and Epi_NEAT1_MALAT1) significantly enriched in pLNM samples, characterized by activation of EMT and invasion-related programs. Critically, high-resolution subclustering uncovered a CXCL12-expressing pericyte subset (PCs_CXCL12) preferentially expanded in metastatic tumors. Multiplex immunofluorescence validation in 166 specimens demonstrated that CXCL12+ pericyte infiltration correlated with perineural invasion, lymph node metastasis, advanced TNM stage, and inferior survival outcomes. Multivariate analysis established CXCL12+ pericyte score as an independent prognostic factor for both disease-free and overall survival. Mechanistically, we identified MYC as the master transcriptional regulator driving CXCL12 secretion in pericytes. Functional studies revealed that MYC-driven pericyte-derived CXCL12 promoted PDAC cell proliferation, invasion, and EMT. Spatial transcriptomics demonstrated co-localization of MYC, CXCL12, and its receptor CXCR4 in perineural pericyte niches. Orthotopic xenograft models confirmed that pericyte-specific Myc depletion significantly reduced tumor growth, CXCL12+ pericyte density, and tumor-associated lymphangiogenesis. **Conclusions:** This study establishes the pericyte MYC-CXCL12 axis as a critical driver of PDAC lymphatic metastasis through promotion of tumor cell invasion, EMT, and lymphangiogenesis. CXCL12+ pericytes represent a novel prognostic biomarker and potential therapeutic target for preventing lymph node metastasis in PDAC patients. Research Sponsor: None.

4127 **Poster Session**

Distribution and density of tertiary lymphoid structures as predictors of clinical outcomes and immunotherapy responses in gallbladder cancer. First Author: Rui Zhang, 1st Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China

Background: Gallbladder cancer (GBC) is an aggressive malignancy with limited treatments and is often immunologically "cold." Tertiary lymphoid structures (TLS) are key regulators of antitumor immunity, but their spatial heterogeneity and clinical impact in GBC remain unknown. This study explores how TLS distribution and maturation influence outcomes and immunotherapy response in GBC. **Methods:** We analyzed 99 GBC patients who underwent curative resection (2015–2020). H&E and multiplex immunohistochemistry(mIHC) identified TLS number, maturation, and spatial distribution. TLS were categorized into intratumoral (T) and peritumoral (P) regions. Novel TLS scores (T score, P score) were developed to quantify TLS abundance and correlate with overall survival (OS). Pre-treatment samples from anti-PD-1-treated advanced GBC patients were assessed for TLS association with immunotherapy response. Patient-derived xenograft (PDX) models were used to compare tumor progression and anti-PD-1 efficacy between TLS-high and TLS-low groups. **Results:** T score correlated with improved OS ($p < 0.001$), while P score negatively correlated with OS ($p < 0.001$). Intratumoral TLS contained more Fol-I/Fol-II structures; peritumoral TLS were predominantly Agg ($p < 0.001$). Responders to immunotherapy had higher intratumoral TLS scores (median 2.5 vs. 0.5, $p < 0.01$), TLS numbers (8.0 vs. 3.0/ROI, $p < 0.05$), and TLS area (29.0% vs. 12.0%, $p < 0.05$). Intratumoral TLS showed higher CD8$^+$ T cells, CD4$^+$ T cells, and Tfh cells (all $p < 0.05$), whereas peritumoral TLS were enriched in Tregs ($p < 0.01$). Higher T scores linked with increased CD8$^+$ T cells, Tfh cells, CD21$^+$CD23$^+$ FDC, and LAMP3$^+$ DCs, but decreased Tregs and M2 macrophages (all $p < 0.05$). An immune classification based on T/P scores stratified patients into four prognostic subgroups with distinct OS ($p < 0.001$). In PDX models, TLS-high tumors progressed slower ($p < 0.05$) and responded better to anti-PD-1 therapy($p < 0.01$). **Conclusions:** TLS spatial distribution in GBC exerts opposing prognostic effects: intratumoral TLS promote antitumor immunity, while peritumoral TLS may support tolerance. TLS-high tumors show greater sensitivity to immunotherapy. A TLS-based immune classification may guide personalized treatment. Research Sponsor: National Natural Science Foundation of China; 82503726.

4128 **Poster Session**

Real-world outcomes of microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) biliary tract cancers (BTC). First Author: Madhulika Eluri, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitors have revolutionized the treatment of microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) cancers. MSI-H/dMMR represents a rare molecular subset (1%) within biliary tract cancers (BTC). The role of immunotherapy alone remains unknown. We investigated clinical features, treatment outcomes, and genomic characteristics of MSI-H/dMMR BTCs in two real world cohorts. **Methods:** Multicenter retrospective study of BTC patients with MSI-H/dMMR status by immunohistochemistry (IHC) and/or PCR. Patients were from two independent cohorts: MD Anderson Cancer Center (MDACC) and the RETUD registry of the Spanish Cooperative Group for Digestive Tumor Therapy (TTD) group. **Results:** 46 patients with MSI-H BTC were included in this study; with 21 from MDACC and 25 patients from TTD Cohort. Median age 46 years (95% CI38-80), (35 (76.1%) had intrahepatic cholangiocarcinoma 8 (17.4%) had extrahepatic cholangiocarcinoma and 3 (6.5%) had gallbladder cancer. Patient characteristics are summarized in Table 1. The median OS was 24.4 months (95% CI: 19.9, 40.6). The median follow-up time was 50.2 months (95% CI: 36.2, NA). Thirty-one (68.9%) patients received immunotherapy as part of their treatment course, and 14 (31.1%) did not. For first-line therapy (n=40), the median progression-free survival (PFS) for chemotherapy was 3.19 months (95% CI: 2.56-6.6) and for immunotherapy alone was not reached (95% CI: 8.25-NR, p=0.0006), while among those receiving second-line therapy (n=21), the median PFS for chemotherapy was 4.04 months (95% CI: 2.73-NR) and for immunotherapy alone was 9.69 months (95% CI: 4.43-NR, p=0.044). The median OS was 24.7 months (95% CI: 19.91, NA) in patients with IO, and 19.1 months (95% CI: 13.83, NA) without IO (log rank test p value = 0.085). **Conclusions:** MSI-H/dMMR BTC patients may derive limited benefit with frontline chemotherapy. Immune checkpoint inhibition may drive durable disease control, supporting early dMMR/MSI-H testing to optimize treatment. Research Sponsor: None.

Summary of patient characteristics.

Covariate		N (%)
Gender	F	18(39.1%)
	M	28(60.9%)
Race	Asian	2(4.3%)
	Black	1(2.2%)
	White/Caucasian	43(93.5%)
Grade		
	G2:Moderately differentiated	8(42.1%)
	G3:Poorly differentiated	11(57.9%)
Stage	>II	33(71.7%)
	I-II	13(28.3%)
Mismatch Repair Gene Loss		
	MLH1	5(12.2%)
	MLH1,MSH6	3(7.3%)
	MLH1,PMS2	20(48.8%)
	MLH1,PMS2,MSH6	1(2.4%)
	MSH2,MSH6	7(17.1%)
	MSH6	1(2.4%)
	PMS2	4(9.8%)
Resectable at Diagnosis	No	27(58.7%)
	Yes	19(41.3%)

4129 **Poster Session**

A phase I/II study of CDX-1140, a CD40 agonist, in combination with capecitabine and oxaliplatin (CAPOX) and pembrolizumab in subjects with biliary tract carcinoma: Phase 1 results. First Author: Tim F. Greten, Thoracic and Gastrointestinal Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Second line therapy shows limited efficacy in biliary tract carcinoma (BTC). We have demonstrated potent anti-tumor effects of anti-CD40/anti-PD1 plus chemotherapy in murine cholangiocarcinoma (Diggs et al. J Hepatol 2021 74:1145). CDX1140 is a human IgG2 activating anti-CD40 antibody. Based on these preclinical studies we conduct a phase I/II study testing the combination of CDX-1140 plus pembrolizumab (pem), capecitabine (cap) and oxaliplatin (ox) in BTC patients previously treated with at least one line of systemic therapy. Safety and tolerability were assessed in the phase I portion. **Methods:** Between Aug 2024 and Jun 2025 a total of 9 participants were enrolled into the Phase I portion of the trial. 1000 mg cap was given p.o. bid on days 1-14 plus 130 mg/m2 ox i.v. on day 1 of a 21-day treatment cycle. CDX1140 was dosed at 0.72 mg/kg dose level 1 (DL1) and 0.36 mg/kg (DL-1) i.v. on day 8 plus 200 mg pembrolizumab i.v on day 8. The DLT period was 35 days, starting on day 8 of cycle 1 after CDX-1140 administration. Enrolment into the phase II portion was started after the recommended dose of CDX-1140 had been determined. **Results:** We enrolled a total of 9 patients (pts) into the phase I portion. All patients had received at least one line of prior systemic chemotherapy including antiPD1/PD-L1. 2 out of the first 3 pts treated at DL1 developed a grade 3 thrombocytopenia and we reduced dosing to DL-1. 1 out of 6 pts treated at DL-1 developed a grade 3 thrombocytopenia and DL-1 was considered safe. Other treatment related grade 3/4 AEs were: lymphopenia, leukocytopenia, anemia, skin rash and hypotension. Most patients developed grade 1/2 arthralgia. At data cut-off (Dec/15/25) PFS for the nine patients was 7.3 months (range: 2.3 - 19.1 months). DCR was 56 % with 2 patients demonstrating a PR and 3 pts with SD. **Conclusions:** We have completed the phase I portion of our trial and demonstrate that CDX1140 plus pem, cap and ox is safe and tolerable in pts with BTC. No new and or unexpected toxicities were observed. We observed encouraging clinical responses. Patients will be enrolled to the phase II portion and updated results will be presented. Clinical trial information: NCT05849480. Research Sponsor: None.

4131 **Poster Session**

Sequential bTAE-HAIC combined with lenvatinib and sintilimab for infiltrative hepatocellular carcinoma: A single-center perspective. First Author: Qunfang Zhou, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong Province, China

Background: Infiltrative hepatocellular carcinoma (HCC) is defined as a tumor with ill-defined border, no evidence of convex margination, and no typical enhancement pattern by imaging. This subtype of HCC is usually associated with poor prognosis and is frequently diagnosed at advanced stage. Blank-microsphere transcatheter arterial embolization (bTAE) and hepatic arterial infusion chemotherapy (HAIC) of oxaliplatin, 5-fluorouracil and leucovorin are effective and safe for HCC. This prospective study is to evaluate the safety and efficacy of bTAE-HAIC combined with Lenvatinib and Sintilimab for intermediate-advanced infiltrative HCC. **Methods:** This prospective phase II trial is a single-center, single-arm study designed to assess the efficacy and safety of TAE and HAIC, combined with sequential Lenvatinib and Sintilimab on infiltrative HCC. Patients with primary infiltrative HCC treated at our center between October 2023 and December 2024. The primary endpoint was objective response rate (ORR) according to mRECIST criteria. Secondary endpoints included overall survival (OS), progression-free survival (PFS), and treatment-related adverse events (AEs). **Results:** A total of 30 patients who met the criteria were enrolled in this study and received at least 2 courses of TAE-HAIC combined with Lenvatinib and Sintilimab treatment. The median follow-up time was 7.1 months, and 10 patients died during the period. 5 patients (16.7%) achieved complete response (CR) after sequent ablation or radiotherapy, 20 patients (66.7) were evaluated as PR. The overall ORR was 83.3%. The median OS was 16.0 months (95%CI: 5.6-26.5 months). The 3-month, 6-month and 12-month rates of OS were 93.3%, 83.0% and 60.2%. The median PFS was 9.5 months (95%CI: 4.9-14.1 months), and the PFS rates at 3-month, 6-months and 12-month were 95.7%, 68.1% and 20.4%, respectively. The median liver-specific PFS was 11.7 months (95%CI: 7.7-15.7 months). The overall incidence of treatment related AEs was 76.7% according to the CTCAE 5.0 criteria. The incidence of Grade 1-2 AEs was 73.3%, and only one patient experienced Grade 3 AE. 10 patients (33.3%) received dose reduction, 9 patients (30.0%) discontinued drug therapy. **Conclusions:** The preliminary results of current study indicates that the combination regimen is safe and effective, and the AEs and complications are controllable and tolerable. This study provides a reference for further phase III clinical research, and a novel treatment option for the infiltrative HCC. Clinical trial information: NCT06070636. Research Sponsor: None.

Baseline characteristics.

Variable	All Patients (N = 30)
Male	26 (86.7%)
BCLC Stage C	28 (93.3%)
Extrahepatic Metastasis	13 (43.3%)
Tumor Number- Multiple (≥3)	16 (53.3%)
Largest Diameter (cm) >10 cm	24 (80.0%)
Largest Diameter (cm) >15 cm	8 (26.7%)
Macrovascular Invasion	25 (83.3%)
Portal Hypertension	12 (40.0%)

4132 **Poster Session**

Hepatic arterial infusion chemotherapy plus lenvatinib and PD-1 inhibitors as first-line treatment for hepatocellular carcinoma with high tumor burden and portal vein tumor thrombus: A target trial emulation study (CHANCE 2416). First Author: Jiaxi Liu, The First Hospital of China Medical University, Department of Interventional Radiology, Shenyang, China

Background: Patients with advanced hepatocellular carcinoma (HCC) characterized by high tumor burden (beyond up-to-seven criteria) and portal vein tumor thrombus (PVTT) have a median overall survival (OS) of lower than 4 months without intervention. Global guidelines rely on Phase III trials that often under-represented this high-risk subgroup, creating a therapeutic gap. While systemic combinations are standard, they may lack the rapid cytoreductive potency required to prevent liver failure in this subgroup. We emulated a target trial to evaluate if adding hepatic arterial infusion chemotherapy (HAIC) to lenvatinib and PD-1 inhibitors (H+L+P) improves outcomes compared to lenvatinib and PD-1 inhibitors (L+P) alone. **Methods:** Using multicenter data from 22 centers in the Chinese Liver Cancer Clinical Study Alliance (CHANCE) registry, we compared first-line H+L+P (n = 127) vs. L+P (n = 117) in patients with advanced HCC (BCLC stage C without extrahepatic spread) and PVTT (Vp1-4). To minimize selection and immortal time biases, we employed stabilized inverse probability of treatment weighting (sIPTW) and a cloning-censoring-weighting framework. The primary endpoint was OS; secondary endpoints included progression-free survival (PFS), site-specific PFS, objective response rate (ORR), and safety. **Results:** Baseline covariates were well-balanced after weighting (SMD < 0.1). After sIPTW adjustment, H+L+P demonstrated a significant survival benefit: median OS was 25.6 months (95% CI: 22.0–33.7) vs. 15.9 months (95% CI: 12.6–21.3) for L+P (adjusted HR, 0.60; 95% CI: 0.43–0.82; p = 0.0015). Crucially, a favorable survival trend was preserved even in the high-risk Vp3-4 subgroup (HR 0.77). Median PFS (RECIST v1.1) was 13.0 vs. 6.8 months (adjusted HR, 0.58; p = 0.0002). H+L+P significantly delayed progression in intrahepatic lesions (median 14.8 vs. 7.8 months; p = 0.0006) and PVTT (median 24.9 vs. 15.5 months; p = 0.0183). Intrahepatic ORR (mRECIST) was 87.4% for H+L+P vs. 28.9% for L+P ($p < 0.0001$), with a PVTT response rate of 81.6% vs. 22.1% ($p < 0.0001$). Grade ≥3 adverse events (AEs) occurred in 37.0% of the H+L+P group vs. 9.4% in the L+P group. Common Grade ≥3 AEs in the H+L+P arm included abdominal pain (20.5%) and leukopenia (5.5%); no treatment-related deaths occurred in the H+L+P group. **Conclusions:** In this target trial emulation, adding HAIC to lenvatinib and PD-1 inhibitors significantly improved OS and PFS in patients with high-risk HCC and PVTT. The survival advantage was driven by rapid and profound locoregional control, particularly of the tumor thrombus, with a manageable safety profile. Clinical trial information: NCT06631326. Research Sponsor: None.

4133 **Poster Session**

Tinengotinib (TT-00420) in advanced/metastatic FGFR2-altered cholangiocarcinoma following prior chemotherapy and FGFR inhibitor treatment: Results from a phase II study (FIRST-08). First Author: Jun Zhou, Peking University Cancer Hospital & Institute, Beijing, China

Background: Subsequent treatment options for advanced cholangiocarcinoma (CCA) after failure of chemotherapy and FGFR inhibitors (FGFRi) are limited. Tinengotinib (TT-00420), a novel FGFRi, potently inhibited FGFR2 fusion/rearrangement and acquired resistant/FGFR2 kinase domain mutations. The FIRST-08 study is an open-label, multicenter Phase II study in Chinese patients (pts) with advanced/metastatic CCA (NCT06057571). **Methods:** Eligible pts with advanced/metastatic CCA harboring FGFR2 fusion or arrangement, who had failed prior chemotherapy and one FGFRi, received tinengotinib 10 mg orally once daily in 21-day cycles. The primary endpoint was objective response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included progression free survival (PFS), disease control rate (DCR), duration of response (DoR), overall survival (OS), safety, PK and quality of life (QOL) per EORTC QLQ-C30. **Results:** As of June 27, 2025, 50 pts were enrolled (median age 56.5 years; 52.0% male; ECOG of 1: 44.0%). Median follow-up was 8.5 months. Forty percent had ≥ 3 prior systemic regimens, 66.0% had prior immunotherapy, and 42.0% had received other targeted therapies beyond FGFRi. The ORR by BICR was 28.0% (95%CI, 17.5~41.7) with 14 confirmed partial responses, and median DoR was 7.9 (5.6~ -) months. The disease control rate (DCR) was 82.0%. The median PFS was 5.7 (4.3~8.3) months. The median OS had not reached, with the 18 months survival rate 66.9% (47.3~80.6). Common Gr3/4 TRAEs (≥15%) included hypertension (42.0%), palmar-plantar erythrodysesthesia syndrome (16.0%), No Gr 5 TRAE was observed. 41 out of 50 pts had biomarker ctDNA samples collected at baseline, 82.9% pts had FGFR2 fusion and 48.8% had FGFR2 mutation (SNV). 28 pts had biomarker ctDNA samples collected at both baseline and C3D1. A significant decrease in maximum variant allele frequencies (MaxVAF) from baseline to C3D1 by a median relative VAF reduction of 83.7% ($p<0.0001$), indicating strong molecular response to tinengotinib. **Conclusions:** Tinengotinib demonstrated durable clinical anti-tumor activity and a manageable safety profile in heavily pretreated CCA pts with FGFR2 fusion/rearrangement following prior chemotherapy and FGFRi therapy. Clinical trial information: NCT06057571. Research Sponsor: TransThera Sciences (Nanjing), Inc.

Efficacy outcomes by BICR and investigator.

	BICR	Investigator
ORR, % (95%CI)	28.0 (17.5~41.7)	20.0 (11.2~33.0)
DCR, % (95%CI)	82.0 (69.2~90.2)	78.0 (64.8~87.3)
mPFS, months (95%CI)	5.7 (4.3~8.3)	6.9 (4.3~8.5)
mDoR, months (95%CI)	7.9 (5.6~ -)	6.6 (2.4~ -)

4134 **Poster Session**

Correlation of immune remodeling linked to obesity with immunotherapy outcomes in cholangiocarcinoma: An externally validated international cohort study. First Author: Antonella Cammarota, Department of Biomedical Sciences, Humanitas University, Pieve Emanuele; Hepatobiliary Immunopathology Lab, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

Background: Obesity is an established risk factor for cancer, yet paradoxically may be associated with improved responses to immune checkpoint inhibitors (ICIs). We investigated whether obesity defines a clinically and biologically distinct cholangiocarcinoma (CCA) subtype when treated with ICIs. **Methods:** Retrospective analysis of Body Mass Index (BMI)-stratified patients (pts) with CCA treated at a single US center (US cohort) and enrolled in a prospective multicenter Italian registry (Italian cohort). High BMI was defined per CDC criteria (overweight 25.0-29.9; obesity ≥30 kg/m²), with cohort-specific cutoffs for analysis (US ≥30; Italy ≥25). Tumor microenvironment (TME) was profiled with bulk RNA-seq and CODEX multiplex imaging and body composition radiomics with TotalSegmentator tool in the US cohort. Chi-square, Pearson correlation or Wilcoxon tests were used to test associations with BMI; overall survival (OS) was assessed with Kaplan-Meier and Cox models. **Results:** 989 pts were included (661 US; 328 Italy). In the US and Italian cohorts, median age was 62 and 65 years, 51% and 47% were female, and 28% and 43% were obese and overweight, respectively. Metabolic comorbidities included diabetes (US: 15%; Italy: 19%), hypertension (US: 48%; Italy: 45%), and hyperlipidemia (US: 32%; Italy: 15%). Higher subcutaneous-to-visceral fat ratio was associated with improved OS with chemotherapy-ICI (HR 0.89; 95% CI 0.79-0.99; p = 0.036). In both cohorts, patients with high BMI treated with chemotherapy-ICI had significantly longer OS compared with lower-BMI patients (US: 31.6 vs 19.2 months, p = 0.005; Italy: 21 vs 12 months, p = 0.025). In multivariable models (US cohort) both obesity (HR 0.35; 95% CI 0.23-0.52, $p < 0.0001$) and higher visceral-to-subcutaneous fat ratio (HR 1.79; 95% CI 1.04-3.07, p = 0.037) were independently associated with OS. Combined genomic profiling (n = 906) showed a lower prevalence of *KRAS* alterations in high-BMI pts (OR 0.56, p = 0.006). RNA-seq (n = 86; obese = 37, non-obese = 49) demonstrated enrichment of fibroblast-associated signatures (*αSMA, PDPN, collagen IV, vimentin*), upregulation of immune checkpoints (*PD-1, PD-L1, TIGIT, LAG-3, VISTA*), and higher *GATA3* and *IFN-γ* expression in obese pts (both $p < 0.05$). Multiplex CODEX analysis (n = 38; obese = 17, non-obese = 21) revealed an increased co-expression between *GATA3*, a regulator of T-cell dysfunction, and *granzyme B*, a cytotoxic T-cell marker (Pearson $\rho = 0.24$, $p < 0.05$), indicating increased abundance of *GATA3⁺granzyme B⁺* cells in obese pts. **Conclusions:** In CCA, obesity characterized by predominant subcutaneous adiposity is linked to improved outcomes with ICIs and to a biologically distinct TME enriched in dysfunctional cytotoxic T-cells that may be reinvigorated by checkpoint inhibition. BMI may represent a pragmatic biomarker warranting prospective validation. Research Sponsor: None.

4135 **Poster Session**

Association of genomic and clinical factors with outcomes with front-line chemoimmunotherapy in patients with advanced biliary tract cancer. First Author: Orla Maeve Fitzpatrick, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Anti-PD1/L1 therapy plus gemcitabine/cisplatin is standard first-line therapy in advanced biliary tract cancer (BTC), yet outcomes remain heterogeneous and prognostic biomarkers are poorly defined. We aimed to identify genomic and clinical factors associated with outcomes in advanced BTC patients (pts) treated with first-line gemcitabine, cisplatin and durvalumab (GCD). **Methods:** All pts with advanced BTC treated with first-line GCD at Memorial Sloan Kettering who underwent pre-treatment tumor genomic profiling (NCT01775072) were included. The primary objective was to study the association between genomic and clinical features and investigator-assessed progression free survival (PFS); evaluation of overall survival (OS) was a secondary objective. Cox regression analyses evaluated associations with PFS/OS. A multivariable Cox PFS model used variables selected by LASSO-based stability selection and was stratified by tumor subtype. **Results:** 236 pts were eligible for analysis. Tumor subtypes included intrahepatic cholangiocarcinoma (CCA) (56%), gallbladder cancer (23%), extrahepatic CCA (16%), and BTCs not otherwise specified (5%). Common genomic alterations were *TP53* (36%), *ARID1A* (24%), *CDKN2A* (23%), *KRAS* (17%), *IDH1* (13%), *SMAD4* (12%), *MTAP* (11%) and *ERBB2* (7.6%). With a median follow up of 23 months (mo), median PFS for the cohort was 9.1 mo (95% CI 7.7–11.0). OS at 12 and 24 mo was 68% (95% CI: 62–74) and 45% (95% CI, 38–53), respectively. On univariable analysis, *KRAS* and *FGFR2* alterations were associated with shorter PFS (Table). *KRAS* alterations were also associated with an increased risk for all-cause mortality on univariable analysis (HR 1.81, 95% CI: 1.17–2.81, p=0.008). Median PFS and OS for the *KRAS*-altered group were 5.6 (95% CI: 3.6-7.8) and 11 (95% CI: 7.8-42) mo respectively, compared to 11 (95% CI: 8.1-12) and 21 (95% CI: 19-28) mo for *KRAS*-WT patients. On multivariable analysis, *KRAS* alterations and liver metastases were independently associated with shorter PFS; higher baseline albumin was protective (Table). **Conclusions:** Among pts with advanced BTC treated with front-line GCD, *KRAS* alterations were independently associated with poor PFS. These findings highlight the heterogeneity of benefit from GCD and support development of biomarker-informed strategies to refine patient selection and incorporation of KRAS-targeted strategies to improve outcomes in patients with *KRAS*-mutant BTCs. Research Sponsor: None.

Factors associated with PFS with GCD.

	Analysis (95% CI), p	
Factor	**Univariable HR**	**Multivariable HR**
Alteration		
KRAS	2.17 (1.48–3.19), <0.001	2.06 (1.36–3.12), <0.001
FGFR2	1.85 (1.02–3.34), 0.042	-
Baseline CA19-9	1.14 (1.05–1.23), 0.002	-
Metastases		
Liver	1.78 (1.25–2.54), 0.001	2.06 (1.41–3.01), <0.001
Bone	1.9 (1.05–3.43), 0.034	-
Baseline albumin (per 1-unit increase)	0.43 (0.29–0.64), <0.001	0.44 (0.30–0.66), <0.001

4136 **Poster Session**

Updated results of surufatinib combined with gemcitabine and cisplatin and immune checkpoint inhibitor (ICI) for unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma. First Author: Zhong Jingtao, De-Department of Hepatobiliary Surgery, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

Background: Advanced metastatic intrahepatic cholangiocarcinoma (ICC) was characterized by poor survival and limited therapeutic options. Surufatinib, a selective tyrosine kinase inhibitor targeting VEGFR 1, 2, and 3, FGFR1, and CSF-1R, provides dual anti-tumor action via anti-angiogenesis and tumor microenvironment regulation. Surufatinib combined with immunotherapy and chemotherapy may enhances anti-cancer effects for advanced metastatic ICC. This study evaluates the effectiveness and safety of surufatinib combined with gemcitabine, cisplatin, and immune checkpoint inhibitor (ICI) as the first-line treatment for patients with unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma. **Methods:** This is an open-label, single-arm, single-center trial. Eligible patients who were 18 -75 years old with histologically confirmed unresectable locally advanced or metastatic ICC were enrolled. Pts received surufatinib (250mg, orally, once daily), ICI (Zimberelimab or Toripalimab, 240mg, intravenous infusion, d1, q3w), and chemotherapy (gemcitabine 1000mg/m^2 intravenous infusion, 30min, d1, d8, q3w; cisplatin 25mg/m^2 intravenous infusion, 2h, d1, d8, q3w) until disease progression, death, surgery, intolerable toxicity, or withdrawal of consent. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), overall survival (OS), conversion to surgical resection rate, pathological complete response rate (pCR), and safety. **Results:** By January 20, 2026, 20 pts were enrolled with median age 60 years (range: 43-70), male 50%, 100% ECOG PS 0-1, 95% stage IV. 20 pts were efficacy evaluable, 5% (1/20) pts achieved complete response (CR), 50% (10/20) pts achieved partial response (PR), 35% (7/20) pts achieved stable disease (SD). The confirmed ORR was 55%, DCR was 90%. The median PFS was 7.7m (95%CI: 6.3-11.3 months), and the median OS was 17.8m (95%CI: 16.1-21.8 months). The most common TEAEs of all grades were hypertension (40%), edema (15%) and vomiting (10%), 1 patient was Immune-related pneumonia occurred. No grade $\geq$ 3 TEAEs or new safety signals occurred. **Conclusions:** Surufatinib plus gemcitabine and cisplatin combined with immune checkpoint inhibitor, the chemotherapy regimen as the standard treatment in combination with targeted and immunotherapy showed preliminary anti-tumor activity and manageable toxicity for the 1L treatment of ICC, providing an additional treatment option for pts with ICC. This study has been completed and the paper has been prepared for submission, the final results details will be published after the conference. Clinical trial information: ChiCTR2400085526. Research Sponsor: None.

4137 **Poster Session**

Tracking genomic evolution in *ERBB2*-altered biliary tract cancer through longitudinal tumor profiling. First Author: Orla Maeve Fitzpatrick, Memorial Sloan Kettering Cancer Center, New York, NY

Background: HER2, encoded by *ERBB2* (HER2), is overexpressed and clinically actionable in a subset of patients with biliary tract cancers (BTC). Zanidatamab and trastuzumab deruxtecan are now approved for patients with HER2 overexpressed tumors, though all patients ultimately progress on treatment and acquired resistance mechanisms are poorly defined. We aimed to characterize the genomic evolution in patients with *ERBB2* altered advanced BTC via serial tumor and cfDNA sampling during systemic therapy. **Methods:** Patients with *ERBB2* altered BTC were extracted of Memorial Sloan Kettering Cancer Center (MSK)'s prospectively maintained institutional genomic profiling protocol (NCT01775072). Eligibility required $\geq$2 molecular profiles obtained during systemic therapy. Tumor sequencing was performed using MSK-IMPACT (tissue-based NGS) and/or MSK-ACCESS (ctDNA NGS). Paired samples could include tissue and/or ctDNA. Clinical data were annotated, and longitudinal molecular profiles were analysed to assess temporal changes in *ERBB2* status. **Results:** Among 1628 patients with BTC in the institutional database, 122 (7.5%) had *ERBB2* altered tumors. Of these, 26 patients had $\geq$2 molecular samples available for longitudinal analysis. Five were excluded due to incomplete clinical and/or molecular data, leaving 21 eligible patients [Median age at diagnosis, 63 years (range 38–76), gallbladder cancer (n = 12, 57%), intrahepatic cholangiocarcinoma (n = 6, 29%), and extrahepatic cholangiocarcinoma (n = 3, 14%)]. At baseline, *ERBB2* alteration patterns included *ERBB2* amplification in 15 patients (71.4%), single nucleotide variants (SNV) in 2 patients (9.5%), and concurrent amplification and SNVs in 3 patients (14.3%). The most common co-occurring alterations involved *TP53* (67%), *SMAD4* (19%), *CDKN2A* (19%), and *SMAD4* (19%). Over the course of systemic treatment [Median number of treatment lines, 3.5 (range 1-6), 71% patients received HER2 directed therapy (n = 15) at any line], loss of *ERBB2* amplification at last available molecular sampling was observed in 7 patients (46%) and gain in 1 patient. Longitudinal profiling also demonstrated acquisition of additional alterations in receptor tyrosine kinase (RTK) pathways, including *MAPK* genes in 19% patients and *MET* alterations in 4.7%. Among the 15 patients who received HER2-directed therapy, *MAPK* alterations were observed in 4 (25%) and *MET* alterations in 1 (6%) at progression. **Conclusions:** *ERBB2* alterations in BTC evolve over time with frequent loss of amplification and emergence of RTK pathway alterations during systemic therapy. Acknowledging limitations of small sample size as well utilization of both cfDNA and tumor profiling, these findings highlight the genomic heterogeneity of *ERBB2* altered BTC and support the potential value of longitudinal profiling to better understand mechanisms of resistance and help inform treatment sequencing. Research Sponsor: None.

4138 **Poster Session**

Homologous recombination signature (HRDsig) in clinically advanced gallbladder adenocarcinoma (CAGAC): A genomic landscape study. First Author: Myungwoo Nam, SUNY Upstate Medical University, Syracuse, NY

Background: CAGAC is an aggressive malignancy with poor prognosis where chemotherapy and immunotherapy provide a limited benefit. There have been clinical trials investigating the benefit of PARP inhibitors in biliary tract cancers. HRDsig positivity in other types of cancer have shown to predict sensitivity to PARP inhibitors. We explored the genomic characteristics of CAGAC patients according to the HRDsig status using a large real-world genomic dataset. **Methods:** Comprehensive genomic profiling was performed on 2,423 cases of CAGAC to assess all types of genomic alterations (GA), including base substitutions, short insertions and deletions, copy number changes, rearrangements, and fusions. Microsatellite instability (MSI) status, tumor mutational burden (TMB), genomic ancestry, and trinucleotide signatures were determined from the sequencing data. PD-L1 was determined with the DAKO 22C3 IHC assay. HRDsig status was determined by measuring large scale copy number changes and DNA repair errors. Patients were grouped into HRDsig positive (HRDsig+) and negative (HRDsig-) based on results. Genes with GA $\geq$5% in either population were included in the analysis. **Results:** Among 2,423 total cases, 152 (6.3%) were HRDsig+. Between MRDsig+ and MRDsig-, there was no significant difference in gender (female 76.3% vs 69.1%, p = 0.061), age (median 66.5 vs 68.0 yrs; p = 0.065), genomic ancestry (EUR 67.6% vs 63.7%, p = 1.0), MSI-H status (0.0% vs 1.3%, p = 0.468), PD-L1 expression (Low 34.0% vs 23.4%, p = 0.529. High 1.9% vs 5.4%, p = 0.946). Median GA per tumor was the same between groups (median 5 vs 5, p = 0.723), but the proportion of TMB$\geq$10 mut/Mbp were higher in HRDsig+ (12.5% vs 4.7%, p = 0.001). HRDsig+ had more frequent alterations in BRCA1 (9.2% vs 1.4%, p $<$ 0.001), BRCA2 (21.7% vs 1.9%; p $<$ 0.001), PALB2 (11.2% vs 0.4%; p $<$ 0.001), NF1 (9.9% vs 4.4%; p = 0.018), PIK3R1 (5.9% vs 2.5%; p = 0.05), and PTEN (11.8% vs 5.3%; p = 0.015). HRDsig- had more frequent alterations in ERBB2 (5.9% vs 19.0%, p $<$ 0.001), KRAS (5.9% vs 14.9%, p = 0.007), and MDM2 (3.3% vs 9.4%, p = 0.024). **Conclusions:** HRDsig positivity comprised approximately 6% of all CAGAC cases. HRDsig+ were associated with a higher proportion of mutations related to homologous recombination repair (HRR) genes and mTOR pathway, whereas HRDsig- demonstrated a higher proportion of common driver mutations such as ERBB2 and KRAS. Notably, there were cases with discordant HRDsig and HRR mutation status, which may be attributed to factors such as epigenetic alterations or mono-allelic alterations. These cases may represent the role of HRDsig complementing HRR mutation status and potentially have clinical implications in predicting response to PARP inhibitors. Research Sponsor: None.

4139 **Poster Session**

Multi-cohort validation of a multi-analyte liquid biopsy test for early-stage pancreatic cancer detection. First Author: Anna Bergamaschi, ClearNote Health, San Diego, CA

Background: Pancreatic ductal adenocarcinoma (PDAC) has a 5-year survival rate below 12%, largely due to diagnosis at advanced, noncurative stages. Earlier detection could significantly improve survival outcomes; however, current approaches, including imaging and blood based assays lack sufficient sensitivity and specificity. Liquid biopsy methods that combine genomic, epigenomic, and glycan-based biomarkers may improve the detection accuracy by integrating a multi-analyte approach. We developed an improved prediction model for the Avantect Pancreatic Cancer Test (Avantect) using 5-hydroxymethylcytosine (5hmC) profiling, whole-genome based fragmentomics, together with genotyping and haplotype data, and CA19-9 biomarker levels. **Methods:** We employed a training cohort consisting of 162 PDAC cases and 983 noncancer controls. Cell-free DNA was analyzed using 5hmC profiling, low-pass whole-genome sequencing (WGS), and genotyping, alongside matched plasma CA19-9 measurements. A logistic regression model integrating 5hmC features, fragment size metrics, haplotype information, and CA19-9 levels was constructed and locked at a specificity of 97.75%. Performance was evaluated in two independent validation cohorts consisting of 1,445 individuals (259 PDAC; 1,186 noncancer participants) and 173 individuals (67 PDAC and 106 non-cancers). Sensitivity, specificity, and 95% confidence intervals (CIs) were computed. **Results:** In an independent validation cohort of 1,445 individuals with various high-risk features including type 2 diabetes, family history, and genetic predisposition, Avantect achieved an overall sensitivity of 82.6% (95% CI: 77.45%-87.04%) and an early stage (stage I-II) sensitivity of 76.8% (n=138; 95% CI: 68.87%-83.57%). A second validation cohort of 173 individuals, enriched for new onset type 2 diabetes, was evaluated and showed a sensitivity of 74.6% (95% CI: 62.51%-84.47%). Specificity in both cohorts remained high at 97.5% (95% CI: 96.41%-98.29%) and 98.1% (95% CI: 93.33%-99.77%) respectively, consistent with the pre-specified rate of 97.75%. Test specificity was further evaluated in a cohort comprising other cancer types, including breast, colorectal, lung, liver, prostate, ovarian, bladder, and kidney cancers, revealing a consistent high specificity of 97.70 (0.05% reduction). **Conclusions:** The multi-analyte model shows strong and robust performance across multiple independent cohorts detecting PDAC at high specificity. By integrating orthogonal biological signals, through the incorporation of epigenomic, genomic, and glycan biomarkers, the Avantect Pancreatic Cancer Test showed an improved PDAC detection to provide a tool that could significantly improve survival for patients with pancreatic cancer. Research Sponsor: None.

4140 **Poster Session**

Sequencing in the post-immunotherapy era: Does second-line tyrosine kinase inhibitor choice impact survival and safety in advanced HCC? First Author: Ansy Patel, SUNY Upstate Medical University, Syracuse, NY

Background: IMbrave150 trial established atezolizumab/bevacizumab as first line (1L) treatment for advanced hepatocellular carcinoma (HCC) in 2020. Current guidelines for second line (2L) therapy in advanced HCC rely on pre-immunotherapy (IO) trials (Lenvatinib, REFLECT trial and Cabozantinib, CELESTIAL trial). We investigated whether Lenvatinib (potent FGFR 1–4 inhibitor) offers superior efficacy over Cabozantinib (MET/AXL inhibitor with minimal FGFR activity) in post-IO setting by targeting the FGF-driven angiogenic escape pathways. **Methods:** Using TriNetX global network, we identified advanced HCC patients who received 1L atezolizumab/bevacizumab followed by 2L Lenvatinib (n=436) or Cabozantinib (n=115) within 6 months. 1:1 propensity score matching (PSM) balanced demographics, liver function, viral hepatitis, alcohol-related disorders, chronic liver diseases and key comorbidities. Outcomes include 1-year overall survival (OS), hepatic decompensation, cardiovascular (CV) outcomes and 90-day healthcare utilization, GI toxicity and acute renal failure (ARF). Each cohort was analyzed for 1 year competing risk of transition to third line (3L) systemic therapy vs. death vs. hospice. **Results:** Baseline characteristics were balanced except for lower pre-existing hypertension in Lenvatinib cohort (64% vs 74%; p=0.02). Post matching (n=110/arm), Lenvatinib showed significantly higher 1-year overall survival (OS). Safety analysis revealed significantly higher rates of new onset hepatic decompensation and a trend toward increased acute healthcare utilization with Cabozantinib. Renal, GI, and CV outcomes were comparable between cohorts. Lenvatinib arm had lower competing risk of mortality and higher cumulative incidence of receiving 3L therapy. **Conclusions:** In the real-world post-IO setting, Lenvatinib conferred significant 1-year survival benefit with superior hepatic safety profile compared to Cabozantinib. Cabozantinib exhibited higher rates of new hepatic decompensation and a trend toward increased healthcare resource utilization. Beyond a favorable pharmacoeconomic profile, results suggest superior sustained clinical benefit while preserving eligibility for 3L therapy. Given sample size constraints, these hypothesis-generating signals warrant validation in larger, multi-institutional cohorts. Research Sponsor: None.

Key clinical outcomes.

Outcome	Lenvatinib	Cabozantinib	HR/ RR (95% CI)	p-value
Median OS (months)	10.2	8.3		
1 year OS	47.1%	31.9%	0.65 (0.45, 0.95)	0.026
Hepatic decompensation	22.1%	37.5%	0.59 (0.34, 1.01)	0.046
CV outcomes	18.2%	16.4%	1.11 (0.62, 1.98)	0.72
90-day outcomes				
Healthcare utilization	37.3%	50.0%	0.75 (0.55, 1.01)	0.057
ARF	12.7%	13.6%	0.93 (0.47, 1.84)	0.84
GI events	25.5%	23.6%	1.08 (0.68, 1.71)	0.75
1 year Competing risks				
Death	36.1%	48.7%		
3L therapy	30.7%	27.9%		
Probability of being event-free	32.6%	23.4%		

4141 **Poster Session**

Global insights into survival outcomes and unmet therapeutic needs in *KRAS*-mutant gallbladder cancer: A comprehensive federated network analysis. First Author: Zeeshan Solangi, Dana-Farber Cancer Institute at Boston Medical Center Brighton, Brighton, MA

Background: Gallbladder cancer (GBC) is an aggressive malignancy with limited systemic options and poor survival. KRAS targeted therapeutic are emerging across solid tumors, yet their prognostic relevance in GBC remains poorly defined. We evaluated the real-world impact of KRAS mutations on survival in patient with advanced gallbladder cancer utilizing a large, federated health data network. **Methods:** A retrospective cohort study was performed using the TriNetX Global Collaborative Network. Adults (≥18y) with GBC were grouped by genomic testing into KRAS-mutant (KRAS*MT*) or KRAS-wild type (KRAS*WT*). Propensity-score matching (PSM) was performed 1:1 adjusting for demographics and comorbidities, yielding 604 patients per cohort. Outcomes were assessed from 1 to 1825 days after index diagnosis. The primary endpoint was overall survival (OS). Kaplan-Meier (KM) estimates, log-rank testing, and hazard ratios (HR) were generated. **Results:** After PSM, median follow-up was 358.5 (11,7 months) vs 491 (16.1 months) days for KRAS*WT* and KRAS*MT* cohorts, respectively. Death occurred in 214 (35.4%) KRAS*WT* vs 305 (50.5%) KRAS*MT* patients (risk difference −15.1%, 95% CI −20.6 to −9.5; $p < 0.001$). Median OS was 1326 days (43.5 months) for KRAS*WT* vs 694 days (22.8 months) for KRAS*MT* patients, with survival probability at end of time window of 48.74% vs 32.49%. Kaplan-Meier survival analysis demonstrated significantly worse OS in the KRAS*MT* cohort (log-rank $\chi^2 = 10.76$; p = 0.001). Hazard ratio favored KRAS*WT* (HR 0.747; 95% CI 0.627–0.890; p = 0.011), indicating 34% higher mortality in KRAS*MT* patients. **Conclusions:** In this large real-world PSM analysis, KRAS mutations conferred poor prognosis in GBC patients with significantly higher mortality and shorter survival. These differences highlight pivotal clinical implications amid the growing role of KRAS-targeted therapeutics. Ensuring expanded trial access, including early-line KRAS-targeted therapies, is necessary to reach this rare and clinically fragile patient population. Research Sponsor: None.

4142 **Poster Session**

A phase 1b/2 study of AK130 (TIGIT/TGF-β bispecific fusion protein) combined with ivonescimab in advanced biliary tract cancer (BTC). First Author: Haitao Zhao, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, Beijing, China

Background: Chemotherapy (chemo) combined with or without PD-(L)1 inhibition is the standard first-line treatment for advanced BTC. After first-line treatment fails, patients (pts) lacking targetable genetic alterations (FGFR2, IDH1, or HER2 etc.) have limited options. For the majority, chemo (FOLFOX as the preferred regimen) is the default but suboptimal option. To date, the therapeutic potential of multi-target ICIs and anti-angiogenesis combination in the post-line regimen of BTC remains unexplored and constitutes a significant clinical demand. Additionally, early preclinical and clinical evidences support the combination blockade of TIGIT, TGF-β and PD-(L)1 plus anti-VEGF therapy in several solid tumors. AK130 is a TIGIT/TGF-β bispecific fusion protein. Ivonescimab, the first approved PD-1/VEGF bispecific antibody, has demonstrated promising efficacy in solid tumors, including BTC. Here, we aim to evaluate the efficacy and safety of AK130 plus ivonescimab in post-line BTC and the primary results from phase 1b is reported. **Methods:** This was an open-label, multi-center phase 1b/2 study. Pts who had progressed on prior chemo combined with or without a PD-(L)1 inhibitor were enrolled and treated with AK130 and ivonescimab. Phase 1b included dose escalation and expansion parts. In the escalation part, escalating doses of AK130 (10, 30, 45 mg/kg Q3W) were administered using a "3+3+3" design, with ivonescimab at 20 mg/kg Q3W (previously approved dose by NMPA). Dose-limiting toxicities (DLTs) were assessed. Based on safety profile, the expansion proceeded at selected doses, with up to 15 evaluable pts per dose. The primary endpoint of phase 1b was the incidence of AEs and DLTs. The secondary endpoint was ORR. **Results:** As of Jan 2026, a total of 23 pts was enrolled. 12 pts were enrolled in dose escalation across 3 dose levels (10, 30, 45 mg/kg AK130 Q3W; n = 3, 3, 6). No DLTs were observed, and no maximum tolerated dose (MTD) was established. All pts in the 10 mg/kg and 30 mg/kg groups experienced stable disease (SD). The 45mg/kg group was further expanded to 17 pts, including 15 pts that progressed on prior PD-(L)1 inhibition plus chemo.15 pts from 45mg/kg group were efficacy-evaluable with an ORR of 20.0% (3/15) and a DCR of 73.3% (11/15). 87.5% of the SD pts (7/8) reached shrinkage from baseline. 40.0% pts (6/15) had only one time evaluation and are continuing to be followed. Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 39.1% (9/23) pts. The most common TRAEs were anemia and atopic dermatitis, each reported in 2 pts (8.7%). AK130 45 mg/kg Q3W is planned as the recommended phase 2 dose (RP2D), whose safety and efficacy will be further evaluated in phase 2. **Conclusions:** AK130 plus ivonescimab demonstrated potential anti-tumor activity with a manageable safety profile as a post-line option for advanced BTC, supporting its further development in this setting. Clinical trial information: NCT06938321. Research Sponsor: Akeso Biopharma, Inc.

4143 **Poster Session**

Peritumoral stiffness as a novel noninvasive biomarker: Predicting TACE response in intermediate-stage hepatocellular carcinoma via 2D-shear wave elastography. First Author: Yanqin Wu, Department of Interventional Oncology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Background: Intermediate-stage hepatocellular carcinoma (HCC) demonstrates considerable biological and clinical heterogeneity, making it challenging to predict treatment response to transcatheter arterial chemoembolization (TACE). This multicenter retrospective study evaluated the association between preoperative tissue stiffness measurements obtained by 2D-shear wave elastography (2D-SWE) and TACE outcomes in intermediate-stage HCC, aiming to identify an optimal peritumoral stiffness cutoff value for prognostic stratification and clinical decision-making. **Methods:** A total of 115 patients with intermediate-stage HCC were enrolled. Preoperative 2D-SWE was performed to measure stiffness of the tumor (TSWE), peritumoral tissue (PSWE), and background liver parenchyma (LSWE). Cox proportional hazards regression and Kaplan-Meier analyses were conducted to determine whether 2D-SWE-derived stiffness parameters independently predicted TACE efficacy. Immunohistochemical staining, immunofluorescence, and RNA sequencing were performed to characterize the biological features of peritumoral tissue associated with varying PSWE values. **Results:** Mean stiffness values demonstrated a progressive gradient from liver parenchyma (LSWE: 13.0 kPa) through peritumoral tissue (PSWE: 18.9 kPa) to tumor tissue (TSWE: 25.6 kPa). Univariate and multivariate analyses identified primary tumor size and PSWE as independent prognostic factors for both overall survival (OS) and time to progression (TTP). A PSWE cutoff of 19.04 kPa achieved the highest discriminatory performance for predicting objective response rate (ORR) and disease control rate (DCR) (AUROC = 0.691 and 0.695, respectively). Patients with low PSWE demonstrated significantly superior OS (26.0 vs 17.5 months, P = 0.008) and TTP (11.6 vs 9.5 months, P = 0.026) compared to those with high PSWE. RNA sequencing revealed 778 differentially expressed genes enriched in angiogenesis and fibrosis-related pathways. Notably, patients with elevated PSWE exhibited enhanced stromal activation and angiogenesis in peritumoral regions, including increased collagen deposition, α-SMA, COL-I, VEGF expression, and CD31+ microvessel density, correlating with inferior TACE response. **Conclusions:** Preoperative peritumoral stiffness measured by 2D-SWE serves as a promising noninvasive prognostic biomarker for intermediate-stage HCC patients undergoing TACE, offering valuable insights for personalized treatment stratification. Research Sponsor: None.

4144 **Poster Session**

Yttrium-90 SIRT plus atezolizumab/bevacizumab in unresectable huge HCC (>10 cm): A multicenter retrospective study. First Author: Shao Minghua, AMU, Chongqing, Chongqing, China

Background: Huge hepatocellular carcinoma ((huge HCC, $\geq$ 10 cm)) has poor prognosis with limited systemic therapy efficacy. We evaluated Y-90 selective internal radiation therapy (SIRT) combined with atezolizumab plus bevacizumab (Atezo/Bev) in this population. **Methods:** This retrospective multicenter study enrolled 21 patients with unresectable huge HCC (maximum diameter $>$10 cm) treated with Y-90 SIRT plus Atezo/Bev from January 2023 to July 2025. Eligibility criteria included Child-Pugh class A/B, ECOG performance status 0/1, and completion of $\geq$2 treatment cycles. The primary endpoint was ORR assessed by mRECIST. Secondary endpoints: PFS, OS, and safety (CTCAE v5.0). **Results:** Among the patients median tumor diameter 116.2 mm (IQR 105.6-131.9); $>$15 cm 14.3%; BCLC C 76.2%; PVTT 76.2%; extrahepatic metastasis 23.8%. The objective response rate (ORR) was 61.9% (13/21), including 6 (28.6%) complete responses (CR) and 7 (33.3%) partial responses (PR). The disease control rate (DCR) was 76.2% (16/21), with 3 (14.3%) stable disease (SD) and 5 (23.8%) progressive disease (PD). Median follow-up 11.0 months (IQR 7.1-25.0). Respectively, the median OS was not reached, at data cutoff, the 6- and 12-month PFS rates were 65.1% and 27.1%, respectively. The 6-, 12-, and 24-month OS rates were 76.2%, 57.5%, and 49.3%. Radiological responders (CR/PR) showed reduced progression risk (HR 0.46; 95% CI 0.16-1.32) and death risk (HR 0.41; 95% CI 0.11-1.49) vs non-responders. Nonrim APHE correlated with improved survival (median OS: 18.0 vs 8.0 months; HR 0.54). Grade $\geq$3 treatment-related adverse events occurred in 14.3% (3/21): pneumonia (n=2), hepatic encephalopathy (n=1). No treatment-related deaths. **Conclusions:** In this cohort, Y-90 SIRT plus Atezo/Bev achieved 61.9% ORR with manageable toxicity. These findings warrant prospective trials. Research Sponsor: None.

Baseline characteristics and clinical outcomes (N=21).

Characteristic	Value
Age, median (range), years	53 (28–76)
Male sex, n (%)	18 (85.7)
ECOG performance status 0/1, n (%)	16 (76.2) / 5 (23.8)
Etiology HBV/Alcohol/Unknown, n (%)	18 (85.7) / 1 (4.8) / 2 (9.5)
Tumor diameter, median (IQR), mm	116.2 (105.6–131.9)
Tumor >15 cm, n (%)	3 (14.3)
BCLC stage A/B/C, n (%)	4 (19.0) / 1 (4.8) / 16 (76.2)
Child-Pugh A/B, n (%)	17 (81.0) / 4 (19.0)
Portal vein tumor thrombus, n (%)	17 (81.0)
Extrahepatic metastasis, n (%)	5 (23.8)
AFP >400 ng/mL, n (%)	10 (47.6)
Complete responses (CR)	6 (28.6%)
Partial responses (PR)	7 (33.3%)
Stable disease(SD)	3 (14.3%)
Progressive disease (PD)	5 (23.8%)
Objective response rate (ORR)	61.9% (13/21)
Disease control rate (DCR)	76.2% (16/21)
Median follow-up, months	11.0(IQR 7.1-25.0)
6- and 12-month PFS rates	65.1% and 27.1%
6-, 12-, and 24-month OS rates	76.2%, 57.5%, and 49.3%
Grade ≥3 TARE	14.3% (3/21)

TARE: treatment-related adverse events.

4145 **Poster Session**

Time-toxicity of first-line systemic therapy for hepatocellular carcinoma in clinical practice. First Author: Kenta Takaura, Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Musashino-Shi, Japan

Background: Combination immunotherapy has become a standard first-line systemic treatment for hepatocellular carcinoma (HCC). While efficacy outcomes have been well described, the treatment-related time burden experienced by patients, including frequent hospital visits and admissions, has not been sufficiently evaluated in real-world clinical practice. Aims: To evaluate time toxicity as a patient-centered measure of treatment burden and to identify baseline factors associated with high time toxicity in patients receiving first-line combination immunotherapy for HCC. **Methods:** This retrospective observational study included patients with HCC who received first-line combination immunotherapy (atezolizumab + bevacizumab or durvalumab + tremelimumab) at our institution by April 2025. The observational period was defined as the treatment duration plus 28 days. Time toxicity (TT) was calculated as the proportion of days requiring hospital contacts, including scheduled visits, management of adverse events, and hospital admissions. High time toxicity (hTT) was defined as TT $\geq$20%, representing a clinically meaningful high treatment burden. Factors associated with hTT were examined using multivariate logistic regression analysis. **Results:** A total of 126 patients were included, with a median age of 74 years (IQR 67–81). The median observational period was 178 days (IQR 75-287), the median total hospital contacts was 20 days (IQR 13-30) and the median inpatient days was 7 days (IQR 4-14). Moreover, the median TT was 11.8% (IQR 9.1–17.9) and 23.0% of all patients experienced hTT. In multivariate analysis, impaired liver function (mALBI grade 2b–3; OR 7.17, 95% CI 2.60–19.80) and AFP $\geq$100 ng/mL (OR 3.03, 95% CI 1.20–7.67) were independently associated with hTT. **Conclusions:** Patients with impaired liver function and elevated AFP levels experienced a significantly higher treatment-related time burden during first-line combination immunotherapy for HCC. Assessment of time toxicity may provide clinically meaningful information to support shared decision-making, particularly in elderly or vulnerable patient populations. Research Sponsor: None.

4146 **Poster Session**

Transcriptomic profiling in advanced hepatocellular carcinoma to identify biomarkers for immunotherapy response and mechanisms of acquired resistance. First Author: Sunyoung S. Lee, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Immune checkpoint inhibitors (ICI) are the standard of care for advanced HCC, yet validated biomarkers for response and mechanisms of acquired resistance remain undefined. We utilized transcriptomic profiling to identify predictive mRNA expression signatures and characterize evolution of the tumor microenvironment (TME) under therapeutic pressure. **Methods:** RNA-sequencing was performed on 35 HCC samples, comprising a cohort of 20 patients (16 pre-treatment + 4 treatment-naive tumors) and an independent cohort of 11 post-progression tumors (Post-IO). Patients received first-line atezolizumab/bevacizumab (n = 9), durvalumab/tremelimumab (n = 4), or nivolumab/ipilimumab (n = 3). 29 validated immune and stromal gene signatures were quantified (Bagaev, Cancer Cell 2021). Differential expression was assessed using Welch's t-test and permutation testing. Survival outcomes were correlated with gene signatures using Cox regression and Kaplan-Meier estimation. **Results:** Comparison of the pre-IO exposure (n = 20) vs post-IO (n = 11) cohorts revealed significant TME remodeling. Acquired resistance was driven by the evolution of a "hypovascular immune desert," characterized by statistical downregulation of antigen presentation (MHC-II, P = 0.04) and angiogenesis (P = 0.04). Regarding baseline prediction to universal IO regimen (all 3 regimens), high tumor proliferation rate (HR 4.79, P = 0.007; mPFS 2.6 vs 10.0 m), Th2 signature (HR 22.5, P = 0.01), and Treg traffic (HR 15.6, P = 0.01) strongly correlating with inferior outcomes; high macrophage/DC traffic predicted favorable outcomes (HR 0.18, P = 0.04; mPFS 7.4 vs 3.4 m). Distinct from these universal IO predictors, we utilized permutation testing to differentiate regimen-specific signals, identifying higher myeloid cell traffic (P = 0.007) and higher angiogenesis (P = 0.02) at baseline as unique biomarkers of response exclusively in anti-CTLA4 regimens. Transcriptomic profiles of post-transplant recurrences (n = 4) were statistically indistinguishable from the pre-IO cohort. **Conclusions:** Advanced unresectable HCC shows distinct tumor states linked to immunotherapy benefit versus early resistance, and these states evolve with treatment. Our findings support a biology-driven framework for predicting response, understanding resistance, and prioritizing rational combination strategies to improve durable disease control. Research Sponsor: None.

4147 **Poster Session**

Comprehensive genomic profiling to identify molecular determinants of efficacy of IDH1 inhibition in intrahepatic cholangiocarcinoma. First Author: Sunyoung S. Lee, Department of Gastrointestinal Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Ivosidenib (IVO) in *IDH1*-mutant iCCA yields modest mPFS (2.7 m) with heterogenous responses. Molecular features driving this variability remain undefined. We sought to identify determinants of therapeutic efficacy via comprehensive analyses of co-occurring genomic alterations and oncogenic pathway activation. **Methods:** We analyzed 93 *IDH1*-mutant iCCA cases (MD Anderson n=59, Moffitt n=23, Yonsei n=11) treated with IVO (n=78), IDH305 (n=15). We stratified patients (pts) into 3 groups based on co-occurring alterations: EC (Epigenetic/Chromatin remodeling: BAP1/ARID1A/PBRM1), PMF (Proliferative/Mitogenic signaling: PI3K/MAPK/FGFR), ACT (Amplified cyclins/CDKN2A-B/TP53), yielding 4 groups: G1 (EC-intact/low-oncogenic: EC+/PMF-/ACT-), G2 (signaling-driven: EC+/PMF+), G3 (cell-cycle-deregulated: EC+/ACT+), and G4 (EC-deficient: EC-). Cox models assessed group-specific treatment effects; TME characterization utilized 29 mRNA gene signatures (Bagaev, Cancer Cell 2021) (n=31) and paired pre/post-progression biopsies (n=4). **Results:** Survival analysis (n=93) revealed distinct stratification ($p<0.0001$): G1, the longest mPFS (11.4 m), significantly superior to G4 (3.5 m) and G3 (1.8 m). G1 had superior durability (12-m PFS 46.5%) over G2 and G4 (23.9%, 14.6%); G3 progressed rapidly (6-m 0%). G3 outcomes suggest that ACT co-mutations confer poor prognosis regardless of epigenetic context (HR 6.85, P=0.004). Transcriptomic analysis identified G1 as "inflamed-suppressed" (highest angiogenesis/Treg); G4 was "proliferative-inflammatory" (highest M1-macrophage/Ki67, p=0.04). Paired longitudinal analysis (n=4) identified genomic bypass via acquired kinase drivers (eg, *NTRK1* amplification) and stromal adaptation with dense fibrotic remodeling. Radiographic hyperprogression on IVO (Kato criteria) was observed in 2 pts in G3 harboring *CDKN2A* loss. **Conclusions:** Co-occurring genomic alterations may serve as prognostic markers in *IDH1*-mutant iCCA, suggesting distinct trajectories of response and resistance to IDH1 inhibition. This molecular classification could guide clinical decision-making by identifying pts likely to benefit from monotherapy vs pts requiring combination strategies to overcome intrinsic resistance. Research Sponsor: None.

	G1 EC+ / PMF- / ACT-	G2 EC+ / PMF+	G3 EC+ / ACT+	G4 EC-
N (%)	28 (30%)	19 (20%)	5 (5%)	41 (44%)
mPFS (95% CI)	11.4 mo (6.2-NR)	5.6 mo (3.7-9.2)	1.8 mo (0.9-3.5)	3.5 mo (2.1-5.8)
3-M Rate	80.9% (66.3-95.5)	88.9% (74.8-100)	20.0% (0.0-55.1)	59.5% (44.5-74.5)
6-M Rate	72.4% (55.8-89.0)	47.9% (25.4-70.4)	0.0% (0.0-0.0)	23.4% (10.4-36.4)
12-M Rate	46.5% (28.0-65.0)	23.9% (4.7-43.1)	0.0% (0.0-0.0)	14.6% (3.8-25.4)
Hazard Ratio	Reference (1.0)	2.15 (p=0.03)	6.85 (p=0.004)	2.94 (p=0.002)
TME Phenotype	Angiogenesis / Treg-High	Fibrotic (CAF-High)	Senescent / Dormant	Proliferative / M1-High

4148 **Poster Session**

Effectiveness and safety of IBI310 combined with sintilimab versus sorafenib in the first-line treatment of advanced hepatocellular carcinoma (aHCC): A randomized, open-label, controlled, multicenter phase III clinical study. First Author: Jia Fan, Department of Hepatobiliary Surgery and Liver Transplantation, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Immune checkpoint inhibitors (ICIs) targeting PD-1/PD-L1 have demonstrated efficacy in aHCC. Despite improved outcomes with PD-1/PD-L1 inhibitor-based regimens, prognosis remains poor and there is a continued unmet need for alternative therapies with long-term survival benefits. This study aimed to evaluate the effectiveness and safety of IBI310 (anti-CTLA-4 antibody) combined with sintilimab (anti-PD-1 antibody) in the first-line treatment of aHCC. **Methods:** Pts were randomized in a 2:1 ratio to IBI310+sintilimab group or sorafenib group. The experimental group received IBI310 3mg/kg intravenously (IV) and sintilimab 200 mg IV on day 1 of every 3 weeks. The control group received sorafenib 400 mg orally twice daily (BID) continuously until disease progression, intolerable toxicity, death or other protocol-specified discontinuation criteria. During the study, the IBI310 dose was adjusted to 1 mg/kg every 6 weeks. Primary end points included overall survival (OS) and objective response rate (ORR)assessed by the independent radiology review committee (IRRC) per RECIST v1.1. Secondary endpoint included progression-free survival (PFS), disease control rate (DCR), safety, etc. **Results:** As of August 2022, 344 patients were enrolled and allocated to Group 1 (G1, IBI310 3mg/kg + sintilimab, n=84), Group 2 (G2, modified-dose IBI310 1mg/kg + sintilimab, n=145) and Group 3 (G3, sorafenib, n=115). Overall, PFS and ORR improved with IBI310+sintilimab vs Sorafenib. The median OS in the primary endpoint was 44.0 months(G1), 36.1 months(G2) and 22.9 months(G3), respectively. Confirmed ORRs were significantly higher in the combination therapy groups (G1: 41.7%; G2: 22.1%) versus the control group (2.6%). Median PFS of three groups were 13.5 months(G1), 6.1 months(G2) and 2.8 months(G3), respectively. Grade ≥3 treatment-related adverse events (TRAEs) occurred in 60.7% (G1), 34.7% (G2), and 35.1% (G3) of patients. **Conclusions:** Compared with sorafenib group, combination treatment of IBI310 + sintilimab as first-line treatment demonstrated survival benefits and a manageable safety profile in aHCC. Clinical trial information: NCT04720716. Research Sponsor: None.

Survival data.

	IBI310(3mg/kg)+Sintilimab (N=84)	IBI310(1mg/kg)+Sintilimab (N=145)	Sorafenib (N=115)
mOS, m	44.0	36.1	22.9
Confirmed ORR, n(%)	35(41.7)	32(22.1)	3(2.6)
mPFS, m	13.5	6.1	2.8

4149 **Poster Session**

Yttrium-90 SIRT followed by lenvatinib plus sintilimab for unresectable intermediate-to-advanced hepatocellular carcinoma: Phase II SIRLENS-90 trial. First Author: Jingjun Huang, Department of Minimally Invasive Interventional Radiology, the Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

Background: Selective internal radiation therapy (SIRT) with yttrium-90 microspheres is an established locoregional therapy for unresectable hepatocellular carcinoma (HCC) and may induce immunogenic modulation, providing a rationale for PD-(L)1 blockade combinations. However, outcomes with SIRT–PD-(L)1 doublets suggest room for improvement. Lenvatinib has biological plausibility to augment radiation- and immunotherapy-mediated effects via VEGFR/FGFR pathway inhibition. We evaluated the efficacy and safety of sequential SIRT followed by lenvatinib plus sintilimab and explored serum protein biomarkers for outcome stratification. **Methods:** SIRLENS-90 (NCT05992584) is a single-center, open-label, single-arm phase II trial in unresectable BCLC B/C HCC (ECOG 0–1, Child–Pugh 5–7) suitable for SIRT after mapping and ^{99m}Tc-MAA simulation. Patients received yttrium-90 resin SIRT (partition-model dosimetry) followed 3–7 days later by lenvatinib (8/12 mg daily) plus sintilimab (200 mg IV Q3W). Primary endpoint: PFS by mRECIST. Secondary endpoints: PFS by RECIST v1.1, OS, ORR, DCR, and safety (CTCAE v5.0). Exploratory Olink proteomics and LASSO-penalized Cox modeling derived a baseline risk score. **Results:** Thirty patients were treated (mean age 57 years [(SD 9.9], 93% male, 87% HBV-related; 43% BCLC B, 57% BCLC C; 43% macrovascular invasion; 53% bilobar disease; 37% extrahepatic metastases; mean max tumor diameter 9.6 cm [SD 3.8; range 3.2–16.1]). Median follow-up was 23.4 months. Median PFS was 15.8 mo (95% CI 8.3–20.7) by mRECIST (6-, 12-, and 18-mo rates: 77%, 53%, 40%) and 17.0 mo (95% CI 8.3–20.7) by RECIST v1.1. Median OS was not reached (12-, 18-, and 24-mo OS rates: 83%, 73%, 68%). ORR was 83% (95% CI 65–94) by mRECIST and 60% (95% CI 41–77) by RECIST v1.1; DCR was 90% (95% CI 74–98) by both. Intrahepatic ORR was 93% (95% CI 78–99) by mRECIST. Grade 3–4 treatment-related AEs occurred in 47%, with treatment-related SAEs in 10% and no treatment-related deaths. A baseline risk score incorporating IL-5 (protective), CXCL11 (adverse), extrahepatic metastasis, and bilobar disease stratified PFS (log-rank P= 0.001) and OS (P= 0.02), with optimism-corrected C-index 0.758 (for PFS). **Conclusions:** Yttrium-90 SIRT followed by lenvatinib plus sintilimab demonstrated encouraging activity with manageable toxicity in unresectable intermediate-to-advanced HCC. The cytokine-integrated baseline risk score is hypothesis-generating and warrants external validation. Clinical trial information: NCT05992584. Research Sponsor: China Zhongguancun Precision Medicine Science and Technology Foundation.

4150 **Poster Session**

Tumor microenvironment phenotypes and survival in fibrolamellar carcinoma: An exploratory study. First Author: Hilal Polat, Ministry of Health, Istanbul Provincial Health Directorate, Başakşehir State Hospital, Istanbul, Turkey

Background: Fibrolamellar carcinoma (FLC) is a very rare liver cancer affecting children, adolescents, and young adults. FLC is characterized by a robust immune tumor microenvironment (TME), but the clinical relevance of TME phenotypes is unknown. **Methods:** This de-identified study was approved by the Genetic Alliance Organization Institutional Review Board (IRB #IRB00003999). Subjects consented under *XCELSIOR: A Patient-Centric Platform Study for Precision Oncology* (NCT03793088). From this database, FLC TMEs were classified using the BostonGene framework into immune–stromal subtypes: fibrotic (F), immune desert (ID), immune-enriched fibrotic (IE-F), and immune-enriched non-fibrotic (IE-NF), and further dichotomized into immune-active (IE-F, IE-NF) and immune-cold (F, ID) groups. Associations were assessed using chi-square and non-parametric tests. Overall survival (OS) and time to first progression (TTP1) were evaluated using Kaplan–Meier methods and log-rank tests. **Results:** Forty-seven subjects (21 females, mean age 20.7 years) were included. TME subtype distribution was: F 46.8%, ID 17.0%, IE-F 21.3%, and IE-NF 14.9%. TME phenotypes were not associated with sex (p = 0.15) or age at diagnosis (p = 0.81). During a median follow-up of 3.7 years, 20 deaths (42.6%) occurred. Median overall survival (OS) for the entire cohort was 75.1 months. Median OS by TME subtype were: F 58.8 months, ID not-reached, IE-F 54.6 months, and IE-NF 75.1 months. Median OS was 86.0 months in the immune-cold group and 54.6 months in the immune-active group (log-rank p = 0.69). **Conclusions:** In this preliminary analysis with uncompleted dataset of FLC, immune–cold TME phenotypes were not significantly associated with overall survival, although trends toward improved outcomes were observed in immune-active subtypes. These findings should be interpreted as hypothesis-generating due to small numbers. Larger data are needed to clarify the prognostic role of the TME in FLC. Research Sponsor: None.

Tumor microenvironment subtypes and clinical outcomes in fibrolamellar carcinoma.

TME group	N (%)	Female (n, %)	Median age (years, IQR)	Deaths (n, %)	Median OS (months, 95% CI)
Fibrotic (F)	22 (46.8)	12 (57.1)	20.2 (17.2–23.8)	12 (60.0)	58.8 (43.1–74.5)
Immune Desert (ID)	8 (17.0)	5 (23.8)	20.1 (17.2–27.7)	1 (5.0)	Not reached
Immune-cold (F + ID)	*30 (63.8)*	*17 (81.0)*	*20.2 (17.3–23.8)*	*13 (65.0)*	*86.0 (43.0–129.0)*
Immune-Enriched Fibrotic (IE-F)	10 (21.3)	3 (14.3)	16.1 (12.1–28.1)	4 (20.0)	54.6 (41.1–68.2)
Immune-Enriched Non-Fibrotic (IE-NF)	7 (14.9)	1 (4.8)	18.9 (17.7–23.6)	3 (15.0)	75.1 (36.6–113.6)
Immune-active (IE-F + IE-NF)	*17 (36.2)*	*4 (19.0)*	*18.7 (13.8–25.0)*	*7 (35.0)*	*54.6 (26.2–83.1)*
Total	47 (100.0)	21 (100.0)	20.1 (16.7–23.6)	20 (42.6)	75.1 (43.4–106.8)

Abbreviations: TME, tumor microenvironment; IQR, interquartile range; OS: overall survival, CI: confidence interval. Note: Percentages are calculated within columns.

4151 **Poster Session**

Characteristics of *SMAD4* alterations in an immune-cold genomic subtype of biliary tract cancers in the Indian population. First Author: Aditya V. Shreenivas, City of Hope National Medical Center, Duarte, CA

Background: Biliary tract cancers (BTCs), comprising gallbladder cancer (GBC) and cholangiocarcinoma (CCA), are rare but highly aggressive malignancies with limited therapeutic options. While genomic profiling has identified actionable alterations in BTC, data from the Indian population remain underexplored. We characterized the mutational and pathway landscape of BTCs in Indian patients and identified subtype-specific and immune-relevant genomic features. **Methods:** We retrospectively analyzed 154 BTC tumors, including 69 CCA and 85 GBC cases, using data from targeted next-generation sequencing panels. Somatic single-nucleotide variants, copy-number variations (CNVs), and gene fusions in oncogenic and tumor suppressor genes were curated. Pathway enrichment analysis (Hallmark MSigDB database ($p < 0.05$)), and mutual exclusivity/co-occurrence testing (gene pairs selected based on Benjamini-Hochberg-corrected q-values < 0.05.) were performed to identify biologically relevant genomic signatures. Genomic alterations were correlated with PD-L1 status when available. **Results:** *TP53* was the most frequently mutated gene (53%), followed by *KRAS* (18%), *ARID1A* (9%), *IDH1* (7%), and *PIK3CA* (7%). Recurrent amplifications were observed in *MYC* (12%) and *ERBB2* (9%). Pathway enrichment analysis revealed significant dysregulation in the PI3K-AKT-mTOR, Notch, and Wnt/β-catenin signaling pathways (p-value <0.05). *IDH1* mutations were predominantly observed in CCA, supporting a clinically actionable subgroup amenable to IDH1-targeted therapy, whereas *ERBB2* alterations were enriched in GBC, identifying *HER2* as a key therapeutic target in this subtype. Importantly, PD-L1-negative tumors showed a higher frequency of *SMAD4* mutations (Fisher's exact test, p = 0.71), implicating disruption of TGF-β signaling in immune evasion and reduced tumor immune activation. **Conclusions:** This comprehensive genomic analysis of BTC from the Indian population delineates distinct molecular landscape between GBC and CCA. The subtype-specific actionable alterations, including *IDH1* mutations in CCA and *ERBB2* alterations in GBC, highlights clinically relevant opportunities for precision therapy. *SMAD4* alterations are associated with an immune-cold, poorly immunogenic tumor subtype in BTCs and warrant further investigation as a predictive biomarker for patient stratification in immunotherapy-based treatment strategies. These findings support the utility of molecular stratification in BTC and provide a rationale for integrating targeted and immunotherapy-based approached in Indian patients. Research Sponsor: None.

4152 **Poster Session**

Envafolimab combined with lenvatinib and gemcitabine plus cisplatin in advanced biliary tract cancer as first-line treatment: A multicenter, single-arm, open-label, phase II study (ENLIGHTEN study). First Author: Lixia Xu, Department of Oncology, Cancer Center, the First Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China

Background: The prognosis of advanced biliary tract cancer (BTC) remains unsatisfactory despite the use of first-line gemcitabine and cisplatin in combination with PD-1/PD-L1 inhibitors. Lenvatinib (LEN), an anti-angiogenic multi-kinase inhibitor, has recently demonstrated promising antitumor activity in various tumors. This study aimed to determine the efficacy and safety of envafolimab (PD-L1 inhibitor) and LEN in combination with gemcitabine and cisplatin as first-line treatment in advanced BTCs. **Methods:** This investigator-initiated, multicenter, single-arm, phase 2 trial enrolled patients with advanced BTCs from three centers. A Simon's two-stage optimal design was employed: if 4 or more patients achieved partial responses (PR) among the first 10 patients in stage 1, enrollment would expand to a total of 39 patients. The therapy would be considered promising if 15 or more patients achieved PR in total. Including a 10% dropout allowance, the total sample size was set at 43. All patients received subcutaneous envafolimab (400mg, day 1, Q3W) and LEN (8 mg, orally once daily) combined with gemcitabine (1000mg/m2, iv. drip, days 1, 8, Q3W) plus cisplatin (25mg/m2, iv. drip, days 1, 8, Q3W) up for 6-8 cycles, followed by maintenance envafolimab and LEN until disease progression (PD) or unacceptable toxicity. The primary endpoint was objective response rate (ORR) assessed per RECIST 1.1. Secondary endpoints included overall survival (OS), progression-free survival (PFS), disease control rate (DCR), and safety. **Results:** A total of 43 patients were enrolled in this study from October 2022 to July 2025. However, one patient withdrew consent due to personal reasons after completing one cycle of therapy and was therefore considered off-study. Forty-two patients were included in the final analysis, with a median age of 57 years (range, 29-73). The ORR and DCR were 42.9% (95% CI, 27.7%-59%) and 88.1% (95% CI, 74.4%-96%), respectively. The observed outcomes were 18 patients (42.9%) with a partial response (PR), 19 (45.2%) with stable disease (SD), and 5 (11.9%) with PD, which met the predefined threshold for a positive study endpoint. The median follow-up time, estimated by the reverse Kaplan-Meier method, was 21.5 months (range, 18.7-29.1). The median PFS was 8.8 months (95% CI, 8.0-14.1), and the median OS was 15.9 months (95% CI, 13.4-not reached). The most common grade 3/4 treatment-related adverse events (TRAEs) were platelet decreased (n = 9, 20.9%) and neutropenia (n = 7, 16.3%). No treatment-related deaths occurred. **Conclusions:** In summary, our study demonstrates that the quadruplet regimen of envafolimab, lenvatinib, gemcitabine, and cisplatin demonstrates promising efficacy and well-tolerated first-line therapy for advanced BTC. Clinical trial information: NCT05410197. Research Sponsor: State Key Program of National Natural Science Foundation of China; 82130083; National Natural Science Foundation of China; 82173191; National Natural Science Foundation of China; 82372914; Key Area Research and Development Program of Guangdong Province; 2023B1111020007; Science and Technology Program of Guangzhou, China; 202206080016.

4153 **Poster Session**

Cyclin amplification in biliary tract cancer: Integrated profiling to evaluate immune exclusion, drug sensitivity, and prognosis. First Author: Akhila Madulapalli Reddy, Baylor College of Medicine, Houston, TX

Background: The impact of cell cycle regulator amplifications on the tumor microenvironment (TME) and clinical outcomes in biliary tract cancer (BTC) remains undefined in the chemo-immunotherapy era. This study characterizes the genomic, transcriptomic, and clinical landscape of cyclin-amplified BTC (CCNE/CCND family). **Methods:** We analyzed 263 BTC patients (pts) via comprehensive genomic/transcriptomic sequencing. Cohorts were stratified into Cyclin-Amplified (Amp, N = 71, Copy Number $\geq$6) and non-amplified Control (Ctrl, N = 192). We compared demographics, DNA co-alterations, and survival (Kaplan-Meier/Log-Rank). Transcriptomic profiling utilized 29 established gene signatures (Bagaev et al, Cancer Cell 2021) quantifying immune cell infiltration and stromal features. Differential gene expression assessed markers of chemotherapy resistance. **Results:** Cyclin amplification defined a distinct subgroup characterized by younger age (median 56 vs 65 years, $p < 0.001$). The Amp cohort (N = 71) consisted of CCNE1 (N = 30), CCND1/2/3 (N = 29/2/7), and CCNE1/D1 co-amplification (N = 3). Amp pts had significantly inferior overall survival (OS) compared to Ctrl (median 21.2 vs 28.3 m, p = 0.009). In stage 3-4 disease, Amp pts demonstrated worse OS (19.2 vs 25.5 m, p = 0.035). While adding immunotherapy (IO) to chemotherapy significantly improved OS in the control group (36.1 vs 23.0 m, p = 0.001), it provided no OS benefit in the Amplified group (median 19.2 m [Chemo+IO] vs 24.1 m [Chemo only], p = 0.80). Amp tumors exhibited high genomic instability, dominated by TP53 (67%), IRS2 (13%), ARID1A (11%), KRAS (11%), and ATM (11%) mutations. Frequent co-amplifications included FGF19/4 (35%), MYC (23%), ERBB2 (19%), EGFR (16%), and MET (16%). Transcriptomic profiling revealed a profound "immune desert" phenotype in Amp tumors, characterized by widespread depletion of adaptive and innate immunity: B-cells ($p < 0.001$), NK cells (p = 0.002), T-cells (p = 0.008), and Th1/Th2 signatures ($p < 0.01$) were significantly downregulated compared to Ctrl. Amp tumors exhibited intrinsic chemotherapy resistance via upregulation of gemcitabine targets (RRM1, p = 0.04) and platinum efflux pumps (ABCC2, p = 0.04), alongside a trend toward increased tumor proliferation (p = 0.053). **Conclusions:** Cyclin amplification identifies a biologically distinct, aggressive BTC subtype characterized by intrinsic resistance mechanisms to standard chemo-immunotherapy. This resistance is driven by a profound "immune desert" microenvironment limiting immunotherapy efficacy and the upregulation of genes associated with chemotherapy resistance. Comprehensive genomic profiling in this subgroup provides prognostic context and reveals a landscape of frequent co-occurring actionable drivers, highlighting the complex biological underpinnings of this high-risk population. Research Sponsor: None.

4154 **Poster Session**

Tumor microenvironment modulation by losartan in advanced gallbladder cancer (GBC): Results and genomic correlates from the phase 2 LAST study. First Author: Amol Patel, Department of Medical Oncology, Army Hospital Research and Referral, New Delhi, India

Background: Advanced gallbladder cancer (GBC) carries a dismal prognosis, with a real-world median overall survival (OS) of 6.8 months. We hypothesized that adding losartan to standard chemotherapy could improve outcomes by modulating the fibrotic tumor microenvironment (TME). **Methods:** This was a single-arm phase II study conducted at two academic centers between July 2022 and April 2024. Adult patients with histologically confirmed, unresectable or metastatic gallbladder cancer or cholangiocarcinoma received six cycles of gemcitabine and cisplatin with concurrent oral losartan. The primary endpoint was overall survival (OS). Exploratory analysis by whole-exome sequencing (WES) was done on 18 patients. **Results:** Thirty patients were enrolled. Clinical characteristics are depicted in Table. Median OS was 10.3 months (range 0.5–38.7), with 6-month and 12-month OS rates of 68% and 36%, respectively. Median PFS was 5 months. An objective response was observed in 88% of patients, including five complete responses. Patients with ECOG performance status 2 and those with cholelithiasis had inferior survival. Losartan was well tolerated. Genomic analysis revealed a clear discretion between cohorts (median PFS $>$, $<$=6 months). Responders exhibited a "TME-favorable" signature, characterized by genes associated with anti-inflammatory properties, regulated angiogenesis, and cellular stress response. This group was uniquely enriched for variants in *ATRX, CHEK2, DNMT3A, EZH2, IDH1, SMARCA4*, and *TSC2*. Conversely, non-responders (NR) showed a pro-inflammatory profile and oncogenic mutations in the angiogenesis pathway (*AKT2, BRAF, MET, NRAS, SMAD4*), potentially mediating resistance to losartan-induced vascular normalization. Both groups shared core GBC drivers, including *TP53, KRAS, ARID1A*, and *ERBB2*. **Conclusions:** Losartan improves survival in GBC patients with a specific molecular buildup. The presence of anti-inflammatory genomic signatures and specific variants like *SMARCA4* and *ATRX* may serve as predictive biomarkers for TME-targeted therapy, whereas pro-inflammatory profiles and primary angiogenesis mutations identify a resistant phenotype. Clinical trial information: CTRI/2023/02/049523. Research Sponsor: INHS ASVINI.

Baseline clinical features (n=30).

Clinical features	n	%
Age in years		
Median (range)	59 (31-75)	
Gender		
Male	11	36
Female	19	64
ECOG PS*		
1	21	70
2	9	30
Gallstones	12	41
Cholecystectomy	10	34
Jaundice at baseline		
Present	8	26
Absent	22	74
Site	26	87
Gallbladder	1	3
Cholangiocarcinoma	3	10
Intra-hepatic		
Extra-hepatic distal CBD**		
Weight in Kgs		
Mean (range)	58 (41-82)	
History of weight loss present	15	52
Co-morbidities		
Diabetes mellitus	7	23
Hypertension	8	26
Hypothyroidism	1	3
Angiotensin receptor blocker		
Losartan	28	94
Telmisartan	2	6
***ERBB2* positive**	2	6
Received Trastuzumab	2	100
Immunotherapy (Durvalumab)	5	17

*PS: Performance status, **CBD: Common bile duct.

4155 **Poster Session**

Optimizing biliary drainage in malignant biliary obstruction: A systematic review and meta-analysis of transpapillary versus suprapapillary stent positioning. First Author: Zainab Rafaqat, Department of Internal Medicine, College of Medicine, University of Oklahoma Health Campus, Oklahoma City, OK

Background: Malignant biliary obstruction causes significant morbidity and poor survival with 5-year survival rates below 10%. Effective biliary drainage is essential to relieve cholestasis, prevent infection, and improve quality of life. Endoscopic stenting is a standard intervention, but the optimal stent position remains unclear. Placement of a stent across the duodenal papilla can lead to duodeno-biliary reflux, subsequent stent dysfunction, while suprapapillary placement may reduce reflux and improve stent patency. We performed a systematic review and meta-analysis to compare the clinical outcomes of trans-papillary versus suprapapillary biliary stent placement in patients with malignant biliary obstruction. **Methods:** We conducted a comprehensive search of major electronic databases to identify studies comparing suprapapillary and transpapillary biliary stent placement. All relevant studies published up to November 2025 were considered. The clinical outcomes assessed included stent occlusion, stent patency, post-ERCP pancreatitis, cholangitis, and overall adverse events. Meta-analysis was performed, and the choice of a fixed-effects or random-effects model was determined based on the presence of heterogeneity across studies. **Results:** A total of 14 studies, including randomized controlled trials and retrospective cohort studies, encompassing 1,169 patients, compared suprapapillary with transpapillary biliary stent placement. Suprapapillary stenting was associated with a significantly lower risk of post-ERCP pancreatitis (OR 0.23, 95% CI 0.11–0.49; I^2 = 0%). Stent occlusion demonstrated a non-significant trend favoring suprapapillary placement (OR 0.68, 95% CI 0.46–1.01; I^2 = 46%). Stent patency duration was longer with transpapillary stents (SMD 0.66, 95% CI 0.27–1.05). Rates of cholangitis were similar between groups (OR 0.86, 95% CI 0.54–1.38). Overall, adverse events were significantly lower with suprapapillary stenting (OR 0.67, 95% CI 0.47–0.94; I^2 = 25%). **Conclusions:** Suprapapillary biliary stent placement appears to be safer than transpapillary stenting, with lower rates of post-ERCP pancreatitis and overall adverse events while still providing effective biliary drainage. However, its superiority over transpapillary placement in terms of stent occlusion and stent patency remains uncertain. These findings highlight the potential advantages of suprapapillary stenting but underscore the need for further large-scale randomized controlled trials before it can be established as the standard of care. Research Sponsor: None.

4156 **Poster Session**

Knowledge distillation–enabled ResNet framework for hepatocellular carcinoma diagnosis on multiphase CT: Toward scalable global deployment. First Author: Hammad Khan, Ayub Medical College, Abbottabad, Pakistan

Background: Hepatocellular carcinoma (HCC) accounts for 85–90% of primary liver cancers and remains a leading cause of cancer-related mortality worldwide. Early and accurate imaging-based diagnosis is critical for staging, treatment selection, and survival. Multiphase contrast-enhanced CT is widely used for HCC detection, yet diagnostic accuracy varies due to lesion heterogeneity and radiologist workload. Deep learning models demonstrate high performance but are computationally intensive, limiting deployment in resource-constrained settings. Knowledge distillation enables transfer of diagnostic capability from large teacher models to lightweight student networks while preserving accuracy. We evaluated a ResNet-based distillation framework for efficient HCC diagnosis using multiphase CT imaging. **Methods:** We analyzed a curated dataset of 140 pathologically confirmed HCC cases, comprising arterial, portal venous, and delayed-phase CT images annotated by two expert radiologists independently . A high-capacity ResNet152 teacher model was trained to detect and localize HCC lesions using hierarchical residual feature learning across multiphase inputs. A compact ResNet18 student model was trained via temperature-scaled knowledge distillation using soft probability targets and regularized cross-entropy loss. Performance was evaluated using accuracy, sensitivity, specificity, F1 score, and AUROC. Computational efficiency and inference latency were assessed to determine real-world deployment feasibility. **Results:** The ResNet152 teacher achieved robust diagnostic performance ($>$ 97% accuracy) for HCC detection across lesion sizes and locations. The distilled ResNet18 preserved near-teacher accuracy, achieving AUROC exceeding 0.93 with balanced sensitivity and specificity ($>$ 93%). Knowledge distillation reduced model parameters by over 80% and substantially lowered inference time, enabling real-time execution on standard clinical hardware. Performance remained consistent across lesion diameter and hepatic segment subgroups, comparable to expert radiologist assessment **Conclusions:** Knowledge distillation enables a lightweight ResNet18 model to retain near–ResNet152 diagnostic performance for HCC detection on multiphase CT while markedly reducing computational requirements. This scalable framework addresses key barriers to AI adoption in oncology imaging and supports global deployment of AI-assisted HCC diagnosis. Prospective multicenter validation is warranted to assess clinical impact on early detection and treatment planning. Research Sponsor: None.

4157 **Poster Session**

Correlative analysis of phase II trial of olaparib and durvalumab in patients with *IDH*-mutated cholangiocarcinoma. First Author: Xin Wang, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: *IDH1/2* mutations occur in ~25% of cholangiocarcinomas (CCAs). Preclinical studies suggest synergy between PARP inhibition and PD-L1 blockade. We previously conducted a phase II trial of olaparib plus durvalumab in advanced *IDH*-mutant CCA. We report matched baseline tissue and serial cell-free DNA (cfDNA)-based correlative analysis of pts samples. The primary objective was to develop a cfDNA methylome signature as a non-invasive biomarker. **Methods:** This single-arm, open-label phase II study (NCT03991832) enrolled patients with unresectable/metastatic *IDH*-mutant CCA and $\leq$2 prior lines of systemic therapy. Patients received olaparib 300 mg orally twice daily and durvalumab 1500 mg IV every 4 weeks. Blood samples were collected at baseline and monthly while on treatment for planned correlatives to examine R2HG, S2HG, and artemin levels using HPLC (High-Performance Liquid Chromatography). Cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) was performed on pts cfDNA samples and case-matched *IDH*-wildtype pts. Formalin-fixed, paraffin-embedded blocks of baseline tumor biopsies were used for multispectral fluorescent IHC (FL-IHC) using a 6-marker panel composed of pan-cytokeratin, CD4, CD8, CD163, PD-L1, and CD68. **Results:** Ten patients were enrolled (median age 63.5 y; 50% female; 90% received prior platinum). Median treatment duration was 1.95 mo (range 1.8–13.5). No complete or partial responses were observed. DCR was 30% (3 patients with stable disease); one patient remained on therapy for 13.5 mo before progression. Median PFS was 1.97 mo (95% CI 1.73–3.93). HPLC from baseline plasma showed lower baseline artemin levels correlated with stable disease (p=0.038), while R2HG/S2HG ratios showed no association with outcome. FL-IHC showed enriched immune cell populations, specifically $CD4^+$ T cells (p=0.0032) and a trend for $CD68^+$ macrophages (p=0.062), in the tumor stroma compared with tumor core. 54 plasma samples (from 8 patients) were profiled with cfMeDIP-seq along with 8 *IDH*-wildtype controls. Using top 100 differentially methylated regions, the circulating tumour DNA methylome exhibited a highly specific signature, accurately discriminating *IDH*-mutant and *IDH*-wildtype CCA regardless of treatment status. The specific differentially methylated gene pathways between groups were comprehensively examined in both on-treatment and baseline plasma samples. **Conclusions:** Advanced *IDH*-mutant CCA harbors an immune-excluded phenotype, which may underlie primary resistance to immunotherapy. Plasma cfDNA methylome signature can accurately discriminate CCA with *IDH* mutations. Clinical trial information: NCT03991832. Research Sponsor: None.

4158 **Poster Session**

The molecular landscape and clinical nomogram of cholangiocarcinoma harboring ESCAT I alterations. First Author: George Laliotis, Johns Hopkins University, Baltimore, MD

Background: Cholangiocarcinoma (CCA) is the second most common primary liver cancer, with rising global incidence and mortality. Despite molecular advances, most patients present with advanced disease unsuitable for curative resection, resulting in poor prognosis. ESCAT I alterations, including FGFR2 fusions, IDH1/IDH2 mutations, BRAF V600E, HER2 amplification, MSI-high, and NTRK fusions, represent validated therapeutic targets with FDA/EMA-approved treatments, occurring in 25% of CCAs. Here, we analyze genomic and transcriptomic data to characterize the molecular landscape and develop an OS nomogram for CCA patients with ESCAT I alterations. **Methods:** In this retrospective study, we analyzed publicly available data from 1928 CCA patients, enrolled in participating institutions between 2012 and 2022, sourced from the cBioPortal for Cancer Genomics. We investigated frequencies of ESCAT I alterations, copy number alterations, mRNA expression, clinicopathological factors, and OS. Transcriptomic profiling and pathway enrichment analysis identified survival-associated genes. A nomogram integrating clinical, pathological, and molecular features was constructed and validated for OS prediction. **Results:** Genomic analysis of 1,845 CCA samples revealed revealed *IDH1* mutations (12%), *FGFR2* fusions (8%), HER2 amplification (6%), *BRAF*V600E (4%), MSI-high (4%), *NTRK1/2/3* fusions (3.4%) and *IDH2* mutations (2%). Notably, ESCAT I alterations were associated with inferior OS (log-rank P = 0.009; mOS altered vs wild-type 33.84 vs 24.31 months). Transcriptomic and GSEA profiling linked these alterations to dysregulation of oncogenic pathways, including DNA damage repair, cell cycle regulation, epithelial-mesenchymal transition, and immune pathways. The prognostic nomogram incorporated age, stage, differentiation, ESCAT I subtype, and top 5 most significantly identified transcriptomic signatures. **Conclusions:** This study provides comprehensive molecular characterization of ESCAT I-altered CCA, revealing distinct genomic and transcriptomic profiles associated with specific alterations and oncogenic pathway dysregulation. The validated nomogram offers a practical tool for personalized OS prediction, potentially guiding treatment selection, surveillance intensity, and clinical trial stratification. These findings emphasize the importance of routine molecular profiling in CCA and support precision medicine integration to improve outcomes and target therapy resistance mechanisms in this population. Research Sponsor: None.

4159 **Poster Session**

First-line GemCis ± immunotherapy vs FGFR inhibition in ctDNA-detected *FGFR2* fusion–positive advanced cholangiocarcinoma: A real-world analysis. First Author: Richard D. Kim, Moffitt Cancer Center Magnolia Campus, Tampa, FL

Background: Advanced cholangiocarcinoma (aCCA) carries a poor prognosis. Approximately 40% of aCCA harbor targetable biomarkers; however, standard first-line (1L) therapy is gemcitabine-cisplatin (GemCis) ± immune checkpoint inhibitors (ICI), regardless of genomic status. Emerging data suggest that oncogene-driven molecular subsets of aCCA may exhibit reduced sensitivity to ICI, raising questions about the benefit of adding ICI to chemotherapy in genomically defined populations. Therefore, we compared outcomes for aCCA pts with ctDNA-detected *FGFR2* fusions (*FGFR2*+) treated with targeted therapy vs. GemCis ± ICI. **Methods:** Real-world data was sourced from InfinityAI Data Library, a database combining de-identified genomic information from Guardant360 (Guardant Health, Palo Alto, CA) and clinical data from administrative claims. aCCA pts with an *FGFR2* fusion detected prior to 1L therapy between Sept. 2018 and June 2025 were analyzed. Outcomes were assessed via real-world time to treatment discontinuation (rwTTD), real-world time to next treatment (rwTTNT) and real-world overall survival (rwOS) in months with 95% confidence intervals. Log-rank tests were used to compare Kaplan-Meier survival curves. **Results:** 149 *FGFR2*+ aCCA pts with treatment and outcomes data were identified. 18.1% (27) were treated with GemCis, 45.6% with GemCis + ICI (68), and 19.5% (29) with FGFRi. *FGFR2*+ pts treated with 1L FGFRi had improved rwTTD, rwTTNT, and rwOS compared to GemCis and GemCis + ICI, with significantly improved rwTTD in those treated with FGFRi vs GemCis + ICI (Table 1). Based on these data, the addition of ICI to GemCis was not associated with improved outcomes in *FGFR2*+ pts. **Conclusions:** Real-world outcomes in ctDNA-detected *FGFR2*+ aCCA did not improve with addition of ICI to 1L GemCis. In contrast, 1L FGFRi was associated with longer treatment duration and delayed need for subsequent therapy. These findings suggest standard chemo-immunotherapy may not be optimal for all biomarker-defined aCCA subgroups and support the use of ctDNA testing to inform biomarker-drive 1L treatment selection abd sequncing strategies, warranting prospective validation. Research Sponsor: None.

Outcomes in FGFR2+ pts by 1L therapy.

	rrwTTD	rrwTTNT	rrwOS
FGFRi vs GemCis	9.1 (4.9-11.5) vs 4.2 (2.3-6.2) HR=0.68, p=0.22	20.8 (8.3-20.8) vs 13.8 (5.6-30.3) HR=0.64, p=0.33	NR (16.9-NR) vs 17.5 (10.3-28.4) HR=0.48, p=0.16
FGFRi vs GemCis + ICI	9.1 (4.9-11.5) vs 5.2 (3.9-7.8) HR=0.62, p=0.03	20.8 (8.3-20.8) vs 8.9 (7.9-NR) HR=0.51, p=0.06	NR (16.2-NR) vs 20.9 (10.7-NR) HR=0.43, p=0.11
GemCis vs GemCis + ICI	4.2 (2.3-6.2) vs 5.2 (3.9-7.8) HR=0.91, p=0.91	13.8 (5.6-30.3) vs 8.9 (7.9-NR) HR=0.8, p=0.61	17.5 (10.3-28.4) vs 20.9 (10.7-NR) HR=0.89, p=0.69

4160 **Poster Session**

Durvalumab or pembrolizumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy for advanced cholangiocarcinoma: A meta-analysis. First Author: Abdullah Esmail, Houston Methodist Neal Cancer Center, Houston, TX

Background: Cholangiocarcinoma (CCA) is a rare, aggressive malignancy of the bile duct epithelium with rising incidence and mortality. Curative surgery is feasible in few cases; for unresectable or metastatic disease, systemic therapy is standard. Gemcitabine plus cisplatin (GemCis) has been the first-line backbone, but phase 3 trials (TOPAZ-1 and KEYNOTE-966) demonstrated overall survival (OS) benefit with added immune checkpoint inhibitors (durvalumab or pembrolizumab). This systematic review and meta-analysis evaluates the efficacy and safety of immunotherapy (IO) plus GemCis versus GemCis alone in advanced CCA. **Methods:** We systematically searched PubMed, Embase, Scopus, and Google Scholar for English-language studies (2009–2025) including randomized controlled trials (RCTs) and cohort studies of first-line GemCis alone or with durvalumab or pembrolizumab in unresectable/metastatic CCA. Primary endpoint: OS. Secondary: progression-free survival (PFS) and grade 3-4 adverse events (AEs) per CTCAE. Kaplan-Meier curves were digitized, and individual patient data reconstructed using IPD tools for pooled estimates. Random-effects models generated hazard ratios (HRs) and pooled medians; heterogeneity assessed via I^2. **Results:** We included 3,703 patients from TOPAZ-1, KEYNOTE-966, ABC-01/02, and six cohort studies: 1,737 on GemCis alone, 1,433 on GemCis + durvalumab, and 533 on GemCis + pembrolizumab. In the full meta-analysis, GemCis + durvalumab showed the best outcomes (median OS 14.1 months, PFS 7.38 months) versus GemCis + pembrolizumab (OS 12.8 months, PFS 6.62 months) and GemCis alone (OS 9.27 months, PFS 5.81 months). Restricting to RCTs only, IO + GemCis improved OS versus GemCis alone (median 12.82 vs. 11.1 months; HR 0.78, 95% CI 0.71–0.86, $p<0.001$), with no significant PFS difference (p=0.20). Grade 3-4 AEs were infrequent across arms; thrombocytopenia was higher with pembrolizumab (p=0.0002), but other severe toxicities were comparable. **Conclusions:** Adding immunotherapy to GemCis significantly enhances survival in unresectable/metastatic CCA, with durvalumab + GemCis providing the most pronounced benefit in this pooled analysis incorporating RCTs and real-world cohorts. Regimens were well-tolerated with manageable toxicity. These findings reinforce chemoimmunotherapy as first-line standard and highlight potential differential efficacy between PD-L1 and PD-1 inhibitors warranting further study. Research Sponsor: None.

4161 **Poster Session**

Real-world analysis of epigenomic molecular tumor-type prediction for biliary tract cancer in CUP. First Author: Daniel Hintz, Guardant Health, Palo Alto, CA

Background: Biliary cancers (BTC) are often diagnosed at advanced stages and can present as metastatic liver tumors, making determination of the primary site difficult, leading to frequent cancer of unknown primary (CUP) designations. Conventional histopathology or imaging may misclassify tumor origin, yet accurate distinction is essential because therapies differ for BTC and CUP. A novel liquid biopsy (LB) molecular tumor type (MTT) classifier using epigenomic signatures predicts tumor origin across 14 solid tumors with graded confidence. This study evaluated concordance, genomic features, and real-world outcomes of high-confidence MTT-BTC predictions in patients (pts) with BTC or CUP using the Infinity AI, a clinical-genomics and epigenomics database. **Methods:** Guardant360 LB results showing high-confidence (>80%) MTT predictions for BTC in pts with BTC or CUP listed on the test requisition form (TRF) were identified. Infinity AI links de-identified clinical, genomic, epigenomic, and administrative claims The LB assay interrogated >700 genes and thousands of methylation regions. First-line (1L) therapies were categorized as chemotherapy (chemo), immunotherapy (IO), or chemo-IO. Real-world time to treatment discontinuation (rwTTD) and time to next treatment (rwTTNT) were compared between TRF-BTC and TRF-CUP cohorts using log-rank tests. **Results:** Among pts with high-confidence MTT-BTC predictions (TRF-BTC n=410; TRF-CUP n=56), MTT accuracy for TRF-BTC was 51.7%. Female proportion was 58% (TRF-BTC) and 64% (TRF-CUP), respectively. Median ages for TRF-BTC and TRF-CUP pts were 68 years, respectively. The most frequent oncogenic mutations in TRF-BTC were *TP53* (34), *ARID1A* (8), *KRAS* (7), and *IDH1* (6); none had *FGFR2* . In TRF-CUP, common mutations included *TP53* (3), *ARID1A* (2), and *IDH2* (2). For TRF-BTC pts, rwTTD was longer with 1L IO+chemo vs IO or chemo alone (7.9 vs 4.3 vs 3.4 mo; $p<0.0001$). TRF-CUP pts showed similar, but non-significant trends. rwTTNT was longer for TRF-BTC pts receiving IO (p=0.00026) and trended higher for TRF-CUP (p=0.069). **Conclusions:** Guardant360 LB epigenomic–based MTT classifier consistently predicted biliary origin in pts labeled as BTC and in a subset labeled as CUP, with broadly concordant genomic features and real-world treatment patterns. CUP pts with high-confidence MTT-BTC predictions demonstrated outcomes that approximated those of TRF-BTC, supporting biologic similarity and suggesting that some CUP cases may represent occult BTC. These findings support consideration of MTT as a tool to refine uncertain diagnoses, guide BTC-aligned therapy selection (including targetable alterations), and improve clinical trial matching. Larger cohorts with longer follow-up and prospective validation are needed to define the impact of MTT-guided management on patient outcomes. Research Sponsor: None.

4162 **Poster Session**

An immune-related pathologic response score as a predictor of survival after immune checkpoint inhibitor–based conversion therapy in hepatocellular carcinoma. First Author: Yi-Jun Lu, Department of Hepatobiliary Surgery and Liver Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Immune checkpoint inhibitor (ICI) based conversion therapy is increasingly utilized in the management of initially unresectable hepatocellular carcinoma (HCC). However, the clinical significance of immune-related pathologic response (irPR) features remain poorly understood in HCC. **Methods:** We enrolled 217 HCC patients undergoing ICI-based conversion therapy followed by curative-intent resection and assigned them to discovery and validation cohorts (2:1). Thirteen immune-related pathological response (irPR) features—tumor-infiltrating lymphocytes, tertiary lymphoid structures, lymphoid aggregates, plasma cell infiltration, granulomas, neutrophils, foamy macrophages, cholesterol clefts, hemosiderin-laden macrophages, giant cells, neovascularization, necrosis, and mature fibrosis—were assessed on H&E-stained tumor bed sections. To explore differences in the tumor microenvironment, bulk mRNA sequencing was performed on FFPE samples from patients in the discovery cohort. **Results:** In the discovery cohort, four irPR features (tumor-infiltrating lymphocytes, lymphoid aggregates, neutrophils, and foamy macrophages) were integrated to construct the immunotherapeutic response score (ITRS), classifying patients as ITRSlow (0–1) or ITRShigh (2–4). $ITRS^{low}$ patients showed significantly improved OS (HR = 4.17; 95% CI 1.64–10.60; P = 0.003) and RFS (HR = 2.07; 95% CI 1.32–3.23; P = 0.001), with longer median RFS (32.3 vs 8.5 months). ITRS remained independently associated with OS (HR = 2.81; 95% CI 1.06–7.43; P = 0.038) and RFS (HR = 2.10; 95% CI 1.32–3.33; P = 0.002) and was validated in an independent cohort. FFPE transcriptomic profiling (n = 41) showed that $ITRS^{low}$ tumors were immune-inflamed, with enrichment of immune-related GO/KEGG pathways and globally higher immune/stromal infiltration (higher ESTIMATE immune/stromal scores, lower tumor purity; all $P < 0.001$). Unsupervised clustering identified hot/cold states, with hot tumors enriched in $ITRS^{low}$ (65.4% vs 13.3%, P = 0.003); $CD8^+$ T-cell infiltration was higher across MCPcounter/CIBERSORT/TIMER and was accompanied by stronger antigen presentation (MHC-II gene sets) and increased $CD8^+$ T-cell activation/cytotoxicity as well as exhaustion signatures (all $P < 0.05$), supporting an immune-active microenvironment linked to favorable outcomes. **Conclusions:** An irPR feature–based ITRS robustly predicts both OS and RFS in HCC patients following ICT. The ITRS is readily applicable in routine diagnostic pathology practice and provides novel insights into the biological mechanisms underlying immunotherapy resistance. Research Sponsor: National Natural Science Foundation of China; 82488101; National Natural Science Foundation of China; 82341027; National Natural Science Foundation of China; 82072715; National Natural Science Foundation of China; 82500694.

4163 **Poster Session**

Comparative outcomes of first-line atezolizumab plus bevacizumab (A+B) and durvalumab plus tremelimumab (D+T) in hepatocellular carcinoma (HCC). First Author: Sarina Ailawadi, Department of Medicine, University Hospitals, Case Western Reserve University, Cleveland, OH

Background: Standard first-line systemic therapy for hepatocellular carcinoma involves immune checkpoint inhibitors, including A+B and the STRIDE regimen consisting of D+T. However, there is limited data comparing outcomes of patients receiving these two regimens. We aimed to compare the survival and safety profiles of patients receiving A+B versus D+T as first-line systemic therapy for advanced HCC in a propensity score matched analysis. **Methods:** We performed a retrospective cohort study using data from TriNetX, a healthcare database of over 150 million patients in the United States. We identified adult patients with a history of HCC and included those who received A+B or D+T as first line treatment. Propensity score matching (PSM) was conducted, matching for patient demographics (age, sex, race), clinical history (alcohol use, ascites, esophageal varices, viral hepatitis), and laboratory parameters [platelets, albumin, bilirubin, INR, alpha-1-fetoprotein (AFP)]. Median overall survival (mOS) and relevant patient safety events were compared between those who received A+B or D+T. **Results:** We identified 2,762 patients who had HCC who were treated with A+B or D+T, of which 2,030 patients received A+B and 723 patients received D+T. Compared to patients in the A+B cohort, those who received D+T were more often older (68.5 vs 66.9 years, standardized mean difference (SMD) = 0.17), had lower platelet counts (186.4 vs 198.6, SMD = 0.11), had higher prevalence of ascites (33.1% vs 20.3%, SMD = 0.29), and alcohol use (23.8% vs 18.8%, SMD = 0.12). After PSM, 723 patients were included in survival analyses, with all variables adequately balanced except for albumin, which was higher in the A+B group (3.6 vs 3.5, SMD = 0.19). At 90 days after starting therapy, D+T was associated with higher incidence of immune-mediated colitis [5.3% vs 2.6%, odds ratio (OR) 2.1; 95% confidence interval (CI), 1.2-3.7], and a higher risk of hospitalization [35.4% vs 27.9%, OR 1.4; 95% CI, 1.1-1.8]. At 6 months, the risk of hypertension and proteinuria was higher in the A+B cohort [21.9% vs 13.7%, OR 0.57; 95% CI, 0.34-0.95], which persisted at 1 year [28.1% vs 16.5%, OR 0.51; 95% CI, 0.32-0.81]. There was no significant difference in mOS between those receiving A+B or D+T [18.3 months vs 22.8 months, hazard ratio (HR) 0.94; 95% CI, 0.79-1.1]. **Conclusions:** In patients with advanced HCC who received A+B or D+T as first-line systemic therapy, we found that A+B was associated with higher risk of hypertension and proteinuria, while D+T was associated with a higher risk of immune-mediated colitis and hospitalization. No significant difference in mOS was observed between the cohorts. These findings suggest that safety profiles, rather than survival differences, may be used to guide optimal first-line treatment regimens. Prospective studies are warranted to further assess differences in patient outcomes. Research Sponsor: None.

4164 **Poster Session**

DEB-TACE combined with apatinib and camrelizumab as second-line therapy for unresectable intrahepatic cholangiocarcinoma: A prospective, single-arm, phase II study. First Author: Xuegang Yang, Sichuan Cancer Hospital & Institute, Chengdu, Sichuan, China

Background: This study aimed to evaluate the efficacy and safety of drug-eluting bead transarterial chemoembolization (DEB-TACE) combined with Apatinib and Camrelizumab as second-line therapy for unresectable intrahepatic cholangiocarcinoma (ICC). **Methods:** This is a prospective, single-arm, phase II study. Eligible patients were those with unresectable ICC who had progressed after first-line gemcitabine-containing chemotherapy. These patients received DEB-TACE combined with Apatinib and Camrelizumab therapy. The primary endpoints were to assess the objective response rate (ORR) and disease control rate (DCR) in accordance with both Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 and modified RECIST (mRECIST) criteria. Secondary objectives included measuring progression-free survival (PFS), overall survival (OS), and safety profiles. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. **Results:** Twenty patients participated in this study. The ORR was 65% (95% confidence interval [CI]: 40.8%–84.6%) per mRECIST and 25% (95% CI: 8.7%–49.1%) per RECIST V1.1. The DCR was 95% (95% CI: 74%–99%) per mRECIST and 85% (95% CI: 62.1%–96.8%) per RECIST V1.1. The median PFS was 7.7 (95% CI: 5.5–9.8) months. The median OS was 13.2 (95% CI: 3.1–23.3) months. Treatment-related adverse events (TRAEs) occurred in all 20 (100%) patients. The most common TRAEs included decreased lymphocyte count, hypertension, and abdominal pain, with grade $\geq$3 TRAEs manageable via appropriate interventions. **Conclusions:** DEB-TACE combined with Apatinib and Camrelizumab as second-line therapy for unresectable ICC demonstrated promising efficacy and an acceptable safety profile, providing a viable treatment option for patients with unresectable ICC progressing after first-line gemcitabine-containing chemotherapy. Clinical trial information: NCT04834674. Research Sponsor: None.

4166 **Poster Session**

Outcomes of combined HCC-cholangiocarcinoma with adjuvant chemotherapy: An NCDB cohort. First Author: Maria Diab, Henry Ford Health/Michigan State University, Detroit, MI

Background: Combined (or mixed) hepatocellular carcinoma-cholangiocarcinomas (cHCC-CCA) are rare liver tumors that are associated with poor prognosis. Patients (pts) presenting with limited disease are candidates for curative intent surgery. However, the role of adjuvant chemotherapy is not established. **Methods:** This retrospective review was based on the National Cancer Data Base (NCDB) participant user file (PUF) from 2014 to 2022. Patients were identified using International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) topography (C22.0–22.1) and histology code 8180 for cHCC-CCA. Adjuvant chemotherapy was defined as chemotherapy administered on or after 6 weeks from surgery. Patients who had neoadjuvant chemo were excluded. Analytical stage variable captures data from pathological stage, and if pathological stage is missing, then clinical stage is captured. Pathological stage data were available only for 13% of pts. Hence, analytical stage was used with about 31% data available. Frequency and proportions were reported for categorical variables. Median overall survival (mOS) and corresponding 95% confidence intervals were reported using Kaplan-Meier (KM) estimates. Cox's proportional hazard model was used to report the adjusted and unadjusted analysis of OS. Hazard ratio (HR) and 95% confidence intervals were reported. All statistical analysis were performed using SAS version 9.4 software. Analysis of the NCDB PUF is exempt from IRB review. **Results:** 2815 pts with cHCC-CCA were identified, of which 2174 pts data were used for final analysis. 394 (18.1%) pts received adjuvant chemotherapy and 1780 (81.9%) did not receive any chemotherapy. 90% were above age 50 years; 76.2% were Caucasians and 67.7% were Male. Of those who received adjuvant chemotherapy, 162 (41.1%) received chemotherapy as single agent and 203 (51.5%) received chemotherapy as multiple agents. Among 668 data on analytic stage, 28.3% were stage 1, 36.8% were stage 2, 20.9% were stage 3 and 14.1% were stage 4. LVI data was also available for 549 patients. Of these, 38.1% had LVI present. Adjuvant chemotherapy was associated with improved OS compared to no chemotherapy (HR = 0.87 (95% CI: 0.77 – 0.99) p = 0.0296) in the entire population. Adjusted OS analysis for adjuvant chemotherapy with analytical stage showed significant survival benefit with adjuvant chemotherapy (HR = 0.73 (9%% CI: 0.56 – 0.96), p = 0.0261). Further adjustment for LVI was not performed due to large missing data. **Conclusions:** Adjuvant chemotherapy is not currently a standard for pts with cHCC-CCA after curative intent surgery. However, it appears to be associated with improved survival. Prospective studies evaluating the role of adjuvant therapy in this pt population are needed. Research Sponsor: None.

4168 **Poster Session**

Performance of a multi-cancer early detection test (MCED) for detecting small hepatocellular carcinoma (HCC) in a screening population. First Author: Gangchao Xu, Department of General Surgery, Huidong People's Hospital, Huizhou, China

Background: Early diagnosis of small HCC (defined as single nodule $\leq$ 3 cm) is crucial, as it represents the optimal window for curative treatments. Abdominal ultrasound with alpha-fetoprotein (AFP) is recommended for HCC surveillance in high-risk population. However, traditional modality detects only ~63% of small HCC, resulting in most HCC being diagnosed at advanced stages. Genie-Seq, a cfDNA-based MCED assay, covers 5 high-mortality cancers including HCC. Here, we report preliminary results evaluating the performance of Genie-Seq for small HCC in an asymptomatic screening population. **Methods:** Participants aged 40-74 years with no clinical suspicion of cancer were enrolled in a prospective, interventional study. All participants underwent Genie-Seq testing and standard-of-care (SOC) screenings according to the China Guidelines for Cancer Screening, including abdominal ultrasound and AFP. Genie-Seq detects cancer signals and localizes tissue-of-origin (TOO) simultaneously. Further HCC-focused diagnostic workup was performed per physician's discretion if: 1) suspicious findings on HCC screening, or 2) positive MCED results with liver as the top-predicted TOO. Diagnostic outcomes were reviewed for cancer status, TOO prediction accuracy, and stage. **Results:** As of December 2025, 1210 participants completed MCED testing and HCC screening. Nine participants were suspected of HCC and underwent further evaluation, with definitive diagnosis achieved in 7. Of these, 4 were confirmed as HCC (3 small HCCs, 1 stage II), 1 had synchronous gastric and colorectal cancers, and 2 had benign hepatic lesions. Genie-Seq identified all HCC cases with 100% TOO prediction accuracy, including 2 that were missed or initially misdiagnosed by traditional imaging. Patient 885 was exclusively identified by MCED, as no nodule was detected by ultrasound. Patient 888 had atypical features on contrast-enhanced CT/Gd-EOB-DTPA MRI (initial suspicion of inflammatory pseudotumor), and Genie-Seq positivity prompted contrast-enhanced ultrasound, leading to definitive diagnosis of small HCC. **Conclusions:** Genie-Seq exhibits excellent performance for small HCC detection in screening population, supporting it as a complementary tool to conventional preventive care and potentially improving curable HCC detection. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co. Ltd.

Diagnostic outcomes of participants achieved diagnostic resolution.

Participants	Suspicious Lesions Detected by Ultrasound	AFP (ng/ml)[1]	MCED Results	Diagnosis	Tumor Stage (AJCC)
0108	Yes	2.96	Negative	Hepatic cysts	
0572	Yes	4.25	Negative	Hepatic cavernous hemangioma	
0640	No	2.6	Positive	Multiple primary cancers	Gastric cancer: IIB Colorectal cancer: I
0723	Yes	58.55	Positive	HCC	II
0885	No	8.16	Positive	HCC	IA
0888	Yes	42.53	Positive	HCC	IB
0971	Yes	9.11	Positive	HCC	IA

[1]AFP levels of $<$ 7 ng/mL were defined as normal.

4169 **Poster Session**

Phase I/II, first-in-human study of yttrium-90 carbon microspheres in patients with unresectable hepatocellular carcinoma: Safety and early efficacy profiles. First Author: Lei Zhang, Department of Radiology, Center of Interventional Radiology and Vascular Surgery, Zhongda Hospital, Medical School, Southeast University, Nanjing, China

Background: Yttrium-90 microsphere selective internal radiation therapy (Y-90 SIRT) plays a significant role in the treatment of unresectable hepatocellular carcinoma. The phase I clinical study evaluated the safety and efficacy of Y-90 Carbon Microspheres Injection in patients with unresectable hepatocellular carcinoma. **Methods:** This multicenter, single-arm, prospective study was conducted across eight centers in China. It enrolled all eligible patients with uHCC who underwent radioembolization between 2023 and 2024. Eligibility criteria included unresectable hepatocellular carcinoma, Child-Pugh A cirrhosis, and an Eastern Cooperative Oncology Group performance status of 0-1. The primary endpoints included the incidence of adverse events and serious adverse events post-infusion, and the objective response rate in the treated area at first assessment according to mRECIST criteria. Among the 40 enrolled patients, 40.0% had an ECOG status of 0. According to China Liver Cancer Staging (CNLC), there were 12 cases (30.0%) in stage Ia, 9 cases (22.5%) in stage Ib, 6 cases (15.0%) in stage IIa, 4 cases (10.0%) in stage IIb, and 9 cases (22.5%) in stage IIIa of liver cancer. The median tumor size was 55.36 mm (range: 11.2–141.2). **Results:** All subjects received radioembolization as primary treatment, with a median tumor target absorbed dose of 450 Gy (range: 196.5 Gy-2000 Gy). According to the SPECT/CT results after treatment with NRT6003 injection, the median tumor absorbed dose was 429.93 Gy (range: 197.1 Gy-2827.7 Gy). As of February 21, 2025, the median follow-up of 9.5 months, a total of 221 treatment-related adverse events were reported, including 16 events of grade ≥3 and 2 serious adverse events (Upper abdominal pain, gastrointestinal bleeding). The best overall objective response rates were 92.5% (37/40) for whole-body and 97.5% (39/40) for local responses. The confirmed objective response rates were 82.5% (33/40) for whole-body and 85% (34/40) for local assessments. Six patients were re evaluated for surgical treatment due to tumor shrinkage. **Conclusions:** In this multicenter Y-90 SIRT study, treatment with Y-90 Carbon Microspheres demonstrated a favorable safety and efficacy were observed in the treatment of unresectable HCC, providing a highly promising treatment option. Clinical trial information: NCT06310590. Research Sponsor: None.

4170 **Poster Session**

Lanreotide for advanced gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in a Korean population: A multicenter prospective observational study (AIM-NETs). First Author: Changhoon Yoo, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are a heterogeneous group of malignancies. Somatostatin analogues (SSAs) are the standard of care for patients with unresectable or metastatic well-differentiated G1/G2 GEP-NETs. However, most pivotal data including the CLARINET trial were derived from Western cohorts. We prospectively evaluated the efficacy and safety of lanreotide in a real-world Korean cohort to bridge this geographic data gap. **Methods:** AIM-NETs is a prospective, observational, multicenter study of patients with unresectable or metastatic GEP-NETs treated with lanreotide. Patients received lanreotide 120 mg deep SC every 4 weeks (dose reduction to 90 mg permitted). Tumor response evaluation was done every 8 to 12 weeks according to the RECIST v1.1. The primary endpoint was the 2-year progression-free survival (PFS) rate. Secondary endpoints included median PFS and overall survival (OS), and safety. **Results:** Between Feb 2021 and Feb 2023, 71 patients were enrolled in five tertiary referral cancer centers in Korea. Median age was 59 years (range 25-82); 53.5% (n = 38) were male. Primary sites included pancreas (n = 40, 56.3%), rectum (8, 11.3%), colon (3, 4.2%) and stomach (3, 4.2%). Only two patients (2.8%) had functioning tumors. Tumor grades were G1 (n = 20, 28.2%), G2 (50, 70.4%) and G3 (1, 1.4%). The 2-year PFS rate was 50.6% (95% CI, 38.2%-63.0%) and median PFS was 26.0 months (95% CI, 15.2-32.7). The 2-year OS rate was 89.9% (82.9%-97.0%); median OS was not reached. The objective response rate was 23.5% (95% CI, 14.1%-35.4%). Higher tumor grade was significantly associated with worse PFS ($p < 0.0001$) and OS ($p < 0.0001$). High somatostatin receptor expression (Krenning score of 3 or higher on baseline Ga-68 DOTATOC scan) did not significantly correlate with PFS (p = 0.358) or OS (p = 0.199). No new safety signal of lanreotide were identified. **Conclusions:** Lanreotide provides robust disease control and a manageable safety profile in Asian patients with advanced GEP-NETs. The observed efficacy, including a favorable ORR, supports lanreotide as a standard of care in this population, aligning with previous clinical trial outcomes. Clinical trial information: NCT04696042. Research Sponsor: Ipsen.

4171 **Poster Session**

Quality of life in patients with gastroenteropancreatic neuroendocrine tumors receiving ^{177}Lu-edotreotide or everolimus: Results from the COMPETE study. First Author: Jaume Capdevila, Hepatobiliary Pancreatic Cancer and Endocrine Tumors Group, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: The Phase 3 COMPETE trial demonstrated a significant treatment effect in favor of ^{177}Lu-edotreotide over everolimus in patients with Grade 1/2, well-differentiated, gastroenteropancreatic neuroendocrine tumors; ^{177}Lu-edotreotide significantly improved progression-free survival (primary endpoint) and objective response rate (secondary endpoint) compared to everolimus. Nowadays, treatment choice also considers the impact of therapy on patients' quality of life (QoL); here, we present QoL results from the COMPETE trial. **Methods:** The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and EORTC QLQ-gastrointestinal neuroendocrine tumors (GI.NET) were completed by patients at baseline, each month during the first year, and every 3 months thereafter until disease progression or end of study. Mean change from baseline, duration of maximum health-related quality of life (HRQoL) improvement (until deterioration), and time to deterioration were calculated. Between-group comparisons were conducted using repeated measure analysis with factors for treatment, randomization stratification factors, visit, baseline value, and treatment-by-visit interaction; all HRQoL analyses were prespecified and exploratory. **Results:** Based on repeated measure analysis, mean change from baseline was in favor of ^{177}Lu-edotreotide: overall mean change (95% confidence interval [CI]) in global health score was 0.9 (-2.7, 4.4) in the ^{177}Lu-edotreotide arm vs -9.9 (-13.9, -6.0) in the everolimus arm (nominal $p<0.0001$) (positive change corresponds to improvement). Time to deterioration in global health status/QoL was longer in the ^{177}Lu-edotreotide arm vs the everolimus arm (Table 1). Similar trends were observed in the EORTC QLQ-C30 and EORTC QLQ-GI.NET subdomains. In the ^{177}Lu-edotreotide arm, 90/207 (43.5%) participants had a clinically meaningful improvement (≥10 points) in global HRQoL score, vs 31/102 (30.4%) participants in the everolimus arm. Among these participants, the median duration of improvement was 22.0 (95%CI: 10.1, not evaluable [NE]) vs 10.2 (95%CI: 3.3, NE) months in the ^{177}Lu-edotreotide and everolimus arm, respectively. **Conclusions:** Consistent with the overall COMPETE outcomes, this analysis demonstrated clinically meaningful and durable HRQoL benefits for ^{177}Lu-edotreotide compared with everolimus. Clinical trial information: NCT03049189. Research Sponsor: None.

Time to deterioration in global health status/QoL (≥10 points).

Parameter / Statistics	^{177}Lu-edotreotide (N=207)	Everolimus (N=102)
Patients with ≥10 points deterioration, n (%)	114 (55.1)	78 (76.5)
Median, months (95% CI)[a]	10.251 (7.359, 15.901)	2.267 (2.004, 3.253)
Nominal stratified p-value[b]	<0.0001	
Stratified hazard ratio (95% CI)	0.392 (0.292, 0.527)	

[a]Estimated via Kaplan-Meier method.
[b]Derived from a two-sided test between the two groups.

4172 **Poster Session**

Organotropic and genomic characterization of pancreatic neuroendocrine carcinoma. First Author: Sara Wallam, Columbia University Irving Medical Center, New York, NY

Background: Pancreatic neuroendocrine carcinoma (PNEC) is a rare, aggressive malignancy. Neuroendocrine carcinomas (NEC) of other primary sites, such as small cell lung cancer (SCLC), have a propensity to metastasize to the brain. Incidence of brain metastases in PNEC is poorly characterized, and most staging recommendations for extrapulmonary NEC do not include routine brain imaging. We evaluated the incidence of brain metastases in PNEC, identified factors associated with brain metastases, and characterized the genomic profile of PNEC. **Methods:** We reviewed the genomic profile of patients with PNEC, pancreatic ductal adenocarcinoma (PDAC), SCLC, and pulmonary large cell neuroendocrine carcinoma (LCNEC), who underwent next generation sequencing (NGS) at Memorial Sloan Kettering Cancer Center (MSKCC). We queried the Surveillance, Epidemiology, and End Results (SEER) database to identify all cases of metastatic PDAC and small cell or large cell PNEC diagnosed 2010-2022. We performed multivariable logistic regression to identify demographic and clinical factors associated with brain metastases. We used chi-squared testing to compare metastatic site frequency between tumor types. **Results:** The SEER query identified 412 cases of metastatic PNEC and 60,668 cases of metastatic PDAC with documented site of metastasis at diagnosis. Compared to PDAC, PNEC had higher rates of metastasis to the brain (8% vs 0.8%, $p<0.001$), bone (16% vs 9%, $p<0.001$), and distant lymph nodes (15% vs 8%, $p<0.001$) but lower rates to the lung (19% vs 25%, p=0.03). The incidence of liver metastases was similar in both tumor types (88% vs 87%). Within the PNEC cohort, lung metastasis was positively associated with brain metastasis (odds ratio [OR] 5.4, 95% confidence interval [CI] 2.4-12.5, $p<0.001$), but liver metastasis was negatively associated with brain metastasis (OR 0.2, 95% CI 0.1-0.5, $p<0.001$). The presence of brain metastases did not impact overall survival. Twenty eight patients with PNEC underwent NGS at MSKCC, including 12 with mixed ductal-neuroendocrine carcinoma or mixed acinar-neuroendocrine carcinoma. TP53 alterations were common (>50%) in all tumor types. RB1 alterations were seen frequently in SCLC (78%), PNEC (54%), and LCNEC (24%), but not in PDAC (2%). KRAS alterations were highly prevalent in PDAC (84%), uncommon in SCLC (3%), and with intermediate frequency in PNEC (36%). **Conclusions:** We found a high incidence of brain metastasis in PNEC, especially in patients with lung metastases, supporting neuroimaging in many patients with this disease. The strong association between lung and brain metastases is also noted in breast cancer, possibly explained by sequential seeding or shared features driving organotropism to these organs. PNEC demonstrated genomic features of both PDAC and SCLC. More research is needed to determine how these genomic features can inform management practices in individual patients. Research Sponsor: None.

4173 **Poster Session**

Cohort-level safety and efficacy results for [^{212}Pb]VMT-α-NET in advanced somatostatin receptor subtype 2 (SSTR2+)–expressing neuroendocrine tumors (NETs): Cohorts 1–3. First Author: Thorvardur Ragnar Halfdanarson, Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background: [^{212}Pb]VMT-α-NET is an alpha-particle radiation-delivering agent targeted to somatostatin receptor type 2 (SSTR2)-expressing tumors. Here, we present safety and efficacy results from the dose-finding phase 1/2a clinical trial (NCT05636618). **Methods:** This phase 1/2a dose-escalation study uses a Bayesian algorithm to identify an optimal dose of [^{212}Pb]VMT-α-NET for participants with advanced, well-differentiated NETs expressing SSTR2. Eligible participants must have unresectable or metastatic disease, documented radiologic progression following at least one prior systemic treatment, and evidence of SSTR2 expression (Krenning Score ³2) in ≥1 lesion confirmed on an FDA-approved somatostatin receptor PET scan. Patients previously treated with systemic peptide receptor radionuclide therapy (PRRT) are excluded from enrollment. During the dose-finding phase, participants may receive up to four administrations of [^{212}Pb]VMT-α-NET at their assigned dose level, and they are monitored for dose-limiting toxicities (DLTs) for 42 days and safety throughout the study. Efficacy is evaluated by investigators according to RECIST criteria v1.1. Dosimetry is included as a supportive analysis. **Results:** As of the 10-Dec-2025 data cut-off (DCO), 56 participants had been enrolled across Cohorts 1, 2, and 3 and received at least one dose of [^{212}Pb]VMT-α-NET: 2 participants in Cohort 1 (2.5 mCi), 46 in Cohort 2 (5 mCi), and 8 in Cohort 3 (6 mCi). No dose-limiting toxicities, grade 5 adverse events, treatment-related discontinuations, serious renal events, dysphagia, or clinically meaningful treatment-related myelosuppression were observed. The median follow-up for all treated participants was 40 weeks (range 6–97). Efficacy has been summarized in this abstract for 25 participants (2 in Cohort 1 and 23 in Cohort 2). Nineteen of these 25 participants remained progression-free at the time of the DCO, with a median efficacy follow-up of 49 weeks (range 6–97). In Cohort 2, investigators observed RECIST v1.1 objective responses in 9 of 23 participants (39%), including 8 confirmed responses. Both participants in Cohort 1 continued to exhibit stable disease after two years of follow-up. Updated safety for all participants and updated efficacy for participants with sufficient maturity beyond the 25 summarized here will be presented at the congress. **Conclusions:** Treatment with [^{212}Pb]VMT-α-NET continues to demonstrate a favorable safety profile across all treated participants (n = 56) and shows signs of sustained efficacy at the 2.5 mCi and 5 mCi dose levels. The therapy has been well-tolerated with no observed dose-limiting toxicities or serious treatment-related adverse outcomes. Based on these encouraging safety and efficacy findings, the study is ongoing, and enrollment into Cohort 3 (6 mCi) remains active. Clinical trial information: NCT05636618. Research Sponsor: None.

4174 **Poster Session**

DISCO update: Diagnostic performance of ^{64}Cu-SARTATE compared to ^{68}Ga-DOTATATE in patients with known or suspected neuroendocrine tumors. First Author: Eva Lengyelova, Clarity, Sydney, NSW, Australia

Background: Diagnostic imaging is critical in the management of neuroendocrine tumors (NETs). ^{64}Cu-SARTATE may provide advantages over existing imaging agents due to its longer half-life and sarcophagine chelator, with a potential to accurately detect additional disease in NETs. **Methods:** This multi-center Phase II study assessed the safety and efficacy of ^{64}Cu-SARTATE (200 MBq) in participants with known or suspected gastroenteropancreatic (GEP)-NETs (NCT04438304). (SARTATE; at 4 ± 1 h and 20 ± 4 h post-injection) were assessed by two independent blinded central readers, and . Discordant lesions (only present on either DOTATATE or SARTATE PET/CT) were subsequently evaluated by an independent assessor against a standard of truth (SOT; biopsy and/or follow-up conventional imaging). The per-lesion sensitivity (SE) for discordant lesions was calculated for both SARTATE and DOTATATE (SE=proportion of true positive foci / [true positive foci + false negative foci]). Lesion detection rate (DR) was calculated for a composite (best-case scenario) lesion detection across both SARTATE time points and for DOTATATE (DR= total number of lesions detected on scan / total number of lesions on scan pair). Values express the averages across readers and both PET/CT time points (for SARTATE). **Results:** 45 participants were enrolled and received SARTATE (41 known and 4 suspected NETs). Most had stage 3 or 4 disease. The mean number of foci detected by SARTATE was 441 vs. 227 by DOTATATE. A total of 238 discordant foci were identified in 34 participants; 223 of these were detected by SARTATE alone and 15 by DOTATATE alone. For the 122 discordant foci with evaluable SOT, the difference in SE for SARTATE vs. DOTATATE was statistically significant 94.7% [95% CI 65.1, 99.5] for SARTATE vs. 5.4% [95% CI 0.5, 34.9] for DOTATATE; $p<0.001$). The lesion DR was 97.2% [95% CI 75.9, 99.5] for SARTATE and 44.4% [95% CI 32.3, 57.5] for DOTATATE. The liver had the highest number of foci detected by both tracers (352 foci on SARTATE vs. 180 on DOTATATE) among all regions. Seven (15.6%) participants experienced 9 SARTATE-related AEs; 8 were Grade 1 and one was Grade 2, with most resolving within 2 days. **Conclusions:** ^{64}Cu-SARTATE was found to be safe and well-tolerated in patients with GEP-NETs. SARTATE lesion detection was higher than that of DOTATATE, with the liver having the highest number of lesions identified. SARTATE was able to detect additional true positive lesions compared to DOTATATE. The enhanced diagnostic performance offered by SARTATE, especially in key organs affected by GEP-NETs, may have important clinical implications to inform treatment decisions. A phase III study of ^{64}Cu-SARTATE in NETs is being planned. Clinical trial information: NCT04438304. Research Sponsor: None.

4175 **Poster Session**

Genomic and biomarker landscape of MTAP deficiency in gastrointestinal cancers. First Author: Rohit Thummalapalli, Memorial Sloan Kettering Cancer Center, New York City, NY

Background: Genomic loss of *MTAP* and *CDKN2A* is frequently observed across cancers, with ongoing development of MTA-selective PRMT5 inhibitors aiming to achieve synthetic lethality in the setting of MTAP loss. However, the biomarker landscape of patients with gastrointestinal (GI) cancers and MTAP deficiency remains poorly defined, and whether subsets of GI cancers harbor non-genomic mechanisms of MTAP deficiency remains unknown. **Methods:** All GI cancer samples sequenced with MSK-IMPACT v7, a DNA-based next generation sequencing (NGS) panel with coverage for *MTAP*/*CDKN2A* were queried. *MTAP* and *CDKN2A* deletions (del) were defined by low read counts in coverage-based copy number analyses. Genomic and pathologic analyses were completed in tumors with high *MTAP* del prevalence: esophagogastric cancers (EGC), pancreatic adenocarcinoma (PDAC), pancreatic neuroendocrine tumors (PanNETs), and biliary tract cancers (BTCs). MTAP immunohistochemistry (IHC) was completed on PDAC, PanNET, small bowel NET, and BTC samples to investigate prevalence of MTAP protein loss. **Results:** Among 8346 GI cancer samples, *MTAP* del was identified in 456 (5.5%), co-occurring with *CDKN2A* del in 98.8% of cases, with 79.8% confirmed homozygous del by FACETS, and was associated with higher tumor purity compared to *MTAP*-intact samples ($p < 0.001$). *MTAP* del prevalence was 14.4% in esophageal squamous cell carcinoma (SCC), 5.9% in esophagogastric adenocarcinoma (EGA), 12.4% in PDAC, 7.4% in PanNET (grade 1 [G1]: 3.4%, G2: 4.3%, G3: 19.4%), 0% in small bowel NET, 10.2% in BTCs (including 11.5% in intrahepatic cholangiocarcinoma [iCCA]), and 0.7% in colorectal cancer. *MTAP* del was associated with wild-type (WT) *KRAS* amplifications (amp) in EGC, *KRAS G12V* and WT *KRAS* amp in PDAC, and *KRAS* mutations and *FGFR2* fusions in iCCA. Among EGA, PDAC, and BTCs, *MTAP* del tumors were associated with higher fractions of genome altered ($p < 0.001$ for each) and rates of whole genome duplication ($p < 0.001$ for each). Among 463 samples profiled by MTAP IHC, MTAP deficiency was found in 29/93 (31%) PDAC, 3/33 (11%) BTC, 15/60 (25%) PanNETs, and 196/277 (71%) small bowel NETs. Analysis of MTAP deficiency and activity of standard systemic therapies, as well as metabolomic and epigenomic profiling of MTAP-deficient GI cancers are ongoing and will be presented. **Conclusions:** *MTAP* genomic del are recurrently identified across GI cancers, most notably in esophageal SCC, PDAC, G3 pancreatic NETs, and iCCA. *MTAP* del are associated with distinct genomic drivers across GI cancers and markers of chromosomal instability more broadly. We found evidence of discrepancy between MTAP loss by NGS and IHC across multiple GI cancers, most notably small bowel NETs, which demonstrate frequent MTAP IHC deficiency in complete absence of genomic loss, suggesting non-genomic mechanisms of MTAP silencing. These observations may help define the role for therapies targeting MTAP deficiency in GI cancers. Research Sponsor: U.S. National Institutes of Health.

4176 **Poster Session**

A multicenter single-arm study of induction EC/EP plus camrelizumab followed by maintenance camrelizumab plus apatinib in treatment-naive advanced or metastatic extrapulmonary neuroendocrine carcinoma. First Author: Yuhong Dai, Department of Oncology, Tongji Hospital, Huazhong University of Science and Technology, Wuhan, China

Background: Extrapulmonary neuroendocrine carcinoma (EP-NEC) is a poorly differentiated and highly aggressive malignancy with poor prognosis. Platinum (cisplatin or carboplatin) plus etoposide (EC/EP) remains the standard first-line regimen. However, clinical outcomes are suboptimal, highlighting the need for more effective strategies. Camrelizumab is a programmed cell death-1 (PD-1) inhibitor, and apatinib is a vascular endothelial growth factor receptor-2 (VEGFR2) inhibitor. Both have demonstrated antitumor activity in multiple solid tumors. Therefore, we investigated a sequential regimen consisting of induction EC/EP plus camrelizumab followed by maintenance camrelizumab plus apatinib in treatment-naive patients with advanced or metastatic EP-NEC. **Methods:** This multicenter, single-arm trial enrolled patients with previously untreated advanced or metastatic EP-NEC. Patients received 4–6 cycles of induction therapy with cisplatin (25 mg/m² iv, d1-3, q3w) or carboplatin (AUC = 5 iv, d1, q3w) plus etoposide (100 mg/m² iv, d1-3, q3w) in combination with camrelizumab (200 mg iv, d1, q3w). Patients without disease progression received maintenance camrelizumab (200 mg iv, q3w) plus apatinib (250 mg, qd) until progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. Tumor response was assessed every 6 weeks per RECIST v1.1. The trial is registered on ClinicalTrials.gov, NCT05142865. **Results:** As of January 2026, 30 patients were enrolled (median age of 59.5 years, range 30–73), and all 30 patients were evaluable for efficacy. The ORR was 66.7% and the DCR was 83.3%. Median PFS was 9.87 months (95% CI, 6.23–NA). Median OS was not reached, and the 1-year OS rate was 74.6%. All patients experienced adverse events (AEs), with grade ≥3 AEs observed in 43.3% (13/30). Grade ≥3 AEs were mainly hematologic toxicities, including anemia (13.3%), neutropenia (13.3%) and thrombocytopenia (13.3%). Common non-hematologic AEs included elevated transaminases (43.3%), mainly grade 1–2, with grade ≥3 events in 10.0%. **Conclusions:** Induction EC/EP plus camrelizumab followed by maintenance camrelizumab plus apatinib showed encouraging activity and manageable safety in treatment-naive advanced or metastatic EP-NEC. Further studies are warranted to confirm these findings. Clinical trial information: NCT05142865. Research Sponsor: Natural Science Foundation of Hubei Province of China; No. 2023AFB1059.

4177 **Poster Session**

Postoperative pancreatic fistula after resection of pancreatic neuroendocrine tumors: Incidence, predictors, and clinical impact. First Author: Oliver Overheu, Department of Hematology and Oncology with Palliative Care, St. Josef Hospital, Ruhr University, Bochum, Germany

Background: Postoperative pancreatic fistula (POPF) remain a major source of morbidity after pancreatic surgery. Data specific to pancreatic neuroendocrine tumors (pNETs) are limited, although these neoplasms differ biologically and surgically from pancreatic adenocarcinoma, potentially influencing POPF risk and outcomes. This study evaluated the incidence, predictors, and clinical impact of POPF in a well-characterized cohort of patients undergoing resection for pNETs. **Methods:** All patients who underwent resection for histologically confirmed pNETs between 2010-2019 at a tertiary center were retrospectively analyzed. Clinicopathological parameters and surgical procedures were assessed for association with POPF occurrence and severity according to the International Study Group on Pancreatic Fistula (ISGPF) criteria. Statistical analyses included χ^2, Fisher's exact, Spearman correlation tests, and multivariable regression analysis; significance was defined as $\alpha = 0.05$. **Results:** Among 106 patients (44% female, mean age 61 ($\pm$ 13.5) years), 85% received a formal pancreatic resection, 15% an atypical resection. More than half (53%) of pNETs were located in the pancreatic tail. The majority (64%) of tumors were G1, only 4% G3, with 72% of diseases in early stages UICC I or II. 12% of pNETs were functional and exclusively insulinomas. 53 patients (50%) developed a POPF, predominantly Grade B (60%), followed by Grade A (34%) and Grade C (6%). No surgery- or POPF-related mortality was observed. POPFs were most frequent after distal pancreatectomy for tail lesions (60% vs. 23% body vs. 17% head; p = 0.065), and in functional pNETs (77% vs. 46% in non-functional pNETs; p = 0.072). Distant metastases were inversely associated with POPF (M0 54% vs. M1 28%; p = 0.043). A nonsignificant trend toward higher POPF rates was observed after atypical resections (73% vs. 48%; p = 0.095). Higher POPF grade was associated with female sex (p = 0.016), and tumor proliferation index (p = 0.046); female sex remained independently associated with POPF grade in multivariable regression analysis (beta = 0.334, p = 0.044). Patients with POPF exhibited lower long-term mortality during follow-up (8% vs. 29%; p = 0.009) and lower mean preoperative chromogranin A levels (82.8 ng/mL vs. 167.8 ng/mL; p = 0.038). **Conclusions:** POPF occurred in half of all pNET resections, most commonly of Grade B severity. Tumor location, functionality, and absence of metastases were associated with higher POPF risk, and female sex with higher grade POPF. The association of POPF with lower long-term mortality likely mirrors the favorable tumor biology and localized disease profile of patients selected for curative surgery. This underscores the long-term oncological benefit of surgical resection in pNETs and provides relevant insights for postoperative risk stratification and perioperative management. Research Sponsor: None.

4178 **Poster Session**

Efficacy and safety of cabozantinib (CABO) in advanced neuroendocrine tumors (NET) according to hormone functional status: Subgroup analysis of phase 3 CABINET trial (Alliance A021602). First Author: Nikolaos Trikalinos, Siteman Cancer Center, Washington University School of Medicine, Saint Louis, MO

Background: In the CABINET trial, CABO significantly prolonged progression-free survival (PFS) compared to placebo (PB) in patients (pts) with advanced, previously treated extrapancreatic NET (epNET) or pancreatic NET (pNET) (Chan et al., NEJM, 2025). Here we report outcomes according to functional status based on NET hormone secretion. **Methods:** Pts with locally advanced or metastatic epNET or pNET were randomized 2:1 in separate cohorts to receive CABO 60 mg daily vs PB. Eligibility included progression by RECIST within 12 months (mo) before registration, $\geq$ 1 prior systemic therapy not including somatostatin analogs (SSA). Pts with functional NET due to hormone secretion and non-functional NET were included. In this post hoc subgroup analysis, we analyzed PFS by blinded independent central review and adverse events for pts receiving CABO vs PB based on functional status. Cox regression models were used with stratification on primary tumor site (epNET vs pNET). Subset analyses to evaluate treatment arm differences were conducted in pts with functional and non-functional tumors. Due to small numbers, separate results for those with unknown functional status are not included. **Results:** Of the total 298 pts enrolled in both cohorts, 74 had a functional NET (CABO, n = 47; PB, n = 27); 179 had a non-functional NET (CABO, n = 123; PB, n = 56); 45 had unknown functional status (CABO, n = 28; PB, n = 17). For functional NET, primary tumor sites were GI tract (n = 50; 68%), pancreas (n = 15; 20%), unknown (n = 4; 5%), lung (n = 3; 4%), and thymus (n = 2; 3%). Secreted hormones that were reported included serotonin (55%), somatostatin (18%), gastrin (16%), glucagon (4%), insulin (4%), ACTH (1%), and vasoactive intestinal peptide (1%). For non-functional NET, primary tumor sites were pancreas (n = 75; 42%), GI tract (n = 42; 23%), lung (n = 30; 17%), unknown (n = 17; 9%), thymus (n = 8; 4%), and other (n = 7; 4%). Concurrent SSA was received by 91% and 53% of pts with functional and non-functional NET, respectively. In both subgroups, CABO was associated with improved PFS compared to PB (for functional NET: stratified hazard ratio [sHR], 0.40; 95% confidence interval [CI]: 0.20-0.82, P = 0.012; for non-functional NET: sHR, 0.26; 95% CI: 0.17-0.41, P $<$ 0.001). The most frequent grade 3/4 adverse events (AEs) attributed to CABO vs PB in pts with functional NET included hypertension (21% vs 11%), diarrhea (9% vs 11%), and fatigue (2% vs 15%); in pts with non-functional NET, grade 3/4 AEs included hypertension (21% vs 4%) and fatigue (18% vs 4%). **Conclusions:** Subset analyses of the CABINET trial suggest that CABO is an effective treatment option for pts with functional and non-functional epNET or pNET. Efficacy and safety results for pts with functional or non-functional NET treated with CABO are consistent with results for the entire trial. Clinical trial information: NCT03375320. Research Sponsor: National Cancer Institute; U10CA180821, U10CA180882; U10CA180820 (ECOG-ACRIN); U10CA180868 (NRG Oncology); U10CA180888 (SWOG); 5U24CA180803 (IROC). https://acknowledgments.alliancefound.org.; Exelixis, Inc.

4180 **Poster Session**

Immune microenvironment signatures as prognostic biomarkers in gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC). First Author: Ruoyu Miao, Emory University School of Medicine, Atlanta, GA

Background: GEP-NEC is an aggressive malignancy with rising incidence and limited therapeutic options. While immune checkpoint inhibitors (ICIs) have become standard of care in small cell lung cancer (SCLC), their role in GEP-NEC remains undefined. Characterizing immune cell signatures in the tumor microenvironment (TME) across different NEC histologies may help identify prognostic biomarkers and guide immunotherapy strategies. **Methods:** We included 4863 NEC tumors that underwent DNA (592-gene panel, whole exome) and RNA (whole transcriptome) sequencing at Caris Life Sciences. Composition of the TME was estimated from bulk RNA sequencing using QuanTIseq method. Overall survival (OS) and IO-associated OS (IO-OS) were derived from insurance claims and calculated from date of tumor biopsy (OS) or IO initiation (IO-OS) to last contact using Kaplan-Meier estimates and Cox proportional hazards models. Statistical significance was determined by Fishers Exact, Chi-square and Mann-Whitney U test with adjustments for multiple comparisons ($P<$ 0.05). **Results:** The cohort was comprised of small cell (SCNEC, n = 2320), large cell (LCNEC, 618), high-grade NEC (HGNEC, 414) and NEC not otherwise specified (NOS, 1511). Primary sites included lung (2642), pancreas (459), non-pancreatic GI (931) and other sites (831). SCNEC had lower Treg, M1 or M2 macrophage and neutrophils, and higher CD4+ T-, NK-, B- and dendritic-cell infiltration than other histologies, suggesting more lymphocyte-driven immune milieu with reduced myeloid-driven suppression. Compared with lung NEC, GEP-NEC demonstrated a more immunosuppressive TME, characterized by lower NK-, B- and dendritic-cell infiltration and higher Treg, M1/M2 macrophage and neutrophils—most pronounced in non-pancreatic GI primaries. Pancreatic NEC had reduced dendritic cells in LCNEC, HGNEC and NOS subtypes and higher neutrophils in HGNEC and NOS. Elevated B-cell infiltration was associated with improved OS in SCNEC of non-pancreatic GI (HR 0.56, 95%CI 0.37-0.85, *P*= 0.032) and lung (HR 0.81, 0.72-0.90, *P*= 0.001) origin. High M2 macrophage and NK-cell scores were associated with prolonged OS in NOS of non-pancreatic GI (M2: HR 0.35, 0.28-0.45, $P<$ 0.001; NK: HR 0.32, 0.26-0.41, $P<$ 0.001) and pancreas (M2: HR 0.46, 0.33-0.62, $P<$ 0.001; NK: HR 0.64, 0.48-0.84, *P*= 0.010) origin. Among patients receiving ICIs (n = 1811, 910 with SCLC), only higher B-cell infiltration was associated with improved IO-OS in SCLC (HR 0.79, 0.68-0.92, *P*= 0.029); data was insufficient to analyze IO-OS for other histologic and anatomic subgroups. **Conclusions:** GEP-NEC exhibits a distinct and relatively immunosuppressive TME compared with lung NEC. B-cell, NK-cell, and macrophage signatures are prognostic across GEP-NEC subtypes. These findings support further evaluation of immune-based stratification and biomarker-driven therapeutic development in GEP-NEC. Research Sponsor: None.

4181 **Poster Session**

Therapy-related myeloid neoplasms after radioligand therapy in neuroendocrine tumors: A multicenter real-world analysis. First Author: Deevyashali Parekh, SUNY Upstate Medical University, Syracuse, NY

Background: Therapy-related myeloid neoplasms (t-MNs), including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), represent a rare but serious long-term hematological toxicity associated with radioligand therapy (RLT). Real-world data on the incidence of t-MNs and associated risk factors following RLT in are limited. We sought to investigate the incidence and risk factors of t-MN in patients with NETs treated with 177Lu-Dotatate. **Methods:** We conducted a multicenter retrospective cohort study using the TriNetX research network. Adult patients with NETs who received 177Lu-Dotatate were identified, with first administration defined as the index date. The primary outcome was development of t-MNs (incident MDS or AML) with a 12-month latency period after target treatment. Incidence was calculated and Cox proportional hazards models were used to evaluate associations between baseline covariates and t-MN risk. Covariates included age, sex, race, primary tumor site (small bowel, colon, pancreas, lung), liver and bone metastases, prior alkylating chemotherapy (temozolomide exposure), chronic kidney disease (CKD), and nicotine or alcohol dependence. Treatment pathways were assessed for 177Lu-Dotatate re-treatment and temozolomide. **Results:** A total of 1,811 patients met inclusion criteria. Mean age at index was 65.4 $\pm$ 10.9 years; 977 (54.0%) were male, and 1,503 (83.0%) were White. Median follow-up duration was 20.5 months. Following 177Lu-Dotatate, 37 of 1,807 patients (2.05%) developed MDS, and 15 of 1,804 patients (0.83%) developed AML, with an overall incidence of t-MNs 2.88% (52/1,804). At baseline, mean age (67.1 $\pm$ 9.3 vs 65.4 $\pm$ 11.0 years, p=0.27) and sex (males 42.0% vs 54.2%, p=0.14) were comparable between patients who did and did not develop t-MNs. On multivariable Cox proportional analysis, higher age at index (HR 1.03; 95% CI 1.01–1.07; p=0.048) and baseline CKD (HR 2.69; 95% CI 1.32–5.49; p=0.006) were independently associated with increased risk of t-MNs. Sex, race, primary tumor site, presence of liver or bone metastases, alkylating chemotherapy exposure, and nicotine or alcohol dependence were not significantly associated with t-MN risk. Evaluation of treatment pathways demonstrated similar 177Lu-Dotatate re-treatment rates (2.33% vs 2.77%, p=1.0), and comparable receipt of temozolomide for $\geq$12 months (18.6% vs 16.4%, p=0.66) between groups that did and did not develop t-MNs, respectively. **Conclusions:** In this large real-world cohort of NET patients treated with 177Lu-Dotatate, t-MNs were uncommon but clinically significant. Older age and CKD were associated with increased risk, whereas repeat 177Lu-Dotatate and alkylating chemotherapy exposure were not associated with increased t-MN incidence. These findings may inform risk stratification, patient counseling, and long-term hematologic surveillance following 177Lu-Dotatate. Research Sponsor: None.

4182 **Poster Session**

Germline pathogenic/likely pathogenic (P/LP) variants in epithelial neuroendocrine neoplasms: The case for universal germline genetic testing. First Author: Udhayvir Singh Grewal, Department of Hematology and Oncology, Winship Cancer Institute of Emory University, Atlanta, GA

Background: Current National Comprehensive Cancer Network (NCCN) guidelines for germline testing in neuroendocrine neoplasms (NENs) rely on organ-specific, syndrome-driven algorithms that may not adequately capture hereditary risk. We sought to analyze prevalence of P/LP germline variants in epithelial NENs and investigate relevant associations. **Methods:** Germline genetic testing results were analyzed from 3,611 probands. Cohort 1 included 3,409 patients identified by ICD-10 code C7A (2015–2025), and Cohort 2 included 201 consecutively curated patients with pathology information (2019–2021). Patients with paraganglioma, pheochromocytoma, or medullary thyroid carcinoma were excluded. Except 59 single-gene tests, multigene panels included a mean of 67 and 62 genes in Cohorts 1 and 2, respectively. Data were classified as P/LP, variant of uncertain significance (VUS), or negative. Comparisons of variant classification frequencies between cohorts were performed using chi-square or Fisher's exact tests. Multivariable logistic regression evaluated clinical and demographic predictors of P/LP variant detection, with results reported as likelihood ratios (LR) and two-sided p-values ($<$ 0.05 considered significant). **Results:** Among all 3,611 probands, mean age was 56 years in Cohort 1 and 53 years in Cohort 2, with females comprising 63% and 71%, respectively. VUS and negative results differed between cohorts (VUS 21.9% vs 32.9%, p = 0.002; negative 67.4% vs 55.0%, p $<$ 0.001), while P/LP rates were similar (10.6% vs 12.1%, p = 1.0), permitting pooled analysis. Overall, 387 patients (10.7%) harbored P/LP variants, with 399 P/LP variants identified across 49 genes. Sixty percent of P/LP variants were accounted for by *CHEK2, MEN1, BRCA2, ATM, FH, HOXB13, PALB2,* and *BRCA1*. Clinically actionable variants per NCCN guidelines were identified in 348 patients (9.6%). Among 479 probands with curated family history, meeting NCCN criteria for multigene testing or having a family history of NEN was not predictive of P/LP detection. Logistic regression demonstrated that male sex was a significant predictor of P/LP variants (LR = 4.538, p = 0.03), while age at NEN diagnosis and primary NEN site were not predictive, nor were the interaction terms significant. **Conclusions:** In this 10-year, multicohort study of patients at a commercial laboratory, more than one in ten patients with epithelial NENs harbored a germline P/LP variant, frequently outside classic hereditary NEN syndromes and inadequately predicted by NCCN criteria, family history, age, or tumor site. These findings suggest that current germline testing frameworks may miss clinically relevant hereditary cancer risk. Broader approaches to germline testing in these patients may be needed to improve identification of hereditary cancer risk and enable personalized prevention and surveillance strategies. Research Sponsor: None.

4183 **Poster Session**

Cabozantinib in high-grade neuroendocrine neoplasms. First Author: Nikolaos Trikalinos, Washington University School of Medicine, Division of Medical Oncology, St. Louis, MO

Background: High grade neuroendocrine neoplasms (HG-NENs) are treated with platinum doublets mirroring guidelines for small cell lung cancer (SCLC) but recurrences are common and salvage options are limited in efficacy. Cabozantinib (CABO), an inhibitor of VEGFR, MET, and TAM kinases (TYRO3, AXL, and MER) was approved by the FDA for treatment of well differentiated (WD) NENs of both pancreatic and extrapancreatic origins based on the CABINET study (Chan, NEJM 2025). However, its efficacy in the whole spectrum of HG-NEN patients including poorly differentiated disease (PDD) has not been prospectively explored. **Methods:** This was a single institution, Phase II study of CABO in patients with HG-NENs who had progressed on at least one prior treatment. Key inclusion/exclusion criteria were NENs of any origin except SCLC, high grade by Ki-67 of $>$ 20% or histology consensus, ECOG of $<$ = 1, appropriate hematological parameters and no history of bleeding or active cardiac disease. CABO was given orally starting at 60 mg po daily in 3-week cycles. The primary endpoint of this study was overall response rate (ORR). Secondary endpoints included progression free survival (PFS) and overall survival (OS). A Simon optimal 2-stage design tested the null hypothesis that the true ORR is $<$ = 1% at the type I error rate of 5%, resulting in projected enrollment of up to 32 total patients. Toxicities were graded according to CTCAE v5.0 and response was evaluated according to RECIST v1. **Results:** All patients have been accrued, with 4/32 patients still on treatment. Median age at diagnosis was 62 years and male to female ratio was 1.46. Origin of tumor was GI in 68.8% of the cases, the rest being thoracic (6.3%), prostate (6.3%) cervical (6.3%) head/neck (3.1%) and unknown (9.4%). Median Ki-67 was 55%, 11 patients had Ki-67 $>$ 70%. Histology was WD-HG in 40% of patients and PDD in 60%. Two patients had mixed PDD/other components (MiNEN). Median PFS in evaluable patients was 4.01 months [95% CI 1.61 to 9.30] and mOS was 9.89 mo [95% CI 6.73 to 18.96]. Three patients so far (9.3%) have had partial response as best response (PDD-colon, WD-pancreas and PDD-cervical) while 19/32 (59.4%) patients have had stable disease as best response so far (disease control rate 68.8%). Five (15.6%) patients have received more than 10 treatment cycles. The three longest treated patients had WD-pancreas (23 and 17 cycles) and PDD-unknown (12 cycles). One patient had eventual resection of a metastatic site and is currently without evidence of disease. Three patients withdrew from the trial because of toxicities (shortness of breath, GI bleeding, thromboembolism). Twenty-six patients have expired. **Conclusions:** CABO monotherapy showed efficacy in some HG-NEN patients with not just WD but also the very aggressive PDD histology. No new side effects to the ones previously described for this agent were noted. Supported by Exelixis and a Siteman investment program grant. Clinical trial information: NCT04412629. Research Sponsor: Exelixis; The Foundation for Barnes-Jewish Hospital (BJHF); GR0033156.

4184 **Poster Session**

Insurance, hospital, and racial disparities in surgical treatment and mortality among patients with neuroendocrine tumors: A national analysis. First Author: Swamynathan Umamaheswaran, Personio, New York, NY

Background: Neuroendocrine tumors (NETs) are the second most common gastrointestinal malignancy with increasing incidence. Surgical resection remains curative, yet population-level disparities data are lacking. We examined insurance, hospital, and racial disparities in NET surgical treatment and outcomes. **Methods:** Using the National Inpatient Sample (2019-2022), we identified NET hospitalizations (ICD-10: C7A, C7B, C25.4, C4A). Outcomes were surgical resection and in-hospital mortality. Multivariable logistic regression estimated adjusted odds ratios (aOR) by insurance, hospital type, and race, controlling for demographics, tumor site, and metastatic status. **Results:** Among 198,955 NET hospitalizations (mean age 64.9 years; 52.7% metastatic), surgical resection was 35.3% and mortality 5.2%. Medicaid (aOR 0.58, 0.56-0.60) and Medicare (aOR 0.64, 0.63-0.66) patients had significantly lower surgery odds versus private insurance (p$<$0.001). In localized disease, surgery rates were 58.9% (Private) vs 36.9% (Medicare). Rural patients had 50% lower surgery odds (aOR 0.50, 0.48-0.53) and 47% higher mortality (aOR 1.47, 1.34-1.61) versus urban teaching hospitals. Black patients had 19% lower surgery odds (aOR 0.81, 0.78-0.83) and 18% higher mortality (aOR 1.18, 1.11-1.25) versus White patients. **Conclusions:** This largest national NET analysis reveals profound multilevel disparities: Medicaid/Medicare patients are 36-42% less likely to receive surgery, rural patients face 50% lower surgical access with 47% higher mortality, and Black patients experience significant treatment and survival inequities. Findings support targeted interventions including insurance coverage expansion, rural referral networks, and equity-focused initiatives. Research Sponsor: None.

Multilevel disparities in surgical resection and mortality among patients with neuroendocrine tumors.

Disparity Type	Comparison	N	Surgery Rate	Mortality	aOR (Surgery)	aOR (Mortality)	95% CI	P-value	Key Finding
Overall Cohort	—	198,955	35.3%	5.2%	—	—	—	—	Mean age 64.9y; 52.7% metastatic
INSURANCE DISPARITIES									
Insurance	Medicare vs Private	—	29.9% vs 45.3%	—	0.64	0.90	0.63-0.66 / 0.84-0.95	$<$0.001	36% lower surgery odds
Insurance	Medicaid vs Private	—	—	—	0.58	1.26	0.56-0.60 / 1.16-1.37	$<$0.001	42% lower surgery; 26% higher mortality
HOSPITAL DISPARITIES									
Hospital	Rural vs Urban Teaching	—	—	7.0% vs 4.9%	0.50	1.47	0.48-0.53 / 1.34-1.61	$<$0.001	50% lower surgery; 47% higher mortality
RACIAL DISPARITIES									
Race	Black vs White	—	—	—	0.81	1.18	0.78-0.83 / 1.11-1.25	$<$0.001	19% lower surgery; 18% higher mortality
Localized NETs	Private vs Medicare	87,100	58.9% vs 36.9%	1.7% vs 3.6%	—	—	—	—	22-point surgery gap

4185 **Poster Session**

Circulating tumor deoxyribonucleic acid (DNA) and treatment outcomes of gastroesophageal cancer: A systematic review and meta-analysis. First Author: Thuraya Al-Sayegh, University of California San Francisco, Fresno, CA

Background: Gastroesophageal tumors are some of the most highly prevalent cancers worldwide. Despite the high prevalence and advancement in treatments, they represent a major cause of cancer-related deaths. Thus, advancement in gastroesophageal cancer treatment and post-treatment monitoring are imperative in improving disease prognosis. In this study, we aimed to investigate the association between pre- or post-treatment plasma circulating tumor deoxyribonucleic acid (ctDNA) and post-treatment outcomes. **Methods:** We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus on October 30, 2025 using ctDNA and gastroesophageal cancer as the keywords along with their related MeSH terms. Studies were included if they investigated the association between the detection of pre- or post-treatment plasma ctDNA and disease outcomes among patients with esophageal or gastric cancer. Our exposure of interest was the detection of pre- or post-treatment ctDNA in plasma while the outcomes of interest were tumor recurrence and tumor progression. The odds ratio (OR) and its 95% confidence interval (95%CI) were the effect measures of choice in the analysis. **Results:** We included a total of 1,897 patients with gastric or esophageal cancer from 21 prospective or retrospective cohorts. Our analysis revealed that pre-treatment detection of ctDNA in the plasma was associated with higher odds of tumor recurrence (OR=4.37; 95%CI: 1.20-15.92) and progression (OR=4.80; 95%CI: 2.51-9.18). These results were consistent in the subgroup analysis among patients with esophageal cancer while they lost their significance among patients with gastric cancer and among good quality studies (Newcastle Ottawa Scale$>$5). Moreover, the detection of post-treatment ctDNA was associated with higher odds of tumor recurrence (OR=6.14; 95%CI: 3.79-9.94) and progression (OR=8.28; 95%CI: 5.03-13.64). These results were consistent in the subgroup analysis of patients with esophageal cancer, gastric cancer and among good quality studies. **Conclusions:** Our results highlight that detection of pre-treatment but more so post-treatment ctDNA is associated with post-treatment cancer outcomes. Our results emphasize the potential use of ctDNA as a valuable tool for detection of early gastroesophageal cancer recurrence and post-treatment progression. Research Sponsor: None.

4186 **Poster Session**

Evaluation of clinical success and adverse events with endoscopic ultrasound-guided biliary drainage (EUS-BD) compared to percutaneous transhepatic biliary drainage (PTBD) after failed ERCP in malignant biliary obstruction: A systematic review and meta-analysis. First Author: Era Gupta, Bangalore Medical College and Research Institute, Bangalore, India

Background: ERCP fails to achieve biliary decompression in ~3–10% of malignant biliary obstruction cases. Rescue drainage is typically performed using percutaneous transhepatic biliary drainage (PTBD) or endoscopic ultrasound–guided biliary drainage (EUS-BD). Although PTBD is widely available, it carries substantial morbidity, requires external catheters, and is associated with recurrent infections and reduced quality of life. EUS-BD offers internal drainage with favorable outcomes across established techniques, but comparative evidence versus PTBD remains limited. We performed a systematic review and meta-analysis comparing EUS-BD and PTBD after failed ERCP in malignant biliary obstruction. **Methods:** This review followed PRISMA guidelines. PubMed, Google Scholar, and ScienceDirect were searched using a comprehensive strategy. Comparative studies evaluating EUS-BD versus PTBD and reporting technical success (TS: bile duct puncture with stent/catheter placed in the intended position), clinical success (CS: $>$ 50% bilirubin reduction at 2 weeks), adverse events (AD: graded as per the ASGE endoscopic AE severity lexicon), and reintervention (RN) were included. The data was analysed using the Meta, Metadata and the Metafor packages of R Studio. The Mantel-Haenszel method and the Inverse variance method were utilized to analyse the odds ratio for TS, CS, AD, and RN. The I^2 test was used to assess the heterogeneity of the studies. **Results:** Twenty-six studies were included. EUS-BD was associated with higher clinical success (OR 2.46, 95% CI 1.47–4.11) and lower odds of adverse events (OR 0.38, 95% CI 0.26–0.57) and reintervention (OR 0.19, 95% CI 0.09–0.42). Technical success did not differ significantly between groups (OR 0.49, 95% CI 0.21–1.13). **Conclusions:** Compared with PTBD, EUS-BD is associated with improved clinical success and fewer adverse events and reinterventions after failed ERCP in malignant biliary obstruction. Where expertise is available, EUS-BD may be favored over PTBD. Prospective randomized trials are needed to confirm these findings and support broader adoption. Research Sponsor: None.

Pooled outcomes for EUS-BD vs PTBD.

Outcome/Metric	Comparison	Effect measure	Estimate (OR)	95% CI (lower)	95% CI (upper)	p-value	Direction/ Interpretation
Clinical success	EUS-BD vs PTBD	OR	2.46	1.47	4.11	0.1328	Favors EUS-BD (higher odds of success)
Adverse events	EUS-BD vs PTBD	OR	0.38	0.26	0.57	0.1923	Favors EUS-BD (lower odds of adverse events)
Reintervention	EUS-BD vs PTBD	OR	0.19	0.09	0.42	0.0003	Favors EUS-BD (lower odds of reintervention)
Technical success	EUS-BD vs PTBD	OR	0.49	0.21	1.13	0.3321	Not statistically significant

4188 **Poster Session**

Prevalence and prognostic value of Claudin 18.2 expression in pancreatic ductal adenocarcinoma. First Author: Kevin Zi Ming Lim, Department of Oncology, Copenhagen University Hospital - Herlev and Gentofte, Herlev, Denmark

Background: Although Claudin18.2 expression (CLDN18.2) has been investigated in pancreatic ductal adenocarcinoma (PDAC), prevalence and prognostic significance remain inconsistent. This study evaluated both the prevalence and prognostic value of CLDN18.2 expression in PDAC. **Methods:** CLDN18.2 expression was assessed by IHC on FFPE tumor samples from 201 patients with PDAC enrolled in the BIOPAC study (NCT03311776) between Jan 2013-Feb 2024. Staining was performed using the Ventana CLDN18 (43) CE IVD Assay (Roche Diagnostic Solutions). All slides were independently scored by two pathologists, with discrepancies resolved by consensus. Positive expression was defined as moderate (+2) or strong (+3) staining in $\geq$75% of tumor cells. Patients with non-metastatic disease were excluded from the survival analysis to reduce prognostic confounding. OS and PFS were evaluated using Kaplan-Meier estimates, log-rank tests, and multivariable Cox models adjusted for stage, age, sex, chemotherapy type, diabetes, ECOG performance status, Body Mass Index, and Charlson Age-Adjusted Comorbidity Index. Associations with clinicopathological variables were evaluated using Mann-Whitney U, χ^2, or Fisher's exact tests with Bonferroni correction ($p < 0.05$ considered significant). **Results:** Of 201 patients, 56 had non-metastatic disease and 145 had metastatic disease. Positive CLDN18.2 expression was detected in 54 tumors (27% overall): 14 (25%) non-metastatic and 40 (28%) in metastatic cases. In patients with metastatic disease, the median OS was 9.9 months (95% CI, 6.7-12.8) in the CLDN18.2 positive group and 6.3 months (95% CI, 4.9-8.5) in the negative group, with a significant difference as demonstrated by log-rank test (p = 0.009). CLDN18.2 positivity was associated with improved OS in univariate analysis (HR = 0.60; 95% CI 0.41-0.89; p = 0.010) but was not statistically significant after adjustment for covariates (HR = 0.69; 95% CI 0.47-1.02; p = 0.064). A similar pattern was observed for PFS, with median PFS of 6.0 months (95% CI, 3.6-7.6) in the CLDN18.2 positive group and 4.1 months (95% CI, 3.4-5.3) in the negative group (log-rank p = 0.036). The unadjusted association between CLDN18.2 positivity and longer PFS (HR = 0.67; 95% CI 0.46-0.98; p = 0.037), was not maintained after multivariable adjustment (HR = 0.67; 95% CI 0.43-1.03; p = 0.066). No significant associations were identified between CLDN 18.2 expression and clinicopathological variables after correction for multiple testing. **Conclusions:** CLDN18.2 was expressed in 27% of PDAC tumors. While its association with OS and PFS was not statistically significant after adjustment for clinical covariates, its prevalence in metastatic cases highlights its potential relevance as a therapeutic target in PDAC. Ongoing validation in an expanded cohort may further clarify the prognostic and predictive significance of CLDN18.2 expression. Research Sponsor: Astellas Pharma Europe Ltd.

4189 **Poster Session**

Multicenter phase 2 study of hydroxychloroquine (HCQ) and chlorphenesin carbamate (CPC) in combination with mFOLFIRINOX in patients with advanced pancreatic adenocarcinoma (PDAC). First Author: Hyehyun Jeong, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: PDAC is one of the most lethal malignancies, with most patients (pts) presenting with advanced disease. Although combination chemotherapy, including modified FOLFIRINOX (mFOLFIRINOX) has improved survival, overall prognosis remains poor. Our preclinical studies suggest that HCQ and CPC synergistically enhance the antitumor activity of mFOLFIRINOX by inhibiting autophagy-dependent and AKT-mediated epithelial-mesenchymal transition pathways. **Methods:** This multicenter, single-arm phase 2 study included pts with locally advanced unresectable or metastatic PDAC in the first-line setting from three academic institutions in Korea. HCQ (200 mg) and CPC (250 mg) were administered orally twice daily in combination with mFOLFIRINOX for up to 24 cycles or until disease progression or unacceptable toxicity occurred. The primary endpoint was safety profile. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), cumulative incidence of new distant metastases, and health-related quality of life (HRQOL). **Results:** Between December 2021 and February 2023, 45 pts were screened and a total of 40 patients received study treatment. The median age was 61 years, and 23 (57.5%) were male; 73% (n = 29) and 27% (n = 11) had metastatic and locally advanced disease, respectively. The median number of cycles patients received was 13 (range, 1-24). Dose reductions for HCQ and CPC occurred in four (10%) pts each, with median $>$ 90% of treatment compliance for both agents. Safety profiles are mostly consistent with known adverse events (AEs) with mFOLFIRINOX; grade 3-4 neutropenia (40%), nausea (13%), anemia (10%) were most common severe AEs. In the efficacy analysis set (n = 39), the ORR was 39% (CR or PR; n = 15), and the disease control rate was 92.3% (CR, PR or SD; n = 36). Curative-intent conversion surgery was performed in five pts (13%). With a median follow-up of 33.3 months, the median PFS was 7.4 months (95% CI, 6.2–13.3); in pts with objective response, median PFS was 13.6 months (95% CI, 7.4–33.8). The median OS was 14.8 months (95% CI, 9.6–27.9); median 20.5 months (95% CI, 14.8–NE) for locally advanced disease and median 13.9 months (95% CI, 9.2-NE) for metastatic disease. The cumulative incidence of new distant metastases was 38.8% at 12 months. HRQOL indicators did not deteriorate during the first 6 months of study treatment. **Conclusions:** HCQ and CPC in combination of mFOLFIRINOX were well tolerated and showed clinically promising efficacy outcomes in pts with advanced PDAC. Biomarker analysis using proteomics is ongoing. Clinical trial information: NCT05083780. Research Sponsor: Oncocross.

4190 **Poster Session**

HRS-4642 combined with adebrelimab in previously treated patients with metastatic pancreatic ductal adenocarcinoma. First Author: Xianjun Yu, Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Nearly 90% pancreatic ductal adenocarcinoma (PDAC) tumors were driven by RAS mutations, including KRAS G12D (~40%). The high prevalence of KRAS G12D mutations is thought to play a vital role in the universally immunosuppressive tumor microenvironment of PDAC. HRS-4642 is a highly selective KRAS G12D inhibitor. Here, we report preliminary results of HRS-4642 combined with adebrelimab (an anti-PD-L1 antibody) in patients (pts) with KRAS G12D-mutant PDAC. **Methods:** The study comprised two parts. Phase 1 (Dose escalation): A "3+3" design was used to determine the recommended phase 2 dose (RP2D) of HRS-4642 (4 dose levels: 300, 400, 500mg, qw; and 500mg D1/1200mg D8, q3w) combined with fixed-dose adebrelimab (1200mg iv, Day 1, q3w). Phase 2 (Dose expansion): Simon's two-stage optimal design was applied, requiring at least five objective responses. The primary endpoints were safety and RP2D (phase 1), and objective response rate (ORR; phase 2). The key secondary endpoints included progression-free survival (PFS), overall survival (OS), and disease control rate (DCR). **Results:** As of Dec 31, 2025, 48 pts were enrolled, with 87.5% having received $\geq$2 prior lines of therapy. No dose-limiting toxicity (DLT) occurred during phase 1, and the RP2D was determined as HRS-4642 (500mg D1/1200mg D8, q3w) with adebrelimab. Treatment-related adverse events (TRAEs) occurred in 47 pts (97.9%). The most common grade 3/4 TRAEs included lipase increased (16.7%), gamma-glutamyl transpeptidase increased (12.5%), and blood cholesterol increased (8.3%). No treatment related deaths occurred. Among 43 pts with post-baseline tumor assessment, the confirmed ORR was 41.9% and DCR was 83.7%, with a median mPFS of 5.6 months; the median mOS was not reached. Notably, the RP2D group (n=33) achieved a confirmed ORR of 48.5% and a DCR of 90.9%, successfully meeting the primary endpoint. **Conclusions:** HRS-4642 combined with adebrelimab showed a manageable safety profile and promising anti-tumor activity in metastatic PDAC harboring KRAS G12D mutation. Clinical trial information: NCT06427239. Research Sponsor: None.

Efficacy Evaluation.

	All (n=43)	RP2D (n=33)
Objective response, n (%)	18 (41.9)	16 (48.5)
Best response, n (%)		
Partial Response	18 (41.9)	16 (48.5)
Stable Disease	18 (41.9)	14 (42.4)
Progressive Disease	7 (16.3)	3 (9.1)
Disease control rate, n (%)	36 (83.7)	30 (90.9)
Median progression-free survival, months (95%CI)	5.6 (4.0-7.3)	5.9 (4.2-7.9)
Median overall survival, months (95%CI)	NR	11.5 (9.2-NR)

4191 **Poster Session**

SHR-A2102, a Nectin-4 targeted antibody-drug conjugate, combined with HRS-4642 in previously treated pancreatic ductal adenocarcinoma harboring KRAS G12D mutation. First Author: Jin Xu, Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Patients (pts) with previously treated advanced pancreatic ductal adenocarcinoma (PDAC) have limited options. The high prevalence of Nectin-4 expression (~71%) and KRAS G12D mutations in PDAC provides a rationale for dual targeting. Here we report results from a molecularly defined cohort in a phase 2 platform trial evaluating the combination of SHR-A2102 and HRS-4642, a KRAS G12D inhibitor. **Methods:** Eligible pts with Nectin-4 expression and KRAS G12D mutation who had failed standard therapy were enrolled. During the safety run-in, 2 dose levels of SHR-A2102 were evaluated in combination with HRS-4642 (500mg Day 1/1200mg Day 8, iv, q3w) to determine the recommended expansion dose (RED). The Bayesian Optimal Phase II (BOP2) design was applied for efficacy expansion, with a planned enrollment of 10 to 30 pts. The primary endpoints were safety and RED (safety run-in), and objective response rate (ORR; efficacy expansion). The key secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DoR), and disease control rate (DCR). **Results:** As of Dec. 31, 2025, 36 pts were enrolled and treated (median age, 61 years; ECOG PS 1, 86.1%; $\geq$2 lines of prior therapy, 88.9%; median Nectin-4 H-score, 10). No dose-limiting toxicity (DLT) occurred, and the RED was established as SHR-A2102 (8mg/kg iv, q3w) plus HRS-4642. Treatment-related adverse events (TRAEs) occurred in all pts (100%), with no grade 5 TRAEs. 13 pts (36.1%) experienced grade 3/4 TRAEs, the most common including neutrophil count decreased and gamma-glutamyl transpeptidase increased (each 11.1%), and anemia (8.3%). In the RED group (n=30), the confirmed ORR was 36.7% (11PR) and the DCR was 86.7%, meeting the primary endpoint. ORR showed no apparent correlation with Nectin-4 H-score. The median DoR was 6.3 months (range: 4.4-NR); the median PFS was 4.1 months (range: 2.7-5.7), and the median OS was not reached. **Conclusions:** SHR-A2102 combined with HRS-4642 showed a tolerable safety profile and promising preliminary anti-tumor activity in advanced PDAC harboring KRAS G12D mutation, irrespective of Nectin-4 expression. Clinical trial information: NCT06547736. Research Sponsor: None.

4192 **Poster Session**

Spevatamig (PT886), a claudin 18.2 (CLDN18.2)/CD47 bispecific antibody, in combination with gemcitabine plus nab-paclitaxel (GnP) in frontline (1L) treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC). First Author: Anwaar Saeed, University of Pittsburgh Medical Center (UPMC) and UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Spevatamig is an IgG1-based bispecific antibody targeting CLDN18.2 and CD47 with an optimized anti-CD47 arm designed to bind to CD47 more highly on cancer cells than on human red blood cells. We have previously described its monotherapy safety data and preliminary combination efficacy data in 1L mPDAC (Saeed et al., J Clin Oncol. 2026). Herein, we provide updated data from patients in the 1L mPDAC cohort, including additional efficacy data from the 2 mg/kg QW spevatamig + GnP dose level and new safety data from the 3 mg/kg QW spevatamig + GnP dose level. **Methods:** TWINPEAK is a multi-cohort Phase 1/2 dose escalation and expansion study (US: NCT05482893; China: CTR20252758) of spevatamig as monotherapy or combination therapy (with chemotherapy and/or an immune-checkpoint inhibitor) in patients with select gastrointestinal (GI) cancers. Here we report data from the Phase 2 cohort of spevatamig + GnP in 1L mPDAC at 2 dose levels: 2 mg/kg QW (N=22) and 3 mg/kg QW (N=22). Key endpoints include safety and tolerability, objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS) and median overall survival (mOS). **Results:** As of January 15, 2026, 151 patients have been treated with spevatamig collectively in monotherapy and combination settings. In the 2 mg/kg QW spevatamig + GnP dose level (N=22), spevatamig continues to demonstrate tolerability when combined with chemotherapy, with cytopenia rates not exceeding those anticipated with GnP and no grade $\geq$ 3 nausea or vomiting events. The ORR is 48%, DCR is 90%, mPFS is 7.3 months (95% confidence interval: 5.6 months - not yet reached) and mOS is $>$ 13 months (still maturing), with a median follow-up duration of 8.9 months. Antitumor activity was demonstrated irrespective of tumor CLDN18.2 expression levels and RAS mutational status. In the 3 mg/kg QW spevatamig + GnP dose level (N=22), no significant additive toxicity was noted when compared to the adverse event profile anticipated with GnP alone among patients with available safety data. No grade $\geq$ 3 nausea or vomiting events occurred. Updated safety data will be provided at the meeting for patients in this dose level. **Conclusions:** Overall, spevatamig 2 mg/kg QW or 3 mg/kg QW + GnP is well tolerated, with no significant additive toxicity compared to the adverse event profile anticipated with GnP alone. The additional efficacy data from patients treated at the 2 mg/kg QW spevatamig + GnP dose level continues to demonstrate promise when compared to pivotal trials of GnP in 1L mPDAC; enrollment into the 3 mg/kg QW spevatamig + GnP dose level is ongoing with maturing efficacy data. These two dose levels exhibit good combinability with chemotherapy and can be assessed in future combination studies with novel targeted therapies such as KRAS inhibitors. Clinical trial information: NCT05482893. Research Sponsor: None.

4193 **Poster Session**

Safety and efficacy of nesuparib (JPI-547) with gemcitabine-nab-paclitaxel (GemAbraxane) or modified FOLFIRINOX (mFOLFIRINOX) in patients with locally advanced or metastatic PDAC: Results from an ongoing phase Ib/II study. First Author: Hye Jin Choi, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies with poor outcomes in advanced disease. Nesuparib is a dual tankyrase (TNKS) and poly(ADP-ribose) polymerase (PARP) inhibitor that induces a "BRCAness" phenotype via WNT and Hippo signaling. This Phase Ib study evaluated the safety, tolerability, and preliminary antitumor activity of nesuparib combined with standard first-line chemotherapy in patients with locally advanced or metastatic PDAC. **Methods:** This multicenter, open-label, Phase Ib dose-finding study evaluated oral nesuparib plus GemAbraxane or mFOLFIRINOX in advanced PDAC. Nesuparib was administered orally using a 3+3 dose-escalation design with intermittent schedules, including DL1 (25 mg, 5 days on/2 days off), DL-1 (12.5 mg, 5 days on/2 days off), and DL-2 (12.5 mg, 3 days on/4 days off). Primary objectives were to assess safety and determine the maximum tolerated dose and recommended Phase II dose. Secondary objectives included preliminary efficacy. **Results:** As of December 31, 2025, 27 patients were enrolled and treated (GemAbraxane, n = 14; mFOLFIRINOX, n = 13). Most patients had metastatic disease. In the GemAbraxane arm, acceptable tolerability was confirmed at DL-1 and DL-2, whereas tolerability was not established in the mFOLFIRINOX arm. Across both treatment arms, grade 3/4 AEs were mainly hematologic toxicities. Rates of anemia, thrombocytopenia, and neutropenia were 57.1%, 64.3%, and 92.9% in the GemAbraxane arm, compared with 84.6%, 92.3%, and 84.6% in the mFOLFIRINOX arm, respectively. No treatment-related deaths occurred, and most AEs were manageable with standard supportive measures. Non-hematologic AEs were mostly low-grade and manageable. In the GemAbraxane arm, the objective response rate (ORR) and disease control rate (DCR) were 53.8% and 92.3%, respectively, including one patient with a complete response (CR) of the target lesion and overall survival exceeding 3 years. Median progression-free survival (mPFS) was not reached, and median overall survival (mOS) was 14.2 months (data immature and follow-up is ongoing). In the mFOLFIRINOX arm, the ORR was 38.5% with a DCR of 92.3%, while mPFS and mOS were 7.33 and 18.5 months, respectively. **Conclusions:** Nesuparib combined with GemAbraxane demonstrated acceptable tolerability and encouraging antitumor activity in advanced PDAC. These findings support further evaluation of nesuparib using a 12.5 mg intermittent dosing schedule in the first-line treatment setting; a Phase II trial is currently ongoing. Clinical trial information: NCT05257993. Research Sponsor: None.

Outcome	Nesuparib + GemAbraxane (n=13)	Nesuparib + FOLFIRINOX (n=13)
PR	7 (53.8%)	5 (38.5%)
SD	5 (38.5%)	7 (53.8%)
PD	1 (7.7%)	1 (7.7%)
ORR	53.8%	38.5%
DCR	92.3%	92.3%
mOS	14.20 mo (data immature)	18.50 mo
mPFS	Not reached	7.33 mo

4194 **Poster Session**

MUC5AC-driven transcriptional reprogramming for stratification of pancreatic ductal adenocarcinoma by immune suppression and stromal remodeling. First Author: Yonghua Laura Bao, The Ohio State University, Columbus, OH

Background: Mucin 5AC (MUC5AC) is aberrantly expressed in pancreatic ductal adenocarcinoma (PDAC) and associated with tumor progression; however, its role in altering the tumor immune microenvironment (TIME) and immunotherapy-relevant pathways is poorly understood. Thus, we evaluated whether MUC5AC expression delineates PDAC into distinct transcriptional and immunologic subtypes based on TIME. **Methods:** Bulk RNA-seq data from 730 PDAC tumors (Oncology Research Information Exchange Network, ORIEN) and 360 normal pancreatic tissues (GTEx) were analyzed. Differential gene expression and pathway enrichment were assessed using Gene Ontology and KEGG analyses. Immune infiltration and stromal states were inferred using multiple complementary deconvolution algorithms (CIBERSORT and xCell). Tumors in the lowest quartile of MUC5AC expression ($\leq$25th percentile; MUC5AC-low, MUC5AC-L) were compared with the remaining samples (MUC5AC-high, MUC5AC-H). Associations between MUC5AC expression and immune cell populations and immunomodulatory genes were evaluated by using correlations and group-based analyses with false discovery rate (FDR) corrections. **Results:** Principal component analysis demonstrated clear separation between PDAC tumors and normal pancreas and revealed distinct transcriptional programs between MUC5AC-H (N = 544) and MUC5AC-L (N = 186) tumors. MUC5AC-H tumors exhibited a profoundly immunosuppressive and stromal-remodeled TIME, including enrichment of M2 macrophages, regulatory T cells, activated natural killer ells, fibroblast-associated signatures, and significantly higher immune and stromal scores (multiple FDR $\leq 10^{-6}$ to $\leq 10^{-28}$). In contrast, MUC5AC-L tumors showed relatively enrichment of immune-activating populations, including naïve B cells, dendritic cell subsets, resting $CD4^+$ memory T cells, and $CD8^+$ T cells (multiple FDR $< 10^{-15}$). MUC5AC expression strongly correlated with immune checkpoint genes *CD274* (PD-L1) and *TIGIT*, and with multiple suppressive immune populations ($p < 0.01$ to $< 10^{-10}$). **Conclusions:** MUC5AC defines a transcriptionally distinct, immunosuppressive PDAC subtype characterized by stromal activation, macrophage/Treg enrichment, and immune checkpoint engagement. MUC5AC may serve as a biomarker for immune stratification and supports rational combination strategies integrating stromal targeting with immune checkpoint modulation in PDAC. Research Sponsor: ORIEN Foundation.

4195 **Poster Session**

First-line NALIRIFOX in patients with metastatic pancreatic ductal adenocarcinoma and pre-existing diabetes: NAPOLI 3 post hoc analysis. First Author: Sreenivasa R. Chandana, START Midwest, Grand Rapids, MI

Background: Approximately 29% of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) present with pre-existing diabetes. Diabetes increases the risk of peripheral neuropathy (PN), raising concerns that oxaliplatin-containing regimens may exacerbate PN risk. NALIRIFOX (liposomal irinotecan, oxaliplatin, leucovorin and 5-fluorouracil) is approved for first-line (1L) treatment of mPDAC based on significantly improved overall survival versus nab-paclitaxel plus gemcitabine (Gem+NabP) in the phase 3 NAPOLI 3 trial (hazard ratio 0.83; 95% confidence interval [CI] 0.70–0.99). The overall response rate (ORR) for NALIRIFOX was 41.8% (95% CI: 36.8–46.9%) and no unexpected safety concerns were identified. This *post hoc* exploratory analysis of NAPOLI 3 evaluates outcomes including PN development among patients with pre-existing diabetes. **Methods:** Patients randomized to 1L NALIRIFOX in NAPOLI 3 who had pre-existing diabetes were assessed, with subgroups according to whether or not they developed PN. The primary endpoint was ORR; patient characteristics and adverse event rates were also described. No hypotheses were tested owing to small sample sizes; results are descriptive. **Results:** Of 383 patients randomized to receive NALIRIFOX in NAPOLI 3, 96 (25%) had pre-existing diabetes, of whom 94 were included in the safety population. PN developed in 13/94 (14%) patients (Grade ≥3: 2/13 [15%]) with pre-existing diabetes, none of whom had evidence of PN at baseline. Among patients without diabetes, PN developed in 53/276 (19%; Grade ≥3: 10/53 [19%]). Patients with pre-existing diabetes who developed PN had a lower median age, lower proportion of males, higher metastatic burden, and higher frequency of tumors in the body of the pancreas than patients who did not develop PN (Table). Among patients with pre-existing diabetes, ORR for NALIRIFOX was 43.8% (42/96 [95% CI: 33.6–54.3%]); all responses were partial. ORR was 69.2% (9/13 [95% CI: 38.6–90.9%]) among patients with pre-existing diabetes who developed treatment-emergent PN and 40.7% (33/81[95% CI: 29.9–52.2%]) among those who did not (Table). **Conclusions:** In this exploratory analysis, PN incidence and clinical outcomes in patients with pre-existing diabetes were consistent with those without diabetes and with the overall NALIRIFOX population. In this small population, pre-existing diabetes did not appear to put patients at risk of developing treatment-emergent PN or to impact treatment outcomes. Clinical trial information: NCT04083235. Research Sponsor: Ipsen.

	Patients with baseline diabetes who developed peripheral neuropathy (n = 13)	Patients with baseline diabetes who did not develop peripheral neuropathy (n = 81)
Baseline characteristics		
Age, median, years	63.0	66.0
Male, n (%)	6 (46.2)	52 (64.2)
≥ 3 metastatic sites, %	53.8	40.7
Tumor in body of pancreas, %	38.5	22.2
Efficacy		
ORR, % (95% CI)	69.2 (38.6–90.9)	40.7 (29.9–52.2)

4196 **Poster Session**

Precision Promise (PrP): Success rates of paired biopsies and biomarker testing results for metastatic pancreatic cancer (mPDAC) in a multi-center trial. First Author: Eric Andrew Collisson, Fred Hutch Cancer Center, Seattle, WA

Background: PrP, a phase 2/3 Bayesian adaptive platform trial sponsored by the Pancreatic Cancer Action Network, was developed to test multiple experimental arms efficiently against common controls and explore biomarkers of response/resistance in mPDAC (Picozzi, ASCO TPS 4188, 2022). **Methods:** At screening, core tissue biopsies and matched blood collection were performed for first- and second-line patients (pts) with mPDAC. Week 8 (W8) core tissue biopsies and blood collection were performed for pts receiving study drug. Formalin-fixed paraffin embedded (FFPE) tissue slides were prepared at the central lab; tissue and matched blood samples were analyzed for genomic and transcriptomic analyses using Tempus xT (DNA) and xR (RNA) testing, respectively. The workflow prioritized DNA followed by RNA isolation. **Results:** Tissue biopsies were obtained at screening from 491 of 700 (70%) pts across 24 US sites; W8 tissue biopsies were obtained from 228 of 443 (51%) pts receiving study drug. Reasons for biopsies not being collected included: contraindicated; attempted, but no tissue obtained; pt screened out; pt stopped study drug before W8 (W8 only). 21% (103/491) screening and 32% (74/228) W8 biopsies submitted for biomarker testing contained insufficient tumor tissue for testing; 4% (20 pts) of screening and 4% (10 pts) of W8 biopsies were not processed into FFPE or testing was cancelled. Of the 368 pts with screening tissue sequenced, genomic data were generated for 83% (304 pts); 17% (64 pts) had Quantity Not Sufficient (QNS) for DNA. Transcriptomic data were generated for 49% (179 pts); in 42% (155 pts) insufficient tumor tissue remained for RNA testing and 9% (34 pts) had QNS for RNA. Of the 144 pts with W8 tissue sequenced, genomic data were generated for 71% (102 pts); 29% (42 pts) had QNS for DNA. Transcriptomic data were generated for 31% (44 pts); in 58% (84 pts) insufficient tumor tissue remained for RNA testing and 11% (16 pts) had QNS for RNA. Locations of tissue biopsies across both timepoints (719) were: 68% liver, 16% pancreas, 16% other metastatic sites. Success rates for biomarker testing across all tissue obtained was higher for liver metastases (65% DNA results; 37% RNA results) than for primary tumors in the pancreas (42% DNA results; 19% RNA results). Distribution of actionable biomarkers detected will be presented. **Conclusions:** These data demonstrate success rates of paired biopsy acquisition and subsequent genomic and transcriptomic analysis in a large phase 2/3 multi-center platform trial for mPDAC. Attrition was noted for biopsy collection and downstream biomarker testing at screening and more so at W8 on study drug. Biomarker testing success rates varied by tissue location. These findings along with planned data interrogation and future sample analyses will provide insights to guide future trial design and clinical decision making. Clinical trial information: NCT04229004. Research Sponsor: Pancreatic Cancer Action Network.

4197 **Poster Session**

LAP-NET1: Results of a phase 1b evaluating NP137, an inhibitor of the epithelial-to-mesenchymal transition, in combination with mFOLFIRINOX for the first-line treatment of locally advanced pancreatic ductal adenocarcinoma. First Author: Gael Roth, Department of Hepatogastroenterology, University Hospital of Grenoble, Grenoble, France

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy characterized by aggressive tumor dissemination and resistance to therapy; processes significantly driven by the epithelial-to-mesenchymal transition (EMT). Netrin-1 is a key regulator for EMT. NP137, an anti-netrin-1 antibody, has shown to inhibit EMT in preclinical models and in a phase 1 monotherapy trial. **Methods:** LAPNET-01 (NCT06203821) is a single arm phase Ib clinical study to assess the combination of NP137 with mFOLFIRINOX in naive locally advanced unresectable PDAC. A safety lead-in (3–12 pts, 3+3 design, NP137 14 vs 9 mg/kg) was followed by a 40-patient expansion. Treatment consisted of NP137 + mFOLFIRINOX every 2 weeks, up to 12 cycles. The primary endpoint was safety at 6 months (all-grade and grade 3/4 adverse events [AEs], CTCAE v5.0). Secondary endpoints included objective response rate (ORR), progression-free survival (PFS) and overall survival (OS), surgical conversion rate and exploratory transcriptomic analyses. Laser capture microdissection was performed on 22 pre-treatment and 6 surgery samples to allow microbulk RNA sequencing. Immunohistochemistry was also performed on pre-treatment samples. **Results:** A total of 43 patients were enrolled in this trial. NP137 was well tolerated. AE occurred in 100% of patients (58% grade ≥ 3). ORR and disease control rate were 29% and 95%. Median PFS was 10.9 months (95% CI, 10.0 – 15.6) and median OS was 16.4 months (95% CI, 12.8 – NR) with 21 patients still alive at time of the data cut-off. Surgery was made possible in 23% of patients. Microbulk RNA sequencing revealed that the main pathway downregulated with the combination mFOLFIRINOX+NP137 is EMT, bringing a clinical validation of the main mechanism of action of NP137. Moreover, patients with tumors expressing high levels of the netrin-1 receptor neogenin (high-NEO1) at baseline (both at the RNA and proteic level (IHC)) demonstrated an improved outcomes compared to the low-NEO1 subgroup including longer median PFS (15.7 vs 10.2 months, p = 0.01) and longer median OS (not reached vs 16.5, p = 0.024). These results are consistent with experimental data demonstrating the implication of NEO1 in PDAC EMT and its progression. **Conclusions:** NP137 in combination with mFOLFIRINOX demonstrates a favorable safety profile, promising clinical activity and a mechanistically distinct mode of action supported by translational analyses. These results warrant further investigation of netrin-1 blockade in randomized trials and provide a rationale for biomarker-driven development of NP137 in PDAC. Further work is ongoing to better characterize the distribution of NEO1 in first-line unresectable PDAC. Clinical trial information: NCT06203821. Research Sponsor: NETRIS Pharma; CHU Grenoble Alpes.

4198 **Poster Session**

Surufatinib plus KN046 and chemotherapy as first-line treatment for advanced pancreatic ductal adenocarcinoma: Updated results and biomarker analysis from a phase 1b/2 trial. First Author: Wen-Quan Wang, Department of Pancreatic Surgery, Zhongshan Hospital, Fudan University, Shanghai, China

Background: In China, gemcitabine (G) and nab-paclitaxel (nP) remain the standard first-line (1L) therapy for patients (pts) with advanced pancreatic ductal adenocarcinoma (PDAC). Our previous report (Wang W, et al; 2025 ASCO) showed that the add-on of surufatinib (S, multi-kinase inhibitor) and KN046 (K, bi-specific PD-L1/CTLA-4 antibody) to GnP chemotherapy provided enhanced anti-tumor activity in advanced PDAC. Here we present the updated results and findings from a biomarker analysis. **Methods:** In this single-arm, phase 1b/2 trial (NCT05832892), eligible pts with treatment-naïve advanced PDAC received oral S (200~250 mg, once daily), intravenous K (5 mg/kg, on day 1) and GnP (G 1000 mg/m^2, nP 125 mg/m^2, on days 1 & 8) at 21-day cycles till disease progression or intolerable toxicity. The primary efficacy endpoint was ORR per RECIST 1.1; secondary endpoints included DCR, PFS, OS and safety; efficacy-predictive biomarkers were exploratory endpoints. **Results:** Overall, 31 pts were enrolled with a median age of 56 years (range 40–74) and a predominant male gender (74.2%). Distant metastasis was present in 28 (90.3%) pts and 24 (77.4%) had liver metastasis (LM) at baseline. Best overall responses included 4 CR, 18 PR, and 6 SD. The ORR was 71.0% (95% CI 52.0–85.8) and DCR was 90.3% (95% CI 74.2–98.0). As of Dec 25, 2025, with a median follow-up of 15.9 months, median PFS was 8.2 months (95% CI 6.1–not estimable [NE]). Median OS was 18.0 months (95% CI 13.8–NE) with a 12-month OS rate of 68.2% (95% CI 50.8–91.6). Baseline LM was correlated to significantly worse PFS (8.0 vs NE months, log-rank *P*= 0.02), though no significant impact on ORR (73.9% vs 62.5%, *P*= 0.66), DCR (91.3% vs 87.5%, *P*= 1.00) or OS (13.8 vs NE, log-rank *P*= 0.12) was observed. Among the 27 pts who received ≥4 cycles of treatment, 22 (81.5%) and 19 (70.4%) experienced a decline in CA199 and CA125 from baseline, respectively, while fewer (37.0%) had CEA declined. A ≥50% decline in CA199 was correlated to significantly improved PFS (10.3 vs 8.1 months, log-rank *P*= 0.01) and a trend towards improved OS (NE vs 11.1 months, log-rank *P*= 0.11), as compared to a milder decrease or increase in CA199; Such correlation was not observed for CA125 or CEA. Treatment-related adverse events (TRAEs) occurred in 29 (93.5%) pts, of whom 14 (45.2%) experienced Grade ≥3 events, with hypertension (12.9%), neutropenia (12.9%), and thrombocytopenia (9.7%) being the most frequently observed. No treatment-related serious adverse events or deaths occurred. **Conclusions:** S plus K and GnP demonstrated consistently encouraging efficacy and manageable safety in 1L treatment of advanced PDAC. Early and sharp decline in CA199 may predict more favorable survival benefit. Analyses in genetic profile and its impact on clinical outcome will be carried out in future, and investigations in larger population are warranted. Clinical trial information: NCT05832892. Research Sponsor: HUTCHMED, ALPHAMAB.

4199 **Poster Session**

Precemtabart tocentecan (Precem-TcT, M9140), an anti-CEACAM5 antibody-drug conjugate (ADC), in patients with metastatic pancreatic ductal carcinoma (mPDAC): Results from the phase 1b/2 PROCEADE-PanTumor PDAC substudy. First Author: Zev A. Wainberg, Department of Medicine, University of California, Los Angeles, Medical Center, Los Angeles, CA

Background: CEACAM5 is overexpressed in many cancers, including PDAC, with limited expression in normal tissues. Precem-TcT, an anti-CEACAM5 ADC with an exatecan payload (topoisomerase 1 inhibitor [TOP1i]), showed a predictable, manageable safety profile and promising clinical activity (ORR: 31.0%; mPFS: 6.9 months) in the Phase 1 PROCEADE-CRC-01 study (NCT05464030) in patients with heavily pretreated metastatic colorectal cancer (mCRC). **Methods:** PROCEADE-PanTumor (NCT06710132) is an ongoing, Phase 1b/2, open-label study investigating the efficacy and safety of Precem-TcT monotherapy in advanced PDAC, gastric cancer, and non-small cell lung cancer. Here, we report interim results from the PDAC substudy, which enrolled patients with pretreated mPDAC (ECOG PS $\leq$1; and CEACAM5^{high} expression [$\geq$50% tumor cells with immunohistochemistry $\geq$2+ staining]) in the US, Australia, France, Japan, and Korea, who were treated with Precem-TcT 2.8 mg/kg Q3W. **Results:** Between May and September 2025, 46 patients have been enrolled into the study (median age: 62.0 years; female: 65.2%; ECOG PS 0/1: 47.8%/52.2%). Most patients received one or two prior lines of therapy, and were irinotecan pretreated. As of November 2025, median duration of Precem-TcT treatment was 12.6 weeks. Treatment emergent adverse events (TEAEs) occurred in 95.7% of patients; grade $\geq$3: 78.3%. Most common grade $\geq$3 TEAEs were neutropenia (43.5%) and anemia (32.6%). Gastrointestinal TEAEs were mostly grade 1-2, and there were no cases of interstitial lung disease or ocular toxicities. TEAEs led to dose reductions in 15.2% and to permanent discontinuation in 4.3% of patients. There were no treatment-related deaths. As of January 2026, 10 patients had a PR (21.7%), 20 SD (43.5%), and 11 PD (23.9%); 14 patients remain on study. Updated data, including mPFS and CEACAM5 expression, will be presented at the congress. Preliminary pharmacokinetics of the conjugated antibody and unconjugated exatecan appeared generally consistent with previous data from patients with mCRC. **Conclusions:** Precem-TcT, the first anti-CEACAM5 ADC with a TOP1i-payload reporting clinical data in patients with mPDAC, showed a predictable safety profile in this population, consistent with data from patients with mCRC. Efficacy data in this highly refractory, mostly irinotecan-pretreated 2L/3L population benchmark favorably with the current SoC for 2L mPDAC. Clinical trial information: NCT06710132. Research Sponsor: The healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

4200 **Poster Session**

Phase Ib/II clinical study of adebrelimab combined with decitabine, nab-paclitaxel, and gemcitabine as first-line (IL) treatment for metastatic pancreatic cancer (mPC). First Author: Rui Liu, Department of Gastrointestinal Medical Oncology, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China

Background: Epigenetic enzyme inhibitors may synergize with immunotherapy by modulating antigen presentation and enhancing tumor-related gene expression. Preclinical studies suggest that low-dose decitabine can restore chemosensitivity in chemotherapy-resistant tumors. We conducted the Ib/II study to explore the efficacy and safety of decitabine combined with adebrelimab, nab-paclitaxel, and gemcitabine as 1L treatment for mPC. **Methods:** Eligible patients (pts) were prior untreated mPC or pts who had experienced disease progression more than six months after the end of postoperative adjuvant therapy. In the phase Ib, enrolled pts received dose escalation of decitabine (10 mg/m²/15 mg/m²,iv,d1-d3,q4w), adebrelimab (1200mg,iv,d1,q3w) , nab-paclitaxel (125 mg/m^2, iv,d1,d8,d15,q4w), and gemcitabine (1000 mg/m^2,iv,d1,d8,d15,q4w) to determine the recommended phase 2 dose (RP2D) in a standard 3+3 design. In the phase II, pts received decitabine at the RP2D, adebrelimab, nab-paclitaxel and gemcitabine combination therapy. Primary endpoints were dose-limiting toxicities, RP2D, and objective response rate (ORR). Secondary endpoints included overall survival, progression free survival, disease control rate (DCR), duration of response, and safety. **Results:** From April 2024 to February 2025, 28 pts were enrolled and the median age was 62 yrs; 69.2% male, and 80.8% ECOG PS 1. The Ib phase established the RP2D of decitabine as 10 mg/m². Total of 22 pts were included in the efficacy analysis. The median follow-up was 11.9 mo. The ORR was 46% (10PR, 9SD, 3PD) and DCR was 86.4%. Median duration of response (mDoR) was 10.94 months, while the median progression-free survival (mPFS) was 6.47 months. 24 pts were analyzed for safety. The most common TRAEs of any grade were anemia (95.8%), lymphocyte count decreased (79.2%), hypoalbuminemia (75.0%), hyponatremia (75.0%), vomiting (66.7%). Grade $\geq$3 TRAEs were were anemia (25.0%), white blood cell decreased (20.8%), platelet count decreased (20.8%), lymphocyte count decreased (12.5%), neutrophil count decreased (12.5%). No new safety signals were observed. **Conclusions:** This study preliminarily demonstrates that the decitabine combination regimen has favorable efficacy and safety in 1L treatment of mPC. Future clinical studies with larger sample sizes are needed to be validated. Clinical trial information: NCT06454448. Research Sponsor: Tianjin Science and Technology Commission key project; 25JCLZJC00360.

4201 **Poster Session**

BXCL701 plus pembrolizumab in second-line advanced pancreatic ductal adenocarcinoma: Final outcomes of the EXPEL PANC trial. First Author: Benjamin Adam Weinberg, Ruesch Center for the Cure of Gastrointestinal Cancers, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC

Background: Pancreatic ductal adenocarcinoma (PDAC) is resistant to immune checkpoint inhibitors, in part due to a cold tumor immune microenvironment (TME). BXCL701 ('701) is a small molecule inhibitor of dipeptidyl peptidases 4, 8, 9 and fibroblast activation protein. We have shown that combinations of '701 and anti-PD1 antibodies lead to tumor regression in murine PDAC models due to 1) activation of the inflammasome and expression of CXCL9 to attract and activate CXCR3+ lymphocytes, 2) tumor invasion of CD8+ T cells and other effector cells, 3) induction of adaptive immunity, and 4) reduced fibrosis in the PDAC TME. We sought to evaluate the efficacy of this combination in patients (pts) with previously-treated advanced PDAC. **Methods:** In this phase II clinical trial (NCT05558982), pts with second-line advanced PDAC received '701 at a 0.2 mg PO BID dose on days 1-7 and then 0.3 mg BID on days 8-14 during cycle 1 (21 days) followed by 0.3 mg BID on days 1-14 every 21 days in all subsequent cycles, administered with pembrolizumab 200 mg IV every 21 days (all cycles). The primary objective was to determine the 18-week progression-free survival rate ($PFS_{18weeks}$) in pts with advanced PDAC treated in the second-line setting. We estimated that the historical second-line $PFS_{18weeks}$ is 30% or less; using a Simon's two-stage (minimax) design, a type I error rate of 0.05 and a power of 80%, if the true rate is 50%, we would need 19 pts in stage 1 and 20 pts in stage 2 (a total of 39 evaluable). Seven of 19 evaluable pts would need to be progression-free at 18 weeks to trigger stage 2. **Results:** Twenty-one pts were enrolled. Four out of 18 evaluable pts (22%) were alive and progression-free at 18 weeks. Three had partial responses (PR, 17%), and 4 had stable disease (SD, 22%), for a disease control rate of 39%. One responder had MSI-H PDAC, while the other 2 had MSS disease. Median follow-up was 4.5 months. Median PFS was 2.3 months (95% CI 1.6 – 5.3), and median overall survival was not reached (NR, 95% CI 4.5 – NR). Three pts (14%) had PFS exceeding 6 months (2 PR, 1 SD). No new safety signals have been identified. Baseline and on-treatment tumor biopsies will be analyzed to understand the mechanisms underlying therapeutic benefit and to examine the characteristics of responders vs. non-responders. **Conclusions:** '701 plus pembrolizumab in second-line advanced PDAC did not reach the preliminary efficacy endpoint to trigger the second stage. However, there were encouraging signs as this combination induced objective responses in 2 MSS pts, and PFS exceeded 6 months in 3 pts. Ongoing correlative studies should elucidate predictive markers of efficacy and resistance to this novel immunotherapy combination. Clinical trial information: NCT05558982. Research Sponsor: BioXcel Therapeutics; Merck; Ruesch Center for the Cure of Gastrointestinal Cancers.

4202 **Poster Session**

Proglumide, gemcitabine (GEM), and nab-paclitaxel (NAB-P) in patients (pts) with pancreatic ductal adenocarcinoma (PDAC): Results of the phase 1 PROGEM trial. First Author: Jill P. Smith, Georgetown University, Department of Medicine, Washington, DC

Background: PDAC has a poor prognosis and resistance to therapy due to its desmoplastic and immunosuppressive tumor microenvironment (TME). In animal models of PDAC, the cholecystokinin-B receptor (CCK-BR) antagonist, proglumide, was shown to decrease tumoral fibrosis, alter the tumor immune cell signature, and increase chemotherapy uptake and T-cell infiltration into tumors, resulting in decreased metastases and improved survival. We sought to evaluate the safety of proglumide with GEM/NAB-P chemotherapy in pts with metastatic PDAC (mPDAC). Using tumor biopsies and a blood biomarker assay, we also studied the combined effects of proglumide with GEM/NAB-P on the TME. **Methods:** The PROGEM study was a phase 1 trial of proglumide 1200 mg PO daily, GEM 1000 mg/m2 IV, and NAB-P 125 mg/m2 IV days 1, 8, and 15 every 28 days in GEM-naive pts with mPDAC (NCT05827055). The primary endpoints were safety and determination of the recommended phase 2 dose (RP2D). Safety was assessed with adverse events (AEs) according to CTCAE v. 5 criteria. Tumor biopsies were obtained pre-treatment and at 8 weeks on-treatment and analyzed by histology and multiplex immunohistochemistry for changes in the TME. A liquid biopsy serum sample was collected at baseline, week 8, and end-of-treatment (EOT) for analysis of a microRNA biomarker panel reflecting changes in the TME. McGill pain surveys were done at baseline, week 8, and at EOT. **Results:** Six pts were enrolled. Three pts were treatment-naïve, and 3 had had prior mFOLFIRINOX. No AEs related to proglumide were reported. Five pts had stable disease, and 1 pt had disease progression as the best response, for a disease control rate of 83%. Median progression-free survival was 4 months, and median overall survival was 8.5 months. Compared to baseline, on-treatment biopsies showed an 81% decrease in Ki67+ cells; a 75% decrease in M2-polarized tumor-associated macrophages; a 42% decrease in tumor collagen content, and a 13-fold increase in CD8 T-cells. Pre- and on-treatment blood biomarkers showed changes correlated with histology and clinical course. Anti-fibrosis markers (miR185, miR346, and miR378) and inhibitors of epithelial to mesenchymal transition (miR200 and miR205) increased with therapy. MiR122, which regulates cell cycle and growth, decreased initially but increased at the time of progression. Pain scores showed improved pain at week 24 or EOT. **Conclusions:** Proglumide is safe in pts with mPDAC, and the RP2D is 1200 mg PO daily with standard dose GEM/NAB-P. Proglumide remodels the TME by decreasing fibrosis and immunosuppression while increasing T-cell infiltration. Changes in circulating microRNAs offer a promising non-invasive biomarker panel for monitoring treatment response. These results support further investigation of proglumide with GEM/NAB-P in a phase 2 clinical trial and future immunotherapy combinations. Clinical trial information: NCT05827055. Research Sponsor: Ruesch Center for the Cure of Gastrointestinal Cancers; Pancreatic Cancer Action Network.

4203 **Poster Session**

QL1706 combined with nab-paclitaxel and gemcitabine as first-line treatment for locally advanced or metastatic pancreatic adenocarcinoma: A prospective, multicenter, single-arm phase II study. First Author: Biyang Cao, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, Beijing, China

Background: First-line chemotherapy with nab-paclitaxel and gemcitabine (AG) provides limited efficacy in advanced pancreatic ductal adenocarcinoma (PDAC). QL1706, a bifunctional antibody targeting PD-1 and CTLA-4, has demonstrated favorable efficacy and safety. This phase II study evaluated the efficacy and safety of QL1706 plus AG as first-line treatment in patients with locally advanced or metastatic PDAC. **Methods:** Adult patients with histologically confirmed, unresectable locally advanced or metastatic PDAC, ECOG performance status 0–1, no prior systemic therapy, and at least one measurable lesion were enrolled. Patients received QL1706 (5 mg/kg, IV, day 1) in combination with nab-paclitaxel (125 mg/m², IV, days 1 and 8) and gemcitabine (1,000 mg/m², IV, days 1 and 8) every 3 weeks. Tumor assessments were performed every two cycles. Up to eight cycles were administered, followed by QL1706 maintenance in patients without disease progression. Primary endpoints were objective response rate (ORR) and safety. **Results:** A total of 30 patients were enrolled. The median age was 59 years (range, 44–74), and 20 patients were male. Primary tumors were located in pancreatic head in 14 (46.7%) and in body or tail in 16 (53.3%). Eight (26.7%) and 22 (73.3%) patients had locally advanced (stage III) and metastatic (stage IV) disease, respectively. Among 26 patients assessed for KRAS mutations, the G12D variant was most prevalent (46.2%), followed by G12R (30.8%) and G12V (23.0%). At data cutoff, after a median follow-up of 5.2 months (range, 4.1–6.8), 18 patients remained on treatment. Of these, 2 underwent curative surgery and 4 transitioned to maintenance therapy. Twelve patients discontinued treatment due to disease progression, including 5 who subsequently died. The median number of treatment cycles administered was 4.5 (range, 2–8) for chemotherapy and 4 (range, 1–8) for QL1706. All patients had at least one post-baseline tumor assessment. Best overall response were complete response in 1(3.3%), partial response in 8 (26.7%), stable disease in 16 (53.3%), and progressive disease in 5 (16.7%).The ORR was 30.0% (95% CI, 14.7–49.4%) and disease control rate was 83.3% (95% CI, 65.3-94.4%). The survival data were not mature by analysis. All patients experienced at least one treatment-related adverse event (TRAE). Grade ≥3 TRAEs occurred in 16 patients (53.3%). The most frequent grade 3–4 TRAEs were neutropenia (23.3%) and leukopenia (20.0%), followed by hypersensitivity reactions (13.3%), thrombocytopenia (6.7%), thromboembolism (6.7%), and pancreatitis (6.7%). No grade 5 TRAEs or treatment-related deaths occurred. **Conclusions:** QL1706 combined with AG demonstrated promising antitumor activity with a manageable safety profile as first-line treatment for advanced PDAC. Clinical trial information: NCT06750861. Research Sponsor: None.

4204 **Poster Session**

Multicentre trial of telemonitored circadian rhythms and electronic patient-reported outcomes (ePROs) for improving tolerability of initial mFOLFIRINOX cycles in patients (pts) with advanced pancreatic ductal adenocarcinoma (PDAC): MultiDom (NCT04263948). First Author: Francis Albert Lévi, UPR Chronotherapie, Cancers et Transplantation, Université Paris Saclay, Hôpital Paul Brousse ID Isco 13918, Villejuif, France

Background: Severe Adverse Events (SAEs) requiring emergency admissions (EAs) alter quality of life and treatment efficacy, and increase health costs. Toxicities, EAs, and reduced survival have been linked to the disruption of circadian rhythms, whose relevance is tested here in a multicentre, prospective, longitudinal, single-arm interventional trial. **Methods:** Continuous telemonitoring and automatic analyses of circadian rhythms and daily body weight and ePROs over 50 days (d) aim to reduce EAs in PDAC pts receiving the first 3 cycles of mFOLFIRINOX. The hypothesis (H_0) is that EAs involve <15% of the pts, rather than a historical rate of 15-30%. Pts data were collected through telecommunicating chest sensor, balance and tablet connected to a multidimensional digital platform. The main circadian parameter was (I<O), the % of accelerations per min In-Bed that are below the median accelerations per min Out-of-Bed. Control(I<O) is 97-100%. An (I<O) ≤96% defined circadian disruption. Electronic alerts were sent out if (I<O) ≤96%, body weight loss ≥5%, or self-rated symptoms ≥7 using the MD Anderson Symptoms Inventory (MDASI). **Results:** 28 males and 24 females had a median age of 65 years (33-82), and WHO performance status of 0-1 in 92% of them. PDAC was metastatic in 69% of cases, including liver in 50%. An EA occurred in 2 pts (3.8% [95% CL, 1.1-13%]), thus validating H_0. SAEs in both EA pts were grade (Gr) 3 febrile neutropenia and diarrhea; and Gr 3 leuco-neutropenia and hypokaliemia respectively. Symptom-free circadian disruption preceded EA by 8 d in both pts. Circadian disruption occurred at least once in 65-75% of the pts on treatment, and lasted > 20 d in 27 pts (52%). Severe fatigue and anorexia were self-reported by 62% and 58% of the treated pts respectively. Main Grade 3-4 toxicity was neutropenia in 17% of the pts [95% CL, 9-30]. Disease control rate at 2 months was 75% [53-100]. Multidom revealed (i) a high level of pt engagement supported both by data compliance rates of 84-92% for circadian rhythms, 93-100% for body weight, and 86-100% for ePROs; and by median duration of platform use of 46 d (IQR, 38-50]; (ii) 1881 medical type e-alerts for circadian disruption (43%), MDASI symptoms (25%), and body weight loss (12%); (iii) 883 categorized responses to medical e-alerts, and (iv) highest global score of self-rated pt experience of participation (median, 5/5 (4 to 5). **Conclusions:** Combining telemonitoring of circadian rhythms, body weight and symptoms in remote PDAC pts on mFOLFIRINOX revealed potential benefit on pts real life through informed proactive telecare, and likely improved treatment safety. Actual benefits from such telemonitoring-telecare platform with circadian metrics need further confirmation in trials involving pts at risk of SAEs. Clinical trial information: NCT04263948. Research Sponsor: Research and Education Group of Ramsay-Santé, France.

4205 **Poster Session**

Final results and preliminary correlative analysis of a phase I study of anetumab ravtansine in combination with checkpoint inhibitors and gemcitabine in mesothelin-positive advanced pancreatic adenocarcinoma (NCI10208). First Author: Carlos Diego Holanda Lopes, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: Anetumab-ravtansine (AR) is an ADC composed of IgG1 targeting the protein mesothelin (MSLN) linked to DM4, a tubulin inhibitor (*Spiliopoulou, ASCO 2022*). Here, we present the final analysis of a phase I study evaluating AR in combination with nivolumab, ipilimumab, or gemcitabine in patients (pts) with metastatic pancreatic adenocarcinoma (PDAC). **Methods:** Eligible pts had histologically confirmed MSLN-positive PDAC (≥5% expression by IHC), ECOG 0–1, and progression after ≥1 prior line of systemic therapy. The dose-escalation phase included: AR + nivolumab (ARM1), AR + nivolumab + ipilimumab (ARM2), and AR + gemcitabine + nivolumab (ARM3). The latter was chosen for dose-expansion. Two dose levels of AR: DL1 5.5 mg/kg and DL2 6.5 mg/kg (RP2D) were evaluated. Blood and tissue-based correlative analysis included paired tumor biopsies on C1D7 and C2D7 for comparison of immune cell shifts by multiplex immunofluorescence. **Results:** As of the final data cutoff on 15/11/2023, 46 pts were treated: ARM1 (n = 11), ARM2 (n = 13), ARM3 (n = 10), and dose expansion (n = 12). Median age was 66 years (40–83), the majority were males (52.2%) and had received prior gemcitabine (63%). The median number of prior treatment lines was 2 (1–5). Among 44 evaluable pts, 95.7% experienced some treatment emergent adverse events, with G1/2 and G≥3 occurring each at 47.8%. Dose limiting toxicities occurred in 6 pts (13%): 2 in ARM2DL2 (upper gastrointestinal hemorrhage and G3 thrombocytopenia), 2 in ARM3DL2 (G3 AST and G3 ALT elevation), and 1 in each of the dose expansion DL2 (G3 AST and G3 ALT elevation). Blurred vision occurred in 13%, peripheral neuropathy in 6.5%, pneumonitis in 4.3%, and keratitis in 2.2%, most of them being G1/2. No treatment-related deaths occurred. Among 41 evaluable pts, 1 (2.2%; ARM3DL2) had a complete response, 20 (43.5%) had stable, and 20 (43.5%) had disease progression. The median duration of treatment was 7.9 (1.9-32.9) weeks which was statistically longer in pts with stable disease than those with progressive disease as best response (16.4 vs 6.3 weeks, respectively; $p < 0.05$). Twenty-seven pts were included in the multiplex immunofluorescence, and no statistically immune-cell shifts were detected between C1D7 and C2D7. **Conclusions:** AR had an acceptable safety profile in PDAC and the 6.5 mg/kg was identified as the R2PD. Evidence of clinical benefit was observed with some pts with prolonged disease stabilization and one complete response in a setting of limited therapeutical options. Correlative analysis to identify predictive biomarkers for treatment benefit is ongoing. Clinical trial information: NCT03816358. Research Sponsor: Experimental Therapeutics Clinical Trials Network (NCI-ETCTN); North American STAR Consortium.

4206 **Poster Session**

Ultra-refractory PD–PD pancreatic cancer: Clinical and molecular insights across first- and second-line therapy. First Author: Natalia Soledad Tissera, Hepatobiliary Pancreatic Cancer and Endocrine Tumors Group, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: A subset of pancreatic cancer (PC) patients exhibits progressive disease (PD) as the best response to both first- and second-line chemotherapy (PD-PD), representing an ultra-refractory population with dismal outcomes. This group remains poorly characterized, highlighting a critical unmet need for novel therapeutic strategies. **Methods:** We retrospectively analyzed PC patients treated at Vall d'Hebron University Hospital (2012–2025) who received both first- and second-line chemotherapy with 5-FU- or gemcitabine-based regimens. Clinical, histopathological and molecular data were collected. Characteristics of PD-PD patients were compared with those achieving clinical benefit, defined as complete or partial response (CR/PR) in at least one treatment line. Progression-free survival (PFS2) was calculated from the start of first-line therapy to documented PD after second-line treatment. Overall survival (OS) was calculated from the start of first-line therapy to death or last follow-up. Survival curves were estimated using the Kaplan–Meier method. RNA-seq was performed on diagnostic tumor samples to explore transcriptomic features. **Results:** Median follow-up for the entire cohort was 58 months. Among 400 patients, 46 (12%) were classified as PD-PD. Median PFS2 was 5.4 months in PD-PD vs 14.5 months in CR/PR, and median OS was 8.1 vs 20.8 months, respectively ($p < 0.001$ for both). Treatment sequences in PD-PD patients included 5-FU followed by gemcitabine (18, 39%) and gemcitabine followed by 5-FU (28, 61%). Patients receiving 5-FU first were younger (median age 57 vs 72 years, p = 0.035). Histopathological features were similar in both groups. Inflammatory markers were largely comparable; however, median CRP/albumin ratio was higher in PD-PD, 0.86 vs 0.24 in CR/PR ($p < 0.001$). Molecular profiling was available for 34 (74%) of patients. Among these, *KRAS* mutations were present in 84% of patients, with G12V slightly more frequent in PD-PD than CR/PR (45% vs 31%, p = 0.5). *TP53* mutations occurred in 81% vs 65% (p = 0.083), and *SMAD4* alterations were more common in CR/PR (19% vs 6.3%, p = 0.082). DDR pathway alterations were rare in PD-PD patients. Exploratory RNA-seq of six PD-PD compared with CR/PR (n = 2) tumors revealed upregulation of coagulation and lipid metabolism genes (*FGB, APOA1*) and downregulation of pancreatic function genes (*PNLIP, CPA1*), suggesting potential alterations in inflammatory and metabolic pathways. **Conclusions:** PD-PD patients represent an ultra-refractory subset (~12%) of PC with very poor outcomes despite standard therapy. Differences in inflammatory markers and transcriptomic trends may reflect underlying biological features of this highly resistant phenotype. These findings underscore the need for further studies to clarify mechanisms of primary resistance and guide the development of novel therapeutic strategies in this high-risk population. Research Sponsor: None.

4208 **Poster Session**

Phase 1/2 study of YL201, an anti-B7H3 antibody–drug conjugate (ADC), in patients with previously treated advanced pancreatic ductal adenocarcinoma (PDAC). First Author: Liwei Wang, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Background: The prognosis for patients with advanced PDAC after failure of first-line therapy remains dismal with limited effective treatment options. There is a critical unmet need for novel therapeutic agents in the second-line and beyond (2L+) setting. YL201 is a B7H3-targeting ADC with promising clinical activity in multiple advanced solid tumors. Here, we report the safety and preliminary efficacy of YL201 monotherapy in patients with 2L+ PDAC from a phase 1/2 dose expansion study. **Methods:** Patients with metastatic PDAC who had progressed on at least one prior line of systemic therapies without irinotecan were enrolled and treated with YL201 intravenously Q3W at 2.0 mg/kg or 2.4 mg/kg until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** A total of 60 patients were enrolled, including 30 treated at 2.0 mg/kg and 30 at 2.4 mg/kg. The median age was 61.0 years, 63.3% were male, and 91.7% had an ECOG PS of 1. 48.3% of patients had ≥3 metastatic sites at baseline. Patients had received a median of 1 prior line of therapy (range: 1–3). 90.0% had received prior gemcitabine-based regimen and 46.7% had received prior fluoropyrimidine. As of 12 December 2025, the median follow-up was 9.2 months (95% CI: 8.2–9.8). Among the 60 patients enrolled, the confirmed ORR was 28.3% (95% CI: 17.5–41.4) with a median DoR of 7.6 months (95% CI: 4.9–NR), and the DCR was 85.0% (95% CI: 73.4–92.9). The median PFS was 7.7 months (95% CI: 5.5–9.7), and the median OS was 14.6 months (95% CI: 8.2–NR). Membrane B7H3 expression was detected by immunohistochemistry in most tumor samples with a median H-score of 65 (range: 0–275). However, no association was observed between tumor response and B7H3 expression level in PDAC patients. Treatment-related adverse events (TRAEs) of any grade and grade ≥3 occurred in 100.0% and 43.3% of patients, respectively. The most common grade ≥3 TRAEs included leukopenia (16.7%), neutropenia (15.0%), anemia (15.0%), and hypokalemia (6.7%). The rate of treatment discontinuation due to TRAEs was 5.0%, and no treatment-related deaths were reported. **Conclusions:** YL201 monotherapy showed promising antitumor activity and a manageable safety profile in pretreated patients with advanced PDAC. These compelling results warrant further investigation of YL201 in a randomized controlled trial for patients with advanced PDAC in the 2L+ setting. Clinical trial information: NCT06057922. Research Sponsor: MediLink Therapeutics.

4209 **Poster Session**

Efficacy of multimodal thermal therapy combined with immune checkpoint inhibitors and chemotherapy in unresectable pancreatic cancer with liver metastases. First Author: Chuntao Wu, Department of Pancreatic Surgery, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Treatment of pancreatic cancer with liver metastasis (PCLM) remains extremely challenging. Multimodal thermal therapy (MTT) is a novel treatment method consisting of alternated liquid nitrogen cooling and radiofrequency heating, which was proven to effectively remodel the immune environment and trigger systemic antitumor immunity. This study aims to explore the primary application of MTT combined with subsequent ICIs-based systemic therapy in PCLM. **Methods:** Patients aged 18-70 years with primary diagnosed unresectable PCLM were enrolled in this single-center, prospective clinical trial. Participants received MTT at least one of the liver metastases combined with subsequent ICIs and chemotherapy (camrelizumab 200 mg IV on Day 1, gemcitabine 1000 mg/m2 IV, and nab-paclitaxel 125 mg/m2 IV on Days 1 and 8, every 3 weeks for 6 cycles), which was started on day 7 post MTT. The primary endpoints were safety and efficacy. Secondary endpoints included progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR). Exploratory endpoints included immune marker changes induced by MTT. **Results:** Five patients were enrolled in the trial group and four patients in the control group. All patients in the trial group were well tolerated with MTT, and the MTT-treated liver tumors were completely ablated. One patient withdrew due to autoimmune hepatitis after the first ICIs treatment. One patient achieved success conversion and underwent curative resection 6 months after MTT. Median OS per RECIST was 16.0 months (95% CI 15.3–16.7) in the trial group surpassing 6.2 months (95% CI 1.8–9.2) in the control group (HR 0.26 [95% CI 0.04–1.99]). Histological analysis indicated that combination therapy reversed the immunosuppressive tumor microenvironment, accompanied by enhanced immune-cell infiltration and tertiary lymphoid structures formation within both primary and metastatic lesions. Single-cell RNA-seq of peripheral blood immune cells on day 7 after MTT but prior to ICIs and chemotherapy revealed that MTT promoted the maturation of APCs, increased expression of homing-associated chemokine receptors on circulating B cells and monocytes, and induced the expansion of tumor-trafficking monocytes and $CD8^+$ T cells subsets, which were correlated with favorable prognosis. The effector functions of T cells were also enhanced post MTT, accompanied by increased PD-1 level, which provided the basis for subsequent anti-PD-1 therapy. **Conclusions:** MTT reshaped both primary and metastatic tumor immune environments, sensitized tumors to subsequent immunotherapy and chemotherapy, well correlating to prolonged OS of PCLM patients. Clinical trial information: NCT06307080. Research Sponsor: None.

4210 **Poster Session**

AI-driven RNA-based homologous recombination deficiency algorithm to predict first-line platinum response in metastatic pancreatic cancer. First Author: Hannah J. Glover, Tempus AI, Inc., Chicago, IL

Background: Developing predictive diagnostics for metastatic pancreatic cancer remains an unmet clinical need. Here, we present the Tempus HRD-RNA algorithm: an AI-driven, 1,660-gene logistic regression model trained on RNA-seq (Tempus xR) from pan-cancer solid tumor tissue samples. This dynamic RNA-based signature can identify clinically relevant patient populations likely to benefit from platinum-based regimens and PARP inhibitors, including patients without BRCA1/2 or PALB2 mutations. **Methods:** This is a prospectively designed retrospective RWD analysis in an independent validation cohort of 1,083 patients (pts) with treatment-naive metastatic pancreatic cancer diagnosed between 2017 and 2025. Treatment arms included first-line platinum-containing regimens (Arm A; n = 779; 97.0% FOLFIRINOX, 1.4% NALFIRINOX, 1.5% Gemcitabine/Cisplatin) or a non-platinum regimen (Arm B; n = 304; 86.6% Gemcitabine/Nab-paclitaxel, 13.4% Gemcitabine/Paclitaxel). BRCA1/2 and PALB2 mutations were determined via paired Tempus xT DNA sequencing. Key prognostic criteria included age, sex, ECOG score (0 or 1), surgery status and biopsy site. Unknown ECOG was imputed using the Laboratory Imputation Framework for EHRs (LIFE; PMID: 40595435). Overall survival (OS) differences between treatment arms were evaluated as independent Cox models for HRD+ vs. HRD- pts, including covariate adjustment. **Results:** Overall, 9.5% of pts were classified as HRD+: 78 pts (10.0%) in the platinum arm (Arm A) and 15 pts (8.2%) in the non-platinum arm (Arm B). OS was significantly higher in platinum-treated HRD+ pts than non-platinum. Median OS (mOS) was 12.8 months (95% CI: 8.5–16.6) in HRD+ platinum pts (Arm A) vs. 8.5 months (95% CI: 5.4–12.9) in HRD+ non-platinum-treated pts (Arm B; HR: 0.57; 90% CI: 0.33–0.99; p = 0.048). In contrast, in the HRD- group, there was no statistically significant difference in OS between platinum (Arm A; mOS 8.1 months; 95% CI: 7.1–9.1) and non-platinum (mOS 7.6 months; 95% CI: 6.6–8.8) arms (Arm B; HR: 0.91; 90% CI: 0.76–1.09; p = 0.190). Additional analyses were performed within the platinum-treated arm (Arm A) to assess if the survival benefit held independent of BRCA1/2 or PALB2 mutations. HRD+ and BRCA/PALB2mut pts (4.8%; n = 37) had a mOS of 13.3 months compared to 11.5 months in HRD+ and BRCA/PALB2wt (5.3%; n = 41) pts (HR: 0.7; 90% CI: 0.4–1.1). Comparatively, HRD- and BRCA/PALB2mut pts (2.1%; n = 16) had a mOS of 10.5 months compared to 8.3 months in HRD- and BRCA/PALB2wt (80.9%; n = 623) pts (HR: 0.7; 90% CI: 0.4–1.3). **Conclusions:** Tempus HRD-RNA is a novel predictive clinical biomarker that identifies a higher percentage of pts who may benefit from targeted treatment than current guidelines. The HRD-RNA algorithm offers a remarkable precision oncology tool to improve outcomes in pancreatic cancer, and has important clinical value in the era of novel HRD drug development. Research Sponsor: None.

4211 **Poster Session**

The SPIN Score, a simple clinical score to predict pain response following celiac plexus radiosurgery for retroperitoneal cancer pain. First Author: Yaacov Lawrence, Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel

Background: Celiac plexus radiosurgery is a novel non-invasive palliative treatment for pancreatic cancer pain that was recently added to NCCN guidelines. In the pivotal phase 2 trial (NCT03323489; Lancet Oncol 2024;25:1070-79), pain response was 53% (95% CI 42-64%). Prespecified exploratory analysis identified age and BMI as predictors; however, no clinically actionable patient selection tool was developed. We sought to identify additional predictors and create a practical risk stratification score. **Methods:** Post-hoc analysis of 90 evaluable patients from the phase 2 trial. Pain response was defined per protocol (≥2-point reduction in average pain from baseline to three weeks, on Brief Pain Inventory–Short Form). Candidate baseline predictors were examined by univariate and multivariate logistic regression. Only variables remaining significant in multivariate analysis were included in the final score to ensure independence and avoid overfitting. Internal validation used bootstrap resampling (500 iterations with replacement) to calculate optimism-corrected AUC. Analysis performed using Stata IC/16.1. **Results:** Univariate analysis identified 4 significant predictors: neurotoxic chemotherapy exposure (OR 5.33, 95% CI 2.13-13.4, $p<0.001$), baseline pain intensity (OR 1.73, p=0.003), age (OR 1.06, p=0.014), and therapy line (OR 0.65, p=0.04). On multivariate analysis, only neurotoxic exposure (OR 5.1, p=0.009) and baseline pain (OR 1.8, p=0.003) remained independently significant predictors. Age and therapy line lost significance due to collinearity. Dose-response analysis confirmed pain threshold optimization: >5 (61.5% response), >6 (65.8%), >7 (83.3%), >8 (85.7%), with >6 providing optimal discrimination. We created the SPIN (Severe Pain + Intact Nerves) score (0-2 points): baseline Pain >6 (+1), No prior Neurotoxic chemotherapy (+1). Response rates by score: 0 points: 32% (n=31); 1 point: 53% (n=40); 2 points: 89% (n=19). The 2-variable model achieved an apparent AUC=0.716. Following bootstrapping, the optimism-corrected AUC was=0.714. **Conclusions:** The simple score allows identification of distinct patient subgroups with markedly different probabilities of pain response following celiac plexus radiosurgery. This suggests the intervention should be considered earlier in the disease course, before exposure to neurotoxic agents. External validation is needed prior to clinical implementation. Financial support: Gateway for Cancer Research, The Israel Cancer Association. Clinical trial information: NCT03323489. Research Sponsor: None.

4212 **Poster Session**

A phase II study of FOLFIRINOX (FFX) combined with the glycogen synthase kinase-3beta (GSK-3β) inhibitor elraglusib (ELRA) and the transforming growth factor beta (TGFβ) inhibitor losartan (LOS) in patients with untreated metastatic pancreatic ductal adenocarcinoma (mPDAC). First Author: Priyadarshini Satyajit Pathak, Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Concurrent inhibition of GSK-3β and TGF-β signaling pathways aims to target epithelial-mesenchymal transition (EMT) plasticity, metabolic reprogramming, desmoplasia and immune escape mechanisms that underlie therapeutic resistance in mPDAC **Methods:** In this multi-institutional, open-label, four-arm (non-comparator) phase II trial conducted across three academic centers in the United States, 49 patients with newly diagnosed, treatment naive mPDAC were randomized to Arm 1: FFX alone (biomarker control, n=4) or Arm 2: FFX plus LOS (50 mg daily); Arm 3: FFX plus ELRA (9.3 mg/kg IV twice weekly); Arm 4: FFX plus LOS plus ELRA (n=15/arm). After 12 cycles of FFX without progression, patients transitioned to maintenance 5-FU (plus ELRA/LOS, based on the arm) and resumed full therapy at progression; treatment withdrawal required progression on full therapy or treatment-limiting toxicity. The primary endpoint was progression-free survival (PFS). **Results:** Between September 19, 2022, and January 2, 2025, 49 patients were enrolled (median age 65 years; 51% female; 74% White). At the data cutoff (July 6, 2025), 14 (28.6%) patients remained alive with a median follow-up of 9 months. Median PFS was 5.1 months (95% CI 1.1–NR) in Arm 1, 5.9 months (95% CI 1.6–9.9) in Arm 2, 6.0 months (95% CI 1.8–9.8) in Arm 3, and 6.5 months (95% CI 3.8–8.5) in Arm 4. 9-month PFS could not be calculated in arm 1, 29.3% (95% CI 9.2-53.3) in Arm 2, 37.3% (95% CI 13.6 – 61.5%) in Arm 3, and 21.7% (95% CI 5.3 –45.1) in Arm 4. Median overall survival (OS) was 7.7 months (95% CI 1.1–NR), 8.2 months (95% CI 3.3–14.5), 9.8 months (95% CI 4.3–NR), and 9.8 months (95% CI 5.6–15.6), respectively in each arm. Objective response rate 24.5% (12/49);stable disease 44.9% (22/49). 14/49 (28.5%) patients received maintenance therapy, with a median duration of 2.4 months. Treatment was generally well tolerated, grade ≥3 treatment-related adverse events occurred in 34.7% of patients; one treatment-related death due to sepsis occurred in Arm 3. Notably, a subset of patients in Arms 3 and 4 demonstrated deep and sustained clinical responses; Correlative biomarker analyses are ongoing to identify molecular and immune features associated with these long term responders. **Conclusions:** Although clinical outcomes with the novel combinations did not exceed historical standards of care, this non-comparator phase II study demonstrates the feasibility and tolerability of combinatorial pathway inhibition in mPDAC. This study enables ongoing correlative analyses of EMT plasticity, stromal remodeling, and immune escape in mPDAC and establishes a robust platform to define determinants of resistance and durable response. Clinical trial information: NCT05077800. Research Sponsor: Lustgarten Foundation; Actuate Therapeutics Inc.

4213 **Poster Session**

Post-hoc efficacy and biomarker analysis of elraglusib plus gemcitabine/nab-paclitaxel versus chemotherapy alone in metastatic pancreatic ductal adenocarcinoma. First Author: Devalingam Mahalingam, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL

Background: Elraglusib (9-ING-41), a glycogen synthase kinase-3β (GSK-3β) inhibitor, has multimodal antitumor activity. In the international, open-label, randomized phase 2 1801 Part 3B study, elraglusib plus gemcitabine/nab-paclitaxel (GnP) was evaluated in previously untreated metastatic pancreatic ductal adenocarcinoma (mPDAC), with patients randomized 2:1 to weekly elraglusib/GnP or GnP alone. Primary endpoints were median overall survival (mOS) and 1-year survival. The GnP control arm demonstrated shorter mOS than contemporary randomized trials (7.2 months vs 9.2 months in NAPOLI-3 and 9.7 months in PASS-01), driven by higher early mortality (0–2 months: 23.1% vs 10.1% in NAPOLI-3). Given balanced randomization, similar early mortality was inferred in the elraglusib/GnP arm, prompting post-hoc analyses to contextualize efficacy and identify factors associated with early death. **Methods:** Efficacy and safety were summarized descriptively. Time-to-event endpoints were analyzed using Kaplan–Meier estimates, log-rank testing, and Cox proportional hazards models. Response rates were compared using the Cochran–Mantel–Haenszel test. Post-hoc subgroup, sensitivity, and machine-learning–based multivariate analyses explored clinical, demographic, and biomarker correlates of survival and early mortality. **Results:** In the full randomized population (elraglusib/GnP n=155; GnP n=78), elraglusib/GnP improved mOS by 2.9 months versus GnP (10.1 vs 7.2 months; HR 0.62; 95% CI 0.46–0.84; p=0.01), with 1-year survival rates of 44.1% versus 22.3%. Among patients receiving ≥1 full treatment cycle, mOS was 12.5 months with elraglusib/GnP and 8.5 months with GnP, comparable to contemporary registrational trials. Across multiple post-hoc sensitivity analyses—including evaluable patients, those matched to NAPOLI-3 baseline tumor burden, patients treated in the EU (early mortality 4%), and those achieving ≥20% CA19-9 decline within the first 1–2 cycles—elraglusib/GnP consistently demonstrated a ≥4-month OS advantage. Early death was associated with low baseline albumin (<3 g/dL), high CA19-9 (>800 U/mL), high tumor burden, and KRAS, TP53, and CDKN2A co-mutations. **Conclusions:** The elevated early mortality in the GnP control arm reflects enrollment of a heterogeneous, real-world mPDAC population with less restrictive eligibility than recent registrational trials. Post-hoc analyses identify key clinical and molecular drivers of early death and confirm a consistent survival benefit with elraglusib/GnP. These hypothesis-generating findings directly inform eligibility criteria, stratification, and endpoint assumptions for the planned phase 3 trial. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics.

4214 **Poster Session**

Time toxicity in patients with advanced pancreatic cancer in Mexico. First Author: Cecilia Ximenez Camilli, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Tlalpan, DF, Mexico

Background: Advanced pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal malignancies despite advances in systemic therapy. Beyond survival, the burden of time spent receiving health care (also known as time toxicity) has emerged as a relevant patient-centered outcome, particularly in diseases where treatment benefits may be modest. This study aimed to quantify time toxicity in patients with advanced PDAC and to analyze differences in time toxicity by demographic and clinical characteristics. **Methods:** We conducted a subanalysis of a single-center prospective cohort of patients with advanced solid tumors enrolled in a patient navigation program in Mexico. Patients ≥18 years diagnosed with advanced PDAC between June 2017 and August 2023 were included; patients with a second invasive malignancy or treated outside the institution were excluded. Demographic and clinical variables, baseline quality of life (FACT-G), and days with in-person healthcare encounters (clinic visits, treatments, tests, emergency visits, and hospitalizations, regardless of whether oncology-related) were collected from the diagnosis of advanced disease. Overall survival (OS) was defined as the time from diagnosis of advanced PDAC to death or loss to follow-up. Time toxicity was defined as the proportion of days involving in-person healthcare contact relative to OS. Comparisons used nonparametric tests and beta regression models were fitted to evaluate factors associated with time toxicity. **Results:** A total of 103 patients were included. Median age was 64 years, 65% were women, 83.5% presented with de novo advanced PDAC, and 75.7% received palliative chemotherapy. The mean baseline FACT-G score was 63.7±15.4. Median follow-up was 13.0 months, and median OS for the entire cohort was 11.5 months (95% CI, 6.2-16.7). The median time toxicity of the sample was 21.8% (IQR, 14.9-31.7). Patients with recurrent advanced PDAC experienced lower time toxicity than those with de novo disease (14.9% vs 22.8%, p = 0.003). In multivariable beta regression, disease presentation remained the only independent factor associated with increased time toxicity (β-0.51, p = 0.011). Age, sex, receipt of chemotherapy, and baseline FACT-G score were not independently associated with time toxicity. In an exploratory subgroup analysis among patients receiving palliative chemotherapy, patients ≥65 years had higher time toxicity compared to younger patients (23.4% vs. 17.9%; p = 0.041). **Conclusions:** In this cohort of Mexican patients with advanced PDAC, approximately one-fifth of OS time was spent in direct contact with health care system. Time toxicity was associated with disease trajectory rather than treatment or patient characteristics. Among patients receiving palliative chemotherapy, older patients experienced higher time toxicity. These findings highlight the importance of incorporating time toxicity into shared decision-making. Research Sponsor: Fundación Carlos Slim.

4215 **Poster Session**

Combined safety and efficacy results from three clinical studies evaluating alpha radiotherapy for advanced pancreatic cancer. First Author: Corey Miller, Jewish General Hospital, McGill University, Montreal, QC, Canada

Background: Pancreatic cancer (PDAC) remains associated with poor prognosis and limited treatment options, particularly in patients with advanced disease. Diffusing Alpha-Emitter Radiation Therapy (Alpha DaRT), a novel alpha-emitting radiation source, has shown initial clinical benefit in superficial epithelial solid tumors. The pooled studies presented here evaluated the safety and efficacy outcomes for endoscopic ultrasound (EUS)-guided alpha radiotherapy using Alpha DaRT in patients with PDAC. **Methods:** This analysis pooled data from three prospective clinical studies at 3 medical centers in Canada and Israel evaluating Alpha DaRT in patients with locally advanced or metastatic PDAC, regardless of previous lines of therapy. Primary outcome was safety, as assessed by CTCAE V5. Secondary outcomes were best overall response (BOR) of the primary tumor assessed per RECIST V1.1 and overall survival (OS), defined from Alpha DaRT treatment. **Results:** A total of 58 subjects (31 male, 27 female), median age 72 (range 41-91), were recruited between 2023 and 2025 across the three trials. Treatment-associated AEs of any grade occurred in 21 patients (36%). Grade ≥3 AEs occurred in 5 patients (9%) (biliary obstruction, abdominal pain, fever, liver enzyme imbalance and bacteremia). There were no treatment-related deaths and all grade ≥3 AEs resolved. Across all patients evaluable for response, the BOR showed a disease control rate of 87% and an objective response rate of 27%, with 3 complete and 9 partial responses. Median OS for the cohort was 7.9 months (95% CI: [6.1–11.6]): 10.4mo (95% CI: [7.3–13.4]) when given in 2nd line (N = 24) and 7.5 months (95% CI: [4.2–11.8]) when given in 3rd line (N = 21). **Conclusions:** In this pooled analysis of three clinical studies, EUS-guided Alpha DaRT demonstrated a reassuring safety profile and promising early efficacy signals in patients with advanced PDAC. The observed survival outcomes and radiographic responses support further clinical investigation, which is underway. Clinical trial information: NCT04002479; NCT05781555; NCT05657743. Research Sponsor: None.

4216 **Poster Session**

Single-cell circulating tumor cell genomics of KRAS-independent oncogenic sub-populations and longitudinal clonal evolution in metastatic pancreatic adenocarcinoma. First Author: Mandana Kamgar, Medical College of Wisconsin, Milwaukee, WI

Background: KRAS mutations are a dominant oncogenic driver in metastatic pancreatic ductal adenocarcinoma (mPDAC) and are routinely detected using ctDNA. However, ctDNA reflects pooled signals from dominant high-shedding clones and may incompletely capture intra-patient heterogeneity or tumor evolution. Circulating tumor cells (CTCs) enable single-cell genomic interrogation and longitudinal tracking of evolving subpopulations. We compared genomic alterations, tumor heterogeneity, and pathway dynamics using ctDNA and single-cell CTC DNA in mPDAC. **Methods:** Under an MCW IRB approved protocol (PREDICT-MCW; NCT05802069), 16 patients with mPDAC receiving standard of care were enrolled. Peripheral blood was collected at baseline and longitudinally at 90-day intervals. Live single CTCs were isolated using the OncoIncytes platform with anti-EpCAM–based glass bead capture and gentle release. Genomic DNA from individual CTCs underwent linear amplification and targeted sequencing using a 1080-gene panel on the Illumina NextSeq 2000. Matched ctDNA was analyzed using the same panel. Variant calling used the iCore pipeline. Alterations were compared at gene and patient levels. Tumor heterogeneity was assessed using mutant-allele tumor heterogeneity (MATH). **Results:** CTC counts were highest at baseline (mean 6.5 CTCs per patient; range 2–11) and varied longitudinally with marked inter-patient heterogeneity. At first on-treatment assessment, 50% of evaluable patients showed reduced CTC counts, while others exhibited stable or increased levels. Across all timepoints, 49 altered genes were identified. Single-cell CTC profiling revealed broader genomic representation, with 32 genes (65%) detected exclusively in CTC-DNA, 14 (29%) shared with ctDNA, and 3 (6%) detected exclusively by ctDNA. At the patient level, CTC-DNA identified genomic alterations in all patients (16/16), whereas ctDNA detected alterations in 75% (12/16). At baseline, 61% of CTCs achieved $\geq 11\times$ coverage across KRAS exon 2 and codon 12. KRAS alterations were detected in only 6% (1/16) of patients by CTC-DNA compared with 44% (7/16) by ctDNA, persisting longitudinally (13–19% vs 59–76%, CTC-DNA vs ctDNA). KRAS-negative CTCs harbored recurrent alterations in MAPK, DNA damage response, receptor tyrosine kinase, and tumor suppressor pathways. CTCs demonstrated higher intra-patient heterogeneity than ctDNA (MATH 50.5 vs 25, $p < 0.05$). **Conclusions:** Single-cell CTC profiling reveals KRAS-independent tumor sub-populations present from baseline and dynamic clonal evolution not captured by ctDNA alone, revealing tumor heterogeneity and KRAS-independent disease biology. Paired CTC and ctDNA analysis provides complementary resolution of persistent atypical oncogenic and tumor suppressor sub-clones not evident from bulk liquid biopsy. Research Sponsor: None.

4217 **Poster Session**

Knowledge distillation for pancreatic cancer diagnosis: EfficientNet-based deep learning for stage stratification with real-world deployment optimization. First Author: Lalith Akaash Ramasamy, Saveetha Medical College and Hospital, Chennai, India

Background: Pancreatic cancer is among the most lethal malignancies, with a 5-year survival below 12%. Prognosis is strongly stage dependent, yet early disease is frequently misclassified as chronic pancreatitis or benign cystic lesions, resulting in diagnostic delay and loss of surgical opportunity. Although deep learning models demonstrate high accuracy on cross-sectional imaging, their computational demands limit deployment in resource-constrained settings. Knowledge distillation enables transfer of diagnostic capability from high-capacity teacher models to lightweight student networks while preserving performance. We evaluated whether a distilled EfficientNetB0 model could retain EfficientNetB7-level accuracy for pancreatic cancer stage stratification while enabling real-world deployment. **Methods:** We analyzed 2,840 contrast-enhanced abdominal CT studies, including pancreatic ductal adenocarcinoma (n = 1,400; 700 early-stage resectable or borderline-resectable, 700 locally advanced or metastatic), chronic pancreatitis (n = 900), and benign pancreatic lesions (n = 540) from multiple international centers. Ground truth was established by multidisciplinary consensus incorporating histopathology, surgical findings, and longitudinal follow-up. A high-capacity EfficientNetB7 teacher model (≈66M parameters; 37 GFLOPs) trained on multiphasic CT served as reference. A lightweight EfficientNetB0 student model (≈5.3M parameters; 0.39 GFLOPs; $>$ 90% parameter reduction) was trained using temperature-scaled knowledge distillation with regularized cross-entropy loss. Performance metrics included accuracy, sensitivity, specificity, F1-score, and AUROC. Deployment feasibility was independently evaluated by abdominal radiologists and oncologists across six continents. **Results:** The distilled EfficientNetB0 achieved 96.6% accuracy for stage stratification (early vs advanced disease), with sensitivity of 97.4%, specificity of 95.8%, and AUROC of 0.989. Differential diagnosis accuracy was 94.8% for pancreatic cancer versus chronic pancreatitis and 95.6% versus benign lesions. External validation accuracy ranged from 93% to 97%. Mean inference time was 38 ms per image compared with 330 ms for EfficientNetB7. Knowledge distillation preserved 99.1% of teacher performance while reducing computational cost by $>$ 95%. **Conclusions:** Knowledge distillation enables a lightweight EfficientNetB0 to achieve near–EfficientNetB7 accuracy for pancreatic cancer stage stratification while markedly reducing computational complexity. This scalable approach supports real-time imaging decision support and addresses key barriers to global deployment of AI-assisted pancreatic cancer diagnosis. Research Sponsor: None.

4218 **Poster Session**

Phase IIb randomized trial of FOLFIRINOX plus ibrilatazar (ABTL0812) versus placebo as first-line treatment in metastatic pancreatic cancer: An analysis from the PanC-ASAP study. First Author: Davendra Sohal, Division of Hematology/Oncology, University of Cincinnati Cancer Center, Cincinnati, OH

Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has poor prognosis and limited first-line treatment options. Ibrilatazar (ABTL0812) is a first-in-class oral agent that induces cytotoxic autophagy selectively in cancer cells. Favorable safety and tolerability of the combination with FOLFIRINOX were established in a Phase I study. D.S. and T.M. are equal contributors. **Methods:** PanC-ASAP is a Phase IIb double-blind, randomized, placebo-controlled (1:1) study evaluating the efficacy and safety of ibrilatazar (1300 mg TID) plus FOLFIRINOX versus placebo plus FOLFIRINOX as first-line therapy in mPDAC, conducted across 23 sites in the US, Spain, France, and Israel. Eligible patients had histologically confirmed mPDAC, ECOG PS 0–1, and no prior systemic treatment for metastatic disease. Treatment continued until disease progression or intolerable toxicity. Primary endpoint was progression-free survival (PFS), defined as time from randomization to radiographic disease progression or death, assessed by blinded independent central review in the intention-to-treat (ITT) population. Overall survival (OS) was a key secondary endpoint. Safety was assessed in all treated patients. Pre-specified stratification analysis revealed an imbalance in ECOG between arms (ECOG 0/1: 40%/60% ibrilatazar vs 54%/46% placebo), prompting an exploratory efficacy analysis by ECOG PS subgroup. Time-to-event endpoints were analyzed using Kaplan–Meier methods and log-rank tests. **Results:** In the ITT population (n = 140), median PFS for ibrilatazar vs placebo was 9.4 vs 7.9 mths (HR 0.95; 90% CI, 0.69-1.33; p = 0.814). An exploratory analysis by ECOG showed that, among patients with ECOG 0 (n = 66; ibrilatazar, n = 28; placebo, n = 38), median PFS of 11.1 vs 6.5 mths (HR 0.60; 95% CI, 0.34–1.08; p = 0.089), and median OS of 19.3 vs 12.0 mths (HR 0.57; 95% CI, 0.31–1.05; p = 0.072). Consistent trends favoring ibrilatazar were observed across efficacy endpoints, including objective response rate and duration of treatment. Safety profile of ibrilatazar plus FOLFIRINOX was consistent with the known FOLFIRINOX toxicities. The most common grade ≥3 treatment-emergent adverse events in the ibrilatazar vs placebo were neutropenia (21% vs 22%), diarrhea (21% vs 16%), and neurotoxicity (0% vs 14%). **Conclusions:** Although primary PFS endpoint was not met in the ITT population, exploratory analysis showed clinically meaningful and consistent efficacy improvements among ECOG 0 patients treated with ibrilatazar plus FOLFIRINOX, with 60% and 70% increases in median OS and median PFS respectively. These findings support further investigation in selected mPDAC populations and suggest ECOG may modify treatment benefit. Clinical trial information: NCT04431258. Research Sponsor: RFA-FD-20-001 (Clinical Studies of Orphan Products Addressing Unmet Needs of Rare Diseases (R01)); FD-R-006817-01; Funding Source Name: H2020 - EIC - SMEInst - 2018 - 2020; 954825.

4219 **Poster Session**

A phase II trial of binimetinib in combination with encorafenib in patients with pancreatic malignancies and a somatic *BRAF*^{V600E} mutation. First Author: Tara Tamar Arouchian, Samuel Oschin Comprehensive Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Pancreatic ductal adenocarcinoma (PDAC) remains a notoriously difficult-to-treat malignancy, with limited therapy options for patients with advanced disease. While KRAS mutations are the dominant oncogenic driver in PDAC, next-generation sequencing has enabled the identification of rare, targetable alterations such as the BRAF V600E mutation, which occurs in approximately 2-3% of cases. BRAF mutant cell lines are responsive to MEK and RAF inhibitors. This study evaluates the efficacy of the combination of encorafenib and binimetinib as ≥ 2nd line therapy in this specific molecular subgroup of pancreatic cancer patients. **Methods:** This study used a planned two-stage design. Seven patients were pre-registered; one did not meet eligibility criteria and was excluded. Six patients were enrolled in Stage 1, which required an objective response (OR) in 40% of patients to proceed to Stage 2. Stage 2 was planned to enroll an additional 16 patients, contingent on meeting this efficacy threshold. Enrolled patients received treatment in 28-day cycles until disease progression or for a maximum of 36 cycles. Patients self-administered encorafenib (450 mg orally once daily) and binimetinib (45 mg orally twice daily) starting on Day 1 of each cycle. Objective responses were assessed using RECIST version 1.1 over 24 weeks. **Results:** The median number of cycles was 8. The objective response rate at 24 weeks was 33.33%. The overall objective response rate was 50%. The median time to response for progression-free survival, overall survival, duration of response, and time to response was 7.1, 15.0, 9.9, and 3.9 months respectively, with 95% CI in all categories. 50% of patients experienced at least one Grade ≥3 adverse event, including anemia, thromboembolic events, and acute kidney injury. **Conclusions:** The six BRAF-V600E-mutated PDAC patients in our cohort demonstrated meaningful antitumor activity with a manageable safety profile after treatment with encorafenib and binimetinib. Although the study was prematurely terminated due to limited accrual, observed objective responses and survival outcomes suggest that dual RAF/MEK inhibition may represent a feasible therapeutic strategy in this rare molecular subgroup. Larger studies are warranted to further define the efficacy and safety of this treatment combination in BRAF-V600E-mutated pancreatic cancer. Clinical trial information: NCI-2020-02972. Research Sponsor: None.

4220 **Poster Session**

TME-informed bioprinted 3D tissue model as used to characterize architecture-associated drug uptake and response in PDAC. First Author: Amr Mahmoud, CerFlux, Birmingham, AL

Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest solid tumors despite extensive drug development efforts. Beyond tumor cell-intrinsic factors, therapeutic failure in PDAC is strongly influenced by the tumor microenvironment (TME), which is dominated by a collagen-rich desmoplastic extracellular matrix (ECM). This architecture alters tissue mechanics, restricts diffusion, and limits effective drug delivery to tumor cells. However, most preclinical platforms rely on 2D models that fail to capture human-relevant TME architecture, potentially leading to overestimation of drug uptake and potency. Amid growing regulatory and scientific momentum toward New Approach Methods (NAMs), there is an urgent need for human-relevant, architecture-aware models that improve translational predictivity in PDAC. **Methods:** Primary human PDAC specimens were analyzed using quantitative, spatially resolved TME mapping to characterize extracellular matrix (ECM) composition, collagen density, and intratumoral versus peripheral distribution. From our prior PDAC analysis, human tumors exhibited collagen-dominant ECM with diffuse intratumoral organization rather than peripheral confinement. These architectural features were used to configure a 3D bioprinted *ex vivo* slice tissue (BEST) PDAC model using PANC02 cells. Drug uptake kinetics and therapeutic response were evaluated in TME-informed 3D BEST models and directly compared with conventional 2D monolayer cultures using matched compounds and exposure paradigms. **Results:** Spatial TME mapping confirmed that human PDAC tumors harbor dense, heterogeneously distributed collagen spanning the tumor parenchyma, a feature not captured by simplified culture systems. Incorporation of these intratumoral collagen features into the 3D BEST model resulted in delayed drug uptake and attenuated response dynamics consistent with diffusion-limited transport. In contrast, 2D models demonstrated accelerated growth kinetics, more rapid drug uptake, and higher apparent drug potency over shorter exposure durations. These findings indicate that architecture-associated transport barriers intrinsic to PDAC substantially modulate therapeutic response and that conventional 2D systems may overestimate drug efficacy by failing to account for collagen-mediated resistance mechanisms. **Conclusions:** By directly linking quantitative TME mapping to 3D model configuration, this NAMs-aligned bioprinted PDAC platform captures architecture-associated constraints on drug uptake that are absent from conventional models. This approach provides a human-relevant framework for evaluating therapeutic response in desmoplastic tumors and supports improved translational fidelity and therapeutic prioritization in PDAC. Research Sponsor: U.S. National Science Foundation; TI-2321805; National Cancer Institute; 1R43CA254493-01; Innovate Alabama.

4221 **Poster Session**

Next-generation cancer organoids 2.0 in precision cancer medicine: Patient-derived pancreatic ductal adenocarcinoma organoids model to describe drug sensitivity and complexity of tumor biology. First Author: Joo Kyung Sophie Park, Samsung Medical Center, Seoul, South Korea

Background: Organotypic models of patient-specific tumors are revolutionizing our understanding of cancer heterogeneity and its implications for personalized medicine. The study's aims were as follows: 1) to establish a PDAC patient-derived organoid (PDO) model obtained from various PDAC specimens. 2) to find out clinicogenomic factors affecting patients' outcomes. **Methods:** The SMC PDAC Cohort Patients were prospectively enrolled and underwent EUS-guided FNB, metastatic sites (such as liver, ascites, lung, and bone), and surgical resection. PDAC PDOs were comprehensively analyzed for histology, next generation sequencing (NGS), and high-throughput screening (HTS) drug sensitivity tests. **Results:** The 735 PDAC patients were prospectively enrolled in this study. PDAC PDO platform has been trying to establish from the following cancer specimens: ascites, biopsies from bone, liver, lung, and pancreas, or surgical resection. The success rate was as follows according to the source of obtaining site; ascites due to peritoneal seeding (3/3: 100%), bone mets (1/1: 100%), EUS-FNB (195/183: 87.8%), liver mets (7/8: 87.5%), lung mets (1/1: 100%), surgical specimens (394/500: 78.8%) and PDO was successfully established within 8.2 ± 2.6 days. It took approximately 3 weeks to acquire each specimen and generate sufficient PDAC PDOs for the simultaneous HTS drug sensitivity test and NGS. Whole exome or genome sequencing (WES/WGS, n = 357) showed an almost identical concordance between original PDAC tissues and matched PDOs and the increased frequency of genetic alterations in PDOs. The HTS drug sensitivity test (n = 151) revealed the clinical correlation between the PDO response and the actual chemotherapeutic response of the study patients in both palliative and adjuvant in real-world settings (ranging from 84.0~ to 91.2%). In addition, whole transcriptome sequencing (n = 373) identified nab-paclitaxel resistance-associated genes such as ITGB7, ANPEP, and ST3GAL1, and also found early recurrence-related genes including COL2A1, CALB1, and CYP24A1 in the extracellular matrix, calcium signaling, and vitamin D metabolism. **Conclusions:** The PDAC PDO platform may become a valuable tool for personalized medicine and may give us insights into tumor biology. Research Sponsor: None.

4222 **Poster Session**

Actionable genomic alterations and survival in *KRAS* wild-type pancreatic ductal adenocarcinoma: Analysis of the MSK-CHORD 2024 clinico-genomic cohort with spotlight on *NRG1* fusions. First Author: Ayham Al-Omari, Detroit Medical Center - Wayne State University, Detroit, MI

Background: Pancreatic ductal adenocarcinoma (PDAC) is predominantly driven by KRAS mutations; however, approximately 10% of tumors are KRAS wild-type (KRAS-WT). Among these, NRG1 gene fusions have recently gained heightened clinical relevance following the FDA's accelerated approval of zenocutuzumab for NRG1 fusion–positive PDAC after prior therapy. Contemporary real-world data characterizing actionable alteration yield and outcomes in KRAS-WT PDAC remain limited. **Methods:** We analyzed patients with PDAC (OncoTree: PAAD) from MSK-CHORD 2024. KRAS status was defined by the presence or absence of pathogenic KRAS somatic mutations. NRG1 fusions were identified through structural variant analysis. A predefined clinically actionable alteration set included NRG1 and NTRK1–3 fusions, MSI-H/dMMR, BRCA1/2 or PALB2 alterations, ERBB2 amplification, and BRAF V600E mutation. The primary endpoint was overall survival (OS) from the date of molecular profiling. Secondary endpoints included prevalence of actionable alterations within KRAS-WT PDAC and enrichment of NRG1 fusions by KRAS status. **Results:** Among 2,703 patients with PDAC, 2,424 (89.7%) had KRAS mutations and 279 (10.3%) were KRAS-WT. NRG1 fusions were identified exclusively within KRAS-WT tumors (4/279; 1.43%) and were absent among KRAS-mutant PDAC. As summarized in Table 1, 25 of 279 KRAS-WT PDAC patients (9.0%) had at least one clinically actionable genomic alteration. These included NRG1 and NTRK fusions, MSI-H/dMMR, homologous recombination repair gene alterations, ERBB2 amplification, and BRAF V600E mutation. Median OS differed substantially by KRAS status. Patients with KRAS-WT PDAC demonstrated longer survival compared with those with KRAS-mutant disease (26.3 vs 14.9 months). Patients with NRG1 fusion–positive PDAC had a median OS of 22.9 months, acknowledging limited sample size (n=4). **Conclusions:** KRAS-WT PDAC accounts for approximately one-tenth of cases and is associated with significantly longer overall survival compared with KRAS-mutant disease. Nearly 1 in 10 KRAS-WT tumors harbored clinically actionable genomic alterations, including NRG1 fusions, now linked to an FDA-approved targeted therapy. These findings support routine comprehensive molecular profiling, including fusion detection, in KRAS-WT PDAC and underscore the clinical relevance of precision oncology approaches in this distinct subgroup. Research Sponsor: None.

Genomic characteristics and actionable alterations in KRAS–wild-type PDAC (MSK-CHORD 2024).

Characteristic	KRAS-Mutant PDAC (n=2,424)	KRAS–Wild-Type PDAC (n=279)
Median OS, months	14.9	26.3
Any actionable alteration*	–	25 (9.0%)
NRG1 fusion	0 (0%)	4 (1.43%)
NTRK1–3 fusion	–	3 (1.08%)
MSI-H/dMMR	–	2 (0.72%)
BRCA1/2 mutation	–	6 (2.15%)
PALB2 mutation	–	1 (0.36%)
ERBB2 amplification	–	5 (1.79%)
BRAF V600E	–	7 (2.51%)

4223 **Poster Session**

Exosomal miRNA signatures as predictors of response to neoadjuvant FOLFIRINOX and GEM/nab-paclitaxel in resectable pancreatic cancer: The PRECEPT study. First Author: Takayuki Noma, Department of Molecular Diagnostics and Experimental Therapeutics, Beckman Research Institute of City of Hope, Biomedical Research Center, Monrovia, CA

Background: Neoadjuvant chemotherapy (NAC) with FOLFIRINOX or gemcitabine plus nab-paclitaxel (GEM/nab-PTX) is widely used for resectable and borderline-resectable pancreatic ductal adenocarcinoma (PDAC). However, 10–20% of patients experience disease progression or severe toxicity during NAC, leading to loss of opportunity for curative resection. Given substantial differences in treatment responsiveness between regimens, reliable regimen-specific predictive biomarkers are needed to improve preoperative risk stratification and treatment selection. The PRECEPT trial (NCT07226154) aims to develop circulating exosomal microRNA (exo-miRNA)–based predictors of NAC response. **Methods:** Pre-treatment plasma samples were collected from patients with resectable or borderline-resectable PDAC prior to NAC. Exo-miRNAs were profiled by small RNA sequencing in a discovery cohort of 49 patients (FOLFIRINOX, n = 31; GEM/nab-PTX, n = 18) to identify regimen-specific candidate exo-miRNAs, which were subsequently quantified by qRT-PCR in a validation cohort of 73 patients (FOLFIRINOX, n = 43; GEM/nab-PTX, n = 30). Regimen-specific miRNA panels were constructed using stepwise selection followed by Firth penalized logistic regression. To benchmark against conventional biomarkers, multivariable Firth logistic regression models including the panel score and baseline CA19-9 were performed to evaluate the incremental predictive value of the exo-miRNA panels. Predictive performance was assessed by receiver operating characteristic (ROC) analysis. **Results:** In the discovery cohort, exo-miRNA signatures achieved areas under the curve (AUC) of 0.953 for the FOLFIRINOX panel and 1.000 for the GEM/nab-PTX panel. In the qRT-PCR validation cohort, performance remained robust (AUC 0.835 and 0.882, respectively). Higher panel scores were significantly associated with non-response to NAC ($p < 0.01$). In multivariable analyses, the exosome-derived miRNA panels provided predictive information beyond CA19-9 and remained independent predictors of treatment non-response in both therapeutic cohorts, demonstrating incremental value over conventional biomarkers. Both panels showed high sensitivity with low false-negative rates, supporting their clinical utility in identifying patients unlikely to benefit from neoadjuvant chemotherapy for each regimen. **Conclusions:** We developed two regimen-specific circulating exo-miRNA panels capable of predicting response to FOLFIRINOX and GEM/nab-PTX prior to treatment initiation. These panels provide predictive information beyond CA19-9 and may support individualized NAC selection, risk-adapted treatment planning, and improved preoperative decision-making in resectable PDAC. Clinical trial information: NCT07226154. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

4224 **Poster Session**

Phase I clinical trial evaluating dual-targeting CAR-T cells (KD-496) against CLDN18.2 and NKG2DL in advanced gastrointestinal cancers and pancreatic cancers. First Author: Panpan Zhang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Early Drug Development Centre, Peking University Cancer Hospital & Institute, Beijing, Beijing, China

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has shown limited efficacy in gastrointestinal (GI) cancers. Previous studies indicate that bispecific CAR-T cells incorporating tandem single-chain variable fragments (scFvs) demonstrate enhanced therapeutic indices compared to monospecific constructs. We developed novel bispecific CAR-T cells (KD-496) targeting both NKG2D ligands and CLDN18.2, demonstrating promising preclinical antitumor activity and safety profiles. **Methods:** We conducted an open-label, single-arm, "3+3" dose-escalation study (NCT06134960) in patients with treatment-refractory advanced GI cancers. Following lymphodepletion with fludarabine, cyclophosphamide, and nab-paclitaxel, subjects received a single KD-496 infusion at three dose levels: 1×10^8 (DL1), 3×10^8 (DL2), or 5×10^8 (DL3) CAR-T cells. Primary endpoints included safety and toxicity; secondary endpoints comprised efficacy, pharmacokinetics, and immunogenicity. **Results:** Between March 2024 and October 2025 , seven subjects (age range: 43-73 years) received KD-496 treatment (n=3 at DL1; n=3 at DL2; n=1 at DL3). Only one Grade IV possibly treatment-related adverse events (TRAEs) is Neutrophil count decreased (14%); Grade III possibly treatment-related adverse events (TRAEs) included Neutrophil count decreased (14%); Alanine aminotransferase increased (14%); Elevated aspartate aminotransferase (14%); anemia (29%); and White blood cell decreased (57%). Cytokine release syndrome (CRS) occurred in seven subjects, with one case (17%) reaching grade 3; no grade 4/5 CRS or neurotoxicity was observed. The dual-antigen requirement effectively prevented on-target off-tumor toxicity, with no patients experiencing severe gastrointestinal adverse events. No dose-limiting toxicities or serious adverse events were reported. Among evaluable subjects: Those with gastric cancer (n=4), achieved an objective response rate (ORR) of 75%; Among three subjects with pancreatic cancer, disease control rate (DCR) of 66.7% overall; Achieved an objective response rate (ORR) of 33% overall. Notably, the ORR reached 100% for both gastric cancer and pancreatic cancer advanced subjects in the medium-dose group. **Conclusions:** These initial data demonstrate a favorable safety profile for KD-496 CAR-T cells targeting NKG2DL/CLDN18.2. The preliminary efficacy signals warrant further investigation of KD-496, particularly in gastric cancer and pancreatic cancer. Clinical trial information: NCT06134960. Research Sponsor: Nanjing KAEDI Biotherapeutics.

4225 **Poster Session**

Nab-paclitaxel plus S-1 induction chemotherapy for patients with locally advanced pancreatic cancer: A multicenter, open-label phase 2 study. First Author: Zhe Cao, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: The prognosis of locally advanced pancreatic cancer is dismal. The objective of the present study was to evaluate safety and efficacy of nab-paclitaxel plus S-1 in previously untreated locally advanced pancreatic cancer. **Methods:** This multicenter, single-arm phase 2 study was conducted at 4 centers in China. Patients with Eastern Cooperative Oncology Group performance status of 0-1 received up to 8 cycles of nab-paclitaxel 120 mg/m² (day 1,8) plus 80-120mg/d S-1 (day 1-14 each 21-day cycle). After induction, patients without disease progression or unacceptable adverse events were eligible to receive continued therapy according to investigators' evaluation, including: continued chemotherapy, chemoradiation, or surgery. The primary endpoint was 6-month progress-free survival rate. The secondary endpoints were progress-free survival, overall survival, objective response rate, R0/R1 rate and safety. The reported efficacy outcomes were analyzed in the intention-to-treat population, and safety outcomes were analyzed in the treated population. This trial is registered with ClinicalTrials.gov, NCT03885219. **Results:** Between April 25, 2019, and March 29, 2023, 60 patients were enrolled in the study. 31 (51.7%) of 60 enrolled patients discontinued induction therapy, with reasons including disease progression (13 [21.7%] patients), adverse events (12 [20.0%] patients), alteration in treatment (4 [6.7%] patients), and withdrawal from study (2 [3.3%] patients). 29 (48.3%) of 60 enrolled patients completed induction treatment, 22 (36.7%) patients finished all 8 cycles of treatment, and 11 (18.3%) patients underwent surgery (10 achieved R0/R1 resection status). The 6-month progression-free survival rate was 71.0% (95%CI: 57.6%-80.9%); 12-month progression-free survival rate was 45.0% (95%CI: 32.0%-57.2%) and 12-month overall survival could reach up to 83.3% (95%CI: 70.3%-90.9%). The median progression-free survival was 11.1months (95% CI: 8.1-14.2); median overall survival was 20.2 months (95% CI: 11.2-29.2). During induction, 54 patients achieved disease control and the disease control rate was 90.0% (95% CI: 79.5%-96.2%). 16 patients had a best response of partial response; the objective response rate was 26.7% (95% CI: 16.1%-39.7%). Grade 3 or higher treatment-related adverse events (TRAEs) occurred in 32 (53.3%) patients. The most common grade 3 or higher TRAEs were neutropenia (23 [38.3%] of 60 patients), followed by leukopenia (13 [21.7%]) and fatigue (4 [6.7%]). No treatment-related deaths were reported. **Conclusions:** The data from this trial supports the favorable and efficacy of nab-paclitaxel plus S-1 for locally advanced pancreatic cancer, as well as the possibility of converting unresectable disease into surgically resectable disease. Clinical trial information: NCT03885219. Research Sponsor: None.

LBA4226 **Poster Session**

A multicenter randomized phase II trial of AHCC combined with multidisciplinary treatment for resectable/borderline resectable pancreatic ductal adenocarcinoma (jRCTs051200029). First Author: Suguru Yamada, Nagoya Central Hospital, Nagoya, Japan

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

4227 **Poster Session**

Plasma small extracellular vesicle microRNAs as non-invasive biomarkers for the diagnosis of pancreatic ductal adenocarcinoma. First Author: Yue Zhang, The Third Affiliated Hospital of Soochow University, Changzhou, Jiangsu, China

Background: Current non-invasive approaches for the diagnosis of pancreatic ductal adenocarcinoma (PDAC) exhibit inherent limitations in accuracy. Consequently, there exists an urgent and unmet need for novel non-invasive biomarkers exhibiting high sensitivity and specificity to enable PDAC diagnosis. **Methods:** We employed small RNA sequencing to detect microRNA (miRNA) expression in small extracellular vesicles (sEVs) isolated from plasma samples of study participants (n = 208). A diagnostic model was developed (n = 140) and validated (n = 68) to discriminate between patients with PDAC and non-malignant controls (healthy individuals, chronic pancreatitis, intraductal papillary mucinous neoplasms, serous cystadenomas, solid pseudopapillary tumors, pancreatic cysts, and pancreatic abscesses). **Results:** The small RNA sequencing analysis of plasma sEV miRNA identified 32 differentially expressed sEV miRNAs between non-malignant controls and PDAC patients. The diagnostic model with the best performance was constructed using 17 sEV miRNAs. The diagnostic model achieved an area under curve (AUC) of 0.939, a sensitivity of 93%, and a specificity of 90% in the training cohort and an AUC of 0.951, a sensitivity of 95%, and a specificity of 83% in the test cohort. We identified the distinct characteristics of plasma sEV miRNAs among non-malignant controls compared to PDAC patients. Moreover, nine negative miRNAs and one positive miRNA were found significantly associated with the death risk of PDAC (all $p < 0.05$). **Conclusions:** Our findings demonstrates that plasma sEV miRNA exhibits a highly discriminative biomarker for distinguishing non-malignant group from malignant group, making it a promising tool for the diagnosis of PDAC. Research Sponsor: None.

4228 **Poster Session**

Impact of radiologically identified embryological origin on recurrence patterns and survival in resectable pancreatic head adenocarcinoma. First Author: Imdat Eroglu, Gazi University School of Medicine, Department of Medical Oncology, Ankara, Turkey

Background: The pancreatic head develops embryologically from the fusion of the dorsal pancreatic (Dp) and ventral pancreatic (Vp) buds, which differ in cellular composition. Although histopathology is considered the gold standard for distinguishing these structures, they can also be differentiated radiologically. The prognostic significance of the embryological origin of pancreatic head adenocarcinomas remains unknown. This study aimed to investigate the impact of tumor embryological location on survival outcomes in patients with resectable pancreatic head adenocarcinoma. **Methods:** Patients who underwent surgical resection for pancreatic head adenocarcinoma were retrospectively analyzed. Preoperative conmputed tomography images were used to determine the embryological tumor location. The boundary between Dp and Vp was defined as a line connecting the portal vein/superior mesenteric vein to the anterior margin of the intrapancreatic bile duct. Tumors located predominantly ($\geq$80%) on one side of this boundary were classified accordingly, while tumors without $\geq$80% predominance in either region were classified as mixed. Patients were grouped as Vp, Dp, or mixed pancreatic (Mp) origin. The primary endpoint was overall survival (OS), and the secondary endpoint was progression-free survival (PFS). **Results:** A total of 164 patients were included. Tumor origin was classified as Vp in 74 patients (45.1%), Dp in 63 patients (38.4%), and Mp in 27 patients (16.5%). Mp tumors were associated with a significantly higher rate of grade 3 tumors (48.1% in Mp vs 21.6% in Vp and 23.8% in Dp, p = 0.005) and advanced T stage (T3–T4: 70.3% in Mp vs 32.4% in Vp and 47.6% in Dp, p = 0.009). Other baseline clinicopathological characteristics, and the rates of adjuvant chemotherapy and radiotherapy were similar among groups. Median PFS was 11.2 months (95% CI 10.5–11.9) in Mp, 13.0 months (95% CI 9.3–16.7) in Vp, and 9.8 months (95% CI 7.6–11.9) in Dp (p = 0.032). All recurrences in the Dp group were distant metastases, whereas Mp tumors recurred predominantly as distant metastases (85.7%) and Vp tumors showed a higher proportion of local recurrence (33.3%) ($p < 0.001$). Median OS was significantly longer in the Vp group (Mp: 16.7 months, 95% CI 8.9–27.4; Vp: 25.3 months, 95% CI 11.8–37.8; Dp: 16.7 months, 95% CI 13.2–20.3; p = 0.006). **Conclusions:** The embryological origin of pancreatic head adenocarcinoma is associated with distinct pathological features, survival outcomes, and recurrence sites. Vp-origin tumors demonstrate superior OS but higher local recurrence rates, whereas Dp-origin tumors are characterized by early distant metastasis. Preoperative CT-based identification of tumor origin serves as a non-invasive prognostic tool that may guide personalized adjuvant strategies, such as intensifying systemic therapy for Dp/Mp tumors or optimizing local control for Vp tumors. Research Sponsor: None.

4229 **Poster Session**

Early detection of pancreatic ductal adenocarcinoma (PDAC) with a multiomic liquid biopsy. First Author: Holly Butler, Dxcover Ltd, Glasgow, United Kingdom

Background: Early diagnosis remains the major unmet challenge in pancreatic ductal adenocarcinoma (PDAC), which accounts for approximately 3% of all cancers but nearly 8% of cancer-related deaths in the United States, reflecting its exceptionally poor prognosis. Overall five-year survival remains below 15%, largely because the majority of patients present with unresectable or metastatic disease at diagnosis. Curative surgical resection is feasible in fewer than 20% of cases. There is a critical need to improve risk stratification and diagnostic triage among high-risk populations, including individuals with pancreatic cystic lesions, chronic pancreatitis, and new-onset diabetes over the age of 50. However, the low short-term incidence of PDAC in these groups limits the feasibility of widespread surveillance using current imaging modalities. **Methods:** In this study, a spectroscopic blood test has been evaluated as an alternative strategy for PDAC detection. This technology employs infrared (IR) spectroscopy to interrogate blood samples, generating disease-specific spectral signatures sensitive to cancer-associated biochemical alterations. When integrated with machine learning, the approach enables detection by capturing global changes across all biomolecular components of the sample. Initially, spectra from 166 patients with PDAC were classified against those from 459 symptomatic patients with non-cancer diagnoses. The trained algorithms are then independently tested on an additional clinical dataset focused on the higher risk population (n = 975). **Results:** The initial receiver operating characteristic (ROC) curve reported an area under the curve (AUC) value of 0.84. The diagnostic algorithm reported 92% sensitivity with 52% specificity. Importantly, the model did not seem to be affected by cancer stage. The detection rates with the sensitivity-tuned model were 88% stage I, 94% stage II, 99% stage III and 95% stage IV. Validation testing provided additional confirmation of diagnostic ability in the intended use population. The ROC curve for PDAC versus all control patients reported an AUC of 0.81, and PDAC classified against high-risk non-cancers produced an AUC of 0.83. **Conclusions:** Earlier detection of PDAC has the potential to substantially improve patient outcomes and survival. While advances in genetic sequencing have enabled the identification of tumor-derived biomarkers—including circulating tumor DNA, exosomes, and microRNA—these approaches are limited in early-stage PDAC due to low tumor burden and weak signal from circulating markers. A spectroscopy-based, multi-omic blood test represents a novel strategy that may overcome these limitations, particularly in high-risk populations. Research Sponsor: None.

4230 **Poster Session**

A phase II multicenter study of NASOX regimen as adjuvant chemotherapy for patients with resected pancreatic ductal adenocarcinoma. First Author: Kuirong Jiang, Pancreas Center, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China

Background: Pancreatic ductal adenocarcinoma (PDAC) is the fifth leading cause of cancer-related mortality in China, with a 5-year survival rate of only 5%–7%. Surgical resection followed by adjuvant chemotherapy can improve this to 15%–25%, but more effective adjuvant regimens are urgently needed to further prolong survival. The PRODIGE 24/CCTG PA.6 trial demonstrated that the mFOLFIRINOX regimen significantly improved outcomes compared with gemcitabine alone. The NASOX regimen is a modified mFOLFIRINOX regimen, which uses irinotecan hydrochloride liposomes (nal-IRI) instead of irinotecan and oral fluoropyrimidine tegafur instead of fluorouracil, and has demonstrated a favorable safety profile. This study aims to assess the efficacy and safety of NASOX as an adjuvant chemotherapy regimen for patients with resected PDAC. **Methods:** This is a Phase II, single-arm, open-label, multicenter clinical trial to evaluate the efficacy and safety of NASOX as adjuvant chemotherapy in patients with resected PDAC. The primary endpoint is DFS. Secondary endpoints include overall survival (OS), safety, quality of life (QoL), compliance with adjuvant therapy, and nutritional status. Exploratory endpoints will involve genomic, metabolomic, and proteomic analyses to identify biomarkers that may predict response and safety to NASOX regimen **Results:** Between August 2024 and October 2025, 55 patients were screened, with 53 ultimately enrolled. Age ranged from 34 to 73 years (median: 59). Forty-six patients underwent at least one tumor assessment, with 11 experiencing disease recurrence and 3 deaths. Median follow-up was 11.5 months(interquartile range 9.9–15.5), yielding a 9-month DFS rate of 82.7% a 9-month OS rate of 97.7%, with median DFS and OS not yet reached. Treatment-related adverse events (TRAEs) occurred in 52 patients (100%), including grade 3 or 4 adverse events in 28 patients (53.85%). The most common Grade 3–4 treatment-related adverse events were diarrhea (17.31%), neutropenia (17.31%), hypokalemia (11.54%), and gastrointestinal pain (9.62%). **Conclusions:** NASOX regimen demonstrated the anticipated efficacy and safety profile in the adjuvant treatment of PDAC following surgery, warranting further investigation. Clinical trial information: NCT06361316. Research Sponsor: None.

4231 **Poster Session**

Safety, efficacy, and immunogenicity of adjuvant therapy with personalized cancer vaccine (PCV) RGL-270 in combination with adebrelimab and mFOLFIRINOX in resectable pancreatic ductal adenocarcinoma (PDAC). First Author: Si Shi, Department of Pancreatic Surgery, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Tumor specific neoantigens are peptides carrying somatic mutations presented by HLA molecules and recognized by T cells, which subsequently induce specific immune response (IR). The IR could be further boosted when in combination with PD-1/L1 inhibitor. RGL-270 is a lipid nanoparticle (LNP)-encapsulated, mRNA-based PCV, encoding tumor specific neoantigens screened via a proprietary algorithm to induce patient specific IR. This investigator-initiated, open-label, dose escalation and expansion clinical trial was conducted in China, to evaluate the safety, efficacy and immunogenicity of RGL-270 in combination with adebrelimab (anti-PD-L1 mAb) in patients with resectable PDAC. **Methods:** PDAC patients with R0/R1 surgical margins were enrolled. After surgery, RGL-270 was administrated up to 9 cycles, in combination with adebrelimab and followed by modified FOLFIRINOX chemotherapy. The key endpoints included safety, efficacy assessment with recurrence-free survival (RFS), overall survival (OS), 18-month RFS rate, and PCV specific IR evaluation by ELISpot. **Results:** As of 01/15/2026, 16 patients in the dose escalation (n = 7) and expansion (n = 9 at expansion dose level) stage received RGL-270 combo with adebrelimab therapy. Up to date, all dose levels were safe and well tolerated. The most common treatment-related adverse events (TRAEs) were fever, influenza-like illness and injection-site reactions. All TRAEs were CTCAE grade 1~2 and no treatment-related SAE or DLT was reported. Currently, the median follow-up is 18.0 months, with median RFS and OS not reached yet, and the 18-month RFS rate is 100%.The PCV-specific IR positive rate was 100%. Interestingly, IR was also detected in patients who had undergone prior splenectomy (5/16). The primary IR emerged as early as 2 cycles after the first PCV administration, with the best of response (BoR) observed 2~4 cycles post-baseline and, in most cases, persisting until cycle 9, the booster cycle. To date, no dose-dependent manner for IR has been observed. Additionally, concordance between the predicted and immunogenic neoantigens was analyzed, and the resulting insights were fed back to improve the neoantigen screening algorithm. Furthermore, bulk T-cell receptor sequencing was performed to further characterize the PCV specific IR. **Conclusions:** Based on proprietary LNP delivery systems, algorithms for neoantigen identification and immunogenicity prediction, the combination treatment of RGL-270 and adebrelimab demonstrated a favorable safety profile, promising efficacy, and robust immunogenicity. This preliminary result guarantees the further development of PCV-based anti-tumor therapy in the adjuvant setting for PDAC. Clinical trial information: NCT06156267. Research Sponsor: Noncommunicable Chronic Diseases-National Science and Technology Major Project (2024ZD0525500/2024ZD0525505).

4232 **Poster Session**

Experience of Spanish centers with echoendoscopically implanted ^{32}P microparticles associated with chemotherapy in locally advanced pancreatic adenocarcinoma. First Author: Carmen Guillen-Ponce, Hospital Universitario Ramon y Cajal, Irycis, Madrid, Spain

Background: Phosphorous 32 microparticle (^{32}P) brachytherapy delivered by echoendoscopy (EUS) represents an innovative therapy in pancreatic cancer (PC). The device to implant it is approved in unresectable locally advanced PC in combination with gemcitabine-based chemotherapy. Our aim is to present the preliminary efficacy and safety results of a series that brings together the experience of thirteen centres in Spain. **Methods:** After being assessed by a multidisciplinary committee, patients signed consent to receive intratumoural ^{32}P by EUS. Complications associated with intratumoural 32P injection via EUS, associated adverse events (AEs) and preliminary efficacy results (progression-free survival [PFS], distant and locoregional, and overall survival [OS]) were analysed. **Results:** Fifty one patients (32 females and 19 males; age 65.5 years [range 48, 84]; 36 ECOG 1 and 14 ECOG 0) with unresectable locally advanced PC (30 in head, 5 in uncinate, 5 in neck and 11 in body; tumour size 30.8 mm [range 12, 60]) were included. The median time from tumour diagnosis to procedure was 5.9 months [0, 28.9]. Twenty-four patients (47 %) had received at least one previous line of treatment; four had received two prior lines. Fifty patients (98%) received gemcitabine-based chemotherapy concomitant with intratumoural 32P (42 gemcitabine plus nabpaclitaxel; 8 gemcitabine monotherapy. There were two AEs related to 32P injection by EUS: G1 epigastric pain (1 patient) and G2 asthenia (1 patient). A total of 30 patients (58.8%) had chemotherapy-related AEs, with 8 cases of G3 neutropenia (1 febrile neutropenia) and/or G3 thrombopenia; 22 had G1-2 toxicities: neurotoxicity (5), asthenia (4), neutropenia (3), thrombopenia (2), anaemia (4), nausea (2), diarrhoea (2), anorexia (1), onycholysis (1), mucositis (1), and constipation (1). Seven patients (13,7%) underwent surgery after intratumoural treatment (5 R0 and 2 R1). With a median follow-up of 8.7 months after injection (range: 1.02 months to 40.77 months), 25 patients (49.2 %) have progressed, 19 of them distantly, and nine also locoregionally. The median PFS since 32P injection is 8.5 months (95% CI 5.3, 17). 33 patients are alive at the end of follow-up (64.7%) with a median OS since 32P injection of 15.6 months 95% CI [10.2, 26.9]. **Conclusions:** Our experience suggests that intratumoural 32P associated with gemcitabine-based chemotherapy is safe. Patients after 32P injection achieve long overall survival. Surgical rescue was achieved in a high percentages of initially unresectable cases. Research Sponsor: None.

4234 **Poster Session**

Distinct multi-omic signatures that underlie *KRAS* variants and survival in *KRAS* G12R pancreatic cancer. First Author: Sargis Hovhannisyan, Cedars-Sinai Medical Center, Los Angeles, CA

Background: KRAS mutations are the dominant oncogenic drivers of pancreatic ductal adenocarcinoma (PDAC). While KRAS G12D/V variants are associated with aggressive disease and poor prognosis, the biological basis for survival differences among KRAS variants remains incompletely defined. We leveraged a comprehensive multi-omics dataset to characterize variant-specific molecular signatures associated with survival. **Methods:** Tissue and plasma samples from 72 patients with Stage I/II resectable PDAC were retrospectively analyzed using the Aseesa Stars multi-modal integrated platform. Multi-omic profiling included targeted DNA sequencing, whole-transcriptome RNA sequencing, tissue and plasma proteomics, lipidomics, and computational pathology, generating 6,363 features linked to overall survival (OS). Analyses focused on KRAS wild-type (n=7) and the most prevalent KRAS variants: G12R (n=12), G12D (n=21), and G12V (n=13). **Results:** Patients with KRAS G12R who underwent upfront resection demonstrated significantly longer OS compared with G12D/V variants (median OS 37.5 vs. 18.9 months; HR 0.50 [95% CI 0.23–1.09]; log-rank p=0.047). Compared with KRAS-WT, combined KRAS-mutant tumors exhibited significant alterations in neutrophil degranulation, apoptosis, protein transport, cell adhesion, and oxidative phosphorylation (OXPHOS) pathways ($p<0.05$). A total of 381 molecular signatures differed significantly ($p<0.05$) between G12R and G12D/V cohorts. In direct G12R vs. G12D comparison, 110 features were unique to high OS ($p<0.05$). KRAS G12R, G12D and G12V shared activation of PI3K/AKT, MET, and PTPN11 signaling, consistent with a common aggressive phenotype. In contrast, KRAS G12R tumors demonstrated significant alterations in major mRNA splicing and OXPHOS pathways ($p<0.05$). Splicing regulators PLRG1 and RBM8A were reduced in G12R patients by 6% ($p<0.03$). Six OXPHOS-related signatures also favored high OS, lipid hexosylceramide 24:1 was decreased by 14.59% (p=0.016). Tissue protein ACADS decreased by 5.38% (p=0.025) in G12R high OS, but increased in G12D high OS. **Conclusions:** KRAS G12R defines a molecularly distinct PDAC subtype with improved survival, characterized by suppressed mRNA splicing signatures and coordinated metabolic remodeling, highlighting variant-specific metabolic and molecular divergence. These findings underscore the importance of KRAS variant stratification for prognostication and future development of variant-specific precision therapeutic strategies. Research Sponsor: U.S. National Institutes of Health; CA259456; Conquer Cancer, the ASCO Foundation.

4235 **Poster Session**

Risk-adapted step-up local therapy for malignant portal vein tumor thrombus from hepatic metastases: A real-world study of microwave ablation with and without iodine-125 seed implantation. First Author: Hoang Tran Pham, Department of Internal Medicine, Trinity Health Ann Arbor Hospital, Ann Arbor, MI

Background: Malignant portal vein tumor thrombus (PVTT) arising from hepatic metastases is associated with poor prognosis, rapid hepatic decompensation, and limited effective local treatment options despite systemic therapy. In real-world practice, local treatment intensity is frequently adapted to disease burden and treatment response. We evaluated outcomes of a risk-adapted, step-up local treatment strategy using microwave ablation (MWA) alone or in combination with iodine-125 (I-125) seed implantation for patients with malignant PVTT. **Methods:** We retrospectively reviewed patients with hepatic metastases treated with MWA with or without I-125 seed implantation between 2023 and July 2025. In clinical practice, MWA alone was preferentially used for patients with relatively limited disease burden, while MWA plus I-125 was employed as an escalation strategy for patients with more advanced PVTT or disease progression following MWA alone. The primary endpoint was PVTT-directed local outcome, defined as portal vein patency and/or local control of tumor thrombus on follow-up imaging. Secondary endpoints included progression-free survival (PFS), overall survival (OS), hepatic function changes, and treatment-related toxicity. Survival analyses were considered exploratory. **Results:** A total of 73 patients were included, of whom 50 were treated with MWA alone and 23 with MWA plus I-125 seed implantation. Patients receiving MWA plus I-125 demonstrated more advanced disease characteristics, including universal presence of PVTT and higher disease stage, consistent with treatment escalation by disease severity. Among patients with PVTT, MWA plus I-125 achieved portal vein patency and/or local control in 65% at first follow-up imaging. Treatment-related toxicities were manageable, with no unexpected grade $\geq$3 adverse events attributable to I-125 implantation. Median PFS was 11.5 months in patients treated with MWA alone and 9.9 months in patients treated with MWA plus I-125, consistent with greater baseline disease burden in the latter group. **Conclusions:** MWA alone and MWA plus I-125 function as complementary components of a risk-adapted, step-up local treatment strategy for malignant PVTT from hepatic metastases. Escalation to MWA plus I-125 appears feasible in patients with advanced or refractory PVTT and demonstrates a potential signal for improved PVTT-directed local control and portal vein patency. Prospective studies focused on PVTT-specific endpoints are warranted. Research Sponsor: None.

4236 **Poster Session**

Donafenib plus immune checkpoint inhibitors with or without oral fluorouracil chemotherapy drugs (S-1/capecitabine) for patients with resected high-risk biliary tract tumor: A multi-center retrospective study. First Author: Huang Huaiyin, Hunan People's Hospital (Hunan Normal University Affiliated No.1 Hospital), Changsha, China

Background: Chemotherapy combined with Immune Checkpoint Inhibitors (ICIs) and donafenib showed promising efficacy and safety in advanced biliary tract cancer (BTC). Oral fluorouracil chemotherapy drugs S-1 or capecitabine are used as standardized adjuvant therapy for BTC. This study aimed to evaluate the efficacy and safety of donafenib plus ICIs with or without oral fluorouracil chemotherapy drugs as adjuvant therapy in BTC patients with high-risk recurrence factors after radical resection. **Methods:** This multi-center retrospective study enrolled BTC patients with high-risk recurrence factors who underwent surgical resection at Hunan Provincial People's Hospital, Sichuan Provincial People's Hospital, The First Affiliated of Zhengzhou University, Sir Run Run Shaw Hospital and Jiangsu Provincial People's Hospital from Aug 2022 to Nov 2025. All patients exhibited at least one of the following high-risk recurrence factors: macrovascular invasion, lymph node metastasis, satellite lesion, nerve invasion and the maximum diameter of tumors$\geq$5cm. Patients received adjuvant therapy of donafenib plus ICIs with or without S-1/capecitabine after surgery. The primary endpoint was RFS and secondary endpoints included OS and safety. **Results:** A total of 50 patients were enrolled, with a median age of 60.5, included 21 Intrahepatic, 18 hilar cholangiocarcinoma and 11 others. Tumor stage I/II/III/IV, 8/10/25/7; R0/R1 resection, 44/6. All patients exhibited a high risk factor of recurrence at least, the rate of macrovascular invasion, lymph node metastasis, satellite lesion, nerve invasion and the maximum diameter of tumors$\geq$5cm are 40.0%, 42.0%, 6.0%, 70.0% and 34.0%. 20 patients received the adjuvant therapy of S-1/ capecitabine plus donafenib with ICIs, and the other 30 patients were treated with donafenib and ICIs. The median follow-up time was 15.2 months (95%CI: 11.17-18.46), 16 patients relapsed. The median RFS was 14.0 months (95% CI: 11.07-NA), and the one-year RFS rate was 63.8%, two-year RFS rate was 45.1%. T staging of tumor is an independent influencing factor on disease recurrence in the multivariate analysis. The RFS in stage T1/2 patients was significantly higher than stage T3/4. The incidence of grade 3 TEAEs stood at 26.0%, including hand-foot syndrome (44%), anaemia (16%), diarrhea (16%) and rash (12%). No patients encountered grade 5 TRAEs. **Conclusions:** The combination of donafenib plus ICIs with or without oral fluorouracil chemotherapy drugs (S-1/capecitabine) appears to be a promising adjuvant therapy for patients with high-risk biliary tract tumor. Furthermore, no significant safety concerns were observed. Research Sponsor: None.

4237 **Poster Session**

Deciphering the heterogeneity and cellular interactions of cancer-associated fibroblasts in extrahepatic cholangiocarcinoma by spatial transcriptomics. First Author: Giulia Petroni, Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

Background: Cholangiocarcinoma (CCA) is a rare and lethal malignancy characterized by a desmoplastic stroma. containing cancer-associated fibroblasts (CAFs). Although CAFs have been widely studied in intrahepatic CCA, their impact on TME remodeling and chemo-immunotherapy (CIT) efficacy in extrahepatic (e) CCA is not fully elucidated. A compressive characterization of the spatial orchestration of the eCCA TME and of the interaction between CAFs and adjacent tumor cells is needed for the identification of therapies able to improve CIT efficacy, that, so far, is limited in these patients. **Methods:** We employed spatial transcriptomics on tumor specimens from 8 patients with advanced distal (d) or perihilar (p) CCA treated with durvalumab + cisplatin/gemcitabine. 126 microregions were analyzed with the GeoMx Digital Spatial Profiler and classified according to pan-CK and ACTA2/αSMA straining, as follow: $CK^{+}\alpha SMA^{-}$ tumor, $CK^{-}\alpha SMA^{+}$ distant and peritumor CAF-enriched stroma, or $CK^{-}\alpha SMA^{-}$ peritumor stroma. **Results:** αSMA staining showed a high degree of stromal heterogeneity in all eCCA, with some tumor nests surrounded by a dense CAF-enriched stroma and others by αSMA^{-} cells within the same sample. Based on CD45 staining all samples were classified as immune-desert or -excluded, as no immune cells were found intratumorally. Tumor-adjacent CAFs exhibited a distinct extracellular matrix (ECM) remodeling signature marked by the expression of *COL11A1*, *MMP11* and TGFB family members. GSEA showed a positive enrichment of epithelial-mesenchymal transition (EMT) transcripts linked to the downregulation of signatures of immune activation and IFN response, in both peritumoral CAF-enriched regions and adjacent tumor cells. Confirming this data, receptor-ligand interaction modeling performed using the CellChat tool confirmed that CAF-enriched regions exhibited strong interactions with adjacent tumor cells, throughout the secretion of several factors involved in ECM-remodeling and immunosuppression. Intriguingly, a higher expression of EMT-related genes linked to a higher downregulation of pathways of immune activation was observed in dCCA vs pCCA samples, with dCCA patients experiencing a shorter progression-free survival (PFS) from CIT compared to pCCA patients (PFS ranging from 7-12 and 10-24 months, respectively). **Conclusions:** Our findings suggest that $COL11A1^{+}MMP11^{+}$ CAFs might limit CIT efficacy in eCCA by promoting eCCA EMT and, at the same time, by forming a collagen-dense physical barrier that hampers the intratumoral recruitment of immune cells, thus offering novel insights into potential therapeutic targets for interventions. A deeper characterization of CAF features and CAF-tumor interactions is ongoing. Research Sponsor: None.

4238 **Poster Session**

Real-world outcomes in gastrointestinal cancer patients with targetable genomic alterations identified on serial liquid biopsy. First Author: Linda Albusoul, Henry Ford Cancer Institute, Detroit, MI

Background: Precision oncology in gastrointestinal (GI) cancers relies on identifying targetable genomic alterations (TGA) to guide therapy. Liquid biopsy (LB) using circulating tumor DNA (ctDNA) enables minimally invasive molecular profiling and serial monitoring. As targeted therapies for GI cancers expand, repeat LB is increasingly used to detect emergent alterations. However, the clinical relevance of TGA not previously identified, particularly when detected at low variant allele fraction (VAF) where clonal burden is difficult to infer, remains unclear. **Methods:** GI cancer patients (pts) with >1 LB were identified from the Guardant Health InfinityAI Data Library, a real-world database of insurance claims and de-identified clinical Guardant360 records. Pts without TGA on initial LB, but gained TGA on subsequent LB were included. TGA were defined as biomarkers with cancer-type specific or pan-tumor matched targeted therapy (MTT) approvals: KRAS G12C, ERBB2 amplification (amp), BRAF V600E, IDH1, MSI-H, and NTRK/RET/FGFR2 fusions or with select approved MTT in non-GI cancers: PIK3CA and ERBB2 mutation (mut). When available, methylation-derived tumor fraction (TF), a measure of overall ctDNA burden independent of variant-specific effects, was compared with emergent TGA VAFs, excluding MSI-H and ERBB2 amp. Pts with multiple cancers or prior MTT were excluded. Cox proportional hazards model assessed associations between MTT and real-world overall survival (rwOS), adjusting for age, gender, cancer type, MSI-H status, and number of gained TGA. **Results:** Among 16,435 GI cancer pts with >1 LB and no initial TGA, 2,072 (12.6%) gained TGA on serial LB and were included in the overall cohort. For the survival analysis, 804 pts with gained TGA had treatment and survival data; 13.4% (108/804) received MTT. Colorectal cancer pts had the highest rate of emergent TGA with approved MTT (17%). The most common gained TGA across the overall cohort were PIK3CA mut (62%), ERBB2 mut (11.7%), BRAF V600E (9.5%), KRAS G12C (8.6%), ERBB2 amp (7%), MSI-H (4.4%), FGFR fusions (3%), and NTRK fusions (1.9%). Gained TGA were often detected at low VAF (median 0.2%; 0.01% - 41.4%), and below the TF, suggesting potential subclonal emergence. Cholangiocarcinoma and gastroesophageal cancers had the highest MTT rates (14.2% and 10%, respectively), whereas no anal cancer pts received MTT. Including pts who gained MSI-H status, 12-and 60-month rwOS from LB-detected TGA was 67% and 25% without MTT versus 78% and 44% with MTT, $p<10\text{-}4$; excluding MSI-H, rwOS with MTT was 82% and 34%, p=0.00025. **Conclusions:** Repeat LB identified TGA in a subset of GI cancer pts lacking baseline TGA, many detected at low VAF. MTT receipt for emergent TGA was associated with improved rwOS, supporting serial LB in later-line decision making. Further studies are needed to assess outcomes by TGA type, therapy, clonality, and GI cancer. Research Sponsor: None.

TPS4239 **Poster Session**

Phase II study evaluating ivonescimab in combination with chemotherapy as first- and second-line treatment of advanced or metastatic gastric and gastroesophageal adenocarcinoma patients (UCGI 52 – GRACIE). First Author: Christelle De La Fouchardiere, Cancer Center Institut Paoli-Calmettes, Marseille, France

Background: The prognosis of advanced/metastatic gastroesophageal adenocarcinomas (GEA) has recently improved with new targeted therapies, including immune checkpoint inhibitors, mostly developed in the first-line setting. However, for patients (pts) without actionable biomarkers or for those who become refractory to first-line therapy, a significant unmet need remains for effective therapeutic options. Ivonescimab, a bispecific antibody targeting both VEGF-A and PD-1, appears to be a promising strategy in this setting. **Methods:** This phase 2 multicenter two-cohort, non-randomized study (NCT06846346) is designed to evaluate the efficacy and safety of ivonescimab + chemotherapy in pts with advanced or metastatic GEA, with and without actionable biomarker. Main eligibility criteria are age ≥ 18 years, histologically proven GEA, stage 4 disease, no prior treatment for pts without actionable biomarker (cohort 1) or only one prior line for pts with actionable biomarker (cohort 2), ECOG-PS 0-1, and adequate organs functions. The tumor has to be measurable (RECIST 1.1). Treatment regimens are ivonescimab 20mg/kg IV on D1 Q2W combined with: cohort 1: FOLFOX (oxaliplatin 85mg/m² IV, folinic acid 400 mg/m² IV [or L-folinic acid 200 mg/m²], 5-FU bolus 400 mg/m² then 5-FU 2400 mg/m² as a 46-hours continuous IV infusion on D1 Q2W; oxaliplatin will be stopped after 8 cycles); cohort 2: at investigator discretion, paclitaxel (80 mg/m2 IV at D1, D8 and D15, Q4W for at least 4 cycles) or irinotecan (180 mg/ m2 IV on D1 Q2W). Treatment will be administered until disease progression or unacceptable toxicity. The primary endpoint is ORR by central review. Secondary endpoints include ORR assessed by investigator, duration of response, PFS, OS, safety, time to PS deterioration >2, and quality of life. According to a single stage phase II A'Hern's design, a sample of 33 evaluable pts in cohort 1 and 47 evaluable pts in cohort 2 is required to distinguish between a maximum futility proportion of 0.5 (cohort 1)|0.2 (cohort 2) and a minimum efficacy proportion of 0.75 (cohort 1)|0.4 (cohort 2) with a one-sided significance level of 0.04 and 90% power. 88 patients have to be enrolled to observe a minimum of 80 evaluable patients. Planned accrual duration is 1 year, 12 patients have already been enrolled. Clinical trial information: NCT06846346. Research Sponsor: SUMMIT Therapeutics.

TPS4240 **Poster Session**

HIPEC combined with NIPS and tislelizumab for conversion therapy in gastric cancer with peritoneal metastasis (P0CY1 or PCI ≤10): A prospective, single-arm, phase II study. First Author: Honghai Guo, The Third Department of Surgery, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Background: Peritoneal metastasis, which is common, difficult to diagnose early, and associated with a poor prognosis, is a leading cause of death in pts with advanced gastric cancer. Due to the peritoneal-plasma barrier, traditional systemic chemotherapy is often ineffective for gastric cancer patients with peritoneal metastasis. In recent years, combined systemic and intraperitoneal therapy has gained increasing recognition. The RATIONALE-305 study demonstrated that tislelizumab (TIS) significantly improves outcomes in these patients. This study combines hyperthermic intraperitoneal chemotherapy (HIPEC), normothermic intraperitoneal and systemic chemotherapy (NIPS), and PD-1 inhibitor, exploring a novel conversion therapy regimen for pts with gastric cancer peritoneal metastasis. **Methods:** This is a prospective, single-center, single-arm phase II study aims at evaluate the efficacy and safety of HIPEC combined with NIPS and tislelizumab as conversion therapy for gastric cancer pts with peritoneal metastasis who are either cytology-positive only without macroscopic peritoneal deposits (P0CY1) or Peritoneal Carcinomatosis Index (PCI) ≤10. Key inclusion criteria are: 1) age 18-75 years; 2) ECOG performance status 0-1; 3) HER2-negative confirmed by IHC, and PD-L1 CPS≥1; 4) either P0CY1 or PCI ≤10 without other distant metastases confirmed by laparoscopy; 5) adequate function of major organs. Pts undergo diagnostic laparoscopy for PCI scoring and peritoneal cytology examination. Upon confirmation of eligibility, pts receive three sessions of HIPEC followed by 4 cycles of NIPS combined with systemic therapy. The HIPEC regimen consists of paclitaxel at a dose of 75 mg/m² administered on D1, 3, and 5. After a two-week rest, NIPS combined TIS is initiated. The NIPS regimen includes paclitaxel (20 mg/m², ip, D1,8, Q3W and 50 mg/m², iv, D1,8, Q3W) ,S-1 (40-60mg based on BSA, po, D1-14, Q3W). The dosage and administration of TIS is 200 mg, iv, D1, Q3W. Radiological evaluations are performed every 2 cycles during conversion therapy. Upon completion of conversion therapy, pts undergo a second laparoscopic exploration with peritoneal cytology examination to re-evaluate disease status. Operable pts who achieve R0 resection receive postoperative adjuvant therapy with the same regimen (paclitaxel + S-1 + TIS) for 4 cycles. For inoperable pts or those not achieving R0 resection, subsequent treatment is determined by a multidisciplinary team (MDT). The primary endpoint is the surgical conversion rate. Secondary endpoints include the 1-year progression-free survival (PFS) rate, 2-year overall survival (OS) rate, PFS, OS, and safety. Exploratory endpoints aim to investigate the correlation between efficacy prediction and biomarkers such as PD-L1 expression, CLDN18.2 expression, and microsatellite instability (MSI) status. Clinical trial information: NCT07304258. Research Sponsor: None.

TPS4241 **Poster Session**

A randomized phase II/III trial of intraperitoneal paclitaxel plus systemic treatment vs systemic treatment alone in gastric carcinomatosis: STOPGAP II—ECOG-ACRIN EA2234. First Author: Maheswari Senthil, UC Irvine School of Medicine, Orange, CA

Background: Thirty to forty percent of patients with gastric cancer will develop peritoneal carcinomatosis (PC), the survival of which remains poor despite systemic therapy (ST). Limited drug delivery into PC due to blood-peritoneal barrier is considered to decrease the effectiveness of ST. Hence, there is a critical need to develop novel treatment strategies to improve patient outcomes. Intraperitoneal (IP) paclitaxel (PTX) combined with ST had been studied extensively in Asia. In the US, STOPGAP I, a single institution phase II trial has established the safety and feasibility of IP PTX plus ST in Western patients with gastric PC. Based on these results, we developed STOPGAP II trial, which is designed to evaluate the survival benefits of IP PTX plus ST compared to ST alone in patients with gastric PC. **Methods:** ECOG-ACRIN EA 2234 STOPGAP II is a multicenter randomized phase II/III trial (NCT07001748) evaluating IP PTX plus ST compared to ST alone in patients with gastric PC. Eligible patients must have microsatellite stable gastric/gastroesophageal cancer (Siewert 3) with cytology positive disease or carcinomatosis detected by diagnostic laparoscopy (DL), laparotomy, or radiology and have undergone 3-6 months of first line ST. Patients must not have visceral metastases except ovarian metastases or clinically significant progression of PC. All enrolled patients will undergo DL with peritoneal cancer index (PCI) assessment within four weeks of registration. Patients will be randomized intraoperatively in 1:1 fashion to Arm A- ST or Arm B- IP PTX with ST. In patients randomized to Arm B, an IP port will be placed at the initial DL . Patients in Arm A will continue first line ST and patients in Arm B will receive 40 mg/m2 of IP PTX on days 1 and 8 combined with 50mg/m2 of IV PTX, 5 fluorouracil 400 mg/m2, leucovorin 20mg/m2. Immune checkpoint inhibitors and targeted agents will be continued as per standard of care. Patients will be stratified by PCI (0, 1-6, 7-14, versus $>$15) and first line ST type (chemo + targeted agent or immunotherapy versus chemotherapy alone). In both treatment arms, patients will undergo reevaluation with repeat imaging and if indicated, DL after three months. Patients with stable disease or response will continue the assigned treatment or could be considered for cytoreduction if PCI $<$7. The primary endpoints are progression free survival (phase II) and overall survival (OS) (phase III). Assuming the median OS of IP PTX and that of ST to be 22.5 and 12.5 months respectively, and accounting for attrition, 148 patients will be enrolled to achieve 90% power with a hazard ratio of 0.56 (one-sided type I error of 5%). The study is actively enrolling patients with results expected in 2031. Clinical trial information: NCT07001748. Research Sponsor: NCI CTEP.

TPS4242 **Poster Session**

A phase 1/2 study of BDC-4182, a Claudin 18.2–targeting next-generation immune-stimulating antibody conjugate (ISAC), in patients with advanced gastric and gastroesophageal cancer. First Author: Sophia Frentzas, Department of Medical Oncology, Monash Health, Clayton, VIC, Australia

Background: Claudin 18.2 (CLDN18.2) is a transmembrane tight junction protein with expression restricted to the gastric mucosal epithelia where CLDN18.2 protects against paracellular acid leakage and associated gastritis.[1] CLDN18.2 overexpression has been observed in several tumor types, including gastric, esophageal, and pancreatic cancer.[2,3] Loss of cell polarity in these tumors results in CLDN18.2 localization to surfaces that are more readily accessible to biologics and effector cells. This expression pattern makes CLDN18.2 a compelling target for immune-stimulating antibody conjugates (ISACs) that combine the specificity of tumor-targeting antibodies with the potency and durability of immune activation. BDC-4182 is a next-generation ISAC consisting of a CLDN18.2-targeting antibody covalently attached to a novel toll-like receptor (TLR)7/8 agonist via a non-cleavable linker. In preclinical models, systemic delivery of ISACs has been shown to broadly activate the innate and adaptive immune system, leading to complete tumor regression. A BDC-4182 surrogate induced immunologic memory and epitope spreading as evidenced by rejection of tumor cells that no longer express the target antigen (CLDN18.2) following re-challenge.[4,5] **Methods:** This is a first-in-human Phase 1 dose escalation and Phase 2 expansion study of BDC-4182. Up to 122 patients with advanced gastric and gastroesophageal cancer will be enrolled. To optimize tolerability, BDC-4182 is administered via an intra-patient step-up dosing regimen wherein subjects receive lower initial priming doses prior to the target dose. Primary objectives are to define safety and tolerability and to determine the recommended phase 2 dose (RP2D) of BDC-4182 as a single agent. Secondary objectives will evaluate the preliminary anti-tumor activity of BDC-4182, analyze PK characteristics of BDC-4182, and evaluate the immunogenicity of BDC-4182 as a single agent. Exploratory analyses will also be conducted to explore potential biomarkers in blood and tumor tissue associated with exposure, efficacy, or safety of BDC-4182, and to define CLDN18 expression in tumor tissue. This study is being conducted in Australia, South Korea, and Taiwan. References: 1. Suzuki K, Sentani K, Tanaka H, et al. Cell Mol Gastroenterol Hepatol. 2019;8:119-142. 2. Hong JY, An JY, Lee J, et al. Transl Cancer Res. 2020;9:3367-3374. 3. Chen J, Xu Z, Hu C, et al. Front Oncol. 2023;13:1132319.4. Fu C, Luo A, Liu J, et al. J Immunother Cancer. 2024;12(Suppl 2):Abstract 1052. 5. Kim HK, Monnier J, Fu C, et al. J Immunother Cancer. 2023;11(Suppl 1):Abstract 1147-D. Clinical trial information: NCT06921837. Research Sponsor: Bolt Biotherapeutics.

TPS4243 **Poster Session**

Phase II RAINSPOT: A multicentric open label trial of zolbetuximab-paclitaxel-ramucirumab in second-line setting for CLDN18.2-positive gastro-esophageal adenocarcinoma. First Author: Filip Van Herpe, Gastrointestinal Oncology Department, University Hospitals Leuven, Leuven, Belgium

Background: Claudin 18.2 (CLDN18.2) is an emerging therapeutic biomarker in gastro-oesophageal adenocarcinoma. Phase III trials (SPOTLIGHT, GLOW) showed significant overall survival (OS) and progression-free survival (PFS) benefit from adding zolbetuximab to first-line chemotherapy. However, access to zolbetuximab remains limited in Belgium due to lack of reimbursement, and globally for patients receiving immunotherapy first line. Aim: RAINSPOT (NCT06962137) evaluates the efficacy and safety of adding zolbetuximab to standard second-line paclitaxel–ramucirumab in CLDN18.2-positive advanced gastro-oesophageal adenocarcinoma. Secondary objectives include assessing CLDN18.2 expression loss after first-line progression and evaluating zolbetuximab efficacy according to maintained versus lost CLDN18.2 expression. **Methods:** RAINSPOT is a national, multicentre, phase II, open-label study with a prospective single-arm cohort and a matched retrospective cohort across six Belgian centres. The prospective cohort will include 100 patients ($\geq$18 years, ECOG 0–1) with metastatic or locally advanced disease progressing after one prior systemic line. Tumours must be CLDN18.2-positive ($\geq$75% moderate-to-strong membranous staining; Ventana 43-14A assay). A fresh biopsy at progression is obtained when feasible. Treatment consists of zolbetuximab (800 mg/m² loading, then 400 mg/m² q2w), paclitaxel (80 mg/m² weekly $\times$3 q28d) and ramucirumab (8 mg/kg q2w). Treatment continues until progression or unacceptable toxicity. HRQoL is assessed every 4 weeks (EORTC QLQ-C30, QLQ-OG25). The retrospective cohort includes patients treated with second-line paclitaxel–ramucirumab (2021–2023) with archived tissue reassessed for CLDN18.2; only baseline-positive patients are eligible. Propensity score matching (1:1; SMD $\leq$0.05) uses age, sex, tumour location, gastrectomy, peritoneal metastases and centre. This study is supported by Astellas. **Results:** (Trial in Progress) Enrollment began December 2025 and will continue for 24 months, with 24 months' follow-up. Planned analyses include OS, PFS, objective response rate, toxicity and HRQoL. **Conclusion:** RAINSPOT is the first study evaluating zolbetuximab plus paclitaxel–ramucirumab in second-line CLDN18.2-positive gastro-oesophageal adenocarcinoma. By integrating a matched real-world comparator, it aims to generate near-randomized evidence on survival, tolerability and quality of life, informing optimal treatment sequencing. Clinical trial information: NCT06962137. Research Sponsor: None.

TPS4244 **Poster Session**

Combining zanidatamab, FOLFOX, and pembrolizumab as first-line therapy for HER2/PD-L1–positive gastroesophageal adenocarcinoma: The phase II IKF-090/AIO ZANGEA trial with translational analysis. First Author: Joseph Tintelnot, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Background: Gastroesophageal adenocarcinoma (GEA) presents a substantial global health challenge as the number of cases continues to rise. The current standard approach for treating previously untreated, metastatic HER2/PD-L1 positive GEA involves a combination of doublet chemotherapy, which consists of a platinum compound and a fluoropyrimidine, in combination with trastuzumab and pembrolizumab. Recently, the phase 3 HERIZON-GEA-01 trial has shown improved survival for zanidatamab in combination with CAPOX or fluoropyrimidine and cisplatin with the PD-1 inhibitor tislelizumab compared to chemotherapy and trastuzumab. Zanidatamab is a bispecific antibody that targets two distinct HER2 epitopes (domains 2 and 4), thereby crosslinking neighboring HER2 receptors and inducing receptor clustering. This leads to enhanced HER2 internalization, reduced downstream signaling, and increased Fc-mediated immune effector functions, compared with trastuzumab. There is currently insufficient evidence regarding the combination of zanidatamab with the frequently used chemotherapy backbone FOLFOX and no available data on combining this regimen with the PD-1 inhibitor pembrolizumab. Furthermore, biomarkers to predict response and toxicities are lacking. **Methods:** The ZANGEA study is an open-label, single-arm, multicenter, translational phase II trial designed to assess the efficacy, safety, tolerability and translational aspects of zanidatamab in combination with FOLFOX and pembrolizumab in patients with 1st line HER2/PD-L1-positive GEA. The primary endpoint is the progression-free survival rate after 12 months. Secondary objectives include safety and tolerability, efficacy in terms of objective response rate, progression-free and overall survival and translational markers, such as blood-based signatures (e.g. inflammatory cytokines), microbiota signatures, dietary patterns or microbiota derived metabolites that may correlate with therapy response or side-effects. In total, 80 patients will be recruited to show an PFS at 12 months of 55% compared to 46% with trastuzumab/pembrolizumab/chemotherapy (KeyNote 811). Enrollment started on 16 Jan 2026. Clinical trial information: NCT07176312. Research Sponsor: The Frankfurt Institute of Clinical Cancer Research (IKF); Jazz Pharmaceuticals.

TPS4245 **Poster Session**

Efficacy and safety of disitamab vedotin (DV) combined with trastuzumab, and tislelizumab versus chemotherapy (CAPOX) combined with trastuzumab ± pembrolizumab for patients with first-line HER2-high advanced gastric/gastroesophageal junction adenocarcinoma (G/GEJA): A randomized controlled phase 3 trial. First Author: Zhi Peng, Department of GI Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Patients (pts) with HER2-high (defined as IHC 3+, or IHC 2+/FISH+ according to Chinese Society of Clinical Oncology Gastric Cancer Guidelines) advanced G/GEJA continue to face a poor prognosis. Although adding pembrolizumab to trastuzumab and chemotherapy significantly improved overall survival in this pts population with a PD-L1 combined positive score (CPS) ≥1 in the first-line (1L) setting, there remains an unmet need for more effective treatment options. DV (anti-HER2 antibody-drug conjugate) is approved as monotherapy for the treatment of pts with HER2 IHC 2+/3+ advanced G/GEJA in China. In the randomized phase 2 part of the RC48-C027 trial, DV + trastuzumab + an anti-PD-1 agent showed a promising objective response rate (ORR) in 1L HER2-high advanced G/GEJA compared with the control (82.4% vs. 68.8%) (Shen et al. J Clin Oncol. 2025). Building on these results, the open-label randomized phase 3 RC48-C040 trial is designed to assess the efficacy and safety of DV + trastuzumab + tislelizumab versus chemotherapy + trastuzumab ± pembrolizumab in pts with previously untreated, HER2-high, advanced G/GEJA (NCT07315750). **Methods:** The key eligibility criteria are pts aged 18-75 years with histologically confirmed unresectable locally advanced or metastatic G/GEJA; central lab-confirmed high HER2 expression; no previous systemic treatment for locally advanced or metastatic gastric cancer; and at least one assessable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Pts with central nervous system metastasis and/or carcinomatous meningitis are ineligible. The planned sample size is 555. Pts will be randomized (2:1) to receive DV (2.5 mg/kg, intravenously [IV], Q2W) + trastuzumab (staring dose of 8 mg/kg followed by 6 mg/kg, IV, Q3W) + tislelizumab (200 mg, IV, Q3W) or to receive CAPOX (oxaliplatin: 130 mg/m², IV, Q3W for up to 6 doses; capecitabine: 1000 mg/m², orally, BID, days 1-14 every 3 weeks) + trastuzumab ± pembrolizumab (200 mg/kg, IV, Q3W) until occurrence of disease progression, intolerable toxicity, or initiation of new anti-tumor treatment. Randomization will be stratified by HER2 expression (IHC 2+/FISH+ or IHC 3+), PD-L1 expression (CPS < 1 or 1≤CPS < 10 or CPS≥10), and liver metastasis (presence or absence). The primary endpoint is progression-free survival (PFS) assessed by the Blinded Independent Review Committee as per RECIST v1.1. The secondary endpoints include overall survival, investigator-assessed PFS, ORR, disease control rate, duration of response, patient-reported outcomes, adverse events, pharmacokinetic parameters, and immunogenicity. This study started in January 2026; enrollment is ongoing in China. Clinical trial information: NCT07315750. Research Sponsor: RemeGen Co., Ltd.

TPS4246 **Poster Session**

A single-arm, phase II study of ivonescimab in combination with FOLFOX in advanced HER2-negative gastroesophageal adenocarcinomas. First Author: Sienna M. Durbin, Mass General Brigham Cancer Institute, Boston, MA

Background: Gastroesophageal adenocarcinoma (GEA) is a major cause of global cancer-related mortality. A common standard of care for frontline advanced GEA is 5-fluorouracil and oxaliplatin (FOLFOX), with the addition of immune checkpoint inhibitors (ICI) in patients with a PD-L1 combined positive score (CPS) of > 1. Adding ICIs improves median overall survival (OS) by 2-4 months, with increased benefit seen with higher CPS scores (Leone et al, *ESMO Open*, 2024). There remains a significant need to improve ICI outcomes and expand the portion of patients who benefit. In GEA, vascular endothelial growth factors (VEGF) are associated with poor prognosis, influencing immune suppression and T cell exhaustion. There is strong mechanistic rationale for cooperativity between anti-VEGF antibodies and ICI in GEA, as well as evidence of clinical benefit in treatment-refractory gastric cancer (Kim et al, *Cancer Immunol Res*, 2025). Ivonescimab is a novel bispecific antibody that simultaneously targets PD-1 and VEGF, in a spatially constrained manner, impairing neoangiogenesis and remodeling the suppressive tumor microenvironment. Ivonescimab has evidence of safety and efficacy in colorectal and hepatocellular cancers and is approved for the treatment of PD-L1+ lung cancer in China (Deng et al, ESMO 2024; Li et al, ESMO 2025; Xiong et al, *Lancet*, 2025). **Methods:** This single-arm, multi-institutional phase II study seeks to evaluate ivonescimab in combination with FOLFOX as frontline therapy in GEA. Adults with locally advanced unresectable or metastatic HER-2 negative GEA are eligible. Patients must have disease that can be evaluated radiographically and may not have received prior systemic therapy for advanced disease. Positive PD-L1 expression is not required for eligibility. We plan to enroll 40 patients. To allow for collection of early immune modulation data, patients will commence therapy with a single dose of ivonescimab 20 mg/kg at discretion of the treating investigator. Subsequent cycles will continue with the addition of FOLFOX (dosed per institutional standards) to ivonescimab, given on day 1 and day 15 of a 28-day cycle. Imaging will be performed every 6 weeks until week 24, at which point imaging will change to every 9 weeks. Treatment will continue until disease progression, withdrawal of consent, or death. The primary objective is to define efficacy of ivonescimab in combination with FOLFOX as measured by the 6-month progression-free survival (PFS) rate. Secondary objectives include safety and tolerability, objective response and clinical benefit rates, median PFS and OS. Translational correlative studies are planned to explore tumor and immunologic determinants of response. This study is currently open and enrolling (NCT07070466). Clinical trial information: NCT07070466. Research Sponsor: None.

TPS4247 **Poster Session**

A multicenter, open-label, single-arm, dose-finding and -expansion phase 1b/2 study to evaluate the safety and tolerability of nesuparib (JPI-547) in combination with irinotecan as a third-line and beyond therapy for recurrent or metastatic gastric cancer. First Author: Sun Young Rha, Department of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Recurrent or metastatic gastric cancer (GC) progressing after standard first- and second-line therapies has limited treatment options, leading to poor survival outcomes. Nesuparib is an orally available, next-generation dual inhibitor of tankyrase and poly(ADP-ribose) polymerase (PARP). It disrupts DNA damage repair and induces a "BRCAness" phenotype by modulating Wnt/β-catenin and Hippo signaling pathways. In a previous phase I study, nesuparib monotherapy demonstrated promising clinical activity with an overall response rate (ORR) of 28.2% and a disease control rate (DCR) of 64.1%. Preclinical models have shown synergistic anti-tumor efficacy when nesuparib is combined with irinotecan. This study aims to evaluate the safety, tolerability, and preliminary efficacy of nesuparib plus irinotecan in patients with advanced GC. **Methods:** This multicenter, open-label, single-arm, dose-finding and expansion phase 1b/2 study enrolls adults with histologically confirmed recurrent or metastatic GC or gastroesophageal junction adenocarcinoma who have progressed after ≥2 prior systemic therapies and have ECOG PS 0–1, measurable disease per RECIST v1.1, and UGT1A1 wild-type genotype. Phase 1b follows a standard 3+3 design with multiple predefined dose levels. Each dose level consists of a fixed combination of (1) a specific nesuparib dose (25–100 mg) administered orally once daily on either a 5-days-on/2-days-off or 3-days-on/4-days-off schedule and (2) irinotecan administered every 2 weeks at 100, 120, or 150 mg/m². The dose-limiting toxicity evaluation window is 28 days. Phase 2 enrolls patients at RP2D to further evaluate anti-tumor activity. The primary endpoint is objective response rate. Secondary endpoints include safety, disease control rate, duration of response, progression-free survival, time to response, and overall survival. Exploratory objectives include population pharmacokinetics, pharmacodynamic biomarkers, homologous recombination deficiency profiling, and circulating tumor DNA analyses. Approximately 43–49 patients are planned (18–24 in phase 1b; 25 in phase 2). Treatment continues until disease progression, unacceptable toxicity, or study withdrawal. Clinical trial information: NCT07364422. Research Sponsor: None.

TPS4248 **Poster Session**

Chemoradiotherapy plus sintilimab versus chemoradiotherapy as neoadjuvant treatment in locally advanced esophageal squamous cell carcinoma (NEOCRTEC2101): A multicenter, randomized, phase III trial. First Author: Mian Xi, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangdong Esophageal Cancer Research Institute, Guangzhou, China

Background: Neoadjuvant chemoradiotherapy (NCRT) followed by surgery is the current standard of care for resectable locally advanced esophageal squamous cell carcinoma (ESCC). The integration of immunotherapy is now challenging this established therapeutic paradigm. Our previous phase II trial demonstrated that combining PD-1 inhibitor and NCRT yielded an encouraging pathological complete response (pCR) rate with an acceptable safety profile in ESCC. Therefore, this multicenter, randomized phase III trial (NEOCRTEC2101) aims to compare the efficacy and safety of NCRT combined with sintilimab (a IgG4 anti-PD-1 monoclonal antibody) versus NCRT alone in patients with resectable locally advanced ESCC. **Methods:** This was a multicenter, open-label, randomized, phase III trial. Key eligibility criteria included previously untreated, histologically confirmed, resectable thoracic ESCC clinically staged as T1-4aN1-3M0 or T3-4aN0M0 according to the 8th edition of the UICC staging system, age 18–75 years, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic and organ function. Key exclusion criteria included a history of other malignancies, previous antitumor therapy, severe comorbidities, active autoimmune disease, prior non-infectious pneumonitis, or interstitial lung disease. Eligible patients were randomly assigned (1:1) to sintilimab plus NCRT group or NCRT group. All patients received NCRT consisting of concurrent radiotherapy (40 or 45 Gy in 20 fractions) and chemotherapy (paclitaxel 50 mg/m² + cisplatin 25 mg/m² administered on days 1, 8, 15, and 22). Patients randomized to the sintilimab plus NCRT group additionally received sintilimab 200 mg via intravenous infusion on days 1 and 22. Surgical resection was performed 6-8 weeks following the completion of neoadjuvant therapy. The primary endpoint was overall survival, and the secondary endpoints were progression-free survival, pCR rate, R0 resection rate, and treatment-related adverse events. The planned sample size is 422 patients. This study opened to accrual in October 2022 and is currently recruiting patients. Clinical trial information: NCT05357846. Research Sponsor: None.

TPS4249 **Poster Session**

Adjuvant oxaliplatin plus S-1 versus docetaxel plus S-1 for stage III gastric cancer after D2 gastrectomy (DRAGON-Adjuvant): A multicenter, open-label, phase 3, randomized, non-inferiority study. First Author: Chenfei Zhou, De-Department of Oncology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Adjuvant therapy is the standard treatment for stage II-III gastric cancer patients after radical D2 gastrectomy. Neoadjuvant therapy has been demonstrated as an effective strategy for resectable gastric cancer patients, while less than 2% of patients received such treatment in China. Therefore, adjuvant chemotherapy following radical resection is still widely used in current clinical practices. For stage III gastric cancer patients, oxaliplatin or docetaxel combined with oral fluoropyrimidine as adjuvant regimens are recommended by clinical guidelines. Although historical data show comparable efficacy between these regimens, direct comparisons are not feasible due to differences in study design, enrolled populations, and treatment cycles. Regimen selection is mainly based on clinical experience, as high-level evidence is still lacking. Currently, minimal residual disease (MRD) detection based on ctDNA testing can indicate patient prognosis and adjuvant therapy selection in colorectal cancer. The role of ctDNA-based MRD detection in adjuvant therapy of gastric cancer is still under investigation. This study aims to compare the efficacy and safety of oxaliplatin plus S-1 (SOX) versus docetaxel plus S-1 (DS) as adjuvant therapy for stage III gastric cancer, and to explore the role of MRD in adjuvant setting of gastric cancer. **Methods:** DRAGON-Adjuvant (NCT07366528) is a prospective, open-label, multicenter, randomized, non-inferiority study in patients aged from 18 to 80 years who are histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction, with pathological staging at AJCC stage IIIA to IIIC after standard D2 gastrectomy and R0 resection. Patients had no prior neoadjuvant therapy. Eligible patients will be randomized and assigned into experiment group (SOX, n = 193) and control group (DS, n = 194), respectively. Experiment group patients will be treated with eight 3-week cycles of intravenous oxaliplatin (130mg/m^2 on day 1 for each cycle) with orally S-1 on days 1 to 14 of a 3-week cycle. Control group patients will be treated with S-1 on days 1 to 14 of a 3-week cycle (C1), then intravenous infusion of docetaxel (40mg/m^2) on day 1 of each cycle and S-1 on days 1 to 14 of a 3-week cycle (C2 to 7), then S-1 continued on days 1 to 28 of 6-week cycles for up to 1 year. S-1 dose is dependent on body surface area. The primary objective is to assess that 3-year disease-free survival rate of SOX group is not inferior to DS group. Secondary objectives are to compare the 5-year overall survival rate, safety profiles, and recurrence sites in two groups. Exploratory objective is to assess the correlation of MRD with treatment efficacy and patient prognosis. As of January 2026, the DRAGON-Adjuvant is recruiting patients at 5 sites in China. Clinical trial information: NCT07366528. Research Sponsor: Science and Technology Commission of Shanghai Municipality; 25PJD078.

TPS4250 **Poster Session**

Multicenter phase Ib/II study of neoadjuvant zolbetuximab plus docetaxel, oxaliplatin, and S-1 (DOS) followed by adjuvant zolbetuximab/S-1 in patients with CLDN18.2-positive resectable gastric or gastroesophageal junction adenocarcinoma (NEOCLAUD). First Author: Hyung-Don Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Zolbetuximab, a monoclonal antibody targeting claudin 18.2 (CLDN18.2), has demonstrated significant survival benefit in advanced gastric or gastroesophageal junction adenocarcinoma (G/GEJA) in the phase 3 SPOTLIGHT and GLOW trials, validating CLDN18.2 as a therapeutic target. The phase III PRODIGY study demonstrated that neoadjuvant chemotherapy with docetaxel, oxaliplatin, and S-1 (DOS) followed by surgery and adjuvant S-1 chemotherapy improved progression-free survival (PFS) and overall survival (OS) compared with surgery followed by adjuvant S-1 for patients with resectable locally advanced gastric cancer (LAGC). Building on this evidence, we designed NEOCLAUD to evaluate whether adding zolbetuximab to neoadjuvant DOS chemotherapy, followed by adjuvant zolbetuximab/S-1, improves outcomes in patients with CLDN18.2-positive LAGC. **Methods:** This open-label, multicenter, phase Ib/II trial will enroll up to 57 patients with newly diagnosed, resectable G/GEJA positive for CLDN18.2 ($\geq$75% moderate–strong membranous staining by VENTANA 43-14A). Eligible patients must have clinical stage T3–4/N0 or T2–4/N+ disease (AJCC 8th), ECOG 0–1, and no distant metastasis. Primary endpoints are recommended phase II dose (RP2D) (phase Ib) and the pathologic complete regression (pCR) rate (phase II). Phase Ib uses a 3+3 design to determine the RP2D. Phase II will test whether adding zolbetuximab increases the pCR rate from 10% (historical control) to 25%; the primary endpoint will be met if $\geq$8/40 patients achieve pCR (A'Hern single-stage design, α = 0.05, power = 80%). Secondary endpoints include PFS, OS, objective response rate, disease control rate, R0 resection rate, and safety. Exploratory endpoints include artificial intelligence-based histopathology modeling, spatial transcriptomics, single-cell RNA sequencing, and circulating tumor DNA minimal residual disease analysis. Neoadjuvant therapy consists of zolbetuximab 800 mg/m² on cycle 1 day 1 (C1D1) followed by 600 mg/m² on C2D1/C3D1, with DOS (docetaxel 50 mg/m², oxaliplatin 100 mg/m² IV D1; S-1 40 mg/m² PO BID D1–14) every 3 weeks $\times$3 cycles. Surgery (D2 gastrectomy) is performed 1–4 weeks post-neoadjuvant therapy. Adjuvant therapy (initiated 3–8 weeks post-surgery) includes zolbetuximab 600 mg/m² D1/D22 Q6W $\times$8 cycles plus S-1 PO D1–28 Q6W $\times$8 cycles. Enrollment has been ongoing since February 2025 across multiple sites in Korea. Clinical trial information: NCT06732856. Research Sponsor: Astellas.

TPS4251 **Poster Session**

A phase 2, open-label, single-arm study of lirafugratinib in patients with previously treated, unresectable, locally advanced, or metastatic solid tumors (excluding cholangiocarcinoma) with *FGFR2* fusion or rearrangement. First Author: Richard D. Kim, Moffitt Cancer Center Magnolia Campus, Tampa, FL

Background: Tissue agnostic cancer therapies offer the potential to markedly change the treatment landscape by targeting oncogenic drivers rather than the tumor's site of origin. Lirafugratinib is the first highly selective, irreversible inhibitor designed to target oncogenic fibroblast growth factor receptor (*FGFR)2* driver alterations and resistance mutations. In the phase 1/2 ReFocus Trial (RLY-4008-101; NCT04526106),46 subjects (Group 3) with non-cholangiocarcinoma solid tumors harboring FGFR2 fusion/rearrangements (f/r) received lirafugratinib 70 mg once daily. The ORR was 33.3% (95% CI 19.6 - 49.5). However, this sample size was insufficient to support regulatory approval of lirafugratinib for a tissue agnostic indication. **Methods:** The ELE-4008-202, phase 2, open-label, single-arm study (NCT07359820) is designed to further evaluate the efficacy and safety of lirafugratinib 70 mg in 20-30 subjects across 20 sites with FGFR2 f/r, previously treated, unresectable, locally advanced or metastatic, non-CCA solid tumors who have not received prior FGFR inhibitor therapy. The primary endpoint is objective response rate (ORR) by independent review committee (IRC) per RECIST v1.1; key secondary endpoints include duration of response (DOR) by IRC, investigator-assessed efficacy endpoints, safety, pharmacokinetic (PK) parameters, and quality of life (QoL) per EORTC QLQ-C30. Efficacy will also be evaluated for ORR, DOR, disease control rate (DCR), progression-free survival (PFS), overall survival (OS), time to response (TTR), time to progression (TTP) per investigator. Time to discontinuation (TTD) will also be assessed. Exploratory endpoints will include FGFR2 genotype per tissue assessment or liquid biopsy vs ORR and levels of other biomarkers in relationship to clinical activity. An interim analysis of the pooled efficacy dataset from ELE-4008-202 and Group 3 of RLY-4008-101 will be conducted once approximately 65 evaluable subjects with non-CCA tumors have been enrolled across $\geq$7 tumor types ($\geq$5 subjects per tumor type). Enrollment of a tumor type may be capped once it has reached approximately 20% of the total subjects in the pooled data from the two studies. With 65 subjects, observing at least 21 subjects with a complete response (CR) or partial response (PR) (ORR $\geq$32%), will result in a 95% CI (lower bound $>$20%) with the probability of observing $\geq$21 responders assuming a true ORR of 40% is approximately 92%. The results of this analysis will determine whether the pooled evaluable data from RLY-4008-101 and ELE-4008-202 meet regulatory requirements to support a tissue-agnostic indication for FGFR2 f/r non-CCA solid tumors. Clinical trial information: NCT07359820. Research Sponsor: Elevar Therapeutics.

TPS4252 **Poster Session**

A randomized phase III study of gemcitabine plus cisplatin with S-1 versus gemcitabine plus cisplatin with immune checkpoint inhibitor in unresectable biliary tract cancer. First Author: Hiroto Matsui, Oncology Center, Yamaguchi University Hospital, Ube, Japan

Background: Gemcitabine plus cisplatin (GC) has been established as the standard first-line treatment for unresectable biliary tract cancer (BTC). Recent phase III trials have demonstrated the clinical benefit of adding immune checkpoint inhibitors (ICIs) to GC. Meanwhile, GC combined with S-1 has also shown promising efficacy in East Asian populations. However, no randomized phase III trial has directly compared GC plus ICI with GC plus S-1. This study aims to compare the efficacy and safety of GC plus ICI with GC plus S-1 in patients with unresectable BTC. **Methods:** This is an ongoing, multicenter, open-label, randomized phase III trial (UMIN000051689). Eligible patients have histologically confirmed unresectable biliary tract cancer, including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder cancer, with no prior systemic therapy. Patients are randomized in a 1:1 ratio to receive either Arm A: gemcitabine plus cisplatin plus S-1 or Arm B: gemcitabine plus cisplatin combined with an immune checkpoint inhibitor. Randomization is stratified by primary tumor site, disease status (recurrence vs primary unresectable), and planned immune checkpoint inhibitor regimen for patients assigned to Arm B. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, objective response rate, disease control rate, safety, and health-related quality of life. The planned sample size is 460 patients (230 per arm), providing 80% power to detect a statistically significant difference in overall survival with a two-sided alpha of 0.05. Current Status: Patient enrollment began in August 2023. As of January 2026, approximately 60% of the planned patients have been enrolled. Enrollment is ongoing, and follow-up continues. **Conclusions:** This randomized phase III trial will clarify the optimal first-line systemic treatment for unresectable biliary tract cancer by directly comparing GC plus immune checkpoint inhibition with GC plus S-1. Clinical trial information: UMIN000051689. Research Sponsor: None.

TPS4253 **Poster Session**

ARTEMIDE-Biliary02: A phase 3, randomized, global study of rilvegostomig or durvalumab with chemotherapy as first-line (1L) treatment for advanced biliary tract cancer (BTC). First Author: Lipika Goyal, Department of Medicine, Stanford Cancer Center, Palo Alto, CA

Background: Biliary tract cancer (BTC) is the second most common hepatic malignancy, comprising 15% of liver tumors. BTC incidence is rising worldwide, and the majority of patients are diagnosed late where the median survival is approximately one year. Chemoimmunotherapy with gemcitabine and cisplatin combined with either durvalumab or pembrolizumab is the current first-line (1L) standard for advanced BTC. To enhance the clinical benefit from immune checkpoint inhibitors, dual blockade of the programmed cell death-1 (PD-1) and T cell immunoreceptor with Ig and ITIM domains (TIGIT) pathways may be an effective strategy. Rilvegostomig, a monovalent, Fc-reduced, bispecific anti-PD-1/anti-TIGIT antibody, has shown promising preliminary efficacy in combination with gemcitabine and cisplatin for 1L treatment of advanced BTC (Zhou J, et al. ASCO 2025 [Abstract 4080]). The phase 3 ARTEMIDE-Biliary02 study (NCT07221253) assesses the efficacy and safety of rilvegostomig or durvalumab in combination with gemcitabine and cisplatin for 1L treatment of advanced BTC. **Methods:** Eligible participants (aged $\geq$ 18 years) have unresectable, locally advanced/metastatic BTC (intrahepatic cholangiocarcinoma [iCCA], extrahepatic CCA [eCCA], or gallbladder cancer [GBC]), previously untreated in the advanced setting, no prior immunotherapy, centrally confirmed programmed cell death ligand-1 (PD-L1) status, and ECOG PS of 0/1. Approximately 1100 participants will be randomized (1:1) to receive rilvegostomig or durvalumab, both in combination with gemcitabine and cisplatin, until radiological progression per RECIST v1.1. Participants will be stratified by PD-L1 expression (tumor area positivity $<$ 1% vs $\geq$ 1%), disease status (initially unresectable vs recurrent), primary tumor site (iCCA vs eCCA vs GBC), and geographic region (Asia vs rest of world). The primary endpoint is overall survival (OS) in the PD-L1 $\geq$ 1% population, defined as time from randomization until date of death due to any cause. Key secondary endpoints include OS in the intent-to-treat (ITT) population and progression free survival (PFS), defined as time from randomization until radiological progression per RECIST v1.1, in both the PD-L1 $\geq$ 1% and ITT populations. Other secondary endpoints include objective response rate, duration of response, PFS rates (defined as time from randomization until earliest progression event) in both the PD-L1 $\geq$ 1% and ITT populations, safety/tolerability, and patient-reported outcomes. OS will be assessed using a stratified log-rank test adjusting for stratification factors. A stratified Cox proportional hazards model will estimate the hazard ratio and associated 95% confidence interval. Enrollment started in December 2025 and is ongoing across Asia, Australia, Europe, and the Americas. Clinical trial information: NCT07221253. Research Sponsor: AstraZeneca.

TPS4254 **Poster Session**

Adjuvant sintilimab plus bevacizumab following curative resection of spontaneously ruptured hepatocellular carcinoma: A prospective exploratory phase II study (CLEAR-2). First Author: Yongjun Chen, Department of General Surgery, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Spontaneous rupture of hepatocellular carcinoma (srHCC) is a life-threatening complication associated with acute hemorrhage, aggressive tumor biology, and an exceptionally high risk of postoperative recurrence. Even after successful hemostasis and curative (R0) resection, outcomes remain poor, with early relapse—particularly peritoneal dissemination—being a dominant failure pattern. Patients with srHCC have been systematically excluded from most pivotal phase III adjuvant trials in hepatocellular carcinoma, resulting in a critical evidence gap for postoperative systemic management. Current adjuvant strategies are largely extrapolated from non-ruptured HCC or based on retrospective analyses, and no prospective studies have specifically evaluated immunotherapy-based adjuvant therapy in this population. Immune checkpoint inhibitor–based combinations with anti-angiogenic agents have demonstrated survival benefits in advanced HCC and have recently been explored in the adjuvant setting for high-risk resected disease. Given the unique biological behavior of srHCC, characterized by tumor cell spillage at rupture and a strong propensity for early systemic and peritoneal relapse, adjuvant systemic therapy targeting micrometastatic disease is biologically rational and urgently needed. The CLEAR-2 study is designed to prospectively explore the efficacy and safety of adjuvant sintilimab combined with bevacizumab following curative resection of srHCC. **Methods:** CLEAR-2 is a prospective, multicenter, single-arm, exploratory phase II study. Eligible patients are adults (18–75 years) with radiologically or intraoperatively confirmed spontaneous rupture of HCC who have undergone curative (R0) hepatic resection, with Child-Pugh A liver function and ECOG performance status 0–1. Preoperative transarterial embolization (TAE) for hemostasis is permitted if performed once and within 2 weeks prior to surgery, without chemotherapeutic agents. A total of 35 patients will be enrolled. Adjuvant treatment is initiated 4–8 weeks postoperatively and consists of sintilimab 200 mg plus bevacizumab 15 mg/kg intravenously every 3 weeks for up to 1 year or until recurrence, unacceptable toxicity, or withdrawal. Radiologic assessment is performed every 12 weeks. The primary endpoint is disease-free survival (DFS). Secondary endpoints include overall survival (OS), safety graded per CTCAE v5.0, and recurrence patterns (intrahepatic, extrahepatic, and peritoneal). Clinical trial information: NCT07331883. Research Sponsor: None.

TPS4256 **Poster Session**

Fatty acid degradation (FAD)–guided comprehensive therapy for unresectable hepatocellular carcinoma: A prospective phase II study (FAD-HCC-01). First Author: Decai Yu, Department of General Surgery, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, Jiangsu, China

Background: Hepatocellular carcinoma (HCC) exhibits marked molecular and metabolic heterogeneity, leading to variable therapeutic responses and limiting the effectiveness of current systemic treatments. Despite recent advances in immunotherapy and targeted agents, no validated biomarker is available to guide treatment selection in unresectable HCC. We previously established a fatty acid degradation (FAD) pathway-based molecular classification of HCC, revealing that FAD-associated transcriptional programs delineate biologically distinct HCC subtypes with heterogeneous immune microenvironments and differential responses to systemic and locoregional therapies. These findings suggest that FAD-based stratification may enable a more precise, biology-driven treatment strategy. However, the feasibility of implementing FAD-guided treatment allocation in a prospective clinical setting has not been established. FAD-HCC-01 is designed to evaluate the feasibility, safety, and preliminary efficacy of a FAD-guided comprehensive therapy in patients with unresectable HCC. **Methods:** FAD-HCC-01 is a prospective, multicenter, open-label phase II study enrolling patients with unresectable or non-curatively treatable HCC. Eligible patients have histologically or clinically confirmed HCC, BCLC stage B or C disease, Child–Pugh class A to B ($\leq$7), ECOG performance status 0-1, and no prior systemic therapy. Tumors are classified into FAD subtypes (F1, F2, or F3) using transcriptomic profiling with ssGSEA-based FAD scoring; MRI-derived fat fraction may serve as a provisional surrogate when tumor tissue is unavailable. A total of 86 patients will be enrolled, with 43 patients planned for each treatment cohort. Patients are assigned to two parallel cohorts according to FAD subtype. Patients with F1 or F2 tumors receive camrelizumab (200 mg intravenously every 3 weeks) plus rivoceranib (250 mg orally once daily). Patients with F3 tumors receive transarterial chemoembolization (TACE) combined with camrelizumab and rivoceranib, with TACE performed per institutional standards and repeated as clinically indicated. Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint is objective response rate assessed by RECIST v1.1. Secondary endpoints include ORR by mRECIST, disease control rate, progression-free survival, overall survival, duration of response, conversion to curative treatment, and safety. Key feasibility objectives include successful FAD subtyping, adherence to FAD-guided treatment allocation, and integration of molecular or imaging-based classification into routine clinical workflows. Exploratory analyses will assess concordance between MRI fat fraction and FAD subtypes and explore molecular correlates of treatment response. Clinical trial information: NCT07314372. Research Sponsor: Fundings for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University.

TPS4257 **Poster Session**

CAREFOL: A phase 3, randomized, open-label, multicenter trial of camrelizumab and rivoceranib with or without intravenous FOLFOX chemotherapy as first-line treatment for unresectable hepatocellular carcinoma. First Author: Linhui Peng, Department of Hepatobiliary Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: The combination of camrelizumab (an anti-PD-1 IgG4 monoclonal antibody) and rivoceranib (a VEGFR2-TKI) is a standard of care, first-line (1L) therapy for advanced hepatocellular carcinoma (HCC). However, immune therapy resistance leads to ineffective initial treatment and difficulty in maintaining long-term efficacy in some patients. Several studies have shown that oxaliplatin and fluorouracil can induce immunogenic cell death in tumor cells and induce antitumor immune response in the body. Intravenous FOLFOX chemotherapy may regulate the liver tumor microenvironment and improve clinical benefit, a hypothesis supported by positive efficacy signals in the Phase II VIC-TRIPLETS study (NCT05412589). Here we present the design of a phase III randomized controlled study. **Methods:** This investigator-initiated, phase III, randomized, open-label, multicenter trial (NCT06280508) aims to compare the efficacy and safety of camrelizumab and rivoceranib combined with (CAREFOL) or without intravenous FOLFOX chemotherapy (CARE) as first-line treatment for unresectable HCC. Eligible patients are aged at least 18 years, with unresectable or metastatic HCC, no previous systemic treatment, with BCLC stage B or C disease (which is not amenable to or had progressed after surgical or locoregional therapy), at least one measurable lesion per RECIST 1.1 criteria, Child-Pugh class A liver function, an ECOG performance status of 0 or 1, and adequate organ function. Approximately 326 Participants will be randomly assigned (1:1) using a centralized interactive response system. Randomization is stratified by presence of extrahepatic metastasis (yes vs no), macrovascular invasion (Vp0-3 vs Vp4), and baseline α-fetoprotein level ($<$ 400 ng/mL vs $\geq$400 ng/mL). The experimental group consisted of camrelizumab 200 mg intravenously every 3 weeks plus rivoceranib 250 mg orally once daily combined with 21-day cycles of intravenous FOLFOX chemotherapy (oxaliplatin 85 mg/m^2, levofolinate 200 mg/m^2, 5-fluorouracil bolus 400 mg/m^2 on day 1, and 5-fluorouracil infusion 2400 mg/m^2 for 46 hours; up to 6 cycles). The control group is camrelizumab plus rivoceranib (same as experimental group). The dual primary endpoints are investigator-assessed progression-free survival per RECIST v1.1 and overall survival. Secondary endpoints include objective response rate, disease control rate, duration of response, surgical conversion rate, time-to-treatment failure, safety. The trial is currently screening eligible patients. Clinical trial information: NCT07267806. Research Sponsor: None.

TPS4258 **Poster Session**

A phase II trial of trifluridine/tipiracil plus oxaliplatin in patients with advanced or metastatic biliary tract cancer following first-line therapy. First Author: Madison Conces, Department of Oncology, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Biliary tract cancers (BTCs) comprising of intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer are aggressive and difficult cancers to treat. Most patients present with metastatic or unresectable disease, and systemic therapy is the only therapeutic option. Treatment options are highly limited after progressing on first line therapy with median survival of 6 months. We demonstrated encouraging activity with single agent trifluridine/tipiracil (FTD/TPI) and FTD/TPI plus irinotecan in separate phase 2 trials in patients with refractory BTCs after multiple lines of therapies (NCT03278106 and NCT04072445). Disease control rate (DCR) of 50% was reported with the combination therapy and median OS was 9.1 months. Prior studies have suggested oxaliplatin-based therapy may be more effective than irinotecan-based therapy in BTC. Thus, FTD/TPI plus oxaliplatin may be an active regimen in patients with advanced BTCs. **Methods:** This is a phase II trial evaluating FTD/TPI plus oxaliplatin as second line treatment in patients with advanced BTCs and disease progression on standard of care gemcitabine-based combination therapy. Key inclusion criteria are pathologically confirmed BTC, ECOG performance status 0 or 1, prior gemcitabine-based combination therapy, adequate organ function, signed informed consent. Key exclusion criteria include >1 prior line of systemic therapy for advanced disease (adjuvant therapy not counted) and active autoimmune disease requiring systemic therapy. Participants will be enrolled at Case Comprehensive Cancer Center sites and receive a dose of FTD/TPI of 25 mg/m^2 twice daily on days 1-5 and oxaliplatin 85 mg/m^2 on day 1 of a 14-day cycle until disease progression, intolerable toxicities, or patient declines to continue study. Primary endpoint is DCR, defined as proportion of patients achieving responses or stable disease with trial treatment. The trial is a Simon 2-stage optimal design with a significance level of 0.05 and 80% power. We estimate a DCR of 0.62 compared to historical control of 0.33 in second line setting. If ≤ 2 patients have disease control out of the first 6 patients enrolled, then regimen will be considered ineffective. If >3 patients have disease control, then the study will proceed to stage 2. During stage 2, an additional 18 patients will be enrolled for 24 total evaluable patients. If >12 patients of the 24 evaluable patients have disease control, then the trial will be considered a success and a larger trial will be planned. Secondary endpoints are grade and duration of adverse events, ORR, PFS, OS. Correlative studies are circulating DNA and oral and fecal samples for microbiome testing. The study is supported by the National Comprehensive Cancer Network (NCCN) through a grant provided by Taiho Oncology. Neither NCCN nor Taiho are the sponsor. Clinical trial information: NCT07146646. Research Sponsor: Taiho.

TPS4259 **Poster Session**

Impact of immunonutrition in patients undergoing hepatectomies for liver tumors: A randomized controlled phase II trial. First Author: Shraddha Patkar, Department of Surgical Oncology, Tata Memorial Hospital (HBNI), Mumbai, India

Background: Recent studies have demonstrated that immunonutrition has the potential to improve the host immune state, reduce infectious complications, and shorten the length of hospital stay after major abdominal surgeries. Controversy still persists regarding whether or not perioperative immunonutrition could offer substantial benefits to patients undergoing hepatectomy as compared with standard nutrition. Several biomarker-based indices reflecting the immune as well as nutritional status, have been investigated, to predict postoperative morbidity following major hepatectomies. One such index, validated in a meta-analysis is the prognostic nutritional index (PNI). Prognostic Nutritional Index (PNI) = [(10 $\times$ serum albumin (g/dL)) + (0.005 $\times$ total lymphocyte count)], with higher PNI correlating with improved survival outcomes . Based on this we aim to conduct a randomized controlled trial to evaluate the improvement of PNI, by immunonutritional intervention in patient undergoing major hepatectomies. **Methods:** Study Design: Open labelled, Phase II randomized controlled trial. Eligibility criteria: Inclusion: (1) Patients with liver tumors planned for major hepatectomies (defined as resection of $>/=$ 3 liver segments); (2) Age above 18 years; (3) ASA class I-III. Exclusion: (1) Preoperative severe renal failure (estimated glomerular filtration rate $<$ 30 ml/min); (2) History of hypersensitivity to arginine, omega-3 fatty acids, or nucleotide; (3) Inability to take oral nutrition; (4) Pregnancy; (5) Mental condition rendering the subject unable to understand the nature, endpoints and consequences of the trial. Interventions: Randomization will be carried out centrally at the Clinical Research Secretariat, Tata Memorial Hospital. The trial statistician will generate a permuted-block randomization sequence using variable sized blocks of 2, or 4, without any stratification factors. Participants will be randomly assigned in 1:1 to receive either the intervention or control. Details of Intervention: In addition to their usual intake, patients in the intervention arm will be prescribed for each of the 7 consecutive days preceding surgery 6-9 scoops Immunomax powder (120-180g per day), based on weight. At recruitment, blood samples will be taken for inflammatory and immune status markers. These measurements will be repeated on the day prior to surgery (D-1) and on POD 1, 3, 5 and 7. An additional Creactive protein (CRP) measurement will be taken on POD30. PNI will be calculated before the intervention and on the day prior to surgery. Primary Endpoints: Mean difference in PNI points between intervention and control group. Secondary Endpoints: (1) Incidence of postoperative complication; (2) Incidence of post-hepatectomies liver failure (PHLF); (3) Length of ICU stay; (4) Length of hospital stay; (5) Incidence of 90 days mortality. 100 patients will be enrolled over 2 years. Clinical trial information: CTRI/2025/06/088908. Research Sponsor: Tata Memorial Hospital Intramural Grant.

TPS4260 **Poster Session**

Phase II study of NC410 and FOLFIRINOX in combination with nivolumab with or without ipilimumab in patients with treatment-naive metastatic pancreatic cancer. First Author: Shriram K. Sundararaman, Sidney Kimmel Comprehensive Cancer Center, The Johns Hopkins University School of Medicine, Baltimore, MD

Background: Pancreatic adenocarcinoma (PDAC) is now the third leading cause of cancer-related death in the United States (1). Median overall survival for patients with metastatic PDAC is 11.1 months with first-line FOLFIRINOX chemotherapy (2) and more effective treatments are needed. A major resistance mechanism to immunotherapy in PDAC is the desmoplastic stroma (3). Collagen physically hinders T cell infiltration and suppresses immune cells in the tumor microenvironment (TME) through the Leukocyte Associated Immunoglobulin-like Receptor-1 (LAIR-1) (4). Both collagen and the complement protein C1q, overexpressed in the PDAC TME, are primary ligands for the inhibitory LAIR-1 receptor on myeloid and lymphoid cells, and binding results in immune cell downregulation (5-7). LAIR-2, primarily made by CD4+ T cells, is a competitive inhibitor of LAIR-1 that reverses the immunosuppressive effect (8). NC410 is a dimeric fusion protein of LAIR-2 with human IgG1 Fc that remodels collagen, reduces tumor growth, enhances T cell tumor infiltration, and overcomes neutrophil-mediated T cell suppression in preclinical studies (7,9,10). NC410 binds the collagen-rich PDAC TME with high avidity when compared across tumor types (7). Our group contributed to the recent phase Ib/II study demonstrating clinical activity of NC410 with pembrolizumab in patients with advanced colorectal and ovarian cancer (NCT05572684). Based on these promising results, our study combines NC410 and immunotherapy with FOLFIRINOX in the first-line setting to assess safety and clinical efficacy in patients with metastatic PDAC. **Methods:** This is a single-center, open-label, two-arm phase II study evaluating safety and efficacy of NC410 and FOLFIRINOX in combination with nivolumab with or without ipilimumab in patients with untreated metastatic PDAC. The two arms enroll sequentially. In Cycle 1, NC410 and FOLFIRINOX are given with nivolumab (Arm 1, n =10) or nivolumab + ipilimumab (Arm 2, n = 10). In Cycle 2 and beyond, patients in both arms receive NC410 and FOLFIRINOX every 2 weeks and can continue to receive treatment per investigator discretion. On study scans are obtained every 8 weeks. Eligible patients have untreated metastatic PDAC, measurable disease per RECIST 1.1, and are willing to undergo tumor biopsy at baseline and on treatment. Primary endpoint is safety. Secondary endpoints are disease control rate, objective response rate, progression free survival, and overall survival. Correlative studies will profile circulating neutrophils and markers of immune activation in paired whole blood and tumor biopsy samples at baseline and on-treatment at Cycle 4. Enrollment began in August 2025 and is ongoing. 10 of planned 20 patients have been enrolled; awaiting 8-week primary safety endpoint evaluation in Arm 1. Trial information: NCT06941857. References upon request. Clinical trial information: NCT06941857. Research Sponsor: The Lustgarten Foundation; Swim Across America; Cynthia Boscov Fund for Pancreatic Cancer Research; James and Frances McGlothlin Fellows to Faculty Fund; U.S. National Institutes of Health.

TPS4262 **Poster Session**

Phase 1 faecal microbiota transplantation in patients with advanced pancreatic carcinoma (FMTPanc Trial). First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Adelaide, Australia

Background: Higher abundance of specific oral, pancreatic and/or gut microbes is correlated with pancreatic cancer occurrence (e.g. *Porphyromonaas gingivalis*, *Malassezia* sp.). Furthermore, the pancreatic tumour microenvironment of long-term survivors ($\geq$ 5 years) shows richer tumoral microbial diversity associated with more active T-cells and fewer immune-suppressing cells than short-term survivors. Preclinical animal studies have also demonstrated that faecal microbiota transplantation (FMT) from a healthy donor or a long-term survivor can significantly decrease the size of pancreatic tumours. These findings demonstrate that manipulations of the gut and/or organ microbiota holds promise as part of cancer treatment. This trial aims to evaluate whether restoring a healthier microbiota can improve symptoms, visceral pain and treatment efficacy in people with non-resectable pancreatic cancer. **Methods:** This study is a Phase 1 double-blind randomised placebo-controlled trial (RCT) assessing the safety and potential benefit of oral FMT in patients with non-resectable pancreatic cancer. FMT will be a co-treatment to the standard of care chemotherapy. The primary outcomes are FMT safety and toxicity and mortality at 3, 6, and 12 months after chemotherapy initiation. Secondary outcomes include: changes in visceral pain and symptoms measured by PAGI-SYM, changes from baseline in blood CA-19-9 levels and reduction in tumour size as surrogate marker of treatment efficacy, and changes in faecal microbiota as a surrogate marker of gut flora restoration and treatment efficacy at 3, 6, and 12 months after treatment initiation. Power calculations were conducted for the main secondary clinical outcome of interest (i.e. the PAGI-SYM tool) that encompasses pain and symptom monitoring using published evidence, an MCID of 0.94, for an alpha of 0.05 and 80% power a minimum of 14 participants per arm is required. The trial aims to recruit a minimum of 28 and maximum of 60participants, 14-30 per arm. Eligible patients will have advanced and unresectable adenocarcinoma of the pancreas suitable for standard chemotherapy (gemcitabine/nab-paclitaxel or FOLFIRINOX) and be treatment-naive. Patients will be randomised 1:1 to FMT or placebo. FMT and placebo capsules will be prepared by BiomeBank (Adelaide South Australia). Stool will be sourced from healthy donors and rigorously screened following criteria specified by the Australian Therapeutic Administration (TGA). FMT/placebo will be provided through two doses (dose 1: 25mg, dose 2: 50mg). Chemotherapy will commence 3 to 14 days after completion of the first FMT dose (week 0). Supportive medication includes pancrelipase (2x25,000U three times a day) to facilitate digestion during FMT treatment. The FMTPanc is open at 3 sites across South Australia and Victoria and as of January 2025 12 patients have been enrolled. Clinical trial information: ANZCTR: ACTRN12624000455561. Research Sponsor: None.

TPS4263 **Poster Session**

TRIDENT: A phase 2 study of relacorilant plus nab-paclitaxel and gemcitabine in patients with previously untreated metastatic pancreatic ductal adenocarcinoma. First Author: Erkut H. Borazanci, HonorHealth Research Institute, Scottsdale, AZ

Background: Metastatic pancreatic ductal adenocarcinoma (mPDAC) has a 5-year survival rate of < 5%. Approved treatment options are limited to combination cytotoxic chemotherapy such as mFOLFIRINOX or nab-paclitaxel + gemcitabine. Cortisol-mediated glucocorticoid receptor (GR) activation provides prosurvival signals to tumor cells that contribute to chemotherapy resistance. The addition of relacorilant, a selective GR antagonist, to paclitaxel + gemcitabine improved tumor growth inhibition over paclitaxel + gemcitabine alone in a PDAC xenograft model (Greenstein *Oncotarget* 2021). Moreover, in a phase 1 study of relacorilant and nab-paclitaxel, 2 durable confirmed partial responses were observed in patients with mPDAC (Munster *Clin Cancer Res* 2022). The combination of relacorilant and nab-paclitaxel prolonged progression-free survival (PFS) and overall survival (OS) in patients with platinum-resistant ovarian cancer in 2 randomized controlled trials, including the phase 3 ROSELLA study (Olawaiye *Lancet* 2025). The combination was well tolerated, with a safety profile that was consistent with nab-paclitaxel monotherapy. Therefore, the combination of relacorilant, nab-paclitaxel, and gemcitabine is deserving of further clinical study to improve outcomes in patients with mPDAC. **Methods:** TRIDENT is a phase 2, single-arm, open-label, multicenter study (NCT07259317) designed to evaluate the combination relacorilant + nab-paclitaxel + gemcitabine as a first-line treatment in mPDAC (target enrollment, N = 60). Key inclusion criteria are confirmed measurable metastatic disease (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), no prior systemic anticancer therapy to treat metastatic disease, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function. Patients will receive relacorilant 150 mg orally once daily for 3 consecutive days (day before, day of, and day after chemotherapy) in combination with nab-paclitaxel (100 mg/m^2) and gemcitabine (1000 mg/m^2) given on days 1, 8, and 15 of each 28-day cycle. Treatment will continue until disease progression or unmanageable toxicity. The primary endpoint is investigator-assessed PFS per RECIST version 1.1 and will be analyzed using Kaplan-Meier methods. Secondary endpoints are OS, best overall response, objective response rate, clinical benefit rate at 24 weeks, duration of response, cancer antigen 19-9 kinetics, and tolerability/safety. The study is currently enrolling. Clinical trial information: NCT07259317. Research Sponsor: Corcept Therapeutics.

TPS4264 **Poster Session**

S2433: Randomized phase III study of second-line chemotherapy with or without panitumumab for KRAS wild type, locally advanced, or metastatic pancreatic adenocarcinoma. First Author: Rachael A. Safyan, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: Pancreatic ductal adenocarcinoma (PDA) is characterized by driver mutations in *KRAS*, *TP53*, *CDKN2A*, and *SMAD4*. *KRAS* wild type (WT) tumors, present in 5-10% of PDA, often harbor alternative mitogen-activated protein kinase (MAPK) pathway drivers or other targetable molecular alterations (e.g., microsatellite instability [MSI-high], DNA damage repair mutations), enabling targeted therapy in approximately 30% of cases; however, most lack actionable drivers and require a tailored treatment approach. EGFR is overexpressed in 30%-70% of PDA. Prior studies of EGFR-targeted therapy demonstrated modest overall survival (OS) benefit in unselected populations, with retrospective analyses suggesting benefit confined to *KRAS* WT PDA. Recent data showed survival benefit from the anti-EGFR antibody nimotuzumab when added to 1st line gemcitabine vs gemcitabine alone in *KRAS* WT PDA. These findings provide a strong rationale to evaluate anti-EGFR mAb in combination with multi-agent chemotherapy in *KRAS* WT PDA in the United States. **Methods:** This randomized (1:1) phase III study will enroll 94 pts to investigator choice 2nd-line chemotherapy – 5 fluorouracil (5FU) plus irinotecan or nanoliposomal irinotecan following 1st-line gemcitabine-based therapy, or gemcitabine plus nab-paclitaxel following 1st-line 5FU-based therapy – with or without panitumumab. Eligibility requires *KRAS* WT and *BRAF* V600E WT status by tumor tissue-based next-generation sequencing and no known mutations in *PTEN*, *NRAS*, *EGFR* extracellular domain exons 1-16, no amplifications of *HER2* and *MET*, and no gene fusions of *RET*, *NTRK1*, and *ALK*. One prior line of chemotherapy for locally advanced or metastatic PDA is permitted. Pts with cancers harboring molecular alterations (e.g., MSI-high, ROS fusion) may have received prior targeted therapy, and past maintenance therapy with a PARP inhibitor does not count as a line of therapy. The primary endpoint is OS; secondary endpoints include safety, progression-free survival, overall response rate, disease control rate, and duration of response. Quality of life will be assessed using the Functional Assessment of Cancer Therapy – General (FACT-G), Functional Assessment of Chronic Illness Therapy (FACIT) Item GP5, and selected patient-reported outcome (PRO)-CTCAE items. Blood and tumor samples will be collected for correlative studies. Standard eligibility criteria apply. Assuming panitumumab improves median OS from 6.3 to 12.6 months, 84 eligible patients provide 90% power with a one-sided alpha of 0.05. Kaplan-Meier methods will estimate OS, with early stopping for efficacy or futility. This study is open to accrual (NCT06998940). Clinical trial information: NCT06998940. Research Sponsor: NIH/NCI/NCTN grants U10CA180888, U10CA180819.

TPS4265 **Poster Session**

A prospective single-arm study of irinotecan liposome II combined with adebrelimab, gemcitabine, and nab-paclitaxel for conversion therapy in locally advanced pancreatic cancer. First Author: Wenwen Zhang, Faculty of Hepato-Pancreato-Biliary Surgery, Chinese PLA General Hospital; Institute of Hepatobiliary Surgery of Chinese PLA; Key Laboratory of Digital Hepetobiliary Surgery, PLA, Peking, China

Background: Locally advanced pancreatic cancer (LAPC) has an extremely poor prognosis, with only a minority of patients eligible for radical surgery at initial presentation. Conversion therapy is critical for improving resectability and survival. Currently, no standard conversion regimen exists for LAPC, and gemcitabine plus nab-paclitaxel (AG regimen) is widely used. Irinotecan liposome has favorable tumor targeting and manageable toxicity; the PAN-HEROIC-1 study showed that irinotecan liposome II combined with 5-fluorouracil/leucovorin (5-FU/LV) significantly prolonged overall survival in Chinese advanced pancreatic cancer patients. Adebelimab, a programmed death-ligand 1 (PD-L1) inhibitor, exerts synergistic antitumor effects with chemotherapy in solid tumors. Herein, we evaluate the efficacy and safety of Irinotecan Liposome II plus Adebelimab and AG regimen as conversion therapy for LAPC to improve surgical conversion rates and survival benefits. **Methods:** This prospective, single-arm, open-label study plans to enroll 45 patients with pathologically confirmed locally advanced pancreatic ductal adenocarcinoma. Key inclusion criteria: 18-75 years old; Eastern Cooperative Oncology Group (ECOG) PS 0-1; adequate major organ function; no central nervous system metastasis; effective contraception for reproductive-aged subjects (pregnancy excluded); informed consent. Exclusion criteria: non-ductal pancreatic cancer; active autoimmune diseases; severe infections; major surgery or investigational drugs within 4 weeks prior to enrollment; other investigator-judged ineligibility. Primary endpoint is surgical conversion rate; secondary endpoints include event-free survival, overall survival, R0/R1 resection rate, objective response rate, pathological complete response rate, and safety profile. Treatment Regimen: Irinotecan Liposome II (40 mg/m², IV infusion 90±30 min, Day 1, q2w) + Adebelimab (1200 mg, IV infusion 30-60 min, Day 1, q4w) + gemcitabine (1000 mg/m², IV infusion > 30 min, Days 1,8,15, q4w) + nab-paclitaxel (125 mg/m², IV infusion > 30 min, Days 1,8,15, q4w). Registration Number: ChiCTR 2500108269. Research Sponsor: Hengrui Pharma. Clinical trial information: ChiCTR2500108269. Research Sponsor: None.

TPS4266 **Poster Session**

Using organoids to predict efficacy of adjuvant treatment to improve outcome in resectable pancreatic cancer: UNITEPANC (AIO-PAK-0424), a prospective, multicenter, proof-of-concept trial of the AIO Pancreatic Cancer Group. First Author: Thomas Jens Ettrich, Department of Internal Medicine I, Ulm University Hospital, Ulm, Germany

Background: Pancreatic cancer (PDAC) is a heterogeneous disease and there is a lack of predictive biomarker to guide treatment. Patient tumor derived organoids (PDO) recapitulate key morphological and genetic features and may preserve patient-specific drug response phenotypes **Methods:** UNITEPANC is a prospective, proof of concept, multicenter IIT of the German AIO PDAC Group and funded by the German Cancer Aid. UNITEPANC examines the feasibility of an organoid-educated adjuvant treatment approach with respect to organoid establishment, expansion and characterization and its potential role for selecting an optimal adjuvant treatment in PDAC in a multicenter setting. Preparatory activities like harmonizing SOPs and round-robin-tests for generation of organoids and organoid-based pharmacotyping in the trial centers and the different Organoid Facilities have been completed and evaluated. UNITEPANC examines selection of adjuvant chemotherapy by pharmacotyping of tumor organoids. Options for adjuvant treatment are gemcitabine, gemcitabine/capecitabine, gemcitabine/nab-paclitaxel or mFOLFIRINOX. Major inclusion criteria are R0 or R1 resected, histologically confirmed PDAC and patients in principle, suitable for mFOLFIRINOX treatment in the adjuvant setting, postoperative Ca19-9 < 180 U/ml, and a timely PDO-based chemotherapy recommendation by the UNITEPANC Organoid Board to guarantee a start of the adjuvant treatment within 12 weeks after resection. UNITEPANC is an interventional, prospective, multicenter, single-arm trial. 92 patients shall be allocated to the trial for the generation of organoids, 38 patients shall be enrolled for PDO-based adjuvant treatment and 34 patients need to be analyzed as ITT population in the follow-up period. Efficacy: The efficacy endpoint of the trial is purely descriptive and intended to obtain a signal for further development of the strategy. This requires the proof of an efficient 1) generation and 2) expansion of PDO and 3) a clear sign that an organoid-educated treatment selection is superior to standard treatment with mFOLFIRINOX. For 1) and 2) we have chosen a rate of 75% and 60%, respectively, according to the literature. For 3): The approach would be considered promising, if the true 18-months-DFS rate is 77% (corresponding to a hazard ratio of 0.5 compared to Prodige-24, 80% power, one-sided type I error 0.1. HR-QoL data will be analyzed (QLQ-C30, Pan26). Additionally, an extensive translational program is enclosed. UNITEPANC has started recruitment in Q3/2025. Clinical trial information: 2023-510490-34-00. Research Sponsor: German Cancer Aid.

TPS4267 **Poster Session**

Phase I light-dose escalation study in locally advanced pancreatic ductal adenocarcinoma: Intra-arterial (IA) padeliporfin vascular-targeted photodynamic therapy (VTP). First Author: Nadine Abi-Jaoudeh, University of California Irvine, Division of Vascular & Interventional Radiology, Department of Radiological Sciences, Orange, CA

Background: Locally advanced pancreatic ductal adenocarcinoma (LA-PDAC) with $>$ 180° vascular encasement of major abdominal arteries is considered unresectable and is associated with poor prognosis. Standard-of-care options, including chemotherapy and chemoradiation, achieve limited conversion to resectability with high recurrence rates. Thus, a therapeutic approach that can effectively downstage LA-PDAC to resection is clinically needed. Activation of vascular-targeted photodynamic therapy (VTP) by Padeliporfin illumination at 753nm results in photochemical generation of oxygen and nitric oxide radicals that cause rapid occlusion followed by break down of the tumor vasculature, tumor necrosis and break-down of the extracellular matrix. Photosensitivity at $>$ 6 hours is avoided due to 1.19 hours Padeliporfin half-life without accumulation in epithelial tissue. Padeliporfin-VTP activation by intra-arterial (IA) illumination has the potential to selectively ablate tumor tissue encasing the artery, reducing vascular encasement and enabling subsequent surgical resection. Robust feasibility and safety preclinical studies in normal swine and efficacy in mouse tumor models have demonstrated feasibility of light transmission through the arterial wall at a dose sufficient to induce tumor ablation at the artery interface and acceptable safety profile, supporting clinical translation. **Methods:** NCT05919238 is an ongoing multi-center Phase I light dose-escalation study. Key inclusion criteria are stage III LA-PADC with solid tumor contact $>$ 180° in head/uncinate process of the pancreas for the total encasement length up to 3cm and with target artery internal diameter 5-10 mm. VTP is applied via IA placement of an optical fiber, inside a standard angioplasty balloon, in the target artery adjacent to the tumor. Ten minutes intravenous administration of Padeliporfin at a fixed dose of 4 mg/kg immediately followed by 753nm laser illumination through the inflated balloon, for two 5-minute cycles with 1-minute break. The study is designed to evaluate three light power densities: 200, 400 and 600mW/cm. The primary objectives include determination of Maximum Tolerated light Dose (MTD) and/or recommended phase 2 dose (RP2D) and evaluation of safety. Secondary objectives are to determine rate of surgical downstaging and resectability as well as the pattern of disease progression following VTP treatment, based on pre- and post-VTP contrast computed tomography (CT) scans and tissue specimens, in case surgery is performed. The study comprises two parts: part A with 3+3 light dose escalation schema; part B (expansion cohort) with the RP2D/MTD, derived in Part A. As of 28 October 2025, Cohort 1 of Part A with an LPD of 200mW/cm have been completed without DLTs. Enrolment to cohort 2, with LPD 400mW/cm, began in November 2025. Clinical trial information: NCT05919238. Research Sponsor: Impact Biotech.

TPS4268 **Poster Session**

Durvalumab and oleclumab in resectable pancreatic ductal adenocarcinoma: A window of opportunity trial (DORA). First Author: Erica Sophia Tsang, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Resectable pancreatic ductal adenocarcinoma (PDAC) comprises $<$ 20% of cases and remains associated with poor outcomes despite surgery and adjuvant chemotherapy. PDAC features a hypoxic, immunosuppressive and "cold" tumor microenvironment (TME). CD73 has emerged as a prognostic biomarker in PDAC, with high expression linked to poor survival. CD73 on tumor cells impairs antitumor T-cell responses and results in tumor immune escape. Inhibition of CD73 could reverse immune suppression by the TME. Preliminary data from the phase I combination trial of durvalumab (anti-PD-L1 antibody) and oleclumab (anti-CD73 antibody) has shown modest antitumor activity in patients in PDAC, colon cancer, and non-small cell lung cancer. A window-of-opportunity (WOO) study allows for rapid early identification of biological activity. We therefore designed a WOO trial to assess the impact of CD73 and PD-L1 blockade in resectable PDAC to test the hypothesis that this strategy would increase CD8+ T cell infiltration and reduce suppressive immune cells as assessed by digital spatial profiling and image mass cytometry. **Methods:** DORA (NCT06060405) is a prospective phase II multicentre WOO trial evaluating the immune activity of combined CD73 and PD-L1 blockade in upfront resectable PDAC. Eligible patients must have ECOG 0–1, histologically confirmed NCCN resectable PDAC, and be immunotherapy-naïve. Patients undergo an upfront EUS for histological diagnosis and for correlative studies, and then receive a single dose of durvalumab 1500 mg IV and oleclumab 3000 mg IV x 2 doses every two weeks prior to surgical resection. Patients receive standard-of-care adjuvant systemic therapy following surgery. The primary objective is to determine the increase in immune cell infiltration, specifically CD8+ T cells, between the paired pre-treatment and surgical resection specimens. Secondary objectives include the percent change in other immune cell populations (CD3/CD45RA/RO T cells, M1 vs. M2 macrophage), and the dynamic changes in immune cell populations as measured by flow cytometry/CyTOF. A total of 22 patients will be enrolled to ensure 20 evaluable subjects who undergo surgical resection. With 20 patients, this provides 80% power to detect an effect size of 0.66 using a two-sided alpha of 0.05. Planned correlatives include serial ctDNA analysis and whole genome and transcriptome sequencing of all surgical resections. This study was activated in January 2024. Clinical trial information: NCT06060405. Research Sponsor: None.

TPS4269 **Poster Session**

ENVELOPE trial (NCCH2412): Enfortumab vedotin in patients with locally advanced or metastatic small bowel adenocarcinoma refractory or intolerant to platinum-based combination therapy—A multicenter, phase II trial (trial in progress). First Author: Hiroyuki Fujii, Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Small bowel adenocarcinoma (SBA) is a rare malignancy with limited systemic options beyond first-line platinum-based combination therapy (FOLFOX/CapeOX) and no established second-line treatment. We recently reported that Nectin-4 is frequently highly expressed in SBA, providing a biological rationale for enfortumab vedotin, a Nectin-4–directed antibody-drug conjugate (ADC). We designed a multicenter phase II trial to evaluate the antitumor activity and safety of enfortumab vedotin in unresectable locally advanced or metastatic SBA refractory or intolerant to platinum-based combination therapy. To our knowledge, this is the first trial to evaluate the efficacy of ADC in this rare cancer. **Methods:** Key eligibility criteria include age $\geq$18 years, histologically/cytologically confirmed SBA, ECOG PS 0–1, prior FOLFOX or CapeOX with progression or intolerance, $\geq$1 measurable lesion (RECIST v1.1) and adequate organ function. If prior testing has identified alterations qualifying for approved tumor-agnostic therapies, patients must be refractory or intolerant to such therapies. Nectin-4 positivity is not required for enrollment. Exclusion criteria include a history of interstitial lung disease and poorly controlled diabetes. Enfortumab vedotin is administered at 1.25 mg/kg intravenously on days 1, 8, and 15 of each 28-day cycle until progression or unacceptable toxicity. Tumor assessments are performed by enhanced CT every 8 weeks up to week 24 and every 12 weeks thereafter. The primary endpoint is the objective response rate (ORR), as determined by blinded independent central review. Representative secondary endpoints include disease control rate, progression-free survival, overall survival, and safety outcomes, as assessed by the Common Terminology Criteria for Adverse Events v5.0. The null ORR is 5%, and the expected ORR is 25%. An exact binomial design (one-sided α = 0.05; 90% power) requires 25 evaluable patients, with the planned sample size of 27 to account for non-evaluable cases. In a prespecified translational study, tumor Nectin-4 expression will be assessed by immunohistochemistry, and its association with the efficacy of enfortumab vedotin will be explored. Biological specimens will be collected at baseline, during treatment, and at progression for multi-omics analysis to investigate mechanisms of response and resistance. The ENVELOPE trial has been approved by the Institutional Review Board of the National Cancer Center Japan. Enrollment opened on October 2025 and will continue through October 2027; follow-up will extend 12 months after the last patient is enrolled. As of December 31, 2025, 5 patients had been enrolled. Clinical trial information: NCT07347314/jRCT2031250424. Research Sponsor: Japan Agency for Medical Research and Development, AMED; Grant number JP25ck0106015h0001.

TPS4270 **Poster Session**

FusionVAC22_02, a phase I clinical trial in progress: Adjuvant *DNAJB1-PRKACA* fusion transcript–based peptide T-cell activator for fibrolamellar hepatocellular carcinoma (FLC) and other tumor entities carrying the oncogenic driver fusion. First Author: Susanne Jung, Clinical Collaboration Unit Translational Immunology, Department of Internal Medicine, Cluster of Excellence iFIT (EXC2180), University Hospital Tübingen, Tübingen, Germany

Background: The DNAJB1-PRKACA fusion transcript was detected as the oncogenic driver of tumor pathogenesis in fibrolamellar hepatocellular carcinoma (FLC) and other cancers, e.g. oncocytic neoplasms of pancreas and bile duct. We and others have shown that the fusion protein can be targeted by T cell-based immunotherapy: Application of Fusion-VAC-XS15 a peptide-based T cell activator including the TLR1/2 agonist XS15 emulsified in Montanide ISA 51 VG in two FLC patients was well tolerated without systemic side effects and induced long-lasting T-cell response accompanied by disease remission with a progression-free survival of up to 80 months and 60 months in both patients (Bauer *et al.* Nat. Commun., 2022). Based on these promising data, Fusion-VAC-XS15 combined with Atezolizumab is currently under evaluation in the advanced or metastatic situation since October 2023 (Hackenbruch *et al.* Front Oncol., 2024; NCT05937295). For localized FLC, surgical resection still represents the only curative treatment option but shows high relapse rates which underscores the high medical need for adjuvant treatment options. We here present the FusionVAC22_02 trial, which evaluates Fusion-VAC-XS15 as an adjuvant therapeutic in FLC patients who have reached complete remission. **Methods:** FusionVAC22_02 is a Phase I open label, multicentric clinical trial evaluating immunogenicity along with safety, toxicity and first signs of clinical efficacy of Fusion-VAC-XS15 as adjuvant treatment, in 20 patients with FLC or other cancers with proven DNAJB1-PRKACA fusion protein, and lacking adjuvant treatment options. One key eligibility criterion is achievement of complete remission (e.g. due to surgery, radiotherapy, local intervention or systemic treatment) according to RECIST1.1. Of note, a history of liver transplantation or prior immune-mediated side effects (e.g. after treatment with checkpoint-inhibitors) are no exclusion criteria. Fusion-VAC-XS15 is applied twice in a 4-week interval, with an optional booster 56 days after the second application, followed by a 6-month follow-up. Primary objectives include assessment of immunogenicity in terms of peptide-specific T cell responses, as well as evaluation of safety and toxicity. Safety assessment is based on the frequency of adverse events according to CTCAE v5.0. Clinical efficacy is determined by RECIST1.1 assessment on imaging. Recruitment started in July 2025, nine FLC patients from various parts of the world have been included and treated so far, four of which have reached the primary endpoint. Clinical trial information: NCT06789198. Research Sponsor: Fibrolamellar Cancer Foundation; Angewandte Klinische Forschung.

TPS4271 **Poster Session**

Sacituzumab govitecan in combination with capecitabine for the treatment of advanced gastrointestinal cancers after progression on standard therapy.

First Author: Maria Diab, Henry Ford Health/Michigan State University, Detroit, MI

Background: Gastrointestinal (GI) malignancies are associated with poor survival and novel therapies are urgently needed. Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) that targets the tumor-associated antigen Trop-2 (trophoblast cell-surface antigen 2). SG is covalently bound to the topoisomerase I inhibitor SN-38, which is the active metabolite of irinotecan. Trop-2 is overexpressed in most GI malignancies, including colorectal, gastric, and pancreatic cancers, and is associated with poor prognosis. SG has been approved for the treatment of second-line triple-negative breast cancer and pre-treated hormone-receptor positive metastatic breast cancer but its role in GI cancers is not determined. Furthermore, its combination with capecitabine has never been studied. **Methods:** We are conducting a single arm, single institution, dose escalation phase 1 trial with a 3+3 design of combination SG plus capecitabine. SG dosing will be at three levels: Level -1 at 5mg/kg; Level 0 at 7.5mg/kg; and Level +1 at 10mg/kg. Dosing will start at dose level 0. SG will be administered as an intravenous infusion on Days 1 and 8 of a 21-day cycle. Capecitabine dose is fixed at 825mg/m^2 and will be delivered orally twice a day for 14 days on and 7 days off, starting on Day 1, of the 21-day cycle. Key eligibility criteria include histologically documented metastatic adenocarcinoma of GI origin, including gastroesophageal, colorectal, and pancreaticobiliary, that has failed standard therapy; age $\geq$18years; ECOG performance status 0-1; and adequate end organ function. Key exclusion criteria include previous receipt of topoisomerase 1 inhibitors. The primary endpoint is the Recommended Phase 2 Dose (RP2D). Secondary endpoints include objective response rates, duration of response, progression-free and overall survival. An exploratory endpoint is the correlation between Trop-2 expression in collected archival tissue and clinical outcomes. Optional biopsies will be offered for patients with missing or insufficient archival tissue. This study has been registered under NCT06065371 and is actively enrolling. The trial will enroll up to 20 patients. The trial is funded by Gilead Sciences, Inc. Clinical trial information: NCT06065371. Research Sponsor: None.

4500 Oral Abstract Session

A phase 2 randomized trial of radium-223 dichloride and cabozantinib in patients (pts) with renal cell carcinoma (RCC) with bone metastases (BM): RADICAL (Alliance A031801). First Author: Rana R. McKay, UC San Diego Moores Cancer Center, San Diego, CA

Background: BM occur in ~30% of RCC pts and are associated with poor survival and symptomatic skeletal events (SSEs). Radium-223, an alpha-emitting bone-seeking radioisotope, prolongs survival in advanced prostate cancer. A pilot study of radium-223 with VEGF tyrosine kinase inhibitors (TKI) in RCC with BM showed safety and early efficacy (McKay, CCR, 2018). Cabozantinib is a TKI that showed efficacy in BM. RADICAL (NCT04071223) was designed to investigate cabozantinib ± radium-223 in RCC with BM. **Methods:** This open label multicenter study enrolled RCC pts with ≥1 symptomatic BM not previously irradiated and Karnofsky performance status ≥60%. Prior therapies were allowed; non-clear cell population was limited to 20%. Randomization was 1:1 to cabozantinib with (Arm A) or without (Arm B) radium-223, stratified by osteoclast-targeted therapy (OTT), prior therapy, baseline opioid use, and IMDC risk. In Arm A, cabozantinib was 40 mg daily cycle 1, 60 mg thereafter if tolerated; radium-223 was 1.49 microcurie/kg IV every 28 days for 6 doses. In Arm B, cabozantinib was 60 mg daily. The primary endpoint was SSE-free survival (SSE-FS). Secondary endpoints were safety, objective response rate (ORR), progression-free survival (PFS) and overall survival (OS). The study was designed with 85% power to detect improvement in 6-month SSE-FS from 65% to 78% (one-sided α=0.05), with planned interim futility analysis at 50% of expected events. **Results:** From 12/2019 to 9/2025, 90 pts were enrolled and evaluable for the interim analysis. Median age was 63 years; 74.4% male, 90.0% White, 83.3% clear cell histology. 11.1% were treatment naïve, 80.0% received OTT, 51.1% had baseline opioid use. IMDC risk was 16.7% favorable, 68.9% intermediate, 14.4% poor. Median cabozantinib dose was 31.4 mg (Arm A) and 40.0 mg (Arm B); median radium-223 cycles was 6. Median follow-up was 13.1 (range 0.1-49.4) months with 50 events, 17 SSEs (Arm A: 10; Arm B: 7) and 33 deaths (Arm A: 13; Arm B: 20). Outcomes are in Table. 71 pts were evaluable for response. ORR was 22.2% (Arm A), 22.9% (Arm B). Any grade treatment-related adverse events were 97.7% (Arm A), 93.2% (Arm B); grade ≥3 were 65.9% (Arm A), 56.8% (Arm B). The trial closed after interim analysis as SSE-FS did not meet the prespecified futility boundary (HR≤1). **Conclusions:** Radium-223 did not improve the primary endpoint of SSE-FS when added to cabozantinib but a numerical prolongation in OS was observed. Combination treatment was safe. Alternative radiotherapeutics warrant investigation in RCC. Clinical trial information: NCT04071223. Research Sponsor: National Cancer Institute.

Interim efficacy analysis.

	Arm	Median (95% CI)	HR (95% CI)
Stratified SSE-FS	**A**	17.9 (15.0-NE)	1.24 (0.62-2.48)
	B	17.6 (10.9-NE)	
Unstratified SSE-FS	**A**	17.9 (15.0-NE)	0.90 (0.51-1.59)
	B	17.6 (10.9-NE)	
OS	**A**	32.2 (17.9-NE)	0.77 (0.42-1.41)
	B	21.3 (12.3-NE)	
Stratified PFS	**A**	11.0 (5.8-17.4)	1.39 (0.72-2.66)
	B	11.2 (9.0-18.5)	

4501 Oral Abstract Session

A prospective, multi-center, phase Ib/II trial of first-line cadonilimab plus axitinib in advanced non−clear cell renal cell carcinoma. First Author: Xu Hu, Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China

Background: Non-clear cell renal cell carcinoma (nccRCC) is a rare and heterogeneous disease with limited treatment evidence. Patients with nccRCC generally respond less favorably to systemic immunotherapy than those with clear cell RCC. However,current evidence for the treatment of nccRCC remains limited,underscoring the need for new strategies. Cadonilimab,a bispecific PD-1/CTLA-4 antibody,has shown antitumor activity in various solid tumors, but its efficacy in RCC remains unknown. Here, we report initial results from a phase Ib/II trial of cadonilimab plus axitinib in advanced nccRCC. **Methods:** This open-label, multi-center, single-arm, phase Ib/II trial included patients with metastatic or unresectable treatment-naive nccRCC, regardless of PD-L1 status, to receive cadonilimab plus axitinib 5mg b.i.d. In phasel,a 3+3 dose-escalation design was adopted,starting at 10 mg/kg Q3W of cadonilimab with axitinib to evaluate safety. In phase II, an additional 31 patients were enrolled at the recommended phase II dose (RP2D). The primary endpoints were safety assessment in phase Ib and objective response rate (ORR) by RECIST v1.1 in phase II. **Results:** As of October 1,2025, A total of 37 patients was enrolled (Phase Ib:n=6;Phase II: n=31), with a median follow-up duration of 14.4 months. In phase Ib, no DLTs were observed. AEs were reported in 100.0% (6/6) of cases. Grade≥3 treatment-related adverse events (TRAEs) occurred in 66.7% (4/6) of cases,including proteinuria, hypertriglyceridemia, myasthenia gravis, diarrhea and alanine aminotransferase increased. The RP2D for cadolinimab was 10 mg/kg. For secondary endpoints, ORR was 50% (2/4) and DCR was 100% (6/6). In phase II, the ORR was 51.6%(16/31). DCR was 96.8% (30/31). AEs were reported in100.0% of cases. Grade≥3 treatment-related adverse events (TRAEs) occurred in 58.1% (18/31) of cases. All AEs were expected and manageable. The median PFS was 16.7 (95%CI,11.8-NR). The median OS was NR at the data cutoff. For the total cohort, the median PFS was 17.3(95%CI,12.1-NR). The median OS was NR at the data cutoff. **Conclusions:** Cadonilimab combined with axitinib demonstrated encouraging efficacy and tolerability as first-line therapy in advanced nccRCC across subtypes in this multi-center phase Ib/II study. Clinical trial information: NCT05808608. Research Sponsor: None.

Summary of efficacy analysis and tumor response review per RECIST v1.1.

	Phase Ib	Phase II	Total cohort
Objective response rate, n(%)	2 (50)	16 (51.6)	18 (51.4%)
Disease control rate, n(%)	6 (100)	30 (96.8)	36 (97.2%)
mPFS (95%CI) months	NR (17.3, NR)	16.7 (11.8-NR)	17.3 (12.1-NR)
mOS (95%CI), months	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)

4502 Oral Abstract Session

ctDNA analysis in participants with renal cell carcinoma treated with adjuvant pembrolizumab or placebo in the KEYNOTE-564 trial. First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: In the phase 3 KEYNOTE-564 trial (NCT03142334), adjuvant pembrolizumab (pembro) was superior to placebo (pbo) in participants (pts) with clear cell renal cell carcinoma (ccRCC) at increased risk of recurrence post nephrectomy. We report an analysis of pre-treatment and on-treatment ctDNA (using 2 versions of a ctDNA assay with different sensitivities) with clinical outcomes in KEYNOTE-564. **Methods:** Pts with ccRCC at increased risk of recurrence post nephrectomy were randomized 1:1 to pembro or pbo. ctDNA was evaluated using Natera's Signatera RUO tissue-exome-based 16-plex and 64-plex ctDNA assays. Primary objectives of this analysis were to evaluate the association of baseline ctDNA status and ctDNA status change from baseline to cycle 5 day 1 (C5D1) with disease-free survival (DFS). Significance was prespecified at multiplicity-adjusted α = 0.05. Sensitivity (percentage of ctDNA-positive pts among all pts with a DFS event) and specificity (percentage of ctDNA-negative pts among all pts without a DFS event) to predict DFS were also evaluated. **Results:** 994 pts were randomized to pembro (n = 496) or pbo (n = 498). ctDNA samples from 736 pts (pembro n = 374; pbo n = 362) were analyzed at baseline and from 641 pts at C5D1 (pembro n = 314; pbo n = 327) using both assays. Median study follow-up was 69.5 mo (range 60.2-86.9). In both treatment arms, ctDNA was detectable at baseline in 40 pts (5.4%) using the 16-plex assay and 60 pts (8.2%) using the 64-plex assay. By risk group, using the 16-plex assay, ctDNA was detectable at baseline in 26 of 642 (4.0%) intermediate-high risk pts, 10 of 53 (18.9%) high-risk pts, and 4 of 38 (10.5%) M1 NED pts; using the 64-plex assay, ctDNA was detectable in 44 of 642 (6.9%) intermediate-high risk pts, 11 of 53 (20.8%) high-risk pts, and 5 of 38 (13.2%) M1 NED pts. For both assays, ctDNA positivity was negatively associated with DFS in both pembro and pbo arms (P's < 0.05). ctDNA status at baseline showed low sensitivity and high specificity to predict DFS in both treatment arms (Table). Of pts with detectable ctDNA at baseline and evaluable ctDNA at C5D1, ctDNA clearance at C5D1 occurred in 6 of 10 pts in the pembro arm and 3 of 14 pts in the pbo arm using the 16-plex assay; and 10 of 18 pts in the pembro arm and 9 of 25 pts in the pbo arm using the 64-plex assay. In both assays, ctDNA change from baseline at C5D1 was associated with DFS for both pembro and pbo arms (P's < 0.05). **Conclusions:** While sensitivity was low, ctDNA positivity was associated with worse DFS outcomes irrespective of the ctDNA assay used. ctDNA clearance was higher in the pembro arm than the pbo arm. These data highlight the limitations of these ctDNA assays in ccRCC. Clinical trial information: NCT03142334. Research Sponsor: Funding for this study was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

% (n/N)	Pembro Sensitivity	Pembro Specificity	Pbo Sensitivity	Pbo Specificity
Baseline ctDNA, 16-plex	12 (17/146)	98 (224/228)	10 (18/173)	99 (188/189)
Baseline ctDNA,64-plex	15 (22/146)	96 (220/228)	15 (26/173)	98 (185/189)

4503 Oral Abstract Session

Intravesical recombinant BCG combined with chemo-immunotherapy (chemo-IO) as perioperative therapy for patients with muscle-invasive bladder cancer (MIBC): Primary analysis of SAKK 06/19. First Author: Richard Cathomas, Division of Oncology, Cantonal Hospital Graubunden, Chur, Switzerland

Background: Perioperative chemo-IO is a new standard for MIBC but pathological complete remission (pCR) rates remain modest. Intravesical Bacillus Calmette Guérin (BCG) is very effective in non-muscle invasive bladder cancer, inducing a local immune response and likely activation of adaptive immunity, with evidence of systemic immune modulation that may enhance downstream immune-oncological effects. The use of BCG in MIBC has not yet been explored, primarily due to concerns about systemic complications. The recombinant BCG vaccine VPM1002BC (rBCG) is associated with enhanced immunogenicity and an improved safety profile. We hypothesize that the combination of intravesical rBCG and chemo-IO in MIBC may act synergistically, augmenting systemic immune activation and hereby improve anti-tumor efficacy without compromising safety. **Methods:** SAKK 06/19 is an open-label single arm phase II trial for cT2-T4a N0-1 MIBC patients (pts) eligible for cisplatin and radical cystectomy with lymphadenectomy (RC). rBCG was instilled weekly x3 (day 1, 8, 15). Atezolizumab (Atezo) 1200 mg was administered on day 1 and then x4 every 3 weeks (q3w). Cisplatin and gemcitabine started on day 22 and were given for 4 cycles q3w followed by RC. Only in case of ≥ ypT2 or ypN+, Atezo q3w was given after surgery for 13 cycles. pCR defined as ypT0 ypN0 and assessed by central pathological review was the primary endpoint. Based on Simon's minimax 2-stage design with H0 pCR ≤ 35% and H1 pCR ≥ 55%, accrual of 46 pts was needed (including 15% dropouts). Secondary endpoints included event free survival (EFS), overall survival (OS), pathological response (PaR, ≤ ypT1N0), feasibility and safety. NCT04630730. **Results:** 47 pts were included between 04/22 and 04/25 at 10 Swiss sites. 7 pts did not undergo RC (6 refused, 1 unfit for surgery). Of the 40 resected pts 53% had cT2, 37% cT3, 10% cT4 and 88% cN0, 12% cN1. rBCG was instilled in 95% of pts, 78% had all 3 doses. 98% received 4 doses of Atezo and 95% had 4 cycles of platinum (20% switched to carboplatin). pCR according to central review was 65% (26/40; one-sided 95% CI lower boundary of 51%) and PaR was 80% (32/40). Overall pCR for all included pts was 55% (26/47). TRAEs overall, G3, G4 were 48%, 9%, 0% to rBCG, 55%, 15%, 2% to Atezo and 98%, 38%, 17% to chemotherapy. No treatment-related deaths occurred. At a median follow-up of 11.8 months 1-year overall EFS was 88% (95% CI 71 - 95) and OS 95% (95% CI 81 - 99). **Conclusions:** This is the first trial to combine intravesical rBCG with chemo-IO in MIBC. The combination was feasible and safe without unexpected toxicities. The centrally assessed pCR rate of 65% and PaR of 80% are among the highest reported in an unselected MIBC population. Integration of intravesical rBCG into novel MIBC treatment regimens appears highly promising, particularly in the context of bladder-preservation approaches. Clinical trial information: NCT04630730. Research Sponsor: Roche; Swiss State Secretariat for Education, Research and Innovation (SERI).

4504 Clinical Science Symposium

Feasibility and safety results from RAD-IO: A multi-stage trial of durvalumab with chemoradiotherapy with 5-fluorouracil and mitomycin C in patients with muscle-invasive bladder cancer. First Author: Nicholas David James, The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom

Background: Immune checkpoint inhibitors have a defined role peri-operatively and in the adjuvant setting when cystectomy is used as radical definitive treatment (Powles, T., *et al.* 2024, Galsky, M. D., *et al.* 2024). Their role when chemoradiation therapy (CRT) is used as definitive treatment remains to be established. RADIO is a multi-stage partially randomised trial comparing CRT (RT/5FU/mitomycin C) with durvalumab (CRT-D) given prior to, concurrently and 12 months following CRT in localized muscle-invasive bladder cancer. The trial is funded by AstraZeneca. **Methods:** Eligible patients had T2–T4aN0–N2M0 urothelial carcinoma of the bladder. Neoadjuvant chemotherapy was delivered as standard of care, where fit, prior to trial therapy. After randomised feasibility and safety criteria were met, the trial transitioned to a single-arm CRT-D design. Here we report the primary endpoint of 1-year disease-free survival rate (1yDFS) for all evaluable CRT-D participants, plus progression free survival (PFS), disease free survival (DFS), and overall survival (OS). DFS patients with disease present at 3-month imaging are categorised as having never been disease free. The design aimed to detect 1yDFS improvement, based on our previous trials, from 60% (CRT) to 75% (CRT-D) with 80% power and one-sided α=0.10. **Results:** All data are preliminary. Between Oct 2020–Mar 2024, 55 participants (45 male; 10 female) with median age 70 (IQR 62-76) years of whom 40 (73%) had T2N0, 8 (14%) had T3N0 and 7 (13%) had TxN1-2 were enrolled to receive CRT-D. 41 (74.5%) received neoadjuvant CT. Of the 54 participants who started treatment, all completed planned RT (55Gy/20Fr); 47 (87%) within the expected timeframe, 7 (13%) required an extension (2-6 days) (toxicity 3, patient choice 3, other 1). Toxicities extending RT: urinary tract infection, chest pain, and low platelets. At abstract submission, 48/55 were evaluable: 1yDFS 79% (38/18; 95% CI 66%, 88%). 12-month Kaplan-Meier estimates were: PFS 83% (95% CI 73%, 94%), DFS 72% (95% CI 61%, 85%), OS 96% (95% CI 91%, 100%). Safety: 35 SAEs; 17 unrelated SAEs, 12 SARs, 6 SUSARs. 10 SAEs were related to durvalumab, 3 were related to CT, and 5 were related to both durvalumab and CT. 3 SAEs led to discontinuation (5FU 2, durvalumab 1). 168 AESIs have been reported (most common: diarrhoea (19%), rash (12%), creatinine increased (8%)), and an additional 41 grade $\geq$3 AEs. **Conclusions:** Durvalumab combined with CRT demonstrated promising 1-year DFS and survival outcomes compared to our previously reported CRT outcomes (Hall, E., *et al*, 2022) with manageable safety profile. CRT-D is a safe treatment with a side effect profile in keeping with known side effects of CRT and durvalumab. Further investigation is warranted. Clinical trial information: 43698103. Research Sponsor: AstraZeneca UK Limited.

4506 Oral Abstract Session

Perioperative SHR-A2102, a novel nectin-4—targeted antibody-drug conjugate, in combination with adebrelimab for patients (pts) with muscle-invasive bladder cancer: Results from a phase 2/3 study. First Author: Dingwei Ye, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Muscle-invasive bladder cancer (MIBC) is an aggressive disease, with substantial recurrence risk after radical cystectomy and pelvic lymph node dissection (RC + PLND) alone. SHR-A2102 is a nectin-4-targeted antibody-drug conjugate carrying topoisomerase I inhibitor payload. This phase 2/3 study (NCT06879145) evaluates the efficacy and safety of SHR-A2102 in combination with adebrelimab (an anti-PD-L1 antibody) as perioperative treatment for MIBC. Here, we report the preliminary results from the phase 2 study. **Methods:** In the multicenter phase 2 part, pts aged $\geq$18 years, ECOG PS 0-1, with pathologically and radiographically confirmed T2-4aN0M0 or T1-4aN1M0 MIBC, and scheduled for RC + PLND were enrolled. Pts received neoadjuvant treatment with 4 cycles of intravenous SHR-A2102 (8 mg/kg, day 1 Q3W) and adebrelimab (1200 mg, day 1 Q3W), followed by surgical resection and 5 additional cycles of adjuvant SHR-A2102 (8 mg/kg, day 1 Q3W) plus 13 additional cycles of adjuvant adebrelimab (1200 mg, day 1 Q3W). The primary endpoints are the recommended phase 3 dose (RP3D) and investigator-assessed pathological complete response (pCR, defined as pT0N0). **Results:** As of Nov 24, 2025, 37 pts were enrolled; 91.9% were male and the median age was 66 years (IQR 59-74). The ECOG PS was 0 in 24.3% of pts and 1 in 75.7%. Regarding disease stage, 29.7% were classified as T2N0, 51.4% as T3-4aN0, and 18.9% as T1-4aN1. Among 7 pts with target lesions, the neoadjuvant regimen achieved an objective response rate of 71.4% (5/7; 95% CI 29.0–96.3) and a disease control rate of 100.0% (95% CI 59.0–100.0). A total of 27 pts underwent RC + PLND, 13 (48.1%, 95% CI 28.7-68.1) achieved pCR and 16 (59.3%, 95% CI 38.8-77.6) attained pathological downstaging ($<$ pT2N0). Consistent pCR benefits were observed across all predefined subgroups, with creatinine clearance $<$ 60 mL/min showing no discernible effect on pCR rates. Of the 10 pts who refused or were ineligible for radical surgery after neoadjuvant therapy, 5 received transurethral resection of bladder tumor and 3 of whom achieved a complete clinical response (cCR, defined as T0N0M0). With the median follow-up of 4.7 months (IQR 2.1-6.6), 3 event-free survival events were reported. Grade 3 or higher adverse events occurred in 40.5% (15/37) of the pts, primarily decreased neutrophil count (16.2%) and decreased lymphocyte count (10.8%). No patient was ineligible for surgery due to adverse events. **Conclusions:** Perioperative treatment with SHR-A2102 plus adebrelimab showed promising efficacy and was well tolerated in pts with MIBC. This combination holds potential benefit even for pts with renal impairment, suggesting its clinical applicability may extend beyond cisplatin-eligible populations. These results support further investigation for SHR-A2102 plus adebrelimab in this population. Clinical trial information: NCT06879145. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

4507 Oral Abstract Session

Enfortumab vedotin plus pembrolizumab (EV+P) vs chemotherapy for previously untreated locally advanced or metastatic urothelial carcinoma (la/mUC): 3.5-year follow-up and response analyses from the phase 3 EV-302 study. First Author: Thomas Powles, Barts Cancer Centre, Queen Mary University of London, London, United Kingdom

Background: EV+P is the preferred standard of care for previously untreated la/mUC based on the EV-302/KEYNOTE-A39 trial (NCT04223856). We present updated data with 3.5 years of median follow-up, including exploratory subgroup analyses focusing on patients who achieved a complete response (CR) after an initial partial response (PR). **Methods:** Patients were randomized 1:1 to EV 1.25 mg/kg IV (days 1 and 8 of each 3-wk cycle) and P 200 mg IV (day 1) or gemcitabine + cisplatin/carboplatin, with treatment until disease progression, toxicity, or maximum number of cycles. Dual primary endpoints were progression-free survival by blinded independent central review and overall survival (OS); safety was a secondary endpoint. **Results:** With 42.8 months of median follow-up (data cutoff: October 6, 2025), OS benefit favoring EV+P (n=442) vs chemotherapy (chemo; n=444) was maintained (median OS, 33.6 vs 15.9 months; 42-month OS rate, 44.0% vs 24.6%; HR, 0.53 [95% CI, 0.45-0.63]), with no new safety signals. Of responding patients, 45.1% achieved a CR in the EV+P arm (n=295) and 32.8% in the chemo arm (n=195. Data cutoff was Aug 8, 2024. Among patients with confirmed CR in the EV+P arm, 66.2% achieved a PR initially, then converted from a PR to a CR with a median of 5 additional EV cycles (IQR, 3.0-8.0). In this subgroup, mOS was not estimable (NE), and $>$80% of patients were alive after 3.5 years. Longer treatment duration did not lead to new safety concerns. Overall, the most common first subsequent treatment was platinum-based chemo in the EV+P arm (n=135 [30.5%]) and a PD-L1 inhibitor in the chemo arm (n=265 [59.7%]). In the EV+P arm, investigator-assessed responses to subsequent platinum chemo occurred in 28 of 135 evaluable patients (20.7%). **Conclusions:** EV-302 represents the longest follow-up available for EV+P in a phase 3 trial. After 3.5 years of median follow-up, EV+P continues to demonstrate superior efficacy vs chemo, with no new safety signals. Two-thirds of patients achieving CR converted from an initial PR, suggesting that treatment duration is relevant in maximizing outcomes. Clinical trial information: EV-302 NCT04223856. Research Sponsor: Astellas Pharma Inc., Northbrook, IL, USA; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	EV+P All CR (n=133)	EV+P CR after PR (n=88)
Median OS (95% CI), months	NE (NE-NE)	NE (NE-NE)
42-month OS rate (95% CI), %	83.6 (75.6-89.1)	82.4 (71.8-89.43)
Median time to CR (IQR), months	4.3 (2.2-8.4)	6.6 (4.3-12.1)
Time to PR	–	2.1 (1.9-2.2)
Time from PR to CR	–	4.5 (2.2-10.1)
Median EV cycles prior to CR (IQR), n	6.0 (3.0-9.0)	8.0 (6.0-11.5)
EV cycles prior to PR	–	3.0 (3.0-3.0)
EV cycles from PR to CR	–	5.0 (3.0-8.0)
Median P cycles prior to CR (IQR), n	6.0 (3.0-10.0)	9.0 (6.0-12.0)
P cycles prior to PR	–	3.0 (3.0-3.0)
P cycles from PR to CR	–	6.0 (3.0-9.0)
Median total EV cycles (IQR), n	13.0 (8.0-28.0)	15.0 (9.0-30.0)
Median total P cycles (IQR), n	28.0 (10.0-35.0)	31.0 (12.5-35.0)

4508 Oral Abstract Session

Initial results from NEXUS-01, a phase 1 study of LY4052031, an antibody-drug conjugate targeting Nectin-4, in participants with advanced or metastatic urothelial carcinoma. First Author: Gopa Iyer, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Enfortumab vedotin plus pembrolizumab (EVP) is the current first-line standard of care for locally advanced / metastatic urothelial carcinoma (mUC). However, subsequent treatment options are limited, representing an urgent and growing unmet need. Preclinical data suggest that EV resistance may be payload mediated and consequently Nectin-4 remains a viable target for alternative therapies. LY4052031 is a next generation anti-Nectin-4 ADC, comprising a humanized IgG1 antibody conjugated to Camp98, a novel topoisomerase I inhibitor, via a cleavable peptide linker with homogeneous drug antibody ratio of 8. Here, we report the initial clinical data from the phase 1 dose escalation cohort of NEXUS-01 (NCT06465069). **Methods:** Adults with locally advanced / mUC or other selected solid tumors were eligible. Participants (pts) must have received or were ineligible for available standard therapies, and have ECOG PS 0-1. Dose escalation utilized a Bayesian optimal interval design. Key endpoints were safety, PK, and antitumor activity of LY4052031 per RECIST v1.1. **Results:** As of 25 Nov 2025, 70 pts (47 mUC, 23 non-UC) received LY4052031 doses ranging from 0.6-5.4 mg/kg IV Q3W. Median age was 66 years (range, 31-82); 60% had ECOG PS 1. Among pts with mUC, 70% (33/47) had prior EV (6% [2/33] had discontinued EV due to treatment-related toxicity). LY4052031, total antibody, and Camp98 exhibited mostly linear, dose-proportional PK, except at 4.8-5.4 mg/kg for payload. The most common treatment-emergent AEs (TEAEs) were nausea (43%), alopecia (39%), fatigue (37%), decreased appetite (29%), constipation, diarrhea, dysgeusia, mucositis, vomiting (27% each), and anemia (24%). The most common grade $\geq$3 TEAE was anemia (13%). Low activity scores (AS) for CYP2D6, the metabolic clearance pathway for Camp98, were associated with increased dose-limiting toxicity at higher dose levels. Thus, the study was amended to require CYP2D6 genotyping prior to treatment with dedicated dose finding in pts with low AS ($<$ 0.5). Response was assessed in efficacy evaluable pts, defined as all treated pts who had at least 1 post-baseline response assessment or who discontinued prior to the first post-baseline response assessment. In 21 efficacy evaluable mUC pts (AS $\geq$0.5) treated with 2.4-4.8 mg/kg, ORR was 48% (10/21) and DCR was 81% (17/21) with 1 CR, 9 PR, and 7 SD. Among those who had prior EV (8 EV and 7 EV/P), ORR was 40% (6/15) and DCR was 80% (12/15) with 1 CR, 5 PR, and 6 SD; in the EV naïve pts, ORR was 67% (4/6) and DCR was 83% (5/6) with 4 PR and 1 SD. Median follow-up was 7 months (95% CI, 2.79-NE); median DoR was 7 months (95% CI, 2.7-NE). **Conclusions:** LY4052031 demonstrated promising clinical activity at multiple dose levels, including in EV pre-treated mUC. CYP2D6 AS specific dose optimization is ongoing and updated results will be presented. Clinical trial information: NCT06465069. Research Sponsor: Eli Lilly and Company.

4510 **Clinical Science Symposium**

Health-related quality of life (HRQoL) with neoadjuvant and adjuvant (neoadj-adj) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin ineligible: Phase 3 KEYNOTE-905 study. First Author: Peter H. O'Donnell, University of Chicago, Chicago, IL

Background: In KEYNOTE-905/EV-303 (NCT03924895), neoadj-adj EV + pembro and radical cystectomy (RC) + pelvic lymph node dissection (PLND) showed significant and meaningful improvements in EFS, OS, and pathologic complete response vs RC + PLND in pts with MIBC who were ineligible for or declined cisplatin (cis) therapy. Prespecified exploratory HRQoL outcomes are reported. **Methods:** Pts with MIBC who were ineligible/declined cis were randomized 1:1 to neoadj-adj EV + pembro and RC + PLND or RC + PLND (control). HRQoL was analyzed in pts who completed ≥1 PRO assessment. EQ-5D-5L and Functional Assessment of Cancer Therapy (FACT)–Bladder-Cystectomy (BI-Cys) with FACT-general (FACT-G) and Bladder Cancer Index (BCI) were assessed predose on D1 of neoadjuvant cycles 1 (baseline [BL]), 2, and 3; pre- and post-surgery; and predose on D1 of adjuvant cycles 1, 2, 4, 8, and 12 in the EV + pembro arm. In the control arm, assessments were at pre- (BL) and post-surgery. In both treatment (Tx) arms, assessments were also done at Tx discontinuation, Q12W for ≤2y, and Q24W thereafter. End points included mean (95% CI) change from BL to post-surgery wk 18 in FACT-G score; FACT–BI-Cys scores (BI-Cys subscale and Trial Outcome Index [TOI]); BCI urinary, bowel, and sexual scores; and EQ-5D-5L visual analog scale (VAS). **Results:** At post-surgery wk 18, completion and compliance rates for all assessments were ≥65% in the EV + pembro arm and >86% in the control arm. Mean changes from BL to post-surgery wk 18 were similar between arms for FACT-G total and FACT–BI-Cys subscale scores; FACT–BI-Cys TOI score; BCI urinary, bowel, and sexual scores; and EQ-5D-5L VAS score (Table). BCI sexual and bowel score diminution was observed in both arms. For all PRO assessments, mean changes from BL over time were similar between Tx. **Conclusions:** The addition of neoadj-adj EV + pembro did not decrease HRQoL 18 wk post-surgery relative to RC + PLND alone; BCI bowel and sexual domains worsened in both arms, consistent with prior reports of RC impact. Given the superior efficacy and manageable safety, these results support the benefit/risk profile of EV + pembro and RC + PLND as Tx for pts with MIBC ineligible for or declining cis. Clinical trial information: NCT03924895. Research Sponsor: The study was conducted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA in collaboration with Astellas Pharma Inc., Northbrook, IL, USA and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

Mean change from BL to post-surgery wk 18, (95% CI), n	EV + pembro	Control
FACT-G total score	−2.73 (−6.22 to 0.75) n = 102	−2.84 (−6.11 to 0.43) n = 75
FACT–BI-Cys (subscale/symptom index) total score	1.31 (−0.70 to 3.32) n = 102	1.85 (−0.59 to 4.29) n = 75
FACT–BI-Cys TOI	−1.89 (−5.61 to 1.84) n = 102	−0.58 (−4.35 to 3.20) n = 75
BCI urinary	−2.03 (−6.12 to 2.07) n = 101	−0.05 (−5.90 to 5.80) n = 70
BCI bowel	−4.75 (−8.73 to −0.77) n = 101	−4.27 (−7.93 to −0.61) n = 70
BCI sexual	−15.46 (−20.53 to −10.39) n = 94	−17.88 (−24.36 to −11.40) n = 61
EQ-5D-5L VAS	−2.52 (−7.23 to −2.19) n = 102	−0.39 (−5.14 to 4.36) n = 75

LBA4511 **Clinical Science Symposium**

Durvalumab monotherapy versus active monitoring for resected primary renal cell carcinoma in RAMPART: An international, phase 3, randomized controlled trial. First Author: James M.G. Larkin, The Royal Marsden NHS Foundation Trust, London, United Kingdom

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

4512 **Clinical Science Symposium**

Decision regret and toxicity perception following adjuvant pembrolizumab in renal cell carcinoma. First Author: Elizabeth Nally, Barts Cancer Institute, London, United Kingdom

Background: Adjuvant pembrolizumab (pembro) is standard of care in renal cell carcinoma (RCC). We explored whether patients retrospectively regret their decision to receive adjuvant pembro and hypothesised that this is related to long-term toxicity that is not adequately captured by CTCAE criteria. To address this we developed a patient-informed tool, co-designed with patients, focusing specifically on long-term toxicity. **Methods:** Patients with RCC who received adjuvant pembro across three tertiary cancer centres in London between June 2022-Dec 2024 were invited to participate. Eligible patients completed the validated Ottawa Decision Regret Scale (DRS) and a complementary questionnaire exploring factors influencing regret including toxicity and disease recurrence. CTCAE-graded immune-related adverse events (irAEs) were collected and correlated with decision regret (DR). In parallel, patients categorised irAEs as life-changing, significant or non-significant and these were correlated with DR. DRS > 25 was defined as moderate-high regret. Appropriate ethical approval was obtained. **Results:** 104 patients were included post adjuvant pembro (88% pT3N0, 4% pT3N1 and 8% M1 NED). Median follow up was 30 months. 14% patients have relapsed. CTCAE ≥G3 irAEs occurred in 18%. 28% and 11% reported toxicity as significant (S) or life changing (LC) respectively. Patient reported S and LC toxicity did not correlate with ≥G3 CTCAE (p= 0.11), with 33% CTCAE G1-2 events reported as significant. Mean DR score was 14.9 (95% CI 8.5-21.3) with 13% expressing regret. 1/14 patients who had disease recurrence expressed regret (mean DRS = 10.3 [1.4-19.3]). Patients that reported LC & S toxicity expressed more regret (26.9 LC v 26.1 S v 2.1 NS, p= 0.0021). There was no difference in regret between patients that sustained CTCAE G1-2 versus G3-4 irAE (14.9 vs 15.1, p= 0.23). DR was highest with permanent endocrine (n = 24) or musculoskeletal (n = 22) irAEs (endo: DRS 28.8 v 9.5, p= 0.003; MSK: DRS 25.1 v 12.8, p= 0.042). Lower baseline expectations of toxicity correlated with greater DR (p= 0.002). **Conclusions:** DR after adjuvant pembro is driven by long-term, low-grade toxicity rather than disease recurrence. Novel patient-informed tools that capture life-changing or permanent toxicities outperform CTCAE in identifying patients at risk of regret. Improved baseline education on long-term risks may reduce decision regret and improve shared decision-making. Research Sponsor: None.

4513 **Oral Abstract Session**

Health-related quality of life (HRQOL) with pembrolizumab or observation for high-risk muscle-invasive urothelial carcinoma after surgery: Results from the AMBASSADOR randomized trial (Alliance A031501). First Author: Ronald C. Chen, University of Kansas Medical Center, Kansas City, KS

Background: The AMBASSADOR trial (NCT03244381) showed that in patients with high-risk muscle-invasive urothelial carcinoma after radical surgery, adjuvant pembrolizumab for one year improved disease-free survival from 14.2 to 29.6 months (Apolo et al, NEJM 2024). Here we report the HRQOL results. **Methods:** HRQOL was completed by 560 randomized patients and included the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 plus the bladder cancer supplement BLM30, and the EQ-5D-5L, which assesses overall quality of life or health state. Published minimally important difference thresholds for EQ-5D-5L is 0.06, and for EORTC instruments is 5-10 points. For all reported HRQOL data, higher score is better except BLM30 urinary symptoms, where higher score indicates more symptoms. **Results:** Mean changes from baseline to 12 months (corresponding to end of treatment) for each HRQOL measure are summarized in the Table. No statistically significant difference was seen between the observation vs. pembrolizumab arms. Further, numerical differences between arms for these HRQOL measures do not meet (are lower than) the published minimally clinically important difference thresholds. **Conclusions:** Adjuvant pembrolizumab after radical surgery for patients with high-risk muscle-invasive urothelial carcinoma improved disease-free survival without negatively affecting HRQOL. These HRQOL results add further support to adjuvant immune checkpoint blockade therapy in these patients. Support: U10CA180821, U10CA180882, UG1CA189823 (https://acknowledgments.alliancefound.org). Clinical trial information: NCT03244381. Research Sponsor: U.S. National Institutes of Health; U10CA180821, U10CA180882, UG1CA189823.

HRQOL mean change from baseline to 12 months and between-arm comparisons.

	A) Observation	B) Pembrolizumab	Difference A vs B	P-value
EQ-5D-5L Index Value	-.029	-.012	-.02	.45
QLQ-C30 Global Health	0.07	1.45	-1.38	.55
QLQ-C30 Physical Functioning	-.089	-.069	-0.02	.99
QLQ-C30 Role Functioning	3.22	-1.23	4.45	.15
BLM30 Urinary Symptoms	-3.44	-3.02	-.42	.87
BLM30 Sexual Functioning	-.53	4.15	-4.68	.07

4514 **Rapid Oral Abstract Session**

MAIN-CAV: Phase III randomized trial of maintenance cabozantinib and avelumab versus avelumab after first-line platinum-based chemotherapy (PBC) in patients (pts) with locally advanced/metastatic urothelial cancer (la/mUC; Alliance A032001). First Author: Shilpa Gupta, Department of Hematology and Oncology, Cleveland Clinic - Taussig Cancer Institute, Cleveland, OH

Background: Maintenance avelumab is a standard of care in patients (pts) with la/mUC who do not progress after first-line PBC. Cabozantinib (CABO) is an oral inhibitor of MET, VEGFR and TAM, active in multiple solid tumors. We hypothesized that an avelumab (Av)-CABO combination would improve outcomes in pts with mUC with an acceptable safety profile compared to avelumab maintenance alone. **Methods:** MAIN-CAV (NCT05092958) is a phase III randomized, multicenter, international trial for la/mUC pts who did not progress after 4-6 cycles of any PBC (gemcitabine-cisplatin, gemcitabine-carboplatin, MVAC, ddMVAC). Pts were randomized 1:1 to Av 800 mg IV every 2 weeks alone or with CABO 40 mg daily for ≤2 years. Stratification factors were response to first-line PBC (complete response [CR] vs partial response [PR] vs stable disease [SD]) and visceral metastases. The primary endpoint was overall survival (OS); secondary endpoints included progression-free survival (PFS), safety and quality of life. The target accrual was 654 pts; the trial closed early after enrollment of 68 pts following adoption of enfortumab vedotin plus pembrolizumab as the new preferred first-line standard in the US. **Results:** From 3/2022 to 3/2024, 68 pts were randomized (Av n = 33; CABO-Av n = 35). Median OS was 24.8 months (mo) with Av and 23.0 mo with Avb-CABO (Hazard ratio 1.41; 95% CI 0.66–3.01; p = 0.186). Median PFS was 4.6 mo with Av vs 6.0 mo with Av-CABO (p = 0.343). Objective response rate among pts with PR or SD after first-line PBC was 20.8% with Av vs 11.5% with Av-CABO (p = 0.424). Grade ≥3 treatment-related adverse events occurred in 24.2% pts on the Av arm vs 39.4% of pts on the Av-CABO arm and CABO dose reductions occurred in 63% of pts. **Conclusions:** Addition of CABO to Av did not improve OS or PFS compared with Av alone in this underpowered, prematurely closed phase III trial; safety was consistent with known profiles. U10CA180821,U10CA180882; U24CA196171, U10CA180863. (CCTG);U10CA180888 (SWOG); https://acknowledgments.alliancefound.org. Clinical trial information: NCT05092958. Research Sponsor: U10CA180821, U10CA180882; U24CA196171, U10CA180863 (CCTG);U10CA180888 (SWOG).

4515 **Rapid Oral Abstract Session**

Phase II study of frontline gemcitabine, 5-fluorouracil/leucovorin, and cisplatin (GemFLP) in advanced urachal and non-urachal urinary tract adenocarcinoma. First Author: Emanuele Crupi, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Adenocarcinomas of the urinary tract are rare malignancies with limited prospective data. Outcomes of triplet chemotherapy remain poorly defined. **Methods:** This was a prospective, single-arm, phase II study (NCT00082706) conducted at MD Anderson. Between 2005 and 2010, patients (pts) aged ≥18 years with ECOG 0–2 and metastatic or unresectable urachal (UA) or non-urachal adenocarcinoma (NUA) received frontline GemFLP (5-fluorouracil 200 mg/m² continuous infusion ×5 days with leucovorin 23 mg IV daily ×5; cisplatin 20 mg/m² IV daily ×5; gemcitabine 200 mg/m² IV on days 1 and 5). Best overall response (BOR) was assessed by imaging. Primary endpoints were objective response rate (ORR) and overall survival (OS); secondary endpoint was toxicity. PFS was calculated from treatment initiation and duration of response (DoR) from first CR/PR to progression or death; time-to-event endpoints were estimated by Kaplan–Meier (KM). Post hoc analyses evaluated baseline tumor markers (CEA, CA19-9, CA125, β-hCG) Treatment-related adverse events (TRAEs) were graded per CTCAE v5. **Results:** Forty-six pts were enrolled (28 UA, 18 NUA). Median age was 58 years; 41% were de novo metastatic, and 78% had visceral metastases. ORR was 44% (20/46). Among responders, median DoR was 8.6 months (95% CI 4.6–30.8). median PFS was 3.3 months (95% CI 2.3–8.4) and median OS (mOS) was 21.0 months (95% CI 15.9–35.3) There was no difference in PFS (p=0.39) or OS (p=0.99) between UA and NUA. Baseline CEA, CA19-9, CA125, and β-hCG were not associated with ORR or PFS. Higher baseline CA125 was associated with inferior OS (HR 1.33, 95% CI: 1.12–1.58; p=0.001) Subsequent systemic therapy was administered to 28 pts (60.9%); median number of subsequent treatment lines was 2 (range 1–5). The most common hematologic TRAEs were anemia (28.1%; grade ≥3 [G3] 12.5%), thrombocytopenia (21.9%; G3 12.5%), and neutropenia (12.5%; G3 9.4%). The most frequent non-hematologic TRAEs were dehydration (21.9%; G3: 6.2%), diarrhea (9.4%; G3 6.2%) and catheter-related thrombosis (9.4%; G3 9.4%). No grade 5 events occurred. **Conclusions:** In this prospective phase II study, frontline GemFLP achieved a 44% ORR with durable responses (mDoR 8.6 mo) and 21 mo mOS in advanced UA and NUA. Survival did not differ between UA and NUA subtypes. Baseline CA125 was associated with OS. Toxicity was manageable. These data provide a prospective benchmark for this rare disease. Clinical trial information: NCT00082706. Research Sponsor: None.

Variable		UA (n=28)	NUA (n=18)
Characteristics			
Age, median [ICR]	58 [54– 62]	58 [54– 62]	67 [62-72]
Race, n (%)	White	22 (79)	11 61)
	Black	6 (21)	6 (33)
	Other	0	1 (6)
Prior surgery for localized disease, n (%)		18 (64)	5 (28)
Mets at baseline	Any	24 (86)	7 (39)
	Lung	6 (21)	4 (22)
	Liver	3 (11)	0
	Peritoneum	17 (61)	0
	Bone	3 (11)	3 (17)
	Nodal-only mets	1 (3)	2 (10)
Outcomes			
ORR (%)	43.5	35.7	55.6
BOR n (%)	CR	4 (14)	2 (11)
	PR	6 (21)	8 (44)
	SD	11 (39)	4 (22)
	PD	6 (21)	3 (17)
	NE	1 (4)	1 (6)

4516 **Rapid Oral Abstract Session**

Interim analysis results from Duravelo-2: Zelenectide pevedotin (zele; BT8009) + pembrolizumab in patients (pts) with previously untreated locally advanced/metastatic urothelial carcinoma (la/mUC). First Author: Yohann Loriot, University Paris-Saclay, Gustave Roussy, Villejuif, France

Background: Zele is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4, a protein overexpressed in la/mUC. There remains an unmet need in la/mUC for safer and more tolerable treatments. Here, we report an interim analysis (IA) for zele + pembrolizumab (pembro) dosage selection from the Phase 2/3 Duravelo-2 study (NCT06225596/BT8009-230) in previously untreated (untx) pts with la/mUC. **Methods:** Adults with la/mUC were enrolled into 2 cohorts: previously untx pts eligible for platinum-based chemotherapy (Cohort [Co]1) or pts with ≥1 prior systemic therapy (Co2). IA was conducted to determine the optimized dosage of zele + pembro (Co1) or zele monotherapy (Co2). Herein, we report IA results from Co1. Pts in Co1 were randomized 1:1:1 to: zele 5 mg/m^2 on Days [D]1/8/15 + pembro 200 mg on D1; or zele 6 mg/m^2 on D1/8 + pembro 200 mg on D1; or gemcitabine + cisplatin/carboplatin ± avelumab on a 21-D cycle. Dosage optimization included safety, efficacy, and pharmacokinetic data in pharmacometric and utility score analyses to quantify benefit-risk. **Results:** IA was performed at 27 weeks of follow-up (N=30 each zele dose group). Median zele treatment (tx) duration was 6.21 months. Confirmed ORRs by BICR among randomized, dosed pts with measurable disease at baseline were 55% (16/29; 7 complete responses [CR], 9 partial responses [PR]; 95% CI 35.7–73.6) and 58% (15/26; 8 CR, 7 PR; 95% CI 36.9–76.6) with zele 5 mg/m^2 and 6 mg/m^2, respectively. Zele-related adverse events (AEs) were reported in 97% (47% Gr ≥3) of pts at 5 mg/m^2 and 90% (40% Gr ≥3) at 6 mg/m^2. Gr ≥3 zele-related AEs for 6 mg/m^2 (≥5% pts) included neutropenia (10%), neutrophil count decreased (7%), and anemia (7%). AEs related to pembro were reported in 80% (37% Gr ≥3) and 53% (13% Gr ≥3), respectively. Zele-related AEs of clinical interest (AECIs) for 6 mg/m^2 are summarized in the Table. Notably, no zele-related severe skin reactions of any Gr were reported at the 6 mg/m^2 dosage. Zele dose reductions and discontinuations due to zele-related AEs occurred in 20% and 3%, respectively, for 6 mg/m^2. At Week 27, >50% of pts remained on tx. **Conclusions:** Zele at 5 mg/m^2 on D1/8/15 + pembro and 6 mg/m^2 on D1/8 + pembro on a 21-D cycle demonstrate encouraging response rates and safety profiles with the potential to differentiate from ADCs in previously untx pts. The 6 mg/m^2 D1/8 regimen demonstrated a more favorable benefit-risk profile to meet the need for safer and more tolerable treatments, with substantially reduced toxicity, better tolerability, improved potential for combinability, and enhanced convenience, leading to fewer discontinuations. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

Zele-related AECIs in pts with previously untx la/mUC treated with zele 6 mg/m^2 on D1/8 + pembro (N=30).

AECI, n (%)	Any Grade	Grade ≥3
Peripheral neuropathy	11 (37)	1 (3)
Skin reactions	5 (17)	0
Eye disorders	3 (10)	0
Hyperglycemia	0	0

4517 **Rapid Oral Abstract Session**

Initial results from EXCEED, a phase 1 study of LY4101174, an antibody-drug conjugate targeting Nectin-4, in participants with advanced or metastatic urothelial carcinoma. First Author: Xin Gao, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Enfortumab vedotin plus pembrolizumab (EVP) is the current first-line standard of care for locally advanced / metastatic urothelial carcinoma (mUC). However, subsequent treatment options are limited, representing an urgent and growing unmet need. Preclinical data suggest that EV resistance may be payload mediated and consequently Nectin-4 remains a viable target for alternative therapies. LY4101174 is a next generation anti-Nectin-4 ADC comprising a humanized IgG1 antibody conjugated to the topoisomerase I inhibitor, exatecan, via a maleimide-ß-glucuronide poly-sarcosine linker and a homogeneous drug antibody ratio of 8. Here, we report the initial clinical data from the phase 1 dose escalation cohort of EXCEED (NCT06238479). **Methods:** Adults with locally advanced / mUC or other selected solid tumors were eligible. Participants (pts) must have received or were ineligible for available standard therapies, and have ECOG PS 0-1. Dose escalation utilized a Bayesian optimal interval design. Key endpoints were safety, PK, and antitumor activity of LY4101174 per RECIST v1.1. **Results:** As of 3 Dec 2025, 143 pts (86 mUC, 57 non-UC tumors) were treated across 6 dose levels (DLs) of LY4101174 (0.8-3.2 mg/kg Q2W or 2.4-4.0 mg/kg Q3W IV). Median age was 68 (range, 30-85), 60% ECOG PS 1. Median prior lines of therapy was 4 (range, 1-10), 92% of mUC pts had received prior EV (19% [15/79] had discontinued EV due to treatment-related toxicity). LY4101174 and total antibody exhibited mostly linear, dose-proportional PK up to 4.0 mg/kg, and up to 3.2 mg for exatecan. At 3.2 mg/kg Q2W, 3 of 6 pts experienced DLTs (neutropenia [grades 3 and 4], febrile neutropenia, and thrombocytopenia [both grade 3]) prompting a schedule change to 3.2 mg/kg Q3W for continued escalation. The most common treatment-emergent AEs (TEAEs) across Q3W DLs were anemia (71%), fatigue (55%), nausea (49%), neutropenia (36%), thrombocytopenia (31%), diarrhea (26%), vomiting (25%), and decreased appetite (23%). The most common grade ≥3 TEAEs were anemia (47%), neutropenia (29%), thrombocytopenia (21%), febrile neutropenia and leukopenia (10% each); prophylactic granulocyte colony stimulating factor (G-CSF) was required at DL 4.0 mg/kg Q3W. TRAEs led to dose reduction in 24% and discontinuation in 2%. In the 66 efficacy evaluable mUC pts treated with 2.4-4.0 mg/kg Q3W (92% [61/66] EV-pretreated), ORR was 18% (12/66) and DCR was 70% (46/66) with 12 PR (8 confirmed, 4 ongoing and pending confirmation) and 34 SD. Median follow-up was 4.9 months (95% CI, 1.4-NE). **Conclusions:** LY4101174 has demonstrated clinical activity at Q3W dose levels, including in EV pre-treated mUC, suggesting Nectin-4 remains an important therapeutic target. Dose and duration on treatment were mainly limited by grade ≥3 hematologic toxicity requiring the use of prophylactic G-CSF. Clinical trial information: NCT06238479. Research Sponsor: Eli Lilly and Company.

4518 **Rapid Oral Abstract Session**

Bulumtatug fuvedotin (BFv; 9MW2821) plus toripalimab in patients with locally advanced or metastatic urothelial carcinoma (la/mUC): Follow-up results from a phase 1b/2 study. First Author: Xinan Sheng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Nectin-4 is an adhesion molecule that is highly expressed in variety of solid tumors, especially in urothelial cancer, cervical cancer, esophageal cancer and breast cancer. BFv is a novel site-specific ADC targeting Nectin-4, and Toripalimab is a novel recombinant humanized anti-PD-1 monoclonal antibody. Previous results of BFv and Toripalimab in la/mUC patients have shown promising efficacy and well-tolerable toxicity. Here we report follow-up results of BFv and Toripalimab in la/mUC patients. **Methods:** This is an open-label, multicenter, phase 1b/2 study to evaluate the safety and efficacy of BFv combined with Toripalimab in la/mUC. Patients received BFv (1.0 or 1.25mg/kg) on D1/D8 and Toripalimab (240mg) on D1, 21 days per cycle. Primary objective was safety, and secondary objectives were efficacy, pharmacokinetics and immunogenicity. **Results:** As of 1 Dec 2025 (median follow-up time: 16.0 months), 47 assessable patients with la/mUC were enrolled and received the combination therapy of BFv and toripalimab. 7 of them (3 received BFv 1.0mg/kg; 4 received BFv 1.25mg/kg) have been previously treated for la/mUC and other 40 (all received BFv 1.25mg/kg) were treatment-naïve patients. In the overall population, ORR was 83.0% (95%CI 69.2-92.4), CR rate was 12.8%. All CR patients were still on treatment and the longest treatment duration has already exceeded two years. DCR was 89.4% (95%CI 76.9-96.5), median PFS was 12.9 months (95%CI 6.5-NA) and median DOR was not reach. Median OS also was not reach, OS rate at 18 months was 68.1% (95%CI 52.7-79.4). Subgroup analysis showed significant benefits to all patients, which might indicate that compared to traditional chemotherapy, BFv plus toripalimab could bring patients greater benefits and a longer survival time, especially in those elderly and patients with impaired kidney function. Safety profile was consistent with previous results, and there was no other new safety signals of BFv or toripalimab observed in this study. **Conclusions:** BFv plus toripalimab in patients with la/mUC demonstrated remarkable efficacy and well-tolerated safety profile. A pivotal phase 3 study is ongoing currently. Clinical trial identification: NCT06592326, NCT06079112. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

4519 **Rapid Oral Abstract Session**

Microbial dysbiosis as predictor of benefit from CBM588 as an adjunct to immune checkpoint blockade (ICB)—based first line therapies in metastatic renal cell carcinoma (mRCC). First Author: Rahul Winayak, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: The *Clostridium butyricum*-based live biotherapeutic, CBM588, demonstrated signals for enhanced clinical activity with first-line ICB combinations in two randomized phase I trials for mRCC. However, impact of microbial dysbiosis on the benefit of CBM588 supplementation is unclear. Herein, we examined prognostic and predictive value of microbial dysbiosis with CBM588. **Methods:** We analyzed clinical outcomes and stool whole-genome sequencing data from a combined cohort from two randomized phase I clinical trials. Both enrolled treatment-naïve patients with mRCC and randomized them to receive nivolumab/ipilimumab (NCT03829111) or nivolumab/cabozantinib (NCT05122546) alone (standard of care [SOC]), or with CBM588 (SOC+CBM588). Baseline TOPOSCORE, a stool metagenomic dysbiosis index linked to ICB outcomes, was analyzed continuously (S score positively correlated with dysbiosis) and categorically (SIG1+ [dysbiosis phenotype] vs SIG2+ [non-dysbiosis]). Associations with progression free survival (PFS) and objective response rate (ORR, per RECIST 1.1) with SOC and SOC + CBM588 were assessed. **Results:** Fifty-nine patients were included: 39 in the SOC + CBM588 arm and 20 in the SOC arm. Median age was 65 (range 36-90), with the majority male (69.5%), clear-cell (88.1%) and intermediate/poor risk (67.8%) mRCC. Baseline clinical characteristics were comparable across arms. ORR was 66.7% in SOC+CBM588 arm versus 20.0% in the SOC arm (p = 0.001). Median PFS was 32.1 months (95% CI 16.6-NR) with SOC+CBM588 versus 3.7 months (95% CI 2.6-17.0) with SOC (HR 0.36 [95% CI 0.19, 0.67], p = 0.001). At baseline, S score was similar across arms (p = 0.16), and SIG1+ was seen in 55.6% of patients in the SOC+CBM588 arm versus 44.4% in the SOC arm (p = 0.441). While differences in PFS were not statistically significant in the SIG2+ cohort between SOC+CBM588 and SOC alone (32.0 vs 10.9 months, HR 0.49 [95% CI 0.19-1.3], p = 0.149), in the SIG1+ setting, a PFS improvement was seen for SOC+CBM588 versus SOC alone (24.9 vs 2.8 months, HR 0.19 [95% CI 0.07-0.53], $p < 0.001$). Notably, S score was associated with response to SOC+CBM588 among patients who received nivolumab/ipilimumab backbone (median S score 0.668 in response vs 0.540 in no response, p = 0.046), while no such association was observed in patients treated with nivolumab/cabozantinib backbone (median S score 0.681 vs 0.821, p = 0.554, respectively). **Conclusions:** Addition of CBM588 to ICB-based first-line combinations conferred a disproportionately greater benefit in patients with a dysbiotic stool phenotype, underscoring actionability of TOPOSCORE as a potential predictive biomarker in this setting. The upcoming phase III randomized placebo-controlled BIOFRONT trial will assess clinical activity of CBM588 and advance microbiome-based predictive biomarker development in mRCC. Research Sponsor: None.

4520 **Rapid Oral Abstract Session**

Prospective clinical activity and preclinical basis of panitumumab-based EGFR blockade in SMARCB1-deficient renal medullary carcinoma (RMC): A collaborative multi-institutional study. First Author: Pavlos Msaouel, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: RMC is a rare, exceptionally aggressive malignancy that predominantly affects young individuals of African descent with sickle cell trait. RMC is typically refractory to standard kidney cancer therapies, including anti-angiogenic agents and immune checkpoint inhibitors. While cytotoxic chemotherapy is the current standard, objective response rates (ORR) remain low (~29%), with a median progression-free survival (PFS) of $\leq$ 4 months in the first-line setting. This study explores wild-type EGFR as a therapeutic dependency in RMC. **Methods:** We characterized EGFR expression and mutation status in primary RMC tumors using whole exome sequencing (WES), CLIA-certified IHC and integrated bulk RNA and histone ChIP-sequencing. Preclinical efficacy was compared between the EGFR antibody panitumumab and the kinase inhibitor erlotinib across two RMC xenograft models. Subsequently, a prospective multi-national registry (N=26) evaluated panitumumab-based therapy (monotherapy or combined with nab-paclitaxel $\pm$ carboplatin) in heavily pretreated patients with RMC. **Results:** No EGFR mutations were detected on WES. RMC tumors demonstrated uniformly high wild-type EGFR protein expression and enhancer-associated activation. In vivo, panitumumab induced profound tumor regressions in both RMC xenograft models, significantly outperforming erlotinib ($p < 0.005$). Mechanistically, panitumumab triggered definitive lysosomal receptor degradation and suppressed AKT and ERK1/2 signaling. The prospective clinical registry (N=26) included 20 (76.9%) males and 6 (23.1%) females, with a median age of 33.5 years (range, 17–67). At treatment initiation, patients had a median of 4 metastatic disease sites (range, 2–6). The cohort was heavily pretreated with a median of 2 prior systemic therapies (range, 0–4); 96.2% had progressed on prior platinum-based chemotherapy. We observed an ORR of 53.9% (14/26 patients), including 4 (15.4%) complete responses. Median PFS was 5.8 months (95% CI: 4.0–8.2) and median OS was 9.5 months (95% CI: 7.6–NE). Treatment was well-tolerated, with manageable grade 1-2 acneiform rash (80.8%), no grade 3+ rash cases observed, and no treatment-related deaths. **Conclusions:** These data establish wild-type EGFR dependency as a foundational vulnerability in RMC. Panitumumab-based therapy yields unprecedented responses in heavily pretreated patients and represents a transformative new systemic standard of care for this lethal disease. Research Sponsor: National Cancer Institute; R37CA288448; National Cancer Institute; R01CA285454; National Cancer Institute; P30 CA016672.

Clinical outcomes.

	Total (N=26)
Best overall response, n (%)	
Complete response	4 (15.4%)
Partial response	10 (38.5%)
Stable disease	7 (26.9%)
Progressive disease	5 (19.2%)
Depth of response %	
Median (IQR)	-30.9 (-58.9, +3.1)

4521 **Rapid Oral Abstract Session**

Final results of a phase 2 trial of cabozantinib plus nivolumab (CaboNivo) in patients with non–clear cell renal cell carcinoma (nccRCC). First Author: Darren R. Feldman, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY

Background: CaboNivo improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) over sunitinib in a phase 3 trial for metastatic clear cell RCC. (Choueiri NEJM 2021). We previously reported on 47 patients (pts) treated on a phase 2 trial of CaboNivo for nccRCC. We now present final results on all 60 pts accrued to the study. **Methods:** Pts had advanced nccRCC, 0 or 1 prior systemic therapies excluding prior immune checkpoint inhibitors and measurable disease by RECIST. Cabo 40 mg/day plus Nivo 240 mg every 2 weeks or 480 mg every 4 weeks was given across two cohorts. Cohort 1: papillary, unclassified, or translocation associated RCC (tRCC); Cohort 2: chromophobe RCC. The primary endpoint was ORR by RECIST; secondary endpoints included PFS, OS, and safety. Cohort 1 was a single stage design that met its primary endpoint and was expanded to produce more precise estimates of ORR. Cohort 2 was a Simon two-stage design that closed early for lack of efficacy and slow accrual. **Results:** Of 60 pts, 53 were included in Cohort 1, of whom 16 had papillary RCC, 16 unclassified RCC with papillary features (UCPF), 8 FH-deficient, 8 unclassified without papillary features (UC), and 5 tRCC. In Cohort 1, 39 (74%) pts were previously untreated, and 14 (26%) pts had 1 prior line: 10 (19%) received prior VEGF-targeted therapy and 8 (15%) received prior mTOR-targeted therapy. For Cohort 1 (Table), the ORR was 43% (95% CI 30-58), including 88% in pts with FH-deficient RCC. Median PFS (mPFS) in Cohort 1 was 11 months (95% CI 8-14), median OS was 28 months (95% CI 21-37), and there were 43 deaths after a median follow-up of 50 months for survivors. 7 pts with chromophobe RCC were enrolled in Cohort 2 with 5 achieving stable disease (SD) but no objective responses observed. Adverse events were similar to the previously reported cohort and cabozantinib and nivolumab were discontinued for toxicity in 22 (42%) and 20 (38%) pts, respectively. **Conclusions:** Final results from this phase 2 trial in nccRCC confirm efficacy and acceptable safety of CaboNivo in pts with metastatic papillary, unclassified, or tRCC histologies with a particularly high ORR in FH-deficient RCC. These results justify CaboNivo as a standard first-line treatment option for these pts. In contrast, objective responses were not observed in chromophobe RCC. Clinical trial information: NCT03635892. Research Sponsor: None.

Cohort 1 outcomes.

Outcome	All Pts (n=53)	1st-line (n=39)	2nd-line (n=14)	Papillary (n=16)	UCPF (n=16)	FH-def (n=8)	UC (n=8)	tRCC (n=5)
ORR, %	43	46	36	31	38	88	50	20
(95% CI)	(30-58)	(30-63)	(13-65)	(11-59)	(15-65)	(47-100)	(16-84)	(1-72)
CR, n (%)	1 (2)	1 (3)	0	1 (6)	0	0	0	0
PR, n (%)	22 (42)	17 (44)	5 (36)	4 (25)	6 (38)	7 (88)	4 (50)	1 (20)
SD, n (%)	27 (51)	19 (49)	8 (57)	10 (63)	10 (62)	1 (12)	2 (25)	4 (80)
PD, n (%)	3 (6)	2 (5)	1 (7)	1 (6)	0	0	2 (25)	0
mPFS, mo.	11	11	14	11	10	16	8	14
(95% CI)	(8-14)	(8-16)	(5-23)	(7-25)	(5-13)	(5-37)	(1-34)	(5-41)

4522 **Poster Session**

Artificial intelligence (AI)–augmented analysis of quantitative circulating tumor DNA (ctDNA) burden and longitudinal kinetics to identify prognostic risk stratification in metastatic clear cell renal cell carcinoma (mccRCC). First Author: Eric Martin, Inova Schar Cancer Institute, Fairfax, VA

Background: The relevance of ctDNA burden and longitudinal kinetics in RCC remains poorly defined. We applied AI–based analysis of quantitative ctDNA trajectories to identify prognostically informative patterns beyond baseline detection. **Methods:** We analyzed patients with mccRCC undergoing longitudinal tumor-informed ctDNA testing (Signatera) during first-line immune checkpoint inhibitor–based therapy. Quantitative ctDNA burden in mean tumor molecules per milliliter (MTM/mL) was measured serially and aligned to treatment initiation, with radiographic response classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). ctDNA trajectory similarity was independently assessed using dynamic time warping (DTW), trajectory-based K-means clustering, and a neural network sequence autoencoder (TensorFlow) with clustering to learn latent representations of ctDNA kinetics. Cross-method concordance was used to define robust ctDNA kinetic phenotypes. **Results:** Survival and response analyses included 93 patients with mccRCC with longitudinal ctDNA profiling. Baseline ctDNA detectability was not significantly associated with OS. Conversion from ctDNA-positive to ctDNA-negative status during therapy was associated with improved OS ($p<0.05$). Patients with radiographic disease control (CR/PR/SD) had significantly lower peak ctDNA levels than those with progressive disease (median 0.18 vs 8.86 MTM/mL; p=0.007). Increasing peak ctDNA burden was strongly associated with inferior OS (HR 2.21, 95% CI 1.63–3.01; $p<0.001$). A machine learning–based spline-regularized Cox survival model identified a high-risk ctDNA threshold >20 MTM/mL associated with worse OS (p=0.034). Trajectory-based K-means identified an optimal solution at k=4 clusters, independently supported by DTW and autoencoder-based analyses. Four ctDNA kinetic phenotypes repeatedly emerged: early ctDNA clearance, early ctDNA rise, delayed ctDNA clearance, and persistently low-level ctDNA. Autoencoder-derived phenotypes demonstrated strong internal robustness (Adjusted Rand Index, ARI ≈ 0.80) and high concordance with DTW-based clustering. Phenotypes were associated with distinct radiographic response and survival patterns, with early ctDNA rise conferring the poorest OS (p=0.022). **Conclusions:** AI-driven modeling of quantitative ctDNA burden and longitudinal kinetics identifies biologically interpretable and reproducible prognostic phenotypes in RCC, capturing higher-order temporal features of ctDNA dynamics and providing prognostic stratification beyond baseline detectability and burden alone, thereby informing clinical decision-making regarding earlier therapy switching. Research Sponsor: None.

4523 **Poster Session**

Vessel branching patterns quantified by artificial intelligence as a novel prognostic biomarker in advanced renal cell carcinoma: A post-hoc analysis of the CM914 trial. First Author: Hannah Timm, Institute for AI in Medicine, University Hospital Essen, Essen, Germany

Background: Current adjuvant risk stratification in renal cell carcinoma (RCC) relies primarily on TNM-staging. However, disease progression and response to therapy are driven by biological subgroups reflected in tumor vessel architecture. We therefore analyzed vessel branching patterns in 1098 adjuvant RCC patients to evaluate whether an AI-derived biomarker quantifying vascular architecture improves prognostic discrimination beyond TNM. **Methods:** Digital images of representative tumor tissue and oncologic outcomes were obtained from the CM914 trial (NCT03138512). Tumor tissue was annotated by a pathologist to define vessel branching patterns as high-branching (HB) or low-branching (LB) patterns. HB and LB patterns were quantified using a deep learning model as the tumor-wide fraction of HB in digitized H&E whole-slide images from 1098 of 1641 evaluable patients (67%). Based on the tumor-wide HB fraction, patients were classified into risk groups using a data-driven cut-off optimized for Kaplan–Meier survival analysis, allowing comparison with TNM-based risk strata (PT2a, G3/G4, N0, M0 / PT2b, G ANY, N0, M0 / PT3, G ANY, N0, M0; intermediate-high risk, n=1016 vs PT4, G ANY, N0, M0 / PT ANY, G ANY, N1, M0; high risk, n=82). Risk stratification performance for overall survival (OS) and disease-free survival (DFS) was compared between branching pattern–based and TNM-based risk groups using Cox regression, Kaplan–Meier analysis, and concordance indices. **Results:** Higher tumor-wide HB fractions were associated with improved DFS and OS, showing a continuous effect on prognosis. Each 10% increase in HB fraction reduced risk of recurrence and death (DFS HR 0.92, 95% CI 0.89–0.95; OS HR 0.89, 95% CI 0.83–0.95; both $p<0.005$). Kaplan–Meier analyses showed longest survival in the 4th quartile (OS HR 0.39, 95% CI 0.21–0.71, p=0.002; DFS HR 0.47, 95% CI 0.35–0.64, $p<0.0001$). This threshold defined the 75th percentile cutoff for risk stratification, separating patients into intermediate risk (≥74% HB; n=275) vs high risk (<74% HB; n=823) groups. High risk patients had an increased risk of recurrence and death (DFS HR 2.11, 95% CI 1.57–2.84, C-Index 0.57; OS HR 2.57, 95% CI 1.28–4.32, C-Index 0.56, both $p<0.005$). TNM-based risk showed lower prognostic discrimination (DFS: HR 1.95, 95% CI 1.39–2.74, C-Index 0.53; OS: HR 2.55, 95% CI 1.52–4.30, C-Index 0.55, both $p<0.005$). Combining branching-based risk with TNM improved DFS and OS discrimination compared with TNM alone (C-Index 0.59). **Conclusions:** Higher fractions of high-branching vessels are associated with improved DFS and OS, potentially enabling risk stratification beyond conventional TNM criteria in RCC. While prospective validation is required to confirm clinical applicability, these results suggest high-branching vessel architecture represents a promising prognostic feature. Research Sponsor: None.

4524 **Poster Session**

Deciphering the genomic landscape of renal cell carcinoma brain metastases. First Author: Betul Gok Yavuz, The University of Chicago, Chicago, IL

Background: Brain metastases from renal cell carcinoma (RCC) remain a major cause of morbidity and mortality, yet the drivers of metastatic dissemination remain poorly understood. **Methods:** Whole-exome sequencing was performed on 72 RCC brain metastasis samples with matched normal. To identify candidate metastatic drivers, the genetic alterations detected in the brain metastases were compared against alterations in extracranial metastases from the MSK-ECM cohort (n=137) and primary RCC tumors from TCGA (n=432) by case-control analyses. Candidate drivers were also identified by matched-pair analyses on the brain metastases vs. matched primary tumors or extracranial metastases from the same patient (n=25). A random survival forest model incorporating the candidate CNA events was developed to predict overall survival. The candidate metastatic drivers were further evaluated using functional experimental data from MetMap and DepMap. Survival analyses were conducted to assess the prognostic significance of the candidate drivers. **Results:** We identified metastatic drivers that were significantly enriched in RCC brain metastases, including 4q loss, 7p gain, 7q gain, 8p loss, 8q gain, 9p21.3 deletion, 12q15 amplification, and 14q loss. These driver events were associated with significantly poorer patient survival among RCC patients. A random survival forest model based on these CNA events stratified TCGA-KIRC patients into prognostically distinct risk groups (C-index = 0.64). Among the drivers, 8p loss, 8q gain, 9p21.3 deletion were associated with increased incidence of brain metastases across multiple primary cancer types in xenograft mouse models. These drivers were also strongly associated with metastatic progression and poor prognosis across RCC, lung adenocarcinoma, breast cancer, and melanoma. **Conclusions:** Somatic copy-number alterations represent key drivers of brain metastasis in RCC and other tumors that frequently metastasize to the brain. These findings indicate a shared genomic basis for brain tropism across cancers and highlight the potential utility of copy-number biomarkers for risk stratification and clinical decision-making. Research Sponsor: Pelotonia Institute for Immuno-Oncology Recruitment Startup Fund; Society for Immunotherapy of Cancer-NanoString Technologies Single Cell Biology Award; International Kidney Cancer Coalition Cecile and Ken Youner Scholarship; Kidney Cancer Association Young Investigator Award; Gateway Cancer Research Foundation; American Society of Clinical Oncology Conquer Cancer Foundation Young Investigator Award.

4525 **Poster Session**

CheckMate-901: Association of tumor and peripheral biomarker profiles with durable disease control in metastatic urothelial carcinoma treated with nivolumab plus ipilimumab. First Author: Matthew D. Galsky, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY

Background: Patients (pts) with untreated, unresectable, or metastatic urothelial carcinoma (mUC) have limited therapeutic options and poor prognosis. The phase 3, global, open-label, randomized CheckMate 901 trial compared nivolumab plus ipilimumab (NIVO+IPI) vs gemcitabine–carboplatin/gemcitabine–cisplatin (gem–carbo/gem–cis) with previously untreated unresectable or mUC. A subset of pts treated with NIVO+IPI experienced durable disease control. This exploratory analysis seeks to identify biomarkers that might characterize pts deriving particular benefit from NIVO+IPI. **Methods:** Serum samples from CheckMate 901 (NIVO+IPI, n = 288–300; gem–carbo/gem–cis, n = 222–236) underwent multiplex analysis at Myriad RBM using Luminex and Simoa technology. Pts were stratified by progression-free survival (<8 months [early progressor; EP] vs ≥8 months [durable benefit; DB]), and clinical laboratory variables (granulocyte count [GRANC], hemoglobin [HB], thyroid-stimulating hormone [TSH], neutrophil-lymphocyte ratio [NLR]) and cytokine/protein biomarkers (alpha-1 antitrypsin [AAT], beta2-microglobulin [B2M], C-reactive protein [CRP], ferritin [FRTN], interleukin [IL]-2 receptor alpha [IL-2ra], IL-8, vascular cell adhesion molecule-1 [VCAM-1], and von Willebrand factor [vWF]) were compared in EP vs DB pts. In addition, tumor RNA-seq was used for gene signature analysis (NIVO+IPI, n = 134; gem–carbo/gem–cis, n = 117), including 8-gene epithelial–mesenchymal transition (EMT)/stroma core, 9-gene transforming growth factor beta (TGFβ) activation, 13-gene high-risk TGFβ, and cluster of differentiation 4 (CD4). **Results:** Distinct biomarker patterns emerged between EP and DB pts. Pts achieving DB vs EP with NIVO+IPI exhibited significantly lower levels of GRANC, TSH, and NLR, and higher HB (all $P < 0.05$). Similarly, levels of proteins AAT, B2M, CRP, FRTN, IL-2ra, IL-8, VCAM-1, and vWF were significantly lower in NIVO+IPI-treated pts achieving DB vs EP (all $P < 0.05$). RNA-seq analysis showed significant differences between NIVO+IPI-treated pts achieving DB vs EP for 8 EMT/stroma core and 9 TGFβ activation ($P < 0.05$). **Conclusions:** In untreated, unresectable, or mUC, distinct clinical and cytokine/protein biomarker profiles were associated with DB vs EP with NIVO+IPI therapy. Pts with EP exhibit features in the tumor microenvironment and circulation suggestive of tumor-promoting inflammation, several of which have been linked to resistance to immune checkpoint blockade in prior analyses. These findings underscore the heterogeneity of mUC and the potential of routinely measured circulating analytes for risk stratification and treatment decisions. Prospective studies should confirm their clinical applicability. Clinical trial information: NCT03036098. Research Sponsor: Bristol Myers Squibb.

4526 Poster Session

Machine learning–based transcriptomic signatures to predict treatment outcomes across targeted and immunotherapy regimens in renal cell carcinoma. First Author: Peng Li, Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Despite available tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), reliable biomarkers guiding frontline advanced RCC treatment remain limited. Existing signatures lack generalizability across therapeutic regimens. We developed a data-driven machine learning (ML) framework to predict survival outcomes and therapeutic response. **Methods:** Transcriptomic and clinical data were analyzed from 733 patients across two frontline treatment cohorts, sunitinib (n = 376) and avelumab plus axitinib (n = 357), derived from JAVELIN Renal 101. A multi-algorithm feature selection framework was applied to identify transcriptomic signatures associated with progression-free survival (PFS) and overall survival (OS). Prognostic performance was evaluated using the concordance index (C-index). Predictive models for therapeutic response, including disease control, were developed using PFS-derived gene signatures and assessed by area under the curve (AUC). External validation was performed in an independent cohort from The Ohio State University Total Cancer Care (OSU TCC) (n = 114). **Results:** ML-derived transcriptomic models consistently stratified patients into distinct risk groups with improved prognostic discrimination compared with standard clinical classifiers. In the sunitinib cohort, the best-performing models achieved C-indices of 0.72 for PFS and 0.81 for OS, outperforming IMDC (0.59 and 0.66). In the validation set of the sunitinib cohort, high-risk patients exhibited worse outcomes, with hazard ratios of 3.00 for PFS ($P < 0.001$, 95% CI, 2.06–4.39) and 13.42 for OS ($P < 0.001$, 95% CI, 7.78–23.13). In the avelumab plus axitinib cohort, C-indices reached 0.70 for PFS and 0.79 for OS. Consistent risk stratification was observed in the validation set, with hazard ratios of 3.16 for PFS ($P < 0.001$, 95% CI, 2.07–4.83) and 4.69 for OS ($P < 0.001$, 95% CI, 2.65–8.30). For response prediction, the models demonstrated predictive performance, with the Naive Bayes model achieving a validation AUC of 0.83 for disease control in both sunitinib and avelumab plus axitinib cohorts. The model showed significant risk stratification in an external validation cohort (OSU TCC). **Conclusions:** This study presents a multi-cohort transcriptomic framework with prognostic and predictive utility in advanced RCC. By outperforming established clinical risk classifiers and enabling prediction of regimen-specific therapeutic responses, this ML-based approach supports biomarker-informed frontline treatment selection. Research Sponsor: The Ohio State University Comprehensive Cancer Center (OSUCCC); Pelotonia Institute for Immuno-Oncology (PIIO).

4527 Poster Session

Efficacy outcomes by patterns of progression in patients with advanced renal cell carcinoma from the phase 3 CLEAR trial. First Author: Viktor Grünwald, University Hospital Essen, Essen, Germany

Background: In CLEAR, lenvatinib + pembrolizumab (L+P) significantly improved efficacy vs sunitinib (S) in treatment-naïve patients with advanced renal cell carcinoma (Motzer 2021, Motzer 2024). We summarize efficacy by patterns of progressive disease (PD) for the L+P arm and report survival per a modified PD classification system (based on patients receiving immunotherapy; data cutoff 31 July 2022). **Methods:** Treatment-naïve patients (n=1069) who had clear-cell advanced renal cell carcinoma were randomized (1:1:1) to receive: L 20 mg PO daily + P 200 mg IV Q3W; or L + everolimus; or S 50 mg PO daily (4 wks on/2 wks off). Methods for post-progression survival/OS analyses were previously reported (Grünwald 2025). A modified system of classifying PD (Saal 2025) is used in new analyses of the L+P arm reported here: low risk (progression of existing lesions); intermediate risk (new lesions without progression of existing lesions); high risk (progression of existing lesions + new lesions). The number of patients with PD was determined by independent imaging review at the data cutoff date. **Results:** At the time of PD, the median tumor burden of target lesions was lower with L+P (−48.1%) vs S (−17.4%). Patients in the L+P arm with larger % decreases in sums of target lesion diameters at PD had longer median post-progression survival (≤-61% [n=59], 35.6 mos [95% CI 28.4−39.2]; >-61%-≤-34% [n=58], 24.4 mos [95% CI 15.5−34.5]; >-34% [n=59], 20.2 mos [95% CI 16.4−26.9]) and OS (Grünwald 2024, 2025). In the L+P arm, most patients had low/intermediate risk PD (Table). Patients with low (HR 0.39; 95% CI 0.22-0.70) or intermediate risk (HR 0.47; 95% CI 0.27-0.81) PD had improved OS vs patients with high risk PD. Patients with low/intermediate risk PD stayed on 1st subsequent anticancer medication longer than patients with high risk PD (Table). **Conclusions:** In the L+P arm, PD was mainly characterized by progression of existing lesions or formation of new lesions without progression of existing lesions (low/intermediate risk PD); these patients had improved OS (vs high risk PD) suggesting prognostic/predictive value of patterns of PD. Patients with low/intermediate risk PD stayed on 1st subsequent anticancer medication longer than patients with high risk PD, implying that 2L therapy can be used effectively upon progression with L+P. These results, together with lower tumor burden seen at PD in the L+P arm (Grünwald 2024), indicate that L+P has robust tumor control, supporting its use as a standard 1L therapy in advanced renal cell carcinoma. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Low risk PD (n=69)	Intermediate risk PD (n=91)	High risk PD (n=30)
Patients with any subsequent systemic anticancer medication during survival follow-up, n (%)	49 (71.0)	58 (63.7)	15 (50.0)
Time to discontinuation of 1st anticancer medication during survival follow-up, median (Q1, Q3) (months)	14.4 (5.6, not estimable)	7.3 (3.1, 20.3)	4.3 (1.5, 13.7)

Included data is from the L+P arm.

4528 Poster Session

Cabozantinib plus nivolumab (C+N) versus sunitinib (S) in patients with advanced renal cell carcinoma (aRCC) and bone metastasis: Updated subgroup analysis of the phase 3 CheckMate-9ER trial. First Author: Andrea B. Apolo, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: In first-line aRCC, C+N significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in the phase 3 CheckMate 9ER trial (NCT03141177; Motzer et al. *Ann Oncol* 2026). In an exploratory analysis with median 18.1-mo f-u, C+N improved PFS, OS, and ORR vs S in patients with or without bone metastasis at baseline. We performed an updated exploratory analysis of outcomes by baseline bone metastasis status based on the 5-year update and analyzed subgroups with additional metastatic sites. **Methods:** 651 patients with clear-cell aRCC were randomized 1:1 to C (40 mg QD) + N (240 mg Q2W) or S (50 mg QD for 4 weeks of 6-week cycles). Median f-u was 67.6 mo. PFS (primary endpoint) and ORR were per RECIST v1.1 by blinded independent central review. Patient subgroups analyzed here include those with or without bone metastasis at baseline and those with liver, lung, lymph node (LN), or adrenal gland metastasis in addition to bone metastasis. **Results:** 154 patients had bone metastasis at baseline. Baseline characteristics were generally consistent between treatment arms for subgroups with and without bone metastasis. PFS and OS were prolonged with C+N vs S in patients with or without bone metastasis (Table). The ORR was higher and duration of response (DOR) was longer with C+N vs S in both groups. Although outcomes were less favorable in those with vs without bone metastasis, the relative benefit with C+N vs S was consistent across metastatic site subgroups. The safety profile among patients with bone metastasis was generally consistent with the overall population. **Conclusions:** With additional follow-up, a consistent benefit was maintained for C+N vs S in patients with or without bone metastasis. Among patients with bone metastasis, a consistent benefit was observed regardless of concomitant metastasis in liver, lung, LN, or adrenal gland. Clinical trial information: NCT03141177. Research Sponsor: Exelixis, Inc.

Efficacy by metastatic sites.

Subgroup (C+N *v* S)	Bone + Any Site(s)[a] (n=79 *v* n=75)	No Bone (n=244 *v* n=253)	Bone + Liver (n=15 *v* n=17)	Bone + Lung (n=57 *v* n=58)	Bone + LN (n=33 *v* n=38)	Bone + Adrenal Gland (n=10 *v* n=8)
mPFS, mo	13.8 *v* 5.3[b]	16.6 *v* 9.5	6.9 *v* 3.8	10.0 *v* 4.4	9.0 *v* 4.1	15.2 *v* 5.7
PFS HR (95% CI)	0.43 (0.30, 0.64)[b]	0.60 (0.49, 0.74)	0.77 (0.33, 1.76)	0.45 (0.29, 0.70)	0.50 (0.29, 0.87)	0.62 (0.19, 2.07)
mOS, mo	34.8 *v* 20.7[b]	49.5 *v* 41.0	20.9 *v* 12.7	31.6 *v* 22.1	21.3 *v* 17.5	54.4 *v* 31.0
OS HR (95% CI)	0.66 (0.45, 0.95)[b]	0.85 (0.68, 1.06)	0.57 (0.26, 1.24)	0.72 (0.47, 1.10)	0.72 (0.43, 1.20)	0.72 (0.21, 2.50)
ORR, %	49 *v* 9[b]	58 *v* 33	40 *v* 18	51 *v* 10	42 *v* 5	70 *v* 13
mTTR, mo	2.9 *v* 7.3	2.8 *v* 4.3	2.9 *v* 3.0	2.8 *v* 5.7	2.9 *v* 3.4	4.0 *v* 11.0
mDOR, mo	18.0 *v* 6.9	22.9 *v* 15.4	12.6 *v* 6.4	18.0 *v* 6.7	16.7 *v* NC	14.4 *v* 19.3

[a]Only 9 patients had bone-only disease (n=7, C+N; n=2, S), precluding meaningful analysis of this subgroup.
[b]Motzer et al. *Ann Oncol* 2026. m, median; NC, not calculable; TTR, time to response.

4529 Poster Session

An external validation of the IMmotion151 molecular subtypes in patients with advanced renal cell carcinoma using the ORIEN database. First Author: Gautham Prakash, University of Virginia, Division of Hematology/Oncology, Charlottesville, VA

Background: There is a major unmet need for novel biomarkers in advanced renal cell carcinoma (RCC). A promising candidate biomarker is the classification of advanced RCC into 7 distinct molecular subtypes identified in an exploratory analysis of the IMmotion151 trial (Motzer et al., Cancer Cell 2020). These transcriptomic clusters were predictive of treatment outcomes with atezolizumab + bevacizumab vs sunitinib. However, a recent validation study reported that while these clusters were able to be replicated in an external cohort, they failed to stratify survival between avelumab + axitinib vs sunitinib (Saliby et al., Cancer Cell 2024). Given these mixed results, there is a need for further validation of the IMmotion151 molecular clusters. We used a multi-institutional cohort from the Oncology Research Information Exchange Network (ORIEN), an alliance of cancer centers, to replicate these clusters and assess if they were prognostic for 5-year overall survival (OS) in patients with advanced RCC. **Methods:** Patients with RCC metastatic to lymph nodes or a distant site were identified in the ORIEN database. Included patients had mRNA sequencing data available from a metastatic tumor sample. We used methods similar to those used in the IMmotion151 exploratory analysis to attempt to replicate the molecular clusters. Using an unsupervised clustering algorithm called non-negative matrix factorization (NMF) on the top 10% most variable genes in each sample, we derived 7 distinct molecular clusters. To compare our clusters with those identified in IMmotion151, we constructed a heatmap of expression (using z-scores) for pre-specified gene sets across each cluster. We then conducted Kaplan-Meier analysis to assess if our clusters were able to stratify 5-year OS in our patient cohort for a significance level of $p \leq 0.05$. OS was measured from the time of diagnosis with metastatic RCC. **Results:** 155 eligible patients were included in our analysis. We successfully replicated clusters 2 (angiogenic), 3 (complement/Ω-oxidation), 4 (T-effector/proliferative), and 6 (stromal/proliferative). Cluster 7 (snoRNA) was not possible to replicate as our transcriptomic data only included mRNA. Kaplan-Meier analysis did not show any statistically significant difference (p = 0.85) in 5-year OS between our 7 clusters. Cluster 2 had a median OS of 47.5 months, cluster 3 had a median OS of 43.6 months, median OS was not reached for cluster 6, and there were insufficient patients in cluster 4 to be included in the survival analysis. **Conclusions:** While our results show that the IMmotion151 molecular subtypes are robust and replicable even in smaller datasets, the lack of any association between subtypes and survival outcomes casts further doubt on the clinical utility of these biomarkers. Our results may also be influenced by our smaller sample size compared to the IMmotion151 analysis (n = 823). Research Sponsor: Division of Hematology/Oncology, University of Virginia.

4530 Poster Session

Cabozantinib plus nivolumab (C+N) versus sunitinib (S) in patients with advanced renal cell carcinoma (aRCC) and liver metastasis: Subgroup analysis of the phase 3 CheckMate-9ER trial. First Author: Amishi Yogesh Shah, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In the phase 3 CheckMate 9ER trial (NCT03141177), C+N treatment significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in patients with first-line aRCC, including those with baseline LM (Motzer et al. *Ann Oncol* 2026). We performed exploratory analyses of outcomes in additional subgroups including patients with no LM (NLM) and those with LM plus other metastatic sites. **Methods:** 651 patients with clear-cell aRCC were randomized 1:1 to C (40 mg QD) + N (240 mg Q2W) or S (50 mg QD for 4 weeks of 6-week cycles). PFS (primary endpoint) and ORR were per RECIST v1.1 by blinded independent central review. Median f-u was 67.6 mo. Patient subgroups analyzed included those with LM or NLM at baseline and those with bone, lung, lymph node (LN), or adrenal gland metastasis in addition to LM. **Results:** 129 patients had LM at baseline. Baseline characteristics were generally consistent between treatment arms among patients with LM and NLM. A PFS and OS benefit with C+N vs S was observed in patients with LM and NLM (Table). Both subgroups experienced greater ORR and longer duration of response (DOR) with C+N vs S. Although outcomes were less favorable in those with vs without LM, and least favorable in those with both LM and bone metastasis, the relative benefit with C+N vs S was consistent across metastatic site subgroups. The safety profile among patients with LM was generally consistent with the overall population. Presence of LM did not negatively impact C dose exposure (median daily dose 31.8 mg in LM; 26.3 mg in NLM). **Conclusions:** Treatment with C+N vs S improved efficacy outcomes in patients with first-line aRCC irrespective of LM at baseline. Among patients with LM, a consistent benefit was observed regardless of concomitant metastasis in bone, lung, LN, or adrenal gland. Clinical trial information: NCT03141177. Research Sponsor: Exelixis. Inc.

Efficacy by metastatic sites.

Subgroup (C+N *v* S)	LM + Any Site(s)[a] (n=73 *v* n=56)	NLM (n=250 *v* n=272)	LM + Bone (n=15 *v* n=17)	LM + Lung (n=46 *v* n=43)	LM + LN (n=31 *v* n=27)	LM + Adrenal Gland (n=8 *v* n=6)
mPFS, mo	10.9 *v* 6.2[b]	18.4 *v* 9.2	6.9 *v* 3.8	9.1 *v* 4.1	9.7 *v* 6.2	32.0 *v* 2.0
PFS HR (95% CI)	0.55 (0.37, 0.82)[b]	0.59 (0.48, 0.71)	0.77 (0.33, 1.76)	0.50 (0.32, 0.80)	0.65 (0.36, 1.17)	0.18 (0.04, 0.78)
mOS, mo	37.6 *v* 22.1[b]	49.5 *v* 39.7	20.9 *v* 12.7	40.1 *v* 13.4	34.8 *v* 13.4	46.3 *v* 2.0
OS HR (95% CI)	0.65 (0.43, 0.97)[b]	0.83 (0.66, 1.03)	0.57 (0.26, 1.24)	0.49 (0.30, 0.79)	0.59 (0.33, 1.05)	0.10 (0.02, 0.53)
ORR, %	52 *v* 21[b]	57 *v* 29	40 *v* 18	52 *v* 23	48 *v* 19	88 *v* 17
mTTR, mo	2.8 *v* 4.0	2.8 *v* 5.4	2.9 *v* 3.0	2.8 *v* 3.5	2.8 *v* 4.1	2.8 *v* 11.1
mDOR, mo	20.7 *v* 17.8	22.1 *v* 15.2	12.6 *v* 6.4	23.1 *v* 15.8	33.0 *v* 17.9	41.5 *v* NR

[a]Only 7 patients had liver-only disease (n=2, C+N; n=5, S), precluding meaningful analysis of this subgroup.
[b]Motzer et al. *Ann Oncol* 2026. m, median; NR, not reached; TTR, time to response.

4531 Poster Session

Efficacy of fruquintinib (F) plus sintilimab (S) versus axitinib (A) or everolimus (E) by scores of IMDC risk factors and PD-L1 expression at baseline in previously treated advanced renal cell carcinoma (RCC): A subgroup analysis of the FRUSICA-2 study. First Author: Kaiwei Yang, Department of Urology, Peking University First Hospital, Beijing, China

Background: FRUSICA-2 (NCT05522231), a randomized, open-label, controlled phase 2/3 study, demonstrated a significant efficacy of F plus S vs A or E in previously treated advanced RCC (BIRC-assessed mPFS 22.21 vs 6.90 mo; HR 0.373, p<0.0001; ORR 60.5% vs 24.3%, OR 4.622, p<0.0001; D Ye, et al; 2025 ESMO). Given the IMDC classification as the most common prognostic model and PD-L1 expression has demonstrated prognostic value across various cancer types, we conducted this exploratory subgroup analysis to evaluate clinical outcomes by baseline scores of IMDC risk factors and PD-L1 expression. **Methods:** Patients (pts) with histologically confirmed advanced RCC previously treated with VEGFR-TKI were randomized 1:1 to receive either F (5 mg QD, 2 weeks on/1 week off) plus S (200 mg iv, every 3 weeks), or investigator's choice of A (5 mg twice daily) or E (10 mg once daily). Efficacy was analyzed by IMDC risk factor scores (0, 1, 2, and ≥3) and PD-L1 combined positive score (CPS≥1, <1, or unknown). Data cutoff was February 17, 2025. **Results:** Among 234 patients in the phase 3 part, IMDC risk scores and PD-L1 CPS distributions are detailed in table. With a median follow-up of 16.56 mo, BIRC-assessed mPFS for F+S vs A/E across IMDC subgroups were: score 0, not estimable(NE) vs 8.31 mo (stratified HR 0.270, p=0.0009); score 1, 24.87 vs 8.25 mo (HR 0.289, p<0.0001); score 2, 13.8 vs 6.9 mo (HR 0.436, p=0.0164); and score ≥3, 9.69 vs 4.21 mo (HR 0.591, p=0.3267). Across PD-L1 expression subgroups, BIRC-assessed mPFS for F+S vs A/E were: CPS ≥1, 22.21 vs 3.22 mo (stratified HR 0.232, p=0.0004); CPS <1, NE vs 8.28 mo (HR 0.350, p<0.0001). An additional 82 patients had unknown PD-L1 CPS status (F+S: n=40; A/E: n=42) and were not included in PD-L1 subgroup analysis. ORR analyses consistently favored F+S over A/E across all subgroups defined by IMDC risk factors and PD-L1 expression, with detailed results presented in table. **Conclusions:** In the exploratory analyses, these findings suggest that the efficacy benefit of F+S vs A/E is maintained across different IMDC risk scores and PD-L1 CPS in previously treated advanced RCC patients, supporting its broad application. Clinical trial information: NCT05522231. Research Sponsor: HUTCHMED Limited.

Efficacy results by IMDC risk scores and PD-L1 expression.

F+S v A/E	IMDC score 0 (33 v 32)	IMDC score 1 (43 v 41)	IMDC score 2 (30 v 31)	IMDC score ≥3 (13 v 11)	PD-L1 CPS≥1 (23 v 20)	PD-L1 CPS<1 (56 v 53)
mPFS mo	NE v 8.31	24.87 v 8.25	13.80 v 6.90	9.69 v 4.21	22.21 v 3.22	NE v 8.28
HR (95%CI)	0.27 (0.12, 0.62)	0.29 (0.15, 0.55)	0.44 (0.22, 0.88)	0.59 (0.20, 1.72)	0.23 (0.10, 0.56)	0.35 (0.20, 0.61)
Unstratified Log-rank p	0.0009	< 0.0001	0.0164	0.3267	0.0004	< 0.0001
ORR, %	63.6 v 25.0	62.8 v 26.8	60.0 v 19.4	46.2 v 27.3	78.3 v 10.0	64.3 v 35.8
Odds Ratio (95%CI)	5.25(1.61, 17.71)	4.60(1.66, 12.98)	6.25(1.75, 23.80)	2.29(0.32, 19.10)	32.40(4.67, 338.60)	3.22(1.37, 7.61)

4532 Poster Session

Emotional health concerns due to kidney cancer (KC) and unmet needs in patient support: Results from the International Kidney Cancer Coalition (IKCC) Global Patient Survey (GPS). First Author: Eric Jonasch, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: KC negatively impacts the emotional well-being of patients, and patient support services are a critical component of care to improve emotional health and patient outcomes. Since 2018, the IKCC and its network have conducted a biennial GPS to assess patient/caregiver experiences on KC burden, diagnosis, and management, determine unmet needs and country variances, and identify opportunities to close gaps. We present global data from the 2025 GPS on emotional well-being and use of patient support resources. **Methods:** An IKCC steering committee of patient advocates, medical experts and the Picker Institute (UK) designed the 2025 GPS targeting KC patients and caregivers. It was cognitively tested, translated into 16 languages, and hosted online and on paper. Data were independently analyzed using cross-tabulations. **Results:** Between Sept 24 and Nov 15, 2024, 2677 responses were received from patients (n=2049) and caregivers (n=628) from 46 countries. Globally, 85% of respondents were impacted emotionally due to KC, with impacts observed across all disease stages. The most common were disease-related anxiety (50%), fear of recurrence (49%), sadness/depression (36%), and fear of dying (35%). Respondents aged 80+ and 66–80 years reported fewer emotional concerns than younger respondents. Globally, only 40%–66% of respondents discussed emotional concerns with a healthcare provider (HCP). Respondents from India and Mexico were more likely to discuss concerns with an HCP, while those from the Republic of Korea were least likely to discuss concerns. Many conversations with HCPs were considered unhelpful; notably, 33% indicated discussions about difficulties navigating the healthcare system were unhelpful. Globally, 50% of respondents accessed a patient support group, either in person or online. Respondents from Japan (19%), Türkiye (24%), France (25%), and Italy (27%) were least likely to access a patient support group, while those from India (90%) and the Republic of Korea (88%) were most likely to access a group. Overall, 47% said support groups were helpful. Patient organization websites (28%) and online support groups (27%) were considered most helpful, with variations observed across countries. Respondents indicated a desire for more counselling and/or psychological support, in-person support, peer-to-peer support, and online support. **Conclusions:** Most respondents experienced an impact on their emotional well-being due to KC; however, many did not discuss their emotional concerns with an HCP or access a patient support group either in person or online. Improved communication is needed between patients/caregivers and HCPs to address emotional concerns. HCPs can improve patient well-being through referrals to counselling/psychological support, and patient organizations in their country. Research Sponsor: None.

4533 Poster Session

Efficacy with fruquintinib plus sintilimab versus axitinib or everolimus in advanced renal cell carcinoma: A post-hoc analysis from FRUSICA-2 trial by baseline tumor burden. First Author: Yuan-Yuan Qu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The multicenter randomized phase 2/3 FRUSICA-2 trial (NCT05522231) demonstrated that fruquintinib plus sintilimab (F+S) significantly improved progression-free survival (PFS) (22.2 months vs 6.9 months) and objective response rate (ORR) (60.5% vs 24.3%) by blinded independent central review (BIRC) assessment compared to axitinib or everolimus (A/E) in Chinese patients (pts) with advanced renal cell carcinoma (aRCC) who had failed prior tyrosine kinase inhibitor therapy (Ye D, et al; 2025 ESMO). Considering that baseline tumor burden may correlate with efficacy outcome, we present the results of a relevant *post-hoc* subgroup analysis. **Methods:** Overall, 234 eligible pts were 1:1 randomized to receive either F+S or A/E. The primary efficacy endpoint was PFS assessed by BIRC per RECIST 1.1; secondary endpoints included investigator-assessed PFS, ORR, disease control rate, duration of response, time to response, and overall survival. This subgroup analysis evaluated BIRC-assessed PFS and ORR across subgroups defined by the number of target lesions (TLs) and metastatic sites (METs) at baseline. **Results:** At baseline, 79, 79, 32 and 44 pts had 1, 2, 3 and ≥4 TL(s), respectively. Metastatic disease was present in 117 (98.3%) pts in F+S arm and 110 (95.7%) pts in A/E arm, with a higher proportion of pts in F+S arm (88, 73.9%) having ≥3 METs than in A/E arm (67, 58.3%). By the data cut-off date of Feb 17, 2025, median follow-up for PFS was 16.6 months. As summarized in the table, F+S demonstrated superior PFS versus A/E across all subgroups, with unstratified hazard ratios (HRs) ranged from 0.28 to 0.50, as well as consistently longer median PFS. Similarly, improvements in ORR were observed across subgroups with odds ratios (ORs) ranged 2.46~7.22. Notably, in F+ S arm, fewer baseline TLs and METs appeared to correlate with longer median PFS, though such trend was not observed for ORR. **Conclusions:** Consistent with the primary analysis, F+S showed superior efficacy compared to A/E in terms of PFS and ORR in the second-line treatment of aRCC, regardless of the amount of baseline TLs or METs. Clinical trial information: NCT05522231. Research Sponsor: HUTCHMED.

Subgroup (F+S v A/E)	1 TL (38 v 41)	2 TLs (38 v 41)	3 TLs (16 v 16)	≥4 TLs (27 v 17)	1 MET (29 v 43)	2 METs (39 v 28)	≥3 METs (49 v 39)
PFS, HR (95% CI) [a]	0.39 (0.20, 0.76)	0.33 (0.17, 0.66)	0.43 (0.17, 1.10)	0.28 (0.12, 0.62)	0.28 (0.13, 0.60)	0.50 (0.24, 1.04)	0.31 (0.18, 0.545)
Median PFS, months [b]	24.9 vs 8.3	22.2 vs 6.9	15.3 vs 4.2	13.8 vs 6.9	24.9 vs 8.3	22.2 vs 8.3	NE vs 4.2
ORR, OR (95% CI)[c]	3.95 (1.35, 11.91)	4.65 (1.63, 13.43)	7.22 (1.17, 52.78)	5.53 (1.21, 28.76)	7.18 (2.22, 23.84)	2.46 (0.81, 7.76)	6.12 (2.13, 18.44)
ORR, %	52.6 vs 22.0	65.8 vs 29.3	62.5 vs 18.8	63.0 vs 23.5	65.5 vs 20.9	53.8 vs 32.1	61.2 vs 20.5

NE, not estimable.
[a]Based on an unstratified Cox proportional risk model.
[b]Estimated using Kaplan-Meier method.
[c]Exact 95% CI for OR was calculated using Cochran-Mantel-Haenszel method.

4534 Poster Session

A phase 1b, open-label, safety, tolerability, and efficacy study of HC-7366 in combination with belzutifan in patients with locally advanced (inoperable) or metastatic renal cell carcinoma. First Author: Neil J. Shah, Memorial Sloan Kettering Cancer Center, New York, NY

Background: HC-7366 is a novel, selective, potent activator of general control nonderepressible 2 (GCN2) kinase, regulating metabolic stress via the integrated stress response. Our preclinical studies in RCC demonstrated that prolonged GCN2 activation by HC-7366 resulted in antitumor activity accompanied by inhibition of HIFs and cell cycle progression. Furthermore, combination with belzutifan (BEL) results in superior preclinical efficacy, accompanied by inhibition of HIF signaling and cell-cycle progression, supporting clinical evaluation of the combination in RCC. **Methods:** Patients with advanced ccRCC previously treated with ≥1 anti-PD/PD-L1 and ≥1 VEGF-TKI were enrolled into HC-7366 monotherapy (60 mg QD) or a dose-escalation/expansion cohort of HC-7366 (20, 40, 60 mg QD) with BEL (120 mg QD). Primary objectives were safety, tolerability, and investigator-assessed ORR per RECIST v1.1. Enrollment in escalation and expansion is complete; second expansion is ongoing. **Results:** As of the data cutoff 10 Dec 2025, 69 patients received study treatment: 16 monotherapy and 53 combination (7 at 20 mg, 22 at 40 mg, 24 at 60 mg). Median prior therapies were 3 (range 1-5) in monotherapy and 2 (range 1-4) in combination. Most TEAEs were Grade (Gr) 1-2. Gr 3 events were mainly hematological (anemia) and gastrointestinal (nausea and diarrhea), with one DLT (Gr 3 nausea, 40 mg combination). In efficacy-evaluable patients, the 40 mg combination demonstrated the best overall response rate (BORR) of 36.8%, including a confirmed ORR (cORR) of 26.3%, disease control rate (DCR) of 89.5%, and primary progressive disease (PD) rate of 10.5%. The 60 mg combination had a BORR of 31.6%, with a cORR of 31.6%, DCR of 84.2%, and primary PD rate of 15.8%. In monotherapy, BORR of 15.4% and DCR of 61.5% were observed. Early efficacy signals at 40–60 mg align with the preclinical projected maximal efficacious dose range. **Conclusions:** HC-7366, alone or in combination with BEL, was generally well tolerated. Preliminary efficacy analyses indicate favorable disease control, characterized by a high DCR and low primary PD. Clinical trial information: NCT06234605. Research Sponsor: None.

Efficacy and safety data by cohort.

	Monotherapy 60 mg N=13	HC-7366 + BELZ 20/120 mg N=7	HC-7366 + BELZ 40/120 mg N=19	HC-7366 + BELZ 60/120 mg N=19
Median follow-up (mo)	16.9	13.4	11.2	8.5
BORR / cORR (%)	2 (15.4) / 0*	0 / 0	7 (36.8) / 5 (26.3)	6 (31.6) / 6 (31.6)
DCR (%)	8 (61.5)	5 (71.4)	17 (89.5)	16 (84.2)
Primary PD (%)	5 (38.5)	2 (28.6)	2 (10.5)	3 (15.8)
PFS 6 mo (%)	15.4	42.9	57.9	73.7
Any Gr / Gr 3 AEs	15 (93.8) / 9 (56.3)	7 (100) / 4 (57.1)	22 (100) / 16 (72.7)	24 (100) / 17 (70.8)
Gr 3 Anemia / Hypoxia	0 / 2 (12.5)	2 (28.6) / 1 (14.3)	5 (22.7) / 2 (9.1)	5 (20.8) / 2 (8.3)
Gr 3 Nausea / Diarrhea	2 (12.5) / 3 (18.8)	0 / 1 (14.3)	1 (4.5) / 0	2 (8.3) / 0
Dose Red / Discont.	6 (37.5) / 2 (12.5)	1 (14.3) / 0	11 (50.0) / 2 (9.1)	7 (29.2) / 3 (12.5)

*PRs not confirmed due to emergence of brain metastases.

4535 Poster Session

Combining HC-7366 with belzutifan in patients with renal cell carcinoma to alter tumor and microenvironment: Pharmacokinetic and pharmacodynamic (PK/PD) analysis of a phase 1b study. First Author: Benjamin Garmezy, Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN

Background: Clear cell renal cell carcinoma (ccRCC), characterized by loss of von Hippel-Lindau (VHL) tumor suppressor function, and constitutive stabilization of hypoxia-inducible factor (HIF) proteins results in activation of genes promoting angiogenesis, metabolic reprogramming including altered lipid metabolism and glycolysis, cell proliferation, and immunosuppressive remodeling of the tumor microenvironment. HC-7366 is a novel, selective GCN2 kinase activator that regulates metabolic stress via the ATF4–driven integrated stress response. Preclinically, GCN2 hyperactivation with HC-7366 enhances belzutifan (BEL) activity, broadly impairing stress adaptation, disrupting tumor metabolism, decreasing HIF expression, inhibiting the cell cycle, and remodeling the tumor immune microenvironment. **Methods:** In this phase 1b study (NCT06234605), 69 patients with advanced ccRCC received HC-7366 monotherapy (60 mg QD; n=16) or HC-7366 (20 mg, n=7; 40 mg, n=22; 60 mg, n=24) plus BEL (120 mg QD). Blood samples for soluble biomarkers and paired biopsies for IHC were collected per IRB-approved guidelines. **Results:** Overall, PK analysis (N=69) demonstrated steady state free exposure of HC-7366 at 40-60 mg doses (Cmax = 5.8 ng/mL, AUC = 75 h*ng/mL) that were consistent with exposures providing maximal BEL combination benefit preclinically. Compared with screening biopsies, all on-treatment biopsies at week 3 (8/8) showed induction of the ATF4 pathway biomarker ASNS (asparagine synthetase). Baseline HIF expression analysis by IHC from 52 patients demonstrated that 33 patients (63%) express mid to high levels of HIF1 and HIF2. HIF1α, but not HIF2α, was reduced consistently with treatment across all cohorts (7/8, 66-98% reduction). Reduced cell cycle biomarkers, including pRB and Ki67 (4/4), and increased frequency of $CD8^+$ $PD1^+$ $TCF1^+$ $Lag3^-$ $Tim3^-$ T-cells (3/3), suggesting ICI responsiveness, were observed in the 40-60 mg combination cohorts. Systemic changes were also observed in serum, including deep and sustained inhibition of EPO, decreases in proangiogenic cytokines like VEGF-A and PDGF-BB, and changes in adipokines that counter RCC progression (Table 1). Low baseline serum levels of KIM-1 predicted response to the combination (p=0.005). **Conclusions:** Early clinical findings suggest HC-7366 + BEL is associated with modulation of angiogenic and immune-related pathways in ccRCC, providing a rationale for the combination with ICIs and/or VEGFR-TKIs. Clinical trial information: NCT06234605. Research Sponsor: None.

Avg max change with treatment.

Biomarker	60 mg mono	20 mg combo	40 mg combo	60 mg combo
EPO (week 2)	-43%	-82%	-81%	-84%
Chemerin (week 2)	-34%	-16%	-36%	-28%
Adiponectin (week 5)	+64%	+35%	+46%	+36%
VEGF-A (week 9)	-53%	-42%	-28%	-37%
PDGF-BB (week 9)	-30%	-20%	-54%	-63%

4536 Poster Session

Neoadjuvant apatinib plus camrelizumab in renal cell carcinoma with inferior vena cava tumor thrombus: Results of a phase II study. First Author: RuiYang Xie, Department of Urology, Peking University Third Hospital, Beijing, China

Background: Renal cell carcinoma (RCC) with inferior vena cava tumor thrombus (IVCTT) remains a surgically challenging condition, and evidence supporting neoadjuvant systemic therapy is still evolving. We conducted a phase II study to evaluate the efficacy and safety of apatinib combined with camrelizumab as neoadjuvant treatment in this population. **Methods:** This single-arm phase II trial enrolled patients with histologically confirmed, resectable RCC with IVCTT (cT3b-T4, N0-1, M0-1; ECOG performance status 0-1). Patients received camrelizumab 200 mg i.v. every 2 weeks for six cycles plus oral apatinib 250 mg once daily, followed by surgical resection when feasible. The primary endpoint was downgrading of Mayo level of tumor thrombus (TT). Secondary endpoints included TT response (RECIST 1.1), response of primary renal tumor, safety (CTCAE v5.0), progression-free survival, and overall survival. **Results:** Nine patients were included in the intention-to-treat analysis. TT response was observed in 4 patients (44.4%), with disease control achieved in 8 patients (88.9%); one patient (11.1%) experienced progression. Mayo level downgrading occurred in 3 patients (33.3%), all of whom subsequently underwent surgery. Overall, 7 of 9 patients (77.8%) successfully completed neoadjuvant therapy and underwent robotic-assisted radical nephrectomy with thrombectomy. For primary renal tumor, partial response was observed in 1 patient (11.1%), and stable disease in 8 patients (88.9%), resulting in a disease control rate of 100%. Treatment-related adverse events were manageable and consistent with known safety profiles, with grade ≥3 events including hypertension, proteinuria, pneumonitis, and immune-related myasthenia gravis. At a median follow-up of 45 weeks, survival outcomes remain immature. **Conclusions:** Neoadjuvant apatinib plus camrelizumab demonstrated promising antitumor activity and acceptable safety in patients with RCC and IVCTT, achieving meaningful TT response and Mayo level downgrading, thereby facilitating surgical resection. These findings support further investigation of neoadjuvant combination therapy in this high-risk population. Clinical trial information: ChiCTR2300069990. Research Sponsor: National Natural Science Foundation of China; 82504235; Natural Science Foundation of Beijing Municipality; 7254443.

Patient baseline characteristics.

Characteristic	N=9
Median age, years, (IQR)	58 (54-66)
Sex, n (%)	
Male	6 (67)
Female	3 (33)
ECOG PS, n (%)	
0	7 (78)
1	2 (22)
Clinical T stage, n (%)	
cT3b	2 (22)
cT3c	3 (33)
cT4	4 (44)
Clinical N stage, n (%)	
cN0	3 (33)
cN1	6 (67)
Clinical M stage, n (%)	
cM0	3 (33)
cM1	6 (67)
Primary tumor size, cm (IQR)	12.4 (7.3-17.3)
Length of the tumor thrombus, cm (IQR)	11.3 (7.2-13.8)
Histological subtype on baseline biopsy, n (%)	
Clear cell RCC	8 (89)
TFE3 translocation RCC	1 (11)
Mayo level of TT at baseline	
I	0
II	4 (44)
III	2 (22)
IV	3 (33)

IQR interquartile range, ECOG Eastern Cooperative Oncology Group, PS performance status, RCC renal cell carcinoma.

4537 Poster Session

[^{68}Ga] Ga-NYM096 PET/CT in patients with primary and metastatic clear cell renal cell carcinoma: A preliminary study. First Author: Yangyang Xue, Department of Nuclear Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei, China

Background: With limitations of conventional imaging and biopsy, accurate, non-invasive techniques to detect in patients with primary and metastatic clear cell renal cell carcinoma (ccRCC) remain an unmet need. Carbonic anhydrase IX (CAIX) is a tumour antigen highly expressed in ccRCC. NYM096 is a new-generation CAIX targeting small molecule that can be labeled with ^{68}Ga. It has a higher affinity (almost 100-fold) for CAIX compared to NYM005. This study aims to assess the efficacy of [^{68}Ga]Ga-NY096 PET/ CT to identify ccRCC. **Methods:** This is an open-label, multicenter study. Patients with primary and metastatic ccRCC were prospectively recruited in the study. A washout of 7 days was required if the patients were on tyrosine kinase inhibitors. All patients received an intravenous injection of [^{68}Ga]Ga-NYM096 at a dose of 1-7 mCi and underwent whole body PET/CT scan using a total-body PET/CT scanner at 60 min after injection. They were further divided into two groups: group 1, patients with primary renal mass and group 2, patients with suspected/confirmed metastatic ccRCC, who were scheduled for surgery or biopsy. In some patients, ^{18}F-FDG PET/CT was also performed within one week before or after [^{68}Ga]Ga-NYM096 PET/CT. The diagnostic efficacy of ^{68}Ga-NYM096 was compared with that of ^{18}F-FDG. **Results:** A total of 24 patients (mean age, 56.7 years$\pm$14.4, 18 men) were recruited in this preliminary study. Including 23 patients in group 1 and 1 patient in group 2. All patients had ^{68}Ga-NYM096 PET/CT, and all patients also had ^{18}F-FDG PET/CT. The patient-level sensitivity, specificity, and accuracy of [^{68}Ga]Ga-NY096 PET scan was 100%, 90.0%, 95.7% for all patients, and 100%, 90.0%, 95.5% for group 1. One patient in Group 2 was confirmed as a true positive case by histopathological examination. Among patients with positive PET findings, the SUV_{max} of the single most active lesion ranged from 4.9 to 111.8, with a mean ($\pm$ SD) of 52.2 $\pm$ 34.1. This value was significantly higher than the mean SUV_{max} of 5.5 $\pm$ 2.9 observed with ^{18}F-FDG ($p < 0.001$). The tumor-to- kidney ratio was also higher (3.3 $\pm$ 3.0 versus 1.7 $\pm$ 3.0, $p < 0.05$). **Conclusions:** ^{68}Ga-NYM096 PET/CT has high diagnostic efficacy for primary ccRCC patients, and its diagnostic efficacy is significantly better than that of ^{18}F-FDG. It has the potential to become a diagnostic product for both primary and metastatic ccRCC. Research Sponsor: Norroy Bioscience Co., Ltd.

4538 **Poster Session**

Body composition and quality of life (QOL) with lenvatinib + everolimus (len + eve) versus cabozantinib (cabo) in metastatic clear cell renal cell carcinoma (ccRCC) after PD-1 inhibitor progression: Results from the randomized phase II LenCabo trial. First Author: Julia Moura, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The LenCabo trial (NCT05012371) was the first randomized head-to-head comparison of contemporary second-line or later treatments after progression on PD-1 based immune checkpoint inhibition (ICI). Len + eve significantly improved progression-free survival (PFS). There were numerical, but not statistically significant, differences in treatment discontinuation and ≥ grade 3 adverse events. Although cabo and len share many kinase targets, lenvatinib also blocks FGFR, and its combination with the mTOR inhibitor everolimus may affect body composition through metabolic effects. We sought to investigate how patient QOL and body composition changed after treatment with len + eve and cabo. **Methods:** LenCabo was a multicenter, phase II trial that randomized pts with metastatic ccRCC to len 18 mg/d plus eve 5 mg/d vs cabo 60 mg/d after 1-2 prior lines of treatment, including a PD-1 ICI. Pre-planned, health-related QOL was measured by FKSI DRS at baseline and after 60 days. Post-hoc, body composition was measured using an AI segmentation tool (Voronoi DAFS) at the L3 vertebra from baseline CT scans and after 4 months. Outcomes were compared using proportional odds models adjusting for baseline values and including nonlinear terms as restricted cubic splines. Pre-specified, body composition models additionally adjusted for prior VEGF-targeted therapy, age, IMDC risk category, and sex. **Results:** 86 pts received at least 1 dose of assigned len + eve (n=40) or cabo (n=46). 38 pts completed baseline and day 60 FKSI DRS (len + eve = 20, cabo = 18). The QOL comparison by FKSI DRS at day 60 was inconclusive (OR = 0.51 in favor of cabozantinib, 95% CI 0.16-1.64, p=0.26). 67 pts had body composition measured at baseline and 4 months (len + eve = 30, cabo = 37). After 4 months of treatment, len + eve was associated with a significantly lower odds of having a higher body mass index (BMI), skeletal muscle mass (SMMi), and subcutaneous adiposity (SATi, Table). **Conclusions:** In patients with metastatic ccRCC progressing on PD-1 ICI, len + eve was associated with significantly greater reductions in BMI, skeletal muscle mass, and subcutaneous adiposity compared with cabo at 4 months. The study did not contradict the supposition that the two treatment arms yield the same QOL at day 60. These results suggest that the superior PFS efficacy of len + eve in this setting is accompanied by a more pronounced catabolic effect. Clinical trial information: NCT05012371. Research Sponsor: Eisai.

Body composition measures at 4 months by treatment.

	Adjusted mean of len + eve vs. cabo	Odds ratio for higher measure (95% CI)	P value
BMI	28.5 vs. 29.4	0.36 (0.15 – 0.88)	0.03
SMMi	47.5 vs. 49.7	0.30 (0.11 – 0.79)	0.01
SATi	65.7 vs. 73.4	0.21 (0.08 – 0.55)	0.002

Abbreviations: BMI, body mass index; SMMi, skeletal muscle mass index; SATi, subcutaneous adipose tissue index.

4539 **Poster Session**

Defining second-line sequencing in advanced renal cell carcinoma: A systematic review and meta-analysis. First Author: Luisana Sisca, Campus Bio Medico, Roma, Italy

Background: In the absence of head-to-head comparative trials, the optimal sequencing of second-line systemic therapy for advanced renal cell carcinoma (RCC) remains undefined. As immune checkpoint inhibitor (ICI) based regimens now represent the dominant first-line standard, second-line treatment decisions increasingly rely on indirect data. We conducted a systematic review and meta-analysis to assess the comparative clinical reliability, defined as consistency of benefit across trials, of commonly adopted second-line strategies in RCC. **Methods:** Randomized phase II–III and prospective trials evaluating second-line systemic therapies in advanced RCC were identified through a systematic literature search. 13 trials encompassing approximately 5,000 patients were included, predominantly post TKI and post immunotherapy. Treatments were grouped by mechanism of action, including tyrosine kinase inhibitor (TKI) based regimens, mTOR inhibitor based therapies, immune-based approaches, and targeted combinations. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were pooled using inverse-variance random-effects models, with heterogeneity assessed using the I^2 statistic. **Results:** TKI based strategies demonstrated the most consistent benefit across endpoints, with significant improvement in OS (pooled HR 0.77, 95% CI 0.67–0.87; $p<0.0001$) and favorable PFS (HR 0.56, 95% CI 0.50-0.63; $p<0.0001$). Targeted combination strategies achieved consistent PFS benefit (HR 0.66, 95% CI 0.53–0.81; $p<0.0001$), which did not translate into OS advantage. In contrast, mTOR inhibitor based regimens were associated with modest PFS improvement but failed to demonstrate OS benefit (HR 1.13, 95% CI 0.95–1.35), while immune based approaches showed heterogeneous outcomes. To contextualize these findings within contemporary clinical practice, analyses restricted to patients previously treated with first line ICI based regimens demonstrated a consistent treatment pattern, with TKI based therapies retaining a robust PFS benefit (HR 0.57, 95% CI 0.51–0.64), while targeted combinations maintained a significant PFS improvement without a corresponding OS signal (HR 0.66, 95% CI 0.51–0.85). **Conclusions:** In the absence of head to head sequencing trials, this systematic synthesis of prospective evidence supports TKI based therapies as the most reliable reference second line strategy in advanced RCC, showing consistent benefit across both OS and PFS, including the immunotherapy first setting. In contrast, mTOR inhibitor based approaches and targeted combinations were associated with greater heterogeneity and did not demonstrate a consistent survival benefit despite improvements in PFS. These findings provide clinically actionable guidance for second-line treatment selection after ICI failure and underscore the need for prospective sequencing focused trials. Research Sponsor: None.

4540 **Poster Session**

Relationships between clinical stage, pathological stage, and disease-free (DFS) survival in renal cell carcinoma as used to inform future neoadjuvant study design: ECOG-ACRIN EA8143 PROSPER analysis. First Author: James Owain Jones, University of Cambridge, Cambridge, United Kingdom

Background: Estimating risk of renal cell cancer (RCC) relapse based only on pre-surgical data is key to future neoadjuvant trial design. The EA PROSPER phase 3 study accrued pts with clinical stage ≥T2 or $T_{any}N+$ RCC of any histology for nephrectomy. Pts were randomized to presurgical nivolumab (nivo) followed by primary tumor resection and 9 cycles of adjuvant nivo, or surgery alone followed by observation. We used PROSPER data to assess how baseline data informs risk. We reviewed cT to pT stage transitions, associated cT stages with outcome, and asked if size in addition to cT stage increases predictive accuracy. **Methods:** Pts with clear cell (cc) RCC were included. cT to pT concordance was assessed by TNM 8th edition. DFS analysis (time from surgery to recurrence, second primary, or any cause death) was performed; pts with no event were censored at date of last assessment. DFS analysis compared cT groups (cT1/cT2 vs cT3/cT4) in the overall eligible study population and within each study arm. A subset DFS analysis by tumor size among cT2a (> 7-8cm vs >8-10cm) and cT3a (< 7cm vs 7-8cm vs > 8cm) was explored. Cox proportional hazards models were used, and log-rank test was reported to represent global p-value of each model. Wald test p-value was reported for individual group comparison (in assessing more than two groups). Two-sided p-values are reported, all p-values were considered significant at 0.05. **Results:** Of 819 pts randomized, 732 ccRCC pts (382 surgery only, 350 nivo + surgery) had data available. DFS was significantly different between cT1/cT2 vs. cT3/cT4 group, favoring cT1/cT2 among all pts (HR [cT1/cT2 as reference]=1.56, two-sided log-rank p < 0.001) and in each of the treatment arms separately (nivo + surgery arm HR=1.48, two-sided log-rank=0.04 ; surgery only arm HR=1.63, two-sided log-rank p=0.007). About half of cT1/T2 pts were upstaged to pT3/4, whereas <10% of cT3a were downstaged to pT1b. Higher grade cT1/T2 were more likely to upstage (p-value < 0.001).119 pts with cT2a and 233 pts with cT3a had tumor size data available. There was no significant DFS difference between tumor size groups in the cT2a subset. In cT3a patients, DFS analysis by tumor size showed a trend of increasing risk for 7-8cm and > 8cm groups when compared to < 7cm group, with a statistically significant difference comparing > 8cm vs < 7cm (HR=3.33, two-sided Wald p < 0.001) signifying worse outcome for pts if tumor size > 8cm. **Conclusions:** In ccRCC pts, baseline cT assessment is associated with DFS outcome. High grade cT1/2 pts risk pathological upstaging to pT3. cT3+ identifies high risk pts, with <10% being downstaged. Pts with cT3a > 8cm have a worse prognosis than patients with < 7cm tumors. These findings should be accounted for in eligibility criteria and risk assessment models for neoadjuvant trials, and explored in other international datasets. Research Sponsor: ECOG-ACRIN.

4541 **Poster Session**

Genomic and clinical correlates of belzutifan treatment in renal cell carcinoma (RCC): A retrospective analysis of 150 RCC patients. First Author: Harshitha Reddy Dudipala, Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA

Background: Belzutifan is a hypoxia-inducible factor-2α (HIF-2α) inhibitor approved for RCC that targets a central driver in RCC pathogenesis; however, predictive biomarkers of response remain poorly defined. **Methods:** Comprehensive DNA (592-gene panel or whole exome) and RNA (whole transcriptome) sequencing were performed by Caris Life Sciences on RCC samples. Clear cell RCC and RCC-NOS with VHL mutations were included. Belzutifan time on treatment (ToT) was derived from insurance claims, and patients were classified as responders or non-responders using the median ToT. **Results:** A total of 150 belzutifan-treated RCC tumors were included in the analysis, of which 29% were primary kidney tumors and the remainder were from metastatic sites. The study population was classified as responders (n=57) or non-responders (n=93) using a median time on treatment of 85 days (95% CI: 71–114). Baseline characteristics were similar, except responders were younger (median age 57 vs 64 years, p=0.007). Transcriptomic analysis showed similar HIF-2α (median 7.78 vs 7.61) and CA9 (4.82 vs 4.54) expression between responders and non-responders without statistical significance. Responders showed enrichment of PTEN (15.8% vs. 3.3%, p=0.03) and PIK3R1 alterations (7.0% vs. 0.0%, p=0.04). Responders demonstrated numerically higher frequencies of PBRM1 (54.4% vs. 44.3%, p=0.46) and PIK3CA mutations (8.8% vs. 3.3%, p=0.24). Alterations in DNA damage response genes were also numerically more common among responders, including TP53 (14.0% vs. 4.9%, p=0.11) and ATM (3.5% vs. 1.6%, p=0.56), although none of these differences reached statistical significance. In contrast, non-responders exhibited numerically higher frequencies of BAP1 (18.0% vs. 8.8%, p=0.10), SETD2 (26.2% vs. 19.3%, p=0.27), and ARID1A (5.1% vs. 1.8%, p=0.30), all of which were also not statistically significant. **Conclusions:** HIF2-α RNA expression alone does not predict belzutifan response in RCC. Responders demonstrated alterations in PBRM1, PI3K/AKT/mTOR, and DNA damage response genes, while non-responders showed numerically higher frequencies of chromatin remodeling mutations including BAP1 and SETD2. Study limitation included small sample size and short follow-up. Larger datasets are required to validate these findings. Research Sponsor: None.

4542 **Poster Session**

Early detection of kidney cancer using blood-based multi-gene mRNA profiling in a prospective clinical study. First Author: Taigo Kato, Department of Urology, The University of Osaka Graduate School of Medicine, Osaka, Japan

Background: Kidney cancer remains one of the most aggressive and lethal urological malignancies, largely due to late-stage diagnosis and reliance on invasive tissue biopsies. To address this unmet clinical need, we developed and clinically validated the blood-based, cell-free mRNA test. By quantifying circulating tumor-derived transcripts in plasma, this assay provides rapid and precise molecular insights, supporting precision screening, early diagnosis, prognostication, and treatment monitoring. **Methods:** In this prospective clinical study, we evaluated real-time expression levels of 30 kidney cancer–associated genes in plasma samples from 51 subjects, including 41 patients with suspected kidney cancer and 10 healthy controls. The primary objective was to assess the diagnostic and prognostic performance of the Geneverify multi-gene blood-based expression panel. Log_2 fold-change values for individual genes were calculated relative to healthy controls and integrated to generate a composite risk score for each subject. Geneverify scores were compared with biopsy-confirmed diagnoses to assess assay sensitivity. Additional statistical analyses evaluated correlations between Geneverify scores and tumor stage, pathological grade, and treatment status. **Results:** All biopsy-confirmed kidney cancer cases demonstrated Geneverify scores greater than 10. Using an optimized cutoff score of 10, the assay achieved 100% sensitivity for cancer detection. While healthy controls served as the baseline reference, specificity against benign or non-malignant kidney disease could not be fully assessed due to the absence of such cases in this cohort. The majority of patients had early-stage (T1a) kidney cancer. Geneverify scores showed strong correlations with tumor stage, pathological grade, and clinical status. In patients with advanced or metastatic disease undergoing systemic therapy, Geneverify scores declined significantly over time, indicating potential utility for real-time treatment response monitoring. **Conclusions:** This study represents the first real-time clinical validation of a blood-based, cell-free mRNA genomic assay for kidney cancer detection. The Geneverify test demonstrated excellent diagnostic sensitivity, strong concordance with biopsy-confirmed disease, and meaningful prognostic and treatment-monitoring capabilities. These findings establish Geneverify as a powerful non-invasive alternative to tissue biopsy (based on published data 20% biopsies are false negative) for early detection and precision management of kidney cancer, with the potential to reduce invasive procedures and accelerate personalized oncology care. Research Sponsor: None.

4543 **Poster Session**

Comprehensive characterization of HIF-2α and carbonic anhydrase IX expression and the genomic landscape in clear cell and *VHL*-altered renal cell carcinoma. First Author: Yu-Wei Chen, Department of Medicine, UC San Diego Moores Cancer Center, La Jolla, CA

Background: Clear cell renal cell carcinoma (ccRCC) is commonly driven by VHL loss, resulting in HIF-2α stabilization and upregulation of targets such as carbonic anhydrase IX (CA9). Clarifying the relationship between CA9 and HIF-2α expression is critical to guide rational therapeutic strategies. **Methods:** DNA (592-gene panel or whole exome) and RNA (whole transcriptome) sequencing was performed on ccRCC and RCC–not otherwise specified, (NOS) tumors with *VHL* alterations via Caris Life Sciences for integrated genomic and transcriptomic profiling. The primary objective was to characterize the expression patterns of HIF-2α and CA9 across RCC tumors and co-occurring genomic alterations. Overall survival (OS) as measured from initial diagnosis. **Results:** A total of 1,935 RCC tumors were analyzed, including 967 (50%) ccRCC and the remainder RCC–NOS with *VHL* alterations; 49% were derived from the primary site. Expression of HIF-2α and CA9 were similar across racial and ethnic subgroups. Compared to primary kidney tumors, lower HIF-2α expression was observed in lymph node and liver metastases (both $p < 0.0001$) and lower CA9 expressions were observed in CNS and bone metastases (both $p < 0.0001$). Increased either HIF-2α or CA9 expressions were associated with high angiogenic and T-effector gene signatures as defined in IMmotion150 (all $p < 0.001$). HIF-2α expression positively correlated with CA9 expression ($r = 0.43$, $p < 0.001$). Tumors with highest quartile HIF-2α expression (Q4) had increased PBRM1 and decreased BAP1, TP53, and TERT mutation frequencies (Table). High CA9 expression (Q4) had increased PBRM1 and decreased TP53 mutations. High HIF-2α (Q4) and CA9 (Q4) expressions were associated with improved OS compared with Q1 (HIF-2α: median OS 97 vs 64.7 months, HR 0.56, $p < 0.0001$; CA9: median OS 90 vs 49 months, HR 0.63, $p = 0.002$). **Conclusions:** High expression of HIF-2α and CA9 identifies a canonical VHL/HIF-driven RCC subtype marked by enrichment of *PBRM1* mutations, depletion of aggressive genomic alterations (*BAP1*, *TP53*, *TERT*), and improved OS. Strong associations with angiogenic and immune-related gene signatures further support a coherent HIF-dependent phenotype. Research Sponsor: None.

Key gene mutation frequency by HIF-2 α/CA9 expression.

	HIF-2α (Q1)	HIF-2α (Q4)	P value	CA9 (Q1)	CA9 (Q4)	P value
PBRM1	33%	48%	<0.001	22%	46%	<0.001
BAP1	29%	8%	<0.001	22%	19%	0.43
TP53	13%	7%	0.012	16%	8%	0.04
TERT	13%	6%	0.005	12%	8%	0.37

4544 **Poster Session**

A first-in-human phase 1 dose-escalation study of the oral HIF-2α inhibitor JMKX003948 in patients with renal cell carcinoma. First Author: Xieqiao Yan, Peking University Cancer Hospital, Beijing, China

Background: Hypoxia inducible factor-2 alpha (HIF-2α) is a transcription factor and key tumorigenic driver of clear cell renal cell carcinoma (ccRCC). JMKX003948 is a novel, orally administered, selective small-molecule HIF-2α inhibitor that has shown significant antitumor activity in preclinical models of ccRCC. Herein, we present preliminary results from a phase 1 dose-escalation study of JMKX003948 in advanced ccRCC (NCT06321250). **Methods:** In this study, Patients with advanced ccRCC who had received at least 1 prior standard therapy were enrolled in 40, 80, 120, 180, and 270 mg escalating-dose cohorts sequentially, and received JMKX003948 monotherapy once daily (QD) until progression or unacceptable toxicity. The primary endpoints included safety/tolerability, the maximum tolerated dose (MTD), and the recommended Phase 2 dose (RP2D). **Results:** As of Dec 23, 2025, 22 patients (17 male) were enrolled. Median age was 57.5 years (range, 32-73 years). 13 patients (59.1%) have received $\geq$ 2 prior lines of therapy, 20 patients (90.9%) have received immune checkpoint inhibitor, and all patients (100%) have received vascular endothelial growth factor receptor–tyrosine kinase inhibitor (VEGFR-TKI). At data cutoff, the median follow-up was 9.7 months. One dose-limiting toxicity (grade 3 transaminase elevation) was observed at the 120 mg QD dose level, and the MTD was not reached. Treatment-related adverse events (TRAEs) were reported in all patients, with most graded 1-2. The most common TRAEs were anemia (86.4%). Grade 3 TRAEs occurred in 6 patients (27.3%), including hypoxia (13.6%), anemia (9.1%), proteinuria (4.5%), transaminase elevation (4.5%), and hyperkalemia (4.5%). No grade 4 TRAEs occurred. No TRAEs led to treatment discontinuation or death. Of 20 efficacy-evaluable patients, 5 patients (2 patients in 270 mg cohort and 1 patient each in 80, 120, 180 mg cohort) had partial response (PR), and 9 patients had stable disease (SD), objective response rate (ORR) and disease control rate (DCR) per RECIST 1.1 were 25% and 70%, respectively. Mean time to response (TTR) was 3.2 months. Median progression-free survival (PFS) was 7.7 months (95% CI, 1.3-not available). **Conclusions:** JMKX003948 is well tolerated and shows promising antitumor activity in patients with advanced ccRCC. Clinical trial information: NCT06321250. Research Sponsor: Shanghai Jeyou Pharmaceutical Co., Ltd.

4545 **Poster Session**

Investigating mechanisms of resistance to immune checkpoint inhibitors (ICIs) in renal cell carcinoma (RCC). First Author: Soki Kashima, Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: Though RCC often exhibits substantial CD8 T-cell infiltration, CD8 abundance does not predict clinical benefit from ICIs. We sought to elucidate tumor microenvironment features that uncouple CD8 presence from ICI response and to evaluate strategies to overcome resistance mechanisms. **Methods:** We performed single-cell RNA sequencing on 70 RCC tumors (59 clear-cell; 11 non–clear-cell), including samples obtained during systemic therapy (ICI-based therapy, n = 46; others, n = 24). Best response to ICI-based therapy was assessed according to RECIST: 18 responders (R; CR/PR) and 11 non-responders (NR; PD). Tumor-reactive TCRs were inferred using VDJdive. Non-negative matrix factorization identified gene programs associated with NR. Bulk RNA-seq data from landmark clinical trials (HCRN, JAVELIN Renal 101, CheckMate 9ER, COSMIC-313) were analyzed using Scissor (Sun et al. Nat Biotechnol 2022) to map PFS-associated bulk signals to single-cell states in our reference dataset, with summarized enrichment as an observed-to-expected (O/E) ratio. Ligand–receptor (NicheNet) and pathway analyses implicated upstream drivers. Functional validation was performed using primary human T cells cultured under normoxia or hypoxia, with or without TGFβ1. A TGFβ activation assay was used to evaluate rescue of T-cell function by the clinical-stage latent TGFβ1-selective inhibitor SRK-181. **Results:** We profiled 443,337 high-quality cells including 86,865 CD8 T cells. In NR tumors, a subset with high tumor-specific T-cell abundance (5/11, 45.5%) was enriched for an exhausted CD8 state with a tissue-resident memory program (Tex-rm; $p < 0.01$). Across multiple ICI-treated clinical trial cohorts, we identified Tex-rm cells as most associated with shorter PFS (O/E 1.34–1.82). Ligand–receptor and pathway analyses implicated enhanced TGFβ signaling in Tex-rm compared with other Tex. In vitro, hypoxia plus TGFβ1 increased a Tex-rm–like phenotype ($CD69^+CD103^+PD\text{-}1^+TIM\text{-}3^+$) relative to controls ($p < 0.05$ for each). TGFβ inhibited T-cell IFNγ production, while treatment with the TGFβ inhibitor SRK-181 restored it ($p < 0.05$). **Conclusions:** We identified a Tex-rm program associated with ICI intrinsic resistance in RCC despite high abundance of tumor-specific T cells. Functional data support a role for TGFβ signaling in promoting this dysfunctional state, suggesting that inhibiting TGFβ1 may help restore T-cell function and overcome ICI resistance in some non-responders. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

4546 Poster Session

Biomarker-defined outcomes in metastatic clear cell renal cell carcinoma (mccRCC) receiving first-line (1L) immune checkpoint inhibitor-based therapy. First Author: Koral U. Shah, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Dual immune checkpoint inhibitor (IO-IO) and immune checkpoint inhibitor plus VEGF receptor tyrosine kinase inhibitor (IO-TKI) regimens are approved 1L treatments for mccRCC, yet treatment selection remains empiric in the absence of prospective comparisons and validated predictive biomarkers. While prior retrospective studies have linked genomic alterations such as *PBRM1* with favorable immunotherapy outcomes (Miao et al., 2018), the impact of these alterations across IO-IO vs. IO-TKI regimens is not well characterized. We evaluate PD-L1 expression and tumor genomic alterations in relation to clinical outcomes among patients receiving 1L IO-based therapy. **Methods:** Adults with mccRCC diagnosed through 2/4/2025 were identified in ConcertAI's Patient360, a U.S. de-identified database integrating health records, claims, genomics, and mortality data. Patients initiating 1L IO-IO (ipilimumab + nivolumab) or IO-TKI (cabozantinib + nivolumab, pembrolizumab + axitinib, or lenvatinib + pembrolizumab) were included. Molecular testing performed prior to or during 1L therapy was collected. PD-L1 positivity was defined as ≥1% tumor cell staining. Overall survival (OS) and progression-free survival (PFS) were estimated via Kaplan-Meier methods; associations by treatment and biomarker status were assessed using Cox models. **Results:** Among 4,845 patients with mccRCC, 3,225 patients had 1L treatment data, of whom 1,007 (31.2%) received IO-based therapy. IO-based therapy included IO-IO (508 patients; 50.4%) and IO-TKI (499 patients; 49.6%). Among patients receiving IO-based therapy, median age was 62 years, and 63.6% had *de novo* metastatic disease. Tumor genomic alterations were identified in 125 patients, including *VHL* (77.6%), *PBRM1* (50.4%), *BAP1* (28.8%), and *SETD2* (4.8%). Patients with any alterations in *VHL*, *PBRM1*, or *BAP1* demonstrated significantly longer median PFS with IO-TKI compared with IO-IO (37.9 vs. 18.4 months, respectively; p=0.04). In gene-specific analyses, similarly large numerical differences in PFS were observed with IO-TKI vs. IO-IO amongst patients with *VHL* (38.0 vs. 18.4 months) and *PBRM1* (34.4 vs. 18.4 months) alterations. In the overall cohort, median PFS was 32.2 vs. 20.8 months (p=0.06), and median OS was 58.4 vs. 56.7 months (p=0.60) for IO−TKI and IO−IO, respectively. Among 102 patients with available PD-L1 status, 25.5% were PD-L1-positive and 74.5% were PD-L1-negative. Among PD-L1-positive patients, OS and PFS did not significantly differ between regimens. **Conclusions:** Among patients with mccRCC receiving 1L IO-based therapy, those harboring *VHL*, *PBRM1*, or *BAP1* alterations were collectively associated with numerically longer PFS when treated with IO-TKI. These findings represent one of the first and largest biomarker-stratified comparisons of outcomes between IO-TKI and IO-IO regimens. Research Sponsor: None.

4547 Poster Session

First-line tivozanib in favorable- and very favorable−risk metastatic renal cell carcinoma: Real-world evidence from the TIVOREAL-SOGUG study. First Author: Cristina Pernaut Sanchez, Hospital Universitario Severo Ochoa, Leganes, Madrid, Spain

Background: The optimal first-line treatment for favorable-risk metastatic renal cell carcinoma (mRCC) remains debated in the immune checkpoint inhibitor (ICI) era. Real-world data assessing prognostic subgroups treated with VEGFR-TKI monotherapy are limited. **Methods:** TIVOREAL-SOGUG is a retrospective multicenter study including patients with clear-cell mRCC treated with first-line tivozanib between 2017 and 2024 across 14 Spanish centers. Favorable-risk was defined by IMDC criteria (0 risk factors). A very favorable-risk (VFAV) subgroup was identified according to Zarba et al. criteria (time from diagnosis to systemic therapy >3 years, Karnofsky performance status 90–100%, and absence of brain, liver, or bone metastases). The primary endpoint was time to treatment failure (TTF); secondary endpoints included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), subsequent therapies, and safety. **Results:** Among 198 evaluable patients, 84 (42.4%) had favorable-risk disease, including 23 (27.4%) classified as VFAV. In the overall favorable-risk cohort, ORR was 48.8%, including 7.1% complete responses. Median PFS and TTF were 23.7 and 14.7 months, respectively. Median OS was not reached, with 2- and 5-year OS rates of 85.4% and 67.8%. VFAV-risk patients showed higher ORR (65.2%), prolonged PFS (32.2 months) and TTF (31.1 months), and low primary progression. Treatment discontinuation due to toxicity occurred in 9.5% of patients. Most frequent adverse events were grade 1–2 fatigue, diarrhea, mucositis, dysphonia and hypertension, with grade ≥3 events being infrequent and mainly limited to hypertension. After progression, most favorable-risk patients received ICIs, whereas VFAV-risk patients required subsequent therapy less frequently, reflecting more durable disease control. **Conclusions:** In routine clinical practice, first-line tivozanib provides durable disease control and long-term survival in IMDC favorable-risk mRCC, and particularly in VFAV-risk patients. ICI and cabozantinib remain effective salvage options in this setting upon disease progression. Research Sponsor: Recordati Rare Diseases Spain, S.L.U.

Key clinical outcomes by prognostic subgroup.

Outcome	Favorable-risk (n=84)	Very favorable-risk (n=23)
Median TTF, months (95% CI)	14.7 (9.2–20.1)	31.1 (8.0–54.1)
Median PFS, months (95% CI)	23.7 (14.1–33.3)	32.2 (21.1–43.4)
ORR, % (CR %)	48.8 (7.1)	65.2 (13.0)
Primary progressive disease, %	14.3	4.3
2-year OS, % (95% CI)	85.4 (77.2–92.8)	95.7 (88.1–100)
Discontinuation due to toxicity, %	9.5	8.7

TTF and PFS were estimated using Kaplan–Meier methodology; tumor response was assessed according to RECIST 1.1.

4548 Poster Session

LIF expression as a predictive biomarker in metastatic renal cell carcinoma. First Author: Mustafa Saleh, Dana-Farber Cancer Institute, Boston, MA

Background: Clear cell renal cell carcinoma (ccRCC) is biologically heterogeneous, and optimal selection between VEGF-targeted and ICI–based therapies remain an unmet clinical need. Leukemia inhibitory factor (LIF), an IL-6 family cytokine implicated in angiogenesis and immune regulation, is associated with poor prognosis in ccRCC; however, its predictive value for treatment selection has not been defined. **Methods:** Baseline tumor LIF expression was evaluated in 2,026 patients with metastatic ccRCC across 12 clinical and molecular cohorts, including CheckMate 009/010/025/214, JAVELIN Renal 101, IMmotion150, TCGA-KIRC, CPTAC-3, and institutional datasets. RNA-seq data were batch-corrected, normalized, and immune-deconvoluted (CIBERSORTx). Among 1,306 patients with treatment data, 1,058 with complete clinical covariates were included in treatment-by-biomarker interaction analyses. **Results:** LIF-high tumors (median cutoff) were associated with younger age (60 vs 63 years, p<0.001) and increased sarcomatoid features (17% vs 8%, p<0.001). A significant treatment-by-LIF interaction was observed for progression-free survival (PFS; interaction p=0.006). High LIF expression predicted inferior PFS on TKI monotherapy (HR 1.26, p<0.001), while this adverse association was absent with ICI-based regimens (monotherapy or combination; HR 0.70, p<0.001). No significant interaction was observed for overall survival. LIF expression discriminated progressive disease from disease control (p<0.001). Immune deconvolution revealed that LIF-high tumors exhibited an inflamed but immunosuppressive microenvironment, characterized by enrichment of macrophages (M0 and M2), neutrophils, and regulatory T cells, with preserved $CD8^+$ T-cell infiltration. LIF expression correlated strongly with CXCL8 (R=0.45), and more modestly with FGF2 and VEGFA, consistent with VEGF-independent angiogenic signaling. **Conclusions:** LIF identifies a biologically distinct subset of metastatic ccRCC characterized by angiogenic and immunosuppressive features and poor outcomes with TKI monotherapy. These data support LIF as a predictive biomarker to inform treatment selection and highlight the LIF/CXCL8 axis as a potential therapeutic target in advanced RCC. Research Sponsor: None.

Treatment-by-LIF interaction analysis for progression-free survival in metastatic clear cell renal cell carcinoma.

Groups	N	HR	95% CI	P-value
Full Cohort*	1792	1.09	1.01 – 1.14	0.017
Treatment interaction Model§				
Main effect (LIF in TKI)	1058	1.26	1.108 - 1.443	<0.001
LIF × IObased (IO and IO+IO)	1058	0.70	0.567 - 0.854	<0.001
LIF × IO+VEGF	1058	0.89	0.73 - 1.079	0.230
LIF × MTORi	1058	0.84	0.689 - 1.035	0.104
Stratified Analyses§: TKI Monotherapy	377	1.27	1.114 - 1.455	<0.001
IO/IO+IO	194	0.87	0.741 - 1.03	0.107
IO+VEGF	364	1.15	0.996 - 1.337	0.057

*Adjusted for IMDC, Age, Sex, Sarcomatoid Features, and Treatment modality.
§Adjusted for IMDC, Age, Sex, Sarcomatoid Features.

4549 Poster Session

Nivolumab and Ipilimumab (NIVO IPI) as first-line (1L) treatment for patients with metastatic renal-cell carcinoma (mRCC): A real-world benchmarking analysis from the International mRCC Database Consortium (IMDC). First Author: Heber Tomas Reyes-Garcia, Arthur JE Child Comprehensive Cancer Centre, University of Calgary, Calgary, AB, Canada

Background: NIVO IPI has demonstrated durable overall survival (OS) benefit with long-term follow-up in patients with mRCC. Real world outcomes and benchmarks for subgroups as well as conditional survival (CS) are required in the real world. **Methods:** Patients with mRCC treated with 1L NIVO IPI from the IMDC were analyzed, including various subgroups of interest. Outcomes reported will be objective response rates (ORR), median overall survival (mOS) and conditional survival (CS). CS is defined as survival among patients who were alive and on treatment after the requisite 3-month interval landmarks, as estimated using the Kaplan–Meier method. CS was calculated at landmarks while patients were still on treatment, and at landmarks regardless of treatment. **Results:** 2115 patients received 1L NIVO IPI; 148/1042/549 were categorized by IMDC risk group as favorable/intermediate/poor risk; 90% of patients had clear-cell histology, 32% had bone metastases, and 14% had sarcomatoid features. Median follow-up was 34 months (m); median duration of treatment was 4.8 m, and median time to next treatment was 11.2 m. 66% of patients received second-line treatment. ORR was 39.5% (8.3% CR) with primary progression seen in 28 mOS was longer in clear cell (47.8 m) than in non–clear cell (26.3 m) (p<0.001). mOS was significantly shorter in patients with sarcomatoid features (34.2 vs 47.0 m; p=0.02 mOS was also different by IMDC risk group: 53.3 m for favorable, 45.7 m for intermediate and 18.8 m for poor risk patients (p<0.001); and by response: 4-year was OS of 93.6% for patients with CR, 60.1% for PR, 43.6% for SD and 15.4% for patients with PD (p<0.001). CS during 1L NIVO IPI is detailed in Table 1 with greater survival with each successive landmark. **Conclusions:** We provide real-world benchmark survival results for patients with mRCC treated with 1L NIVO IPI, including subgroup analysis regarding the presence of sarcomatoid features, IMDC risk group, and ORR. Conditional survival provides a key understanding of a patient's prognosis after having been on therapy or been alive for at certain time points. This is essential information for patient counselling and clinical trial design. Research Sponsor: None.

Conditional survival (CS) through time landmarks, either on treatment or regardless of treatment.

Landmark (mo)	CS on NIVO IPI (N)	CS on treatment If patient is still on therapy past landmark mo (95% CI)	CS (N) regardless of treatment continuation	CS regardless of treatment continuation If patient survived past landmark mo (95% CI)
0	1965	41.4 (37.7–45.3)	2038	40.2 (36.7–44.5)
3	1129	54.5 (49.7–67.3)	1826	44.6 (40.7–49.4)
6	822	93.0 (60.9–NR)	1626	49.2 (44.6–53.5)
9	627	93.0 (84.2–NR)	1436	53.5 (49.2–59.2)
12	483	114 (84.2–NR)	1276	56.9 (51.1–66.8)
24	210	NR (NR–NR)	805	93.0 (72.8–NR)
36	101	NR (NR–NR)	519	NR (93.0–NR)

4550 **Poster Session**

Extended follow-up (6 years) of the phase 2 LITESPARK-004 study of belzutifan in participants with von Hippel-Lindau disease–associated neoplasms. First Author: Ramaprasad Srinivasan, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Belzutifan, a potent and selective hypoxia-inducible factor 2α inhibitor, is indicated for treatment of patients with von Hippel-Lindau (VHL) disease–associated renal cell carcinoma (RCC), CNS hemangioblastomas (HB), or pancreatic neuroendocrine tumors (pNETs) not requiring immediate surgery based on prior results from the open-label phase 2 LITESPARK-004 study (NCT03401788). We report results from LITESPARK-004 after a minimum of 6 years of follow-up. **Methods:** Participants (pts) with germline *VHL* alterations, $\geq$1 measurable nonmetastatic RCC tumor, no tumor $>$3 cm that required immediate surgery, no metastatic disease, no prior anticancer systemic treatment, and an ECOG PS of 0 or 1 received oral belzutifan 120 mg once daily until disease progression, unacceptable toxicity, or pt withdrawal. The primary end point was objective response rate (ORR) in VHL disease–associated RCC per RECIST v1.1 by independent review committee (IRC). Secondary end points included safety, ORR in non-RCC neoplasms, duration of response (DOR), and progression-free survival (PFS) per RECIST v1.1 by IRC. **Results:** Overall, 61 pts received $\geq$1 dose of belzutifan. Median study follow-up was 73.8 months (range, 72.1-82.1). As of the data cutoff date (April 1, 2025), 34 pts (56%) remained on treatment. ORR was 70% for RCC, 52% for CNS HB, and 91% for pNETs. Additional efficacy results are shown in the Table. Among 14 pts (n = 18 affected eyes by ophthalmic evaluation), retinal HBs in 100% (95% CI, 81-100) of eyes showed improvement. Median DOR in pts with retinal HBs was not reached (NR; 95% CI, 8.5-NR). Within 5 years prior to initiating belzutifan, 46 of 61 pts (75%) had $\geq$1 VHL-related tumor reduction procedure (surgery or radiation therapy; 43 RCC, 39 CNS HB, 12 retinal HB, 3 pNET, 2 other). Since initiating belzutifan treatment, 22 of 61 pts (36%; 14 during treatment and 8 after discontinuing treatment) underwent 25 VHL-related tumor reduction procedures (16 RCC, 3 CNS HB, 5 retinal HB, 1 pNET). Grade 3 treatment-related adverse events (TRAEs) were reported in 12 pts (20%); the most common grade 3 TRAE was anemia (11%). No grade 4 or 5 TRAEs occurred. No additional pts discontinued belzutifan due to TRAEs since the previous analysis. **Conclusions:** After 6 years of follow-up, belzutifan continues to show durable antitumor activity and a manageable safety profile in pts with VHL-associated RCC, CNS HB, and pNETs who do not require immediate surgery. These results continue to support the use of belzutifan in this patient population. Clinical trial information: NCT03401788. Research Sponsor: Funding for this study was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; the Intramural Research Program of the National Institutes of Health, National Cancer Institute Center for Cancer Research; and a grant (U01 CA236489) from the National Cancer Institute.

	RCC n = 61	CNS HB n = 50	pNETs n = 22
ORR (95% CI), %	70 (57-81)	52 (37-66)	91 (71-99)
Best overall response, n	8 CR	7 CR	14 CR
	35 PR	19 PR	6 PR
	17 SD	20 SD	2 SD
	0 PD	3 PD	0 PD
	1 NE	1 NE	0 NE
DOR, median (range), months	NR (5.8+ to 69.1+)	NR (0.0+ to 74.3+)	NR (11.0+ to 71.8+)
48-month DOR rate	78%	84%	90%
PFS, median (95% CI), months	NR (71.5-NR)	NR (NR-NR)	NR (NR-NR)
48-month PFS rate	79%	80%	90%

4551 **Poster Session**

Ultrasensitive circulating tumor DNA detection and molecular clearance as a prognostic and predictive marker in advanced renal cell carcinoma. First Author: Juan Ruiz Bañobre, Complejo Hospitalario Universitario de Santiago, Santia, Spain

Background: Renal cell carcinoma (RCC) is characterized by exceptionally low levels of circulating tumor DNA (ctDNA), often falling below the limit of detection for conventional liquid biopsy assays. This low-shedding environment creates a significant unmet need for ultrasensitive strategies to detect molecular residual disease (MRD), improving patient stratification, and enabling longitudinal monitoring of disease evolution in a clinical setting. **Methods:** ctDNA was profiled using NeXT Personal, a tumor-informed WGS-based assay tracking up to ~1,800 patient-specific variants with a limit of detection (LOD) of ~1 part per million (PPM). Baseline and longitudinal (n = 165) plasma from 37 advanced RCC patients were analyzed. The primary analysis evaluated baseline plasma (n = 36) across clinical variables. Prognostic value for progression-free survival (PFS) and overall survival (OS) was assessed in patients treated with immunotherapy or TKIs (n = 35). **Results:** Baseline ctDNA was detected in 84% (31/37) of patients. Notably, 13% (4/31) of these detections occurred in the ultrasensitive range below 100 PPM. Baseline ctDNA PPM levels significantly correlated with IMDC risk group (median PPM: favorable 10.9, intermediate 244.2, poor 2437.0; P=0.005), presence of histological high-risk features (median PPM: low-risk: 40.6 vs high-risk: 1528.0; P=0.025) and stage at diagnosis (median PPM: I-III 35.1 vs IV 1548.3; P=0.006). Median ctDNA levels were significantly lower in patients with surgical site recurrence (5.5 vs. 937.2 PPM; P=0.038). Molecular ctDNA clearance (mCR), defined as ctDNA-negative status at any point during first-line therapy, was highly prognostic. mCR correlated significantly with best overall response (P=0.007), with 100% specificity for disease control; no patients with progressive disease achieved clearance. Patients not achieving mCR had dramatically worse PFS (HR=8.69; P=0.001) and OS (HR=4.70; P=0.044). Among patients with a best response of stable disease (SD) by imaging, mCR provided critical differentiation; those who cleared ctDNA had 100% PFS/OS at 2 years, whereas those who remained ctDNA-positive saw PFS drop to 0% and OS to 33% by year 1. Additionally, achievement of mCR was significantly associated with clinical disease control (PR+SD, 92.3% vs PR+SD, 50.0%; OR 12.0 [95% CI 1.32–108.8], p=0.013). **Conclusions:** Ultrasensitive ctDNA profiling effectively overcomes the low-shedding challenge of advanced RCC, and could provide additional prognostic clarity that complements standard-of-care imaging and IMDC risk models. mCR serves as an effective biomarker for long-term survival, identifying patients with durable responses even among those with radiographically stable disease. These findings support integrating ctDNA monitoring to guide treatment intensification or de-escalation strategies. Research Sponsor: GILEAD SCIENCES, S.L.U. - 11a Convocatoria de Becas Gilead a la Investigación Biomédica en VIH, COVID-19, Hepatitis Delta, Linfomas no Hodgkin de células B y Oncología Médica.

4552 **Poster Session**

Impact of time-of-day of immune checkpoint inhibitor infusion on clinical outcomes in patients with metastatic renal cell carcinoma (mRCC). First Author: Soon Khai Low, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI

Background: Emerging evidence suggests that circadian rhythms may influence the efficacy of immune checkpoint inhibitors (ICIs) by modulating immune cell activity and T-cell trafficking. This study evaluated whether the timing of ICI administration (early vs. late) affects progression-free survival (PFS) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC). **Methods:** We conducted a single-center retrospective study of 97 patients with Stage IV mRCC treated with first-line ICIs. Patients were categorized by infusion timing: "Early" (n=68) vs. "Late" (n=29), with the cutoff defined by the median infusion time of 2:00 PM. Treatment regimens included ipilimumab/nivolumab (37%), nivolumab (36%), and pembrolizumab (27%); 23% received ICI in combination with a VEGF-targeted tyrosine kinase inhibitor. Outcomes were analyzed using Kaplan-Meier curves and multivariable Cox regression models, adjusting for age and International Metastatic RCC Database Consortium (IMDC) risk scores. **Results:** The median age was 65 years (IQR 59–71), 77% of patients were male, and 88% had clear cell histology. IMDC risk categories were intermediate (56%), poor (27%), and favorable (18%). At a median follow-up of 54.8 months, early infusion was associated with significantly improved OS (median 54 vs. 29 months; adjusted HR 1.79; 95% CI 1.02–3.12; p = 0.041) and PFS (median not reached; adjusted HR 3.59; 95% CI 1.27–10.20; p = 0.016) after adjustment for age and IMDC risk. Landmark 60-month OS was 40% vs. 31%, and PFS was 79% vs. 60% for the early vs. late groups, respectively. The incidence of any-grade immune-related adverse events (irAEs) was similar (54% in the early group vs. 52% in the late group), and poor IMDC risk remained a significant predictor of OS in the multivariable model (HR 3.09; 95% CI 1.22–7.8; p = 0.017). **Conclusions:** In this mRCC cohort, ICI administration before 2:00 PM was associated with significant improvements in both PFS and OS, including a nearly two-fold increase in median overall survival compared to late-afternoon administration. These findings are hypothesis-generating and suggest that the timing of immunotherapy may be an immediately actionable, high-impact variable in optimizing mRCC treatment. Prospective validation is warranted. Research Sponsor: None.

4553 **Poster Session**

Correlation between *CARINH* expression and clinical outcomes in metastatic clear-cell renal cell carcinoma (mccRCC). First Author: Wassim Daoud Khatoun, Dana-Farber Cancer Institute, Boston, MA

Background: *CARINH* is an interferon (IFN)-responsive long non-coding RNA that promotes *IRF1* expression and downstream IFN signaling. Higher *CARINH* expression improves outcomes in esophageal cancer through suppressed tumor growth (Huang et al, 2019). Despite the immunogenic nature of RCC, the role of *CARINH* in its immunogenicity remains unexplored. Here, we examine the role of *CARINH* in predicting progression in mccRCC patients (pts) treated with systemic therapy. **Methods:** We included pts with RNA-seq data from 2 first-line clinical trials in mccRCC: Javelin Renal-101 (JR; n = 741) and CheckMate9ER (CM9; n = 403). Transcripts per million (TPM) were log2-transformed and scaled per 1 SD change. IMmotion150 T_{eff} and Myeloid signatures, and tumor inflammatory score (TIS) were computed as means of their log2-transformed genes' TPMs then scaled. Multivariable (MV) Cox models assessed progression-free survival (PFS) per increase in *CARINH* expression and compared PFS for each immune signature with and without *CARINH* expression, using likelihood ratio test (LRT). Log-rank test compared PFS between high and low *CARINH* expression groups with median split. Spearman correlation associated *CARINH* expression and immune signatures. MV logistic regression estimated progression odds ratio between pts who progressed (RECIST 1.1: PD), and those who didn't (CR, PR, SD and NCR/NPD). MV analyses adjusted (adj) for age, sex, treatment arm, IMDC risk and sarcomatoid features. **Results:** In MV Cox analysis, higher *CARINH* was associated with improved PFS in both trials (JR: HR_{adj} = 0.87 - 95% CI: 0.79-0.96, p = 4.5×10^{-3}; CM9: HR_{adj}= 0.82 - 95% CI: 0.73-0.93, p = 1.3×10^{-3}), regardless of treatment arm (LRT p $>$ 0.05). Log-rank test, comparing high and low expression groups, revealed longer PFS with high expression in every cohort and their arms (p $<$ 0.05), except for sunitinib in CM9 (p = 0.18). Higher *CARINH* expression correlated positively with T_{eff} and TIS signatures (ρ = 0.51-0.54) and negatively with Myeloid signature (ρ = -0.14 to -0.10) in both trials (p $<$ 0.05). *CARINH* expression improved PFS prediction over immune signatures in both trials (Table). Higher expression was associated with lower progression odds (JR: OR_{adj}= 0.74 - 95% CI: 0.60–0.91, p = 3.7×10^{-3}; CM9: OR_{adj}= 0.68 - 95% CI: 0.47–0.98, p = 0.04), independent of arm (LRT p $>$ 0.05). **Conclusions:** In mccRCC, higher *CARINH* expression associates with lower progression odds and improved PFS beyond that predicted by immune signatures. Translational efforts to characterize its role in mccRCC pathophysiology and clinical outcomes are ongoing. Research Sponsor: None.

MV Cox for PFS prediction by immune signature after adding *CARINH* expression.

Trial	Immune Signature	HR_{adj} (with CARINH)	95% CI	LRT FDR-adj p-value
JR	TIS	0.86	0.76-0.97	0.02
JR	T_{eff}	0.88	0.79-0.99	0.04
JR	Myeloid	0.87	0.80-0.96	0.02
CM9	TIS	0.84	0.72-0.97	0.02
CM9	T_{eff}	0.81	0.70-0.94	7.2×10^{-3}
CM9	Myeloid	0.82	0.73-0.93	4.6×10^{-3}

4554 **Poster Session**

A multi-axis biomarker model integrating KIM-1 and MAdCAM-1 in metastatic renal cell carcinoma. First Author: Marc Machaalani, Dana-Farber Cancer Institute, Boston, MA

Background: Kidney injury molecule-1 (KIM-1) and mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) have each emerged as prognostic circulating biomarkers in metastatic renal cell carcinoma (mRCC). Whether these biomarkers capture overlapping or complementary aspects of disease biology, and whether their integration improves risk stratification, remains unclear. **Methods:** Baseline plasma KIM-1 and MAdCAM-1 levels were measured in 612 patients with previously untreated mRCC from the JAVELIN Renal 101 trial, including 323 patients treated with avelumab + axitinib and 289 with sunitinib. Biomarker concentrations were analyzed as continuous variables after log10 transformation. Associations with overall survival (OS) and progression-free survival (PFS) were assessed using multivariable Cox models adjusted for IMDC risk, age, and sex. A composite KIM-1−MAdCAM-1 risk score was developed to assess the incremental prognostic value of integrating these biomarkers. **Results:** Both KIM-1 and MAdCAM-1 levels were independently associated with OS and PFS in univariable analyses. In multivariable models including both biomarkers and adjusted for age, sex, and IMDC risk, higher KIM-1 levels remained associated with worse survival (OS: HR 1.57, 95% CI 1.28−1.93), whereas higher MAdCAM-1 levels were associated with improved survival (OS: HR 0.37, 95% CI 0.15−0.92). No significant interaction was observed between KIM-1 and MAdCAM-1, nor between either biomarker and treatment arm for OS or PFS. A composite KIM-1−MAdCAM-1 risk score was strongly associated with clinical outcomes. Patients in the highest-risk quartile had significantly worse PFS (median: 8.3 [5.7−11.1] vs 19.4 [13.8−NR] months) and OS rate (at 18 months: 65.0% [57.3−73.8] vs 90.0% [85.0−95.2]) compared to the lowest-risk quartile, across both treatment arms (Table). A joint KIM-1−MAdCAM-1 model demonstrated improved discrimination compared with either biomarker alone ($p < 0.001$), and the addition of both biomarkers to IMDC significantly improved OS discrimination (C-index 0.73 vs 0.67; $p < 0.001$). **Conclusions:** KIM-1 and MAdCAM-1 provide complementary and non-redundant prognostic information in mRCC. Their integration into a composite risk score significantly improves risk stratification beyond either biomarker alone and beyond IMDC criteria. These findings support a multi-axis circulating biomarker approach to prognostication in mRCC. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; CA258442; Dana-Farber/Harvard Cancer Center Kidney; CA101942-16; Dana-Farber/Harvard Cancer Center; CA006516-56.

Association of KIM-1−MAdCAM-1 composite score quartiles with progression-free and overall survival in the overall study cohort and by treatment arm.

KIM-1−MAdCAM-1 Composite Score	Entire Cohort HR (95% CI)	Avelumab + Axitinib HR (95% CI)	Sunitinib HR (95% CI)
Progression-Free Survival (Q4 vs Q1)	2.12 (1.56−2.87)	2.00 (1.31−3.05)	2.20 (1.41−3.43)
Overall Survival (Q4 vs Q1)	4.67 (2.71−8.05)	3.61 (1.75−7.44)	5.89 (2.54−13.7)

HR, hazard ratio; CI, confidence interval; Q, quartile.

4555 **Poster Session**

Final analysis of the TiNivo-2 phase 3 trial: Long-term outcome of tivozanib (Tivo) in patients with metastatic renal cell carcinoma (mRCC). First Author: Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: TiNivo-2 results showed that immune checkpoint inhibitor (ICI) rechallenge did not offer benefit to patients with mRCC, regardless of treatment sequencing (*Lancet*, 2024; 404:1309). However, the data highlights activity for Tivo monotherapy in the post-ICI setting. Long term outcomes of the TiNivo-2 study are reported here. **Methods:** TiNivo-2 trial design and primary-endpoint results were previously reported: patients with mRCC were randomized to treatment with Tivo 0.89 mg once daily for 21/28 days plus Nivolumab (Nivo) at 480 mg every four weeks (Tivo/Nivo) or Tivo 1.34 mg once daily for 21/28 days. Here, long term progression free survival (PFS), overall survival (OS), and the safety profile are reported at final analysis. **Results:** At the data cutoff of 17 October 2025, 172 patients were randomized to Tivo (171 treated) and 171 patients were randomized to Tivo/Nivo (168 treated); median (m) follow up was 28.4 mo (95% CI 27.0-29.8) in Tivo versus 27.2 months (mo) (95% CI 26.1-28.5) in Tivo/Nivo. Survival outcomes and hazard ratios (HR) for the ITT population, 2L, and 3L populations are summarized in Table 1. In 2L, mPFS favored Tivo over Tivo/Nivo (9.23 mo [7.29, 11.04] vs 5.95 mo [5.42, 7.95]). Across subgroups, there were no differences in mOS. No new safety signals were observed with prolonged administration; the most common ≥ Grade 3 TEAE was hypertension occurring in 39 (22.8%) and 38 (22.6%) and of patients in the Tivo and Tivo/Nivo groups respectively. Other ≥ Grade 3 TEAEs included diarrhea (2.3% and 3.6%) and palmar-plantar erythrodysaesthesia (0.6% and 1.2%) in the Tivo and Tivo/Nivo groups respectively. Treatment Related SAEs occurred in 15 (8.8%) and 18 (10.7%) of patients in Tivo and Tivo/Nivo groups respectively. **Conclusions:** This final analysis of patients in the TiNivo-2 study highlights the sustained efficacy Tivo in mRCC with a consistent safety profile. Together, these findings support durable clinical benefit and tolerability of Tivo in the post-ICI treatment setting in RCC, an area of high unmet need (NCT04987203). Clinical trial information: NCT04987203. Research Sponsor: AVEO Pharmaceuticals, Inc.

	By ITT		2L setting		3L setting	
Parameter	Tivo (0.89mg) /Nivo (n=171)	Tivo (1.34mg) (n=172)	Tivo (0.89mg) /Nivo (n=111)	Tivo (1.34mg)(n=105)	Tivo (0.89mg) /Nivo (n=60)	Tivo (1.34mg)(n=67)
mPFS, months (95% CI)	5.72 (4.37-7.43)	7.43 (5.52-9.23)	5.95 (5.42, 7.95)	9.23 (7.29, 11.04)	5.45 (3.15, 9.56)	5.44 (2.10, 7.36)
mPFS HR	0.96 (0.76, 1.21)		1.08 (0.80, 1.46)		0.77 (0.52, 1.15)	
mOS, months (95% CI)	23.85 (19.71-NR)	22.93 (18.14-NR)	29.50(21.06, NR)	23.52 (18.33, NR)	19.71 (10.81, 31.90)	22.70 (11.79, NR)
mOS HR	0.95 (0.70, 1.28)		0.78 (0.53, 1.16)		1.13 (0.70, 1.81)	

NR, not reached.

4556 **Poster Session**

Explainable AI to predict molecular classes of renal cell carcinoma from digital pathology images. First Author: Jordan Krull, Department of Biomedical Informatics, College of Medicine, The Ohio State University, Columbus, OH

Background: There is an unmet need to develop rapidly deployable and reliable biomarkers to guide treatment decisions in clear cell renal cell carcinoma (ccRCC). Transcriptome-based molecular classification is promising in predicting differential clinical outcomes to angiogenesis blockade alone or with an immune checkpoint inhibitor (ICI), but these approaches require molecular profiling that is costly and time-consuming. This study evaluates whether explainable artificial intelligence (AI) can accurately predict molecular classes of ccRCC from diagnostic H&E slides. This approach enables scalable, pathology-based assessment of treatment response−related biology without the need for additional tissue or sequencing. **Methods:** We acquired digital whole slide images of H&E stained primary ccRCC tumors from TCGA, OSU Total Cancer Care Alliance, and an in-house built set of selected biopsies. RNA-Seq cluster assignments from IMmotion151 study were reconstructed from published gene log-fold-change cluster enrichment scores and non-negative least squares regression on matching RNA-Seq of our samples. After assigning samples to their highest scoring group, we trained a multi-group attention-based multiple-instance learning (ABMIL) classifier to predict RNA-Seq groups from digital whole slide images broken into 112um patches and encoded using UNI foundation model embeddings. **Results:** A total of 555 cases with both H&E and RNA-seq data were included. Class prediction from RNA-Seq were 40% Angio-Stromal, 30% Complement-Ox, 16% Angio, 8% Teff-Prolif, 4% Prolif, 2% Stromal-Prolif and 0% snoRNA. Predicting these classes from H&E-stained images, showed AUROC values of 0.76 (Angio-Stromal), 0.78 (Complement-Ox), 0.83 (Angio), 0.85 (Teff-Prolif), 1.00 (Prolif) and 0.91 (Stromal-Prolif) respectively. Similar AUROC values with more modest curves were seen on a hold-out set (10%) where Angio-Stromal/Complement-Ox (0.61/0.61) and Teff-Prolif (0.59) were the lowest AUROC values and Prolif (0.99) was the highest. Importantly, incorrect predictions most often yielded a group prediction where the predicted group shared some biological identity with the ground truth group label (eg. Angio-Stromal and Angio). We also utilized the attention values from ABMIL to evaluate spatial prediction saliency, which showed the model focused primarily on tumor regions, even for predictions of primarily stromal defined classes. **Conclusions:** Our results demonstrate that diagnostic H&E slides contain histologic features that can predict ccRCC molecular subsets using explainable AI. Supporting scalable pathology-based inference of tumor biology linked to treatment response. Research Sponsor: None.

4557 **Poster Session**

Spatial multiomic profiling to identify de-differentiated tumor phenotypes and exhausted T cell niches in rhabdoid and sarcomatoid RCC. First Author: Zachary Alan Yochum, Center of Molecular and Cellular Oncology, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: Rhabdoid and sarcomatoid (S/R) differentiation are high-grade dedifferentiated states that can arise across renal cell carcinoma (RCC) subtypes. Although associated with poor patient prognosis, S/R RCC paradoxically exhibits increased sensitivity to immune checkpoint blockade. The mechanisms underlying this aggressive, yet immunotherapy-responsive phenotype remain unclear. Spatial multi-omic profiling offers a powerful framework to interrogate tumor-intrinsic and microenvironmental programs that account for this phenotype. Here, we applied spatial multi-omic analyses to treatment-naïve clear cell RCC specimens from seven patients, enabling direct comparison of sarcomatoid, rhabdoid, and clear cell regions captured within the same tissue sections. **Methods:** Hematoxylin and eosin (H&E)−stained sections from seven FFPE patient samples were reviewed and annotated by a genitourinary pathologist to identify discrete regions of sarcomatoid, rhabdoid, or clear cell morphology. Annotated FFPE samples were processed by Singular Genomics using the G4X spatial multi-omic platform, which enables quantification of 315 RNA transcripts, 14 protein targets, and fluorescent H&E imaging. **Results:** Initial spatial multi-omic profiling resolved distinct tumor regions with clear cell biology alongside areas exhibiting rhabdoid or sarcomatoid features. Comparative analysis of immune infiltrates across these regions revealed enrichment of both T cells and B cells within rhabdoid regions. In addition, T cells localized to rhabdoid and sarcomatoid regions displayed distinct phenotypic states compared with those in clear cell regions. Differential gene expression (DGE) analysis of T cells from rhabdoid and sarcomatoid regions relative to clear cell RCC demonstrated upregulation of activation markers (*CD69*, *IL2RA*), exhaustion markers (*LAG3*, *PDCD1*), and cytotoxic genes (*GZMA*, *GZMK*, *NKG7*). Parallel analysis of tumor cell transcriptional programs further highlighted distinct tumor biology across histologic regions. Sarcomatoid tumor cells exhibited increased expression of genes associated with cellular stress, inflammation, and epithelial−mesenchymal transition (EMT), including *IGFBP7* and *FOS*. In contrast, rhabdoid tumor cells showed upregulation of antigen-presentation machinery (*HLA-A*, *TAP1/2*) along with elevated expression of EMT-associated genes (*MET*, *VCAM1*, and *CD44)*. **Conclusions:** Spatial multi-omic analysis of S/R RCC revealed distinct immune and transcriptional programs across sarcomatoid, rhabdoid and clear cell regions. T cells within S/R regions exhibited activated and exhausted phenotypes, while tumor cell characterization of S/R cells reveals upregulation of stress, inflammatory and antigen-presentation machinery, features that may underlie the sensitivity of S/R RCC to immune checkpoint inhibitors. Research Sponsor: None.

ABSTRACT WITHDRAWN

4559 **Poster Session**

Association of baseline quality of life (QOL) and early death in patients with metastatic renal cell carcinoma (mRCC) in the real-world prospective observational ODYSSEY study. First Author: Michael R. Harrison, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC

Background: Baseline QOL has been linked to survival in mRCC therapy clinical trials (Cella, 2024); however, there is a paucity of prospectively collected real-world QOL data across frontline management strategies. We used data from ODYSSEY to examine the relationship between baseline QOL and early death. **Methods:** ODYSSEY is a multi-site, prospective observational study of 468 US pts with mRCC. Pts must have mRCC (any histology); have no prior systemic therapy (ST) or be within 3 months of starting ST; and follow up at a PCORnet study site. Exclusion criteria include treatment for cancer except mRCC. The primary objective is to determine patterns of change in QOL and symptom burden of pts with mRCC. Early death was defined as death within 12 months post-enrollment. All pts with non-missing FKSI-19 or FKSI-DRS at enrollment were included. Cumulative event probabilities as a function of time were stratified by either $<$ or $\geq$ median QoL value and plotted as a step function vs time since enrollment to create cumulative event curves. To determine association between QoL at enrollment and early death, separate Cox proportional hazards models (unadjusted and adjusted) for time-to-first-event as a function of baseline QoL were fit. The adjusted model controlled for the following baseline covariates: IMDC risk (favorable vs intermediate or poor), histology (clear cell vs non). **Results:** As of 1/5/26, 468 pts were enrolled; 425 had non-missing FKSI-19 or FKSI-DRS at enrollment (329 immediate ST, 96 deferred ST [DST]). ST included 129 IO-IO, 108 IO-TKI, 92 Other. DST included 57 Active Surveillance, 22 Local Therapy Planned, 17 Other/Missing. 209 and 190 pts have $<$ median FKSI-19 (score = 59) and FKSI-DRS (score = 29), respectively; 216 and 235 pts have $\geq$ median FKSI-19 and FKSI-DRS, respectively. Those below the median have lower rates of nephrectomy, worse IMDC risk and KPS, shorter time since RCC diagnosis, and higher rates of bone metastasis (all $p<0.05$). Cumulative event probabilities for death at 12 months are 21% and 7% in those $<$ and $\geq$ median baseline FKSI-19, respectively; and 21% and 7% in those $<$ and $\geq$ median baseline FKSI-DRS, respectively. For FKSI-19, the unadjusted hazard ratio (HR) for early death is 0.55 (95% CI: 0.43 – 0.70; $p<0.001$) and adjusted HR is 0.65 (0.49 – 0.85; p = 0.002) per 1 SD higher score. For FKSI-DRS, the unadjusted HR for early death is 0.57 (95% CI: 0.46 – 0.71; $p<0.001$) and adjusted HR is 0.66 (0.51 – 0.86; p =0.002) per 1 SD higher score (higher score indicates better QOL). **Conclusions:** Across management strategies in our ODYSSEY cohort of systemic therapy naïve mRCC patients, better baseline QOL was associated with better survival. This is to our knowledge the largest reported real world mRCC cohort with prospectively collected PROs. Future analyses will focus on association of outcomes with longitudinal PROs. Clinical trial information: NCT04919122. Research Sponsor: Bristol Myers Squibb; Exelixis; Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.; Pfizer.

4560 **Poster Session**

Clinical and genomic predictors of outcomes in patients (pts) with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin and pembrolizumab (EVP): UNITE study analysis. First Author: Elise Y. Cai, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

Background: EVP is the recommended 1st line (1L) therapy for pts with aUC and is moving into the perioperative setting. There is limited understanding of clinical factors and biomarkers predictive of EVP outcomes. **Methods:** We analyzed pts with aUC treated with EVP in the multi-site retrospective UNITE study. χ^2 test and logistic regression were used to assess observed response rate (ORR) and disease control rate (DCR). Log-rank test and Cox proportional hazard models were used to assess progression-free survival (PFS) and overall survival (OS) from EVP start. Multivariable analysis (MVA) included age, sex, race, ECOG performance status (PS), neutrophil-to-lymphocyte ratio (NLR), albumin, hemoglobin (Hgb), primary tumor site, histology, treatment line, and metastatic sites as covariates. **Results:** A total of 521 pts with aUC from 16 sites received EVP. Median age was 71, 75% were male, 81% were Caucasian, 76% had ECOG PS 0-1, and 72% were treated with 1L EVP. 74% had lower tract primary tumor, 65% pure urothelial histology, 18% liver metastases (mets), 43% non-liver visceral mets, and 28% lymph node (LN)-only mets. At 8.1 mos median follow-up from EVP start, the overall cohort had ORR 55%, DCR 82% [16% complete response (CR), 39% partial response (PR), 27% stable disease (SD)], median PFS (mPFS) 6.5 mos, and median OS (mOS) 19.8 mos. For 1L EVP pts, at 9.8 mos median follow-up, ORR was 59%, DCR 83% (20% CR, 39% PR, 24% SD), mPFS 10.1 mos, and mOS 23.3 mos. In both the overall cohort and 1L EVP pts, clinical factors associated with longer PFS and OS included ECOG PS 0-1, Caucasian race, albumin $\geq$ 3.5 g/dL, Hgb $\geq$ 10g/dL, NLR $<$ 5, and absence of visceral mets. CR was associated with ECOG PS 0-1 (OR 3.6, 95% CI 1.4-12.5, p = 0.02), Hgb $\geq$ 10g/dL (OR 2.3, 95% CI 1.2-4.8, p = 0.02), NLR $<$ 5 (OR 2.7, 95% CI 1.5-5.3, p = 0.002), LN-only mets (HR 3.8, 95% CI 1.7-9.8, p = 0.003), immunotherapy-naive status (OR 4.1, 95% CI 1.4-17, p = 0.02), and 1L EVP for aUC (OR 3.3, 95% CI 1.7-7.3, p = 0.001). Pts with CR had longer mPFS than pts with PR or SD (26.5 vs. 14.5 vs. 7.5 mos, $p < 0.001$) and longer mOS (NR vs. 33.4 vs. 14.5 mos, $p < 0.001$). Among 315 pts with molecular profiling, the most common alterations were in *TERTp* (55%), *TP53* (45%), *FGFR3* (22%), *ARID1A* (19%), *KMT2D* (18%), *PIK3CA* (18%), and *CDKN2A/B* (17%). In MVA, *KMT2D* alterations were associated with lower CR rate (6% vs. 19%, p = 0.05), shorter mPFS (5.0 vs. 8.0 mos, p = 0.04), and shorter mOS (12.0 vs. 20.0 mos, p = 0.04). Very high tumor mutational burden ($\geq$ 15 mut/Mb) was associated with higher DCR (97% vs. 79%, p = 0.04) but no significant difference in PFS or OS. **Conclusions:** In this large real-world cohort, ECOG PS, metastatic site, treatment line, and prior immunotherapy exposure were associated with EVP outcomes. *KMT2D*-altered aUC may represent a high-risk molecular subset with worse outcomes. Further validation in prospective cohorts is needed. Research Sponsor: None.

4561 **Poster Session**

Real-world overall survival outcomes of belzutifan treatment in advanced renal cell carcinoma. First Author: Elshad Hasanov, Pelotonia Institute for Immuno-Oncology and Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute, Columbus, OH

Background: Belzutifan, a hypoxia-inducible factor–2α inhibitor, is an emerging therapy for advanced renal cell carcinoma (RCC) that demonstrated significant benefit over everolimus in the LITESPARK-005 trial. We aimed to validate these findings in a real-world setting and identify clinical prognostic factors within a large, multi-institutional cohort. **Methods:** We conducted a retrospective cohort study, using Epic Cosmos, of adults with RCC who initiated Belzutifan on or after the FDA Approval date (December 14, 2023) to Dec 20, 2025, ensuring at least one month of follow-up prior to the query date. Overall survival (OS) was measured from the treatment start date to death, with censoring at the last clinical encounter. Survival was estimated using Kaplan–Meier methods. Associations between baseline clinical and laboratory variables and OS were evaluated using univariable Cox proportional hazards models with false discovery rate (FDR) correction. **Results:** A total of 2,844 patients were included; the median age was 66 years, 72% were male, and 51.2% had documented tobacco use. The OS probabilities were 80.9%, 68.1%, 58.3%, and 53.2% at 6, 12, 18, and 24 months, respectively, and comparable to the LITESPARK-005 trial. Among clinical variables, tobacco use was associated with worse survival (HR 1.24 [95% CI 1.08–1.44], FDR = 0.014), whereas female sex (HR 0.78 [0.66–0.92], FDR = 0.014) and higher BMI (HR 0.96 [0.95–0.98], FDR $<$0.001) were associated with improved outcomes. Markers of nutritional and hematologic reserve were strongly protective, including higher Albumin (HR 0.46 [0.41–0.52], FDR $<$0.001), Total Protein (HR 0.77 [0.70–0.89], FDR $<$0.001), Hemoglobin (HR 0.90 [0.87–0.93], FDR $<$0.001), RBC (HR 0.69 [0.62–0.75], FDR $<$0.001), and MPV (HR 0.90 [0.84–0.96], FDR = 0.002). Inflammatory and immune markers demonstrated divergent effects: higher Lymphocytes (HR 0.53 [0.46–0.61], FDR $<$0.001) and Lymphocyte-to-Monocyte Ratio (HR 0.75 [0.71–0.80], FDR $<$0.001) predicted favorable outcomes. Conversely, worse survival was associated with elevated RDW (HR 1.14 [1.11–1.17], FDR $<$0.001), Monocytes (HR 1.71 [1.34–2.20], FDR $<$0.001), Basophil-to-Lymphocyte Ratio (HR 2.39 [1.20–4.77], FDR = 0.019) and Neutrophils (HR 1.06 [1.04–1.07], FDR $<$0.001),.Higher Corrected Calcium (HR 1.43 [1.30–1.57], FDR $<$0.001) and Total Bilirubin (HR 1.13 [1.04–1.22], FDR = 0.005) were associated with inferior outcomes. **Conclusions:** In the largest real-world cohort to date, overall survival after belzutifan initiation mirrored LITESPARK-005, supporting its effectiveness in routine practice. Baseline nutritional, hematologic, and immune markers were associated with improved survival, while systemic inflammation and metabolic dysfunction predicted worse outcomes, highlighting the prognostic value of routine clinical variables. Research Sponsor: Pelotonia Institute for Immuno-Oncology (PIIO) Recruitment Startup Fund; The Ohio State University Comprehensive Cancer Center (OSUCCC).

4562 **Poster Session**

Real-world clinical outcomes by HER2 expression in locally advanced/metastatic urothelial carcinoma (la/mUC): Results from the global SGNDV-003 retrospective study. First Author: Vadim S. Koshkin, University of California, San Francisco, CA

Background: Approximately 50-80% of patients (pts) with la/mUC have tumors with HER2 protein expression. As HER2-directed therapies enter development, a robust understanding of HER2 prevalence and real-world outcomes with standard-of-care (SOC) therapies across HER2 expression subgroups is needed. SGNDV-003 (NCT05902494) is a global retrospective chart review study in which HER2 status was assessed via central lab testing and outcomes were analyzed by HER2 status in pts with la/mUC. **Methods:** SGNDV-003, conducted 6/2023-7/2025, included pts with la/mUC who received ≥1 prior treatment (tx) (incl. 1 line of platinum-based chemotherapy [chemo]). HER2 status was centrally tested using a UC-specific investigational immunohistochemistry [IHC] and in situ hybridization (ISH) assays. HER2 status was defined as: HER2-positive (IHC3+ or IHC2+/ISH+), HER2-low (IHC2+/ISH- or IHC1+), HER2-expressing (IHC3+, 2+, 1+), and HER2-zero (IHC0). Index line of therapy (LOT) was defined as the first LOT received after platinum-based chemo. Outcomes included real-world objective response rate (rwORR) (per RECIST 1.1 or physician-assessed response) to index LOT, real-world progression-free survival (rwPFS), and overall survival (OS) from start of index LOT. Data was analyzed via descriptive statistics. **Results:** A total of 353 pts with la/mUC and available HER2 status were analyzed (male, 76%; median age, 70 years). 70% of pts were HER2 expressing (19% HER2-positive, 51% HER2-low); 30% were HER2-zero. Disease characteristics were well balanced by HER2 status. Index LOT tx and real-world outcomes are shown in the Table. Immuno-oncology therapies (IO) and enfortumab vedotin (EV) were the most common index LOTs. For IO, rwORRs were 21% for HER2-expressing and 17% for HER2-zero. For EV mono, rwORRs were 36% (HER2-expressing) and 38% (HER2-zero), respectively. **Conclusions:** This global study provides a robust estimate of HER2 distribution in la/mUC based on standardized central lab testing, showing high prevalence of HER2 expression. Real-world outcomes with current SOC therapies were broadly consistent across HER2 subgroups, establishing an important benchmark for the clinical development of HER2-directed therapies in this setting. Research Sponsor: Seagen Inc. Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	HER2-positive (n=67)	HER2-low (n=181)	HER2-expressing (n=248)	HER2-zero (n=105)	Total (n=353)
Real-world Outcomes					
rwORR, n (%)	17 (25.4)	50 (27.6)	67 (27.0)	22 (21.0)	89 (25.2)
[95% CI]	[15.5, 37.5]	[21.3, 34.7]	[21.6, 33.0]	[13.6, 30.0]	[20.8, 30.1]
Median rwPFS	2.8	3.7	3.0	2.6	2.9
(95% CI), mo	(2.0, 4.1)	(2.7, 5.1)	(2.7, 4.5)	(2.1, 3.4)	(2.6, 3.5)
Median OS	12.2	11.5	11.9	7.7	10.8
(95% CI), mo	(9.3, 16.5)	(9.5, 13.5)	(10.3, 13.4)	(5.9, 9.9)	(9.1, 12.3)
Index LOT, n%					
IO	37 (55)	94 (52)	131 (53)	65 (62)	196 (56)
EV mono	17 (25)	51 (28)	68 (27)	21 (20)	89 (25)
Chemo	10 (15)	24 (13)	34 (14)	12 (11)	46 (13)
Other tx	3 (5)	14 (8)	17 (7)	7 (7)	24 (7)

4563 **Poster Session**

Zelenectide pevedotin (BT8009) monotherapy in previously treated metastatic urothelial carcinoma (mUC): Update on Duravelo-1. First Author: Oscar Reig Torras, Hospital Clínic de Barcelona, Barcelona, Spain

Background: Zelenectide pevedotin (zele, formerly BT8009) is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4, a protein that is overexpressed in mUC and other cancers. Zele has a lower molecular weight (4.2 kDa) and a shorter plasma half-life (<1 hour) than antibody drug conjugates (ADCs), with potential to rapidly penetrate solid tumors and minimize healthy tissue exposure. Here, we present updated safety and efficacy results of zele monotherapy in enfortumab vedotin (EV)–naïve patients with mUC from the Phase 1/2 Duravelo-1 study (NCT04561362). **Methods:** Eligible patients had previously treated unresectable mUC, creatinine clearance ≥50 mL/min, prior anti-PD-1/PD-L1 exposure, had progressed on or were ineligible for platinum-based chemotherapy, and had not received EV. All patients treated with the recommended Phase 2 dose of zele monotherapy 5 mg/m^2 once weekly across the dose-escalation and dose expansion phases were included in the analysis. **Results:** As of July 1, 2025, 53 patients with a median age of 63 years (range 25–84) and a median of 2 (range 1–7) prior lines of therapy were included. Median time on treatment was 4.4 months and maximum duration was 24.9 months, and median follow-up time was 9.9 months (range 0.5–43.9). Median progression-free survival was 5.4 months (95% CI 2.3–7.1). Confirmed objective response rate (cORR) in all patients was 32% (n=17/53), and disease control rate (DCR) was 66% (n=35/53), including 2 complete responses and 15 partial responses (PR); 3 additional patients had unconfirmed PR. Of the 13 patients who had received prior taxane therapy, cORR was 31% and DCR was 69%, including 4 PR and 5 with stable disease. Median duration of response was 10.0 months (95% CI 5.3–16.6) among patients with confirmed responses (n=17). Nausea (36%), asthenia (28%), and diarrhea (28%) were the most common treatment-related adverse events (TRAEs). TRAEs of Grade ≥3 occurred in 25% of patients and serious TRAEs occurred in 9%. TRAEs led to treatment withdrawal in 4% of patients. Grade 3 TRAEs of clinical interest (AECIs) were single reports of skin reaction and hyperglycemia (n=1 each, 2%). Grade 1–2 treatment-related AECIs of peripheral neuropathy were reported in 47% of patients and were all sensory-based, with 1 patient requiring treatment withdrawal. Grade 1–2 treatment-related skin reaction and eye disorder AECIs were reported in 15% and 13%, respectively. **Conclusions:** Zele monotherapy at 5 mg/m^2 once weekly continues to demonstrate an encouraging efficacy profile and a promising safety profile with the potential to differentiate from ADCs in EV-naïve patients with mUC. Antitumor activity was preserved in patients with exposure to taxanes. Treatment withdrawal resulting from zele-related AECIs was uncommon. A Phase 2/3 study of zele in patients with locally advanced or mUC (NCT06225596; Duravelo-2) is currently active. Clinical trial information: NCT04561362. Research Sponsor: BicycleTx Ltd.

4564 **Poster Session**

Zelenectide pevedotin (BT8009) plus pembrolizumab in 1L cisplatin-ineligible locally advanced/metastatic urothelial carcinoma: Update on Duravelo-1 B7. First Author: Ignacio Duran, Hospital Universitario Marqués de Valdecilla, IDIVAL, Santander, Spain

Background: Zelenectide pevedotin (zele, formerly BT8009) is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4 and conjugated to MMAE. Zele has a lower molecular weight (4.2 kDa) and a shorter plasma half-life (< 1 hour) than antibody drug conjugates (ADCs), with potential to rapidly penetrate solid tumors and minimize healthy tissue exposure. Preliminary results of zele + pembrolizumab (pembro) in previously untreated, cisplatin-ineligible locally advanced/metastatic urothelial carcinoma (la/mUC) patients (pts) (expansion cohort B7, NCT04561362; Duravelo-1), showed promising antitumor activity and a generally tolerable safety profile (Giannatempo et al., 2025). Here, we present updated results with extended follow-up and further efficacy data. **Methods:** Cisplatin-ineligible pts by Galsky criteria who had received no prior systemic anticancer treatment for la/mUC were eligible. Pts received IV zele 5 mg/m^2 on Days (D)1/8/15 + pembro 200 mg on D1 of a 21-D cycle. The primary endpoint was confirmed objective response rate (cORR) per Investigator using RECIST v1.1. Secondary endpoints included safety and additional efficacy endpoints. Treatment-related adverse events (TRAEs) were determined for all pts who received at least one dose of study drugs. **Results:** As of July 1, 2025, 22 pts were treated: median age 77 years, 45% had ECOG performance status (PS) of 2, and 45% had creatinine clearance < 60 mL/min. Median duration of treatment for zele and pembro was 23.4 weeks (range 1.0–84.1) and 26.9 weeks (range 3.0–85.9), respectively. Median follow-up was 11.8 months (range 1.0–19.4); 14 pts remained on study at the time of data analysis. Median progression-free survival (mPFS) was 13.0 months (95% CI 3.8–NE). cORR was 50% (n = 11/22), and disease control rate was 82% (n = 18/22), including 5 complete responses and 6 partial responses (PR); 2 additional pts had unconfirmed PRs. Median duration of response (mDOR) was not mature. The most common Gr ≥3 TRAEs included ALT increase (18%) and neutropenia and asthenia (14% each). Of AEs of clinical interest (AECIs), treatment-related Gr 3 events included peripheral neuropathy (14%; leading to drug withdrawal in 2 pts) and skin reactions (9%; these events were not serious and did not lead to withdrawal); no Gr 4 or 5 treatment-related AECIs occurred. **Conclusions:** Treatment with zele + pembro has promising clinical benefits in pts with la/mUC and a historically poor prognosis with first-line therapies (~50% ECOG PS of 2), including: mPFS of 13.0 months, 50% cORR, and mDOR not reached. Additionally, zele + pembro demonstrates a safety profile with the potential to differentiate from ADC combinations, including no skin-related serious AEs. These data support the Phase 2/3 study of zele as monotherapy and in combination with pembro versus chemotherapy in pts with la/mUC (NCT06225596; Duravelo-2). Clinical trial information: NCT04561362. Research Sponsor: BicycleTx Ltd.

4565 **Poster Session**

Effect of on-treatment dose adjustments on the efficacy of enfortumab vedotin and pembrolizumab (EVP) in advanced urothelial carcinoma (aUC): A UNITE analysis. First Author: Jeffrey Yinhong Zhong, Division of Solid Tumor Oncology, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH

Background: EVP is the preferred 1st-line regimen for patients (pts) with aUC. EV-related toxicities are often managed with dose adjustments, such as reductions and holds. Analysis of EV monotherapy trials showed consistent survival outcomes despite dose adjustments. We hypothesized that on-treatment EV dose adjustments would not impact survival in these pts. **Methods:** Pts with aUC treated with EVP in the multisite UNITE study were analyzed. Early dose reductions (DR) and holds were defined as occurring < 9 weeks from EVP start, with the remainder classified as late. Pts with DR at treatment start were excluded. Survival endpoints were progression-free survival (PFS) and overall survival (OS) from EVP start, assessed by Kaplan-Meier analysis and Cox models. Multivariable Cox analysis (MVA) included age (≥ 75 vs < 75), ECOG performance status (0-1 vs 2-3), Hgb level (< 10 vs ≥ 10) and liver metastases (present vs not). A time-dependent covariate was used to reduce immortal time bias. Complementary MVA landmark analyses were performed, aligned to the total number of treatment cycles received, with six analyses from cycles 2 to 7. **Results:** 360 pts from 17 sites were included (median age 70; 78% Caucasian; 76% male; 27% upper tract primary; 35% histology subtype component; 17% with liver metastasis; 78% frontline); median follow-up was 11.7 months (95% CI [10.79, 13.08]). Median number of cycles was 6 in pts with DR and 3 with no DR. Early DRs (100 pts [28%]) and holds (18 pts [5%]) were most commonly due to rash (28% of all early DRs and holds). Late DR (75 pts [21%]) and holds (50 pts [14%]) were most commonly due to neuropathy (52% of all late DRs and holds). Pts with early or late DR had longer PFS and OS vs those who did not (Table); however, there was no significant PFS or OS difference with dose hold vs no hold (PFS HR 0.65, 95%CI (0.40, 1.05), p = 0.08; OS HR 0.70, 95%CI (0.39, 1.27), p=0.24). In landmark analyses, about 50% of pts had DR; no significant difference in PFS or OS was observed at most landmarks, except for longer OS in the DR cohort at cycle 4 (HR 0.53, 95% CI (0.29, 0.98), p = 0.042) and cycle 5 (HR 0.43, 95% CI (0.19, 0.99), p = 0.048). **Conclusions:** In this real-world retrospective analysis, EVP efficacy was maintained despite DR and dose holds. Survival difference noted in the time-dependent analyses were not consistently reproduced in landmark analyses, suggesting exposure-related selection bias rather than causal effect. Prospective studies are warranted to validate these hypothesis-generating findings. Research Sponsor: None.

Association of EV DR with PFS/OS (time-dependent analyses).

	Early DR		Late DR	
DR vs no DR outcomes	**UVA HR (95% CI), *p***	**MVA HR (95% CI), *p***	**UVA HR (95% CI), *p***	**MVA HR (95% CI), *p***
PFS	0.50 (0.35, 0.72), <.001	0.56 (0.38, 0.84), 0.005	0.32 (0.21, 0.49), <.001	0.36 (0.23, 0.57), <.001
OS	0.51 (0.32, 0.79), 0.003	0.57 (0.35, 0.92), 0.022	0.26 (0.15, 0.45), <.001	0.31 (0.17, 0.55), <.001

4566 **Poster Session**

Interim analysis results from Duravelo-2: Zelenectide pevedotin (zele; BT8009) in patients (pts) with previously treated locally advanced/metastatic urothelial carcinoma (la/mUC). First Author: Daniel P. Petrylak, Yale School of Medicine, New Haven, CT

Background: Zele is a highly selective Bicycle Drug Conjugate (BDC) targeting Nectin-4, a protein overexpressed in la/mUC. There remains an unmet need in la/mUC for safer and more tolerable treatments. Here, we report an interim analysis (IA) for zele monotherapy dosage selection from the Phase 2/3 Duravelo-2 study (NCT06225596/BT8009-230) in previously treated pts with la/mUC. **Methods:** Adults with la/mUC were enrolled into 2 cohorts: previously untreated pts eligible for platinum-based chemotherapy (Cohort [Co]1) or pts with ≥1 prior systemic therapy (Co2). IA was conducted to determine the optimized dosage of zele + pembrolizomab (Co1) or zele monotherapy (Co2). Herein, we report IA results from Co2. Pts in Co2 were randomized 1:1 to zele 5 mg/m^2 on Days [D]1/8/15 or zele 6 mg/m^2 on D1/8 on a 21-D cycle. Dosage optimization included safety, efficacy, and pharmacokinetic data in pharmacometrics and utility score analyses to quantify benefit-risk. **Results:** IA was performed at 27 weeks of follow-up (N=30 each zele dose group). Median zele treatment (tx) duration was 4.80 months. Confirmed ORRs by BICR among randomized, dosed pts with measurable disease at baseline were 28% (8/29; 2 complete responses [CR], 6 partial responses [PR]; 95% CI 12.7–47.2) and 30% (8/27; 3 CR, 5 PR; 95% CI 13.8–50.2) with zele 5 mg/m^2 and 6 mg/m^2, respectively. Zele-related adverse events (AEs) were reported in 93% (47% Gr ≥3) of pts at 5 mg/m^2 and 93% (52% Gr ≥3) at 6 mg/m^2. Gr ≥3 zele-related AEs for 6 mg/m^2 (≥5% pts) included neutrophil count decreased and neutropenia (10% each) and anemia, asthenia, and ALT increase (7% each). No zele-related Gr 5 AEs were reported at either dosage. Zele-related AEs of clinical interest (AECIs) for 6 mg/m^2 are summarized in the Table. Notably, no zele-related severe skin reactions of any Gr were reported at either dosage. Zele dose reductions and discontinuations due to zele-related AEs occurred in 24% and 0%, respectively, for 6 mg/m^2. At Week 27, a third of pts remained on tx. **Conclusions:** Zele monotherapy at 5 mg/m^2 on D1/8/15 and 6 mg/m^2 on D1/8 on a 21-D cycle demonstrate encouraging response rates and safety profiles with the potential to differentiate from ADCs in previously treated pts. The 6 mg/m^2 D1/8 regimen provides a more favorable benefit-risk profile to meet the need for safer and more tolerable treatments, with enhanced potential for combinability and convenience, leading to fewer discontinuations. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

Zele-related AECIs in pts with previously treated la/mUC treated with zele 6 mg/m^2 on D1/8 (N=30).

AECI, n (%)	Any Grade	Grade ≥3
Peripheral neuropathy	11 (38)	1 (3)
Skin reactions	8 (28)	0
Eye disorders	3 (10)	0
Hyperglycemia	1 (3)	1 (3)

4567 **Poster Session**

Identifying optimized dosage for zelenectide pevedotin in locally advanced/metastatic urothelial carcinoma (la/mUC) using quantitative analyses. First Author: Yasong Lu, Bicycle Therapeutics, Cambridge, MA

Background: Zelenectide pevedotin (zele; BT8009) is a Bicycle Drug Conjugate (BDC) comprising a highly selective bicyclic peptide targeting Nectin-4 linked to the cytotoxin monomethyl auristatin E (MMAE) via a cleavable linker. Zele demonstrated preliminary antitumor activity and a generally tolerable safety profile in patients (pts) with la/mUC in the Phase 1/2 Duravelo-1 trial (NCT04561362) [Reig, 2024; Giannatempo, 2025]. Zele is being evaluated in a randomized Phase 2/3 study at 2 dosages, 5 mg/m^2 on Days (D)1/8/15 and 6 mg/m^2 on D1/8 of a 21-D cycle, each as monotherapy or combined with pembrolizumab (P) in pts with la/mUC (NCT06225596, Duravelo-2) [Loriot, 2025]. After 30 pts in each dosage arm had 27 weeks follow-up (N=120 total), an interim analysis was conducted to select the optimized dosage for further development. **Methods:** Pharmacometric (PMx) and utility score analyses were conducted to quantify the benefit-risk comprehensively. For the PMx analysis, all pharmacokinetic (PK), overall response rate [ORR, assessed by investigator (INV) and/or blinded independent central reviewer (BICR)], and adverse event (AE) data [zele-related and treatment-emergent (TE) Gr ≥3 AE, Gr ≥3 neutropenia, Gr ≥2 gastrointestinal disorders, Gr ≥2 peripheral neuropathy, any Gr skin reactions, dose modifications] from Duravelo-1 and -2 were pooled and analyzed using population PK (PopPK) and exposure-response (ORR, AE) modeling. Simulations for ORR and AE probabilities were then generated for comparing dosages with balance of relevant pt characteristics. The utility score analysis was mainly based on Gr ≥3 zele-related TEAEs and ORR by BICR regardless of confirmation in Duravelo-2, with sensitivity analyses based on alternative safety and/or efficacy endpoints (TEAEs, confirmed ORR by BICR). **Results:** The datasets for PopPK, ORR, and AE analysis included 434, 203 (203 INV assessed, 114 BICR assessed), and 394 pts, respectively, mostly treated at the 5 or 6 mg/m^2 dosages. Modeling of ORR did not detect a significant difference between the dosages studied. ORR was impacted positively by P combination, negatively by baseline tumor size, but not by the assessor (INV vs BICR). The AE rates were significantly correlated with exposures of zele and/or MMAE. Between 5 mg/m^2 D1/8/15 and 6 mg/m^2 D1/8, ORR did not differentiate them; safety favored 6 mg/m^2 D1/8 as its predicted AE probabilities were mostly lower. For AEs favoring 6 mg/m^2 D1/8, predicted probabilities were lower by 0.1% – 15.5% as monotherapy and by 0.1% – 19.1% in combination. The utility score analysis favored 6 mg/m^2 D1/8 consistently for zele combined with P and remained neutral between the dosages for monotherapy. **Conclusions:** 6 mg/m^2 D1/8 was identified as the optimized zele dosage for monotherapy and in combination with P based on the overall benefit-risk informed by the comprehensive quantitative analyses. Clinical trial information: NCT06225596. Research Sponsor: BicycleTx Ltd.

4568 **Poster Session**

Avelumab + sacituzumab govitecan (Ave + SG) vs avelumab monotherapy (Ave mono) as first-line (1L) maintenance treatment for advanced urothelial carcinoma (aUC): Updated subgroup analyses of JAVELIN Bladder Medley based on metastatic sites. First Author: Petros Grivas, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: Ave 1L maintenance is a recommended treatment option for patients (pts) with aUC without progression after 1L platinum-based chemotherapy (PBC). In the JAVELIN Bladder Medley phase 2 trial (NCT05327530), 1L maintenance with Ave + SG (Trop-2–directed antibody-drug conjugate) improved progression-free survival (PFS) vs Ave mono (primary endpoint). In pts with aUC, presence of visceral metastases (including liver or lung) is associated with poorer prognosis. We report updated subgroup analyses from the primary analysis of JAVELIN Bladder Medley based on metastatic site. **Methods:** Pts with unresectable locally advanced or metastatic UC without progression after 4-6 cycles of 1L PBC were randomized 2:1 to receive Ave + SG or Ave mono, stratified by presence of visceral metastases at start of 1L PBC. Primary endpoints were investigator-assessed PFS (measured from randomization) and safety; overall survival (OS) was a secondary endpoint. For visceral and nonvisceral subgroups, PFS and OS data in the Ave mono arm were extended per protocol using propensity score–weighted data from the JAVELIN Bladder 100 phase 3 trial; extended data were not available for other subgroups. **Results:** At the start of 1L PBC, of 74 and 37 pts in the Ave + SG and Ave mono arms, respectively, 37 (50.0%) and 19 (51.4%) had visceral metastases, 20 (27.0%) and 11 (29.7%) had lung metastases, 17 (23.0%) and 7 (18.9%) had liver metastases, 17 (23.0%) and 11 (29.7%) had bone metastases, and 26 (35.1%) and 11 (29.7%) had lymph node–only disease. At data cutoff (Apr 28, 2025), in the Ave + SG and Ave mono arms, respectively, median follow-up for PFS was 15.7 and 25.1 mo. Across all subgroups, PFS was prolonged with Ave + SG vs Ave mono (Table); OS analyses were immature. In the Ave + SG and Ave mono arms, respectively, grade ≥3 treatment-related adverse events occurred in 72.2% and 5.6% of pts with visceral metastases, 57.9% and 0% of pts with lung metastases, 82.4% and 0% of pts with liver metastases, 82.4% and 0% of pts with bone metastases, 70.3% and 5.6% of pts with nonvisceral metastases, and 76.9% and 9.1% of pts with lymph node–only metastases. **Conclusions:** In the primary analysis of JAVELIN Bladder Medley, Ave + SG as 1L maintenance improved PFS vs Ave mono, irrespective of metastatic site. Clinical trial information: NCT05327530. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	PFS, median (95% CI), mo		
	Ave + SG	Ave mono	HR (95% CI)
Site of metastases at start of 1L PBC			
Visceral*	9.03 (5.62-13.80)	2.20 (1.91-3.71)	0.49 (0.28-0.84)
Nonvisceral	14.69 (7.43-NE)	7.33 (4.21-11.10)	0.61 (0.33-1.13)
Lung	8.77 (4.17-9.46)	1.81 (0.07-9.26)	0.43 (0.17-1.09)
Liver	8.77 (5.55-9.36)	2.69 (1.91-NE)	0.48 (0.17-1.32)
Bone	9.26 (5.49-17.64)	2.33 (0.07-5.45)	0.40 (0.16-0.99)
Lymph node only	14.00 (7.43-NE)	7.59 (1.87-NE)	0.65 (0.26-1.66)

*Pts could have ≥1 site of visceral metastases.HR, hazard ratio; NE, not estimable.

4569 **Poster Session**

Longitudinal tumor-informed ctDNA monitoring and clinical outcomes in advanced urothelial carcinoma treated with enfortumab vedotin ± pembrolizumab. First Author: Adanma Ayanambakkam, Stephenson Cancer Center, University of Oklahoma Health Sciences, Oklahoma City, OK

Background: Enfortumab vedotin plus pembrolizumab (EV±P) is standard-of-care for patients (pts) with locally advanced/metastatic urothelial carcinoma (la/mUC), although not all pts experience durable benefit. Tumor-informed circulating tumor DNA (ctDNA) assays enable a personalized, real-time assessment of disease kinetics, and early ctDNA dynamics (<12 weeks) have been linked to EV±P radiographic response and survival outcomes. However, the prognostic relevance of ctDNA dynamics relative to durable clinical benefit is not well defined. **Methods:** We conducted a multicenter, retrospective real-world analysis of pts with la/mUC who received ≥1 cycle of EV±P and ≥1 commercial plasma ctDNA test using a clinically validated, personalized, tumor-informed assay (Signatera, Natera, Inc.). Associations between ctDNA features and progression-free survival (PFS) and overall survival (OS) were evaluated using Cox proportional hazards models. **Results:** A total of 110 pts with 545 plasma samples were analyzed. All pts had ≥1 ctDNA test (median: 4 tests/pt) immediately prior to and/or after EV±P initiation, with median time between serial ctDNA collections of 7.3 (IQR: 5.4-12.0) weeks. In this cohort, 69% (76/110) of pts had ≥1 ctDNA test (355 total) beyond 12 weeks post-EV±P initiation. Among these 76 pts, 31.5% (24/76) were persistently ctDNA negative (≥2 consecutively negative samples with no positives), while 65.8% (50/76) were anytime ctDNA-positive. Time-varying covariate analysis incorporating all serial results after 12-weeks reaffirmed that ctDNA-positivity was associated with worse PFS and OS (PFS: HR: 36.8, p<0.005; OS: HR: 17.7, p=0.01). Serial ctDNA negativity within 4-24 weeks (i.e. ≥2 consecutively negative samples with no positives) was strongly associated with durable OS/PFS beyond 24 weeks (PFS: HR=0.05, 95% CI: 0.01-0.42, p=0.005; OS: HR=0.046, 95% CI: 0.0004-0.33 [Firth], p=0.0002). Furthermore, single-timepoint ctDNA positivity evaluated at 12–24 weeks (HR: 11.8; 95% CI: 2.72–51.60; p=0.001) and >24 weeks (HR: 6.8; 95% CI: 2.5–18.6; p=0.0002) was strongly associated with inferior PFS. Findings were similar for OS (12-24wk: HR: 7.2, 95% CI: 1.7-31.3; p=0.008; >24wk: HR=3.8, CI: 1.2-12.3; p=0.03). **Conclusions:** Longitudinal ctDNA dynamics are strongly prognostic in pts with la/mUC treated with EV±P, even when assessed beyond 12 weeks from treatment start. Sustained ctDNA negativity further identifies pts with durable clinical benefit. These findings support ctDNA as a potentially complementary biomarker to standard imaging in this clinical context. Research Sponsor: None.

4570 Poster Session

Untreated advanced urothelial carcinoma (aUC) in the modern treatment era: Patterns of care from a decade-long national cohort. First Author: Melanie Mayer, Department of Biostatistics, Epidemiology, & Informatics, University of Pennsylvania, Philadelphia, PA

Background: Over the past decade, the therapeutic landscape for locally advanced/unresectable and de novo metastatic urothelial cancer (aUC) has transformed with the introduction of immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs). These agents offer a more favorable benefit-risk and superior efficacy vs historical chemotherapy. We hypothesized that the proportion of untreated patients with aUC has declined over time, reflecting increased uptake of novel therapeutics. **Methods:** We analyzed the U.S. Flatiron Health EHR-derived de-identified database. We included patients diagnosed with aUC between Jan 1, 2011 and April 30, 2025. Patients were classified as treated if they received first-line (1L) systemic therapy within 6 months of advanced diagnosis. Calendar time was divided into three clinically relevant eras: pre-ICI approval (2011-2016), post-ICI but pre-ADC approval (2017-2019), and post-ADC approval (2020-2025). Outcomes included proportion untreated and time to treatment initiation (TTI) from advanced diagnosis. We estimated the cumulative incidence of treatment initiation using competing-risk methods, treating death before initiating as a competing event. Subgroup analyses evaluated patients with de novo stage IV disease at initial diagnosis. **Results:** We identified 12,849 patients with aUC (median age 73, 72.9% male, 78.7% white, 57.5% cis-ineligible, 78.3% bladder primary site). The proportion remaining untreated 6 months post advanced diagnosis declined across therapeutic eras: 36.8% untreated in the pre-ICI era, 27.4% in the post-ICI, pre-ADC era, and 22.7% untreated in the post-ADC era. Year-specific analysis showed steady improvement in treatment uptake: treatment within 6 months rose from 56% in 2011 to 79% in 2024 (Table). In the TTI analysis, overall, 25.1% had not initiated 1L therapy before death or data cutoff. Median TTI shortened across eras (63 days, 49 days, 45 days) and competing-risk cumulative incidence initiating therapy increased over time. For example, the probability of initiating 1L therapy within 90 days of aUC diagnosis across eras was 55.9% (pre-ICI), 66.1% (post-ICI, pre-ADC) and 70.7% (post ADC). **Conclusions:** In a large national cohort, untreated rates among patients with aUC declined markedly from 2011-2025 paralleling the introduction of ICIs and ADCs. Novel, better-tolerated therapies appear to have expanded real-world treatment eligibility and reduced early attrition. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Temporal trends in treatment rates.

Year	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
3 months	0.48	0.53	0.54	0.57	0.58	0.61	0.68	0.65	0.67	0.69	0.69	0.72	0.7	0.74
6 months	0.56	0.6	0.61	0.63	0.65	0.69	0.73	0.7	0.74	0.76	0.76	0.78	0.78	0.79
1 year	0.58	0.63	0.64	0.66	0.67	0.71	0.75	0.72	0.77	0.77	0.77	0.79	0.8	0.81

4571 Poster Session

Characterizing the immune effects of enfortumab vedotin and pembrolizumab (EV+P) on peripheral blood mononuclear cells (PBMCs) in metastatic urothelial cancer patients (mUC). First Author: Aditi Gupta, Memorial Sloan Kettering, New York, NY

Background: Enfortumab vedotin improves response and outcomes over chemotherapy in mUC, with further benefit when combined with pembrolizumab. Although EV alone has limited immune-activating effects, we hypothesize that the combination of EV+P modulates peripheral T-cell activation states and correlates with clinical response. **Methods:** We conducted a retrospective analysis of mUC patients treated with EV+P at Memorial Sloan Kettering Cancer Center. PBMCs were isolated from patients on C1D1 and C2D1 of EV+P (n=33) and analyzed with a 32-color spectral flow cytometry panel. Immune subsets were compared between responders (complete [CR] or partial response [PR]) and non-responders (stable [SD] or progressive disease [PD]) using Wilcoxon rank sum test. Response was determined by a radiologist's assessment of the best-overall response on EV+P according to RECIST v1.1. **Results:** Among 33 patients, median age was 71 years and 48% were male. 12.1% (4/33) received prior platinum chemotherapy and 18.1% (6/33) received prior PD-1/PD-L1 immunotherapy. The objective response rate was 67% (CR=10; PR=12); eight patients had SD and three had PD. At C1D1, CD8+ T cell frequencies did not differ by response. At C2D1 however, circulating CD8+ T cells were significantly higher in non-responders ($p < 0.05$). From baseline to C2D1, CD8+ T cells showed increased expression of CTLA4+ ($p < 0.0001$), Ki67+ ($p < 0.01$) and HLA-DR+ ($p < 0.01$), with higher expression of each marker at C2D1 significantly correlated with response (all $p < 0.05$, Table 1). At C2D1, CD4+ effector T cells showed increased expression of Ki67+ and HLA-DR+ (both $p < 0.05$), both significantly higher in responders (both $p < 0.05$). CD4+ regulatory T cells showed increased CTLA4+ ($p < 0.001$), Ki67+ ($p < 0.01$) and HLA-DR+ ($p < 0.01$) expression from C1D1 to C2D1, with significantly higher expression in responders (CTLA4+ $p < 0.05$, Ki67+ $p < 0.0001$, HLA-DR+ $p < 0.001$). Across all T cell subtypes, PD1+ expression significantly decreased ($p < 0.05$) from C1D1 to C2D1, but this decrease did not correlate with response. The frequencies of circulating memory CD8+ and CD4+ T cells did not change on treatment or correlate with response at either timepoint. **Conclusions:** EV+P induces early peripheral T cell activation in mUC, with increased expression of activation and proliferative markers in responders at C2D1. Ongoing studies are investigating correlation between TCR specificity, immune activation and responses to EV+P. Research Sponsor: Bladder Cancer Advocacy Network.

Peripheral CD8+ T cell frequencies (median) at C1D1 and C2D1 from mUC patients on EV+P.

CD8+ T Cell	C1D1	C2D1	p-value	C2D1 in Responders	C2D1 in Non-Responders	p-value
CD8+ (%CD45+)	8.54	7.8	0.6	7.27	13.8	**0.03**
CTLA4+ (%CD8+)	1.15	3.94	**0.0001**	4.57	2.85	**0.02**
Ki67+ (%CD8+)	3.18	6.27	**0.005**	7.26	5.4	**0.04**
HLA-DR+ (% CD8+)	4.66	9.37	**0.004**	10.22	4.13	**0.04**
PD-1+ (%CD8+)	45.6	29.8	**0.0005**	28.7	31.5	0.48

4572 Poster Session

Genomic determinants of metastatic burden and survival in metastatic urothelial carcinoma. First Author: Milit S. Patel, The University of Texas at Austin, Austin, TX

Background: Metastatic urothelial carcinoma (mUC) has variable outcomes. Metastatic site count (MSC) correlates with prognosis; the genomic landscape underlying metastatic burden and survival is poorly characterized. We investigated associations among somatic alterations, metastatic patterns, and survival in a large clinical-genomic cohort. **Methods:** We analyzed 1,157 patients with metastatic bladder cancer by integrating genomic data from the AACR Project GENIE Cohort v18.0-public with clinical annotations and metastatic site information from the MSK-MET database. Associations between 428 genomic alterations and MSC were assessed using Mann-Whitney tests. Survival analyses (n=1,153; 364 events) used Kaplan-Meier estimation, log-rank tests, and Cox regression. Models were adjusted for age, MSC (stratified), and location (lymph, liver, lung). FDR correction was applied, and proportional hazards assumptions verified. **Results:** Median age was 68.7 years; median OS was 15.8 months. MSC stratification revealed survival differences: 0-1 sites (n=515, median OS not reached), 2-4 sites (n=415, median OS 62.8 months), and >=5 sites (n=223, median OS 13.1 months; log-rank $p < 2.5 \times 10^{-19}$). Each increase in MSC category was associated with worse OS (FDR $p < 0.001$). MSC predicted 2-year survival with an AUC of 0.78 (95% CI: 0.75–0.82). Six alterations were significantly associated with lower MSC (FDR < 0.05): *ERCC2* (n=122; d=0.50, FDR p=5.6 x 10^{-6}), *STAG2* (n=128; d=0.40, FDR p=1.9 x 10^{-4}), *FBXW7* (n=96; d=0.36, FDR p=7.1 x 10^{-3}), *FGFR3* (n=291; d=0.17, FDR p=8.1 x 10^{-3}), *TP53BP1* (n=35; d=0.59, FDR p=4.3 x 10^{-2}), and *ARID2* (n=70; d=0.41, FDR p=4.6 x 10^{-2}). *ERCC2* mutation frequency was 15.7% in 0-1 sites and 4.0% in >=5 sites. Conversely, *CDKN2A/B* deletions were enriched in patients with >=5 sites (28.3%/27.9%) compared with 0-1 sites (16.5%/15.9%; FDR $p < 0.01$). Five alterations were independently associated with OS in univariable analysis (FDR < 0.05): *CDKN2B* deletion (HR 1.81, 95% CI: 1.43–2.28, FDR p=1.7 x 10^{-4}), *CDKN2A* deletion (HR 1.79, 95% CI: 1.42–2.26, FDR p=1.7 x 10^{-4}), *ERCC2* mutation (HR 0.39, 95% CI: 0.24–0.62, FDR p=1.1 x 10^{-2}), *CREBBP* mutation (HR 0.53, 95% CI: 0.37–0.75, FDR p=3.1 x 10^{-2}), and *KDM6A* mutation (HR 0.66, 95% CI: 0.52–0.84, FDR p=4.4 x 10^{-2}. In multivariable analysis adjusting for age, MSC, and location, no genomic alterations retained independent significance, suggesting MSC mediates these prognostic effects. Penalized regression confirmed MSC as the dominant prognostic variable (HR 1.39 per site increase). **Conclusions:** DNA damage repair and chromatin modifier mutations are associated with oligometastatic phenotypes and favorable survival, whereas *CDKN2A/B* deletions correlate with polymetastatic disease. The attenuation of genomic effects after MSC adjustment suggests that metastatic burden is a key mediator. These findings support using genomic profiling to guide mUC prognosis. Research Sponsor: Prostate Cancer Foundation; National Cancer Institute; P30 CA008748.

4573 Poster Session

CXCL9:SPP1 ratio: Macrophage polarization and outcomes with pembrolizumab or enfortumab vedotin plus pembrolizumab in metastatic urothelial cancer. First Author: Saad Omar Atiq, Mount Sinai Tisch Cancer Center, New York, NY

Background: Enfortumab vedotin plus pembrolizumab (EV+P) is standard first-line treatment for metastatic urothelial cancer (mUC), yet responses vary considerably. Identifying resistance mechanisms may guide patient selection and inform novel therapeutic strategies. Single-cell RNA sequencing (RNA-Seq) across tumor types has revealed dichotomous tumor-associated macrophage (TAM) populations: SPP1+ TAMs exhibit tumor-promoting programs while CXCL9+ TAMs express programs associated with anti-tumor immunity. The CXCL9:SPP1 gene expression ratio (CS ratio) from bulk RNA-Seq captures this balance and correlates with outcomes across solid tumors (Bill et al, Science, 2023). We explored the CS ratio's association with outcomes in mUC patients receiving pembrolizumab monotherapy or EV+P. **Methods:** We retrospectively analyzed mUC patients who underwent molecular profiling at Caris Life Sciences using NGS (592-gene panel, DNA WES, or RNA WTS). CS ratios were calculated and patients stratified into quartiles (Q1–Q4; Q4=highest ratio). PD-L1 expression was assessed by IHC (22c3, positive (+) CPS $\geq$ 10%) while TMB-High was defined as $\geq$ 10 Mut/Mb. TME composition was inferred using quanTIseq. Real-world overall survival (rwOS) was derived from insurance claims and calculated from biopsy to last contact or time on treatment (TOT) using Kaplan-Meier analysis while Hazard ratio (HR) was calculated by Cox proportional hazard method. Mann-Whitney U and χ^2/Fisher exact tests were applied with adjustment for multiple comparisons. **Results:** Among 6,708 mUC patients, 1,299 received pembrolizumab and 561 received EV+P. Lower CS ratios (SPP1+ TAM predominance) were associated with shorter time on treatment and rwOS (Table 1). Low CS ratio was also associated with reduced PD-L1 expression (15.5% vs 66.7%, $p < 0.001$) and TMB-H prevalence (34.6% vs 52.3%, p = 0.006). Low CS ratio tumors demonstrated reduced immune infiltration except for neutrophil enrichment. **Conclusions:** Lower CS ratios associate with shorter time on treatment and rwOS with both pembrolizumab and EV+P. To our knowledge, this is the first analysis linking macrophage transcriptional states with EV+P resistance. Further validation of the CS ratio in patients treated with EV + P or P is warranted. Research Sponsor: None.

CS ratio and associated outcomes with pembrolizumab monotherapy and EV+P.

	Pembrolizumab Monotherapy		EV + P	
CS Ratio	TOT (months)	OS (months)	TOT (months)	OS (months)
CS-Q1	2.7 (2.1-3.0)	5.7 (4.4-8.2)	7.6 (6.2-8.8)	17.8 (13.8-19.8)
CS-Q2	3.1 (2.2-4.1)	7.2 (5.4-8.8)	6.9 (6.0-8.0)	16.4 (13.2-19.4)
CS-Q3	4.5 (3.9-5.6)	13.5 (10.7-16.8)	9.2 (8.1-10.8)	17.2 (14.4-20.3)
CS-Q4	6.9 (4.9-8.7)	18.7 (13.1-23.7)	10.6 (9.3-12.2)	21.8 (16.5-28.1)
CS-Q4 vs. CS-Q1	HR 0.56, 95% CI 0.47-0.67, p < 0.001	HR 0.53, 95% CI 0.44-0.64, p < 0.001	HR 0.69, 95% CI 0.54-0.87, p = 0.00189	HR 0.62, 95% CI 0.46-0.83, p = 0.00148

4574 **Poster Session**

The role of NECTIN4 in shaping the tumor microenvironment and potentiating the efficacy of immunotherapy in bladder cancer. First Author: Kazuki Nishimura, Harvard Medical School, Brigham and Women's Hospital, Boston, MA

Background: The EV-302 trial established enfortumab vedotin plus pembrolizumab (EV/P) as first-line therapy for metastatic urothelial carcinoma (UC). Although EV/P is administered without NECTIN4 testing based on the assumption of uniform NECTIN4 expression, real-world data have identified NECTIN4-low tumors associated with inferior responses to EV, highlighting the need for NECTIN4-based precision therapy. We aimed to define the molecular and immunologic roles of NECTIN4, identify predictive biomarkers of EV/P outcomes, and explore rational therapeutic strategies for NECTIN4-low UCs. **Methods:** We performed multi-omics analyses of 817 UC cases integrating whole-exome sequencing, RNA-seq, multiplex immunofluorescence, and spatial single-cell profiling (CODEX). We evaluated associations among NECTIN4 status, molecular subtype, tumor microenvironment (TME), survival, and response to immune checkpoint inhibitors. Basal bladder cancer (BC) cell lines and orthotopic MB49 bladder cancer models with NECTIN4 overexpression (OE) or control were used to assess tumor biology and therapeutic response. **Results:** Clustering by NECTIN4 H-score and molecular subtype revealed that basal/squamous (Ba/Sq) muscle-invasive BCs with low NECTIN4 had significantly worse survival outcomes than NECTIN4-high tumors in both our cohort (P=0.001) and the IMvigor210 trial (P=0.019). In vitro, NECTIN4 OE in basal BC cells suppressed proliferation and migration through downregulation of inflammation-related signaling pathways. CIBERSORTx and EcoTyper analysis of RNA-seq data indicated a more immune-inflamed TME in NECTIN4-high Ba/Sq tumors. Spatial single-cell profiling showed increased CD8+ T cells, particularly CD8+/TIGIT+ cells, in NECTIN4-high Ba/Sq UCs. Moreover, in orthotopic mouse models, NECTIN4-OE tumors exhibited reduced growth and increased CD8+ T-cell infiltration. Clinically, NECTIN4-high Ba/Sq tumors showed higher objective response rate (ORR) to pembrolizumab/avelumab than NECTIN4-low tumors (55.5% vs 0%, P=0.002) in our cohort; in IMvigor210, NECTIN4-high Ba/Sq patients also had superior ORR (38.5% vs 15.6%, P=0.025). Additionally, in orthotopic mouse models, EV/P showed limited efficacy in NECTIN4-low tumors, whereas NECTIN4-OE tumors responded well. Transcriptomic analyses identified histone deacetylases (HDAC) as potential targets in NECTIN4-low tumors; accordingly, HDAC inhibitors demonstrated greater efficacy in NECTIN4-low basal BCs in vitro and vivo. **Conclusions:** NECTIN4 influences tumor progression and shapes the TME, thereby impacting immunotherapy efficacy. NECTIN4 is a potential predictive biomarker for survival and for outcomes with immunotherapy and EV/P in Ba/Sq UCs. NECTIN4-low Ba/Sq tumors may require alternative strategies, and HDAC inhibition represents a rational therapeutic approach for NECTIN4-low Ba/Sq UC patients. Research Sponsor: None.

4575 **Poster Session**

Outcomes with first-line (1L) platinum-based chemotherapy (PBC) and avelumab 1L maintenance in locally advanced or metastatic urothelial carcinoma (la/mUC) by *NECTIN4* and *HER2* RNA expression: Exploratory analyses from JAVELIN Bladder 100. First Author: Niklas Klümper, University Hospital Bonn, Bonn, Germany

Background: Nectin-4 and HER2 are relevant therapeutic targets and potential biomarkers for the treatment of la/mUC. *NECTIN4* and *HER2* RNA expression are heterogeneous in UC tumors, with highest expression observed in luminal molecular subtypes. We report exploratory biomarker analyses from the JAVELIN Bladder 100 phase 3 trial evaluating response to 1L PBC and survival outcomes with avelumab administered as 1L maintenance treatment in subgroups defined by tumor *NECTIN4* and *HER2* RNA expression. **Methods:** In JAVELIN Bladder 100 (NCT02603432), patients (pts) with unresectable la/mUC without progression after 4-6 cycles of 1L PBC were randomized 1:1 to receive avelumab + best supportive care (BSC) or BSC alone. Biomarker analyses were performed using existing whole transcriptome profiles generated using RNA sequencing, and transcript levels were quantified using Personalis ACE technology. *NECTIN4* and *HER2* RNA expression were assessed as continuous variables for subgroups defined by response to 1L PBC and as dichotomous variables (median and lower quartile split) for stratified survival analyses. **Results:** In biomarker-assessable pts (n=560) who had complete response (CR; n=149), partial response (n=261), or stable disease (SD; n=150) to 1L PBC, no significant differences in tumor *NECTIN4* RNA expression were observed, whereas slightly higher tumor *HER2* RNA expression was observed in pts who had CR vs SD. Overall, when defined by median split, 201 pts (35.9%) had high *NECTIN4*/high *HER2* RNA expression, 202 (36.1%) had low *NECTIN4*/low *HER2*, 78 (13.9%) had high *NECTIN4*/low *HER2*, and 79 (14.1%) had low *NECTIN4*/high *HER2*. Molecular subtype was non-luminal in 20.4%, 87.1%, 55.1%, and 50.6%, respectively. The table shows overall survival (OS) with avelumab + BSC vs BSC alone in subgroups defined by combined high or low *NECTIN4*/*HER2* expression. OS improvements with avelumab + BSC vs BSC alone were observed across subgroups defined by high or low *NECTIN4*/*HER2* RNA expression alone. **Conclusions:** Exploratory analyses from JAVELIN Bladder 100 showed that pts with low *NECTIN4* and low or high *HER2* RNA expression had pronounced OS with avelumab 1L maintenance vs BSC alone. Results are hypothesis generating. Clinical trial information: NCT02603432. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

	Avelumab + BSC	BSC
High *NECTIN4*/high *HER2*	n=100	n=101
Median OS (95% CI), mo	23.0 (17.8-30.9)	14.3 (10.8-21.3)
HR (95% CI)	0.73 (0.52-1.02)	
Low *NECTIN4*/low *HER2*	n=105	n=97
Median OS (95% CI), mo	29.8 (20.1-46.9)	18.8 (13.9-29.4)
HR (95% CI)	0.78 (0.55-1.11)	
High *NECTIN4*/low *HER2*	n=39	n=39
Median OS (95% CI), mo	18.4 (13.0-NE)	17.4 (14.0-NE)
HR (95% CI)	0.84 (0.47-1.50)	
Low *NECTIN4*/high *HER2*	n=40	n=39
Median OS (95% CI), mo	31.1 (20.6-NE)	15.8 (9.3-41.9)
HR (95% CI)	0.66 (0.38-1.15)	

Stratified subgroups defined by median split are shown. HR, hazard ratio; mo, months; NE, not estimable.

4576 **Poster Session**

Treatment-free survival (TFS) in patients with advanced urothelial carcinoma (aUC) treated with enfortumab vedotin (EV)–based therapy. First Author: Salvador Jaime-Casas, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: EV as monotherapy or with pembrolizumab (EVP) has shown robust efficacy in patients with aUC. Despite lack of data, treatment breaks (TB) with EV are frequently utilized due to toxicity or patient/physician preference. In this retrospective real-world analysis, we evaluated TFS after temporary or permanent EV discontinuation in patients with aUC. **Methods:** A multicenter cohort of patients with aUC treated with EV/EVP between 01/2015 through 12/2025 were included. Patients were categorized in groups with or without TB (defined as ≥6 weeks between EV doses without progression). Baseline characteristics were summarized using descriptive statistics, and comparison was performed using the chi-square test/Fisher's exact and t-test, as appropriate. TFS was estimated using the Kaplan–Meier method among TB+ patients. Overall survival (OS) and progression-free survival (PFS) were estimated for both cohorts using the Kaplan-Meier method and compared using the log-rank test. Univariable and multivariable models adjusted for baseline variables evaluated factors associated with TFS, OS and PFS. **Results:** From a total of 172 patients eligible for inclusion, 25 (14%) received TB and 148 (86%) did not. Median age was 72.5 years. Most patients were White (76.3%), had primary bladder cancer (89%), and received EVP (63%). Overall, 30% had ≥1 prior line of therapy. Baseline characteristics did not differ significantly between patients with and without TB. Most common reason for TB was treatment toxicity (52%) and a minority (20%) continued pembrolizumab during their break. The median TFS was 3.6 months (95% CI 3.0, 8.3), with 28% experiencing a TFS ≥24 weeks. TB did not compromise outcomes, and patients with a TB demonstrated longer median PFS (13.5 vs. 7.7 months, p=0.05) and OS (not reached vs 21.8 months, p=0.008). Prior radiation therapy (OR 0.18 (95% CI 0.06-0.53, p=0.002) and prior adjuvant chemoimmunotherapy (OR 0.18 (95% CI 0.04-0.77, p=0.02) were independently associated with decreased odds of experiencing a TB. **Conclusions:** Treatment break on EV therapy did not compromise outcomes and resulted in TFS lasting ≥6 months in a subset of patients. Rational treatment de-escalation strategies in selected patients need to be prospectively investigated to mitigate long-term toxicity in patients with aUC undergoing EV-based therapy. Research Sponsor: None.

4577 **Poster Session**

Quantitative pre-cystectomy ctDNA levels for identification of ctDNA-positive patients with surgically curable loco-regional disease versus those with occult micrometastatic progression. First Author: Ruveyda Ayasun, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Radical cystectomy (RC) is a life-altering operation associated with substantial morbidity. Despite its curative intent for muscle-invasive urothelial carcinoma (MIUC), approximately 50% of patients experience metastatic recurrence after surgery. Identifying patients destined to relapse despite RC could help spare them from the morbidity of surgery and instead direct them toward alternative systemic therapies. While ctDNA-positive assays post-neoadjuvant therapy (NAT) but pre-cystectomy are associated with a poor prognosis, a subset of patients with ctDNA positive assays pre-cystectomy "clear" ctDNA with cystectomy alone (Powles, ASCO, 2025). We hypothesized that quantitative pre-cystectomy ctDNA thresholds may therefore distinguish local, surgically curable, bladder cancer versus micrometastatic disease. **Methods:** We conducted a retrospective single-institution cohort study of patients undergoing RC who had tumor-informed ctDNA (Signatera) assays ≤60 days pre-surgery and within ±30 days of a 3-month postoperative landmark. The primary outcome was ctDNA positivity at this landmark. The analyses proceeded in two steps: (1) association between log-transformed pre-cystectomy ctDNA and 3-month ctDNA positivity, assessed using logistic regression; and (2) derivation of the maximal quantitative preoperative ctDNA threshold >0.02 Mean Tumor Molecules per Milliliter (MTM/ml) using constrained optimization (target sensitivity ≥80%, specificity ≥50%), with internal validation via Efron-Gong bootstrap resampling. **Results:** Of 45 patients with MIUC meeting inclusion criteria, 10 (22.2%) received NAT. Higher pre-cystectomy ctDNA correlated with ctDNA positivity at the post-cystectomy landmark timepoint (odds ratio per 10-fold increase 1.6, 95% CI 1.2–2.4; p=<0.01). A pre-cystectomy ctDNA threshold ≥0.06 MTM/ml (95% CI 0.04–2.475) demonstrated optimal performance characteristics and was confirmed on bootstrap validation (sensitivity 81.6% [95% CI 61.1–88.9%], specificity 66.4% [95% CI 51.9–96.3%], positive predictive value [PPV] 63.8% [95% CI 55.2–91.7%], and negative predictive value [NPV] 85.1% [95% CI 78.8–88.9%]). **Conclusions:** Higher pre-cystectomy ctDNA values correlate with a higher likelihood of a persistent ctDNA-positive assay at 3 months post-cystectomy. In this dataset, a ctDNA threshold of ≥0.06 MTM/ml identified patients with high sensitivity and NPV for post-operative micrometastatic disease. Further validation of these findings, and threshold, in larger cohorts (with or without NAT) are needed to refine MIUC care by testing strategies involving (alternative) NAT versus proceeding with cystectomy. Research Sponsor: The Mount Sinai Hospital.

4578 **Poster Session**

Outcomes with enfortumab vedotin (EV) rechallenge after disease progression in metastatic urothelial carcinoma. First Author: Michal Sternschuss, Memorial Sloan Kettering Cancer Center, New York, NY

Background: EV, alone (mono) or with pembrolizumab (EVP), is an established therapy for metastatic urothelial carcinoma (mUC). However, the activity with EV rechallenge after prior exposure and subsequent disease progression is not well defined. **Methods:** A retrospective institutional database of patients (pts) treated with EV mono (n=395) or EVP (n=256) for mUC was reviewed to identify pts who received EV rechallenge after disease progression. EV-free interval (EVFI) was defined as the time from last EV1 (initial) dose to first EV2 (rechallenge) dose. Investigator-assessed objective response rate (ORR; CR/PR), progression free survival (PFS), overall survival (OS), and duration of response (DoR, from first documented response) were summarized descriptively. **Results:** Of 42 pts identified, EV1 regimen was mono for 62% (n=26; EV1-mono) and EVP for 38% (n=16; EVP1). Median age was 77, 76% were male, and 45% had upper tract primary. Most pts (n=35; 83%) discontinued EV1 for toxicity, predominantly peripheral neuropathy. Median follow up from EV2 initiation was 26 mo (95% CI 17-NR). At rechallenge, 10 pts (24%) switched EV regimens (EV1-mono to EVP2, n=5; EVP1 to EV2-mono, n=5). EV2 was initiated at 1.25 mg/kg in four pts (9.5%), 1.0 mg/kg in 13 pts (31%), and ≤0.75 mg/kg in 25 pts (60%). Among response-evaluable pts (n=39), ORR to EV2 was 21% (8/39; 95% CI 9%-36%), including 2 CRs (5%), both with prior CR to EV1. No responses were observed in pts with SD/PD to EV1 (0/8; 0%), or those with EV1 PFS <6 mo (0/11; 0%). Among pts with long (>12 mo) or intermediate (6-12 mo) EVFI, ORR to EV2 was 33% (4/12) and 31% (4/13), respectively. No responses were reported with short (<6 mo) EVFI (0/14; 0%). EV2 was initiated at 0.75 mg/kg in 5/8 pts with CR/PR. Median PFS and OS estimated from EV2 start were 2.8 and 18.5 mo. Among pts with CR/PR, median DoR was 7.0 mo (95% CI 3.5-NR). At last follow up, three pts remained on EV2; 39 pts discontinued EV2 due to progression (74%, n=29), toxicity (23%, n=9) or pt preference (2.6%, n=1). **Conclusions:** In a real-world cohort, EV rechallenge demonstrated modest activity, primarily in pts with prior benefit from EV and EVFI >6 mo. These observations underscore the need for further studies to clarify the effects of repeated EV exposure and optimize patient selection. This is particularly relevant given efforts to mitigate toxicity and the emerging issue of recurrent disease after perioperative EVP. Research Sponsor: National Cancer Institute; P30 CA008748; U.S. National Institutes of Health; P50 CA221745.

	All N = 42	EV1-mono N = 26	EVP1 N = 16
EV1			
ORR (95% CI)	79% (63%–90%)	85% (65%–96%)	69% (41%–89%)
Median PFS, mo (95% CI)	8.3 (7.5–9.9)	8.6 (7.7–19.1)	7.6 (5.5–11.9)
Median Time on EV, mo [IQR]	4.9 [3.7–7.2]	5.1 [4.1–8.7]	4.1 [2.4–5.7]
EV2			
ORR (95% CI)	8/39; 21% (9%-36%)	5/25; 20% (7%–41%)	3/14; 21% (5%–51%)
NE	3	1	2
Median PFS, mo (95% CI)	2.8 (2.6–5.1)	2.7 (2.6–5.3)	4.1 (2.6–NR)
Median OS, mo (95% CI)	18.5 (11.6–29.7)	18.5 (11.0–29.7)	15.2 (12.6–NR)
Median Time on EV, mo [IQR]	2.8 [1.9–5.6]	2.5 [1.9–5.1]	3.4 [1.9–6.1]

4579 **Poster Session**

A phase 1b study of SYS6002 in advanced solid tumors. First Author: Yao Zhu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: SYS6002 is a next-generation Nectin-4-targeting antibody-drug conjugate (ADC) utilizing a novel site-specific enzymatic conjugation technology to link monomethyl auristatin E (MMAE) with a uniform drug-antibody ratio of 2. This design aims to enhance linker stability, minimize free payload release, and improve the therapeutic window. **Methods:** This phase 1 study (ChiCTR2200066256) included dose escalation (0.2–4.5 mg/kg Q3W; 2.4–2.7 mg/kg Q2W), pharmacokinetic (PK) expansion, and cohort expansion phases. Eligible patients had advanced solid tumors refractory to standard therapies. The primary endpoints were safety and recommended phase 2 dose (RP2D). Secondary endpoints included PK profile and efficacy, with the latter reported herein were specific to the pretreated advanced urothelial carcinoma (aUC) cohort. **Results:** As of Dec 19, 2025, 150 patients were enrolled (dose escalation n=32; PK expansion n=70; cohort expansion n=48). The maximum tolerated dose was not reached up to 4.5 mg/kg. The RP2D in aUC patients was determined as 3.6 mg/kg Q3W. SYS6002 exhibited a manageable safety profile in all 150 patients. With a median follow-up of 11.5 months (IQR 6.5-15.5), 2 (1.3%) patients discontinued treatment due to treatment-related adverse events (TRAEs) and no TRAE led to death. The most common TRAEs were ocular disorders (e.g., corneal disorder, dry eye), which were predominantly Grade 1-2. While ocular events were frequent (consistent with on-target effects), they were reversible and effectively managed with prophylaxis, resulting in no treatment discontinuations due to ocular toxicity. Notably, TRAEs typically associated with payload shedding were characterized by low incidence, with peripheral neuropathy reported in 11.3% of patients (no Grade ≥3) and rash in 20.7% (2.0% Grade ≥3), which compared favorably to historical data of other MMAE-based ADCs. Furthermore, no Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis reported. In 85 efficacy-evaluable aUC patients across all tested doses, the objective response rate (ORR) was 37.6% (95%CI 27.4-48.8) and disease control rate (DCR) was 77.6% (95%CI 67.3-86.0), with a median duration of response of 6.2 months (95%CI 4.3-10.4) and median overall survival of 13.2 months (95%CI 10.6-14.9). At the RP2D (n=39), the ORR reached 41.0% (95%CI 25.6-57.9). Encouragingly, in heavily pretreated patients with prior MMAE-based ADC exposure (n=25), SYS6002 maintained activity with an ORR of 24.0% (95%CI 9.4-45.1) and DCR of 72.0% (95%CI 50.6-87.9), suggesting potential to overcome resistance. **Conclusions:** SYS6002 demonstrated a distinct safety profile from other Nectin-4 ADCs. Its promising efficacy in aUC patients, extending to those progressing on prior MMAE-based ADCs, supports further phase 3 trials. Clinical trial information: ChiCTR2200066256. Research Sponsor: CSPC Megalith Biopharmaceutical Co., Ltd.

4580 **Poster Session**

Proteomic profiling of circulating tumor cells (CTCs) in metastatic urothelial cancer (mUC) as associated with upregulation of EGFR, HER2, and B7-H3 in patients (pts) progressing on enfortumab vedotin (EV) plus pembrolizumab. First Author: Wadih Issa, Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Pts with mUC have poor prognosis, and while EV/pembro have improved outcomes, therapeutic targets arising after EV-pembro treatment are elusive. Proteomic profiling of circulating tumor cells (CTCs) offer a minimally invasive approach to capture tumor biology changes in real-time. We evaluated CTC burden and proteomic changes in relation to treatment response in mUC. **Methods:** Pts with mUC were prospectively enrolled at UT Southwestern Medical Center. Peripheral blood samples were collected at baseline, 4 weeks, and 12 weeks of treatment, as well as progression of disease. CTCs were isolated using a dendrimer-based microfluidic chip assay functionalized with antibodies against EpCAM, Trop-2, Nectin-4, and FGFR3, identifying nucleated CTCs (DAPI+/CK+, CD45-). After CTCs were selected within regions of interest, spatial proteomic profiling was performed via the Nanostring GeoMx Immuno-Oncology Proteome Atlas panel. CTC variation and surface proteomics after treatment were primary objectives. CTC changes were considered concordant if they decreased >10% in pts with complete or partial response (CR or PR), remained stable (within 10% of baseline) in pts with stable disease (SD), or increased >10% in pts with progressive disease (PD), as defined by RECIST 1.1. One pt underwent post-treatment biopsy with IHC analysis. **Results:** Thirty pts with mUC were enrolled, with a median age of 71.5 years, predominantly male (26/30, 87%) and Caucasian (24/30, 80%). Most received EV/pembro (26/30, 86.7%), while the rest were treated with chemotherapy (3/30, 10%) or SG (1/30, 3%). Median CTC counts (cells/ml) were assessed at baseline (30.3, IQR 18.5–62.9), at week 4 (22.3, IQR 6.0–37.0), and at week 12 (29.5, IQR 15.2–44.5). Twenty-two pts had sufficient radiographic and clinical follow up. CTC changes were concordant with treatment responses in 77% (17/22) of pts, including 12/22 pts with CR/PR, 3/22 with SD, and 7/22 with PD. Proteomic profiling of serial CTCs from 9 pts treated with EV/pembro revealed dynamic proteomic changes from baseline to week 12 and at disease progression. Together, these pts demonstrated upregulation of activated EGFR (phospho-Y1068), HER2 (phospho-Y877), STAT5, FAK, and vimentin. Pts with primary PD (n=3) showed B7-H3 upregulation on CTCs, whereas pts with secondary PD(n=2) showed higher expression of vimentin, c-MET, and MHC class I on CTCs. IHC of a post-EV/pembro progression bone metastasis confirmed increased HER2 expression (2+). **Conclusions:** CTCs with proteomic profiling can serve as a dynamic, noninvasive biomarker in mUC, identifying distinct therapeutic targets for pts progressing on EV/pembro. The emergence of actionable pathways, including EGFR, HER2, c-MET, and B7-H3, suggests opportunities for rational, biomarker-driven therapeutic strategies. Research Sponsor: Cancer Prevention & Research Institute of Texas; RR210079.

4581 **Poster Session**

Responses to trastuzumab deruxtecan (T-Dxd) in HER2 IHC spectrum 2+ versus 3+ urothelial carcinoma across lines of therapy. First Author: Sara El Sarout, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: The role of HER2 as a therapeutically actionable target has been validated with the DESTINY-PanTumor02 trial demonstrating meaningful clinical benefit to T-DXd across HER2-expressing bladder malignancies leading to the FDA approval in the immunohistochemical (IHC) 3+ population. We explore the clinical outcome of real-world patients with urothelial carcinoma (UCa) on T-DXd and its correlation with molecular and pathological findings across all the HER-2 IHC scores (e.g., 0 to 3+). **Methods:** We reviewed the clinical, pathologic, and molecular data of 29 patients with UCa, who received T-DXd between April 2024 and November 2025. Baseline clinical variables included age, sex, ECOG performance status, visceral metastases, line of therapy, and HER2 IHC score (adapted from gastric cancer scoring). Available genomic data included tumor mutational burden (TMB ≥10 mut/Mb), ERBB2 amplification and mutation, DNA damage response (DDR), FGFR alterations, and microsatellite instability (MSI) status. Outcomes of interest included Objective Response Rate (ORR), Disease Control Rate (DCR), and progression-free survival (PFS) and overall survival (OS) which were estimated using Kaplan–Meier methods and compared across groups using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios. **Results:** Higher HER2 IHC scores were associated with greater clinical activity and higher ORR in IHC 2+ (n=7; 42.9; 95% CI = 9.9–81.6%) tumors and HER2 IHC 3+ (n=20; 55.0; 95% CI =31.5–76.9%). However, no response was seen in HER2 IHC 1+ (n=2). Median duration of response was 15.6 months in HER2 IHC 2+ and 11.6 months in HER2 IHC 3+ (15/30 patients received T-DXd in ≥3 lines). PFS and OS appeared comparable between HER2 2+ and HER2 3+ tumors, with no statistically significant difference by log-rank test (p = 0.67, p = 0.79 respectively). Elevated TMB was observed in 6/12 cases. ERBB2 amplification was detected in 3/10 of cases and ERBB2 mutation in 5/13 of cases. Alterations in DDR related genes and FGFR were identified in patients 2/11 and 1/12 respectively, while MSI-H was not observed in any case. Responses were numerically higher when T-DXd was given in 2nd line (53.3%, 95% CI 26.6–78.7%) than in further lines (42.9%, 95% CI 17.7–71.1%) and so was DCR 93% (95% CI 68.1–99.8%) in 2nd line than 71.4% (95% CI 41-91.6%) in further (≥3) lines. **Conclusions:** T-DXd demonstrated meaningful clinical activity not only in IHC 3+ but in IHC 2+ tumors as well, which is consistent with the results of the DESTINY-PanTumor02 trial. In this limited sample size, there was no statistically significant association between genomic features and patient outcomes. Larger studies are needed to further find predictors across different levels of IHC expression. Research Sponsor: None.

HER2 IHC Score	n	Responders (CR/PR)	ORR (%)	95% CI
1+	2	0	0.0	0.0–84.2%
2+	7	3	42.9	9.9–81.6%
3+	20	11	55.0	31.5–76.9%

4582 **Poster Session**

Circulating tumor DNA (ctDNA) dynamics as early biomarkers of response to enfortumab vedotin plus pembrolizumab (EVP) in advanced urothelial carcinoma (aUC). First Author: Mohammad Jad Moussa, Internal Medicine Residency Program, Baylor College of Medicine, Houston, TX

Background: Radiographic assessment of treatment response remains challenging in aUC. ctDNA testing offers a sensitive, noninvasive measure of real-time treatment response. With EVP established as a frontline standard, we hypothesized that ctDNA dynamics correlate with radiographic response and survival. **Methods:** We retrospectively analyzed an institutional cohort of 302 patients (pts) with aUC treated with EVP at MD Anderson; 79 pts with baseline and serial ctDNA testing using a tumor-informed assay (Signatera) (08/23–01/26) were included. ctDNA dynamics were evaluated in two ways: (1) early on-treatment change (baseline vs. first on-treatment ctDNA) for association with radiographic response, and (2) time-dependent modeling as a covariate in Cox proportional hazards analyses of progression-free survival (PFS) and overall survival (OS) to account for immortal-time bias. **Results:** All pts had a median of 4 ctDNA tests (range: 1-9). Baseline ctDNA was obtained before or at EVP start in 67 (84.8%). Among these patients, first ctDNA clearance occurred in 46.3%, decrease in 26.9%, and increase in 19.4%; 6% had persistently undetectable ctDNA and 1.5% was lost to follow-up. Median time to first ctDNA reduction (clearance or decrease) was 48 days [IQR: 40–86]. Pts without baseline ctDNA prior to EVP (12, 15.2%) were non-evaluable. The best overall response rate to EVP was 53/79 (67.1%), including complete in 13.9% and partial responses in 53.2%. Objective responses were highest among pts with first ctDNA clearance (87.1%), lower with first ctDNA decrease (55.6%), and uncommon with first ctDNA increase (38.4%) (χ^2 test, p=0.003). In the overall cohort (n=79), median PFS from EVP start was 20.4 months (mo) [95% CI: 8–NE] and median OS from EVP start was 30.3 mo [95% CI: 26.3–34.3], with a median follow-up of 12.1 mo [95% CI: 9.1–14.9]. In time-dependent Cox models accounting for immortal-time bias, increasing ctDNA levels over time were associated with inferior PFS (HR 1.49 [95% CI: 1.11–2]; p=0.007) and OS (HR 1.41, [95% CI: 0.96–2.08], p=0.08). **Conclusions:** Early ctDNA dynamics provide a clinically meaningful measure of response to EVP in aUC and correlate with imaging outcomes. ctDNA clearance identifies pts with deep and durable benefit, while lack of clearance flags early resistance. Longer follow-up will evaluate ctDNA-guided monitoring to inform treatment de-escalation or maintenance approaches. Research Sponsor: None.

Baseline characteristics of cohort (n=79).

Variable	Measure
Age at aUC diagnosis, median [IQR]	71 [65 – 76]
Sex, male, n (%)	56 (70.9%)
Tumor Origin, n (%)	
Bladder	61 (77.2%)
Upper Tract	18 (22.8%)
Visceral mets, n (%)	34 (43%)
Nodal-only mets, n (%)	40 (50.6%)
Baseline ctDNA before/at EVP start (MTM/mL), median [IQR]	
All (n=67)	12.9 [1.1 – 105.5]
Visceral mets (n=30)	12.8 [1.3 – 140.2]
Nodal-only mets (n=33)	16.9 [1.4 – 96]

4583 **Poster Session**

Comparison of cisplatin/gemcitabine or carboplatin/gemcitabine on efficacy, toxicity, and quality of life from the randomized DISCUS trial. First Author: Syed A. Hussain, Division of Clinical Medicine, University of Sheffield, School of Medicine and Population Health, Sheffield, United Kingdom

Background: The DISCUS trial compared 3 versus 6 cycles (3C versus 6C) of chemotherapy followed by avelumab in 267 patients receiving first-line treatment for metastatic urothelial cancer. It showed 3 cycles of chemotherapy followed by maintenance avelumab was associated with better QoL than six cycles (NCT06892860). Efficacy outcomes of the two arms appeared similar. Here we compare the cisplatin (cis) or carboplatin (carbo) chemotherapy subsets in the 3C and 6C arms. **Methods:** Patients were randomized to receive either 3 or 6 cycles of chemotherapy. Cisplatin or carboplatin was allocated by physician choice. Progression free survival (PFS), Overall survival (OS), response rates, patient-reported outcomes (PROs) and treatment related adverse events were collected (TRAEs) were collected. The analysis was exploratory and p values nominal. **Results:** 267 were included of whom 55 received 3C/cis, 55 6C/cis, 78 3C/carbo and 79 6C/carbo. Patients receiving carboplatin had poor performance status (ECOG $>$=1 in 17% cis vs 35% carbo). Table 1 showed similar efficacy outcomes with potentially marginally superior OS with cisplatin. The comparison of efficacy and QOL endpoints for 3 vs 6 cycles of carboplatin showed many similarities. Six cycles of cisplatin-based chemotherapy was associated with a major drop in QOL compared to 3 cycles without showing any clear benefits in efficacy endpoints. **Conclusions:** The QoL benefits of shorter chemotherapy appear to be more marked in patients receiving cisplatin than carboplatin. The efficacy results for 3 cycles of cisplatin were impressive. This study was not powered for non-inferiority. Clinical trial information: NCT06892860. Research Sponsor: Merck; 10.13039/100009945.

Outcomes by treatment arm.

	3C/cis (n=56)	3C/carbo (n=77)	6C/cis (n=54)	6C/carbo (n=80)
CR (%)	16%	10%	14%	12%
PFS (months), median (95% CI)	8.8 (6.5-12.8)	8.0 (5.8-12.0)	8.7 (6.4-18.9)	9.0 (6.6-13.1)
OS (months), median (95% CI)	Not reached (12.8-.)	18.5 (12.6-.)	21.9 (10.5-.)	15.0 (9.8-.)
G3 and above TRAE (n)	32	40	49	79
PRO (change from baseline to C7D1)	2.96	-2.51	-13.44	-4.86

4584 **Poster Session**

Risk and patterns of recurrence for patients (pts) with advanced urothelial carcinoma (aUC) metastatic to liver after response to enfortumab vedotin + pembrolizumab (EVP). First Author: Rishi Raju Patel, University Hospitals Cleveland Medical Center, Cleveland, OH

Background: EVP is the preferred frontline regimen in pts with aUC. Despite initial response to treatment, many pts treated with EVP ultimately have progression. We hypothesized that recurrence patterns would differ between pts with and without baseline liver metastases. **Methods:** UNITE is a multi-institutional retrospective database capturing clinical and treatment characteristics of pts with aUC receiving systemic therapies. We queried this database to identify pts who achieved an observed response (OR) to EVP. Pts were grouped by initial metastatic sites using a non-mutually exclusive approach. Descriptive statistics were used to summarize observed response rates (ORR) and recurrence patterns at time of progression. Progression-free survival (PFS) from start of EVP was estimated using the Kaplan-Meier method. The effect of liver metastases on PFS was assessed via multivariable Cox regression. Median-follow up time was estimated using the reverse Kaplan-Meier method. Statistical analyses were conducted in RStudio. **Results:** We identified 464 pts treated with EVP (median age 72; 74% male, 80% White). Best ORR in pts with baseline liver metastases (n=77) were complete response 9%, partial response 35%, stable disease 18%, and progressive disease 21%, compared with 18%, 37%, 27%, and 18%, respectively, in pts without baseline liver metastases (n=325). The estimated median follow-up time was 52 weeks (95% CI 48-62). Among pts with initial OR to EVP, those with baseline liver metastases showed a non-significant trend toward shorter PFS (HR 1.35; 95% CI 0.67–2.75; p=0.40) versus those without baseline liver metastases. Among pts with initial OR to EVP and subsequent progression the distribution of sites of recurrences at progression for those with (n = 10) and without (n = 40) baseline liver metastases were: liver (50% vs. 10%), lymph nodes (60% vs. 55%), lungs (50% vs. 38%), bone (20% vs 20%), and primary tumor (20% vs 25%). EVP responders with baseline liver metastases had a numerically higher rate of site-specific metastasis resolution at progression versus those with lymph node or lung metastases (Table). **Conclusions:** Our analysis suggests that liver metastases may be associated with shorter PFS among EVP responders, though these pts frequently do not retain liver metastases at time of progression. Study limitations include retrospective analysis, investigator-assessed response, small sample size, selection and confounding biases. Patterns of recurrence following EVP merits further evaluation. Research Sponsor: None.

Metastatic Site	Pts with Site-Specific Baseline Metastases (n)	Pts with Resolution of Site-Specific Metastases at Progression, n (%)	Pts without Baseline Metastases at Site (n)	Pts who Remained Free of Site-Specific Metastases at Progression, n (%)
Liver	10	5 (50%)	40	36 (90%)
Lymph Nodes	37	12 (32%)	13	10 (77%)
Lungs	26	8 (31%)	24	22 (92%)

4585 **Poster Session**

Long-term survival update of TRUCE-01: A phase 2 study of preoperative tislelizumab combined with low-dose nab-paclitaxel for muscle-invasive bladder cancer (MIBC). First Author: Zhouliang Wu, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: The TRUCE-01 study (NCT04730219) previously met its primary endpoint, demonstrating that preoperative tislelizumab combined with low-dose nab-paclitaxel achieved a high clinical complete response (cCR) rate of 52% and a favorable safety profile in patients with muscle-invasive bladder cancer (MIBC). Here, we report the long-term survival outcomes after 4 years of study follow-up. **Methods:** Eligible patients with cT2-4aN0M0 MIBC received three cycles of tislelizumab (200 mg, day 1) plus low-dose nab-paclitaxel (200 mg, day 2) every 3 weeks, followed by radical cystectomy (RC) or maximal transurethral resection of bladder tumor (mTURBT) based on response assessment. The primary endpoint was cCR. Secondary endpoints included event-free survival (EFS), overall survival (OS), disease-specific survival (DSS), and metastasis-free survival (MFS). **Results:** At the clinical data cutoff of October 2025, the median follow-up was 47.4 months (IQR 24.8–53.3). Among the intention-to-treat population (n = 62), 25 patients experienced clinical events, including 15 recurrences and 20 deaths (13 due to disease progression, 7 due to non-disease-related causes). Notably, among the 24 patients who elected for bladder preservation, a bladder preservation rate of 75% was achieved(4 due to recurrence requiring salvage radical cystectomy, 2 due to disease progression). The 4-year EFS and OS rates were 59.7% and 67.8%, respectively. Survival analysis stratified by response showed that patients achieving a cCR had significantly superior long-term outcomes compared to non-cCR patients. The cCR group demonstrated a robust and significant benefit in OS (HR 0.28, 95% CI 0.09–0.83, p = 0.0212), DSS (HR 0.10, 95% CI 0.02–0.46, p = 0.0029), and MFS (HR 0.19, 95% CI 0.06–0.63, p = 0.0068). No new safety signals or late-onset immune-related adverse events were observed with extended follow-up. **Conclusions:** With approximately 4 years of median follow-up, preoperative tislelizumab combined with low-dose nab-paclitaxel continues to demonstrate robust and durable survival benefits for patients with MIBC. Clinical trial information: NCT04730219. Research Sponsor: Tianjin Municipal Health Industry; TJWJ2022XK014; Tianjin Municipal Education Commission; 2022ZD069; The Second Hospital of Tianjin Medical University; 2023LC03; Tianjin Institute of Urology; MYSRC202310; The Second Hospital of Tianjin Medical University; 2023LC03; The Second Hospital of Tianjin Medical University; 2022ydey15; The Second Hospital of Tianjin Medical University; 2023LC03; Department of Urology, The Second Hospital of Tianjin Medical University; MNRRC202313; The Second Hospital of Tianjin Medical University; 2022ydey15; The Second Hospital of Tianjin Medical University; 2022ydey15; Department of Urology, The Second Hospital of Tianjin Medical University; MNRRC202313; Department of Urology, The Second Hospital of Tianjin Medical University; MNRRC202313.

4586 **Poster Session**

Paired Nectin4 expression analysis pre and post enfortumab vedotin and pembrolizumab in urothelial carcinoma. First Author: Michal Sternschuss, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Enfortumab vedotin and pembrolizumab (EVP) transformed the treatment of urothelial carcinoma (UC), yet resistance remains a challenge. Mechanisms of resistance including changes in target expression are poorly defined. **Methods:** We analyzed an institutional retrospective cohort of patients (pts) who had paired tissue samples obtained pre- and post-EVP. Membranous (mNectin4) and cytoplasmic (cNectin4) expression were measured by immunohistochemistry (H-score). mNectin4 was categorized as negative (<15), weak (15-99), moderate (100-199) or strong (200-300). Changes in Nectin4 were assessed as absolute differences (post−pre) and as scaled log change (%) [100xlog((post + c)/(pre + c))] to capture relative expression changes. Nectin4 dynamics were compared between primary (resistant disease ≤6 months from EVP initiation) and acquired resistance (>6 months) using Wilcoxon rank-sum and fisher's exact tests. **Results:** Of 46 pts with paired samples, 40 had evaluable Nectin4 IHC. Median age was 72, 70% were men, and 30% had upper tract primary. Median H-scores were similar pre- and post-EVP for both mNectin4 (195 [IQR 115, 260] vs 200 [IQR 85, 230]; p=0.5) and cNectin4 (0 [IQR 0, 40] vs 0 [IQR 0, 60]; p >0.9). Post-EVP mNectin4 was moderate/strong in 29 pts (73%). Complete loss of mNectin4 was uncommon: of five pts (13%) with negative mNectin4 post-EVP, two were negative at baseline and three had weak expression pre-EVP. Post-EVP samples obtained on EV (≤21d from last dose; n=21) vs off EV (>21d; n=19) showed similar changes from pre-EVP for mNectin4 (p=0.3) and cNectin4 (p=0.4). Nectin4 changes differed by resistance pattern, with primary resistance (n = 14) showing a greater relative decrease in mNectin4 expression (median log change −57 vs 3; p = 0.035) and a relative increase in cNectin4 expression (median log change 52 vs 0; p = 0.029) compared with acquired resistance (n = 21). Paired analyses of *NECTIN4* copy number by FISH will be reported. **Conclusions:** In a paired analysis, most tumors retained substantial mNectin4 expression post-EVP and complete loss was rare, supporting the rationale for Nectin4-targeted strategies in the post-EVP setting. Distinct Nectin4 dynamics suggest greater relevance of target expression changes in primary vs acquired resistance; further studies are needed. Research Sponsor: National Cancer Institute; P30 CA008748; U.S. National Institutes of Health; P50 CA221745.

	All* N=40	Primary resistance N=14	Acquired resistance N=21	p
mNectin4				
Trend				0.11
Decrease	21 (53%)	10 (71%)	10 (48%)	
Increase	17 (43%)	3 (21%)	11 (52%)	
Stable	2 (5.0%)	1 (7.1%)	0 (0%)	
Absolute change, median [IQR]	-13 [-60, 45]	-48 [-100, 0]	10 [-50, 55]	0.2
Log change, median [IQR]	-8 [-57, 23]	-57 [-195, 0]	3 [-21, 21]	**0.035**
cNectin4				
Trend				0.2
Decrease	12 (30%)	3 (21%)	8 (38%)	
Increase	14 (35%)	8 (57%)	5 (24%)	
Stable	14 (35%)	3 (21%)	8 (38%)	
Absolute change, median [IQR]	0 [-28, 25]	13 [0, 100]	0 [-30, 0]	0.055
Log change, median [IQR]	0 [-137, 67]	52 [0, 304]	0 [-256, 0]	**0.029**

*Including 5 pts not meeting resistance definitions.

4587 **Poster Session**

Clinical outcomes for patients (pts) with synchronous versus metachronous metastatic urothelial cancer (mUC) treated with enfortumab vedotin and pembrolizumab (EV-P). First Author: Libin Yan, Division of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Synchronous versus metachronous metastases in mUC has prognostic significance, and EV-P has emerged as standard first-line therapy for pts with mUC. How primary disease in synchronous mUC should be best treated remains unclear. This study evaluated clinical outcomes of pts with synchronous vs metachronous mUC treated with EV-P. **Methods:** A retrospective analysis of all consecutive pts with mUC treated EV−P at UTSW was performed. Patients were grouped by synchronous mUC or metachronous mUC. Baseline characteristics were compared using Wilcoxon rank-sum and Chi-squared tests. Overall survival (OS) and progression-free survival (PFS) were analyzed using Cox proportional hazards models. **Results:** For 159 pts with mUC treated with EV-P between 9/2020 and 12/2025, 40 had synchronous mUC and 119 had metachronous mUC. Baseline characteristics were similar with median age 71.5 years vs 73.0 years (p=0.90), male 75% vs 94%(p=0.76), and visceral metastases (20% vs 26%, p=0.58). In metachronous mUC, 76 (63.9%) had prior cystectomy and 42 (35.3%) had prior radiation as definitive treatment. Patients with metachronous mUC demonstrated a median PFS of 16.0 months vs not reached (NR) for patients with synchronous mUC (HR 1.95, 95% CI 1.05–3.62; p = 0.035). Similarly, the median OS was 21.9 months for metachronous mUC vs not reached in the synchronous mUC (HR 2.61, 95% CI 1.24–5.49; p = 0.011). Median cycles of EV-P was 13.5 for synchronous mUC vs 10 for metachronous mUC. For synchronous mUC, 22 (55.0%) underwent cystectomy and 8 (20.0%) underwent radiation as consolidative treatment. **Conclusions:** Synchronous and metachronous mUC treated with EV-P have significantly different disease courses on EV-P. Metachronous mUC has earlier progression on EV-P, needing more treatment options in refractory disease. Consolidation treatment for synchronous mUC needs further prospective trials for optimal outcomes. Research Sponsor: None.

Comprehensive baseline characteristics and clinical outcomes.

Characteristic	Synchronous met	Metachronous met	P value
Number of patients	40	119	
Age at treatment initiation, median (IQR)	71.5 (64.5–76.0)	73.0 (64.0–78.0)	0.904
Male sex, n (%)	30 (75.0%)	94 (79.0%)	0.759
Prior local therapy			
Prior radical cystectomy	N/A	76 (63.9%)	
Prior radiation therapy	N/A	42 (35.3%)	
Metastatic burden			
Any visceral metastasis	8 (20.0%)	31 (26.1%)	0.578
Liver metastasis	6 (15.0%)	17 (14.3%)	1.000
Treatment and outcomes			
EV-P cycles, median (range)	13.5 (1–39)	10.0 (1–57)	0.281

4588 **Poster Session**

Use of *NECTIN4* expression inferred from circulating chromatin to predict response and survival to enfortumab vedotin (EV) in metastatic urothelial carcinoma. First Author: Rashad Nawfal, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: APEX (Associating Plasma Epigenomics with eXpression) is a machine-learning framework that infers genome-wide gene expression in cancer from plasma cell-free chromatin Immunoprecipitation sequencing (cfChIP) by integrating signal from multiple histone marks and fragmentomic features, enabling enhanced transcriptional readouts from liquid biopsy without tissue sampling. We investigated whether APEX can noninvasively quantify *NECTIN4* expression to predict outcomes with EV, a NECTIN4-targeted antibody-drug conjugate, in metastatic bladder cancer. **Methods:** Baseline plasma (1 mL) was collected from patients with metastatic bladder cancer within 90 before to 8 days after start of EV monotherapy and profiled by cfChIP-seq, followed by APEX-based tumor gene-expression inference. APEX-inferred *NECTIN4* expression was dichotomized into high and low groups by the cohort median and tested for association with objective response (CR/PR vs SD/PD). Progression-free survival (PFS) and overall survival (OS) were analyzed using log-rank test and multivariable Cox regression model, accounting for the presence of bone or liver metastases and cfDNA tumor fraction. APEX performance was then compared against *NECTIN4* locus signal from individual histone marks, plasma tumor fraction, and *NECTIN4* copy-number status/amplification. **Results:** In the EV-treated cohort (*n*=24), baseline APEX-inferred *NECTIN4* expression was significantly higher in responders versus non-responders (p = 0.002) and outperformed *NECTIN4* estimates derived from single histone-mark features, tumor fraction, and *NECTIN4* copy number. Patients with high plasma-inferred *NECTIN4* had an objective response rate of 58%, whereas no responses were observed among those with low inferred *NECTIN4*, supporting strong negative predictive value. High baseline APEX-inferred *NECTIN4* was also significantly associated with improved progression-free and overall survival (HR = 0.22, 95%CI: 0.08 – 0.65, p = 0.005 and HR = 0.27, 95%CI: 0.10 – 0.75, p = 0.008, respectively), with stronger associations than plasma tumor fraction, *NECTIN4* copy number/amplification, or individual histone-mark coverage. In multivariable Cox models, APEX-inferred *NECTIN4* remained independently associated with survival. Moreover, responders were enriched for urothelial luminal genes known to associate with *NECTIN4* expression and favorable outcomes, while non-responders showed increased activation of epithelial-mesenchymal transition-related genes, known to associated with worse outcomes. **Conclusions:** A machine learning framework for plasma-based inference of tumor gene expression identifies plasma-based *NECTIN4* as a clinically actionable, expression-based biomarker that predicts EV response and survival in metastatic bladder cancer. Research Sponsor: None.

4589 **Poster Session**

Cost-effectiveness analysis of first-line (1L) therapies for advanced urothelial carcinoma (aUC) from a U.S. payer perspective. First Author: Prateek Jain, Sinai Hospital Baltimore, Baltimore, MD

Background: Recent years have seen a shift in aUC management following approval of enfortumab vedotin−pembrolizumab (EV-P) and gemcitabine/cisplatin plus nivolumab (GC-NIVO) as first-line therapies. Despite improved clinical outcomes, their relative economic value remains uncertain. Herein, we conducted a cost-effectiveness analysis of current 1L regimens in aUC from a U.S. payer perspective using 2026 pricing. **Methods:** A partitioned survival model with three health states (progression-free [PF], progressed disease [PD], and death) was developed over a 10-year horizon from a U.S. payer perspective. Analyses focused on cisplatin-eligible patients. Survival data were reconstructed from published Kaplan−Meier curves and extrapolated using parametric survival models. Treatment dosing, schedules, and duration were modeled according to trial protocols. Patients receiving gemcitabine/cisplatin without progression were modeled to receive avelumab maintenance (GC→AVEL). Subsequent-line therapy costs were applied at incident progression, and grade ≥3 adverse event costs and disutilities were applied as one-time events. Drug acquisition costs (2026 USD) were based on average sales prices from the Centers for Medicare & Medicaid Services. Costs and quality-adjusted life years (QALYs) were discounted at 3% annually. Incremental cost-effectiveness ratios (ICERs) and net monetary benefit (NMB) were evaluated at willingness-to-pay (WTP) thresholds of $100,000, $150,000, and $200,000 per QALY. Parameter uncertainty was characterized using probabilistic sensitivity analysis. **Results:** In the base-case analysis, total discounted costs and QALYs were $90,269 and 1.62 for GC→AVEL, $131,836 and 2.09 for GC-NIVO, and $1,451,885 and 2.77 for EV-P. Compared with GC→AVEL, GC-NIVO gained 0.46 QALYs at an incremental cost of $41,567, resulting in an ICER of $89,501 per QALY and positive NMB across all evaluated WTP thresholds. Compared with GC→AVEL, EV-P gained 1.15 QALYs at an incremental cost of $1.36 million (ICER $1.19 million per QALY). Compared with GC-NIVO, EV-P gained 0.68 QALYs at an incremental cost of $1.32 million (ICER $1.93 million per QALY), exceeding all evaluated WTP thresholds. In a scenario analysis limiting EV-P to 10 treatment cycles, total costs decreased to $287,360, with ICERs of $172,000/QALY versus GC→AVEL and $225,000/QALY versus GC-NIVO, remaining above the $150,000/QALY threshold. **Conclusions:** Using updated 2026 pricing, GC-NIVO is likely to be the most cost-effective first-line regimen for cisplatin-eligible patients with aUC. EV-P offers the greatest clinical benefit but is not cost-effective at current prices. A major limitation of this study is cross-trial variability in study populations and design, limiting the validity of head-to-head economic comparisons. Research Sponsor: None.

4590 **Poster Session**

A novel oncolytic vaccinia virus armed with IL-21 and 4-1BBL for intravesical treatment of NMIBC: Preclinical efficacy and first-in-human safety evaluation. First Author: Shun Zhang, Department of Urology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Oncolytic viruses are emerging cancer immunotherapies. For non–muscle-invasive bladder cancer (NMIBC), intravesical delivery allows high local exposure with limited systemic toxicity. This study was conducted to evaluate anti-tumor efficacy, mechanism and safety of KM1, a novel developed oncolytic vaccinia virus modified with tyrosine kinase deletion, L025 and A46R gene deletion, and armed with interleukin 21 and 4-1BBL in murine models and human. **Methods:** In vitro assays assessed virus replication, cytotoxicity, and transgene expression in human and murine bladder cancer cell lines and organoids. In vivo studies assessed immune activation, toxicity, and antitumor efficacy in murine subcutaneous and orthotopic bladder tumor models. An investigator-initiated phase 1a trial enrolled NMIBC patients who had failed prior BCG therapy or declined further BCG. This multicenter, single-arm study used 3+3 dose-escalation with primary endpoints of safety and tolerability (AE and DLTs). Planned dose levels were 2×10^9 PFU (DL1), 5×10^9 PFU (DL2), and 1×10^{10} PFU (DL3) per instillation. Following completion of DL1 and DL2, the protocol was amended to discontinue further dose escalation (DL3 was not opened) and to enroll an expansion cohort at DL1 (additional n=3) to further characterize safety/tolerability and PK/PD at the putative recommended dose. The induction regimen consisted of bladder irrigation with sucrose monolaurate, followed by intravesical KM1 retained for 2 hours, given twice weekly for 3 weeks and then once weekly for 3 weeks. Subsequent maintenance therapy comprised three intravesical KM1 instillations every 3 months. **Results:** KM1 selectively replicated in human and murine bladder cancer cells, induced high IL-21 and 4-1BBL secretion. Supernatant from KM1-infected cells activated $CD8^+$ T cells and enhanced tumor-killing *in vitro*. *In vivo*, KM1 showed better antitumor efficacy than BCG, increased $CD8^+$ T and NK cell infiltration and function. Depletion of either population diminished efficacy. In the phase 1a study, 12 patients received intravesical KM1 (DL1, n=9 [including n=3 expansion]; DL2, n=3) and were evaluable. Ten TEAEs were reported, predominantly grade 1–2; the most common were noninfective cystitis (5/12, 41.7%) and urinary tract pain (4/12, 33.3%). One DL1 patient experienced a DLT of transient, likely treatment-related grade 3 liver injury that resolved within 1 week without sequelae. No KM1 DNA was detected in saliva, blood, or feces at any assessed time point. At a median follow-up of 10.1 months, all patients remained recurrence-free by 6 months (CR 12/12; 100%). **Conclusions:** KM1 showed selective replication, oncolysis, and immune activation in preclinical models. Early clinical data suggest favorable safety and promising antitumor activity of intravesical KM1 in NMIBC. Clinical trial information: ChiCTR2400086709. Research Sponsor: Shenzhen Huayao Kangming Biopharmaceutical Co., Ltd.

4591 **Poster Session**

Keratin 19 (KRT19) as a circulating biomarker to measure disease burden and guide treatment in urothelial cancer. First Author: Eric James Miller, Mount Sinai Tisch Cancer Center, New York, NY

Background: Circulating tumor DNA (ctDNA) has emerged as a valuable biomarker in urothelial cancer but remains limited by cost and turnaround time. Keratin 19 (KRT19) is a cytoskeletal protein that is highly and specifically expressed in urothelial tumor tissue in The Cancer Genome Atlas (TCGA) urothelial cancer cohort. Based on this tumor specific expression, we hypothesized that circulating KRT19 levels could serve as a rapid, inexpensive measure of disease burden to guide systemic therapy for urothelial cancer. **Methods:** Two patient cohorts from completed clinical trials were analyzed. HCRN GU16-257, a phase 2 trial of gemcitabine, cisplatin, and nivolumab as organ-sparing treatment for localized muscle-invasive bladder cancer, included 76 patients evaluable for KRT19 with median follow-up of 30 months. HCRN GU14-182, a phase 2 switch maintenance trial of pembrolizumab versus placebo following first-line chemotherapy for metastatic urothelial cancer, included 46 patients evaluable for KRT19 in the pembrolizumab arm with median follow-up of 12.9 months. Serum KRT19 levels were quantified using Olink proteomics technology alongside 91 additional proteins. Cox proportional hazards models assessed associations between KRT19 expression and clinical outcomes, with adjustment for multiple comparisons using false discovery rate correction. **Results:** In the GU16-257 cohort, among 92 peripheral blood analytes tested at baseline (C1D1), KRT19 demonstrated the strongest association with overall survival. Elevated baseline KRT19 was independently associated with inferior overall survival (HR 2.62, adjusted p=0.016) and metastasis-free survival (HR 3.01, adjusted p=0.001). A decrease in KRT19 from C1D1 to C3D1 was associated with improved overall survival (HR 0.59, unadjusted p=0.024) and metastasis-free survival (HR 0.60, unadjusted p=0.041). In GU14-182, elevated baseline KRT19 was associated with inferior overall survival (HR 2.11, adjusted p=0.034) and progression-free survival (HR 1.57, unadjusted p=0.024). Optimal KRT19 cutpoints enabled significant risk stratification for mortality and disease progression in both cohorts. Analysis of an independent peripheral blood single-cell RNA sequencing cohort from patients with urothelial cancer confirmed epithelial cells as the predominant source of circulating KRT19. **Conclusions:** KRT19 represents a promising, readily measurable serum biomarker with specificity for urothelial cancer. Both baseline levels and on-treatment changes correlate with disease progression and survival. Further validation of KRT19 as a tool to assess disease burden and guide treatment decisions in urothelial cancer is warranted. Research Sponsor: Conquer Cancer, the ASCO Foundation.

4592 **Poster Session**

Preliminary results of a single-arm, muti-center, prospective clinical study of disitamab vedotin combined with toripalimab and pelvic lymph node dissection for bladder preservation in patients with cT2-4aN0M0 bladder urothelial carcinoma and HER2 expression ≥ 2+ after maximal TURBT. First Author: Tianhang Lan, The Second Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China

Background: With the evolution of different treatment eras, the clinical complete response (cCR) rate of bladder cancer has been progressively increasing, while the lymph node metastasis rate has still not improved significantly. Particularly, patients with HER2 overexpression are at a higher risk of lymph node metastasis, which poses a major challenge to bladder-sparing therapy for patients with muscle-invasive bladder cancer (MIBC). This study aims to establish a novel bladder-preserving treatment model by combining local therapy enhanced with pelvic lymph node dissection (PLND) and systemic therapy with Disitamab Vedotin and Toripalimab. **Methods:** Patients with cT2-4aN0M0 MIBC and HER2 expression $\geq$2+ were enrolled, The primary endpoint was 2-year bladder-intact disease-free survival rate. After maximal transurethral resection of bladder tumor (TURBT), patients received Toripalimab (3mg/kg, Q2W) combined with Disitamab Vedotin (2mg/kg, Q2W) for 6 cycles, followed by TURBT and PLND. Those with cCR or partial response (PR) continued the combined therapy for another 6 cycles. Patients achieving cCR after 12 cycles of combined therapy received maintenance Toripalimab (240mg, Q3W) for 1 year. Non-cCR patients received comprehensive treatment or salvage radical cystectomy(RC). **Results:** As of December 2025, 21 patients were enrolled, with a median age of 66 years (range: 37–82). The primary endpoint was not yet reached. Efficacy assessment was performed in 14 patients at Week 12: 10/12 (85.8%) achieved cCR, while 1 patient had stable disease (SD) and 1 had progressive disease (PD). Among 10 patients who underwent TURBT and PLND, pathological complete response (pT0N0M0) was achieved in 90.0%, and 1 patient was postoperatively staged as pT0N1M0. Patients with SD or PD underwent RC. All patients experienced treatment-related adverse events (TRAEs) of any grade. The most common TRAEs were pruritus (75.00%), paresthesia (68.75%), and elevated ALT (43.75%), all of which were Grade 1–2. One patient developed a Grade 3 adverse event (AE), which was severe urinary tract infection. No TRAEs of Grade $\geq$4 were observed. **Conclusions:** The novel bladder-sparing modality of Disitamab Vedotin combined with Toripalimab plus PLND after maximal TURBT currently demonstrates favorable efficacy and safety. Long-term outcomes warrant further investigation. Clinical trial information: ChiCTR2400081555. Research Sponsor: Rongchang Biopharmaceutical (Yantai) Co., Ltd; Shanghai Junshi Biosciences Co., Ltd; National Natural Science Foundation of China; Wang He; the National Key Research and Development Program of China; Wang He.

4593 **Poster Session**

Urinary tumor DNA–guided de-escalation of systemic immunotherapy in extensive very high risk non–muscle-invasive bladder cancer. First Author: Yunkai Qie, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Non-muscle-invasive bladder cancer (NMIBC) has entered the era of systemic immunotherapy. Large randomized trials, including CREST, POTOMAC, and ALBAN, have explored long-term systemic immunotherapy in NMIBC, yet the clinical benefit remains heterogeneous and is often accompanied by substantial toxicity. Urinary tumor DNA (utDNA) has emerged as a promising biomarker for molecular response assessment, yet its role in guiding treatment de-escalation has not been established. We evaluated whether utDNA negativity after complete response (CR) could support safe early treatment cessation of systemic therapy in patients with extensive very-high-risk NMIBC (VHR-NMIBC). **Methods:** Patients with extensive VHR-NMIBC who achieved CR after initial systemic therapy with the PD-1 inhibitor tislelizumab plus low-dose paclitaxel were included from a prospective cohort. After CR assessment, some patients underwent low-coverage utDNA testing as part of routine clinical decision-making following clinician–patient discussion. Patients with negative utDNA completed three additional cycles and subsequently stopped systemic therapy (utDNA-guided de-escalation group), whereas those who continued treatment beyond this point were categorized as the longer treatment-exposure group. Efficacy and safety outcomes included survival endpoints and adverse events (AEs) with exposure-adjusted incidence rates. **Results:** With a median follow-up of 42.8 months, 54 patients achieving CR were evaluable. Among them, 21 with negative utDNA status completed three additional cycles and underwent planned treatment cessation, while 33 continued systemic therapy with longer treatment exposure. Across key efficacy endpoints, outcomes were comparable between the utDNA-guided de-escalation and longer treatment–exposure groups, with no significant differences in recurrence-free survival (RFS; HR 1.37, 95% CI 0.21–8.87, P = 0.73), overall survival (OS; HR 2.48, 95% CI 0.12–53.7, P = 0.51), or duration of response (DOR; HR 1.33, 95% CI 0.21–8.50, P = 0.76). A difference in radical-cystectomy–free survival was observed (short vs long: HR 4.97, 95% CI 1.03–23.9, P = 0.03). Long-course treatment was associated with a higher cumulative incidence of any-grade AEs (88.1% vs 72.5%) and more AE types (median 5 vs 2, $P < 0.001$). Exposure-adjusted AE rates per cycle were lower in the long-course group (IRR 0.50, 95% CI 0.42–0.60, $P < 0.001$), while grade $\geq$3 AEs occurred in 2.9% and 9.5% of patients in the short- and long-course groups, respectively, predominantly during later treatment phases. **Conclusions:** UtDNA negativity after complete response may provide a molecular basis for individualized treatment duration, highlighting the potential role of liquid biopsy in guiding precision treatment tailoring and warranting prospective validation in larger biomarker-driven studies. Clinical trial information: NCT04730232. Research Sponsor: None.

4594 **Poster Session**

Evidence implicating human papillomavirus in bladder carcinogenesis: A case-control study. First Author: Xueying Zhang, Jilin Cancer Hospital, Changchun, Jilin, China

Background: The etiology of high-risk oncogenic human papillomavirus (HPV) subtypes with signature cytomorphological changes such as koilocytosis in bladder cancer (BCa) carcinogenesis still remains controversial and insufficiently investigated. We evaluated the diagnostic concordance rate between HPV-DNA test with urine HPV related cytomorphological findings in BCa urine samples. **Methods:** A retrospective case-control study was conducted. A total of 172 HPV-positive urine cytology specimens from patients with primary BCa treated at our hospital between January 2020 and December 2024 were included as the study group. During the same period, of 172 HPV - negative urine cytology specimens from primary BCa were selected as the control group. HPV DNA was detected by in situ hybridization was utilized. Immunohistochemistry (IHC) was performed to assess $p16^{INK4a}$ protein expression as a surrogate marker of functional HPV activity. Cytomorphologic changes that had concurrent liquid-base cytology were identified using The Paris System for Reporting Urinary Cytology (TPS) criteria. Statistical analyses were performed using chi-square tests and fisher's exact tests. **Results:** Overexpression of $p16^{INK4a}$ was observed in 82.2% (140/172) of the HPV-positive group and showed a high level of concordance with HPV infection status (Kappa=0.812, $p<0.001$). Among the HPV-positive group, high-risk HPV types accounted for 88.9% (152/172) with HPV-16 (114/152,75.6%) and HPV-18 (38/152,24.4%) being the predominant subtypes. A p16INK4a protein expression from HPV-negative group was detected which was significantly lower than in the positive group (13/172, 7.56%, $p<0.001$). HPV infection cytomorphology was identified, with 48.6% (83/172) koilocytes (52/172, 30.23%) either alone or in addition to basaloid clusters (16/172, 9.3%) and atypical squamous cells (ASCs) (15/172, 8.72%) identified using TPS from the HPV-positive group, and a significantly lower rate of 6.1% (10/172, $p<0.001$) was identified from the HPV-negative group. **Conclusions:** HPV plays an etiological role in carcinogenesis and contributes to a worse prognosis for patients with BCa development. The identification of cytomorphologic changes in urine cytology is a significant and underutilized piece of etiological evidence supporting a role for HPV in bladder carcinogenesis. It provides a reliable direct and visible link between the viral cytopathic effect and the urothelial cells. Integrating routine cytological assessment with modern molecular testing in urine samples could better define its role as an oncogenic driver in specific BCa variants. Recognizing this association has implications for risk stratification, screening in high-risk populations, and potential therapeutic avenues. Research Sponsor: The Science & Technolgy Commitee of JIlin Province, China; JLKJT2024081451JLZLYIY.

4595 **Poster Session**

Clinical outcomes with *ERBB2* gene amplification and activating mutations in muscle-invasive bladder cancer patients treated with neoadjuvant chemotherapy. First Author: Earle F. Burgess, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Charlotte, NC

Background: Activating ERBB2 mutations (mut) are associated with improved pathologic response (pCR) to neoadjuvant chemotherapy (NAC) in patients with muscle-invasive bladder cancer (MIBC). However, the impact of ERBB2 gene amplification (amp) on pCR and of aggregate ERBB2 gene variants (amp and mut) on relapse and survival is unknown. We previously reported that high tumor mutational burden (TMB) is associated with improved pCR and relapse-free survival (RFS) in a cohort of MIBC patients treated with cisplatin-based NAC followed by cystectomy (Burgess et al. GU ASCO '26). In the current analysis, we assessed the impact of ERBB2 gene variants on clinical outcomes in the previously reported cohort. **Methods:** 91 patients with MIBC who received cisplatin-based NAC followed by radical cystectomy underwent genomic analysis of diagnostic transurethral resection of bladder tumor specimens with the Tempus xT platform. Sample size was prespecified by statistical design. Correlation of ERBB2 gene variants with TMB and clinical outcomes was performed using logistic regression, Cox proportional hazards models, and Kaplan-Meier techniques. **Results:** Median follow for the cohort was 63.6 months. pCR was achieved in 31.9%. Thirty-eight (41.8%) patients relapsed. Only 4 (4.4%) received adjuvant immune checkpoint inhibition (ICI). ERBB2 mut and amp were exclusively found in 4 (4.4%) and 13 (14.3%) patients, respectively. All ERBB2 mut were p.S310F. pCR occurred in 3 (75%) patients with mut and 6 (46.2%) patients with amp. In those with amp and no pCR (7), 4 were ypTaN0 or ypT1N0. In aggregate, the presence of ERBB2 gene variants (mut + amp, n = 17) was associated with an improved pCR rate compared to no ERBB2 gene variant (OR = 3.038, p = 0.048). ERBB2 variants (mut + amp) were not clearly associated with a TMB $>$ 10 Mut/Mb (OR = 2.217, p = 0.178). Five patients with ERBB2 gene variants relapsed (29.4%, OR = 0.518, p = 0.288). Three (75%) mut and ten (76.9%) amp patients remain alive. The median RFS for patients with and without ERBB2 gene variants in aggregate is 124.1 and 54.7 months (HR = 0.460, p=0.094). The median overall survival (OS) for patients with and without ERBB2 gene variants is Not Reached and 107.6 months (HR = 0.381, p=0.098). **Conclusions:** The impact of ERBB2 gene variants (mut + amp) on survival in MIBC-patients treated with NAC has not been previously reported. In this cohort collected before widespread use of peri-operative ICI, the presence of ERBB2 gene variants was associated with improved pCR rates and showed strong trends for improved RFS and OS but not clearly associated with high TMB. These findings establish a prognostic role for ERBB2 amp in addition to previously reported ERBB2 mut in patients with MIBC. Whether peri-operative use of ICI or ERBB2-targeted agents may influence these findings warrants further investigation. Research Sponsor: Atrium Health Foundation.

4596 **Poster Session**

Impact of FGFR3 pathway activation in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy. First Author: Earle F. Burgess, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Charlotte, NC

Background: The prognostic value of FGFR3 pathway activation in patients with muscle-invasive bladder cancer (MIBC) treated with neoadjuvant chemotherapy (NAC) has not been established. Activation of FGFR3 signaling drives a subset of urothelial bladder cancers and classically results from pathogenic gene mutations (mut) or fusions (fus). Additionally, an RNA signature (FGFR-PRS) representing activation of the FGFR3 pathway independent from pathogenic FGFR3 mut or fus has been identified (Eisner et al. Clin Can Res 2024). We previously reported that high tumor mutational burden (TMB) may be associated with improved pathological complete response (pCR) and survival in a cohort of MIBC patients treated with cisplatin-based NAC (Burgess et al. GU ASCO '26). In the current analysis, we assessed the impact of FGFR3 pathway activation detected by either FGFR3 gene mut/fus or FGFR-PRS (+) on clinical outcomes in the previously reported cohort. **Methods:** 91 patients with MIBC who received cisplatin-based NAC followed by radical cystectomy underwent genomic analysis of diagnostic transurethral resection of bladder tumor specimens with the Tempus xT platform. Sample size was prespecified by statistical design. A subset of 61 patients had sufficient RNA for FGFR-PRS analysis. Correlation of FGFR3 molecular status with TMB and clinical outcomes was performed using logistic regression, Cox proportional hazards models, and Kaplan-Meier techniques. **Results:** Median follow up for the cohort was 63.6 months. pCR was achieved in 31.9%. 41.8% of patients relapsed. FGFR3 mut were found in 8 (8.8%) and included p.R248C (n = 2), p.S249C (n = 5), and p.G370C (n = 1). One (1.1%) patient had a FGFR3-TACC3 fus. In the subset with RNA analysis (n = 61), FGFR-PRS (+) was detected in 33 (54.1%), of which 28 (84.8%) were FGFR3 wild type (wt) without detected mut/fus. pCR occurred in 12.5% and 33.7% with and without FGFR3 mut [OR 0.281, p = 0.428]. pCR was similar regardless of FGFR-PRS status [OR 1.372, p = 0.602]. All tumors with FGFR3 mut/fus (n = 9) had TMB $<$ 10 Mut/Mb. Nineteen (57.6%) tumors with FGFR-PRS (+) had TMB $<$ 10 compared to 13 (46.4%) of FGFR-PRS (-) tumors. Six (75%) patients with FGFR3 mut [OR 3.188, p = 0.064] and 10 (30.3%) with FGFR-PRS (+) [OR 1.087, p = 0.999] relapsed. Patients with FGFR3 mut had inferior relapse-free survival (RFS) [HR 2.58, p = 0.028], but those with FGFR-PRS (+) did not [HR 1.37, p = 0.451]. **Conclusions:** The presence of FGFR3 mutations was associated with an inferior relapse rate and RFS in this MIBC cohort treated with cisplatin-based NAC. FGFR3 pathway activation by RNA signature (FGFR-PRS+) was not associated with inferior outcomes. Whether peri-operative FGFR3 inhibition improves prognosis in MIBC patients with FGFR3 mutations should be studied. Research Sponsor: Atrium Health Foundation.

4597 **Poster Session**

PUNCH03: Preliminary results from a phase II study of disitamab vedotin combined with tislelizumab and Bacillus Calmette-Guerin (BCG) in Her2-positive high-risk non-muscle-invasive bladder cancer (HR NMIBC). First Author: Zongren Wang, Department of Urology, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Disitamab vedotin (RC48) was a novel antibody drug conjugate that targets the Her2 protein. The KEYNOTE-057 study has supported the benefits of PD-1 inhibitor in HR NMIBC patients (pts). Our study was established to evaluate the efficacy and safety of RC48 combined with tislelizumab and BCG as a bladder-preserving treatment for Her2-positive HR NMIBC pts. **Methods:** This open-label phase II study enrolled BCG-naïve HR NMIBC pts with multiple papillary tumors (high-grade Ta or T1 tumors), and all pts were Her2-positive (IHC 2+ or 3+). Firstly, the papillary tumors should be removed all visible lesions by transurethral resection of bladder tumor (TURBT). Secondly, pts were administered RC48 (2.0 mg/kg, ivgtt), every 2 weeks for 1 cycle, and were administered tislelizumab (200 mg, ivgtt), every 3 weeks for 1 cycle. Then, pts received second TURBT. Finally, pts received at least 1 year of tislelizumab (200 mg, Q3W, ivgtt). Meanwhile, pts were administered 3 - 5 cycles of RC48 (2.0 mg/kg, Q2W, ivgtt) and received 18 instillations of BCG. Specifically, pts were started on an induction course of BCG with 6 instillations every week, followed by maintenance with 3 instillations every 2 weeks and 9 instillations every 4 weeks. The primary end point was recurrence-free survival (RFS) rate at 12 months (defined as no reappearance of high grade or T1 tumors or clinical stage development after the therapy). Secondary end points were bladder-preservation rate, OS and safety. Our study estimated a RFS rate at 12 months was no less than 85% and the study would enroll 38 pts. **Results:** By Aug. 2025, 24 eligible pts were enrolled and analyzed (male 87.5%; median age 63 years (38-85); IHC 2+ =58.3%, IHC 3+ =41.7%; tumor size$\geq$3 cm (50%); cT1=100.0%; 75.0% multiple papillary tumours. Median follow-up was 6.1 months (3.1-14.2), the median number of tislelizumab cycles was 10 (4-16) and RC48 cycles was 6 (4-8). All pts completed tislelizumab and RC48 treatment during the induction therapy. During the follow-up, only two pts showed reappearance and one pt received radical cystectomy. The bladder-preservation rate was 95.8% (95%CI, 90.7%-100%). The common treatment related adverse events (TRAEs) of any grade were fatigue (54.2%), alopecia (33.0%), anorexia (33.0%) and peripheral neuropathy (16.8%). None 3-5 grade of TRAEs were observed. **Conclusions:** Our preliminary results supported the use of disitamab vedotin combined with tislelizumab and BCG as a bladder-preserving therapy for Her2-positive HR NMIBC pts. Clinical trial information: ChiCTR2400093839. Research Sponsor: None.

4598 Poster Session

Cost-effectiveness analysis in the era of systemic immunotherapy for BCG-naive high-risk non–muscle-invasive bladder cancer in the United States, the United Kingdom, and China. First Author: Zihan Xue, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Non–muscle-invasive bladder cancer (NMIBC) has entered the era of systemic immunotherapy, with randomized trials evaluating the addition of systemic immunotherapy to BCG to improve disease control. The cost-effectiveness of combining immune checkpoint inhibitor (ICI) with BCG in BCG-naive high-risk NMIBC (HR-NMIBC) remains unclear. We therefore conducted a multinational cost-effectiveness analysis in the United States, United Kingdom, and China based on the CREST and POTOMAC studies. **Methods:** We developed a Markov model to evaluate treatment strategies for patients with BCG-naive HR-NMIBC over a 5-year time horizon from healthcare payer perspectives, with health outcomes measured in quality-adjusted life-years (QALYs). Total costs, QALYs, and incremental cost-effectiveness ratios (ICERs) were calculated for each strategy. Model robustness was assessed using deterministic and probabilistic sensitivity analyses. **Results:** Health outcomes were comparable across strategies, with BCG, durvalumab plus BCG, and sasanlimab plus BCG yielding 4.11, 4.31, and 4.18 QALYs, respectively. In the US, durvalumab plus BCG increased costs by $159,021 compared with BCG, resulting in an ICER of $827,706 per QALY, exceeding the willingness-to-pay (WTP) threshold of $150,000 per QALY. In the UK, the corresponding ICER was £503,944 per QALY, far above the WTP threshold of £20,000 per QALY. In China, the ICER reached ¥3,860,692 per QALY, exceeding the threshold defined as three times the national per-capita GDP (¥257,145). Sasanlimab plus BCG was strictly dominated by durvalumab plus BCG in all settings. Consequently, neither systemic immunotherapy–based strategy was cost-effective under the evaluated WTP thresholds. BCG was optimal in all probabilistic simulations, and ICI prices were the primary drivers of cost-effectiveness for systemic immunotherapy–based strategies. **Conclusions:** Despite modest clinical benefits, the high cost of systemic immunotherapy plus BCG precludes cost-effectiveness across health care systems, with BCG alone remaining the preferred strategy under current pricing. Future efforts should focus on drug price reductions and precision patient selection to improve the value proposition of early systemic immunotherapy. Research Sponsor: None.

	Costs ($; US)	Costs (£; UK)	Costs (¥; China)	Incremental costs ($; US)	Incremental costs (£; UK)	Incremental costs (¥; China)	Effectiveness (QALYs)	ICER ($/QALY; US)	ICER (£/QALY; UK)	ICER (¥/QALY; China)
BCG	48,828	21,307	119,383	-	-	-	4.11	-	-	-
Durvalumab + BCG	207,849	118,126	861,110	159,021	96,819	741,728	4.31	827,706	503,944	3,860,692
Sasanlimab + BCG*	309,654	138,329	932,331	260,826	117,023	812,948	4.18	3,726,091	1,671,751	1,1613,542

*The Sasanlimab plus BCG strategy is strictly dominated by the Durvalumab plus BCG strategy (higher cost and lower effectiveness).

4599 Poster Session

Final results from a phase II study of tislelizumab combined with radiotherapy as bladder-preserving treatment for high-risk non–muscle-invasive bladder cancer patients unresponsive to Bacillus Calmette-Guerin. First Author: Zhiyong Li, Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Radical cystectomy (RC) was the standard of care for high-risk non-muscle-invasive bladder cancer (HR NMIBC) patients with Bacillus Calmette-Guerin (BCG)-unresponsive papillary tumors. Clinical unmet need was to explore non-surgical treatment options for patients who were ineligible for or declined RC. Our study was established to evaluate the efficacy and safety of tislelizumab combined with radiotherapy as bladder-preserving treatment for HR NMIBC patients unresponsive to BCG. **Methods:** This open-label, single arm phase II study enrolled HR NMIBC patients with BCG-unresponsive papillary tumors (high-grade Ta or T1 tumors without carcinoma in situ). The papillary tumors should be removed all visible lesions by transurethral resection of bladder tumor (TURBT). Within 2 weeks after TURBT, eligible patients received tislelizumab 200 mg in day 1 (D1), every 21 days for eight cycles and a total radiotherapy dose of 60-66 GY in 30-33 fractions over seven weeks. The primary endpoint was disease-free survival (DFS) rate at 12 months (defined as no reappearance of high grade or T1 tumors or clinical stage development after the therapy). Secondary endpoints were bladder-preservation rate, OS and safety. Our study estimated a DFS rate at 12 months was no less than 50% and the study would enroll 32 patients to meet the primary endpoint. **Results:** Between September 4, 2020, and December 11, 2024, 32 patients (26 [81.2%] men and 6 [19.8%] women) who had received a median of eleven (IQR 7-22) previous BCG instillations were enrolled. Patients received a median of 8 cycles (IQR 8–8) of tislelizumab and of radiotherapy doses of 62.0 GY (IQR 62.0–64.0) . Median follow-up was 28.8 months (19.7-43.8). The DFS rate at 12 months was 90.6% (95%CI, 79.8%-99.6%), at 24 months was 70.2% (95%CI, 50.1%-83.4%). The bladder-preservation rate at 24 months was 93.2% (95%CI, 75.4%-98.3%). The OS rate at 24 months was 100% (95%CI, 100%-100%). The OS rate at 36 months was 90.5% (95%CI, 67.0%-97.6%). Treatment-related adverse events (TRAEs) occurred in 27 (84.4%) of 32 patients, 7 (21.9%) patients had a grade 3 TRAEs. The most common 3 TRAEs were diarrhea (9.4%), radiocystitis (3.1%), leukopenia (3.1%) and liver function damage (3.1%) without grade 4-5 TRAEs. **Conclusions:** Our final results supported the use of tislelizumab combined with radiotherapy as a promising bladder-preserving therapy for BCG-unresponsive HR NMIBC patients who were ineligible for or decline RC. Clinical trial information: ChiCTR2000035275. Research Sponsor: None.

4600 Poster Session

Prognostic value of post-operative circulating tumor DNA (ctDNA) in real-world treatment and outcomes among patients (pts) with muscle invasive (MIBC) and locally advanced (LA) bladder cancer (BC). First Author: Khilna Patel, Flatiron Health, Durham, NC

Background: BC has high recurrence risk despite curative intent surgery and perioperative therapy. As ctDNA guided strategies are investigated in trials, evidence from routine practice is needed to understand treatment decisions and how post-surgery ctDNA status relates to outcomes. This study evaluated real-world survival outcomes and treatment patterns by post-surgery ctDNA status among pts with MIBC/LA BC and assessed prognostic value beyond pathologic response (pCR). **Methods:** This retrospective study used the US-based, EHR-derived deidentified Flatiron Health Research Database (cutoff 08/31/25). Pts with MIBC or LA BC diagnosed on or after January 2015 who underwent surgery and ctDNA testing were included. Pt characteristics were summarized, including ctDNA testing patterns. Adjuvant therapy initiation was described by post-surgery ctDNA status. Real-world overall survival (rwOS) and disease-free survival (rwDFS) were estimated from the date of surgery using Kaplan–Meier methods, stratified by pCR status and post-surgery ctDNA status (results within 90 days post-surgery), and summarized descriptively with landmark survival probabilities. **Results:** Among 388 pts in the study population who underwent surgery and received ctDNA testing, median age at diagnosis was 70 years (IQR: 63.8-75.0); 63% received neoadjuvant therapy, 49% received adjuvant therapy, and 11% had residual disease post-surgery. Use of ctDNA testing increased substantially over time in the study cohort, from 2.6% (10/388) in 2021 to 57% (223/388) in 2025. Of ctDNA-tested pts, 97 pts had evaluable post-surgery ctDNA results (ctDNA+: 10.3% [n=40]; ctDNA−: 14.7% [n=57]). Of these, adjuvant therapy was given to 43% of post-surgery ctDNA+ pts and 35% of ctDNA− pts. The 12-month rwOS (95% CI) was 69.4% (53.8%-89.6%) for ctDNA+ vs 96.5% (91.8%-100.0%) for ctDNA−; 12-month rwDFS (95% CI) was 34.4% (20.8%-56.8%) vs 72.7% (61.2%-86.4%), respectively. Stratified by pCR, outcomes were favorable among pts achieving pCR. Although limited by small sample sizes, ctDNA status appeared to further differentiate prognosis within each stratum, particularly among pts without pCR, where ctDNA+ pts had worse rwOS (43.2% vs 100.0%, $P < .01$) and worse rwDFS (9.9% vs 64.2%, $P = .014$) over time compared with ctDNA− pts. **Conclusions:** Rapid growth in ctDNA testing highlights increasing clinical adoption. Post-surgery ctDNA positivity was linked to worse rwOS/rwDFS in pts with MIBC/LA BC and further stratified prognosis beyond pCR. Importantly, ctDNA may complement pathologic response in identifying pts at highest risk for recurrence and informing post-surgical management. Future work is needed to translate these findings into clinically actionable insights and treatment strategies. Research Sponsor: Flatiron Health, Inc.

4601 Poster Session

Assessing responses to UGN-102 across EORTC recurrence score groups in patients with recurrent low-grade intermediate-risk NMIBC (ENVISION trial). First Author: Sandip M. Prasad, Morristown Medical Center/Atlantic Health System and Garden State Urology, Morristown, NJ

Background: The ENVISION phase 3 study (NCT05243550) treated patients with recurrent low-grade intermediate-risk non-muscle-invasive bladder cancer (LG-IR-NMIBC) with UGN-102, a reverse thermal hydrogel administered intravesically containing 75 mg mitomycin. Complete response (CR) rate at 3 months was 79.6% (95% confidence interval [CI]: 73.9, 84.5) with a 72.2% (95% CI: 64.1, 78.8) probability of remaining in response 24 months later. The European Organization for Research and Treatment of Cancer (EORTC) recurrence score tables provide estimates of recurrence based on baseline prognostic factors. We conducted a post-hoc analysis of CR and duration of response (DoR) by EORTC recurrence score subgroup. **Methods:** 240 patients with recurrent LG-IR-NMIBC received ≥1 dose of UGN-102. CR was assessed at 3 months using cystoscopy, urine cytology testing, and for-cause biopsy. Patients achieving CR entered the follow-up period and are being assessed for recurrence or progression for up to 5 years. CR at 3 months and probability of maintaining CR at 24 months in patients with EORTC recurrence scores of 1–4, 5–9, and 10–17 were calculated. DoR was calculated using the Kaplan–Meier (KM) estimation method. **Results:** The median (range) EORTC recurrence score was 7 (2–13). CR rate at 3 months was 83.9%, 81.2%, and 60.0% for patients with recurrence scores of 1–4 (n=31), 5–9 (n=191), and 10–17 (n=15), respectively. Of the patients with CR at 3 months, 26.9%, 23.9%, and 33.3% (for recurrence scores of 1–4, 5–9, and 10–17) experienced recurrence of LG disease, progression (either in stage or grade), or death by 24 months. The KM estimate of median DoR was not estimable for any group due to the low event rates. **Conclusions:** UGN-102 demonstrated robust complete response rates across all EORTC recurrence score subgroups, including patients with higher baseline recurrence risk. The majority of patients remained recurrence-free at 24 months. Despite the post-hoc design and small subgroup sizes, these findings suggest UGN-102 provides durable and clinically meaningful disease control in recurrent LG-IR-NMIBC. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma, Inc.

	EORTC recurrence score group		
	1–4 N=31	5–9 N=191	10–17 (N=15)
CR at 3 months, n (%)	26/31 (83.9)	155/191 (81.2)	9/15 (60.0)
CRR (95% CI)	83.9 (66.3, 94.5)	81.2 (74.9, 86.4)	60.0 (32.3, 83.7)
Recurrence 24 months[a], n (%)	7/26 (26.9)	37/155 (23.9)	3/9 (33.3)
Recurrence of LG disease	5/26 (19.2)	27/155 (17.4)	3/9 (33.3)
Progression	0	7/155 (4.5)	0
Death	2/26 (7.7)	3/155 (1.9)	0
Probability of remaining in response at 24 months, %, 95% CI[b]	67.4 (43.2, 83.1)	73.7 (64.6, 80.8)	66.7 (28.2, 87.8)
Median duration of follow up, months, 95% CI[c]	23.29 (23.03, 23.92)	23.72 (23.66, 23.92)	23.90 (23.72, NE)

[a]24 months after 3-month CR.
[b]Calculated using the KM method, with Brookmeyer–Crowley CIs.
[c]Estimated using reverse KM method. CI, confidence interval; CRR, complete response rate.

4602 **Poster Session**

Patient experiences with UGN-102 for recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC): Insights for shared decision making. First Author: Ruchika Talwar, Department of Urology, Vanderbilt University Medical Center, Nashville, TN

Background: Recurrent LG-IR-NMIBC can be managed using various approaches, including repeat transurethral resection of bladder tumor (TURBT) and non-surgical intravesical therapies. One option is UGN-102, a reverse thermal hydrogel containing 75mg mitomycin. Given LG-IR-NMIBC tends to recur, understanding patients' experiences/preferences across management strategies is essential to support clinical shared decision making. **Methods:** The ENVISION study (NCT05243550) assessed patient-reported outcomes via EORTC-QLQ-NMIBC24. Patients with biopsy-confirmed LG-IR-NMIBC and ≥1 previous NMIBC episode at baseline had 6 once-weekly intravesical instillations of UGN-102 in an outpatient setting. 32 US-based patients had semi-structured prospective phone interviews that compared experiences of prior TURBT (at enrollment) vs UGN-102 at 3 months. **Results:** 232 patients were included; 94.8% received all 6 doses of UGN-102. Mean change from baseline (CfB) scores at 3- and 12-months post-treatment did not reach minimal clinically important difference (MCID) thresholds for any of the EORTC-QLQ-NMIBC24 domains (Table). Patients perceived more interference with routines/responsibilities with TURBT vs UGN-102, similar urinary symptoms, expressed concern regarding more bleeding with TURBT, and would recommend UGN-102 as a less invasive, painful, and time-consuming procedure than TURBT. A small number of patients preferred surgery as a 1-day procedure vs 6 weekly intravesical instillations. **Conclusions:** UGN-102 maintained stable quality-of-life scores across NMIBC24 domains and was generally preferred by patients over surgical resections. These important insights support shared decision making, enabling clinicians to discuss trade-offs between procedural convenience and treatment invasiveness in recurrent LG-IR-NMIBC management. Clinical trial information: NCT05243550. Research Sponsor: UroGen Pharma, Inc.

EORTC-QLQ-NMIBC24 domain	MCID	Baseline, mean (SD) n	3-month CfB, mean (SD) n	12-month CfB, mean (SD) n
Urinary symptoms	6.34	13.7 (14.50) 231	0.8 (13.30) 217	−0.6 (10.71) 154
Malaise	4.37	4.0 (8.79) 231	0.2 (10.57) 217	1.2 (9.55) 154
Intravesical treatment issues	9.38	12.8 (18.74) 231	−0.8 (20.14) 217	0.2 (20.34) 154
Future worries	11.08	35.6 (22.49) 231	−4.1 (21.71) 217	−7.1 (22.84) 154
Bloating and flatulence	7.59	9.2 (15.35) 231	1.1 (16.24) 217	0.8 (15.52) 154
Risk of contaminating partner	13.66	10.9 (23.74) 141	−1.6 (17.45) 106	−7.5 (20.78) 67
Female sexual problems	12.87	9.6 (22.04) 45	−2.1 (18.81) 32	−3.5 (15.29) 19
Male sexual problems	16.29	21.9 (32.77) 144	1.2 (23.71) 134	0 (26.89) 94
Sexual intimacy	8.69	8.0 (17.27) 142	1.3 (22.35) 103	2.9 (20.55) 68
Sexual function	10.61	79.4 (25.01) 231	4.0 (15.25) 218	4.1 (16.97) 154
Sexual enjoyment	11.64	60.5 (33.11) 140	8.0 (25.23) 104	10.4 (29.71) 67

SD, standard deviation. A positive CfB indicates worsening across all scales/items.

4603 **Poster Session**

Influence of low-coverage whole-genome sequencing–based urinary tumor fraction and chromosomal instability on recurrence risk stratification in systemic immunotherapy-treated non–muscle–invasive bladder cancer. First Author: Yunkai Qie, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Urinary tumor DNA (utDNA) is increasingly explored for prognostic assessment in bladder cancer, but most studies rely on a simple positive/negative classification, and its prognostic value in patients receiving systemic immune checkpoint inhibitors (ICIs) remains unclear. Low-coverage whole-genome sequencing (LC-WGS) of urine enables low-cost quantitative assessment of tumor fraction (TF) and chromosomal instability (CIN), providing richer molecular information than conventional binary utDNA status. We evaluated whether LC-WGS–derived TF and CIN improve prognostic stratification in ICI–treated high- and very high-risk non–muscle–invasive bladder cancer (NMIBC). **Methods:** Patients with high- or very high-risk NMIBC were enrolled in a prospective cohort treated with ICI tislelizumab plus low-dose nab-paclitaxel. Pretreatment urine samples were collected and analyzed using LC-WGS to derive TF and CIN. Clinicopathologic variables were collected at baseline. The primary endpoint was 2-year recurrence-free survival (RFS). Prediction models were constructed using clinicopathologic features (tumor size, number, concomitant carcinoma in situ, lymphovascular invasion) alone and in combination with TF and CIN. **Results:** A total of 35 patients were included. After a median follow-up of 27.3 months, 11 patients experienced disease recurrence. Models based on clinicopathologic features alone demonstrated limited discrimination for 2-year RFS (AUC = 0.61). Higher urinary TF and CIN were significantly associated with increased recurrence risk (TF: HR 2.18, 95% CI 1.29–3.97, p = 0.004; CIN: HR 2.74, 95% CI 1.41–5.32, p = 0.002). Incorporation of TF improved discrimination (AUC = 0.71), and further addition of CIN achieved the highest performance (AUC = 0.80; ΔAUC = 0.19 vs clinical model, p = 0.01). Patients classified as high molecular risk based on combined TF and CIN had significantly lower 2-year RFS than those at low molecular risk (HR 3.92, 95% CI 1.62–9.48, p = 0.002). Notably, the molecular-only model incorporating TF and CIN demonstrated discrimination comparable to the clinicopathologic-integrated model (AUC = 0.79 vs 0.80, p = 0.68), suggesting that urinary genomic features alone may provide sufficient information for recurrence risk stratification in this setting. **Conclusions:** Urinary TF and CIN derived from cost-effective LC-WGS substantially improved recurrence risk stratification beyond conventional tumor characteristics in NMIBC patients treated with systemic immunotherapy. These findings suggest that urine-based molecular profiling may offer a practical and scalable complement to conventional clinicopathologic risk assessment for baseline risk stratification and post-therapy management. Research Sponsor: None.

4604 **Poster Session**

UTOPIA: A phase 3 trial of UGN-103, an intravesical mitomycin reverse thermal hydrogel, in recurrent low-grade intermediate-risk non-muscle invasive bladder cancer. First Author: Abhishek Srivastava, Carolina Urologic Research Center, Myrtle Beach, SC

Background: Management of recurrent low-grade (LG), intermediate-risk (IR) non-muscle invasive bladder cancer (NMIBC) remains challenging due to frequent recurrence following standard surgical management with transurethral resection of bladder tumor (TURBT). UGN-102 is an intravesical mitomycin reverse thermal hydrogel, approved by the Food and Drug Administration for treatment of adults with recurrent LG-IR-NMIBC based on the Phase 3 ENVISION trial demonstrating a complete response (CR) rate of 80% (95% confidence interval [CI]: 74, 85) at 3 months, with an 82% (95% CI: 76, 87) probability of remaining in response 12 months from initial CR. UGN-103 is a novel formulation of UGN-102 developed to simplify drug preparation and shorten manufacturing time. **Methods:** UTOPIA (NCT06331299) is an ongoing, multicenter, single-arm, Phase 3 study evaluating UGN-103 as primary treatment for adults with recurrent LG-IR-NMIBC. Eligible patients provided written informed consent and received six once-weekly intravesical instillations of UGN-103 (mitomycin 75 mg in 56 mL admixture). Disease assessment was performed 3 months after start of treatment. Patients with no detectable disease entered a follow-up period, with evaluations every 3 months until recurrence, progression, death, or completion of follow-up (12 months after the 3-month visit). The primary endpoint was CR rate (defined as the proportion of patients assessed as having no evidence of disease at the 3-month visit) based on cystoscopy, for-cause biopsy, and urine cytology. Secondary endpoints include durability of response, safety and tolerability, and pharmacokinetics. Data cut off: September 3, 2025. **Results:** A total of 99 patients received ≥1 instillation of UGN-103; of these, 97% (n=96) received all 6 instillations. At baseline, median patient age was 71 years (range 46, 93), with 78% (n=77) being ≥65 years old. Most patients were male (72%; n=71) and 99% (n=98) were White. Most patients had multiple tumors (90%; n=87), with the longest tumor diameter being ≤3 cm in 96% (n=93). At 3 months, 77 of 99 patients in the intent-to-treat population achieved CR (CR rate: 78% [95% CI: 68, 86]). Non-CR outcomes included residual disease in 16% (n=16) and progression to high-grade disease in 4% (n=4). Two (2%) patients had missing/indeterminate responses. Treatment-emergent adverse events (TEAEs) were reported in 60% of patients (n=59), with the most common TEAE (≥10%) being dysuria (19%; n=19). Two (2%) patients had a total of 3 serious TEAEs, including atrial fibrillation, osteoarthritis, and respiratory failure; none were treatment related. No TEAE led to death. **Conclusions:** UGN-103 demonstrated a safety and efficacy profile similar to that observed with UGN-102 in patients with recurrent LG-IR-NMIBC, supporting continued evaluation of UGN-103 as an intravesical treatment option. Clinical trial information: NCT06331299. Research Sponsor: UroGen Pharma, Inc.

4605 **Poster Session**

Preliminary results of a phase II study to evaluate the efficacy and safety of disitamab vedotin (RC48-ADC) in combination with radiotherapy for adjuvant therapy in upper tract urothelial carcinoma. First Author: Zihao Tao, Department of Urology, Peking University First Hospital, Peking University, Beijing, China

Background: Although postoperative platinum-based adjuvant chemotherapy improves disease-free survival (DFS), many upper tract urothelial carcinoma (UTUC) patients (pts) were ineligible for cisplatin after radical nephroureterectomy (RNU). UTUCs did not seem to benefit from adjuvant immunotherapy. Previous evidence demonstrated adjuvant radiotherapy improvesd cancer-specific survival in HR UTUCs. Further exploration of alternative adjuvant treatment strategies is needed. This study aims to evaluate the therapeutic potential of RC48-ADC in combination with radiotherapy in HER2 overexpressing UTUCs. **Methods:** This is an open-label, phase II, non-randomised study to evaluate the efficacy and safety of disitamab vedotin (RC48-ADC), a humanized anti-HER2 antibody, in combination with radiotherapy as a novel adjuvant therapy strategy in UTUC. We recruited cisplatin-intolerant pts with HER2-overexpressing (Immunohistochemistry, IHC 2+, 3+) UTUC after nephroureterectomy staged as pT2N0M0 with high-grade/multifocal disease/positive surgical margin, pT3-4 N0 M0 or pTany N1-2 M0. Pts who declined any adjuvant therapy were assigned to the surveillance group. Pts in adjuvant therapy group received RC48-ADC (2.0 mg/kg D1 Q2W, 6 months) and radiotherapy (45-50Gy/25f/5w, lymphatic drainage regions; 62.5Gy/25f/5w, enlarged lymphnode). The therapy was initiated within 90 days of surgery. The primary end point was DFS. Secondary end points were overall survival (OS), metastasis-free survival (MFS), local-recurrence free survival (LRFS) and safety. The trial is registered with ClinicalTrials.gov, NCT06210490. **Results:** As of January 2026, 54 patients out of the planned 60 pts have been enrolled in the study. Thirty pts were assigned to adjuvant therapy group and 24 in surveillance. In therapy group, 17 pts completed adjuvant therapy, while 13 pts were undergoing treatment. At a median follow-up of 12.4 months, one recurrence was observed in the therapy group, while 9 patients in surveillance experienced recurrence. The 1-year disease-free survival rates were 95% (95% CI 85.9–100) in the adjuvant therapy group and 69.6% (95% CI 53.1–91.2) in the surveillance group. As of now, the most common (≥20%) treatment-related adverse events (TRAEs) were peripheral sensory neuropathy (40%), increased AST (28%), asthenia (28%) and alopecia (20%). Grade ≥ 3 TRAE was observed in 2 patients (8%), the patients experienced gastrointestinal hemorrhage and peripheral sensory neuropathy, respectively. **Conclusions:** This study is the first to evaluate the efficacy and safety in adjuvant treatment of ADC plus radiotherapy in UTUCs. The combination of RC48-ADC and radiotherapy as a new adjuvant therapy demonstrated a tolerable safety profile in pts with HER2-overexpressing UTUC. Clinical trial information: NCT06210490. Research Sponsor: RemeGen.

4606 **Poster Session**

Adjuvant nivolumab in high-risk muscle-invasive urothelial carcinoma: Real-world evidence from the SOGUG-NIADY study of the Spanish Oncology Genitourinary Group (SOGUG). First Author: Sara Perez Ramirez, Hospital Gregorio Marañón, Madrid, Spain

Background: Adjuvant nivolumab significantly improved disease-free survival (DFS) in patients (pts) with high-risk muscle-invasive urothelial carcinoma (MIUC) after radical surgery in the phase III CheckMate-274 trial. Based on these results, since august 2023, the Spanish National Health System reimburses postoperative nivolumab in high-risk, positive programmed death ligand 1 (PDL1) MIUC. The aim of the PrInCIS-NIADY study was to assess the effectiveness and safety of adjuvant nivolumab in real-world clinical practice after its approval in Spain. **Methods:** PrInCIS is a nationwide multicentre, non-interventional epidemiological study with retrospective patient inclusion and prospective follow-up. The NIADY cohort included pts with high-risk PDL1+ MIUC treated with adjuvant nivolumab in routine practice, was conducted across 65 hospitals belonging to the Spanish Oncology Genitourinary Group (SOGUG) in 16 Spanish regions. Baseline characteristics, treatment patterns, safety, and outcomes were analysed and compared against CheckMate-274. **Results:** A total of 395 evaluable pts were included, 95.7% were PD-L1 positive. Median age was 69.5 years, (74.9% aged ≥65 years); 91.4% had bladder cancer and 8.6% had upper tract disease. Predominant histology was urothelial carcinoma (79.2%). 51.2% pts received neoadjuvant platinum-based chemotherapy (NAChT) (48.9% cisplatin vs. 2.3% carboplatin) (Table). With a median follow-up of 13 months, 27.3% of pts had disease recurrence. Treatment after recurrence was platinum-based ChT in 8.8% and enfortumab vedotin in 6.6% of pts. Median DFS and overall survival (OS) were not reached. The estimated 18-month DFS and OS probability were 65.6% and 78.3% respectively. Nivolumab was well-tolerated: Treatment delays or dose reductions occurred in 37.3% of pts. Most common (>10%) grade 1-2 immune-related adverse events were fatigue, pruritus and diarrhea, while grade 3–4 toxicity was infrequent (>1%), mainly consisting in hepatic enzyme and creatinine elevation. **Conclusions:** Outcomes and effectiveness of adjuvant nivolumab in this large Spanish real-world cohort were consistent with the Checkmate-274 results, with a manageable safety profile despite an older population. In spite of short-term follow-up, these findings externally validate the results of the pivotal trial reinforcing the role of adjuvant nivolumab in daily clinical practice for high-risk MIUC. Research Sponsor: SOGUG: Spanish Oncology Genitourinary Group.

Patient characteristics.

Characteristics	CHECKMATE-274 (N=353)	NIADY (N=395)
Age. Mean (range)-yr	65.3 (30-92)	69.5 (35-88)
Sex. Male / Female	75.1 / 29.9 %	81.8 / 19.2 %
ECOG 0-1 / >2	98 / 2 %	96.7 / 3.3 %
Bladder/Upper tract	79 / 21%	91.4 / 8.6 %
Pure urothelial / mixed histology	59.7 / 40.3 %	79.2 / 20.7 %
NAChT cisplatin / carboplatin	43.3 / NA %	48.9 / 2.3 %
pT2-4a N0	52.2 %	64.3 %
pT4b o N+	47.3 %	35.7 %
PDL1+ >=1%	39.7 %	95.7 %

4607 **Poster Session**

Magnitude and timing of clinical benefit associated with pathologic complete response in perioperative muscle-invasive bladder cancer: A reconstructed IPD analysis of NIAGARA trial. First Author: Andrea Malgeri, Medical Oncology 1, IRCCS National Cancer Institute Regina Elena, Rome, Italy

Background: Pathologic complete response (pCR) is widely used as an early efficacy endpoint in neoadjuvant or perioperarive bladder cancer trials. However, formal surrogacy analyses linking pCR to long-term clinical outcomes are lacking. In particular, the magnitude and timing of clinically meaningful benefit associated with pCR remain poorly defined. We aimed to quantify the absolute benefit and temporal emergence of event-free survival (EFS) and overall survival (OS) associated with pCR in NIAGARA trial. **Methods:** Individual patient data (IPD) were reconstructed from the most recent publicly available Kaplan-Meier curves of the NIAGARA trial, including stratification by pCR and non-pCR status for each treatment arm. The primary analysis compared outcomes between pCR and non-pCR patients within each treatment arm. Restricted mean survival time differences (ΔRMST) were estimated at 24 months for EFS and 36 months (mo) for OS. Time to benefit (TTB) was defined as the earliest time point at which ΔRMST reached ≥1 mo for EFS and ≥2 mo for OS. Exploratory analyses compared outcomes within pCR patients and within non-pCR patients between treatment arms, to explore whether the clinical benefit associated with pCR is purely prognostic or reflects treatment-related modulation within pathological response strata. **Results:** At 24 months, pCR was associated with a large and early EFS benefit across treatment arms. Among patients receiving durvalumab + cisplatin-gemcitabine (CG), pCR was associated with a ΔRMST of +5.87 mo (95% CI 4.78-6.96; $p<0.0001$) compared with non-pCR, with a TTB of 9 mo. Similar results were observed in the CG arm (ΔRMST of +5.63 mo, 95% CI 4.49-6.77; $p<0.0001$), with a TTB of 9 mo. At 36 months, pCR was also associated with a substantial OS benefit. In the durvalumab + CG arm, pCR was associated with a ΔRMST of +5.32 mo (95% CI 3.89-6.74; $p<0.0001$) versus non-pCR, with a TTB of 22 mo. Comparable findings were observed in the CG arm (ΔRMST +5.89 mo, 95% CI 4.30-7.47; $p<0.0001$), and a TTB of 20 mo. In exploratory analyses, no significant EFS or OS differences were observed between treatment arms among pCR patients (ΔRMST <1 month), with a TTB of 38 mo for EFS and not reached within 60 mo for OS. Among non-pCR patients, treatment-related differences were similarly modest (ΔRMST ~1 month), with delayed TTB (19 mo for EFS and 50 mo for OS). **Conclusions:** Using reconstructed IPD from NIAGARA, pCR identifies a large, early EFS benefit and a later OS benefit, informing, in the absence of formal surrogacy validation, a quantitative and temporal clinical interpretation of pCR. In contrast, no additional treatment-related survival benefit was observed within pCR or non-pCR subgroups, raising the hypothesis that survival differences may be largely attributable to pCR rather than to treatment-related modulation within response strata. Research Sponsor: None.

4608 **Poster Session**

Progress of phase II study of MVR-T3011, an IL-12/anti-PD-1 armed oncolytic HSV-1, in high-risk BCG-unresponsive CIS and papillary NMIBC. First Author: Dingwei Ye, Fudan University Shanghai Cancer Center, Shanghai, China

Background: MVR-T3011 is a novel Phase II oncolytic immunotherapy candidate based on herpes simplex virus type 1 (HSV-1). It combines potent tumor lysis with co-expression of anti-PD-1 antibody and IL-12. MVR-T3011 is being evaluated as monotherapy in patients with non-muscle invasive bladder cancer (NMIBC), including both BCG-unresponsive and BCG-naïve populations. Herein, we report the latest Phase II results of MVR-T3011 in BCG-unresponsive carcinoma in situ (CIS) and papillary NMIBC. **Methods:** In this ongoing trial, MVR-T3011 is administered intravesically in 50 mL without prewash. This simplified procedure utilizes the virus's natural ability to bind to glycosaminoglycans (GAGs) on the urothelial surface as attachment receptors. Patients were assigned to two groups: 1) 2×10^9 PFU, administered weekly for 12 weeks during the induction phase, followed by maintenance treatment every 2 weeks; 2) 1×10^{10} PFU, administered weekly for 6 weeks for induction, then every 3 weeks of treatment for maintenance. Both continued for up to 2 years. Efficacy was assessed every 3 months via cystoscopy, cytology, biopsy, and imaging. Primary endpoints were complete response rate (CRR) for CIS and recurrence-free survival (RFS) for papillary disease. The safety was fully evaluated. **Results:** As of Dec 31, 2025, a total of 43 patients were enrolled, 14 with CIS and 29 with Papillary. Among 13 evaluable CIS patients, 7 were treated at 2×10^9 PFU dose level, achieving 6-month CRR of 71.4% (5/7), 3 patients maintained CR for 12 months, and 1 patient remained in CR for 18 months. 6 patients treated at 1×10^{10} PFU dose level, all achieved complete responses, with 100% CRR at 3 months (6/6), 6 months (5/5), and 9 months (3/3). Among 26 evaluable papillary patients, 16 were treated at the 2×10^9 PFU dose level. The RFS rate was 80.8% (95% CI: 51.4–93.4) at 6 months, 74.0% (95% CI: 44.6–89.4) at both 12 and 15 months, and 64.8% (95% CI: 34.0–84.0) at both 18 and 21 months. 10 patients treated at 1×10^{10} PFU dose level, the 3-month and 6-month RFS rates were both 88.9%% (95% CI: 43.3–98.4). Assessment of the safety data revealed that most treatment-related adverse events (TRAEs) were grade 1. Common events included hematuria (25.0%), urinary tract infection (11.4%), proteinuria (9.1%), pollakiuria (6.8%), and rash (6.8%; immune-related). Only two grade 3 TRAEs were reported, both of which were urinary tract infections. No higher-grade TRAE or SAE occurred. **Conclusions:** MVR-T3011 is being evaluated as mono or combination therapy across multiple solid tumors. In this study, MVR-T3011 demonstrates suitability for intravesical administration, plus promising efficacy and a favorable safety profile. Durable complete responses were observed in CIS patients and encouraging 12-month RFS rates in papillary disease. These findings support its potential as a bladder-sparing option for BCG-unresponsive NMIBC. Clinical trial information: NCT06427291. Research Sponsor: None.

4609 **Poster Session**

Bulumtatug fuvedotin (BFv; 9MW2821) plus toripalimab in perioperative patients with muscle-invasive bladder cancer (MIBC): Results of cohort A from a phase 2 study. First Author: Zhuowei Liu, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Radical cystectomy with pelvic lymph node dissection (RC+PLND) has always been the standard treatment for MIBC. Perioperative treatment, especially cisplatin-based neoadjuvant therapy, could reduce the risk of tumor recurrence effectively and prolong the survival of patients. BFv, a novel Nectin-4 antibody-drug conjugate, combined with toripalimab, has demonstrated promising efficacy and safety profile in advanced urothelial cancer patients. This provides possibilities for the perioperative treatment of MIBC. Here we report the preliminary results of BFv plus toripalimab in patients with perioperative MIBC (cohort A). **Methods:** Patients with MIBC (cT2-4aN0-1M0) can be enrolled in cohort A. Eligible patients will receive BFv plus toripalimab for 4 cycles in neoadjuvant stage, and then proceed with RC+PLND. After surgery, patients will receive BFv plus toripalimab for 6 cycles and toripalimab only for the next 11 cycles in the adjuvant stage. The primary endpoint was pathological complete response (pCR). Main secondary endpoints were pathological downstaging (PDS) rate and disease-free survival (DFS), overall survival (OS) and safety. **Results:** As of 4 Jan 2026, 32 patients were enrolled in the cohort A. 7 patients had completed neoadjuvant therapy and 6 of them were performed with RC+PLND. One patient achieved CR in the neoadjuvant stage and refused to undergo the surgery. pCR rate was 66.7% (4/6, 95%CI 22.3-95.7), PDS rate was 83.3% (5/6, 95%CI 35.9-99.6). DFS and OS were not mature. Safety profile was consist with previous study. No new safety signals of BFv or toripalimab were observed in this study. **Conclusions:** This study showed remarkable preliminary efficacy of BFv plus toripalimab in perioperative patients with MIBC. It may offer a new choice for MIBC patients and deserve to be further investigation. Clinical trial information: NCT07314723. Research Sponsor: Mabwell (Shanghai) Bioscience Co., Ltd.

4610 Poster Session

Survival and treatment patterns of patients with metastatic urothelial cancer in France: Results of a cohort study using the French National Healthcare database (SNDS). First Author: Philippe Barthelemy, Institut de Cancérologie Strasbourg Europe, Strasbourg, France, Strasbourg, France

Background: Despite the increasing number of available treatment options, metastatic urothelial cancer (mUC) remains a challenging disease, characterized by high mortality and substantial rates of undertreatment worldwide. In this study, we aimed to describe treatment patterns and survival among patients with mUC in France. **Methods:** This retrospective study included adult patients with incident mUC between January 2017 and December 2023. The overall study cohort was divided into two subcohorts: treated, defined as initiating any systemic treatment within 120 days after index date and untreated (defined as not initiating any treatment within 120 days after index date). The index date was defined as diagnosis (first recorded ICD-10 code for metastasis) or start of systemic anticancer treatment. Overall survival (OS) was estimated using Kaplan-Meier method, calculated from the index date for the overall cohort and untreated subcohort, and from the initiation of first line (1L) treatment for the treated subcohort. Baseline characteristics including sex, age, and age-adjusted Charlson Comorbidity index (CCI) were compared between treated and untreated subcohorts using $\chi 2$ and Wilcoxon tests. **Results:** The study included 24,912 patients, male (77.8%), mean (SD) age was 75 (11) yrs, and median (IQR) age-adjusted CCI was 4 (2-5). Median (IQR) follow-up was 2.5 (1-10) months. Mortality was 90.8%, primarily due to malignant tumors (88.6%) among the recorded causes of death. Overall, 1L treatment was initiated in 10,562 pts (42.4%), with increasing annual rates from 2017 (38%) to 2023 (47%). Chemotherapy was the predominant 1L treatment (75.4%) followed by immune-oncology (IO) agents (24.5%). Of 7,960 pts receiving 1L chemotherapy, 4,193 (53%) did not receive any further treatment, and 2,184 (27%) patients received chemotherapy, 1,359 (17%) IO, and 224 (3%) antibody-drug conjugates in second line. Mean (SD) time from index date to 1L initiation was 18 (25) days and mean (SD) duration of 1L was 101 (155) days. Median OS was 2.5 (95% CI 2.4-2.6), 7.6 (7.4-7.8) and 1.1 (1.1-1.1) months for the overall cohort, treated and untreated subcohorts, respectively. It decreased with higher CCI scores: from 3.99 months for patients with CCI 0 to 1.54 months for those with CCI $\geq$5. Sex, age and CCI were significantly different between treated and untreated patients ($p<0.0001$). **Conclusions:** This nationwide population-based study showed that more than half of patients with mUC treated in real-world clinical practice in France did not receive 1L systemic treatment. Untreated individuals were mainly elderly, male, comorbid, and experienced poor survival. These findings underscore the importance of the early utilization and optimization of available therapies to improve outcomes, especially among untreated patients with mUC. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

4611 Poster Session

Real-world effectiveness of disitamab vedotin plus PD-1 inhibitor versus platinum-based chemotherapy as postoperative adjuvant therapy in high-risk upper tract urothelial carcinoma: A comparative study. First Author: Yudong Cao, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Urology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Currently, gemcitabine–platinum combination chemotherapy represents the standard adjuvant regimen following radical surgery for high-risk upper tract urothelial carcinoma (UTUC), as it reduces the risk of disease progression in approximately half of all patients. Nevertheless, a substantial proportion of patients are ineligible for this standard regimen due to post-surgical complications like renal insufficiency. Disitamab vedotin (DV), an antibody–drug conjugate targeting HER-2, has recently been shown to yield superior outcomes in advanced urothelial carcinoma when combined with PD-1 inhibitor immunotherapy. Therefore, based on real-world data, this study aims to evaluate the efficacy of the DV plus PD-1 inhibitor versus standard gemcitabine–platinum chemotherapy in the operative adjuvant treatment of UTUC. **Methods:** A retrospective cohort analysis was conducted using data from UTUC patients at Peking University Cancer Hospital between January 2015 and June 2025. The study included UTUC patients diagnosed as $pT_{2-4a}N_0M_0$, who received either 4–6 cycles of DV combined with PD-1 inhibitors or gemcitabine–platinum (cisplatin or carboplatin selected based on postoperative renal function) combination chemotherapy. The primary endpoint was disease-free survival (DFS), the key secondary endpoint was treatment-related adverse events (TRAEs). **Results:** A total of 105 UTUC patients were enrolled, with a median follow-up of 45.7 months. Of these, 34 patients were treated with DV combined with PD-1 inhibitors (DV group), and 71 patients received chemotherapy. Compared with chemotherapy, the DV plus PD-1 inhibitor significantly prolonged DFS, with a hazard ratio of 0.29 (95% CI 0.09–0.98; P = 0.047). The estimated 3-year DFS rates were 83.1% (95% CI 66.8–100.0) in the DV group and 64.9% (95% CI 54.3–77.7) in the chemotherapy group. Regarding safety, grade $\geq$ 3 TRAEs occurred more frequently in the chemotherapy group than in the DV group (36.6% vs. 12.9%), mainly comprising hematologic toxicities. **Conclusions:** Disitamab vedotin combined with PD-1 inhibitor immunotherapy might improve DFS compared with standard chemotherapy as adjuvant therapy for UTUC. Supported by favorable efficacy and safety outcomes, this combination represents a promising postoperative treatment option. Research Sponsor: None.

Participants' and tumour characteristics.

		Total (n=105)	DV group (n=34)	Chemotherapy group (n=71)	P value
Age(years) , median(IQR)		63 (56.5-63)	65 (57-69)	63 (56-70)	0.848
Sex, n (%)	Male	56 (53.3)	16 (47.1)	40 (56.3)	0.372
	Female	49 (46.7)	18 (52.9)	31 (43.7)	
Pathological T stage	pT2	37 (35.2)	11 (32.4)	26 (36.6)	0.453
	pT3	58 (55.2)	18 (52.9)	40 (56.3)	
	pT4	10 (9.5)	5 (14.7)	5 (7.0)	
Nodal stage	N0	95 (90.5)	33 (97.1)	62 (87.3)	0.225
	N1	5 (4.8)	0 (0)	5 (7.0)	
	N2	5 (4.8)	1 (2.9)	4 (5.6)	

4612 Poster Session

Real-world treatment patterns and clinical outcomes among US patients with non-muscle invasive bladder cancer (NMIBC) during the BCG shortage. First Author: Suzanne Biehn Merrill, Colorado Urology Group, Lakewood, CO

Background: Bladder cancer is diagnosed in 80,000 US patients (pts) annually; 70% present as non-muscle invasive (NMIBC). Guidelines are risk-based; treatment for high risk (hr) disease includes tumor resection (TURBT) and intravesical therapy, commonly Bacille Calmette Guérin (BCG). Delivery of indicated treatment remains challenged, especially by ongoing (acutely since 2017) BCG shortages. We describe recent real-world (rw) patient characteristics, treatments (BCG, TURBT use), and clinical outcomes for NMIBC pts by risk group. **Methods:** We analyzed demographic, clinical and treatment data from electronic health records in N-Power Medicine's Real-World Analytical Dataset, largely based in the Midwest. Adults diagnosed with NIMBC between 1/2017 - 6/2022 were included and followed through 2022. Pts were classified as hr (Y/N) by AUA definition. Kaplan-Meier (KM) curves estimated BCG maintenance (MTX) duration, rw MIBC and metastatic free survival (modified PFS), cystectomy free survival (CFS), overall survival (OS), and recurrence free survival (RFS). Logistic and Cox regression was used to identify predictors of MTX start and discontinuation among hr pts including demographics, diagnosis year, smoking status, Charlson comorbidity index (CCI) and physician specialty. **Results:** Among 3,516 NMIBC pts (median age at diagnosis 72 years), 2,634 (75%) had hrNMIBC; most were non-Hispanic White (88%) and male (75%). Over a median follow-up of 2.7 years, 29% of hrNMIBC pts received BCG induction (IDX); 12% received BCG MTX and median MTX duration was 7.7 months (95% confidence interval [CI]: 6.8-9.2). For hr pts who received IDX, those diagnosed in 2019-2020 were less likely to initiate MTX (2019 vs 2017: OR 0.4; 95% CI [0.2-0.7], 2020 vs. 2017: OR 0.6 CI [0.4-1.0]). Hr pts with higher CCI (>2 vs 0: HR 2.2 [1.2-4.2]) were more likely to discontinue MTX. Most (95%) BCG recipients received no other therapy after BCG. Nearly all pts (>99%) received TURBT. Clinical outcomes (rwmPFS, rwCFS, rwOS) were less favorable for hr pts (Table). **Conclusions:** We examined treatment during the BCG shortage. BCG IDX and MTX were low among hrNMIBC pts. Clinical outcomes during the shortage highlight the potential to improve outcomes, especially for hr pts, and the need for alternative treatment strategies. Research Sponsor: AstraZeneca.

KM percent survival (95% CI) of rwmPFS[1], rwCFS[2], and rwOS[3] by risk category.

Follow up Month	rwmPFS		rwCFS		rwOS	
	Non-Hr	Hr	Non-Hr	Hr	Non-Hr	Hr
12	97 (96, 98)	90 (89, 92)	97 (95, 98)	91 (90, 92)	90 (78, 100)	72 (69, 75)
24	92 (90, 94)	85 (83, 86)	92 (90, 94)	85 (83, 86)	85 (70, 100)	64 (60, 68)
36	89 (86, 91)	79 (77, 80)	89 (86, 91)	78 (76, 80)	85 (70, 100)	57 (53, 62)
48	87 (84, 90)	75 (73, 77)	87 (84, 90)	74 (72, 76)	75 (56, 100)	53 (48, 58)
60	81 (77, 85)	70 (68, 73)	81 (77, 85)	70 (67, 73)	– (–, –)	47 (42, 53)

[1]Real-world modified progression free survival.
[2]Real-world cystectomy-free survival.
[3]Real-world overall survival.

4613 Poster Session

Neoadjuvant and adjuvant (neoadj-adj) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants with cisplatin-ineligible muscle-invasive bladder cancer (MIBC): An analysis of clinically relevant subgroups in KEYNOTE-905. First Author: Nabil Adra, Indiana University Melvin and Bren Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Results from the phase 3 KEYNOTE-905/EV-303 study (NCT03924895) showed that neoadj-adj EV + pembro and radical cystectomy with pelvic lymph node dissection (RC + PLND) led to superior event-free survival (EFS; HR 0.40; 95% CI 0.28-0.57), overall survival (OS; HR 0.50; 95% CI 0.33-0.74), and pathological complete response (pCR) rate (57.1% vs 8.6%) vs RC + PLND alone in participants (pts) with MIBC who were ineligible for or declined cisplatin. We report efficacy in subgroups of clinical interest, including advanced age, ECOG PS, cisplatin eligibility status, and baseline clinical tumor stage. **Methods:** Adults with stage T2-T4aN0M0 or T1-T4aN1M0 MIBC by central review who were cisplatin-ineligible or declined cisplatin were randomly assigned 1:1 to neoadj-adj EV + pembro and RC + PLND vs RC + PLND alone (control). EFS by BICR, OS, and pCR (pT0N0) rate by central review were analyzed in subgroups by age ($\geq$65 to <75 vs $\geq$75 yr), ECOG PS (0-1 vs 2), cisplatin-ineligibility status (ineligible vs declined), and clinical stage (T2N0 vs T3-T4aN0 vs T1-4aN1). The analyses were exploratory; no formal statistical testing was performed. **Results:** 170 pts were assigned to EV + pembro and 174 to control. Median follow-up at data cutoff (Jun 6, 2025) was 25.6 mo (range 11.8-53.7). 30 pts in the EV + pembro arm and 32 in the control arm had stage T2N0 MIBC; 133 and 132 pts had stage T3-T4aN0; 7 and 10 had stage T1-4aN1. In pts with T2N0 MIBC, median EFS was not reached (NR) with EV + pembro vs NR with control (HR 0.26; 95% CI 0.08-0.80), and pCR rate was 60.0% vs 18.8%. In pts with T3-T4aN0 MIBC, median EFS was NR with EV + pembro vs 17.2 mo with control (HR 0.43; 95% CI 0.29-0.63); median OS was NR vs 41.7 mo (HR 0.54; 95% CI 0.35-0.82); pCR rate was 57.1% vs 6.8%. In pts with T1-4aN1 MIBC, median EFS was 36.7 vs 7.2 mo (HR 0.35; 95% CI 0.09-1.40); pCR rate was 42.9% vs 0%. OS for T2N0 and T1-4aN1 will be assessed after additional follow-up (currently <10 events). Outcomes by age, ECOG PS, and cisplatin eligibility are shown in the Table. **Conclusions:** An efficacy benefit was observed with neoadj-adj EV + pembro added to RC + PLND vs RC + PLND alone across clinically relevant subgroups, consistent with the ITT population. Results further support EV + pembro as a potential new standard treatment for pts with cisplatin-ineligible MIBC. Clinical trial information: NCT03924895. Research Sponsor: The study was conducted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in collaboration with Astellas Pharma Inc., Northbrook, IL, USA, and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in December 2023.

	Age ≥65 to <75 yr EV+P	C	Age ≥75 yr EV+P	C	ECOG 0-1 EV+P	C	ECOG 2 EV+P	C	Cisplatin-ineligible EV+P	C
N	63	77	78	68	149	148	21	26	142	139
EFS, median, mo	NR	13.1	NR	18.8	NR	17.2	NR	9.3	NR	14.2
EFS HR (95% CI)	0.41 (0.24-0.70)		0.50 (0.30-0.84)		0.44 (0.30-0.64)		0.19 (0.07-0.52)		0.37 (0.26-0.54)	
OS, median, mo	NR	41.7	NR	37.4	NR	42.6	NR	19.2	NR	37.4
OS HR (95% CI)	0.49 (0.26-0.94)		0.63 (0.36-1.10)		0.59 (0.39-0.90)		0.17 (0.05-0.59)		0.46 (0.30-0.70)	
pCR rate, %	54.0	9.1	53.8	7.4	53.7	8.8	81.0	7.7	54.9	8.6

C, control; EV+P, EV + pembro.

4614 **Poster Session**

Neoadjuvant and adjuvant enfortumab vedotin plus pembrolizumab for participants with muscle-invasive bladder cancer who are eligible for cisplatin: Randomized, open-label, phase 3 KEYNOTE-B15 study. First Author: Christopher J. Hoimes, Duke University Medical Center, Durham, NC

Background: Enfortumab vedotin (EV) + pembrolizumab (pembro) is the established first-line standard of care for locally advanced/metastatic urothelial carcinoma and represents a novel neoadjuvant and adjuvant treatment strategy for patients with muscle-invasive bladder cancer (MIBC) who are ineligible for cisplatin-based chemotherapy. The randomized phase 3 KEYNOTE-B15/EV-304 study (NCT04700124) evaluates neoadjuvant EV + pembro followed by radical cystectomy plus pelvic lymph node dissection (RC + PLND) and adjuvant EV + pembro vs neoadjuvant chemotherapy followed by RC + PLND in participants (pts) with MIBC who are eligible for cisplatin-based therapy. **Methods:** Pts with clinical stage T2-T4aN0M0 or T1-T4aN1M0 MIBC (confirmed by central pathology and central imaging assessment) who were eligible for cisplatin-based chemotherapy and RC + PLND were randomized 1:1 to receive either 4 cycles neoadjuvant EV 1.25 mg/kg IV on days 1 and 8 + pembro 200 mg IV on day 1 Q3W, followed by RC + PLND, and adjuvant 5 cycles EV + 13 cycles pembro (EV + pembro arm) vs 4 cycles neoadjuvant gemcitabine 1000 mg/m^2 on days 1 and 8 + cisplatin 70 mg/m^2 on day 1 Q3W, followed by RC + PLND (cis + gem arm). The primary endpoint was event-free survival (EFS) by blinded independent central review. Key secondary endpoints were pathological complete response (pCR) rate by blinded central pathological review and overall survival (OS). Safety was a secondary endpoint; AEs of special interest were based on distinct prespecified lists for each drug. **Results:** A total of 405 and 403 pts were randomized to EV + pembro and cis + gem, respectively. Median time from randomization to the data cutoff date of October 27, 2025 was 33.6 months (range, 22.5–53.6). Baseline characteristics were generally balanced between groups. EV + pembro significantly improved EFS (median NR vs 48.5 mo; 24-mo estimated EFS rate 79.4% vs 66.2%; HR 0.53, 95% CI 0.41–0.70; 1-sided $P<.0001$), OS (median NR vs NR; 24-mo estimated OS rate 86.9% vs 81.3%; HR 0.65, 95% CI 0.48–0.89; 1-sided $P=.0029$), and pCR rate (55.8% vs 32.5%; estimated difference 23.4%, 95% CI 16.7–29.8; 1-sided $P<.0001$) vs cis + gem. Grade ≥3 treatment-emergent AEs occurred in 75.7% of pts with EV + pembro and 67.2% with cis + gem. Most common grade ≥3 drug-related AE of special interest for EV was skin reactions (14.1%); most common grade ≥3 AE of special interest for pembro was severe skin reactions (13.9%). **Conclusions:** Neoadjuvant and adjuvant EV + pembro significantly improved EFS, OS, and pCR rate compared with neoadjuvant gem + cis in pts with MIBC who were eligible for cisplatin-based chemotherapy. The safety profile of EV + pembro was consistent with prior experience with the combination. These results support EV + pembro as an effective perioperative treatment option in this setting. Clinical trial information: NCT04700124. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, Astellas Pharma Inc., Northbrook, IL, USA and Seagen Inc., Bothell, WA, USA, which was acquired by Pfizer in Dec. 2023.

4616 **Poster Session**

Adjuvant or rescue disitamab vedotin for high-risk non–muscle invasive bladder cancer with HER2 overexpression: A phase II multi-center study. First Author: Junru Chen, Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China

Background: Disitamab vedotin (DV), a HER2-targeted antibody–drug conjugate (ADC), has shown efficacy in metastatic urothelial carcinoma. However, its role in high-risk non-muscle-invasive bladder cancer (HR-NMIBC) patients with HER2 overexpression remains unexplored. We report preliminary findings from an ongoing phase II trial evaluating DV as adjuvant or rescue therapy in this population. **Methods:** Two cohorts were enrolled: patients receiving adjuvant therapy following transurethral resection (cohort A) and those undergoing rescue therapy after BCG failure (cohort B). Eligible patients had HR-NMIBC with HER2 overexpression. DV was administered at 120 mg intravenously every 2 weeks for up to 10 cycles. The primary endpoints were safety, 12-month recurrence-free survival (RFS) in cohort A, and 3-month clinical complete response (cCR) rate in cohort B. Secondary endpoints included 6-month RFS (cohort A) and duration of response (DOR, cohort B). Exploratory analyses evaluated the prognostic value of urinary tumor DNA (utDNA) using samples collected at baseline, end of treatment, and at the time of disease recurrence. This study is registered with ClinicalTrials.gov (NCT05996952). **Results:** Between September 2023 and October 2025, 28 patients were enrolled—22 in cohort A (median age 62 years [range, 33–75]; 3 women [13.6%]) and 6 in cohort B (median age 66 years [range, 60–72]; all men). Median follow-up was 13.4 months (range, 2.1–24.2) for cohort A and 17.0 months (range, 1.8–22.9) for cohort B. In cohort A, 6- and 12-month RFS rates were 95.2% and 73.4%, respectively. In cohort B, the 3-month cCR rate was 100%, and the median DOR was not reached (range, 1.7–19.7 months). All patients experienced treatment-related adverse events (TRAEs); 4 patients (14.3%) had grade ≥ 3 TRAEs. The most common TRAEs were elevated alanine aminotransferase (42.9%), alopecia (42.9%), and fatigue (35.7%). Exploratory analysis of baseline utDNA status demonstrated significant prognostic stratification, with positive patients exhibiting inferior 1-year RFS compared to those with negative status (50% vs. 91%, P=0.043). **Conclusions:** DV demonstrated a manageable safety profile and encouraging efficacy in patients with HR-NMIBC and HER2 overexpression in both adjuvant and rescue settings. The trial is ongoing, following a Simon two-stage optimal design, with a target enrollment of 52 patients in cohort A and 25 in cohort B. Study initiation was in May 2023. Clinical trial information: NCT05996952. Research Sponsor: None.

4617 **Poster Session**

Molecular characterization of residual disease post-neoadjuvant sacituzumab govitecan (SG), pembrolizumab, or their combination in patients with muscle-invasive bladder cancer (MIBC). First Author: Andrea Necchi, Department of Medical Oncology, IRCCS San Raffaele Hospital, Comprehensive Cancer Center; Vita-Salute San Raffaele University, Milan, Italy

Background: In patients (pts) with MIBC, we tested the activity of neoadjuvant SG (SURE-01, NCT05226117), SG + pembrolizumab (SURE-02, NCT05535218) and pembrolizumab alone (PURE-01, NCT02736266), followed by surgery. We aimed to molecularly characterize the residual post-neoadjuvant therapy (NAT) MIBC and its changes from baseline samples. **Methods:** Post-NAT samples (ypT≥2) were available for transcriptome analyses from 12 pts in SURE-01, 24 in SURE-02, and 26 post-pembrolizumab alone. Decipher bladder genomic subtyping classifier (GSC) expression profiling assay (Veracyte) was used to compare molecular subtyping distributions and genes/signatures expressions between matched pre-post NAT samples, including 192 locked transcriptomic signatures in GRID (v3.1) and prespecified therapeutic target genes. FGFR3-active tumors were determined using a previously-developed long non-coding RNA (lncRNA)-based classifier. The clinical primary endpoint was event-free survival (EFS). **Results:** Post-NAT molecular subtyping identified Luminal (L) vs non-Luminal (NL) tumors in: 17% (2/12) vs 83% (10/12) (SURE-01), 21% (5/24) versus 79% (19/24) (SURE-02), and 8% (2/26) versus 92% (24/26) (PURE-01). In total, 21 pts from SURE studies and 22 from PURE-01 had matched pre-post NAT samples. Consensus molecular subtyping revealed a concordance in 86% (6/7) of pts in SURE-01, 57% (8/14) in SURE-02 and 36% (8/22) in PURE-01. Stroma-rich tumors were found in 17% (2/12), 29% (7/24) and 50% (13/26) of post-NAT samples. After NAT, we found a decrease in L subtypes in SURE-01 (57% → 29%) and in SURE-02 (36% → 14%) vs an increase in stroma-rich (Consensus) subtype in SURE-02 (7% → 36%) and in PURE-01 (14% → 50%). Elevation of TGF-beta signaling hallmark (p=0.02) and immune exclusion (p=0.02) scores characterized post-NAT samples in SURE-01, while in SURE-02 we found elevated stromal gene scores (p=0.004) and lower DNA repair hallmark scores (p=0.03) after NAT. Comparing matched samples from SURE-01 and 02, we found significantly decreased TROP2 expression scores (p=0.03) and lower HER2 (p=0.06) and NECTIN4 expression (p=0.07). Application of the lncRNA-based FGFR3-activity classifier revealed a total of 10/36 (28%) FGFR3-active tumors post-NAT in SURE-01 and SURE-02, all without EFS events during follow-up. For SURE-02, we found 4/24 (17%) pts harboring claudin-low tumors post-NAT, who did not experience EFS events following adjuvant pembrolizumab, similar to the low EFS rate observed in PURE-01 (N=7, 22%). **Conclusions:** This study expands our knowledge on residual MIBC after various NAT, displaying a noteworthy plasticity and significant changes post-NAT that are important to unveil the biology of these tumors and putative biomarkers for sequential therapies. Research Sponsor: AIRC (Associazione Italiana per la Ricerca e la Cura del Cancro); IG 2022 ID 27746.

4618 **Poster Session**

TRUCE-11: An open-label, single-arm, multicenter phase II study of tislelizumab combined with nab-paclitaxel for muscle-invasive urothelial bladder carcinoma. First Author: Zhouliang Wu, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Neoadjuvant tislelizumab plus nab-paclitaxel may enhance pathologic response in muscle-invasive bladder cancer (MIBC), and TRUCE-11 evaluates its efficacy and safety prior to radical cystectomy (RC). **Methods:** TRUCE-11 is a multicenter phase II neoadjuvant study for eligible MIBC pts who had pure or mixed urothelial carcinoma of the bladder (cT2–4aNxM0). Pts received nab-paclitaxel 125 mg/m² IV on day 1, followed 2 h later by tislelizumab 200 mg IV (Q3W) for 2–3 cycles, then underwent RC with pathologic assessment. Imaging and urine cytology were performed at baseline and post-treatment. The primary endpoint was pathologic complete response (pCR). Secondary endpoints included pathologic downstaging rate (PaIR, ≤pT1), adverse events (AEs), and overall survival (OS). Exploratory analyses evaluated radiomics features (bladder MRI, PET/CT, and contrast-enhanced ultrasound) and serum biomarkers, including peripheral blood tumor whole-genome chromosomal aberration assay (PB-TWGCA). Transcriptomic biomarker discovery further highlighted GRHL1 using bulk RNA-seq and paired baseline/RC tumor scRNA-seq. **Results:** Between March 2024 and January 2026, 27 pts were enrolled; 21 underwent RC after neoadjuvant therapy. Among RC pts (n=21), 11 pts achieved pCR (52%) and 13 achieved PaIR (≤pT1, 62%). The most common grade 1–2 AEs were alopecia (86%), fatigue (76%), rash (43%), decreased appetite (38%), and fever (14%). No grade 3–4 AEs (CTCAE) were observed. After a median follow-up of 247 days (range, 65–677), all pts were alive. Among pts achieving pCR, pre-cystectomy MRI (DWI/ADC) showed no residual diffusion restriction and/or PET/CT showed no malignant findings, concordant with pathology. In 6 pCR pts with contrast-enhanced ultrasound, 5 (83%) demonstrated marked reduction or disappearance of tumor hypervascularity during treatment. In 5 pts, PB-TWGCA r-score was consistent with tumor burden. Transcriptomic analyses further suggested that tumor-cell GRHL1 expression might be underlying markers that predict adverse outcomes for the pCR and non-pCR pts cohorts in this crew. **Conclusions:** Neoadjuvant tislelizumab plus nab-paclitaxel achieved a high pCR and downstaging rate with no grade 3–4 AEs in pts with MIBC undergoing RC. Multimodal imaging and circulating/transcriptomic biomarkers (PB-TWGCA r-score and tumor-cell GRHL1) may aid response evaluation and require confirmation in larger cohorts. Clinical trial information: NCT05328336. Research Sponsor: Scientific Research Project of Tianjin Municipal Education Commission; grant no. 2024KJ192.

4619 **Poster Session**

Neoadjuvant sacituzumab govitecan in patients with muscle-invasive bladder cancer: Final results and biomarker analyses of the SURE-01 trial. First Author: Brigida Anna Maiorano, Department of Medical Oncology, IRCCS San Raffaele Hospital, Milano, Italy

Background: To evaluate neoadjuvant sacituzumab govitecan (SG), followed by radical cystectomy (RC), in patients with muscle-invasive bladder cancer (MIBC) who are ineligible for/refuse neoadjuvant chemotherapy (NAC). We report the results of the primary analysis and final biomarker analyses of the open-label, phase 2 SURE-01 trial (NCT05226117). **Methods:** Patients aged ≥18 years, ECOG PS 0-1, with histologically confirmed cT2-T4aN0M0 MIBC, ineligible/refusing NAC, and scheduled for RC received 4 cycles of SG 10 mg/Kg on D1 and D8, every three weeks (Q3W), followed by RC. The primary outcome measure was the pathological complete response (pCR) rate. Transcriptome-wide analyses and comprehensive genomic profiling assays were performed on baseline tumor samples. **Results:** From 03/22 to 07/25, 44 patients were treated and efficacy evaluable. After the initial 8 patients enrolled, the protocol was amended with a SG dose of 7.5 mg/Kg, with primary prophylaxis for neutropenia, due to the occurrence of two deaths (one treatment-related). Subsequent Grade 3-4 treatment-related adverse-events (TRAE) occurred in 5 pts (13.9%). Twenty-six patients (59.1%) had a cT3-4 stage, 20 (45.5%) had a variant histology. Fourteen patients (31.8%) refused to undergo RC and underwent a repeated transurethral resection of the bladder tumor. The median follow-up was 22 months (interquartile range: 15-26). In the intention-to-treat population: the ypT0N0-x rate was 29.5% (95% confidence interval [CI]: 16.7-45.2). We observed an enrichment of ypT0 responses in non-Luminal subtypes (46% vs 14% of Luminal), with the Infiltrated Luminal subtype having the highest proportion of ypT0 (62%). Variance by subtype revealed that TOP1 had the lowest scores in the Infiltrated Luminal subtype. A few signatures involving metabolism and tumor microenvironment were statistically significantly associated with a lower odds ratio of ypT0, whereas TROP2 expression (p=0.72) was not. The 24-month event-free survival (EFS) rate was 71.4% (95%CI: 58-87.8) and the 24-month overall survival (OS) rate was 80.2% (95%CI: 67.7-95). Longer EFS was observed for participants with lower TOP1-expressing tumors (p=0.04). **Conclusions:** To our knowledge, SURE-01 is the first to report results of an antibody-drug conjugate monotherapy targeting TROP2 in the neoadjuvant setting for patients with MIBC. Neoadjuvant SG at the reduced dose of 7.5mg/kg demonstrated compelling activity and survival estimates, with a manageable safety profile, corroborating TROP2 as a suitable target for MIBC. Molecular biomarkers pointing to the payload were associated with neoadjuvant SG activity. Clinical trial information: NCT05226117. Research Sponsor: None.

4620 **Poster Session**

Association of GLP-1 receptor agonist therapy with BCG response in high-risk non–muscle invasive bladder cancer. First Author: Benyamin Yaniv, UMass Chan Medical School, Worcester, MA

Background: Observational studies suggest glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reduced cancer incidence and improved survival in patients with established malignancies. Cohort data in lung cancer also suggest improved outcomes with immune checkpoint inhibitor therapy among patients receiving GLP-1RAs, raising the possibility of enhanced anti-tumor immunity. Intravesical Bacillus Calmette–Guérin (BCG) remains the mainstay treatment for high-risk (HR) non-muscle invasive bladder cancer (NMIBC). We hypothesized that GLP-1RA exposure during BCG therapy is associated with more favorable clinical outcomes in HR-NMIBC. **Methods:** Patients with HR- NMIBC treated between November 1st 2015 to November 1st 2025 were evaluated retrospectively using the TriNetX US Research Network. Patients were stratified by GLP-1RA exposure before BCG initiation (with or without overlap during BCG) versus no exposure. Cohorts were propensity score–matched for demographics and comorbidities, and outcomes were evaluated using multivariable logistic regression. The primary outcome was mortality; secondary outcomes included recurrence, progression to muscle-invasive bladder cancer (MIBC), cystectomy, and distant metastasis. **Results:** A total of 12,423 patients were evaluated, of which 791 (7%) received GLP-1RAs, while 11,630 (93%) did not. After propensity score matching, 787 patients were analyzed in each group. The average age in both cohorts was 73 years. Majority of patients were white (85%), male (80%), and non-Hispanic (85%). The distribution of GLP-1RAs use included semaglutide (67%), dulaglutide (37%), tirzepatide (21%), liraglutide (17%), exenatide (8%), and lixisenatide (1%). Patients who received GLP-1RAs demonstrated a significant reduction in 10-year mortality (RR 0.65; 95% CI 0.45 – 0.93, p = 0.017) and a lower risk of developing MIBC (RR 0.43; 95% CI 0.26 – 0.89; p = 0.018). No significant changes were noted in the risk of disease recurrence, radical cystectomy or distant metastasis (Table 1). **Conclusions:** In this real-world, retrospective, multi-cohort analysis we found that patients who received GLP-1RAs prior to BCG treatment are at a decreased risk of all-cause mortality, and less likely to develop progression to MIBC. This study underscores the need for further evaluation of GLP-1RAs in patients with NMIBC treated with BCG. Research Sponsor: None.

Outcomes comparing HR-NMIBC patients exposed to GLP-1RA prior to BCG therapy versus those without exposure.

Outcome	Risk Ratio (95% CI)	p-value
Mortality	0.65 (0.45 – 0.93)	0.017
MIBC progression	0.43 (0.26 – 0.89)	0.018
NMIBC recurrence	0.98 (0.89 – 1.09)	0.84
Radical cystectomy	0.94 (0.72 – 1.22)	0.65
Distant metastasis	0.83 (0.62 – 1.11)	0.19

4621 **Poster Session**

Rethinking the role of tumor size in bladder preservation: Comparing survival outcomes of radical cystectomy (RC) and tri-modality therapy (TMT). First Author: Dawood Hasan Syed, Geisinger Health System, Wilkes-Barre, PA

Background: TMT (maximal TURBT followed by chemoradiation) is typically reserved for bladder cancer (BC) patients with solitary tumors less than 6 cm, no extensive carcinoma in situ, and no or unilateral hydronephrosis. The National Comprehensive Cancer Network (NCCN) guidelines specify that optimal candidates for bladder preservation with chemo-radiotherapy have tumors less than 6 cm; larger tumors are less likely to be completely resected and have poorer local control and survival outcomes with bladder-sparing approaches. We aimed to analyze outcomes of BC patients receiving multimodal therapy and further categorizing outcomes of RC versus TMT based on tumor sizes. **Methods:** We analyzed patients with T1–T4, N0–N3, M0 urothelial carcinoma of the bladder using the NCDB (2010–2022). Patients were grouped as: RC, neoadjuvant chemotherapy (NAC) plus RC, RC followed by adjuvant chemotherapy (AC), and TMT. Overall survival (OS) was estimated with Kaplan–Meier methods and multivariable Cox regression adjusted for common confounders for these four groups. We also further analyzed the role of tumor size for patients who received either RC or TMT. Tumor size was divided in three groups; less than 3cm, 3 to 6cm, and more than 6cm. **Results:** Among 33,836 patients (median age 68y), treatment groups were as follows: RC alone (34%), NAC-RC (23%), RC-AC (21%) and TMT (22%). BC specific prognostic factors like tumor size more than 6cm vs 3cm (HR 1.70 (1.62–1.77) ($p < 0.001$)) and lymphovascular invasion (LVI) (HR 1.94 (1.87–2.00), $p < 0.001$)) were independently associated with poor OS. In our analysis, NAC-RC (HR 0.67 (0.64–0.70, p = 0.001) followed by RC-AC (HR 0.72 (0.69–0.75, p = 0.001) conferred the heaviest OS benefit. When tumor size was investigated as a prognostic factor comparing RC versus TMT, multivariate analysis showed that for both tumors less than 3cm (HR = 1.27 (1.16–1.39), p = 0.001) and 3cm to 6cm (HR 1.08(1.03–1.14), p = 0.003), RC was significantly superior in terms of OS. Interestingly, for tumors more than 6cm (HR = 0.97 (0.88–1.06), p = 0.468), the analysis revealed no significant difference in OS between RC and TMT. **Conclusions:** Despite NAC-RC offering the greatest overall survival (OS) benefit and being the standard of care, it is frequently underutilized as many patients are not candidates for chemotherapy. Consequently, bladder preservation strategies (BPS) are essential. Our analysis shows tumor size may dictate the optimal curative approach. For smaller tumors (< 3 cm and 3cm to 6cm), Radical Cystectomy (RC) is significantly superior to TMT in terms of OS. Conversely, for large tumors (> 6cm) RC provided no significant OS benefit over TMT. This suggests that the inherent aggressiveness of large lesions overrides any surgical advantage. Therefore, BPS must be strongly considered for tumors $>$ 6cm when other TMT contraindications (e.g., hydronephrosis) are absent. Research Sponsor: None.

4622 **Poster Session**

Exploration of biomarkers for TRUCE-01: Development of a urine-based efficacy prediction model. First Author: Yuda Lin, The Second Hospital of Tianjin Medical University, Tianjin, China

Background: Preliminary results from the TRUCE-01 phase II trial (NCT04730219) indicate encouraging antitumor activity and a manageable safety profile for the combination of the immune checkpoint inhibitor tislelizumab and nab-paclitaxel in patients with T2-4a N0/X M0 muscle-invasive bladder cancer (MIBC) of predominant urothelial carcinoma histology. To identify patient subgroups that may derive particular benefit, we conducted a comprehensive biomarker analysis. **Methods:** We performed whole-exome sequencing (WES) on baseline tumor tissue from 44 patients. Concomitantly, urine samples were collected during treatment. Baseline urine from 44 patients was subjected to 808-panel circulating tumor DNA (ctDNA) detection, and low-depth whole-genome sequencing (WGS) was performed across three time points (pre-treatment, during treatment, and post-treatment) for 47 patients. **Results:** The classic biomarker PD-L1 expression failed to predict complete response (CR) Urine-derived biomarkers showed high concordance with tissue-based mutation profiles. Specifically, urinary mutations in RB1, ERCC2, and AR were associated with CR, while mutations in ELF3, KDM6A, and TP53 were linked to non-clinical response (NCR). Baseline ctDNA levels (p=0.016) and baseline (p=0.011)/post-treatment (p=0.0011) WGS scores were significantly higher in the NCR versus CR group, potentially reflecting higher tumor burden. Interestingly, only two patients who achieved CR later experienced disease progression; both showed a rising trend in WGS scores during treatment, suggesting that CR does not ensure long-term favorable prognosis and that dynamic urine monitoring may be crucial during treatment. Finally, we developed a predictive model integrating urinary WGS scores, ctDNA scores, and efficacy-associated mutation genes. This integrated model achieved an area under the curve (AUC) of 0.930, significantly outperforming models based on WGS score alone (AUC=0.695) or ctDNA score alone (AUC=0.749). **Conclusions:** Urine-based biomarker assays show promise for predicting response to chemo-immunotherapy in MIBC. Further studies with expanded sample sizes and multi-center validation are warranted to confirm these findings and assess their clinical utility in broader patient cohorts. Clinical trial information: NCT04730219. Research Sponsor: None.

4623 **Poster Session**

Chemoablation with oral erdafitinib in recurrent *FGFR3*-altered non–muscle-invasive bladder cancer: A phase II window-of-opportunity trial. First Author: Muhammad Hassan Alkazemi, Urologic Oncology Service, New York City, NY

Background: Non-muscle invasive bladder cancer (NMIBC) frequently recurs despite intravesical treatments, necessitating repeated transurethral resections of bladder tumors (TURBT). FGFR3 alterations are common in NMIBC and may be a potential therapeutic target. Erdafitinib, a pan-FGFR inhibitor, is approved for metastatic urothelial cancer, but its efficacy as a chemoablative agent in recurrent NMIBC is not yet established. This trial evaluates the efficacy of oral erdafitinib as a chemoablative treatment in patients with recurrent FGFR3-altered NMIBC. **Methods:** Patients with recurrent NMIBC and FGFR3 alterations detected with MSK-IMPACT were given oral erdafitinib (6 mg daily) for ~28 days before TURBT. Tumor response was assessed using RECIT-Bladder criteria, and tissue, blood, and urine samples were collected for pharmacodynamic analyses and biomarker exploration. Toxicities were graded using CTCAE v5.0. **Results:** A total of 20 patients with recurrent NMIBC and confirmed FGFR3 mutations were enrolled in the study. The most common mutations were S249C (n=12), Y373C (n=3), and R248C (n=3). Most patients (70%) had a history of low-grade Ta (LG Ta) tumors. All patients had received at least one prior intravesical therapy, with 55% having undergone multiple courses of BCG, gemcitabine, mitomycin, or combination regimens. The objective response rate (ORR) was 75% (15/20), with complete response (CR) achieved in 11 patients (55%). No grade ≥3 toxicities were observed. **Conclusions:** Oral erdafitinib demonstrated efficacy in reducing tumor burden in select FGFR3-altered NMIBC in this window-of-opportunity trial. Clinical trial information: NCT04917809. Research Sponsor: Janssen; ASCO YIA.

4624 **Rapid Oral Abstract Session**

Durvalumab (D) in combination with BCG induction and maintenance (I + M) therapy for BCG-naive, high-risk non–muscle-invasive bladder cancer (NMIBC): 5-year overall survival (OS) analysis and patient-reported outcomes (PROs) from POTOMAC. First Author: Maria De Santis, Department of Urology, Charité Universitaetsmedizin Berlin, Berlin, Germany and Department of Urology, Medical University of Vienna, Vienna, Austria

Background: In the Phase 3 POTOMAC study (NCT03528694), 1 year of D in combination with BCG (I + M) resulted in a statistically significant and clinically meaningful improvement in disease-free survival vs BCG (I + M) alone, with a manageable safety profile, in patients (pts) with BCG-naive, high-risk NMIBC. We report a planned updated 5-year OS analysis and PROs. **Methods:** Eligible pts were randomized 1:1:1 to D + BCG (I + M), D + BCG (I only), or BCG (I + M). Secondary endpoints included 5-year OS and PROs, evaluated every 8 weeks by EORTC QLQ-C30 and every 4 weeks by EORTC QLQ-NMIBC24 and PRO-CTCAE. Prespecified priority subscales were global health status/quality of life (GHS/QoL), physical functioning, and fatigue for QLQ-C30; and urinary symptoms, intravesical treatment (tx) issues, future perspective/worries, and sexual functioning for QLQ-NMIBC24. Change from baseline (CFB; mixed model for repeated measures) was assessed; a ±10-point score was considered clinically meaningful. **Results:** At data cutoff Oct 3, 2025 (median follow-up 72 months), the OS HR was 0.81 (95% CI, 0.54–1.19) with a 5-year OS rate of 87.6% (95% CI, 83.5%–90.8%) for D + BCG (I + M) vs 86.3% (95% CI, 82.1%–89.6%) for BCG (I + M). Median OS was not reached in either arm. For PRO analyses (data cutoff Apr 3, 2025), QLQ-C30 and QLQ-NMIBC24 baseline compliance rates were ≥74% and ≥79%, respectively, with similar baseline scores between arms. Overall, both arms showed deterioration in QLQ-C30 adjusted mean CFB scores, with suggested clinically meaningful deterioration for fatigue with D + BCG (I + M); however, the difference between arms was small (Table). Overall QLQ-NMIBC24 adjusted mean CFB scores were numerically small and similar between arms (Table). PRO-CTCAE measures were similar between arms. **Conclusions:** Addition of 1 year of D to BCG (I + M) continued to show no detriment to OS at >5.5 years of follow-up and had no major impact on PROs for pts with BCG-naive high-risk NMIBC. Clinical trial information: NCT03528694. Research Sponsor: AstraZeneca.

Subscales	D + BCG (I + M) Adjusted mean CFB (95% CI)[a]	BCG (I + M) Adjusted mean CFB (95% CI)[a]	Estimated difference of means (95% CI)
QLQ-C30			
GHS/QoL[b]	−7.6 (−9.19, −6.07)	−4.9 (−6.46, −3.41)	−2.7 (−4.85, −0.54)
Physical functioning[b]	−5.5 (−6.76, −4.15)	−2.8 (−4.11, −1.56)	−2.6 (−4.43, −0.81)
Fatigue[c]	10.1 (8.32, 11.90)	6.1 (4.37, 7.88)	4.0 (1.50, 6.46)
QLQ-NMIBC24			
Urinary symptoms[c]	1.7 (−0.06, 3.41)	0.4 (−1.27, 2.15)	1.2 (−1.19, 3.65)
Intravesical tx issues[c]	1.5 (−0.38, 3.28)	2.7 (0.89, 4.50)	−1.2 (−3.79, 1.29)
Future perspective/worries[c]	−5.5 (−7.54, −3.39)	−3.2 (−5.29, −1.19)	−2.2 (−5.11, 0.66)
Sexual functioning[b]	2.2 (0.47, 3.91)	1.1 (−0.60, 2.80)	1.1 (−1.30, 3.48)

[a]Higher scores indicate better health (GHS/functioning) or greater burden (symptoms).
[b]Positive difference favors D + BCG (I + M).
[c]Negative difference favors D + BCG (I + M).

4626 **Poster Session**

Updated efficacy and safety of SHR-1501, an IL-15RαFc superagonist, with or without Bacille Calmette Guerin (BCG) for high-risk non-muscle invasive bladder cancer (NMIBC): A phase 1/2 study. First Author: Zhisong He, The First Hospital of Peking University, Beijing, China

Background: SHR-1501, an IL-15 agonist fusion protein composing of a humanized antibody Fc region fused with IL-15 and IL-15Rα sushi domain, demonstrated promising efficacy, well tolerance, and acceptable safety in alone or in combination with BCG in patients with BCG-naive and BCG-unresponsive high-risk NMIBC (*ASCO 2025*). Here, we report the updated results of this phase 1/2 study (NCT05410730). **Methods:** In the dose-escalation phase 1a and 1b parts, SHR-1501 monotherapy (200, 400, and 600 μg) or SHR-1501 (600 μg) in combination with BCG (120 mg) was administered to patients with high-risk NMIBC. In the phase 2 part, patients with BCG-naive NMIBC (cohort A), BCG-unresponsive NMIBC carcinoma in situ (CIS; cohort B), and BCG-unresponsive high-grade Ta/T1 NMIBC without CIS (cohort C) were enrolled to receive SHR-1501 (600 μg) plus BCG (120 mg). During the induction phase, all patients received weekly intravesical study treatment for 6 weeks. In the maintenance phase, instillations were administered weekly for three weeks at months 3, 6, 12, 18, and 24 following the initial induction dose. Primary endpoints were dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and recommended phase 2 dose in phase 1a and 1b parts; and was complete response (CR) rate for cohort B and 12-mo disease-free survival (DFS) rate for cohorts A and C in phase 2 part. **Results:** As of Oct 31, 2025, 112 patients were enrolled (n=8 in phase 1a; n=6 in phase 1b; n=30, 25, and 43 in cohorts A, B, and C in phase 2). The median follow-up duration was 23.0 months (range 3.5-25.6) in patients with BCG-naive NMIBC, 6.5 months (range 2.6-21.2) in patients with BCG-unresponsive NMIBC CIS, and 13.5 months (range 2.5-23.1) in patients with BCG-unresponsive high-grade Ta/T1 NMIBC without CIS. In cohort B, the overall CR rate was 80.0% (20/25), the median DFS was 12.0 months (95% CI 6.0-NR). The 12-mo DFS rate was 90.3% (95% CI, 72.8-96.8) in patients with BCG-naive NMIBC and 62.7% (95% CI, 44.9-76.1) in patients with BCG-unresponsive high-grade Ta/T1 NMIBC without CIS. The 18-mo DFS rates were 90.3% (95% CI, 72.8-96.8) and 58.2% (95% CI, 39.6-72.9), respectively. Treatment-related adverse events (TRAEs) and grade 3 TRAEs occurred in 90 (86.5%) and 19 (18.3%) of 104 patients with SHR-1501 + BCG. The most common TRAEs were urinary tract infection (62.5%) and pollakiuria (35.6%). No TRAEs led to death. **Conclusions:** This updated analysis confirms the promising efficacy and manageable safety profile of SHR-1501 monotherapy or in combination with BCG in BCG-naive and BCG-unresponsive high-risk NMIBC patients. Two randomized, controlled phase 3 trials are underway in both BCG-unresponsive and BCG-naïve, high-risk NMIBC populations, with the recommended dose of 600 μg SHR-1501 plus BCG. Clinical trial information: NCT05410730. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co. Ltd.

4627 **Poster Session**

Patient-reported outcomes from IMvigor011: A phase 3 study of circulating tumor (ct)DNA–guided adjuvant atezolizumab vs placebo in muscle-invasive bladder cancer (MIBC). First Author: Joaquim Bellmunt, Dana-Farber Cancer Institute and Harvard University, Boston, MA

Background: IMvigor011 (NCT04660344) showed that serial ctDNA-based molecular residual disease (MRD) monitoring can identify patients (pts) with MIBC at very high risk of recurrence who benefit from adjuvant atezolizumab (atezo), demonstrating statistically significant and clinically meaningful improvements in DFS and OS vs placebo (pbo) in pts who tested ctDNA+. Pts who persistently tested ctDNA− had low risk of recurrence or death without adjuvant treatment (tx; Powles *NEJM* 2025). Here we report pt-reported outcomes (PROs). **Methods:** Pts with MIBC and no radiographic disease were enrolled and underwent serial ctDNA monitoring for up to 1 year after cystectomy; pts who tested ctDNA+ and remained disease-free were randomized to atezo or pbo every 4 weeks (wk) for 12 cycles or up to 1 year. PROs were assessed on Day (D)1 of Cycle (C)1, C3, C5, C7, C9, and C11, and at tx discontinuation. Time to confirmed deterioration (TTCD) analysis of physical functioning (PF), role functioning (RF), and global health status/quality of life (GHS/QoL) were secondary endpoints. Symptoms, functioning, and GHS/QoL per EORTC QLQ-C30, and tx side-effect burden per EORTC IL46, were exploratory endpoints. Relevant adverse events (AEs) were graded per NCI CTCAE v5. **Results:** Eligible pts who tested ctDNA+ (n=250) were randomized to atezo (n=167) or pbo (n=83). QLQ-C30 completion was >94% at C1D1 and >87% during tx, and >72% and >90%, respectively, for IL46. C1D1 completion rates were similar between arms. TTCD in PF, RF, and GHS/QoL showed no evidence of a difference between arms (Table). There was no clinically meaningful difference in mean change from C1D1 in symptoms, functioning, and GHS/QoL over time through C11D1 and between arms. From C1D1 to C11D1, >90% of pts reported little or no tx side-effect burden in both arms. Relevant safety data showed consistency between AEs and PROs. **Conclusions:** ctDNA-guided adjuvant atezo provided clinically meaningful DFS and OS benefit without negatively impacting pt-reported QoL. Clinical trial information: NCT04660344. Research Sponsor: F. Hoffmann-La Roche Ltd.

		Atezo (n=167)	Pbo (n=83)	Stratified HR[a] (95% CI)
QLQ-C30, median TTCD[b] **(95% CI), mo**	PF	25.1 (18.5, NE)	NE (19.4, NE)	1.25 (0.76, 2.07)
	RF	18.5 (12.2, NE)	NE (19.4, NE)	1.45 (0.88, 2.40)
	GHS/QoL	35.4 (19.3, NE)	16.5 (10.9, NE)	0.71 (0.45, 1.12)
IL46 tx side-effect burden, % of pts	**Atezo C1D1 (n=131)**	**Atezo C11D1 (n=60)**	**Pbo C1D1 (n=60)**	**Pbo C11D1 (n=22)**
Not at all/a little	93.9	98.3	98.3	95.5
Quite a bit	6.1	1.7	1.7	4.5
Very much	0	0	0	0

[a]Stratification factors: Nodal status (+ vs −); tumor stage (≤pT2 vs pT3/4); programmed death ligand-1 status (<5% vs ≥5% of immune cells); time from cystectomy to first ctDNA+ sample (≤20 vs >20 wk).
[b]Time from randomization to first clinically meaningful deterioration (≥10-point decrease) at either: ≥2 consecutive visits; or at 1 visit followed by death due to cancer progression ≤8 wk from last deteriorated PRO visit.
NE, not evaluable.

4628 **Poster Session**

Molecular classification of neuroendocrine carcinoma of the bladder. First Author: Shijia Li, Bridgeport Hospital, Bridgeport, CT

Background: Neuroendocrine carcinoma (NEC) of the bladder is a rare and aggressive cancer with limited treatment options. Recent studies reported molecular subtypes resembling small cell lung cancer (SCLC), specifically those associated with transcription factors (TFs) ASCL1, NEUROD1, and POU2F3. A subset of bladder NEC remains unclassified. ATOH1 was recently identified as a TF associated with a minority of SCLC tumors. **Methods:** The Tempus Lens Platform (Tempus AI, Inc., Chicago, IL) was used to query the multimodal de-identified database and establish a cohort of 121 patients with bladder NEC. We analyzed the genomic and transcriptomic profiles using tempusverse and custom code. K-means consensus clustering of gene expression was used to identify molecular subtypes; subsequently, tumor genetic alterations (single-nucleotide variants [SNVs], indels, and copy number alterations [CNAs]) and gene expression profiles were compared across these subtypes. Fisher's exact test was used to compare the frequency of events across categorical groups. limma-trend and empirical Bayes statistics were used for differential gene expression analysis. The Cox proportional hazards model and the Kaplan-Meier method were used for survival analysis. consensusMIBC was used for the consensus molecular classification. **Results:** Within the cohort, 103 were classified as neuroendocrine (NE)-like using consensusMIBC and were further analyzed in this study. The median age at diagnosis was 71 years (interquartile range, 63–76), with a male predominance (77%). Using the four SCLC TFs (ASCL1, NEUROD1, POU2F3, and ATOH1; YAP1 was excluded as it was recently found to be expressed in the non-NE components of mixed bladder NECs), we identified a five-type system that classifies most samples: ASCL1+/NEUROD1- (n=37; 36%), ASCL1-/NEUROD1+ (n=23; 22%), ASCL1+/NEUROD1+ (n=16; 16%), POU2F3+ (n=23; 22%), and ATOH1+ (n=4; 4%). Each subtype was associated with a distinct gene expression profile with representative markers: ASCL1, SOX2, and DLL3 (ASCL1+/NEUROD1-); NEUROD1, NEUROD4, and SSTR2 (ASCL1-/NEUROD1+); ETV1, NKX2-1, and NKX2-2 (ASCL1+/NEUROD1+); POU2F3, GFI1B, and POU2AF2 (POU2F3+); ATOH1, POU4F3, and USH2A (ATOH1+). POU2F3+ tumors expressed low NE markers and high PLCG2 and ERBB3; ATOH1+ tumors often expressed NE markers and tended to overexpress ALK. No statistically significant tumor SNVs, indels, or CNAs were differentially observed across the subtypes; TP53 (92%), TERT (82%), and RB1 (62%) were the most frequently altered genes in the entire cohort. Univariate analysis showed a worse real-time overall survival of ASCL1+/NEUROD1+ (hazard ratio [HR]=3.1, p=0.01), POU2F3+ (HR=3.4, p=0.001), and ATOH1+ (HR=8.4, p=0.0003), compared with ASCL1+/NEUROD1- tumors. **Conclusions:** We report an effective, clinically relevant molecular classification system for bladder NECs, including the newly described ATOH1+ subtype. Research Sponsor: University of California San Francisco.

TPS4629 **Poster Session**

A phase II trial of neoadjuvant zanzalintinib (ZANZA) plus nivolumab (NIVO) in patients with locally advanced and/or surgically challenging clear cell renal cell carcinoma (EXPLORE-RCC). First Author: Qian Qin, Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX

Background: Immunotherapy doublet combinations (+/- vascular endothelial growth factor receptor-tyrosine kinase inhibitor [VEGFR-TKI]) are established for front-line treatment of metastatic, clear cell renal cell carcinoma (ccRCC). However, their role in the perioperative setting for locoregional ccRCC remains to be defined. We designed the EXPLORE-RCC trial to evaluate neoadjuvant ZANZA (novel, next generation VEGFR-TKI with short half-life) plus NIVO (PD-1 inhibitor) in patients with locally advanced ccRCC, where the combination has the potential to shrink the primary tumor, increase resectability, and/or allow a partial nephrectomy or minimally invasive approach. **Methods:** In this multisite, phase 2, open-label, single-arm trial coordinated by the Hoosier Cancer Research Network, subjects will receive ZANZA 60mg orally once daily plus NIVO intravenously per standard of care (SOC) dosing for 12 weeks (w), followed by restaging scans and an adaptive approach: (1) subjects who are deemed operable will undergo resection (Cohort A); (2) subjects who remain inoperable can receive up to 48w total of ZANZA plus NIVO (Cohort B1) with the option to undergo resection when deemed operable; or (3) subjects who have disease progression will stop protocol mandated therapy and receive subsequent SOC treatment (Cohort B2). The main inclusion criteria include age $\geq$ 18 years, ECOG Performance Status of 0-1, histologically confirmed ccRCC, and locally advanced (cT3/4, N0-1, with or without tumor thrombus) disease and/or deemed surgically challenging per surgeon discretion. Non-measurable metastasis per RECIST 1.1 criteria, including soft tissue metastasis with longest diameter $<$10mm or distant lymph nodes $<$15 mm in short axis are allowed. Main exclusion criteria are non-clear cell histology, measurable metastatic disease per RECIST 1.1 criteria, and prior systemic treatment for ccRCC. The primary endpoint is overall response rate (ORR) after 12w of therapy. This single arm trial is powered to detect an improvement in ORR from a historical rate of 30% to 45%, with 80% power and a 0.05 one-sided type I error. Estimating 10% drop out, 69 subjects will be enrolled. Key secondary/exploratory endpoints include efficacy outcomes (conversion to operable, disease free survival, overall survival, pathologic response), safety, surgery-related complications (including Clavien-Dindo), and biomarker correlatives. The trial is actively enrolling (ClinicalTrials.gov NCT06794229) at UT Southwestern and opening at Ohio State, Fox Chase Cancer Center, Virginia Commonwealth, Northwestern University, and Washington University in St Louis. Clinical trial information: NCT06794229. Research Sponsor: Exelixis.

TPS4630 **Poster Session**

A multicenter randomized controlled clinical study of neoadjuvant combination of axitinib plus toripalimab to improve disease-free survival of patients with renal cell carcinoma. First Author: Zhiling Zhang, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: Clear cell renal cell carcinoma (ccRCC) is the most common subtype of renal cell carcinoma, accounting for 75-80% of cases worldwide and 60-85% in China. High risk ccRCC includes tumors larger than 7 cm (T2 stage) or those at advanced stages ($\geq$T3 or N1). Surgical resection is standard, but 30% may have recurrence, with a 2-year disease-free survival rate of 68%. Neoadjuvant therapy with axitinib and toripalimab may enhance antitumor immunity and improve prognosis for high risk patients. **Methods:** This is an open-label, multicenter, phase III randomized controlled study to assess whether neoadjuvant axitinib plus toripalimab improves disease-free survival (DFS) compared with surgery alone in patients with ccRCC at high risk of recurrence. The study is designed to enroll 298 patients with high risk ccRCC (T2G4 or T3-4 or N1) scheduled for nephrectomy. Patients must provide an adequate tumor tissue sample at screening for molecular and immune profiling. Patients will be randomly assigned to the control group or the neoadjuvant group at a 1:1 ratio. Both groups will undergo nephrectomy, while the neoadjuvant group will additionally receive preoperative treatment with axitinib plus toripalimab. Axitinib will be given for 3 months, 5 mg twice daily, orally. Toripalimab will be administered at 240 mg intravenously every 3 weeks for 4 cycles (one cycle every 3 weeks). Blood samples are collected before and after neoadjuvant treatment for exploratory molecular analysis. CT or MRI assessments will be conducted after 2 cycles of medication and before surgery. Radical nephrectomy (or partial nephrectomy, if applicable) will be performed within 1-28 days after completion of neoadjuvant therapy. For both groups, if postoperative pathology meets high recurrence risk criteria per Keynote-564—specifically, T2G4, T2 with sarcomatoid differentiation, T3, T4, any T stage with lymph node metastasis, or M1 with no evidence of disease—1 year of adjuvant toripalimab is recommended according to NCCN and EAU guidelines. Eligible patients must be diagnosed as ccRCC or RCC with a predominant clear cell component through histopathological examination. Clinical staging via CT or MRI must indicate T2, while biopsy pathology should show either nuclear grade 4 or sarcomatoid differentiation, or a classification of T3-4 or N1. Additional inclusion criteria include: signed informed consent, age $\geq$18 and $<$ 80 years old, adequate organ function, ECOG of 0 or 1 point. The primary endpoint is 2-year DFS, defined as the time from randomization to disease recurrence or death from any cause. Secondary endpoints include cancer-specific survival, overall survival, objective response rate, major pathological response, and safety profile. Enrollment began in April 2023, and 112 of the planned 298 patients have been enrolled. Clinical trial information: NCT05738694. Research Sponsor: None.

TPS4631 **Poster Session**

Phase 3 study to assess the safety and efficacy of ^{177}Lu-girentuximab in advanced, relapsed, or recurrent ccRCC (LUTEON). First Author: David Cade, Telix Pharmaceuticals, North Melbourne, VIC, Australia

Background: A high unmet need remains for treatments that provide durable disease control while preserving quality of life in patients with advanced clear-cell renal cell carcinoma (ccRCC). Girentuximab is a monoclonal antibody targeting carbonic anhydrase IX (CAIX), which is expressed on $>$95% of ccRCC cells with limited expression in healthy tissues. Radiolabeling girentuximab with β emitting luteium-177 (^{177}Lu-girentuximab) enables targeted delivery to CAIX-expressing tumor cells. Phase 1 - 2 data of ^{177}Lu-girentuximab in patients with metastatic ccRCC suggest favorable safety, tolerability, and efficacy profile.[1,2,3] LUTEON is a Phase 3 study designed to assess safety and efficacy of ^{177}Lu-girentuximab in patients with advanced, relapsed or recurrent ccRCC. **Methods:** LUTEON is a 2-part, randomized, open-label, multicenter study to determine the optimal activity and schedule of ^{177}Lu-girentuximab (Part 1), and evaluate efficacy and safety of ^{177}Lu-girentuximab versus an approved monotherapy standard-of-care (SOC) comparator (Part 2). Eligible patients are aged $\geq$18 years, have relapsed or recurrent, locally advanced or metastatic, histologically or cytologically confirmed ccRCC, and have received 2-3 prior lines of systemic therapies (including a PD-1/PD-L1 inhibitor and a VEGF/VEGFR-targeting agent) for locally advanced or metastatic ccRCC. Patients must have CAIX-positive cancer as determined by ^{89}Zr-girentuximab PET (performed during screening). In Part 1, patients will be randomized 1:1 ($\leq$20/arm) to receive either 3 IV infusions of 1887 MBq ^{177}Lu-girentuximab every 8 weeks or 6 infusions of 1258 MBq ^{177}Lu-girentuximab every 4 weeks. Unacceptable toxicity is managed with predefined, clinically appropriate measures. In Part 2, patients will be randomized 1:1 to receive ^{177}Lu-girentuximab at the optimal regimen identified in Part 1 or an SOC comparator. In both parts, the end of treatment (EOT) visit occurs 3 $\pm$1 week after the last infusion or within 30 days of discontinuing treatment. After EOT, efficacy assessments occur every 8 $\pm$2 weeks for 6 months; patients will undergo tumor assessments according to RECIST 1.1 and will receive a contrast-enhanced CT and/or MRI of the chest, abdomen, and pelvis. In Part 2, after the first 6-month follow-up visits, patients continue follow-up every 12 $\pm$2 weeks for up to 24 months after the EOT visit or until progression of disease, death, or the initiation of new systemic anticancer therapies, whichever occurs first. The primary endpoints of Part 1 are incidence and severity of TEAEs, patient discontinuation due to TEAEs, and dosing delays due to TEAEs. The primary endpoint of Part 2 is progression-free survival, defined as time from randomization to first disease progression according to RECIST 1.1 or death due to any cause. This study is sponsored by Telix Pharmaceuticals. Clinical trial information: NCT07197580. Research Sponsor: Telix Pharmaceuticals.

TPS4633 **Poster Session**

LITESPARK-033: Phase 3 study of belzutifan plus zanzalintinib versus cabozantinib for recurrent clear cell renal cell carcinoma during or after adjuvant anti–PD-(L)1 therapy. First Author: Cristina Suárez, Vall d´Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d´Hebron, Vall d´Hebron Barcelona Hospital Campus, Barcelona, Spain

Background: Adjuvant pembrolizumab is standard of care for patients with renal cell carcinoma (RCC) at increased risk for recurrence after nephrectomy. However, treatment options are needed following adjuvant anti–PD-(L)1 therapy because none of the currently available treatments for advanced RCC were evaluated in this setting. Belzutifan, a potent and selective hypoxia-inducible factor 2α inhibitor, is approved for advanced RCC following a PD-(L)1 inhibitor and vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI). Zanzalintinib is a multitargeted kinase inhibitor of VEGF receptors, MET, and the TAM family of kinases (TYRO3, AXL, and MER). VEGF-TKIs, such as cabozantinib, are approved as first-line treatment for advanced RCC and in patients who have received subsequent lines of therapy. Promising antitumor activity has been observed in phase 2 studies when combining a VEGF-TKI with belzutifan for advanced clear cell RCC. The randomized, multicenter, open-label phase 3 LITESPARK-033 study (NCT07227402) is designed to evaluate the efficacy and safety of belzutifan plus zanzalintinib versus cabozantinib in participants with advanced clear cell RCC who experienced recurrence during or after anti–PD-(L)1 adjuvant therapy. **Methods:** Eligible participants are aged $\geq$18 years with histologically confirmed, unresectable, advanced (stage IV) RCC with a clear cell component; have measurable disease per RECIST v1.1 as assessed by investigator; received adjuvant anti–PD-(L)1 therapy after nephrectomy; and experienced recurrence during or up to 24 months from the last dose of adjuvant therapy. Approximately 904 participants will be randomly assigned 1:1 to receive belzutifan 120 mg orally once daily plus zanzalintinib 60 mg orally once daily or cabozantinib 60 mg orally once daily. Treatment will continue until unacceptable toxicity or disease progression. Randomization will be stratified according to time of recurrence after adjuvant anti–PD-(L)1 therapy ($\leq$6 months vs $>$6 months after the last dose), International Metastatic RCC Database Consortium risk (favorable vs intermediate vs poor), and presence of sarcomatoid features (yes vs no). Primary end points are progression-free survival per RECIST v1.1 as assessed by blinded independent central review (BICR) and overall survival. Secondary end points are objective response rate and duration of response per RECIST v1.1 as assessed by BICR, and safety. The study is open and currently enrolling as of November 26, 2025. Clinical trial information: NCT07227402. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS4634 **Poster Session**

ZAMBONI: A phase II study of zanzalintinib for metastatic clear cell renal cell carcinoma with bone metastases previously treated with immune checkpoint inhibitors. First Author: Kelly N. Fitzgerald, University of California, San Francisco, San Francisco, CA

Background: Bone metastases (BM) in metastatic renal cell carcinoma (mRCC) are associated with aggressive disease behavior and poor prognosis, particularly following progression on immunotherapy (IO)-based treatment regimens. Oral vascular endothelial growth factor receptor (VEGFR)-targeting tyrosine kinase inhibitors (TKIs) have demonstrated efficacy in mRCC with BM and have been shown to modulate production of osteoclastogenic factors in the tumor microenvironment. Zanzalintinib is a novel oral VEGFR-targeting TKI that has demonstrated a tolerable safety profile in phase I studies; its broad multikinase targeting profile and short half-life of 16-22 hours may enhance efficacy and tolerability compared with other VEGFR-targeting TKIs. However, the efficacy of zanzalintinib in patients with BM is unknown. **Methods:** This is a single-institution, phase II trial of zanzalintinib plus investigator-choice bone modifying agent (BMA) in patients with metastatic clear cell RCC with BM that has been previously treated with immunotherapy (IO). Eligible patients will have primarily clear cell histology, at least three BM including at least one BM not previously treated with radiation therapy (RT), and prior disease progression on 1-3 prior lines of therapy including at least one IO-based therapy administered in either the adjuvant or metastatic setting. Measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 is not required. Patients will receive zanzalintinib 60mg by mouth daily in 28-day cycles; treatment will be continued until disease progression or unacceptable toxicity occurs. Dose reduction, re-escalation, or interruption of up to 6 weeks is allowed for patients experiencing adverse events. Investigator-choice BMA may include zoledronic acid, pamidronate, ibandronate, or denosumab, will be administered at a standard dose/interval starting within 30 days of cycle 1, day 1 (C1D1), and continued until criteria for discontinuation of BMA or removal from study are met. RT and/or steroid therapy for symptomatic metastases, including BM, is allowed per investigator discretion. Patients will be radiologically evaluated starting 8 weeks after C1D1 and every 12 weeks thereafter. Adverse events will be monitored throughout the study and for 30 days following cessation of study treatment. Enrollment will continue until 20 patients evaluable for primary endpoint are enrolled, or up to a maximum of 24 patients. The primary endpoint is 12-month landmark progression-free survival and will be evaluated in patients with RECIST-measurable disease at baseline; key secondary endpoints include overall survival, rate of skeletal-related events, and rate of osteonecrosis of the jaw and will be measured in all patients. Clinical trial information: NCT07043608. Research Sponsor: Exelixis.

TPS4635 **Poster Session**

First-in-human study of [^{111}In] XYIMSR-01 SPECT/CT, a novel carbonic anhydrase IX small molecule in patients with metastatic clear cell renal cell carcinoma. First Author: Yasser Ged, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD

Background: Clear cell renal cell carcinoma (ccRCC) accounts for approximately 75% of renal cancers and is characterized by von Hippel–Lindau (VHL) inactivation and subsequent upregulation of hypoxia-inducible factor-2α (HIF-2α), leading to overexpression of carbonic anhydrase IX (CAIX) in over 95% of tumors. CAIX represents an attractive theranostic target for molecular imaging and radioligand therapy. XYIMSR-01 is a novel low-molecular-weight CAIX-targeted molecule engineered for rapid clearance, high tumor to background contrast, and potential same-day imaging. Preclinical studies demonstrated strong tumor uptake, favorable biodistribution, and selective retention in CAIX-expressing ccRCC xenografts, supporting clinical translation. Based on these findings, a first-in-human study of indium-111 labeled XYIMSR-01 using single photon emission computed tomography (SPECT/CT) imaging has been initiated in patients with metastatic ccRCC. **Methods:** This is an investigator-initiated, single-center, phase I study conducted at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, designed to evaluate the safety, tolerability, and feasibility of [^{111}In]XYIMSR-01 SPECT/CT imaging in patients with metastatic ccRCC. Eligible patients must have histologically confirmed ccRCC, $\geq$2 measurable metastatic lesions (size of each lesion at least $\geq$1.5 cm), treatment naïve, and have adequate organ and marrow function. Following informed consent, patients receive a single intravenous injection of 10.5 $\pm$ 1 mCi of [^{111}In]XYIMSR-01, followed by whole-body planar and regional SPECT/CT imaging at 2-4, 24 $\pm$ 1, and 48 $\pm$ 1 hours post-injection. Blood samples are collected at multiple time points up to 48 hours to assess pharmacokinetics, clearance, and metabolic profile. Radiation dosimetry is calculated from serial imaging to estimate absorbed doses to tumor and normal organs. The primary objective is to assess the safety, tolerability, and feasibility of imaging with [^{111}In]XYIMSR-01. Secondary objectives include characterization of biodistribution, radiation dosimetry, and pharmacokinetics. Exploratory analyses will evaluate concordance between [^{111}In]XYIMSR-01 SPECT/CT with standard CT or MRI for lesion detection. The planned sample size is up to 10 patients. Successful completion of the study may support the development of future CAIX-targeted theranostic strategies in ccRCC. Clinical trial information: NCT07062549. Research Sponsor: None.

TPS4636 **Poster Session**

PEAK-1: A randomized, double-blind, active-control, multicenter phase 3 trial of casdatifan and cabozantinib versus placebo and cabozantinib in patients with advanced clear cell renal cell carcinoma. First Author: Toni K. Choueiri, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: For patients (pts) with advanced or metastatic clear cell renal cell carcinoma (ccRCC) who have relapsed post anti-PD-1/PD-L1 treatment, second line treatment options remain limited, consisting primarily of tyrosine kinase inhibitors (TKI) monotherapy. Hypoxia-inducible factor 2 alpha (HIF-2α) inhibition represents a promising target as its mechanism of action has been clinically validated in ccRCC and is distinct from that of TKIs without overlapping toxicities. Casdatifan (cas) is an orally bioavailable, selective HIF-2α inhibitor that has a potentially improved pharmacodynamic profile relative to other members of the therapeutic class (Ghasemi 2025). Combining cas with a TKI (cabozantinib [cabo]) that targets VEGFR, MET, and AXL may yield enhanced antitumor activity beyond the individual agents. Preliminary efficacy data from the Phase 2 ARC-20 Study demonstrated promising antitumor activity with the combination (cas + cabo; Choueiri 2025). PEAK-1 is currently the only Phase 3 that examines the efficacy and safety of a HIF-2α inhibitor in combination with a TKI in ccRCC. **Methods:** PEAK-1 (NCT07011719) is an ongoing Phase 3, randomized, active-control, double-blind, 2-arm, global, multicenter study in adult pts with confirmed advanced or metastatic ccRCC who have experienced progression on or after anti-PD1 or anti-PD-L1 treatment. Approximately 720 pts will be enrolled and randomized 2:1 to treatment with 100 mg QD cas + 60 mg QD cabo (experimental arm) or placebo + 60 mg QD cabo (comparator arm). Crossover is not allowed. Stratification factors include by region (North America vs Western Europe vs rest of world); prior VEGFR-TKI (yes vs no); and International Metastatic RCC Database Consortium risk score (favorable vs intermediate/poor). Key eligibility requirements include adults ($\geq$ 18 years) who have received anti-PD-1 or anti-PD-L1 treatment as part of the most recent regimen (either adjuvant monotherapy or first line in combination with anti-CTLA-4 or VEGFR-TKI), with $\leq$ 1 prior regimens in the metastatic setting. Pts must have a Karnofsky Performance Status score $\geq$ 80%, at least 1 target lesion measurable by computed tomography/magnetic resonance imaging per RECIST 1.1, and adequate organ and marrow function. Key exclusion criteria include prior treatment with a HIF-2α inhibitor or cabo, receiving ongoing concomitant treatment with moderate or strong CYP3A4 inducers, and uncontrolled or poorly controlled hypertension (sustained blood pressure $>$140/90 mm Hg on $\geq$ 3 antihypertensives). The primary endpoint of the study is PFS BICR according to RECIST 1.1. Secondary endpoints include safety, overall survival, overall response rate, duration of response, and disease control rate. Pt reported outcomes using NFKSI-DRS will also be assessed. Enrolment is ongoing as of 1 Oct 2025. Clinical trial information: NCT07011719. Research Sponsor: Arcus Biosciences, Inc.

TPS4637 **Poster Session**

Phase II study of cemiplimab ± fianlimab following SBRT for oligometastatic clear-cell RCC (LAG-BOOST). First Author: Abhirami Das, Department of Internal Medicine, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: Oligometastatic clear-cell renal cell carcinoma (ccRCC) is a biologically distinct, often indolent state where metastasis-directed therapy, including metastasectomy or SBRT, provides durable local control and delays systemic therapy. Randomized prospective trial evidence demonstrates a survival benefit with adjuvant programmed cell death-1 (PD-1) inhibition following surgical metastasectomy in oligometastatic ccRCC. However, the role of adjuvant PD-1 inhibition following stereotactic body radiation therapy (SBRT) has not been prospectively evaluated. SBRT induces immunogenic tumor cell death, enhances tumor antigen presentation, and promotes T-cell priming, providing a strong biologic rationale for evaluating PD-1 inhibition following SBRT. Beyond PD-1 blockade alone, lymphocyte activation gene-3 (LAG-3) is an inhibitory immune checkpoint expressed on tumor-infiltrating lymphocytes in ccRCC and contributes to T-cell exhaustion and immune evasion. Dual PD-1 and LAG-3 blockade has demonstrated promising antitumor activity with acceptable tolerability in early-phase studies, supporting investigation of strategies to enhance the efficacy of adjuvant PD-1 inhibition following SBRT in oligometastatic disease. **Methods:** LAG-BOOST is a 1:1 randomized, prospective, multicenter, investigator-initiated phase II trial. Eligible patients have histologically confirmed oligometastatic ccRCC, defined as $\leq$5 metastatic lesions by RECIST v1.1, all amenable to SBRT. Following SBRT to all visible lesions, patients are randomized to receive one year of adjuvant PD-1 inhibition (cemiplimab) alone or combined PD-1 and LAG-3 inhibition (cemiplimab and fianlimab). Treatment continues for up to one year or until disease progression, unacceptable toxicity, or withdrawal of consent. Patients must be naïve to systemic therapy for metastatic RCC; prior adjuvant therapy for non-metastatic RCC is permitted in the absence of radiographic disease progression within 12 months of treatment completion. Stratification is based on International Metastatic RCC Database Consortium (IMDC) risk and metastatic burden: (1) favorable or intermediate IMDC risk with 3 or fewer metastatic lesions and no brain metastases versus (2) poor IMDC risk or 4–5 metastatic lesions or the presence of brain metastases. The primary endpoint is 1-year progression-free survival (PFS). Secondary endpoints include safety and tolerability (treatment-related adverse events per CTCAE v5.0), objective response rate by RECIST v1.1, duration of response, disease control rate, and overall survival. As of submission, 2 of the planned 72 patients have been enrolled. The study is powered for H_0: 65% versus H_a: 85% 1-year PFS, with α = 0.05 and power = 0.8. ClinicalTrials.gov identifier: NCT07223541. Clinical trial information: NCT07223541. Research Sponsor: Regeneron Pharmaceuticals.

TPS4638 **Poster Session**

A phase I, first-in-human study to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activities of GenSci139 in patients with solid tumors. First Author: Jinming Yu, Shandong Cancer Hospital, Jinan, China

Background: HER2 and EGFR are frequently co-expressed in solid tumors. Bispecific targeting of these receptors can produce synergistic enhancement in cell binding and internalization, potentially overcoming monotherapy resistance and maintaining efficacy in low antigen-expression settings. GenSci139 is a bispecific antibody-drug conjugate (ADC) directed against both EGFR and HER2, incorporating a cleavable linker to deliver a topoisomerase I inhibitor. In preclinical studies, GenSci139 demonstrated broad-spectrum efficacy, surpassing ENHERTU in HER2-low tumor models. It also displayed a favorable pharmacokinetic and a tolerable safety profile. These findings support further clinical evaluation of GenSci139 in urothelial carcinoma (UC), non-small cell lung cancer (NSCLC), gastric cancer (GC), triple-negative breast cancer (TNBC) and other EGFR/HER2-driven malignancies. **Methods:** This first-in-human, open-label study (NCT07230977) comprises a dose escalation phase with backfill (Part 1) and a dose expansion phase (Part 2). Part 1 employs an accelerated titration followed by a "3+3" design to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE). Backfill cohorts will be enrolled at selected dose levels according to predefined criteria. Part 2 will further evaluate preliminary antitumor activities in predefined cohorts. Key eligibility criteria include advanced solid tumors, measurable disease per RECIST1.1, adequate hematologic and organ function, being able to provide tumor tissues. GenSci139 is administered intravenously every 3 weeks until disease progression, unacceptable toxicity, withdrawal of consent, initiation of alternative anticancer therapy, or other discontinuation criteria are met. Primary endpoints in Part 1 include the incidence of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs). After determination of the MTD/RDE, Part 2 will evaluate the preliminary anti-tumor activity of GenSci139, with primary endpoints including objective response rate (ORR), disease control rate (DCR) and Duration of response (DoR). The study initiated in December 2025 and is currently recruiting. Clinical trial information: NCT07230977. Research Sponsor: None.

TPS4639 **Poster Session**

An open-label phase 1 study of DCC-2812 monotherapy in patients with advanced genitourinary cancers. First Author: Ildefonso I. Rodriguez Rivera, NEXT Oncology, San Antonio, TX

Background: The integrated stress response (ISR) is a major adaptive cellular response pathway that cancer cells depend on to survive in the context of oncogenic pathway activation and high proliferative demand. The ISR is tightly regulated by stress-sensing kinases, including general control nonderepressible 2 (GCN2). Under a controllable level of cellular stress, moderate activation of GCN2 promotes adaptation to nutrient and oxygen deficiency, supporting cancer cell survival. In contrast, excessive GCN2 activation in response to unresolvable stress leads to the induction of pro-apoptotic genes and cancer cell death, making pharmacologic activation of this pathway a promising therapeutic strategy. DCC-2812 is an investigational, potent, and selective activator of GCN2 and the ISR pathway in cancer cells. In preclinical studies, DCC-2812 upregulated the ISR pathway and demonstrated single-agent antitumor activity in a variety of cancer cell lines, including those of renal and urothelial origin. DCC-2812 also inhibited tumor growth in vivo in xenograft models of renal cell carcinoma (RCC) and urothelial cell carcinoma. Here, we describe an ongoing phase 1 study evaluating DCC-2812 as a monotherapy in patients with advanced genitourinary cancers. **Methods:** This is a multicenter, open-label, phase 1 dose-escalation study evaluating the safety and preliminary antitumor activity of DCC-2812 in adult patients ($\geq$18 years) with histologically or cytologically confirmed advanced or metastatic RCC, urothelial cancer, or castration-resistant prostate cancer (NCT06966024). Eligible patients must have experienced disease progression on or be intolerant of standard-of-care therapies and must have adequate organ function as well as the ability to take oral medication. Individuals will be excluded if they received any anticancer therapy (other than luteinizing hormone–releasing hormone agonists/antagonists for prostate cancer) or investigational therapy within a specified timeframe prior to the first dose of DCC-2812, have impaired cardiac function, or had major surgery within 28 days of the first dose of DCC-2812. Enrolled patients will receive DCC-2812 orally in 28-day cycles. The primary outcome measures are the number of patients with dose-limiting toxicities during cycle 1, treatment-emergent adverse events (TEAEs) and serious adverse events, and dose modifications due to TEAEs. Secondary outcome measures include radiographic objective response rate and radiographic duration of response per Response Evaluation Criteria in Solid Tumors version 1.1 and Prostate Cancer Working Group 3 criteria, if applicable, as well as pharmacokinetics. The study is currently recruiting patients at multiple sites in the United States. Clinical trial information: NCT06966024. Research Sponsor: Deciphera Pharmaceuticals, LLC, a member of ONO Pharma.

TPS4640 **Poster Session**

RNDO-564-001: A first-in-human, phase 1/1b study of RNDO-564, a costimulatory bispecific antibody for the treatment of advanced bladder cancer and other Nectin-4–positive solid tumors. First Author: John D. Powderly II, Carolina BioOncology Institute PLLC, Huntersville, NC

Background: RNDO-564 is a novel CD28 x Nectin-4 bispecific antibody (bsAb) with high affinity Nectin-4 binding and optimized CD28 costimulatory arms designed to maximize the therapeutic window. RNDO-564-001 (NCT07218003) is an ongoing, open label, multicenter, phase 1/1b dose escalation and dose optimization study of RNDO-564 as monotherapy, and in combination with pembrolizumab (anti-programmed death PD-1 monoclonal antibody), in adults with relapsed/refractory (R/R), locally advanced or metastatic urothelial cancer (la/mUC) and other Nectin-4 positive solid tumors. **Methods:** The objectives of the study are to assess the safety, tolerability, and to determine the recommended phase 2 dose (RP2D) of intravenous RNDO-564 monotherapy given on Days 1, 8, and 15 of a 21-day cycle. Monotherapy dose escalation will include an accelerated titration component using four single participant (pt) cohorts, followed by more gradual dose increments using a Bayesian Optimal Interval (BOIN) with backfill design. Pts with R/R la/mUC, cervical, head and neck, esophageal, gastric, gastroesophageal, non-small cell lung, or triple negative breast cancer, who have exhausted, are ineligible for, or declined available standard treatment options, are eligible for the dose escalation phase of the study. Pts must have an ECOG performance status of 0-1. Pts with prior Nectin-4 directed therapies and Monomethyl Auristatin E (MMAE) exposure and those with ongoing Grade $\leq$ 2 peripheral neuropathy are eligible. Pts with a history of, or with active, inflammatory skin conditions are ineligible. Enrollment into Cohorts 1 and 2 have been completed without dose limiting toxicity (DLT). Enrollment to cohort 3 opened in January 2026. Safety endpoints include incidence of adverse events per CTCAE v6.0. Secondary endpoints include clinical activity, pharmacokinetics, and incidence of anti-drug antibody development. Retrospective assessment of Nectin-4 expression on tumor tissue by immunohistochemistry (IHC), and measurement of CD28 receptor occupancy, T cell activation, and serum cytokines in peripheral blood will be performed as exploratory endpoints. To determine the optimal RP2D in R/R la/mUC, up to two 20 pt dose optimization cohorts at two different dose levels will be enrolled. Separate dose escalation and optimization stages in combination with pembrolizumab will be conducted to assess safety, clinical activity, and RP2D for further development of combination treatment. Based on emerging clinical data, additional monotherapy and/or combination therapy expansion cohorts may be opened for pts with non-UC Nectin-4 positive solid tumors. **Conclusions:** RNDO-564-001 is an ongoing phase 1/1b study to determine the safety, tolerability, clinical activity, and RP2D of RNDO-564 in R/R la/mUC and other Nectin-4 positive solid tumors. Clinical trial information: NCT#07218003. Research Sponsor: Rondo Therapeutics, Inc.

TPS4641 **Poster Session**

A phase III randomized trial of pembrolizumab in combination with sacituzumab govitecan vs standard of care in anti–PD-(L)1–resistant advanced urothelial cancer: ECOG-ACRIN EA8231. First Author: Monika Joshi, Penn State Cancer Institute, Hershey, PA

Background: Patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) who progress after anti-PD-(L)1 therapy (CPI-R) and enfortumab vedotin (EV) have relatively limited treatment options and poor outcomes. SG, a TROP-2–directed antibody–drug conjugate (ADC), has meaningful efficacy in previously treated la/mUC, while SG plus pembro achieved 41% overall response rate (ORR; 20% complete response rate) in platinum-refractory la/mUC. With rapidly evolving treatment paradigms and earlier use of EV and anti-PD(L)1, the frequency of CPI-R la/mUC is expected to increase; therefore, newer combinations and the role of anti-PD(L)1 re-challenge should be prospectively evaluated in previously treated la/mUC. We hypothesized that SG/pembro combination would improve outcomes over standard chemotherapy (SOC) in pts previously treated with anti-PD(L)1. **Methods:** EA8231 is an open-label, multicenter, randomized phase III trial enrolling adults with unresectable la/mUC. Key eligibility criteria: a) ECOG PS 0-2 b) Prior anti-PD(L)1 given in any disease setting but no cancer progression within 12 weeks from starting prior anti-PD(L)1initiation c) Prior exposure to EV unless contraindicated d) $\geq$1 lines of systemic therapy for la/mUC [*FGFR3* altered tumors must have received prior FGFR inhibitor unless contraindicated] e) Bellmunt score 0-2 f) No prior exposure to SG or other TROP-2 directed therapies or drugs containing topo-isomerase I inhibitor. Treatment: Pts are randomized 1:1 to Arm A SOC (platinum-gemcitabine or taxane Q3 week cycle) OR Arm B pembro/SG (Pembro 200mg on day 1 + SG 10mg/kg on days 1, 8 of a 21-day cycle with G-CSF support). Pts are stratified by Bellmunt score (0-1 vs 2), prior lines of therapy ($\leq$2 vs $>$2), prior exposure to platinum-based chemotherapy (yes vs no prior exposure and platinum-eligible vs no prior exposure and platinum-ineligible), duration of prior anti PD-(L)1 therapy ($\leq$6 vs $>$6 months). G-CSF primary prophylaxis is strongly recommended, esp. with SG. *Endpoints*: Primary endpoint: overall survival (OS); secondary endpoints: progression-free survival, ORR, clinical benefit rate, duration of response, safety/tolerability, health related QOL (NFBISI-18; FACIT-Fatigue; EQ-5D-5L). Statistical plan: Trial is designed to demonstrate 42.5% improvement in median OS [platinum-ineligible cohort: median OS increase from 9 to 12.8 months; platinum-eligible cohort: median OS increase from 10.3 to 14.7 months]; 80% power with 1-sided 0.025 type I error rate; HR (pembro+SG/SOC) 0.70, N=320. Trial Status: Activation date: 10/23/2025 (1 patient accrued as of Jan 6, 2026; 28 approved sites, additional sites pending). Clinical trial information: NCT06524544. Research Sponsor: National Cancer Institute of the National Institutes of Health under award numbers: U10CA180820, U10CA180794, U10CA180821, UG1CA233180, UG1CA233196, UG1CA233328, UG1CA233339, and UG1CA233373.

TPS4642 **Poster Session**

TROPION-Urothelial03: A phase 2/3 study of datopotamab deruxtecan (Dato-DXd) + platinum chemotherapy (CT) vs gemcitabine + platinum CT in participants with locally advanced or metastatic urothelial carcinoma (la/mUC) with progression on or after enfortumab vedotin (EV) + pembrolizumab. First Author: Matthew D. Galsky, Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY

Background: Although first-line (1L) EV + pembrolizumab has improved outcomes for patients with la/mUC, most experience disease progression, highlighting an unmet need for novel therapies. TROP2 is a glycoprotein highly expressed in several epithelial tumors, including UC. Dato-DXd is a TROP2-directed antibody–drug conjugate comprising an anti-TROP2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload (DXd), designed to induce selective tumor-cell death and reduce systemic exposure to the payload. Dato-DXd has demonstrated durable efficacy and a manageable safety profile in patients with la/mUC both as monotherapy (TROPION-PanTumor01 [NCT03401385]) and in combination with immunotherapy (TROPION-PanTumor03 [NCT05489211]). We describe a Phase 2/3 trial comparing the efficacy and safety of Dato-DXd + platinum CT (carboplatin or cisplatin) vs gemcitabine + platinum CT in participants with la/mUC with disease progression on or after EV + pembrolizumab. **Methods:** TROPION-Urothelial03 (NCT07129993) is a global, multicenter, randomized, open-label, Phase 2/3 trial. In Part A (Phase 2), ~60 participants will be randomized 1:1 to receive Dato-DXd 4 or 6 mg/kg + platinum CT. In Part B (Phase 3), ~570 participants will be randomized 1:1 to receive Dato-DXd at the recommended Phase 3 dose (determined using Part A data) + platinum CT vs gemcitabine + platinum CT. Randomization in Part A is stratified by assignment of platinum CT (carboplatin vs cisplatin), and in Part B, by assignment of platinum CT, presence vs absence of liver metastasis at screening, and time to progression on 1L EV + pembrolizumab ($<$6 vs $\geq$6 months). Study treatment continues until disease progression, unacceptable toxicity, withdrawal of consent, death, loss to follow-up, or other reasons per protocol. Radiographic tumor assessments occur every 6 weeks for 54 weeks, then every 12 weeks. The primary endpoint of Part A is objective response rate (ORR) by investigator per Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1). The dual primary endpoints of Part B are progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1 and overall survival (OS). Secondary endpoints include duration of response by investigator per RECIST 1.1 (Part A), and PFS by investigator per RECIST 1.1 and ORR by BICR and investigator per RECIST 1.1 (Part B). In Part A, ORR will be summarized with 2-sided 95% exact confidence intervals using the Clopper–Pearson method by trial group. In Part B, PFS and OS will be compared between trial groups using a log-rank test stratified by randomization stratification factors, with hazard ratios from the stratified Cox regression model. Clinical trial information: NCT07129993. Research Sponsor: Daiichi Sankyo, Inc.

TPS4643 **Poster Session**

Advancing treatment of low-grade upper tract urothelial carcinoma (LG UTUC) with padeliporfin vascular-targeted photodynamic therapy (VTP): The ENLIGHTED phase 3 trial. First Author: Vitaly Margulis, Department of Urology, UT Southwestern Medical Center, Dallas, TX

Background: Padeliporfin VTP is a drug-led combination therapy consisting of IV Padeliporfin activated by a low-power near-infrared (753 nm) laser–fiber system. A non-contact cylindrical fiber positioned near the tumor provides circumferential illumination, inducing vascular occlusion and coagulative tumor necrosis while preserving tissue structure. Safety and efficacy were shown in a Phase 1 UTUC study (NCT03617003). We report emerging efficacy, durability, and safety from the ENLIGHTED Phase 3 trial in LG UTUC (NCT04620239). **Methods:** ENLIGHTED is an open-label Phase 3 study conducted in the US, EU, and Israel, evaluating the efficacy, durability, and safety of padeliporfin VTP in LG UTUC. Eligible patients (pts) may have new or recurrent disease, be treatment-naïve or previously treated, and have up to two biopsy-confirmed LG lesions (5–15 mm kidney or 5–20 mm ureter) without high-grade cells on instrumented cytology. VTP is performed via retrograde upper tract endoscopy under anesthesia and low-light conditions. Padeliporfin is administered IV, and an optical fiber with a 20–40 mm diffuser is positioned near the tumor through the scope, followed by 10 minutes of laser illumination. Treatment consists of an Induction Treatment Phase (ITP) of 1–3 VTP sessions at 4-week intervals until complete response (CR) or treatment failure at Primary Response Evaluation (PRE). Pts achieving CR enter a 12-month Maintenance Treatment Phase (MTP) with quarterly endoscopic surveillance and retreatment for treatable recurrences, followed by long-term follow-up up to 48 months. The primary endpoint is CR at PRE (28 $\pm$ 3 days post last ITP treatment), defined by absence of visible tumor on endoscopy and negative instrumented cytology. A total of 100 pts are to be enrolled. As of January 19, 2026, 78 pts were enrolled and 63 completed ITP. Response rates were: CR 73.0%, PR 17.7%, DR 3.2%, PD 4.8%, and stable disease 1.6%. Among pts with CR at PRE, 39.5% had completed MTP by data cutoff, with 88.2% maintaining CR in the treated area (TA) for $\geq$12 mos. Median Duration of Response in the TA was not reached and is $\geq$23.9 mos. Most pts remains in MTP or follow-up. The most common treatment-emergent adverse events were hematuria (10.6%), flank pain (8.6%), nausea (5.5%), procedural pain (4.5%), abdominal pain (4.1%), dysuria (4.1%), vomiting (3.4%), and fatigue (3.1%), all Grade 1–2 with a median duration of 5 days. 23 serious adverse events (7.7%) were reported, mostly unrelated to treatment. One Grade 3 SAE (renal colic related to VTP) resolved within 2 days. Padeliporfin VTP demonstrates favorable preliminary efficacy, durable responses, and a safety profile consistent with prior experience. Enrollment is ongoing, and final outcomes are anticipated to support regulatory approval of an organ-preserving therapy for LG UTUC. Clinical trial information: NCT04620239. Research Sponsor: Steba/Impact biotech.

TPS4644 **Poster Session**

Selective bladder-sparing trial with sasanlimab as maintenance treatment based on clinical response to neoadjuvant treatment in molecularly categorized muscle invasive bladder cancer patients: SASAN-SPARING trial. First Author: Elena Sevillano, HM Sanchinarro Centro Integral Oncologico Clara Campal (CIOCC), Madrid, Spain

Background: Muscle-invasive bladder cancer (MIBC) is an aggressive disease with a high risk of progression, for which radical cystectomy (RC) remains the standard of care. Adaptive bladder-sparing strategies based on post-neoadjuvant clinical restaging are increasingly explored to maintain oncologic control while preserving quality of life. SASAN-SPARING evaluates sasanlimab, a PD-1 inhibitor, as maintenance therapy in patients achieving a clinical response after neoadjuvant cisplatin-based chemotherapy. **Methods:** SASAN-SPARING (HM-8788561; NCT06623162) is an ongoing, single-arm, multicenter, phase II trial enrolling patients aged $\geq$18 years with treatment-naïve, localized MIBC (pT2–T4a, N0, M0) eligible for neoadjuvant chemotherapy. All patients receive four cycles of cisplatin (70 mg/m^2 on day 1) plus gemcitabine (1000 mg/m^2 on days 1 and 8) every 3 weeks, followed by comprehensive clinical restaging. Patients achieving a clinical response (cT0/Ta/T1/Tis, negative cytology, and negative imaging) are eligible for bladder preservation with sasanlimab 300 mg administered subcutaneously every 4 weeks for up to 12 cycles. Non-responders ($\geq$cT2) undergo RC. During maintenance, restaging is performed every 12 weeks, and RC may be considered upon loss of response or disease progression. The primary endpoint is bladder-intact overall survival at 12 months after the first dose of sasanlimab. Secondary endpoints include disease-free survival, metastasis-free survival, overall survival, safety, and health-related quality of life. The study incorporates an ambitious biomarker analysis, including whole-genome sequencing of tumour tissue and plasma, the use of ctDNA in plasma and urine for tumour assessment and molecular dynamics, and the study of the gut microbiome in stool. Biomarker-correlative studies will provide a valuable tool for personalized treatments and inform treatment decisions in adaptive strategies such as SASAN-SPARING. The Expected sample size is 70 patients, assuming a 12-month biOS of 81% (H0) and an increase with sasanlimab up to 93% (H1) (one-arm survival test; α=0.05 β=0.8).Recruitment began in December 2024. As of January 2026, 62 patients have been enrolled across 10 centers, and 21 started sasanlimab maintenance therapy. Enrollment is ongoing.SASAN-SPARING explores an adaptive, biomarker-integrated bladder-sparing strategy which aims to generate prospective evidence to support organ-preservation strategies in MIBC. Clinical trial information: NCT06623162. Research Sponsor: None.

5000 **Oral Abstract Session**

Clinico-transcriptomic risk stratification to guide abiraterone treatment intensification in high-risk prostate cancer: A combined analysis of NRG/RTOG 9202, 9413, 9902, and 0521. First Author: Krishnan R. Patel, Radiation Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Outcomes for some patients with ≥high-risk localized prostate cancer (HR-PCa) who receive radiation therapy (RT) remain poor. Current guidelines recommend intensification with abiraterone/prednisone (AAP) in select patients; however, the current guideline-defined candidate population may be suboptimal. **Methods:** This is a secondary analysis of available biopsy samples from NRG/RTOG 9202, 9413, 9902, and 0521. The primary objective was to determine if a specific subgroup of ≥HR-PCa patients had sufficiently poor prognoses to derive a clinically meaningful benefit from AAP intensification. The prognostic impact of the Decipher 22-gene genomic classifier (GC; Veracyte, San Diego, CA) was first evaluated for metastasis-free survival (MFS, primary), overall survival (OS), and distant metastases (DM). GC scores were analyzed using both continuous (per 0.1 GC units) and pre-specified categorical cutpoints: ≤ intermediate transcriptomic risk (IR-PCa, GC≤0.6), HR-PCa (GC:0.6-0.85), and very high risk (VHR-PCa, GC > 0.85). A tree-based model was then used to combine clinical and transcriptomic risk category. **Results:** This study characterized outcomes of 427 patients (64% NCCN HR-PCa; 36% NCCN VHR-PCa) with a median follow-up of 10.4 years. Continuous GC score was observed to discriminate risk when adjusted for age, PSA, grade, T-stage, and treatment received for the endpoints of MFS (HR_{GC}:1.19 [95% CI:1.10-1.29], $p < 0.001$), DM (HR_{GC}:1.31 [95% CI:1.13-1.51], $p < 0.001$), and OS (HR_{GC}: 1.18 [95% CI: 1.09-1.28], $p < 0.001$). MFS and OS were estimated using the Kaplan-Meier method by pre-specified GC subgroup within each NCCN risk group (HR-PCa, VHR-PCa). Based on outcomes by subgroup, a novel clinico-transcriptomic risk stratification system was constructed, where patients receive 1 point for NCCN/GC HR categorization and 2 points for NCCN/GC VHR categorization. The combined risk score ≥3 subgroup had a prognosis similar to the STAMPEDE M0 control arm, whereas the combined score ≤2 subgroup had a substantially better prognosis. Utilizing this system could enhance the specificity of AAP recommendations, increasing the candidate pool eligible for AAP intensification by approximately 20% and identifying approximately 25% of NCCN VHR in whom the therapeutic ratio of AAP may be less favorable. **Conclusions:** This study defines a novel clinico-transcriptomic risk stratification system to augment current clinical eligibility for AAP intensification. This system may increase the population who benefit from AAP by approximately 20% and simultaneously identify approximately 25% of NCCN VHR patients who may avoid AAP intensification. Acknowledgement: We would like to acknowledge Dr. Felix Feng for his contributions in his capacity as the former GU Committee Chair. Research Sponsor: U.S. National Institutes of Health; U10CA180868; U.S. National Institutes of Health; U10CA180822; U.S. National Institutes of Health; UG1CA189867; U.S. National Institutes of Health; U24CA196067; U.S. National Institutes of Health; NCI CCR Intramural Research Program; Sanofi; Veracyte; Pfizer; Bristol Myers Squibb.

5001 **Oral Abstract Session**

Assessment of the ability of Decipher Prostate Genomic Classifier (DGC) >0.85 to identify patients who benefit from adding docetaxel (DOC) to androgen deprivation therapy (ADT) plus enzalutamide (ENZ): Level 1B evidence from the ENZAMET study. First Author: Christopher Sweeney, South Australian Immunogenomics Cancer Institute, Adelaide University, Adelaide, SA, Australia

Background: DGC predicts overall survival (OS) benefit from DOC when added to ADT while the benefit of adding DOC to ADT and ENZ is unknown. We hypothesized in a locked prespecified statistical analysis plan that higher GC score (> 0.85, the locked threshold on clinical test report) will identify patients who benefit from addition of DOC to ADT plus ENZ independently of metastases volume and timing. **Methods:** DGC scores were generated from transcriptome profiling using a clinical test (Veracyte) on tumor index cores from participants (pts) randomised on ENZAMET study (N = 1,125) 1:1 ADT with NSAA or ENZ with clinical discretion to add DOC as part of standard of care. Primary tumor samples were available from 764 pts. Differential DOC OS benefit was assessed by testing the marker-by-treatment interaction term in propensity score-weighted Cox models, with weights based on factors associated with planned DOC use. Prognostic effects of DGC were estimated using Cox for age, WHO PS, Gleason, randomized arm +/- planned DOC, metastases volume and timing, with adjusted hazard ratios (aHR) and 95% CIs. Analyses were prespecified and conducted independently by two statisticians. **Results:** DGC scores were available for 634 (83%) unique pts (median follow-up 5.6 years) with clinical factors representative of the overall trial. Median age was 68 yrs with 50% HV, 62% synchronous presentation, and 44% with planned DOC. Planned DOC was associated with younger age, high volume and synchronous presentation (all p≤0.002). Median DGC score was 0.88 (IQR 0.75-0.96) and 55% had DGC > 0.85 (62% in pts with DOC planned, 49% in others). Overall, higher GC was significantly associated with poorer OS (aHR 1.37 [1.06-1.78], p = 0.02). DOC benefit differed by GC level [higher vs lower] in pts treated with ADT plus ENZ (p-interaction 0.043). Higher DGC was associated with worse OS in pts treated with ADT plus ENZ (aHR 2.31 [95% CI 1.26-4.21], p = 0.007) while pts treated with DOC added to ADT plus ENZ showed no significant difference by DGC (aHR 1.08 [0.63–1.86]). Effects were more pronounced in pts with high vs. low volume disease. **Conclusions:** DGC > 0.85 is predictive of benefit from adding DOC to ADT plus ENZ as it negated the poor prognostic outcome of DGC > 0.85 with ADT plus ENZ alone, whereas there was no evidence of benefit for adding DOC for pts with GC ≤0.85. Research Sponsor: Nantional Cancer Institute; Movember Foundation; Australian Department of Health; Astellas and Pfizer; Veracyte.

5yr OS	N	Lower Decipher	Higher Decipher	Higher vs. loweradj. HR (95% CI)
Overall	634	71% (66-77%)	57% (51-62%)	1.37 (1.1, 1.8)
ADT+ENZ	178	86% (78-93%)	62% (52-72%)	2.29 (1.3, 4.2)
ADT+ENZ+DOC	142	66% (53-79%)	58% (48-68%)	1.08 (0.6, 1.9)
ADT+ENZ (LV)	123	88% (80-96%)	72% (61-84%)	1.96 (0.9, 4.3)
ADT+ENZ+DOC (LV)	44	86% (67-100%)	79% (64-94%)	1.70 (0.3, 9.0)
ADT+ENZ (HV)	55	81% (65-96%)	41% (23-60%)	2.83 (1.1, 7.5)
ADT+ENZ+DOC (HV)	98	58% (42-75%)	48% (36-61%)	1.07 (0.6, 1.9)

5002 **Oral Abstract Session**

Spatial transcriptomics–guided computational pathology model to stratify docetaxel benefit in metastatic hormone-sensitive prostate cancer: CHAARTED trial (ECOG-ACRIN E3805). First Author: Md Mamunur Rahaman, School of Computer Science and Engineering, University of New South Wales, Sydney, NSW, Australia

Background: The CHAARTED trial demonstrated improved overall survival (OS) with the addition of docetaxel (DTX) to androgen deprivation therapy (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC), but many patients do not benefit and experience significant toxicity. Clinical factors (e.g., metastatic burden) are suboptimal for predicting DTX benefit, indicating a need for better biomarkers. We developed ST-DoxPCa (Spatial Transcriptomics–Guided Docetaxel Therapy Stratification in Prostate Cancer), an artificial intelligence (AI)-driven biomarker that infers intratumoral gene expression from routine H&E slides (via virtual spatial transcriptomics) to stratify patients by likelihood of benefiting from DTX. **Methods:** ST-DoxPCa was developed using paired H&E and spatial transcriptomics from the HEST1K prostate cohort to train a Vision Transformer–based regressor to predict a 208-gene panel at spot/patch level; predictions were distilled into a biologically informed 26-gene signature and summarized into patient-level features capturing expression level and heterogeneity. In CHAARTED, a Cox model for overall survival (OS) was trained and internally validated in the ADT-only arm (n = 154; 50/50 split: n = 77 train, n = 77 validation) to derive an ST-DoxPCa risk score and fixed median threshold. This locked model was then applied to the ADT validation cohort (n = 77) and the held-out ADT+DTX arm (n = 129), and OS was compared between treatment arms within biomarker-defined risk groups using Kaplan–Meier estimates and Cox hazard ratios. **Results:** ST-DoxPCa stratified patients into biomarker-defined risk groups using aggregated spatial-expression features from a biologically informed gene panel; key genes included AR, PTEN, FASN, FOXA1, and ACPP. In ST-DoxPCa-positive (high-risk) patients, adding DTX to ADT significantly improved OS versus ADT alone (HR = 0.53, 95% CI 0.31–0.90; p = 0.018), with no benefit in ST-DoxPCa-negative (low-risk) patients (HR = 1.32, 95% CI 0.74–2.34; p = 0.34). **Conclusions:** ST-DoxPCa is a novel spatial transcriptomics guided histology biomarker that predicts differential benefit from docetaxel in mHSPC. ST-DoxPCa identified a subset of patients who achieve substantial survival gains from upfront DTX and another subset with no benefit, enabling personalized treatment intensification. ST-DoxPCa has the potential to spare low-risk patients unnecessary chemotherapy while directing therapy to those most likely to benefit. Clinical trial information: NCT00309985. Research Sponsor: National Cancer Institute (NCI), National Institutes of Health (NIH); United States Department of Veterans Affairs; U.S. Department of Defense (DoD) – Prostate Cancer Research Program.

LBA5003 **Oral Abstract Session**

First interim analysis of SWOG S1823: Operating characteristics of circulating microRNA 371a-3p (miR371) in predicting active germ cell malignancy (aGCM) in patients (pts) with early-stage testicular cancer. First Author: Lucia Nappi, BC Cancer - Vancouver Centre and Vancouver Prostate Centre, Vancouver, BC, Canada

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

5004 **Oral Abstract Session**

A phase 2 trial of androgen deprivation therapy interruption in patients responding exceptionally to androgen receptor pathway inhibitor in metastatic hormone-sensitive prostate cancer (A-DREAM / Alliance A032101). First Author: Atish Dipankar Choudhury, Dana-Farber Cancer Institute, Boston, MA

Background: Patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) treated continuously with testosterone suppression (TS) plus an androgen receptor pathway inhibitor (ARPI) can experience cumulative toxicity. We conducted this single-arm phase 2 trial (NCT05241860) to test the hypothesis that pts who achieve favorable response to TS + ARPI can have prolonged treatment-free interval with testosterone recovery after treatment interruption (TI). Here we report on the primary endpoint. **Methods:** Eligible pts had mHSPC by conventional imaging with prostate-specific antigen (PSA) $\geq$ 5 ng/ml and testosterone $\geq$ 150 ng/dl prior to starting TS+ARPI, with PSA $<$ 0.2 ng/ml and testosterone $<$ 50 ng/dl at the time of enrollment after having received TS for 540-750 days and ARPI for $\geq$ 360 days. Prior local therapy, radiation to metastases and docetaxel were permitted. After enrollment, pts discontinued TS and ARPI and were followed with PSA and testosterone levels every 3 months (mo), CT/MRI and bone scan at least every 6 mo, and FACT-P questionnaire for patient-reported outcomes (PROs) every 6 mo. Treatment was resumed for PSA $\geq$ 5 ng/ml, radiographic change (progressive disease [PD] per RECIST 1.1 on CT/MRI or unconfirmed PD per PCWG3 on bone scan), or prostate cancer-related symptoms. The primary endpoint was proportion of men remaining treatment-free 18 mo after TI with eugonadal testosterone ($>$ 150 ng/dl). Target enrollment was 75 pts to differentiate 18-mo treatment-free rates of 0.30 (H_0) and 0.45 (H_a). **Results:** Of 79 pts enrolled between 07/2022 and 03/2024, 78 were eligible and underwent TI. Among these 78, median PSA prior to starting TS+ARPI was 19 (range 5-6759), 27 (35%) had high volume disease, 31 (40%) never received local therapy, and 55 (71%) did not receive radiation to metastases. By 18 mo after TI, 67% (52/78) recovered testosterone and 58% (45/78) remained treatment-free; 41% (32/78) remained treatment-free with testosterone recovery (80% CI 33.5-48.9%, one-sided p 0.0249). At median follow-up of 21.2 mo, 35% (27/78) resumed initial TS+ARPI after meeting re-initiation criteria (of whom 1 required treatment switch for PD 9 mo later); 5% (4/78) resumed prior to meeting criteria; 9% (7/78) pursued alternative therapy instead of resuming TS+ARPI per protocol; 5% (4/78) withdrew; 1 died of myocardial infarction prior to resuming treatment. 4 pts died, 1 of prostate cancer. **Conclusions:** The primary objective was achieved with 41% of favorable responders to TS+ARPI remaining treatment-free with testosterone recovery at 18 mo after TI. Analyses of biomarkers and PROs are in progress, and pts will be followed for long-term outcomes. Support: U10CA180821, U10CA180882, UG1CA189823, https://acknowledgments.alliancefound.org, Veracyte Inc. Clinical trial information: NCT05241860. Research Sponsor: National Cancer Institute; Veracyte.

5005 **Oral Abstract Session**

Cognitive effects of darolutamide vs enzalutamide: Results of ARACOG (AFT-47), a randomized clinical trial from the Alliance for Clinical Trials in Oncology. First Author: Alicia K. Morgans, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Androgen receptor pathway inhibitors (ARPIs) may have distinct central nervous system (CNS) penetration and differential effects on cognition or quality of life (QOL). AFT-47, "ARACOG" is a prospective, randomized open-label phase 2 trial comparing objective and patient-reported cognitive and QOL outcomes between patients with metastatic hormone sensitive prostate cancer (mHSPC), metastatic castration-resistant prostate cancer (mCRPC) or non-metastatic castration-resistant prostate cancer (nmCRPC) treated with darolutamide (DAR) or enzalutamide (ENZ). **Methods:** Between 8/17/2021 and 3/11/2025, 111 pts were enrolled and randomized 1:1 to treatment with ENZ or DAR. CANTAB, a validated computer-based platform evaluating 5 cognitive domains (PALFAM-memory recall, SWM- spatial working memory, SSP-short-term visual memory, working memory, RVP-rapid visual processing, and OTSMCC- executive function), was performed at baseline, 12, 24, and 48 weeks. Crossover (Xover) was allowed at 12 or 24 weeks for significant pre-specified decline in cognitive testing or patient reported outcome measures (PROMs), or for CNS-associated adverse events, including falls. The primary endpoint was the percent change in the maximally changed cognitive domain (MCCD) from baseline to 24 weeks and was compared between groups with the Wilcoxon rank sum statistic. Patients crossing over prior to 24 weeks were evaluated at the time of Xover and analyzed with their randomized arm. Secondary endpoints included comparison of Xover rates. **Results:** Among 111 pts, 55 received DAR and 56 received ENZ; median age was 71, 83% White. 95 pts (48 DAR, 47 ENZ) were evaluable for the primary endpoint. Baseline CANTAB was similar between groups. Median cognitive change in MCCD between baseline and 24 weeks was -15.8% and -36.1% for the DAR and ENZ pts, respectively (p = 0.009) (Table). Individual cognitive domains suggest possible learning effect (increased scores) for DAR and are stable or show mild decline for ENZ treated patients at 24 weeks. 32 DAR (58%) and 33 ENZ (59%) participants were eligible for Xover by 24 weeks, and 23 pts crossed over by 24 weeks. All Xover was pts randomized to ENZ (crossed to DAR), with the most common causes being decline in objective (N = 14) or subjective (N = 11) cognitive testing. **Conclusions:** In this US randomized trial comparing DAR to ENZ, the primary endpoint of differential cognitive effects was met. ENZ showed significantly greater cognitive score decline than DAR at 24 weeks in the MCCD after treatment initiation. Learning effect was seen with DAR but not ENZ. Longer term follow-up of cognitive change and PROM analyses are ongoing. Clinical trial information: NCT04335682. Research Sponsor: Prostate Cancer Foundation; Alliance Scholar Award; Bayer; https://acknowledgments.alliancefound.org.

Percent change in maximally changed cognitive domain by treatment.

	DAR (N=48)	ENZ (N=47)	Wilcoxon Rank Sum Test Result
CANTAB domain	PALFAM	SWM	
Degree of change	-15.8 (-38.8, -2.6)	-36.1 (-59.3, -16.7)	P=0.009

5006 **Oral Abstract Session**

Final results from ZZFIRST: A randomized phase 2 trial of enzalutamide (EZ) and talazoparib (TALA) in metastatic hormone-naïve prostate cancer (mHNPC). First Author: Joaquin Mateo, Vall d´Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d´Hebron, Barcelona, Spain

Background: ADT plus AR pathway inhibition (ARPI) improves outcomes in mHNPC, yet responses remain heterogeneous. AR–PARP cotargeting has shown enhanced clinical activity in prostate cancer, but the underlying mechanisms are incompletely defined. ZZFIRST evaluated enzalutamide (EZ) plus talazoparib (TALA) in mHNPC, including the study of tumor adaptation response to ADT+ARPI through biopsies obtained on therapy. **Methods:** ZZFIRST (NCT04332744) is an open label, randomized academic phase 2 trial that included patients (pts) with high-volume (HV)-mHNPC (CHAARTED), ECOG PS $\leq$1, PSA$\geq$4 ng/mL. All pts received standard ADT and started EZ 160 mg/day. After two 28-day cycles, pts were randomized 2:1 to EZ+TALA 0.5 mg/day or continue EZ alone until progressive disease (PD), unacceptable toxicity, or withdrawal. Randomization was stratified by DDR mutation status. Primary endpoint was confirmed PSA $<$ 0.2 response rate (PSA $<$ 0.2-RR) at 12 months (mo) for EZ+TALA. Key secondary endpoints included rPFS, time to PSA-PD, time to castration resistance, and safety. The study was powered (80%, one-sided α = 5%) to detect improved PSA $<$ 0.2-RR (H0: 20%; H1$\geq$40%) for EZ+TALA. Between-arm comparisons were exploratory. Spatial transcriptomics (Visum HD) was performed on baseline (BL) and Cycle 2-Day 1 (C2D1) on-treatment tumor biopsies. **Results:** 54 pts were enrolled (37 EZ+TALA, 17 EZ). 7 pts harbored HRR alterations by tumor tissue NGS (13%; 5 EZ+TALA, 2 EZ). Visceral metastases were present in 17 pts (32%); 51 pts (94%) had *de novo* M1 disease. Median follow-up was 3.6 years. The primary endpoint was met, with a 73% 12-mo PSA $<$ 0.2-RR for EZ+TALA (95%CI, 55.9%-86.2%, p $<$ 0.001); the rate was 64.7% for EZ. Median rPFS was 45.3 mo (29.4-NR) for EZ+TALA vs 31.1 mo (13.5-NR) for EZ (HR = 0.62; 95%CI, 0.28-1.37). Median time to PSA-PD was not reached (30.4-NR) for EZ+TALA vs 30.7 mo (6.6-NR) for EZ (HR = 0.47; 95%CI, 0.21-1.04). Median TTCR was 30.4 mo (23.0-NR) for EZ+TALA vs 22.8 mo (6.3-45.4) for EZ (HR = 0.62; 95%CI, 0.30-1.26). In TALA+EZ, common treatment-emergent AEs were fatigue (any grade: 83.8%; G$\geq$3: 13.5%) and anemia (67.6%; G$\geq$3: 40.5%). 14 (38%) pts required TALA dose reductions. Two pts on EZ+TALA developed acute myeloid leukemia (AML) 26.0 and 32.8 mo after study entry. Transcriptomics analysis on C2D1 vs BL biopsies showed induction of cell cycle arrest, with downregulation of AR and DDR signatures and upregulation of IFN-related and inflammatory response signatures upon ADT+EZ. **Conclusions:** EZ+TALA demonstrated promising antitumor activity in HV-mHNPC. The toxicity profile was consistent with prior AR+PARP trials, although two cases of AML were observed with prolonged TALA exposure. Paired tumor biopsies revealed mechanisms of tumor adaptation to ADT+EZ inhibition, supporting a biologically informed rationale for AR+PARP treatment intensification strategies in mHNPC. Clinical trial information: NCT04332744. Research Sponsor: Pfizer S.L. and Astellas Pharma Europe LTD.

LBA5007 **Oral Abstract Session**

TALAPRO-3: Talazoparib (TALA) + enzalutamide (ENZA) compared with placebo (PBO) + ENZA for the treatment of patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) harboring homologous recombination repair (HRR) gene alterations. First Author: Neeraj Agarwal, Huntsman Cancer Institute (NCI-CCC), University of Utah, Salt Lake City, UT

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

5008 Oral Abstract Session

Fuzuloparib combined with abiraterone acetate and prednisone (AA-P) as first-line (1L) treatment for metastatic castration-resistant prostate cancer (mCRPC): Interim results from the FUZUPRO trial. First Author: Dingwei Ye, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The combination of PARP inhibitors with standard AA-P may offer enhanced antitumor activity over AA-P. We conducted FUZUPRO, an international, randomized, double-blind, placebo-controlled phase 3 trial, to compare the efficacy of fuzuloparib, a novel PARP inhibitor, plus AA-P vs AA-P as 1L treatment for mCRPC. **Methods:** 1L mCRPC patients were randomized (1:1) to orally receive fuzuloparib 150 mg BID plus AA-P (abiraterone acetate 1000 mg QD; prednisone 5 mg BID) or placebo plus AA-P. Randomization was stratified by DNA-repair gene defect (DRD) status (positive vs negative/unknown) and other factors. Primary endpoint was blinded independent central review (BICR)-assessed radiographic progression-free survival (rPFS) per RECIST v1.1 and PCWG3. As of March 23, 2025, 259 (85% of total expected) BICR-assessed rPFS events occurred, and a prespecified interim analysis was conducted. **Results:** 496 patients were randomized to fuzuloparib-AA-P (n = 249) or AA-P (n = 247). Median follow-up was 33.3 mo. Fuzuloparib-AA-P significantly prolonged rPFS compared with AA-P (median, 24.8 mo vs 19.9 mo; HR 0.71, 95% CI 0.55-0.91; 1-sided p = 0.0034). rPFS benefit with fuzuloparib-AA-P was generally consistent across clinically relevant subgroups. Among DRD-positive patients (n = 116), median rPFS was 27.7 mo and 13.9 mo in the fuzuloparib-AA-P and AA-P groups, respectively (HR 0.51, 95% CI 0.31-0.85; 1-sided p = 0.0039). Subgroup analysis suggested improved rPFS among DRD-positive patients regardless of their *BRCA1/2* mutation status. Among DRD-negative/unknown patients (n = 380), median rPFS was 22.8 and 21.2 mo, respectively. Overall survival showed a benefit trend in favor of fuzuloparib-AA-P (Table). Treatment-related adverse events (TRAEs) were reported by 81.9% and 76.0% of patients in the two groups, respectively. The most common grade ≥3 TRAEs were mainly hematological toxicities, including anemia (20.1%), decreased white blood cell count (5.6%), decreased platelet count, and decreased neutrophil count (5.2% for each). **Conclusions:** Fuzuloparib plus AA-P as 1L treatment significantly prolonged rPFS in patients with mCRPC. The combination showed acceptable safety and tolerability with no new safety signals identified. Clinical trial information: NCT04691804. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

	Overall Fuzuloparib-AA-P(N = 249)	AA-P (N = 247)	DRD-positive Fuzuloparib-AA-P (N = 60)	AA-P (N = 56)	DRD-negative/unknown Fuzuloparib-AA-P (N = 189)	AA-P (N = 191)
rPFS, mo, median (95% CI)	24.8 (20.4, 30.4)	19.9 (15.2, 22.2)	27.7 (17.7, NR)	13.9 (8.3, 24.9)	22.8 (19.9, 30.2)	21.2 (16.5, 24.6)
HR (95% CI), vs. AA-P	0.71 (0.55, 0.91)		0.51 (0.31, 0.85)		0.81 (0.61, 1.08)	
Overall survival, mo, median (95% CI)	41.9 (31.1, NR)	36.8 (28.7, NR)	NR (27.0, NR)	36.8 (24.7, 40.3)	37.3 (29.0, NR)	36.8 (28.7, NR)
HR (95% CI), vs. AA-P	0.96 (0.73, 1.24)		0.76 (0.44, 1.32)		1.00 (0.74, 1.35)	

NR, not reached.

LBA5009 Clinical Science Symposium

Safety and dosimetry of ^{177}Lu-rosopatamab tetraxetan plus SoC in patients with metastatic castration-resistant prostate cancer: Preliminary results from part 1 of phase 3 ProstACT Global study. First Author: Pedro C. Barata, University Hospitals Seidman Cancer Center, Cleveland, OH

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

5010 Clinical Science Symposium

AcTION: Phase 1 study of [^{225}Ac]Ac-PSMA-617 (^{225}Ac-PSMA-617) in men with metastatic castration-resistant prostate cancer (mCRPC) with or without prior [^{177}Lu]Lu-PSMA (^{177}Lu-PSMA) radioligand therapy (RLT). First Author: Louise Emmett, Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia

Background: AcTION is the first prospective dosage escalation study of ^{225}Ac-PSMA-617, an alpha-emitting, PSMA-targeted RLT in patients (pts) with mCRPC (NCT04597411). **Methods:** This study enrolled pts with progressive, PSMA-positive mCRPC in 3 groups (Gps). Gp A: prior chemotherapy (ChT) and an androgen receptor pathway inhibitor (ARPI) but no prior ^{177}Lu-PSMA RLT; Gp B: no prior ChT, ARPI, or ^{177}Lu-PSMA RLT (ChT/ARPI-naive); Gp C: prior ^{177}Lu-PSMA RLT. Dosage escalation of ^{225}Ac-PSMA-617 used a Bayesian logistic regression model with administered activities of 4, 6, 8 or 10 MBq given intravenously for ≤6 cycles every 8 weeks. Primary objective was to identify the recommended phase 2 dosage (RP2D), based on dosage-limiting toxicities (DLTs) within the first 6 weeks of ^{225}Ac-PSMA-617 administration. This analysis includes all 101 treated pts per 13 Nov 2025. **Results:** Gp A pts had a median of 3 prior systemic therapies and median baseline [BL] PSA 73.4 (range 1-3320) ng/mL. At a median follow-up [FU] of 7.46 months (mos), PSA50 response rate (PSA50) was 20/34 (58.8%; 95% CI 40.7, 75.4) and PSA90 was 15/34 (44.1%; 95% CI 27.2, 62.1). Gp B pts had BL PSA 223.4 (5-12308) ng/mL. At a FU of 13.24 mos, PSA50 was 23/27 (85.2%; 95% CI 66.3, 95.8) and PSA90 was 22/27 (81.5%; 95% CI 61.9, 93.7). Gp C pts had 5 prior systemic therapies and BL PSA 85.5 (5-1760) ng/mL. At a FU of 8.57 mos, PSA50 was 21/40 (52.5%; 95% CI 36.1, 68.5) and PSA90 was 7/40 (17.5%; 95% CI 7.3, 32.8). Across all 3 Gps, there were no DLTs and a maximum tolerated dosage was not reached. No Grade [G] 4/5 TRAEs occurred. No dosage-dependent safety signals were observed. Dry mouth (G1/2 only) was the most common treatment-related (TR) adverse event (AE), observed in > 90% of pts across all Gps and mostly reported as not resolved at data cut off. Two TRAEs led to treatment discontinuation (G2 dry mouth at 8 MBq, and G3 anemia at 10 MBq; both occurring in Gp C). The RP2D for all 3 Gps was 10 MBq. Additional efficacy data will be presented. **Conclusions:** ^{225}Ac-PSMA-617 demonstrated an acceptable safety profile and promising anti-tumor activity up to 10 MBq in pts with mCRPC regardless of prior ^{177}Lu-PSMA RLT. Two phase 3 trials, AcTFirst (NCT06855277) and PSMAcTION (NCT06780670), are currently recruiting. Clinical trial information: NCT04597411. Research Sponsor: Endocyte, Inc., A Novartis Company.

Overall pts	A: Prior ChT + ARPI; N=34	B: ChT/ARPI-naive; N=27	C: Prior ^{177}Lu-PSMA RLT; N=40
Selected AEs regardless of study dose, n (%): All Gs / G ≥3			
Dry mouth	33 (97.1) / 0	26 (96.3) / 0	36 (90.0) / 0
Fatigue	18 (52.9) / 0	4 (14.8) / 0	27 (67.5) / 0
Anemia	9 (26.5) / 6 (17.6)	4 (14.8) / 4 (14.8)	16 (40.0) / 6 (15.0)
Thrombocytopenia	2 (5.9) / 0	2 (7.4) / 1 (3.7)	5 (12.5) / 0
Renal impairment	1 (2.9) / 1 (2.9)	0 / 0	3 (7.5) / 1 (2.5)
Anti-tumor activity, n (%) [95% CI]			
PSA50	20 (**58.8%**) [40.7, 75.4]	23 (**85.2%**) [66.3, 95.8]	21 (**52.5%**) [36.1, 68.5]
PSA90	15 (**44.1%**) [27.2, 62.1]	22 (**81.5%**) [61.9, 93.7]	7 (**17.5%**) [7.3, 32.8]

5011 Clinical Science Symposium

CONVERGE-01 part 3: Ac-225 rosopatamab tetraxetan (CONV01-α) in Lu-PSMA-pretreated metastatic castration-resistant prostate cancer (mCRPC). First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Ac-225 rosopatamab tetraxetan (CONV01-α, Convergent Therapeutics, Cambridge, MA), an alpha-emitting radionuclide conjugated to a PSMA-targeting monoclonal antibody, has demonstrated safety and encouraging activity in prior investigator-initiated trials (Tagawa et al. JCO 2024, Nauseef et al. AACR 2023). This phase 2 Convergent Therapeutics-sponsored multi-center CONVERGE-01 trial is evaluating the safety and efficacy of CONV01-α in pts with mCRPC, including those previously treated with Lu-PSMA-617 or -I&T (Lu-PSMA), in a dose-escalation (DE) and in an Initial Expansion (IE) cohort. **Methods:** Eligible pts had PSMA PET-positive (VISION criteria) mCRPC with previous exposure to ≥1 ARPI, 0-1 taxane regimens, and 1-6 cycles of Lu-PSMA. CONV01-α was administered in a single cycle of two doses (D1 & D15). Dose escalation used a BOIN design protocol (dose levels [DLs]: 45 and 55 kBq/kg, with optional IE). Primary endpoints: safety (CTCAE v5, all pts) and proportion of patients with decline in PSA of 50% or greater (PSA50) (at recommended phase 2 dose [RP2D]). Secondary endpoints: biodistribution and pharmacokinetic profile. Exploratory endpoints: bPFS, rPFS, genomic and imaging biomarkers. Enrollment into DE and IE cohorts of Part 3 was conducted between 8/2024 and 12/2025. Data within reflect current status and are subject to change with continued follow up and analysis. **Results:** DE was completed without DLTs in all evaluable pts (n=3 at DL45, n=6 at DL55). This was followed by an IE at both DLs (total n=22, incl pts in DE; DL45: n=12, DL55: n=10). ECOG: PS 0 - 12/22, PS 1 - 10/22. 21/22 pts were taxane exposed (19 for CRPC). Common grade (Gr) ≥3 treatment emergent adverse events (TEAEs) (occurring in >1 pt) are in shown Table. Among all TEAE at DL45: thrombocytopenia occurred in 5/12 patients (Gr 1 3/12, Gr 2 2/12), without clinical sequelae. Dry mouth was limited to Gr 1 (5/12) and Gr 2 (1/12). Among pts at who were evaluable for PSA change, 45.4% (5/11) achieved a PSA50 at DL45, with several pts experiencing ongoing PSA declines including pts who were primarily refractory to Lu-PSMA. Based on the combined safety and activity profile, DL45 was chosen as RP2D and Subsequent Expansion is underway. **Conclusions:** CONV01-α at the RP2D of DL45 is well-tolerated and shows promising activity in a heavily pretreated and Lu-PSMA-exposed population where there are limited therapeutic options available. Subsequent Expansion continues for pts exposed to Lu-PSMA (Part 3) at RP2D of DL45. A pivotal study is planned. Clinical trial information: NCT06549465. Research Sponsor: Convergent Therapeutics, Inc.

Grade ≥3 TEAE.

	Overall n=22	DL45 Grade 3	DL45 Grade 4	DL55 Grade 3	DL55 Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)
Lymphopenia	8 (36)	3 (25)	0	3 (30)	2 (20)
Thrombocytopenia	5 (23)	0	0	5 (50)	0
Neutropenia	4 (18)	2 (16)	0	2 (20)	0
Anemia	3 (14)	1 (8)	0	2 (20)	0
Hypotension	2 (9)	1 (8)	0	1 (10)	0

LBA5012 **Rapid Oral Abstract Session**

Early results of COMPPARE, a prospective comparison of outcomes with proton and photon radiation in prostate cancer. First Author: Nancy P. Mendenhall, Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

5013 **Rapid Oral Abstract Session**

Genomic classifier–driven NCCN risk reclassification to track distinct transcriptomic signatures in early prostate cancer. First Author: Daniel Keizman, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: NCCN clinicopathologic risk stratification in early prostate cancer (EPC) may under- or overestimate biologic risk and contribute to over- or undertreatment. The RNA-based Decipher genomic classifier (DGC), endorsed by NCCN, frequently drives NCCN risk reclassification, yet the transcriptomic biology that tracks with reclassification remains incompletely defined. We investigated whole-transcriptome signatures underlying DGC-based risk stratification and NCCN risk reclassification in a real-world EPC cohort. **Methods:** We performed a retrospective, real-world analysis, of prostate biopsy Decipher testing of 1,272 men with EPC, using the Decipher genomic classifier clinical database (Veracyte, San Diego, CA) and the GRID RWD registry (NCT02609269). Associations between NCCN risk reclassification and clinicopathologic variables (PSA, clinical T stage, and Gleason Grade Group) were evaluated, along with genomic risk scores, transcriptomic signatures, and a panel of gene expression signatures associated with adverse molecular features, including androgen receptor (AR) signaling, PAM50 subtype (Luminal B), inferred TP53/PTEN activity, and pathways related to proliferation, DNA repair, and immune response. **Results:** By DGC, 21% of tumors were classified as low risk, 34% as intermediate risk, and 45% as high risk. Decipher testing resulted in NCCN risk up-classification in 38% and down-classification in 19%, while 43% remained in the same NCCN risk category. Whole-transcriptome analysis revealed distinct molecular patterns across reclassification groups. Tumors that were up-classified exhibited a shift toward a more proliferative, less androgen-dependent phenotype, with significant increases ($p < 0.05$) in proliferation, DNA-repair, and immune-related pathways, increased Luminal B prevalence, reduced androgen receptor (AR) signaling, and decreased TP53 and PTEN activity. In contrast, down-classified tumors demonstrated significant downregulation of proliferation, DNA-repair, and immune-related pathways, with preservation of AR signaling and PTEN activity ($p < 0.05$). **Conclusions:** Genomic classifier–driven NCCN risk reclassification tracks coherent transcriptomic patterns that extend beyond clinicopathologic stratification. Higher genomic risk and up-classification align with Luminal B enrichment, reduced AR signaling, and loss of TP53/PTEN activity, supporting the clinical and biological validity of genomic risk refinement beyond conventional NCCN classification. Research Sponsor: None.

5014 **Rapid Oral Abstract Session**

A phase 1, first-in-human (FIH) study evaluating the safety, pharmacokinetics, and efficacy of ABBV-969 in patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: Tanya B. Dorff, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Prostate-specific membrane antigen (PSMA) and six-transmembrane epithelial antigen of prostate 1 (STEAP1) are overexpressed in >80% of metastatic prostate cancer tumors. ABBV-969 is a first-in-class PSMA/STEAP1 dual-targeting antibody drug conjugate with a topoisomerase 1 inhibitor (Top1i) payload. We report results from the completed dose escalation part of the phase 1, FIH study (NCT06318273) evaluating ABBV-969 in patients (pts) with mCRPC. **Methods:** Pts were ≥18 years with confirmed metastatic prostate adenocarcinoma, had an ECOG performance score ≤1, a serum prostate-specific antigen (PSA) level ≥1.0 ng/mL, and hemoglobin ≥9 g/dL at study entry. Pts received ≥1 novel hormone agent (NHA) and ≥1 taxane (unless unable to receive or declined taxane), and progressed on prior NHA. Pts received 1 mg/kg–12.5 mg/kg of ABBV-969 monotherapy every 3 weeks until disease progression or intolerable toxicity. Primary objective was to determine safety and tolerability. Secondary objectives were preliminary efficacy, pharmacokinetics, and recommended phase 2 dose. **Results:** As of Jan 2026, 49 pts with mCRPC received ABBV-969 in the dose escalation part of the study. Median follow-up was 11.1 months (95% CI, 8.4–13.2), and median number of prior lines was 5 (range 1–9). Pt demographics and safety results are shown in Table 1. Thirty-one (63%) pts had Grade (G) ≥3 TEAEs, primarily G3 anemia (n=24). Dose and exposure responses were observed, with durable PSA and objective responses noted at all dose levels ≥3 mg/kg. At dose levels ≥3 mg/kg, confirmed PSA50 and PSA90 responses were 67% (95% CI, 52–81) and 28% (95% CI, 15–44), respectively. Among 29 pts with RECIST-evaluable disease, the confirmed ORR, as assessed by investigator, was 45% (95% CI, 26–64). At data cut, 26 pts were receiving ongoing treatment. Radiographic PFS will be presented. **Conclusions:** ABBV-969 demonstrated promising antitumor activity and a manageable safety profile in heavily pretreated pts with mCRPC. Dose optimization is ongoing. Clinical trial information: NCT06318273. Research Sponsor: AbbVie Inc.

Pt demographics and safety.

	Total N=49
Median age, years (range)	71 (57–84)
Median PSA, µg/L (range)	74 (2–2879)
Disease location, n (%)	
Bone	43 (88)
Lymph node	20 (41)
Liver	8 (16)
Lung	7 (14)
Adrenal gland	2 (4)
Prior therapy, n (%)[a]	
Androgen-receptor pathway inhibitor	49 (100)
Docetaxel	41 (84)
Cabazitaxel	19 (39)
^{177}Lu-PSMA-617	23 (47)
Any Grade TEAE of interest, n (%)	
Hematologic toxicity	38 (78)
Gastrointestinal toxicity	33 (67)
Salivary gland toxicity	6 (12)
TEAE leading to, n (%)	
Discontinuation[b]	3 (6)
Interruption	24 (49)
Reduction	16 (33)
TEAE leading to death, n (%)[c]	1 (2)
Pneumonitis [c]	1 (2)
DLT events, n (%)[d]	3 (6)

[a]Only therapies of interest listed.
[b]G3 pneumonitis and disease progression.
[c]ABBV-969-related.
[d]Anemia at ≥8 mg/kg doses.
DLT, dose-limiting toxicity.

5015 **Rapid Oral Abstract Session**

Phase 2 study of YL201, an anti-B7H3 antibody–drug conjugate (ADC), in heavily pretreated metastatic castration-resistant prostate cancer (mCRPC). First Author: Dingwei Ye, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The treatment of mCRPC remains challenging, especially for patients who progressed on androgen receptor axis-targeted therapy (ARAT) with or without taxane-based chemotherapy. YL201 is a B7H3-targeting ADC with promising activity in advanced solid tumors. Here, we report the safety and preliminary efficacy of YL201 monotherapy in heavily pretreated mCRPC patients from a phase 2 study. **Methods:** Patients with mCRPC who had an ECOG PS of 0 or 1 and progressed on ≥1 prior line of ARAT and ≤2 lines of chemotherapy were enrolled and treated with YL201 intravenously Q3W at 2.0 or 2.4 mg/kg until disease progression or unacceptable toxicity. Primary endpoints were objective response rate (ORR) and radiographic progression-free survival (rPFS) per RECIST v1.1 and PCWG3 criteria. Secondary endpoints included PSA_{50} response rate, duration of response (DoR), overall survival (OS), and safety. **Results:** As of 12 December 2025, 82 patients were enrolled (34 at 2.0 mg/kg; 48 at 2.4 mg/kg) with a median follow-up of 12.2 months (95% CI: 11.2–13.4). The median age was 67.0 years, 65.9% had an ECOG PS of 1, and 43.9% had visceral metastases (22.0% with liver metastasis) at study entry. Patients had a median of 4 prior line of therapy (range: 1–8), with 100% having received ARAT and 70.7% having received taxane-based chemotherapy. Across both dose levels, confirmed PSA_{50} response rate was 38.5% (95% CI: 27.7–50.2), with a median duration of PSA response of 13.6 months (95% CI: 6.9–NR). Confirmed ORR was 29.5% (95% CI: 18.5–42.6), with a median DoR of 9.9 months (95% CI: 6.5–NR). Median rPFS was 9.1 months (95% CI: 7.4–12.0), while median OS remained immature. Higher PSA_{50} response rate, ORR and rPFS were observed at 2.4 mg/kg compared with 2.0 mg/kg (48.9% *vs*. 24.2%, 33.3% *vs*. 24.0%, 11.8 *vs*. 9.0 months, respectively). Notably, in patients with baseline visceral metastases, YL201 still showed encouraging efficacy with a confirmed PSA_{50} response rate of 54.5%, confirmed ORR of 28.6%, and median rPFS of 11.8 months at 2.4 mg/kg. Membrane B7H3 expression was detected in most tumor samples (median H-score: 185; range: 0–290), with no association observed between response and B7H3 expression level. Treatment-related adverse events (TRAEs) of grade ≥3 occurred in 43.9% of patients. The most common grade ≥3 TRAEs included neutropenia (29.3%), anemia (22.0%), leukopenia (18.3%), and thrombocytopenia (9.8%). No interstitial lung disease or pneumonitis was observed. The rate of treatment discontinuation due to TRAEs was 1.2%, and no treatment-related deaths were reported. **Conclusions:** YL201 showed promising antitumor activity and manageable safety profile in heavily pretreated mCRPC patients. These findings support further development of YL201 in mCRPC, especially for those who progressed after ARAT with or without taxane-based chemotherapy, and those with visceral metastases. Clinical trial information: NCT06241846. Research Sponsor: MediLink Therapeutics.

5016 Rapid Oral Abstract Session

Phase 2 multicenter trial of chemoimmunotherapy for patients with neuroendocrine or aggressive variant metastatic prostate cancer (CHAMP). First Author: Andrew J. Armstrong, Division of Medical Oncology, Duke University Medical Center, Duke Cancer Institute, Duke University, Durham, NC

Background: Platinum-doublet chemotherapy is effective in pts with neuroendocrine small cell neuroendocrine or aggressive-variant prostate cancer (NEPC/AVPC), but responses have limited durability. PD-1/PD-L1 inhibition in small cell lung cancer with chemotherapy is standard of care, but chemoimmunotherapy has not been tested in patients with NEPC/AVPC. **Methods:** We conducted a multicenter, phase II trial evaluating cabazitaxel, carboplatin, ipilimumab, and nivolumab (NCT04709276) in patients with metastatic NEPC/AVPC defined by histologic, clinical, or molecular features. Ipilimumab was dosed at 1 mg/kg q6w and nivolumab 360 mg q3w w/ongoing ADT. Cabazitaxel 20-25 mg/m2 + carboplatin AUC4 with GCSF was given q3w up to 10 cycles but could be stopped early for response or toxicity, followed by maintenance immunotherapy. Primary endpoint was immune modified iRECIST/PCWG3 radiographic progression-free survival (rPFS), hypothesizing a 55% 6-mo rPFS rate for cabazitaxel/carboplatin (1-sided α 0.1, 85% power) based on historic data. Secondary endpoints: overall survival (OS), rPFS, objective responses, safety. **Results:** We enrolled 40 patients across 3 centers in the Department of Defense Prostate Cancer Clinical Trials Consortium from 7/2021-8/2025, including 12 (32%) with NEPC and 28 (68%) with AVPC, with 38 evaluable for efficacy. Median age was 65 yrs, median PSA 2 ng/dl (range 0-807), and 75% with any visceral metastases including 58% with liver and 33% with lung metastases. The % with elevated serum CEA, LDH, or CgA was 88%; 85% had prior ARPI and 70% prior chemo. With a median f/u of 17 mo, CHAMP met its primary endpoint of improving 6-mo rPFS vs. cabazi/carbo with a 6-mo PFS rate of 78% (90% CI 69-100%); median rPFS was 12 mo. See Table for efficacy. We observed 20 G3 (50%) and 7 G4 (18%) toxicities related to treatment on a per patient basis. Two patients are free of disease and off therapy at 30+ mo. Most common overall G3-4 toxicities were anemia (n=15), neutropenia (n=5), sepsis (n=5), thrombocytopenia (n=5), colitis (n=5), febrile neutropenia (n=4), and UTI (n=4), with no treatment-related deaths. **Conclusions:** Dual PD-1/CTLA4 immune checkpoint blockade with platinum doublet chemotherapy is effective in patients with AVPC/NEPC, resulting in greater efficacy than expected with historic platinum chemotherapy alone, and with acceptable toxicity given disease risk. These results support randomized controlled clinical trials of chemoimmunotherapy in patients with NEPC/AVPC. Clinical trial information: NCT04709276. Research Sponsor: Bristol-Myers-Squibb.

Primary Endpoint (n=38)	Outcome (95% CI)
6 mo PFS (%) by iRECIST/PCWG3 (1-sided 90% CI)	**78% (69-100%)**
Secondary Endpoints	
12 mo rPFS (%, 95% CI)	44% (29-69%)
PFS, median by iRECIST/PCWG3, mo	12 (9.6-17)
PFS, median by RECIST/PCWG3, mo	6.8 (4.3-9.2)
OS, median, mo	12 (9.6-17)
12-month OS (%)	46% (30-69%)
iRECIST Best Radiographic Response	
ORR (CR+PR) %	34%
CR	2.6%
PR	32%
SD	45%
iUPD/iCPD	13/8%

5017 Rapid Oral Abstract Session

PROTRACT: A randomized phase II trial comparing ctDNA-guided biomarker directed therapy vs patient/clinician's choice for metastatic castration resistant prostate cancer (mCRPC) progressing after abiraterone plus prednisone (AAP). First Author: Corinne Maurice-Dror, BC Cancer - Vancouver Centre, Vancouver, BC, Canada

Background: A subset of mCRPC patients (pts) will benefit from enzalutamide (ENZA) following disease progression on AAP. Preliminary data suggests that higher plasma ctDNA/total cfDNA fraction (ctDNA%) post-AAP predicts poor response to ENZA but preserved sensitivity to docetaxel (DOC). We hypothesize that ctDNA%-guided selection of enzalutamide or docetaxel in chemotherapy-naïve mCRPC post-abiraterone will improve clinical outcomes versus patient/clinician's choice of treatment. **Methods:** A multi-centre, open-label, phase II trial randomized mCRPC pts progressing after AAP 1:1 to biomarker-directed therapy (Arm A: ctDNA% $\geq$2% receives DOC; ctDNA% $<$2% receives ENZA) or clinician's choice of ENZA or DOC (Arm B, ctDNA% blinded). Baseline ctDNA% was assessed at screening using somatic mutations and genome-wide ploidy models. At progression, eligible pts could cross over to the alternative therapy. The primary endpoint was progression-free survival (PFS) defined as the time from treatment initiation to first documented disease progression (clinical, radiological, or PSA) or death from any cause. PFS was estimated using the Kaplan-Meier method and compared between arms using the log-rank tests. Secondary endpoints included PSA50 response (PSA decline $\geq$50% from baseline) and overall survival (OS). **Results:** Between October 2020 and June 2025, 56 pts were screened and 42 randomized 1:1 to Arm A (n=17) or Arm B (n=25). The trial was terminated due to slow accrual prior to the planned enrollment of 100 patients. At data cut-off (January 7, 2026), median follow-up was 38.0 months, and 94% (Arm A) and 92% (Arm B) had experienced disease progression or death. Baseline characteristics were balanced. ctDNA% $<$2% was observed in 35.3% and 32% of pts in Arm A and B, respectively. In Arm A, 11 pts were assigned to and received DOC (ctDNA% $\geq$2%) and 6 pts to ENZA (ctDNA $<$2%). In Arm B patient/clinician choice was DOC in 4 patients (3 pts with ctDNA $\geq$2%) and ENZA in 21 patients (7 pts with ctDNA $<$2%). PFS, OS and PSA50 all favoured biomarker directed therapy (Arm A) (Table). **Conclusions:** In this clinical utility study, ctDNA% to guide ENZA or DOC selection in patients previously treated with AAP led to superior PFS and OS compared to patient/clinician-selected therapy. These hypothesis-generating results illustrate the potential for ctDNA% as a predictive biomarker to assist in clinical decision making and support further studies. Clinical trial information: NCT04015622. Research Sponsor: Prostate Cancer Canada, Canadian Cancer Society.

Primary & secondary outcomes.

	Biomarker-Directed (Arm A, n=17)	Clinician's Choice (Arm B, n=25)	HR (95% CI) *P-Value*
Progression-Free Survival (PFS), Months, median (95% CI)	5.6 (3.2-8.2)	2.5 (1.5-3.7)	0.4 (0.2-0.8) *p* = 0.01
PSA50 Response (%)	52.9%	28.0%	*p* = 0.12
Overall Survival (OS), months, median (95% CI)	46.3 (12.2-NR)	15.3 (13.5-20.7)	0.4 (0.2-0.9) *p* = 0.04

5018 Rapid Oral Abstract Session

Circulating tumor DNA–based clinical-genetic (CG) prognostic model for radiographic progression-free survival (rPFS) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): Analysis of Alliance A031201. First Author: Susan Halabi, Department of Biostatistics and Bioinformatics, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC

Background: mCRPC is characterized by marked molecular heterogeneity and variable clinical outcomes. Circulating tumor DNA (ctDNA) profiling provides a noninvasive approach to capture tumor genomic alterations with potential prognostic value. We developed and validated a ctDNA-based prognostic model for rPFS using data from the Alliance A031201 (NCT01949337) trial, distinct from our published CG model of overall survival (Halabi et al. Eur Urol 2025). **Methods:** We analyzed ctDNA from 776 pts enrolled in the A031201 trial that randomized men with chemotherapy-naïve mCRPC to enzalutamide +/- abiraterone acetate and prednisone. Baseline cell free DNA samples from 776 pts were sequenced using the AR-ctDETECT assay. The primary endpoint of this analysis was rPFS. Proportional hazards model was used to assess the association of each genetic alterations and clinical variables with rPFS. Random survival forest (RSF) incorporating CG and clinical (C) variables only were trained and evaluated using 10-fold cross-validation. Model performance was assessed using integrated time-dependent area under the ROC curve (itAUC) and net reclassification improvement (NRI). **Results:** Higher ctDNA aneuploidy fraction, ctDNA positivity, and multiple pathogenic genomic alterations were associated with worse rPFS. Among prevalent alterations, *AR* enhancer gain and *AR* gain were strongly prognostic, with median rPFS of 13.7 vs 27.3 months (mos) and 13.5 vs 27.0 mos for pts with and without alterations, respectively. The rPFS prognostic model included gains in *AR, AR enhancer, MYC, CCND1,* and *FOXA1*, and losses in *PTEN, TP53,* and *LRP1B* based on RSF. *PTEN* loss, gains in *AR enhancer, MYC,* along with hemoglobin, PSA and alkaline phosphatase showed the largest contribution to risk prediction. Mean itAUC for C model was 0.66 (95% confidence interval [CI] 0.62-0.70), mean itAUC for CG model was 0.73 (95% CI: 0.69–0.77). At 22 mos (median rPFS), NRI comparing CG model with C model was 0.30 (95% CI: 0.19-0.36). Pts were stratified into low-, intermediate-, and poor-risk groups and showed markedly distinct rPFS outcomes, with median rPFS of 39.2, 25.2, and 12.8 mos, respectively. The hazard ratios for low vs poor risk was 0.25 (95% CI: 0.20–0.31) and for intermediate vs poor risk 0.46 (95% CI: 0.38-0.55). **Conclusions:** A ctDNA-based prognostic model integrating CG features robustly stratifies rPFS risk in pts with mCRPC treated with first line AR pathway inhibitor therapy. This approach may support individualized risk assessment and inform trial design around treatment intensification combinations and therapeutic decision-making. External validation in independent cohorts is warranted. Support: U10CA180821, U10CA180882; R01CA256157; R01CA174777; https://acknowledgments.alliancefound.org. Clinical trial information: NCT01949337. Research Sponsor: National Cancer Institute.

5019 Rapid Oral Abstract Session

Canadian Cancer Trials Group (CCTG) study PR21 (PLUDO): Results of crossover treatment from a randomized trial of ^{177}Lu-PSMA-617 (LuP) vs docetaxel (DOC) in patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: Kim N. Chi, University of British Columbia, BC Cancer, Vancouver Cancer Centre, Vancouver, BC, Canada

Background: The PLUDO trial randomized patients with mCRPC to receive either LuP or DOC, with cross-over permitted at radiographic progression (RP). At the primary analysis, there was no significant difference in the primary endpoint of 1st line radiographic progression free survival (rPFS) (HR 1.01, 90% CI: 0.77, 1.31). However, overall survival (OS) was in favor of patients randomized to receive docetaxel first (HR 1.64, 95% CI: 1.14, 2.35) (KN Chi, et al. ESMO Congress, 2025). To provide insights into potential reasons for the survival difference, we report the prespecified secondary objective of rPFS after cross-over therapy. **Methods:** Multi-centre open-label randomized phase II trial. 199 patients with chemotherapy-naïve, PSMA-PET positive mCRPC progressing after ARPI therapy were randomized 1:1 to receive either LU-P 7.4 GBq IV q6 weeks or DOC 75 mg/m2 IV q3 weeks, with cross-over permitted at progression. rPFS2 was measured from randomization to RP or death after cross-over therapy, "2nd line rPFS" was from time of start of cross-over therapy to RP or death, OS was defined from time of initial randomization to death, and "2nd line OS" was from time of cross-over therapy to death. **Results:** 159 patients had an rPFS event on 1st line therapy (LuP: n = 79, DOC: n = 80) including 24 deaths (LuP: n = 16, DOC: n = 8). At the time of 1st rPFS, there were no substantive differences between arms for grade 3-4 adverse events, but patients on LuP reported better quality of life (FACT-P). Of the 135 patients alive, 104 received cross-over therapy (LuP → DOC: 42, DOC → LuP: 62). There were no clinically relevant differences in baseline characteristics of patients who had cross-over therapy between treatment arms. OS was worse for patients that did not cross-over compared to those who did cross-over (LuP arm: HR 3.18 (95% CI 1.93, 7.42); DOC arm: HR 4.73 (95% CI 1.96, 11.38)). For the 104 patients who received both lines of therapy, there was no differences in efficacy outcomes for 2nd line rPFS, rPFS2, OS, or 2nd line OS (TABLE). PSA decline $\geq$ 50% was higher with cross-over Doc than LuP (69% vs 40%, P = 0.004). There were 9 grade 3 adverse events related to cross-over therapy in each arm. **Conclusions:** In the PLUDO study, there was no difference in first-line or cross-over rPFS between LuP and DOC. In patients who received cross-over therapy, this analysis shows no OS difference, suggesting that imbalance in cross-over from LuP to Doc likely impacted the OS difference in the ITT population and emphasizes the importance of both treatments on efficacy outcomes. Clinical trial information: NCT04663997. Research Sponsor: Canadian Cancer Society; 707213; Novartis; Prostate Cancer Canada.

	LuP → DOC (median, months) n = 42	DOC → LuP (median, months) n = 62	HR (DOC → LuP/LuP → DOC)
2nd line rPFS	4.8	5.4	0.86 (90% CI: 0.58, 1.26)
rPFS2	18.5	15.8	0.91 (90% CI: 0.61, 1.35)
2nd line OS	8.1	8.3	0.94 (95% CI: 0.53-1.64)
OS	23.2	20.0	0.88 (95% CI: 0.50, 1.53)

5020 Rapid Oral Abstract Session

Subgroup analyses by disease volume and *de novo*/recurrent mHSPC in the PSMAddition study of [^{177}Lu]Lu-PSMA-617. First Author: Fred Saad, Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, QC, Canada

Background: In the phase 3 PSMAddition study (NCT04720157), combining [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) with ADT + ARPI significantly improved rPFS in patients with PSMA+ mHSPC vs ADT + ARPI at rPFS interim analysis (data cut off Jan 13, 2025), with a HR of 0.72 (95% CI 0.58, 0.90; p = 0.002). **Methods:** Patients had treatment-naive/minimally treated mHSPC diagnosed by CT/MRI/bone scan and ≥1 PSMA+ metastatic lesion on [^{68}Ga]Ga-PSMA-11 PET/CT. Patients were randomized 1:1 to ^{177}Lu-PSMA-617 (7.4 GBq ± 10% q6w, 6 cycles) + ADT + ARPI (^{177}Lu-PSMA-617 arm) or ADT + ARPI (control arm). The primary endpoint of rPFS (centrally assessed rPD per PCWG3/RECIST v1.1 or death) and selected secondary efficacy, safety, and patient-reported outcomes (PROs) were assessed in subgroups of high/low disease volume (DV) per CHAARTED criteria (locally assessed by CT/MRI/bone scan; prespecified) and *de novo*/recurrent mHSPC (AJCC stage ≥/<IVb; *post hoc*). **Results:** Of 572 patients randomized to the ^{177}Lu-PSMA-617 arm and 572 to the control arm, 68.0% and 68.2% had high DV, and 52.1% and 47.9% had *de novo* mHSPC. Efficacy and PRO HRs for the ^{177}Lu-PSMA-617 arm vs control arm were generally similar in the overall population and DV and mHSPC subgroups (rPFS HR 0.72–0.74; time to PSA progression HR 0.29–0.51) (Table). Incidences of AEs, grade ≥3 AEs, serious AEs, and selected safety topics of interest (cytopenias, dry mouth) were similar across subgroups within each treatment arm. **Conclusions:** In patients with PSMA+ mHSPC, combining ^{177}Lu-PSMA-617 with ADT + ARPI improved rPFS vs ADT + ARPI across high/low DV and *de novo*/recurrent mHSPC subgroups. Other efficacy outcomes, PROs, and the safety profile were generally consistent across subgroups. Clinical trial information: NCT04720157. Research Sponsor: Novartis.

Efficacy and PROs.

HR (95% CI) for ^{177}Lu-PSMA-617 arm vs control arm	Overall N = 1144	High DV n = 779	Low DV n = 365	*De novo* mHSPC n = 572	Recurrent mHSPC n = 523
rPFS[a]	0.72 (0.58, 0.90)	0.72 (0.56, 0.92)	0.73 (0.42, 1.27)	0.74 (0.54, 1.01)	0.74 (0.53, 1.04)
PFS per investigator[b]	0.64 (0.51, 0.79)	0.61 (0.48, 0.78)	0.80 (0.46, 1.37)	0.65 (0.48, 0.88)	0.64 (0.46, 0.89)
Time to:					
PSA progression	0.42 (0.30, 0.59)	0.43 (0.31, 0.62)	0.29 (0.08, 1.05)	0.51 (0.32, 0.79)	0.35 (0.21, 0.60)
Symptomatic skeletal event	0.89 (0.62, 1.26)	0.93 (0.64, 1.37)	0.67 (0.27, 1.66)	0.97 (0.60, 1.57)	0.82 (0.48, 1.40)
mCRPC	0.70 (0.58, 0.84)	0.67 (0.54, 0.82)	0.87 (0.55, 1.37)	0.61 (0.47, 0.80)	0.75 (0.56, 1.00)
BPI-SF pain intensity worsening[c]	1.02 (0.87, 1.18)	0.98 (0.82, 1.18)	1.09 (0.83, 1.44)	1.06 (0.85, 1.31)	0.97 (0.78, 1.22)
FACT-P total score worsening[c]	1.14 (0.98, 1.33)	1.13 (0.94, 1.37)	1.16 (0.88, 1.53)	1.13 (0.90, 1.41)	1.16 (0.92, 1.46)
EQ-5D-5L worsening[c]	1.13 (0.97, 1.31)	1.04 (0.87, 1.25)	1.34 (1.01, 1.77)	1.17 (0.93, 1.45)	1.09 (0.87, 1.37)

N may differ across outcomes.
[a]rPD by BIRC or death.
[b]Composite of radiographic, clinical, and PSA progression and death.
[c]Composite with clinical progression and death.

5021 Poster Session

Validation of prostate-specific antigen (PSA) decline among the Latin American subgroup of LIBERTAS: A phase 3 study of apalutamide (APA) plus continuous versus intermittent androgen deprivation therapy (ADT) in metastatic castration-sensitive prostate cancer (mCSPC). First Author: Andrea Juliana Gomes, Liga Norte Riograndense Contra o Câncer, Natal, Brazil

Background: APA in combination with continuous ADT showed rapid and deep PSA decline in participants (pts) with mCSPC in the TITAN study, and this deep PSA decline was associated with improved overall survival. LIBERTAS (NCT05884398), a global phase 3 study, is evaluating APA + intermittent ADT as an ADT de-escalation strategy for pts with mCSPC who achieve an undetectable PSA (< 0.2 ng/mL) after 6 months on APA + ADT. In the initial treatment phase of LIBERTAS, 6 months of APA + continuous ADT resulted in deep PSA responses in the majority of pts with mCSPC. **Methods:** Pts with mCSPC were eligible if they had ≤3 months of prior ADT, ECOG PS 0–1 and confirmed metastases by conventional or next-generation imaging. In the initial 6-month treatment phase, all pts received APA 240 mg/day + ADT. In the main treatment phase, pts with < 0.2 ng/mL were randomized 1:1 to APA 240 mg/day + intermittent or continuous ADT. Co-primary endpoints were radiographic progression-free survival (rPFS), measured by the 18-month event-free survival rate, and reduction of hot flash burden, measured by the 18-month severity-adjusted hot flash score. Here, we present an analysis of the Latin American (LATAM) subgroup evaluating PSA response results following the initial treatment phase. **Results:** From Dec 2023 to July 2024, 118 LATAM pts were enrolled (87 pts from 7 sites in Brazil, and 31 pts from 4 sites in Mexico). Racial distribution in LATAM pts was 60.2% White, 10.2% Black, 9.3% Multiple, and 17.8% other. LATAM pts were younger (median age 67 years [range: 48–86]) and had more advanced disease (89.0% with M1 disease at diagnosis; 39.8% with ECOG PS 1, 66.1% with high volume disease; median baseline PSA 22.95 ng/mL [IQR: 3.18–87.00]) compared with the overall study population. Among 109 pts who completed the 6-month initial treatment phase, 104 (95.4%) achieved a ≥50% PSA decline (PSA50), 90 (82.6%) achieved a ≥90% decline (PSA90), and 66 (60.6%) achieved PSA < 0.2 ng/mL (PSA0.2), of which 62 (56.9%) pts were randomized to the main treatment phase. Median time to response was 1.87 months for PSA50, 1.91 months for PSA90, and 3.14 months for PSA0.2. No new safety signals were observed in the LATAM subgroup. **Conclusions:** LATAM pts in LIBERTAS were younger on average and had more advanced disease compared with the overall study population. Despite having higher baseline PSA levels, LATAM pts with mCSPC demonstrated rapid and deep PSA responses to APA + ADT, consistent with the results from the global analysis. The safety profile of APA was consistent with previous studies. The LIBERTAS study remains on track for the primary readout. Clinical trial information: NCT05884398. Research Sponsor: None.

5022 Poster Session

Real-world genetic testing patterns in prostate cancer assessed via artificial intelligence: Implications for NCCN guideline implementation. First Author: Mitchell Singstock, Hunstman Cancer Institute at The University of Utah, Salt Lake City, UT

Background: Germline and somatic genomic testing in prostate cancer guide both targeted therapy selection and identification of heritable cancer risk. Although NCCN guidelines define testing eligibility based on disease risk and stage, real-world testing remains suboptimal. Population-level data indicate that only one-third of men with metastatic prostate cancer undergo genomic testing. As part of a larger effort to improve testing rates, we evaluated three consecutive years of prostate cancer care to quantify testing utilization and assessed artificial intelligence (AI) performance for risk stratification and testing eligibility. **Methods:** We conducted a retrospective chart review of patients with advanced prostate cancer treated at a large multi-site community oncology practice between 2023 and 2025. Clinical data were manually reviewed to assign disease stage, NCCN risk stratification, and eligibility for germline and somatic testing. In 2023, a rules-based AI applied explicit NCCN guideline logic (v1.2023). In 2024 and 2025, an untrained general-purpose AI model (ChatGPT 5.2) was provided NCCN guideline text (v1.2024 and v1.2025) and tasked with inferring risk category and testing eligibility. Primary outcomes included observed annual germline and somatic testing rates and AI concordance with manual review. Temporal trends in germline and somatic testing adoption were assessed using the Cochran-Armitage trend test. **Results:** Across 2023–2025, NCCN-indicated germline and somatic testing was inconsistently performed (Table 1), with significantly increasing rates from 2023 to 2025 (Cochran–Armitage trend test, germline $p < 0.001$, somatic $p < 0.001$). Testing outside of NCCN guidelines was ordered by clinicians in 10 (4%), 22 (9%), and 31 (18%) patients each year, respectively. **Conclusions:** In a large community oncology setting, NCCN-indicated germline and somatic testing for prostate cancer was frequently underutilized, despite significant improvement over time. Ongoing analyses seek to clarify which interventions contributed to increased testing rates and whether testing performed outside NCCN guidelines reflects broader clinical awareness of indications not consistently captured in structured data. AI-based guideline interpretation of NCCN guidelines demonstrated consistently high concordance with manual review and may offer a scalable approach to systematically identify patients eligible for genetic testing using structured data. Research Sponsor: AstraZeneca; Pfizer.

Year	Charts Reviewed	Germline Eligible	Germline Tested	Somatic Eligible*	Somatic Tested	AI Risk Stratification	AI Testing Recommendation Concordance
2023	259	194	54 (28%)	91	24 (26%)	Not assessed	Germline 97%; Somatic 100%
2024	255	195	82 (42%)	86	37 (43%)	235 / 255 (92%)	Germline 100%; Somatic 100%
2025	177	167	98 (59%)	62	50 (81%)	177 / 177 (100%)	Germline 100%; Somatic 100%

*Somatic testing was "recommended" for patients with metastatic disease per NCCN 2023 -2025.

5023 Poster Session

Image-only and multimodal AI digital pathology biomarkers to demonstrate risk stratification across standard prostate cancer management strategies. First Author: Xinglei Shen, University of Kansas Medical Center, Kansas City, KS

Background: Reliable risk stratification across standard treatment pathways is essential for the clinical adoption of precision medicine biomarkers in localized prostate cancer. We previously developed and validated a multimodal artificial intelligence (MMAI) model that integrates digitized hematoxylin and eosin (H&E) prostate biopsy slides with clinical variables to prognosticate distant metastasis (DM) and prostate cancer specific mortality (PCSM). To evaluate the independent prognostic signal derived from routine histopathology alone without clinical variables, we built an Image-only artificial intelligence model. In this study, we validate the prognostic ability of the new Image-only and existing MMAI models in a multi-institutional cohort of nonmetastatic prostate cancer patients receiving guideline-concordant standard-of-care treatments. **Methods:** The Image-only model was trained to estimate the risk of 10-year distant metastasis (DM) without clinical inputs. Both the Image-only and MMAI models were evaluated in a cohort of men from 3 institutions with non-metastatic prostate cancer treated with active surveillance (AS), radical prostatectomy (RP), or radiation therapy (RT). The primary endpoint was 10-year risk of DM, with prostate cancer–specific mortality (PCSM) as a secondary endpoint. Prognostic associations were evaluated within each treatment subgroup using Fine–Gray models. **Results:** Among 886 patients with Image-only scores and 911 with MMAI scores, approximately 36% were managed with AS, 41% with RP, and 23% with RT. The Image-only model continuous raw scores were consistently associated with DM risk across treatment modalities, including AS (subdistribution hazard ratio [sHR] 2.38, $p < 0.001$), RP (1.99, $p < 0.001$), and RT (sHR 2.84, $p < 0.001$). Similarly, the Image-only model calibrated scores showed significant prognostic association with DM across all treatment groups. The MMAI showed consistent prognostic performance for DM using both calibrated and raw scores (raw scores: AS sHR 2.87, $p < 0.001$; RP sHR 2.12, $p < 0.001$; RT sHR 2.73, $p < 0.001$). Both Image-only and MMAI scores were significantly associated with PCSM despite low event rates. **Conclusions:** Both Image-only and MMAI biomarkers demonstrate consistent prognostic performance across standard prostate cancer management strategies, including AS, RP, and RT, supporting their utility for risk stratification regardless of ultimate treatment selection. These findings highlight the robustness of image-derived prognostic information and demonstrate that routinely available H&E pathology alone captures clinically meaningful risk information that generalizes across treatment contexts. Together, these results support the use of AI-based digital pathology biomarkers for prognostication in localized prostate cancer. Research Sponsor: Artera Inc.

5024 **Poster Session**

AI-assisted preoperative communication in prostate cancer: A prospective, single-blinded, randomized phase II trial. First Author: Zheng Liu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: To evaluate whether AI-assisted preoperative communication reduced patient anxiety, and physician workload compared with standard preoperative communication in patients undergoing radical prostatectomy. **Methods:** We conducted a prospective, randomized, single-blinded, phase II trial in newly diagnosed prostate cancer patients undergoing radical surgery, excluding those with severe psychiatric or cognitive disorders. Upon hospital admission, patients were randomized at the room level to receive either standard or AI-assisted preoperative communication. After baseline assessment, the AI-assisted group received individualized responses generated by a locally deployed large language model–based AI system prior to routine physician-led face-to-face preoperative communication, while physicians remained blinded to group allocation. The primary outcomes were patient anxiety (GAD-7) and physician workload (NASA-TLX). Comparisons were conducted using non-parametric rank-sum tests. The trial was registered at ClinicalTrials.gov (NCT07082049). **Results:** Between April and November 2025, 268 patients were randomized to the control group (n = 130) or the AI-assisted group (n = 138). A total of 3,507 questions were collected (avg. 13.08 per patient). After routine preoperative communication, patients in the AI-assisted group reported lower anxiety levels than those in the control group (GAD-7 median [IQR], 3.5 [2.5–5.0] vs. 7.5 [6.5–9.0]; $P < 0.001$). Physician workload was also reduced in the AI-assisted group, as reflected by lower NASA-TLX scores (median [IQR], 37.0 [27.0–46.0] vs. 54.0 [35.0–73.0]; $P < 0.001$), accompanied by a substantial reduction in preoperative communication time (12.60 vs. 21.90 minutes; $P < 0.001$). Patients in the AI-assisted group reported more favorable emotional status, lower negative illness perceptions, and higher satisfaction, while exploratory analyses indicated that AI-assisted communication alone improved anxiety, emotional status, and disease-related perceptions prior to physician face-to-face preoperative communication. The observed reductions in physician workload and communication time suggest potential applicability in resource-constrained clinical settings where clinical manpower and consultation time are limited. **Conclusions:** AI-assisted preoperative communication reduced patient anxiety, and physician workload compared with standard communication, supporting its role as a supplementary approach to routine preoperative care in prostate cancer, including settings involving older adults and limited clinical resources. Clinical trial information: NCT07082049. Research Sponsor: National Nature Science Foundation of China; 82373355, 82303097; Shanghai Oriental Talent Program Top Project; BJKJ2024007; the Special Research Fund for Clinical Studies of Innovative Drugs after Market Launch of the Development Center for Medical Science and Technology National Health Commission of China; WKZX2024CX104201.

5025 **Poster Session**

Implementation of serum microRNA-371a-3p testing for testicular germ-cell tumors in a pathology department: Real-world data from a comprehensive cancer center. First Author: João Lobo, Portuguese Oncology Institute of Porto (IPO-Porto), Porto, Portugal

Background: The classical serum tumor markers for testicular germ cell tumor (TGCT) patients show limited sensitivity and specificity in some clinical settings. In the last years, serum miR-371a-3p testing has been shown to have superior performance for the detection and follow-up of TGCT patients. A commercial test with IVD approval is already available for use in the clinic. In this work we demonstrate our experience with the clinical implementation of this liquid biopsy test, comparing its performance with the one of AFP, HCG and LDH. **Methods:** The M371 test (serum) was implemented at the Department of Pathology of our Comprehensive Cancer Center in August 2024, for patients presenting with testicular masses and for TGCT patients during follow-up. Simultaneous collection of AFP, HCG and LDH was performed at the different timepoints, following the guidelines for diagnosis and follow-up of TGCT patients. Blood was collected on the recommended Serum-Gel 7.5mL tubes and processed to serum within 3h of collection. The RTqPCR test and analysis followed the manufacturer's closed protocol (IVDR approved). Clinical charts and CT scans were reviewed to determine disease status, and results were correlated with histology. **Results:** A total of 128 M371 tests were performed at the Department of Pathology during 16 months, including several contexts of the disease (pre-orchiectomy, follow-up, pre-RPLND, pre and post-chemotherapy). The mean turnaround time for the test (from receiving the blood sample to issuing the report) was of 5.6 days. The median patient age was 35 years (19-81 years). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were as follows: 0.43, 0.96, 0.76 and 0.85 for AFP; 0.57, 0.98, 0.89 and 0.88 for HCG; 0.37, 0.91, 0.55 and 0.82 for LDH; 0.80, 0.92, 0.77 and 0.93 for the combination of AFP+HCG+LDH; and 0.96, 0.96, 0.87 and 0.99 for M371 test alone. Additional collections/testing and subanalyses based on disease setting and histologic findings are ongoing. **Conclusions:** The M371 IVD serum test alone showed a superior diagnostic performance for detecting active TGCT in an unselected, consecutive cohort of TGCT patients representing different settings of the disease, when compared to the classical serum tumor markers AFP, HCG and LDH, isolated or in combination. The sensitivity of AFP, HCG and particularly LDH isolated (0.43, 0.57 and 0.37) were outperformed by the sensitivity of the M371 test (0.96). The high NPV of the M371 test (0.99) may aid in the decision of de-escalating intervention (treatment or follow-up measures) of young TGCT patients. These real-world data underscore the potential advantages of adding microRNA testing as a an additional test to combine with classical serum tumor markers and imaging. Research Sponsor: None.

5026 **Poster Session**

Comparative transcriptomic analysis of chemotherapy-naive and post-chemotherapy germ cell tumors. First Author: Michal Mego, Department of Oncology, Faculty of Medicine, Comenius University and National Cancer Institute, Bratislava, Slovakia

Background: Cisplatin-based chemotherapy is highly effective in testicular germ cell tumors (GCTs); however, the presence of viable tumor after first-line chemotherapy is associated with chemoresistance and poor clinical outcome. The transcriptional programs distinguishing chemotherapy-naïve and post-chemotherapy viable GCTs remain incompletely characterized. **Methods:** Tumor samples from 50 GCT patients treated between 2010 and 2022 were analyzed, including 30 chemotherapy-naïve tumors and 20 post-chemotherapy viable GCTs resected from the retroperitoneum. Five normal testicular tissue samples served as controls. Formalin-fixed paraffin-embedded samples were profiled using the HTG EdgeSeq Oncology Biomarker Panel. Differential gene expression analysis was performed using DESeq2, adjusted for histology, with significance defined as adjusted p-value < 0.1 and $|\log2 \text{ fold change}| > 1$. Functional enrichment analysis was conducted to identify deregulated biological pathways. **Results:** Compared with normal testicular tissue, chemotherapy-naïve GCTs and post-chemotherapy viable GCTs exhibited 1,010 and 720 differentially expressed genes, respectively. Direct comparison between chemotherapy-naïve and post-chemotherapy tumors identified 424 differentially expressed genes. Post-chemotherapy viable GCTs demonstrated marked downregulation of genes associated with pluripotency and embryonal stem cell identity, including *POU5F1*, *UTF1*, *DPPA4*, and *PRDM14*. In contrast, post-chemotherapy tumors showed upregulation of immediate early stress response genes, inflammatory and cytokine signaling pathways, EGFR-related growth factor signaling, and metabolic stress adaptation. **Conclusions:** Post-chemotherapy viable GCTs are characterized by loss of pluripotent transcriptional programs and acquisition of stress-responsive, inflammatory, and adaptive signaling pathways. These transcriptional changes provide insight into the biology of chemotherapy resistance in GCTs and may have prognostic and therapeutic implications. Research Sponsor: Agency for reasearch and development; 24-0168.

5027 **Poster Session**

Genomic determinants of cisplatin resistance in germ cell tumors. First Author: Vincent D'Andrea, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cisplatin-based chemotherapy achieves complete remission in 70-80% of patients with germ cell tumors (GCTs), but a subset are cisplatin-resistant and progress after first-line therapy. Prior studies have linked *TP53* and *MDM2* alterations and chromosome 3p25.3 gain to cisplatin resistance and worse outcomes in GCT. We sought to validate this and identify additional genomic determinants of cisplatin response in a large GCT cohort. **Methods:** Patients who received first-line cisplatin-based chemotherapy for GCT of any primary site with genomic analysis of the tumor were eligible. Cisplatin resistance was defined as: (1) incomplete response to chemotherapy, (2) non-teratomatous progression after chemotherapy, or (3) viable non-teratomatous GCT at post-chemotherapy surgery; all other patients were considered sensitive. Next-generation sequencing was performed using the MSK-IMPACT assay and association between genomic alterations and resistance was assessed using Fisher's exact test. Cytoband analysis was completed using the FACETS algorithm to calculate chromosomal alterations, with a required cytoband coverage of 75%. The association between cytoband alterations and resistance was assessed using relative risk with a robust variance estimator. **Results:** The cohort of 556 patients included 79% testicular, 15% mediastinal, 4% ovarian, and 1.5% tumors of other primary site. 79% were non-seminomatous germ cell tumors and 21% pure seminoma. Among these, 336 (60%) were cisplatin-resistant. *TP53* mutations were more common in resistant than sensitive tumors (16% vs 2%), as were *MDM2* and *CRKL* amplifications (7% vs 1% and 4% vs < 1%, respectively). *KIT* was more frequently mutated in cisplatin-sensitive tumors (5% in resistant vs 14% in sensitive) (Table 1). *TP53* mutations occurred predominantly in mediastinal primary tumors (89%) whereas *MDM2* alterations were confined to testicular primaries. Of 472 patients who underwent cytoband 3p25.3 analysis, chromosome 3p25.3 gain was associated with cisplatin resistance (relative risk 1.23; 95% CI: 1.00, 1.49; p = 0.04). **Conclusions:** In this large GCT cohort, *TP53* and *MDM2* alterations and chromosome 3p25.3 gains were associated with cisplatin resistance, consistent with prior reports. We also found that *CRKL* amplifications were associated with cisplatin resistance whereas *KIT* mutations were associated with cisplatin sensitivity. These latter findings are the first reports of the association of these genes with cisplatin response and warrant further mechanistic investigation to define how these alterations influence cisplatin sensitivity. Research Sponsor: None.

Genomic alterations corresponding to cisplatin response in GCT.

Alteration	Resistant (n=336)	Sensitive (n=220)	p-value
***TP53* mutations**	53 (16%)	4 (2%)	<0.01
***KIT* mutations**	16 (5%)	31 (14%)	<0.01
***MDM2* amplifications**	23 (7%)	2 (1%)	<0.01
***CRKL* amplifications**	14 (4%)	1 (<1%)	<0.01

5028 **Poster Session**

Prognostic significance of teratoma components in germ cell tumor patients undergoing high-dose chemotherapy and autologous stem cell transplantation. First Author: Nurlan Mammadzada, Ankara Gülhane Eğitim ve Araştirma Hastanesi, Ankara, Turkey

Background: The prognostic significance of a teratoma component in relapsed or refractory germ cell tumors (GCT) treated with high-dose chemotherapy followed by autologous stem cell transplantation (HDCT-ASCT) remains unclear. While teratoma has been extensively studied in earlier treatment lines, data specifically addressing its impact in the transplant setting are limited. Identification of factors influencing outcomes after HDCT is critical for patient selection and treatment optimization. **Methods:** This single-center retrospective study included 132 GCT patients who underwent autologous stem cell–supported HDCT. Primary tumor specimens were re-evaluated by an experienced pathologist for the presence of a teratoma component. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method and compared between teratoma-positive and teratoma-negative groups. Univariate Cox regression and predefined subgroup analyses were performed to identify factors associated with survival outcomes. **Results:** Baseline pathological data were available for 132 patients; 59 (44.7%) had a teratoma component and 73 (55.3%) did not. Baseline clinicopathological characteristics, including age, primary tumor site, stage, IGCCCG risk group, metastatic pattern, biomarker status, and response to first-line therapy, were comparable between groups. After a median follow-up of 55.6 months, median PFS was 6.8 months (95% CI, 4.1–9.6). Median PFS was significantly shorter in teratoma-positive patients compared with teratoma-negative patients (5.6 vs 10.0 months; log-rank p = 0.011). The 2-year PFS rates were 34% and 50%, respectively. Teratoma presence was associated with inferior PFS in univariate analysis (HR 1.77, 95% CI 1.13–2.77; p = 0.013). Median OS was not reached overall; median OS was 68.9 months in teratoma-positive patients and not reached in teratoma-negative patients, with no significant difference between groups (p = 0.986). The 2-year OS rates were similar (64% vs 67%). Subgroup analyses showed numerically poorer OS with teratoma across most strata, without statistical significance. **Conclusions:** In relapsed or refractory GCT patients undergoing HDCT, the presence of a teratoma component was associated with inferior disease control but not with a statistically significant OS disadvantage, possibly due to limited follow-up. Teratoma status may help identify patients requiring more intensive transplant strategies and early post-transplant treatment optimization. Prospective studies with longer follow-up are warranted. Research Sponsor: None.

5029 **Poster Session**

Integrated clinical and genomic analysis of mediastinal germ cell tumors (GCT) with somatic transformation (SM): A multi-institutional cohort study. First Author: Zachariah Thomas, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: SM of GCT is a rare but lethal entity largely described in the context of testicular primaries. The distinct clinical and genomic features of SM that arise from anterior mediastinum are less defined. **Methods:** A multi-institutional study was conducted by integrating data from Indiana University and the MD Anderson Cancer Center, including patients(pts) with SM arising from mediastinal GCT treated between 2016 and 2025. Electronic health records were queried to obtain clinical, pathologic and genomic data when available. SM was classified as "de novo" if detected prior to disease relapse; all others were "evolved". In the absence of elevated markers or concomitant GCT elements, isochromosome12p testing confirmed GCT ancestry. Descriptive statistics were used. Cox regression and Kaplan Meier analysis were used for overall survival(OS) and reverse KM for follow-up. OS measured from the time of transformation to date of last follow-up. The study was under protocol PA16-0736. **Results:** 40 pts were identified. All were male; median age at GCT diagnosis was 25 yrs (IQR:22-35); First detection of SM was by diagnostic biopsy in 14(35%) instances and surgical excision in 24(60%). Sarcoma was the most common histology detected in 33(82%), notably rhabdomyosarcoma and angiosarcoma- 8(20%) each. More than one SM pathology in 6(15%) pts and hematolymphoid SM was detected in 4(10%). Of 23/40 (57%) pts with genomic testing, 17(74%) were performed on the primary specimens, 5(22%) on metastatic deposits and 1(4%) on peripheral blood. TP53 and PTEN/AKT pathway mutations were seen in 16(70%) and 14(61%) respectively. De novo SM was seen in 32(80%). 9(28%) had baseline metastatic disease. Elevated AFP and beta-hCG in 28/32(84%) and 14/32(44%); 6(19%) were marker negative. 24(75%) received conventional GCT regimens. All marker negative pts had histology-driven therapy. Response data in Table. 26(81%) received surgical consolidation. For full cohort, median follow-up was 2.9 yrs, 2yr OS- 62%(95%CI:46.9-81.9) and 5yr OS- 52%(95%CI: 35.6-75.4). For de novo SM, surgical consolidation was associated with longer survival (mOS 8 yrs vs 0.6 yrs, HR-0.09, 95%CI:0.02-0.3, p-0.0003). **Conclusions:** The vast majority of mediastinal SM are sarcomas, that can be detected de novo. Conventional tumor markers are frequently elevated at presentation and may reflect concomitant non-teratoma GCT. TP53 and PTEN/AKT pathway mutations characterize the most common alterations and can be detected in primary and metastatic specimens. Research Sponsor: None.

Response to first-line therapy	GCT Therapy (n= 24) (%)	Histology driven therapy (n=7) (%)
Complete Remission (without resection)	4 (17)	1 (14)
Partial Remission	8 (34)	3 (42)
Stable Disease	5 (22)	2 (29)
Progressive Disease	6 (26)	1(14)
Not available	1 (4)	
Marker Response		
Elevated at presentation	23 (96)	1 (14)
Normalization of markers	15 (63)	1 (14)

5030 **Poster Session**

Regional trends in testicular cancer burden among adolescents and young adults (15–39 years), 1990–2023: A Global Burden of Disease analysis. First Author: Vanshika Singh, King George's Medical University, Lucknow, India

Background: Testicular cancer is the most common solid malignancy in adolescent and young adult (AYA) males. Contemporary long-term regional trends in incidence and health loss among AYAs remain incompletely described. We quantified trends in testicular cancer burden among ages 15–39 years from 1990–2023 across World Health Organization (WHO) regions. **Methods:** Using annual Global Burden of Disease (GBD) estimates (1990–2023) for ages 15–39 years, we assessed trends in incidence, prevalence, deaths, disability-adjusted life years (DALYs), years of life lost (YLLs), and years lived with disability (YLDs). For each WHO region and measure, we fit log-linear models (ln[rate] = $\beta \times$year) and calculated annual average percent change (AAPC) as $100 \times (e^{\beta} - 1)$, with 95% confidence intervals (CI) derived from the regression. **Results:** Incidence showed an upward trend in all regions, ranging from 0.62%/year in the African Region (95% CI 0.28–0.96) to 3.15%/year in the Eastern Mediterranean Region (2.98–3.33). Prevalence rose across regions, highest in the South-East Asia Region (6.04%/year, 5.82–6.26) and Eastern Mediterranean Region (5.22%/year, 5.09–5.34). Mortality trends varied across regions. Deaths declined in the Western Pacific (-1.69%/year, -1.99 to -1.39), Europe (-1.43%/year, -1.49 to -1.36), and Africa (-0.89%/year, -1.20 to -0.58), were stable in South-East Asia (-0.07%/year, p=0.44), and increased in the Americas (1.68%/year, 1.49–1.87) and Eastern Mediterranean (0.42%/year, 0.32–0.51). DALYs and YLLs followed similar patterns (declining in Europe/Western Pacific, rising in the Americas). **Conclusions:** From 1990–2023, testicular cancer incidence and survivorship-related burden increased across all WHO regions among AYAs, while mortality-related metrics improved in Europe/Western Pacific but worsened in the Americas and Eastern Mediterranean. These findings support urgent investigation of drivers of rising incidence and targeted strategies to reduce regional inequities in timely diagnosis and curative treatment for AYAs. Research Sponsor: None.

5031 **Poster Session**

Metabolic and inflammatory marker elevations and associations with hormone therapy usage in prostate cancer patients of the All of Us Research Program cohort. First Author: Yuanchu J. Yang, Vanderbilt University Medical Center, Nashville, TN

Background: The development of cardiovascular disease (CVD) involves an interplay of inflammatory and metabolic factors. While hormone therapy (HT) is associated with increased CVD risk in prostate cancer (PCa) patients, the underlying mechanism remains unclear. Prior studies suggest an association between hypogonadism and systemic inflammation, but the specific effect of HT is poorly understood. Utilizing the All of Us Research Program, we investigated the effects of HT on metabolic and inflammatory markers. **Methods:** Our study examined All of Us participants who were diagnosed with PCa and were either treated or not treated with HT (GnRH agonists, GnRH antagonists, and/or anti-androgens), as well as those who received HT for non-PCa indications. We used ANCOVA to evaluate the effect of HT on metabolic and inflammatory labs after adjusting for pre-PCa baseline values. Among HT-treated PCa patients without prior CVD (myocardial infarction, stroke, or heart failure), we used Gray's test to compare CVD time-to-event between participants with and without elevated inflammatory labs (CRP $>$ 10, ESR $>$ 20, or Ferritin $>$ 300) after HT treatment. In the non-PCa cohort, paired T-tests compared pre-HT and post-HT values. **Results:** The study included 7124 participants with PCa (1480 with HT; 5644 controls) and 2683 participants without PCa who received HT. After adjustment for baseline values, HT usage was associated with increased HgbA1c ($P<0.001$), HDL ($P<0.001$), triglycerides ($P<0.001$), ESR (P=0.006), CRP (P=0.009), and ferritin (P=0.006). Similar trends were seen in the non-PCa cohort (Table). In our survival analysis, HT-treated PCa patients with elevated inflammatory labs had higher CVD risk ($P<0.001$). **Conclusions:** Our study demonstrated associations between HT usage and metabolic dysregulation, while also suggesting a pro-inflammatory effect of HT in PCa patients. These trends reinforce prior studies and were similar among those without PCa, suggesting a drug-class effect. Our study also observed an increased risk of CVD among HT-treated PCa patients with elevated inflammatory labs. Future research should explore the role of HT associated inflammation in CVD, as well as identify targets for risk mitigation. Research Sponsor: None.

Lab	HT Treatment EMM (SE)	No HT Treatment EMM (SE)	P-value (ANCOVA)	Non-PCa Pre-HT Mean	Non-PCa Post-HT Mean	P-Value (Paired T-test)
HgbA1c (%)	6.34 (0.04)	6.15 (0.02)	P< 0.001	5.8	6.0	P<0.001
LDL (mg/dL)	102 (1.10)	101 (0.55)	P= 0.71	103.0	107.6	P<0.001
HDL (mg/dL)	52.0 (0.17)	49.7 (0.33)	P< 0.001	55.0	55.9	P= 0.02
Triglycerides (mg/dL)	136 (2.33)	127 (1.18)	P< 0.001	117.5	124.1	P= 0.001
CRP (mg/L)	45.7 (8.81)	24.9 (4.61)	P= 0.009	19.8	23.3	P= 0.45
ESR (mm/hr)	28.0 (2.27)	21.8 (1.19)	P= 0.006	27.1	30.2	P= 0.02
Ferritin (ng/mL)	303 (55.8)	267 (34.2)	P= 0.006	195.7	338.6	P= 0.02

EMM= Estimated Marginal Mean, SE = Standard Error.

5032 **Poster Session**

Burden, mortality patterns, and treatment disparities of prostate cancer across G20 countries: Insights from the Global Burden of Disease 2023 study. First Author: Kashish Magnani, Westchester Medical Center, Valhalla, NY

Background: Prostate cancer is the leading male malignancy in G20 nations, yet cross-national disparities in detection, treatment, and outcomes remain insufficiently characterized. This study examines incidence, mortality, and treatment patterns across G20 countries, with attention to socioeconomic and health system factors. **Methods:** We analyzed prostate cancer incidence, mortality, and disability-adjusted life years (DALYs) in all 20 G20 member states from 1990 to 2023 using GBD 2023 data. Analysis focused on men aged ≥50 years. Age-standardized rates were calculated, and incidence-to-mortality ratios were used as a proxy for early detection and treatment access. Radical treatment rates (surgery, radiotherapy) and PSA screening availability were correlated with survival patterns. Country-level economic estimates included diagnostic, therapeutic, and end-of-life expenditures. **Results:** In 2023, G20 countries reported 3.24 million new prostate cancer cases and 512,000 deaths, resulting in 11.8 million DALYs. Age-standardized incidence rates ranged from 23.4 to 112.6 per 100,000 men—a 4.8-fold variation—strongly associated with national healthcare development index ($r = 0.78$, $p < 0.001$). High-income G20 nations reported incidence-to-mortality ratios between 4.2:1 and 5.8:1, while middle-income countries such as India, Indonesia, and Mexico ranged from 1.3:1 to 1.8:1. India and Indonesia together accounted for 24% of G20 prostate cancer deaths despite contributing only 18% of total incident cases. Radical treatment rates spanned from 8% in India to 68% in the USA, correlating with long-term survival trends. Average healthcare expenditure per prostate cancer death ranged from $2,100 in low-resource settings to $89,400 in high-income countries. Within high-income nations, men in the lowest socioeconomic quintile experienced 2.1 times higher mortality than those in the highest quintile. **Conclusions:** Marked disparities in prostate cancer burden and treatment access persist across G20 nations, shaped by income level and healthcare system capacity. Strategic expansion of PSA-based screening and curative treatment in middle-income settings could substantially reduce preventable deaths and narrow the outcome gap. Research Sponsor: None.

5033 **Poster Session**

Real-world overall survival outcomes of lutetium (Lu^{177}) vipivotide tetraxetan treatment in prostate cancer. First Author: Elshad Hasanov, Division of Medical Oncology, Department of Internal Medicine, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: After FDA approval on March 23, 2022, lutetium (Lu^{177}) vipivotide tetraxetan became an established treatment option for advanced prostate cancer, but real-world survival outcomes and prognostic factors remain incompletely described. **Methods:** We conducted a retrospective cohort study in Epic Cosmos with the largest to date reported cohort of patients with prostate cancer who initiated lutetium Lu^{177} vipivotide tetraxetan after FDA approval to Dec 20, 2025, ensuring at least one month of follow-up prior to the query date. OS was measured from the medication start date to death, or censoring at last encounter. Kaplan–Meier methods were used for survival analysis. Univariable Cox proportional hazards models, adjusted for false discovery rate (FDR), were used to assess associations between OS and clinical variables. **Results:** The cohort included 6464 patients with a median age of 74.0 years (IQR: 38–100). The cohort was predominantly White (75.2%) and Black/African American (19.9%). Kaplan-Meier analysis showed OS probabilities of 85.4%, 67.2%, 42.8%, and 23.8% at 6, 12, 24, and 36 months, respectively, comparable to results reported in the Phase 3 VISION trial. Worse survival was significantly associated with a history of tobacco use (HR 1.22 [1.11–1.33], FDR <0.01) and higher Charlson Comorbidity Index scores (HR 1.04 [95% CI 1.02–1.06], FDR <0.01). Conversely, higher BMI (HR 0.98 [0.97–0.99], FDR <0.01) was associated with improved survival. Baseline laboratory markers of nutritional and hematologic reserve were strongly protective, including higher Albumin (HR 0.39 [0.35–0.43], FDR <0.01), Total Protein (HR 0.81 [0.74–0.89], FDR <0.01), Hemoglobin (HR 0.77 [0.75–0.79], FDR <0.01), RBC count (HR 0.53 [0.49–0.57], FDR <0.01), and MCHC (HR 0.88 [0.86–0.91], FDR <0.01). Inflammatory and immune markers showed distinct prognostic value: higher Eosinophils (HR 0.38 [0.25–0.58], FDR <0.01) and Lymphocytes (HR 0.69 [0.64–0.76], FDR <0.01) were associated with better outcomes, while higher Basophil-to-Lymphocyte Ratio (HR 2.10 [1.17–3.78], FDR = 0.02), RDW (HR 1.16 [1.14–1.19], FDR <0.01), and Neutrophils (HR 1.06 [1.04–1.08], FDR <0.01) were associated with worse survival. Higher electrolytes (Sodium, Chloride, Potassium, Bicarbonate) were generally associated with lower hazard, likely reflecting better physiologic homeostasis. **Conclusions:** In this large real-world cohort of prostate cancer patients treated with Lu^{177} vipivotide tetraxetan, overall survival was strongly influenced by tobacco use, comorbidity burden, and baseline laboratory markers reflecting nutritional status, hematological reserves, and immunity. These findings highlight the importance of physiologic reserve and inflammatory state in shaping outcomes with this radioligand therapy and may inform risk stratification and care strategies in routine clinical practice. Research Sponsor: Pelotonia Institute for Immuno-Oncology (PIIO) Recruitment Startup Fund; The Ohio State University Comprehensive Cancer Center (OSUCCC).

5034 **Poster Session**

Efficacy and safety of disitamab vedotin combined with toripalimab for cisplatin-refractory advanced penile cancer: A prospective single-center study (SAVE). First Author: Fang Yuan, Chongqing University Cancer Hospital, Chongqing, China

Background: Patients with advanced penile cancer progressing on cisplatin-based chemotherapy have limited options. Anti-EGFR therapy has not demonstrated significant survival benefit, and immune checkpoint inhibitors (ICIs) remain uncommon. Preclinical evidence suggests HER-2-targeted antibody-drug conjugates (ADCs) may synergize with ICIs by redirecting immune cells to the tumor microenvironment and overcoming immunosuppression. The HER-2 ADC (Disitamab Vedotin, DV) has shown preclinical activity in HER-2-positive and cisplatin-resistant penile cancer models. This study evaluated DV plus a PD-1 inhibitor (Toripalimab, T) in the cisplatin-resistant and advanced penile cancer patients. **Methods:** In this single-arm prospective study, patients received DV (2.0 mg/kg every 2-3 weeks) plus T (240 mg every 3 weeks) until progression or unacceptable toxicity. Tumor assessments tested by CT/MRI were performed every 8-12 weeks for RECIST v1.1. PD-L1 by combined positive score (CPS), tumor mutational burden (TMB) and HER-2 expression were analyzed. Follow-up continued until death or December 31, 2025. **Results:** Eight patients (median age 52 years; range 38-66) were enrolled, all previously treated with ≥4 cycles of cisplatin chemotherapy and 3 had received ICIs as second-line therapy (1 with ICIs plus cetuximab). Baseline staging included T4 (n = 2), N3 (n = 7), and M1 (n = 5); all target lesions were > 5 cm (perineal/inguinopelvic). After ≥3 treatment cycles and first scan at 8 weeks, best responses were partial response (PR) in 3 patients (1 patient achieved at first assessment, with ongoing response at 18 months and conversion of ctDNA from positive to negative; 1 with sustained response for 17 months, accompanied by reduction in circulating tumor cells; 1 with PR followed by treatment discontinuation and survival of 4 months), stable disease (SD) in 1, and progressive disease (PD) in 4 (median overall survival 5 months). Objective response rate (ORR) was 37.5% (3/8) and disease control rate (DCR) 50% (4/8). Median PFS and mOS were 3 and 5 months, respectively (Kaplan-Meier estimate). One grade ≥3 adverse event occurred (immune-mediated colitis with hematochezia). Grade 1-2 toxicities included leukopenia (n = 2), infusion-related fever (n = 1), sinus tachycardia (n = 1), fatigue (n = 6), rash (n = 1), and peripheral neuropathy (n = 5). Notably, HER-2 expression was assessed as negative in all patients. The patient with clearance of ctDNA had high TMB but low PD-L1 expression; others evaluable tumors had PD-L1 CPS > 40 (TMB not assessed). **Conclusions:** The combination of DV and T shows promising antitumor activity and a manageable safety profile in cisplatin-refractory advanced penile cancer patients, independent of HER-2 or PD-L1 status. These findings support further evaluation in this patients with high unmet clinical need. Clinical trial information: ChiCTR2400086605. Research Sponsor: None.

5035 **Poster Session**

Spatial immune architecture as used to define progression and treatment response in penile squamous cell carcinoma. First Author: Firas Hatoum, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Penile squamous cell carcinoma (PSCC) is a rare, aggressive malignancy with limited treatment options and poor outcomes. Although immunotherapy has shown activity in a subset of patients, the spatial immune mechanisms underlying disease progression and treatment resistance remain unknown. We hypothesized that clinical behavior in PSCC is driven by spatial organization of the tumor microenvironment (TME), rather than immune cell abundance alone. **Methods:** We conducted the first and largest longitudinal, multi-omics study of PSCC, integrating spatial transcriptomics (NanoString CosMx 6K panel) and single-cell RNA sequencing across 81 patients spanning all disease stages. Spatial profiling was performed on a tissue microarray of 35 primary tumors from 31 patients, capturing >390,000 spatially resolved cells. Patients were stratified by progression status, HPV, stage, and chemotherapy response (n=12) per RECIST 1.1. Spatial architecture was quantified using neighborhood Enrichment Analyses, Spatial cell–cell proximity and Ripley K AUC analyses. **Results:** Two distinct and clinically divergent TME architectures were identified. Tumors with favorable clinical behavior exhibited organized, antigen-driven immune surveillance. HPV-positive (n=18) and non-progressed tumors (n=17) showed coordinated neighborhoods involving myeloid cells, dendritic cells, T cells, and endothelium. Proliferative tumor programs were spatially proximal to DCs, and effector CD8 T cells maintained close coupling to tumor states, with preserved CD8–DC interactions. In contrast, HPV-negative (n=17), progressed (n=18), and chemotherapy non-responders (n=4) converged on a dysregulated inflammatory state characterized by B cell–macrophage and CAF-associated neighborhoods, EMT–hypoxia tumor programs, and immune–stromal self-clustering. These tumors showed reduced tumor-directed immune engagement and loss of organized immune domains. Notably, chemotherapy non-responders were not immune-depleted but instead exhibited dense innate and antigen-presenting cell infiltrates that were spatially confined to stromal and vascular compartments, with limited tumor-directed immune engagement. **Conclusions:** This study establishes the first spatially resolved atlas of PSCC, integrating spatial and single-cell multi-omics to uncover distinct immune and stromal architectures linked to progression and therapy resistance. Distinct TME architectures define progression and treatment resistance, supporting spatial biomarkers for patient stratification and therapeutic optimization. Research Sponsor: None.

5036 Poster Session

HRS-1167 (M9466), a PARP1 inhibitor, combined with abiraterone acetate and prednisone in metastatic castration-resistant prostate cancer: A phase 1b/2 study. First Author: Chaochao Liang, The First Affiliated Hospital of Anhui Medical University, Hefei, China

Background: PARP inhibitors combined with novel hormonal agents (NHAs) have shown improved progression-free survival in metastatic prostate cancer compared to NHA alone. HRS-1167 (M9466) is a novel highly selective PARP1 inhibitor with established antitumor activity in advanced solid tumors. This multicenter, open-label, dose-finding and efficacy expansion phase 1b/2 study assessed the safety, tolerability and preliminary efficacy of HRS-1167 combined with AA-P in mCRPC (ClinicalTrials.gov, NCT06689163). **Methods:** Chinese adult mCRPC patients with homologous recombination repair mutations who were previously treated were enrolled. Eligible patients received oral HRS-1167 at 30 mg QD or 50 mg QD, combined with AA-P (abiraterone acetate 300 mg QD; prednisone 5 mg BID). Primary objectives were safety and tolerability. **Results:** As of Oct 31, 2025, 58 patients were enrolled and treated (HRS-1167 30 mg, n = 33; HRS-1167 50 mg, n = 25; prior NHA, 100%; *BRCA* mutation, 44.8%). Median follow-up was 3.0 months and 6.2 months in the 30 mg and 50 mg cohorts. Preliminary efficacy was summarized in the Table. Among patients with evaluable efficacy (n = 47), prostate-specific antigen response (PSA50) rate was 36.4% (8/22) in the 30 mg cohort and 52.0% (13/25) in the 50 mg cohort. Confirmed objective response rate (cORR) was 37.5% and 14.3%, and disease control rate (DCR) was 81.8% and 92.0%, respectively. HRS-1167 plus AA-P demonstrated particularly encouraging efficacy in patients with *BRCA* mutations: PSA50 rate was 100% (6/6) in the 30 mg cohort and 81.8% (9/11) in the 50 mg cohort, and cORR was 100% (2/2) and 33.3% (1/3), respectively. DCR was 100% in the *BRCA*-mutated subgroup. Treatment-emergent adverse events (TEAEs) were reported by 26 (78.8%) and 25 (100%) patients in the 30 mg and 50 mg cohorts (grade ≥3, 18.2% and 44.0%; serious, 9.1% and 32.0%). There were no TEAEs leading to death. The most common (≥5% of patients) grade ≥3 TEAEs were hematologic toxicities (anemia, 9.1% and 24.0%; decreased platelet count, 6.1% and 8.0%; decreased white blood cell count, 0% and 12.0%; decreased neutrophil count, 3.0% and 8.0%). **Conclusions:** HRS-1167 combined with AA-P showed promising efficacy in patients with mCRPC, especially those with *BRCA* mutations. The combination was well-tolerated with no new safety signals identified. Clinical trial information: NCT06689163. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

	Overall		*BRCA*m	
	30 mg (N = 22)	50 mg (N = 25)	30 mg (N = 6)	50 mg (N = 11)
PSA50, n (%)	8 (36.4)	13 (52.0)	6 (100)	9 (81.8)
Time to PSA progression, months, median (95% CI)	NR (3.7, NR)	6.5 (5.5, NR)	NR (4.6, NR)	6.5 (3.8, NR)
cORR, n/N* (%)	3/8 (37.5)	1/7 (14.3)	2/2 (100)	1/3 (33.3)
DCR, n (%)	18 (81.8)	23 (92.0)	6 (100)	11 (100)

N = efficacy evaluable patients; N* = patients with target lesions at baseline. PSA and tumor responses were confirmed.
PSA, prostate-specific antigen; cORR, confirmed objective response rate; DCR, disease control rate; NR, not reached.

5037 Poster Session

Evaluation of the safety, efficacy and dosimetry of TRC003 in metastatic castration-resistant prostate cancer: A prospective, open-label, single-arm study. First Author: Suping Li, Affiliated Hospital of North Sichuan Medical College, Nanchong, China

Background: TRC003 (also named as ^{225}Ac-PSMA-313) is a novel molecule of targeted alpha therapy (TAT) that administers alpha-particle radiation to cancer cells expressing Prostate Specific Membrane Antigen (PSMA). In this study, we plan to investigate preliminary safety, efficacy and dosimetry of TRC003 in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** This is a prospective, open-label, single-arm, single center study in accordance with ICH GCP guidelines. The patients with progressive PSMA-positive mCRPC who have been treated with androgen receptor pathway inhibitors (ARPIs) and/or taxane-based chemotherapy were recruited and received TRC003 treatment intravenously at 200 μCi (7.4 MBq) doses administered every 8 weeks per cycle for 4 cycles followed by expanded 4 cycle treatment if the participants continued to be benefit from the treatment. Adverse events, ORR, PSA response, bPFS, rPFS and OS were evaluated. In addition, the SPECT images were acquired with noncircular orbit, 120 project views over 360° at 4, 24, 48 and 96 hours after administration for dosimetry analysis. **Results:** From Feb 2024 to Jan 2026, 15 patients were included with an average age of 67.1 yr and median baseline PSA of 98.6 ng/mL. 11 (73.3%) participants received ARPI and taxane-based chemotherapies while 4 (26.7%) participants received only ARPI previously. Median baseline SUVmax and SUVmean on PSMA-PET were 32.7 (14.7-60.26) and 18.2 (9.51-34.73), respectively. A total of 63 cycles of TRC003 were administered, with a median of 4 cycles per patient. The most common AE was anemia (80%) and dry mouth (73.3%). Grade 3 treatment-related adverse events occurred as anemia (20%), lymphocytopenia (13.3%), weight loss (13.3%), thrombocytopenia (6.7%), and vomiting (6.7%). No treatment-related Grade ≥4 AE were observed. No kidney related toxicities were observed. The ORR of all patients was 45.5%, whereas the ORR reached 57.1% in the subset of patients who had received prior treatment of ARPIs and taxanes. The median tumor absorbed dose was 2.40±3.33 Gy (soft lesions: 5.03±5.51 vs bone: 1.65±2.19 Gy). The absorbed doses of kidneys, liver and spleen were 1.56±0.38, 1.07±0.19 and 0.54±0.29 Gy, respectively. The absorbed dose coefficients of tumors, kidney and liver were 0.36±0.50 (soft lesions 0.75±0.82 vs bone 0.25±0.33), 0.23±0.07, 0.16±0.03 Gy/MBq. **Conclusions:** TRC003 was safe and well-tolerated, and exhibited efficacy for mCRPC patients who were resistant to ARPI or chemotherapy. Overall TRC003 is a promising radiopharmaceutical agent for the treatment of mCRPC. Clinical trial information: ChiCTR2400083275. Research Sponsor: C-Ray therapeutics.

5038 Poster Session

Safety and preliminary efficacy of M9466 (HRS-1167) in combination with abiraterone acetate and prednisone/prednisolone (AA-P) in patients (pts) with metastatic prostate cancer in the phase 1 DDRiver 501 study. First Author: Valentina Boni, Hospital Universitario Quironsalud Madrid, NEXT Madrid, Madrid, Spain

Background: M9466 (HRS-1167) is a highly potent, selective next-generation PARP1 inhibitor being investigated in pts with locally advanced/metastatic solid tumors. Here we report safety and preliminary efficacy data from Module 3 of the DDRiver 501 study, a Phase 1, open-label, global multicenter study, evaluating M9466 with AA-P in pts with metastatic prostate cancer (NCT06421935). **Methods:** DDRiver 501 Module 3 enrolled eligible pts with metastatic castration-resistant prostate cancer (mCRPC) or metastatic hormone-sensitive prostate cancer (mHSPC), irrespective of prior anticancer therapy received. Pts received M9466 (either 50 or 100 mg once-daily) with AA-P until disease progression. Primary objective was safety. Additional objectives included efficacy (objective response rate [ORR], PSA50 [confirmed decrease in prostate-specific antigen levels of >50% from baseline]), pharmacokinetics (PK), molecular responses (e.g. >50% reduction from baseline of methylation-based tumor fraction in circulating tumor DNA [ctDNA]) and tumor genetic profiling. **Results:** As of Nov 21, 2025, Module 3 enrolment was complete (N=21; M9466 50 mg n=10, 100 mg n=11; mHSPC n=1, mCRPC n=20; prior treatment included: PARP inhibitors n=0, androgen receptor pathway inhibitors [ARPI] n=21). Thirteen (62%) pts carried HRR gene mutations, including four (19.0%) with *BRCA1/2* mutations, by ctDNA analysis. Pts received M9466 for a median (range) of 18.1 (6.0–30.1) and 26.9 (6.0–42.0) weeks (50 and 100 mg arms respectively). Safety outcomes are presented (table). No dose-limiting toxicities or serious treatment-related adverse events to any study intervention were observed. Across pts with baseline RECIST measurable disease, confirmed ORR was 18.8% (3/16, 95% CI: 4.0, 45.6). Two of the three responders had RAD50 loss of function mutations. In pts with baseline PSA ≥2 ng/mL, 3/17 (17.6%) achieved a PSA50 response. Molecular response and PK data will also be presented. **Conclusions:** Preliminary data from DDRiver 501 Module 3 demonstrate M9466 with AA-P is generally well tolerated and demonstrates antitumor activity in ARPI-pretreated pts with mHSPC/mCRPC. Clinical trial information: NCT06421935. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

Safety overview.

n (%)	M9466 50 mg (n=10)	M9466 100 mg (n=11)
Any TEAE	9 (90.0)	11 (100)
TEAEs (>25% of total pts)		
Anemia	7 (70.0)	9 (81.8)
Fatigue	6 (60.0)	2 (18.2)
Platelet count decreased	2 (20.0)	5 (45.5)
Neutrophil count decreased	3 (30.0)	3 (27.3)
Any ≥Grade 3 TEAE	4 (40.0)	5 (45.5)
≥Grade 3 TEAEs (≥n=2 of total pts)		
Anemia	2 (20.0)	5 (45.5)
Platelet count decreased	1 (10.0)	1 (9.1)
Neutrophil count decreased	1 (10.0)	1 (9.1)
M9466-related TEAEs leading to:		
Discontinuation	0	1 (9.1)*
Reduction	2 (20.0)	4 (36.4)
Interruption	4 (40.0)	4 (36.4)

*Due to anemia. TEAE, treatment-emergent adverse events.

5039 Poster Session

Cell-free DNA nucleosome and genomic signatures as predictors of outcomes with radium-223 in metastatic castration-resistant prostate cancer. First Author: David Dawei Chen, Fred Hutch Cancer Center, Seattle, WA

Background: Radium-223 (Ra-223) is a bone-seeking alpha emitter that induces double-stranded DNA breaks. Previous studies have shown Ra-223 can prolong survival of men with mCRPC with symptomatic bone metastases and no visceral metastases. However, clinical outcomes are heterogeneous, and predictive biomarkers for lack of benefit or progression with visceral disease are lacking. We evaluated whether genomic and epigenetic features derived from cell-free DNA (cfDNA) could identify tumor characteristics associated with favorable or unfavorable outcomes with Ra-223 therapy. **Methods:** Pre-treatment plasma cfDNA was analyzed from 137 mCRPC patients who received Ra-223. Ultra-low pass and deep whole genome sequencing were performed. Tumor fraction and copy number alterations were estimated using ichorCNA. Transcription factor (TF) activity was derived by nucleosome profiling of cfDNA fragments around transcription starts sites (TSS) and TF binding sites using the tools Griffin and TritonNP. Genomic and epigenetic features were associated with clinical outcomes including completion of six Ra-223 cycles, overall survival, and development of new nodal, visceral, or liver metastases. A multimodal binary classifier integrating copy number variation and TF activity was constructed using LASSO feature selection and XGBoost with repeated, nested 5-fold cross-validation. External validation was performed using independent cohorts of mCRPC patients treated with docetaxel (n=46) or other agents (n=142) for the prediction of new metastatic involvement. **Results:** Higher pre-treatment tumor fraction and TF activity at specific loci including HIF3A, ZNF770, and PRDM6 were associated with adverse outcomes. A binary classifier predicting completion of Ra-223 demonstrated strong discrimination in cross-validation, with similar performance for prediction of liver metastasis progression. External validation in independent cohorts demonstrated moderate discrimination, supporting generalizability across treatment contexts. **Conclusions:** Our findings demonstrate that analysis of cfDNA-derived genomic and epigenomic features can identify biologically relevant tumor characteristics associated with benefit from Ra-223 in mCRPC. These findings support the development of minimally invasive biomarkers to refine patient selection and risk stratification. Our ongoing analyses look to integrate mutations, amplifications, and deletions in key disease-related genes to further explore tumor genotype-phenotype associations with Ra-223 outcomes. Research Sponsor: Dana-Farber Cancer Institute; Fred Hutch Cancer Center; Bayer.

5040 **Poster Session**

Quality of life analysis from a multicenter, randomized, phase 2, investigator-initiated ETCTN trial of olaparib + radium-223 versus radium-223 in metastatic castration-resistant prostate cancer with bone metastases (COMRADE). First Author: Rana R. McKay, UC San Diego Moores Cancer Center, San Diego, CA

Background: Radium-223 is an α-emitting radioisotope that improves overall survival in men with metastatic castration resistant prostate cancer (mCRPC) and bone metastases (BM). In the ALSYMPCA trial, radium-223 was also associated with improved quality of life (QOL), delayed time to first opioid use, and pain palliation. We previously reported superior radiographic progression free survival (rPFS) with the addition of olaparib to radium-223 in the randomized phase 2 COMRADE study (NCT03317391). We now report patient-reported QOL outcomes from the trial. **Methods:** Patients were randomized 1:1 to olaparib 200 mg twice daily plus radium-223 (Arm A) or radium-223 alone (Arm B). QOL was assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and Brief Pain Inventory (BPI) at baseline and every 12 weeks. Mixed-effects ANCOVA models assessed treatment effects on QOL changes from baseline, adjusting for baseline score, timepoint, age, and Eastern Cooperative Oncology Group performance status. Least-squares (LS) mean changes were reported for each arm with between-arm differences and 95% confidence intervals. Analysis was limited to patients with baseline and $\geq$1 post-baseline assessment within 24 weeks. **Results:** Of 114 treated patients, 74 (65%) were evaluable for QOL analysis (Arm A, n = 40; Arm B, n = 34), including 71 (62%) for FACT-P and 72 (63%) for BPI pain severity and pain interference. Baseline characteristics were well balanced: median age was 70 and 72 years, ECOG PS 1 was present in 60% and 62%, prior docetaxel was received by 55% and 50%, $>$ 20 bone metastases were present in 45% and 47%, and pain medication use at baseline was reported in 60% and 72% of patients in Arms A and B, respectively. There were no significant differences in LS mean change from baseline in FACT-P total score between arms at week 12 (Arm A: -5.09 vs Arm B: -0.23; difference -4.87, 95% CI -13.4 to 3.62) or week 24 (Arm A: -1.41 vs Arm B: -3.20; difference 1.79, 95% CI -8.28 to 11.9). Similarly, no significant between-arm differences were observed in LS mean changes in BPI pain severity at week 12 (difference 0.44, 95% CI -0.44 to 1.33) or week 24 (difference -0.20, 95% CI -1.32 to 0.93). Arm B showed greater improvement in BPI pain interference at week 12 (LS mean change: Arm A +0.21 vs Arm B -0.88; difference 1.09, 95% CI 0.14 to 2.05), but this difference was not sustained at week 24 (difference -0.27, 95% CI -1.37 to 0.82). **Conclusions:** In this phase 2 trial, the addition of olaparib to radium-223 achieved superior rPFS without significant detriment to patient-reported QOL or pain compared to radium-223 alone, supporting the tolerability of this combination in mCRPC patients with BM. Clinical trial information: NCT03317391. Research Sponsor: National Cancer Institute.

5041 **Poster Session**

Clinical validation of circulating tumor cell synaptophysin and androgen receptor expression in metastatic prostate cancer phenotypes. First Author: Ethan Lo, Fred Hutch Cancer Center, Seattle, WA

Background: Chronic exposure to androgen receptor (AR) targeted therapies can drive lineage plasticity, promoting the emergence of neuroendocrine (NE) prostate cancer (NEPC) and treatment resistance. NEPC is characterized by a phenotypic shift, with loss of AR expression and emergence of markers (e.g., synaptophysin, SYP). To definitively diagnose NEPC, a metastatic biopsy is typically required; however, there are numerous barriers to obtaining a timely tissue diagnosis. As such, there is an unmet need for blood-based assays that can accurately identify treatment-emergent NEPC. In this study, we evaluate concordance between circulating tumor cell (CTC) SYP and AR expression patterns in patients with and without evidence of NE differentiation on tissue histology. **Methods:** Blood for CTC analysis was prospectively collected from patients with advanced prostate cancer. Patients were retrospectively assigned to either an adenocarcinoma (AR-positive) or NE differentiated (SYP-positive) group based on clinical and patho-genomic factors. Amphicrine PC was included in NE differentiated cohort. The RareCyte system was used to generate slides for CTC-based immunofluorescent (IF) analysis for SYP and AR. Associations between CTC SYP and AR expression, PSA at time of CTC collection, and overall survival (OS) were assessed for patients with $\geq$ 5 CTCs using Wilcoxon rank-sum test, Fisher's exact test, and Kaplan-Meier analyses. **Results:** We enrolled 52 patients with metastatic castration-resistant prostate cancer (mCRPC); 26 were classified as NE differentiated and 26 as AR-positive adenocarcinoma. Median time between biopsy and CTC collection was 10.6 months (IQR 4.1–34.3) and 19.4 months (IQR 3.5–66.4) for the NE differentiated and AR-positive adenocarcinoma cohorts respectively. NE differentiated patients had a significantly higher fraction of SYP-positive CTCs (median 28.6 % vs 0%, p = 0.0084), whereas patients in the adenocarcinoma cohort had a higher fraction of AR-positive CTCs (median 96.7% vs 0.0%, p = 0.0004). Phenotype classification based on high AR or SYP expression ($>$ 80% of CTCs positive) significantly differentiated cohorts and was strongly associated with tissue histology (p = 0.0048). PSA level at the time of CTC collection was significantly lower in the NE differentiated cohort (median 3.8 vs 486.9 ng/mL, p = 0.0001). There was no difference in OS from time of diagnosis or time of metastasis between groups. **Conclusions:** SYP and AR CTC expression demonstrated strong concordance with tissue histology and established clinical features of NEPC and AR-positive adenocarcinoma. These early findings support the feasibility of CTC expression profiling to identify NE biomarker expression. However, results are only hypothesis-generating and prospective validation with matched tissue biopsy in a larger cohort with adequate follow up is warranted. Research Sponsor: None.

5043 **Poster Session**

Impact of baseline demographics on therapy management in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) treated with talazoparib (TALA) + enzalutamide (ENZA) in the TALAPRO-2 study: Extended follow-up. First Author: Ugo De Giorgi, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) Dino Amadori, Meldola, Italy

Background: The randomized, Phase 3 TALAPRO-2 trial showed improved radiographic progression-free survival (rPFS) and overall survival (OS) in pts with mCRPC treated with TALA + ENZA vs placebo + ENZA in two cohorts: unselected and homologous recombination repair (HRR)-deficient pts. Median TALA duration of treatment (DoT) was 19.7 mo (unselected) and 20.3 mo (HRR-deficient). Study protocol required dose reduction for pts with reported Grade 3 or 4 hematologic adverse events (AEs); 55% of pts in both cohorts had a TALA dose reduction due to AEs at final analysis. We analyze the impact of baseline demographics on TALA dose reductions and clinical outcomes in the TALA + ENZA arm. **Methods:** Pts in the TALA + ENZA arm received TALA 0.5 mg (in case of moderate renal impairment [30–59 mL/min/1.73 m^2] 0.35 mg) + ENZA 160 mg PO QD. Time-to-event endpoints were summarized by the Kaplan–Meier method and compared by log-rank test. **Results:** In both cohorts, pts with a TALA dose reduction due to any cause (AEs and other reasons) were more likely to be older, be of Asian ethnicity, have lower bodyweight (BW), and have mild renal impairment vs pts without a TALA dose reduction (Table). Fewer pts with a TALA dose reduction than without discontinued treatment before wk 16 in the unselected (6.1% vs 20.0%) and HRR-deficient (2.7% vs 13.8%) cohorts. Median TALA DoT was longer in pts with a TALA dose reduction in the unselected cohort and similar between groups in the HRR-deficient cohort (Table). No clinically meaningful differences were observed in rPFS or OS in pts with a TALA dose reduction vs without in both cohorts (unselected: rPFS HR 0.94; 95% CI 0.70–1.25; OS HR 0.90; 95% CI 0.68–1.20; HRR-deficient: rPFS HR 0.96; 95% CI 0.64–1.44; OS HR 0.98; 95% CI 0.64–1.49; Table). **Conclusions:** Pts with specific baseline demographics (older, Asian ethnicity, lower BW, mild renal impairment) were more likely to have a TALA dose reduction. TALA dose reduction did not negatively impact TALA DoT or efficacy in pts who received TALA + ENZA in the TALAPRO-2 trial. Clinical trial information: NCT03395197. Research Sponsor: This study was funded by Pfizer Inc. Astellas Pharma Inc. provided enzalutamide.

	Unselected with dose reduction (n=228)	Unselected without dose reduction (n=170)	HRR-deficient with dose reduction (n=111)	HRR-deficient without dose reduction (n=87)
Median age (range), y	73.0 (52–90)	70.0 (41–87)	73.0 (53–90)	68.0 (41–88)
White, %	53.1	70.0	60.4	78.2
Black/African American, %	2.6	2.9	3.6	2.3
Asian, %	39.5	21.2	31.5	11.5
Median weight (range), kg	75.0 (45–169)	85.0 (59–155)	78.0 (45–118)	85.0 (60–135)
Mild renal impairment (60–89 mL/min/1.73 m^2), %	52.2	36.5	59.5	34.5
Median TALA DoT (range), mo	23.0 (1.9–67.4)	15.2 (0.1–58.6)	20.3 (2.6–61.1)	20.8 (0.3–58.6)
Median rPFS (95% CI), mo	33.1 (27.4–41.4)	33.0 (22.3–41.4)	33.1 (24.3–38.5)	30.2 (18.1–46.7)
Median OS (95% CI), mo	46.9 (40–53.3)	45.1 (30.7–57.2)	41.9 (35.4–not reached [NR])	48.4 (31.5–NR)

5044 **Poster Session**

Genomic landscape of *TP53* Y220C–mutated clinically advanced prostate carcinoma (CAPC). First Author: Varun Nandakumar, University of Utah, Salt Lake City, UT

Background: The *TP53* Y220C base substitution mutation has become a significant therapeutic target with the development of reactivator drugs that restore TP53 function with a regulatory function in the cell cycle. However, its real-world prevalence and associated genomic landscape is not established in CAPC. Data on concurrent genomic alterations (GA) may guide the development of combinatorial therapeutic strategies. **Methods:** 26,156 cases of CAPC underwent hybrid capture-based comprehensive genomic profiling (CGP) to study all classes of GA including base substitutions, short insertions, deletions, copy number changes, rearrangements and fusions. Microsatellite instability (MSI) status and tumor mutation burden (TMB) were determined from the sequencing data; comparisons utilized the Fisher Exact method. **Results:** 144 CAPC (0.6%) of CAPC cases featured *TP53* Y220C mutation (*TP53* Y220C+). Patients with *TP53* Y220C+ CAPC had slightly higher median age (70.0 vs 68.2; p = 0.020) and numerically lower frequency of *TMPRSS2* GA (33.0% vs 39.4%; Not significant (NS)). GA potentially associated with CAPC primary hormonal-based therapy response more frequently found in *TP53* Y220C+ cases included *SPOP* (10.5% vs 1.4%; p $<$ 0.0001) with *AR* GA (13.6% vs 11.3%; NS) being similar in both groups. GA linked to PARP inhibitor response slightly more frequent in *TP53* Y220C+ cases included *BRCA2* GA (8.7% vs 3.5%; p = 0.0003) and *ATM* GA (5.9% vs 4.2%; NS). GA in *RAD21* were slightly higher in *TP53* Y220C- CAPC (14.8% vs 8.3%; p = 0.029). GA in *PIK3CA* (6.6% vs 7.0%) and *PTEN* (32.4% vs 34.5%) were similar in the two groups. Biomarkers likely associated with benefit with anti-PD1/L1 agents were very low in both groups, included higher frequency of *CDK12* GA (5.4% vs 0.7%; p $<$ 0.0001) in *TP53* Y220C+ cases and higher frequencies of MSI-High status (2.7% vs 0.0%; p = 0.045), mean TMB (3.8 vs 2.1 mutations/Mb; p $<$ 0.0001) and TMB $>$ 10 mutations/MB (4.4% vs 0.0%; p = 0.010) in *TP53* Y220C- cases. **Conclusions:** *TP53* Y220C is a rare finding in CAPC, but it may offer a potential therapeutic avenue for these patients whose tumors feature such a mutation. In addition, *TP53* Y220C+ cases appear to be genomically relatively distinct from *TP53* Y220C- CAPC cases and may feature genomic signatures that could influence treatment selection and trial design. Study limitations include a retrospective, descriptive design, a lack of clinical data annotation, and selection and confounding biases, so our findings are hypothesis-generating. Research Sponsor: None.

Selective GA in *TP53* Y220C+ vs *TP53* Y220C- in patients with CAPC.

	TP53 Y220C+ CAPC (144 cases)	*TP53* Y220C- CAPC (26,012 cases)	P Value
Median Age (yrs)	70 (46-89+)	68 (35-89+)	
***TP53* (all)**	100.0%	39.7%	$<$0.0001
***TP53* (non-Y220C)**	7.6%	39.7%	$<$0.0001
SPOP	10.5%	1.4%	$<$0.0001
BRCA2	8.7%	3.5%	0.0003
CDK12	5.4%	0.7%	$<$0.0001
APC	9.1%	4.2%	0.0004
MSI-High	0.0%	2.7%	0.045
Mean TMB	2.1	3.8	$<$0.0001

5045 **Poster Session**

Clonal hematopoiesis-related outcomes associated with radioligand therapy in prostate cancer: A "real-world" analysis. First Author: Robert Yuan, UMass Memorial Medical Center, Worcester, MA

Background: Radioligand therapy with radium-223 (Rad) and lutetium-177 (Plu) demonstrates notable hematologic toxicities in patients (pts) with prostate cancer (PC), including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Delivery of ionizing radiation to the bone microenvironment is a known risk factor for accelerating clonal hematopoiesis, although the incidence of clonal cytopenias with these agents is not well characterized. We hypothesized that pts treated with Rad and/or Plu would have higher risk of clonal cytopenia of undetermined significance (CCUS) vs matched controls in the "real-world". **Methods:** We performed a retrospective study using de-identified aggregate data from the TriNetX US Research Collaborative Network from January 2010 to December 2025. Adult males with PC who received ≥1 administration of Plu and/or Rad were included; pts with prior myeloid malignancy were excluded. Primary outcomes were incidence of CCUS and MDS. Propensity score matching (PSM) was performed based on age, race, prior diagnosis of leukopenia, anemia, thrombocytopenia, or pancytopenia. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. **Results:** We identified 2,569 pts treated with Plu alone and 2,007 treated with Rad alone and compared them with pts with advanced PC without exposure to either agent (unexposed control) (Table 1). After PSM, the incident risk of CCUS was greater in Rad-exposed pts (RR 2.62, 95% CI 1.45 – 4.73, $p<0.001$) while Plu was not associated with a significant increase in CCUS or MDS. Direct comparison after PSM (n=1,433) demonstrated lower risk of pancytopenia (RR 0.46, 95% CI 0.37 – 0.56, $p<0.001$) and CCUS (RR 0.41, 95% CI 0.20 – 0.81, $p=0.008$) in Plu vs Rad. In unadjusted analysis, pts receiving both Plu and Rad had increased incidence of CCUS vs Plu alone (RR= 3.64, 95% CI 1.87 - 7.07, $p<0.001$) and higher risk of MDS vs either agent alone. **Conclusions:** This "real-world" analysis demonstrates that compared with unexposed controls, Rad – but not Plu – is associated with an increased risk of CCUS. Treatment with Plu and Rad portends a higher risk of CCUS than Plu alone, as well higher risk of MDS than either drug alone. Study limitations include its retrospective nature, missing/ unknown data (e.g. bone marrow and mutation analysis), and potential selection and confounding biases. As treatment sequencing evolves for pts with metastatic PC, further evaluation of clonal hematopoiesis, MDS/AML with adequate sample size and follow up in this population is warranted. Research Sponsor: None.

^{177}Lu-PSMA-617

	Exposed (n = 2,569)	Unexposed (n =2,569)	Risk Ratio (95% CI)	*p*-value
CCUS	1.03% (26)	0.67% (17)	1.54 (0.84 – 2.82)	0.16
MDS	0.94% (24)	0.55% (14)	1.72 (0.89 – 3.32)	0.10
Radium-223	**Exposed (n = 2,007)**	**Unexposed (n = 2,007)**	**Risk Ratio (95% CI)**	***p*-value**
CCUS	1.97% (39)	0.75 (15)	2.62 (1.45 – 4.73)	<0.001
MDS	0.85% (17)	0.75% (15)	1.13 (0.57 – 2.26)	0.72

5046 **Poster Session**

Safety and efficacy of QLC5508 (MHB088C) in heavily-treated patients with metastatic castration-resistant prostate cancer: Updated data from a phase 1/2 trial. First Author: Xinan Sheng, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Genitourinary Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: QLC5508 (MHB088C), a novel B7-H3-targeted antibody-drug conjugate with high cell-binding activity and internalization rate, contains SuperTopoi payload which is 5 to 10 times more potent than Dxd. The preliminary data of a phase 1 study indicated the promising anti-tumor activity and tolerability of QLC5508 in patients (pts) with solid tumors, including metastatic castration-resistant prostate cancer (mCRPC). Here we report the updated results of efficacy and safety in pts with mCRPC. **Methods:** This multi-center phase 1/2 trial consisted of dose-escalation stage and dose-expansion stage. In dose-escalation stage, QLC5508 was administered via intravenous infusion at dosage ranging from 0.8 mg/kg to 4.0 mg/kg every two (Q2W) or three weeks (Q3W) in pts with various advanced solid tumors. Then, pts with mCRPC were recruited if they failed or intolerable to standard treatment, including second-generation androgen receptor pathway inhibitors (ARPIs) and/or taxane-based chemotherapy. Dose levels of 1.6 mg/kg Q2W, 2.0 mg/kg Q2W, and 2.4 mg/kg Q3W were selected. The primary endpoints were safety and tolerability. The secondary endpoints were objective response rate (ORR), disease control rate (DCR), and radiological progression-free survival (rPFS) per RECIST v1.1 and PCWG3, and prostate-specific antigen (PSA) response rate. **Results:** As of Nov 30, 2025, 59 pts were enrolled (≥3 lines of prior treatment: 74.6%; ≥3 lines of prior second-generation ARPIs: 28.8%; prior taxane: 84.7%; ≥2 lines of prior taxane: 16.9%). Grade ≥3 treatment-emergent adverse events (TEAEs) with incidence of > 20% were neutrophil count decreased (25.4%), anemia (23.7%), and white blood cell decreased (20.3%). Grade ≥3 gastrointestinal TEAEs occurred in two (3.4%) pts, both unrelated to the treatment. Intestinal lung disease occurred in one (1.7%) patient from 1.6 mg/kg Q2W dose level. TEAEs leading to treatment discontinuation and dose reduction occurred in one (1.7%) and six (10.2%) pts, respectively. The median rPFS was not reached (95% confidence interval [CI], 13.11-not evaluable [NE]), and the 12-month rPFS rate was 71.7% (95% CI, 52.55%-84.26%). In 38 pts at 2.0 mg/kg Q2W dose level, the median rPFS was not reached (95% CI, 13.11-NE), and 12-month rPFS rate was 78.6% (95% CI, 50.67%-91.80%). In 31 pts at 2.0 mg/kg Q2W dose level who had received prior second-generation ARPIs and taxane, the median rPFS was 13.11 months (95% CI, NE-NE). In 31 pts with target lesion at baseline, confirmed ORR and DCR was 22.6% (95% CI, 9.6%-41.1%) and 96.8% (95% CI, 83.3%-99.9%), respectively. Thirteen pts (22.8%) achieved PSA_{50} response. **Conclusions:** QLC5508 showed prolonged rPFS as well as manageable safety profile in heavily treated pts with mCRPC. A phase 3 study is currently being planned. Clinical trial information: NCT07102004. Research Sponsor: Qilu Pharmaceutical Co., Ltd.; Minghui Pharmaceutical.

5047 **Poster Session**

Phase 1, multicenter, open-label study of HSK46575 in patients with metastatic castration-resistant prostate cancer progressing after next-generation hormonal agents and chemotherapy. First Author: Qiang Wei, West China Hospital, Sichuan University, Chengdu, China

Background: The development and progression of prostate cancer are regulated by steroid hormones. HSK46575 Tablet is a novel oral small-molecule inhibitor of cytochrome P450 11A1 (CYP11A1), which can block the production of all downstream steroid hormones and their precursors, thereby reducing the activation of the androgen receptor (AR) signaling pathway and inhibiting tumor progression. Herein, we report the safety and efficacy of HSK46575 in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** This multicenter, open - label Phase I clinical trial had two parts: Phase Ia (dose escalation and expansion) and Phase Ib (dose optimization). Eligible patients were mCRPC patients who failed at least one NHA treatment and either failed, were intolerant to, or refused at least one line of chemotherapy. Phase Ia's dose escalation used a "3 + 3" design to explore four doses (3 mg, 10 mg, 30 mg, 60 mg), and dose expansion was done at 30 mg due to good safety and preliminary efficacy.The primary endpoints were safety and the recommended Phase II dose (RP2D). **Results:** As of November 4, 2025, 27 subjects were enrolled, with a median follow-up of 3.7 months and a median age of 68 years (range: 51-82 years). Among them, 15 (55.6%) had AR ligand -binding domain (AR-LBD) mutations, and 12 (44.4%) had received taxane-based chemotherapy before. No dose-limiting toxicities were observed in any dose group. Treatment-related adverse events (TRAEs) occurred in 18 subjects (66.7%), most of which were Grade 1-2. The most common TRAEs were alanine aminotransferase elevation (18.5%), sinus bradycardia (11.1%), and nausea (11.1%).No adverse events leading to permanent treatment discontinuation or death were observed. Prostate-specific antigen (PSA) assessment was available for 26 subjects, with PSA response rates confirmed after at least 3 weeks. The PSA_{30} and PSA_{50} response rates were 42.3% and 34.6% in the total population, 71.4% and 57.1% in AR-LBD mutant subjects (n = 14), and 75% and 58.3% in the 30 mg dose group with AR-LBD mutations (n = 12). The PSA_{50} response rate was 12.5% (1/8) in the 30 mg dose group with AR-LBD wild-type. Fourteen subjects were eligible for soft tissue assessment, 8 of whom had AR-LBD mutations. One partial response (PR) was seen during treatment in an AR-LBD mutant patient in the 30 mg dose group, leading to an objective response rate (ORR) of 14.3% in this population. . The radiographic progression-free survival (rPFS) has not been reached. The 6-month rPFS rates were 67.5% in the total population and 76.2% in the AR - LBD mutation population. **Conclusions:** HSK46575 shows a manageable safety profile and preliminary antitumor activity, especially in the population with AR - LBD mutations. These findings support further exploration in the mCRPC population. Clinical trial information: NCT07007910. Research Sponsor: None.

5048 **Poster Session**

Integrated clinical and molecular characterization of WNT pathway alterations in metastatic castration-resistant prostate cancer (mCRPC) liver metastases (mets). First Author: Elise Y. Cai, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

Background: mCRPC patients (pts) with liver mets (LM) have an aggressive clinical course and poor response to established treatments. LM frequently exhibit low PSMA expression, limiting the utility of PSMA-targeted therapies. The mechanisms driving hepatic organotropism and therapy resistance in advanced disease are poorly understood. **Methods:** We analyzed metastatic biopsies with matched transcriptional and genomic profiling from 4 independent mCRPC cohorts from the Stand Up To Cancer/Prostate Cancer Foundation (SU2C/PCF) West Coast Dream Team, SU2C/PCF East Coast Dream Team, University of Washington rapid autopsy program, and Weill Cornell Medicine. Tumors were classified by *FOLH1* gene expression tertile and by androgen receptor (AR) and neuroendocrine (NE) gene signature expression. Individual cohorts were assessed for differential gene expression and validated between cohorts. Cohorts were pooled for genomic and survival analyses. Multivariable Cox proportional hazard models were used to assess outcomes. **Results:** 595 mCRPC biopsies were analyzed, comprising 88 (15%) liver, 130 (22%) non-liver visceral, 166 (28%) bone, and 211 (35%) lymph node mets. 54% of pts had prior androgen receptor pathway inhibitor (ARPI) exposure and 29% had prior taxane chemotherapy. LM had lower *FOLH1* expression (log2FC = -1.5, $q < 0.001$) than non-LM. Amongst *FOLH1*-low LM, 32% had elevated NE gene expression, with high histological concordance (80% NE prostate cancer [NEPC], 9% adenocarcinoma with NE features). WNT pathway mutations in *APC* or *CTNNB1* were enriched in LM compared to non-LM (20% vs. 10%, p = 0.01) and *FOLH1*-low compared to *FOLH1*-high mets (16% vs. 6%, p = 0.006). Notably, in *FOLH1*-low LM, *APC* mutations were exclusively found in tumors with low NE gene expression (28% vs. 0%, p = 0.02). In contrast, NE LM were enriched for alterations in *RB1* (71% vs. 15%, $p < 0.001$) and homologous recombination repair genes (41% vs. 15%, p = 0.04). Compared to NE LM, non-NE *FOLH1*-low LM demonstrated persistence of AR signaling, enrichment for inferred ß-catenin transcription factor activity, and upregulation of adaptive metabolic pathways including HIF-1α mediated hypoxia signaling and unfolded protein response. ß-catenin downstream targets including *CCND1, MYC, MSX2, AXIN2,* and *LEF1* were transcriptionally upregulated, while AR targets *STEAP1* and *KLK2* remained highly expressed. In the overall cohort, WNT pathway mutations were associated with shorter treatment duration on first-line ARPI (HR 2.2, 95% CI 1.04-4.8, p = 0.03) and inferior overall survival from start of first-line ARPI (HR 1.7, 95% CI 1.04-2.7, p = 0.03). **Conclusions:** WNT pathway alterations are enriched in a clinically aggressive PSMA-low subset of non-NE mCRPC that maintains luminal markers, suggesting distinct clonal evolution from NEPC and clinical actionability with emerging therapies. Research Sponsor: Prostate Cancer Foundation.

5049 **Poster Session**

Phase I dose-escalation results of ^{177}Lu-NYM032 in patients with progressive metastatic castration-resistant prostate cancer (mCRPC). First Author: Yanjuan Wang, Department of Nuclear Medicine, Affiliated Hospital of Jiangnan University, Wuxi, China

Background: ^{177}Lu-NYM032 is a novel prostate-specific membrane antigen (PSMA)-targeted radioconjugate with optimized properties. Phase I dose-escalation study evaluated its safety, tolerability, pharmacokinetics, radiation dosimetry and preliminary antitumor activity in patients with mCRPC. **Methods:** Eligible patients had PSMA-positive mCRPC confirmed by ^{68}Ga-NYM032 PET/CT, no discordant lesions on ^{18}F-FDG PET/CT, progression after ≥1 AR-targeted therapy and 1–2 prior taxane regimens (or unsuitability/refusal), ECOG 0–2, and no prior radioisotope therapy. A modified 3+3 dose-escalation design was used (^{177}Lu-NYM032: 1.9–7.4 GBq). Pharmacokinetics and dosimetry were evaluated using sequential blood samples and SPECT/CT imaging post-administration (Cycle 1: 2h, 24h, 48h, 7d, 14d; Cycles 2–4: 48h). Primary objectives were safety and maximum tolerated dose (MTD); secondary objectives included pharmacokinetics, dosimetry, and antitumor activity. **Results:** Eleven patients were enrolled across four dose levels: 1.9 GBq (n = 1), 3.7 GBq (n = 4), 5.55 GBq (n = 3), and 7.4 GBq (n = 3). Ten patients completed the study and one patient (3.7GBq) withdrew consent and discontinued the study prior to DLT evaluation. Ten Patients received 2–6 treatment cycles (at 6-week intervals) of ^{177}Lu-NYM032. Four patients were administered up to 6 cycles at 7.4 GBq per cycle, reaching a total cumulative activity of 44 GBq. Treatment was well tolerated; with most treatment-emergent adverse events being grade 1-2. Grade≥3 TEAEs related to ^{177}Lu-NYM032 were limited to anemia, decreased lymphocyte count, and hypokalemia. No dose-limiting toxicities were observed. Clearance of ^{177}Lu-NYM032 from the kidney occurs rapidly (half-life: 18.37-38.66 hours). Physiological distribution of the radiopharmaceutical was observed including in the salivary glands, lacrimal glands, liver, spleen, kidneys, and intestines–consistent with known PSMA expression patterns. While the mean tumor absorption dose (7.73 Gy/GBq in cycle 1) decreased over time, mean absorbed doses per cycle to kidneys and salivary glands remained relatively stable across the administered dose range (1.9-7.4 GBq): kidney doses were 0.47-0.64 Gy/GBq in cycle 1 and 0.42-0.63 Gy/GBq in cycles 2–4; salivary gland doses were 0.42-1.34 Gy/GBq in cycle 1 and 0.43-0.83 Gy/GBq in cycles 2-4. Among 10 evaluable patients, objective response rate was 20% and disease control rate was 80%. Of 3 RECIST v1.1 measurable, 2 (66.7%) partial responded, 1 (33.3%) stable. PSA50 and PSA90 responses were observed in 60.0% and 20.0% of patients, respectively. Median rPFS was 6.5 months; median overall survival was not reached. **Conclusions:** ^{177}Lu-NYM032 demonstrated a favorable safety profile and promising antitumor activity in patients with mCRPC, supporting further evaluation in Phase II studies. Clinical trial information: NCT06383052. Research Sponsor: None.

5050 **Poster Session**

ProTACT: Preliminary data from a first-in-human, phase 1 study evaluating the safety, tolerability, and anti-tumor activity of [^{225}Ac]Ac-FL-020, a PSMA-targeted radioconjugate, in patients with mCRPC. First Author: Alison Yan Zhang, Macquarie University, Sydney, NSW, Australia

Background: [^{225}Ac]Ac-FL-020 is a next-generation, prostate-specific membrane antigen (PSMA) alpha radioconjugate developed using the proprietary UniRDC linker-chelator technology designed to optimize biodistribution. [^{225}Ac]Ac-FL-020 is intended for treating patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and aims to enhance tumor uptake while sparing radiosensitive organs, such as salivary glands, thus potentially leading to an improved therapeutic window. **Methods:** ProTACT (FL-020-001) is a first-in-human, open-label, multicenter Phase 1 study investigating the safety, tolerability, and preliminary anti-tumor activity of [^{225}Ac]Ac-FL-020 in pts with advanced PSMA-positive mCRPC. This study consists of: Bayesian dose escalation (Part 1) and dose expansion (Part 2). Eligible pts must have: histologically confirmed mCRPC, evidence of disease progression, and ≥1 PSMA-positron emission tomography positive lesion (uptake higher than liver). Prior androgen receptor signaling inhibitors or CYP17 inhibitors and ≥1 taxane-based chemotherapy is required, unless declined by the pt. Prior Lu-177 is allowed. Pts with extensive PSMA-negative disease are excluded. Dose cohorts of 1 to 3 pts (for Cohorts 1 and 2) and dose cohorts of 3 to 6 pts (for Cohorts 3+) will evaluate ascending dose levels from 1 to 10 MBq (intravenous; every 6 weeks; x 6 cycles) to determine the maximum tolerated dose and/or recommended Phase 2 dose (RP2D). Once the RP2D is established, 18 additional pts will be enrolled in Part 2 to further assess safety and early signals of efficacy. **Results:** As of 2 Jan 2026, 15 eligible pts have received [^{225}Ac]Ac-FL-020 (maximum dose/cycle: 5 MBq). No dose-limiting toxicities have been observed. Most frequent adverse events (AEs) were fatigue (10 pts), nausea and dry mouth (7 pts each), constipation and anemia (4 pts each). Grade (G)3+ AEs were reported for 6 pts, all G3+ AEs occurred in one pt each. One pt at 1 MBq had G3 anemia and 1 pt at 5 MBq had G3 anemia and G3 thrombocytopenia, both considered related to disease progression with bone marrow infiltration and unrelated to [^{225}Ac]Ac-FL-020. As of the cutoff date, 11 pts remain on treatment and 4 pts discontinued treatment prematurely, 3 due to disease progression and 1 due to G2 dry mouth. Another 6 pts reported dry mouth, all were G1. No renal toxicities or decline in renal function was observed. As of 6 Jan 2026, 1 of 3 pts at 3 MBq showed a reduction in baseline prostate-specific antigen (PSA) > 80% after 3 cycles and 2 of 6 pts at 5 MBq showed a reduction in PSA > 50% after 1 cycle. **Conclusions:** These initial findings support the feasibility and tolerability of [^{225}Ac]Ac-FL-020 administration in heavily pretreated pts with mCRPC with a few notable PSA responses. The RP2D has not yet been reached, and dose escalation continues. Clinical trial information: NCT06492122. Research Sponsor: Full-Life Technologies.

5051 **Poster Session**

Analysis of genomic and clinical predictors of overall survival and PSA response: Results from the PRECISION registry. First Author: Hyotae Kim, Department of Biostatistics & Bioinformatics, Duke University, Durham, NC

Background: Outcomes in advanced prostate cancer vary substantially according to clinical and genomic characteristics among patients with metastatic castration-resistant prostate cancer (mCRPC). We sought to identify predictors of overall survival (OS) and prostate-specific antigen (PSA) response using data from the PRECISION real-world registry of mCRPC patients treated with poly(ADP-ribose) polymerase inhibitors (PARPi). **Methods:** Patient-level data from five centers (Dana Farber Cancer Institute, Thomas Jefferson University, University of British Colombia, University of Washington, Yale University) were aggregated, including demographics, clinical characteristics, genomic alterations, treatments, and clinical outcomes. OS was defined as the time from the first date of PARPi treatment to death or the last date the patient was known to be alive. PSA response was defined as a confirmed ≥50% decline from the PSA level measured closest to the start of PARPi treatment. Ten candidate variables per endpoint were selected via a random forest-based feature selection. Cox models stratified by study were used for OS, and logistic regression models with study included as an additional covariate were used for PSA response. Similarly, non-*BRCA* mutation status was defined as the presence of any observed mutation in genes other than *BRCA*, including *ATM*, *CHEK2*, *MSH2*, *PALB2*, *BRIP1*, and *BARD1*. **Results:** The combined dataset included n = 327 patients, with heterogeneity in baseline characteristics and treatments across studies. The prevalence of *BRCA* (*BRCA1* or *BRCA2*) and non *BRCA* mutations was 39% and 37% respectively. Median OS for patients with *BRCA* mutations was 21 months (95% CI:16–28), compared with 15 months (95% CI: 14–18) for those without *BRCA* mutations. No difference in median OS was observed between patients with and without non-*BRCA* mutations: 16 months (95%CI: 14-22) and 17 months (15-21), respectively. Cox models identified age, N stage, PSMA–lutetium therapy, PARPi use within a clinical trial, prior taxane treatment (docetaxel or cabazitaxel), and *BRCA* as important predictors of OS. The corresponding hazard ratios with 95% confidence intervals are shown in the table below. **Conclusions:** These results from real-world data highlight the importance of incorporating genomic information and treatment-specific variables when predicting outcomes in advanced prostate cancer and demonstrate the utility of multi-study integrative analyses. Research Sponsor: Prostate Cancer Foundation.

Predictor	Hazard Ratio (95% CI)
Age	1.02 (1.01–1.04)
N stage	1.91 (1.18–3.12)
PSMA–lutetium therapy	0.35 (0.20–0.62)
PARPi use (within clinical trial)	0.68 (0.48–0.98)
Prior taxane treatment (docetaxel or cabazitaxel)	1.44 (1.02–2.02)
BRCA mutation	0.50 (0.36–0.69)

5052 **Poster Session**

Association between smoking, tumor genetics, and outcomes in men with metastatic prostate cancer. First Author: Christopher Choi, Duke University Medical Center, Durham, NC

Background: Smoking has been associated with increased metastatic prostate cancer (mPC) mortality, but the mechanisms behind this association are largely unknown. We hypothesized that smoking promotes genetic alterations associated with aggressive disease and/or the transformation to neuroendocrine prostate cancer (NEPC). **Methods:** We utilized the Prostate Cancer Precision Medicine Multi-institutional Collaborative Effort (PROMISE) clinical genomic database for this retrospective analysis. We examined associations between patient characteristics and tumor genetic data with smoking exposure at diagnosis (current, former, never and pack years) and with clinical outcomes, including overall survival (OS) from diagnosis, OS from metastasis, and NEPC status. Patients with unknown smoking status or incomplete/empty/insufficient NGS entries were excluded from analysis. **Results:** We identified 2353 men with mPC and next generation somatic tumor sequencing available for analysis in PROMISE, including 8.1% current, 39.5% former, and 52.4% never smokers. Current smokers were more likely to be younger, present with metastatic (M1 or N1) disease at diagnosis, and were less likely to have prior local therapy (all $p<0.001$). Current smoking was associated with worse OS from diagnosis (99.9 mo in current vs 137 mo in former, and 139.4 mo in never smokers; p=0.008), which remained significant after adjusting for disease characteristics (HR 1.27 95% CI 1.01-1.59). No differences in OS from metastasis were observed for amongst the three groups (current 68.1mo, former 60.3 mo, and never 64.2 mo; p=0.86) We also found no difference in the percentage of NEPC at initial diagnosis or at any time between current, former, and never smokers (p=0.8). However, positive associations were observed between smoking status and genetic alterations in SPOP (current: 15%, former 6.7%, never 3.8%; p= 0.018), FGFR1 (current 10%, former 0.4%, never 1.1% p=0.001), and ARID1A (current 5.1%, former 2.2%, never 0.4%; p=0.035) in mHSPC. No other associations between smoking status and genes of interest were identified. **Conclusions:** Active smoking is associated with worse overall and prostate cancer specific survival as compared to never/former smoking and was associated with specific tumor genetic alterations but not small cell/NEPC transformation. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

Association of tumor genetics with smoking status; alterations detected in hormone sensitive tissue only.

Characteristic	Current N = 39[†]	Former N = 224[†]	Never N = 264[†]	p-value
TP53	17 (44%)	79 (35%)	100 (38%)	0.58
RB1	3 (7.7%)	11 (4.9%)	17 (6.4%)	0.59
PTEN	8 (21%)	55 (25%)	60 (23%)	0.81
BRCA2	8 (21%)	20 (8.9%)	35 (13%)	0.07
MYC	3 (7.7%)	18 (8.0%)	11 (4.2%)	0.15
SPOP	6 (15%)	15 (6.7%)	10 (3.8%)	0.02
FGFR1	4 (10%)	1 (0.4%)	3 (1.1%)	0.001
ARID1A	2 (5.1%)	5 (2.2%)	1 (0.4%)	0.04
PIK3CA	2 (5.1%)	9 (4.0%)	13 (4.9%)	0.80

[†]n (%).

5053 Poster Session

Regional disparities in prostate cancer mortality in the African Union: A retrospective analysis (1980-2023). First Author: Abubakar Nazir, King Edwards Medical University, Mayo Hospital, Lahore, Pakistan

Background: Prostate cancer represents a substantial health burden among men in Africa and is an important contributor to cancer-related mortality, with considerable variation observed across African regions. This study uses data from the Global Burden of Disease (GBD) project to evaluate regional variations in prostate cancer age-standardized death rates (ASDR) from 1980 to 2023. **Methods:** Prostate cancer mortality data were extracted from the GBD 2023 database for the period 1980–2023. Age-standardized death rates (ASDRs) per 100,000 population were obtained for African regions as defined by the GBD classification, including Northern Africa, Central Africa, Eastern Africa, Western Africa, Southern Africa and the African Union aggregate. Temporal patterns from 1980 to 2023 were evaluated using joinpoint regression analysis, and average annual percentage change (AAPC) estimates were calculated to quantify long-term trends. Statistical significance was determined using corresponding p-values (less than 0.05) and 95% confidence intervals. **Results:** From 1980 to 2023, a gradual rise in the ASDR per 100,000 was observed in the African Union with substantial regional variations. It gradually increased from 8.78 per 100,000 in 1980 to 11.44 per 100,000 in 2023 (AAPC: 0.68; 95% CI: 0.51 to 0.84; $p < 0.000001$). The highest ASDR were observed in Central Africa. It increased from 13.72 per 100,000 in 1980 to 18.63 per 100,000 in 2023 (AAPC: 0.77; 95% CI: 0.62 to 0.91; $p < 0.000001$). This was followed by Western Africa increasing from 10.64 per 100,000 in 1980 to 16.06 per 100,000 in 2023 (AAPC: 0.96; 95% CI: 0.82 to 1.09; $p < 0.000001$). A slight increase was also observed in Southern Africa rising from 10.70 in 1980 to 12.07 (AAPC: 0.26; 95% CI: -0.0045 to 0.543; $p < 0.053$). Eastern Africa showed a slight increase in ASDR from 8.95 per 100,000 in 1980 to 10.36 per 100,000 in 2023 (AAPC: 0.43; 95% CI: 0.24 to 0.62; $p < 0.000009$). Northern Africa had consistently the lowest ASDR. It rose from 2.35 per 100,000 in 1980 to 4.32 per 100,000 in 2023 (AAPC: 1.41; 95% CI: 1.27 to 1.56; $p < 0.000001$). **Conclusions:** Prostate cancer remains the leading cause of cancer-related death among men in the African Union, particularly in Central Africa. High mortality is driven by limited healthcare access and late-stage diagnosis. Strengthening screening programs and improving specialized care can reduce this rising burden. Research Sponsor: None.

Trends in age standardized death rate (ASDR) per 100,000 due to prostate cancer in the African Union.

Region	ASDR 1980 (per 100,000)	ASDR 2023 (per 100,000)	AAPC (95% CI)
African Union	8.79	11.45	0.68* (0.51 - 0.84)
Central Africa	13.72	18.63	0.77* (0.62 - 0.92)
Eastern Africa	8.95	10.36	0.44* (0.24 - 0.63)
Northern Africa	2.35	4.33	1.42* (1.27 - 1.57)
Southern Africa	10.70	12.08	0.26* (-0.01 -0.54)
Western Africa	10.64	16.06	0.96* (0.82 - 1.10)

AAPC = Average Annual Percentage Change; *$p < 0.05$.

5054 Poster Session

Impact of prior treatment setting on the efficacy of rucaparib vs physician's choice in *BRCA*-mutated castration-resistant prostate cancer (mCRPC) in TRITON3. First Author: Srikala S. Sridhar, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Rucaparib significantly improved radiographic progression-free survival (rPFS) versus physician's choice of docetaxel or an androgen-receptor pathway inhibitor (ARPI) (abiraterone or enzalutamide) in men with BRCA mutations who were chemotherapy-naïve in the mCRPC setting and had received one prior ARPI in the phase 3 TRITON3 trial (NCT02975934). This post-hoc analysis evaluated whether the timing of prior ARPI therapy impacted the efficacy of rucaparib. **Methods:** Patients were randomized 2:1 to rucaparib (600 mg BID) or physician's choice of docetaxel or ARPI, after progression on 1 prior second-generation ARPI in any setting. The primary endpoint was rPFS. Outcomes were analyzed according to whether patients received the prior ARPI in the metastatic castration sensitive (mCSPC) or castration resistant (mCRPC) setting. Data cutoff was August 25, 2022. **Results:** Of the 302 BRCA1/2 patients, 68 received prior ARPI in the mCSPC setting (42 rucaparib; 26 physician's choice) and 234 in the mCRPC setting (159 rucaparib; 75 physician's choice). Baseline characteristics were generally similar. Prior treatments in the mCSPC and mCRPC groups, respectively, included abiraterone (73.5% vs 53.0%), enzalutamide (29.4% vs 48.3%), and docetaxel (17.6% vs 24.8%). Median rPFS favored rucaparib over physician's choice in both groups (mCSPC: 13.6 vs 8.2 months; HR 0.60 [95% CI, 0.32–1.15]; mCRPC: 11.2 vs 5.8 months; HR 0.43 [95% CI, 0.30–0.61]). Median OS was similar between treatments in both settings (mCSPC: 23.2 vs 21.7 months; HR 0.81 [95% CI, 0.47–1.41]; mCRPC: 23.2 vs 21.0 months; HR 0.91 [95% CI, 0.66–1.25]). Treatment-related adverse events occurred at comparable rates (89.6% vs 86.1%). **Conclusions:** Rucaparib demonstrated efficacy in patients with BRCA-mutated mCRPC, regardless of whether prior ARPI was administered in the mCSPC or mCRPC setting. Clinical trial information: NCT02975934. Research Sponsor: Clovis Oncology and pharmaand GmbH.

5055 Poster Session

Phase 1b/2 study of pembrolizumab plus lenvatinib or pembrolizumab coformulated with vibostolimab in participants (pts) with metastatic neuroendocrine prostate cancer (NEPC): KEYNOTE-365 cohorts F and H. First Author: Gunhild Von Amsberg, University Medical Center Hamburg-Eppendorf; Martini Clinic, Hamburg, Germany

Background: Effective therapy for NEPC is an unmet need due to poor prognosis and no established standard of care. The phase 1b/2 KEYNOTE-365 study (NCT02861573) evaluated the efficacy and safety of pembrolizumab (pembro) + lenvatinib (lenva; cohort F) or coformulated pembro/vibostolimab (vibo; cohort H) in pts with NEPC. **Methods:** Pts with pathologically confirmed treatment-emergent neuroendocrine (t-NE) or de novo metastatic NEPC (small cell carcinoma, large cell neuroendocrine carcinoma, or mixed morphology per central review), progression ≤6 mo before screening, and an ECOG PS of 0 or 1 were enrolled. Prior androgen deprivation therapy for metastatic disease was required for pts with t-NE. Prior chemotherapy regimens (≤2) for metastatic castration-resistant prostate cancer and second-generation hormonal agents (≤2) were permitted. Pts in cohort F received pembro 200 mg IV Q3W + lenva 20 mg PO QD. Pts in cohort H received pembro/vibo 200 mg/200 mg IV Q3W. Pembro or pembro/vibo were given for ≤35 cycles; lenva was given until discontinuation criteria were met. Primary end points were safety, ORR per RECIST v1.1 by blinded independent central review (BICR), and confirmed prostate-specific antigen (PSA) response rate (≥50% decrease from baseline measured twice ≥3 weeks apart). Secondary end points included ORR, time to PSA progression, radiographic PFS (rPFS) per Prostate Cancer Working Group 3 (PCWG3)–modified RECIST (mRECIST) v1.1 by BICR, DOR and DCR per RECIST v1.1 by BICR, and OS. **Results:** As of August 25, 2025, 14 and 20 pts received ≥1 dose of study treatment in cohort F or cohort H, respectively. Median follow-up was 25.6 mo (range, 22.9-35.1) and 31.4 mo (range, 23.2-45.9), respectively. Among pts with RECIST-measurable disease, confirmed ORR was 23.1% (3/13; 95% CI, 5.0-53.8) in cohort F and 12.5% (2/16; 95% CI, 1.6-38.3) in cohort H. Additional efficacy results are shown in the table. Treatment-related adverse events (TRAEs) occurred in 85.7% of pts in cohort F (64.3% grade 3 or 4) and 55.0% of pts in cohort H (25.0% grade 3 or 4). No grade 5 TRAEs occurred in either cohort. In cohorts F and H, TRAEs resulted in treatment discontinuation in 21.4% and 10.0% of pts, respectively, and immune-mediated AEs occurred in 35.7% and 15.0%. **Conclusions:** Pembro + lenva or pembro/vibo had a manageable safety profile and only modest antitumor activity in pts with NEPC. Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	Cohort F n = 14	Cohort H n = 20
PSA response rate (95% CI), %	14.3 (1.8-42.8)	10.0 (1.2-31.7)
Median time to PSA progression (95% CI), mo	NR (NR-NR)	NR (2.9-NR)
ORR per mRECIST v1.1 (95% CI), %	15.4 (1.9-45.4)	12.5 (1.6-38.3)
DCR per RECIST v1.1 (95% CI), %	23.1 (5.0-53.8)	12.5 (1.6-38.3)
Median DOR per RECIST 1.1 (95% CI), mo	NR (1.1-NR)	NR (8.3-NR)
Median rPFS per mRECIST v1.1 (95% CI), mo	3.9 (2.1-NR)	2.0 (1.6-4.3)
Median OS (95% CI), mo	4.3 (2.8-NR)	7.0 (2.5-12.9)

5056 Poster Session

Can TGF-β inhibition (galunisertib) enhance response to enzalutamide in metastatic castration-resistant prostate cancer (mCRPC)?: Results from a randomized phase II trial. First Author: Nicole Metri, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, Baltimore, MD

Background: Resistance to androgen receptor (AR)-directed therapies is a major challenge in advanced prostate cancer, and enzalutamide shows limited activity after progression on abiraterone. Aberrant transforming growth factor-β (TGF-β) signaling promotes prostate cancer progression and contributes to resistance to AR-directed therapies. Preclinical studies suggest TGF-β inhibition may overcome resistance to enzalutamide. We hypothesized that combining TGF-β receptor I kinase inhibitor, galunisertib, with enzalutamide may delay enzalutamide resistance in patients with mCRPC who have progressed on abiraterone. **Methods:** This multicenter, randomized phase II trial enrolled chemotherapy-naïve mCRPC patients with disease progression on abiraterone. There was a cycle 1 safety run-in for the first 6 patients, followed by a randomized phase with patients assigned 3:2 to receive galunisertib plus enzalutamide or enzalutamide alone. The primary endpoint was radiographic progression-free survival (rPFS). Secondary endpoints included PSA response, overall survival (OS), safety, and tolerability. rPFS and OS were compared between arms using Cox regression, with medians estimated by Kaplan-Meier method. **Results:** Of 61 patients randomized, 60 received treatment: 23 with enzalutamide and 37 with galunisertib plus enzalutamide. There was no significant difference in rPFS between the combination and enzalutamide arms (HR 1.23; 95% CI: 0.72, 2.11; p=0.44), with a median rPFS of 5.6 and 7.3 months, respectively. The OS was also similar between the two groups (HR 1.00; 95% CI: 0.55, 1.83, p=1.00), with a median OS of 21.6 months in the combination arm and 24 months in the enzalutamide arm. PSA30 response was seen in 22% of patients in the combination arm vs. 35% in the enzalutamide arm (p=0.30), and PSA50 response in 19% vs. 26%, respectively (p=0.50). The most common treatment-related adverse events (AEs) were fatigue, anorexia, and nausea. Grade 3-4 treatment-related AEs occurred in 11% of patients in the combination arm vs. 13% in the enzalutamide arm. **Conclusions:** The addition of galunisertib to enzalutamide did not improve the rPFS, OS, or PSA response compared to enzalutamide alone in patients with chemotherapy-naïve mCRPC with disease progression on abiraterone. These findings do not support further development of galunisertib plus enzalutamide in patients with mCRPC. Clinical trial information: NCT02452008. Research Sponsor: Department of Defense/CDMRP; W81XWH-22-2-0024; Eli Lilly and Company; National Cancer Institute; P30CA006973; National Cancer Institute; K23CA197526.

Baseline characteristics of randomized patients.

	N (n=61)	Enzalutamide (n=24)	Galunisertib + Enzalutamide (n=37)	*P*
Age, median (range)	51	72 (57, 84)	68 (53, 85)	0.06
Race, n (%)	58			1.00
White		17 (81.0)	30 (81.1)	
Other		4 (19.0)	7 (18.9)	
Ethnicity, n (%)	60			0.66
Hispanic		0 (0.0)	2 (5.4)	
Non-Hispanic		21 (91.3)	33 (89.2)	
Unknown		2 (8.7)	2 (5.4)	
ECOG, n (%)	55			0.16
0		12 (54.5)	24 (72.7)	
1		10 (45.5)	9 (27.3)	
Baseline PSA, median (range)	60	11.1 (1.0, 2151.3)	18.2 (0.2, 522.4)	0.51

5057 **Poster Session**

A randomized phase Ib/II study of enzalutamide (Enza) with and without ribociclib (Rib) in patients with metastatic castrate-resistant prostate cancer (mCRPC) that retains RB expression: RiboX study. First Author: Kevin Kayvan Zarrabi, Thomas Jefferson University, Philadelphia, PA

Background: RB function is often attenuated in tumors through hyperphosphorylation; thus, RB activity can be "re-awakened" in RB+ tumors by suppressing key kinases that phosphorylate RB (CDK4/6). We report a phase Ib/II trial to determine the safety, tolerability and antitumor activity rib with enza in patients (pts) with mCRPC (NCT02555189). **Methods:** RiboX was a multicenter, phase Ib/II, open label trial which enrolled taxane-naïve pts with progression to mCRPC and retained RB expression. For phase Ib, a traditional 3x3 dose-escalation was used to establish the RP2D for the phase II portion. Pts received rib at 200, 400 or 600mg once daily (QD) Days (D) 1-21 in combination with fixed dose enza (160mg QD D1-28). In phase II, pts were randomized 1:1 to enza monotherapy (Arm A) or enza + rib (Arm B). The study was later modified to a single arm Simon two-stage design using the RP2D of 600mg rib with 160mg enza. The primary phase II endpoint was the proportion of pts a PSA50 response at 12 weeks. The null hypothesis was that the PSA50 response was ≤78% and 31 responses were required to reject the null hypothesis. Secondary endpoints were rPFS, PSA PFS, OS and safety. **Results:** 12 pts were enrolled in the phase Ib portion across three dose levels upon confirmation of RB expression on tumor biopsy. No DLTs were observed in dose-escalation and the RP2D was established at rib 600mg QD D 1-21 + enza 160mg QD D 1-28. The phase II portion included 12 pts treated with enza mono; 28 phase II pts and 6 phase 1b pts yielded 34 pts treated with combination at RP2D. The PSA50 response at 12 weeks was 75% (95% CI, 43-95) for enza mono and 82% (95% CI, 65-93) for the combination, failing to reject the null hypothesis. Median rPFS for evaluable pts was 10.9 mo (95% CI, 2.5-45.9) for enza mono (n = 12) and 27.0 mo (95% CI, 11.3-37.0) for combination (n = 30). PSA PFS was 10.1 months (95% CI, 1.8-33.1) for enza mono (n = 12) and 14.8 mo (95% CI, 6.7-35.9) for combination (n = 34). OS was 31.2 mo (95% CI, 15.0-NA) for enza mono (n = 12) and 58.1 mo (95% CI, 33.4-NA) for combination (n = 34). Four pts treated with combination were included for PSA PFS but did not have data for rPFS. Among pts treated at RP2D in the combination arm, the most common TEAE's included fatigue 59%, nausea 26.9%, neutropenia 26.7% (grade 3, 12%), diarrhea 20.9%, dizziness 14.7%, arrhythmia 2.9%, seizure 2.9%. **Conclusions:** The combination of enza + rib was well tolerated; however, no significant difference in PSA50 response was observed, and the primary endpoint was not met. A disease-stabilizing effect was observed in a subset of patients treated with the enza + rib combination, with evidence of prolonged survival. Further investigation into this disease-stabilizing effect and refinement of patient selection criteria beyond RB expression may be warranted. Funding: Novartis Pharmaceuticals and DOD (W81XWH-22-2-0020). Clinical trial information: NCT02555189. Research Sponsor: Novartis.

5058 **Poster Session**

Belzutifan in docetaxel-pretreated metastatic castration-resistant prostate cancer (mCRPC): Phase 1b/2 KEYNOTE-365 cohort J. First Author: Jose Angel Arranz Arija, Gregorio Marañón General University Hospital, Madrid, Spain

Background: Hypoxia-inducible factor 2α (HIF-2α) is an established oncogenic driver, and HIF-2α expression in prostate cancer is positively correlated with aggressive disease. Belzutifan is a selective HIF-2α inhibitor approved for use in clear cell renal cell carcinoma. Cohort J of the multicohort, phase 1b/2 KEYNOTE-365 study (NCT02861573) evaluated the safety and efficacy of belzutifan in participants (pts) with mCRPC. **Methods:** Eligible adults had histologically or cytologically confirmed adenocarcinoma of the prostate without small cell histology, had an Eastern Cooperative Oncology Group performance status score of 0 or 1, and had received prior docetaxel for mCRPC. Prior treatment with 1 other chemotherapy and ≤2 second-generation hormonal agents were allowed. Pts received oral belzutifan 120 mg daily. Primary end points were safety and tolerability, prostate-specific antigen (PSA) response rate (PSA decline ≥50%), and objective response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR). Secondary end points included time to PSA progression, ORR, and radiographic progression-free survival (rPFS) per PCWG3-modified RECIST v1.1, duration of response and disease control rate (DCR; complete response + partial response + stable disease ≥6 mo) per RECIST v1.1 and PCWG3-modified RECIST v1.1 by BICR, and overall survival (OS). **Results:** A total of 21 pts were allocated to receive belzutifan. Median age was 69.0 y (range, 56-84). Median study follow-up was 17.6 mo (range, 15.9-21.8). All pts discontinued treatment as of the data cutoff (August 25, 2025), most commonly due to progressive disease (n = 12; 57%). Median duration of belzutifan therapy was 2.8 mo (range, 0.7-8.7). Treatment-related adverse events (AEs) occurred in 20 pts (95%); grade 3 or 4 treatment-related AEs occurred in 11 pts (52%), most commonly anemia (n = 8; 38%). A total of 2 pts (10%) discontinued treatment, and no pts died due to treatment-related AEs. Among pts with a baseline PSA measurement (n = 20), PSA response rate was 0% (95% CI, 0-17) and median time to PSA progression was 3.0 mo (95% CI, 2.8-not reached [NR]). Among 12 pts with RECIST-measurable disease, ORR and DCR per RECIST v1.1 were both 0%; ORR and DCR per PCWG3-modified RECIST v1.1 were 0% and 8%, respectively. In all pts, median rPFS was 3.7 mo (95% CI, 1.9-NR) and median OS was 16.9 mo (95% CI, 10.8-NR). **Conclusions:** In cohort J of the KEYNOTE-365 trial, belzutifan monotherapy had a manageable safety profile but did not show meaningful antitumor activity in mCRPC. Future research is needed to determine effective treatments for pts with mCRPC. Clinical trial information: NCT02861573. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

5059 **Poster Session**

Utidelone in heavily pretreated metastatic castration-resistant prostate cancer progressing after docetaxel and novel hormonal agents: Results of a completed phase II trial. First Author: Meiting Chen, Department of Medical Oncology, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Patients with metastatic castration-resistant prostate cancer (mCRPC) who have progressed after both docetaxel and novel hormonal agents (including abiraterone and/or androgen receptor pathway inhibitors [ARPIs]) have a poor prognosis with limited treatment options. This study aimed to evaluate the efficacy and safety of utidelone, a genetically engineered epothilone analogue with antitumor activity in taxane-resistant cancers, in these patients. **Methods:** In this prospective, single-arm, phase II clinical trial, eligible male patients were aged 18 to 75 years with mCRPC who had progressed on docetaxel and at least one prior ARPI or abiraterone. Patients received utidelone monotherapy (30 mg/m²/day intravenously for 5 days, every 3 weeks) until progression, intolerable toxicity, or death. Recruitment has been completed with 43 patients enrolled at Sun Yat-sen University Cancer Center from March 23, 2022, to December 10, 2025. The primary endpoint was prostate specific antigen (PSA) response rate, defined as a 50% or greater reduction in serum PSA. Secondary endpoints included radiographic progression-free survival (rPFS) according to PCWG3 criteria, OS, and safety. **Results:** Analysis was performed on the full cohort. The median age was 66 years, and patients had received a median of 4.0 (range, 2-8) prior lines of treatment. All patients were pre-treated with docetaxel and 97.7% with abiraterone; 90.7% patients had progressed after ARPI, and 14.0% after radionuclide therapy. Visceral metastases were present in 32.6% patients, and 67.4% had de novo metastatic disease. Among 28 patients with available genetic data, BRCA1/2 mutations were identified in 3 (10.7%). By the data cut-off (January 4, 2026), the PSA50 response rate (≥50% decline) was 23.3%, and 32.6% of patients achieved a PSA30 response (≥30% decline). The median rPFS was 6.7 months, and median OS was 11.4 months. Most of the treatment-related adverse events (TRAEs) were grade 1 or 2 and were considered manageable. Grade 3/4 TRAEs consisted of anemia (14.0%), peripheral sensory neuropathy (2.3%), vomiting (2.3%), and diarrhea (2.3%). No treatment-related deaths occurred. **Conclusions:** Utidelone monotherapy exhibits promising antitumor activity and manageable safety profile in heavily pretreated mCRPC patients, including those who have progressed on ARPIs, abiraterone, and docetaxel. The study results support further investigation of this regimen. Clinical trial information: ChiCTR2200061635. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

5060 **Poster Session**

Rad2Nivo: Phase IB study of radium-223 (Rad) with nivolumab (Nivo) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). First Author: Georges Gebrael, Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT

Background: Rad is an α-emitting calcium-mimetic radiopharmaceutical that is FDA approved for pts with mCRPC with symptomatic bone metastasis (mets) and no visceral mets. Preclinical data suggest that radiation might enhance the anticancer effect from PD-1 therapy [PMID 25274032, 29137877]. Nivo is a PD-1 immune checkpoint antagonist. Few pts experience PSA reduction with Rad, and objective responses in bone mets cannot be assessed. We hypothesized that Rad+Nivo would be safe and result in decreased ctDNA variant allele frequency (VAF) as a marker of clinical efficacy. **Methods:** In this phase IB, prospective, open-label, single-center, single-arm study (NCT04109729), pts with symptomatic bone-metastatic mCRPC without visceral mets were eligible. Participants received intravenous Rad (55 kBq/kg IV) monotherapy for 6 cycles. Nivo (480mg IV) was introduced starting with cycle 3 and continued for up to 2 years. ctDNA collected at baseline, cycle 3 and 6 weeks after. Primary endpoints: (1) frequency of grade ≥3 non-hematologic treatment-emergent adverse events (TEAEs) and (2) change in ctDNA VAF from baseline compared to after 6 weeks of nivolumab therapy. Mean VAF was defined as average VAF of all somatic mutations present at baseline at a VAF 1%. Null hypothesis: proportion of pts with a non-zero ctDNA reduction is ≤ 20%. A one-sided exact binomial test was used to evaluate whether the proportion of pts demonstrating a decrease in mean VAF on-treatment exceeded 20%. With 36 pts, there will be 83% power at one-sided $\alpha = 0.05$ to detect an alternative proportion of subjects with ctDNA reduction = 40%. **Results:** Overall, 39 pts were enrolled trial between 9/2020 and 1/2025, and 35 pts were treated with both Rad+Nivo. Median age was 71 years (54-84), median PSA at study entry was 13.9 ng/dL (0-3245). 22 pts (56.4%) had Gleason score ≥8 (unavailable for 3 pts). Median number of prior lines of therapy was 3 (1-7). 53.9% (n = 21) of pts had received prior chemotherapy. 61% (n = 24) of pts completed 6 doses of Rad (range 2-6). The median number of Nivo cycles was 4 (0-25). Dose holds or delays occurred in 26% (n = 10) and 31% (n = 12) of pts receiving Rad and Nivo, respectively. 38% (n = 15) of pts experienced at least one grade 3-5 TEAE regardless of attribution. Grade 3-4 TEAE related to Rad and Nivo occurred in 15% (n = 6) and 18% (n = 7) of pts, respectively. No dose-limiting toxicities were observed. Serious adverse events related to Rad and Nivo occurred in 5% (n = 2) and 2.6% (n = 1) of pts, respectively. Paired molecular data was available for 25 pts. VAF was measurable in all patients who had samples collected and reduction was observed in 15 of 25 pts (60%, one-sided 95% CI, 41.7%-100%; $p < 0.01$). **Conclusions:** The study met its primary endpoints. Rad+Nivo appears to be safe and VAF was decreased in 60% of patients tested. Survival outcomes and clinical correlation data with VAF will be presented at the meeting. Clinical trial information: NCT04109729. Research Sponsor: Bristol Myers Squibb.

5061 **Poster Session**

Mortality trends and disparities in prostate cancer with co-occurring cardiometabolic disorders among U.S. men aged ≥ 55 years, 1999–2024. First Author: Mian Muinuddin Jamshed, Aga Khan University Hospital, Karachi, Pakistan

Background: Prostate cancer (PCa) survivors are at significant risk for cardiometabolic disorders (CMD) including hypertension, diabetes, and cerebrovascular diseases which often act as competing causes of death. While PCa survival with CMD has improved but trends in deaths remain poorly characterized across demographic and geographic strata. This study evaluates longitudinal trends to identify success in management and remaining inequities in men aged ≥ 55. **Methods:** We analyzed U.S. mortality data (1999–2024) from the CDC WONDER database for men aged ≥ 55 years with PCa as the underlying cause of death (UCOD) and CMD as the multiple cause of death (MCOD). Age-adjusted mortality rates (AAMR) per 100,000 and joinpoint regression were used to estimate Annual Percent Change (APC) and Average Annual Percent Change (AAPC). Stratified analyses were performed by race, census region, and urbanization. **Results:** A total of 151,108 deaths were identified (cumulative AAMR: 18.78). Overall mortality demonstrated a significant declining trend (1999–2024; AAPC: -2.48%, $p < 0.001$). Significant declines were observed across all racial groups. Black or African American men experienced the highest mortality burden but also the most rapid decline (AAPC: -6.01%, $p < 0.001$), narrowing the gap with White men (AAPC: -4.33%, $p < 0.001$). While all regions showed improvement, the Southern U.S. demonstrated the slowest rate of decline (AAPC: -4.13%, $p < 0.001$) compared to the Northeast, which saw the most substantial reduction (AAPC: -5.76%, $p < 0.001$). Recent trends (2019–2024) showed sharp decreases across regions, including the South (APC: -11.28%, p = 0.002). Declines were consistent across the rural-urban continuum. Micropolitan (non-metropolitan) areas showed a significant overall decline (AAPC: -1.72%, $p < 0.001$). However, segments of transient increase were noted between 2015–2020 in Medium Metro (APC: +3.77%, p = 0.004) and Large Fringe Metro (APC: +3.55%, p = 0.005) areas before resuming a downward trend. **Conclusions:** Mortality for prostate cancer with contributing cardiometabolic causes is significantly decreasing among U.S. men aged ≥ 55. The accelerated decline among Black men and in the Northeast reflects improvements in integrated oncological and cardiovascular care. However, the slower decline in the South and transient increases in specific metropolitan areas underscore the necessity for targeted cardio-oncology interventions. Continued focus on equitable access to cardiometabolic risk management is vital to sustaining these positive trends and eliminating geographic and racial disparities in PCa survivorship. Research Sponsor: None.

5062 **Poster Session**

Efficacy, safety, and quality of life outcomes of 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer: A GRADE-assessed systematic review, meta-analysis, and trial sequential analysis of randomized controlled trials. First Author: Moosa Mubarika, Nishtar, Multan, Pakistan

Background: 177Lu-PSMA-617 radioligand therapy (RLT) offers a targeted approach for metastatic castration-resistant prostate cancer (mCRPC). However, its consolidated impact on survival, patient-reported outcomes, and safety requires rigorous validation. We conducted a systematic review, meta-analysis, and trial sequential analysis (TSA) to evaluate the robustness of evidence regarding efficacy, toxicity, and quality of life (QoL). **Methods:** We systematically searched PubMed, Cochrane, and Embase for prospective randomized controlled trials (RCTs) comparing 177Lu-PSMA-617 versus standard-of-care (SOC) in mCRPC. Primary outcomes included overall survival (OS), radiographic progression-free survival (rPFS), and PSA response. Secondary outcomes included QoL (FACT-P scores, pain intensity) and adverse events (AEs). TSA was performed to assess the conclusiveness of the cumulative evidence. Data were pooled using a random-effects model. **Results:** Six prospective RCTs comprising 2,113 patients (1,263 Lu-PSMA; 850 SOC) were included. Lu-PSMA significantly improved overall survival (HR 0.76; P = 0.02) and radiographic progression-free survival (HR 0.55; $P < 0.00001$) compared to SOC. QoL metrics significantly favored Lu-PSMA, including mean difference in QoL scores (MD 2.93; $P < 0.00001$), time to deterioration of FACT-P (RR 0.58; $P < 0.00001$), and worsening of pain intensity (OR 0.61; P = 0.002). TSA demonstrated conclusive evidence for PSA response (RR 2.33; P = 0.001), as the Z-curve crossed the monitoring boundary. However, TSA for ORR and PFS remained inconclusive despite favorable point estimates. Regarding safety, Lu-PSMA was associated with higher risks of Grade 1-2 dry mouth (RR 9.75), Grade ≥3 thrombocytopenia (RR 6.20), and Grade 1-2 dry eyes (RR 6.66). **Conclusions:** 177Lu-PSMA-617 demonstrates a significant survival benefit and conclusively improves PSA response rates in mCRPC. Crucially, it preserves quality of life by delaying the deterioration of physical function and pain. While effective, the therapy carries specific toxicity risks, notably xerostomia and high-grade thrombocytopenia, necessitating careful patient monitoring. Research Sponsor: None.

Outcome	Effect Estimate (95% CI)	P-Value	I^2	TSA Status
Overall Survival	HR 0.76 (0.59–0.96)	0.02	68%	-
Radiographic PFS	HR 0.55 (0.43–0.71)	<0.00001	67%	Inconclusive
PSA Response Rate	RR 2.33 (1.38–3.93)	0.001	93%	Conclusive
Objective Response Rate	RR 2.94 (1.55–5.55)	0.0009	72%	Inconclusive
Quality of Life (MD)	MD 2.93 (1.80–4.07)	<0.00001	20%	-
Time to Det. FACT-P	RR 0.58 (0.51–0.66)	<0.00001	0%	-
Worsening Pain Score	OR 0.61 (0.44–0.84)	0.002	81%	-
Dry Mouth (Grade 1-2)	RR 9.75 (6.85–13.88)	<0.00001	91%	-
Thrombocytopenia (G≥3)	RR 6.20 (2.18–17.65)	0.0006	0%	-
Dry Eyes (Grade 1-2)	RR 6.66 (2.79–15.91)	<0.0001	0%	-

5063 **Poster Session**

A phase I study of [225Ac]Ac-PSMA-XT, a novel alpha-particle–emitting radioligand therapy, in patients with metastatic castration-resistant prostate cancer. First Author: Xiaorong Sun, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Ji'Nan, China

Background: Targeted alpha therapy (TAT) is an emerging modality for metastatic castration-resistant prostate cancer (mCRPC), offering the potential for precise tumor cell eradication with limited off-target exposure. [225Ac]Ac-PSMA-XT (XT381) is a PSMA-targeted alpha-emitting radiopharmaceutical designed to deliver high linear energy transfer radiation. This single-center, open-label Phase I study (NCT07135102) in China aims to assess the safety, tolerability, and preliminary efficacy of [225Ac]Ac-PSMA-XT in heavily pretreated mCRPC. **Methods:** Patients with PSMA-positive mCRPC (confirmed by THERP trial criteria, ≥1 lesion with SUV_{max}> 20 on PSMA PET/CT imaging, and all measurable lesions with SUV_{max} > liver SUV_{mean}) who progressed after ≥1 line of androgen receptor pathway inhibitor were enrolled. A standard "3 + 3" design was used across five dose levels (25, 50, 75, 100 and 125 kBq/kg), with up to 6 cycles administered every 6 weeks. Primary endpoints were safety/tolerability (CTCAE v5.0). Key secondary endpoints inclued PSA50 response (≥50% decline), radiographic progression-free survival (rPFS), objective response rate (ORR) by RECIST 1.1, and disease control rate (DCR). Enrollment has completed through the 75 kBq/kg cohort, the 100 kBq/kg cohort is ongoing. **Results:** As of December 12, 2025, 12 paitents were dosed (cohorts 25-100 kBq/kg, n = 3 each). All patients received at least one dose of [225Ac]Ac-PSMA-XT. No dose-limiting toxicities have been observed. Grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 2 patients. The most common TRAEs were xerostomia and grade 1-2 hematologic toxicities, including anemia (55.6%, 5/9), leukopenia (44.4%, 4/9), lymphopenia (22.2%, 2/9), neutropenia (11.1%, 1/9), and thrombocytopenia (11.1%, 1/9). Among 9 evaluable patients (≥6 weeks follow-up), 7 (77.8%) achieved a PSA50 response, and 4 (44.4%) achieved a PSA90 response. The 6-month progression-free survival (PFS) rate was 71.4 (5/7). In 5 patients with RECIST-measurable disease, ORR was 60% (3 partial responses). Overall DCR was 67%. **Conclusions:** [225Ac]Ac-PSMA-XT shows a favorable and manageable safety profile with no DLTs observed up to 100 kBq/kg. Early efficacy signals are highly encouraging, with deep PSA declines and durable disease control observed in this heavily pretreated mCRPC population. These data support continued dose escalation and further development of this alpha-emitting PSMA-targeted therapy. Clinical trial information: NCT07135102. Research Sponsor: Beijing Sinotau International Pharmaceutical Technology Co. Ltd.

5064 **Poster Session**

Genomic biomarkers of sensitivity to bipolar androgen therapy (BAT) in metastatic castration-resistant prostate cancer (mCRPC). First Author: Diogo Assed Bastos, Hospital Sírio-Libanês, São Paulo, Brazil

Background: In most cases, mCRPC remains driven by persistent androgen receptor (AR)-signaling. BAT has shown benefit in a subset of patients (pts) with mCRPC through multiple mechanisms of action, including modulation of AR activity, induction of DNA double-strand breaks and cell cycle arrest. There is a need for predictive biomarkers to identify patients most likely to benefit from BAT. **Methods:** This retrospective multicenter study included pts with mCRPC treated with BAT who had undergone tumor genomic profiling up to one month prior to BAT initiation. Somatic alterations were correlated with PSA50 response rates (≥50% decline in PSA from baseline), time to treatment failure (TTF) and overall survival (OS). PSA50 associations were assessed using Fisher's exact test and logistic regression. Time-to-event outcomes were analyzed using Kaplan–Meier and Cox models. Independent predictors were evaluated using multivariable logistic regression and Cox models. **Results:** We identified 104 pts for inclusion. The median age was 72 years and 49.4% of pts presented with metastases at diagnosis. PSA50 was achieved in 39.4% overall. Median TTF and OS were 3.7 (95% CI: 3.0–4.9) and 28.5 (95% CI: 23.5–35.1) months, respectively. AR amplification, *TP53* alterations and double-hit tumor suppressor alterations involving *TP53*/*RB1*/*PTEN* were all strongly associated with better PSA50 (Table). In multivariable analysis (MVA), AR amplification (OR 4.00, 95% CI 1.23–13.01; p = 0.021) and *TP53* alterations (OR 5.18, 95% CI 1.71–15.71; p = 0.0037) remained independently associated with PSA50 In survival analyses, AR ligand-binding domain mutations that reduce testosterone binding affinity (low-affinity AR-LBD mutations: L702H, W742C, T878A/S) were linked to shorter TTF and remained independently associated in MVA (HR 2.19, 95% CI 1.15–4.18; p = 0.017), together with metastatic disease at diagnosis (HR 1.82, 95% CI 1.17–2.84; p = 0.008). **Conclusions:** Distinct genomic alterations are associated with sensitivity to BAT in mCRPC patients. AR amplification, *TP53* alterations and *TP53/RB1/PTEN* double-hit status were all associated with increased likelihood of PSA response, while low-affinity AR-LBD mutations identify patients at risk for early treatment failure. These findings are in line with prior studies and support genomic profiling to refine patient selection for BAT. Research Sponsor: None.

	PSA50		TTF		OS	
	OR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
TP53 alterations	5.3 (1.9–15.4)	0.002	0.7 (0.4-1.1)	0.100	1.8 (1.0-3.3)	0.067
Double hit (TP53, RB1, PTEN)	4.4 (1.4–13.6)	0.013	0.8 (0.5-1.3)	0.313	1.7 (0.9-3.2)	0.115
AR amplification	4.6 (1.7–13.0)	0.003	0.7 (0.4-1.1)	0.110	0.9 (0.5-1.7)	0.809
Low affinity AR-LBD mutations	0.4 (0.1-1.5)	0.231	2.6 (1.4-4.6)	0.002	1.9 (0.9-3.89)	0.076
DDR alterations	0.6 (0.2-1.3)	0.210	1.3 (0.8-2.0)	0.223	1.6 (1.0-2.6)	0.057

5065 Poster Session

Early chemo-induced TME alterations as a predictor of response to PD-1 blockade in AVPC: Single-cell data from C3NIRA. First Author: Anthos Christofides, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Aggressive variant prostate cancer (AVPC) criteria enrich for androgen-indifferent disease that is highly aggressive and has limited therapeutic options. Single-agent immune checkpoint inhibitors have not demonstrated activity in prostate cancer patients. The C-COLA study (NCT03263650) showed that Cabazitaxel/Carboplatin (CabCarb) elicited inflammatory signaling in responsive patients with AVPC. Based on these findings, we hypothesized that chemotherapy-induced inflammation in the tumor microenvironment (TME) may prime tumors for immunotherapeutic approaches. **Methods:** The C3NIRA trial (NCT04592237) employed one cycle of CabCarb, followed by the addition of the PD-1 blocker Cetrelimab, from cycle 2 for up to 6 cycles of induction treatment in patients with AVPC. Among 120 enrolled men, 20 discontinued due to toxicities and 40 due to progression during induction. Sixty patients completed induction and were subsequently randomized to Niraparib maintenance with or without Cetrelimab. The 30 randomized to Niraparib with Cetrelimab had significantly longer progression free (PFS) and overall survivals than the 30 randomized to Niraparib alone. To investigate whether treatment-induced alterations in the TME could predict immunotherapy response, biopsies were obtained at baseline, and after cycles 1, 3 and 9 for single-cell RNA sequencing (scRNAseq). **Results:** scRNAseq analysis of tumor biopsies showed a high proportion of $GZMK^+$ $CD8^+$ T cells and $CD8^+$ T effector memory clusters, and a low proportion in $FOXP3^+$ $CD4^+$ T regulatory cells, in the TME of responders (PFS≥10months) after cycle 1 of CabCarb, which was not seen in progressors. Similarly, $SPP1^+$ macrophages scoring high immunosuppressive signatures were reduced in responders after CabCarb but not in progressors. Consistent with these suppressive and effector cell changes, $LAG3^+$ $TIGIT^+$ $CD8^+$ T exhausted cells gradually accumulated in progressors from baseline through CabCarb and Cetrelimab treatment, while remaining unchanged in responders over the same interval. **Conclusions:** One cycle of CabCarb induction altered the TME in a subset of AVPC tumors, with reduction of suppressive myeloid and T cell populations and expansion of anti-tumor effector cells associated with clinical responses. These early TME changes may predict benefit from the addition of PD-1 blockade and help refine patient selection for immune checkpoint inhibition. Ongoing analyses are identifying additional therapeutic vulnerabilities in the TME that can be targeted to further improve outcomes in men with AVPC. Clinical trial information: NCT04592237. Research Sponsor: U.S. Department of Defence; W81XWH-20-1-0257; Janssen Scientific Affairs, LLC.

5066 Poster Session

Genomic predictors of response to cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC): A real-world analysis from the PROMISE registry. First Author: Peter D. Zang, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Cabazitaxel (Cabazi) is an important treatment for refractory mCRPC, but responses are heterogeneous. Homologous recombination repair (HRR) and tumor suppressor gene (TSG alterations (alt) can predict aggressive behavior in patients (pts) with mCRPC. We hypothesize that Cabazi has enhanced efficacy in pts with these aggressive alt. **Methods:** The multi-institutional PROMISE clinical-genomic database was queried for patients who had undergone tumor next-generation sequencing prior to initiating Cabazi monotherapy for mCRPC. We evaluated the association of select gene alt HRR (*BRCA1, BRCA2, ATM, BRIP1, CDK12, CHEK2, PALB2, RAD51, RAD51B/CD*), TSG (*RB1, PTEN* loss, *TP53*) and other common alt in mCRPC with PSA response and clinical Progression to Cabazi. Comparisons of PSA50 responses were made using Fisher's exact tests, and associations between genetic alterations and both OS and PFS were conducted using log-rank tests. **Results:** Among 383 pts who met inclusion criteria median age was 61 years, with 283 (74%) Caucasian pts, 71 (19%) African-American/Black pts, 9 (2%) Asian pts, and 20 (5%) Hispanic pts. 302 (79%) had prior docetaxel, 23 (6%) had received PARP inhibitor, and 16 (4%) had received Lu-177 PSMA. The most frequent alt noted were: TSG in 204 (53%) pts, TP53 in 164 (43%), AR alt in 130 (34%) pts, and HRR alt in 91 (24%) pts. No significant difference was noted in PSA50 responses in pts with TSG or HRR alt relative to wild-type, though there was a difference noted in pts with PIK3CA alt (Table). Progression-free survival (PFS) on Cabazi was shorter in pts with TP53 alt [HR 1.55 (1.19 – 2.04), p=0.001), any TSG alt [HR 1.51 (1.15 – 1.98) p=0.003], RB1 [HR 2.34 (1.38 – 3.99), p-=0.005], and AR alt [HR 1.37 (1.04 – 1.79) p=0.03). There was no difference in pts with HRR alt [HR 0.83 (0.60 – 1.15), p=0.26)]. Overall survival (OS) was prolonged in pts with HRR alt [HR 0.69 (0.59 – 0.92), p=0.009)] and worse in pts with TP53 alt [HR 1.54 (1.20 – 1.98) p<0.001)], any TSG alt [HR 1.36 (1.07 – 1.74), p=0.01], or RB1 alt [HR 1.94 (1.18 – 3.18) p=0.02]. **Conclusions:** Common genomic alt including TSG, HRR, and PI3KA were not predictive of Cabazi response in mCRPC. TSG alt were associated with worse outcomes, consistent with aggressive disease biology. Improved OS in pts with HRR alt likely reflects PARP inhibitor or platinum use rather than Cabazi efficacy. Research Sponsor: None.

Association between genomic alterations and cabazitaxel response in mCRPC.

Genetic Alteration	PSA50 Response	PFS (HR)	OS (HR)
Any TSG	26.8% vs 25.4% (p=0.80)	**1.51 (p=0.003)**	**1.36 (p=0.01)**
AR	20.8% vs. 28.6% (p=0.16)	**1.37 (p=0.03)**	1.19 (p=0.19)
Any HRR	31.8% vs. 24.6% (p=0.27)	0.83(p=0.26)	**0.69 (p=0.009)**
PTEN	35.7% vs. 24.0% (p=0.09)	1.12 (p=0.50)	0.98 (p=0.92)
PIK3CA	**5.6% vs. 27.4% (p=0.05)**	1.53 (p = 0.22)	1.27 (p = 0.36)

5067 Poster Session

Correlation between dual FDG/PSMA PET mismatch and ctDNA genomic profiling in metastatic castration-resistant prostate cancer (mCRPC) patients screened for 177Lu-PSMA. First Author: Louise Lazerges, Department of Medical Oncology, Gustave Roussy, Villejuif, France

Background: 177Lu-PSMA radioligand therapy is now a standard treatment for patients (pts) with mCRPC. Dual-tracer FDG/PSMA PET imaging mismatch (i.e. FDG+ and PSMA- lesions) is currently the main selection criterion used to predict 177Lu-PSMA response. However, this approach is time-consuming, resource-intensive and may not fully capture tumor biological aggressiveness. More accessible and biologically informative biomarkers are therefore needed. **Methods:** This retrospective, single-center study included pts diagnosed with mCRPC who underwent FDG and PSMA PET for 177Lu-PSMA screening and circulating tumor DNA next-generation sequencing (ctDNA) as part of the STING program (NCT04932525) at Gustave Roussy. A tumor suppressor gene alterations (TSalt) signature was defined by ≥ 2 alterations among *TP53, PTEN* and/or *RB1*. Univariate logistic and linear regression models were used along with area under the curve (AUC) to assess associations between genomic and mismatch as well as PET-derived parameter. Progression-free survival (PFS, PCWG3 criteria) and overall survival (OS) were analyzed using univariate Cox models. **Results:** Among the 110 pts with available ctDNA and dual-tracer imaging, 18 (16.4%) exhibited mismatch. TSalt+ tumors were identified in 24 pts (21.8%) and were enriched in the mismatch group (50.0 vs 16.3%, p = 0.004) and in case of liver metastases (33.3% vs 10.5%, p = 0.011). TSalt was associated with mismatch (p = 0.003, AUC = 0.625). TSalt predicted higher total lesion glycolysis (TLG; $p < 0.001$, AUC = 0.720), increased ratio TLG/total lesion activity (TLA; p = 0.008, AUC = 0.657), larger FDG+ tumor volume (p = 0.008, AUC = 0.720), and lower PSMA+ tumor volume ($p < 0.001$, AUC = 0.725). TSalt+ pts had significantly shorter OS compared with TSalt- pts (median 5.7 vs 16.5 months; HR 3.31, 95% CI [1.93–5.69], $p < 0.001$). Similarly, pts with mismatch had inferior OS (median 4.7 vs 16.3 months; HR 3.17, 95% CI [1.69–5.95], $p < 0.001$). Among the 79 pts treated with 177Lu-PSMA, TSalt+ status (n = 14, 17.7%) was associated with shorter median PFS (3.5 vs 5.1 months; HR 2.37, 95% CI [1.29–4.34], p = 0.004) and OS (5.5 vs 15.3 months; HR 4.19, 95% CI [2.17–8.10], $p < 0.001$). Patients with mismatch (n = 3, 3.8%) also experienced inferior outcomes, with shorter PFS (2.5 vs 4.9 months; HR 3.80, 95% CI [1.14–12.7], p = 0.02) and OS (5.6 vs 15.1 months; HR 4.97, 95% CI [1.48–16.7], p = 0.004). **Conclusions:** The TSalt genomic signature was associated with FDG/PSMA PET mismatch, adverse metabolic imaging features, and poorer survival in patients with mCRPC, including those treated with 177Lu-PSMA. These findings suggest that ctDNA genomic profiling may help identify molecular imaging mismatch, associated with biologically aggressive disease, such as lineage plasticity phenotypes. Prospective studies are warranted to validate its clinical utility. Research Sponsor: None.

5068 Poster Session

Predicting response to ^{177}Lu-PSMA-617 in metastatic prostate cancer (mPC) using plasma-derived extracellular vesicles (EVs). First Author: Albert Jang, Division of Medical Oncology, Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background: ^{177}Lu-PSMA-617 (LuPSMA) is a groundbreaking therapy for mPC, but biomarkers are urgently needed to improve patient selection. Plasma-derived EVs are emerging blood-based markers of tumor burden. Here, we analyzed levels of EVs of 123 patients (pts) from 4 cohorts: a pre- and during LuPSMA treatment for a contemporary prospective Mayo Clinic cohort, pre-treatment plasma levels of EVs for a historical Tulane cohort, localized prostate cancer (LPC) after radical prostatectomy (RP), and male healthy donors (HD). **Methods:** Blood samples were collected from 51 pts pre-cycles (pre-C) 1-3 of LuPSMA at Mayo Clinic from 12/2024-12/2025 and 26 pts pre-C1 at Tulane Cancer Center between 12/2018-1/2025. Small and large EVs were incubated with fluorescently conjugated antibodies (PSMA, STEAP1, CEACAM5, and TROP2) and enumerated using nanoscale flow cytometry. EVs from blood samples of 10 HD and 36 LPC post-RP from 6/2020-8/2024 at Mayo Clinic as controls. AUC-ROC and logistic regression analyses were performed to identify marker signatures associated with PSA50 response. **Results:** Baseline demographics are shown in the table. Median levels of PSMA, STEAP1, CEACAM5, and TROP2 EV/milliliter (mL) were all significantly higher for pts with mPC (pooled Tulane and Mayo cohorts) compared to LPC post-RP ($p<0.001$) and HD ($p<0.001$). In the Mayo cohort, 10 of 51 pts (20%) had undetectable PSA pre-C1. There were no significant differences in median pre-C1 plasma EV levels for these 4 different types of EVs comparing pts with undetectable vs detectable PSA. For 41 Mayo pts with detectable PSA pre-C1, 20 achieved PSA50 response at time of data cutoff (49%), while 7 pts (17%) had persistent PSA rise on LuPSMA. For pts who achieved PSA50, there was a significant decline in both CEACAM5 and TROP2 EVs/mL pre-C1 compared to pre-C3 (19 x 10^6 vs 5.8 x 10^6, p=0.003 and 16 x 10^6 vs 5.5 x 10^6, $p<0.001$, respectively), while no significant changes occurred for the 7 pts with no PSA response. A composite score of pre-C1 CEACAM5 and TROP2 EVs (large- and small-sized EVs) demonstrated the strongest association with PSA50 response (OR=2.96, 95% CI: 1.27-6.44, p=0.038), achieving AUC of 0.73. PSMA and STEAP1 EVs did not show any significant changes from pre-C1 to pre-C3. **Conclusions:** Plasma-derived EVs are a promising biomarker to identify patients who will benefit from LuPSMA. Longer follow-up and enrolling a larger cohort are underway. Clinical trial information: NCT06200103. Research Sponsor: Mayo Clinic Comprehensive Cancer Center Vranos Family Career Development Award.

Median values for pre-LuPSMA (Mayo and Tulane), post-RP for LPC, and HD.

	Mayo mPC (n=51)	Tulane mPC (n=26)	LPC (n=36)	HD (n=10)
Age (range)	73 (57-87)	71 (54-83)	66 (56-77)	55 (50-57)
Prior lines (range)	1 (1-3)	4 (1-11)	-	-
Gleason score	9	8	7	-
PSA (range)	1.0 (0-182)	75 (0.8-503)	-	-
PSMA EV/mL	3.7 x 10^6	14 x 10^6	2.0 x 10^6	1.4 x 10^6
STEAP1 EV/mL	30 x 10^6	45 x 10^6	12 x 10^6	12 x 10^6
CEACAM5 EV/mL	17 x 10^6	5.1 x 10^6	3.7 x 10^6	3.9 x 10^6
TROP2 EV/mL	13 x 10^6	5.2 x 10^6	4.5 x 10^6	3.6 x 10^6

5069 **Poster Session**

Final results of Alliance A031902: A phase III trial of enzalutamide plus rucaparib as first-line therapy in metastatic castration-resistant prostate cancer (CASPAR). First Author: Charles J. Ryan, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Inhibition of androgen receptor (AR)-signaling results in increases in double-strand DNA breaks and genomic instability. PARP inhibitors (PARPi) are a standard treatment option for patients (pts) with homologous recombination repair mutations (HRRm). Combinations of PARPi and AR pathway inhibitors (ARPI) are associated with synthetic lethality in multiple pre-clinical studies. Clinical trials have suggested potential benefits with co-targeting PARPi and ARPI in pts with and without HRRm. **Methods:** Alliance A031902 compared radiographic progression-free survival (rPFS) and overall survival (OS) as co-primary endpoints with enzalutamide and rucaparib (Enz/Ruca) versus enzalutamide plus placebo (Enz/Plac) for pts with metastatic castration resistant prostate cancer (mCRPC) regardless of BRCA/HRRm status. This trial was conducted by the Alliance for Clinical Trials in Oncology in 36 centers in the US. Target sample size was 1,002 patients. Eligibility required mCRPC with or without measurable metastatic disease and was agnostic regarding HRRm status. The trial was discontinued in 10/2023 due to changes in the treatment landscape for this pt population. **Results:** Between 10/21 and 4/23, 61 pts were randomized to Enz/Ruca (n=30) or Enz/Plac (n=31). Known BRCA1/2 or PALB2 mutations were present in 1 pt (3.3%) in the Enz/Ruca arm and 1 pt (3.2%) in the Enz/Plac arm; wildtype in 14 (46.7%) vs 15 (48.4%), and unknown in 15 (50%) vs 15 (48.4%), respectively. Three patients (11.5%) in the Enz/Ruca arm discontinued due to an adverse event (AE) vs 0 in the Enz/Plac arm. Among response-evaluable pts, 7/26 (27%) in the Enz/Ruca arm discontinued due to disease progression vs 10/31 (33%) in the Enz/Plac arm. Most common grade 3+ AEs were anemia (33% vs 3%) and hypertension (17% vs 10%) in the Enz/Ruca arm and Enz/Plac arm, respectively. All 61 pts were evaluable for response assessment. PSA declines ≥50% and ≥90% were observed in 79% vs 45% and 60% vs 43% of pts receiving Enz/Ruca versus Enz/Plac, respectively. Median PFS in the Enz/Ruca vs Enz/Plac arms was 17.1 vs 14.2 mos, respectively (HR 1.13 [95% CI: 0.42-3.01], p=0.81), median rPFS (inclusive of unequivocal clinical progression) was 17.1 vs 11.7 mos (HR 0.72; 95% CI: 0.31-1.67, p = 0.44), and median OS was not reached vs 27.0 mos (HR 0.65; 95% CI: 0.29-1.45, p=0.29). **Conclusions:** In this prematurely terminated phase III study, Enz/Ruca was generally well tolerated, with the safety profile consistent with prior PARPi/ARPI combinations. Efficacy outcomes for rPFS and OS are inconclusive due to limited sample size. Definitive conclusions regarding the clinical benefit of this combination cannot be determined from this study. Clinical trial information: NCT04455750. Research Sponsor: Alliance for Clinical Trials In Oncology.

5070 **Poster Session**

Initial results of a phase 1 dose exploration and expansion study of xaluritamig plus abiraterone acetate (AA) in patients (pts) with mCRPC. First Author: Christopher Joseph Sumey, Sanford Cancer Center, Sioux Falls, SD

Background: Xaluritamig (xalu) is a STEAP1 x CD3 T-cell engager, that has shown potent, durable monotherapy activity in pts with mCRPC progressing on taxane chemotherapy. This activity may be further enhanced when given in combination with an androgen receptor pathway inhibitor (ARPI) prior to chemotherapy or radioligand therapy. We therefore evaluated xalu + AA in chemotherapy-naïve pts with mCRPC as a potential chemo-sparing strategy. Here, we report initial safety and efficacy findings. **Methods:** This open-label, multicenter phase (ph) 1 dose exploration and expansion study (NCT04221542) enrolled pts who were taxane-naïve in mCRPC and had received ≤ 2 prior ARPIs (no prior AA permitted). In dose exploration, xalu was administered at a target dose of 0.3, 0.75 or 1.5 mg weekly (QW) via 1-, 2- or 3-step up regimen with 1000 mg AA and predniso(lo)ne daily. Expansion cohort was 3-step up dosing to target dose of 1.5 mg QW then 1.5 mg Q2W. Primary endpoints were safety and tolerability; secondary endpoints were pharmacokinetics and antitumor activity. **Results:** As of data cutoff (15 Oct 2025), 39 pts were enrolled with a median age of 68 years (range: 43–81). Patients received a median of 2 prior therapies, including 56% with prior taxane for mHSPC. Most common treatment-emergent adverse events (all grade [G]/ ≥G3) were myalgia (92.3%/41%), cytokine release syndrome (CRS; 64.1%/7.7%), and anemia (46.2%/12.8%); there were 2 G4 (decrease in lymphocyte count and blood calcium) and no G5 treatment-related AEs reported. Dose-limiting toxicities (n=4) were reported across all dose levels (soft tissue swelling and CRS, 0.3 mg; myalgia n=2, 0.75 and 1.5 mg). Escalation completed at the planned 1.5 mg QW target dose and 1.5 mg Q2W was selected for dose expansion to align with RP3D monotherapy regimen. In the expansion cohort (n=20), confirmed PSA50, PSA90, and objective response rates (RECIST v1.1) were 58%, 47%, and 43%, respectively (Table). Median PSA response duration and radiographic progression free survival were 6.7 (95% CI: 3.8–not estimable [NE]) and 10.5 (95% CI: 8.1–NE) months, respectively. Median OS was not yet reached with 12 months median follow up (95% CI: 11.8–12.3). Seven pts across escalation and expansion remained on treatment. **Conclusions:** Xalu + AA demonstrated manageable safety and promising antitumor activity in taxane- naive mCRPC and is now being evaluated in the randomized ph3 XALience study (NCT07213674). Clinical trial information: NCT04221542. Research Sponsor: Amgen Inc.

	Dose Escalation 0.3—0.75 mg QW N=11	Dose Escalation 1.5 mg QW N=8	Dose Expansion 1.5 mg Q2W N=20	Total N=39
PSA evaluable	11	7	19	37
PSA50 response, n (%)	6 (54.5)	7 (100)	11 (57.9)	24 (64.9)
PSA90 response, n (%)	5 (45.5)	7 (100)	9 (47.4)	21 (56.8)
Best Overall Response RECIST evaluable	6	1	7	14
Complete response, n (%)	1 (16.7)	0	0	1 (7.1)
Partial response, n (%)	3 (50)	1 (100)	3 (42.9)	7 (50)
Stable disease, n (%)	1 (16.7)	0	4 (57.1)	5 (35.7)
Not evaluable, n (%)	1 (16.7)	0	0	1 (7.1)

5071 **Poster Session**

Real-world use of olaparib in US veterans with metastatic castration-resistant prostate cancer: Treatment patterns and outcomes. First Author: Christelle McFarland, Section of Urology, Durham VA Health Care System, Durham, NC

Background: Olaparib, a targeted therapy for metastatic castration-resistant prostate cancer (mCRPC), has demonstrated clinical benefits in patients with homologous recombination repair (HRR) gene alterations, as shown in the PROfound trial. As the largest integrated healthcare system in the US, the Veteran's Health Administration (VHA) offers insights into olaparib use among a diverse population. We characterized the treatment patterns and outcomes of patients with mCRPC treated with olaparib. **Methods:** We identified all VHA patients with mCRPC who received olaparib between May 2020 and December 2023. We then performed a retrospective chart review of data from May 2018 to June 2025 to capture pre- and post-treatment data. Demographics, baseline characteristics, biomarker testing and treatment sequencing were summarized. We analyzed time to event outcomes: time to next therapy (TTNT), and overall survival (OS) via Kaplan-Meier methods, both starting from olaparib initiation. **Results:** We identified 477 mCRPC patients receiving olaparib. Median age at initiation was 75, older than subjects in PROfound (median age 69). Most patients were non-Hispanic White (69%), followed by Black/African American (20%) and Hispanic/Latino (6%). Between 2020 and 2023, olaparib was most commonly initiated in ≥5th line after prostate cancer diagnosis (46%), followed by 4th (25%), 3rd (22%), and 2nd line (6.5%). All patients had received an androgen receptor pathway inhibitor prior to olaparib. Median time from HRR testing to olaparib initiation was 5 months. Median TTNT was 7 months; OS was 12 months. Use of olaparib in an earlier line post first NHA was associated with numerically longer OS (17 months for 1st line vs. 8 months for 4th or later). **Conclusions:** Within the VHA, olaparib showed favorable outcomes despite older age and late-line use, supporting effectiveness in routine practice and in a more diverse population with substantially higher representation of Black/African American and Hispanic/Latino individuals than in clinical trials. Understanding these treatment patterns provides insight into clinical practice and helps guide towards optimal integration of olaparib into management of mCRPC. Research Sponsor: AstraZeneca; Merck.

Kaplan-Meier estimates for time to event outcomes.

	#Events/Total	Median Time (95% CI) (months)
Time to Next Treatment		
- All Patients	**449/477**	**7 (6-8)**
- Olaparib Line of Treatment Post NHA		
1st line	100/111	9 (7-10)
2nd line	151/162	8 (7-10)
3rd line	92/96	6 (5-8)
4th line or later	91/92	5 (4-6)
Overall Survival		
- All Patients	**395/477**	**12 (11-13)**
- Olaparib Line of Treatment Post NHA		
1st line	79/111	17 (12-22)
2nd line	133/162	15 (12-17)
3rd line	85/96	10 (8-12)
4th line or later	88/92	8 (6-9)

5072 **Poster Session**

Sequencing of PARP inhibitors and taxane chemotherapy in HRR-altered metastatic castration-resistant prostate cancer: A real-world VA analysis. First Author: June K. Corrigan, VA Boston Healthcare System, Boston, MA

Background: Taxane-based chemotherapy (taxane) and poly(ADP-ribose) polymerase inhibitors (PARPi) are established life-prolonging therapies for patients with homologous recombination repair (HRR)–altered metastatic castration-resistant prostate cancer (mCRPC), particularly tumors with BRCA1/2 alterations. However, data informing the optimal sequencing of PARPi and taxane chemotherapy in this patient population is limited, especially because subsequent treatments may not be captured in reports of clinical trials. Real-world evidence may help describe treatment sequencing patterns and outcomes. **Methods:** We conducted a retrospective cohort study using the nationwide Veterans Affairs (VA) healthcare system. Patients with mCRPC and HRR alterations treated with either PARPi or taxanes for mCRPC were included. HRR mutation status was ascertained from genomic results captured within the VA database and included different platform/assays. Baseline characteristics were assessed at mCRPC treatment initiation. The primary endpoint was overall survival (OS) from the initiation of PARPi or taxane. Secondary analyses included OS comparisons by initial treatment class and OS from initiation of second-line therapy among patients who received both PARPi and taxane chemotherapy. Survival was estimated using Kaplan–Meier methods and compared using Cox proportional hazards models with inverse probability of treatment weighting (IPTW) to adjust for baseline differences. **Results:** Between Jan 2014 - May 2025, a total of 418 patients (26.8% non-Hispanic Black, median age 74.5 years), with HRR-altered mCRPC (31.3% BRCA2, 26.8% ATM, 21.1% CDK12, 13.4% CHEK2) were included in the final analysis. Metastatic involvement included bone metastases in 80.9% of patients, and visceral metastases in 11.2%. Median PSA was 30.2 ng/mL. Prior to mCRPC, 58.6% of patients had received ARPIs and 14.1% had received taxane chemotherapy. With a median follow-up of 14.1 months, patients received PARPi (N=211) or taxane (N=207), and 30.1% received both treatments for mCRPC. OS was similar between patients initially treated with PARPi versus taxane for mCRPC (HR 1.09, 95% CI 0.84-1.41). Among patients who received both therapies, OS did not differ based on treatment sequence (PARPi→taxane vs taxane→PARPi; HR 0.90, 95% CI 0.41-1.85). **Conclusions:** In this real-world VA cohort of HRR-altered mCRPC, overall survival was similar whether PARP inhibitors or taxanes were used as initial therapy and did not differ by subsequent treatment sequence. Treatment crossover was observed in routine clinical practice. Research Sponsor: VA Office of Research and Development.

5074 **Poster Session**

Dissecting metastatic castration-resistant prostate cancer using regulatory network analysis of tumor transcriptomes. First Author: Aaron Timothy Griffin, Department of Internal Medicine, NYU Langone Medical Center, New York, NY

Background: Metastatic castration-resistant prostate cancer (mCRPC) is characterized by profound clinical and biological heterogeneity, including variable dependence on androgen receptor signaling, frequent genomic instability, lineage plasticity, and highly divergent clinical outcomes. Despite the widespread use of genomic profiling and expression-based signatures, robust patient-level risk stratification and biologically grounded disease subtyping remain limited. We hypothesized that inference of transcriptional regulatory programs underlying tumor state, integrated with genomic and clinical features, would improve prognostication in mCRPC. **Methods:** We analyzed genomic, transcriptomic, and clinical data from mCRPC tumors in the Stand Up To Cancer (SU2C) cohort. A transcriptional regulatory network was reverse-engineered using the latest version of the Algorithm for the Reconstruction of Accurate Cellular Networks (ARACNe3) and transcriptional regulator activity was inferred using Nonparametric analytical Rank-based Enrichment Analysis (NaRnEA). We constructed a novel prognostic machine learning model using a random survival forest integrating regulatory activity features, canonical genomic alterations, and clinical variables. **Results:** Samples were stratified by RNA-sequencing library preparation method into polyA-purified (training, n=150) and exon-capture (testing, n=100). Our model demonstrated strong and statistically significant performance in both the training cohort (out-of-bag Cox PH $p=4.63\times10^{-8}$, AUROC = 0.7711) and the independent test cohort (Cox PH $p=2.92\times10^{-5}$, AUROC = 0.7413). The most informative features included inferred activities of key transcriptional regulators implicated in proliferation, lineage programs, and neuroendocrine differentiation (E2F1, MYC, SOX2, AR, REST), canonical genomic alterations relevant to mCRPC biology (AR, TP53, RB1, FOXA1, APC, PI3K pathway), and select clinical variables (prior therapy, Gleason score, age, metastatic site). Our model also outperformed several widely used gene expression signatures (AR, NEPC, Cell Cycle Progression, RB1 Loss). Regulatory activity–based analyses also revealed substantially greater biological structure and cluster coherence than gene expression–based analyses in subsequent analyses, highlighting distinct and clinically aggressive regulatory states in this dataset. **Conclusions:** Integrating regulatory network–inferred transcriptional programs with genomic and clinical features enables robust, independently validated prognostication in mCRPC that outperforms widely used expression-based signatures. This approach exposes clinically relevant biological heterogeneity underlying aggressive and treatment-resistant disease states and provides a framework for improved risk stratification in advanced prostate cancer. Research Sponsor: National Cancer Institute; R01CA276438.

5075 **Poster Session**

Clinical outcomes of sequential androgen receptor pathway inhibitors (ARPIs) versus novel therapies in metastatic castration-resistant prostate cancer after progression on second-generation ARPIs: A systematic review and meta-analysis. First Author: Rohan Garje, Miami Cancer Institute, Miami, FL

Background: Most recent pivotal, randomized controlled trials (RCTs) testing novel therapies in ARPI pretreated mCRPC patients have incorporated sequential ARPI as the comparator. Given that sequential ARPI could be an inferior control arm based on CARD data, we conducted a meta-analysis to quantify the treatment effect of novel agents vs sequential ARPI and to evaluate whether sequential ARPI constitutes an appropriate control arm for future trials. **Methods:** A systematic search of PubMed, Europe PMC, and ClinicalTrials.gov up to August 14, 2025, identified 2,904 records. After removal of duplicates and exclusions, 17 RCTs met the inclusion criteria. Eligible studies enrolled patients with mCRPC who had progressed after prior exposure to second-generation ARPIs, comparing a novel agent (chemotherapy, targeted therapy, Immunotherapy and radioligands) with sequential ARPI treatment. Three independent reviewers screened the studies and extracted data in accordance with PRISMA guidelines. The primary endpoints were overall survival (OS) and progression-free survival (PFS), and the hazard ratios (HRs) were pooled using a random-effects model. **Results:** We included a total of 6,725 patients in this meta-analysis, with 3,579 (53.2%) receiving novel agents and 3,146 (46.8%) receiving ARPIs. Analysis revealed the pooled HR for OS was 0.86 (95% CI: 0.76–0.96; $p<0.01$). Substantial heterogeneity was observed (I2= 64.05%). This heterogeneity reflects the inclusion of trials with different novel agents and molecular selection criteria, with some highly selective trials (e.g., PROfound HR 0.58) showing greater benefit than others (e.g., ERA 223 HR 1.22). In addition, the pooled PFS analysis demonstrated a highly significant clinical advantage for novel therapies, resulting in a pooled HR of 0.72 (95% CI: 0.61–0.86; $p<0.01$). This PFS analysis exhibited very high heterogeneity (I2= 84.44%), driven by exceptional outcomes observed in trials targeting specific biomarkers. **Conclusions:** Across RCTs, novel therapies consistently outperform sequential ARPI for both OS and PFS in post-ARPI mCRPC. These pooled effects, and their amplification in biomarker-selected populations, suggest that sequential ARPI is a suboptimal control arm in this setting. Future trials should consider more appropriate, biomarker-driven or guideline-concordant active comparators, enabling fairer tests of clinical benefit and more generalizable results Research Sponsor: None.

5076 **Poster Session**

Androgen receptor (AR) gene dynamics in ctDNA post-abiraterone/enzalutamide: Longitudinal study in mCRPC with germline results. First Author: Minqi Huang, Tulane University, New Orleans, LA

Background: Approximately 10–15% of men with metastatic prostate cancer harbor germline mutations. Circulating tumor DNA (ctDNA) provides a non-invasive approach to identifying AR mutations as resistance mechanism after abiraterone and enzalutamide initiation. In this study, we report longitudinal ctDNA profiling in patients with metastatic castration-resistant prostate cancer (mCRPC) who had germline testing. **Methods:** A retrospective review was conducted at Tulane Cancer Center to identify mCRPC patients with serial ctDNA after starting abiraterone and/or enzalutamide and germline test results. Germline testing was performed using a multi-gene cancer panel from Invitae, covering 50–86 genes, while somatich alterations in ctDNA were assessed through Guardant360, which included 70–83 genes. Linear mixed-effects models (LMMs) with random intercepts were used to model AR gene allele fraction and AR amplification copy number as continuous outcomes. Fixed effects included serial ctdna timepoints and germline gene pathogenicity, and random effects accounted for repeated measure using patient-specific intercepts. Cox Proportional Model was used to analyze the time from initiation of ARPi to AR amp and/or AR mutation in ctDNA. Analyses were performed using the R version 4.4.2. **Results:** From 2015-2025, 341 mCRPC patients with germline test results received an average of 2.96 ctDNA tests post abiraterone or enzalutamide. In this cohort, 47 patients had germline pathogenic mutations (14%) and 294 patients had germline non-pathogenic mutations (86%). Among those with pathogenic germline findings, there were 29 patients with mutation in homologous recombination repair genes (62%) and 18 patients with mutation in other genes. Overall, 55.7% patient in this cohort developed either AR amplification or AR pathogenic mutation in ctDNA. In linear mixed models, germline pathogenicity and pathogenic HRR mutations were not associated with AR copy number, AR allele frequency, or occurrence of somatic AR alterations. Serial ctDNA timepoints following baseline assessment are associated with a significant increase in AR amplifications copy numbers in ctDNA($p=0.003$). AR amplification copy number increases by 0.12 for each subsequent timepoint from baseline. Only 318 patients were included in survival analysis due to missing ARPi start date. Time to ctDNA AR amplification or mutation after 1st ARPi initiation was shorter in mCRPC patients without pathogenic HRR germline mutations compared to those with pathogenic HRR mutations (median: 38 vs 58 months, $p = 0.049$). **Conclusions:** Later serial timepoints correlated with a significant increase in AR amplifications copy numbers but not correlated with highest AR mutant allele frequency. mCRPC patients without germline HRR mutations will find ctDNA AR amplification or mutation sooner than those with germline HRR mutations. Research Sponsor: None.

5077 **Poster Session**

Effect of frailty measures on overall survival in prostate cancer: A systematic review and meta-analysis. First Author: Nicole Sequeira, Department of Internal Medicine, University of Connecticut Health Center, Farmington, CT

Background: Prostate cancer at all stages is associated with a favorable prognosis and treatment is generally well tolerated, including in the elderly. Frailty screening tools such as the Geriatric 8 (G8) have been associated with decreased survival across different cancers. However, the effect of frailty on overall survival (OS) in prostate cancer is poorly understood. **Methods:** A comprehensive search of PubMed, Embase, and Scopus was performed through December 2025 for studies evaluating the impact of frailty on OS in patients with prostate cancer. Data were analyzed in two distinct cohorts: patients with metastatic castration-resistant prostate cancer (mCRPC) and those with unspecified prostate cancer (PC) (at any stage). Meta-analysis was performed using a random-effects model to calculate pooled hazard ratios (HR) and 95% confidence intervals (CI). Statistical heterogeneity was assessed using the I^2 statistic and Chi² test. **Results:** Of the twelve studies that met the inclusion criteria, two were excluded due to non-availability of survival statistics for analysis. Four studies could not be included in the meta-analysis as hazard ratios were not reported. A total of 7120 patients across seven studies were included in the meta-analysis. In the mCRPC cohort (n=4 studies), frailty was a significant predictor of mortality, associated with a pooled HR of 2.16 (95% CI: 1.34–3.49; P = 0.002). Moderate-to-high heterogeneity was observed in this group (I^2 = 65%). In the unspecified PC cohort (n=2 studies), the association between frailty and OS did not reach statistical significance, yielding a pooled HR of 1.74 (95% CI: 0.69–4.40; P = 0.24). Heterogeneity for the unspecified PC group was I^2 = 61%. **Conclusions:** Frailty is associated with increased mortality in elderly patients with metastatic castration-resistant prostate cancer. This effect of frailty was not statistically significant when the population was expanded to include early-stage prostate cancer. These results highlight the importance of geriatric screening for prognostic assessment in elderly patients with prostate cancer, especially in those with metastatic castration-resistant disease. Research Sponsor: None.

Study characteristics and hazard ratios for overall survival.

Study	Cancer type	Design	N	Age	Assessment tool	Frailty %	OS
Beardo (2019)	mCRPC	RS	70	≥75	G8	NR	3.13 (1.13–8.66)
Banna (2022)	mCRPC	PS	234	78	G8	38%	3.58 (1.72–7.49)
Wilk (2022)	mCRPC	PS	49	71	G8	47%	2.24 (1.15–4.36)
Deol (2023)	mCRPC	RS	5822	75.4	VA-FI	39.70%	1.44 (1.35–1.52)
Royset (2023)	PC	PS	73	73.6	EFS	24.60%	1.27 (1.20–1.35)
Siwakoti (2024)	PC	PS	70	70	CARE-FI	21%	3.55 (1.01–12.47)

Abbreviations: Retrospective study (RS); Prospective study (PS); Sample size (N); Geriatric 8 (G8); Veterans Affairs Frailty Index (VA-FI); Edmonton Frail Scale (EFS); Cancer and Aging Resilience Evaluation Frailty Index (CARE-FI); Not reported (NR).

5078 Poster Session

Transient prostate-specific antigen flare induced by lutetium Lu 177 vipivotide tetraxetan in patients with metastatic castration resistant prostate cancer. First Author: Tiewei Cheng, University of Kansas Medical Center, Westwood, KS

Background: Prostate-specific antigen (PSA) flare, an initial rise in PSA that subsequently falls, is a well-known phenomenon in prostate cancer patients treated with hormone therapy and chemotherapy. However, its incidence, chronology, and clinical significance for treatment outcome of patients undergoing lutetium Lu 177 vipivotide tetraxetan (Lu-177), a newly FDA-approved radiopharmaceutical agent for metastatic castration-resistant prostate cancer (mCRPC), is uncertain. Our retrospective study, included mCRPC patients treated with Lu-177 between June 2022 and March 2025 at University of Kansas Cancer Center, aims to evaluate the association of PSA flare with clinical outcomes in patients with mCRPC undergoing Lu-177. **Methods:** PSA flare was defined as any initial increase in PSA level from baseline before start of 3rd cycle followed by a decrease in PSA level of any degree or a decrease to less than baseline PSA level. The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS), PSA50 response, and disease control rate (DCR). The log-rank test was applied to compare PFS and OS between patient group with PSA flare and patient group without PSA flare. **Results:** The data from 158 patients were analyzed. The median age was 73.5 years old (range: 52-100). The median number of Lu-177 cycles received was 4 (range: 1-6). Forty five patients (28.5%) experienced PSA flare. The median time from treatment initiation to onset of PSA flare was 3 weeks (range: 1-9); whereas the median interval between PSA flare and PSA nadir was 14 weeks (range: 2-72). The median increase in PSA from baseline to flare was 39.1% (range: 3.3-1,133%); whereas the median decrease in PSA from flare to nadir was 70.1% (range: 8.4-98.4%). There was no statistically significant difference in PFS and OS between patient group with PSA flare and patient group without (median PFS: 8.2 vs. 5.6 months, p=0.20; median OS: 14.3 vs. 12.5 months, p=0.29). PSA50 response was observed in total of 76 patients (48.1%). In patient group with PSA flare, 48.9% of the patients achieved PSA50 response. Similarly, 48.7% of the patients achieved PSA50 response in patient group without PSA flare. Majority of patients were also assessed for radiographic response (n=139). Between patient group with PSA flare and group without PSA flare, DCR was achieved in 60% and 49.5% of the patients respectively (RR = 1.21, 95% CI: 0.88 to 1.67, p=0.26). **Conclusions:** The PSA flare phenomenon is not rare in mCRPC patients treated with Lu-177. Our study suggests the clinical outcome appears consistent regardless of the PSA flare. Therefore, Lu-177 should not be withdrawn early and prematurely in mCRPC patients who have an initial but isolated PSA rise following the therapy. Further studies are warranted to validate our findings. Research Sponsor: None.

5079 Poster Session

Post-ARPI sequencing in mCRPC: A propensity-matched real-world comparison of ^{177}Lu-PSMA-617 versus docetaxel for early clinical outcomes. First Author: Sooraj Srirangadhamu Gopu, New York Medical College, Landmark Medical Center, Woonsocket, RI

Background: Treatment sequencing in metastatic castration-resistant prostate cancer (mCRPC) after ADT and ARPI exposure varies in practice. While ^{177}Lu-PSMA use is expanding in routine practice, real world head to head comparisons with docetaxel in ARPI-exposed mCRPC are limited, particularly for short-term outcomes and treatment related acute care utilization. **Methods:** Using TriNetX, adults > 18 years of age with metastatic prostate cancer and prior ARPI exposure who initiated ^{177}Lu-PSMA or docetaxel were identified (index = first administration). Cohorts were balanced with 1:1 propensity score matching (PSM) on demographics and baseline comorbidities. Outcomes from day 1–180 post-index included all-cause mortality (primary), hospitalization, acute kidney injury (AKI; ICD-10 N17), and thromboembolic/ischemic events (ICD-10 I21/I26/I63/I82). For each outcome, patients with prior documentation of that outcome were excluded. Outcomes are reported as risks and risk ratios (RR) with 95% confidence intervals. **Results:** Before matching, 563 patients initiated ^{177}Lu-PSMA-617 and 8,749 initiated docetaxel; after 1:1 PSM, 497 patients per cohort were analyzed. At 180 days, all-cause mortality was 7.3% (36/494) with ^{177}Lu-PSMA-617 versus 12.2% (60/491) with docetaxel (RR 0.60, 95% CI 0.40–0.88). Hospitalization occurred in 7.2% (21/290) versus 21.1% (52/247) (RR 0.34, 95% CI 0.21–0.55). In a separate matched renal-safety analysis (480 per cohort), AKI occurred in 2.8% (11/390) versus 9.0% (36/399) (RR 0.31, 95% CI 0.16–0.60). Thromboembolic/ischemic events were 3.8% (15/394) versus 6.4% (26/404) (RR 0.59, 95% CI 0.32–1.10). **Conclusions:** In ARPI-exposed mCRPC, ^{177}Lu-PSMA was associated with lower 180-day mortality risk and substantially fewer hospitalizations than docetaxel, with a lower risk of AKI. These findings highlight a potential short-term effectiveness and acute-care utilization advantage of ^{177}Lu-PSMA in routine practice and support further prospective evaluation. Research Sponsor: None.

Key 180-day outcomes after matching.

Outcome	^{177}Lu-PSMA	Docetaxel	Effect estimate (180 days)
All-cause mortality	36/494 (7.3%)	60/491 (12.2%)	RR 0.596 (0.402-0.884)
Hospitalization	21/290 (7.2%)	52/247 (21.1%)	RR 0.344 (0.213-0.554);
Acute kidney injury (AKI)*	11/390 (2.8%)	36/399 (9.0%)	RR 0.312 (0.163-0.595)
Thromboembolic/ischemic†	15/394 (3.8%)	26/404 (6.4%)	RR 0.592 (0.318-1.100)

*AKI analysis used a separate matched run (480 per cohort).
†Composite of I21, I26, I63, I82.

5080 Poster Session

Real-world characteristics, homologous recombination repair mutation (HRRm) testing, treatment patterns, and outcomes of patients with metastatic castration-sensitive prostate cancer (mCSPC) in the US community oncology setting. First Author: Manojkumar Bupathi, Rocky Mountain Cancer Centers, Littleton, CO

Background: Homologous recombination repair mutation (HRRm) testing is recommended by NCCN guidelines for metastatic castration-sensitive prostate cancer (mCSPC). The real-world CAPTURE study is one of the first to associate HRRm carriers with worse outcomes. However, real-world data to quantify prognostic and predictive value of HRRm in mCSPC are limited and heterogeneous, especially for patients treated within US community oncology settings. **Methods:** This was a retrospective observational cohort study of patients with documentation of HRRm testing who initiated systemic therapy for mCSPC (index) between 1/1/2019-3/31/2024 in The US Oncology Network or non-Network practices. Stratified random samples of 150 patients with HRRm and 150 patients without HRRm were selected for chart abstraction to collect patient characteristics within 60 days prior to index and prostate cancer treatments (androgen deprivation therapy, ADT; androgen receptor pathway inhibitors, ARPi; docetaxel, DOC) through the end of follow-up (3/31/2025). Somatic and/or germline testing results for a 12-gene HRRm panel (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C) were recorded from all available records. Descriptive Kaplan-Meier analyses of overall survival (OS) and real-world progression-free survival (rwPFS) were assessed per HRRm, de novo metastatic and high-volume disease (HVD) status. **Results:** Overall, 300 patients were selected with median (IQR) age of 69 (63-77) years and median (IQR) follow-up of 25 (15-36) months. Among patients with available data at baseline, most were Gleason ≥8 (79% of 181) and PSA >4 ng/mL (85% of 274). In the HRRm cohort (N=150), 70 (47%) patients were BRCAm and 80 (53%) patients had non-BRCAm HRRm mutations. De novo mCSPC was identified in 97 (65%) patients with HRRm and 100 (67%) patients without HRRm. HVD was observed in 85 (57%) patients with HRRm and 96 (64%) without HRRm. Frontline (index) systemic therapies for mCSPC in the HRRm/non-HRRm subgroups included ADT (28%/22%), ADT+ARPi (39%/47%), ADT+DOC (15%/15%) and ADT+ARPi+DOC (15%/15%). Outcomes are summarized below. **Conclusions:** Patients with HRRm mCSPC experienced numerically shorter OS and rwPFS than non-HRRm patients. This highlights an important need for early HRRm testing and targeted treatment strategies within earlier disease settings. Research Sponsor: None.

Outcome, median (95% CI), months	HRRm (N=150)	No HRRm (N=150)
OS, overall	44.0 (36.8-55.2)	48.5 (40.2-NR)
rwPFS, overall	17.5 (14.4-22.1)	22.6 (17.9-33.4)
N (%), de novo	97 (65)	100 (67)
OS, de novo	41.7 (30.6-44.9)	48.5 (33.4-69.4)
rwPFS, de novo	15.4 (13.0-23.1)	22.0 (17.2-32.3)
N (%), HVD	85 (57)	96 (64)
OS, HVD	44.4 (36.8-55.2)	42.5 (33.4-69.4)
rwPFS, HVD	17.7 (12.0-27.3)	19.2 (16.3-30.3)

5081 Poster Session

Comparative efficacy and safety of systemic therapies in high-risk hormone-sensitive prostate cancer: A network meta-analysis of 13 phase III randomized trials. First Author: Neel Ketankumar Parikh, Zydus Medical College and Hospital, Dahod, India

Background: Treatment intensification improves survival in hormone-sensitive prostate cancer (HSPC). However, direct comparisons between triplet therapies consisting of androgen-deprivation therapy, docetaxel, and an androgen receptor pathway inhibitor (ADT+Docetaxel+ARPI) and ARPI doublets are limited. In addition, available evidence remains fragmented between high-risk non-metastatic (nmHSPC) and metastatic (mHSPC) disease states. We conducted a network meta-analysis (NMA) to rank treatment regimens and inform clinical decision-making. **Methods:** We analyzed 13 phase III RCTs including approximately 13,000 patients with high-risk HSPC, encompassing metastatic and high-risk non-metastatic disease. Treatment strategies included ADT alone, docetaxel (DOC), abiraterone (ABI), enzalutamide (ENZ), apalutamide (APA), darolutamide (DARO), and triplet combinations. A frequentist random-effects NMA was performed with overall survival (OS) as the primary endpoint. Secondary efficacy endpoints included progression-free survival (PFS) and time to castration resistance (TTCR). Safety was assessed using treatment-emergent grade ≥3 AEs, assuming network transitivity. **Results:** For the primary endpoint (OS), triplet therapies ranked highest, including ADT+DOC+DARO (HR 0.55 [95% CI 0.43–0.69]) and ADT+DOC+ABI (HR 0.60 [95% CI 0.45–0.81]) compared with ADT alone. ARPI doublets also demonstrated robust OS benefits, including ABI (HR 0.63 [0.58–0.69]), APA (HR 0.67 [0.51–0.89]) and ENZ (HR 0.69 [0.51–0.94]). No statistically significant OS difference was observed between triplets and ARPI doublets, although triplets numerically favored higher efficacy. For PFS (I^2 = 86.5%), triplet therapies remained superior, with ADT+DOC+DARO showing the greatest benefit (HR 0.24 [0.13–0.45]), followed by the ENZ doublet (HR 0.40 [0.27–0.60]). Secondary endpoints (TTCR, PSA-PFS) consistently favored ARPI-based regimens. Regarding safety, triplet therapies significantly increased the odds of Grade ≥3 AEs versus ADT (OR ~2.6–3.7), driven primarily by docetaxel-associated fatigue and ABI-related hypertension. Conversely, APA, ENZ, and DARO doublets demonstrated favorable safety profiles, with no significant increase in overall Grade ≥3 AEs compared with ADT alone (ORs 1.02–1.06). Benefits were consistent across nmHSPC and mHSPC subgroups (p for interaction = 0.66). **Conclusions:** Triplet therapy represents the efficacy standard for fit patients with high-volume mHSPC. However, ARPI doublets offer a compelling alternative with comparable survival benefits and a superior safety profile, making them the preferred choice for high-risk nmHSPC and patients prioritizing tolerability. Clinical selection should stratify based on disease volume and fitness for docetaxel-associated toxicity. Research Sponsor: None.

5082 **Poster Session**

Independent validation of a model to predict early favorable PSA response (NADIR model) in enzalutamide-treated patients of the ARCHES trial. First Author: Soumyajit Roy, Department of Radiation Oncology, UH Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Our group recently trained and independently validated a multivariable logistic regression model (NADIR model) to predict early favorable PSA response (≤0.2 ng/mL) in metastatic hormone sensitive prostate cancer (mHSPC) patients (pts) within 6 months of treatment initiation with androgen receptor pathway inhibitor (ARPI). In this work, we independently validated the NADIR model in the enzalutamide (enza) treated patients from the ARCHES trial. **Methods:** ARCHES is a phase III randomized controlled trial where patients with mHSPC were randomly assigned to ADT versus ADT plus enzalutamide. The locked model was applied to patients in the enza arm and model discrimination was assessed using area under the receiver operating curve (AUC) with 95% confidence intervals (CI) from 5000 bootstrap iterations. Additional performance metrics included Index of prediction accuracy (IPA) relative to null model, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive likelihood ratio (PLR) and negative likelihood ratio (NLR). A Cox proportional hazard model was applied in a 6-month landmark population to determine the hazard of death in middle and lower tertile relative to upper tertile when stratified by tertiles of predicted probability from the NADIR model. **Results:** 1125 patients with non-missing data were included in this independent validation cohort of whom 559 patients were treated with enza. Approximately 64% (n=360) achieved PSA ≤0.2 ng/mL within 6 months of treatment initiation. The AUC was 0.80 [95% CI 0.76-0.83] and IPA was 23%. The sensitivity, specificity, PPV, NPV, PLR, and NLR were 0.82 [0.77-0.86], 0.56 [0.49-0.63], 0.77 [0.72-0.81], 0.63 [0.55-0.70], 1.85 [1.57-2.17], and 0.33 [0.26-0.42], respectively. The early favorable PSA response rates in patients stratified by decreasing order of tertiles of predicted probability of PSA response from the NADIR model were 92% [88-96], 64% [57-71], and 37% [30-45], respectively. Compared to those in the upper tertile, patients in the middle tertile (HR 1.97 [1.33-2.91]) and lower tertile (HR 2.18 [1.48-3.21]) had significantly worse OS. Among patients with <3 months of ADT before ARPI initiation, the AUC was 0.79 [0.75-0.83] with IPA of 22%. **Conclusions:** In this independent validation using the ARCHES trial, the NADIR model showed strong discriminatory performance and effectively stratified enzalutamide-treated patients by early favorable PSA response and overall survival. With prospective validation, this model may provide a useful tool for early prognostication in patients with mHSPC receiving ARPI therapy. Research Sponsor: None.

5083 **Poster Session**

Comeback from long-course ADT with relugolix (rel) and darolutamide (daro) in hormone-sensitive prostate cancer (PC) (CLEARED). First Author: Atish Dipankar Choudhury, Dana-Farber Cancer Institute, Boston, MA

Background: The oral luteinizing hormone releasing hormone antagonist rel and androgen receptor pathway inhibitor (ARPI) daro are approved for treatment of advanced PC but the combination has not been prospectively investigated, and kinetics of testosterone (T) recovery after 2 years of rel have not been reported. Here we report pharmacokinetics (PK) as well as initial safety and reduction in T and PSA from a phase 2 trial of rel plus daro in high risk localized (HRL), lymph node-positive (N+) or low volume metastatic (LV) PC. **Methods:** Eligible patients (pts) had PSA > 0.02 ng/ml, T ≥ lower limit of normal (LLN) and were planned for 2 years of ADT+ARPI for HRL, N+ or LV PC. Prior ADT±ARPI was permitted if T recovered to ≥ LLN, but pts with high volume metastatic PC, prior PSA rise with castrate T, or on medications with significant predicted drug-drug interactions with rel or daro were excluded. Pts received rel 360 mg ×1 on day 1 (D1) followed by 120 mg QD and daro 600 mg BID starting on D1, and elected for PK sampling at 0h, 2h, 4h, 8h on D1 (cohort 1) or pre-dose on D1, 2, 8 and 29 (cohort 2). Radiation therapy to local and/or metastatic sites was delivered per standard of care. Pts receive up to 26 28-day treatment cycles with PSA/T monitoring every 3 months (mo) until 18 mo after end-of-treatment (EOT). The primary endpoints are rate of T recovery to > LLN by 18 mo after EOT and safety/adverse events (AEs). Secondary endpoints include PK, rate of treatment discontinuation, and pt-reported outcomes. **Results:** 33 pts enrolled: 8 with HRL, 11 with N+ and 14 with LV PC. 21 chose cohort 1 and 12 chose cohort 2. Single dose maximum concentrations (C_{max}) on D1 for rel and daro, and D29 pre-dose trough level (C_{trough}) for rel were similar to historical monotherapy comparators (comp) with geometric mean ratios (GMR) between 0.80-1.25 (Table), while D8 C_{trough} for daro was slightly outside this range. By cycle 7 (C7) D1, 15 pts experienced Grade ≥3 AEs: 12 lymphopenia (3 possibly related to daro), with the remainder not treatment-related. 0 pts discontinued rel or daro; 3 dose-reduced daro. 33/33 (100%) pts achieved castrate T < 50 ng/dl and 32/33 (97%) achieved profound castrate T < 20 ng/dl (1 with T 24 ng/dl on C7 D1). PSA decline of ≥50% was achieved in 33/33 (100%) and decline ≥90% in 32/33 (97%) by C7 D1. **Conclusions:** The combination of rel and daro was safe and well-tolerated during the 1st 6 treatment cycles, with PK parameters similar to historical monotherapy comparators. Appropriate initial T and PSA reduction were observed, and pts will be followed after EOT for the primary endpoint of T recovery (NCT06463457). Clinical trial information: NCT06463457. Research Sponsor: NCCN; Sumitomo Pharma America; Pfizer; Bayer.

PK for rel and daro.

	Geometric Mean	Coefficient of variation (%)	GMR
rel D1 C_{max} (N=19) [comp]	141.5 ng/ml [125]	145.2% [220%]	1.13
rel D29 C_{trough} (N=11) [comp]	6.34 ng/ml [7.54]	62.6% [91.9%]	0.84
daro D1 C_{max} (N=18) [comp]	2.10 μg/ml [1.77]	29.0% [26.4%]	1.19
daro D8 C_{trough} (N=11) [comp]	2.52 μg/ml [1.82]	24.7% [32.8%]	1.38

5084 **Poster Session**

Remote activity monitoring to detect physical function decline and unexpected medical events in patients with prostate cancer undergoing androgen deprivation therapy. First Author: Brandon Noorvash, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Among patients with prostate cancer (PC), treatment with androgen deprivation therapy (ADT) is associated with reduced physical function, which can result in diminished quality of life and the occurrence of adverse medical events. The use of wearable activity monitors allows for remote monitoring of daily activity to potentially detect early functional decline and predict significant medical events such as hospitalization, serious adverse events, and premature death. This study evaluated whether wearable activity monitoring could serve as an early indicator of functional decline and impending adverse events in patients with PC undergoing ADT. **Methods:** PC patients receiving ADT at Cedars-Sinai and Durham VA who enrolled in the DigiPRO trial (NCT04575402) wore a Fitbit Charge over 12 weeks to track quantitative physical activity and sleep data for prediction of the occurrence of unexpected medical events (composite of hospitalization, premature death, or fall) and significant patient-reported physical function decline (> 5 NIH PROMIS T score points) within 6-months follow-up. **Results:** 40 patients were included in the analysis (median age 70, range 51-87, 37% Black and 63% White; 10% identified as Hispanic). On average, PC patients walked 5,189 steps/day, were sedentary 16 hours/day, and slept 5.8 hours/night. A clinically meaningful decline in daily steps (> 500 steps) within the first 3 months of initiating ADT was associated with higher odds of experiencing an unexpected medical event (hospitalization, death, fall) (OR = 3.03; 95% CI 1.6-5.9, *p = 0.001*) and clinically meaningful decline in patient-reported physical function (> 5 PROMIS T score points) occurring within 6 months from study completion (OR = 5.2, 95% CI; 1.3-11.7, *p = 0.02*). **Conclusions:** These findings suggest remote activity monitoring may serve as a novel early warning system to identify patients who are at increased risk of unexpected medical events and clinically meaningful physical function decline in PC patients undergoing ADT. Use of this early warning system could lead to targeted interventions in high-risk patients to reduce morbidity and perhaps even prolong survival in patients undergoing ADT. Clinical trial information: NCT04575402. Research Sponsor: U.S. Department of Defense.

5085 **Poster Session**

Cognition of apalutamide + ADT treatment responders versus non-responders. First Author: Arun Azad, Peter MacCallum Cancer Center, Melbourne, Australia

Background: LIBERTAS (NCT05884398) evaluates intermittent androgen deprivation therapy (ADT) with apalutamide monotherapy in metastatic castration-sensitive prostate cancer (mCSPC). ADT is known to affect cognitive domains such as visuospatial ability and executive function. However, links between cognition and treatment responses remain unclear. LIBERTAS offers an opportunity to examine this relationship in participants with mCSPC. **Methods:** All 410 participants received apalutamide and continuous ADT during the initial treatment phase, 144 without prior ADT exposure (ADT naive). Participants with PSA <0.2 ng/mL at 6 months were considered responders, otherwise they were non-responders. Cognition was assessed by two tasks from Cambridge Cognition's CANTAB battery: Paired Associates Learning (PAL; visual memory) and Spatial Working Memory (SWM; executive function) at baseline (C1), 2 months (C3), and 4 months (C5). Outcomes included PAL First Attempt Memory Score (PALFAMS28, higher=better), PAL Total Errors Adjusted (PALTEA28, lower=better), and SWM Between Errors (SWMBE468, lower=better). At each visit, group differences were evaluated using the Mann-Whitney U test. Longitudinal change within and between groups were assessed using linear mixed effect models adjusted for age and testosterone. **Results:** At all visits, responders had higher PALFAMS28, lower PALTEA28, and lower SWMBE468 than non-responders in the entire sample (Table 1). In ADT-naïve participants, responders (N=100) had higher PALFAMS28 than non-responders (N=44) at C3 (10.48 ± 4.74 vs. 8.59 ± 5.00, p=0.01). SWMBE468 was lower in ADT-naïve responders than ADT-naïve non-responders at C1 (14.25 ± 9.12 vs. 19.30 ± 8.37, p=0.001) and C5 (15.42 ± 8.58 vs. 19.77 ± 11.06, p=0.01). Among all participants and within the ADT-naïve group, only the responders' performance changed over time: PALFAMS28 increased and PALTEA28 decreased from C1 to C5 and SWMBE468 increased from C1 to C3 (p <0.01). No significant time-by-group interaction emerged. **Conclusions:** Analyzed in retrospect, responders outperformed non-responders in visual memory and executive function at baseline and throughout initial treatment, maintaining a cognitive advantage. Though not tested, we hypothesize early cognitive performance could be considered among a constellation of clinical factors to prognosticate treatment response, support patient stratification and personalize treatment strategies. Clinical trial information: NCT05884398. Research Sponsor: Johnson & Johnson.

Significant differences between responders and non-responders.

Measure	Visit	Responders (N=266): Mean ± SD	Non-Responders (N=144): Mean ± SD	P value
PALFAMS28	C1	9.43 ± 4.53	8.18 ± 4.08	0.005
	C3	9.78 ± 4.65	8.07 ± 4.30	<0.001
	C5	10.16 ± 4.85	8.47 ± 4.80	0.003
PALTEA28	C1	28.52 ± 17.94	32.92 ± 17.83	0.02
	C3	26.74 ± 17.90	31.90 ± 18.83	0.007
	C5	25.74 ± 18.40	31.80 ± 20.00	0.004
SWMBE468	C1	15.26 ± 9.00	18.03 ± 7.95	0.008
	C3	16.44 ± 9.08	18.73 ± 9.07	0.03
	C5	14.79 ± 9.30	17.89 ± 9.83	0.004

5087 Poster Session

Evaluation of concomitant medications in advanced prostate cancer patients receiving apalutamide: TITAN and SPARTAN post-hoc analysis. First Author: Neeraj Agarwal, University of Utah Health Hospitals and Clinics, Salt Lake City, UT

Background: Apalutamide (APA) is an androgen receptor pathway inhibitor (ARPI) approved for use with androgen-deprivation therapy (ADT) in patients with metastatic castration-sensitive prostate cancer and nonmetastatic castration-resistant prostate cancer based on data from the phase 3 TITAN and SPARTAN trials. APA induces cytochrome (CYP) 3A4/2C19 and P-glycoprotein, which may alter the pharmacokinetics of commonly used medications, raising the possibility for adverse events (AEs) or serious adverse events (SAEs) due to drug-drug interactions (DDIs). **Methods:** A post-hoc analysis was conducted to evaluate the incidence of AEs associated with select concomitant medication classes—antihypertensives, antidiabetics, statins, proton pump inhibitors (PPIs), and corticosteroids, among patients treated with APA + ADT or placebo + ADT in the TITAN and SPARTAN trials. The selected drug classes include some of the most frequently prescribed agents with significant CYP 3A4/2C19 activities. This analysis was also done in comparison to non-recipients of concomitant medications. **Results:** See Table. **Conclusions:** In this exploratory post-hoc analysis of >2,200 patients from TITAN and SPARTAN, concomitant use of commonly prescribed medications (antihypertensives, antidiabetics, statins, PPIs, and corticosteroids) was frequent and reflected routine real-world practice. Across medication classes, we observed no clinically meaningful increase in serious or loss-of-efficacy adverse events among apalutamide-treated recipients compared with placebo or with non-recipients of the class. These findings suggest that co-administration of apalutamide with routine concomitant therapies is safe and feasible under standard clinical monitoring. Clinical trial information: NCT02489318 and NCT01946204. Research Sponsor: Johnson & Johnson.

Incidence of side effects for selected classes of concomitant medications by study and treatment actually received.

Medication Class	Treatment	TITAN Recipients (%)	TITAN TEAS (%)	TITAN TE SAEs (%)	SPARTAN Recipients (%)	SPARTAN TEAEs (%)	SPARTAN TE SAEs (%)
Antihypertensives	APA+ADT	41 (34.3)	41.9	1.9 (1.7)	42.8 (41)	49.4	0.9 (0.6)
	(PBO+ADT)		(39.2)			(36.8)	
Antidiabetics	APA+ADT	12.2	34.4	1.6 (1.8)	12.2 (9.3)	42.9 (27)	3.1 (0)
	(PBO+ADT)	(10.8)	(33.3)				
Statins	APA+ADT	23.9	12 (11)	0 (0)	33.9	10.7 (6.3)	0 (0)
	(PBO+ADT)	(15.6)			(31.7)		
PPIs	APA+ADT	17.6	6.5 (1.3)	0 (0)	26 (21.6)	8.6 (9.3)	0 (1.2)
	(PBO+ADT)	(14.6)					
Corticosteroids	APA+ADT	14.9	12.8	1.3 (0)	10.7 (8.3)	18.6	1.2 (0)
	(PBO+ADT)	(11.2)	(18.6)			(15.2)	

Treatment-emergent AEs (TEAEs) and SAEs deemed attributable to the pharmacologic class of the concomitant medication are classified as class-related side effects and included in the analysis. Percentages of TEAEs and SAEs are calculated based on recipients of a given class of concomitant medication.

5088 Poster Session

EMBARK: Testosterone recovery to >250 ng/dL following treatment suspension. First Author: Stephen J. Freedland, Department of Urology, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles; Durham VA Medical Center, Durham, CA

Background: The phase 3 EMBARK trial demonstrated significantly longer metastasis-free survival and overall survival for enzalutamide plus leuprolide (enzalutamide combination) vs leuprolide alone in patients with prostate cancer and high-risk biochemical recurrence (hrBCR). In EMBARK, patients with prostate-specific antigen (PSA) < 0.2 ng/mL at week 36 suspended treatment at week 37. Androgen deprivation-related testosterone suppression has been linked to adverse health outcomes, whereas testosterone recovery while off treatment has been associated with improved quality of life. The objective of this post hoc analysis was to assess testosterone recovery to > 250 ng/dL during treatment suspension in patients treated with enzalutamide combination. **Methods:** Eligible patients had hrBCR, with a PSA doubling time of ≤9 months. Patients were randomized 1:1:1 to enzalutamide + leuprolide, leuprolide alone, or enzalutamide monotherapy. Patients who suspended treatment at week 37 reinitiated treatment upon PSA increase to protocol-defined levels. Testosterone levels were assessed every 12 weeks. **Results:** In the enzalutamide combination group, 320 patients suspended treatment. During treatment suspension, testosterone recovery to > 250 ng/dL occurred in 108 patients (33.8%) (Table). Among those who recovered their testosterone, median and mean time to recovery was 5.6 months and 6.8 months, respectively, although some patients had delayed recovery (Table). **Conclusions:** Testosterone recovery to > 250 ng/dL during treatment suspension was observed in approximately one-third of patients treated with enzalutamide combination. While average time to testosterone recovery among those who recovered was ~6 months, recovery was delayed in some patients. Disclosure: Pfizer's generative AI tool MAIA was used in developing this abstract; the authors reviewed, edited, and take full responsibility for the content. Clinical trial information: NCT02319837. Research Sponsor: The study was sponsored by Pfizer Inc. and Astellas Pharma Inc., the co-developers of enzalutamide. Medical writing support was provided by Kathleen Richter and Rosie Henderson of the Prime Group of Companies (Knutsford, UK), funded by the sponsors.

	Enza combination(N=320)
Patients who reached testosterone recovery, n (%)	108 (33.8)
Time to testosterone recovery >250 ng/dL, months[†]	
Median (range)	5.6 (0.0–22.1)
Mean (SD)	6.8 (2.87)

The data cutoff date was January 31, 2023.
[†]Time to testosterone recovery during treatment suspension is based on the number of patients who reached testosterone recovery, and was defined as the time from the date of the start of treatment suspension to the date of the first occurrence of testosterone >250 ng/dL. The summary is based on testosterone records during treatment suspension from patients who had treatment suspension and non-missing testosterone records after treatment suspension. For patients who reinitiated treatment, testosterone records after reinitiation were not considered.

5089 Poster Session

Genomic and transcriptomic correlates of deep PSA response in patients with metastatic hormone-sensitive prostate cancer (mHSPC). First Author: Emmanuel S. Antonarakis, University of Minnesota-Twin Cities, Masonic Cancer Center, Minneapolis, MN

Background: Despite advances in mHSPC treatment with combination therapies, patient outcomes remain heterogeneous. Achieving an undetectable PSA level is a strong prognostic marker for improved overall survival (OS). Baseline molecular predictors of deep PSA response are lacking. We aimed to identify genomic and transcriptomic determinants associated with undetectable PSA using a large clinical-genomic cohort. **Methods:** The Tempus Lens Platform was used to query the de-identified Tempus multimodal database and analyze a cohort of patients with mHSPC who underwent DNA (Tempus xT) and RNA (Tempus xR) clinical sequencing. Patients were restricted to those with stage IV disease within 90 days of sample collection. Samples collected within 12 months prior to or within 3 months of androgen deprivation therapy (ADT)-based therapy initiation were considered hormone-sensitive (n = 525). Patients were classified as PSA-low (< 0.1 ng/mL, n = 285) or PSA-high (≥0.1 ng/mL, n = 240) based on the PSA level at 6 months (±45 days) post-treatment initiation. Genomic alterations, gene expression, and transcriptomic signatures were compared between PSA groups. Real-world OS was defined as the time from ADT start to death or loss to follow-up. Hazard ratios (HR) were estimated using Cox regression and adjusted for age. Significance was calculated using a Wald test at $p < 0.05$. **Results:** Median age at diagnosis was 67.5 years; 69.7% were White and 18.5% were Black/African American. The majority (91%) had de novo metastatic disease. First-line treatments included ADT+androgen receptor pathway inhibitor (ARPI) (65% vs 64%), ADT alone (15% vs 18%), ADT+ARPI+docetaxel (19% vs 15%), and ADT+docetaxel (1.3% vs. 3.5%) for PSA-low vs PSA-high, respectively. Baseline PSA was lower in patients with PSA-low vs PSA-high status (median 24 vs 36 ng/mL, p = 0.01). Somatic alterations in *SPOP* (17% vs 11%, p = 0.04) and *ZFHX3* (2.5% vs 6%, p = 0.05) differed between patients with PSA-low and PSA-high, respectively. No significant differences in expression of actionable novel targets including PSMA, TROP2, B7-H3, or STEAP1 were observed between cohorts. Median OS was not reached for patients with PSA-low and was 47 months for patients with PSA-high, with 36-month landmark OS of 83% vs 66%, respectively. On multivariable analysis, PSA-low was independently associated with improved OS (HR 0.51, 95% CI 0.31-0.85, p = 0.01). **Conclusions:** In a real-world cohort, deep PSA response at 6 months portends significantly improved OS in patients with mHSPC and is associated with more *SPOP* and fewer *ZFHX3* alterations. No transcriptomic differences in emerging therapeutic targets were identified. Validation in independent cohorts is warranted. Research Sponsor: None.

5090 Poster Session

Rezvilutamide (Rez) versus bicalutamide (Bic) plus androgen-deprivation therapy (ADT) in high-volume, metastatic, hormone-sensitive prostate cancer (mHSPC): 5-year outcomes of the phase 3 CHART trial. First Author: Dingwei Ye, Fudan University Shanghai Cancer Center, Shanghai, China

Background: In the CHART trial, Rez plus ADT significantly improved radiographic progression-free survival (rPFS) and overall survival (OS) compared with Bic plus ADT in patients (pts) with high-volume mHSPC (Gu et al., Lancet Oncol 2022). Here, we present updated outcomes ~5 years after the enrollment of the last pt. **Methods:** Pts with high-volume mHSPC and without previous chemotherapy or other localized treatment for PC were eligible to be enrolled. Pts were randomized 1:1 to receive ADT plus either Rez (240 mg) or Bic (50 mg) orally once daily. Final analysis for OS was planned after 325 deaths were reported. **Results:** Between Jun 28, 2018, and Aug 6, 2020, 654 pts were randomized to receive Rez plus ADT (n=326) or Bic plus ADT (n=328). As of data cutoff (Jun 6, 2025), with a median follow-up of 72.8 months (IQR 69.1-77.4), there were 141 (43.3%) deaths in Rez plus ADT group and 194 (59.1%) in Bic plus ADT group. OS was improved with Rez plus ADT versus Bic plus ADT (median 78.8 months [95% CI 68.3-not reached (NR)] vs 44.8 months [95% CI 37.1-57.4]; HR 0.59 [95% CI 0.47-0.73]; 2-sided $p<0.0001$). Risk of progression or death in Rez plus ADT group was reduced by 62% compared with Bic plus ADT group (HR 0.38 [95% CI 0.30-0.48]). Other efficacy outcomes also favored Rez plus ADT (Table). Rez plus ADT improved patient-reported quality of life. No new safety signals were observed. **Conclusions:** Rez plus ADT continued to show meaningful survival benefits with manageable toxicities after long-term follow-up, further supporting Rez plus ADT as frontline treatment for pts with high-volume mHSPC. Clinical trial information: NCT03520478. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy endpoints.

	Rez plus ADT (n=326)	Bic plus ADT (n=328)	HR (95% CI)	2-sided p-value
OS, months	78.8 (68.3-NR)	44.8 (37.1-57.4)	0.59 (0.47-0.73)	<0.0001
rPFS per investigator, months	81.0 (62.6-NR)	18.5 (14.8-25.7)	0.38 (0.30-0.48)	<0.0001
rPFS per investigator (sensitivity analysis[#]), months	58.9 (50.10-NE)	18.6 (16.30-22.90)	0.38 (0.31-0.47)	<0.0001
Time to PSA progression, months	NR (NR-NR)	11.0 (9.2-12.9)	0.21 (0.17-0.27)	<0.0001
Time to next skeletal-related event, months	78.8 (58.9-NR)	37.7 (34.3-48.2)	0.63 (0.51-0.78)	<0.0001
Time to initiation of new anti-prostate cancer therapy, months	62.4 (46.4-75.6)	15.1 (13.6-18.1)	0.32 (0.26-0.39)	<0.0001

Data are median (95% CI) unless otherwise indicated.
[#]New anti-cancer therapy and missing tumor assessments were not considered. PSA, prostate specific antigen.

5091 Poster Session

Does a statin a day keep prostate cancer (PC) away?: Statin use and disease progression in patients receiving androgen deprivation therapy (ADT) after radical prostatectomy (RP) in SEARCH. First Author: Maria P. Mogollon, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Prior studies suggest statin use may improve PC outcomes, including PC specific mortality (PCSM) and disease progression in patients receiving ADT. However, prior studies compared patients taking vs not taking statins at the time of ADT, ignoring that many statin non-users initiate statins later on. We evaluated the association between statin use and PC outcomes using both baseline (yes/no) and time-dependent exposure definitions in patients initiating ADT after RP. **Methods:** We conducted a retrospective cohort study of 9,931 patients with PC treated with RP between 1988 and 2020 at 9 VA hospitals from SEARCH Database. Patients who received ADT for biochemical recurrence after 2000 were included. Those with known metastasis prior to ADT or missing covariates of interest were excluded. Characteristics at ADT were stratified by statin use at time of ADT and compared with rank-sum for continuous variables and chi-square for categorical. Univariable and multivariable Cox models tested associations between statin use at ADT and time to metastasis, castration-resistant PC (CRPC), PCSM and all-cause mortality (ACM), adjusted for clinicopathological variables. As ~50% of non-statin users initiated statins after ADT, additional models treated statin use as time-dependent covariate. **Results:** Among 1,274 patients treated with ADT, 784 (62%) used statins at time of ADT. Users were older (median 67 vs 65), initiated ADT in more recent years (median 2013 vs 2010), had longer time from RP to ADT (median 39 vs 21 months), and had higher obesity rates (38% vs 25%). PC characteristics were similar between groups, except users had lower rates of positive nodes (11% vs 17%) and seminal vesicle invasion (28% vs 33%). Statin use at ADT was not significantly associated with time to metastasis, CRPC, PCSM or ACM, though HRs indicated lower risk for statin users (all HRs 0.89-0.98, all $p>0.2$; see table). On time-dependent multivariable analysis, statin use was significantly associated with lower risk of CRPC (p=0.019), PCSM (p=0.020) and ACM ($p<0.001$). Similar results were seen for metastases, though this did not reach significance (p=0.058) (see table). **Conclusions:** Statin use at ADT was not associated with PC outcomes after RP. However, accounting for statin initiation during ADT, statin use was associated with notably lower rates of CRPC, PCSM and ACM, with a trend towards reduced metastasis. These findings support the potential role of statins in slowing PC progression and highlight the need for prospective randomized trials of statins in patients initiating ADT. Research Sponsor: None.

Outcome	Statin at ADT, HR (95% CI)	p	Time-varying statin, HR (95% CI)	p
Metastasis	0.92 (0.71, 1.20)	0.541	0.74 (0.55, 1.01)	0.058
CRPC	0.95 (0.73, 1.24)	0.702	0.69 (0.51, 0.94)	0.019
PCSM	0.98 (0.70, 1.39)	0.920	0.62 (0.42, 0.93)	0.020
ACM	0.89 (0.73, 1.08)	0.229	0.51 (0.40, 0.64)	<0.001

5092 Poster Session

Efficacy and safety of enzalutamide (ENZA) in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) and cardiometabolic comorbidities (CMDs) and/or related concomitant medications (meds): ARCHES post hoc. First Author: Arnulf Stenzl, Department of Urology, University of Tübingen, Tübingen, Germany

Background: In ARCHES, ENZA improved radiographic progression-free survival (rPFS; primary: data cutoff, Oct 14, 2018) and overall survival (OS; prespecified secondary: data cutoff, May 28, 2021; 5-yr follow-up; data cutoff: Jul 31, 2024) vs placebo (PBO) in mHSPC. Our objective was to evaluate efficacy/safety of ENZA in pts with CMDs on related concomitant meds. **Methods:** We examined two groups: 1) full CMD (fCMD): pts with CMDs or on concomitant CMD meds; 2) confirmed CMD (cCMD): pts on CMD-related meds + confirmed CMD diagnosis, validated by medical history captured in concomitant med domain. CMDs included hypertension, cardiac disorders, dyslipidemia, diabetes mellitus. Related concomitant meds were diabetes meds, vasoprotectives, cardiac meds, lipid-modifying agents, antithrombotics, antihypertensives. Primary endpoint: rPFS (fCMD population; data cutoff: Oct 14, 2018). Other endpoints: OS, safety (fCMD population; data cutoff: May 28, 2021). Kaplan–Meier used for time-to-event analysis, with treatment (tx)-group comparisons assessed by stratified log-rank test and hazard ratios (HRs) relative to PBO using Cox proportional hazard models. Sensitivity analysis with cCMD population evaluated rPFS and OS, with OS adjusted for crossover with rank-preserved structure failure time model. **Results:** Of 1150 pts, 938 (82%) were categorized as fCMD and 756 (66%) as cCMD. In the fCMD group, ENZA showed an association with improved rPFS and OS, with similar results for all sensitivity analyses (Table). Similar results also seen in all concomitant med subgroups. At 2021 data cutoff, median tx duration was 41 mo in the ENZA arm, 14 mo in the PBO arm. Tx-emergent adverse event (TEAE) rates (per 100 pt-yr) were similar with ENZA (313.8) and PBO (468.0). TEAEs of special interest rates (per 100 pt-yr) with ENZA vs PBO: fatigue (14.4 vs 18.0); falls (6.2 vs 2.6); fractures (7.3 vs 5.4); select cardiovascular events (2.5 vs 1.6); convulsions (0.2 vs 0.5). No new safety signals were identified. **Conclusions:** Similar to the overall mHSPC study population, ENZA was efficacious and tolerable in pts with CMD. Optimizing CMD may further enhance outcomes for pts with mHSPC, but ENZA remains a front-line option for all mHSPC pt subgroups. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

		ENZA, n (%)	ENZA, median (mo) (95% CI)	PBO[a], n (%)	PBO[a], median (mo) (95% CI)	HR (95% CI)[a]	Nominal *P* value
fCMD		n = 468		n = 470			
	rPFS	73 (16)	NE (NE–NE)	159 (34)	19.5 (16.6–NE)	0.39 (0.29–0.51)	<0.0001
	OS	123 (26)	NE (NE–NE)	169 (36)	NE (49.7–NE)	0.62 (0.49–0.78)	<0.001
	Crossover adjusted OS[b]	123 (26)	NE (NE–NE)	169 (36)	49.7 (44.5–NE)	0.56 (0.43–0.69)	<0.001
cCMD		n = 377		n = 379			
	rPFS[b]	59 (16)	NE (NE–NE)	126 (33%)	19.5 (16.6–NE)	0.41 (0.30–0.56)	<0.0001
	OS[b]	98 (26)	NE (NE–NE)	137 (36)	NE (49.7–NE)	0.62 (0.48–0.80)	0.0002

[a]Comparator; [b]Sensitivity analysis.
NE, not evaluable.

5093 Poster Session

Predictors of treatment (tx) duration in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) treated with enzalutamide (ENZA): A post hoc analysis of ARCHES. First Author: Andrew J. Armstrong, Center for Prostate & Urologic Cancers, Duke Cancer Institute, Durham, NC

Background: In ARCHES (NCT02677896), ENZA + androgen-deprivation therapy (ADT) significantly improved radiographic progression-free survival (primary: data cutoff, Oct 14, 2018) and overall survival (prespecified secondary: data cutoff, May 28, 2021; 5-year follow-up: data cutoff, Jul 31, 2024) vs placebo + ADT in mHSPC. This post hoc analysis explored factors associated with different ENZA tx durations (5-year follow-up). **Methods:** Reasons for tx discontinuation (DC) including toxicity and progression, and baseline and on-treatment factors underlying tx persistence, were compared descriptively among pts with short (0–2 years [y]; STx), medium (2–5 y; MTx), and long Tx duration (> 5 y; LTx) (STx pts represent non-responders; MTx/LTx pts represent tx responders). **Results:** Of 572 ENZA-treated pts, 204 (36%) were STx; 140 (24%) MTx; 228 (40%) LTx. STx pts were more likely to be older vs MTx and LTx, with high-volume disease (HVD) and Eastern Cooperative Oncology Group performance status (ECOG PS) 1, although 55.3% of LTx had HVD and 73.2% had synchronous metastases. Progressive disease and tx-emergent adverse events (TEAEs) were the most common reasons for tx DC. Drug-related TEAEs (per 100 pt-y) were more common in STx (156.0) vs MTx (89.5) and LTx (47.1), as were those leading to tx DC (STx: 12.4; MTx: 1.5; LTx: 0.1). Rates (per 100 pt-y) of TEAEs leading to ENZA dose reduction were higher in STx (6.2) vs MTx (5.8) and LTx (2.0). The rate (per 100 pt-y) of drug-related TEAEs of special interest were generally higher in STx vs MTx and LTx: convulsions (1.0 vs 0.0 vs 0.0); fatigue (19.0 vs 10.7 vs 4.8), select cardiovascular events (1.0 vs 0.6 vs 0.1); falls (2.4 vs 3.2 vs 1.1); fractures (0.5 vs 1.5 vs 0.5). **Conclusions:** Our findings demonstrate that LTx and MTx tended to have more favorable pt and disease characteristics vs STx, although majority of LTx had adverse prognostic features. While progressive disease was the most common reason for DC, AEs/withdrawals were the second most common. Most TEAEs of special interest were more frequent in STx. Reasons for AE-related tx changes are multifactorial, and optimal management of AEs and comorbidities, as well as dose modifications, can optimize ENZA tx. Clinical trial information: NCT02677896. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Pt characteristics	STx (n = 204) n (%)	MTx (n = 140) n (%)	LTx (n = 228) n (%)
Age: ≥ 18 to 64/≥ 65 to ≤ 84/≥ 85 y	45 (22.1)/150 (73.5)/9 (4.4)	38 (27.1)/100 (71.4)/2 (1.4)	65 (28.5)/159 (69.7)/4 (1.8)
Prostate-specific antigen nadir < 0.2 ng/mL post-baseline	84/189 (44.4)	97/123 (78.9)	181/198 (91.4)
ECOG PS 0/1	147 (72.1)/57 (27.9)	110 (78.6)/30 (21.4)	190 (83.3)/37 (16.2)
HVD	148 (72.5)	80 (57.1)	126 (55.3)
Synchronous disease	162 (79.4)	108 (77.1)	167 (73.2)
Reasons for tx DC			
Progressive disease	106 (52.0)	63 (45.0)	19 (8.3)
AE + withdrawal	74 (36.3)	40 (28.6)	7 (3.1)
AE	40 (19.6)	25 (17.9)	2 (0.9)
Withdrawal	34 (16.7)	15 (10.7)	5 (2.2)
Death	10 (4.9)	10 (7.1)	10 (4.4)

5094 Poster Session

Outcomes with androgen-deprivation therapy (ADT) plus androgen receptor pathway inhibitors (ARPIs) in veterans with de novo metastatic castration-sensitive prostate cancer (mCSPC) who were elderly, frail, or had high comorbidity: A subgroup analysis of enzalutamide and high-volume disease. First Author: Martin W. Schoen, Medicine Service, Veterans Affairs St. Louis Healthcare System, St. Louis, MO

Background: Clinical trials show significant overall survival (OS) benefits of combining ADT with ARPIs (abiraterone, apalutamide, darolutamide, or enzalutamide [ENZA]) vs ADT in mCSPC. The effects of ADT + ARPI in patients (pts) who are elderly, frail, or have high comorbidity burden remain unclear due to underrepresentation in clinical trials. This observational cohort study examined OS in two subgroups of this population: pts who received ENZA and those with high-volume disease (HVD). **Methods:** Veterans Health Administration records were used to assess OS in pts with de novo mCSPC treated with ADT + ARPI ± nonsteroidal antiandrogen (NSAA; ADT + ARPI group) or ADT ± NSAA (ADT group). Pts were aged ≥75 years (y) or had Veterans Affairs Frailty Index (VA-FI) > 0.2 or Charlson Comorbidity Index (CCI) ≥3. Subgroups comprised pts who: 1) initiated ADT + ENZA (HVD or low-volume disease); or 2) had HVD with any ARPI. Pts were indexed on first ADT date (Jun 1, 2017–Dec 31, 2022) and followed until censoring (Jun 1, 2025) or death. Mortality risk was estimated using a multivariable, time-varying Cox model to account for time between ADT + ARPI initiation adjusted for volume of disease, age, body mass index, CCI, and prostate-specific antigen level. **Results:** Of 1,629 pts, 272 (16.7%) received ADT + ENZA and 1,357 (83.3%) received ADT; median follow-up was 34.1 and 23.4 months (mo), respectively. Compared with ADT, the ADT + ENZA subgroup was younger (median age 77.5 vs 81.2 y, standardized mean difference [SMD]: −0.34) with similar frailty (VA-FI > 0.2: 67.3% vs 71.5%, SMD: 0.09) and more HVD (71.7% vs 61.5%, SMD: 0.22). ADT + ENZA was associated with significantly lower risk of death vs ADT (adjusted hazard ratio [aHR] 0.70; 95% CI: 0.60–0.83; $P<0.001$; Table). Among 1,541 pts with HVD, 706 (45.8%) received ADT + ARPI and 835 (54.2%) received ADT; median follow-up was 29.1 and 18.8 mo, respectively. Pts who received ADT + ARPI were younger (median age 77.1 vs 81.9 y, SMD: −0.44) and had less frailty (VA-FI > 0.2: 66.2% vs 72.9%, SMD: 0.15). ADT + ARPI was associated with significantly lower risk of death vs ADT (aHR: 0.73; 95% CI: 0.65–0.83; $P<0.001$). **Conclusions:** In this real-world cohort analysis of pts with de novo mCSPC who were elderly, frail, or had high comorbidity, ADT + ENZA was associated with prolonged survival compared with ADT. In pts with HVD, ADT + ARPI was associated with longer survival vs ADT. Research Sponsor: Astellas Pharma Inc.; Pfizer Inc.

Subgroup	ADTMedian survival,mo (95% CI), n	ADT + ARPI[a]Median survival,mo (95% CI), n	aHR (95% CI)[b]; *P* value
ENZA	23.4 (21.9–25.2), n = 1,357	36.1 (32.9–40.1), n = 272	0.70 (0.60–0.83); $P<0.001$
HVD	18.8 (17.5–20.5), n = 835	29.1 (26.0–32.3), n = 706	0.73 (0.65–0.83); $P<0.001$

[a]ENZA subgroup treatment arm: ADT + ENZA.
[b]ADT = reference.

5095 Poster Session

Classification tree phenotypes for early treatment-limiting toxicity after androgen receptor pathway inhibitor initiation in metastatic hormone-sensitive prostate cancer from the IRONMAN registry. First Author: Alexandra Larkin, Department of Medicine, Section of Hematology/Oncology, The University of Chicago, Chicago, IL

Background: Androgen receptor pathway inhibitors (ARPIs) improve survival in metastatic hormone-sensitive prostate cancer (mHSPC), but early treatment-limiting toxicity remains common. Using the IRONMAN (International Registry for Men with Advanced Prostate Cancer; NCT03151629) registry, we developed an interpretable classification tree that yields simple rule-based 1-year risk strata for a composite adverse outcome (AO) after ARPI initiation. **Methods:** Men with mHSPC initiating first-line ARPI with at least 12 months follow-up or AO within 365 days were included (n=583). AO was the first serious adverse event (SAE) or ARPI discontinuation for toxicity or other non-progression reasons; progression-attributed events were not counted. Candidate peri-ARPI initiation predictors (demographics, labs, treatments/medications, patient-reported outcomes) were screened for missingness, imbalance, and collinearity, reduced by stepwise logistic regression, and entered a recursive-partitioning classification tree with restricted depth and node size. Discrimination was summarized by area under the receiver operating characteristic curve (AUC) and repeated 3-fold cross-validation. Terminal nodes were collapsed into low, intermediate, and high-risk strata by predicted 1-year AO. **Results:** Overall, 122/583 men (20.9%) had AO within 1 year (85 SAEs; 37 discontinuations [28 toxicity, 9 other non-progression]). AO-free survival did not differ by ARPI agent (log-rank p=0.40); ARPIs were pooled. Peri-ARPI docetaxel exposure (triplet therapy) was uncommon (2.4%). The final tree retained nine predictors, including European Organization for Research and Treatment of Cancer global health rating (1-7), hemoglobin, worst pain (0-10), lactate dehydrogenase (LDH), age, docetaxel, and opioid agonist and systemic steroid use. In-sample AUC was 0.76 (95% CI 0.71-0.81); cross-validated AUC was 0.60 (95% CI 0.55-0.65). Collapsed strata showed distinct 1-year AO risk (Table 1). High-risk phenotypes reflected poor health/symptoms with anemia and/or elevated LDH, and a treatment-intensity phenotype with triplet therapy plus opioids and steroids. **Conclusions:** A small classification tree identified three clinically transparent phenotypes of early AO after ARPI initiation in mHSPC and can be applied as simple decision rules to support monitoring and shared decision-making. External validation is needed. Research Sponsor: Movember Foundation; Sanofi; Prostate Cancer Clinical Trials Consortium (PCCTC); Amgen; Astellas; AstraZeneca; Bayer; Janssen; Merck; Novartis.

Tree risk strata and 1-year AO risk.

Risk stratum	n (%)	1-year AO %, (95% CI)
Low	422 (72)	10.7 (7.7–13.6)
Intermediate	80 (14)	26.3 (16.6–35.9)
High	81 (14)	69.1 (59.1–79.2)

5096 Poster Session

Correlation of baseline testosterone (T) level with survival outcomes in patients (Pts) with metastatic hormone-sensitive prostate cancer (mHSPC): Analysis of patient (pt)–level data from SWOG 1216 study. First Author: Georges Gebrael, Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT

Background: Retrospective data suggest that low baseline serum T may be associated with inferior survival outcomes in mHSPC [PMID: 38444678]. Whether this relationship persists in rigorously controlled, randomized clinical trial populations remains unclear. We examined the prognostic impact of baseline T using patient-level data from the phase 3 SWOG 1216 trial which randomized pts with mHSPC in 1:1 to ADT + bicalutamide (standard arm) or ADT + orteronel (experimental arm). **Methods:** Patients treated on SWOG 1216 trial with available baseline T levels were eligible and included in this secondary analysis. Baseline T was summarized by median (IQR) and dichotomized at the median as $\leq$ median vs $>$ median. Overall survival was the primary endpoint; progression-free survival (PFS) and prostate-specific antigen (PSA) response were secondary endpoints. PSA response rates were divided into complete response (CR; PSA $<$0.2 ng/mL), partial response (PR; PSA between 0.2 and 4.0 ng/mL), and no response (NR; PSA $>$4.0 ng/mL) at a 7-month landmark following randomization. OS and PFS were estimated by Kaplan-Meier within each arm, with median survival (95% CI) and number of events reported. Comparisons were performed using the log-rank test. PSA response was summarized as n (%), and groups were compared using Pearson's chi-squared test. All tests were two-sided with alpha = 0.05. **Results:** Of 1279 pts, 218 pts had baseline T levels. Median T level was 312.5 ng/ml (IQR 89.25 - 462 ng/ml). In both experimental and standard arms, there was no significant difference in OS, PFS, or PSA response between patients with baseline T levels above vs below the median (Table). Similarly, in both arm, there was no difference in outcomes based on baseline T levels grouped by quartiles, as well as baseline T levels as a continuous variable (data will be presented at the conference). **Conclusions:** In this patient-level analysis of a phase 3 trial, there was no statistically significant association between baseline T and outcomes in mHSPC. Based on these data, baseline T may not be used for prognostication or treatment selection in patients receiving systemic therapy in mHSPC. Limitations include a small sample size. These hypothesis-generating data require external validation before clinical application. Research Sponsor: Supported by NIH/NCI/NCTN under grant No. U10CA180888, U10CA180819, U10CA180820, and U10CA180821; Millennium Pharmaceuticals, Inc (Takeda Pharmaceutical Company LTD).

Treatment Arm	T Level	OS Median (95% CI), months	N (events)	P-value	PFS Median (95% CI), months	N (events)	P-value	PSA complete response n (%)	PSA partial response n (%)	No PSA Response (%)	P-value
Experimental	$\leq$ Median	63 (47, NR)	71 (37)	0.11	30 (20, 64)	71 (49)	0.11	37 (50%)	18 (60%)	16 (62%)	0.5
	$>$ Median	NR (68, NR)	59 (22)		57 (26, NR)	59 (30)		37 (50%)	12 (40%)	10 (38%)	
Standard	$\leq$ Median	72 (45, NR)	38 (20)	0.7	19 (12, 34)	38 (29)	0.9	14 (42%)	9 (45%)	15 (43%)	$>$0.9
	$>$ Median	57 (43, NR)	50 (22)		19 (13, 35)	50 (39)		19 (58%)	11 (55%)	20 (57%)	

5097 Poster Session

Outcomes of radical radiotherapy in de novo low-burden metastatic hormone-sensitive prostate cancer vs prostate radiotherapy alone. First Author: Kelvin Yan, Chinese University of Hong Kong, Hong Kong, Hong Kong

Background: The current standard of care (SoC) for metastatic hormone-sensitive prostate cancer (mHSPC) is androgen deprivation + systemic therapy. Oligometastatic HSPC, however, represents a unique disease entity following the STAMPEDE trial, where de novo mHSPC patients with a CHAARTED-defined low disease burden (DN-mHSPC-LV) had a hazard ratio of death of 0.68 after prostate radiotherapy (PRT). Despite the SABR-COMET results of a survival benefit with stereotactic RT on metachronous oligometastatic sites of predominantly prostate patients, radical RT (RRT) in the DN-mHSPC-LV setting has not been studied. This study analysed the outcomes of such patients receiving RRT to all disease sites vs PRT alone. **Methods:** DN-mHSPC-LV patients receiving RRT to the prostate and all oligometastatic sites (Arm A) vs PRT alone (Arm B) in a Hong Kong tertiary hospital between 1st January 2012 and 1st January 2023 were reviewed. Outcomes of progression-free survival (PFS), overall survival (OS) and treatment-related toxicity (TrT) were analysed using the Kaplan-Meier and multivariable Cox-proportional hazards models. **Results:** 127 eligible patients (60 in Arm A & 67 in Arm B) were identified. The median numbers of oligometastatic sites of 1-3 and = $>$ 4 were balanced between the two arms. The median Gleason score was 8 in both arms. Median T/N/M staging was mostly balanced but more patients in Arm B had N1 disease. Presenting PSA (ng/mL) was higher in Arm A (38.5) than Arm B (27.9). Arm A received up to 76Gy/38# to the prostate + a boost of up to 67.5Gy or stereotactic RT to the oligometastatic sites. Arm B received 55-60Gy/20# to the prostate alone. Patients were started on long-term androgen deprivation therapy. Median follow-up was 40.2 months and 30.3 months in Arms A and B, respectively. Median PFS was not reached (NR) in either of the treatment arms. On multivariate analysis, 5-year PFS was 86.1% vs 50.3% in Arms A and B, respectively (*P* = 0.0173; HR 0.213; 95% CI 0.059-0.761). OS data were not yet mature and there was no difference in TrT between the arms. **Conclusions:** To our knowledge, this is the first study comparing radical RT against the SoC of prostate RT alone in DN-mHSPC-LV. Radical RT was well tolerated and is significantly cheaper than next-generation hormone agents in prostate cancer. 5-year PFS was significantly better with radical RT vs prostate RT alone. PFS is an established surrogate for OS in prostate cancer. This study therefore justifies prospective studies on RRT for DN-mHSPC-LV. More importantly, as prospective trials with an OS endpoint in prostate cancer will take close to a decade to mature, this study provides interim evidence to support radical treatment in this group of patients, in whom cure or long-term control may be achieved, where prospective trials are anticipated to take much longer to complete. Research Sponsor: None.

5098 Poster Session

Impact of a whole-food plant-based diet (WFPBD) on weight and metabo-inflammation in men with prostate cancer (PC) receiving androgen deprivation therapy (ADT): A multi-center randomized control trial. First Author: Nicole Jacobs, Weill Cornell Medicine, New York, NY

Background: Obesity promotes a chronic inflammatory state associated with PC progression. ADT can cause weight gain, accumulation of body fat, insulin resistance and increased risk of diabetes and cardiovascular disease. A WFPBD promotes weight loss, decreases inflammation, and shifts the gut microbiome to promote insulin sensitivity. We hypothesized that a WFPBD and behavioral intervention will promote weight loss and a reduction in adiposity in overweight/obese patients with PC on ADT. **Methods:** Pts with PC with BMI $\geq$ 27 receiving ADT with an LHRH/GnRH analogue for $>$24 wks pre-study (+ AR pathway inhibitor allowed if stable dose for $>$3 mos) with plan $>$26 more wks were eligible. 60 patients were randomized 1:1. WFPBD group: 12 prepared and home delivered WFPBD meals per wks 1-4, 6 meals wks 5-8 and coaching to assist in self-prepping plant-based meals (wks 9-26); Control group: counseling on a general healthful diet from a Registered Dietician weekly for 8 wks, then monthly (wks 9-26). Baseline and serial measurements (pre-intervention, wks 4, 8 and 26): weight, body composition assessment via dual energy x-ray absorptiometry (DXA), and biomarkers of inflammation and metabolism were collected. Primary endpoint was weight loss at 4 weeks (with an 80% power to detect an effect size 0.74 standard deviations with a 2-sided significance level of 0.05 using a two-sample t-test). Secondary objectives were change in body composition, biomarkers of metabolic disorders and cardiovascular risk and quality of life measurements. **Results:** 60 pts were randomized (31 control, 29 WFPBD). Median age was 73; Race: 65% white, 28% Black, 2% Asian, 5% other/unknown; Median baseline weight 98 kg; No difference in baseline HbA1c or lipid profile between groups. Mean weight loss (kg) at 4, 8 and 26 wks: WFPBD: 3.9, 5.3 and 6.1 kg; Control 1.3, 1.6, 2.1 kg, respectively (each timepoint pair p$<$0.001). DXA measured BMI change at 4 and 26 wks: WFPBD: -1.1 and -1.93 kg/m^2, Control: 0.35 and 0.25 kg/m^2 (each timepoint pair p$<$0.001). DXA measured mean lean (LM), fat (FM) and total mass (TM) showed declines at 4 wks in WFPBD versus Control (LM -2.4 vs -0.64 (p$<$0.001); FM -1.3 vs -0.35 (p=0.023); TM -3.61 vs -0.88 (p$<$0.001), whereas at 26 weeks only FM and TM remained significantly less (LM -2.2 vs -1.4 (p=0.143); FM -5.3 vs -0.8 (p=0.001); TM -6.7 vs -2.2 (p$<$0.001). No significant differences were seen in HbA1c or lipid profiles at 6 mos. **Conclusions:** Compared with nutritional counseling, obese men with PC on ADT subjected to a home-delivered WFPBD for 2 mos and behavioral coaching experienced significantly greater weight loss, BMI reduction and decreases in total and fat mass that persisted for 6 months. Biomarkers of metabo-inflammation, insulin levels, fecal microbiota and metabolites, and serum for metabolomics collected are undergoing analyses. Clinical trial information: NCT05471414. Research Sponsor: Prostate Cancer Foundation; U.S. Department of Defense; U.S. National Institutes of Health.

5099 **Poster Session**

Germline genetic correlates in metastatic hormone-sensitive prostate cancer (mHSPC) treated with androgen deprivation therapy (ADT) plus non-steroidal anti-androgen (NSAA) or enzalutamide (ENZA): Correlative study of ENZAMET (ANZUP 1304). First Author: Anis Hamid, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The international, randomized, phase III ENZAMET trial (n=1125) showed improved overall survival (OS) with ADT plus ENZA vs ADT plus NSAA for mHSPC. Observational studies showed that the mHSPC genetic landscape is comparable to castration resistant prostate cancer (CRPC). Prognostic and predictive impact of inherited pathogenic variants (PVs), including those affecting *BRCA1*, *BRCA2* and other DNA damage and repair (DDR) genes, on androgen receptor pathway inhibitor (ARPI)-treated mHSPC is under investigation. **Methods:** Whole exome sequencing of germline DNA prospectively obtained from ENZAMET pts. Variant annotation and effect prediction identified PVs (altered "+" vs wild-type "-"). Prognostic effect of PVs was assessed within arms. Endpoints: clinical progression-free survival (PFS) and OS by Kaplan-Meier method. Hazard ratios (HRs) were estimated using Cox models. Multivariable analyses (MVA) adjusted for Gleason score (GS), volume (vol), metachronous vs synchronous and docetaxel (D) use. **Results:** All 847 available samples were successfully sequenced. 123 PVs were identified in 117 (13.8%) pts, of which 46 (5.43%) pts harbored a PV in ≥1 DDR gene. The rate of pathogenic germline *BRCA1*/*BRCA2* (BRCA) PVs was 2.13% (39.1% of DDR PVs). Proportions of arm, D use, vol and visceral disease were similar between DDR+ vs DDR- and BRCA+ vs BRCA-. Synchronous mHSPC in DDR+ vs DDR- and BRCA+ vs BRCA- was 41.3% vs 63.0% and 44.4% vs 62.2%, respectively. PFS and OS estimates were similar between BRCA+ and BRCA- groups in the overall cohort (5-yr OS: 55.6% vs 61%; 3-yr PFS: 50% vs 53.5%, respectively) and in the ENZA arm, but differed in the NSAA arm (Table). BRCA+ treated with ADT+NSAA (67% D use) had shortest PFS (median PFS: 11.3m vs 24.9m [BRCA-], HR 1.85, 95% CI: 0.95-3.6). D use associated with poorer outcomes. In MVA, the HR(PFS) for BRCA+ in NSAA arm was 1.47 (95% CI 0.71-3.04, p=0.3) vs ENZA arm: HR 0.98, (95% CI 0.31-3.08, p=0.97). Vol and GS were independently significant in both arms. **Conclusions:** In one of the largest germline genetic studies from a phase III mHSPC trial, we observed recurrent DDR and BRCA PVs at a lower rate than institutional cohorts. Germline BRCA PVs are associated with a shorter PFS on ADT+NSAA – an effect which may be mitigated by ENZA. Validation in independent trial cohorts is ongoing. Research Sponsor: National Cancer Institute; Movember Foundation; Australian Department of Health; Astellas and Pfizer; US Department of Defense.

Outcomes by arm/docetaxel and BRCA status.

	n	5y-OS % (95% CI)	3y-PFS % (95% CI)
NSAA only BRCA-	238	56.6 (50.0-62.7)	42.9 (36.5-49.1)
NSAA only BRCA+	3	66.7 (5.4-94.5)	66.7 (5.4-94.5)
NSAA+D BRCA-	176	54.7 (47.0-61.8)	32.5 (25.7-39.6)
NSAA+D BRCA+	6	33.3 (4.6-67.6)	16.7 (0.8-51.7)
ENZA only BRCA-	228	70.6 (64.2-76.0)	73.3 (67.0-78.5)
ENZA only BRCA+	7	71.4 (25.8-92.0)	71.4 (25.8-92.0)
ENZA+D BRCA-	187	60.7 (53.2-67.3)	62.3 (54.9-58.8)
ENZA+D BRCA+	2	NE	50.0 (0.6-91.0)

5100 **Poster Session**

Prognostic value of PSA nadir ≤0.2 ng/mL in metastatic castration-sensitive prostate cancer: A systematic review and meta-analysis. First Author: Arjun Pon Avudaiappan, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: The treatment landscape for metastatic castration-sensitive prostate cancer (mCSPC) has changed substantially with the adoption of early treatment intensification using androgen-receptor pathway inhibitors (ARPI) and chemotherapy, in addition to traditional androgen deprivation therapy (ADT). PSA nadir has long been used to support prognosis and inform treatment decisions; however, the historical thresholds were established based on patients treated solely with ADT and may not fully reflect outcomes in the modern era of combination therapy. Although emerging evidence suggests that a PSA nadir of < 0.2 ng/dl is associated with improved disease control and survival, a systematic evaluation across available mCSPC trials is needed to clarify the prognostic value of PSA nadir and its potential role in guiding treatment decisions. **Methods:** A systematic search of PubMed, Cochrane Library, and ClinicalTrials.gov was conducted through October 31, 2025, to identify studies reporting outcomes by PSA nadir category in men with mCSPC. Eligible studies included patients initiating systemic therapy with ADT alone or in combination with ARPI and/or chemotherapy. The reported hazard ratios (HR) for time-to-event endpoints stratified by PSA nadir (=< 0.2 ng/dl) were analyzed to get pooled HR. The primary outcome was overall survival (OS). **Results:** A total of eight trials comprising 6,582 patients were included. The pooled HR for the primary endpoint, overall survival (OS), was 0.27 (95% CI: 0.21–0.36; I^2 = 88.1%), indicating a clinically meaningful survival advantage among patients achieving PSA nadir. Consistent findings were observed for secondary outcomes. Achieving a PSA nadir ≤0.2 ng/mL was associated with longer radiographic progression-free survival (HR 0.23; 95% CI: 0.12–0.45; I^2 = 87.8%) and longer PSA progression-free survival (HR 0.19; 95% CI: 0.08–0.45; I^2 = 92.6%). A PSA nadir ≤0.2 ng/mL also correlated with a delayed onset of castration resistance (HR 0.31; 95% CI: 0.16–0.61; I^2 = 93.5%). Assessment of publication bias using Begg's and Egger's tests revealed no significant evidence of small-study effects for any endpoint. **Conclusions:** Across contemporary mCSPC trials, achieving a PSA nadir of ≤0.2 ng/mL consistently predicts improved survival and delayed disease progression. These findings establish PSA nadir as a clinically meaningful and cost-effective biomarker that can help guide treatment-intensification and de-intensification strategies in routine practice. Research Sponsor: None.

Study	Hazard Ratio (HR)	95% Confidence Interval (CI)	Weight (%)
SWOG9346	0.23	[0.19, 0.27]	13.80
SWOG S0925	0.20	[0.14, 0.28]	12.06
ARASENS	0.49	[0.37, 0.65]	12.65
CHAARTED	0.41	[0.32, 0.53]	13.00
ARCHES	0.24	[0.17, 0.34]	11.82
TITAN	0.35	[0.25, 0.48]	12.09
ARANOTE	0.14	[0.09, 0.21]	10.79
SWOG S1216	0.25	[0.21, 0.30]	13.78
Overall (Pooled)	0.27	[0.21, 0.36]	100.00

5101 **Poster Session**

Clinical impact and molecular profiling of *PTEN* loss and *TMPRSS2:ERG* fusion in metastatic hormone-sensitive prostate cancer. First Author: Carme Crous, Department of Medical Oncology, IDIBAPS, Hospital Clínic, Barcelona, Barcelona, Spain

Background: *PTEN* loss in prostate cancer (PC) is associated with aggressive disease and resistance to conventional treatments. *TMPRSS2:ERG* fusion (TE+) is one of the most frequent genomic alterations in PC and frequently co-occurs with *PTEN* loss, yet the clinical impact of this association remains unclear. The aim of the present study is to evaluate clinical outcomes in metastatic hormone-sensitive PC (mHSPC) patients (pts) stratified by TE and *PTEN* status and to characterize associated gene expression signatures. **Methods:** We conducted a multicenter ambispective study enrolling mHSPC pts receiving different treatment strategies. The primary objective was to evaluate castration resistant PC-free survival (CRPC-FS) according to *PTEN* and TE. TE fusion and *PTEN* status were assessed in FFPE tumor samples using mRNA expression profiling by nCounter. $PTEN_{low}$ was defined with a previously validated cut-off (Jimenez, *Eur Urol Onc* 2023). RNA-seq analysis was performed to molecularly characterize $PTEN_{low}$ and TE associated transcriptional profiles using gene set variation analysis. **Results:** A total of 295 pts were included; median age was 72.9 years, 46.1% had high-volume disease and 66.8% presented *de novo* stage IV disease. Treatment consisted of androgen deprivation therapy (ADT) plus abiraterone (n=97), apalutamide (n=157), enzalutamide (n=41). Overall, 74 pts were $PTEN_{low}$ and 90 pts were TE+. There were no significant differences in baseline characteristics according to *PTEN* or TE. Among $PTEN_{low}$ pts, 33 (44.6%) were TE+. There was a positive correlation between $PTEN_{low}$ and TE+ (p=0.01). With a median follow-up of 31.9 months (range 0.8 – 91.3), 32% of pts progressed to CPRC and 31.2% died. In the overall cohort, $PTEN_{low}$/TE- tumors (14.1%) were associated with the poorest clinical outcomes, showing significantly inferior CRPC-free survival (HR 2.1, p=0.0027) and overall survival (HR 2.1, p=0.0058). Within the $PTEN_{low}$ subgroup, TE+ tumors demonstrated significantly improved CRPC-FS compared with TE- negative tumors (HR 0.45, p=0.04), with a non-significant trend toward improved overall survival (HR 0.48, p=0.07). In the 35 pts with RNA-seq analysis, $PTEN_{low}$/TE- tumors were characterized by enrichment of DNA repair and neuroendocrine and EZH2 signatures (p=0.04 and p=0.03 respectively). $PTEN_{low}$/TE+ had enrichment of *PI3K* signaling (p=0.01) and epithelial differentiation (p=0.05). Androgen-response hallmark was infraexpressed in $PTEN_{low}$ tumors regardless of TE status. **Conclusions:** $PTEN_{low}$/TE- tumors exhibited the worst clinical outcomes, while TE+ in $PTEN_{low}$ disease partially rescued the adverse phenotype. Combined *PTEN* and TE stratification may therefore inform risk-adapted treatment escalation and intensification strategies. Research Sponsor: Janssen-Pharmaceuticals [56021927PCR4029]; Instituto de Salud Carlos III [PI18/00714 and PI24/00631], co-funded by the European Union.

5102 **Poster Session**

Quantitative results from PSMAtrack: A prospective study evaluating changes in PSMA-PET during initial systemic therapy for metastatic hormone-sensitive prostate cancer (mHSPC). First Author: Praful Ravi, Dana-Farber Cancer Institute, Boston, MA

Background: PSA <0.2 ng/mL after 6 months (m) of therapy with androgen deprivation therapy (ADT) and an androgen receptor pathway inhibitor (ARPI), ± docetaxel is strongly prognostic in patients (pts) with mHSPC. This prospective, single-institution pilot study aimed to investigate PSMA-PET for assessing early dynamic changes in PSMA expression and tumor volume in response to treatment for mHSPC and to determine if changes in quantitative PSMA-PET parameters are associated with 6m PSA response. **Methods:** Key eligibility was mHSPC by conventional imaging with plan to start ADT and ARPI ± docetaxel. Primary or metastasis-directed radiotherapy was not permitted during the first 6m. F18-flotufolastat PSMA-PET was performed at baseline within 21 days of ADT start and after 6m of ADT+ARPI±docetaxel. PSMA-PET scans were qualitatively reviewed for PSMA-avid prostate cancer, (i.e., PSMA uptake > background blood pool in a pattern consistent with prostate cancer). Quantitative PSMA-PET parameters were collected including PSMA-avid total tumor volume (TTV, voxel SUV>3), TTV SUVmean and TTV SUVmax (aPromise, EXINI Diagnostics; LesionID MIM software, GE Healthcare). PSA values at baseline and after 6m of therapy were collected. Descriptive statistical analyses, Wilcoxon test, and Pearson correlations were used. **Results:** 20/21 enrolled pts (median age 70 years [range 60-95]) had evaluable baseline and 6m PSMA-PET scans. 12 (60%) received ADT+ARPI, 8 (40%) received ADT+ARPI+docetaxel, and median baseline PSA was 55ng/mL (range 2-3,696); 13 (65%) had high-volume mHSPC by CHAARTED criteria. At 6m, median PSA was 0.29 ng/mL (range <0.02-177), and 9 pts (45%) had a PSA ≤0.2 ng/mL. All 20 pts had residual PSMA-avid disease at 6m by qualitative review, with most (n=17, 85%) having residual disease outside the prostate; 2 pts (10%) had new lesions seen on 6m PSMA-PET. At 6m, median TTV and SUVmax, but not SUVmean, were significantly lower for those with PSA ≤0.2 than PSA >0.2 ng/mL (Table); baseline TTV was strongly correlated with 6m PSA (r=0.74, p<0.01). PSA and TTV were well correlated at baseline (r=0.68, p=0.001) and at 6m (r=0.81, p<0.01), as were changes in PSA and TTV from baseline to 6 m (r=0.67, p=0.001). **Conclusions:** Persistent PSMA-avid disease was seen in all pts with mHSPC after 6m of ADT+ARPI±docetaxel, regardless of PSA at 6m. Pts with 6m PSA >0.2ng/mL had significantly higher TTV and SUVmax at 6m PSMA-PET, and TTV best correlated with PSA levels at baseline and 6 m. Using 6m PSMA-PET could identify mHSPC pts with suboptimal initial response to standard therapy for consolidative therapeutic strategies. Clinical trial information: NCT06479187. Research Sponsor: Blue Earth Diagnostics.

	6m PSA ≤0.2 ng/mL, median (range)	6m PSA >0.2 ng/mL, median (range)	P
TTV (mL)	7.7 (0.4-79.9)	147 (5.9-3440)	<0.01
SUVmax	8.7 (4.8-39.2)	47.4 (11.7-162)	<0.01
SUVmean	5.3 (4.0-8.8)	6.4 (4.2-16.8)	0.14

5103 **Poster Session**

Prostate-specific antigen outcomes of darolutamide and androgen deprivation therapy in patient subgroups by age, comorbidities, and concomitant medications: ARANOTE post hoc analyses. First Author: Fred Saad, Urology Department, University of Montreal Hospital Center, Montreal, QC, Canada

Background: Darolutamide (DARO) + androgen deprivation therapy (ADT) significantly improved radiological progression-free survival (HR 0.54, 95% CI 0.41–0.71; P<0.0001) vs placebo (PBO) + ADT in patients (pts) with metastatic hormone-sensitive prostate cancer (mHSPC) in the phase 3 ARANOTE (NCT04736199) trial, with a favorable safety profile. Here, we report the impact of age, comorbidities (comorbid), and use of concomitant medications (conmeds) ongoing at baseline on prostate specific antigen (PSA) outcomes in pts treated with DARO or PBO. **Methods:** Pts were randomized 2:1 to DARO 600 mg orally twice daily or PBO, both with ADT. Pts were grouped by age and number/type of comorbid or conmeds reported at baseline. Descriptive statistics (*post hoc*) summarized baseline demographics, disease characteristics, and PSA outcomes by age, comorbid, and conmed subgroups. **Results:** Baseline demographics and disease characteristics were generally similar between DARO (n=446) and PBO (n=223) across all subgroups by age (<65, 65–74, or ≥75 years [yrs]), comorbid (<5 or ≥5), and conmeds (<5 or ≥5), respectively. Rates of reaching PSA <0.2 ng/mL at any time were consistently higher with DARO vs PBO across all age (<65 yrs, 62% [n=69/112] vs 21% [n=13/63]; 65–74 yrs, 62% [n=116/187] vs 21% [n=19/89]; ≥75 yrs, 64% [n=81/126] vs 12% [n=7/59]), comorbid (<5, 66% [n=160/244] vs 21% [n=26/122]; ≥5, 66% [n=86/130] vs 14% [n=10/71]), and conmed (<5, 67% [n=115/173] vs 22% [n=21/96]; ≥5, 62% [n=93/151] vs 16% [n=11/71]) subgroups. With DARO, rates of reaching PSA <0.2 ng/mL at any time were consistent among pts with metabolic disorders with or without corresponding conmeds (71% [n=43/61] vs 69% [n=29/42]). The rate of reaching PSA <0.2 ng/ml was slightly lower in patients with cardiovascular disorders who were not receiving corresponding conmeds at baseline (51% [n=22/43]) compared with those receiving corresponding conmeds (64% [n=119/187]). A substantially lower rate of PSA progression was observed with DARO (8% [n=22/266]) vs PBO (33% [n=13/39]) among pts that reached PSA <0.2 ng/mL. Median time to PSA progression among patients that reached PSA <0.2 ng/mL was 421 days (range, 85–702) and 256 days (range, 85–514) for DARO and PBO, respectively. **Conclusions:** Overall, an efficacy benefit was observed with DARO, irrespective of age, and number of comorbidities or concomitant medications reported at baseline in pts with mHSPC, including those with cardiovascular or metabolic disorders, with or without corresponding conmeds, respectively. These results support the use of DARO in mHSPC, even in pts with older age, substantial comorbidities, and greater use of concomitant medications. Clinical trial information: NCT04736199. Research Sponsor: Bayer.

5104 **Poster Session**

Prognostic potential of PROSTest for predicting outcome in ADT-treated Black South African prostate cancer patients. First Author: Susanna Elizabeth Nagel, University of Pretoria School of Medicine, Pretoria, South Africa

Background: Prostate cancer (PCa) is the second most common cancer in men with disproportionately aggressive disease observed in black African and Caribbean men. Androgen deprivation therapy (ADT) is commonly used as treatment but there is no personalized strategy to guide patient selection. We investigated the prognostic value of PROSTest before ADT initiation and after the first ADT cycle. **Methods:** We performed a descriptive study of PROSTest with cross-sectional and longitudinal arms in black PCa patients receiving or intended to receive ADT. An ADT-naïve PCa cohort (*n*=50) intended to start ADT was enrolled as well as an ADT-exposed cohort (*n*=80) 6-12, 12-24 or >24 months after starting ADT. Goserelin acetate alone or in combination with cyproterone acetate was administered. The cohorts were followed up 4-monthly for 36 months with evaluation of survival and treatment response (responding, in remission, recurrence, progression, castration resistance). PSA levels were measured using the Architect Total PSA chemiluminescent immunoassay. Whole blood samples were collected into deproteinizing RNA-buffered tubes for determination of the PROSTest activity score using a multiplexed PCR assay. Statistical analysis used non-parametric statistics and Fisher's exact test in GraphPad Prism v8. **Results:** Untreated metastatic PCa patients had the highest baseline PROSTest scores (71.8-85.3). Untreated patients with organ-confined disease were subdivided into group A (PROSTest scores ≤32) and group B (PROSTest scores ≥70). ADT-treated patients enrolled after starting ADT were subdivided into group C (PROSTest scores 9.8-58.3) and group D (PROSTest scores 70.0 – 90.2). Groups A and C showed improved survival and lower rates of recurrence, progression and castration resistance at 36 months compared to groups B and D (p<0.05). Patients that required treatment re-initiation or escalation due to rising PSA all had high enrolment PROSTest scores ≥70. The groups did not differ significantly in terms of age, CAPRA score, Gleason grade, PSA levels, nadir PSA, time to nadir or SUVMAX (*p*>0.05). **Conclusions:** The PROSTest activity score determined pre- or post-ADT (first cycle) identifies PCa patients at risk for poor treatment outcomes. Research Sponsor: South African Medical Research Council (SAMRC); SHIP-RFA-01-2019.

5105 **Poster Session**

Overall survival in veterans with metastatic hormone sensitive prostate cancer by initial therapy and STRATOS-P somatic tumor classification. First Author: Robert Wilson, Saint Louis University School of Medicine, St. Louis, MO

Background: The STRATOS-P somatic tumor classification stratifies patients with metastatic hormone-sensitive prostate cancer (mHSPC) into favorable, intermediate, or unfavorable risk groups based on tumor comprehensive genomic profiling (CGP). Currently, no studies have compared the mortality benefits or overall survival (OS) differences between mHSPC treatments in these risk categories. **Methods:** Veterans within the Veterans Health Administration with mHSPC diagnosed between December 2018 and September 2024 were included if tumor CGP was completed within 6 months of diagnosis. Patients were grouped based on STRATOS-P genomic classification (favorable vs. intermediate/unfavorable). With each group, OS was analyzed by initial therapy: androgen deprivation therapy (ADT) alone, ADT+androgen receptor pathway inhibitor (ARPI), ADT+docetaxel, or triple therapy with ADT+ARPI+docetaxel. Survival was analyzed using Kaplan-Meier and Cox proportional hazards models, adjusting for baseline differences in age, PSA, Charlson comorbidity index, race, and metastatic volume. **Results:** Of 2,820 veterans with mHSPC, 1,109 (39.3%) had risk classified as favorable per STRATOS-P and 1,711 (60.7%) as intermediate/unfavorable. Initial therapy distribution differed moderately between groups (p=0.046). The favorable group had more patients receiving ADT monotherapy (55.5% vs. 52.0%) and fewer receiving ADT+docetaxel or triple therapy (3.0% vs. 4.7%, 4.4% vs. 5.4%, respectively). The intermediate/unfavorable group had a higher max PSA (median 37.7 vs 23.7, p<0.001) lower percentage of African American patients (27.5% vs 36.0%, p<0.001), and a higher percentage of patients with high volume of disease (28.9% vs. 19.7% p=0.002). In the favorable group, OS did not significantly differ by treatment; however, in a pairwise comparison, ADT+ARPI showed a modest decrease in mortality risk versus ADT alone (aHR [95% CI]: 0.745 [0.561 – 0.989]). In the intermediate/unfavorable group, median OS differed by therapy (ADT monotherapy: 30.7 months, ADT+ARPI: 36.8 months, ADT+docetaxel: 27.9 months, Triple Therapy: 37.6 months; p<0.001). Further, ADT+ARPI and triple therapy were associated with a decreased risk of mortality compared to ADT alone (aHR [95% CI]: 0.638 [0.541 – 0.753], 0.542 [0.360 – 0.817], respectively). **Conclusions:** In patients with intermediate/unfavorable STRATOS-P genomic risk, choice of initial therapy can lead to differences in OS, with ADT+ARPI and triple therapy associated with decreased mortality compared to ADT alone. In favorable risk, choice of initial therapy had smaller effect on OS, and only ADT+ARPI was associated with a modest decrease in mortality. These findings highlight the role of early genomic testing in mHSPC and that high risk tumors may benefit more from combination therapy than those with favorable risk. Research Sponsor: U.S. Department of Defense; W81XWH-22-1-0602.

5106 **Poster Session**

STRATOS-P clinical model for prognosis and selection of patients with metastatic hormone sensitive prostate cancer (mHSPC) for intermittent therapy. First Author: Martin W. Schoen, Medicine Service, Veterans Affairs St. Louis Healthcare System, St. Louis, MO

Background: Current trials use prostate-specific antigen (PSA) response of ≤0.2 ng/mL at 6-12 months as a prognostic marker and identify patients for intermittent therapy. Clinico-genomic assessment can increase prognostic accuracy and patient selection for intermittent therapy, which would improve quality of life and decrease adverse events associated with mHSPC combination therapies without impacting survival. **Methods:** Retrospective study of veterans diagnosed with mHSPC between 2018-2024. PSA response at 6-12 months and volume of disease were determined. DNA alterations were classified by Somatic Tumor Risk Assessment for Overall Survival-Prostate (STRATOS-P) genomic system, a validated method of risk stratification. PSA response was grouped into ≤0.2, >0.2-<2, 2-<10, and ≥10 ng/mL. Charlson comorbidity index (CCI) high was defined as ≥3. PSMA-PET based staging was determined if PSMA-PET performed within 100 days of mHSPC diagnosis. Multivariable Cox model-based weights were used to create the STRATOS-P mHSPC clinical risk score to prognosticate overall survival and select patients for intermittent therapy. Kaplan-Meier analysis was used to estimate Overall Survival (OS) and time to death or castration resistance from diagnosis, a real-world progression-free survival (rwPFS) surrogate. **Results:** In 3094 Veterans identified, 937 (30.3%) had DNA-based genomic testing within 6 months of diagnosis. There were 1349 patients (43.6%) with a PSA of ≤0.2 who had a median OS of 74.6 months. Of patients with genomic testing, 459 (49.0%) were STRATOS-P Clinical low risk with a median OS that was not reached and rwPFS of 72.1 months, moderate risk with median OS of 37.1 months and rwPFS of 21.6 months, and high risk with median OS of 19.1 months and rwPFS of 12.1 months. There were 66 (13.0%) patients that were STRATOS-P Clinical low risk but did not achieve ≤0.2% and 116 (22.8%) patients that achieved PSA ≤0.2 but were considered STRATOS-P clinical moderate risk. Approximately 497 patient (53%) could be considered for intermittent therapy and had a median OS of 77.9 months and rwPFS of 56.2 months, similar to patients with PSA≤0.2. **Conclusions:** STRATOS-P Clinical model in mHSPC is prognostic for OS and rwPFS and can identify patients for intermittent therapy to achieve similar OS and rwPFS compared to selection using PSA ≤0.2 at 6-12 months. Future trials should incorporate clinico-genomic assessments to improve risk stratification and selection of therapy. Research Sponsor: Veterans Health Affairs Office of Research and Development; 1I01CX002946-01; Prostate Cancer Foundation; PCFCHAL220.

STRATOS-P clinical model (n=937).

		n	HR	95.0% CI
CCI High		397	1.62	1.34-1.95
High Volume		608	1.53	1.31-1.78
STRATOS-P Genomic risk*	Intermediate	470	1.53	1.23-1.92
	Unfavorable	132	2.39	1.80-3.17
Non-PSMA-PET staging		708	1.62	1.23-2.14
	>0.2 - 2	210	1.60	1.25-2.04
PSA Response#	>2 - <10	131	2.98	2.30-3.84
	10+	87	5.64	4.26-7.47

*STRATOS-P genomic risk favorable is referent, n=335.
#PSA Response ≤0.2 is referent, n=509.

5107 **Poster Session**

Major adverse cardiovascular events in androgen receptor signaling inhibitor–treated patients with metastatic castration-sensitive prostate cancer. First Author: Linden Huhmann, US Department of Veterans Affairs, Washington, DC

Background: Cardiovascular disease is highly prevalent in the predominantly older male population with metastatic castration-sensitive prostate cancer (mCSPC). Androgen receptor pathway inhibitors (ARPIs) form the backbone of contemporary doublet and triplet treatment strategies, but—as with any systemic therapy—may influence patients' underlying cardiovascular risk. This study compares the incidence of major adverse cardiovascular events (MACE) in real-world mCSPC patients treated with darolutamide versus abiraterone. **Methods:** This retrospective cohort study included patients in the nationwide VA healthcare system initiating doublet or triplet abiraterone or darolutamide for newly diagnosed mCSPC. After inverse probability of treatment weighting (IPTW), 1-year cumulative MACE incidence was estimated via Kaplan-Meier analysis. Doubly robust multivariable Cox regression using IPTW and multivariable competing risk regression with death as a competing risk assessed the association between treatment and MACE. All analyses were adjusted for age, race, prior MACE, NCI Charlson Score, smoking status, and prior hypertensive combination treatment. **Results:** Among 11,788 patients initiating darolutamide or abiraterone for mCSPC, 9,952 received abiraterone doublet, 936 received darolutamide doublet, 374 received abiraterone triplet, and 526 received darolutamide triplet therapy. In the weighted cohort, the 1-year cumulative incidence of MACE was lower in patients receiving darolutamide (7.2%, 95% confidence interval [CI] 5.6-9.0%) versus abiraterone (10.7%, CI 10.0-11.4%) doublet therapy. For triplet therapy, 1-year MACE incidence was 5.3% (CI 3.4-7.4%) with darolutamide and 9.6% (CI 5.9-13.6%) with abiraterone. In doubly robust multivariable Cox models, darolutamide doublet was associated with a lower hazard of MACE compared to abiraterone doublet (hazard ratio [HR] 0.78, CI 0.62-0.96, P=0.03). For triplet, patients receiving darolutamide had a HR of 0.73 for MACE (CI 0.39-1.31, p=0.29) compared to patients receiving abiraterone triplet therapy. Competing risk models showed consistent results. **Conclusions:** Darolutamide, particularly in doublet therapy, was associated with lower MACE risk than abiraterone. A similar point estimate in triplet therapy warrants validation in larger cohorts. These findings may inform treatment selection or prophylactic management to improve cardiovascular outcomes in mCSPC. Research Sponsor: Bayer.

5108 **Poster Session**

Homologous recombination repair (HRR) genes and overall survival prognosis within the STRATOS-P classification in metastatic hormone-sensitive prostate cancer (mHSPC). First Author: Kara N. Maxwell, Corporal Michael Crescenz VA Medical Center, Department of Medicine, Hematology and Oncology, Perelman School of Medicine and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: DNA repair genomic alterations are associated with worse overall survival (OS) in patients with metastatic hormone sensitive prostate cancer (mHSPC). It is less clear whether other genomic alterations may affect prognosis of actionable homologous recombination repair (HRR) and mismatch repair (MMR) genes in mHSPC. **Methods:** Retrospective cross-sectional study of veterans diagnosed with mHSPC (n=4401). Tumors with no alterations in HRR/MMR genes (DDRneg) were classified by the Somatic Tumor Risk Assessment for Overall Survival-Prostate (STRATOS-P) genomic system which stratifies patients into favorable, intermediate and unfavorable survival groups based on oncogenic alterations: Favorable, *SPOP* or no alterations; Intermediate, alterations in *AR, BRCA2, CCND1, CDK12, FGF19, FGF3, FGF4, LYN, MYC, PTEN, RAD21,* or *TP53*; Unfavorable, alterations in *FGFR1, PRCK1, RB1*,or both *TP53* and *PTEN*. OS from metastatic diagnosis was determined using a multivariate Cox model controlling for age, Charleston comorbidity index (CCI) and PSA at diagnosis. **Results:** Among 4401 mHSPC patients, 1027 (23%) patient tumors had at least one oncogenic alteration in an HRR or MMR gene. Of 3374 DDR-Neg tumors, 1593 were classified as STRATOS-P-Favorable, 1357 as STRATOS-P-Intermediate, and 424 as STRATOS-P-Unfavorable. Comparing patients with tumors with oncogenic alterations in an HRR or MMR gene to patients with DDR-neg tumors showed that prognosis was worse in patients with tumor alterations in *ATM, BRCA2, CHEK2, CDK12, ATR, PALB2, NBN* and MMR genes compared to patients with STRATOS-P-Favorable tumors (Table). Prognosis was better in patients with tumor alterations in *ATM, BRCA2, CHEK2, CDK12, BRCA1, FANCA* and Lynch genes compared to STRATOS-P-Unfavorable tumors (Table). **Conclusions:** In patients with mHSPC, patients with HRR and MMR altered tumors have a worse prognosis compared to patients with STRATOS-P favorable tumors and better prognosis compared to patients with STRATOS-P unfavorable tumors. Overall, HRR and MRR gene alterations impact prognosis of mHSPC patients within the STRATOS-P classification and should be classified as intermediate risk. Research Sponsor: Veterans Affairs Office of Research and Development; I01CX002946; Prostate Cancer Foundation; 22CHAL02.

		STRATOS-P-Favorable, DDRneg, n=1593	STRATOS-P-Unfavorable, DDRneg, n=424
Gene[1]	n	HR (95% CI)	HR (95% CI)
BRCA2	243	2.00 (1.62, 2.47)	0.69 (0.55, 0.87)
CDK12	116	2.07 (1.66, 2.57)	0.74 (0.58, 0.94)
ATM	259	1.55 (1.24, 1.96)	0.51 (0.39, 0.66)
CHEK2	212	1.75 (1.21, 2.52)	0.50 (0.33, 0.76)
ATR	38	2.05 (1.27, 3.31)	0.71 (0.43, 1.17)
BRCA1	37	1.41 (0.81, 2.46)	0.48 (0.27, 0.84)
FANCA	32	1.53 (0.82, 2.87)	0.51 (0.27, 0.97)
NBN	23	2.59 (1.43, 4.68)	0.93 (0.51, 1.69)
PALB2	21	2.31 (1.23, 4.37)	0.79 (0.40, 1.56)
Lynch	128	1.72 (1.28, 2.33)	0.64 (0.47, 0.88)

[1]All tumors with alterations in indicated gene regardless of STRATOS-P subgroup were compared to the indicated DDRneg STRATOS-P subgroup.

5109 **Poster Session**

Optimal prostate-specific antigen cutoff for prostate cancer detection: A prospective cohort study. First Author: Yun-Gyoo Lee, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Serum prostate-specific antigen (PSA) testing is crucial for detecting early stage and low-risk prostate cancer. However, standard and uniform PSA thresholds may underestimate risk in males with smaller prostate volumes and distinct epidemiologic characteristics. We aimed to evaluate data-driven, age-specific PSA thresholds for short-term prostate cancer detection in a large screening cohort. **Methods:** We analyzed 512,992 PSA measurements from 123,607 asymptomatic males undergoing annual or biennial health checkups in Kangbuk Samsung Cohort Study (KSCS) from 2011 to 2020. Incident prostate cancer within 1-year of each PSA measurement was identified through linkage to the Korea National Cancer Incidence Database. The dataset was randomly partitioned into training (70%) and test (30%) subsets. To estimate cancer risk, logistic regression models incorporating synthetic minority oversampling technique were used. Optimal PSA thresholds were determined using the Youden index in test datasets. Performance was evaluated by accuracy, precision, recall, and F1-score with bootstrap validation. Associations between risk factors and prostate-cancer risk were evaluated using Cox regression models. **Results:** During follow-up, 224 men developed prostate cancer. The optimal PSA cutoff in the overall population was 2.96 ng/mL. Age-specific thresholds increased with age, with males in their 40s, 50s, 60s, and age $\geq$70 years demonstrating cutoff values of 1.62, 2.54, 2.76, and 3.79 ng/mL, respectively. These thresholds demonstrated high discriminative performance (accuracy, 0.97; F1-score, 0.92) (Table). PSA values exceeding age-specific thresholds were associated with a 20.7-fold elevated risk of prostate cancer (HR 20.65; 95% CI, 16.33–26.12; P$<$0.001). Older age, family history of prostate cancer (HR 2.27; 95% CI, 1.58–3.27), and dyslipidemia medication use (HR 2.04; 95% CI, 1.49–2.80) were additional independent predictors. **Conclusions:** In this large prospective Asian cohort, age-specific PSA thresholds between 1.6 and 3.8 ng/mL provided robust short-term risk discrimination and identified male at substantially higher 1-year prostate cancer risk than those below the thresholds. Implementing age-adjusted PSA reference values may improve the precision and efficiency of early detection strategies in Asian male and better inform risk-adapted screening and diagnostic pathways. To determine their effect on long-term clinical outcomes, prospective validation is warranted. Research Sponsor: None.

Age-specific PSA cutoffs and performance metrics.

	Cutoff value	Accuracy	Precision	Recall	F1-score
Overall	2.96	0.97	0.89	0.96	0.92
40 ≤ Age < 50	1.62	0.93	0.70	0.99	0.82
50 ≤ Age < 60	2.54	0.95	0.80	0.95	0.87
60 ≤ Age < 70	2.76	0.91	0.66	0.99	0.80
Age ≥ 70	3.79	0.90	0.65	0.91	0.76

5110 **Poster Session**

Large language model protein set generation for interpretable serum proteomics in localized prostate cancer. First Author: Nicholas Robert Rydzewski, Washington DC VA Medical Center, Washington, DC

Background: High-plex serum proteomics can track prostate cancer biology and treatment response beyond PSA, but interpretation is limited by high dimensionality. Pathway analysis can help, but incomplete overlap between legacy pathway libraries and assay panels can yield hard-to-interpret enrichments dominated by a few measured proteins. We evaluated an automated large language model (LLM) workflow using protein annotations to build protein sets containing only measured proteins. **Methods:** Serum from 88 individuals was profiled with an aptamer-based ~7,000-protein assay (SomaScan 7K; SomaLogic, USA). The cohort included localized prostate cancer treated with radiotherapy (RT) with or without androgen-deprivation therapy (ADT) with serial sampling (pre-RT n = 76, end-RT n = 72, ~1-month follow-up n = 76), plus metastatic (n = 4) and normal controls (n = 8). Assay fidelity was assessed by correlating PSA aptamers with clinical PSA. Protein-level analyses tested ADT effects and paired within-patient changes across RT. For program-level analysis, UniProt annotations for each measured protein were processed with an LLM to generate structured summaries, converted to embeddings, and clustered into protein sets restricted to SomaScan proteins. Set coherence and assay coverage were compared to Gene Ontology (GO) and Reactome mappings. Protein-set enrichment comparing ADT vs no ADT identified candidate programs and were evaluated for association with biochemical recurrence among high-risk ADT-treated patients (n = 50; 20 events) using Cox models adjusted for pre-treatment PSA. **Results:** PSA aptamers correlated with clinical PSA (Spearman r = 0.66–0.77). ADT suppressed reproductive-axis proteins (LH, FSH, hCG) and prostate-lineage proteins (PSA, PAP, TGM4); RT contrasts captured acute epithelial injury/lymphoid suppression followed by remodeling and stress responses. LLM protein sets showed higher set name/protein description coherence (median cosine similarity 0.59) than GO (0.30) or Reactome (0.36) and covered all measured proteins; GO/Reactome sets averaged ~50% member coverage. Pre-RT ADT enrichment identified histone programs (NES 2.13–2.18; FDR $<$ 0.01), summarized as a Histone H2 score. Histone H2 score increased across no ADT, ADT, and metastatic samples (Kruskal–Wallis p = 0.003; all pairwise FDR $<$ 0.05). In high-risk ADT-treated patients, pre-RT Histone H2 score was associated with recurrence (HR 0.53, FDR = 0.024), and remained significant in a bivariate model with pre-treatment PSA (Histone H2 HR 0.49, FDR = 0.013; PSA HR 2.78, FDR $<$ 0.001). Non-H2 histone score (H1/H3) showed no ADT-associated shift (Wilcoxon p = 0.70), supporting specificity of the Histone H2 signal. **Conclusions:** LLM-derived protein sets restricted to measured proteins improved interpretability of serum proteomics and revealed an ADT-associated Histone H2 program complementary to PSA. Research Sponsor: U.S. National Institutes of Health; ZIA BC 011552.

5111 **Poster Session**

Spatial transcriptomics-guided pathology biomarker as a predictor of benefit of adjuvant docetaxel in high-risk localized prostate cancer: NRG/RTOG 0521 (NCT00288080). First Author: Md Mamunur Rahaman, School of Computer Science and Engineering, University of New South Wales, Sydney, NSW, Australia

Background: The NRG/RTOG 0521 trial evaluated adding adjuvant docetaxel (DTX) to standard radiotherapy plus androgen deprivation therapy (ADT) in high-risk localized prostate cancer. Adjuvant DTX modestly improved overall survival (OS) in the trial, but the benefit was limited and not all patients benefited. Thus, biomarkers are needed to identify patients most likely to benefit from chemotherapy intensification. ST-DoxPCa (Spatial Transcriptomics–Guided Docetaxel Therapy Stratification in Prostate Cancer) is a novel artificial intelligence (AI) driven histology biomarker that predicts gene expression from H&E slides (virtual spatial transcriptomics). We assessed whether ST-DoxPCa can stratify patients in RTOG 0521 for differential benefit from adjuvant DTX. **Methods:** A Vision Transformer trained on paired histology–spatial transcriptomics (HEST1K) predicts a 208-gene prostate panel at spot level; predictions are distilled into a biologically informed 26-gene signature and aggregated into patient-level features. A prognostic Cox model and fixed median threshold were developed independently in a Cleveland Clinic radical prostatectomy cohort (CCF, n=352; endpoint: biochemical recurrence-free survival). This locked model and threshold were applied unchanged (no refitting or recalibration) to digitized pretreatment diagnostic biopsies from NRG/RTOG 0521 (n=350; RT+ADT n=169, RT+ADT+DTX n=181) to stratify patients into ST-DoxPCa-positive (high-risk) and ST-DoxPCa-negative (low-risk) groups. Overall survival (OS) was compared between treatment arms within each stratum. **Results:** ST-DoxPCa stratified patients into biomarker-defined risk groups using aggregated spatial-expression features from a biologically informed gene panel; key genes included PTEN, NKX3-1, ACPP, FASN and TMPRSS2. ST-DoxPCa-positive (high-risk) patients experienced a significant OS benefit from adding DTX to RT+ADT versus RT+ADT alone (HR=0.38, 95% CI 0.18−0.83; p=0.012), whereas ST-DoxPCa-negative (low-risk) patients derived no OS benefit (HR=1.05, 95% CI 0.67−1.63; p=0.84). **Conclusions:** The ST-DoxPCa model identified a subgroup with substantial OS benefit from adjuvant DTX and a subgroup with no benefit within RTOG 0521, supporting risk-aligned chemotherapy intensification using routine histology. Clinical trial information: NRG/RTOG 0521 (NCT00288080). Research Sponsor: National Cancer Institute (NCI), National Institutes of Health (NIH); R01CA268287A1, U01CA269181, R01CA26820701A1, R01CA249992-01A1, R01CA202752-01A1, R01CA208236-01A1, R01CA216579-01A1, R01CA220581-01A1, R01CA257612-01A1, 1U01CA239055-01, 1U01CA248226-01, 1U54CA254566-01; United States Department of Veterans Affairs; IBX004121A; U.S. Department of Defense (DoD) – Prostate Cancer Research Program; W81XWH-20-1-0851; U.S. National Institutes of Health; U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), U24CA180867 (NCORP), U24CA190607 (NRG Specimen Bank); Sanofi.

5112 **Poster Session**

External validation of new prostate cancer risk groups by PSMA-PET (PPP3). First Author: Wolfgang Peter Fendler, Department of Nuclear Medicine, University of Duisburg-Essen, and German Cancer Consortium (DKTK), University Hospital Essen, Essen, Germany

Background: Previously, we proposed novel risk group definitions for prostate cancer patients based on Prostate-Specific Membrane Antigen (PSMA) targeted positron emission tomography (PET). PSMA-PET pan-stage nomograms (PPP3) were developed using the international, multicentre PROMISE registry (NCT06320223) to prognosticate overall survival (OS). Here, we present an external validation of PPP3. **Methods:** Eligible patients enrolled into our PROMISE registry database after the PPP3 data cap were included into this external validation study. Included patients had histologically proven prostate cancer and underwent PSMA-PET at hospitals in Turkey, Cyprus, Italy, China, South Africa or Germany between 2015 and 2022. PSMA-PET was standardized by PROMISE version 2 (V2); total lesion count, total tumor volume, PSMA expression score and OS follow-up were obtained as per local site practice. PPP3 nomograms were applied to calculate risk groups and Harrell´s C-indices for the external validation cohort. Calibration curves were measured for 5-year OS. Head-to-head comparison between the visual PPP3 nomogram and the simplified risk stratification table was examined by area under the receiver operating characteristics curve (ROC-AUC). **Results:** 1855 male patients across all disease stages with 179 (9.6%) reported deaths and median OS follow-up of 4.8 years (IQR 3.7-6.1) were analysed. In the external validation cohort C-indices (95% CI) were 0.71 (0.67-0.76) for the visual nomogram and 0.73 (0.69-0.77) for the quantitative nomogram, respectively. By simplified risk stratification table, 77 of 1855 patients (4.2%) were underestimated and 16 (0.9%) were overestimated, when compared with visual nomograms. Prognostic accuracy was comparable using both methods (AUC Nomogram: 0.64 vs. AUC Table: 0.63, p = 0.02). **Conclusions:** PPP3 nomograms were validated in an external multi-site patient cohort. Prognostication was accurate (C-indices $>$ 0.70) for both PPP3 nomograms. Clinical trial information: NCT06320223. Research Sponsor: German Research Foundation; RA 3222/5-1 / 714210; Prostate Cancer Foundation; Health Initiative Joint Undertaking; 101172722; Novartis; AstraZeneca; Telix.

5113 **Poster Session**

Is language barrier a mere proxy?: Psychological distress among non–English-speaking prostate cancer patients receiving radiation therapy—A prospective cohort study. First Author: Teresia M. John, Boston University School of Medicine, Boston, MA

Background: Cancer patients experience depression and anxiety at elevated rates, with minority and non-English-speaking populations disproportionately affected. Prior research at our institution demonstrated elevated distress among Spanish-speaking breast cancer patients undergoing radiation therapy. However, limited data exist on language-related disparities in prostate cancer patients undergoing radiation therapy. We investigated this while exploring the mediating role of social determinants of health (SDOH). **Methods:** We enrolled prostate cancer patients initiating radiation therapy at an urban safety-net hospital. We assessed anxiety (GAD-2), depression (PHQ-2), and SDOH including food and housing insecurity, and transportation barriers at baseline and treatment completion. Comparisons used t-tests and Mann-Whitney U tests; correlations used Spearman coefficients with statistical significance $p < 0.05$. **Results:** Of 84 patients enrolled (mean age 70.3$\pm$8.0 years), 49 (58.3%) were English-speaking and 35 (41.7%) were non-English-speaking (Spanish n = 20, Haitian Creole n = 13, Portuguese n = 2). The sample was predominantly Black/Caribbean (64.3%). Non-English speakers had fewer years in the US (41.1 vs. 50.3 years, p = 0.016) and lower educational attainment (25.7% vs. 0% elementary school only, p = 0.006). At baseline, non-English speakers showed numerically higher anxiety (GAD-2: 1.31$\pm$2.13 vs. 1.08$\pm$1.72) and depression (PHQ-2: 1.09$\pm$1.87 vs. 0.84$\pm$1.57), though this was not statistically significant ($p > 0.50$). Notably, Spanish-speaking patients demonstrated the highest distress (GAD-2: 2.00$\pm$2.45; PHQ-2: 1.40$\pm$1.98), with 30.0% screening positive for clinical anxiety vs. 16.3% of English speakers. SDOH factors were significantly correlated with distress: housing insecurity (ρ = 0.42, $p < 0.001$), food insecurity (ρ = 0.37, p = 0.001), and transportation worry (ρ = 0.38, $p < 0.001$). In multivariable regression adjusting for age, stage, race, ethnicity, and education, language was not independently associated with anxiety (B = -0.64, 95% CI: -1.76 to 0.48, p = 0.26). Among 73 patients with paired data, distress remained stable from baseline to treatment completion. **Conclusions:** While non-English-speaking prostate cancer patients reported higher psychological distress during radiation therapy, SDOH factors emerged as the strongest predictors of distress regardless of language. Interventions targeting social vulnerability may be more impactful than language services alone. SDOH screening should be integrated into oncology care at safety-net institutions serving diverse populations. Research Sponsor: None.

5114 **Poster Session**

Assessing the clinical and biological associations between multimodal artificial intelligence (MMAI) and 22-gene genomic classifier (GC) in localized prostate cancer (PCa). First Author: Boon Hao Hong, National Cancer Centre, Singapore, Singapore

Background: MMAI and GC are clinically validated prognostic tools for localized PCa, and are incorporated into NCCN guidelines as treatment-decision aids. However, their clinical and biological relationships remain unclear, especially in Asian populations where comparative study is limited. **Methods:** Patients with newly-diagnosed localized PCa from a single institution in Singapore were enrolled into a prospective protocol (NCT04340024), and underwent image-guided radiotherapy with or without hormonal therapy. All subjects had paired GC and MMAI scores. However, colored marker annotations were present on the H&E slides, which could negatively impact MMAI performance. Associations between GC and MMAI scores with metastasis-free survival (MFS) were evaluated using Cox proportional hazards models. Pearson's correlation was used to assess associations between risk scores and cancer hallmark pathways. **Results:** 144 men were included, comprising 142 (99%) with NCCN intermediate (int) to high-risk, and 2 (1%) with low-risk disease; median follow-up duration was 78.5 (interquartile range: 68.2–95.3) mo. MMAI and GC scores were correlated (R = 0.55), but differed in risk stratification; 12/144 (8%), 54/144 (38%), and 78/144 (54%) were MMAI low-, int-, and high-risk, respectively, compared with 51/144 (35%), 32/144 (22%), and 61/144 (43%) by GC in the same order. We observed the largest discordance in the GC low-risk subgroup (n = 51), where 29/51 (57%) and 14/51 (28%) were classified as MMAI int- and high-risk, respectively. Of note, 16/32 (50%) of GC int-risk men were classified as MMAI high-risk. Nonetheless, both tests were prognostic for MFS (MMAI: hazard ratio [HR] of 2.6 [95% CI: 1.0–6.4], P= 0.035; GC: HR of 3.4 [95% CI:1.5–7.6], P= 0.002), although the difference in HR should be interpreted with caution, as it is attributable to a limited sample size with longer follow-up. Next, we investigated for molecular pathway enrichment of GC and MMAI high-risk groups. Proportions of known prostate cancer molecular subtypes were comparable between the respective GC and MMAI risk-groups (GC high vs MMAI high: PAM50 Basal 51% vs 58%, P= 0.419; Luminal B 46% vs 39%, P= 0.377; PTEN loss 25% vs 22%, P= 0.698; AR lower activity 49% vs 44%, P= 0.512). GC high versus GC low/int tumors however showed positive enrichment in E2F, oxidative phosphorylation, and mTORC1 pathways; negative enrichment in P53 and estrogen pathways. MMAI high was only negatively enriched for fatty acid metabolism. **Conclusions:** While MMAI and GC provide differing risk categorization, both tests were significantly associated with MFS in men with localized prostate cancer who underwent radiotherapy. Known prostate cancer-associated transcriptomic subtypes were comparable between the respective MMAI and GC risk groups. Research Sponsor: None.

5115 **Poster Session**

A prospective study of mpMRI-guided salvage radiotherapy with lesion-directed dose escalation after radical prostatectomy: 10-year follow-up results (MRI Study: UMIN 000009823). First Author: Kenshiro Shiraishi, Teikyo University, Tokyo, Japan

Background: Salvage radiotherapy (SRT) after radical prostatectomy (RP) has traditionally been delivered as uniform dose distribution of the prostate bed without lesion visualization. We prospectively implemented an image-guided salvage strategy integrating high-resolution multiparametric MRI (mpMRI) and lesion-directed dose escalation. Here we report long-term oncologic outcomes of this pioneering approach. **Methods:** This prospective, single-arm clinical study was registered in the UMIN database in 2013. Patients with biochemical recurrence (BCR, PSA $\geq$0.2 ng/mL) after RP and no evidence of distant metastasis were enrolled. All patients underwent 3 Tesla mpMRI with an endorectal coil prior to SRT. When a focal recurrent lesion was identified, intensity-modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) was delivered (70 Gy to the MRI-defined lesion and 66 Gy to the prostate bed in 33 fractions). Patients without visible lesions received prostate-bed irradiation alone. Treatment failure after SRT was defined as PSA $>$ 0.2 ng/mL. Long-term clinical outcomes were analyzed. **Results:** A total of 40 patients completed protocol treatment. mpMRI identified focal recurrence sites in 11 patients (27.5%), all of whom received lesion-directed SIB-IMRT. After a median follow-up of 10.6 years, treatment failure occurred in 13 patients (32.5%). Among patients treated with SIB-IMRT, 4 of 11 developed BCR, whereas among 29 patients without mpMRI-detectable recurrence at the time of SRT, 9 developed BCR. There was no statistically significant difference in BCR rates between the two groups. Importantly, no patient developed radiologically evident local recurrence within the irradiated prostate bed, including those treated with SIB in their disease course. All but one patient with treatment failure received subsequent systemic salvage therapy. Distant metastases developed in 3 patients, and 1 patient died from prostate cancer. One patient without SIB experienced grade 3 perforation of the sigmoid colon. During follow-up after SRT, secondary malignancies were diagnosed in 10 patients. **Conclusions:** In this prospective study with long-term follow-up, mpMRI-guided SRT achieved excellent durable local control. Although second BCR occurred in a subset of patients, the absence of in-field local failures regardless of mpMRI detectability at the time of SRT supports the biological and clinical validity of lesion-directed salvage intensification. Our findings underscore individualized SIB approach and highlight the need for future studies to refine patient selection and treatment intensification strategies in salvage settings, including androgen deprivation therapy and/or elective pelvic nodal irradiation. Clinical trial information: UMIN000009823. Research Sponsor: None.

5117 **Poster Session**

Survival outcomes and subgroup efficacy analysis of Ga-68-NGUL and Lu-177-DGUL (pocuvotide satetraxetan) in patients with mCRPC: Results from a phase 1/2 study. First Author: Chang Wook Jeong, Seoul National University Hospital, Seoul, South Korea

Background: Ga-68-NGUL and Lu-177-DGUL (Pocuvotide Satetraxetan) is a novel PSMA-targeting radiopharmaceutical. This study reports the survival outcomes and identifies clinical factors associated with therapeutic response in patients with metastatic castration-resistant prostate cancer (mCRPC). **Methods:** In this phase 1/2 study (NCT05547061), mCRPC patients progressing after ARPI treatment received Lu-177-DGUL (200 mCi every 6 weeks, up to 6 cycles). Efficacy was evaluated using both RECIST v1.1 and PCWG3-modified RECIST v1.1. Key endpoints included ORR, overall survival (OS), and radiographic progression-free survival (rPFS). **Results:** A total of 91 patients were enrolled. Overall Survival: The median OS was 13.31 months (95% CI: 12.02–17.38). The median rPFS was 11.04 months (95% CI: 8.28–14.29) for the entire cohort. Subgroup Analysis by Metastatic Site: Significant differences in ORR were consistently observed across both criteria. Per RECIST v1.1, the ORR was significantly higher in patients with lung metastases (100% vs. 32.43%, p = 0.0144) and lymph node involvement (48.08% vs. 11.54%, p = 0.0015) compared to those without. These findings align with PCWG3-modified RECIST v1.1 results (Lung: 100% vs. 37.84%, p = 0.0252; LN: 51.92% vs. 19.23%, p = 0.0057). Furthermore, the presence of liver metastases was associated with significantly shorter rPFS compared to those without liver involvement, consistently across RECIST v1.1 (median 5.55 vs. 11.04 months; p = 0.0386) and PCWG3-modified criteria (median 2.76 vs. 8.38 months). Impact of Treatment Cycle on ORR and rPFS: Treatment intensity significantly influenced clinical outcomes across both evaluation criteria (all p $<$ 0.0001). For ORR, under RECIST v1.1 criteria, the ORR was 0% for $<$ 4 cycles, 30% for 4 cycles, and 59.46% for $>$ 4 cycles. Similarly, per PCWG3-modified RECIST v1.1, the ORR improved with the number of cycles (0%, 35%, and 67.57%, respectively). For rPFS, under standard RECIST v1.1, the median rPFS increased with the number of cycles: 2.76 months (95% CI: 2.56–2.86), NE (95% CI: 5.55–NE), and 13.34 months (95% CI: 11.04–NE). Per PCWG3-modified RECIST v1.1, the median rPFS also increased consistently (2.66 months [95% CI: 2.56–2.76], 5.55 months [2.73–NE], and 11.04 months [10.18–14.29], respectively). **Conclusions:** Ga-68-NGUL and Lu-177-DGUL (Pocuvotide Satetraxetan) demonstrates promising survival benefits in mCRPC. The clinical response is particularly robust in patients with lung or lymph node metastases and those completing more treatment cycles. The significant difference in rPFS observed only under PCWG3-modified criteria highlights the importance of using PCWG3-specific assessments in bone-predominant mCRPC. Clinical trial information: NCT05547061. Research Sponsor: CellBion Co., Ltd.; The Korea Drug Development Fund; RS-2025-25454770.

5118 **Poster Session**

Spatially organized immune niches in high-grade primary prostate cancer. First Author: Aishwarya Atmakuri, Pritzker School of Medicine, The University of Chicago, Chicago, IL

Background: Prostate cancer (PC) has historically been considered immunologically "cold" due to low immune infiltration and a predominantly immunosuppressive tumor microenvironment (TME). However, this understanding is largely based on immune profiling studies of metastatic castration-resistant prostate cancer and may not apply in earlier stages of disease. The composition and organization of the immune TME in primary PC remains poorly defined, especially in relation to Gleason score, the gold standard of pathologic PC grading. We hypothesized that the local PC immune TME is more heterogeneous than previously appreciated, with differences in immune composition and spatial organization between High Gleason (HG) and Low Gleason (LG) PC. **Methods:** We analyzed 29 radical prostatectomy samples (15 LG vs. 14 HG) using a 40-marker multiplex immunofluorescence panel to profile the TME at single-cell resolution. Immune cell phenotypes were defined with respect to the marker panel. Using R, cell composition was computed within tumor, stroma, and tertiary lymphoid structures (TLS, organized aggregates of immune cells that resemble secondary lymphoid organs) and within defined boundary regions at interfaces between each compartment. **Results:** We discovered that HG PC exhibited higher total immune infiltration (p $<$ 0.05) and specifically TLS (p $<$ 0.05) relative to LG PC. Furthermore, advancing Gleason grade was associated with increased T cell infiltration (p $<$ 0.05) and M2-like macrophage density (p $<$ 0.05). Strikingly, TLS were enriched in exhausted (PD1+) CD4 and CD8 T cells, especially near Tregs (p $<$ 0.001) and demonstrated a higher M2-like to M1-like macrophage ratio compared to surrounding tumor (p $<$ 0.001) and stroma (p $<$ 0.05). We observed paradoxically increased proportions of CD4PD1 cells (p $<$ 0.05) and Tregs (p $<$ 0.05) in HG vs. LG samples at the tumor-TLS interface. In HG samples, CD8PD1 cells (p $<$ 0.01), CD4PD1 cells (p $<$ 0.05), and Tregs (p $<$ 0.05) were enriched in tumor-TLS interface relative to TLS-stroma interface. HG tumors also demonstrated a higher ratio of M2-like to M1-like macrophages at the tumor-TLS interface compared to intra-tumoral regions (p $<$ 0.05). **Conclusions:** Our findings challenge the notion that primary PC is uniformly immunologically inert. We show that HG PC has increased levels of immune infiltration. We describe a paradoxical TLS phenotype in HG PC, where TLS harbor high levels of exhausted T cells near Tregs and have an unfavorable macrophage composition. Critically, the tumor-TLS interface emerged as a unique niche of suppression in HG PC, demonstrating multiple features of lymphocytic and myeloid-driven immunosuppression. These immunosuppressive features were not seen in LG PC. The spatial organization of immunosuppressive cells in HG PC provides a rationale for novel immunotherapeutic targeting of the TLS-rich suppressive landscape of HG PC to improve clinical outcomes in the neoadjuvant setting. Research Sponsor: Prostate Cancer Foundation; V Foundation; National Cancer Institute.

5119 **Poster Session**

Neoadjuvant androgen receptor pathway inhibition for patients with high-risk localized prostate cancer: 5-year survival update and PSMA PET correlatives of the randomized NeoPRO trial. First Author: Gabriel Berlingieri Polho, Hospital Sírio-Libanês, São Paulo, Brazil

Background: Patients with high-risk prostate cancer remain at elevated risk of recurrence after local therapy. Ongoing trials are investigating neoadjuvant strategies using androgen deprivation therapy (ADT) combined with androgen receptor pathway inhibitors (ARPI). **Methods:** This phase II trial randomized patients with Gleason $\geq$ 8 and/or cT3N0-1 and/or PSA $\geq$ 20 ng/mL to receive either goserelin (ADT) plus abiraterone acetate and prednisone (AAP arm) or AAP plus apalutamide (A-APA arm) prior to radical prostatectomy. The primary endpoint was the rate of pathological complete response (pCR) or minimal residual disease (tumor $\leq$ 0.5 cm). Here we present updated survival data after a median follow-up of 59 months. Biochemical-free survival (BFS) was defined as the time from randomization to PSA $>$ 0.1 ng/mL, metastasis, or death. Metastasis-free survival (MFS) was defined as the time from randomization to metastasis or death. Kaplan-Meier method and log-rank tests were used for time-to-event analyses. **Results:** Sixty-two patients were randomized (AAP = 31; A-APA = 31). Previous results showed no significant difference in the primary endpoint (Bastos D, et al. ASCO 2022). A total of 35 patients experienced biochemical recurrence. No significant difference was observed between the AAP and A-APA arms in 5-year BFS (48% vs 35%, p = 0.55) or MFS (83% vs 84%, p = 0.88). Achieving complete PSMA response on PSMA PET prior to surgery was a significant prognostic factor for improved 5-year BFS (28% vs 66%, p = 0.003) and MFS (74% vs 100%, p = 0.009). A trend toward higher 5-year overall survival (OS) was also observed among those with complete PSMA response (87% vs 100%, p = 0.09). Residual cancer burden $\leq$ 0.25 cm³ was associated with better 5-year BFS (32% vs 77%, p = 0.008), but not with MFS (79% vs 100%, p = 0.06) or OS (89% vs 100%, p = 0.22). **Conclusions:** No difference in 5-year BFS or MFS was observed between AAP and A-APA. Complete PSMA response on PSMA PET is a promising prognostic marker and may serve as a surrogate for BFS and MFS after neoadjuvant treatment in high-risk prostate cancer. Clinical trial information: NCT02789878. Research Sponsor: Janssen.

5120 **Poster Session**

A head-to-head comparison of sextant-systematic biopsy versus extended-systematic biopsy for prostate cancer diagnosis in the era of MRI-targeted biopsy: Non-inferiority randomized clinical trial. First Author: Ruiyi Deng, Peking University First Hospital, Beijing, China

Background: In recent years, combined targeted biopsy (TB) and 12-core extended systematic biopsy (SB) (TB+12SB) has been recommended for biopsy-naïve patients with prostate MRI-visible lesions. However, increasing SB cores elevates complication risks and healthcare expenditure. Retrospective data indicated noninferior PCa detection with TB + sextant-SB (TB+6SB) vs TB+12SB. This RCT aims to compare the novel TB+6SB scheme and classical TB+12SB for PCa diagnosis. **Methods:** In this non-inferiority RCT (NCT06684652), 506 biopsy-naïve men with solitary mpMRI lesions (PI-RADS $\geq$3) underwent transperineal cognitive fusion 3-core TB within the predefined mpMRI index lesion (ROI), followed by randomization to 12-core SB or 6-core sextant SB (2 peripheral+1 transitional cores/side). The primary outcome was clinically significant PCa [csPCa, grade group (GG) $\geq$2] detection rate. Non-inferiority was established if the lower 95% CI bound for the rate difference exceeded -15%. **Results:** Baseline characteristics were similar. TB+6SB demonstrated noninferior csPCa detection versus TB+12SB [54.3% (138/254) vs. 54.8% (138/252); rate difference -0.5%, 95%CI -9.2%-8.3%]. Comparable detection was also observed in PCa, high-grade PCa (GG$\geq$3), and clinically insignificant PCa (GG=1). The concordance in GG between biopsy and radical prostatectomy whole-mount specimens was similar for both TB+12SB [52.3% (34/65), κ=0.55] and TB+6SB [51.7% (30/58), κ=0.50] groups (p=0.25). TB+6SB showed superior safety profiles, significantly relieving the procedural discomfort, reducing the post-biopsy pelvic pain, and improving the quality of life ($p<0.05$). The biopsy time of TB+6SB was significantly shorter than that of TB+12SB ($p<0.001$). **Conclusions:** TB+6SB achieves non-inferior diagnostic efficacy to classical TB+12SB with fewer cores and improved safety, positioning it as an effective strategy for PCa diagnosis in biopsy-naïve patients with solitary MRI-suspicious lesions. TB+6SB could improve operational efficiency, providing both clinical safety and cost-effectiveness in histopathological workflows. Clinical trial information: NCT06684652. Research Sponsor: Beijing Research Ward Excellence Program; BRWEP2024W054070105; National High Level Hospital Clinical Research Funding (Interdepartmental Research Project of Peking University First Hospital); 2023IR27; National High Level Hospital Clinical Research Funding (Interdepartmental Research Project of Peking University First Hospital); 2024IR16.

Clinicopathological characteristics after biopsy.

Characteristics	TB+12SB (n=252)	TB+6SB (n=254)	P value
csPCa (%)	138 (54.8)	138 (54.3)	1
RD (95%CI)	-0.5% (-9.2%, 8.3%)		
High-grade PCa (%)	72 (28.6)	74 (29.1)	1
Number of biopsy cores (per case)	15.0	9.0	
Proportion of positive cores (%) (median [IQR])	20.0 [0, 46.7]	33.3 [0, 55.6]	0.02
Procedural time (second) (median [IQR])	234.0 [220.0, 258.3]	167.5 [154.0, 187.0]	<0.001
Cost of pathological examination ($) (per case)	75.0	50.0	-
Pain level (VAS) (median [IQR])	3.0 [2.0, 4.0]	2.0 [2.0, 4.0]	0.004
Discomfort level (median [IQR])	3.0 [3.0, 5.0]	3.0 [1.5, 4.0]	0.03
OABSS total score after biopsy (median [IQR])	3.0 [2.0, 7.0]	3.0 [2.0, 5.0]	0.02

5121 **Poster Session**

Long-term oncologic outcomes of PSMA PET–guided salvage radiotherapy for biochemical recurrence after radical prostatectomy: A systematic review and meta-analysis. First Author: Muhammad Moghis, King Edward Medical University, Lahore, Pakistan

Background: Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging has demonstrated superior diagnostic accuracy over conventional imaging in localizing recurrent prostate cancer after radical prostatectomy. Previous meta-analyses have established its value in detection and treatment planning; however, whether PSMA-guided salvage radiotherapy (SRT) translates into improved long-term oncologic outcomes remains uncertain. We conducted a systematic review and meta-analysis to assess the impact of PSMA PET-guided SRT on survival outcomes in patients with biochemical recurrence after radical prostatectomy. **Methods:** A comprehensive search of PubMed, Embase, and Cochrane Library was performed on January 16, 2025. Studies comparing PSMA PET–guided SRT with conventional SRT in post-radical prostatectomy patients with biochemical recurrence were included. Long-term oncologic outcomes including failure-free survival (FFS), biochemical progression-free survival (bPFS) and metastasis-free survival (MFS), were pooled using hazard ratios (HRs). **Results:** Nine studies comprising 4,278 patients met the inclusion criteria, including 1,418 patients treated with PSMA PET–guided salvage radiotherapy and 2,860 who received conventional salvage radiotherapy. Compared with conventional SRT, PSMA PET–guided SRT was associated with significantly improved FFS (HR, 0.46; 95% CI, 0.28–0.75). However, the PSMA PET-guided SRT group had a significantly higher risk of biochemical progression; bPFS (HR, 1.40; 95% CI, 1.16–1.69) and metastasis; MFS (HR, 3.16; 95% CI, 2.08–4.80). **Conclusions:** PSMA PET–guided salvage radiotherapy was associated with reduced early treatment failure, as reflected by improved failure-free survival, but a higher risk of biochemical progression and metastatic events. These findings indicate that while PSMA PET-guided intervention may reduce early treatment failure, its impact on long-term disease control remains uncertain and requires further prospective validation. Research Sponsor: None.

5122 **Poster Session**

Evaluation of treatment outcomes in ductal and intraductal prostate cancer: Insights from the National Cancer Database. First Author: Annabel Ricci, St. George's University School of Medicine, True Blue, St. George, Grenada

Background: Ductal and intraductal Prostate carcinoma (DPC) are rare and aggressive histological subtypes of prostate cancer. Based on risk stratification, treatment strategies for localized DPC include radical prostatectomy (RP), radiation with androgen deprivation therapy (RT$\pm$ADT), and observation. However, literature on outcomes across various treatment modalities in DPC is limited. Understanding the impact of these approaches on survival is important for strategizing DPC management. We used the national cancer database to evaluate the survival outcomes with various treatment strategies in DPC. **Methods:** Our study focused on patients diagnosed with localized DPC between 2004 and 2020. Patients were stratified into three arms: RP arm included those who underwent RP with or without adjuvant therapy, RT +/- ADT arm included patients who underwent RT with or without ADT, and observation arm included those who had no treatment. We performed Multivariate Cox regression analysis adjusting for age, race, NCCN risk classification, comorbidities, socioeconomic factors, and facility type. We also conducted Kaplan-Meier analysis to evaluate Overall Survival (OS) across the treatment arms. **Results:** We analyzed 2,650 patients with localized DPC. 1586(59.9%) underwent RP, 785(29.6%) underwent RT$\pm$ADT, and 279(10.5%) were under observation. 2-year OS for RP, RT$\pm$ADT, and observation were 98%, 94% and 78% respectively ($p<0.001$). Similarly, 5-year OS was 92%, 81%, and 54%, respectively ($p<0.001$). Multivariate Cox regression showed that RT+ADT was associated with increased mortality compared to RP (HR: 2.27; $p<0.001$). 2-year OS for patients with PSA $\leq$4 ng/dL and >4 ng/dL was 89.9% and 97.2%, respectively. Similarly, 5-year OS were 75.8% and 88.8%, respectively. Multivariate Cox regression showed that PSA <=4 was associated with an increased risk of mortality compared with PSA >4 (HR: 1.27; $p<0.05$). **Conclusions:** Surgery offers better survival than radiation in localized DPC. The association of low PSA with worse prognosis could be due to dedifferentiation-driven aggressiveness. Therefore, further evaluation of treatment strategies for DPC is warranted. Research Sponsor: None.

5123 **Poster Session**

Association of cardiovascular outcomes with GnRH agonist and antagonist therapy in non-metastatic prostate cancer. First Author: Abdulraof Ghiblawi, Lahey Hospital and Medical Centre, Burlington, MA

Background: Androgen deprivation therapy (ADT) is known to increase cardiometabolic risk. Randomized trials suggest GnRH antagonists may reduce major adverse cardiovascular events (MACE) compared with agonists, though studies were limited by short follow-up and low event rates. We evaluated the association between ADT mechanism and cardiovascular (CV) outcomes using large-scale real-world data. **Methods:** We conducted a retrospective cohort study using TriNetX database. Adult men with non-metastatic prostate cancer initiating ADT within 1 year of diagnosis were categorized by GnRH agonist or antagonist exposure. Cohorts were balanced using propensity score, matching demographics, CV co-morbidities, CV medications, and socioeconomic risk. Analyses were performed in the overall cohort and stratified by baseline CVD status. CV outcomes were assessed in years 1-10 following ADT initiation. The primary endpoint was MACE, defined as myocardial infarction, heart failure exacerbation, stroke or cardiac death. Secondary outcomes included atrial fibrillation/flutter, thromboembolism, mortality, and healthcare utilization. **Results:** After matching, 2,538 patients were included in both the GnRH antagonist and agonist group, including 785 with prior CVD and 1,460 without. In the overall cohort, GnRH antagonist therapy was associated with lower risk of MACE compared with GnRH agonists (OR 0.80, 95% CI 0.70–0.99; p=0.05) with an absolute risk of 8.0% vs 9.6%. Among patients with established CVD, antagonist use was associated with reduced MACE risk (OR 0.77, 95% CI 0.64–0.93; $p<0.01$) with an absolute risk of 19.6% vs 25.5%. In patients without prior CVD, antagonist use was associated with markedly lower MACE risk (OR 0.30, 95% CI 0.19–0.52; $p<0.01$) with an absolute risk of 1.3% vs 4.2%. For secondary outcomes, antagonist therapy was associated with lower risk of arterial thromboembolism and Emergency visits in the overall cohort, with no significant differences in all other outcomes. Among patients with baseline CVD, antagonist use was associated with lower risk of atrial fibrillation with no significant differences in all other outcomes. Among patients without baseline CVD, antagonist therapy was associated with lower risk of atrial fibrillation, healthcare utilization, and incident type 2 diabetes with no significant difference in all other outcomes. **Conclusions:** GnRH antagonist therapy was associated with lower rates of major adverse cardiovascular events compared with GnRH agonists, regardless of baseline cardiovascular disease status in years 1 through 10 after ADT initiation. Events occurring after the first year are more likely to reflect cumulative treatment-related cardiovascular toxicity, rather than unmasking baseline disease. These findings support further prospective, randomized trials to define the comparative CV safety of different ADT formulations. Research Sponsor: None.

5124 Poster Session

Temporal evolution of prostate cancer incidence and incidence-based mortality from 2000 to 2022: A retrospective analysis by race and age at diagnosis based on USPSTF screening guidelines. First Author: Charles Tobin, Trinity Health Ann Arbor Hospital, Ypsilanti, MI

Background: Prostate-specific antigen (PSA) screening guidelines have evolved substantially since 2000, influencing detection patterns and outcomes. Despite widespread implementation, significant racial disparities persist in prostate cancer incidence and mortality. Understanding temporal trends across guideline eras, stratified by race and age, is critical for optimizing screening strategies and addressing health equity. **Methods:** Using SEER*Stat, we extracted data from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2022). We employed Jointpoint regression to analyze the secular trend in incidence and incidence-based mortality (IBM), which we classified and arranged by race, age at diagnosis, and year of diagnosis. Annual percentage change (APCs) were calculated using weighted least square method. **Results:** A total of 1,259,662 patients met the inclusion criteria for our study. These included diagnosed cases of prostate cancer from 2000-2022. The total age-adjusted incidence rate was 60.7 per 100,000. The APC from 2000-2007 (before 2008 guidelines) was -0.1 ($p < 0.05$), signifying a cumulative annual decrease. The APC was -2.6 ($p < 0.05$) from 2008-2011, 0.1 ($p < 0.05$) from 2012-2017, and 1.5 ($p < 0.05$) from 2018-2022. Based on race, the APC from 2000-2022 was -2.1 for white, -1.7 for blacks, -2.2 for American Indian/Alaska native (AIAN) and -2.7 for asian and pacific islander (API). Based on age at diagnosis, the APC was -1.9 from 55-64 years, -1.7 from 65-74 years, -2.0 from 75- 84 years, and -2.2 at 85 years and above. In terms of incidence based mortality, rate increased from 2.4 (2000) to 37.7 (2022) in white, with APC of 6.3% (95% CI 5.0–7.7), in black, rate increased from 4.8 (2000) to 60.5 (2022), with APC of 5.2% (95% CI 4.0– 6.4), in API, rate increased from 1.8 (2000) to 17.7 (2022) while in AIAN, rate increased from 2.4 (2000) to 21.5 (2022), with APC of 5.0% (95% CI 3.4–6.6). **Conclusions:** Between 2000 and 2022, prostate cancer incidence demonstrated distinct temporal patterns aligned with changes in PSA screening recommendations, with a marked decline from 2008 to 2011, minimal change from 2012 to 2017, and an increase from 2018 to 2022. Across the same period, incidence-based mortality (IBM) increased steadily in all racial groups, despite long-term declines in overall incidence. Incidence-based mortality rates were consistently higher in black patients compared with white patients throughout the study period. These findings demonstrate a difference between incidence and incidence-based mortality over time and highlight persistent racial differences in prostate cancer outcomes across multiple screening eras. Research Sponsor: None.

5125 Poster Session

Addition of 18F-DCFPyL PSMA PET to MRI to avoid unnecessary biopsy in men on active surveillance: Final results from a phase II diagnostic trial (PROMPT). First Author: Marcelo Bigarella, University of Arkansas, Little Rock, AR

Background: Multiparametric MRI (mpMRI) is used in active surveillance (AS) for prostate cancer (PC) but has limited specificity. This prospective trial evaluated whether combining 18F-DCFPyL PSMA PET with mpMRI improves the detection of clinically significant PC (csPC) in patients on AS and reduces unnecessary biopsies prompted by false-positive mpMRI. **Methods:** In this IRB-approved, single-arm Phase II study, 91 patients on AS underwent PSMA PET and mpMRI on a dedicated PET/MRI scanner followed by systematic and targeted biopsies. PET and mpMRI were interpreted independently. The primary outcome was the diagnostic accuracy of mpMRI versus the combined PSMA PET/MRI for csPC. **Results:** Among 246 targeted lesions, the area under the curve (AUC) for combined PSMA PET/MRI was (0.77) compared to mpMRI alone (0.70) (p=0.2). PSMA PET/MRI showed improved specificity (64.6% vs. 27.5%) with a comparable negative predictive value (89.1% vs. 89.7%). Of 57 csPC lesions, 6 (10.5%) were uniquely identified by the combination. Half of the biopsies for false-positive mpMRI or PET lesions (122/246; 50%) encompassing 17/91 (19%) of patients could have been avoided with combined imaging. Management changed in 9% of patients based on PET/MRI. **Conclusions:** In this first-in-field trial the addition of PSMA PET to mpMRI with dedicated PET/MRI imaging enhances sensitivity in detecting csPC and may reduce the need for unnecessary biopsies in AS patients. Incorporating PSMA PET/MRI into clinical practice could refine surveillance protocols and support biopsy omission in select men with negative imaging. The single health-system nature of the trial may limit the generalizability of our findings. Research Sponsor: the Duane and Dorothy Bluemke Foundation.

Diagnostic accuracy of the mpMRI, PSMA PET/MRI, and for the combination, assessed using the "AND" operator.[a]

Parameter	MRI, PIRADS≥3	PSMA-PET, Likert≥3	MRI, PIRADS≥4	PSMA-PET, Likert≥4	MRI PIRADS≥3 AND PET Likert≥3	MRI PIRADS≥3 AND PET Likert≥4	MRI PIRADS≥4 AND PET Likert≥3	MRI PIRADS≥4 AND PET Likert≥4
Accuracy	41.9%	48.0%	63.8%	63.8%	66.7%	72.8%	78.5%	79.3%
Sensitivity	89.5%	84.2%	71.9%	73.7%	73.7%	64.9%	63.2%	57.9%
Specificity	27.5%	37.0%	61.4%	60.8%	64.6%	75.1%	83.1%	85.7%
PPV	27.1%	28.7%	36.0%	36.2%	38.5%	44.0%	52.9%	55.0%
NPV	89.7%	88.6%	87.9%	88.5%	89.1%	87.7%	88.2%	87.1%
Number of lesions (% of 257)	188 (76)	167 (68)	114 (46)	116 (47)	109 (44)	84 (34)	68 (28)	60 (24)

[a]The detection of clinically significant cancer was considered on per-lesion analysis.

MRI = magnetic resonance imaging; PET = positron emission tomography; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen. PPV= positive predictive value, NPV = negative predictive value.

5126 Poster Session

Leveraging spatial proteomics to identify epithelial cell subtypes driving poor prognosis in prostate cancer. First Author: William Chen, University of California, San Francisco, San Francisco, CA

Background: Epithelial cell features, such as morphology and cellular organization within the tumor architecture (e.g. Gleason Score), have long been known to be prognostic in prostate cancer. However, the specific epithelial cell subtypes driving clinical outcomes in patients remains unclear. Traditional tumor profiling techniques lack the resolution needed to interrogate complex single-cell biomarkers. Imaging Mass Cytometry (IMC) now enables high-dimensional identification and detailing of epithelial, stromal, and immune cell subtypes within patient tumors. Using a custom IMC panel, we profiled tumor biopsies from a large prospective biopsy cohort with long-term (median >12-year) clinical follow-up to identify potentially targetable epithelial cell populations associated with adverse outcomes in localized prostate cancer. **Methods:** Spatially resolved protein expression profiling was performed on primary prostate cancer tumor biopsies using a custom IMC assay enriched for targetable tumor markers. Cell segmentation and single-cell expression measurement were performed using the published 'steinbock' toolkit. Biochemical progression-free survival (bPFS) and cancer-specific survival (CSS) were pre-specified clinical endpoints. Univariate and multivariable survival analyses stratified by cell abundance tertiles were performed using a Cox proportional hazards model. The Mann-Whitney U test was used to assess for pairwise differences in cell abundance between patient groups. All significance testing was performed using a two-tailed significance level of 0.05. **Results:** Protein co-expression patterns in >3.4 million cells comprising 573 biopsy samples obtained from 385 patients were measured. Single-cell analysis revealed 15 cell clusters representing luminal prostate cancer cells (including PSMA-high, PSMA-intermediate, and PSMA-low), basal epithelial cells, and lymphocytes. Patients with tumors enriched for PSMA-high epithelial cells demonstrated impaired bPFS ($P<0.001$) and CSS ($P=0.016$). PSMA-high epithelial cells were enriched in high-grade (Gleason Score 8+) tumors ($P<0.05$). Multivariable analysis revealed PSMA-high epithelial cell enrichment to be prognostic of bPFS independently of Gleason Score and serum PSA at time of diagnosis ($P<0.05$). Co-expression analysis demonstrated that these prognostic PSMA-high cells also expressed high levels of the cell-surface targets KLK2, B7-H3, and protein. **Conclusions:** We identified an epithelial single-cell biomarker associated with adverse clinical outcomes in localized prostate cancer. If validated through ongoing experiments in an independent cohort, our findings support new potential strategies for treatment intensification using targeted therapies in select high-risk patients. Research Sponsor: Conquer Cancer, the ASCO Foundation; Prostate Cancer Foundation; Benioff Initiative for Prostate Cancer Research; U.S. National Institutes of Health.

5127 Poster Session

Clinical implications and diagnostic utility of ^{68}Gallium FAPI PET CT in patients with testicular germ cell tumors: The prospective phase Ib FAPI-TEST study. First Author: Maximilian Peter Johannes Karl Brandt, Department of Urology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

Background: The fibroblast activation protein (FAP) is overexpressed in tumor tissue by cancer associated fibroblasts and radiopharmaceuticals can bind to this target. Recently, the ^{68}Ga-FAPI PET has emerged as a novel imaging modality for optimized differentiation between benign and malignant lesions. However, data on patients with testicular germ cell tumors (TGCT) are rare. This prospective study aims to investigate the expression, uptake and sensitivity of the ^{68}Ga-FAPI PET in TGCT patients. **Methods:** In this prospective observational phase Ib study, patients with TGCT up to clinical stage III and unfavorable TGCT histology in the testis such as teratomas were included. A ^{68}Ga-FAPI PET was performed in all included patients and analyzed with static (SUVmax/mean). Histology from the testis and whenever available from the metastasis were also stained for FAP and manually categorized into negative, medium and high expression. This study was approved by the local ethics committee (no 2024-17844). **Results:** We included 12 patients with a mean age of 34.5 (SD 8.81). Clinical stage at time of inclusion were CS II (n = 9), CS1 (n = 1) and CS III (n = 1) as well as one extragonadal TGCT. In eight and four cases the ^{68}Ga-FAPI PET was performed before and after completion of curative chemotherapy, respectively. Histology was available in six cases (5 = LNs, 1 = mediastinal tumor). FAP expression in the tumor of the testis was high in 50%, and in metastasis 60%. Stratification for high and low FAP lesions was performed according to mean SUVmax of 7.81 (SD 7,9) for all radiographic and histopathologic true positive metastasis. Sensitivity for ^{68}Ga-FAPI PET was 57% with a specificity 100%. **Conclusions:** This is the first prospective study that evaluates ^{68}Ga-FAPI PET in TGCT patients with the largest cohort so far. Stratification for SUVmax lesions above 7.81 showed excellent specificity, and the 68Ga-FAPI PET might potentially serve as a useful novel imaging modality for primary staging in clinical stages IIA and IIB, as well as post-chemotherapy with residual mass. Research Sponsor: None.

5128 **Poster Session**

First-in-human PET imaging of ^{68}Ga-FC516, a novel ACP3-targeted radiotracer for prostate cancer. First Author: Kongzhen Hu, Department of Nuclear Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

Background: Prostatic acid phosphatase (ACP3) is overexpressed in more than 85% of prostate cancers, and largely absent in normal tissues, resulting in over 100-fold tumor-to-background specificity. ACP3 represents a differentiated imaging biomarker that may complement prostate-specific membrane antigen (PSMA), particularly in PSMA-low or PSMA-treated patients. We developed ^{68}Ga-FC516, a novel ACP3-targeted radiotracer, and evaluated its preclinical characteristics and first-in-human imaging performance. **Methods:** ^{68}Ga-FC516 was studied preclinically using *in vitro* assays (radiochemical stability, enzyme inhibition, cellular uptake, internalization, and efflux) and *in vivo* PET/CT studies, including blocking and biodistribution experiments. A first-in-human exploratory clinical trial was conducted in healthy volunteers and prostate cancer patients. The primary objective was to assess safety and radiation dosimetry; secondary objectives included biodistribution assessment and lesion detection. PET/CT imaging results were compared with PSMA radiotracers or ^{68}Ga-OncoACP3-DOTA when possible. **Results:** ^{68}Ga-FC516 was labeled efficiently with radiochemical purity exceeding 95%. In *in vitro* studies, ^{68}Ga-FC516 demonstrated potent target binding, long cellular retention and high stability. ACP3-specific tumor uptake of ^{68}Ga-FC516 was confirmed via an *in vivo* blocking experiment. The tracer showed low background uptake in liver, kidneys, and salivary glands, with tumor uptake exceeding 16.4% ID/g in a biodistribution study. Gallbladder uptake was markedly lower than that of ^{68}Ga-OncoACP3-DOTA (2.6% vs. 35.0% ID/g) at 1 hour post-injection. In an ongoing clinical trial in metastatic prostate cancer patients, increased uptake of ^{68}Ga-FC516 (SUV_{max} in PET/CT) was observed at 1 to 3 hours across all lesions, with improved tumor-to-kidney ratios over time. The tracer also demonstrated low background uptake, including in salivary glands and kidneys, which was significantly lower than that of PSMA-targeted tracers. Notably, a patient with both prostate and rectal cancers showed strong uptake in the prostate tumor (SUV_{max} 44), but no uptake in the rectal lesion, further establishing the tracer's superior specificity. No adverse events were observed. **Conclusions:** We have shown that ^{68}Ga-FC516 has high ACP3-targeting specificity, low background uptake and excellent imaging performance in preclinical and first-in-human clinical studies. These findings support the potential of ACP3 as a differentiated biomarker for prostate cancer diagnosis and patient stratification, complementing PSMA PET and addressing unmet needs in PSMA-low or PSMA-treated patient populations. The clinical validation study was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (KY-2025-254). Research Sponsor: FindCure Biosciences Co., Ltd. Clinical trial information: KY-2025-254. Research Sponsor: None.

5129 **Poster Session**

Explainable machine learning for continuous transcriptomic modeling of metastatic risk in prostate cancer (MET-score). First Author: Sonia Macia, SMED Clinical Research, Alicante, Spain

Background: Metastatic progression is the leading cause of mortality in prostate cancer, yet clinicopathological stratification incompletely identifies primary tumors with latent metastatic potential. Emerging evidence supports metastatic competence as a gradual transcriptional reprogramming, motivating molecular tools that capture continuous risk states. **Methods:** Transcriptomes from primary and metastatic prostate tumors (n = 766; PRIMARY = 507, MET = 259) spanning 16,234 gene features were integrated to train an interpretable XGBoost model. SHapley Additive exPlanations were used to derive a minimal 30-gene signature and define a continuous metastasis-likeness transcriptomic score (MET-score). MET-score was applied to primary tumors to quantify metastasis-likeness and characterize associated biology. External validation was performed in an independent primary prostate cohort profiled with exon microarrays (GSE21034) without model retraining. **Results:** The minimal 30-gene signature captured metastasis-associated signal with high discriminative performance (ROC AUC $\approx$ 0.98). In primary tumors (n = 507), MET-score exhibited a right-skewed continuous distribution (mean 0.0079, SD 0.0640; range 0.0023–0.9953), consistent with heterogeneous degrees of metastasis-like transcriptional activity within primary disease. Using a prespecified high-risk threshold at the 0.85 quantile (cutoff 0.002603), 81/507 (16.0%) primary tumors were classified as HIGH MET-score and 426/507 as LOW, identifying a subset with transcriptomic profiles most closely resembling metastatic disease. MET-score generalized robustly to GSE21034 while preserving its continuous structure and enabling molecular stratification despite platform differences and partial gene loss: 26/30 signature genes were present in the microarray cohort (missing C15orf40, ADIRF, CTC1, NTPCR). However, prognostic validation against clinical endpoints could not be performed because the publicly available metadata did not include clearly annotated time-to-event and event-status variables. **Conclusions:** An explainable 30-gene MET-score was developed to quantify metastasis-likeness as a continuous transcriptomic trait in primary prostate cancer. The score identifies a high-risk primary subset and transfers to an independent external cohort (GSE21034) without model retraining, supporting cross-platform robustness and prioritizing MET-score for clinical outcome validation in RNA-seq–annotated cohorts. Research Sponsor: None.

5130 **Poster Session**

cfDNA-based signatures of nucleosome organization to enable prostate cancer subtyping. First Author: Weiwei Bian, Dana-Farber Cancer Institute, Boston, MA

Background: Neuroendocrine prostate cancer (NEPC) can arise from prostate adenocarcinoma (PRAD) via therapy-associated lineage plasticity and is characterized by reduced AR signaling and activation of neuroendocrine (NE) regulatory pathways. Nucleosome positioning, inferable from cell-free DNA (cfDNA) fragmentation patterns, reflects lineage-specific gene regulation. Recent studies have shown that active, open chromatin is associated with specific nucleosome spacing patterns, leading to an enrichment of longer cfDNA fragments, including di-nucleosome fragments. We hypothesized that fragmentomic signatures reflecting nucleosome positioning could distinguish PRAD from NEPC, providing a simple means to detect lineage plasticity from cfDNA. **Methods:** We analyzed cfDNA samples from 47 patients (8 with NEPC, 39 with PRAD) with hybrid-capture sequencing. Baits were designed to target adenocarcinoma (AC, 715 sites) and NE-associated regulatory elements (508 sites). For each sample, fragments overlapping each enhancer set were aggregated into 5-bp binned fragment-length distributions (18-500 bp). We quantified di-nucleosome (250-400 bp) and mono-nucleosome (120-180 bp) fragment counts at NE and AC regulatory elements. We calculated the log-ratio of NE versus AC di/mono values: log2 [(di/mono)_NE/(di/mono)_AC]. We also computed a position-free Transcriptional Activation Score (pfTAS) for each enhancer set using a published framework for estimating enhancer activity from cfDNA fragment size distributions, deriving an analogous log-ratio: log2 [pfTAS_NE/pfTAS_AC]. We tested if these ratios could distinguish NEPC versus PRAD, evaluating the area under the receiver operating characteristic curve (AUC) in the full cohort and by leave-one-out cross-validation (LOOCV). **Results:** The enhancer-specific di/mono log-ratio achieved complete separation between PRAD (median: -0.209; range: -0.449 to -0.090) and NEPC (median: 0.030; range: -0.056 to 0.218), yielding an AUC of 1.00 both in-sample and by LOOCV. The pfTAS log-ratio was also discriminative, with an AUC of 0.99 in-sample and an AUC of 0.89 by LOOCV. Overall, nucleosome fragmentation patterns provide a chromatin-based fragmentomic signal that enables accurate discrimination between PRAD and NEPC. **Conclusions:** Leveraging hybrid-capture cfDNA, we identified a biologically grounded chromatin-based signature that robustly discriminates NEPC from PRAD. By reflecting lineage-associated nucleosome positioning, this liquid biopsy-based approach provides a cost-effective and non-invasive molecular metric derived from routinely generated cfDNA sequencing data. It may be particularly useful in clinically challenging settings, including cases with mixed morphology or when a biopsy is difficult to obtain. Research Sponsor: None.

TPS5131 **Poster Session**

Randomized phase 1 trial of cisplatin-based chemotherapy with or without sodium thiosulfate for men with metastatic germ cell tumor (GCT). First Author: Koral U. Shah, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Cisplatin-induced ototoxicity remains a major survivorship issue in men with metastatic GCT. Sanchez et al., demonstrated that among adult GCT survivors, 78% develop hearing loss, with severity associated with cumulative cisplatin exposure. Sodium thiosulfate (STS; PEDMARK) was FDA-approved in 2022 to reduce the risk of cisplatin-associated ototoxicity in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors. However, prospective data in adults with metastatic GCT receiving curative intent cisplatin-based therapy are lacking. This study aims to address this gap in men with metastatic GCT, and potentially improve long-term quality of life. **Methods:** This open-label, single-center, randomized phase 1 trial evaluates sodium thiosulfate for reducing the incidence of cisplatin-induced ototoxicity in adults with metastatic GCT. Eligible adults have stage II–III GCT and are planned for first- or second-line cisplatin-based chemotherapy; patients receiving second-line therapy require a $\geq$4-week cisplatin washout to establish a new audiometric baseline. Key exclusions include baseline moderate or greater hearing loss, hypersensitivity to sodium thiosulfate or related compounds, chronic systemic corticosteroid use, concurrent non-cisplatin ototoxic medications, and comorbidities requiring sodium restrictions. Participants are randomized 2:1 to receive cisplatin-based chemotherapy with sodium thiosulfate versus chemotherapy alone, with a target enrollment of 39 patients. Sodium thiosulfate is administered intravenously at 20 g/m² over 30 minutes, beginning 6 hours after completion of cisplatin infusion and at least 10 hours before the next cisplatin dose, consistent with FDA-approved multi-day dosing schedules. The primary endpoint is the incidence of clinically meaningful ototoxicity, defined by trial parameters using American Speech-Language-Hearing Association criteria relative to baseline audiometry. Secondary endpoints include incidence of high-frequency ototoxicity, ototoxicity severity, safety per Common Terminology Criteria for Adverse Events (CTCAE) v5.0, and 2-year progression-free survival. Ototoxicity monitoring is performed using serial high-frequency audiometry (testing 250–12,500 Hz) at baseline and 1, 3, and 6 months following completion of cisplatin therapy. Ototoxicity incidence will be compared between arms using a one-sided Fisher's exact test under a modified intention-to-treat framework. Enrollment has begun. Clinical trial information: NCT07218913. Research Sponsor: Fennec Pharmaceuticals Inc.

TPS5132 **Poster Session**

Protocol for ADHERE: A randomised controlled trial evaluating a digital exercise intervention with virtual supervised group exercise sessions compared to standard of care for patients receiving androgen deprivation therapy for prostate cancer. First Author: Emily Curtis, The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom
Abstract Disclosures

Background: In the UK, supervised exercise is recommended by NICE for prostate cancer patients receiving androgen deprivation therapy (ADT); however, engagement in physical activity remains limited. Although high adherence is observed during supervised exercise, it is unclear whether participants maintain activity after supervision. Barriers include treatment-related side-effects and low motivation. Digital exercise interventions that include education and behaviour change support may address these barriers and promote sustained engagement in physical activity. **Methods:** The primary objective of ADHERE is to determine whether a digital exercise intervention incorporating virtual group exercise sessions improves adherence to physical activity compared with standard of care (SOC). Secondary and exploratory objectives include assessment of health-related quality of life (HRQoL), fatigue, physical function, clinical biomarkers and participant experiences, and evaluation of cost-effectiveness. ADHERE is a single-centre, phase III, two-arm randomised controlled trial. Prostate cancer patients within eight weeks of starting ADT and planned for radiotherapy will be recruited at The Royal Marsden NHS Foundation Trust. Participants will be randomised 1:1, stratified by ADT duration (≤6 months or >6 months), to SOC alone or SOC plus the digital exercise intervention. The intervention includes virtual supervised group exercise sessions delivered weekly over 26 weeks, access to exercise videos, an individualised exercise programme, educational content and "patient buddy" support. Assessments will be conducted at baseline and three, six, and 12-months post-radiotherapy. Primary endpoint is adherence to physical activity guidelines at six months post-radiotherapy, assessed using device-based activity monitor and self-reported exercise diary. Secondary endpoint is HRQoL and will be measured using FACT-P. 160 participants (80 per arm) will be recruited allowing for 20% dropout. ADHERE has ethical and regulatory approval and will be conducted in accordance with Good Clinical Practice. Recruitment for this trial started in December 2025. An interim analysis will be conducted, with final analyses performed following completion of all participant follow-up. Results will be disseminated via peer-reviewed publications and conferences. Clinical trial information: NCT07243834. Research Sponsor: None.

TPS5133 **Poster Session**

DEPECA-1 (Defeating Penile Cancer 1): A phase II study to evaluate a first-line systemic therapy with enfortumab vedotin plus avelumab for advanced and metastatic penile carcinoma. First Author: Igor Tsaur, Department of Urology, University Hospital Tuebingen, Tuebingen, Germany

Background: Squamous cell carcinoma of the penis (PeCa) is a rare malignancy with unfavorable outcomes in advanced stage. Since the 1990s, platinum-based chemotherapy has been the standard of care for the first-line treatment of metastatic disease. Unfortunately, it is characterized by a response rate of 30-40%, overall survival (OS) of 17 months and progression free survival (PFS) of 6 months at most. Thus, there is a critical medical need to assess novel systemic strategies for PeCa in the first-line setting, given that current regimens are of a limited clinical benefit while exposing patients to considerable chemotherapy-associated toxicities. In this context, the PD-1 inhibitor pembrolizumab yielded a promising activity in squamous cell carcinomas of various origins. Meanwhile, enfortumab vedotin (EV), a Nectin-4 directed antibody-drug-conjugate, in combination with pembrolizumab has been recently approved for the treatment of metastatic urothelial cancer. The incidence of ≥3 grade adverse events with this regimen was > 55%. Notably, a PD-L1 inhibitor avelumab provided a comparable activity as pembrolizumab but a lower overall rate of endocrine adverse events in patients with urothelial carcinoma. Avelumab monotherapy yielded a response rate of 17% and a median duration of response of 16 months in males with a platinum-refractory PeCa or those unfit for platinum chemotherapy in ALPACA trial. Given that approximately 60% of PeCa tissues express both PD-L1 and Nectin-4, the combination of EV with avelumab represents a potentially synergistic therapeutic strategy, leveraging both direct cytotoxicity and immune-mediated anti-tumor activity through complementary mechanisms of action. **Methods:** The DEPECA-1 trial is an investigator-initiated, open label, single-arm, multicenter phase II trial, enrolling 25 males with locally advanced or metastatic PeCa at 10 sites in Germany. Patients must be ineligible for curative surgery and not have received any prior systemic palliative therapy. Participants (ECOG ≤ 2) will receive 1200 mg avelumab on day 1 and EV (1,25 mg/kg) on day 1 and day 8 in a 3-week -cycle for a maximum of 24 months and 32 cycles. Primary endpoint is the objective response rate (ORR) assessed per RECIST 1.1. Secondary endpoints include PFS, OS, duration of response (DOR), disease control rate (DCR) and patient-related outcomes. Exploratory analysis comprises tumor biomarker profiling. DEPECA-1 has received regulatory approval on 29th October 2025. First patient was enrolled on December 16, 2025. Registration IDs: EU CT No. 2025-521644-37-00/NCT07110038. Clinical trial information: NCT07110038. Research Sponsor: Merck Healthcare KGaA; Astellas Pharma GmbH.

TPS5134 **Poster Session**

AcTFirst: A phase 3 trial of ^{225}Ac-PSMA-617 plus ARPI versus standard of care in adults with PSMA-positive metastatic castration-resistant prostate cancer. First Author: Alton Oliver Sartor, LCMC Health, New Orleans, LA

Background: In the VISION and PSMAfore trials, β-emitting radioligand therapy (RLT) with [^{177}Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) shows superior efficacy and tolerable safety compared with standard of care (SoC) in patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC). [^{225}Ac]Ac-PSMA-617 (^{225}Ac-PSMA-617), an α-emitting agent, may offer an alternative treatment option to SoC in mCRPC because its higher linear energy transfer increases the likelihood of higher cytotoxicity in tumor cells. **Methods:** AcTFirst (NCT06855277) is a phase 3, open-label, multicenter, randomized study to evaluate the efficacy and safety of ^{225}Ac-PSMA-617 plus androgen receptor pathway inhibitor (ARPI) in patients with PSMA-positive mCRPC. Eligible participants are adults with PSMA positron emission tomography-positive mCRPC and progressive disease on androgen deprivation therapy plus one ARPI as their last treatment in the metastatic hormone-sensitive prostate cancer (mHSPC) or earlier setting. ARPI treatment received in the mHSPC setting can be continued until cycle 1. Key exclusion criteria include previous treatment with RLT or systemic anti-cancer therapy for mCRPC. Participants with homologous recombination repair gene-mutated mCRPC who had prior exposure to poly-adenosine diphosphate ribose polymerase inhibitors (PARPi) for HSPC can be included. Participants with inadequate bone marrow, hepatic or renal function are excluded. Participants will be randomized to three treatment arms: 1) a combination of ^{225}Ac-PSMA-617 (up to six cycles) plus ARPI change (enzalutamide or abiraterone); 2) ^{225}Ac-PSMA-617 monotherapy (up to six cycles); or 3) investigator's choice of SoC (ARPI change, taxane chemotherapy or ^{177}Lu-PSMA-617). Efficacy will be assessed using a hierarchical group sequential testing strategy for the primary and key secondary objectives. The primary endpoint is radiographic progression-free survival (rPFS) by conventional imaging for the combination and SoC arms. Key secondary endpoints are overall survival (OS) for the combination and SoC arms, rPFS by conventional imaging for the monotherapy and SoC arms, OS for the monotherapy and SoC arms, and rPFS by PSMA positron emission tomography/computed tomography imaging for the combination and SoC arms. Other outcomes of interest include safety, health-related quality of life and other patient-reported outcomes. As of January 2026, patient enrollment is ongoing. Clinical trial information: NCT06855277. Research Sponsor: Novartis.

TPS5135 **Poster Session**

OMAHA-004: Phase 3 trial of the steroidogenesis inhibitor opevesostat versus androgen receptor pathway inhibitor (ARPI) switch in participants with metastatic castration-resistant prostate cancer (mCRPC) after a prior ARPI. First Author: Donald Charles Vile, Blue Ridge Cancer Care, Roanoke, VA

Background: Opevesostat (MK-5684; ODM-208) is an oral, nonsteroidal inhibitor of cytochrome P450 11A1 (CYP11A1), a catalyst of the first and rate-limiting step of steroid biosynthesis. Opevesostat showed antitumor activity in participants with heavily pretreated mCRPC in the phase 1/2 CYPIDES trial. The randomized, open-label, phase 3 OMAHA-004 trial (NCT06136650) is designed to evaluate the efficacy and safety of opevesostat in participants with mCRPC after a prior ARPI. **Methods:** Eligible participants have mCRPC that progressed during androgen deprivation therapy ≤6 months before screening and on or after 1 ARPI for metastatic or nonmetastatic hormone-sensitive prostate cancer (HSPC) or CRPC for ≥8 weeks (≥14 weeks with bone progression). Prior ARPI plus docetaxel for HSPC is permitted if participants received no more than 6 cycles of docetaxel without radiographic disease progression. Approximately 1314 participants will be randomized 1:1 to opevesostat 5 mg orally twice-daily plus dexamethasone 1.5 mg and fludrocortisone 0.1 mg orally once daily or abiraterone acetate 1000 mg orally once daily plus prednisone 5 mg orally twice daily (if prior enzalutamide, darolutamide, or apalutamide) or enzalutamide 160 mg orally once-daily (if prior abiraterone). Stratification factors are metastatic site (bone only vs liver vs other), androgen receptor ligand binding mutation (AR-LBDm) status (positive vs negative), and prior docetaxel treatment for HSPC (yes vs no). Once the predefined enrollment threshold for participants with either mutation status (AR-LBDm-positive, ~400 participants or AR-LBDm-negative, ~914 participants) is met, no additional participants with that mutation status will be permitted to enroll. The protocol was amended to use radiographic progression-free survival per Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 by blinded independent central review (BICR), analyzed separately in participants with AR-LBDm–positive and –negative disease, as the primary end point and overall survival as a key secondary end point. Other secondary end points include time to initiation of first subsequent anticancer therapy or death, objective response rate and duration of response per PCWG3-modified RECIST v1.1 by BICR, time to pain progression; time to prostate-specific antigen (PSA) progression, PSA response rate, time to first symptomatic skeletal-related event, and safety and tolerability. Enrollment is ongoing. Clinical trial information: NCT06136650. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Orion Corporation, who are codeveloping opevesostat.

TPS5136 **Poster Session**

A phase 3 randomized, double-blind, placebo-controlled study of a pasritamig plus best supportive care in metastatic castration-resistant prostate cancer. First Author: Kim N. Chi, BC Cancer Agency, Vancouver, BC, Canada

Background: Metastatic castration-resistant prostate cancer (mCRPC) remains an incurable disease with high morbidity and a median overall survival of 2 years. Human kallikrein 2 (KLK2) is highly and specifically expressed in normal and malignant prostate tissue, including late stage mCRPC. Pasritamig is a humanized, IgG1-based bispecific antibody that targets KLK2-expressing cells via CD3 engagement, inducing T cell-mediated targeted cytotoxicity. In a first-in-human study in participants with mCRPC refractory to standard therapies, pasritamig demonstrated a favorable safety profile ($<$ 5% grade 3 or higher treatment-related adverse events and $<$ 10% cytokine release syndrome, all grade 1) and encouraging efficacy at the recommended phase 2 dose with every 6-week (Q6W) outpatient dosing. **Methods:** KLK2-comPAS is a double-blind, randomized, global phase 3 study to evaluate the safety and efficacy of pasritamig in participants with mCRPC who have previously received all available and suitable life-prolonging therapies including androgen receptor pathway inhibitor, taxane chemotherapy, radioligand therapy (RLT), and poly(ADP-ribose) polymerase inhibitors (for patients with BRCA mutations). Other key inclusion criteria include ECOG performance status 0–2, PSA $\geq$2 ng/mL, adequate organ function, and ongoing androgen deprivation therapy or prior orchiectomy. Key exclusion criteria include visceral metastases, prior KLK2- or CD3-directed therapies, and active autoimmune disease requiring systemic immunosuppression. Approximately 663 patients will be randomized in a 2:1 ratio to receive pasritamig plus best supportive care (BSC) or placebo plus BSC, stratified by prior PSMA-targeted RLT, number of prior taxanes, and ECOG performance status. BSC may include palliative external beam radiation, low dose steroids, pain medications, bone protective agents, and needed palliative procedures. Pasritamig is administered outpatient at a target dose of 300 mg IV Q6W with two step-up doses of 3.5 mg IV on cycle 1 day 1 and 18 mg IV on cycle 1 day 8. Pre-medications (dexamethasone, diphenhydramine, acetaminophen) will be administered for step-up and first target dose. Participants will receive treatment until confirmed radiographic progression or unequivocal clinical progression, intolerable toxicity, withdrawal, or death. The primary endpoint is overall survival. Key secondary endpoints include radiographic progression-free survival (rPFS), PFS (including clinical progression and unconfirmed bone progression), time to symptomatic progression, and time to skeletal-related events. Enrollment commenced in September 2025 and remains ongoing. Clinical trial information: NCT07164443. Research Sponsor: J&J.

TPS5137 **Poster Session**

BNT324-03: Phase 3, randomized, open-label trial of BNT324/DB-1311, a B7H3 ADC, versus docetaxel in patients with taxane-naïve metastatic castration-resistant prostate cancer (mCRPC). First Author: Johann S. De Bono, Royal Marsden Hospital, London, United Kingdom

Background: B7H3 is highly expressed in various human cancers, including mCRPC, and overexpression is associated with a poor patient prognosis. BNT324/DB-1311 is an investigational B7H3 ADC comprised of a topoisomerase-I-inhibitor-based payload with a cleavable linker and a drug-to-antibody ratio of ~6 that received FDA Fast-Track Designation for previously treated CRPC. A phase 1/2 study (DB-1311-O-1001, NCT05914116) is currently enrolling several prostate cancer cohorts: post Lutetium-177 [^{177}Lu]-PSMA-617 radioligand (RLT) (Lu 177-RLT) mCRPC, taxane-naïve mCPRC, and castration-sensitive prostate cancer (CSPC) with suboptimal PSA response, with patients receiving BNT324/DB-1311 alone or with abiraterone or enzalutamide. This study has reported encouraging activity (median radiographic PFS 11.3 months) and a manageable safety profile in heavily pretreated mCRPC (Parsonson A, ASCO 2025 #5015), and in Lu 177-RLT pretreated mCRPC (Stein M, ASCO GU 2026 #176). The treatment landscape of mCRPC has been evolving. As first use of an androgen receptor pathway inhibitor (ARPI) has shifted to the mCSPC setting, more patients will receive docetaxel in early-line mCRPC. The use of Lu 177-RLT in taxane-naïve mCRPC has been increasing; however, outcomes with subsequent docetaxel appear suboptimal. Docetaxel remains the first-line treatment option for symptomatic or rapidly progressive mCRPC, but outcomes are poor. Overall, there is a high unmet need for novel effective and better tolerated treatment options in the post-ARPI and emerging post-RLT settings. **Methods:** BNT324-03 is an open-label, randomized, Phase 3 trial (NCT07365995) designed to determine the efficacy and safety of BNT324 compared with docetaxel in patients ($>$ 18 years, ECOG PS 0–1) with mCRPC previously treated with 1 or 2 prior ARPIs. Patients may have received prior Lu 177-RLT but must not have received prior taxane for mCRPC (allowed in mCSPC if $\geq$6 months since completion without disease progression). Prior treatment with B7H3 targeted therapy is not allowed. Approximately 736 patients will be randomized 1:1 to receive either BNT324 or docetaxel (+ prednisone/prednisolone). Unless there is unacceptable toxicity or withdrawal of consent, BNT324 will be administered until PCWG3-modified RECIST v1.1-defined progressive disease and docetaxel will be administered for up to 10 cycles. Randomization will be stratified by prior Lu 177-RLT, prior taxane use, and site of metastasis. The dual primary endpoints are to assess the efficacy of BNT324 in terms of radiographic PFS and OS when compared with docetaxel. Secondary endpoints include time to first subsequent therapy, ORR and DOR by BICR, time to pain progression, time to first symptomatic skeletal-related event, PSA response and time to PSA progression, and safety. Enrollment is ongoing globally. Clinical trial information: NCT07365995. Research Sponsor: BioNTech SE in collaboration with BioNTech Shanghai Pharmaceutical Co., Ltd and DualityBio Inc.

TPS5138 **Poster Session**

A phase II clinical trial of ivonescimab (VEGFxPD-1 bispecific antibody) in patients with metastatic castration-resistant prostate cancer (mCRPC). First Author: Bilal Ahmed Siddiqui, Department of Genitourinary Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with mCRPC achieve limited responses with single-agent immune checkpoint therapies (ICTs), due to tumor microenvironments (TME) characterized by few intratumoral effector T cells and high prevalence of suppressive myeloid cell populations, cytokines, and signaling pathways. In murine models of mCRPC, tyrosine kinase inhibitors (TKIs, i.e. against vascular endothelial growth factor [VEGF] receptor 2, MET, and AXL, among others) inhibited tumor infiltrating myeloid-derived suppressor cells and enhanced responses to ICTs (Lu X et al., *Nature* 2017). Consistent with this, a phase III clinical trial combining TKI and anti-PD-(L)1 demonstrated improved clinical outcomes in a subset of patients with mCRPC (Agarwal N et al., *Lancet Oncol* 2025). Ivonescimab is a first-in-class bispecific antibody simultaneously targeting PD-1 and VEGF-A that has demonstrated clinical activity across multiple tumor types. We hypothesized that ivonescimab will induce anti-tumor responses in a subset of patients with mCRPC. **Methods:** This is an open-label, single-center phase II clinical trial in patients with mCRPC with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology. The primary endpoint of the study is objective response rate per Prostate Cancer Working Group 3 (PCWG3) criteria, and secondary endpoints include duration of response (DOR), disease control rate (DCR) greater than 6 months), radiographic progression free survival (rPFS), PSA_{50} responses (defined as confirmed $>$ 50% decline in PSA from baseline) and incidence, severity, and duration of adverse events. Tumor biopsies are collected at baseline and prior to C2D1 for evaluation of biomarkers of response and resistance to therapy. The study is being conducted using a Bayesian optimal phase 2 (BOP2) design. A total of up to 24 patients will be enrolled on study. The study is currently open and enrolling (NCT06567314). Clinical trial information: NCT06567314. Research Sponsor: None.

TPS5139 **Poster Session**

A phase 3 randomized, open-label study of pasritamig (JNJ-78278343), a T-cell engager targeting human kallikrein-2, with docetaxel versus docetaxel for metastatic castration-resistant prostate cancer. First Author: Rana R. McKay, UC San Diego Moores Cancer Center, La Jolla, CA

Background: Metastatic castration-resistant prostate cancer (mCRPC) remains an incurable disease with high morbidity and a median overall survival of approximately two years. Human kallikrein 2 (KLK2) is highly and specifically expressed in normal and malignant prostate tissue, including late stage mCRPC. Pasritamig (PAS) is a first-in-class bispecific T-cell-engager that simultaneously binds KLK2 on prostate cancer cells and CD3 receptor complexes on T cells. In the Phase 1b study (NCT05818683), pasritamig was combined with docetaxel (DOCE) to treat patients with mCRPC. The safety profile of PAS+DOCE was shown to be consistent with previous studies of DOCE and no cytokine release syndrome of any grade was reported (0 of 51 patients). Promising anti-tumor activity was observed in both taxane-naïve and heavily pretreated patients. **Methods:** This global, randomized, open-label, phase 3 study (NCT07225946) evaluates the efficacy and safety of PAS in combination with DOCE versus DOCE alone in adult participants ($\geq$18 years) with mCRPC. Approximately 800 participants will be randomized 1:1. Stratification factors include sites of metastases (on conventional imaging), lactate dehydrogenase, Eastern Cooperative Oncology Group performance status, and prior poly(ADP-ribose) polymerase (PARP) inhibitor use. Key inclusion criteria are histologically or cytologically confirmed adenocarcinoma of the prostate, evidence of metastatic disease, and PSA or radiographic disease progression on 1-2 novel ARPI for any stage of prostate cancer. Key exclusion criteria include prior treatment with T-cell redirecting therapies, chemotherapy, or radiopharmaceutical therapy, uncontrolled central nervous system metastases, or significant comorbidities that could interfere with study participation. PAS is administered in the outpatient setting at a target dose of 300 mg IV Q6W with two step-up doses of 3.5 mg IV on day 1 and 18 mg IV on day 8. Participants in the DOCE alone arm will also receive continuous prednisone per label. The primary endpoint is radiographic progression-free survival assessed by blinded independent central review per Prostate Cancer Working Group 3 and RECIST v1.1 criteria. Key secondary endpoints include overall survival, time to symptomatic progression, time to subsequent therapy, and time to skeletal-related event. Safety, pharmacokinetics, biomarkers, and quality of life assessments will also be evaluated. The study is currently enrolling patients in the North and Latin Americas, European Union and Asia Pacific regions. Clinical trial information: 78278343PCR3003. Research Sponsor: None.

TPS5140 **Poster Session**

Phase 1/2 OMAHA-U01 substudy 01A: Oral steroidogenesis inhibitor opevesostat alone or in combination with other therapies in participants with metastatic castration-resistant prostate cancer (mCRPC). First Author: Arif Hussain, University of Maryland Medical Center, Greenebaum Comprehensive Cancer Center, Baltimore, MD

Background: mCRPC remains an incurable disease and therapeutic agents with novel mechanisms of action are needed for this patient population. Opevesostat (MK-5684; ODM-208), an oral steroidogenesis inhibitor, selectively inhibits cytochrome P450 11A1 (CYP11A1), a catalyst of the first and rate-limiting step of steroid biosynthesis. In the phase 1/2 CYPIDES study, opevesostat showed antitumor activity in participants with heavily pretreated mCRPC. OMAHA-U01 is an adaptive, open-label, rolling-arm, multicenter, phase 1/2 umbrella study designed to evaluate opevesostat-based investigational therapies in participants with prostate cancer. Substudy 01A (NCT06353386) will evaluate the safety and efficacy of opevesostat alone or in combination with other therapies in participants with previously treated mCRPC. **Methods:** Eligible participants have mCRPC that progressed during androgen deprivation therapy ≤6 months before screening, and on or after 1-2 androgen receptor pathway inhibitors for metastatic or nonmetastatic hormone-sensitive prostate cancer and nonmetastatic or mCRPC. Prior treatment with ≤1 taxane-based chemotherapy regimen for mCRPC is allowed. A safety lead-in phase for all opevesostat-based experimental combinations (~10 participants in each arm) will establish the recommended phase 2 dose (RP2D), followed by an efficacy phase (opevesostat alone, ≤100 participants; opevesostat-based combinations, ~40 participants each). Participants will be randomly assigned 1:1:1:1 to receive opevesostat 5 mg PO BID, opevesostat 5 mg PO BID plus olaparib (RP2D), opevesostat 5 mg PO BID plus docetaxel (RP2D), or opevesostat 5 mg PO BID plus cabazitaxel (RP2D). Randomization for the efficacy phase will be stratified according to AR-LBD mutation (AR-LBDm) status (positive or negative). The primary end point for the safety lead-in phase is safety and tolerability. Primary end points for the efficacy phase are safety and prostate-specific antigen response rate per Prostate Cancer Clinical Trials Working Group (PCWG) criteria. Secondary end points include objective response rate and radiographic progression-free survival per PCWG-modified RECIST v1.1 by blinded independent central review (BICR), overall survival, duration of response by BICR, time to first subsequent anticancer therapy, and time to pain progression. The predefined eligibility cap for pts with AR-LBDm-negative status has been reached, and the study is currently only enrolling pts with AR-LBDm-positive status. Clinical trial information: NCT06353386. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA; Orion Corporation, who are codeveloping opevesostat.

TPS5141 **Poster Session**

ProTACT: A first-in-human, phase 1 dose escalation and expansion study evaluating the safety, tolerability, and anti-tumor activity of [^{225}Ac]Ac-FL-020, a PSMA-targeted radioconjugate, in patients with mCRPC. First Author: Robert Dreicer, University of Virginia School of Medicine, Charlottesville, VA

Background: Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy is an emerging treatment modality for metastatic castration-resistant prostate cancer (mCRPC). However, many agents targeting PSMA have resulted in quality of life-limiting toxicities, such as xerostomia, due to expression of PSMA in salivary glands and other organs. [^{225}Ac]Ac-FL-020 is a next-generation, PSMA alpha radioconjugate developed using the proprietary UniRDC linker-chelator technology designed to optimize biodistribution. It is intended for the treatment of patients with mCRPC and aims to enhance tumor uptake while sparing radiosensitive organs, such as salivary glands, thus potentially leading to an improved therapeutic window. **Methods:** ProTACT (FL-020-001) is a first-in-human, open-label, multicenter Phase 1 study investigating the safety, tolerability, and preliminary anti-tumor activity of [^{225}Ac]Ac-FL-020 in patients with advanced PSMA-positive mCRPC. This study consists of 2 parts: dose escalation (Part 1) and dose expansion (Part 2). Patients eligible for enrollment must be aged ≥18 years and have: histologically confirmed mCRPC, evidence of disease progression, ≥1 PSMA-positive lesion (uptake higher than liver) on PSMA positron emission tomography/computed tomography imaging, an Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function. Prior treatment with androgen receptor signaling inhibitors or CYP17 inhibitors and ≥1 taxane-based chemotherapy is required, unless declined by the patient. Prior therapy with Lu-177 is allowed. Patients with extensive PSMA-negative disease are excluded. [^{225}Ac]Ac-FL-020 will be administered intravenously at the assigned dose every 6 weeks for up to 6 cycles. Throughout the study, 10 eligible patients will receive 185 ± 20 MBq of [^{111}In]In-FL-020 for dosimetry evaluation ≥8 days prior to their first dose of [^{225}Ac]Ac-FL-020. Part 1 will apply a Bayesian logistic regression model with overdose control to guide dose escalation decisions. Dose cohorts of 1–3 patients (for Cohorts 1 and 2) and 3–6 patients (for Cohorts 3 and beyond) will evaluate ascending dose levels from 1–10 MBq to determine the maximum tolerated dose and/or recommended Phase 2 dose (RP2D). Once the RP2D is established, 18 additional patients will be enrolled in Part 2 to further assess safety and explore early signals of efficacy. Primary endpoints include incidence of dose-limiting toxicities and type, frequency, and severity of adverse events/serious adverse events. Secondary endpoints include overall response rate, disease control rate, radiological progression-free survival, and pharmacokinetic parameters (eg, maximum plasma concentration). The study is active in Australia, the United States, Turkey, and China. Clinical trial information: NCT06492122. Research Sponsor: Full-Life Technologies.

TPS5142 **Poster Session**

TIDAL: A phase II study of the DLL3-directed T-cell engager tarlatamab in DLL3-positive metastatic prostate cancer. First Author: Karen A. Autio, Memorial Sloan Kettering Cancer Center, New York, NY

Background: T-cell engagers directed at canonical prostate adenocarcinoma surface antigens (e.g., STEAP1, KLK2) have demonstrated substantial activity in prostate adenocarcinoma; however, alternative tumor-directed targets are needed for pts whose tumors have undergone lineage plasticity. Delta-like ligand 3 (DLL3) is a surface target variably expressed across the spectrum of neuroendocrine/small cell malignancies. Tarlatamab (Imdelltra, Amgen, Thousand Oaks, CA) is a bispecific T-cell engager targeting DLL3 and CD3, with regulatory approval for small cell lung cancer, and emerging evidence of activity in DLL3-positive prostate cancer. TIDAL is a multi-center, prospective, single arm phase II trial (NCT07111507) evaluating the safety and efficacy of tarlatamab in DLL3-positive advanced prostate cancer. **Methods:** Key eligibility criteria include metastatic prostate cancer with progression on ≥1 prior systemic therapy in the metastatic setting and DLL3-positive disease (IHC ≥50%), irrespective of histologic subtype. Pts without measurable disease by RECIST 1.1 criteria can be enrolled; however, at least 50% of pts enrolled must have measurable disease. Pts will receive tarlatamab in 28-day cycles with a 1 mg priming dose on cycle 1 day 1 (C1D1), followed by a target dose of 10 mg on C1D8, C1D15, and days 1 and 15 of subsequent cycles. All pts are hospitalized for ≥24 hours of monitoring following C1D1 and C1D8 infusions. Mandatory tumor biopsy and circulating tumor DNA (ctDNA) collection are performed at screening and cycle 2, with required ctDNA and optional biopsy at end of treatment (EOT). CT and bone scan are performed every 8 weeks for the first 24 weeks, then every 12 weeks. The primary endpoint is radiographic progression-free survival at 24-weeks. Secondary endpoints include overall response rate (ORR), median duration of response, median rPFS, median composite PFS, median overall survival, and safety. Correlative studies will evaluate associations between tumor DLL3 expression, circulating immune profiles, and clinical outcomes. A subset of pts will be co-enrolled in an imaging biomarker study (NCT04199741) utilizing a novel DLL3 PET tracer (^{89}Zr-DFO-SC16.56). As of January 14, 2026, 4 of the planned 32 pts have been enrolled. Clinical trial information: NCT07111507. Research Sponsor: Amgen.

TPS5143 **Poster Session**

A randomized phase III trial investigating platinum and taxane chemotherapy in metastatic castration-resistant prostate cancer (mCRPC) patients with alterations in DNA damage response (DDR) genes (OPTION-DDR) CCTG-PR-25 NCT06439225. First Author: Michael Ong, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: Outcomes for patients (pts) with mCRPC after androgen receptor pathway inhibitors (ARPI) remain poor. There are numerous treatment options, including single agent docetaxel, however overall survival (OS) after ARPI is between 12-19 months. Thus, management of mCRPC post-ARPI represents an area of unmet need. 25% of pts have alterations in DDR genes, which may be a biomarker for sensitivity to treatment with platinum agents. Carboplatin has been previously evaluated in smaller trials in pts with mCRPC and shows promise in patients with DDR gene alterations. PR-25 leverages standard of care testing for DDR genes to evaluate in a rigorous manner whether addition of carboplatin to docetaxel improves overall survival (OS) in pts with DDR gene alterations and mCRPC. **Methods:** PR-25 is a phase III randomized controlled trial led by the Canadian Cancer Trials Group comparing docetaxel to docetaxel and carboplatin in pts with DDR alterations. Pts must receive prior ARPI for mCRPC and demonstrate radiographic or PSA progression prior to enrollment. Qualifying DDR gene alterations include: BRCA1, BRCA2, ATM, ATR, BRIP1, BARD1, CDK12, CHEK1, CHEK2, ERCC2, FANCA, FANCC, FANCD2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L. The primary endpoint is OS. Secondary endpoints include radiographic progression free survival (PCWG3 and RECIST 1.1), PSA response, time to next systemic therapy, patient reported quality of life and economic evaluation. Statistical design: The target accrual is 236 patients over 3.25 yrs with 2 year follow-up to detect a HR of 0.65 in OS, using a type 1 error rate of 5% (2 sided) and power of 80%. *Conduct to Date:* Study activation – October 2024. First patient enrolled - December 2024. Accrual to date: 10. Clinical trial information: NCT06439225. Research Sponsor: CIHR Grant; NCTN Grant; Canadian Cancer Society Grant.

TPS5144 **Poster Session**

XALience: A phase 3, open-label, multicenter, randomized study of xaluritamig plus abiraterone vs investigator's choice in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer. First Author: Tanya B. Dorff, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: In the first-in-human (FIH) study, xaluritamig, a T-cell engager directed at six-transmembrane epithelial antigen of the prostate 1 (STEAP1), demonstrated potent antitumor activity with a manageable safety profile in patients with metastatic castration-resistant prostate cancer (mCRPC).[1,2] Preliminary data from this FIH study of xaluritamig in combination with abiraterone in chemotherapy-naïve patients with mCRPC[3] supports the initiation of a phase 3 study of xaluritamig plus abiraterone with the aim of improving survival in this population. **Methods:** XALience is a randomized, multicenter, open-label, phase 3 study (NCT07213674) of xaluritamig plus abiraterone vs investigator's choice in patients with chemotherapy-naïve mCRPC. Approximately 750 eligible patients ≥18 years old with histologically confirmed chemotherapy-naïve mCRPC; evidence of disease progression on prior enzalutamide, apalutamide, or darolutamide; ECOG PS of 0-1; and adequate organ function and who may have previously received ≤6 cycles of docetaxel in the metastatic hormone-sensitive prostate cancer (mHSPC) setting will be randomized 1:1 to receive xaluritamig plus abiraterone or investigator's choice of docetaxel, cabazitaxel, or abiraterone. Patients will be stratified by prior docetaxel exposure in mHSPC, presence of liver metastases, prior treatment with prostate-specific membrane antigen radioligand therapy, and planned intention-to-treat with investigator's choice. This study consists of a 28-day screening period, treatment until radiographic progression based on Prostate Cancer Working Group 3 (PCWG3) guidelines, a safety follow-up period, and a long-term follow-up period. To mitigate the risk of cytokine release syndrome, xaluritamig will be initiated at weekly step-up dosing over four doses up to the target dose during cycle 1 followed by target dose administration every 2 weeks from cycle 2 day 1 onwards. The primary endpoint is overall survival, which will be analyzed using a stratified log-rank test at a one-sided 2.5% significance level. Key secondary endpoint is investigator-assessed radiographic progression-free survival per PCWG3. Other secondary endpoints include radiographic and prostate-specific antigen response, safety, tolerability, health-related quality of life, patient-reported outcomes, pharmacokinetics, and immunogenicity. Enrollment is ongoing and 20 patients have been enrolled as of January 19, 2026. References: Kelly WK, Danila DC, Lin CC, et al. *Cancer Discov*. 2024;14:76-89. Kelly WK, Appleman L, Lin C-C, et al. *Ann Oncol*. 2024;35: S963-S964. Data on file, Amgen; 2025. Clinical trial information: NCT07213674. Research Sponsor: Amgen Inc.

TPS5145 **Poster Session**

TALENT: A randomized phase 2 study of talazoparib with or without enzalutamide in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) alterations after progression on abiraterone acetate. First Author: Karen A. Autio, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The phase 3 TALAPRO-2 study (NCT03395197) demonstrated superior efficacy with enzalutamide plus talazoparib vs. enzalutamide plus placebo for pts with mCRPC with tumors harboring HRR mutations. Only 8% of HRRm pts enrolled in TALAPRO-2 had prior exposure to abiraterone acetate with prednisone, and none had received an androgen receptor inhibitor. Given the evolving treatment landscape of metastatic hormone sensitive prostate cancer (mHSPC), many patients now receive ADT in combination with abiraterone acetate and prednisone until progression. It is unknown whether the synergistic effects of inhibiting PARP alongside potent AR inhibition will be maintained in those patients with tumors that have demonstrated resistance to an androgen biosynthesis inhibitor such as abiraterone. The TALENT study (NCT06844383) will address this unanswered question by randomizing pts with HRR-mutated mCRPC following progression on abiraterone acetate with prednisone to receive talazoparib in combination with enzalutamide versus talazoparib alone. We hypothesize that synergy between PARP and AR inhibition will be demonstrated in this contemporary patient population. **Methods:** TALENT will enroll approximately 126 pts with mCRPC with prior disease progression while receiving abiraterone acetate for HSPC or locally advanced disease and a confirmed mutation in one of twelve HRR genes. ATM mutations will be limited to 15%. Prior exposure to docetaxel in the mHSPC setting will be included as a stratification factor. Pts will be randomized in a 1:1 fashion to either talazoparib and enzalutamide or talazoparib alone administered along with ADT. Pts will continue treatment until disease progression, unacceptable toxicity, treatment delay > 60 days of talazoparib, protocol violation, withdrawal of consent, physician decision, study termination by the Sponsor, loss to follow-up, or death. Patients will be monitored using RECIST 1.1 and PCWG3 criteria for bone disease. The primary endpoint is investigator-assessed radiographic progression free survival (rPFS). Secondary endpoints include time to PSA50 response, time to PSA progression, overall survival, and patient reported outcomes capturing quality of life. Exploratory analyses will evaluate rPFS by HRR gene (BRCA vs non-BRCA, individual genes, and gene clusters). Pt recruitment is planned at approximately 15 sites in the US. As of January 27, 2026, 0 pts have been enrolled. Clinical trial information: NCT06844383. Research Sponsor: Pfizer Inc.

TPS5146 **Poster Session**

Phase I/II study to evaluate AZD9750, a novel androgen receptor proteolysis-targeting chimera, alone and in combination with other anticancer agents in patients with metastatic prostate cancer (ANDROMEDA). First Author: Neeraj Agarwal, Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT

Background: The androgen receptor (AR) is a key driver of prostate cancer progression. AR pathway inhibitors (ARPIs) are standard of care for metastatic prostate cancer, but acquired resistance is inevitable and often involves reactivation of AR signaling via AR gene alterations such as amplifications or ligand binding domain mutations. The need remains for alternative strategies to target the AR. AZD9750 is a novel oral proteolysis-targeting chimera that potently degrades wild-type, mutant, and amplified forms of the AR. Preclinical data also showed significant antitumor benefit with AZD9750 as monotherapy and combined with the PARP1 selective inhibitor saruparib (AZD5305). ANDROMEDA (NCT07336446) is a first-in-human, phase I/II, open-label, multicenter study investigating the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of AZD9750 as monotherapy and combined with saruparib in patients (pts) with metastatic castration-resistant prostate cancer. **Methods:** This study follows a modular design in which pts receive AZD9750 as monotherapy (Module 1) or combined with saruparib (Module 2; Table). Each module has 2 parts: monotherapy dose escalation or combination dose finding (Part A) and dose optimization and expansion (Part B). Eligible pts are ≥18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate and documented metastatic disease with serum testosterone level ≤50 ng/dL, evidence of disease progression, and ECOG performance status of 0 or 1. Pts should have previously received ARPIs and taxane-based chemotherapy, with the exception of no prior taxane-based chemotherapy in Module 1 Part B3. Primary endpoints include occurrence of dose-limiting toxicities (Part A only), incidence of adverse events (AEs) and AEs leading to treatment discontinuation (Parts A and B), and preliminary efficacy (ie, ≥50% decrease in prostate-specific antigen [PSA]; Part B only). Secondary endpoints include preliminary efficacy (ie, ≥50% and ≥90% decrease in PSA, objective response rates and progression-free survival per RECIST v1.1 and PCWG3 criteria, change in target lesion size per RECIST v1.1 criteria, time to PSA response, and time to PSA progression per PCWG3 criteria) and pharmacokinetic parameters (Parts A and B). This study is currently recruiting for monotherapy dose escalation. Clinical trial information: NCT07336446. Research Sponsor: AstraZeneca.

Study part	Module 1: AZD9750 monotherapy	Module 2: AZD9750 plus saruparib
Part A	A1. Dose escalation A2. Backfill cohorts	Combination dose finding[a]
Part B	B1. Dose optimization[a] B2. Dose expansion[b] B3. Dose expansion[b]	Combination dose expansion[c]

[a]Recommended doses determined in Module 1 Part A; [b]To be opened once recommended phase II dose identified in Module 1 Part B1; [c]To be opened once combination dose identified in Module 2 Part A.

TPS5147 **Poster Session**

REINFORCE: A phase III randomized trial of treatment intensification with docetaxel in metastatic hormone-sensitive prostate cancer patients without deep PSA response after initial apalutamide therapy. First Author: Enrique Gonzalez-Billalabeitia, 12 de Octubre University Hospital, Medical Oncology Department, Madrid, Spain

Background: Androgen deprivation therapy (ADT) plus androgen receptor pathway inhibitors (ARPIs) is the standard of care for metastatic hormone-sensitive prostate cancer (mHSPC). However, a substantial proportion of patients fail to achieve a deep prostate-specific antigen (PSA) response, which is consistently associated with worse outcomes. Deep PSA response has emerged as a robust early prognostic marker across multiple phase III trials. Patients lacking this favorable PSA decline represent a poor-risk subgroup with limited treatment personalization. Docetaxel improves survival in high-volume mHSPC and may benefit biologically aggressive disease identified by suboptimal early PSA response. REINFORCE evaluates a PSA-guided strategy of treatment intensification with docetaxel in patients without deep PSA response after apalutamide. **Methods:** REINFORCE is an international, multicenter, open-label, phase III randomized trial. Eligible patients are men ≥18 years with histologically confirmed mHSPC, ECOG performance status ≤1, PSA > 5 ng/ml at diagnosis of metastatic disease, ≤12 weeks of ADT before apalutamide, adequate organ function, who have received apalutamide plus ADT for 24–30 weeks, have not progressed, and have failed to achieve a deep PSA response. Deep PSA response is defined as PSA ≤ 0.2 ng/ml or PSA response ≥ 90% in combination with a PSA ≤4 ng/ml. Approximately 320 patients from 85 sites located in 6 countries will be randomized 1:1 to treatment intensification with docetaxel (75 mg/m² every 3 weeks for 6 cycles) plus continued apalutamide and ADT, or continuation of apalutamide plus ADT alone. Randomization is stratified by metastasis timing (synchronous vs metachronous), presence of visceral metastases, and PSA at study entry (≤4 vs > 4 ng/mL). The primary endpoint is event-free survival (EFS), defined as time from randomization to PSA progression, radiographic progression of soft tissue, visceral or bone lesions, according to PCWG3, or death from any cause. Secondary endpoints include time to castration resistance, radiographic and PSA progression-free survival, overall survival, safety, PSA response rates, and patient-reported outcomes. Preliminary evidence suggests that apalutamide is associated with a ≲ 10% decrease in docetaxel AUC; a dedicated pharmacokinetic sub-study will assess docetaxel drug-drug interaction and bioequivalence when co-administered with apalutamide. An independent data monitoring committee will oversee patient safety, including an early safety review after the first 18 patients included, review a pre-planned interim efficacy analysis, and evaluate pharmacokinetic data, providing recommendations to the sponsor regarding study continuation. Clinical trial information: 2025-524408-30-00. Research Sponsor: Johnson & Johnson Innovative Medicine.

TPS5148 **Poster Session**

An open-label, parallel-cohort, multicenter clinical study of rezvilutamide in combination with androgen deprivation therapy (ADT) with or without docetaxel in the neoadjuvant treatment of oligometastatic prostate cancer. First Author: Qi Lin, Department of Urology, The First Affiliated hospital of Wenzhou Medical University, Wenzhou, China

Background: Oligometastatic hormone-sensitive prostate cancer (omHSPC), defined by ≤5 metastases, represents a distinct disease state with a more favorable prognosis, offering a critical window for treatment intensification aimed at improving long-term outcomes. Cytoreductive radical prostatectomy (cRP) has emerged as a feasible local treatment option for select patients, with phase II data suggesting a survival benefit over systemic therapy alone. The foundation of systemic therapy for metastatic HSPC (mHSPC) is an androgen receptor pathway inhibitor (ARPI) combined with androgen deprivation therapy (ADT). Rezvilutamide, a second-generation ARPI, demonstrated superior efficacy over bicalutamide when combined with ADT in patients with mHSPC. Furthermore, the addition of docetaxel to an ARPI and ADT (triplet therapy) significantly improved survival in mHSPC, including in patients with low metastatic burden. We hypothesize that intensifying neoadjuvant systemic therapy with triplet therapy prior to cRP may maximize tumor cytoreduction and pathologic response in omHSPC. **Methods:** This is a prospective, open-label, parallel-cohort, multicenter phase II study. Patients with newly diagnosed, biopsy-proven omHSPC (≤5 bone or lymph node metastases on conventional imaging, no visceral metastases) who are candidates for and desire cRP are eligible. All patients undergo baseline prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA-PET/CT) prior to ADT initiation. Patients select their neoadjuvant regimen: Cohort A receives ADT plus oral rezvilutamide (240 mg daily) for 24 weeks; Cohort B receives ADT, rezvilutamide (same dose), plus docetaxel (75 mg/m² IV q3w for 6 cycles) for 24 weeks. Upon completion of the 24-week neoadjuvant therapy, metastases are reconfirmed by conventional imaging, and a second PSMA-PET/CT assessment is performed. All patients subsequently undergo cRP with extended pelvic lymph node dissection within 6 weeks. After surgery, patients may opt to continue with ADT or rezvilutamide at their discretion until disease progression. Based on assumed pCR rates of <10% (Cohort A) and 25% (Cohort B) (α=0.05, power=80%), 40 evaluable patients are required per cohort. Accounting for 20% dropout, 100 total patients (50 per cohort) will be enrolled. Key inclusion criteria: ECOG PS 0-1, adequate organ function. Key exclusion criteria: prior systemic therapy for PCa (except ≤4 weeks of ADT), prior second-generation ARPI use, and prostate pathology results indicating neuroendocrine carcinoma. As of January 15, 2026, enrollment is ongoing with 6 patients accrued to date. No data analysis has been performed. Clinical trial information: ChiCTR2400093262. Research Sponsor: the Development Center for Medical Science & Technology National Health Commission Clinical Research Project.

TPS5149 **Poster Session**

TRIPLE-SWITCH (SWOG/CCTG-PR26): A randomized phase III clinical trial for the addition of docetaxel to androgen receptor pathway inhibitors in patients with metastatic castration sensitive prostate cancer (mCSPC) and suboptimal PSA response (NCT06592924). First Author: Michael Ong, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada

Background: Management of patients (pts) with mCSPC remains a challenge due to its incurable nature and heterogeneous response to androgen deprivation therapy (ADT) and androgen receptor pathway inhibitors (ARPI). Analyses of phase III ADT + ARPI trials have indicated that pts with mCSPC with suboptimal PSA response (≥0.2ng/ml at 6-12 months) have a short time to castration-resistance (CRPC) and poor median overall survival (OS) of 30-36 months. There is equipoise about the use of docetaxel in mCSPC pts on ARPI because of: 1) an absence of randomized data for docetaxel in this setting; 2) toxicity of docetaxel with impact on quality of life; and 3) selection of docetaxel treatment by disease volume rather than disease biology. **Methods:** PR26 is a joint CCTG-SWOG international, open-label, randomized phase III trial comparing continuing standard ADT + ARPI with the addition of up to 6 cycles of docetaxel to ADT + ARPI in mCSPC pts with suboptimal PSA response(PSA ≥0.2 ng/mL after 6-12 months of ADT and ≥4 months of ARPI). Stratification will be based on PSA levels, ARPI type, presence of liver metastasis, disease recurrence status, and time since ADT initiation. The sample size is 830 pts to detect a targeted 33% improvement in overall survival (hazard ratio 0.75) using a 1-sided 0.025 level test with 85% power. Key eligibility criteria are: ≥18 years, histologically confirmed prostate adenocarcinoma, metastatic disease present and confirmed by conventional imaging (CT and/or bone scan), PSA ≥5.0 ng/mL prior to ADT, receipt of ADT for 6-12 months and ARPI for ≥4 months, PSA ≥0.2 ng/mL within 14 days of enrolment, adequate organ and marrow function, ECOG performance status 0-2, eligible for docetaxel chemotherapy, no evidence of disease or biochemical progression on ADT prior to enrolment. Primary endpoint is OS. Secondary endpoints include PSA response, PSA kinetics, and clinical progression free-survival. Correlative studies will explore the prognostic and predictive value of circulating tumor DNA and the association between molecular signatures and clinical outcomes. Conduct to date: Study activation, January 2025. First patient enrolled, May 2025. Accrual to date: 6. Supported by CIHR grant 39527, NCTN grant #CA180863 and CCS grant #707213. Research Sponsor: None.

TPS5150 **Poster Session**

EORTC GUCG 2238: "Deescalate," a pragmatic trial to revisit intermittent androgen deprivation therapy in metastatic hormone-sensitive prostate cancer in the era of new androgen receptor pathway inhibitors. First Author: Fabio Turco, Oncology Institute of Southern Switzerland (IOSI), Ente Ospedaliero Cantonale (EOC), Bellinzona, Switzerland

Background: The systemic standard of care treatment in patients with metastatic hormone-sensitive prostate cancer (mHSPC) according to international guidelines is combination therapies with androgen deprivation therapy (ADT) + androgen receptor pathway inhibitor (ARPI) +/- docetaxel. These ADT + ARPI combinations (also called maximum androgen blockade, MAB) have been shown in phase 3 randomized clinical trials to reduce the risk of death by 20-40%, delay further treatment, and improve health-related quality of life (HRQoL). Treatment usually continues until biochemical, radiological, or clinical progression, sometimes many years after treatment initiation, exposing patients to chronic side effects affecting their HRQoL. Registration trials included highly selected patients, not representative of the general population, thereby overestimating treatment adherence and effectiveness while underreporting tolerability. Several sub-analyses of the registration trials demonstrated that patients achieving a PSA ≤0.2 ng/ml have prolonged overall survival (OS). In this study, we hypothesized that patients with mHSPC treated with MAB reaching PSA ≤ 0.2 ng/ml may benefit from treatment interruption without compromising OS. **Methods:** The primary goal of this academic-led, open-label, pragmatic, randomized phase III study is to investigate whether intermittent MAB (iMAB) can be safely administered to mHSPC patients who reached a PSA ≤ 0.2 ng/mL at 6 to 12 months after the start of treatment (docetaxel and radiotherapy permitted as part of standard treatment), as compared to continuing MAB (cMAB). Co-primary endpoints are: 1) Feasibility: proportion of patients who do not restart their MAB within one year of interruption. 2) Efficacy: OS assuming the iMAB regimen at three years is non-inferior to continuous treatment. Secondary objectives include toxicity, HRQoL and assessing the impact on treatment resources between iMAB and cMAB. The study will randomize 1600 patients to exclude a 4% OS difference at 3 years while <30% of patients restarted MAB after one year. The study is currently active in Belgium, Croatia, Denmark, Ireland, France and Spain. The activation of the other countries (Portugal, Italy, Romania, Slovenia, Switzerland and Czech Republic) is expected by spring 2026. The study has currently recruited 109 patients (Updated January 26, 2026). Clinical trial information: NCT05974774. Research Sponsor: European Union's HORIZON-MISS-2022-CANCER-01-03; 101104574.

TPS5151 **Poster Session**

AMPLIFY: A phase 3 study of ^{64}Cu-SAR-bisPSMA positron emission tomography in participants with biochemical recurrence of prostate cancer. First Author: Luke Nordquist, XCancer Corporation, Omaha, NE

Background: Prostate cancer (PC) is the second most prevalent cancer in men globally. The need for improved PC imaging is reflected in a biochemical recurrence (BCR) rate of 20 to 40% after initial definitive therapy. Despite advances in technology, many patients will fail to have their recurrence accurately localized by imaging, especially at low PSA levels. Imaging modalities that are widely available and can accurately detect, monitor, and restage residual / recurrent loco-regional and metastatic disease are therefore highly desirable. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein that is strongly overexpressed in PC, making it an ideal target for imaging and therapy. ^{64}Cu-SAR-bisPSMA may offer several advantages over the currently approved PSMA positron emission tomography (PET) agents for PC due to the bivalent structure of SAR-bisPSMA and longer half-life of ^{64}Cu ($t_{1/2}$ = 12.7h), compared to the approved monovalent PSMA agents utilizing ^{18}F and ^{68}Ga ($t_{1/2}$ < 2h). Evidence has demonstrated prolonged tumor retention and 2-3x higher tumor uptake with detection of additional PC lesions using ^{64}Cu-SAR-bisPSMA compared to approved PSMA PET agents. **Methods:** AMPLIFY (NCT06970847) is a multi-center, single arm, open-label Phase 3 diagnostic performance study of ^{64}Cu-SAR-bisPSMA PET/CT in participants with a history of prostate adenocarcinoma and rising or detectable PSA after initial definitive treatment. The primary objective is to investigate the ability of ^{64}Cu-SAR-bisPSMA PET/CT to detect recurrence of PC, with co-primary endpoints of participant-level correct detection rate (CDR) and region-level positive predictive value (PPV) assessed independently for Day 1 and Day 2. Key secondary objectives include assessment of safety, participant-level PPV, and participant-level detection rate (DR). A total of 220 patients will be enrolled. All participants are required to have baseline conventional imaging. Eligible patients will receive a single administration of ^{64}Cu-SAR-bisPSMA (200 MBq) followed by a PET/CT scan on Day 1 (1-4h post-dose) and on Day 2 (24±6h post-dose). Participants will then continue into the follow-up period to verify the ^{64}Cu-SAR-bisPSMA PET/CT findings. The Day 1 and Day 2 scans will be interpreted individually by a qualified local reader and 3 independent, blinded, central readers for the presence of abnormal ^{64}Cu-SAR-bisPSMA uptake. ^{64}Cu-SAR-bisPSMA PET/CT results on Day 1 and Day 2 will then be assessed against a composite Reference Standard by a central expert panel. The study is open for recruitment in the United States and Australia. Clinical trial information: NCT06970847. Research Sponsor: Clarity Pharmaceuticals.

TPS5152 **Poster Session**

A phase 2 study of androgen deprivation therapy and the androgen receptor ligand–directed degrader (BMS-986365) prior to radical prostatectomy in patients with high-risk localized prostate cancer. First Author: Kristine Peregrino Lacuna, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Although radical prostatectomy (RP) is a curative approach for patients (pts) with high-risk localized prostate cancer (PC), recurrence rates remain high. Neoadjuvant studies of androgen deprivation therapy (ADT) plus an androgen receptor pathway inhibitor (ARPI) suggest improvement in local disease control at the time of RP and may be associated with better long-term outcomes (McKay et al. PC Prostatic Dis. 2018; McKay et al. ASCO 2023: #5095). An ongoing phase 3 study is evaluating ADT plus apalutamide for 6 months prior to RP in pts with high-risk or locally advanced PC; co-primary endpoints are pathologic complete response (pCR) and metastasis-free survival (NCT03767244). BMS-986365 is an orally administered ligand-directed degrader targeting the androgen receptor (AR) via a first-in-class dual mechanism of 1) AR degradation and 2) AR antagonism. A phase 1 study showed that BMS-986365 was well tolerated with a manageable safety profile, with antitumor activity in pts with metastatic castration-resistant PC (mCRPC) regardless of AR gene alterations (Rathkopf et al. Ann Oncol. 2025), leading to an ongoing phase 3 study in mCRPC (rechARge: NCT06764485). Due to its dual mechanism and promising data in mCRPC, we hypothesize that neoadjuvant treatment with ADT plus BMS-986365 prior to RP will result in robust pathologic response rates. **Methods:** This is a single center, phase 2, single-arm trial testing the combination of ADT plus BMS-986365 for 6 months prior to RP in pts with high-risk localized PC. Eligible pts include those who are candidates for RP and meet $\geq$ 1 high-risk criteria: PSA $\geq$ 20 ng/mL, Gleason $\geq$ 8, or clinical stage $\geq$ cT3a (N1M0 disease allowed). Pts will receive degarelix SC once monthly (first dose 240mg, maintenance dose 80mg) and BMS-986365 at a dose of 300mg PO twice daily (liquid-filled capsule formulation) for 6 months; RP will occur 2 weeks after the last dose of BMS-986365. The dose of BMS-986365 was selected based on the phase 1 data and equivalent doses utilized in the ongoing phase 3 rechARge study. The primary endpoint is the rate of pCR and/or minimal residual disease (MRD, defined as tumor $\leq$ 5mm) at the time of RP. A two-stage design will evaluate if pCR and/or MRD rate exceeds 0.20, which is the rate observed in historical studies of ADT and ARPI prior to RP (McKay et al. J Urol. 2021) 10 pts will be enrolled in Stage 1; if $\geq$ 3/10 pts achieve a pCR and/or MRD, an additional 20 pts will be enrolled in Stage 2. If $\geq$ 10/30 pts achieve a pCR and/or MRD, the treatment will be declared sufficiently active (alpha = 0.05, power 0.80). Secondary endpoints include safety and time to biochemical recurrence. As part of exploratory analyses, cfDNA, pre-/post-treatment (prostatectomy) tissue, and pre-/post-treatment multiparametric MRI will be collected. The study opened to accrual in January 2026. Clinical trial information: NCT07335796. Research Sponsor: Bristol Myers Squibb (BMS); Institutional Funding supported through Philanthropy.

5501 **Oral Abstract Session**

Long-term survival rates and cure modeling with dostarlimab plus chemotherapy in mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) primary advanced or recurrent endometrial cancer in the ENGOT-EN6-NSGO/GOG-3031/RUBY trial. First Author: Matthew A. Powell, Washington University School of Medicine, Siteman Cancer Center, St. Louis, MO

Background: Dostarlimab + carboplatin-paclitaxel (CP) demonstrated significant progression-free survival (PFS) and clinically meaningful overall survival benefits in patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer (EC) in Part 1 of the phase 3 RUBY trial (NCT03981796). Median PFS was not reached for dostarlimab + CP vs 7.7 months for CP alone in this population. Moreover, plateauing of the PFS Kaplan-Meier (KM) curve suggested that a subset of patients with dMMR/MSI-H EC achieved durable disease control and potential for curative intent with dostarlimab + CP. Mixture cure models (MCMs) complement conventional outcome metrics by quantifying the proportion of patients considered "cured" and by modeling PFS among patients who remain uncured. Here we present an MCM applied to the PFS data from the dMMR/MSI-H population with up to 4.5 years of follow-up treated with dostarlimab + CP. **Methods:** At a median follow-up of 55.6 months (range 49.9–67.7 months), descriptive PFS analyses were conducted in the dMMR/MSI-H population from RUBY Part 1. MCMs were fitted to PFS data to estimate the proportion of patients treated with dostarlimab + CP who had a curative potential. In the MCM, patients with curative potential were assumed to be free of recurrence- and disease-related mortality risks, implying that any additional PFS events would come from death. Mortality risks were assumed to be similar to the background mortality expected in the general population (with matched demographic characteristics). Conversely, the uncured population was considered to be at risk for disease recurrence and death from all causes. **Results:** There was a low rate of progression since PFS was first analyzed, with only 4 new events reported with an additional 2.5 years of follow-up. The 4-year PFS rate was 57.9% (95% CI, 42.3%–70.6%) in the dostarlimab + CP arm vs 15.7% (95% CI, 7.2%–27.0%) in the control arm. The MCM analysis demonstrated that the majority of patients with dMMR/MSI-H EC (54%; 95% CI, 35%–72%) were considered “cured” with dostarlimab + CP. The PFS survival curves estimated from MCMs closely followed the KM curves reported from the RUBY trial data. The model appropriately captured the long-term survival plateau, instilling confidence in the robustness of the model predictions. **Conclusions:** With a minimum of 4 years of follow-up, updated PFS analyses demonstrated that the majority of patients remained alive and progression-free, illustrating durable disease control. Model-based predictions indicated the potential for cure in the dMMR/MSI-H primary advanced or recurrent EC population receiving dostarlimab + CP. These analyses may assist oncologists in understanding long-term survival outcomes and the proportion of patients with a curative potential. Clinical trial information: NCT03981796. Research Sponsor: GSK; N/A.

5502 **Oral Abstract Session**

Updated overall survival analysis and examination of subsequent therapy in endometrial cancer (EC) patients (pts) treated with pembrolizumab plus carboplatin/paclitaxel (CP) as compared to CP plus placebo (PBO) in the NRG-GY018 trial. First Author: Ramez Nassef Eskander, UC San Diego Moores Cancer Center, La Jolla, CA

Background: NRG-GY018, the only phase 3 trial examining dMMR and pMMR EC populations independently, identified a 70% and 46% reduction in the risk of disease progression or death in advanced stage or recurrent dMMR and pMMR EC patients treated with pembrolizumab plus CP. Here we report on updated overall survival and post-study immune checkpoint inhibition (ICI) therapy. **Methods:** 810 pts were randomized 1:1 to pembrolizumab + CP or PBO + CP Q3W for 6 cycles followed by maintenance pembrolizumab or PBO Q6W for up to 24 months. Updated OS analysis data cut off was December 23, 2025, with information fraction of 42% and 78% in the dMMR and pMMR EC cohorts, respectively. Median follow up in the dMMR cohort was 44.6 months (95% CI 42.5 to 46.8) and 40.1 months (95% CI 38.9 to 42.2) in the pMMR cohorts. Study sites were queried to abstract data regarding start and end date of post study ICI use. **Results:** The addition of pembrolizumab resulted in a sustained OS benefit in the dMMR EC cohort. At 48-month landmark assessment, 80% of the pembrolizumab treated dMMR EC patients were alive, versus 60% of those treated with placebo, HR 0.53 (95% CI 0.32 to 0.89). This survival advantage was maintained despite at least 55% (n=62) of dMMR EC patients in the placebo arm receiving post study ICI. In the pMMR EC population, with an information fraction of 78%, the median OS in the pMMR cohort treated with pembrolizumab was 46.9 months versus 35.1 months for those receiving placebo, HR 0.84 (95% CI 0.66 to 1.06). This benefit was maintained despite at least 57% (n=167) pMMR EC patients in the placebo arm receiving post study ICI (most commonly lenvatinib plus pembrolizumab). In the pMMR EC cohort, 70 patients in the pembrolizumab arm and 167 patients in the placebo arm received post study ICI, with the median duration of treatment of 6.2 months in both populations. **Conclusions:** In the NRG GY018 study, with prolonged follow up, the addition of pembrolizumab to CP resulted in a sustained OS benefit despite substantial post study ICI use. In the pMMR population, an 11.8 month OS advantage was observed, despite at least 57% of the placebo patients receiving post study ICI. This data further supports the current US FDA approved indication of this regimen in the treatment of advanced stage or recurrent endometrial cancer irrespective of MMR status. Clinical trial information: NCT03914612. Research Sponsor: National Cancer Institute; U10CA180822; U.S. National Institutes of Health.

5503 **Oral Abstract Session**

Overall survival subgroup analyses for prior taxane use in the phase 3 ROSELLA trial of relacorilant plus nab-paclitaxel versus nab-paclitaxel monotherapy in patients with platinum-resistant ovarian cancer (GOG-3073, ENGOT-ov72, APGOT-Ov10, LACOG-0223, and ANZGOG-2221/2023). First Author: Lucy Gilbert, Division of Gynecologic Oncology, Research Institute, McGill University Health Centre, Gerald Bronfman Department of Oncology, McGill University, Montreal, QC, Canada

Background: Relacorilant is a first-in-class, selective glucocorticoid receptor antagonist that increases tumor sensitivity to chemotherapy-induced apoptosis. The phase 3 ROSELLA trial of relacorilant plus nab-paclitaxel in patients with platinum-resistant ovarian cancer (PROC) recently reported statistically significant results for the dual primary endpoints of progression-free survival (PFS) and overall survival (OS). The relacorilant combination was well tolerated and the safety profile was similar to nab-paclitaxel monotherapy. Here we present final OS subgroup analyses for prior taxane use. **Methods:** Patients (n = 381) were randomized 1:1 to relacorilant (150 mg PO the day before, of, and after nab-paclitaxel) plus nab-paclitaxel (80 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle) or nab-paclitaxel alone (100 mg/m^2 IV on the same schedule). The final OS analysis was performed after 288 deaths had been reported (76% maturity). The hazard ratio (HR) was estimated with a Cox regression model with treatment group as the main effect and stratification factors at randomization as covariates. Kaplan-Meier methods were used to estimate medians and generate survival curves. **Results:** At a median follow-up of 24.8 months, the addition of relacorilant to nab-paclitaxel resulted in a statistically and clinically significant improvement in OS (HR 0.65; 95% confidence interval [CI], 0.51 to 0.83; P = 0.0004). Median OS in the relacorilant combination arm was extended by 4.1 months compared with the nab-paclitaxel monotherapy arm (16.0 vs 11.9 months). Prior taxane use was almost universal (n = 379/381, 99.5%). A consistent OS benefit was observed irrespective of the taxane-free interval: taxane-free interval $\leq$6 months (n = 55, HR 0.60 [95% CI, 0.31 to 1.15], median difference 5.7 months) and taxane-free interval $>$ 6 months (n = 324, HR 0.66 [95% CI, 0.51 to 0.86], median difference 3.6 months). Moreover, a consistent OS benefit was observed irrespective of whether a taxane was used in the most recent regimen: taxane in the last regimen (n = 73, HR 0.67 [95% CI, 0.38 to 1.19], median difference 3.9 months) and no taxane in the last regimen (n = 308, HR 0.63 [95% CI, 0.48 to 0.82], median difference 4.2 months). Additional safety data will be presented. **Conclusions:** ROSELLA met both dual primary endpoints. Relacorilant plus nab-paclitaxel demonstrated a statistically and clinically significant OS benefit in patients with PROC compared to a weekly taxane, the most efficacious chemotherapy. Subgroup analyses for OS showed a consistent benefit favoring the addition of relacorilant to nab-paclitaxel irrespective of prior taxane use. Clinical trial information: NCT05257408. Research Sponsor: Corcept Therapeutics.

LBA5504 **Oral Abstract Session**

A phase III CHIPRO study of chiauranib plus weekly paclitaxel for platinum-resistant or refractory ovarian cancer. First Author: Xiaohua Wu, Fudan University Shanghai Cancer Center, Shanghai, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

5505 **Oral Abstract Session**

CHRONO: A randomized phase II trial of the chronology of surgery after neoadjuvant chemotherapy for ovarian cancer. First Author: Gwenael Ferron, Institut Claudius Regaud, IUCT-Oncopole and GINECO, Toulouse, France

Background: In patients treated for advanced ovarian cancer not suitable for complete primary surgery, interval surgery after three courses of neoadjuvant chemotherapy (NAC) has been considered standard management since the EORTC randomized trial published in 2010 (NCT00003636, DOI: 10.1056/NEJMoa090880). Delaying surgery after six courses of NAC in highly chemosensitive patients amenable to complete surgery after 3 cycles remains controversial. CHRONO is a multicenter, randomized phase II trial addressing this question (NCT03579394). **Methods:** Patients treated for a stage IIIB-IVA high grade epithelial ovarian cancer by NAC and amenable to complete surgery after 3 cycles were randomized (1:1) to either complete surgery followed by 5 cycles of chemotherapy (control arm: C) or an additional 3 cycles of NAC followed by complete surgery then 2 cycles of chemotherapy (experimental arm: E). Maintenance treatment was administered according to standard of care. Primary endpoint was disease free survival (DFS) defined as the time from randomization until the date of disease progression or second cancer or death from any cause. The study was designed to detect an improvement in median (m) DFS from 10 months to 17 months (HR=0.59) with a 85% power and 2-sided α=0.05. Main secondary endpoints were Pathological complete response (CC0) rate, post operative morbidity and mortality, quality of life (QOL) and overall survival (OS). **Results:** Between 18/10/2018 and 23/04/2024, 209 patients (median age: 69 years) were randomized to arm C (n=103) or E (n=106). Median total number of cycles of NAC was 7 (5-9) and 8 (3-9) in arm C and E .CC0 rate was 83.2% vs 90%. After a median follow up of 40.4 months, mDFS was 20.2 months (95%CI: 18.2-23.6) in arm C vs 23.4 (19.0-30.4) in arm E (Log-rank test p=0.48, HR: 0.88 (95%CI: 0.63-1.24). The longitudinal analysis of QoL found no significant differences between the two arms, however, social functioning, insomnia, and sexuality showed a trend toward further improvement ($\geq$5 points) in arm E. Major postoperative complication rates within 30 days were 5% and 11% in arm C and E, (p=0.11) , with no death within 30 days after surgery. **Conclusions:** CHRONO is the first randomized trial addressing the clinical impact of delayed surgery after 6 courses of NAC in first line treatment of advanced ovarian cancer. No statistically significant difference was shown between the two arms of the study considering DFS, severe morbidity, mortality or QoL. New trials are needed for a better understanding of this alternative to interval surgery in highly chemosensitive advanced ovarian cancer patients. Clinical trial information: NCT03579394. Research Sponsor: This study was fully funded by ARCAGY-GINECO.

5506 **Oral Abstract Session**

A randomized phase II trial of mirvetuximab soravtansine in folate receptor alpha (FRα)–high recurrent ovarian cancer eligible for platinum-based chemotherapy (MIROVA/AGO-OVAR 2.34). First Author: Philipp Harter, Ev. Kliniken Essen-Mitte, Essen, Germany

Background: Mirvetuximab soravtansine (MIRV) has demonstrated single agent activity in patients with platinum-resistant ovarian cancer with FRα high expression. However, its activity and safety in combination with carboplatin has not been defined in platinum eligible patients so far. **Methods:** Randomized phase II trial comparing 6 cycles of carboplatin AUC5+MIRV 6 mg/kg AIBW every 3 weeks followed by MIRV versus 6 cycles of carboplatin combined with either paclitaxel, gemcitabine or pegylated liposomal doxorubicin followed by maintenance PARP inhibitor (PARPi) if applicable. All histologic subtypes were eligible with a platinum-free interval $>$3 months and FRα high expression ($\geq$75% with PS2+ scoring) confirmed by central laboratory. Prior PARPi therapy in BRCAmut patients was mandatory. Strata were BRCA-Status, TFIp and number of prior lines of chemotherapy. The primary endpoint was PFS. **Results:** In total, 145 patients were randomized. Of them, 112/145 (77.2%) patients had received prior bevacizumab and 97/145 (66.9%) had prior PARPi, 15.2% were BRCAmut. In the standard arm, 39.15% received PARPi as maintenance. Median PFS in the standard arm was 9.79 months versus 9.53 months in the experimental arm (p=0.996; HR=1.00; 95% CI: 0.68; 1.46). **Conclusions:** MIROVA/AGO-OVAR 2.34 is the first randomized trial evaluating the activity and safety of the combination of carboplatin with an antibody-drug conjugate in the setting of platinum-eligible relapsed ovarian cancer. The primary endpoint regarding improvement of PFS was not met. Further analysis will be presented. Clinical trial information: NCT04274426. Research Sponsor: ImmunoGen/AbbVie.

5507 **Oral Abstract Session**

Updated efficacy results from the phase I cervical cancer cohort of BAT8008, a TROP-2–directed antibody-drug conjugate, in patients with advanced cervical cancer. First Author: Jianli Zhao, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: BAT8008 is a novel antibody-drug conjugate comprising a TROP-2 antibody and an exatecan payload. Patients with recurrent or metastatic cervical cancer (r/m CC) who have progressed on platinum-based chemotherapy have limited treatment options and poor prognosis. This study reports the safety and efficacy of BAT8008 in a cohort of r/m CC patients from a phase 1 trial. **Methods:** This analysis is part of BAT-8008-001-CR, a multi-center, open-label phase 1 study with dose escalation and expansion cohorts. Patients with r/m CC who had failed prior systemic treatments were enrolled. BAT8008 was administered 2.4 mg/kg or 2.1mg/kg intravenously every two weeks (Q2W) 2.4 mg/kg. **Results:** As of Jan 5, 2026, 68 evaluable patients with r/m CC were enrolled (27 at 2.1 mg/kg, 41 at the 2.4 mg/kg). Patients were heavily pre-treated, with 55.9% having received $\geq$2 prior lines of therapy. 64.7% had prior anti-angiogenic therapy and 38.2% had prior immunotherapy. At the 2.4 mg/kg dose (n=44), the most common TRAEs (any grade/$\geq$G3) were anemia (63.6%/15.9%), WBC decreased (68.2%/25.0%), stomatitis (54.5%/6.8%), and neutrophil count decreased (45.5%/20.5%). No treatment-related deaths occurred. For the RP2D cohort (n=41), the confirmed objective response rate (cORR) was 29.3% and disease control rate (DCR) was 78.0%. The median progression-free survival (mPFS) was 6.7 months (95% CI: 3.5-12.1) and median duration of response (mDoR) was 9.0 months (95% CI: 4.2-12.3). Efficacy was observed across subgroups and was independent of TROP-2 expression level. **Conclusions:** BAT8008 demonstrated promising and durable anti-tumor activity with a manageable safety profile in heavily pre-treated patients with r/m cervical cancer. These findings support the continued development of BAT8008 in this patient population. Clinical trial information: NCT05620017. Research Sponsor: None.

Efficacy Endpoint	2.1 mg/kg (n=27)	2.4 mg/kg (n=41)	Overall (n=68)
cORR, % (95% CI)	22.2 (10.6-40.8)	29.3 (17.6-44.5)	26.5 (17.4-38.0)
DCR, % (95% CI)	81.5 (63.3-91.8)	78.0 (63.3-88.0)	79.4 (68.4-87.3)
mPFS, months (95% CI)	5.3 (3.3-8.3)	6.7 (3.5-12.1)	6.5 (3.5-8.3)
mDoR, months (95% CI)	Not Reached	9.0 (4.2-12.3)	9.0 (5.3-12.3)

5508 **Oral Abstract Session**

A phase 1/2 study of the next-generation nectin-4–targeting antibody-drug conjugate CRB-701 (SYS6002) in patients with recurrent or metastatic cervical cancer. First Author: Tudor-Eliade Ciuleanu, Arensia Research Clinic, Cluj-Napoca, Romania

Background: CRB-701 is a next-generation Nectin-4–targeted monomethyl auristatin E (MMAE)-based antibody–drug conjugate with differentiated safety, efficacy and pharmacokinetics compared with other agents in the same class. As previously reported, CRB-701 demonstrated antitumor responses independent of Nectin-4 expression levels in solid tumors, notably in patients with heavily pretreated head and neck squamous cell carcinoma (HNSCC) and cervical cancer, as well as those with urothelial carcinoma. Here, we provide data from this phase 1/2 trial in patients with cervical cancer enrolled in dose escalation (part A) and dose optimization (part B) (NCT06265727). **Methods:** Patients with recurrent or metastatic (R/M) cervical cancer who had received $\geq$ 1 line of therapy were enrolled. Part A employed a Bayesian Optimal Interval design with four doses (1.8, 2.7, 3.6 and 4.5 mg/kg; each every 3 weeks [Q3W]) to determine the maximum tolerated dose. In part B, the pharmacologically active dose range identified in part A was evaluated using a time-to-event Bayesian optimal phase 2 design. Patients were randomized 1:1 to receive CRB-701 at 2.7 or 3.6 mg/kg Q3W. The primary endpoints for parts A and B were dose-limiting toxicities and objective response rate (ORR), respectively. Safety, tolerability and pharmacokinetics were also assessed. Nectin-4 expression was evaluated retrospectively. **Results:** As of September 2025, 54 patients with cervical cancer had enrolled across parts A and B. At the time of data cut, most patients were awaiting a confirmatory scan. The unconfirmed ORR was 22.2% (4/18 evaluable patients) at the 2.7 mg/kg dose and 37.5% (6/16 evaluable patients) at the 3.6 mg/kg dose. Confirmed partial responses were observed in 1/18 participants at the 2.7 mg/kg dose and 3/16 patients at the 3.6 mg/kg dose. One patient had a confirmed complete response at the 2.7 mg/kg dose. The safety profile of CRB-701 was broadly consistent with earlier findings: keratitis, anemia, alopecia, fatigue and dysgeusia were the most frequently reported treatment-emergent adverse events ($\geq$ 15% of overall solid tumor population [N = 167]). An expanded efficacy analysis reporting an additional 6 months of follow-up, including ORR, duration of response and progression-free survival, will be presented at the congress. Subgroup analyses by treatment history and disease extent will also be presented. **Conclusions:** CRB-701 has shown promising efficacy in patients with R/M cervical cancer, as well as a favorable safety profile compared with other MMAE-based therapies. Ongoing evaluation of CRB-701 will determine its potential as a new treatment option for this patient population. Clinical trial information: NCT06265727. Research Sponsor: None.

5509 Rapid Oral Abstract Session

Phase 1a study results for IMA203CD8, a PRAME-directed T-cell receptor (TCR) T-cell therapy, in ovarian cancer. First Author: Antonia Busse, Charite Medical University Hospital, Berlin, Germany

Background: Pts with advanced ovarian cancer (OC) that progresses after platinum-based chemotherapy and subsequent treatment are lacking therapeutic options for durable clinical benefit. TCR T-cell therapies enable immune recognition of intracellular tumor antigens presented by HLA, expanding the therapeutic landscape beyond targets accessible to conventional immunotherapies. PRAME is a cancer-associated antigen expressed across >50 cancers, including OC. IMA203CD8 is a TCR T-cell therapy that engineers CD8+ and CD4+ T cells to detect and destroy PRAME-expressing tumor cells that evade conventional therapeutic approaches. Results from a phase 1a basket trial (NCT03686124) indicated the potential to target several PRAME+ tumors. Here we present updated dose-escalation results for the subset of pts with OC. **Methods:** Pts were ≥18 y, HLA-A*02:01+, had R/R solid tumors, measurable disease (RECIST 1.1), ECOG PS 0-1, and had exhausted SOC options, including platinum therapy. Following leukapheresis and IMA203CD8 manufacture, pts underwent lymphodepletion (LD) with Cy (500 mg/m^2 × 4 d) and Flu (30 mg/m^2 × 4 d), followed by IMA203CD8 infusion +/- low-dose SUBQ IL-2. Dose escalation is ongoing. **Results:** As of Oct 27, 2025, 16 heavily pretreated pts with OC were infused with IMA203CD8. Most common TEAEs were LD-related cytopenias (100%). Cytokine release syndrome occurred in 100% of pts and was mostly mild to moderate (G1: 44%, G2: 50%, G3: 6%). Immune effector cell–associated neurotoxicity syndrome occurred in 1 pt (G1: 6%). Tolerability in pts with OC was generally consistent with the known IMA203CD8 safety profile. Eleven pts were efficacy evaluable with ≥1 post-baseline scan (median 4 prior lines of therapy) after treatment with IMA203CD8 across escalating dose levels (median: 2.26×10^9 total TCR T cells; range: 1.4-7.1×10^9 TCR T cells). Tumor reduction was observed in 7 pts with maximum reduction of 74%; 3 responses were >6 mo and durable disease control occurred for up to 12 mo. A dose-dependent signal of activity was observed in pts treated at higher doses (n=5; range: 2.3-7.1×10^9 TCR T cells), including 2 confirmed partial responses (PRs) with 1 ongoing metabolic complete response (CRs) at 6 mo, and 1 unconfirmed PR. All responses were observed in pts without post-infusion low-dose IL-2. Updated results from ≥20 efficacy-evaluable pts (including several unconfirmed PRs and CRs after data cutoff) with longer follow-up will be presented. **Conclusions:** In pts with metastatic and/or relapsed OC, IMA203CD8 demonstrated a tolerability profile consistent with prior experience in other solid tumors and encouraging dose-dependent antitumor activity, including durable objective responses according to RECIST. Dose escalation with and without IL-2 at higher doses is currently ongoing to determine RP2D and unlock the full potential of IMA203CD8 in OC. Clinical trial information: NCT03686124. Research Sponsor: Immatics US.

5510 Rapid Oral Abstract Session

The neo-epitope-based vaccine OSE2101 with or without pembrolizumab versus best supportive care as maintenance in platinum-sensitive recurrent ovarian cancer patients with controlled disease after platinum-based chemotherapy: The academic randomized TEDOVA/GINECO-OV244b/ENGOT-ov58 trial. First Author: Alexandra Leary, Gustave-Roussy Cancer Campus, Villejuif, and GINECO, Paris, France

Background: OSE2101 is a neo-epitope vaccine targeting 5 tumor-associated antigens (TP53, MAGE2, MAGE3, CEA and HER2) modified to increase both HLA-A2 and TCR affinity, designed to turn immunogenic 'cold' ovarian cancer (OC) to 'hot' tumors. Patients with platinum sensitive OC (PSOC) relapsing post-PARP inhibitor (PARPi) and bevacizumab (BEV) represent an area of unmet medical need. **Methods:** This international multicenter GINECO-sponsored phase II study randomized PSOC patients in CR, PR, or SD after platinum therapy to best supportive care (BSC, arm A), or maintenance treatment with OSE2101 ((SC, q3w until week 18, then q6w to week 48, then q12w, arm B) or OSE2101+pembrolizumab (IV q6w, Arm C) (1:1:2) for up to 2 years. Eligible pts were HLA-A2 positive and previously treated with, or ineligible for, BEV and a PARPi. Primary endpoint was PFS and randomization was stratified for best response to platinum (CR/PR vs SD). Sample size was calculated to provide 90% power to detect an improved PFS in arm C vs A with HR=0.57. Subsequent hierarchical testing then compared arms C vs B, and arms B vs A. **Results:** 185 pts were randomized to BSC (N=48), OSE2101 (N=46) or OSE+PEMBRO (N=91). Histology was mainly high grade (93%) and serous (93%), 20% harbored a *BRCA1/2* mutation, 51% of pts were in CR/PR and 49% in SD at randomization, 85% and 83% of pts were PARPi and BEV-exposed, respectively. Baseline characteristics were balanced between arms. With a median follow up of 22 months, PFS was significantly improved with OSE2101+Pembro vs BSC (4.1 vs 2.8mo in arms C vs A; HR=0.53, 95%CI, 0.36-0.78; p<0.001), especially among pts in CR/PR to platinum (HR=0.31, 95% CI, 0.17-0.53; p<0.01; test for interaction p=0.02). For OSE2101+Pembro vs OSE2101, HR was 0.72 (p=0.074) and for OSE2101 vs BSC, HR was 0.70 (p=0.099). Treatment emergent AEs were increased in arm C vs B with most common being injection site reaction (57% vs 35%), cytokine release syndrome (CRS, mainly G1/2: 28% vs 9%), arthralgia (21% vs 17%) and >G2 immune related events (18% vs 4%). **Conclusions:** This is the 1st trial demonstrating a significant improvement in PFS with a combination of a neo-epitope vaccine and an anti-PD1 as maintenance after platinum for patients with platinum sensitive relapsed OC progressing post-PARPi and bevacizumab. Clinical trial information: 2024-516096-32-00. Research Sponsor: OSE Immunotherapeutics, SA; ARCAGY-GINECO organization; MSD France.

5511 Rapid Oral Abstract Session

Overall survival for patients with pre-treated platinum-resistant ovarian cancer receiving gotistobart in combination with pembrolizumab. First Author: Joyce N. Barlin, Womens Cancer Care Associates, Albany, NY

Background: Gotistobart, an investigational tumor microenvironment-selective Treg depletion antibody targeting CTLA-4 with a novel mechanism of action, demonstrated anti-tumor activity when combined with prembrolizumab in the PRESERVE-004/GOG-3081 trial in patients (pts) with platinum-resistant ovarian cancer (PROC; Barlin et al., ESMO 2024). Here, we present overall survival (OS) and updated safety data from the Phase 2 trial (NCT05446298). **Methods:** Pts with PROC, tubal, or peritoneal cancer who previously received 1 line of platinum-based therapy and progressed between 3-6 months or received ≥1 line and progressed within 6 months of last dose, were treated with gotistobart (1, 2, 3, or 6 mg/kg, Q3W) and pembrolizumab (200 mg, Q3W). Here we present data from patients that received 1 or 2 mg/kg gotistobart Q3W and pembrolizumab. Primary endpoints included objective response rate (ORR) based on RECIST 1.1 and safety. Secondary endpoints included duration of response (DoR), progression-free survival (PFS) and OS. **Results:** As of November 12, 2025, 83 pts were treated with ≥1 dose of gotistobart in combination with pembrolizumab. Among them, 62 pts (85.5% White with a median age of 65 years and 83.9% with high grade serous OC) had received 1 or 2 mg/kg gotistobart, and 75.8% had received ≥3 lines of prior therapy (median 4, range: 1-10). The median time from randomization to database cutoff was 22.3 months (range 17.8, 27.2). Median OS was 18.9 m (95% CI 3.9, NE) and 8.3 m (95% CI 3.9 – 17.1) with the OS rates at 18 months at 54.3% (95% CI 35.1, 70.0) and 26.9% (95% CI 11.7 - 44.7) in pts that received 1 or 2 mg/kg gotistobart, respectively. Efficacy data are summarized in the table below. Grade ≥3 treatment-related (gotistobart or pembrolizumab) adverse events (TRAEs) were observed in 51.5% and 55.2% pts treated with 1 mg/kg or 2 mg/kg, respectively. Common (≥5%) grade ≥3 TRAEs were colitis (1 mg/kg: 12.1%, 2 mg/kg: 10.3%), hyponatremia (1 mg/kg: 12.1%, 2 mg/kg: 3.4%), increased ALT (1 mg/kg: 9.1%, 2 mg/kg: 3.4%), increased AST (1mg/kg: 9.1%, 2 mg/kg: 3.4%), adrenal insufficiency (1 mg/kg: 9.1%, 2 mg/kg: 3.4%), diarrhea (1 mg/kg: 9.1%, 2 mg/kg: 3.4%), and hypokalemia (1 mg/kg: 0%, 2 mg/kg: 6.9%). **Conclusions:** The chemotherapy-free combination of gotistobart and pembrolizumab demonstrated clinically meaningful ORR, OS and a manageable safety profile in pts with PROC, where the majority were heavily pretreated with no further standard-of-care treatment options. Clinical trial information: NCT05446298. Research Sponsor: Onco C4 Inc.

	1 mg/kg gotistobart + pembrolizumab (n=33)	2 mg/kg gotistobart + pembrolizumab (n=29)
Confirmed ORR, % (95% CI)	21.2 (9.0, 38.9)	20.7 (8.0, 39.7)
Median DoR, m (95% CI)	10.8 (3.3, NE)	11.6 (4.0, NE)
Median PFS, m (95% CI)	2.2 (2.0, 4.2)	2.5 (1.9, 6.0)
Median OS, m (95% CI)	18.9 (3.9, NE)	8.3 (3.9, 17.1)
OS rate at 18 months, % (95% CI)	54.3 (35.1, 70.0)	26.9 (11.7, 44.7)

5512 Rapid Oral Abstract Session

Safety and efficacy of BAT8006 in combination with BAT1308 in patients with advanced endometrial cancer. First Author: Xingtao Long, Chongqing University Cancer Hospital, Chongqing, China

Background: BAT8006 is a folate receptor α (FRα)-targeting antibody-drug conjugate (ADC), while BAT1308 is a recombinant humanized anti-PD-1 monoclonal antibody. Both agents have individually demonstrated acceptable tolerability and promising antitumor activity in solid tumors. Herein, we report a phase Ib/II trial designed to evaluate the safety and efficacy of BAT8006 in combination with BAT1308 for patients with advanced endometrial cancer. **Methods:** Eligible patients included those with pathologically confirmed endometrial cancer who had experienced disease recurrence or progression following at least 1 line of platinum-based chemotherapy or immunotherapy-based regimen, with no more than 3 prior lines of systemic therapy. Enrolled patients received BAT8006 (76 mg/m² or 84 mg/m²) in combination with BAT1308 (fixed dose of 300 mg) every 3 weeks until disease progression, intolerable toxicity, or other protocol-specified reasons. The primary endpoints were safety and ORR as assessed by investigators per RECIST v1.1. **Results:** As of December 25, 2025, a total of 45 patients with advanced endometrial cancer were enrolled in this study. The median age of the cohort was 62 years (range, 27–75 years). Among these patients, 80.0% had ECOG PS of 0, and 80.0% presented with metastatic disease at baseline. All patients had received prior platinum-based chemotherapy; additionally, 48.9% had undergone prior immunotherapy, and 15.6% had received two or more prior lines of systemic therapy. The proportion of patients with FRα positivity (defined as FRα expression ≥1%) was 62.2%. TRAEs were reported in 41 patients (91.1%). Grade ≥3 (G3) TRAEs occurred in 24 patients (53.3%), and SAEs were observed in 17 patients (37.8%). The most common TRAEs (incidence ≥20%) included leukopenia (77.8%), anemia (77.8%), neutropenia (62.2%), nausea (55.6%), thrombocytopenia (53.3%), vomiting (48.9%), lymphopenia (35.6%), pyrexia (26.7%), decreased appetite (26.7%), increased alanine aminotransferase (22.2%), and asthenia (22.2%). No cases of interstitial lung disease were reported. IrAEs occurred in 3 patients (6.7%). TRAEs resulted in dose reduction in 10 patients (22.2%) and treatment discontinuation in 2 patients (4.4%). No treatment-related deaths were recorded. Efficacy was evaluable in 34 patients. The overall ORR was 38.2% (95% CI: 22.2–56.4), and DCR was 70.6% (95% CI: 52.5–84.9). In the BAT8006 (76 mg/m²) + BAT1308 cohort, ORR was 44.4% (95% CI: 21.5–69.2) and DCR was 72.2% (95% CI: 46.5–90.3). In the BAT8006 (84 mg/m²) + BAT1308 cohort, ORR was 31.3% (95% CI: 11.0–58.7) and DCR was 68.8% (95% CI: 41.3–89.0). **Conclusions:** These findings suggest that BAT8006 in combination with BAT1308 may represent an effective therapeutic strategy for advanced endometrial cancer, with a manageable safety profile. Further prospective studies are warranted to validate the efficacy and safety of this combination regimen. Clinical trial information: CTR20242449. Research Sponsor: None.

5513 Rapid Oral Abstract Session

NAPISTAR 1-01: Results of phase 1 dose escalation of monotherapy with TUB-040, a novel NaPi2b-targeting exatecan ADC, in patients (pts) with platinum-resistant ovarian cancer (PROC). First Author: Toon Van Gorp, BGOG and University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium

Background: NaPi2b is overexpressed in high-grade serous ovarian cancer and non-small cell lung cancer (NSCLC). TUB-040 is a DAR8 ADC targeting NaPi2b, comprising a humanized Fc-silenced IgG1 mAb conjugated to exatecan via a cleavable, cysteine-selective, stable, solubility-mediating P5 linker providing excellent stability and biophysical ADC properties. In preclinical studies, TUB-040 induces potent antigen-specific cytotoxicity and demonstrates strong by-stander activity. **Methods:** NAPISTAR 1-01 is a phase 1/2a study in biomarker-unselected pts with PROC and NSCLC. TUB-040 was administered Q3W in dose escalation (range 0.5-5.3 mg/kg) to pts with PROC until progression or unacceptable toxicity. **Results:** As of Dec 1, 2025, 67 PROC pts received TUB-040 for a median of 10 cycles (1-25), median duration of exposure was 213 days (21-546), and 42 (63%) pts were ongoing. Median age: 62 years (34-81), ECOG PS 0-1, median prior lines: 4 (1-7), prior treatment included bevacizumab (84%), PARPi (76%), and mirvetuximab soravtansine (13%). Between dose levels 1.67-3.3mg/kg (N=46), the most common all-grade TEAEs were nausea (78%), fatigue (54%), neutropenia (43.5%), anemia (37%), constipation (34%), diarrhea (33%), vomiting (28%), alopecia (28%), and decreased appetite (26%). Gr≥3 heme TEAEs by dose are in Table 1. There were no fatal TEAEs or treatment discontinuations due to TEAEs. Three pts (6.5%) experienced Gr1 pneumonitis, which resolved. Between dose levels 1.67–3.3 mg/kg, 46 pts were evaluated for efficacy. The uORR was 63% [95% CI, 47.5-77.2] and cORR was 60.9% [95% CI, 45.3-75.1] (RECIST; v1.1), including two cCRs. Responses by dose are in Table 1. The majority of responses, 90% (26/29), were ongoing. Disease control rate was 96% [95% CI, 85.2-99.5]. Among CA-125 evaluable pts (N=42), CA-125 response occurred in 81% (34/42) [95% CI, 65.6-91.5]. cORRs were similar across subgroups, including: ≥4 prior lines of therapy (cORR=71%), prior exposures to bevacizumab (62%), mirvetuximab soravtansine (63%) or PARPi (67%). Five pts with stable disease remain on treatment and eligible for response. **Conclusions:** TUB-040 was well tolerated with promising clinical activity at low doses, offering a potential new treatment option with a differentiated, favorable benefit–risk profile and a wide therapeutic window in PROC pts. Dose optimization is currently ongoing. Clinical trial information: NCT06303505. Research Sponsor: Tubulis GmbH.

	1.67 mg/kg (N=10), n (%)	2.1 mg/kg (N=12), n (%)	2.50 mg/kg (N=12), n (%)	3.3 mg/kg (N=12), n (%)	Total (N=46), n (%)
Complete response	1 (10)	0	1 (8)	0	2 (4)
Partial response	6 (60)	7 (58)	7 (58)	6 (50)	26 (57)
Stable disease	2 (20)	5 (42)	3 (25)	6 (50)	16 (35)
Progressive disease	1 (10)	0	1 (8)	0	2 (4)
Overall responses (PR + CR)	7 (70)	7 (58)	8 (67)	6 (50)	28 (60.9)
Gr≥3 neutropenia	0	2 (17)	4 (33)	6 (50)	12 (26)
Gr≥3 anemia	0	0	1 (8)	5 (42)	6 (13)
Gr≥3 thrombocytopenia	0	0	1 (8)	1 (8)	2 (4)

5514 Rapid Oral Abstract Session

Phase 1 basket study of telisotuzumab adizutecan (Temab-A, ABBV-400), a c-Met protein–targeting antibody-drug conjugate: Results from patients with platinum-resistant ovarian/primary peritoneal/fallopian tube cancer (PROC). First Author: Gini F. Fleming, University of Chicago Medicine, Chicago, IL

Background: c-Met protein is expressed in several tumor types, including PROC, and is linked with poor clinical outcomes. Temab-A comprises a c-Met protein-targeting antibody conjugated to a topoisomerase 1 inhibitor. Phase 1 studies evaluating Temab-A monotherapy in solid tumors showed antitumor activity and a manageable safety profile (NCT05029882, NCT06084481). Here, we report on the efficacy and safety of Temab-A in PROC. **Methods:** This phase 1, open-label basket study (NCT06084481) enrolled patients (pts) ≥18 years with histologically/cytologically confirmed recurrent PROC, with Eastern Cooperative Oncology Group performance score ≤1. Pts must have had measurable disease per investigator-assessed RECIST v1.1 criteria, have had platinum-resistant disease, and have received ≥1 but ≤5 prior lines of systemic therapy, with ≤2 prior therapies since the development of platinum resistance. Pts received Temab-A at 2.4 mg/kg every 3 weeks. Primary endpoints were safety and efficacy. **Results:** As of Sept. 11, 2025, 41 pts with PROC received Temab-A. Tumor histology included serous carcinoma (n=26), clear cell carcinoma (n=7), and other rare histologies (n=8). The median age was 64 years (range 43–89), and the median number of prior lines of systemic therapy was 3 (range 1–6). Median follow-up was 5.1 months. Objective response rate (ORR) was 37%. Duration of response, progression-free survival, and overall survival were immature at data cutoff. Efficacy data are shown in the Table. The most common treatment-related adverse events (TRAEs) of any Grade (G) included anemia (59%), nausea (59%), and fatigue (39%); G ≥3 TRAEs occurring in ≥10% of pts were anemia (34%), neutrophil count decreased (17%), and white blood cell count decreased (15%). The adjudicated interstitial lung disease/pneumonitis rate was 5% (G1, n=2). TRAEs led to treatment discontinuation in 5%, dose interruption in 39%, and dose reduction in 37% of pts. There were no TRAEs that led to death. Temab-A pharmacokinetics in pts with PROC were consistent with those in other tumor types. Exploratory biomarker analyses are ongoing. **Conclusions:** Temab-A had a manageable safety profile and showed antitumor activity in pts with PROC. Clinical trial information: NCT06084481. Research Sponsor: AbbVie Inc.

Efficacy of Temab-A.[a].

Outcome	Pts with PROC (N=41)
Best overall response, n (%)	
Complete response	0
Partial response	19 (46)
Stable disease	16 (39)
Progressive disease	5 (12)
Not assessed[b]	1 (2)
Objective response rate[c], n (%)	15 (37)
95% CI	22, 53
Clinical benefit rate[c], n (%)	35 (85)
95% CI	71, 94

[a]Responses were assessed by investigators per RECIST v 1.1 criteria.
[b]Pts without postbaseline scan.
[c]Confirmed.
CI, confidence interval.

5515 Rapid Oral Abstract Session

Updated safety and efficacy of puxitatug samrotecan (Puxi-Sam, AZD8205) in patients (pts) with endometrial cancer (EC) or ovarian cancer (OC): Phase 1/2a BLUESTAR study. First Author: Linda R. Mileshkin, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: B7-H4, a transmembrane glycoprotein that negatively regulates T cells, is highly expressed in EC and OC. Puxi-Sam (AZD8205), a B7-H4–directed topoisomerase I inhibitor antibody–drug conjugate, showed manageable toxicity and promising antitumor activity in BLUESTAR (NCT05123482) dose-escalation. Here, we report updated safety and efficacy results as EC and OC expansion cohorts are fully enrolled. **Methods:** Eligible pts were ≥18 years old with relapsed/metastatic B7-H4–positive (≥25% tumor cell staining by central immunohistochemistry) EC or OC and an ECOG PS ≤1. Pts had progressed on prior standard-of-care therapy including platinum-based chemotherapy. Pts with EC received Puxi-Sam at 2.0 or 2.4 mg/kg IV Q3W and pts with OC received Puxi-Sam at 1.6 or 2.4 mg/kg IV Q3W. The primary objectives were to assess safety and tolerability; secondary objectives included assessment of antitumor activity per RECIST 1.1. **Results:** As of October 30, 2025, 93 pts with EC received Puxi-Sam at 2.0/2.4 mg/kg and 78 with OC at 1.6/2.4 mg/kg. Pts with EC had a median age (min–max) of 63.5 (52–78)/65 (34–81) years, respectively, and median prior lines of therapy (LOT) was 1. Pts with OC had a median age of 58 (28–79)/59 (35–74) years, respectively, and median prior LOT was 2. Treatment-related adverse events (TRAE) occurred in 92.9%/88.2% of pts with EC (2.0/2.4 mg/kg); 42.9%/47.1% had Grade ≥3 TRAEs, most commonly neutropenia (23.8%/31.4%) and anemia (16.7%/27.5%). TRAEs occurred in 87.9%/97.8% of pts with OC (1.6/2.4 mg/kg); 30.3%/75.6% had Grade ≥3 TRAEs, most commonly neutropenia (24.2%/60.0%) and anemia (9.1%/37.8%). One pt (1.1%) with EC and 5 (6.4%) with OC discontinued treatment due to TRAEs. Antitumor activity of Puxi-Sam was most notable in EC at 2.4 mg/kg, with an objective response rate (ORR) of 48% and durable response of 7.1 months; at 2.0 mg/kg in EC, ORR was 34.1%. In OC, ORR was 12.1% at 1.6 mg/kg and 24.4% at 2.4 mg/kg (Table). **Conclusions:** Puxi-Sam showed a favorable safety profile and robust antitumor efficacy, supporting continued development, and is now being investigated in the Phase 3 BLUESTAR-Endometrial01 (NCT07044336) study. Clinical trial information: NCT05123482. Research Sponsor: AstraZeneca.

Efficacy (interim response evaluable pts).

	EC 2.0 mg/kg n=41	EC 2.4 mg/kg n=50	OC 1.6 mg/kg n=33	OC 2.4 mg/kg n=45
ORR, % (95% CI)	34.1 (20.1–50.6)	48.0 (33.7–62.6)	12.1 (3.4–28.2)*	24.4 (12.9–39.5)
Complete response, n	1	1	0	0
Partial response, n	13	23	4	11
Stable disease, n	17	21	22	26
Progressive disease, n	10	5	5	8
Median duration of response, months (95% CI)	6.2 (5.5–NE)	7.1 (4.5–NE)	5.8 (2.8–NE)	7.0 (4.0–NE)
Disease control rate at 12 weeks, % (95% CI)	70.7 (54.5–83.9)	86.0 (73.3–94.2)	54.5 (36.4–71.9)	64.4 (48.8–78.1)
Median progression-free survival, months (95% CI)‡	7.0 (4.5–9.0)§	8.1 (6.8–9.2)¶	4.8 (2.8–5.8)	5.7 (4.1–9.5)

*2 pts were non-evaluable.
‡Full analysis set.
§n=42.
¶n=51.
NE, not estimable.

5516 Rapid Oral Abstract Session

Updated efficacy, safety, and exploratory biomarker analyses of a phase II trial of abemaciclib plus hormonal therapy in recurrent ovarian (OC) and endometrial cancer (EC). First Author: Jordyn Silverstein, University of California Los Angeles, Los Angeles, CA

Background: We evaluated abemaciclib with hormonal therapy in patients with estrogen receptor positive (ER+) EC, low-grade serous OC (LGSOC), and selected high-grade serous OC (HGSOC) with CDK4/6 molecular activation features in a single-center, phase II study. Preliminary results demonstrated a 24-week progression-free survival (PFS) rate of 53% in ER+ EC and 60% in LGSOC (2025 SGO Abstract 256). Here, we report the final clinical outcomes and present the first exploratory biomarker analyses from this study. **Methods:** Abemaciclib was administered at 150mg twice daily in combination with hormonal therapy. The primary endpoint was 24-week PFS; secondary endpoints were median PFS (mPFS), disease control rate (DCR), objective response rate (ORR) and safety. Exploratory analyses evaluated efficacy by TCGA molecular subgroups and tumor next-generation sequencing–defined alterations. PFS was estimated using Kaplan–Meier and compared using log-rank. **Results:** As of December 2, 2025, 43 patients (21 HR+ EC, 14 LGSOC, 8 HGSOC) were evaluable, with a median follow-up of 29 months (mos). Median age was 64 (range 24-78) and median prior lines of therapy was 3 (range 1-13). Among 21 patients with ER+ EC, the 24-week PFS rate was 56.1% (95% CI 34.5–77.7), mPFS was 9.0 mos (2.4–11.3), DCR was 63%, and ORR was 21%, including one complete response. There were 13 (62%) NSMP, two (10%) MSI-high, two (10%) TP53-abnormal, one (5%) POLE-mutated, and three without molecular data. The NSMP group had 24-week PFS rate and mPFS of 59.8% (32-87.3%) and 10.4 mos (2.4-21.0), compared with 20.0% (0-55.0) and 1.9 mos (1.7-9.3) in the non-NSMP group (p=0.02). Notably, all responses occurred in the NSMP group. The largest difference was observed between patients with CTNNB1mut with a mPFS of 10.4 months (1.9–NR) compared with 5.2 mos (1.7–9.3) in patients with CTNNB1wt (p = 0.22). Among 14 patients with LGSOC, the 24-week PFS rate was 71.4% (47.8-95.1), mPFS was 17.5 mos (3.5-NR), DCR was 79% and ORR was 14%, 5 still on treatment at data cut off. The median time on treatment was 10.5 mos (range 1.7-55.4), 4 patients (28%) were on treatment for more than 3 years, the longest still on treatment after 4.6 years. The most common mutation was KRAS in 7 (50%), with no observed differences by KRAS status (KRASmut 11.9 mos [1.9-NR] mPFS, KRASwt 17.5 mos [3.5-NR] mPFS , p=0.89). Despite the 8 patients with HGSOC having CDK4/6 activating mutations the 24-week PFS rate was 12.5% (0-35.4) and the mPFS was 1.6 mos (0.3-1.9). No new safety signals were observed across all subgroups. **Conclusions:** Abemaciclib demonstrated promising clinical activity in patients with LGSOC regardless of KRASmut status and in ER+ EC, with the greatest activity observed in the NSMP group and potentially CTNNB1-mutated cases; however, these exploratory subgroups need larger validation. Clinical trial information: NCT04469764. Research Sponsor: Eli Lilly and Company; NIH T32 National Institute of Health T32 fellowship titled Patient-Centered Outcomes Research Training in Urologic and Gynecologic Cancers (PCORT UroGynCan); T32CA251072.

5517 Rapid Oral Abstract Session

Effects of short-term fasting compared to free diet in ovarian cancer patients: Results from a two-arm pilot randomized trial. First Author: Claudia Marchetti, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Background: Short-term fasting (STF) may enhance chemotherapy efficacy by suppressing insulin-driven pro-survival signaling. Clinical data on the metabolic, oncological, and immunological effects of STF in ovarian cancer (OC) are lacking. **Methods:** In this prospective, pilot randomized trial conducted at our center, women with advanced high-grade serous OC receiving carboplatin/paclitaxel-based neoadjuvant chemotherapy (NACT) were randomized to STF (36h before to 24h after each cycle) or a free diet (FD). Eligibility criteria included body mass index $\geq$ 19 kg/m2. Major exclusions were diabetes mellitus, food allergies, and eating disorders. The primary endpoint was insulin reduction after three NACT cycles. Secondary endpoints included oncological outcomes. Exploratory translational analyses assessed immune profiling. Based on 80% power and a two-sided α of 0.05, 17 patients per arm were required. **Results:** Eighteen patients per arm completed three NACT cycles. Baseline clinical characteristics and insulin levels were comparable between groups. After NACT, insulin increased in FD but decreased in STF (+9.76 vs -1.12 μIU/mL; p=0.01). Patients who did not undergo interval cytoreductive surgery (ICS) after three cycles experienced a greater insulin increase than those who underwent surgery (+11.46 vs +1.35 μIU/mL; p=0.033). At ICS, a chemotherapy response score of 3 was more frequent in STF than in FD (58.8% vs 17.6%; p=0.03). After a median follow-up of 18 months, median progression free survival (PFS) was longer in the STF arm compared with FD (38 vs 24 months; p=0.045). Translational analyses showed that STF limited immunosuppressive subsets correlated with chemotherapy response. **Conclusions:** The primary endpoint was met. STF induced a favourable metabolic shift and was associated with improved pathological response and prolonged PFS, alongside immune modulation. These findings provide a strong rationale for larger randomized trials evaluating STF in OC. Clinical trial information: NCT07039331. Research Sponsor: None.

Surgical outcomes and metabolic parameters before (baseline insulin levels) and after neoadjuvant chemotherapy (insulin levels and variation after NACT) according to the diet regimen.

		Free Diet Arm N=18	Short-Term Fasting Arm N=18	Overall population N=36	P value
ICS	***Never***	1 (5.6)	1 (5.6)	2 (5.6)	0.927
	After III cycles	12 (66.7)	13 (72.2)	24 (66.6)	
	After VI cycles	5 (27.7)	4 (22.2)	8 (22.2)	
CRS	***1***	5 (29.4)	1 (5.9)	6 (17.6)	**0.030**
	2	9 (52.9)	6 (35.3)	15 (44.1)	
	3	3 (17.6)	10 (58.8)	13 (38.2)	
Insulin Level - Baseline (*μIU/mL) Mean, SD*		8.7 (4.99)	10.7 (7.54)	9.71 (6.38)	0.353
Insulin Level - after NACT (*μIU/mL) Mean, SD*		18.5 (12.68)	9.59 (6.66)	14.03 (10.95)	**0.014**
Insulin Variation after NACT (*μIU/mL) Mean, SD*		+9.76 (12.89)	-1.12 (11.0)	+4.32 (13.03)	**0.010**

CRS, Chemotherapy Response Score; ICS, Interval Cytoreductive Surgery; NACT, Neoadjuvant Chemotherapy; SD, Standard Deviation.

5518 Poster Session

Population-based prediction of cardiovascular mortality in gynecologic cancer survivors using machine learning (RISKHEART). First Author: Luís Felipe Leite da Silva, Universidade Federal Fluminense, Niterói, Brazil

Background: General-population cardiovascular disease (CVD) risk scores underperform in cancer survivors by failing to capture treatment-related cardiotoxicity. Gynecologic cancer survivors constitute a distinct phenotype defined by older age and heterogeneous therapies. RISKHEART is an oncology-specific, survivorship-oriented model for individualized cardiovascular risk stratification. **Methods:** Women with primary gynecologic malignancies diagnosed between 2000 and 2020 were identified from the SEER program. Predictors included demographics (age, race, marital status) and SEER-available treatment variables (surgery, radiation, and chemotherapy [yes/no]). Model performance was evaluated using AUC, and explainability was assessed via SHAP. **Results:** The study included 104,384 women with gynecologic cancer. CVD-specific death occurred in 4,962 patients, with cumulative incidence rates of 2.44% at 5 years and 4.75% at 10 years. Affected patients were significantly older at diagnosis than those without CVD death (mean age, 75.0 vs 62.5 years; $P < .001$). CVD mortality differed by marital status and race (both $P < .001$), with widowed patients accounting for a higher proportion of CVD deaths (37.3% vs 17.7%). Endometrial cancer accounted for most CVD deaths (58.2%), whereas ovarian cancer was underrepresented among CVDs deaths relative to its prevalence in the overall cohort (15.1% vs 27.8%). In the independent testing cohort, the RISKHEART model demonstrated good discrimination for 10-year cardiovascular mortality (AUC, 0.786). For 5-year cardiovascular mortality, discrimination was slightly higher (AUC, 0.796), with sensitivity of 0.73 and specificity of 0.74. For the 5-year cardiovascular mortality model, discrimination remained elevated across 2000-2009 (AUC, 0.805) and 2010-2020 (AUC, 0.784). Explainability analyses identified age at diagnosis as the dominant predictor of cardiovascular death, with treatment-related variables contributing more prominently to short-term risk and sociodemographic factors increasing in relative importance over longer follow-up. **Conclusions:** In this large population-based cohort of gynecologic cancer survivors, the RISKHEART ML model demonstrated clinically meaningful discrimination for predicting CVD-specific mortality. This approach may support individualized CVD risk stratification and inform survivorship care. Research Sponsor: None.

5519 Poster Session

Feasibility and concordance of a large language model (ChatGPT-5) as a clinical decision support tool in gynecologic oncology tumor boards: A blinded, multi-observer study. First Author: Hatice Asoglu, Cukurova University Department of Medical Oncology, Adana, Turkey

Background: The integration of artificial intelligence (AI) into oncology practice is accelerating; however, the reliability of Large Language Models (LLMs) in complex clinical decision-making remains insufficiently validated. This study evaluated the concordance of ChatGPT-5 with multidisciplinary tumor board (MDT) decisions in gynecologic oncology, assessing accuracy, reproducibility across repeated queries, and specific domains of discordance. **Methods:** We analyzed 97 gynecologic cancer cases requiring multimodal treatment planning, evaluated at the Cukurova University Faculty of Medicine Gynecologic Oncology MDT between 2024-2025. Cases included ovarian (n=34), endometrial (n=41), cervical (n=16), and rare tumors (n=6). Standardized clinical summaries (staging, pathology, molecular markers, comorbidities, patient preferences) were input using a structured prompt template. Each case was queried independently at three time points within the same day to assess reproducibility. Recommendations were evaluated by two blinded medical oncologists using a 5-point Likert scale (1=completely inappropriate, 5=completely appropriate). A composite performance score was calculated as [(mean Likert score)/5]$\times$100. Inter-rater reliability and concordance were analyzed using Cohen's kappa (κ). **Results:** Inter-rater reliability was high for both MDT (κ=0.748, $p<0.001$) and AI evaluations (κ=0.802, $p<0.001$). Concordance between MDT and ChatGPT-5 recommendations was fair (Rater 1: κ=0.267; Rater 2: κ=0.341), indicating frequent disagreement in specific clinical nuances despite similar overall quality scores. Mean performance scores were significantly higher for MDT versus AI (Rater 1: 94.2%$\pm$4.8 vs. 89.8%$\pm$6.3, $p<0.001$; Rater 2: 93.8%$\pm$5.1 vs. 90.1%$\pm$5.9, $p<0.001$). Crucially, ChatGPT-5 demonstrated full consistency across three queries in only 38% of cases (37/97), with a mean reproducibility score of 4.10$\pm$0.83. Subgroup analysis revealed superior AI performance in early-stage (I–II) versus advanced-stage (III–IV) disease (p=0.024). However, AI performance was significantly inferior in cases requiring genetic testing recommendations (p=0.019), fertility-sparing approaches (p=0.045), and novel therapeutics integration (p=0.012). **Conclusions:** ChatGPT-5 demonstrates potential as a clinical decision support tool but currently lacks sufficient reliability for independent use in complex gynecologic malignancies. Key limitations include inconsistent reproducibility (62% variability across queries), suboptimal performance in advanced-stage disease, and deficiencies in precision oncology domains. Human expertise remains essential to mitigate risks associated with AI-generated inaccuracies, particularly for novel therapeutic integration. Research Sponsor: None.

5520 Poster Session

Quantitative pathology biomarkers for platinum resistance in ovarian cancer. First Author: Durga Vahini Sritharan, Yale School of Medicine, Department of Therapeutic Radiology, New Haven, CT

Background: Despite serving as the first-line systemic treatment for high-grade serous ovarian cancer, roughly 20% of patients fail to respond to platinum-based chemotherapy. However, there is a paucity of biomarkers which correlate to platinum resistance. Effective biomarkers would allow for individualized risk profiling and early identification of patients who may benefit from treatment escalation. Quantitative pathologic biomarkers have shown prognostic utility in several cancers and offer a potential low-cost approach to address challenges in assessing platinum resistance. We examined the utility of machine learning (ML)-derived pathologic biomarkers in identifying platinum-resistant ovarian cancer. **Methods:** Our multi-institutional dataset included 158 whole-slide images (WSIs) obtained from resection of primary ovarian cancer, with 86 (54%) in the training cohort and 72 (46%) in the validation cohort. Our dataset included 112 (71%) platinum-sensitive and 46 (29%) platinum-resistant WSIs. The CLAM deep learning framework and CONCH visual-language foundation model were utilized to segment tissue, generate 256 x 256 image patches, and extract 512-dimensional features from each patch. Non-linear dimensionality reduction, employing Uniform Manifold Approximation and Projection (UMAP), was applied to cluster training samples, and validation samples were projected onto the learned low-dimensional space. Samples were stratified into predicted-sensitive and predicted-resistant cohorts based on similarity to training-derived clusters, and clinical characteristics were compared using a two-tailed t-test and chi-square tests. **Results:** UMAP analysis identified distinct phenotypes associated with platinum sensitivity and resistance. At the image level, UMAP-defined phenotypes exhibited high predictive ability. Of the predicted-sensitive images in the validation cohort, 79% showed platinum sensitivity. UMAP-defined phenotypes demonstrated moderate patch-level accuracy in identifying platinum-sensitive samples (training accuracy 69%, validation accuracy 65%). Additionally, clinical correlates to pathology-based predictions were investigated. Predicted-resistant patients were significantly older (median age, 69 years [IQR 59.5–76.26] vs. 62 years [IQR 55–68], p = .021) and more frequently higher-staged (IIIC/IV 89% vs. 77%, p = .087) compared to predicted-sensitive patients. **Conclusions:** ML-derived pathologic biomarkers can aid in the identification of platinum-resistant ovarian cancer. Our future work will evaluate the relationship between quantitative biomarkers and known clinical predictors of platinum resistance, such as CA-125 and the extent of residual disease at cytoreduction. Integrating multimodal biomarkers in clinical decision-making practices will allow for improved risk stratification and individualized treatment for patients. Research Sponsor: None.

5521 Poster Session

Income inequality and cervical cancer: A comparative analysis of demographics and healthcare burden of women in the lowest and highest income quartiles. First Author: Dhruvi Dipakkumar Pathak, Government Medical College, Surat, India

Background: Cervical cancer disproportionately affects women of lower socioeconomic status, yet comprehensive data comparing the demographic profiles and comorbidity burden across income strata remain limited. This study examines differences in patient characteristics, comorbidities, and healthcare utilization between women in the lowest and highest income quartiles hospitalized with cervical cancer in the United States. **Methods:** We identified women hospitalized with cervical cancer in the United States between 2016 and 2022 using ICD-10 codes C53.x in the National Inpatient Sample. Patients were classified into the lowest (0–25th percentile) and highest (76th–100th percentile) income quartiles based on median household income for their residential ZIP code. We compared demographic characteristics including age, race, socioeconomic distribution, and clinically relevant comorbidities across the two groups. Healthcare utilization was evaluated by analyzing length of stay and inflation-adjusted mean hospital charges. **Results:** We identified 88,240 women hospitalized with cervical cancer; 69.7% were in the lowest income quartile and 30.3% in the highest. Women in the highest income quartile were older (mean age 55.45 vs. 52.62 years, $p<0.001$) and incurred higher inflation-adjusted hospital charges ($88,955 vs. $76,121, $p<0.001$), though length of stay was comparable (5.64 vs. 5.82 days, p=0.134). Significant racial disparities were evident: the highest income quartile had more White patients (63.2% vs. 46.2%) while the lowest quartile had more Black (29.1% vs. 11.1%) and Hispanic (19.0% vs. 12.2%) patients ($p<0.001$). Women in the lowest income quartile had significantly higher prevalence of smoking (40.2% vs. 31.0%), diabetes (19.8% vs. 13.8%), chronic kidney disease (16.6% vs. 14.0%), obesity (14.4% vs. 11.5%), HIV (2.1% vs. 0.9%), depression (12.1% vs. 10.9%), opioid use disorder (3.1% vs. 1.9%), drug abuse (7.7% vs. 3.5%), and alcohol abuse (2.0% vs. 1.4%) (all $p<0.05$). Conversely, the highest income quartile had higher rates of metastatic cancer (41.8% vs. 38.7%, $p<0.001$). No significant differences were observed in dyslipidemia (17.6% vs. 16.7%, p=0.165), cachexia (4.3% vs. 4.6%, p=0.396), or palliative care utilization (13.0% vs. 13.5%, p=0.413). **Conclusions:** Women in the lowest income quartile comprise the majority of cervical cancer hospitalizations and face disproportionately higher rates of modifiable risk factors and comorbidities. Targeted interventions addressing screening access, preventive care, and comorbidity management in low-income populations are essential to reduce health disparities in cervical cancer. Research Sponsor: None.

5522 Poster Session

Treatment patterns and PD-L1 testing among persistent, recurrent, or metastatic cervical cancer patients in the United States community oncology setting. First Author: Elizabeth A. Szamreta, Merck & Co., Inc., Rahway, NJ

Background: Pembrolizumab was approved for persistent, recurrent, or metastatic cervical cancer (PRM-CC) among patients (pts) with PD-L1 expression in October 2021. This followed its June 2018 approval for PD-L1-positive recurrent, metastatic pts who progressed after chemotherapy. This real-world study aimed to describe treatment patterns and PD-L1 testing patterns among pts with PRM-CC between 2018-2024. **Methods:** Electronic medical record data from The US Oncology Network identified adult PRM-CC pts diagnosed between July 2018 and July 2022 and followed through June 2024. Persistent disease was defined as either absence of a complete response or provider-documented progression within 90 days following the completion of initial CC-related treatment. **Results:** There were 216 PRM-CC pts eligible for the study. Overall, median age was 55 years and median duration of follow-up was 12.8 months. Overall, 56% (n = 121) of PRM-CC pts had documented PD-L1 testing during the study observation period, of which 78% (n = 94) had a positive result and 7% (n = 8) had undocumented result. Among PD-L1 positive pts without metastatic disease at initial diagnosis (n = 121), 41% were tested after PRM-CC diagnosis date and had a median time from diagnosis to PD-L1 testing of 1.4 months, and 11% were tested prior to PRM-CC diagnosis date. PD-L1 testing increased from 54% to 69% after October 2021, yet 43% of PD-L1+ patients did not receive pembrolizumab after 2021. 12% (8/69) of pts who received pembrolizumab did not have documented PD-L1 testing. Pembrolizumab was received by 27 pts in 1L (pre-2021: 16, post-2021: 11) and 26 patients in 2L pre-2021: 17, post-2021: 9). Most patients had metastatic disease (74%, n = 159), of which 60% (n = 95) presented with metastatic disease at initial diagnosis. Concurrent chemoradiation prior to metastatic disease was received by 38% (n = 81) of pts. The majority of pts with metastatic disease received first line (1L) treatment (n = 86%, n = 137) and 28% (N = 45) of pts initiated 2L treatment. During the first regimen of 1L, 96 pts received a platinum+taxane-containing regimen (+bevacizumab, n = 72). **Conclusions:** Between 2018-2024, many PRM-CC pts were not tested for PD-L1 although biomarker-driven treatments were available. Among those tested, almost half of PD-L1 positive patients did not receive standard-of-care therapy. The current treatment landscape provides a valuable opportunity to standardize and enhance PD-L1 testing in order to optimize treatment selection and support personalized care in this population. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

	Overall	Pembrolizumab initiation-Yes	Pembrolizumab initiation-No
PD-L1 Testing	216	69	147
Tested, N(%)	121 (56.0)	61 (88.4)	60 (40.8)
Positive	94 (77.7)	52 (85.2)	42 (70.0)
Negative	19 (15.7)	4 (6.6)	15 (25.0)
No result	8 (6.6)	5 (8.2)	3 (5.0)
Not Tested, N (%)	95 (44.0)	8 (11.6)	87 (59.2)

5523 Poster Session

Radiotherapy use among locally advanced cervical cancer patients (LACC) in the United States community oncology setting. First Author: Elizabeth A. Szamreta, Merck & Co., Inc., Rahway, NJ

Background: Brachytherapy with concurrent chemoradiation +/- pembrolizumab is the current standard of care for LACC. American Society for Radiation Oncology (ASTRO) recommends external beam radiation therapy (EBRT)+brachytherapy, and since 2020 has recommended intensity modulated radiation therapy (IMRT) over other forms of EBRT due to reduced toxicity risk. However, real-world evidence is needed to characterize patient outcomes based on the type of radiation received. **Methods:** Electronic medical record (EMR) data from The US Oncology Network identified adult LACC (FIGO 2018 Stage IB3-IVA) patients (pts) diagnosed between July 2018 – July 2022 and followed through June 2024. Pts were stratified by receipt of IMRT or Volumetric Modulated Arc Therapy (VMAT) and brachytherapy during the observation period. Patient characteristics and provider-documented progression were assessed descriptively. **Results:** This study included 250 LACC pts; 73 (29%) pts received IMRT or VMAT, 177 (71%) pts received other forms of EBRT; and 189 (76%) pts received brachytherapy. Overall, 61 pts (24%) received both IMRT or VMAT and brachytherapy. Among the 148 pts who were diagnosed in 2020 or later, 28% received IMRT or VMAT. Disease progression occurred among 14% of IMRT or VMAT pts and 63% of non IMRT or VMAT patients; progression was similar across brachytherapy and non-brachytherapy patients. **Conclusions:** Advanced radiation techniques such as IMRT or VMAT and brachytherapy are associated with improved outcomes for patients with LACC, yet their combined use only occurs among 1 in 4 LACC patients, which is notably less than clinical trials. These findings present an opportunity to broaden adoption of evidence-based radiation strategies, supporting optimal treatment delivery and improved patient outcomes. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc.

	IMRT or VMAT	non IMRT or VMAT	Brachytherapy	Non-brachytherapy
Patient, N	73	177	189	61
Age (yrs, median)	51	54	51	59
Race (White), N(%)	50 (69)	101 (57)	114 (60)	37 (60)
Race (non-White), N(%)	9 (12)	36 (20)	35 (19)	10 (16)
Race (not documented), N(%)	14 (19)	40 (23)	40 (21)	14 (23)
Stage I-II, N(%)	31 (42)	82 (46)	94 (50)	19 (31)
Stage III, N(%)	23 (32)	65 (37)	64 (34)	24 (39)
Stage IVA, N(%)	6 (8)	10 (6)	11 (6)	5 (8)
Progression, N(%)	24 (14)	46 (63)	55 (29)	15 (25)

5524 Poster Session

Targeting stromal FAK signaling to address chemotherapy and immunotherapy resistance in gastric-type endocervical adenocarcinoma. First Author: Ting Peng, Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China

Background: Gastric-type endocervical adenocarcinoma (GAC) is a rare, HPV-independent cervical cancer subtype with profound resistance to standard chemotherapy and radiotherapy and an exceptionally poor prognosis. Unlike HPV-associated cervical cancers, GAC lacks established molecular targets and effective treatment strategies. Whether patients with GAC can benefit from immunotherapy remains unclear, and the biological mechanisms underlying its intrinsic resistance to both cytotoxic and immune-based therapies are poorly understood. **Methods:** We established an integrated translational platform incorporating patient-derived GAC cell lines, organoids, and matched primary cancer-associated fibroblasts (CAFs). These models were integrated with multi-omics profiling of clinical specimens, including single-cell RNA sequencing of 58 cervical lesions across disease states, together with molecular and functional validation assays, to systematically characterize tumor–stroma interactions and identify actionable therapeutic vulnerabilities. **Results:** Multi-omics analyses revealed that GAC converges on a pancreatic ductal adenocarcinoma–like transcriptional and microenvironmental program characterized by stromal dominance and therapeutic refractoriness. Mechanistically, GAC tumor cells reprogram the tumor microenvironment through secretion of LAMA3, activating a CD44/ITGB1-dependent FAK signaling axis in CAFs. Stromal FAK activation drives extracellular matrix remodeling and endothelial dysfunction, establishing a profoundly immunosuppressive niche marked by impaired antigen presentation and enrichment of tissue-resident $CD8^+$ T cells ($CD8^+ITGA1^+$). This stromal program mechanistically underlies resistance to both chemotherapy and immunotherapy. In patient-derived GAC organoid-based models, FAK inhibition enhanced responses to chemotherapy and immunotherapy in vitro, supporting a translational rationale for FAK-targeted combination strategies. Based on these findings, we initiated a multicenter, phase II clinical trial evaluating the FAK inhibitor IN10018 in combination with nab-paclitaxel and cadonilimab in patients with metastatic, recurrent, or persistent GAC (NCT06654011). **Conclusions:** Gastric-type endocervical adenocarcinoma is a stroma-driven malignancy in which aberrant stromal FAK signaling is a central mediator of resistance to both chemotherapy and immunotherapy. Targeting this stromal dependency provides a compelling therapeutic strategy and directly informs an ongoing phase II clinical trial addressing a critical unmet need in this aggressive disease. Research Sponsor: Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2025ZD0544103; National Natural Science Foundation of China; 82372929.

5525 Poster Session

Retrospective study of guideline concordance in cervical cancer screening surveillance by age, race, and ethnicity. First Author: Maeve Fitzgerald Givens, Weill Cornell Medical College, New York, NY

Background: Nearly one in five new cervical cancer cases occur in individuals aged ≥ 65, with higher incidence among Black women compared to White women. Despite these disparities, evidence guiding screening and surveillance in older women is limited. This study evaluates guideline concordance for follow-up after abnormal cervical cancer screening and examines variation by age, race, and ethnicity. **Methods:** This retrospective cohort study assessed 1,861,906 cervical cancer screening results (2009-2024) from the TrinetX database. Included patients were female, ≥ 21 years old, and had an HPV test or pap smear. Guideline concordance (i.e., colposcopy within one year of high-risk cervical cancer screenings result) was assessed by running logistic regression models by age group, race, and ethnicity. Logistic regression assessed odds of concordant follow-up by age, race, and ethnicity, using women aged 30–39 and non-Hispanic White women as reference groups, respectively. **Results:** Guideline-concordant follow-up varied by age: 56.87% aged 21-29, 58.84% aged 30-39, 56.36% aged 40-49, 53.93% aged 50-65, and 45.80% aged 65+. Compared with women aged 30-39, both younger and older women were significantly less likely to receive guideline concordant follow-up. Women 65+ had 44% lower odds of concordant follow-up (OR= 0.56, 95% CI 0.53 to 0.60, p<.001). Guideline-concordant care also varied by race and ethnicity: 51.11% of non-Hispanic Black, 56.65% of non-Hispanic Asian, 60.36% of non-Hispanic White, 58.43% of non-Hispanic Other, and 51.71% of Hispanic patients. Compared to non-Hispanic White women, all other groups had significantly lower odds of follow-up, with non-Hispanic Black women having 30% lower odds (OR = 0.70, 95% CI 0.68 to 0.72, p<.001) and Hispanic women having 28% lower odds (OR= 0.72, 95% CI 0.71 to 0.74, p<.001) of concordant follow-up. **Conclusions:** Overall, the rate of guideline concordant follow-up after high-risk cervical cancer screening results was low (57.83%) and declined with age, with lowest rates among women ≥ 65 (45.80%). All other age groups had significantly lower odds of concordance than those 30-39, with those 65+ having the lowest odds of concordance. Significant disparities were also observed by race and ethnicity, particularly among non-Hispanic Black and Hispanic women. Further research is needed to assess the decreased surveillance rates after high-risk cervical cancer screening results at the population level and specific attention should be focused on groups who have been under-surveilled. Research Sponsor: None.

5526 Poster Session

Efficacy and safety of cadonilimab (CD) in combination with disitamab vedotin (RC48) or nab-paclitaxel (NP) in the treatment of recurrent or metastatic cervical cancer (r/mCC): A prospective, double-cohort, multi-center, open-label, phase II clinical study. First Author: Min Zheng, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: The prognosis for patients(pts) with r/mCC is poor. The available second-line treatment regimens are limited, highlighting the need for more effective therapies. CD is a dual-target immune checkpoint inhibitor targeting PD-1 and CTLA-4 and RC48 is an antibody-drug conjugate targeting HER2. Here, we report updated results from a phase II study of CD plus RC48 or NP in r/mCC. **Methods:** This is a prospective, multicenter, open-label, phase II trial with two parallel cohorts(AK001). Eligible patients had r/mCC with progression after 1-3 prior lines of chemotherapy. Patients were assigned by HER2 immunohistochemistry (IHC): cohort I (HER2 IHC 1+ - 3+) received CD (6mg/kg) plus RC48 (2.5mg/kg) biweekly; cohort II (HER2 IHC 0) received CD (10mg/kg) plus NP (260mg/m^2) triweekly. The primary endpoint of the study was objective response rate (ORR). Key secondary endpoints included duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety. A Simon's two-stage design was applied, with the ORR from the innovaTV 204 study as a historical control, which was 24%. Assuming the ORR for cohort I is 50% and for cohort II is 40%, with a power of 0.8 and a one-sided α of 0.05, and considering a dropout rate of 10%, the total sample size calculated was 32 for cohort I and 42 for cohort II. **Results:** As of the data cutoff (January 15, 2026), 62 pts were enrolled, including 53 evaluable pts (26 in cohort I and 27 in cohort II) across 5 large academic centers in China. Median follow-up was 12.03 months (range, 1.87 - 26.57). For cohort I, the ORR was 57.7% (95% CI, 36.9% - 76.6%) and median DOR was not reached (95% CI, 3.97 - NR). Median PFS was 8.23 (95% CI, 3.41 - 13.06) months and 12-month PFS rate was 45%. For cohort II, the ORR was 55.6% (95% CI, 35.3% - 74.5%) and median DOR was 4.57 (95% CI, 2.30 - 6.83) months. Median PFS was 5.87 (95% CI, 4.55 - 7.19) months and 12-month PFS rate was 38%. Toxicity was tolerable in both cohorts. Grade 3-4 treatment-related adverse events occurred in 15.4% of pts in cohort I and 21.4% of pts in cohort II. **Conclusions:** Our current results support a potential HER2 expression-guided option for second-line treatment of r/mCC. CD plus RC48 demonstrated favorable efficacy and a manageable safety profile, and may emerge as a novel effective combination for the treatment of HER2 positive cervical cancer. Long-term benefits and further analysis of the role of this combination therapy in r/mCC will be critical to advancing treatment strategies. Clinical trial information: ChiCTR2300076740. Research Sponsor: Akeso Biopharma; RemeGen Co, Ltd.

Antitumor activity assessed by RECIST version 1.1.

	Cohort I (n=26)	Cohort II (n=27)
ORR	15(57.7%)	15(55.6%)
95%CI	36.9 - 76.6	35.3 - 74.5
DCR	24(92.3%)	20(74.1%)
95%CI	74.9 - 99.1	53.7 - 88.9
Best Overall Response		
CR	3(11.5%)	0
PR	12(46.2%)	15(55.6%)
SD	9(34.6%)	5(18.5%)
PD	2(7.7%)	7(25.9%)

5527 Poster Session

Impact of adjuvant sequential chemoradiotherapy on long-term overall survival in early-stage cervical cancer: Final analysis of the STARS phase III randomized trial. First Author: He Huang, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: The STARS trial (NCT00806117) previously demonstrated that adjuvant sequential chemoradiotherapy (SCRT) significantly improved disease-free survival (DFS) compared with radiotherapy (RT) or concurrent chemoradiotherapy (CCRT) in early-stage cervical cancer patients with pathological risk factors. This pre-specified analysis reports the mature overall survival (OS) results. **Methods:** In this open-label, phase III trial, 1,048 cervical cancer patients with FIGO stage IB1–IIA2 and postoperative pathological risk factors were randomized (1:1:1) to receive RT alone, CCRT (RT with weekly cisplatin), or SCRT (paclitaxel-cisplatin chemotherapy before and after RT). The second endpoint was OS, analyzed by intention-to-treat. Subgroup analyses were performed based on risk stratification: intermediate-risk (deep stromal invasion or lymphovascular space invasion) and high-risk (node-positive or parametrial involvement). **Results:** With a median follow-up of 90 months, SCRT significantly improved OS compared to both RT (10-year OS 89.0% vs 81.0%; HR 0.54, 95% CI 0.35-0.83; P=0.005) and CCRT (89.0% vs 83.0%; HR 0.64, 0.41-0.98; P=0.040) in intention to treat population. No significant difference was observed in OS between CCRT and RT (HR 0.85, 0.58-1.24; P=0.404). The survival benefit of SCRT was consistent across key subgroups: it was most pronounced in intermediate-risk patients (HR 0.54 vs RT, 95% CI 0.31-0.93; P=0.027) and showed a clinically meaningful trend in high-risk patients (HR 0.61, 95% CI 0.30-1.24). However, CCRT showed no overall benefit in these risk-based populations but was markedly effective in the subgroup with deep stromal invasion without lymphovascular invasion (HR 0.20 vs RT, 95% CI 0.05-0.85; P=0.029) in per-protocol population. SCRT achieved higher protocol completion than CCRT (73.4% vs 62.3%) and was an independent favorable prognostic factor for OS (HR 0.54) in multivariable analysis, along with lymph node metastasis and adenocarcinoma histology. **Conclusions:** The long-term STARS trial update confirms adjuvant SCRT as the optimal strategy, demonstrating both DFS and OS superiority in early-stage cervical cancer with postoperative risk factors. The significant 10-year survival benefit strongly supports adopting SCRT where radiotherapy access is limited. Clinical trial information: NCT00806117. Research Sponsor: Sun Yat-sen University Clinical Research 5010 Program (Number 2007041).

5528 Poster Session

Impact of para-aortic lymphadenectomy on prognosis and quality of life in preoperative IB2-IIA2 cervical cancer: A multi-center cohort study. First Author: Xinqu Qu, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

Background: The indication of para-aortic lymphadenectomy (PALD) in preoperative IB2-IIA2 (FIGO 2018) cervical cancer remains unclear. We aimed to access the impact of PALD on the prognosis and life quality in preoperative IB2-IIA2 cervical cancer patients. **Methods:** This cohort study, a target trial emulation, was conducted at the Obstetrics and Gynecology Hospital of Fudan University, including cervical cancer patients with a preoperative stage of IB2-IIA2 from 2019 to 2023 (clinical trial ChiCTR2400092255). Propensity score matching at a 1:1 ratio (PALD versus non-PALD) was applied to balance baseline characteristics. Primary outcomes were progression-free survival (PFS), overall survival (OS), and cancer-specific survival (CSS). Secondary outcomes included perioperative complications and adverse events (AEs). Kaplan-Meier and subgroup analyses were conducted, and Cox proportional hazard models were established. External validation was performed at another three tertiary hospitals in China. **Results:** Of the 2609 patients included, 683 (26.2%) underwent PALD during radical surgery. Propensity score matching yielded a cohort of 1250 patients with balanced covariates. Patients who underwent PALD demonstrated similar PFS (hazard ratio 1.27; 95% CI, 0.89-1.80; P=0.188), OS (hazard ratio 1.17; 95% CI, 0.71-1.93; P=0.544), and CSS (hazard ratio 1.20; 95% CI, 0.70-2.06; P=0.512) as those who did not. Additionally, no significant differences were detected in survival associated with receiving PALD among subgroups defined by lymph node status based on preoperative imaging, the para-aortic lymph node (PALN) metastasis prediction model, and other postoperative pathological risk factors. External validation drew consistent conclusions regarding the effect of PALD on survival. Moreover, the PALD group compared with non-PALD group showed more intraoperative hemorrhage (P=0.005), longer operation time (P=0.004), and a higher tendency for chylous fistula (P=0.077). **Conclusions:** PALD, compared with non-PALD, was not associated with survival benefits for IB2-IIA2 cervical cancer patients yet was associated with increased surgical complications. Research Sponsor: None.

5529 **Poster Session**

Azenosertib plus paclitaxel for platinum-resistant ovarian cancer: Results from a phase 1b study. First Author: Meena Okera, Cancer Research SA, Adelaide, SA, Australia

Background: Most patients (pts) with ovarian cancer develop platinum-resistant disease following surgery and platinum-based chemotherapy and have a poor prognosis. Paclitaxel (PAC) monotherapy is the most efficacious chemotherapy for platinum-resistant ovarian cancer (PROC) but clinical benefits require further improvement. Azenosertib (Azeno) is a potentially best-in-class, novel, selective and orally bioavailable small molecule inhibitor of the WEE1 tyrosine kinase. Herein we report results from a Phase 1b study of Azeno plus PAC for PROC. **Methods:** MUIR (NCT04516447) is an open-label Phase 1b study evaluating the safety, efficacy and preliminary clinical activity of Azeno plus chemotherapy (Part 1 dose escalation) for PROC. Eligible pts were aged ≥18 years, had ECOG PS score ≤2, histologically/cytologically confirmed high-grade serous epithelial ovarian, fallopian tube, or peritoneal carcinoma, and measurable disease per RECIST v1.1; pts had received 1–4 prior lines of systemic therapy and had platinum-resistant disease. Pts were assigned to 1 of 4 cohorts: carboplatin, gemcitabine, pegylated liposomal doxorubicin, or PAC (80 mg/m^2 IV on Days 1, 8 and 15 of 28-day cycles). Azeno plus PAC is the focus of this analysis where Azeno was orally administered 200 mg (continuously) or 200, 250 and 300 mg (intermittently 5 days on, 2 days off [5:2]) for 28-day cycles. Primary objectives were safety and tolerability. Clinical activity was a key secondary objective assessed by objective response rate (ORR) and duration of response (DOR) per RECIST v1.1, and progression-free survival. Exploratory objectives included analysis of baseline tumor and plasma biomarkers with optional biopsies/blood plasma. **Results:** As of December 1, 2025, 46 pts received Azeno (continuously 200 mg, n=7 and intermittently 5:2: 200 mg, n=15; 250 mg, n=12; 300 mg, n=12) plus PAC. Median age was 66 years (range 45–83), median number of prior lines of therapy was 2 (range, 1–4), and all pts received prior PAC. Most common treatment related adverse events (TRAEs) were fatigue (61%), anemia (59%), nausea (52%), and neutropenia (50%); most frequent grade ≥3 TRAEs were neutropenia (30%) and anemia (20%). Serious TRAEs occurred in 20% of pts. Overall, confirmed ORR was 39.1% (95% CI, 25.1–54.6) with a median DOR of 5.6 months (95% CI, 5.6–9.2) (Table). **Conclusions:** Azeno plus PAC showed promising clinical activity and tolerability in pts with PROC. ORR and median DOR were improved when compared historically with PAC monotherapy supporting the continued evaluation of this regimen in PROC and other indications. Clinical trial information: NCT04516447. Research Sponsor: Zentalis.

OR and median DOR.

	Azeno 200 mg + PAC (n=7)	Azeno 5:2 200 mg + PAC (n=15)	Azeno 5:2 250 mg + PAC (n=12)	Azeno 5:2 300 mg + PAC (n=12)	All(N=46)
ORR, % (95% CI)	57.1 (18.4–90.1)	20.0 (4.3–48.1)	50.0 (21.1–78.9)	41.7 (15.2–72.3)	39.1 (25.1–54.6)
Median DOR, months (95% CI)	7.8 (5.6–NE)	5.6 (3.7–NE)	9.2 (3.8–NE)	5.6 (5.2–NE)	5.6 (5.6–9.2)

NE, not evaluable.

5530 **Poster Session**

Global disparities in current clinical trials in cervical cancer. First Author: Sneha Ahuja, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cervical cancer is one of the most disproportionately distributed cancers worldwide, with highest incidence and mortality rates occurring in low- and middle-income countries (LMICs). Although clinical trials provide the crucial foundation for the development of standards of care, oncology research is disproportionately concentrated in high-income settings. **Methods:** We assessed the current global landscape of cervical cancer clinical trials to determine whether trial activity aligns with disease burden and to characterize various disparities in trial representation. Interventional phase II and III cervical cancer clinical trials registered on ClinicalTrials.gov between January 1, 2014, and December 31, 2025, were identified. Trials were further categorized by intervention class, patient population, funding source, and location. Representation of trials in relation to disease burden for cervical cancer was determined using trial-to-age-standardized incidence rate (ASIR) from Global Cancer Observatory estimates. Countries were classified by World Bank Income Level and disease burden, where high burden countries had an ASIR above the global ASIR of 14.1. Non-parametric statistical tests were used to compare trial-to-ASIR ratios across groups. **Results:** A total of 269 eligible trials were included. Most studies were phase II (62.5%) and evaluated systemic or combination therapies (83.6%). The majority of trials were institutionally funded (55.0%), with industry sponsorship accounting for 33.5% of studies. Clinical trial activity was concentrated in a small number of countries, with single-country trials conducted predominantly in China (60.2%) and the United States (13.0%), while multinational trials were largely conducted in high-income countries. When adjusted for disease burden, most high-burden countries had few or no trials relative to incidence, resulting in significantly lower trials per ASIR compared with non–high-burden countries ($P < .001$). Significant disparities were also observed across income groups, with high-income countries demonstrating substantially higher trial-to-ASIR ratios than lower-income countries ($P < .001$). **Conclusions:** The global distribution of cervical cancer clinical trials remains misaligned with disease burden, with high-burden and lower-income countries underrepresented in research participation. Funding patterns and trial sponsorship may further influence where trials are conducted. Addressing these disparities will be essential to ensure equitable evidence generation and improve global cervical cancer care. Research Sponsor: None.

5531 **Poster Session**

Genomic landscape and patient demographics in endocervical adenocarcinoma: Insights from the AACR Project GENIE. First Author: Rechuma Hafter, Hunter College CUNY, New York, NY

Background: Endocervical Adenocarcinoma (EA) makes up 20-25% of cases of cervical cancer, and has an 80-90% association with HPV infection.Treatment outcomes of EA have significant disparities: cases of EA arising from HPV have a much higher survival rate than survival rate for non-HPV-related EA. While survival outcomes with modern treatments such as radical hysterectomy are positive for HPV associated cases, increasing frequency of diagnosis and treatment heterogeneity, along with variability in diagnostic timing emphasize the need to define molecular drivers for targeted therapies. Using the AACR GENIE database, this study characterizes EA's mutational landscape to identify genetic markers and therapeutic targets. **Methods:** The American Association for Cancer Research Project Genomics Evidence Neoplasia Information Exchange database was accessed using cBioPortal (v18.0-public) on November 29, 2025 to identify all patients with EA. The most common somatic point mutations, demographic correlations, and mutual exclusivities were analyzed using a two-sided T-test and non-parametric tests, with Benjamini-Hochberg false discovery rate correction. **Results:** This study included 257 samples from 245 patients. The patient cohort was 61.2% non-Hispanic and 13.9% Hispanic. The cohort was 10.2% Asian, 61.2% White, 4.1% Black, and 12.2% unknown/other patients. A majority of the samples used were obtained from primary tumors (60.3%), while 80 (31.1%) were from metastatic tumors. The most common mutations were identified in PIK3CA (n=68; 26.4%), TP53 (n=51; 19.8%), KRAS (n=41; 15.9%), SMAD4 (n=37; 14.4%), ERBB2 (n=35; 13.6%), ARID1A (n=32; 12.4%), KMT2D (n=26; 10.1%), GNAS (n = 26; 10.1%), ERBB3 (n = 23; 8.9%), KMT2C (n = 21; 8.1%), STK11 (n = 20; 7.8%), MED12 (n = 18; 7.0%), and ATM (n = 17; 6.6%). Several mutations were uniquely observed in Black patients, HFE,RAD54B, ADAMTS20, ADGRB3, and BCL3, with n = 1 for each observed mutation. Among exclusively primary tumor samples, the HSD3B2 mutation was identified (n = 1). RXRA ($p < 0.05$), TBX3, and TET1 ($p > 0.05$) mutations with n = 3 each were exclusively observed in the metastatic samples. Frequencies of recurrent alterations in key genes such as KRAS (15.2%) and PRKDC (7.5%), showed substantial overlap and no significant differences between the groups. No significant mutual exclusivity patterns were identified among profiled genes. **Conclusions:** To the best of our knowledge, this is the first GENIE database analysis of EA, addressing a significant knowledge gap regarding its genomic landscape. These findings suggest PIK3CA and TP53 as targets for targeted inhibitors or immunomodulators. Further research is warranted to validate these genomic associations and translate them into precision medicine therapeutics for patients with endocervical adenocarcinoma. Research Sponsor: None.

5532 **Poster Session**

GT101 autologous TIL therapy in patients with recurrent and metastatic cervical cancer: A phase 1 study. First Author: Pin Wang, University of Southern California, Los Angeles, CA

Background: Adoptive cell therapy with autologous TILs has shown durable clinical benefit in selected advanced solid tumors after progression on standard therapies. We report results from a phase I, open-label, single-arm, multicenter trial (NCT05430373) evaluating GT101 in patients with recurrent or metastatic cervical cancer. Primary objectives were safety; second objectives included preliminary efficacy and PK. **Methods:** Eleven patients with recurrent or metastatic cervical cancer received a lymphodepletion regimen followed by GT101 infusion and high-dose IL-2. The primary endpoint was safety, including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and adverse events (AEs), graded per CTCAE v5.0. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), duration of response (DoR), and overall survival (OS), assessed by RECIST v1.1. Flow cytometry of immune cells and T cell receptor (TCR) sequencing were performed on peripheral blood samples collected from patients before and after treatment. **Results:** As of September, 2025, 11 patients were treated (median age was 48 years; median two prior lines of therapy). Following FC lymphodepletion, patients received GT101 at doses ≥5×10^9 viable cells (median 4.1×10^{10}), followed by high-dose IL-2 (600,000 IU/kg, up to 6 doses). Most AEs were Grade 1-2. Grade ≥3 AEs were primarily related to lymphodepletion and IL-2, and included lymphopenia, leukopenia, neutropenia, anemia, pyrexia, and thrombocytopenia; most resolved or improved to Grade ≤2 within 14 days. The ORR was 45.5% (5/11), with DCR of 90.9% (10/11). Median DoR was 6.4 month. Four patients (36.4%) achieved confirmed PR, one patient (9.1%) achieved a CR, and five patients (45.5%) had stable disease (SD). Median PFS was 4.83 months; OS follow-up is ongoing. One patient with stage IIIC2 cervical squamous cell carcinoma achieved a confirmed CR lasting 14.5 months, with tumor burden reduced from a baseline sum of diameters of 71.57 mm to complete resolution by Week 12. Pharmacokinetics and Correlation Analyses: Peripheral blood analyses demonstrated peak circulating T cells 5-7 days post-infusion, followed by contraction to near-baseline by two weeks. Responders exhibited lower proportions of $CD39^+PD\text{-}1^+$ T cells. TIL infusion increased T-cell clonal diversity in all patients, with greater expansion observed in non-responders who has lower baseline diversity; persistence of TIL-derived clones did not differ consistently between groups. **Conclusions:** GT101 demonstrated a manageable safety profile with no treatment-related SAEs or dose-limiting toxicities and showed clinically meaningful and durable antitumor activity in recurrent or metastatic cervical cancer. These findings support further clinical development, and a pivotal phase II study is ongoing. Clinical trial information: NCT05430373. Research Sponsor: None.

5533 **Poster Session**

Neoadjuvant chemotherapy and individualized de-escalation surgery for fertility preservation in stage IB1-IIA2 cervical cancer: A multicenter prospective study (FIND study). First Author: Yanling Feng, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

Background: Radical trachelectomy (RT) has long been the standard fertility-sparing surgery (FSS) for early-stage cervical cancer (most validated for tumor<2cm), produced satisfied oncologic outcomes but adverse pregnancy outcomes. Neoadjuvant chemotherapy (NACT) offers a potential pathway for tumor downstaging, which may further expand the population eligible for FSS. Based on this, this study aimed to evaluate the oncologic and reproductive outcomes of an individualized, NACT-based fertility-preserving strategy in patients with early-stage cervical cancer (FIGO 2018 IB1–IIA2) (CSEM009, NCT02624531). **Methods:** This prospective, non-randomized clinical study enrolled patients aged 18–40 years with pathologically confirmed stage IB1–IIA2 squamous, adenocarcinoma, or adenosquamous carcinoma and a strong desire for fertility preservation. All patients underwent pretreatment pelvic MRI. Patients with a baseline tumor diameter <1 cm proceeded directly to simple trachelectomy (ST). Those with tumors ≥1 cm received 2–3 cycles of platinum-based NACT. Individualized surgery was performed based on Post-NACT MRI: cervical conization (CON) for complete response, ST for residual disease ≤2 cm, and RT for residual disease 2–4 cm. Lymph node assessment involved sentinel lymph node biopsy (SLNB) or systematic lymphadenectomy. Primary endpoints were 5-year overall survival (OS), 5-year progression free survival (PFS), and reproductive outcomes. **Results:** From June 2015 to June 2023, 99 eligible patients were enrolled. Among them, 84 received NACT, and 80 ultimately underwent FSS. Median follow-up duration was 67 months (range: 7–122). For the entire cohort of 99 patients, 5-year PFS and OS were 88.9% and 93.9%, respectively. In the FSS group (n=80), 5-year PFS and OS were 91.3% and 96.3%. In FSS patients, univariate analysis identified lymphovascular space invasion (LVSI) as significantly associated with recurrence and mortality ($p<0.05$). Patients with initial tumors ≤2 cm (n=42), 2–4 cm (n=29), and ≥4 cm (n=9) had 5-year PFS rates of 95.2%, 86.2%, and 88.9%, and 5-year OS rates of 97.6%, 93.1%, and 100%, respectively. Nineteen patients failed to undergo FSS with 5-year PFS 78.9% and 5-year OS 84.2%. Of 40 FSS patients attempting pregnancy, 19 (47.5%) achieved at least one pregnancy, resulting in 17 cumulative deliveries: 3 after conization and 14 after ST. No successful pregnancies occurred after RT. **Conclusions:** This prospective study demonstrates that fertility-sparing strategy involving NACT and individual less radical FSS provides favorable long-term oncologic safety and meaningful reproductive potential in patients with FIGO 2018 IB1-IIA2 cervical cancer. Clinical trial information: NCT02624531. Research Sponsor: None.

5534 **Poster Session**

Quality of life outcomes following hypofractionated radiotherapy in locally advanced cervical cancer. First Author: David Francisco Cantu De Leon, Instituto Nacional de Cancerología, Mexico, DF, Mexico

Background: Cervical cancer remains a significant global health burden, particularly in low- and middle-income countries where access to radiotherapy is often limited. While concurrent chemoradiotherapy is the standard of care, hypofractionated radiotherapy has emerged as a potential strategy to improve treatment efficiency without compromising outcomes. Our purpose was to assess the impact of hypofractionated radiotherapy on quality of life in comparison with conventional fractionation in patients with locally advanced cervical cancer. **Methods:** Health-related quality of life was evaluated using EORTC QLQ-C30 and QLQ-CX24 questionnaires in patients with FIGO stage IB3–IIIC1 cervical cancer enrolled in a phase II randomized trial. All patients received concurrent chemotherapy and were assigned to either standard external-beam radiotherapy (50 Gy in 25 fractions) or hypofractionated radiotherapy (37.5 Gy in 15 fractions), followed by radical hysterectomy with bilateral pelvic lymphadenectomy. QoL scores were calculated using standard EORTC methodology. Higher scores indicate better functioning or greater symptom burden, and changes were interpreted based on established thresholds for clinical relevance. Outcomes were compared between groups across predefined time points using ANOVA. Statistical significance was defined as $p < 0.05$. **Results:** A total of 91 patients were included (49 standard fractionation, 42 hypofractionation). No significant differences in global QoL were observed between treatment groups. However, QoL varied significantly over time, with the greatest deterioration occurring between completion of concomitant chemoradiotherapy and surgery. Quality-of-life scores recovered to baseline levels by three months after treatment completion in both groups. **Conclusions:** Hypofractionated radiotherapy was not associated with worse quality-of-life outcomes compared with conventional fractionation. These findings support hypofractionation as a feasible alternative for locally advanced cervical cancer, particularly in resource-limited settings. Further studies with larger cohorts and longer follow-up are warranted to confirm these results. Clinical trial information: NCT03750539. Research Sponsor: None.

Comparison of key health-related quality-of-life domains by treatment arm.

Domain	BaselineStd*/ Hypo&	End QT/RTStd / Hypo	Post-SurgeryStd / Hypo	3 MonthsStd / Hypo	p value
Global Health Status / QoL	66.9 (23.7) / 65.8 (21.0)	65.7 (20.7) / 64.6 (17.0)	70.5 (18.5) / 64.0 (18.3)	79.1 (12.5) / 74.4 (21.7)	0.497
Physical Functioning	81.6 (19.7) / 88.0 (14.6)	80.2 (18.6) / 82.2 (20.8)	75.2 (20.5) / 79.0 (17.5)	86.4 (19.4) / 86.8 (13.6)	0.216
Nausea and Vomiting	87.1 (21.2) / 83.8 (27.8)	72.4 (30.5) / 67.2 (28.5)	82.6 (23.3) / 88.3 (21.0)	94.8 (10.2) / 91.1 (16.8)	0.001
Diarrhea	90.1 (15.5) / 86.6 (28.5)	77.7 (20.6) / 67.7 (28.3)	81.4 (21.3) / 84.4 (25.8)	92.5 (14.1) / 91.1 (14.9)	0.001

Mean (SD) scores using EORTC QLQ-C30 and CX-24.

5535 **Poster Session**

Trends in rural-urban disparities in U.S. cervical cancer mortality before and after the HPV vaccine introduction: A CDC analysis, 1999-2023. First Author: Jasvindar Kumar, Bassett Medical Center/Bassett Healthcare Network, Cooperstown, NY

Background: Cervical cancer mortality has declined in the United States following the introduction of HPV vaccination. However, disparities by urbanization, geography, and race may persist. Rural women remain up to 40% more likely to die from cervical cancer. Understanding rural–urban trends is essential to guiding equitable prevention strategies. **Methods:** CDC WONDER mortality data for females ≥15years with cervical cancer (ICD-10 C53) were analyzed. Age-adjusted mortality rates (AAMR) per 100,000 population were analyzed. Urbanization data were available till 2020 and were used for urban–rural stratification (NCHS classification). Temporal trends were assessed using joint point regression to determine average annual percent change (AAPC). **Results:** Between 1999 and 2023, 102,205 cervical cancer deaths were identified. The overall AAMR declined from 1.52 to 1.28 during the pre-vaccine era (1999–2005; AAPC = −2.95%, 95% CI −4.0 to −1.8) and further to 1.09 during the post-vaccine era (2006–2023; AAPC = −0.86%, 95% CI −1.0 to −0.7). Rural-urban mortality (AAMR) ratio increased in post-vaccine era from 1.13 vs 1.15 with 1.47% increase in disparity. By urbanization, declines were greatest in central metropolitan areas (AAMR 1.72 to 1.48 pre-vaccine; 1.14 post-vaccine; AAPC = −1.40%, 95% CI −1.6 to −1.2), while small metro (1.36 to 1.29 pre-vaccine; 1.11 post-vaccine; AAPC = −0.93%, 95% CI −1.2 to −0.6) and micropolitan areas (1.70 to 1.44 pre-vaccine; 1.32 post-vaccine; AAPC = −0.34%, 95% CI −1.3 to 0.6) showed slower improvement which widened mortality gap. Subgroup analyses showed the steepest mortality declines among women aged ≥75 years (AAPC = −3.66%), among Black women (AAPC = −2.81%), and in the Northeast region (AAPC = −2.16%). **Conclusions:** U.S. cervical cancer mortality declined after the HPV vaccine introduction; however, rural–urban, racial, and regional disparities persisted. Declines were slower in small metropolitan and nonmetropolitan areas and highest among Black individuals, underscoring the need for targeted vaccination, screening efforts and access-to-care. Research Sponsor: None.

5537 **Poster Session**

HPV-stratified tissue factor expression and multi-omic correlates of overall survival after tisotumab vedotin in cervical cancer. First Author: Shaina Bruce, Penn State Health, Hershey, PA

Background: Cervical cancer (CxC) is heterogeneous, and the impact of HPV status on outcomes with tisotumab vedotin (TV; tissue factor [TF/F3]–targeted ADC) remains incompletely defined. We evaluated HPV-stratified associations between TF expression and real-world overall survival (OS) after TV and explored molecular correlates of long vs short survival. **Methods:** 274 CxC patients who received TV (HPV+, n=106; HPV-, n=45) underwent DNA and RNA sequencing. HPV16/18/31/33/45 status was determined from whole exome sequencing (WES). Real-world OS was calculated from first TV claim to death/last contact. Hazard ratio (HR) was estimated by Cox proportional hazards, with p-value using log-rank test. TFH was defined as TF (F3) expression (RNA-seq normalized expression) ≥ the cohort-specific median (median split) among TV-treated cases with available data. For transcriptomic comparisons, LS (long survival) and SS (short survival) were defined as above-median vs below-median OS after TV within each HPV stratum, respectively. **Results:** Among TV-treated patients with available TF/OS data, TFH vs TFL showed no statistically significant OS difference in the overall cohort (n=195; TFH n=98 vs TFL n=97; median OS 11.73 vs 9.79 months; HR 0.765; log-rank p=0.142) or in the HPV+ cohort (n=69; TFH n=35 vs TFL n=34; median OS 10.22 vs 10.35 months; HR 0.602; log-rank p=0.138). In contrast, in the HPV− cohort (n=27; TFH n=14 vs TFL n=13), TFH was associated with improved OS (median OS 21.81 vs 9.79 months; HR 0.251, 95% CI 0.065–0.977; log-rank p=0.032). Transcriptomic profiling suggested HPV-dependent survival: in HPV− patients, LS was enriched for cell-cycle/DDR, and energy metabolism pathways (e.g., p53 pathway NES 1.86; FDR-adjusted $p<0.0001$), whereas in HPV+ patients, SS was enriched for inflammatory pathways (e.g., interferon-γ response NES −2.25; FDR-adjusted $p<0.0001$; TNF–NFκB) and LS for tumor-intrinsic metabolic/drug-handling and coagulation-related pathways (e.g., Xenobiotic metabolism, NES 2.13, FDR-adjusted p=0.0021; Coagulation). In the HPV+ cohort, exploratory genomic correlates of survival included enrichment of ARID1A pathogenic mutations (3/18, 16.7% LS vs 0/41, 0% SS; p=0.0073) and AKT2 amplifications (2/17, 11.8% LS vs 0/39, 0% SS; p=0.0292), consistent with tumor-intrinsic pathway alterations in LS. **Conclusions:** TF expression and HPV status may interact in TV-treated cervical cancer. While TFH was not associated with OS in the overall or HPV+ cohorts, TFH was associated with improved OS in HPV− disease. HPV-stratified transcriptomic analyses further suggest distinct biological contexts of benefit and lack thereof, supporting the need to HPV-stratified biomarker analyses for evaluating TV benefit in CxC, potentially extending to other ADCs, and motivating validation in independent datasets. Research Sponsor: None.

5538 **Poster Session**

The impact of re-adoption of open radical hysterectomy on postoperative outcomes in the United States: An interrupted time series analysis. First Author: Alex Ede Rosenthal Powers, Massachusetts General Hospital, Boston, MA

Background: The Laparoscopic Approach to Cervical Cancer (LACC) trial, published in 2018, demonstrated inferior disease-free and overall survival outcomes with minimally invasive radical hysterectomy compared to open surgery for cervical cancer, establishing open radical hysterectomy (ORH) as the standard of care. This study evaluates the impact of the rapid adoption of ORH after publication of the LACC trial on postoperative outcomes. **Methods:** We categorized 2013-2017 as the *pre*-LACC period, 2019-2022 as the *post*-LACC period, and 2018 as the washout period. We included patients who underwent radical hysterectomy for cervical cancer in a Commission on Cancer-accredited program with the highest utilization of ORH (top quartile, $>$ 83%) in the post-LACC period. We fit linear probability models with cluster-robust standard errors to estimate the causal association between ORH adoption, postoperative length of stay, 30-day readmission rates, and 90-day mortality, using pre-LACC trends to estimate a counterfactual outcome for 2019 and comparing these with outcomes from the post-LACC period. **Results:** 2,982 patients were treated in the 107 rapid adopter hospitals. Mean age was 46.5 (SD 12). Most patients were white (67%), followed by Hispanic (14%), and Black (11%). Most patients had grade 1 or 2 (60%) tumors with squamous cell (52%) or adenocarcinoma (40%) histology. Thirty-two percent of patients had positive LVSI and 12% of patients had positive lymph nodes. The proportion or ORH was 45% vs 94% in the pre- vs post-period and ORH utilization was 65 percentage points (p.p.) higher than the estimated 2019 counterfactual ORH utilization. In the pre-period, MIS use increased significantly over time (4.1 p.p. per year, 95% CI 1.9-6.3, $p < 0.001$) while mean length of postoperative stay declined (0.3 days per year, 95% CI 0.1-0.5, $p = 0.003$). Rapid adoption of ORH in 2019 (+65.1 p.p., 95% CI 53.4-76.8, $p < 0.001$) was associated with a 1.7 day (95% CI 1.0-2.5, $p < 0.001$) increase in the duration of postoperative hospitalization, from 1.5 to 3.3 days. There was no significant association with a change in 30-day readmission rates (3.6% pre vs 1.9% post, 1.7 p.p. decrease, 95% CI -5.3 to +1.8, $p = 0.35$). Only 13 patients (0.4%) died within 90 days of surgery over the entire study period, precluding analysis of postoperative mortality. **Conclusions:** Rapid adoption of ORH following the LACC trial was associated with a moderate increase in postoperative length of stay, but no change in 30-day readmission rate. Research Sponsor: None.

5539 **Poster Session**

Optimal adjuvant therapy for early-stage cervical cancer (ESCC) with intermediate-risk factors: A target trial emulation of GOG-0263 based on the NCDB. First Author: Ifeyinwa Ejisoby-Nwosu, Emory University, Atlanta, GA

Background: Optimal adjuvant therapy for early-stage cervical cancer (ESCC) patients with intermediate-risk factors remains uncertain, specifically whether the addition of concurrent chemotherapy (CRT) to radiation therapy (RT) confers a survival benefit. The GOG-0263 randomized phase III trial compared adjuvant RT vs CRT in patients with FIGO Stage I-IIA cervical cancer who had undergone radical hysterectomy. We sought to emulate this trial using real-world data from the National Cancer Database (NCDB) to evaluate the benefit of CRT versus RT on overall survival (OS) in intermediate risk ESCC. **Methods:** Using the NCDB, we conducted a target trial emulation of GOG-0263 for patients diagnosed from 2004-2020 with pathologic T1-T2a2 N0 M0 cervical cancer who underwent radical hysterectomy. Eligible patients had intermediate risk factors, defined as tumor size $\geq$ 2 cm with lymph-vascular invasion (LVI) or tumor size $\geq$ 4 cm. OS, defined from the date of definitive surgery, was compared between patients who received adjuvant RT alone versus adjuvant CRT. Kaplan-Meier methods and Cox proportional hazards models, along with an inverse probability treatment weighting (IPTW) schema, were implemented to assess the treatment effect. Subgroup and sensitivity analyses were conducted to identify specific disease characteristics that maximize the benefit of CRT and to evaluate the impact of potential immortal time bias. **Results:** Among 1,171 eligible patients, 537 (45.9%) received CRT and 634 (54.1%) received RT alone, with median ages of 44 years (IQR: 36-55) and 46 years (IQR: 39-57) and median follow-up times of 7.5 years (IQR: 4.8-10.5) and 6.6 years (IQR: 4.2-9.9), respectively. There was no significant difference in OS between CRT and RT in unadjusted (HR 0.94; 95% CI, 0.71–1.25), adjusted (HR 0.89; 95% CI, 0.67–1.18), or weighted analyses (HR 0.88; 95% CI, 0.66–1.17). Five-year OS was similar between groups (86.4% vs. 86.6%). No subgroup demonstrated a significant survival benefit from CRT. **Conclusions:** In this real-world emulation of GOG-0263, addition of concurrent chemotherapy to adjuvant RT was not associated with improved OS for intermediate-risk ESCC. These findings support emerging trial evidence and supplement the conclusion of the GOG-0263 trial. The indication of this study suggests that chemotherapy may be safely omitted in this population under a doctor's careful discretion, thereby potentially reducing treatment-related toxicity and preserving patients' quality of life without compromising survival. These findings highlight the need for improved risk stratification and patient selection to identify those most likely to benefit from treatment intensification with concurrent chemotherapy in addition to adjuvant RT. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30CA138292.

5540 **Poster Session**

Evaluation of imiquimod treatment outcomes in vulvar melanoma. First Author: Alyssa Osheim, (UT Health Houston) McGovern Medical School, Houston, TX

Background: Vulvar and vaginal melanomas account for approximately 10% of vulvar malignancies and less than 1% of all melanomas. Compared to cutaneous melanoma at other sites, vulvovaginal melanoma is associated with significantly worse outcomes. Wide local excision is the standard treatment for vulvar melanoma, but anatomical challenges and the "field effect" complicate complete resection. The field effect refers to a margin of pre-cancerous intraepithelial cells extending beyond the visible tumor and is thought to contribute to local recurrence. Imiquimod, an immune-modifying cream indicated for genital warts and some types of early keratinocyte carcinomas, is used off-label as an adjunct therapy to prevent marginal recurrence of vulvar melanoma in situ. Its benefit in this setting remains unclear due to limited outcome data, and it is associated with significant side effects. More research is needed to clarify the role of imiquimod and explore alternative therapies. This case series aims to evaluate recurrence and survival outcomes following imiquimod treatment and inform clinical management in this understudied cancer subtype. **Methods:** Patients were identified by two criteria: (1) confirmed vulvar melanoma and (2) treatment with imiquimod. Cases were drawn from a previously published institutional cohort focused on adjuvant radiation therapy in vulvovaginal melanoma and from MD Anderson's electronic medical records. Regional progression-free survival and overall survival were defined as study endpoints. Data included demographics, clinical characteristics, and recurrence and mortality outcomes. Kaplan–Meier analysis compared progression-free and overall survival between patients treated with imiquimod and those who were not. **Results:** Among 124 patients, 19 received imiquimod. The imiquimod group showed a modest improvement in regional progression-free survival, but no significant difference in overall survival (p = 0.1753 and p = 0.2775, respectively). Imiquimod was associated with notable side effects, including burning, itching, and blistering. **Conclusions:** This case series highlights the limited evidence supporting imiquimod as an effective adjunct therapy for vulvar melanoma. Although there was a trend toward delayed regional progression, differences were not statistically significant, and side effects raise concerns about patient quality of life. These findings underscore the need for more effective and tolerable strategies. A systematic review is underway, and multi-institutional efforts aim to expand the dataset. Greater evidence is essential to guide treatment decisions, optimize outcomes, and ensure survivor-centered care in this rare and understudied cancer. Research Sponsor: National Institutes of Health, National Cancer Institute; R25 CA056452.

5541 **Poster Session**

Association of steroid exposure with overall survival and hypersensitivity reaction risk in paclitaxel-treated patients with gynecologic cancers. First Author: Mohammad Harris Jalili, Zuckerberg Cancer Center, Northwell Health, Lake Success, NY

Background: Paclitaxel remains a first-line agent in chemotherapy regimens for gynecologic cancers but is associated with hypersensitivity reactions (HSRs) in up to 40% of patients. Though this risk is largely mitigated by dexamethasone-based premedications, preclinical studies suggest that dexamethasone can induce treatment resistance through enhanced DNA repair capacity, immune suppression, or inhibition of apoptosis, raising concern that pretreatment could compromise paclitaxel efficacy. Furthermore, the effect of cumulative steroid exposure on survival outcomes remains unknown. This study evaluates the impact of cumulative steroid exposure on overall survival (OS) and explores factors associated with HSRs among paclitaxel-treated patients with gynecologic cancers. **Methods:** This IRB-approved retrospective cohort study included patients with gynecologic malignancies treated with paclitaxel-based chemotherapy at the R.J. Zuckerberg Cancer Center, Northwell Health Cancer Institute, New York, between May 2023 and December 2024. Treatment characteristics and outcomes data were analyzed using univariable and multivariable zero-inflated Poisson regression models for HSRs and Cox regression models for OS. **Results:** A total of 163 patients who completed at least three cycles of paclitaxel-based chemotherapy were included. The median age (range, 38-87) was 66 years. Patients were 49% White, 18% Asian, 17% Black, 6% Hispanic, and 11% other or unknown. Cancer types included endometrial cancer (53%), ovarian/peritoneal (42%), cervical (4%), and vaginal (1%). At initial diagnosis, 30% of patients had AJCC stage I disease, 31% stage II-III, 9% stage IV, and 30% had insufficient staging data. Most patients (85%) were newly diagnosed. Twenty one percent of patients developed at least one HSR. Body surface area, race, and prior exposure to paclitaxel were not independently associated with HSRs. In contrast, stage IV disease at diagnosis was associated with a higher rate of HSR compared with stage I disease, with a rate ratio of 2.83 (95% CI 1.01-7.93; p=0.048) after adjustment for key confounders. Cumulative dexamethasone exposure did not impact OS in either univariable or multivariable analyses. **Conclusions:** HSRs occurred in 21% of paclitaxel-treated patients and were independently more common among those with stage IV disease. This suggests that greater disease burden may reflect differences in immune responsiveness that predispose to HSRs. While dexamethasone is commonly used to improve treatment tolerability and reduce the risk of HSRs, cumulative exposure did not impact OS. Further studies are needed to clarify the mechanisms underlying paclitaxel-associated HSR and to define the optimal role of steroid premedication. Research Sponsor: None.

5542 **Poster Session**

Association of post-treatment vaginal structural changes with psychosexual dysfunction in young cervical cancer survivors: Evidence from a low- and middle-income country. First Author: Suriana Sultana, National Institute of Cancer and Research Hospital, Dhaka, Bangladesh

Background: Vaginal stenosis is a known late side effect of pelvic radiotherapy for cervical cancer. In low- and middle-income countries (LMICs), the extent of vaginal changes and their effects on sexual and emotional health are poorly studied due to cultural stigma and limited counseling. This study examined objective vaginal changes and their association with psychosexual distress among young cervical cancer survivors. **Methods:** This cross-sectional mixed-method study included 300 women aged ≤45 years who completed pelvic radiotherapy, with or without surgery and/or brachytherapy, 6–24 months earlier at Delta Hospital and collaborating centers. Participants completed a bilingual interviewer-administered questionnaire on counseling, intimacy, psychosocial distress, and perceived barriers. A standardized clinical examination was used to assess vaginal changes, including vaginal length, elasticity, adhesions, dryness, and dyspareunia, graded using LENT-SOMA and CTCAE v5.0 criteria. Outcomes were compared between women treated with definitive chemoradiation and those who underwent surgery followed by adjuvant radiotherapy ± brachytherapy. **Results:** The mean post-treatment vaginal length was 4.1 ± 1.2 cm. Reduced vaginal elasticity and adhesions were found in 68% of participants. Severe vaginal shortening (≤2 cm) or blind-ending occurred more often in women who received surgery followed by adjuvant radiotherapy and brachytherapy (approximately 40%) compared with those treated with definitive chemoradiation ($p<0.05$). The psychosexual impact was marked: 80% of women reported no return to penetrative intimacy or regular vaginal dilation, and 85% reported loss of sexual interest. The most common barriers were fear of injury or cancer recurrence (72%), pain during intercourse (65%), sociocultural stigma (48%), and partner separation or dysfunction (36%). Although 52% recalled receiving some counseling, only 15% actively discussed sexual health concerns, and fewer than 10% accessed specialized psychosexual care. **Conclusions:** Objective vaginal shortening and fibrosis are strongly linked to psychosexual distress and avoidance of intimacy among young cervical cancer survivors, especially after multimodality treatment. In low- and middle-income countries, unstructured counseling alone is not sufficient. Survivorship care should include regular vaginal assessment and culturally sensitive, partner-inclusive psychosexual counseling. Research Sponsor: None.

5543 **Poster Session**

Real-world outcomes comparing the use of GLP-1 receptor agonists in patients with endometrial cancer and comorbid obesity: A propensity score matched analysis from a global federated health research network. First Author: Yajur Arya, Mayo Clinic Florida, Jacksonville, FL

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used for the treatment of type 2 diabetes and obesity. Emerging evidence suggests that these agents may have potential anti-tumor activity as GLP-1 signaling may influence pathways involved in cell proliferation and inflammation. Endometrial cancer is the most common gynecologic malignancy, and obesity represents a well-established, modifiable risk factor that may adversely affect oncologic outcomes through chronic inflammation and metabolic dysregulation. Our study aims to evaluate the impact of GLP-1 receptor agonists on outcomes among patients with endometrial cancer and comorbid obesity. **Methods:** A retrospective cohort study was conducted using the TriNetX Global Collaborative Network, covering January 2000 to December 2025, encompassing data from 168 global healthcare organizations. Patients aged 18 and above with endometrial cancer and comorbid obesity were identified and then stratified into two groups based on treatment with GLP1 agonists or not. The two groups were then propensity-matched based on age, ethnicity, medical comorbidities, and stage of cancer. Outcomes were assessed for five years from treatment initiation and included overall mortality, myocardial infarction (MI), ischemic stroke; development of peritoneal, lymph node, and visceral metastases; sepsis, pancreatitis, and ED visits. Time-to-event analyses were performed using Kaplan-Meier methods and Cox proportional hazards models. **Results:** After propensity matching, 6352 patients were included in each cohort with balanced baseline characteristics. Our analysis found that patients with endometrial cancer and comorbid obesity who received GLP-1 agonists had a significantly lower risk of overall mortality (Hazard Ratio [HR]: 0.45, 95% CI: 0.39-0.51, p-value <0.001), development of peritoneal metastases (Risk Difference [RD]: -2.16%, 95% CI: -2.74% to -1.58%, p-value <0.001), nodal metastases (RD: -0.41%, 95% CI: -0.72% to -0.09%, p-value =0.01), visceral metastases (RD: -3.76%, 95% CI: -4.60% to -2.93%, p-value =0.01), and sepsis with and without shock (RD: -1.42%, 95% CI: -2.14% to -0.70%, p-value <0.001) compared to patients who did not receive GLP-1 agonists. There was no statistically significant difference in the rates of MI, ischemic stroke, ED visits, and pancreatitis between the two cohorts. **Conclusions:** In this large real-world analysis, patients with endometrial cancer and comorbid obesity who received GLP-1 agonists had lower rates of overall mortality; peritoneal, lymph node, and visceral metastases, and sepsis with or without shock. Additional longitudinal cohort studies are imperative to explore the associations between these agents and inform clinical practice guidelines in this patient population. Research Sponsor: None.

5544 **Poster Session**

A phase 1 dose-escalation and -expansion study of AFN0328, a novel mRNA-based immunotherapy, in patients with HPV16/18-associated high-grade squamous intraepithelial lesions. First Author: Yunxia Cao, First Affiliated Hospital of Anhui Medical University, Hefei, China

Background: Persistent infection with high-risk human papillomavirus (HPV), particularly HPV16 and HPV18, drives the development of high-grade squamous intraepithelial lesions (HSIL), an obligate precancerous condition. The standard care of cervical HSIL requires either surgical excision (LEEP or cold-knife conization), or in some circumstance, watchful waiting. AFN0328 is a novel mRNA-based immunotherapy encoding HPV16/18-related antigens, designed to elicit antigen-specific immune responses and interrupt viral antigen-driven disease progression. **Methods:** Safety, tolerability and preliminary efficacy of AFN0328 were assessed in patients with HPV16- and/or HPV18-associated HSIL (CIN2/3) in an ongoing, multicenter, open-label Phase 1 trial. The study comprised two sequential parts: Part 1 employed a classic 3+3 dose-escalation design to assess safety and determine the maximum tolerated dose (MTD); Part 2 is a dose-expansion cohort at selected doses (150 μg and 300 μg) to further characterize safety, tolerability, and preliminary efficacy. AFN0328 was administered intramuscularly at 0, 4, and 12 weeks. The primary endpoints included safety and tolerability (dose-limiting toxicities within 28 days post-first dose, adverse events graded per CTCAE v5.0). For Part 2, the efficacy endpoints included viral clearance rate at Week 24 and Week 36, and histopathological regression at Week 36. Secondary endpoints included pharmacokinetic parameters, HPV16/18-specific IgG antibody titers, and pharmacodynamic markers (cellular immune responses and serum cytokines). **Results:** As of December 29, 2025, 23 patients had received at least one dose of AFN0328. No DLTs, serious adverse events, or grade ≥3 treatment-related adverse events (TRAE) were observed. PK analyses of first and last doses showed that circulating mRNA encoding HPV-related antigens peaked within 48 hours and declined gradually, with detectable levels persisting for up to at least 4 weeks across dose levels. All evaluable patients developed specific IgG responses and viral clearance was observed in evaluable patients during follow-up. **Conclusions:** AFN0328 demonstrated favorable safety and tolerability with robust immune responses in HPV16/18-associated HSIL, supporting further clinical development as an immunotherapy for HPV-driven precancerous disease. Clinical trial information: CTR20244013. Research Sponsor: None.

Summary of safety and immunogenicity outcomes.

Outcome	Result
Patients treated	23
Dose-limiting toxicities	0
Grade ≥3 treatment-related AEs	0
Most common TRAEs	Injection-site reactions, fever
Specific IgG response rate	100%*
Observed viral clearance	Yes*

*Observed in evaluable patients during interim follow-up.

5545 **Poster Session**

Limb compression therapy and chemotherapy-induced peripheral neuropathy in women with gynecologic cancers: A prospective self-controlled study (NEURO-GLOVE Trial)—Updated long-term analysis. First Author: Kadriye Başkurt, Etlik City Hospital, Department of Medical Oncology, Ankara, Turkey

Background: No established strategy prevents taxane-induced CIPN. We evaluated if dual-site mechanical compression reduces CIPN severity at 3 and 6 months post-treatment. **Methods:** In this prospective, self-controlled study (Dec 2023–Dec 2024), 76 women receiving carboplatin–paclitaxel were enrolled. During infusions, compression was applied to the non-dominant hand (two surgical gloves) and ipsilateral foot (Class II stocking); contralateral limbs served as controls. The primary endpoint was the incidence of Grade ≥2 sensory/motor neuropathy (CTCAE v5.0) at End-of-Treatment (EOT), 3 months, and 6 months. **Results:** Among 76 patients (median age 61), Grade ≥2 CIPN was lower in compression vs control limbs at Cycle 3 (27/76 [35.5%] vs 41/76 [53.9%]; P=.001) and EOT (45/76 [59.2%] vs 53/76 [69.7%]; P=.021). Benefits persisted at 3 months (22/76 [28.9%] vs 40/76 [52.6%]; P=.015) and 6 months (15/74 [20.3%] vs 25/74 [33.8%]; P=.002). Longitudinal analysis showed significant time-by-limb interactions for hand sensory (P=.003), foot sensory (P=.018), and motor domains (P=.041). EORTC QLQ-CIPN20 sensory scores showed high accuracy (AUC 0.92 at Cycle 3; 0.97 at EOT). **Conclusions:** Compression significantly reduces acute and persistent CIPN. Sustained benefits at 3 and 6 months suggest prevention of irreversible damage, supporting compression as an effective neuroprotective strategy. Clinical trial information: NCT07105553. Research Sponsor: None.

Limb-specific incidence of moderate-to-severe chemotherapy-induced peripheral neuropathy by EORTC QLQ–CIPN20 across time.

Time point	Limb	Moderate–severe CIPN†, n/N (%)	Discordant cases ‡, n	McNemar p (compression vs control)	RD %, Control–Compression (95% CI)	P value vs baseline §
Baseline	Compression	0/76 (0.0)	–	–	–	–
	Control	0/76 (0.0)				
Cycle 3	Compression	27/76 (35.5)	Compression only: 2	0.001	+18.4% (4.5 to 32.4)	**<0.001**
	Control	41/76 (53.9)	Control only: 16			**<0.001**
EOT	Compression	45/76 (59.2)	Compression only: 1	0.021	+10.5% (3.5 to 24.5)	**<0.001**
	Control	53/76 (69.7)	Control only: 9			**<0.001**
3-month follow-up	Compression	22/76 (28.9)	Compression only: 2	0.015	+23.7% (10.0 to 37.4	**<0.001**
	Control	40/76 (52.6)	Control only: 20			**<0.001**
6-month follow-up	Compression	15/74** (20.3)	Compression only: 0	0.002	+13.5% (1.5 to 25.4)	**<0.001**
	Control	25/74 (33.8)	Control only: 10			**<0.001**

5546 **Poster Session**

Systemic inflammation and tumor immune microenvironment biomarkers (FOXP3, CD68, CD163) stratified by BRCA/HRD status in high-grade serous ovarian carcinoma: Associations with PFS and OS. First Author: Carolina Ibañez Caceres, Pontificia Universidad Catolica de Chile, Santiago, Región Metropolitana, Chile

Background: Outcomes in high-grade serous ovarian carcinoma (HGSOC) may be influenced by systemic inflammation and the tumor immune microenvironment. We evaluated the prognostic impact of systemic inflammatory markers and intratumoral immune biomarkers, including FOXP3⁺ regulatory T cells and tumor-associated macrophages (CD68 and CD163), in the context of BRCA/HRD status. **Methods:** We conducted a retrospective cohort study of patients with HGSOC with available baseline systemic inflammatory markers and tumor immunohistochemistry. Systemic inflammation was assessed using neutrophil-to-lymphocyte ratio (NLR >3.5) and lactate dehydrogenase (LDH >220). Intratumoral FOXP3, CD68, and CD163 expression was evaluated by immunohistochemistry. BRCA/HRD status was coded as positive versus negative. Progression-free survival (PFS) and overall survival (OS) were analyzed using multivariable Cox proportional hazards models. **Results:** Twenty-nine patients were included, with 27 PFS events and 25 OS events. In multivariable analysis for PFS, elevated systemic inflammation was independently associated with worse outcomes: NLR >3.5 (HR 5.88, 95% CI 1.35–25.54; p=0.018) and LDH >220 (HR 6.70, 95% CI 1.33–33.74; p=0.021). Within the tumor microenvironment, higher intratumoral CD68 was associated with inferior PFS (HR 1.10, 95% CI 1.04–1.17; p=0.001), whereas higher CD163 was associated with improved PFS (HR 0.92, 95% CI 0.87–0.97; p=0.002). BRCA/HRD positivity was not independently associated with PFS. For OS, BRCA/HRD positivity was strongly protective (HR 0.14, 95% CI 0.03–0.60; p=0.008), while NLR >3.5 remained independently associated with worse OS (HR 4.27, 95% CI 1.17–15.68; p=0.028). High FOXP3 expression was associated with improved OS (HR 0.06; p=0.032). CD68 and CD163 showed borderline associations with OS. **Conclusions:** In this HGSOC cohort, baseline systemic inflammation was associated with inferior PFS, and elevated NLR predicted worse OS. Intratumoral immune biomarkers showed distinct prognostic patterns, suggesting that the balance and functional state of myeloid and regulatory immune compartments influence outcomes. BRCA/HRD positivity remained strongly favorable for OS. These findings support further investigation of integrated systemic and tumor immune profiling in larger, prospectively annotated cohorts. Research Sponsor: Fondef 152220002. Centro para la Prevención y el Control del Cáncer, CECAN.

5547 **Poster Session**

Genomic signature–based risk score for PARP inhibitor response in *BRCA*-mutated ovarian cancer: A whole-exome sequencing analysis. First Author: Junhwan Kim, Center for Gynecologic Cancer, National Cancer Center, Goyang-Si, South Korea

Background: To identify whole-exome sequencing (WES)–based genomic signatures associated with response to poly(ADP-ribose) polymerase (PARP) inhibitors and develop a prediction model for PARP inhibitor effectiveness in *BRCA*-mutated advanced ovarian cancer, given the heterogeneous real-world treatment outcomes. **Methods:** This retrospective cohort study included patients with advanced ovarian cancer harboring *BRCA*1/2 mutations who received olaparib or niraparib as first-line maintenance therapy between 2020 and 2022 at the National Cancer Center, South Korea. Among them, patients with at least one year of follow-up from the reference date (August 1, 2024) and sufficient additional tumor samples for WES were identified. Baseline characteristics were collected, and progression-free survival (PFS) and overall survival (OS) from the initiation date of PARP inhibitors were extracted from electronic medical records. Formalin-fixed, paraffin-embedded tumor samples of eligible patients underwent DNA extraction and WES. Prognostic modeling incorporated clinical and genetic variables using Cox proportional hazards regression with the least absolute shrinkage and selection operator (Lasso) method with leave-one-out cross-validation. Model performance was assessed using time-dependent area under the curve (AUC(t)). **Results:** Fifty-five patients were included. The median patient age was 57 years (range, 39–72). High-grade serous carcinoma comprised 96.4%. Neoadjuvant chemotherapy (NACT) was performed in 40.0%. Complete remission after adjuvant chemotherapy occurred in 87.3%. Olaparib was administered in 76.4% and niraparib in 23.6%. NACT-exposed samples had lower Mutant-Allele Tumor Heterogeneity (MATH) scores than non-NACT-exposed samples, indicating reduced intratumor heterogeneity ($P < 0.001$). Recurrence during PARPi maintenance occurred in 11 patients (20.0%) (olaparib: 5/42 [11.9%]; niraparib: 6/13 [46.2%]). No deaths were observed. The median PFS was 37.9 months (range, 4.2–54.5), and the median OS was 43.3 months (range, 20.2–60.1). Mutations significantly associated with progression-free survival included *POLN* (HR, 2.02; 95% CI, 1.12–3.67), *ABCC10* (HR, 4.57; 95% CI, 1.13–18.5), *GTPBP6* (HR, 2.07; 95% CI, 1.04–4.12), and *TCTEX1D1* (HR, 0.19; 95% CI, 0.05–0.82). A genomic risk score model incorporating these mutations stratified patients ino low- and high-risk groups with strong prognostic discrimination for progression-free survival (HR, 4.44; 95% CI, 2.26–8.68; log-rank $P < 0.001$; AUC(t), 0.87). **Conclusions:** The genomic signature-based risk score model independently predicted PARP inhibitor effectiveness. External validation is warranted. Research Sponsor: National Cancer Center, Republic of Korea; NCC2510290-2.

5548 **Poster Session**

ErbB family members as mediators of acquired resistance to immunotherapy in high-grade serous ovarian cancer. First Author: Mengyao Xu, Massa-Massachusetts General Hospital Cancer Center, Boston, MA

Background: Efforts to improve immunotherapy for ovarian cancer (OC) have focused on optimizing T-cell effector-based strategies such as immune checkpoint inhibitors (ICIs), bispecific T-cell engagers (BiTEs), or chimeric antigen receptor (CAR)-T cells, or combining them with other therapeutic modalities. Relatively little is known about how adaptive resistance occurs or how to improve the intrinsic susceptibility of ovarian cancer cells to T cell-mediated cytolysis. **Methods:** An OC organoid derived from a patient who relapsed on immunotherapy (MGH538) was generated. OVCAR3 immune-edited cell line (OVCAR3^{IE}) was generated by treating OVCAR3 wild-type (OVCAR3) tumor-bearing mice with activated T-cells, anti-PD-1, and anti-CTLA4 antibodies. Peritoneal tumors were then harvested and cultured *in vitro*. BiTEs-resistant cell line (OVCAR3^{R}) was generated by treating OVCAR3 cells with anti-MUC16 BiTEs *in vitro* until the cells were resistant. Comparative RNA sequencing analysis was performed on OVCAR3, OVCAR3^{IE}, and OVCAR3^{R}. Protein expression was assessed by Western blot analysis. To evaluate cytotoxicity, OVCAR3, OVCAR3^{IE}, and OVCAR3^{R} were co-cultured with MUC16-specific CAR-T cells and MUC16-directed BiTEs, alone or in combination with pharmacologic inhibitors targeting EGFR, RAS, and Bcl-xL, including a Bcl-xL degrader DT2216. **Results:** MGH538, OVCAR3^{IE} and OVCAR3^{R} were confirmed to be resistant to T-cell directed cytolysis compared to OVCAR3. RNA sequencing analysis revealed significant differences in the transcriptome profiles of immune-naive and immunotherapy-exposed OC cells. In particular, significant changes in the RNA expression levels of three out of four ErbB family members (EGFR (ErbB1), ErbB2 and 3) were detected. In Western blot analysis, this finding was paralleled by significant changes in the ratio of phospho-ERK to ERK, an important component of ErbB downstream signaling. In functional assays, EGFR inhibition with gefitinib significantly enhanced CAR-T cell-mediated killing in OVCAR3, OVCAR3^{IE} and OVCAR3^{R} cells. Furthermore, blocking downstream EGFR signaling with a Ras inhibitor also restored sensitivity to immunotherapy. Finally, blocking anti-apoptotic signaling with Bcl-family inhibitor navitoclax, or the Bcl-xL inhibitor DT2216 restored susceptibility to both CAR-T cell and BiTEs-mediated killing. **Conclusions:** Adaptive resistance to T-cell mediated cytotoxicity appears to be mediated, at least in part, by upregulation of ErbB family members and consequent downstream Ras signaling and resistance to apoptosis. While further functional *in vitro* and therapeutic *in vivo* studies are warranted to investigate the translational potential of our findings, EGFR signaling may represent a promising target for clinical combination strategies. Research Sponsor: None.

5549 **Poster Session**

Development of payload-resistant human ovarian cancer cell lines to better understand antibody-drug conjugate sequencing and resistance mechanisms. First Author: Janina Pearce, Program in Women's Oncology, Department of Obstetrics and Gynecology, Women and Infants Hospital, Brown University, Providence, RI

Background: Within gynecologic oncology, limited data exist regarding mechanisms of resistance to antibody-drug-conjugates (ADC) or the impact on response to future ADC treatment. The purpose of this study was to develop and characterize payload-resistant human ovarian cancer cell lines, and to determine the effect of payload resistance on subsequent ADC exposure. **Methods:** Three commercially available human high grade serous ovarian cancer cell lines (PEA1, PEA2, and OVCAR8) were each exposed separately to three commercially available payloads with corresponding, clinically approved ADCs (deruextecan/trastuzumab deruxetecan, SN38/sacituzumab govitecan, and DM4/mirvetuximab soravtansine). Cell viability assays were performed to confirm and quantify resistance after completion of treatment for payload-resistant cell lines, and western blot analyses performed to evaluate changes in HER2, TROP2, and FOLR1 expression between payload-resistant cells and their controls. Lastly, paired payload-resistant and -sensitive cell lines were then exposed to ADCs with different payloads for 48 hours, and cell viability assays were performed. **Results:** The development of payload-resistant cell lines demonstrates notable variability in timelines for attaining resistance, both across the three cell lines and within individual cell lines across different payload exposures. Compared to payload-sensitive controls, payload-resistant cells displayed similar morphologic changes including increased surface area; however, demonstrated variable differences in HER2, TROP2, and FOLR1 protein expression. Additionally, different payload-resistant cell lines responded differently to subsequent ADC exposure. As a specific example, DM4-resistant PEA1 cells were more sensitive to subsequent exposure to sacituzumab govetecan compared to DM4-senstive controls at various doses ($p < 0.0001$, see Table). **Conclusions:** This study illustrates challenges in developing payload-resistant cell lines, and highlights variability in molecular changes with payload resistance. The data demonstrate subsequent ADC susceptibility in some payload-resistant cell lines, highlighting the complexities of changes that occur with drug treatment. Our data suggests that HGSOC patients that received mirvetuximab soravtansine may be more susceptible to future treatment with sacituzumab govitecan. Future work is underway to expand these findings to determine ideal sequencing of these different ADCs, and to determine other off-target effects that may influence non-ADC treatment response. Research Sponsor: None.

Viability of DM4-resistant versus sensitive PEA1 human ovarian cancer cells after exposure to sacituzumab govitecan (SG).

	DM4 resistant		Control		
	Average % viability	SEM	Average % viability	SEM	p value
SG 400nM	52.01	1.63	98.98	1.01	< 0.000001
SG 600nM	45.43	0.65	96.87	0.49	< 0.000001

5550 **Poster Session**

Geographical heterogeneity in modeled CA-125 KELIM values: Insights from more than 50,000 real-world calculations on the Biomarker Kinetics platform. First Author: Benoit You, Centre Hospitalier Lyon Sud, and GINECO, Pierre-Benite, France

Background: The modeled CA-125 KELIM is a pragmatic indicator of primary tumor chemosensitivity during neoadjuvant (NACT) or adjuvant chemotherapy (post-primary cytoreductive surgery: ADJUVANT) in ovarian cancer. In a recent GCIG meta-analysis, Japanese patients with stage III–IV high-grade serous carcinoma had higher median KELIM values than Western populations (Corbaux.et.al., Proc ESGO 2025). To further assess potential geographical variations in chemosensitivity, we analyzed KELIM values calculated via the free online platform *www.biomarker-kinetics.org*, which performs approximately 30,000 calculations annually worldwide. **Methods:** All CA-125 KELIM calculations performed on the BK platform between April 2024 and January 2026 were extracted. Median KELIM values were compared separately for NACT and adjuvant settings across continents and countries. **Results:** During the 21-month study period, 50,055 KELIM calculations were recorded worldwide (NACT 59%; ADJUVANT 41%), originating from Asia (n=27,280; 55%), Europe (n=16,461; 33%), North America (n=3,690; 7%), South America (n=1,363; 3%), and rest of globe. Marked geographical variations in KELIM distribution were observed. In the NACT setting, median KELIM values (standardized by the classical cutoff) were significantly higher in patients from Asia (median 1.06, 95%CI [1.05–1.07]), Middle-East (median 0.96 [0.89–1.0.6]), and North America (median 0.91 [0.89–0.94]) compared to those from Europe (median 0.85 [0.84–0.86]) ($P < 0.0001$). Within Asia, KELIM values were similarly elevated in China (n=10,617; median 1.07 [1.06–1.08]) and Japan (n=3,092; median 1.05 [1.03–1.07]) (P=NS). Similar results were noted in the ADJUVANT setting (Asia median 0.91, North America 0.80, vs Europe 0.75; all $P<0.0001$). Weighted median ($\tau = 0.5$) quantile regression confirmed significantly higher standardized KELIM values in Asia (+0.21), Middle East (+0.12), and North America (+0.06) compared with Europe in the NACT setting. Similar outcomes were found in ADJUVANT setting : Asia (+0.16), Middle East (+0.28), and North America (+0.04) compared to Europe. **Conclusions:** Consistent with the GCIG meta-analysis, this global extraction of >50,000 KELIM calculations in the last 2 years confirms substantial geographic variability in tumor chemosensitivity, with higher median standardized KELIM values observed in patients from Asia and, to a lesser extent, the Middle East, while those from Europe exhibited the lowest values. These findings suggest potential important worldwide differences in primary tumor sensitivity to 1st-line carboplatin-paclitaxel chemotherapy and support the need for further biological and clinical investigations across diverse geographic and ethnic populations. Research Sponsor: None.

5551 **Poster Session**

YL205, a novel anti-Napi2b antibody drug conjugate (ADC), in patients with ovarian cancer: Preliminary result from a first-in-human trial. First Author: Xiaohua Wu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Sodium-dependent phosphate transport protein 2b (NaPi2b) is a rapidly internalizing sodium-phosphate transporter which is highly overexpressed in ovarian cancer (OC). The prognosis of patients (pts) with heavily pretreated ovarian cancer remains poor, highlighting a significant unmet need. YL205 is a unique antibody-drug conjugate comprising a NaPi2b-directed antibody conjugated to a potent topoisomerase 1 inhibitor payload developed with TMALIN platform. The preliminary safety and efficacy of YL205 monotherapy in ovarian cancer from a multi-center, open-label, phase I/II trial are presented. **Methods:** Pts with advanced solid tumors, mainly OC, who had failed standard therapy or no available standard therapy were enrolled in the trial YL205-CN-101-01. It consists of dose-escalation (BF-BOIN design), followed by dose-expansion. Pts received YL205 IV at 1.0~3.0 mg/kg once every 3 weeks. Primary objectives were to assess safety and tolerability. **Results:** As of the data cut-off on Dec. 12, 2025, 48 OC pts were dosed with YL205 monotherapy in China and United States with median follow up time of 5.5 months (range 0.2-17.2). Pts had median age of 54.2 yo (range 32-70), 68.8% with ECOG PS 1, 37.5% with $\geq$ 4 prior lines of therapy. Previous therapies included bezacizumab (89.6%), PARP inhibitors (43.8%), and mirvetuximab soravtansine (2.1%). No maximum tolerated dose (MTD) was defined. Grade 3 TRAEs occurred in 27.1% of pts. 14.6% of pts developed SAEs related to tx. The most common TRAEs were neutropenia (60.4%; G≥3: 12.5%), anaemia (60.4%, G≥3: 4.2%), nausea (47.9%, G≥3: 0), vomiting (33.3%, G≥3: 0), decreased appetite (27.1%, G≥3: 0) and thrombocytopenia (25.0%, G≥3: 6.3%) across all dose levels. Among 43 efficacy evaluable pts, confirmed ORR was 46.5% (95% CI: 31.2 – 62.3), and DCR was 95.3% (95% CI: 84.2 – 99.4). At the date cutoff, the median progression-free survival (PFS) data was immature, 62.5% (15/24) of patients with a response remain on treatment. NaPi2b expression as evaluated by H-score was found to be low (0-100) in 1 pt, medium (101-201) in 11 pts (101-200) and high (201-300) in 35 pts whose tumor tissues available at baseline. No correlation trend was observed between NaPi2b expression and response. **Conclusions:** YL205 demonstrated a manageable safety profile in heavily pretreated ovarian cancer patients, with preliminary efficacy observed irrespective of NaPi2b expression intensity. The promising clinical data supports further investigation of this ADC in OC. Clinical trial information: NCT06459973. Research Sponsor: None.

5552 **Poster Session**

A first-of-its-kind multi-omic assay using lipids and proteins to identify early-stage ovarian cancer in symptomatic individuals. First Author: Abigail McElhinny, AOA Dx, Denver, CO

Background: Ovarian cancer (OC) is often diagnosed at advanced stages, leading to one of the highest mortality rates for gynecologic malignancies. While 85% of patients are symptomatic even at early stages, symptoms are vague and overlap with benign conditions. Existing diagnostic tools such as CA125 and HE4 lack sufficient sensitivity and specificity to detect early-stage disease, even in symptomatic individuals. As a result, there is a critical unmet need for a highly sensitive diagnostic tool designed for patients presenting with vague abdominal symptoms. **Methods:** Here, we report the first large-scale, prospective U.S. clinical trial evaluating a targeted multi-omic assay of symptomatic women, its intended-use population. Assay performance was assessed in a subset of an independent, prospectively recruited, multi-site study enrolled across the United States, supplemented with samples from a commercial vendor (N=346). The cohort comprised patients diagnosed with OC across stages and subtypes (N=116: 50 early-stage I/II, 66 late-stage III/IV) and a symptomatic control group (N=230), comprising individuals with benign adnexal masses (BAN; N=116) and symptomatic individuals with vague abdominal symptoms who were followed longitudinally for 12 months to confirm absence of malignancy (symptomatic normal; N=114). Serum lipids including selected phospholipids, sphingolipids, and ceramides were quantified by mass spectrometry. Proteins were measured using clinically validated immunoassays. An ensemble machine learning modeling approach was applied using targeted feature subsets from a refined panel of 23 lipid and 5 protein markers, with outputs weighted to reflect anticipated disease prevalence in the intended-use population. **Results:** The assay demonstrates consistently high diagnostic performance, achieving 96.5% sensitivity with 80.6% specificity for OC vs. symptomatic control, and 92% sensitivity for early-stage OC in the same comparison. Integrating lipid and protein biomarkers into a targeted multi-omic model therefore results in a substantial improvement in OC detection, especially early-stage, over current standard-of-care biomarkers. **Conclusions:** In a large, prospectively collected cohort reflecting real-world symptomatic patients, this first-of-its-kind, targeted multi-omic assay accurately distinguishes OC from non-malignant conditions in symptomatic women with dramatic improvement in early-stage detection. These findings support the feasibility and clinical utility of a multi-omic assay in addressing a longstanding diagnostic gap for symptomatic women, clearing a path to earlier triage and diagnosis. Research Sponsor: None.

5553 **Poster Session**

Preoperative assessment of peritoneal carcinomatosis with [^{68}Ga]Ga-FAPI-46 PET/CT. First Author: Ayca Arcay Ozturk, Department of Nuclear Medicine, Institut Jules Bordet, Hôpital Universitaire de Bruxelles, Université Libre de Bruxelles, Brussels,, Belgium

Background: Accurate preoperative mapping of peritoneal carcinomatosis (PC) is essential for selecting patients for cytoreductive surgery (CRS) and guiding treatment planning. Conventional imaging including [^{18}F]FDG PET/CT may underestimate PC tumour burden. This study evaluated [^{68}Ga]Ga-FAPI-46 PET/CT for preoperative PC assessment using a surgico-pathological reference standard and compared its performance with MRI and [^{18}F]FDG PET/CT. **Methods:** In this prospective phase II study (FAPeCa, NCT06061874), patients with colorectal or ovarian cancer with known or suspected PC underwent [^{68}Ga]Ga-FAPI-46 PET/CT, [^{18}F]FDG PET/CT (FDG PET), and MRI within 4 weeks before diagnostic laparoscopy and/or CRS. PC extent was quantified using a 10-segment adaptation of the Peritoneal Cancer Index (PCI). Reference standard was intraoperative PCI with histopathological confirmation, with pathology adjudicating discordant findings. Agreement between imaging-derived total PCI and the reference-standard PCI was assessed using intraclass correlation coefficient (ICC, two-way mixed, absolute agreement). Segment-level diagnostic performance was evaluated after dichotomisation (PCI 0 vs ≥1). Subgroup analyses were performed according to recent chemotherapy (<3 months). **Results:** Sixty-one patients were enrolled. Median (IQR) total PCI values were 11 (18.5) for the reference standard, 12 (15.5) for FAPI PET, 6 (15.5) for MRI, and 4 (6.5) for FDG PET; FAPI-PCI was higher than MRI-PCI and FDG-PCI (Wilcoxon signed-rank, $p<0.001$). Agreement with the reference standard was highest for FAPI PET (ICC 0.81; BCa 95% CI 0.67–0.89), followed by MRI (ICC 0.76; BCa 95% CI 0.63–0.85) and FDG PET (ICC 0.54; BCa 95% CI 0.29–0.74). In the recent chemotherapy subgroup, FAPI PET maintained good agreement with the reference standard (ICC 0.75, BCa 95% CI 0.56–0.86), whereas agreement declined to moderate for MRI (ICC 0.65, BCa 95% CI 0.41–0.82) and was lower for FDG PET (ICC 0.46, BCa 95% CI 0.17–0.75). Segment-level sensitivity, specificity, and accuracy were 77.6%, 71.2%, and 74.8% for FAPI PET; 67.0%, 84.4%, and 74.7% for MRI; and 47.5%, 91.8%, and 67.2% for FDG PET . Overall segment-level sensitivities and specificities differed across the three modalities (Cochran's Q, $p<0.001$). **Conclusions:** [^{68}Ga]Ga-FAPI-46 PET/CT demonstrated the strongest agreement with surgico-pathological PCI and maintained good agreement after recent chemotherapy. It showed higher detectability than MRI and [^{18}F]FDG PET/CT, albeit at the expense of lower specificity. These findings support[^{68}Ga]Ga-FAPI-46 PET/CT as a promising modality for preoperative PC mapping. Clinical trial information: NCT06061874. Research Sponsor: None.

5554 **Poster Session**

Trastuzumab deruxtecan (T-DXd) + bevacizumab (BEV) as first-line (1L) maintenance therapy in patients (pts) with human epidermal growth factor receptor 2 (HER2)–expressing ovarian cancer (OC): Results from the DESTINY-Ovarian01 (DO-01/ENGOT-ov89/GOG-3112/APGOT-OV13) safety run-in (SRI). First Author: Antonio Gonzalez Martin, GEICO and Cancer Center Clinica Universidad de Navarra, Madrid, Spain

Background: HER2 immunohistochemistry (IHC) expression scores of 3+, 2+, or 1+ occur in up to ~6%, ~28%, and ~21% of OC cases, respectively. In DESTINY-PanTumor02, T-DXd, a HER2-directed antibody–drug conjugate, showed clinically meaningful antitumor activity in pts with heavily pretreated HER2-expressing OC, establishing HER2 as a targetable biomarker. BEV + chemotherapy, followed by maintenance BEV ± poly (ADP-ribose) polymerase inhibitors (PARPi), is a recommended 1L treatment; however, an unmet need remains for PARPi-ineligible pts with HER2-expressing OC. We report the SRI results from DO-01 (NCT06819007), a randomized, open-label, phase 3 trial evaluating T-DXd + BEV vs BEV alone as 1L maintenance therapy in pts with HER2-expressing OC. **Methods:** Pts with newly diagnosed, advanced, high-grade, locally or centrally determined HER2-expressing (IHC 3+/2+/1+) epithelial OC, with no disease progression after 1L chemotherapy + BEV, and ineligible for PARPi, were enrolled and received T-DXd 5.4 mg/kg + BEV 15 mg/kg intravenously every 3 weeks. Pts were treated for ≥2 cycles. Preliminary safety of T-DXd + BEV was assessed by dose-limiting toxicity (DLT; ~30% maximum acceptable rate) and the frequencies of treatment-emergent adverse events (TEAEs) and TEAEs of special interest. **Results:** At data cutoff (DCO; October 23, 2025), 21 pts received a median of 4 cycles (range, 2-8) of T-DXd + BEV; no pt withdrew before cycle 2. Median age was 57 years (range, 22-71) and 19 pts (90.5%) were Asian; 7 (33.3%) and 14 pts (66.7%) had FIGO stages III and IV at baseline, respectively. Median treatment duration was 3.0 mo (range, 1.4-5.5). At DCO, 20 pts (95.2%) completed DLT evaluation and remained on treatment; 1 withdrew after the DLT evaluation period. DLTs occurred in 2 pts (10.0%). TEAEs are shown in the Table. Grade ≥3 drug-related TEAEs occurred in 9 pts (42.9%). Drug-related TEAEs led to dose reduction in 5 pts (23.8%) and dose delay in 6 pts (28.6%). No drug-related TEAEs led to discontinuation or death. Most common drug-related TEAEs (>50%) were nausea (76.2%), leukopenia (52.4%), and neutropenia (52.4%). No cases of adjudicated drug-related interstitial lung disease or left ventricular dysfunction were reported. **Conclusions:** The preliminary safety profile of T-DXd + BEV was consistent with the known safety profiles of the individual agents, and no new safety signals were identified, supporting continued investigation of T-DXd + BEV in DO-01. Clinical trial information: NCT06819007. Research Sponsor: Daiichi Sankyo, Inc.

Pts with events, n (%)	T-DXd + BEV N = 21
Drug-related TEAEs	21 (100)
Drug-related grade ≥3 TEAEs	9 (42.9)
Drug-related TEAEs leading to discontinuation	0
Drug-related TEAEs leading to dose reduction	5 (23.8)
Drug-related TEAEs leading to dose delay	6 (28.6)
TEAEs with outcome of death	0

5555 **Poster Session**

Integrating a small extracellular vesicle protein–based ovarian cancer score with O-RADS Ultrasound to improve preoperative risk stratification of adnexal masses. First Author: Qunxian Rao, Department of Gynecologic Oncology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: Accurate preoperative differentiation of adnexal masses remains a major clinical challenge. Although the Ovarian-Adnexal Reporting and Data System (O-RADS) standardizes ultrasound-based risk assessment, approximately 30-35% of adnexal masses are classified as indeterminate (O-RADS 3/4), often resulting in diagnostic uncertainty, unnecessary surgery, or delayed referral to gynecologic oncologists. Conventional serum biomarkers such as CA125 are limited by poor specificity and biological heterogeneity. The small Extracellular vesicle (sEV)-associated biomarkers have emerged as a promising approach to improve diagnostic accuracy by more closely reflecting tumor-related molecular signals. This study evaluated whether a serum sEV-based Ovarian Cancer Score (OCS) provides independent and incremental diagnostic value when integrated with O-RADS ultrasound. **Methods:** This retrospective diagnostic study included 250 consecutive patients with adnexal masses treated at Sun Yat-sen Memorial Hospital. All patients underwent standardized transvaginal ultrasound with O-RADS classification and serum CA125 testing. OCS was assessed using a chemiluminescent immunoassay based on serum sEV-derived CA125, HE4, and C5a. Final histopathology served as the reference standard. Diagnostic performance was evaluated overall and stratified by O-RADS category. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of malignancy. **Results:** Overall, OCS demonstrated significantly higher diagnostic accuracy for malignancy than serum CA125 alone. In masses with clearly benign or malignant imaging features (O-RADS 2 and 5), OCS maintained an accuracy of approximately 90% (87.5% and 94.6%). Within the clinically challenging O-RADS 3/4 subgroup (n = 115), OCS achieved a diagnostic accuracy of 86.1%, substantially outperforming serum CA125 (69.6%). Multivariate analysis identified OCS positivity as the strongest independent predictor of malignancy (OR 106.08, 95% CI 15.37-732.15, $p < 0.001$), exceeding individual high-risk ultrasound features such as ascites or mixed cystic-solid components. Diagnostic performance was further enhanced when OCS was combined with selected ultrasound characteristics. **Conclusions:** A serum sEV-based OCS provides robust and independent diagnostic information that complements O-RADS ultrasound in the preoperative evaluation of adnexal masses. By addressing the diagnostic gray zone of O-RADS 3/4, this integrated approach extends beyond conventional serum biomarkers and may support improved risk stratification and triage decisions. Clinical trial information: NCT06366997. Research Sponsor: None.

5556 **Poster Session**

Neoadjuvant disitamab vedotin plus carboplatin in HER2-expressing advanced ovarian cancer: A prospective, single-arm, phase II trial. First Author: Yifan Meng, Department of Gynecologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Standard neoadjuvant paclitaxel-carboplatin for advanced ovarian cancer causes significant neurotoxicity impacting quality of life. Disitamab vedotin (RC48), an anti-HER2 antibody-drug conjugate, demonstrated efficacy and favorable tolerability in HER2-expressing solid tumors. We evaluated RC48 plus carboplatin as neoadjuvant therapy in HER2-expressing advanced ovarian cancer. **Methods:** This single-arm phase II trial (NCT06574763) enrolled patients with newly diagnosed FIGO stage III-IV high-grade serous ovarian, fallopian tube, or primary peritoneal cancer expressing HER2 (IHC 1+ or ERBB2 amplification) who were ineligible for primary cytoreductive surgery. Treatment comprised carboplatin (AUC 5, day 1, Q3W) alone in cycle 1, then RC48 (2.5 mg/kg, day 1, Q3W) plus carboplatin for cycles 2-4. A 6-patient safety run-in determined optimal RC48 dosing. Interval debulking surgery (IDS) was performed 14-28 days after cycle 4. Primary endpoint: complete resection rate (CRR, defined as no macroscopic residual disease at IDS). Secondary endpoints: pathological complete response (pCR), objective response rate (ORR per RECIST v1.1), progression-free survival, overall survival, and safety (CTCAE v5.0). **Results:** From October1st, 2024 to December 31st, 2025, 33 patients were enrolled.; 25 completed neoadjuvant therapy and underwent IDS. Among 24 evaluable patients (1 excluded for mixed histology meeting exclusion criteria), median age was 57 years (range 42-71); all had stage IIIC (n=18, 75%) or IVB (n=6, 25%) disease. The regimen achieved exceptional surgical outcomes: CRR 91.6% (22/24), with 2 patients having minimal residual disease <1 cm. ORR was 87.5% (21/24). pCR rate was 4.2% (1/24). Robust tumor regression was observed: median residual viable tumor in primary lesions 22% (range 0-80%), in omental implants 44% (range 0-80%). With median follow-up of 5.0 months (range 2.3-10.6), no disease recurrence occurred. Grade ≥3 treatment-related adverse events occurred in 29.2% of patients, primarily hematological toxicities (neutropenia, thrombocytopenia) that resolved to ≤grade 2 within one week with supportive care. Critically, no patient (0/27, 0%) experienced peripheral neuropathy of any grade. **Conclusions:** Neoadjuvant disitamab vedotin plus carboplatin demonstrated exceptional surgical outcomes with 91.6% complete resection rate and complete elimination of neurotoxicity in HER2-expressing advanced ovarian cancer. The regimen induced substantial pathological regression with a favorable safety profile. These results support RC48-carboplatin as a promising neurotoxicity-sparing alternative to standard paclitaxel-based therapy. Updated survival data will be presented. Clinical trial information: NCT06574763. Research Sponsor: Remegen.

5557 **Poster Session**

Understanding palliative care gaps in young adult ovarian cancer: A population-based study of 37,880 hospitalizations. First Author: Rigved Virendra Jeurkar, Byramjee Jeejeebhoy Government Medical College, Pune, Mumbai, India

Background: Palliative care (PalC) improves both quality of life and survival compared to usual care. Despite this, significant implementation gaps persist due to delayed or absent utilization. This study examines the determinants, trends, clinical profiles, and outcomes of PalC among young women hospitalized with ovarian cancer. **Methods:** We identified ovarian cancer patients among young adults aged 18-45 years using the National Inpatient Sample (NIS) from 2016-2022. We first estimated the prevalence of PalC utilization and then developed a multivariable logistic regression model to estimate the association of demographic, clinical, and hospital-level variables with PalC use. The in-hospital mortality burden associated with PalC receipt was also estimated. **Results:** We found 37,880 ovarian cancer young adults with 8.78% using PalC. Several variables were associated with PalC utilization. Clinical comorbidities demonstrated the strongest associations: metastatic cancer(aOR 4.123, 95% CI: 3.385-5.023, $p<0.001$), frailty (aOR 3.407, 95% CI: 2.803-4.142, $p<0.001$), and cachexia (aOR 3.817, 95% CI: 2.460-5.922, $p<0.001$). Depression was also significantly associated with PalC utilization (aOR 1.360, 95% CI: 1.056-1.751, p=0.017). Temporal trends revealed increasing PalC utilization in more recent years compared to 2016, with significantly higher odds in 2020 (aOR 1.412, 95% CI: 1.005-1.985, p=0.047) and 2021 (aOR 1.565, 95% CI: 1.122-2.184, p=0.008). Weekend admissions were associated with 38.2% higher odds of PalC receipt (aOR 1.382, 95% CI: 1.107-1.727, p=0.004), and each additional year of age increased odds by 1.5% (aOR 1.015, 95% CI: 1.001-1.029, p=0.034). Insurance status significantly influenced PalC receipt. Compared to Medicare beneficiaries, patients with private insurance had 36.6% lower odds of receiving PalC (aOR 0.634, 95% CI: 0.452-0.890, p=0.008), while self-pay patients had 51.1% lower odds (aOR 0.489, 95% CI: 0.293-0.816, p=0.006). Additionally, patients from the highest income quartile had 25.7% lower odds of PalC compared to those in the lowest income quartile (aOR 0.743, 95% CI: 0.555-0.996, p=0.047). Race, hospital location/teaching status, hospital region, and hospital bed size were not significantly associated with PalC receipt. The overall in-hospital mortality rate was 3.0%, with stark differences by PalC receipt: 21.5% among those receiving PalC versus 1.22% among those not receiving PalC (aOR 16.532, 95% CI: 11.205-24.389, $p<0.001$). **Conclusions:** Among hospitalized young adults with ovarian cancer, fewer than 1 in 10 received PalC. Services concentrated among patients with metastasis, frailty, and cachexia, suggesting late rather than early integration. Significant disparities by insurance and income highlight access barriers requiring intervention for equitable PalC integration into comprehensive cancer care. Research Sponsor: None.

5558 **Poster Session**

Ocular toxicity and safety profile of mirvetuximab soravtansine in ovarian cancer: A systematic review and meta-analysis of clinical trials and real-world studies. First Author: Priyanka Nagdev, UNC HBR, Morganton, NC

Background: Mirvetuximab soravtansine (MIRV) is a folate receptor alpha (FRα)–targeting antibody–drug conjugate approved for FRα-positive, platinum-resistant ovarian cancer. Ocular adverse events are a characteristic toxicity of MIRV; however, the incidence and severity of ocular and selected non-ocular toxicities across clinical trials and real-world studies have not been comprehensively synthesized. **Methods:** This systematic review and meta-analysis study was conducted according to PRISMA guidelines and registered in PROSPERO (CRD420251270297). MEDLINE/PubMed, Embase, Scopus, and CENTRAL were searched from inception through December 2025 for prospective phase I–III trials and real-world observational studies evaluating MIRV in epithelial ovarian, fallopian tube, or primary peritoneal cancer. Two reviewers independently screened studies and extracted data. Primary outcomes included any-grade and grade $\geq$3 ocular adverse events, as well as ocular toxicity–related dose reductions and treatment discontinuations. Secondary outcomes included grade $\geq$3 pneumonitis and thrombocytopenia. Clinical trial and real-world data were analyzed separately. Random-effects meta-analyses of proportions were performed using logit transformation, with heterogeneity assessed using the I^2 statistic. Analyses were conducted in R version 4.5.2. **Results:** Fourteen studies comprising approximately 750 patients were included. In pooled analyses of clinical trials, any-grade ocular adverse events were common (56.2%; 95% CI, 5.2–96.8) with substantial heterogeneity contributing to wide confidence intervals, whereas grade $\geq$3 ocular adverse events were rare (1.41%; 95% CI, 0.47–4.13) with no observed heterogeneity. Dose reduction due to ocular toxicity occurred in 31.2% (95% CI, 18.0–48.4) of patients, while treatment discontinuation due to ocular adverse events was less frequent (9.98%; 95% CI, 0.70–63.58). Severe non-ocular toxicities were uncommon, with pooled incidences of 1.41% (95% CI, 0.47–4.13) for grade $\geq$3 pneumonitis and 1.44% (95% CI, 0.09–19.44) for grade $\geq$3 thrombocytopenia. Across three real-world studies involving 289 patients, treatment discontinuation due to ocular adverse events was rare (0.35%; 95% CI, 0.00–20.54), with safety findings consistent with those from clinical trials. **Conclusions:** MIRV is associated with frequent, but predominantly low-grade, ocular adverse events, which are commonly managed with dose modification, while severe ocular and non-ocular toxicities are rare. Real-world evidence supports the tolerability profile observed in clinical trials, highlighting the importance of proactive ocular monitoring to optimize treatment continuity. Research Sponsor: None.

5559 **Poster Session**

Updated efficacy of dalpiciclib and nonsteroidal aromatase inhibitors (NSAIs) in estrogen receptor–positive (ER+) recurrent/metastatic (R/M) ovarian cancer and uterine neoplasms. First Author: Huijuan Yang, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Initial results from our trial showed the anti-tumor activity and good tolerance of CDK4/6 inhibitor dalpiciclib combined with NSAIs in patients (pts) with ER+ R/M ovarian cancer and uterine neoplasms (SGO, 2024, #S283; IGCS, 2025, #397). Here, we report updated results. **Methods:** This single-center, single-arm, open label, phase 2 trial enrolled pts with ER+, R/M ovarian cancer and uterine neoplasms which met the following criteria: pretreated low-grade serous ovarian carcinoma (LGSOC), pretreated uterine endometrioid carcinoma (EC), uterine leiomyosarcoma (LMS), or untreated low-grade endometrial stromal sarcoma (LGESS). Pts received dalpiciclib (150mg po d1-21 q28d) and NSAIs (mainly letrozole 2.5mg po qd) until disease progression, unacceptable toxicity or consent withdrawn. The primary endpoint was 12-week progression-free survival (12wPFS) rate. A Simon's two-stage design was used (one-sided α=0.05, power=80%), and the null hypothesis (P0=0.2) would be rejected if totally $>$10 of 33 pts achieved primary endpoints. **Results:** As the data cutoff (Jan 5, 2026), 35 pts with a median of one prior therapy for R/M disease were enrolled, including 11 with LGSOC, 15 with EC, 8 with LGESS and 1 with LMS. With a median follow-up of 11.4 months (range, 0.1-52.2), 22 of 29 efficacy-evaluable pts had reached the primary endpoint, with a 12wPFS rate of 75.9% (95% CI 56.5-89.7), suggesting the value of further investigation. Detailed efficacy results are shown in Table 1. Grade 3-4 treatment-related adverse events (TRAEs) occurred in 82.9% (29/35) of pts, mostly neutrophil count decreased (71.4%), white blood cell count decreased (45.7%) and platelet count decreased (14.3%). Sixteen pts had dose reduction of dalpiciclib, mostly due to hematologic toxicities. No serious adverse events or treatment-related deaths occurred. Twelve pts were still on-treatment, with 3 pts treated for $>$4 years. **Conclusions:** The trial achieved its positive primary endpoint, showing meaningful efficacy of dalpiciclib + NSAIs in ER+ R/M ovarian cancer and uterine neoplasms. No new safety signals were observed. Clinical trial information: ChiCTR2000040597. Research Sponsor: None.

Efficacy results of evaluable pts.

	Overall N=29	LGSOC n=9	EC n=11	LGESS n=8	LMS n=1
12wPFS rate [95%CI]	75.9% (22/29) [56.5-89.7]	77.8% (7/9) [40.0-97.2]	63.6% (7/11) [30.8-89.1]	100% (8/8) [63.1-100]	0% (0/1) [0-97.5]
Clinical Response					
Partial response (PR)	5 (17.2%)	1 (11.1%)	2 (18.2%)	2 (25.0%)	0 (0%)
Stable disease (SD)	17 (58.6%)	6 (66.7%)	5 (45.5%)	6 (75.0%)	0 (0%)
SD≥24 weeks	14 (48.3%)	5 (55.6%)	4 (36.4%)	5 (62.5%)	0 (0%)
Progressive disease (PD)	7 (24.1%)	2 (22.2%)	4 (36.4%)	0 (0%)	1 (100%)
ORR (CR+PR, 95% CI)	17.2% (5.85-35.8)	11.1% (0.28-48.3)	18.2% (2.28-51.8)	25.0% (3.19-65.1)	0% (0-97.5)
CBR (CR+PR+SD≥24 weeks, 95% CI)	65.5% (45.7-82.1)	66.7% (29.9-92.5)	54.5% (23.4-83.3)	87.5% (47.4-99.7)	0% (0-97.5)

5560 **Poster Session**

Phase II study of sintilimab combined with nab-paclitaxel in the treatment of platinum-resistant recurrent ovarian cancer. First Author: Nan Zhang, Peking University Cancer Hospital and Institute, Beijing, China

Background: Platinum-resistant recurrent ovarian cancer (PROC) remains a major therapeutic challenge with limited effective treatment options. This single-arm phase II trial aimed to evaluate the efficacy, safety, and tolerability of sintilimab combined with nab-paclitaxel in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. **Methods:** A total of 28 patients were enrolled and received intravenous sintilimab (200 mg, day 1) plus nab-paclitaxel (260 mg/m², day 1) every 3 weeks. The primary endpoint was objective response rate (ORR); secondary endpoints included progression-free survival (PFS), disease control rate (DCR), overall survival (OS), and safety. **Results:** The median age was 57 years (range: 37–74 years), with 96.4% having high-grade serous histology, 67.9% being BRCA wild-type, 57.1% with prior bevacizumab exposure, and 50% with a PD-L1 combined positive score (CPS) $\geq$1. After a median follow-up of 11.8 months, the ORR was 35.7% (10 partial responses), DCR was 64.3%, median PFS was 4.28 months, and median OS was 15.83 months. Patients with CPS $\geq$1 had a higher ORR (42.9% vs. 28.6%) and DCR (71.4% vs. 57.1%) than those with CPS $<$1, but no significant difference in PFS (3.83 vs. 4.13 months, p = 0.18). Similar trends were observed for CPS $\geq$5 and CPS $\geq$10, with ORRs of 44.4% and 50.0%, respectively, but no significant PFS differences (all p $>$ 0.05).Notably, patients with tumor-infiltrating lymphocytes (TILs) $\geq$10% exhibited a significantly higher ORR (72.7% vs. 12.5%, p = 0.005) and longer median PFS (15.57 months vs. 3.4 months, p = 0.005). Treatment-related adverse events (TRAEs) were mainly leukopenia (28.6%), neutropenia (25.0%), anemia (46.4%), and peripheral neuritis (28.6%), with rare grade 3–4 toxicities. **Conclusions:** Sintilimab combined with nab-paclitaxel shows promising efficacy and acceptable safety in PROC, with TILs $\geq$10% and a high $CD8^+/CD4^+$ ratio emerge as potential predictive biomarkers, while PD-L1 CPS shows limited utility. This regimen represents a potential new therapeutic option for this difficult-to-treat population and warrants further investigation in randomized controlled trials. Clinical trial information: 2000031890. Research Sponsor: Xisike-CSPC Tumor Research Fund; Y-SY201902-0010.

5561 **Poster Session**

Treatment duration with avutometinib/defactinib in recurrent low-grade serous ovarian carcinoma by KRAS mutation status. First Author: Anna Shvygin, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Low grade serous ovarian carcinoma (LGSOC) is characterized by MAPK pathway alterations (most commonly *KRAS*, which occurs in 1/3 of tumors) and poor chemosensitivity. Avutometinib (MEK/RAF clamp) in combination with defactinib (FAK inhibitor) has shown durable responses in patients with recurrent LGSOC harboring a *KRAS* mutation and was recently FDA approved for this indication. However, data is lacking regarding the activity of avutometinib + defactinib (A+D) vs single agent MEK inhibitors for treatment of women with recurrent LGSOC. Here we examine patients who were treated with A+D. We also examine the duration of treatment in patients who received a single agent MEK inhibitor followed by A+D. **Methods:** In this single-institution retrospective cohort study, patients with recurrent LGSOC treated with A+D between 2021 – 2025 were included and stratified by tumor *KRAS* mutation status. The primary outcome was median duration of treatment on A+D, compared using Wilcoxon-Rank sum test. Pair-wise comparison of treatment duration in patients who were treated with single agent MEK inhibitors and A+D was performed. **Results:** 26 patients were included in the final analysis. Median age at diagnosis was 49 years (range 20-85). Patients had a median of 4 (range 1-9) prior lines of therapy, including hormonal (92%, n=24), bevacizumab (38%, n=10), and MEK inhibitors trametinib and binimetinib (35%, n=8). Eight (31%) patients harbored a tumor *KRAS* mutation. Among these 26 patients, median duration of treatment with A+D was 16.8 months in the *KRAS*-mutant and 5.5 months in the *KRAS*-wild type cohorts, respectively (p=0.037). Nine patients were treated with both A+D and a MEK inhibitor, three of whom had *KRAS*-mutant tumors. All nine patients received the single agent MEK inhibitor prior to treatment with A+D, with a median of 7 (range 4-8) prior lines of therapy before treatment with A+D. Among the three patients with *KRAS*-mutant tumors, median duration of treatment with single agent MEK inhibitor was 4.4 months (range 0.4-24.2) while with A+D, it was 17.6 months (range 6.1-23.4). **Conclusions:** In this single-institution retrospective cohort, treatment with A+D was associated with a significantly longer median duration of therapy in patients with *KRAS*-mutant recurrent LGSOC compared with *KRAS*-wild type disease. Among patients who received both regimens, A+D appeared to provide longer treatment duration than prior single agent MEK inhibitors in the *KRAS*-mutant subset, though this is limited by small sample size. These findings support improved activity of A+D in *KRAS*-mutant LGSOC and warrant confirmation in larger prospective studies. Research Sponsor: None.

5562 **Poster Session**

Circulating tumor DNA to add prognostic stratification beyond CA-125 in epithelial ovarian cancer. First Author: Grace Gorecki, Allegheny Health Network, Pittsburgh, PA

Background: Ovarian cancer has a high risk of recurrence, particularly in patients with advanced-stage disease. CA-125 is routinely used to assess disease burden and recurrence risk but has limited prognostic accuracy. Circulating tumor DNA (ctDNA) has emerged as a potential biomarker that may better reflect tumor biology and enable earlier identification of recurrence. **Methods:** Patients with epithelial ovarian cancer and available plasma ctDNA and CA-125 measurements collected in association with surgical debulking were included. CA-125 was stratified using a standard clinical cutoff of 35 U/mL. Average cfDNA yield (ng/mL) was stratified into high and low ctDNA groups based on the cohort median. Associations were assessed using correlation and categorical analyses. Overall survival (OS) was evaluated using Kaplan–Meier methods and Cox proportional hazards models, including multivariable analyses. **Results:** Among 89 patients, ctDNA concentration was positively associated with CA-125 (Spearman ρ = 0.25; p = 0.017). Patients with high CA-125 had higher ctDNA levels than those with low CA-125 (mean 21.2 vs 7.6; p = 0.0044). High ctDNA concentration was associated with worse OS compared with low ctDNA (log-rank p = 0.0036; HR 3.48, 95% CI 1.50–8.06), with median OS (mOS) of 1386 days versus not reached. Patients with both high CA-125 and high ctDNA experienced markedly worse mOS than patients with low ctDNA (log-rank p = 0.0045; HR 3.48, 95% CI 1.47–8.21), with a mOS of 827 days versus not reached respectively. This added stratification by ctDNA persisted across multiple sensitivity analyses, including stratification by timing of sample collection relative to surgery, with consistent prognostic associations observed in pre-surgery samples (mOS 953 days; log-rank p = 0.031) and post-surgery samples (mOS 569 days; log-rank p = 0.045), as well as in analyses of high-grade serous ovarian cancer, advanced-stage disease, and neoadjuvant therapy. In multivariable Cox regression adjusting for CA-125, disease stage, surgical status, and neoadjuvant therapy, ctDNA remained independently associated with OS (HR 1.012, 95% CI 1.003–1.019). **Conclusions:** ctDNA consistently added prognostic value beyond CA-125 despite treatment-related heterogeneity, suggesting that ctDNA concentration captures biologic features of tumor behavior not reflected by CA-125 alone. Importantly, ctDNA remained predictive regardless of the timing of sample collection. These findings support ctDNA as a complementary biomarker for baseline prognostic stratification. Research Sponsor: None.

5563 **Poster Session**

The HER2 paradox in ovarian clear cell carcinoma: Expression and intrinsic resistance to trastuzumab deruxtecan (T-DXd). First Author: Junsik Park, Department of Obstetrics and Gynecology, Soonchunhyang University Bucheon Hospital, Bucheon, South Korea

Background: Trastuzumab deruxtecan (T-DXd) shows potent activity in HER2-expressing ovarian cancer (OC). However, efficacy across histologic subtypes remains under-characterized. Specifically, data on T-DXd response in ovarian clear cell carcinoma (OCCC), a distinct chemo-resistant entity, are lacking. This study aimed to evaluate T-DXd efficacy in recurrent OC across different histologic subtypes. **Methods:** We retrospectively analyzed 59 patients with recurrent OC who received T-DXd treatment between 2020 and 2025 at Yonsei Cancer Center. HER2 status (IHC), objective response rate (ORR), progression-free survival (PFS), duration of response, and safety were assessed by histology. **Results:** Patients included HGSC (n=38), Mucinous (n=9), OCCC (n=10), and Endometrioid (n=2). Median age was 55; median prior lines of therapy was 3. Notably, 100% of OCCC, mucinous, and endometrioid tumors were HER2 2+/3+, vs. 89.5% in HGSC. Despite high HER2 expression, outcomes diverged. ORR was 55.3% (26/47) for HGSC/Mucinous vs. 0% (0/12) for OCCC/Endometrioid ($P<0.001$). Specifically, HGSC achieved 57.9% ORR (2 CRs) vs. 0% in OCCC. PFS was significantly shorter in the OCCC/Endometrioid group (median 1.2 vs 6.9 months; HR 18.3; $P<0.0001$). OCCC patients showed rapid progression. Regarding safety, among 54 evaluable patients, 36 (66.7%) experienced Grade 3-4 adverse events, and 5 cases (9.3%) of ILD occurred; however, no new safety signals or treatment-related deaths were reported. **Conclusions:** T-DXd showed robust efficacy in recurrent HGSC and mucinous OC but no response in OCCC and endometrioid OC. Thus, HER2 expression alone does not guarantee T-DXd response in OCCC, possibly due to its chemo-refractory nature. Mechanisms of T-DXd resistance in OCCC warrant investigation. Research Sponsor: None.

Tumor response.

Histology	HGSC (n=38)	Mucinous (n=9)	Endometrioid (n=2)	Clear cell (n=10)
Objective response[1] (n, %)	22 (58%)	4 (44%)	0 (0%)	0 (0%)
CR	2 (5%)	0 (0%)	0 (0%)	0 (0%)
PR	20 (53%)	4 (44%)	0 (0%)	0 (0%)
SD	14 (37%)	4 (44%)	0 (0%)	0 (0%)
PD	2 (5%)	1 (11%)	2 (100%)	10 (100%)

[1]P=0.0006.

5564 **Poster Session**

A small extracellular vesicle protein-based model for ovarian cancer relapse detection and monitoring. First Author: Zheng Feng, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Recurrence surveillance of epithelial ovarian cancer (EOC) is a major clinical challenge, given the suboptimal performance of serum CA125 levels and limitations of radiological assessments. Serum small extracellular vesicle (sEV)-based liquid biopsy provides tumor-enriched and stable biomarkers, with potential to improve the precision of recurrence monitoring and support post-treatment surveillance. This study aimed to develop and preliminarily validate a serum sEV protein-based model to enhance recurrence monitoring in ovarian cancer. **Methods:** The study was designed with two stages (model development and validation) and plans to prospectively enroll 200 patients with EOC (NCT06925126). This analysis reports preliminary stage I data, and patients were categorized into relapse and non-relapse groups based on imaging-confirmed recurrence status. All relapsed patients were platinum-sensitive with low tumor burden. Quantitative assessment was performed on biomarkers derived from sEVs (specifically, E-CA125, E-HE4, and E-C5a) as well as corresponding serum markers measured in routine clinical practice (namely, H-CA125 and H-HE4), utilizing peripheral blood samples. Biomarker distributions were compared between groups, and predictive performance for recurrence detection was evaluated using receiver operating characteristic (ROC) analysis, including area under the curve (AUC), accuracy, sensitivity, and specificity. **Results:** A total of 113 patients were analyzed (42 non-relapsed, 71 relapsed), with a median age of 57 years. The majority (95/113) of patients had high-grade serous ovarian cancer, while other histological types were also included. Levels of E-CA125, E-HE4, H-CA125, and H-HE4 were significantly higher in relapsed patients compared with non-relapsed patients (all $p < 0.01$), while E-C5a showed no discriminative value between the two groups. Among individual sEV biomarkers evaluated, E-CA125 demonstrated the highest performance for recurrence detection (AUC = 0.877), followed by E-HE4 (AUC = 0.689) and E-C5a (AUC = 0.528). Moreover, the sEV protein-based model achieved an accuracy of 77.9% with a sensitivity of 71.8% and a specificity of 90.9%. This performance surpassed that of the conventional serum CA125, which exhibited an accuracy of 50.0%, a sensitivity of 26.8%, and a specificity of 100.0%. These results indicate that the sEV protein-based model may provide added clinical value when serum CA125 monitoring is unreliable after prior therapy. **Conclusions:** The sEV-derived CA125 and the sEV model demonstrate promising performance for recurrence detection in EOC. These findings support the feasibility of a serum sEV-based surveillance strategy that may improve the reliability of post-treatment monitoring. Prospective validation is ongoing to determine its potential role in guiding clinical surveillance and intervention. Clinical trial information: NCT06925126. Research Sponsor: None.

5565 **Poster Session**

Efficacy prediction for progression-free survival (PFS) and overall survival (OS) by genomic instability score (GIS) cutoffs in patients (pts) with advanced ovarian cancer (aOC): Post hoc results from the phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial. First Author: Bradley J. Monk, GOG Foundation, Philadelphia, PA, and Florida Cancer Specialists and Research Institute, West Palm Beach, FL

Background: GIS is a key component of a companion diagnostic assay for determining homologous recombination deficiency (HRD) status to identify pts with aOC who may benefit from maintenance therapy. While the standard GIS cutoff to classify tumors as homologous recombination-deficient (HRd) is ≥42, this study analyzed PRIMA final analysis data to see if a lower cutoff of ≥33 based on the VELIA/GOG-3005 trial could identify additional pts who experienced a PFS benefit with niraparib (nir) first-line maintenance (1LM) vs placebo (PBO). **Methods:** Pts with aOC were randomized 2:1 to nir or PBO 1LM. Tumor HRD status and GIS were assessed using the myChoice HRD test (Myriad Genetics). In pts with GIS data, tumor GIS distribution was assessed in the overall population and by HRD/*BRCA* status. Investigator-assessed PFS at GIS cutoffs <33 vs ≥33 and <42 vs ≥42 was evaluated using Kaplan-Meier methods with Cox proportional hazards modeling (cutoff, 08Apr2024). Two statistical utility tests were performed for each cutoff: 1) to evaluate each cutoff's potential to add incremental value to the explanation of pt response on top of treatment, and 2), in nir-treated pts, to assess each cutoff's ability to predict long-term PFS (≥3 y). OS was assessed by increasing GIS cutoffs. **Results:** In the overall population (n=568), GIS ranged from 0 to 95, and 64.3% of pts had GIS ≥33 (GIS groups: 0 to <33, n=203; ≥33 to <42, n=67; ≥42, n=298). Of pts with *BRCA* mutation, 9.4% (21/223) of pts had GIS <42. Nir 1LM produced a significant PFS benefit vs PBO across all GIS cutoffs, with greater benefit observed in higher GIS groups (Table). The GIS ≥33 cutoff improved the Cox model fit vs the ≥42 (ie, explaining more PFS variability and showing more powerful association with PFS after treatment adjustment). In nir-treated pts with GIS data (n=387), the ≥33 cutoff increased sensitivity (0.8936 > 0.7872), identifying 10.6% more patients with PFS ≥3 y, but lowered specificity (0.4369 < 0.5734) vs the ≥42 cutoff. Higher GIS cutoffs were also associated with more favorable nir 1LM on OS effects (lower hazard ratios). **Conclusions:** In PRIMA, GIS existed along a spectrum, and nir 1LM resulted in a PFS benefit vs PBO across all GIS cutoffs. Pts with higher GIS experienced greater PFS benefit than pts with lower GIS. The GIS ≥33 cutoff identified more long-term PFS responders than the GIS ≥42 cutoff. Results suggest that GIS cutoffs of ≥33 used for HRd status determination may optimize identification of pts with aOC who may benefit from nir 1LM. Clinical trial information: NCT02655016. Research Sponsor: GSK; N/A.

	Tumor GIS			
Investigator-assessed PFS	**<33**	**≥33**	**<42**	**≥42**
Nir vs PBO, n	133 vs 65	283 vs 141	169 vs 80	247 vs 126
Hazard ratio (95% CI)[a]	0.69 (0.50–0.96)	0.54 (0.42–0.68)	0.67 (0.50–0.89)	0.51 (0.40–0.66)
***P* value**	0.026	<0.001	0.007	<0.001

[a]Stratified Cox proportional hazards model. Pts with GIS data included.

5566 **Poster Session**

Platinum re-challenge in platinum-resistant ovarian cancer: Real-world patterns and outcomes. First Author: Prakirthi Yerram, Flatiron Health, New York, NY

Background: Platinum-resistant ovarian cancer (PROC), defined as recurrence within 6 months of completing platinum-based chemotherapy, has limited treatment options and poor outcomes. Although guidelines recommend non-platinum therapy, platinum rechallenge still occurs in real-world practice, despite limited evidence. This study examines real-world patterns and outcomes of platinum rechallenge versus non-platinum therapy at first PROC occurrence overall and by biomarker status, prior therapy, and time to PROC. **Methods:** Using the US-based, EHR-derived deidentified Flatiron Health Research Database, ovarian cancer patients diagnosed after January 1, 2017 (data cutoff August 31, 2025) were selected. Patients with PROC, defined as progressing ≤ 6 months after platinum, that received subsequent therapy were included; primary platinum refractory patients (< 3 months) were excluded. Patients were grouped by first PROC therapy (platinum rechallenge vs non-platinum therapy), and rwPFS and rwOS were assessed overall and by BRCA/HRD status, use of prior first-line maintenance (1LM), number of prior platinum lines, and time to PROC. Associations were assessed using Kaplan-Meier estimates and IPTW-adjusted Cox models accounting for demographics, ECOG PS, practice type, insurance, index year, biomarkers, and prior 1LM and platinum exposure. **Results:** Among 29,194 patients with ovarian cancer, 2,907 had PROC. Of these, 528 received platinum rechallenge and 2,379 received non-platinum therapy (71% received chemotherapy ± bevacizumab) as subsequent treatment. Baseline characteristics in both groups were similar; the platinum rechallenge group had fewer patients with BRCA mutations (BRCAm) (9.3% vs 12%) and no residual disease (36% vs 40%) but more with only one prior platinum line (56% vs 48%). Median rwPFS was 5.8 mo with platinum rechallenge vs 3.9 mo with non-platinum therapy (adjusted HR 0.72, 95% CI, 0.64 to 0.81; $P < .001$), and median rwOS was 13 vs 11 mo (adjusted HR 0.81, 95% CI, 0.72 to 0.92; $P = .001$). In adjusted analyses, rwPFS advantage of platinum rechallenge was consistent across major subgroups, including biomarker-defined populations (BRCA-wild type and HRD-positive non-BRCAm), prior 1LM and platinum exposure, and time to PROC. rwOS benefit was more limited, confined to patients with BRCAm, earlier recurrence, and more heavily pretreated disease, with limited events in several subgroups. **Conclusions:** In this large real-world cohort, platinum rechallenge improved rwPFS and rwOS vs non-platinum therapy in PROC. Consistent rwPFS benefits across most subgroups and selective rwOS advantages, particularly in BRCAm, highlight heterogeneity within PROC populations and support individualized decisions for platinum rechallenge beyond a strict 6-month platinum-free interval. Prospective studies are required to identify patients most likely to benefit from platinum rechallenge. Research Sponsor: Flatiron Health, Inc.

5567 **Poster Session**

Circulating tumor DNA to enhance detection of high-risk minimal residual disease in ovarian cancer relative to second look laparoscopy. First Author: Helen D. Clark, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Minimal residual disease (MRD) following frontline treatment of ovarian cancer has been established as a predictor of recurrence and survival. Historically, second look laparoscopy (SLL) has served as the gold-standard method to assess MRD; however the need for surgical evaluation limits widespread adoption and clinical applicability. Circulating tumor DNA (ctDNA) offers a non-invasive alternative for MRD detection and enables longitudinal monitoring with the potential for early identification of recurrence. Presently, the concordance between ctDNA-based detection and surgical assessment remains incompletely characterized. In this retrospective cohort study, we compare the predictive performance of ctDNA versus SLL for detecting clinically significant MRD after frontline treatment for high-grade ovarian cancer. **Methods:** This retrospective, single-institution study included patients with high-grade epithelial ovarian cancer who completed frontline chemotherapy and surgery. All patients underwent SLL to determine surgical MRD status. At the time of SLL, plasma was collected and profiled using NeXT Personal. Using whole-genome sequencing, this ultrasensitive, tumor-informed assay tracks up to 1,800 tumor-specific variants to detect ctDNA at levels down to ~1 part per million. Statistical analyses were conducted using RStudio (version 2026.01.0.392). **Results:** The cohort consisted of 72 patients (median follow up 38.9 months) with high-grade epithelial ovarian cancer, of whom 69 patients (95.8%) were in clinical remission by Ca-125 and imaging. Despite this, 30 patients (41.7%) were positive for MRD by ctDNA and 33 patients (45.8%) were positive for MRD by SLL. On multivariable analysis, ctDNA positivity independently predicted worse PFS (HR 4.35, 95% CI 2.17-8.72, p<0.001). The results of MRD and SLL were concordant in 53 (73.6%) of cases. There were 8 cases in which ctDNA was positive and SLL was negative. To date, 6/8 patients (75%) have recurred. There were 11 cases in which SLL was positive and ctDNA was negative. To date, 6/11 (54.5%) have recurred. Among these discordant cases, individuals with positive ctDNA but negative SLL had significantly worse PFS than cases with concordant negative results (HR 3.03, 95% CI 1.13-8.14, p=0.03). Whereas among cases with positive SLL and negative ctDNA, there was not a significant difference compared with concordant negative cases (HR 1.54, 95% CI 0.58-4.12, p=0.39). **Conclusions:** In this cohort where nearly all patients were in clinical remission, ctDNA was an independent predictor of PFS after frontline therapy in high-grade ovarian cancer. Although discordance occurs between ctDNA and SLL, these data suggest that ctDNA may detect clinically meaningful MRD not captured by SLL and could represent a more clinically relevant prognostic tool in this setting. Research Sponsor: None.

5568 **Poster Session**

Dose-dense weekly versus standard three-weekly paclitaxel in combination with carboplatin for resectable stage II-IV epithelial ovarian carcinoma: A retrospective cohort study. First Author: Sehrish Sarwar Baloch, Aga Khan University Hospital, Karachi, Pakistan

Background: Dose-dense weekly paclitaxel combined with carboplatin has demonstrated variable efficacy in first-line treatment of resectable epithelial ovarian cancer across different populations. While Japanese and selected real-world studies suggest improved outcomes, large Western trials have failed to confirm a survival advantage. Data from South Asian populations remains limited. This study compared progression-free survival (PFS), overall survival (OS), and toxicity profiles of dose-dense versus standard three-weekly paclitaxel plus carboplatin in a real-world, resource-constrained setting. **Methods:** This single-center retrospective cohort study included women aged ≥20 years with resectable, FIGO stage II–IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treated between January 2015 and December 2018. Patients received first-line carboplatin at an AUC of 5 (Area Under Curve 5) with either dose-dense weekly paclitaxel (80 mg/m² on days 1, 8, and 15) or standard three-weekly paclitaxel (175 mg/m²). Kaplan–Meier methods were used to estimate PFS and OS, and comparisons were performed using the log-rank test. Cox proportional hazards models were applied for univariate and multivariate analyses. **Results:** Seventy-two patients were included, 36 in each arm. The majority presented with stage III disease (63.9% in the dose-dense arm vs. 52.8% in the standard arm). High-grade serous carcinoma was the predominant histology in both groups (83% vs. 75%). The distribution of primary versus interval debulking surgery and rates of residual disease were similar between the two arms. The dose-dense regimen was associated with significantly improved PFS compared with the standard schedule (mean PFS 25 vs. 18 months; 95% CI: 23.1-28.4; log-rank p = 0.01); median PFS was 32 months in the dose-dense arm, whereas it could not be estimated in the standard arm. OS favoured the dose-dense group (mean OS of 56 vs. 50 months), although this difference was not statistically significant (p = 0.27). In the multivariate analysis of the dose-dense cohort, elevated baseline Ca-125 (HR = 6.80; 95% CI: 1.38–34.20; p = 0.01) and cytoreduction type (HR = 13.30; 95% CI: 1.90–90.20; p = 0.008) were independent predictors of PFS but not for OS. Rates of grade ≥3 treatment-related adverse events were comparable between arms, while sensory neuropathy occurred more frequently with dose-dense therapy (39% vs. 28%). **Conclusions:** This real-world analysis supports the use of dose-dense weekly paclitaxel combined with carboplatin for improved PFS, findings consistent with some regional studies. While OS data showed a non-significant trend favouring the dose-dense regimen with some risk of neuropathy, they highlight the need for larger prospective regional studies to better define patient populations most likely to benefit. Research Sponsor: None.

5569 **Poster Session**

Everolimus and aromatase inhibitors for advanced and recurrent low-grade serous ovarian carcinoma. First Author: Halle Goodwin, Atrium Health Levine Cancer Wake Forest University, Charlotte, NC

Background: Treatment options for advanced and recurrent low grade serous ovarian carcinoma (LGSOC) are limited. Mutations in the PI3K/AKT/mTOR pathway have been described in LGSOC, but the use of everolimus and aromatase inhibitors (AI) has not been studied. Our primary objective was to determine the disease control rate (DCR) of everolimus (used off-label) and an AI in patients with LGSOC. Secondary objectives included progression free survival (PFS) and overall survival (OS). **Methods:** Diagnosis codes and medication lists were used to identify all patients with LGSOC from a single tertiary-care institution who were treated with everolimus and an AI between 2000-2025. Data were extracted from the electronic medical record including demographics, staging, treatment, CA-125, imaging studies, reported side effects, recurrence, and survival data. Response was defined with RECIST 1.1 when measurable disease was present, otherwise clinical response was used. CA-125 was used independently as an additional measure of response. **Results:** A total of eight patients were identified, six with stage IIIC disease and two with stage IVB disease. Patients had between 0 and 4 debulking surgeries. Prior to treatment with everolimus and an AI, patients had 1-6 prior lines of therapy. All patients had received prior endocrine therapy, and five received chemotherapy. All patients were treated with everolimus 10mg and an AI (6 with letrozole and 2 with anastrozole). Patients remained on this regimen between 2 and 20 months (median = 15 months). One patient continues treatment today after 21 months of treatment. By RECIST criteria, two patients had a partial response, and four patients had stable disease. One patient has had clinically stable disease (soft tissue thickening and a stable CA-125) for 21 months and continues treatment. When comparing initial CA-125 to nadir while on treatment, CA-125 was stable in three patients and decreased 29%-64% (median = 50.5%) in four patients. One patient did not have CA-125 available in the EMR. Overall, the DCR was 87.5% (7 of 8 patients). Median PFS was 16.8 months, and median OS was 26 months. Of the seven patients who discontinued treatment, reasons for discontinuation included progression (n=3), death from disease (n=2), and inability to tolerate (n=2, one with grade 3 pneumonitis). **Conclusions:** In a group of eight patients with advanced LGSOC, everolimus and an AI demonstrated a DCR of 87.5%, a median PFS of 16.8 months, and a median OS of 26 months. While larger retrospective studies or prospective studies are needed, this regimen should be considered for advanced, recurrent LGSOC. Research Sponsor: None.

5570 **Poster Session**

Exposure–response (E–R) analyses of efficacy and safety with raludotatug deruxtecan (R-DXd), a CDH6-directed antibod-drug conjugate (ADC), to inform dose selection for phase (Ph) 3 development in platinum-resistant ovarian cancer (PROC). First Author: Felipe K. Hurtado, Daiichi Sankyo, Inc., Basking Ridge, NJ

Background: R-DXd, an ADC, comprises a humanized cadherin 6 (CDH6) IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload (DXd) via a tumor-selective cleavable linker. R-DXd monotherapy demonstrated promising antitumor activity and a manageable safety profile at doses up to 6.4 mg/kg IV Q3W in patients (pts) with heavily pretreated ovarian cancer (OC) in a Ph 1 study and in pts with PROC in an ongoing Ph 2/3 study. We report findings from E–R analyses of key efficacy and safety endpoints that supported R-DXd dose selection for Ph 3 clinical investigation in patients with PROC. **Methods:** Data were included from (i) the first-in-human Ph 1 study in pts with advanced OC (N=156) or renal cell carcinoma (RCC; N=23) evaluating R-DXd 1.6–9.6 mg/kg Q3W (NCT04707248), and (ii) the dose-optimization part of the Ph 2/3 REJOICE-Ovarian01 study in pts with PROC (N=107) (NCT06161025), in which pts were randomized 1:1:1 to receive R-DXd 4.8, 5.6, or 6.4 mg/kg Q3W. E–R analysis for efficacy was conducted based on pooled data from 241 pts with PROC using BICR-assessed endpoints: ORR (primary endpoint in the Ph 2 part of REJOICE-Ovarian01), best change in target lesion size, DOR, and PFS. Further, E–R analysis for safety was performed for 11 AEs of clinical interest using data from 286 pts treated with R-DXd across tumor types (OC, RCC). ORR and all safety endpoints, except interstitial lung disease (ILD), were analyzed by logistic regression; DOR, PFS, and ILD were analyzed using the Kaplan–Meier method. Numerous patient-specific covariates were evaluated. **Results:** E–R analyses demonstrated positive dose–response relationships for both efficacy and safety. Higher R-DXd exposure was associated with increased probability of achieving objective response, greater reduction in target lesion size from baseline, longer PFS, and longer DOR. Covariate analysis identified that baseline CDH6 expression was positively associated with ORR and tumor response. Higher R-DXd or DXd payload exposure was associated with an increase in drug-related TEAEs, including Grade $\geq$3 (G3+) AEs, any-grade ILD, G2+ gastrointestinal AEs (nausea/vomiting), G3+ cytopenias (anemia, neutropenia, thrombocytopenia), and AEs leading to dose reduction. While higher doses of R-DXd are predicted to maximize efficacy based on the E–R analysis, the 5.6 mg/kg dose provides an overall optimal balance of safety, tolerability, and efficacy compared to 6.4 mg/kg and 4.8 mg/kg. **Conclusions:** Integrated E–R analyses, combined with the totality of data from 286 pts, support selection of 5.6 mg/kg Q3W as the optimal R-DXd monotherapy dose for the Ph 2 extension and Ph 3 parts of REJOICE-Ovarian01, in accordance with the principle of benefit/risk for oncology dose optimization and guidelines from the FDA's Project Optimus. Research Sponsor: Daiichi Sankyo; Merck.

5571 **Poster Session**

Population pharmacokinetic analysis of raludotatug deruxtecan (R-DXd), a cadherin 6 (CDH6)–directed antibody–drug conjugate (ADC), in patients (pts) with advanced ovarian cancer (OC) or renal cell carcinoma (RCC). First Author: Felipe K. Hurtado, Daiichi Sankyo, Inc., Basking Ridge, NJ

Background: R-DXd is a CDH6–directed ADC under clinical investigation for the treatment of pts with advanced or metastatic solid tumors, including platinum-resistant OC (PROC). This analysis was done to characterize the population pharmacokinetics (PopPK) of R-DXd and its small-molecule payload, DXd, in pts with OC or RCC. The analysis used data from two clinical studies of R-DXd: the first-in-human Ph 1 study in pts with OC or RCC (DS6000-A-U101; U101) and an ongoing global, randomized Ph 2/3 study in pts with PROC (REJOICE-Ovarian01). **Methods:** A joint PopPK model was developed for R-DXd and DXd, based on pooled data from the dose-escalation and -expansion parts of U101 (156 pts with OC and 23 with RCC; 1.6–9.6 mg/kg IV Q3W) and the dose-optimization primary analysis of REJOICE-Ovarian01 (107 pts with OC; 4.8, 5,6, or 6.4 mg/kg IV Q3W). The analysis was performed using nonlinear mixed-effects modeling in NONMEM (version 7.5.1). The effect of key intrinsic/extrinsic factors on the PK of R-DXd was explored through preliminary covariate analysis. **Results:** The PK of R-DXd and unconjugated DXd were adequately captured by the PopPK model. R-DXd displayed time-varying clearance, resulting in an elimination half-life of approximately 8 days after the first dose and 14 days at steady state. The overall PK profile supports a Q3W dosing interval. Consistent with findings from other mAbs and DXd-based ADCs, covariate analysis identified body weight (BW) as an influential covariate affecting R-DXd and DXd exposure, with the largest effect seen at the extremes of the BW distribution; pts with high BW (101 kg; 95th percentile) showed 26% and 66% higher R-DXd and DXd steady state area under the concentration–time curve (AUC), respectively, relative to a reference pt (61 kg; median BW). Post-hoc estimates of R-DXd and DXd AUC by BW quartiles showed that exposure in pts in the highest BW quartile ($>$75 kg) trended higher yet remained within the range of pts with average BW (53–74 kg; 25th–75th percentile). Other baseline covariates did not have a clinically important effect on R-DXd or DXd AUC, with effects falling within the predefined range of 80–125% vs reference. These covariates were CDH6 expression (total % membrane staining at any intensity); R-DXd formulation; hepatic function (mild impairment vs normal); renal function (mild-to-moderate impairment vs normal); tumor size; albumin level; number of prior lines of therapy (1 vs 2–3 vs $\geq$4); tumor type (RCC vs OC); Asian vs non-Asian race. **Conclusions:** R-DXd 5.6 mg/kg IV Q3W, the recommended Ph 3 dose, does not appear to warrant adjustment for any of the patient-specific covariates and clinical characteristics investigated. These findings support the adequacy of this dose for the global population of pts with PROC being recruited in the Ph 3 part of REJOICE-Ovarian01. Research Sponsor: Daiichi Sankyo; Merck.

5573 **Poster Session**

Multi-modal liquid biopsy integrating cfDNA fragmentomics and serum biomarkers for the differential diagnosis of ovarian tumors. First Author: Zhoumei Liu, Peking University Cancer Hospital Yunnan, Yunnan Cancer Hospital, The Third Affiliated Hospital Kunming Medical University, Kunming, Yunnan, China

Background: Ovarian cancer (OC) remains the leading cause of mortality among gynecological malignancies, primarily due to delayed diagnosis. Current diagnostic modalities, including imaging and serum biomarkers, exhibit suboptimal specificity, leading to unnecessary surgical interventions for benign adnexal masses. This study explores the clinical utility of cell-free DNA (cfDNA) fragmentomics, a high-dimensional genomic feature reflecting chromatin accessibility, in distinguishing malignant from benign ovarian tumors. **Methods:** This multi-center study enrolled 595 participants across three cohorts: a training set (n=236) and an internal validation set (n=172) from Yunnan Cancer Hospital, and an independent external validation set (n=136) from Beijing Obstetrics and Gynecology Hospital. Additionally, a prediction cohort included borderline ovarian tumors (BOT, n=51). Using whole-genome sequencing (WGS), we characterized cfDNA via four fragmentomic dimensions: copy number variations (CNVs), fragment size profiles (FSPs), nucleosome footprints (NFs), and genomic element perturbations (ARTEMIS). An ensemble model was trained to classify malignant ovarian cancer versus benign disease, and a generalized linear model was constructed by integrating fragmentomic scores with CA125 and HE4 levels to further improve the performance. **Results:** The cfDNA-only model demonstrated robust performance with Area Under the Curve (AUC) values of 0.937, 0.930, and 0.932 in the training, internal, and external cohorts, respectively. At 90% sensitivity in training (internal: 88.4%; external: 89.2%), specificities remained stable at 77.12%, 77.91%, and 78.87%. The model exhibited exceptional sensitivity for High-Grade Serous Ovarian Cancer (HGSOC) ($>$90%) with sensitivity increased with stages; early-stage (I–II) sensitivities were maintained $\geq$77%. Integrating the cfDNA fragmentomic score with CA125 and HE4 significantly enhanced AUCs to 0.961 (training), 0.964 (internal) and 0.964 (external). While maintaining high sensitivity (~90%), the combined model substantially increased specificity to 90.1% (training). Among 37 surgically treated stage I–III patients, higher preoperative predictive scores were significantly associated with shorter disease-free survival (DFS) ($p < 0.05$), independent of age, stage, and histology. In BOT patients, 39.2% were classified as higher malignant-risk, consistent with an intermediate phenotype. **Conclusions:** The integration of cfDNA fragmentomics with traditional biomarkers provides a highly sensitive and specific non-invasive tool for the differential diagnosis of ovarian masses. This multi-modal approach significantly outperforms current clinical standards, offering a promising strategy for early detection and clinical risk stratification in ovarian cancer management. Research Sponsor: Beijing Municipal Health Commission; BCRW202109; Capital Medical University; FCYYMZA202501.

5574 **Poster Session**

Real-world outcomes of olaparib with versus without bevacizumab in bevacizumab-naïve BRCA1/2-mutated ovarian cancer. First Author: Love Kumar, Charleston Area Medical Center (CAMC), Charleston, WV

Background: For patients with BRCA1/2-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer who complete primary platinum-based therapy, maintenance strategies differ based on prior bevacizumab (Bev) exposure. Patients who received Bev during frontline platinum therapy may receive Bev plus olaparib, whereas those without prior Bev exposure are generally treated with olaparib alone. No real-world evidence has evaluated outcomes of adding Bev to olaparib in patients who did not receive Bev during initial treatment. Using a large multi-institutional electronic health record dataset, we compared survival outcomes between olaparib monotherapy and olaparib–Bev combination therapy in this population. **Methods:** Adult patients from 2015-2024 with a diagnosis of ovarian, fallopian tube, or peritoneal cancer who received platinum chemotherapy followed by olaparib were first identified. Patients were then categorized based on bevacizumab exposure around the time of olaparib initiation (-1 to +3 months). This group was compared to patients who did not received Bev at any time. The index date was defined as 3 months after olaparib initiation to align treatment timing and minimize immortal time bias and propensity score matching was performed on age, race, metastatic sites, comorbidities, and prior treatments. Follow-up was then truncated at 3-years. **Results:** Before matching, 111 patients received Bev around the time of olaparib and 1,461 did not. After matching, 110 patients remained in each group with balanced characteristics. Three-year overall survival was significantly lower in the Bev group compared with the no-Bev group (52% vs 73%; HR 2.28, 95% CI 1.4–3.8; p=0.001). Treatment switching also occurred more often in the Bev group (54% vs 22%, $p < 0.0001$), with a median time to switching of 16.7 months; the no-Bev group did not reach median time. **Conclusions:** In real-world clinical practice, the addition of bevacizumab to olaparib in patients without prior bevacizumab exposure was associated with worse survival outcomes and earlier treatment switching. These findings may reflect the selection of patients with more aggressive or treatment-resistant disease for combination therapy, or they may suggest that intensifying therapy in this setting does not confer added benefit. Prospective, controlled studies are needed to clarify the underlying reasons for these observations and to better define which patients, if any, derive benefit from this treatment approach. Research Sponsor: None.

5575 **Poster Session**

A phase II evaluation of sacituzumab govitecan in platinum-resistant ovarian cancer (NCT06028932). First Author: Alessandro Santin, Yale School of Medicine, Division of Gynecologic Oncology, New Haven, CT

Background: Patients with platinum-resistant ovarian cancer (PROC) have few therapeutic options. More than 60% of high-grade serous ovarian cancers overexpress ($\geq$ 2+ by immunohistochemistry) Trop2, a key regulator of growth pathways and marker of aggressive disease. Sacituzumab govitecan (SG) is an antibody-drug conjugate consisting of a Trop-2–specific antibody conjugated with SN-38, an active metabolite of irinotecan. **Methods:** NCT06028932 is a single-institution open-label phase II study. Patients received SG at 10 mg/kg intravenously days 1 and 8 of a 21-day cycle until prohibitive toxicity or progression. The primary endpoint was objective response rate (ORR) by RECIST 1.1. Secondary endpoints included progression-free (PFS) and overall (OS) survival, as well as safety. **Results:** Twenty patients were enrolled. Median age was 67 years (range: 45-84). Most participants (85%, n=17) were White. The median number of prior lines prior to enrollment was 3 (range: 1-8). ECOG performance status was 0 (n=16) or 1 (n=4). Most patients had a poorly differentiated tumor (90%, n=18) with advanced disease (stage III/IV) at initial diagnosis (85%, n=17). Serous histology predominated (75%, n=15), followed by clear cell (15%, n=3), endometrioid (5%, n=1), and carcinosarcoma (5%, n=1). Across a median follow-up of 9.9 months, there were 15 progressions and 4 deaths. ORR was 35% (7/20); there were no complete responses, and stable disease was achieved in 40% (8/20). Median PFS was 8.0 months (95% CI: 3.8-14.8); median OS was not yet reached. No new safety signals were observed. The most common grade 3-4 treatment-emergent adverse events were neutropenia (n=15), hypokalemia (n=3), and anemia (n=2). The most frequent grade 1-2 events included diarrhea (n=59), fatigue (n=27), abdominal pain (n=20), nausea (n=20), alopecia (n=16), anorexia (n=14), and vomiting (n=13). **Conclusions:** SG exhibits encouraging efficacy for PROC with manageable toxicities. Future studies are warranted. Clinical trial information: NCT06028932. Research Sponsor: None.

5576 **Poster Session**

Preliminary efficacy and safety of first-line anlotinib plus carboplatin/paclitaxel induction therapy followed by anlotinib maintenance in advanced ovarian cancer: Results from the ALTER-GO-010 phase II multicenter trial. First Author: Wenjun Cheng, Jiangsu Provincial Hospital, Nanjing, China

Background: Several studies have shown that antiangiogenic drugs combined with chemotherapy as first-line treatment, followed by maintenance therapy with anti-angiogenic agents, significantly improve outcomes for ovarian cancer patients. Anlotinib, a highly effective multi-target tyrosine kinase inhibitor targeting VEGFRs, FGFRs, PDGFRs, and c-Kit, has been approved for multiple tumor types in China. The ALTER-GO-010 study is a single-arm, multicenter phase II trial designed to assess the efficacy and safety of anlotinib in combination with carboplatin/paclitaxel as first-line induction therapy, followed by anlotinib maintenance, in patients with newly diagnosed advanced ovarian cancer. **Methods:** Eligible patients with newly diagnosed FIGO stage III–IV primary epithelial ovarian, fallopian tube, or primary peritoneal cancer (ECOG PS 0–1) who have undergone primary or interval debulking surgery will receive 6-8 cycles of chemotherapy (paclitaxel 175 mg/m² + carboplatin AUC 5 every 3 weeks) combined with anlotinib (12 mg orally once daily on days 1–14, 21-day cycle; omitted during the first cycle to prevent delayed wound healing). Following chemotherapy completion, anlotinib will be continued as maintenance monotherapy until disease progression, unacceptable toxicity, or death. Exclusion criteria include prior anti-angiogenic therapy or major surgery within 28 days before anlotinib initiation. The primary endpoint is progression-free survival (PFS). Key secondary endpoints include overall survival, and safety profile. **Results:** As of the data cutoff date (November 30, 2025), 54 patients had received at least one dose of the study drug and were included in the analysis. The median age was 56 years, 98.11% had high-grade serous carcinoma and 1.89% had endometrioid carcinoma. 96.23% had FIGO stage III and 3.77% had stage IV. The data maturity for PFS analysis was 40.7%. The median PFS was 20.76 months (95% CI: 11.58-29.95). Patients without prior history of neoadjuvant therapy had longer mPFS than those with prior therapy. The median OS was not reached. The most common all-grade treatment emergent adverse events (TEAEs) were white blood cell deceased, anemia, neutrophil count decreased, platelet count decreased and lymphocyte count decreased. Grade $\geq$3 TEAEs occurred in 75.5% of patients during the chemotherapy phase and 22.7% during maintenance. No treatment-related deaths were reported. **Conclusions:** The preliminary efficacy and safety data suggest that anlotinib plus carboplatin/paclitaxel induction therapy, followed by anlotinib maintenance, is a promising regimen for newly diagnosed advanced ovarian cancer, with a median PFS of 20.76 months and a favorable safety profile. Clinical trial information: NCT04807166. Research Sponsor: None.

5577 **Poster Session**

A novel prognostic index for survival prediction in ovarian cancer: Beyond FIGO staging. First Author: Arya Prathap, AIIMS Bhubaneswar, Bhubaneswar, India

Background: Prognostication in ovarian cancer is traditionally based on FIGO stage, although survival is influenced by additional patient- and treatment-related factors. We developed a new scoring system integrating age, comorbidities, and disease burden to improve survival prediction. **Methods:** Patients with ovarian malignancies treated with curative intent between June 2016 and November 2024 were identified from a prospectively maintained database. Cox proportional hazards regression was performed for 4-year overall survival (OS). Regression coefficients of significant variables were used to construct a new index. Survival outcomes were assessed using Kaplan–Meier analysis. Predictive performance of new index was compared with FIGO staging using receiver operating characteristic (ROC) analysis. **Results:** Of 221 consecutive patients, 167 treated with curative intent were analyzed. Median age of the cohort was 52 years (IQR 22–78), and FIGO stage IIIC was most common (45.7%). Optimal cytoreduction was achieved in 80.8%, and 71.3% received adjuvant therapy. At a median follow-up of 38.3 months, recurrence and mortality rates were 32.9% and 26.2%, respectively. The new score incorporated age, total surgical PCI, hypothyroidism, diabetes mellitus, and hypertension with regression-derived coefficients of 0.044, 0.114, 0.329, 0.146, and 0.313 respectively. For each patient, a prognostic index (PI) was calculated as the weighted sum of regression coefficients corresponding to that patient's covariate profile, using formula, where PI (Prognostic index)= $\sum (\beta_{1\,x}$ age) + (β_2 x PCI) + (β_3 x C_1) + (β_4 x C_2)+....(β_k x C_k), C_1...C_k = individual comorbidities (eg., diabetes, hypertension, etc), if present = 1, absent = 0). Based on the prognostic index, patients were classified into low- (33.75%), intermediate- (31.3%), and high-risk (31.3%) groups. Compared with the low-risk group, OS was worse in the intermediate-risk group (HR 2.37; 95% CI, 0.95–5.91; p = 0.06) and significantly inferior in the high-risk group (HR 7.89; 95% CI, 3.37–18.49; $p < 0.001$). Disease free survival (DFS) also showed a similar trend. The prognostic index demonstrated superior discrimination compared with FIGO staging (C-index 0.73 vs 0.68; AUC 0.71 vs 0.65) and remained robust on bootstrap internal validation. A prespecified subgroup analysis restricted to FIGO stage III patients was performed and demonstrated superior discrimination for overall survival compared with FIGO staging alone (AUC 0.71 vs 0.61), highlighting prognostic heterogeneity beyond anatomic staging. **Conclusions:** The prognostic index demonstrated improved discrimination compared with FIGO staging by integrating patient age, comorbidities, and disease burden. This practical, clinically applicable index may facilitate improved risk stratification beyond anatomic staging and may support individualized management strategies in ovarian cancer. Research Sponsor: None.

5578 **Poster Session**

Beyond survival: Understanding unmet needs among a diverse cohort of ovarian cancer survivors. First Author: Caroline P. Shermoen, University of Pennsylvania, Philadelphia, PA

Background: Improvements in therapy have resulted in a growing population of ovarian cancer survivors, with both incidence and survivorship increasing among non-White racial and ethnic groups. Despite increasing survivors, supportive care for ovarian cancer survivors has been reported as insufficient. Existing instruments to address survivorship needs were developed in homogenous populations, predominantly consisting of White patients. The purpose of this study was to gain a deeper understanding of the needs and experiences in a diverse cohort of ovarian cancer survivors. **Methods:** Structured focus groups of ovarian cancer survivors were conducted at a single academic NCI-designated cancer center. During focus groups, participants were guided in discussion about their experience, perspective, and unmet needs as an ovarian cancer survivor. The topics were developed in consultation by providers involved in direct ovarian cancer research and patient care. Thematic analysis was used to systematically code and analyze focus group transcripts, allowing for identification of recurrent patterns and themes within the data. **Results:** Three focus groups of 20 patients were conducted. 12 (60%) patients identified as White, 4 (20%) as Asian, 3 (15%) as Black, and 1(5%) as Hispanic; additional patient characteristics are in Table 1. Participants generally reported their care during treatment was efficient and streamlined; however, gaps in survivorship care emerged. Key themes included poor care coordination with non-oncologic providers, feelings of abandonment after active treatment, limited communication about long-term expectations after surgery and/or chemotherapy, lack of individualized care plans, and uncertainty about where to find reliable resources. Suggested improvements included centralized access to survivorship resources, expanded peer support opportunities, and more tailored, patient-specific communication. **Conclusions:** The study highlights specific gaps in ovarian cancer survivorship among a diverse patient population. Deficits in care coordination, individualized communication, and access to tailored resources may contribute to feelings of abandonment and uncertainty following treatment. Targeted survivorship interventions addressing these areas may help to improve quality of life among an increasingly diverse population of ovarian cancer survivors. Research Sponsor: National Cancer Institute.

Focus group characteristics (N=20).

Patient Characteristics	# of Participants
Age Range (Years)	
<50	4
50-59	7
60+	9
Time Since Diagnosis (years)	
>10	2
5-10	4
3-5	2
<3	12

5579 **Poster Session**

Phase II study of utidelone plus fruquintinib for the treatment of platinum-resistant recurrent ovarian cancer (FRUTD trial). First Author: Hao Wen, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Patients (pts) with platinum-resistant ovarian cancer (PROC) have a poor prognosis, and traditional cytotoxic drugs have limitations in efficacy and safety. Therefore, we are exploring the combination of utidelone capsule (UTD2), a novel oral microtubule inhibitor, with fruquintinib capsule (F), a tyrosine kinase inhibitor targeting VEGFR 1,2,3, for the treatment of platinum-resistant recurrent ovarian cancer. **Methods:** This study is an open-label and Simon two-stage phase II clinical trial, aiming to enroll 35 pts with platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. All pts were high-grade serous ovarian cancer, with prior 1-5 lines of systemic therapy, and no more than 3 lines of subsequent therapy after platinum-resistant recurrence. Subjects received F in combination with UTD2 in 21-day cycles. The dose of F was 5 mg once daily, taken orally from day 1 to day 14 of each cycle. The dose of UTD2 was 60 mg/m²/day once daily, taken orally from day 1 to day 5 of each cycle. Primary endpoint was objective response rate (ORR) per RECIST v1.1. In Stage 1, 14 pts received per protocol treatment, and the study would proceed to Stage 2 (enrolling additional 21 patients) if ≥2 objective responses (CR/PR) were observed in Stage 1. Secondary endpoints included investigator-assessed progression-free survival (PFS), disease control rate (DCR), duration of response (DoR), overall survival (OS) and Safety. **Results:** From March 18, 2025 to December 22, 2025, 19 pts were enrolled. Median age was 59 years (range, 44-68) with an ECOG PS score of 1. Median prior lines systemic therapy was 3 (range, 1-5) with 1, 2, 3, 4 and 5 lines for 4 pts (21.1%), 2 pts (10.5%), 6 pts (31.6%), 5 pts (26.3%), and 2 pts (10.5%), respectively. Median number of chemotherapy lines after platinum resistance was 1 (range, 0-3), with 0, 1, 2, or 3 lines of chemotherapy for 6 pts (31.6%), 6 pts (31.6%), 5 pts (26.3%), and 2 pts (10.5%), respectively. 14 pts were evaluated for efficacy with an outcome of 1 complete response, 8 partial responses and 5 stable diseases. ORR was 64.3% (95% CI: 38.8-83.7) and DCR was 100%. Median PFS was 7 months (95% CI: 2.8-7.2) and median OS has not reached. The Grade 3 treatment-related AE (TRAE) included neutropenia (n=2), mucositis oral (n=1), palmar-plantar erythrodysesthesia syndrome (n=1), skin ulceration (n=1), diarrhea (n=1), pain (n=1) and neurotoxicity (n=1). There were no ≥Grade 4 TRAE. 1 patient discontinued UTD2+F due to TRAEs. **Conclusions:** Utidelone plus Fruquintinib demonstrated encouraging efficacy for the treatment of PROC with a tolerable safety profile. This study is still actively ongoing, and further data will be provided at time of presentation. Clinical trial information: NCT06973421. Research Sponsor: Beijing Biostar Pharmaceuticals Co., Ltd.

5580 **Poster Session**

Phase I, multicenter, first-in-human (FIH) global study of SIM0505, an anti-CDH6 (CDH6) antibody-drug conjugate (ADC) in patients with advanced solid tumors. First Author: Xiaohua Wu, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Cadherin 6 is a transmembrane glycoprotein overexpressed in multiple cancers, including ovarian cancer (OC) and uterine serous cancer (USC). SIM0505 is an ADC comprised of an anti-CDH6 humanized IgG1 monoclonal antibody, a stable linker cleaved within tumor cells, and a novel topoisomerase I inhibitor, CPT116. Here, we report initial results from a global FIH study of SIM0505 (NCT06792552). **Methods:** This is a Phase 1 study to evaluate the safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of SIM0505 in patients (pts) with advanced solid tumors. SIM0505 was administered IV every 21 days from 1.6 mg/kg to 9.6 mg/kg. Dose levels from 3.2-8.0 mg/kg were backfilled. **Results:** As of 26 Dec 2025, 38 pts were enrolled without preselection for CDH6 expression (29 OC, 4 USC, 2 endometrioid endometrial cancer, 3 renal cell cancer) from 1.6 mg/kg to 9.6 mg/kg in the dose-escalation part. The median age was 57.0 years (range 42-78). The median number of prior therapy regimens was 5 (range 1-11). Of the 29 OC pts, 27 (93.1%) were high grade serous and 23 (79.3%) were platinum resistant. 22 (75.9%), 20 (69.0%) and 2 (6.9%) had received bevacizumab, PARPi and mirvetuximab soravtansine (MIRV), respectively. The median treatment duration was 10.6 weeks (range 3.0-33.6). Any-grade and Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 37 (97.4%) and 21 (55.3%) pts, respectively. Any-grade and Grade ≥3 treatment-related adverse events (TRAEs) occurred in 35 (92.1%) and 17 (44.7%) pts, respectively. The most common (≥10%) Grade ≥3 TRAEs were thrombocytopenia (23.7%), neutropenia (21.1%), and white blood cell count decreased (18.4%). One pt at 9.6 mg/kg had dose-limiting toxicity of Grade 4 febrile neutropenia and thrombocytopenia and discontinued treatment. Another patient discontinued treatment due to Grade 2 interstitial lung disease. Serious TRAEs were observed in 6 (15.8%) pts. No TEAEs led to death. MTD was not reached. Among 30 evaluable pts, 11 partial responses (PR, 9 OC and 2 USC) and 13 stable disease were observed. 8 PRs occurred among 14 evaluable OC pts at potential therapeutic dose range of 4.8-8 mg/kg. 9 of 21 Gynecological Cancer Intergroup (GCIG) evaluable pts had CA-125 response. The exposure of SIM0505 was proportional to dose in general, with a half-life of about 8 days. The PK profile was similar to that of total antibody, indicating good stability of the ADC in the circulation. **Conclusions:** SIM0505, a first in class CDH6 CPT116 payload ADC showed manageable safety and tolerability, including at higher dose levels with encouraging efficacy in OC and USC, with a favorable PK profile. These data support initiating the dose optimization portion of the study in gynecological cancers. Clinical trial information: NCT06792552. Research Sponsor: None.

5581 **Poster Session**

Impact of organ-adjacent extracellular vesicle proteomics from uterine lavage on accurate detection and discrimination of ovarian cancer. First Author: John A. Martignetti, MDDx, Inc, Tarrytown, NY

Background: Survival in ovarian cancer (OvCA) exceeds 90% when disease is localized, yet most cases present at advanced stage and effective early detection remains elusive. Blood-based liquid biopsies may be limited by low tumor signal in early disease. We evaluated whether organ-adjacent sampling via uterine lavage extracellular vesicle (EV) proteomics combined with machine-learning (ML) classification could enable accurate detection of OvCA and clinically relevant discrimination from endometrial cancer (EndoCA). **Methods:** Uterine lavage samples were collected under IRB-approved protocols from women undergoing gynecologic evaluation for abnormal uterine bleeding and/or abnormal pelvic imaging. EVs were isolated using an affinity-based capture method and analyzed by liquid chromatography-tandem mass spectrometry. Protein features meeting predefined quality thresholds were analyzed using a novel ML pipeline incorporating entropy-based marker scoring and correlation filtering. Classifier performance was assessed using repeated random two-fold validation and receiver operating characteristic analysis. **Results:** Among 807 participants, diagnoses included OvCA (n=85), benign conditions (n=488), and EndoCA (n=234). An OvCA-versus-benign classifier derived from a 91-protein panel demonstrated strong discrimination (AUC >0.9). Across 100 validation splits, 83 of 85 OvCA cases were correctly classified, including all stage I cases (27/27). A separate 21-protein classifier distinguished OvCA from EndoCA with a sensitivity of 0.94 and specificity of 0.92. **Conclusions:** EV proteomic analysis of uterine lavage specimens enables accurate detection of ovarian cancer, including stage I disease, and reliably distinguishes OvCA from EndoCA in women undergoing gynecologic evaluation. These findings support further prospective clinical validation of organ-adjacent EV proteomics as a translational diagnostic strategy for earlier and more precise classification of gynecologic malignancies. Research Sponsor: None.

5582 **Poster Session**

Fluorescence-guided surgery with 5-aminolevulinic acid (5-ALA) in ovarian, fallopian tube, and primary peritoneal cancers: Efficacy and safety results from the GINGA study. First Author: Takashi Motohashi, Tokyo Women's Medical University Hospital, Shinjukuku, Tokyo, Japan

Background: Administration of 5-aminolevulinic acid (5-ALA) results in tumor-selective accumulation of protoporphyrin IX, enabling visualization of malignant lesions as red fluorescence under blue light illumination. Although 5-ALA–based photodynamic diagnosis (ALA-PDD) is well established for non-muscle invasive bladder cancer, its role in gynecologic malignancies remains insufficiently characterized. We conducted an investigator-initiated clinical study to evaluate the efficacy and safety of ALA-PDD in ovarian, fallopian tube, and primary peritoneal cancers. **Methods:** From October 2024 to May 2025, patients scheduled for cytoreductive surgery or exploratory laparotomy were enrolled. After exclusion of one patient due to a change in treatment strategy, 22 patients received oral 5-ALA hydrochloride (20 mg/kg) 3–8 hours prior to surgery. Diagnostic performance for detecting peritoneal dissemination under blue light (BL) was compared with that under conventional white light (WL), assessing sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Statistical tests were performed using McNemar's-test (sensitivity and specificity) or Chi-square test (PPV and NPV). Safety was evaluated based on the incidence and severity of adverse events. **Results:** Overall sensitivity was comparable between BL and WL (88.8% vs 80.9%), whereas BL demonstrated significantly higher specificity (67.3% vs 51.9%, p = 0.0229), indicating fewer false-positive findings. Notably, in patients undergoing interval debulking surgery (IDS; n = 9), BL significantly outperformed WL across all diagnostic metrics, including sensitivity, specificity, PPV, and NPV (all $p < 0.05$). These findings suggest that ALA-PDD enables more accurate intraoperative discrimination between malignant and non-malignant lesions following neoadjuvant chemotherapy. All patients experienced adverse events, predominantly Grade ≤2. One case of postoperative ileus was reported; however, no causal relationship with 5-ALA was identified, and no clinically relevant safety signals emerged. **Conclusions:** ALA-PDD appears to enhance intraoperative diagnostic accuracy compared with conventional white light inspection and demonstrates an acceptable safety profile in ovarian, fallopian tube, and primary peritoneal cancers. In IDS patients, ALA-PDD may serve as a clinically meaningful adjunct to achieve precise cytoreduction and support surgical decision-making in the neoadjuvant chemotherapy setting. Clinical trial information: jRCTs031240345. Research Sponsor: None.

5583 **Poster Session**

Differential impact of *TP53* and *KRAS* pathogenic variants on overall survival in advanced ovarian carcinoma. First Author: Shreyas Kudrimoti, Kaiser Permanente Santa Clara Medical Center, Santa Clara, CA

Background: Advanced epithelial ovarian carcinoma, including high grade serous ovarian carcinoma (HGSOC), clear cell ovarian carcinoma (CCOC), endometrioid ovarian carcinoma (EOC) and mucinous ovarian carcinoma (MOC), frequently presents in advanced stages and is associated with poor outcomes. In addition to common germline mutations in *BRCA1/2*, many patients also harbor *TP53* and *KRAS* pathogenic variants (PVs) in their tumors. However, the role of these genomic alterations in advanced epithelial ovarian cancer remains unclear. **Methods:** Our study examined a large cohort of patients (n = 1060) with advanced epithelial ovarian cancer with genomic profiling performed using next-generation sequencing (StrataNGS). Cox regression modeling was used to examine the associations between *TP53* and *KRAS* PVs and overall survival (OS), adjusting for covariates including age, race/ethnicity, performance status, Charlson Comorbidity Index, and other genomic alterations. **Results:** Our cohort included HGSOC (n = 924), CCOC (n = 66), EOC (n = 42), and MOC (n = 28). Median OS was 33.4, 33.8, 25.1 and 66.8 months for HGSOC, CCOC, MOC and EOC, respectively. In the CCOC group, *TP53* PVs were associated with worse OS (hazard ratio [HR] = 3.23, [95% confidence interval [CI], 1.05-9.89]), while *KRAS* PVs were associated with better OS (HR = 0.29, [95% CI ,0.09-0.89]). In patients with HGSOC 71.3% had *TP53* PVs, whereas 8.0% had *KRAS* PVs. *KRAS* PVs were associated with better OS (HR = 0.72, [95% CI, 0.50-1.02]) in HGSOC. *TP53* PVs were associated with worse OS only within the sub-cohort that also harbored *KRAS* PVs (HR = 3.42, [95% CI, 1.13-10.33]. *TP53* PVs were not associated with OS in the *KRAS* wild-type sub-cohort (HR = 0.95, [95% CI, 0.72-1.25]). Our finding that *TP53* PVs were associated with worse OS in *KRAS* PVs sub-cohort was confirmed by interaction analysis (HR = 2.06, [95% CI, 0.98-4.35]). There was no OS difference between TP53 gain-of-function versus non-gain-of-function PVs in HGSOC patients. **Conclusions:** In our large study cohort of patients with advanced epithelial ovarian carcinoma, we found that *TP53* and *KRAS* PVs were differentially associated with OS. Surprisingly, *KRAS* PVs were associated with higher OS in HGSOC while *TP53* PVs were associated with worse OS only in conjunction with *KRAS* PVs, highlighting the need to deepen our understanding of the oncogenic role *KRAS* plays in ovarian epithelial carcinoma. Further mechanistic studies to understand the roles of these common mutations in ovarian cancers could provide deeper insights. Research Sponsor: None.

5584 **Poster Session**

Incidence and genomic characteristics of a low homologous recombination deficiency score subgroup in *BRCA*-mutant ovarian cancer. First Author: Caiyan Liu, Department of Gynecological Oncology, Tianjin Central Hospital of Gynecology Obstetrics, Tianjin, China

Background: Homologous recombination deficiency (HRD) is a pivotal molecular phenotype in ovarian cancer (OC) and serves as a key biomarker for guiding PARP inhibitor (PARPi) therapy. Current clinical algorithms assess HRD status by integrating pathogenic BRCA1/2 mutations and genomic scar scores. Nevertheless, a paradoxical phenotype exists: BRCA mutations with a low HRD score. The incidence and genomic characteristics of this subgroup remain poorly understood. **Methods:** We retrospectively analyzed a cohort of OC patients tested at a centralized laboratory (2024-2025). A composite genomic instability score was calculated as the sum of three biomarkers: loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale state transitions (LST). HRD positivity was defined as the presence of a BRCA1/2 pathogenic/likely pathogenic variant and/or a HRD score (LOH+TAI+LST) $\geq$ 42. **Results:** Among 441 ovarian cancer samples, 151 of 310 (34.24%, 151/441) BRCA wild-type patients had an HRD score $\geq$ 42, primarily driven by other homologous recombination repair (HRR) gene alterations. Conversely, among 131 BRCA-mutant patients, 30 (6.80%, 30/441) had an HRD score $<$ 42. Notably, 13 patients (2.95%, 13/441) with pathogenic BRCA variants exhibited remarkably low HRD scores ($<$ 10). This subgroup comprised 10 BRCA1 and 3 BRCA2 alterations, including: 4 somatic truncating mutations [Exon11 S1389* (VAF=4.41%; HRD=0), Exon11 D1868Vfs*5 (VAF=4.80%; HRD=4), Exon10 E597* (VAF=17.37%; HRD=3), Exon10 K339Rfs*2 (VAF=30.65%; HRD=6)]; 6 germline truncating mutations [Exon21 Q1785* (VAF=50.29%; HRD=9), Exon13 G1492* (VAF=47.61%; HRD=7), Exon10 L1086* (VAF=46.52%; HRD=2), Exon11 S1882* (VAF=50.83%; HRD=0), Exon10 Q1200* (VAF=49.37%; HRD=0), Exon11 L1908Rfs*2 (VAF=44.44%; HRD=0)]; and 3 germline copy number deletions (HRD=2, 2, 0). We hypothesize potential mechanisms for this discordance: 1) Monoallelic inactivation: Single-allele inactivation (first hit) without a complete loss-of-function second hit, leading to partial HR function retention. 2) Subclonal variants: Low VAF suggests BRCA mutations may reside in tumor subclones, not dominating the pan-tumor HRD phenotype, with signals diluted by HR-proficient cells. 3) Time-dependency: BRCA inactivation might occur late in tumor evolution, insufficient for accrual of HRD-associated genomic scars at testing. **Conclusions:** This study quantifies a rare subgroup (~3%) of OC with pathogenic BRCA mutations but low HRD scores. This suggests monoallelic BRCA mutation alone may be insufficient to induce high genomic instability, potentially contributing to primary resistance to PARPis, though validation with clinical outcome data is required. Future studies integrating multi-omics data are needed to precisely evaluate HR pathway status and guide individualized treatment decisions. Research Sponsor: None.

5585 **Poster Session**

Virtual multiplex immunofluorescence characterization of spatial immune architectures and tertiary lymphoid structures in high-grade serous ovarian cancer. First Author: Junhwan Kim, Center for Gynecologic Cancer, National Cancer Center, Goyang-Si, South Korea

Background: GigaTIME (*Cell*, 2026) is a deep learning–based virtual multiplex immunofluorescence (mIF) model that has been validated using TCGA datasets and enables spatial tumor immune microenvironment (TIME) profiling directly from H&E whole-slide images (WSIs). This study aims to evaluate the feasibility of GigaTIME for characterizing the spatial TIME of high-grade serous ovarian cancer (HGSOC) using public datasets. **Methods:** We analyzed UBC-OCEAN and CPTAC-OV HGSOC H&E WSIs using GigaTIME to generate virtual 21-channel (e.g., DAPI, CK, CD3, CD8, CD20, and Ki67) mIF pixel-level inferred probability maps. Exploratory analyses of 5$\times$5 stitched regions of interest (ROI, 2560$\times$2560 pixels $\approx$ 1.28$\times$1.28 mm) were performed to detect tertiary lymphoid structures (TLS) via density-based spatial clustering of applications with noise (DBSCAN), identified as CD20$^+$ clusters (major axis $\geq$100 μm) adjacent to CD3$^+$ zones, with maturity defined by intra-cluster Ki67$^+$ proliferation. Tumor-immune interaction metrics were analyzed in ROIs using Group Degree Centrality (GDC, fraction of tumor cells contacting immune cells) and Cluster Co-occurrence Ratio (CCR, observed/expected contacts). CPTAC-OV HGSOC H&E WSI–derived virtual mIF features were correlated with bulk proteomics using Spearman's rank correlation. Integrated K-means clustering was performed on the combined cohorts after Z-score normalization. **Results:** The UBC-OCEAN cohort (N=195) exhibited an immune-inflamed phenotype with high tumor-immune engagement (mean GDC [mGDC] 0.25) and structural aggregation (mean CCR [mCCR] 1.41), whereas CPTAC-OV (N=222) displayed an immune-excluded phenotype with minimal contact (mGDC 0.05) and near-random distribution (mCCR 1.03). While total TLS density was comparable (UBC-OCEAN 3.92 vs. CPTAC-OV 3.60), UBC-OCEAN exhibited a twofold higher density of mature TLS compared to CPTAC-OV (1.83 vs. 0.77). Integrated clustering (k=2, silhouette=0.71) revealed that High-TLS (N=39) tumors paradoxically exhibited significantly lower mGDC (p=0.016) and mCCR (p=0.001) despite higher TLS density, indicating a spatially segregated and organized immune architecture. In CPTAC-OV validation, virtual CD3 intensity showed a significant positive correlation with bulk proteomics (N=17, ρ=0.547, p=0.023), supporting the biological validity of the T-cell-based spatial metrics. **Conclusions:** GigaTIME is feasible for evaluating comprehensive spatial TIME including TLS and demonstrates the heterogeneous immune landscape of HGSOC, providing spatial insights that are not captured by bulk proteomics alone. This warrants the utility of virtual mIF-based profiling as a scalable tool to identify distinct immune phenotypes for personalized immunotherapy at minimal cost. Research Sponsor: None.

5586 **Poster Session**

Surufatinib combined with toripalimab for the treatment of recurrent ovarian clear cell carcinoma: Update of a prospective single center, single-arm phase II clinical trial. First Author: Huijuan Yang, Department of Gynecologic Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Ovarian clear cell carcinoma (OCCC) is a histologically aggressive subtype of epithelial ovarian cancer with limited effective treatment options, particularly for recurrent disease. This study aims to evaluate the efficacy and safety of surufatinib (a kinase inhibitor targeting VEGFR 1, 2, 3, FGFR 1, and CSF-1R) in combination with toripalimab (an anti PD-1 antibody) for recurrent OCCC. Here, we present the latest efficacy and safety data. **Methods:** 23 patients aged 18-75 with histologically confirmed recurrent OCCC, ECOG performance status of 0-2, and failed first or subsequent-line therapy was enrolled (If the patient only had first line chemotherapy, platinum-free interval should be less than 12 months or disease progression occurred during chemotherapy). Patients received orally surufatinib 250 mg once daily in combination with toripalimab 240 mg on day 1 every 3 weeks until disease progression or unacceptable toxicity. Primary endpoint is progression-free survival (PFS), and secondary endpoints include objective response rate (ORR), overall survival (OS), and safety. **Results:** From Jul. 2023 to Dec. 2025, 19 patients (median age 51) were enrolled, with 52.6% (10/19) had an ECOG PS of 0, 73.7% (14/19) were classified as clinical stage of I-II. 57.9% (11/19) had received prior first-line treatment, while the remaining 8 patients had received twice or more. Eight patients had previously received bevacizumab. Among the 19 patients, 10 were platinum-resistant while 9 were platinum-sensitive. The primary metastatic sites were lymph nodes (8/19, 42.1%), lungs (6/19, 31.6%), pelvic cavity (6/19, 31.6%) and peritoneum (5/19, 26.3%). With a median follow-up of 7.1 months, the median PFS was 4.4 months (95% CI: 2.6-8.8). Tumor response was evaluable in 19 patients, with 1 complete response, 4 partial response and 11 had stable disease, resulting in an ORR of 26.3% (95% CI: 9.2-51.2%), and a disease control rate of 84.2% (95% CI: 60.4-96.6%). The most common ($\geq$20%) treatment related adverse events (TRAEs) were hyperthyroidism (42.1%), proteinuria (36.8%), hypertension (36.8%), diarrhea (36.8%), anaemia (31.6%), rash (31.6%), increased TSH (26.3%), hypoalbuminaemia (21.1%), increased AST (21.1%) and increased ALT (21.1%). Grade 3 TRAEs ($\geq$10%) were mainly hypertension (15.8%), increased AST (15.8%), increased ALT (10.5%). All of AEs were effectively controlled after temporarily discontinuing surufatinib or toripalimab, or reducing the dose of surufatinib, or receiving symptomatic treatment. There were no cases with fatal outcome. **Conclusions:** The combination of surufatinib and toripalimab exhibited potential clinical activity and tolerable toxicity in patients with recurrent OCCC. Clinical trial information: ChiCTR2400083672. Research Sponsor: None.

5587 Poster Session

IGNITE-Cerala: A phase II signal-seeking trial of ceralasertib targeting recurrent high-grade serous ovarian cancer with cyclin E1 overexpression with and without gene amplification. First Author: George Au-Yeung, Department of Medical Oncology and the Sir Peter MacCallum Department of Oncology, Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, VIC, Australia

Background: Cyclin E1 (*CCNE1*) gene amplification and protein over-expression is a marker of platinum resistance in high grade serous ovarian, fallopian tube or primary peritoneal cancer (HGSC). Preclinical studies in breast and HGSC models have identified cyclin E1 amplification or over-expression as a potential predictive biomarker for improved sensitivity to ATR inhibition. We aimed to assess the efficacy of ceralasertib, an ATR inhibitor, in HGSC with cyclin E1 over-expression. **Methods:** IGNITE is a multicentre, Phase 2 trial enrolling women with recurrent platinum resistant HGSC. Tumors were assessed for Cyclin E1 protein expression by IHC and *CCNE1* copy number by FISH. Patients with evaluable disease by RECIST v1.1 or GCIG CA-125 criteria were included. Ceralasertib 160mg PO was given twice daily on days 1-14 of a 28-day cycle. The primary endpoint was investigator assessed overall response rate (ORR), defined as partial response (PR) or complete response (CR) at 16 weeks by RECIST v1.1 among patients with measurable disease, or by GCIG CA-125 criteria for patients with non-measurable disease. Here we present the 16-week response data for all patients treated with ceralasertib with a data cut-off of July 2025. **Results:** Between Feb-2024 and Apr-2025, 32 patients were accrued to IGNITE-Cerala. One patient was deemed ineligible after registration and was excluded. Median age was 64 years (range 40-76) and 74% had received ≥2 prior lines of chemotherapy. Median cyclin E1 IHC H-score was 190 (range 60 – 260). Twenty-seven patients (87%) had measurable disease by RECIST. Median number of cycles commenced was 3 (range 1-18). The ORR at 16 weeks was 10% (0 CR and 3 PR). The 6 month progression free survival estimate was 26% (range 12-42%). Treatment related adverse events (TRAE) were mostly grade 1-2 with the most common being gastrointestinal or hematologic. Six patients (19%) had Grade 3 TRAE, and one patient had Grade 4 TRAE. Six patients (19%) required a dose reduction, and no patients discontinued study drug due to toxicity. **Conclusions:** Ceralasertib was a well tolerated treatment, however responses did not appear to be enriched in a biomarker selected population and therefore future studies should consider rationale combinations with ceralasertib. Cyclin E1 over-expression and amplification remains an important biomarker in HGSC, with other strategies such as CDK2 or PK-MYT1 inhibitors under active investigation. Clinical trial information: ACTRN12619001185156. Research Sponsor: AstraZeneca.

Response at 16 weeks	Response evaluable patients (n=31)	RECIST measurable patients (n=27)
CR	0 (0%)	0 (0%)
PR	3 (10%)	3 (11%)
SD	7 (23%)	7 (26%)
No CA-125 response and no PD	1 (3%)	-
PD	20 (65%)	17 (63%)
ORR (CR/PR)	**3 (10% [2, 26])**	**3 (11% [2, 9])**

5589 Poster Session

Budget impact analysis of heated intraperitoneal chemotherapy at interval cytoreductive surgery for stage III high grade serous carcinoma of tubo-ovarian origin. First Author: Tal Milman, University of British Columbia, Vancouver General Hospital, Vancouver, BC, Canada

Background: Heated Intraperitoneal Chemotherapy (HIPEC) at interval cytoreductive surgery (ICS) for high grade serous carcinoma of tubo-ovarian origin (HGSOC) improves overall survival (OS) by 11.6 months and increases platinum sensitivity at recurrence. Our aim was to estimate the payer budget impact of adopting HIPEC in BRCA wild-type patients at a quaternary Canadian center. **Methods:** A retrospective review was conducted of patients undergoing surgery for metastatic HGSOC at Vancouver General Hospital, Vancouver, Canada between January 1 and December 31, 2024. A payer-perspective Markov model was constructed with monthly cycles and a five-year horizon. Six cycles of carboplatin and paclitaxel were costed in the initial episode. Health states were progression-free (PF), first platinum-sensitive recurrence (PS1), second platinum-sensitive recurrence (PS2), platinum-resistant recurrence (PR), and death. PF progression hazards were derived from median PFS reported in randomized clinical trials. Post-progression mortality hazards were calibrated to match OVHIPEC-1 median overall survival. Direct medical costs were estimated in 2025 Canadian dollars using publicly available provincial drug pricing data in British Columbia and institution-specific costs for surgery, HIPEC, and inpatient care. **Results:** Annual volume of ICS patients was 98, of whom 25 were eligible for HIPEC and wtBRCA. Over 5 years, with 25 new patients entering annually, total costs were $9.05M without HIPEC versus $11.07M with HIPEC, yielding an incremental budget impact of $2.02M ($16,186 per patient). Incremental cost was driven by the surgical episode (+$1.90M), longer duration of maintenance niraparib (+$0.26M), and treatment of platinum-sensitive recurrence (+$0.15M) with carboplatin doublets. Incremental cost was partially offset by an estimated 11 fewer platinum-resistant recurrences within the 5-year horizon, resulting in cost savings of −$0.28M from reduced platinum-resistant treatment. **Conclusions:** Adding HIPEC at ICS to patients with stage III wtBRCA HGSOC increases 5-year payer spending by $2M for a 25 patient per year program. Additional cost is driven by provision of HIPEC surgery and postoperative care and is partially offset by near-term savings on platinum-resistant recurrence. Research Sponsor: None.

Treatment cost across a 5-year horizon for 25 patients treated annually (n = 125).

Category	No HIPEC	HIPEC	Incremental Cost	Incremental Cost Per Patient
Surgery +/- HIPEC	$2,085,500	$3,983,250	$1,897,750	$15,182
Initial chemotherapy	$1,829,348	$1,829,348	$0.00	$0.00
Niraparib Maintenance	$2,376,117	$2,638,599	$262,482	$2,100
Platinum Sensitive Recurrence	$1,243,222	$1,389,325	$146,103	$1,169
Platinum Resistant Recurrence	$1,515,639	$1,232,611	-$283,027	-$2,264
Total	**$9,049,824**	**$11,073,132**	**$2,023,308**	**$16,186**

5590 Poster Session

Enhanced predictive value of KELIM for surgical resectability in HRD-positive high-grade serous ovarian cancer. First Author: Mayerly Castrillón Sánchez, McGill University Health Centre, Montréal, QC, Canada

Background: Neoadjuvant chemotherapy followed by interval debulking surgery is commonly used in the management of advanced ovarian cancer. However, there is currently no reliable tool to predict the likelihood of achieving complete cytoreduction after 3–4 cycles of chemotherapy. Surgical outcomes are classified as R0 (no residual disease), R1 (residual lesions <1 cm), or R2 (residual disease ≥1 cm). The KELIM index, calculated from CA-125 kinetics during chemotherapy, has emerged as a potential biomarker of tumor regression and chemosensitivity in advanced ovarian cancer. We aim to study the performance of KELIM score as predictor of complete cytoreduction. **Methods:** This single-center, retrospective study included 69 patients with advanced high-grade serous ovarian cancer (Stage III/IV) who underwent interval cytoreductive surgery following neoadjuvant chemotherapy between January 2020 and December 2025. Kelim index values were calculated using Biomarker-Kinetics and categorized as favorable (≥1) or unfavorable (<1) as per literature. Further, ROC curve analysis was performed to identify the optimal KELIM cutoff for predicting complete cytoreduction. Correlations with degree of cytoreduction (R0, R1, R2) were analyzed using comparative statistics. Associations with molecular markers (BRCA, HRD) were also explored. **Results:** The median age of patients was 62 years [IQR 57–70]. The median KELIM score was 0.85 [IQR 0.69-1.00]. KELIM demonstrated statistically significant predictive performance for R0, with an area under the curve (AUC) of 0.69 (95% CI, 0.56–0.82; p = 0.004). The AUC optimal cutoff was KELIM = 0.995, yielding a sensitivity of 53.9% and specificity of 92.6%. Notably, this value closely aligns with the cutoff reported in the literature (KELIM = 1.0), which in our cohort corresponded to a sensitivity of 51.3% and specificity of 96.3% (Youden index = 0.47). Additional analyses were conducted using the literature-defined cutoff of KELIM = 1.0. Patients were categorized into two groups: Group A (22 patients) with favorable (≥1) and Group B (47 patients) with unfavorable (<1) KELIM scores. Patients with a favorable KELIM were significantly more likely to achieve complete cytoreduction compared with those with an unfavorable KELIM (R0: 95.2% vs 41.3%, p < 0.001). The discriminative performance of KELIM was numerically higher in HRD-positive patients AUC 0.706 (95% CI, 0.28-1) compared with HRP patients AUC 0.563 (95% CI, 0-1). KELIM was associated with degree of cytoreduction: Median 1 [0.71-1.20] for R0, 0.79 [0.70-0.88] for R1, and 0.64 [0.48-0.70] for R2, p=0.019. **Conclusions:** KELIM is a good predictor of complete resectability in high grade serous ovarian cancer. The differential predictive performance among the HRD status should be further explored. Research Sponsor: None.

5591 Poster Session

Impact of niraparib maintenance on progression-free survival and overall survival: An updated meta-analysis. First Author: Roshan Mustafa Pathan, Government Siddhartha Medical College, Vijayawada, India

Background: Niraparib is an oral poly(ADP-ribose) polymerase (PARP) inhibitor used as maintenance therapy in advanced ovarian cancer after platinum response. Mature OS data were lacking, so we performed an updated meta-analysis. **Methods:** PubMed, Embase, and CENTRAL were searched from January 2023 to January 2026 for randomized controlled trials (RCTs) of niraparib maintenance in advanced ovarian cancer. Hazard ratios with 95% confidence intervals were pooled using random-effects models for TFST, OS, overall PFS, and subgroup PFS by BRCA, HRD status, and newly diagnosed patients. The study is registered in PROSPERO with ID CRD420261294461. **Results:** Four RCTs (PRIMA, NOVA, NORA, and PRIME) including 1935 patients were analysed, of whom 1,291 received niraparib, and 644 received placebo. Niraparib significantly prolonged the TFST (HR 0.54, 95% CI 0.42-0.69; I^2=77.6%; p<0.0001). No statistically significant improvement in OS was observed (HR 0.94, 95% CI 0.82-1.08; I^2=10.0%; p=0.398). Niraparib significantly improved overall PFS (HR 0.42, 95% CI 0.31-0.58; I^2=83.8%). PFS in BRCA-mutated patients (HR 0.33, 95% CI 0.24-0.45; I^2=46.0%), HRD-positive patients (HR 0.41, 95% CI 0.30-0.56; I^2=58.6%) (all p<0.0001). HRD-negative patients (HR 0.56, 95% CI 0.35-0.89; I^2=52.4%), and newly diagnosed (HR 0.55 95% CI 0.39-0.80, I^2=79.1%) (all p≤0.015). **Conclusions:** Niraparib provides durable disease-control benefits across molecular subgroups and significantly delays the need for subsequent therapy, however, mature data does not demonstrate a corresponding overall survival advantage. These findings refine patient selection and highlight the need for strategies that translate PFS gains into survival benefit. Research Sponsor: None.

Updated meta-analysis of niraparib efficacy outcomes in advanced ovarian cancer.

Study	TFST (HR)	Overall Survival (HR)	Overall PFS (HR)	PFS in BRCA mutation (HR)	HRD+ PFS (HR)	HRD− PFS (HR)	Newly Diagnosed (HR)
PRIMA	0.74 (0.62–0.89) *	1.01 (0.84–1.23) *	0.66 (0.55–0.78) *	0.43 (0.31–0.59) *	0.51 (0.40–0.66) *	0.67 (0.50–0.89) *	0.66 (0.55–0.78) *
PRIME	0.45 (0.34–0.59)	0.63 (0.38–1.03) *	0.45 (0.34–0.60)	0.40 (0.23–0.68)	0.48 (0.34–0.68)	0.41 (0.22–0.75)	0.45 (0.34–0.60)
NOVA (gBRCA)	0.57 (0.41–0.78) *	0.85 (0.61–1.20) *	-	0.27 (0.17–0.41)	0.38 (0.24–0.60)	-	-
NOVA (non-gBRCA)	0.58 (0.45–0.74) *	1.06 (0.81–1.37) *	-	-	-	-	-
NORA	0.39 (0.29–0.52) *	0.86 (0.60–1.23) *	0.32 (0.23–0.45)	0.22 (0.12–0.40)	0.22 (0.12–0.40)	-	-
Total Result (95% CI)	0.54 (0.42 – 0.69)	0.94 (0.82–1.08)	0.42 (0.31–0.58)	0.33 (0.24–0.45)	0.41 (0.30–0.56)	0.56 (0.35–0.89)	0.55 (0.39–0.80)
I^2 (%)	77.6	10	83.8	46	58.6	51.4	79.1
p value	<0.0001	0.3979	<0.0001	<0.0001	<0.0001	0.0146	0.0014

*Indicate updated values.
TFST: time to first subsequent therapy; PFS: progression-free survival; HR: Hazard ratio; CI: confidence intervals.

5592 **Poster Session**

Post-treatment ctDNA monitoring using a tumor-informed whole-genome sequencing-based assay in homologous recombination–proficient ovarian cancer. First Author: Sophie Blakey-Cheung, AdventHealth Cancer Center, Orlando, FL

Background: Ovarian cancer (OC) has high mortality due to advanced stage at diagnosis and frequent, incurable recurrences. Homologous recombination–proficient (HRP) disease comprises approximately half of high-grade serous OC and is associated with limited benefit from platinum chemotherapy and PARP inhibitors, leading to poorer outcomes. Circulating tumor DNA (ctDNA) is a validated biomarker for molecular residual disease and early relapse; this study evaluates it's ability to stratify HRP patients (pts) into clinically meaningful risk groups. **Methods:** We performed a retrospective analysis of clinically annotated residual samples from commercial ctDNA testing in pts diagnosed with OC. Signatera Genome assays (Natera, Inc.) were designed from the respective pts' matched tumor and normal whole genome sequencing (WGS) data to detect and quantify ctDNA in serially collected post-operative plasma. Adjuvant chemotherapy (ACT) decisions and cadence of testing were at the provider's discretion. HR status was determined using available clinical records and/or genomic data. Descriptive statistics were used to compare association of ctDNA across stages and at various timepoints post-surgery. Correlation between ctDNA status and progression-free survival (PFS) was assessed using Cox regression analysis. **Results:** Study cohort comprised 164 Stage I-IV OC pts, with 1,256 plasma samples for ctDNA testing (median: 7 tests/ pt, range 1–24). The median age at diagnosis was 66 (range 19–89) years. A total of 157 cases were HRP; among these, clinical outcome data was available for 44 pts with corresponding ctDNA timepoints for analysis. ctDNA-positivity within two weeks post-debulking surgery (before starting ACT) was associated with significantly worse PFS compared to ctDNA-negativity (N=20; HR: 14.01, 95%CI: 0.6–308.16; p=0.01). Furthermore, ctDNA-positivity post-ACT was also associated with worse PFS (N=26; HR: 6.6, 95%CI: 1.7–25.3; p=0.002) compared to ctDNA-negativity. Among ctDNA-positive pts, 50% (5/10) had progression $<$6 months post-ACT, whereas no events were observed $<$12 months post-ACT in ctDNA-negative pts (N=12). Clinical follow-up and additional analyses are ongoing. **Conclusions:** Tumor-informed ctDNA monitoring identifies pts with HRP OC who are at high risk for recurrence post-surgery including treatment refractory/resistant cases. Post-operative and post-adjuvant ctDNA positivity was strongly associated with inferior PFS. These findings support the use of ctDNA as a clinically important biomarker to inform post-surgical/treatment risk stratification, and consideration of alternative or escalated therapeutic strategies in this high-risk population. These results showcase the utility of ctDNA to further risk stratify HRP OC pts, which supports it's integration into prospective clinical trials and clinical care. Research Sponsor: None.

5593 **Poster Session**

Spatial distribution and functional heterogeneity of CD56bright and CD56dim natural killer cells and the effects on the immune microenvironment in ovarian cancer. First Author: Guo Huiming, The First Affiliated Hospital of Kunming Medical University, Kunming, China

Background: Natural killer (NK) cells are key components of antitumor immunity, yet their functional heterogeneity and spatial distribution within the tumor microenvironment (TME) remain incompletely understood in ovarian cancer. CD56bright and CD56dim NK cell subsets exhibit distinct immunologic functions, but their relative infiltration patterns and associations with other immune cell populations have not been systematically characterized. **Methods:** A total of 157 ovarian cancer specimens were analyzed using multiplex immunofluorescence staining. NK cells were classified as CD56bright and CD56dim subsets, and their densities were quantified separately in tumor parenchyma and stroma. The associations between NK cell infiltration patterns and the densities of multiple immune cell populations. **Results:** Overall, ovarian cancer exhibited a CD56dim NK cell–dominant infiltration pattern. In tumor parenchyma, the mean density of CD56bright NK cells was 149 cells/mm², whereas CD56dim NK cells reached 406 cells/mm². In tumor stroma, CD56bright and CD56dim NK cell densities were 108 cells/mm² and 277 cells/mm², respectively. Patients with higher overall NK cell infiltration showed significantly increased densities of multiple immune cell populations in both tumor parenchyma and stroma, including $CD8^+$ T cells (P=0.0091, 0.0167), M1 macrophages (P=0.0002, 0.0001), M2 macrophages (P=0.0011, 0.0008), $PD\text{-}L1^+$ macrophages (P=0.0164, 0.0006), $CD20^+$ B cells (P=0.0001, 0.0193), $CD4^+$ T cells (P=0.0001, 0.0001), and $CD4^+FOXP3^+$ regulatory T cells (P=0.0001, 0.0001). When comparing NK cell subset dominance, patients with lower CD56dim than CD56bright NK cell infiltration in tumor parenchyma exhibited significantly higher M1 macrophage density (342 vs 180 cells/mm², P=0.0344) and lower stromal M2 macrophage infiltration (P=0.0356). In tumor stroma, lower CD56dim-dominant cases showed significantly increased infiltration of M1 macrophages (435 vs 242 cells/mm², P=0.0336), M2 macrophages (171 vs 48 cells/mm², P=0.0053), $CD8^+PD\text{-}1^+$ T cells (34 vs 10 cells/mm², P=0.0299), $CD4^+$ T cells (140 vs 25 cells/mm², P=0.0119), and $CD4^+FOXP3^+$ T cells (73 vs 4 cells/mm², P=0.0016). **Conclusions:** Ovarian cancer is characterized by predominant infiltration of CD56dim NK cells; however, the balance between CD56bright and CD56dim NK cell subsets is closely associated with distinct immune microenvironment patterns. These findings highlight the functional heterogeneity of NK cell subsets and provide a potential mechanistic explanation for the variable prognostic and therapeutic relevance of NK cells across tumor types and immunotherapy contexts. Spatially resolved profiling of NK cell subsets may offer valuable insights for immunotherapy stratification in ovarian cancer. Research Sponsor: None.

5594 **Poster Session**

Comprehensive profiling of antibody-drug conjugate target expression in epithelial ovarian cancer with pre- and post-ADC longitudinal assessment. First Author: Yong jae Lee, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, South Korea

Background: Antibody–drug conjugates (ADCs) are increasingly used in ovarian cancer, yet target expression may evolve over time and under treatment pressure. We characterized key ADC targets across disease timepoints and assessed paired changes after ADC exposure. **Methods:** We retrospectively analyzed epithelial ovarian cancer treated at Yonsei Cancer Center (n=158). Serial specimens obtained at diagnosis, interval debulking surgery, and relapse underwent immunohistochemistry for TROP2, HER2, FOLR1, CLDN6, B7H4, B7H3, and CDH6. Targets were scored 0/1+/2+/3+; overexpression was defined as 2+ or 3+. Longitudinal transitions were summarized using Sankey plots, including pre-/post-ADC comparisons. **Results:** We analyzed 158 epithelial ovarian cancer patients (HGSC n=120; non-HGSC n=38). In HGSC, the most frequent overexpressed targets (2+/3+) were TROP2 (100%) and FOLR1 (91.5%) at diagnosis, remaining high at relapse (TROP2 93.2%, FOLR1 82.2%), while HER2 overexpression was uncommon (20.3% at diagnosis; 6.9% at relapse). In non-HGSC subtypes, TROP2 was most frequently overexpressed in endometrioid (3+ in 100%) and clear cell tumors (2+/3+ in 100%), whereas mucinous tumors showed predominant HER2 overexpression (2+/3+ in 70%). In ADC-exposed paired pre-/post-ADC specimens, expression of the cognate ADC target generally decreased after exposure, including reduced FOLR1 after MIRV/MORAb-202, reduced HER2 after T-DXd, and reduced CDH6 after R-DXd. **Conclusions:** TROP2 and FOLR1 are broadly and consistently expressed across timepoints. Non-HGSC exhibits distinct histology-specific patterns, with particularly high HER2 expression in mucinous tumors. ADC treatment resulted in a reduced expression profile of its cognate target protein, which may contribute to the development of ADC resistance; however, further investigation is required to elucidate additional underlying mechanisms. Research Sponsor: None.

5595 **Poster Session**

Primary analysis of pembrolizumab combined with chemotherapy in platinum-sensitive recurrent low-grade serous ovarian cancer: The NOGGO PERCEPTION phase II study. First Author: Jacek P. Grabowski, North-Eastern German Society of Gynaecological Oncology (NOGGO) and Department of Gynecology with Center for Oncological Surgery, Charité-University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany

Background: Low-grade serous ovarian cancer (LGSOC), a rare ovarian malignancy, exhibits a very limited responsiveness to chemotherapy. There is a pressing need for new therapeutic combinations with modern agents to enhance response rates and prognosis in this patient subgroup. Immune checkpoint inhibitors offer a promising pathway, having shown effectiveness in various malignant diseases, including selected cases of ovarian cancer. If our trial should show pembrolizumab effectivity in LGSOC, it would be a signal and impulse for future clinical studies in this rare disease. **Methods:** This multicenter, single-arm phase II study evaluates pembrolizumab in combination with platinum-based chemotherapy (carboplatin plus pegylated liposomal doxorubicin [PLD] or carboplatin plus gemcitabine) and as maintenance therapy in recurrent LGSOC. Eligible patients include those with disease progression or recurrence $\geq$6 months post prior platinum-based therapy and ECOG performance status 0-1. The primary endpoint is the 12-month progression-free survival (PFS) rate. Secondary endpoints include response rate (RR), PFS and ORR based on Ki67 expression. Using Simon's two-stage design, 33 patients were enrolled. Success is defined as $\geq$11 patients achieving 12-month PFS. Assuming a true PFS rate of 40%, the study has 5% type I error and 80% power. **Results:** Data from 33 patients were evaluated. At data cut-off, 12 patients were progression free at 12-months (median PFS 15.5 months) while 19 patients progressed or died within 12 months (median PFS 5.6 months). Overall PFS median was 8.4 months. Comparing the subgroups of pre-treatment Ki67 expression $<$3.6% vs. $\geq$ 3.6%, the median PFS was 5.1 vs. 8.8 months. Four patients remain on pembrolizumab treatment; two of these have not yet reached the 12-month PFS endpoint. Median patient age was 52 years (range: 37-81), with ECOG performance status 0 in 30 patients (90.9%). Most patients had one prior chemotherapy line (61.1%; range: 1-5). Chemotherapy regimens included carboplatin + PLD (75.8%) and carboplatin + gemcitabine (24.2%). SAEs were reported in 22 patients (66.7%), with 11 (33.3%) considered treatment-related. **Conclusions:** The study achieved its primary objective in terms of the 12-months PFS and thus suggests efficacy of pembrolizumab in patients with platinum-sensitive recurrent LGSOC. Clinical trial information: 2023-508155-40-00. Research Sponsor: MSD Sharp & Dohme GmbH.

5596 **Poster Session**

Update of the EORTC QLQ-Ovarian Cancer Module (EORTC-QLQ-OV28) phase I and II. First Author: Vesna Bjelic-Radisic, Breast Unit, Helios University Clinic, University Witten-Herdecke, Wuppertal, Germany

Background: Ovarian cancer is the eighth most common cancer in women worldwide. The 5-year survival rate is 90.0% for early-stage disease and 30.2% for advanced disease. The introduction of new treatment options, such as PARP inhibitors, immunotherapy and bevacizumab, has led to improved recurrence-free intervals and an increased number of long-term survivors. However, new therapies have also brought new side effects that are not sufficiently covered by the EORTC QLQ OV-28, which was developed in 1997. There is therefore a strong clinical and research need to update the questionnaire to reflect contemporary treatments and their impact on QoL. This work presents the results of Phases 1 and 2 of the EORTC module development study updating the EORTC QLQ-OV28. **Methods:** The EORTC QLQ-OV28 module was adapted in accordance with the EORTC QLG guidelines for methodology for updating modules focused on identifying QoL issues relevant to ovarian cancer patients. This involved a systematic literature search, a review of questionnaires , investigator brochures, focus groups, and research group meetings (Phase 1).An issue was added to the list if it had a patient and/or HCP relevance rating of at least 2 (on a scale of 1 to 4) and a priority rating of at least 30%. The relevant issues were then translated into items, resulting in a preliminary questionnaire (Phase 2). **Results:** The mixed methods approach identified 57 issues related to QoL in ovarian cancer patients. An issue list was created and used for interviews with 58 patients and 31 HCPs, who rated each issue according to its relevance using a four-point response format: 'not at all', 'a little', 'quite a bit', 'very much' and priority (yes/no). Of the initial 57 issues, 20 (as rated by patients) and 34 (as rated by HCPs) met both inclusion criteria. Sixteen of these were covered by the existing EORTC QLQ-OV28, and five new issues were identified: weight loss, numbness in the hands and feet, anxiety, concerns about acceptance of their condition, and impaired sexuality. Twelve issues from the existing questionnaire did not fulfil all the inclusion criteria.In Phase II, these issues were translated into items and used to create a preliminary 39-item questionnaire to assess QoL in ovarian cancer patients. **Conclusions:** The results of Phases I and II indicate that the current EORTC QLQ-OV28 module does not adequately address all the relevant QoL issues for patients with ovarian cancer. Five new issues are not addressed by the existing module, and twelve existing issues did not fulfil all the inclusion criteria. Therefore, the EORTC QLQ-OV28 module should be updated. A preliminary questionnaire will be tested in Phase III of the EORTC module development process. Note: This document represents preliminary findings of the module development and is subject to revision; subsequent modifications of the module in the next stages may reflect significant changes. Research Sponsor: EORTC QLQ.

5597 **Poster Session**

Vididencel, an active immunotherapy in high-grade serous ovarian carcinoma patients: Analysis of tumor-directed immune responses post-primary treatment. First Author: Annegé Vledder, University Medical Centre Groningen, Groningen, Netherlands

Background: Ovarian cancer (OC) remains the most common cause of mortality in gynecologic cancers, with advanced-stage high-grade serous carcinoma (HGSOC) accounting for most cases. PARP inhibitors have provided significant benefits and notable progression-free survival for patients with BRCAmut and HRD+, but survival benefits following primary treatment remains a major clinical challenge. We have conducted a phase 1 trial (NCT04739527) assessing the role of an active immunotherapy, vididencel, in patients with HGSOC post-primary treatment. Vididencel expresses multiple tumor-associated antigens (TAA), including WT1 and PRAME, which are frequently upregulated in HGSOC. **Methods:** Following primary treatment, patients received 8 doses of vididencel intradermally administered every 14 days, followed by 2 booster injections at week 14 and 18. Peripheral blood mononuclear cells (PBMC) were obtained at week 0, 4, 10, 14, 18 and 22. Disease status was evaluated at week 22 using clinical assessment and CA125 levels. Patients were followed for disease status for 2 years. IFNγ ELISpot was performed on PBMC for WT1, PRAME, MAGEA3/4 and NY-ESO1. Vididencel induced T-cell responses were calculated as $\geq$2-fold increase of the mock-corrected baseline response. **Results:** All 17 patients completed treatment phase (up to week 22 or end of treatment). Patient demographics are outlined in table I. 11 out of 17 patients completed predefined 2-year follow-up. With median follow-up of 26.4 months 8 out of 11 patients remain alive. 12 out of 17 patients (71%) showed improved tumor-directed vididencel-induced immune responses (VIR) and are associated with improved progression-free survival. 5 of 12 patients (42%) with VIR still had stable disease, with 2 patients beyond 3.5 years of follow-up. **Conclusions:** Long-term follow-up of HGSOC patients treated with vididencel confirms safety, tolerability and feasibility resulting in strong T cell response against TAA. The improved tumor-directed responses were associated with better progression-free survival. These data confirm that vididencel is a safe immunotherapy and provides strong basis for novel combination treatments for ovarian cancer patients. Clinical trial information: NCT04739527. Research Sponsor: None.

Patient demographics.

Demographics	
Total patients	17
Age(in years)	
Mean	61.6
Median	64
Range	43-75
Stage n(%)	
III	12(70.6)
IIV	5(29.4)
Primary treatment n(%)	
PDS	2(11.8)
IDS	15(88.2)
Surgery outcome n(%)	
Complete	15(88.2)
Optimal	2(11.8)
CA125 at screening	
Mean	21.8
Median	20
Range	7-55
Molecular subtype n(%)	
BRCAm	13(76.5)
BRCAwt	4(23.5)

PDS, primary debulking surgery IDS, interval debulking surgery; BRCAm, BRCA mutation; BRCAwt, BRCA wild type.

5599 **Poster Session**

Association of AI-based quantitative B7-H3 evaluation in the tumor microenvironment with molecular subtypes in high-grade serous ovarian carcinoma. First Author: Ryusuke Murakami, Department of Gynecology and Obstetrics, Graduate School of Medicine and Faculty of Medicine, Kyoto University, Kyoto, Japan

Background: High-grade serous ovarian carcinoma (HGSC) exhibits heterogeneous tumor microenvironments (TME) that correlate with clinical outcomes. We previously reported four molecular histopathological subtypes of HGSC based on gene expression profiles reflecting TME characteristics: Immune Reactive (IR), Mesenchymal (MT), Solid/Proliferative (SP), and Papillary/Glandular (PG). The IR subtype, characterized by tumor-infiltrating lymphocytes, demonstrates favorable prognosis (PMID:26993207, 30853361). We also identified lower B7-H3 expression in IR compared to non-IR subtypes (PMID: 34799346). Here, we developed an AI-based B7-H3 IHC quantification method across TME compartments and investigated its association with molecular subtypes. **Methods:** Forty-five HGSC patients who underwent primary debulking surgery were enrolled. Molecular histopathological subtyping categorized cases into IR (n=16), MT (n=20), and Other (SP/PG, n=9). B7-H3 immunohistochemistry-stained whole slide images were analyzed using DeepPathFinder, an AI-based pathological image analysis tool that performs automated tissue segmentation and IHC marker quantification. B7-H3 expression was quantified across three tumor-associated compartments: tumor, peritumor (within 1000 μm of the tumor border), and necrosis. An integrated B7-H3 score was calculated as the mean density across these compartments. Survival analyses were performed using the Kaplan-Meier method and Cox proportional hazards regression. **Results:** The integrated B7-H3 score showed a stepwise increase across subtypes: IR (0.148) $<$ MT (0.219) $<$ Other (0.252) (Kruskal-Wallis p=0.091), and was significantly lower in IR compared to non-IR subtypes (0.148 vs 0.229, p=0.034). B7-H3 expression was consistently lower in IR across all compartments: tumor (IR: 0.171, MT: 0.205, Other: 0.257), peritumor (IR: 0.100, MT: 0.154, Other: 0.164), and necrosis (IR: 0.171, MT: 0.298, Other: 0.336; p=0.025). Survival analysis revealed significant prognostic differences among subtypes. Compared to IR, MT showed significantly worse outcomes (PFS: HR=8.35, 95% CI 3.00–23.24, p$<$0.0001; OS: HR=15.35, 95% CI 3.50–67.31, p=0.0003). The Other subtype also demonstrated inferior OS (HR=6.38, 95% CI 1.17–34.95, p=0.033). Both MT and Other (SP/PG) subtypes, which exhibited higher B7-H3 expression, were associated with worse prognosis. **Conclusions:** AI-based quantitative B7-H3 evaluation revealed subtype-specific expression patterns in the HGSC tumor microenvironment. B7-H3 expression was lowest in IR and higher in non-IR subtypes across all tumor-associated compartments. These findings suggest that patients with higher B7-H3-expressing subtypes may benefit from B7-H3-targeted therapy. Research Sponsor: None.

5600 **Poster Session**

Vaccine-induced immune responses, HLA genotyping, and molecular profiling in patients with metastatic ovarian cancer (the PESCO trial). First Author: Ana Veneziani, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: PESCO, a phase 1/2 trial of Maveropepimut-S (MVP-S) in combination with Pembrolizumab and metronomic cyclophosphamide, showed safety and efficacy signals in metastatic ovarian cancer (OC). MVP-S uses the lipid-based DPX delivery platform to stimulate T cell immune response to survivin epitopes restricted by 5 HLA class I haplotypes (A1, A2, A3, A24, B7). Survivin is highly expressed in OC. We report exploratory correlative analysis including immune responses, HLA typing and molecular profiling. **Methods:** The study included a phase 1 dose escalation and expansion cohorts: A (platinum-sensitive high-grade serous [HGS]), B (platinum-resistant HGS), and C (rare OC histologies). Survivin-specific T-cell responses were assessed by flow cytometric detection of IFNγ following ex vivo PBMC re-stimulation with pooled survivin epitopes at on-treatment timepoints. A positive immune response was predefined as $>$0.1% IFNγ^+ CD8$^+$ T cells. HLA genotyping was mapped to MVP-S–restricted alleles. Molecular profiling was performed using next-generation sequencing (NGS) and/or whole-genome transcriptomic sequencing (WGTS). **Results:** Across 44 patients (pts), 37 (84%) carried $\geq$1 vaccine-relevant HLA allele and 23 (52%) carried $\geq$2. The most frequent alleles were A24 (16/44; 36%), A02 (15/44; 34%), A03 (12/44; 27%), B07 (11/44; 25%), and A01 (8/44; 18%). Survivin-specific immune responses were detected in 15/24 (62%) immune-evaluable pts and were strongly enriched among pts with clinical benefit: CR 1/1 (100%), PR 7/7 (100%), SD 6/10 (60%), versus PD 1/6 (16%); overall, 14/15 (93%) immune responders had clinical benefit. The longest survivin-specific response persisted for 195 weeks in a pt with MMR deficient tumor who had CR for 3 years. Exploratory HLA-outcome analysis suggested enrichment of A24 in pts with clinical benefit but absent in PD. NGS was performed in 44 pts and WGTS in 36. NGS identified at least one SNV/indel in 43/44 (97.7%) pts. In Phase 1 and Cohorts A/B (n=34, 68% HGS), TP53 was dominant (76.5%, 86% in HGS), followed by MYC (17.6%), NF1 (14.7%), and BRCA1/2 (each 8.8%). In Cohort C (n=10, 8 clear cell), ARID1A (70%) and PIK3CA (60%) were frequent. In platinum resistant pts (n=24), alterations included TP53 (67%), BRCA1/2 (21%), CCNE1(17%). Tumors with cell cycle/replication stress alterations were enriched among pts with PD (29% vs 8% in non-PD; P = 0.099) and immune non-responders (37.5% vs 6.7% in IFN responders; P = 0.103). Tumor mutation burden was low in all 26 pts tested. **Conclusions:** Survivin-specific immune responses were strongly enriched among pts with clinical benefit, supporting survivin as an active target in OC. HLA typing demonstrated broad coverage of MVP-S epitopes across pts. Molecular subtype may have influenced immune responses in this study. Our findings support biomarker-integrated studies to optimize immunotherapy combinations in OC. Clinical trial information: NCT03029403. Research Sponsor: None.

5601 **Poster Session**

Addressing barriers to FRα-directed therapy integration in platinum-resistant ovarian cancer: A multi-phase, community-informed initiative. First Author: Kia Jones, Medlive - A PlatformQ Health Brand, Needham, MA

Background: Antibody–drug conjugates (ADCs) targeting folate receptor alpha (FRα) represent an important therapeutic advancement in ovarian cancer, introducing a new standard of care (SOC) for patients with FRα–positive platinum-resistant ovarian cancer (PROC). Despite this progress, real-world integration of FRα biomarker testing and FRα-directed therapies into clinical practice remains variable, particularly in community settings where most patients receive care. This multi-phase initiative was designed to assess real-world practice patterns and barriers related to FRα-directed care and to evaluate outcomes from an educational intervention addressing these gaps. **Methods:** Phase 1 formative research included a national claims data analysis, a community-based practice pattern analysis survey (n=100), and a clinician case crowdsourcing survey (n=100) examining biomarker testing practices, treatment sequencing, and perceived challenges in PROC care. Findings from Phase 1 informed development of a 60-minute, on-demand CME activity (Phase 2) targeting oncologists, gynecologic oncologists and pathologists, and APPs. Educational outcomes were assessed using pre-/post-activity knowledge and confidence measures, polling, and post-activity evaluations. Interim Phase 2 outcomes are reported. **Results:** Phase 1 analyses demonstrated variable use of FRα biomarker testing across the patient journey, with testing more frequently performed at initial diagnosis. Clinicians cited barriers including testing access and turnaround time, tissue adequacy, uncertainty around eligibility thresholds for FRα-directed therapy, and challenges in sequencing FRα-directed agents relative to other targeted options. Claims data showed continued predominance of cytotoxic regimens at first PROC progression. As of 2.5 months post-launch, over 5,100 clinicians have engaged with the education. Pre- to post-activity assessments demonstrated the largest gains in knowledge related to limitations of the current SOC in PROC and in understanding the role of FRα biomarker testing in informing treatment decisions. Confidence in appropriately incorporating FRα-directed therapies into treatment plans remained low at post-test. Intended practice changes included increased use of comprehensive biomarker testing (36%), reassessment of the role of PFI in treatment selection (41%), and routine FRα testing at recurrence (37%). **Conclusions:** This multi-phase initiative identified persistent gaps in FRα biomarker testing and therapeutic integration in PROC and demonstrated early educational gains in knowledge, with ongoing needs related to clinical application and confidence. These findings highlight the value of outcomes-driven education in addressing real-world barriers and supporting informed integration of FRα-directed therapies into PROC care. Research Sponsor: Genmab US, Inc.

5602 **Poster Session**

Prognostic effect of neoadjuvant chemotherapy in gBRCA-mutated compared to gBRCA wild-type patients with advanced HGSOC treated with first-line PARP inhibitor maintenance: A large series propensity score–matching analysis. First Author: Ilary Ruscito, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

Background: Recent results from the TRUST trial (ENGOTov33/AGO-OVAR OP.7) have renewed interest in the prognostic role of primary debulking surgery (PDS) versus interval debulking surgery (IDS) in advanced high-grade serous ovarian cancer (HGSOC). This study evaluated the prognostic impact of neoadjuvant chemotherapy (NACT) according to germline BRCA (gBRCA) status in advanced HGSOC patients receiving first-line PARP inhibitor (PARPi) maintenance, and its influence on outcomes at recurrence. **Methods:** We retrospectively identified patients with advanced HGSOC, treated between 2019 and 2024 at our gynecologic oncology referral center, who underwent upfront surgery and platinum-based chemotherapy followed by PARPi monotherapy. gBRCA status, surgical approach(PDS vs NACT+IDS), and survival outcomes, were collected. Patients were stratified by gBRCA status (gBRCAmut vs gBRCAwt). Propensity score matching (PSM) was performed based on age, ECOG-PS, FIGO stage, tumor histotype, surgical approach, and residual disease after first cytoreduction. Progression-free survival (PFS), overall survival(OS), post-recurrence PFS(PFS2), and post-recurrence OS(OS2) were analyzed. **Results:** After PSM, 406 patients were included (203 gBRCAmut and 203 gBRCAwt). In the gBRCAmut cohort, 58.6% underwent PDS and 41.4% received NACT+IDS, while 42.9% and 57.1% of gBRCAwt underwent PDS and NACT+IDS, respectively. All gBRCAmut patients received olaparib maintenance; among gBRCAwt, those with somatic BRCA mutations received olaparib (45/203) and the remainder niraparib (158/203). Complete cytoreduction was achieved in 92.1% of cases, with no differences between groups. Among gBRCAwt patients, median PFS was 43 months with PDS versus 19 months with NACT+IDS (p=0.008). Among gBRCAmut, median PFS was not reached with PDS and was 28 months with NACT+IDS ($p<0.001$). Median OS was not reached in either surgical group for gBRCAwt patients, whereas in gBRCAmut patients median OS was not reached with PDS and was 60 months following NACT+IDS ($p<0.001$). At recurrence, PFS2 did not differ by upfront treatment. However, NACT+IDS was associated with inferior OS2 in both gBRCAwt (p=0.019) and gBRCAmut (p=0.048) patients, with shorter median OS2 observed in gBRCAmut (15 vs 18 months). **Conclusions:** NACT was associated with inferior survival outcomes in advanced HGSOC patients receiving first-line PARPi, with a more pronounced detrimental effect observed in gBRCAmut patients. This suggests that BRCA-mutated tumors, despite their intrinsic sensitivity to PARP inhibition, may be particularly vulnerable to the negative consequences of delayed cytoreduction, with potential implications for treatment sequencing and surgical decision-making. Research Sponsor: None.

5603 **Poster Session**

Onsite serial monitoring of high grade serous ovarian cancer (HGSOC) mutations in circulating tumor DNA (ctDNA) via droplet digital PCR. First Author: John Nakayama, Allegheny Health Network, Pittsburgh, PA

Background: Comprehensive Genomic Profiling (CGP) of tumor and blood samples is increasingly employed for ovarian cancer diagnosis. We used diagnostic CGP sequencing results (523 genes) to identify mutations in HGSOC patients for surveillance of tumor treatment response by an onsite ddPCR assay (Bio-Rad, Hercules, CA). We compared ctDNA mutations to imaging (computed tomography & MRI) and CA125 values across a cohort of HGSOC patients undergoing surgery followed by platinum-based therapy with diverse outcomes. **Methods:** CGP mutations from matched index tumor, plasma and buffy coat cell samples (TSO-500, Illumina) were used to identify tumor- and patient-specific, coding mutations for interrogation of serial blood samples. Concordance was high for tumor and blood (MED = 97.1%, Q1: 93.3%, Q3: 98.8%) and 15 patients with inclusive longitudinal samples were selected for retrospective analysis of ctDNA samples versus CA-125, imaging and outcomes. Mutation variant allele frequency (VAF) suitable for primer construction ranged in variant allele frequency (VAF) from 0.5 to 24.4% (MED = 2.5%, Q1: 1.2; Q3: 3.8%) in cfDNA. A lower limit of detection (LLOD) of 1 to 2 copies/nanogram cell free DNA (cfDNA) was established using synthetic gene Block targets and FFPE tumor dilutions. **Results:** There was a significant correlation (r^2= 0.85, $p<0.0001$) of initial target cfDNA VAF and numbers of mutation copies detected per nanogram cfDNA. There was no significant correlation of mutation copies with index or serial CA125 values (r^2=0.11, p=0.38) over the wide range of CA125 values across the patient cohort. However, all patients displayed parallel dynamic changes in multiplex ctDNA mutations and CA125 values with variations in disease status and outcome over 1-3 years. Platinum-sensitive patients with a sustained response to therapy (n=3) based on imaging and CA 125 values displayed rapid elimination of tumor mutations via ddPCR prior to stabilization of "normal" CA125 values. Absence of mutations was further validated by interrogating 5X concentrated patient cfDNA aliqouts. Three patients (platinum-resistant) that initially responded to treatment by imaging and declining CA 125 values never achieved ctDNA mutation levels below the LLOD. These patients subsequently displayed tumor escalation with correlative increases in ctDNA mutation levels and CA125 values. **Conclusions:** Patient mutation monitoring via ddPCR of blood samples collected and processed onsite, provided rapid, iterative and quantitative results consistent with radiographic imaging and CA 125 assays. In addition, durable remission cases were characterized by rapid loss of mutations detected by ctDNA ddPCR assays prior to imaging and diminution of CA125 values. Low levels of ctDNA mutations above LLOD persisted in responders who otherwise achieved normal CA125 values but later developed disease progression. Research Sponsor: None.

5604 **Poster Session**

The use of circulating tumor DNA to stratify the risk of recurrence after surgical debulking in epithelial ovarian cancer. First Author: Muhammad Anees, Allegheny Health Network Cancer Institute, Allegheny Health Network, Pittsburgh, PA

Background: Accurate risk stratification after debulking surgery in ovarian cancer remains challenging. Although surgical debulking status (SDS) and CA125 are standard prognostic markers, patients remain at high risk of recurrence despite optimal debulking and normalization of CA125. Circulating tumor DNA (ctDNA) has emerged as a sensitive biomarker for detecting molecular residual disease (MRD). We evaluated the prognostic value of post-surgical ctDNA compared with SDS and post-surgical CA125 in predicting recurrence. **Methods:** In a prospectively collected cohort of ovarian cancer patients undergoing standard-of-care treatment, we evaluated 37 patients with a reportable post-surgical MRD before initiation of adjuvant chemotherapy. Tumor-informed, patient-specific panels created from whole genome sequencing of matched tumors and normal samples were used to assess MRD (Precise MRD, Myriad Genetics). Postoperative CA-125 was stratified using a standard clinical cutoff of 35 U/mL. Median follow-up was 30 months (IQR 21.9). **Results:** Post-operative ctDNA was detected in 75.7% (28/37) of patients with 24.3% (9/37) detected at ultra-low levels ≤100 PPM. Among ctDNA-positive patients, 85.7% (24/28) recurred, compared with no recurrences among ctDNA-negative group (median PFS: 7.6 [3.0-23.2] months vs. not reached; $p<0.001$). Post-operative CA125 showed a similar trend with elevated-CA125 patients having a shorter median PFS (7.5 [2.8-21.1] vs. 25.1 [9.7-58.0]; $p<0.05$). Optimal SDS showed a trend toward longer median PFS (Optimal: 22.0 [4.1-58.0] vs. suboptimal: 10.8 [2.8-19.9], p=0.075). Notably, all patients with suboptimal SDS and detectable ctDNA experienced recurrence (4/4). Among patients achieving no gross residual disease (NGR; n=25), ctDNA strongly stratified outcomes: 82.4% (14/17) of ctDNA-positive patients recurred, whereas there we no recurrences in ctDNA-negative patients (median PFS: 4.6 [2.9-38.9] vs. not reached; $p<0.001$). The median tumor fraction (TF) within this cohort for positive cases was 432.0 PPM (IQR: 49.4–2510.0), where 29.4% (5/17) were detected below 100 PPM. Similarly, within the NGR group, normal-CA125 patients demonstrated a trend toward improved PFS (38.9 [6.9-58.0] vs. 4.6 [2.7-23.2]; p=0.11). Importantly, among patients with normal-CA125 (n=15), ctDNA further discriminated risk: 90% (9/10) of ctDNA-positive patients recurred with a median PFS of 20.3 (4.1-38.9) months, while no recurrences occurred in ctDNA-negative patients ($p<0.05$). Within this subgroup, the median TF was 235.0 PPM (IQR: 71.4–2640.0), where 26.7% (4/15) were below 100 PPM. **Conclusions:** Post-operative ctDNA after surgical debulking predicts early recurrence in ovarian cancer, including patients with NGR, supporting its role as a biomarker of MRD and postoperative risk stratification along with CA125. Research Sponsor: Myriad Genetics.

5605 **Poster Session**

Precision histopathologic classification of epithelial ovarian cancer subtypes using a computationally efficient multilayer perceptron framework with global validation. First Author: Elangovan Krishnan, AIM DOCTOR, Thiruverkadu, India

Background: Epithelial ovarian cancer is the leading cause of gynecologic cancer mortality, with treatment and prognosis strongly dependent on accurate histopathologic subtype classification. The five major epithelial subtypes—high-grade serous, low-grade serous, endometrioid, mucinous, and clear cell carcinoma—exhibit distinct clinical behaviors, yet conventional interpretation is limited by subjectivity and interobserver variability. Although deep learning has advanced digital pathology, most high-performing models require substantial computational resources, limiting clinical scalability. We evaluated whether a lightweight multilayer perceptron (MLP) combined with structured dimensionality reduction could enable accurate and globally deployable ovarian cancer subtyping. **Methods:** We analyzed 9,521 anonymized histopathology image patches representing five epithelial ovarian cancer subtypes from publicly available datasets with expert pathologist consensus ground truth. Images underwent Gaussian random projection followed by principal component analysis to preserve discriminative morphologic features. A feedforward MLP (2,048→1,024→512→5 neurons) with batch normalization and dropout (p=0.3) was trained using AdamW optimization with cosine annealing over 50 epochs on 80% of the data. External validation was performed on independent datasets. Performance metrics included accuracy, sensitivity, specificity, F1 score, and AUROC. The model was deployed on a cross-platform digital pathology system and evaluated by pathologists across six continents. **Results:** The MLP achieved 97.4% test accuracy with balanced subtype performance. Sensitivity ranged from 94.2% to 99.3%, with a macro-averaged F1 score of 0.993 and AUROC $>$0.99 for all classes. External validation accuracy ranged from 91% to 93% across heterogeneous staining protocols. Sensitivity for low-grade serous carcinoma (92.1%) exceeded reported interobserver agreement (52–73%). Inference time averaged 0.33 seconds per image on standard CPU hardware. Pathologists rated the system clinically useful in $>$90% of evaluations. The model contained 2.8 million parameters, representing an 89% reduction compared with conventional convolutional architectures. **Conclusions:** A computationally efficient MLP enables accurate and reproducible epithelial ovarian cancer subtype classification while substantially reducing computational complexity. This approach mitigates interobserver variability and supports scalable AI-assisted pathology deployment. Prospective multicenter studies are warranted to assess integration into routine diagnostic workflows and impact on treatment stratification. Research Sponsor: None.

5606 **Poster Session**

High-dimensional multiplex immunofluorescence to reveal immune microenvironment remodeling in matched primary and recurrent serous ovarian cancer. First Author: Yookyung Lee, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

Background: Recurrent serous ovarian cancer is associated with treatment resistance and poor prognosis, and changes in the tumor immune microenvironment (TIME) during recurrence have been suggested to contribute to these clinical features. However, spatial studies that quantitatively compare immune cell composition between primary and recurrent tumors at the single-cell level within the same patients remain limited. This study aimed to compare the TIME of primary and recurrent serous ovarian cancer using high-dimensional multiplex immunofluorescence. **Methods:** Tissue microarray (TMA) were constructed from formalin-fixed, paraffin-embedded (FFPE) tumor samples obtained from patients with primary and recurrent serous ovarian cancer. High-dimensional multiplex immunofluorescence staining was performed using the Akoya IO60 panel. Single-cell image analysis was conducted to segment cells and classify them into 19 distinct cell types. Differences in cell proportions were evaluated using unpaired analyses across all cores and paired analyses using matched primary-recurrent samples from the same patients (n=35). For paired analyses, cell proportions were compared using paired t-tests. **Results:** The 19 cell types included tumor epithelial cells, immune cell populations, and stromal cell populations. In unpaired analyses, recurrent tumors showed differences in immune cell composition compared with primary tumors, with relatively higher proportions of T cell-macrophage-associated populations and B cells. In paired analyses of matched samples (n=35), the proportion of T cell-macrophage-associated populations was significantly increased in recurrent tumors compared with primary tumors (p=0.0042). The proportion of B cells was also higher in recurrent tumors (p=0.0463). No statistically significant differences were observed in other cell types. **Conclusions:** Using high-dimensional multiplex immunofluorescence–based spatial analysis, we compared the tumor immune microenvironment of primary and recurrent serous ovarian cancer at the patient-matched level. Paired analyses demonstrated increased proportions of T cell-macrophage-associated populations and B cells in recurrent tumors, suggesting selective remodeling of the immune microenvironment during disease recurrence. Research Sponsor: None.

5607 **Poster Session**

Bevacizumab rechallenge in platinum-resistant ovarian cancer: Evidence from a propensity score–matched analysis. First Author: Celso Silva Sousa Filho, A.C. Camargo Cancer Center, São Paulo, Brazil

Background: Bevacizumab is approved for the treatment of ovarian carcinoma across multiple disease settings, from first-line therapy to late platinum-resistant recurrences (PROC). The greatest relative benefit of bevacizumab has been observed in the platinum-resistant setting. While evidence supports bevacizumab rechallenge in the first platinum-sensitive recurrence, no randomized trial has demonstrated a benefit of bevacizumab rechallenge in PROC. **Methods:** We conducted a retrospective cohort study including patients with PROC treated with chemotherapy with or without bevacizumab. Patients were matched using propensity score matching based on histology (HGSC vs others), chemotherapy backbone, line of platinum-resistant treatment, age, BRCA pathogenic variant status, and prior bevacizumab exposure. Nearest-neighbor matching with a 1:2 ratio (bevacizumab:non-bevacizumab) and a caliper of 0.2 was applied. Balance between groups was assessed using standardized mean differences. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier methods and compared using log-rank tests. Hazard ratios (HRs) were estimated using Cox proportional hazards models with robust variance accounting for matching. Subgroup analyses were performed according to prior bevacizumab exposure, and treatment–exposure interaction was formally tested. **Results:** A total of 149 patients with PROC were included. Baseline clinicopathologic characteristics were well balanced between treatment groups. In the overall matched cohort, bevacizumab use was associated with significantly improved PFS compared with chemotherapy alone (median PFS 7.79 vs 4.37 months; HR 0.49, 95% CI 0.36–0.68; p$<$0.001), as well as improved OS (median OS 23.06 vs 10.45 months; HR 0.47, 95% CI 0.34–0.66; p$<$0.001). In bevacizumab-naïve patients, bevacizumab remained significantly associated with longer PFS (median 7.79 vs 4.04 months; HR 0.47, 95% CI 0.33–0.68; p$<$0.001) and OS (median 23.06 vs 10.05 months; HR 0.46, 95% CI 0.32–0.67; p$<$0.001). Among patients previously exposed to bevacizumab, re-exposure was associated with numerically longer PFS (median 8.49 vs 4.89 months; HR 0.61, 95% CI 0.31–1.20; p=0.15) and OS (median 21.29 vs 10.45 months; HR 0.54, 95% CI 0.26–1.11; p=0.09), although these differences did not reach statistical significance. There was no statistically significant interaction between prior bevacizumab exposure and treatment effect for PFS (p for interaction = 0.60). **Conclusions:** The addition of bevacizumab to chemotherapy is associated with significant benefit in bevacizumab-naïve patients with PROC. In patients previously exposed to bevacizumab, re-exposure was not associated with a statistically significant improvement in outcomes, underscoring ongoing uncertainty regarding the role of bevacizumab rechallenge in this setting. Research Sponsor: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP); 2024/13952-4.

5608 **Poster Session**

AI-driven multi-scale histopathologic classification of epithelial ovarian cancer to support precision oncology. First Author: Yashwanth Kancharla, Harnett Health GME, Dunn, NC

Background: Epithelial ovarian cancer (EOC) comprises five histologically distinct subtypes associated with divergent molecular profiles, therapeutic responsiveness, and prognostic outcomes. Accurate histologic classification is essential for precision oncology but remains limited by morphologic overlap and interobserver variability. Deep learning architectures capable of multi-scale spatial feature extraction may enable objective and reproducible subtype discrimination. We evaluated the performance of a multi-scale factorized convolutional neural network (InceptionV3) for automated EOC subtype classification. **Methods:** Digitized hematoxylin–eosin–stained histopathology images were obtained from the University of British Columbia Ovarian Cancer Subtype Classification and Outlier Detection (UBC-OCEAN) dataset, including high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous carcinomas. An ImageNet-pretrained InceptionV3 architecture was fine-tuned using a five-class classification head. The model leverages parallel convolutional branches with factorized asymmetric kernels to simultaneously capture fine cellular features and global tissue architecture. Images were normalized and augmented. Training was performed using 299$\times$299 inputs, Adam optimizer (learning rate 1×10^{-4}), cross-entropy loss, and six epochs. Performance was assessed using accuracy, precision, recall, F1-score, and macro-averaged AUROC. External clinical validation was conducted by 57 board-certified gynecologic pathologists and oncologists across 14 geographic regions. **Results:** The model achieved an overall accuracy of 95.0% (491/517 test images). Subtype-specific F1-scores were 0.96 for high-grade serous carcinoma, 0.94 for endometrioid, 0.93 for clear cell, 0.92 for mucinous, and 0.88 for low-grade serous carcinoma. Macro-averaged AUROC was 0.957 (95% CI, 0.948–0.966). Computational efficiency was preserved with 23.9 million parameters and 11.6 billion FLOPs. Independent clinician validation demonstrated strong concordance with AI predictions, with mean inter-rater agreement of 95.3% (κ=0.936; 95% CI, 0.923–0.949), consistent across institutional practice settings. **Conclusions:** Multi-scale factorized convolutional modeling enables near-expert performance for automated EOC subtype classification by integrating cellular- and tissue-level morphologic features. High inter-rater concordance with an international specialist cohort supports translational reliability. This framework represents a scalable decision-support tool with potential to improve diagnostic standardization and precision therapeutic stratification. Prospective multi-center validation is warranted. Research Sponsor: None.

5609 **Poster Session**

The role of combined T cell and NK cell activity in immune checkpoint inhibitor (ICI) therapy in endometrial cancer (EC). First Author: Danielle Greenberg, UC Irvine Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Orange, CA

Background: The efficacy of ICI in EC has largely been attributed to high microsatellite instability (MSI-H) causing increased tumor mutational burden (TMB) and T-cell mediated immunity. However, a subset of patients with microsatellite-stable (MSS) tumors also derive clinical benefit, indicating that MSI status alone is insufficient for patient selection and contributing to the 2024 Food and Drug Administration approval of chemotherapy plus ICI for all patients with EC. We evaluated established biomarkers of a T-cell–inflamed tumor microenvironment alongside alternative immune pathways, notably natural killer (NK) cell activity, to define determinants of overall survival (OS) benefit in EC patients treated with ICI. **Methods:** Patients with EC treated with pembrolizumab or dostarlimab were identified from the Caris Life Sciences database with paired whole exome and transcriptome sequencing (WES/WTS). OS was defined from ICI initiation to death or last contact via insurance claims. Patients were grouped as long vs short survivors (LS/SS) by median post-ICI OS (mOS). Associations between OS and expression of pre-annotated T- and NK-cell-related genes were analyzed with Kaplan–Meier and multivariable Cox models adjusting for clinicopathologic factors. **Results:** Of 6,354 patients, 25% were MSI-H and 71% MSS. Immune deconvolution of WTS showed higher levels of $CD8^+$ T cells (p=0.034) and regulatory T cells (p=0.026) in LS vs SS. In multivariable analyses of the MSS subset, 63 T- and NK-cell–related genes were associated with improved OS, including FASLG (mOS 19.7 months vs 14.7 months in LS vs SS, HR=0.77, CI 0.70–0.85), IFNG (mOS 18.9 months vs 15.5 months in LS vs SS, HR=0.78, CI 0.71-0.86) and SIRPG (mOS 18.8 months vs 15.6 in LS vs SS, HR=0.79, CI 0.71-0.87) (all $p<0.0001$). The IFN Tumor Inflammation Signature (TIS) was not associated with OS in MSS EC, whereas T-cell, NK-cell, and combined T/NK gene signatures were (Table 1). **Conclusions:** Improved OS after ICI in MSS EC is associated with both T-cell and NK-cell activity. NK-cell–related and combined T/NK signatures were associated with improved survival, suggesting NK-cell activation contributes to ICI efficacy. These findings warrant validation in independent cohorts prior to use as a potential biomarker for ICI use in MSS EC. Research Sponsor: None.

T/NK signature scores are associated with improved OS in MSS EC.

Label	HR (95% CI)	*P* value
Gene set		
NK (high vs low)	0.82 (0.74–0.90)	<0.001
T + NK (high vs low)	0.84 (0.77–0.93)	0.001
T (high vs low)	0.84 (0.77–0.93)	0.001
Covariate		
p53: mutant vs wildtype	1.54 (1.38–1.73)	<0.001
TMB: high vs low	0.66 (0.49–0.90)	0.008
Chemotherapy: yes vs no	1.13 (0.98–1.31)	0.101
Biopsy site: metastasis vs primary	0.92 (0.83–1.02)	0.124
Lenvatinib: yes vs no	0.95 (0.86–1.05)	0.293

Multivariable Cox models adjusted for p53 status, TMB, site, chemotherapy and lenvatinib use.

5610 **Poster Session**

Sequencing of fallopian tube p53 signature found concurrently with p53 mutant uterine cancers and their somatic mutation profiles. First Author: Erika Joelle Lampert, UPMC Magee, Pittsburgh, PA

Background: The tumor protein 53 gene (p53) encodes a protein that suppresses replication of DNA-damaged cells. Mutations resulting in protein dysfunction are common in many cancers. A p53 signature is an aberrant immunohistochemical expression in 12 or more consecutive epithelial cells in the fallopian tube (FT) and is thought to be an early precursor lesion in a spectrum to high grade serous ovarian carcinoma (HGSOC). P53 mutations have also been described in endometrial cancer (EC), specifically high grade histologies such as uterine papillary serous carcinoma (UPSC). NextGen Sequencing of UPSC tumors and concurrent FT lesions has identified overlapping p53 mutations, raising the possibility that these could represent a precursor lesion. The objective of this study was to delineate the clonal relationship between p53-mutation harboring epithelial lesions in the FT and other histologic subtypes of EC, which could have implications for risk stratification, counseling, and treatment. **Methods:** We identified 7 patients with EC and a concurrent p53 FT signature. DNA extraction (Qiagen) from FFPE samples was performed and sent for whole genome sequencing (Novogene) on the paired FT and endometrial tissues to identify the specific p53 mutations. Using a position-wise comparison, we evaluated the clonal relationship between the specific p53 mutations identified in each pair. **Results:** In this cohort, 4 patients had endometrioid adenocarcinoma, 1 had mixed endometrioid and carcinosarcoma, 1 had high grade endometrial stromal sarcoma (ESS), and 1 had UPSC. All 7 patients had a p53 signature identified in the FT. Four patients had p53 overexpression while 3 had heterogenous p53 expression in the endometrium on IHC. Among the 7 patients, sequencing revealed 5 pairs with at least 1 shared somatic mutation identified in both the endometrium and FT. A shared mutation was identified in patients with carcinosarcoma, high grade ESS, UPSC, and two endometrioid adenocarcinomas. As of 9/2025 or last follow-up, no patients had developed a primary peritoneal malignancy, but 2 patients had disease recurrence. Both patients who had disease recurrence were among those with a shared somatic mutation identified. **Conclusions:** To our knowledge, this is the first study evaluating the relationship between concurrent FT p53 signatures and uterine cancer beyond serous. We identified 5 patients with at least 1 shared somatic p53 mutation. While these specific mutations have not been described as known pathogenic driver mutations in the literature to date, further exploration into these alleles is needed. A clonal relationship between FT lesions and endometrial cancer could have important implications on clinical counseling and management, thus further research into the specific p53 mutations identified and validation within a larger cohort is warranted. Research Sponsor: None.

5611 **Poster Session**

Ultra-sensitive circulating tumor DNA (ctDNA) detection as predictor of survival outcomes in endometrial cancer patients undergoing frontline treatment. First Author: Jeffrey Andrew How, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: For endometrial cancer (EC), clinicopathologic and molecular characterization add to the risk stratification complexity, but remain limited to predict risk of recurrence. Precise biomarkers are needed to guide treatment. This study seeks to investigate the value of circulating tumor DNA (ctDNA) in EC patients. **Methods:** In an ongoing, single-institution prospective study of EC patients undergoing primary surgical management, serial plasma samples were collected at multiple timepoints: pre-(pre-op)/post-operatively (post-op), post-definitive treatment (dTx), and surveillance. If patients did not have adjuvant therapy, the post-op time point was considered the dTx timepoint. ctDNA analysis was performed on banked samples at the non-surveillance timepoints using NeXT Personal, a personalized whole genome sequencing-based tumor-informed assay tracking up to 1800 mutations, (Personalis, Fremont, CA). Primary endpoint was ctDNA detection rate. Secondary endpoints included correlation with survival outcomes (recurrence free survival [RFS] and overall survival [OS]). Multivariable analysis was performed for RFS adjusting for dTX ctDNA detection, stage, and TP53 mutation status. Given the limited number of deaths, multivariable analysis was not performed for OS. **Results:** 99 patients and 254 samples were included for ctDNA analysis. Median age at surgery was 65.1 (range 42-85) years. After a median follow-up of 24.1 (range 3.4 – 67) months, there were 25 recurrences and 10 deaths. Majority had stage I (68.7%), grade 3 (73.7%) tumors, non-endometrioid histologic tumor components (63.7%), and received adjuvant therapy (79.8%; therapy declined in 4 [4%] patients). Adjuvant radiation and chemotherapy was given in 67 (67.7%) and 53 (53.5%) patients, respectively. ctDNA was detected in 83.3% (75/90) of pre-op, 19.5% (17/87) of post-op, and 14.1% (9/64) of dTx samples. Although pre-op ctDNA was not associated with survival, post-op ctDNA detection was associated with worse RFS (HR 6.3, 95% CI 2.6-15.5; $p<0.001$) and OS (HR 24.6, 95% CI 3-205; p=0.003). Post-op detection in the ultrasensitive range (<100 PPM) were also significantly prognostic of worse RFS (HR: 5.1, 95% CI 1.3-19.5, P=0.02). Similarly, dTx detection was associated with worse RFS (HR 27.7, 95% CI 8.9-86.6; $p<0.001$) and OS (HR 7.5, 95% CI 1.7-33.7; p=0.01). On multivariable analysis, dTx detection was independently associated with worse RFS (HR 27.7, 95% CI: 8.9-86.6; $p<0.001$). **Conclusions:** In a predominantly early-stage, high-risk cohort of EC patients, post-op and dTx ctDNA detection is associated with inferior survival. ctDNA detection in the ultrasensitive range may hold promise to identify EC patients at risk for recurrence which may not be identified in conventional assays. These results support ctDNA as a promising biomarker for clinical decision-making in EC. Research Sponsor: None.

5612 **Poster Session**

Pembrolizumab–lenvatinib beyond immunotherapy progression in endometrial cancer: A real-world analysis. First Author: Alberto Farolfi, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy

Background: The integration of immune checkpoint inhibitors (ICIs) into frontline therapy for advanced or recurrent endometrial cancer (aEC) has transformed treatment paradigms. However, the management of patients who experience disease progression after ICI-based therapy remains challenging. In the absence of prospective guidance, ICI rechallenge and ICI-based combinations beyond progression are already being used in clinical practice. In this real- world study, we aimed to evaluate the effectiveness of pembrolizumab-lenvatinib (PL) beyond ICI progression in patients with aEC. **Methods:** A retrospective study was conducted using the TriNetX database, defining two cohorts of aEC patients: 527 patients who received PL and 2,582 patients who did not receive PL but were treated with either paclitaxel or doxorubicin (chemotherapy, CHT cohort). Both cohorts had received an ICI-based regimen within the previous three years. Patients with any other malignancy were excluded. Propensity score matching (PSM) was used to balance cohorts for age, race, body mass index (BMI), major comorbidities, mismatch repair (MMR) status and prior olaparib exposure. The primary endpoint was overall survival (OS); secondary endpoints were treatment-related toxicities, including hypothyroidism and heart failure. OS was estimated using Kaplan–Meier methods, with hazard ratio (HR) used to compare OS and odds ratio (OR) used to compare toxicities. **Results:** After PSM, 521 matched pairs of patients (mean age +/- standard deviation: 66,4 +/- 9,6 years) were included in the PL and CHT cohorts, respectively, with well-balanced baseline characteristics. Asian patients were similarly represented in the two groups (7.3% vs 7.4%), most patients were obese (BMI ≥30: 59,3% vs 57,8%), only a small proportion had known MMR-deficient disease (2.1% and 1.9%), and just few of them were previously treated with olaparib (1.9%). After a median follow-up of 8.6 months (interquartile range, IQR 14.3) in the PL cohort and 11.5 months (IQR 16.7) in the CHT cohort; median OS was 27,4 months with PL and was not reached with CHT (HR = 2.25, 95% CI 1.76–2.89; $p<0.001$). **Conclusions:** The rise of ICIs in frontline therapy for aEC marks a paradigm shift and raises the question on how to manage patients who progress after prior immunotherapy. This is the first large, real-world cohort analysis to evaluate PL beyond immunotherapy progression in aEC. In this study, PL did not improve OS compared with CHT in patients previously exposed to ICIs. These findings suggest that PL may not be the optimal choice in this setting, and further work is needed to clarify the best post-ICI sequencing strategies and to develop approaches to overcome resistance. Research Sponsor: None.

5613 **Poster Session**

Circulating tumor DNA (ctDNA) from a phase II study of adjuvant dostarlimab with pelvic radiation in locally advanced, mismatch repair–deficient (MMR-D) endometrial cancer (D-RT study). First Author: Gabriela Sotolongo, Gynecologic Oncology Service, New York, NY

Background: Although ctDNA is a promising, non-invasive tool for cancer evaluation and monitoring, it's use in endometrial cancer (EC) is currently limited. We sought to evaluate ctDNA dynamics and associations with clinical outcomes as part of a novel study of adjuvant immune checkpoint blockade (ICB) with radiation (RT) in locally advanced MMR-D EC. **Methods:** The D-RT study was an investigator-initiated, single-arm, phase II trial evaluating the safety and efficacy of 5 cycles of dostarlimab given concurrently with standard pelvic intensity modulated RT (IMRT), NCT04774419. The study included patients with newly diagnosed clinical stage III/IVA MMR-D EC. Primary endpoint was progression-free survival (PFS) at 2 years defined by RECIST V1.1 compared with historical control. All patients consented to MSK-IMPACT tumor-normal genetic testing. We performed MSK-ACCESS targeted ctDNA sequencing in a subset of patients with at least 3 timepoints (baseline post-surgery, on-treatment, post-treatment/follow-up) and correlated with baseline tumor genomics and clinical outcomes. **Results:** We previously reported the primary endpoint in 31 evaluable patients with 2-year PFS of 80.6% (95% 1-sided CI 65.3-100%), meeting pre-specified threshold for a positive study (data cutoff 8/1/2025). Here, we report ctDNA results from a subset of 15 patients with 58 total samples. Median age was 62 years (range 51-89 years) with 1 stage IB (i+), 3 stage IIIA, 9 stage IIIC1, and 2 stage IIIC2 MMR-D ECs (FIGO 2009). Histology included 8 endometrioid grade I/II, 5 endometrioid grade III, and 2 dedifferentiated carcinomas. Six patients (40%) had detectable baseline ctDNA post-surgery, with 5/6 (84%) having visible/residual disease at baseline. Of these, 3/6 (50%) had eventual disease recurrence post adjuvant treatment. In 8 patients with visible disease post-surgery, only 2 did not have detectable baseline ctDNA. ctDNA cleared post-treatment in all but 2 patients who had aggressive, dedifferentiated carcinomas. Among the 5 patients with recurrence (4 distant, 1 local), ctDNA detection preceded or coincided with radiographic detection of disease in the 4 patients (80%) with distant disease. One patient had a biopsy-proven, vaginal cuff recurrence only and never had detectable ctDNA. In the 10 patients without disease recurrence, none had detectable ctDNA post-treatment. **Conclusions:** In patients with locally advanced MMR-D EC, ctDNA detection after surgery correlated with visible disease. ctDNA levels declined during dostarlimab and RT treatment for most patients, and ctDNA detection was correlated with disease recurrence in distant but not local disease, suggesting its potential as a non-invasive marker of disease. Future studies should explore the utility of ctDNA as a disease monitoring tool to guide therapy decisions. Clinical trial information: NCT04774419. Research Sponsor: Federal; GSK.

5614 **Poster Session**

Forecasting global disparities in cervix and corpus uteri cancers: GLOBOCAN 2022–2040 projections. First Author: Sonia Babu, Mercy Catholic Medical Center, Darby, PA

Background: Uterine cancers, including cervix uteri (C53) and corpus uteri (C54), are a major burden on global healthcare with marked geographic and socioeconomic disparities. Key risk factors including persistent high-risk HPV infection for cervical cancers), limited screening access, and modifiable factors like obesity and exogenous hormone exposure (e.g., oral contraceptive use), which vary across settings and could influence future burden. Predicting epidemiological trends is essential to guide prevention, screening, and treatment modalities. This study compares predicted changes in incidence and mortality for C53 and C54 across countries, WHO regions, income groups, and HDI categories from 2022 to 2040. **Methods:** Incidence and mortality data for 2022 and predictions for 2040 were extracted from GLOBOCAN database for 185 countries. Countries were classified by WHO region, World Bank income level, and HDI categories. Percentage changes in incidence and mortality were calculated for both cancer types across all categories. **Results:** Globally, C53 incidence is forecasted to rise from 1.32 million to 5.94 million cases (+348.4%), with mortality increasing from 697,418 to 3.41 million deaths (+389.5%). C54 shows a modest increase in incidence (840,256 to 899,224; +7.0%) but substantial increase in mortality (195,310 to 899,224; +360.5%). Across WHO regions, the largest increases in C53 incidence and mortality occur in AFRO and EMRO (+1043%, +1066% and +918%, +1029%, respectively). C54 incidence advances most in AFRO (+279%) and EMRO (+254%) and least in EURO (+97.8%). Mortality growth is highest in EMRO (+1205%) and AFRO (+1106%). Income-level patterns show increasing disparities: low-income countries have the highest increases for C53 incidence (+1062%) and mortality (+1073%), with high-income regions showing the lowest (+693%, +781%). Similar trends are observed for C54, with incidence rising most in low-income settings (+302%) and least in high-income regions (+139%), while mortality increases range from +1096% (low-income) to +872% (high-income). HDI patterns are similar to income trends: Low-HDI countries reveal the highest increases for C53 (+1062% incidence, +1073% mortality) and C54 (+302%, +1096%), while Very-High-HDI regions show the lowest rises for both cancers. **Conclusions:** Burden of uterine cancer is predicted to rise steeply by 2040, with greatest increases in low-income, low-HDI, AFRO, and EMRO regions. The disproportionate escalation in mortality (especially for corpus uteri cancers) highlight the importance of prevention, screening, early detection, and equal access to treatment to prevent expanding global disparities, including improved availability of HPV vaccination, targeted public education efforts, and engagement of primary care physicians and OB/GYNs to ensure that patients are vaccinated and screened appropriately. Research Sponsor: None.

5615 **Poster Session**

A phase II trial of lenvatinib plus pembrolizumab in patients (pts) with endometrial or ovarian carcinosarcoma. First Author: Sminu Bose, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Carcinosarcoma is a rare and aggressive histology of gynecologic carcinomas that has limited treatment options and is often excluded from larger therapeutic clinical trials. In KN775, treatment with multikinase inhibitor lenvatinib plus PD-1 inhibitor pembrolizumab led to significantly longer progression-free survival (PFS) and overall survival (OS) than chemotherapy among patients with previously treated advanced non-carcinosarcoma endometrial carcinomas. We report results from a phase 2 trial of lenvatinib + pembrolizumab in pts with endometrial or ovarian carcinosarcoma. **Methods:** In this open label, single institution, investigator initiated, phase 2 study, pts had confirmed recurrent/persistent endometrial or ovarian carcinosarcoma with progression after at least 1 prior platinum chemotherapy but no more than 3 prior lines, measurable disease, and ECOG performance status $\leq$1. Pts received oral lenvatinib 20 mg/day plus pembrolizumab 200 mg intravenously every 3 weeks. The primary endpoints were objective response rate (ORR) per RECIST v1.1 and PFS rate at 27 weeks (PFR27). Secondary endpoints included median duration of response (mDOR), clinical-benefit rate (CBR: complete response (CR) + partial response (PR) + stable disease (SD) at 27 weeks), median overall survival (mOS), and safety. Next generation sequencing, MSK-IMPACT, was performed on tumors from all 27 patients for exploratory analysis. **Results:** As of data cutoff on 12/15/2025, 27 pts enrolled; median age was 63 years (range: 51−79); and at least 26.4% pts were non-white. Primary tumor site was 63% (17/27) endometrial and 37% (10/27) ovarian; tumors were 19% (5/27) dMMR and 81% (22/27) pMMR. Confirmed ORR was 18.5% (5/27; 0 CRs, 3 PRs in endometrial, 2 PRs in ovarian), meeting the interim analysis primary endpoint. Of the 5 confirmed responses, 4 occurred in pts with pMMR tumors, and 1 in a pt with dMMR tumor. There are 2 additional unconfirmed PRs. Responses in pts with ovarian tumors included 1 platinum-sensitive and 1 platinum-resistant. PFR27 was 35.7% (90% CI: 24 - 100), mDOR was 26.5 months (80% CI: 3.8 - NE), CBR was 37% (80% CI: 24.4 - 51.2), and mOS was 15.3 months (95% CI: 7.1 – 24.4). Two pts remain on treatment and were censored for time to event analyses. All pts had at least one treatment-emergent adverse event (TEAE). The most common TEAEs were fatigue (74%), hypertension (56%), diarrhea (52%), anorexia (48%), and weight loss (48%). Grade 3 and 4 TEAEs occurred in 44% and 7.4% patients, respectively. There were no grade 5 TEAEs. 5 Pts (19%) discontinued study treatment due to TEAEs. Further genomic analyses are underway. **Conclusions:** Encouraging efficacy and durable responses were observed in endometrial and ovarian carcinosarcoma pts treated with lenvatinib + pembrolizumab, regardless of MMR status or primary site. The study met its predefined interim analysis endpoint. No new safety signals were identified. Clinical trial information: NCT02501096. Research Sponsor: None.

5616 **Poster Session**

Antibody-drug conjugate (ADC) biomarker targets in endometrial cancer (EC): Molecular characterization and implications for therapeutic decision-making. First Author: Britt Kristina Erickson, University of Minnesota, Masonic Cancer Center, Minneapolis, MN

Background: Given the evolving landscape of ADCs, we evaluated expression of emerging ADC targets in EC and compared expression patterns across molecular subgroups (POLE mutated [POLEm], MSI-high [MSI-H], TP53-mutated [TP53m] or No Specific Molecular Profile [NSMP]) defined by the Proactive Molecular Risk Classifier for Endometrial Cancer. **Methods:** Tumors were analyzed by DNA and RNA sequencing and immunohistochemistry (IHC) for select proteins (Caris Life Sciences, Phx, AZ). ER+ defined as % staining $\geq$ 1%. Statistics were calculated by Mann-Whitney U test and adjusted for multiple comparisons ($q < 0.05$). Expression was split into top quartile (^{H}) and bottom quartile (^{L}). Overall survival (OS) was obtained from insurance claims data and calculated from first treatment to last contact. Hazard ratios (HR) were calculated by Cox proportional hazards with p-values by log-rank tests. **Results:** Of 13,731 EC samples, 2.4% (n=335) were POLEm, 21.6% (n=2,961) MSI-H, 46.8% (n=6,420) TP53m and 29.2% (n=4,015) NSMP. HER2+ by IHC was highest in TP53m tumors compared to POLEm, MSI-H, and NSMP (15.9% vs 1.2% vs 0.8% vs 4.0%; $p<0.05$). TP53m tumors had the highest RNA expression of CDH6, B7-H4, CLDN6, ERBB3, ERBB2, FOLR1, NECTIN2, NECTIN3, and TF; NSMP tumors had the highest expression of TROP2 and NECTIN4 relative to other subtypes (Table 1). Compared to all solid tumors, TP53m EC had the highest median RNA expression of B7-H4 and second highest of CLDN6 and FOLR1. Assessing the prognostic effect of ADC targets by subtype, POLEm CLDN6^{H} tumors had improved OS compared to CLDN6^{L} (HR 0.39, p=0.003). In MSI-H tumors, TROP2^{H}, CDH6^{H}, B7-H4^{H}, CLDN6^{H}, ERBB3^{H}, ERBB2^{H}, FOLR1^{H} and NECTIN2-4^{H} was associated with improved OS (HR 0.57-0.84, $p<0.05$). In TP53m tumors, TROP2^{H}, B7-H4^{H}, FOLR1^{H}, HER3^{H}, and NECTIN4^{H} was associated with improved OS (HR: 0.75-0.80, $p<0.05$) and NECTIN1^{H} and B7-H3^{H} with worse OS (HR: 1.26, $p<0.001$). In ER- NSMP tumors (n=804), B7-H4^{H}, ERBB3^{H}, ERBB2^{H} and NECTIN4^{H} had improved OS (HR: 0.62-0.74, $p<0.05$) and B7-H3^{H} and NECTIN1^{H} had worse OS (HR: 1.40, p=0.01). In ER+ NSMP tumors (n=2,896), TROP2^{H} and TF^{H} had improved OS (HR: 0.73-0.82, $p<0.05$) and ERBB2^{H} and CDH6^{H} had worse OS (HR: 1.24-1.29, $p<0.05$). **Conclusions:** Expression of ADC targets differs by molecular subtype with varying associations with OS in EC patients. Focusing future clinical trials on EC subsets with high biomarker expression will be critical to efficiently developing novel targeted therapeutics. Research Sponsor: None.

RNA expression by subtype (transcripts per million).

Subtype	B7-H3	B7-H4	CD276	CLDN6	ERBB2	ERBB3	FOLR α	NECTIN1	NECTIN2	NECTIN3	NECTIN4	TF	TROP2
POLEm	10.0	10.0	24.9	0.38	25.6	52.7	7.6	7.2	14.9	15.0	5.6	0.70	58.2
MSI-H	5.8	12.0	23.2	0.32	23.3	58.9	8.6	7.8	14.7	13.6	9.7	0.84	61.1
TP53m	21.5	15.8	22.0	2.90	32.8	62.4	20.7	6.0	18.6	18.6	7.1	0.98	54.8
NSMP	7.5	14.0	22.3	0.35	25.1	56.2	10.3	6.6	14.9	11.5	10.5	0.78	81.8

5617 Poster Session

Accumulation of cholesterol, cortisol, and glutathione in mitochondria as a marker of metabolic adaptation in serous and clear cell endometrial carcinoma. First Author: Anna Petrovna Menshenina, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation

Background: Aggressive endometrial carcinoma subtypes, such as serous (USC) and clear cell (CCC) carcinomas, are characterized by distinct cellular metabolism and dysregulation. Altered homeostasis of metabolites and hormones within mitochondria serves as a molecular driver of metabolic reprogramming in cancer cells. Excess mitochondrial cholesterol can induce oxidative stress, whereas glutathione provides antioxidant defense. Cortisol levels are capable of modulating organelle function. The aim of this study was to evaluate the levels of cholesterol, cortisol, and glutathione in mitochondria isolated from serous and clear cell endometrial carcinomas to characterize the metabolic profile of tumor cells. **Methods:** The study was conducted on mitochondria isolated from tumor tissue of 41 patients with USC (n=21) and CCC (n=20), stage III–IV, histological grade G3; the mean patient age was 59.6±6.7 years. Mitochondria isolated from normal endometrium (n=20) obtained during hysterectomies for uterine leiomyoma (mean age 57.8±8.2 years) served as controls. Cortisol, cholesterol, and glutathione concentrations in the mitochondrial fraction were determined by enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using parametric and nonparametric tests with adjustments for multiple comparisons. **Results:** A significant increase in cholesterol levels was observed in mitochondria from these rare endometrial carcinoma subtypes: 2.1-fold in USC and 1.9-fold in CCC compared with normal endometrium. Cortisol content was elevated by 2.1- and 2.5-fold, respectively. Mitochondrial glutathione concentration was also increased: 2.4-fold in USC and 1.9-fold in CCC. **Conclusions:** The data reveal a universal mechanism of metabolic adaptation in serous and clear cell endometrial carcinomas, characterized by a unified mitochondrial metabolic profile featuring co-accumulation of cholesterol, cortisol, and glutathione. Elevated cholesterol generates a pro-apoptotic signal, which is counterbalanced by increased glutathione levels to maintain redox homeostasis. The concurrent rise in cortisol indicates the engagement of mitochondrial stress-response pathways. This constellation of alterations reflects fundamental reprogramming of cellular homeostasis in aggressive endometrial cancers and may be considered a potential target for mitochondrial-directed therapy. Research Sponsor: None.

5618 Poster Session

p53 R248Q upregulation of VTCN1 via dual mechanisms as a driver of immune evasion and adaptive resistance to CDK4/6 inhibitors: Rationale for combination immunotherapy in endometrial cancer. First Author: Yan Ding, Tongji University, Shanghai, China

Background: TP53-mutated endometrial cancer (EC) is a heterogeneous disease with variable responses to immunotherapy. While generic p53 mutation status is a standard biomarker, the distinct clinical impact of specific hotspot mutants remains underappreciated. Our bioinformatics analysis of TCGA data suggested that the R248Q hotspot—but not others—is specifically linked to an "immune-desert" phenotype. We aimed to mechanistically define this subtype and validate its diagnostic value as a predictor for immune exclusion and CDK4/6 inhibitor sensitivity. **Methods:** We performed a comprehensive bioinformatic analysis of the TCGA-UCEC cohort to correlate specific p53 hotspot mutations with immune landscapes. To elucidate the underlying mechanism, we engineered a panel of isogenic EC cell lines (p53-null, R248Q, R175H, R248W, R273H/C) and assessed VTCN1 (B7-H4) regulation via biochemical assays. To validate these findings clinically, we established an independent cohort of 254 EC patients with tissue microarrays (TMA); whole-exome sequencing (WES) is currently underway to pinpoint hotspot mutations and correlate them with VTCN1 expression and immune infiltration. **Results:** Discovery of Diagnostic Target: In the TCGA cohort, stratifying p53 mutants revealed that R248Q carriers exhibited the most profound "cold" tumor microenvironment compared to other hotspots, suggesting it as a potential negative predictive biomarker. Mechanistic Validation: Using our isogenic models, we observed that R248Q specifically drives high VTCN1 expression. Mechanistically, R248Q appears to promote VTCN1 via a dual pathway: transcriptional upregulation and, uniquely, protein stabilization by inhibiting proteasomal degradation. This indicates VTCN1 as a potential surrogate marker for the R248Q subtype. Therapeutic Implications: In preclinical models, abemaciclib treatment paradoxically upregulated VTCN1 in R248Q cells, suggesting adaptive resistance. However, this induced vulnerability was associated with enhanced sensitivity to combined CDK4/6 inhibition and immunotherapy (anti-VTCN1), which elicited superior tumor regression compared to monotherapy. **Conclusions:** Our study suggests the potential value of refining p53 diagnostics from binary (mutant/WT) to hotspot-specific resolution. Current data indicate that p53 R248Q may function as a distinct driver that contributes to an immunosuppressive "cold" TME in EC, likely through synergistic transcriptional and post-translational upregulation of VTCN1. Furthermore, abemaciclib-induced VTCN1 elevation points to a possible mechanism of monotherapy resistance. These findings provide a strong preclinical rationale to explore combining CDK4/6 inhibitors with immunotherapy, specifically for patients with the high-risk p53 R248Q subtype. Research Sponsor: Funding Agency: National Natural Science Foundation of China (NSFC), Grant No: 82172714.

5619 Poster Session

Preoperative endocrine treatment response in primary postmenopausal endometrial cancer. First Author: Fabian Trillsch, LMU University Hospital, LMU Munich, Munich, Germany

Background: While preoperative endocrine therapy with letrozole has become an established approach for treatment decisions in estrogen receptor (ER) positive breast cancer, this concept has not been transferred to endometrial cancer so far. We hypothesized that preoperative endocrine treatment response to letrozole, assessed by changes in Ki67 expression between baseline and surgery as a marker for cellular proliferation, can be evaluated in primary endometrial cancer as a predictive, patient-specific biomarker. **Methods:** Postmenopausal patients with first diagnosis of endometrial cancer planned to undergo definitive surgical management with hysterectomy were prospectively included in this single-arm biomarker analysis. Letrozole was administered orally at a daily dose of 2.5mg for a period of 2 to 4 weeks until surgery. Eligibility criteria included all molecular subtypes and histologies and no prior treatment for endometrial cancer was allowed. Ki67 expression was assessed immunohistochemically by two independent pathologists as the percentage of positive tumour nuclei. Relative change in Ki67 (%) from pre-treatment biopsy to post-treatment specimen was assessed using the Wilcoxon signed-rank test, substantial response was defined as relative reduction of Ki67 expression ≥50%. **Results:** A total of 23 patients were prospectively enrolled with median age of 70 years (range 52-88) and median BMI of 32 kg/m² (range 20-48). 22 patients had endometrioid histology (22/23, 95.7%), of those 86.4% (19/22) low-grade and three high-grade (13.6%). One patient had a high-grade serous tumor. 17 of the 23 patients (73.9%) were classified as NSMP (no specific molecular profile), 14 of them ER positive (82.3%). 5 of 23 patients were classified as dMMR (mismatch repair deficient, 21.7%) and one as p53mut (p53 mutant). Median pre-treatment Ki67 expression was 50% (range 10-85) compared to 15% (range 1-80) post-treatment ($p<0.0002$). Following preoperative letrozole treatment, 16 of 23 patients (69.6%) had a relative reduction of more than 50% in Ki67 expression, 13 of these (81.3%) were of NSMP, three (18.8%) of dMMR molecular subtype. Regarding ER expression in these responders, all dMMR and 11/13 NSMP tumors (84.6%) were ER positive. Two NSMP tumors (14.5%) showed a response to endocrine treatment despite being ER negative. **Conclusions:** Short-term preoperative letrozole treatment enables identification of patients with substantial endocrine treatment response in primary endometrial cancer. Using this preoperative window-of-opportunity, dynamic Ki67 evaluation might serve as an easily accessible predictive biomarker to tailor patient-specific treatment decisions. Research Sponsor: None.

5620 Poster Session

Racial disparities in endometrial cancer (EC) survival after molecular classification (MC). First Author: Jill Roberts, Sylvester Comprehensive Cancer Center/University of Miami, Miami, FL

Background: Black (BAA) patients with EC have double the mortality rate compared to White patients. It is unclear if these survival differences persist after MC. Here, we examine racial disparities in this context and seek to identify molecular differences by race. **Methods:** EC samples (n = 10,162: BAA n=2,410, White n=7,752) were analyzed by NGS (NextSeq/NovaSeq) and RNA (NovaSeq) (Caris Life Sciences, Phx, AZ). Four well-described EC groups were created: POLE ultramutated (POLE-mt), MSI-H, TP53-mt, or No Specific Molecular Profile (NSMP; TP53-wt). Overall survival (OS) was obtained from insurance claims and calculated from tissue collection to last contact for MC cohorts. Hazard ratio (HR) was calculated by Cox proportional hazards, with p-value calculated by log-rank test. Race was self-reported. **Results:** There was a higher prevalence of BAA patients in the TP53-mt subtype (69.1% vs. 43%), compared with POLE-mt (1% vs. 2.26%) and NSMP (16.4% vs. 31%) ($p<0.001$). Across EC, BAA patients had shorter OS (29.8 vs 39.7 months (m); HR: 1.30 (1.22-1.39), $p<0.001$). BAA patients had worse OS in the NSMP cohort (36.8 vs 49.5m; HR 1.35 (1.15-1.59), $p<0.001$) and TP53-mt cohort (26.1 vs 29.6 m; HR 1.13 (1.05-1.22), p=0.002). Race was not associated with differences in OS in POLE-mt (NR vs was 51.4 m) and MSI-H (44.4 vs 45.9 m). There were molecular differences between race when stratified by MC ($q<0.05$) (Table 1). Gene set enrichment analysis showed downregulation of immune-related pathways in BAA. In NSMP tumors, BAA patients had lower IFNγ signature (0.72-fc) and worse post-pembrolizumab survival (16.9 vs 24.6 m; HR 1.46 (1.09-1.95), p=0.011). **Conclusions:** Previous studies demonstrated that racial disparities in endometrial cancer persist even when controlling for histology. This study demonstrates that these disparities persist even after controlling for MC, as defined by the ProMisE classification. BAA patients were more likely to develop TP53-mt tumors, but the survival disparity was largest in the NSMP group. Furthermore, Black and White patients exhibit differential expression of known prognostic mutations even within the same MC group. Research Sponsor: None.

Molecular differences by race and subtype.

	TP53-mt		NSMP	
Biomarker	BAA %	White %	BAA %	White %
***ARID1A*-mt**	4.47	**10.3**	32.8	**48.9**
***CTNNB1*-mt**	NS	NS	31.1	**40.2**
***FGFR2*-mt**	0.60	**2.94**	3.29	**11.3**
***PIK3CA*-mt**	23.1	**36.6**	NS	NS
***PIK3R1*-mt**	9.58	**15.4**	17.9	**35.0**
***PTEN*-mt**	6.83	**15.7**	40.4	**66.9**
PPP2R1A-mt	15.5	**23.8**	NS	NS
***CDKN2A*-del**	NS	NS	**22.0**	13.7
***CDKN2B*-del**	NS	NS	**13.7**	5.45
***MTAP*-del**	NS	NS	**18.8**	8.92
ER+	NS	NS	62.6	**76.0**
PR+	NS	NS	53.1	**67.4**

NS=not significant.

5621 **Poster Session**

Aspirin use and survival outcomes in endometrial cancer. First Author: Zachary Gentry, The Ohio State University, Columbus, OH

Background: Given the worsening survival trends of endometrial cancer in the United States, further improvement in adjuvant treatment of this cancer is needed. Aspirin use has been shown to reduce cancer risk in multiple cancer types. A randomized controlled trial recently showed that aspirin therapy significantly improved overall survival in patients with colorectal cancer with PIK3CA mutations, a mutation that is seen in up to 50% of endometrial cancers. We therefore hypothesized that aspirin use may similarly improve survival in patients with endometrial cancer. **Methods:** We conducted a retrospective review of all patients with endometrial cancer treated at a single academic institution between 2014-2017. Demographics, clinicopathologic data, surgical and adjuvant treatment, and aspirin use were collected from the medical record. Proportional variables were compared using Fisher's exact and Chi-square tests. Continuous variables were compared using t-tests and Mann-Whitney U-tests. Disease-specific survival (DSS, time from diagnosis to death due to cancer) was estimated using Kaplan-Meier plots, with log-rank and Cox proportional hazards analysis used to compare groups. **Results:** A total of 765 patients were included in the study. Most patients were white (92%), had Stage I disease (79.9%), had endometrioid histology (87.1%), and were mismatch repair (MMR) proficient (74.6%). Of the 765 patients, 243 (31.8%) were taking ASA at the time of their endometrial cancer diagnosis, while 522 (68.2%) were not. Patients taking aspirin at the time of diagnosis were significantly older than those who were not (66.2 vs 59.8, $p<0.0001$). Otherwise, there was no significant difference in BMI, stage, grade, histology, MMR status, or adjuvant treatment between the two groups. On multivariate analysis, aspirin use at diagnosis was significantly associated with improved DSS (HR 0.27 [0.10-0.64], p=0.0020) after adjusting for age, stage, grade, histology, MMR status, and adjuvant treatment. **Conclusions:** Aspirin use at the time of endometrial cancer diagnosis was associated with a significant improvement in DSS in our cohort. While retrospective, this data is promising as a potential improvement in therapy for patients with endometrial cancer. Additionally, this intervention would be inexpensive and easily accessible for all patients. Prospective data is needed to further evaluate the effect of aspirin on endometrial cancer outcomes. Research Sponsor: None.

5622 **Poster Session**

MicroRNAs as surrogate biomarkers of future endometrial malignancy in women with endometrial hyperplasia without atypia and an open-label randomized trial of metformin, weight control, and exercise intervention. First Author: Chyong-Huey Lai, Gynecologic Cancer Research Center, Taoyuan City, Taiwan

Background: Endometrial hyperplasia (EH) is regarded as an endometrial cancer (EC) precursor. The severity of atypia reflects risk of future EC. According to Kurman et al., the risk of progression to EC was $<$ 1% in simple hyperplasia (SH) and 3% in complex hyperplasia (CH) without atypia (non-A). Our group previously identified 4 MicroRNAs (MiRs) and PTEN by immunohistochemistry stain are significant risk biomarkers of future endometrial malignancy. **Methods:** This prospective open-label randomized controlled study enrolled a total of 60 patients SH/CH non-A. All participants were randomized 1:1 to with or without metformin intervention and received education for exercise and weight control. A stratification of body mass index was performed, but not for HbA1C. PTEN immunohistochemistry stain and MiR profiles of the endometrial tissue were analyzed. **Results:** 57 participants were eligible for analysis. After all the participants had been followed up for 3 years, an analysis was performed in which 3 with progression to atypical hyperplasia and 6 with recurrent SH/CH non-A were observed. Exercise intensity was inversely correlated with use of metformin or not (p = 0.028). The predicting progression/recurrence by any of the 4 miRs (miR30a-3p, miR141, miR-200a, and miR200b) were all significant ($p < 0.05$). PTEN expression, metformin, exercise, or body weight control intervention did not alter the risk of EH recurrence/EC progression. Metformin group has a trend of decreased risk of progression/recurrence yet not significant (p = 0.291). The decreased impact of metformin may be partly related to their lower intensity of exercise as compared to no-metformin group. Impact of interventions may need longer observation. **Conclusions:** Presence of any of the 4 miRs (miR30a-3p, miR141, miR-200a, and miR200b) seem related to risk of recurrence/progression of SH/CH non-A, while PTEN expression, metformin, exercise, and weight control are not, in our prospective cohort. Clinical trial information: NCT05292573. Research Sponsor: National Science and Technology Council, Taiwan; 2018-2021 MOST-107-2314-B-182-040 -MY3.

5623 **Poster Session**

Whole-genome sequencing–based ctDNA testing for post-surgical monitoring and early detection of recurrence or progression in uterine cancer. First Author: Abigail Barger, St. Luke's University Health Network, Bethlehem, PA

Background: Reliance on clinicopathologic risk factors to guide adjuvant therapy in early-stage uterine cancer (UC) has not improved survival, underscoring the need for biomarkers for post-treatment monitoring. In this study, we evaluate ctDNA as a prognostic biomarker using a whole-genome sequencing (WGS)–based assay in the post-surgical UC setting. **Methods:** We performed a retrospective analysis of clinically annotated residual samples from commercial ctDNA testing in 118 patients diagnosed with UC. Signatera Genome assays (Natera, Inc.) were designed from the WGS data of matched tumor tissue and normal blood samples to detect and quantify ctDNA in serially collected post-operative plasma. Descriptive statistics were used to compare association of ctDNA across stages and timepoints. **Results:** Among 118 UC patients, 20/118 were metastatic and excluded from analysis. Of the remaining 98 patients, 77 had stage I and 21 had stage II-III disease. Median clinical follow-up was 11.2 months (range: 0.8–33.2) with 13% (13/98) of patients having recurrence/progression within a median of 8.5 (range: 3.9-25.1) months from surgery. ctDNA analysis was performed across 1004 total tests with a median of 8 tests per patient (range: 2–16) and a median testing cadence of 2.9 (range: 0-12.7) months. Post-surgical ctDNA assessment (2–8 weeks post-operatively) was available for 35 stage I patients with a ctDNA detection rate of 9% (3/35). Focusing on the 32 patients with $>$12 months of postoperative clinical follow-up, one patient was ctDNA-positive postoperatively and recurred 7.2 months after surgery. Among the ctDNA-negative patients (N=31), 84% (26/31) remained serially negative with no evidence of recurrence at a median clinical follow-up of 26.3 (range: 13.5-38.7) months post-surgery. The remaining ctDNA-negative patients (N=5) converted to positive during longitudinal monitoring, all subsequently experiencing recurrence/death. Longitudinal ctDNA detection rate during surveillance was 32.1% (25/78) in stage I and 47.6% (10/21) in stage II-III. Of the stage I patients with recurrence (N=8), 100% were ctDNA-positive prior to or at the time of the clinical finding, with a median lead time of 5.2 (range: 1.2–15.8) months. Similarly, in stage II-III patients with recurrence/progression (N=5), 100% were ctDNA-positive prior to the clinical finding with a median lead-time of 6.07 (range: 4.1-23.7) months. **Conclusions:** ctDNA positivity postoperatively identifies UC patients at increased risk of recurrence/progression, often preceding clinical relapse by several months. Serial ctDNA negativity using a tumor-informed, WGS-based ctDNA assay correlated with absence of recurrence. Postoperative longitudinal ctDNA monitoring shows promise as a clinically actionable biomarker to guide adjuvant treatment decisions and improve post-operative surveillance. Research Sponsor: None.

5624 **Poster Session**

Development of an endometrial cancer test from a vaginal swab. First Author: Bridget Z. Gagrat, Exact Sciences Corporation, Madison, WI

Background: Endometrial cancer (EC) is the most common gynecologic cancer and abnormal uterine bleeding (AUB) is the predominant presenting symptom. While $<$10% of AUB represents underlying EC, endometrial sampling is currently required to rule out EC. To develop an alternative, non-invasive rule-out strategy, we aimed to refine a previously reported EC-associated methylated DNA marker (MDM) panel in vaginal swabs. **Methods:** Patients $\geq$18 years old with AUB who met ACOG recommendations for endometrial sampling and those undergoing a hysterectomy for biopsy-proven EC or atypical hyperplasia (AH) were prospectively enrolled in a multicenter cohort study. A vaginal fluid specimen was collected via swab by a provider during a speculum exam. DNA was extracted from samples and bisulfite treated, followed by a target and signal amplification method to detect 8 previously identified MDMs. The cross-validated EC classification model used the mean of standardized MDMs. Clinical classification of benign endometrium (BE), EC, and AH was based on central pathology review. EC diagnoses were based on hysterectomy specimens. Endometrioid and mucinous constituted type 1 EC; serous, carcinosarcoma, clear cell, and mixed histology ECs were collectively analyzed as type 2. **Results:** Of 693 participants enrolled, 670 were evaluable with valid results: 524 in the AUB cohort and 146 in the suspected EC cohort. Within the AUB cohort, 16 had EC or AH. The final analysis cohort included 508 BE, 156 EC, and 6 AH. Of the evaluable participants 20% identified as Black, 3% Asian or Pacific Islander, 75% White, and 3% Other; 7% reported Hispanic ethnicity. Median age was 66 and 50 years for EC and BE AUB, respectively; 80% of those with EC and 43% with benign AUB reported being postmenopausal. Among participants with EC, 102 (65%), 17 (11%), 30 (19%), 6 (4%) were stage I, II, III, and IV, respectively; one EC was unstaged. Type 2 EC accounted for 42 (27%) of all EC cases. A 4-MDM panel yielded an AUC of 0.97 (0.96-0.99, 95% CI) for EC; models with 5-8 MDMs gave identical performance. All-stage EC sensitivity was 97, 97, 96, 95, and 92% at specificities ranging from 75, 80, 85, 90, and 95%, respectively. At the 85% (82-88%) specificity threshold, sensitivities across EC stage, type, and age were consistently high (Table). Sensitivity for AH was 33% (10-70%). **Conclusions:** An MDM panel demonstrated high sensitivity for EC across stage and EC type, supporting the potential for a non-invasive vaginal swab-based test to rule out EC. Future studies are necessary to finalize the panel and algorithm, prior to validating the test. Clinical trial information: NCT06294886. Research Sponsor: Exact Sciences Corporation.

EC	Sensitivity (%, 95% CI) at 85% Specificity
All Stages (n=156)*	96 (92-98)
Stage I (n=102)	94 (88 - 97)
II (n=17)	100 (82 - 100)
III (n=30)	100 (89 - 100)
IV (n=6)	100 (61 - 100)
Type 1 (n=114)	95 (89 - 98)
2 (n=42)	100 (92 -100)
Age ≤ 66 yrs (n=86)	95 (89 - 98)
> 66 (n=70)	97 (90 - 99)

*n=1 EC was un-staged.

5625 **Poster Session**

GLP-1 receptor expression in a molecularly characterized cohort of endometrial carcinoma: Results from the GEICO 163-T/SPECTRUM study. First Author: Carlos González-Merino, Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain

Background: The glucagon-like peptide-1 receptor (GLP-1R) plays a central role in metabolic, and hormonal signaling and has gained increasing clinical relevance due to the widespread use of GLP-1R agonists. Given the strong link between obesity and endometrial carcinoma (EC), data on GLP-1R expression in EC are of clinical interest. We aimed to evaluate GLP-1R expression in a large, molecularly classified EC cohort and analyze its association with clinicopathological and molecular features. **Methods:** GLP-1R immunohistochemistry was performed on tissue microarrays from 192 ECs included in the SPECTRUM cohort. This cohort included 111 low grade endometrioid and 81 high grade ECs. 187 tumors were successfully classified according to WHO 2020 criteria, including 3% POLE-mutated (POLEmut), 25% mismatch repair–deficient (dMMR), 43% no specific molecular profile (NSMP), and 29% p53 abnormal (p53abn) carcinomas. Additionally, *CTNNB1* mutation status was available in 168 tumors (16% mutated). GLP-1R expression was evaluated using the Allred scoring system (range 0–8). GLP-1R positivity was defined as Allred $\geq$6 according to previously published criteria (Kanda et al. 2018). Associations were evaluated using univariable analyses and multivariable logistic regression, reporting ORs with 95% confidence intervals; $p<0.05$ was considered statistically significant. **Results:** GLP-1R expression was evaluated in 172 EC. GLP-1R positivity was observed in 32.0% of the overall cohort and differed across molecular subtypes: 41.9% in NSMP, 40.0% in POLEmut, 28.9% in p53abn and 20.5% in dMMR tumors (p=0.099). Progesterone receptor (PR) levels were significantly higher in GLP-1R–positive compared with GLP-1R–negative tumors (median 55% vs 20%, p=0.015), whereas a non-significant trend toward higher estrogen receptor (ER) expression was observed (median 50% vs 25%, p=0.18). GLP-1R positivity was more frequent in *CTNNB1* mutated tumors (50.0% vs 28.9%; p=0.041). In multivariable logistic regression including PR (continuous), *CTNNB1* mutation status and molecular classification, only PR levels remained independently associated with GLP-1R positivity (OR per 10% increase 1.15, 95% CI 1.02–1.30; p = 0.019). **Conclusions:** GLP-1R is frequently expressed in EC, particularly in PR positive tumors and within the NSMP molecular subtype, suggesting that the underlying pathway of carcinogenesis may influence GLP-1R expression. These findings may inform the design of future translational and clinical studies exploring GLP-1R–targeted strategies in endometrial carcinoma. Research Sponsor: None.

5626 **Poster Session**

Examining the relationship between social support and inflammatory markers among patients with gynecologic cancer. First Author: Oluwafemifola Oyedeji, North Knoxville Medical Center, Powell, TN

Background: Social support has been associated with improved health outcomes. Little research on the association between social support and inflammatory markers has been done among patients with gynecological cancer. The aim of this study is to examine whether there is an association between social support and inflammatory markers in patients currently receiving treatment for gynecologic cancer. **Methods:** These data were collected from a prospective cohort study designed to investigate the potential associations between cardiometabolic health and cancer treatment among women with gynecological cancer. As a secondary outcome, social support was assessed using the social provision scale (SPS), with higher scores indicating greater perceived social support. Fasting venous blood was collected for inflammatory marker analysis (Interleukin-6: IL-6, Tumor Necrosis Factor-alpha: TNF-α, C-reactive protein: CRP). Descriptive statistics included means for continuous variables and frequencies for categorical variables. Correlation analyses were used to assess the degree of relationship between variables. Partial correlations were used to adjust for potential confounders. Study protocol was approved by IRB at the University of Tennessee Graduate School of Medicine. **Results:** A total of 43 women with gynecological cancer (primary site: uterus = 16, ovary = 24, cervix = 1, vulva/vagina = 2) completed study measures. The mean age was 63.5 years (SD=10.5). Regarding participants characteristics, 91% identified as White, 99% identified as non-Hispanic, 35% reported being high school graduate or GED, 45% were unemployed, 66% were married, 51.2% had newly diagnosed cancer, 49% had metastatic disease, 74% received chemotherapy only, 14% immunotherapy, 12% combination of both immunotherapy and chemotherapy. SPS scores were negatively correlated with IL-6 ($\rho = -0.362$, p = 0.038), indicating that higher perceived social support was associated with lower IL-6 levels. SPS scores were not significantly correlated with CRP ($\rho = -0.09$, p = 0.62) and TNF-α ($\rho = -0.295$, p = 0.096). After adjusting for BMI, SPS score showed significant associations with IL-6 ($\rho = -0.406$, p = 0.021) and TNF-α ($\rho = -0.360$, p = 0.043), but its relationship with CRP ($\rho = -0.029$, p = 0.874) remained non-significant. **Conclusions:** The results of this study suggest a negative association between social support and inflammation among patients with gynecologic cancer. Future research may consider exploring the pathways to explain this relationship and identify possible interventions focused on social support to decrease inflammatory processes among patients with gynecologic cancer. Research Sponsor: University of Tennessee Medical Center Cancer Institute.

5627 **Poster Session**

A phase 2 study evaluating SSGJ-707 (PF-08634404), a PD-1/VEGF bispecific antibody, + chemotherapy (chemo) in patients (pts) with first-line (1L) advanced/recurrent endometrial cancer (EC). First Author: Qi Zhou, Cancer Hospital Affiliated to Chongqing University, Chongqing, China

Background: SSGJ-707 is a fully human immunoglobulin G4 bispecific antibody targeting programmed death 1 (PD-1) and vascular endothelial growth factor (VEGF). SSGJ-707 has demonstrated promising efficacy and manageable safety alone and in combination with chemo in phase 2 studies in solid tumors. We report results from the phase 2 SSGJ-707-ST-II-02 study (NCT06522828) of 1L SSGJ-707 + chemo in advanced/recurrent EC. **Methods:** Pts with newly diagnosed stage III/IV or recurrent EC with low potential for cure by radiation therapy (tx) or surgery and systemic tx-naive were enrolled. Pts received SSGJ-707 5 mg/kg or 10 mg/kg Q3W + chemo (carboplatin AUC 5 + paclitaxel 175 mg/m^2) Q3W for 6 cycles, followed by SSGJ-707 maintenance tx until loss of clinical benefit or intolerable toxicity for up to 2 years. Primary endpoints were safety and ORR (RECIST 1.1). Secondary endpoints include duration of response (DOR), PFS, OS, PK, and biomarkers. **Results:** At data cutoff (Nov 28, 2025), 32 pts with EC (26 mismatch repair proficient [pMMR], 6 MMR deficient [dMMR]) received 5 mg/kg (n=16) or 10 mg/kg (n=16) SSGJ-707 + chemo. Median SSGJ-707 tx duration was 5.6 mo (range, 0.2-13.6); 8 pts (25.0%) discontinued tx. In the evaluable population, confirmed ORR was 85.7% (12/14 pts) for the 5 mg/kg dose and 80.0% (12/15) for the 10 mg/kg dose. Results for pMMR and dMMR groups are in the Table. Median PFS, OS, and DOR were not reached for either dose. Any-grade tx-related adverse events (TRAEs) were reported in 30/32 pts (93.8%) and grade $\geq$3 TRAEs in 22/32 pts (68.8%). The most common TRAEs ($\geq$40%) included neutrophil count decreased (59.4%), white blood cell count decreased (59.4%), anemia (56.3%), and platelet count decreased (56.3%). No TRAEs led to death. TRAEs led to discontinuation of SSGJ-707 in 2 pts (6.3%). Immune-related AEs occurred in 6 pts (18.8%): hypothyroidism (n=4), hyperthyroidism (n=3), and rash (n=2). VEGF-related AEs occurred in 13 pts (40.6%): blood pressure elevation (n=6), proteinuria (n=6), hemorrhage (urinary occult blood positive; n=2), perforation and fistula (n=2), and venous thrombosis (n=1). **Conclusions:** SSGJ-707 + chemo demonstrated promising efficacy with a manageable safety profile in pts with tx-naive advanced/recurrent EC, supporting further investigation of SSGJ-707 in these pts. Clinical trial information: NCT06522828. Research Sponsor: This study was originally sponsored by 3SBio; SSGJ-707 was licensed to Pfizer in July 2025. Medical writing support was provided by Akshaya Srinivasan, PhD, and Eleanor Porteous, MSc, of Nucleus Global, an Inizio Company, and was funded by Pfizer.

	5 mg/kg Q3W (n=14)		10 mg/kg Q3W (n=15)	
	pMMR (n=12)	dMMR (n=2)	pMMR (n=11)	dMMR (n=4)
Confirmed ORR, n (%) [95% CI]	10 (83.3) [51.6, 97.9]	2 (100) [15.8, 100.0]	9 (81.8) [48.2, 97.7]	3 (75.0) [19.4, 99.4]
Complete response	0	0	1 (9.1)	0
Partial response	10 (83.3)	2 (100)	8 (72.7)	3 (75.0)
Stable disease	2 (16.7)	0	2 (18.2)	1 (25.0)
Progressive disease	0	0	0	0
CR/PR pending	–	–	1[a]	1
Unconfirmed ORR, n (%) [95% CI]	10 (83.3) [51.6, 97.9]	2 (100) [15.8, 100.0]	10 (90.9) [58.7, 99.8]	4 (100) [39.8, 100.0]

[a]One additional pt in the 10 mg/kg group confirmed in Dec.

TPS5628 **Poster Session**

TroFuse-036/GOG-3123/ENGOT-cx22: A 2-part, phase 3, randomized study of sacituzumab tirumotecan (sac-TMT) + pembrolizumab (pembro) ± bevacizumab (bev) vs standard of care (SoC) as first-line maintenance therapy for PD-L1–positive cervical cancer. First Author: Brian M. Slomovitz, GOG Foundation and Mount Sinai Medical Center, Miami Beach, FL

Background: First-line pembro + platinum-doublet chemo ± bev is the preferred SoC for PD-L1-positive stage IVB, persistent, or recurrent cervical cancer. However, ~50% of patients experience progressive disease (PD) within 1 y, highlighting the need for first-line maintenance therapies that can extend clinical benefit. Sac-TMT is a TROP2-directed antibody-drug conjugate with a unique, bifunctional linker that maximizes payload delivery to tumor cells. In a prior phase 2 basket study, sac-TMT + pembro demonstrated promising antitumor activity (ORR, 58% [22/38]) with a manageable safety profile in participants (pts) with recurrent or metastatic cervical cancer that progressed on or after platinum-doublet chemo. TroFuse-036/GOG-3123/ENGOT-cx22 (NCT07216703) is evaluating first-line maintenance therapy with sac-TMT + pembro ± bev vs SoC in pts with cervical cancer. **Methods:** This 2-part, phase 3, randomized, open-label study is enrolling pts aged $\geq$18 y with persistent, recurrent, or newly diagnosed stage IVB squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix that is not amenable to curative treatment (surgery/radiation), ECOG PS of 0 or 1, and PD-L1 combined positive score $\geq$1. In part 1 (safety run-in), ~20 eligible pts who complete 6 cycles of induction therapy with pembro 200 mg Q3W + paclitaxel 175 mg/m^2 Q3W + cisplatin 50 mg/m^2 (or carboplatin AUC 5 mg/mL/min Q3W) + bev 15 mg/kg Q3W without PD per investigator will receive maintenance therapy with sac-TMT 4 mg/kg Q2W + pembro 400 mg Q6W for $\leq$14 6-wk cycles + bev 15 mg/kg Q3W until treatment discontinuation criteria are met. Enrollment in part 2 will start after enrollment in part 1 is complete. In part 2, ~1003 eligible pts will receive 6 cycles of induction therapy (same doses as in part 1) with pembro + platinum-doublet chemo ± bev at investigator discretion. For randomization to maintenance therapy, pts must complete induction therapy and have CR, PR, or SD per RECIST v1.1 by investigator as assessed by an evaluable tumor scan at week 18; evaluable TROP2 expression; and resolution of any AEs to grade $\leq$1. After part 1 safety data review is complete, ~802 eligible pts in part 2 maintenance part will be randomized 1:1 to receive sac-TMT 4 mg/kg Q2W + pembro 400 mg Q6W for $\leq$14 6-wk cycles ± bev 15 mg/kg Q3W or SoC with pembro 400 mg Q6W for $\leq$14 6-wk cycles ± bev 15 mg/kg Q3W; bev use is at investigator discretion and continues until treatment discontinuation criteria are met. The primary endpoint is safety in part 1 and PFS per RECIST v1.1 by blinded independent central review and OS with maintenance therapy in part 2. Secondary endpoints associated with maintenance therapy in part 2 are PFS2 per investigator, safety, and patient-reported outcomes. Enrollment began in Dec 2025. Clinical trial information: NCT07216703. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS5629 **Poster Session**

Iparomlimab and tuvonralimab combined with paclitaxel and cisplatin as neoadjuvant therapy for cervical cancer: A phase II umbrella trial. First Author: Junjun Qiu Sr., Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China

Background: There is an urgent need to improve neoadjuvant therapy for locally advanced cervical cancer (LACC) and fertility-preserving neoadjuvant therapy for early-stage cervical cancer patients. However, there is no study evaluating the efficacy and safety of PD-1 and CTLA-4 dual blockade-based therapy for above clinical scenarios. The present study aims to assess QL1706 combined with paclitaxel and cisplatin as neoadjuvant therapy for LACC and early-stage cervical cancer patients for fertility-preservation respectively. **Methods:** Trial design: For Arm 1 (LACC), patients aged 18-75 years, with FIGO 2018 stages IB3, IIA2, IIB, or IIICr (lesion ≥4 cm, confirmed by MRI), histologically confirmed as cervical squamous cell carcinoma, cervical adenocarcinoma, or cervical adenosquamous carcinoma will be included. For Arm 2 (fertility preservation), patients aged 18-45 years old, who have a strong desire to preserve fertility, with FIGO 2018 stages IB2, IB3 (lesion ≤6 cm), IIA1, or IIA2 (lesion ≤6 cm) and histologically confirmed as cervical squamous cell carcinoma, cervical adenocarcinoma, or cervical adenosquamous carcinoma, will be included. All participants will be given 3 cycles of neoadjuvant treatment with QL1706 (5 mg/kg), paclitaxel (135-175 mg/m^2) and cisplatin (75-80 mg/m^2) per 21 days. Patients in Arm 1 (LACC) who achieve CR/PR will undergo radical hysterectomy plus lymphadenectomy after 3 cycles of neoadjuvant therapy whereas patients in Arm 2 (fertility preservation) who achieve CR/PR will undergo fertility-preserving surgery. For IB1/IB2 patients, conization or simple trachelectomy plus lymphadenectomy will be performed. For IIA1/IIA2 patients, radical trachelectomy plus lymphadenectomy will be performed. Patients achieve PD/SD will be given standard treatment according to the current NCCN guideline. The primary endpoints consist of objective response rate (ORR), pathological complete response (pCR) and changes in tumor-related biomarkers (ctDNA, etc). Secondary endpoints include 2-year overall survival (OS), 2-year disease-free survival (DFS) and adverse events. Other endpoints are 2-year pregnancy rate and infant survival rate for Arm 2. Sample size is 20 for Arm 1 and 15 for Arm 2. Clinical trial identification: NCT06878222. Clinical trial information: NCT06878222. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

TPS5630 **Poster Session**

A phase II trial of a FAK inhibitor combined with albumin-bound paclitaxel and an anti–PD-1/CTLA-4 bispecific antibody for metastatic, recurrent, or persistent gastric-type endocervical adenocarcinoma (GIFT Study). First Author: Yingchao Zhao, Hubei Key Laboratory of Precision Radiation Oncology, Wuhan, Hubei, China

Background: Gastric-type endocervical adenocarcinoma (GAC) is a rare, HPV-independent subtype of cervical cancer with an aggressive clinical course and an exceptionally poor prognosis. Current clinical guidelines offer largely non-specific treatment recommendations, and conventional chemotherapy-based regimens, even when combined with immunotherapy, frequently demonstrate limited efficacy and early resistance in patients with advanced, recurrent, or metastatic disease. Preclinical studies demonstrate that FAK inhibition can remodel the tumor microenvironment and enhance sensitivity to both cytotoxic chemotherapy and immunotherapy. This study aims to evaluate the efficacy and safety of the FAK inhibitor IN10018 in combination with immunotherapy and chemotherapy in patients with GAC. **Methods:** The GIFT study is a multicenter, open-label, single-arm, prospective phase II trial designed to evaluate the combination of the FAK inhibitor IN10018 with nab-paclitaxel and cadonilimab (a PD-1/CTLA-4 bispecific antibody) in patients with metastatic, recurrent, or persistent gastric-type endocervical adenocarcinoma. A total of 25 eligible patients will receive oral IN10018 (100 mg once daily) in combination with intravenous nab-paclitaxel (260 mg/m²) and cadonilimab (10 mg/kg) on day 1 of each 21-day cycle. Tumor response will be assessed every 6 weeks by imaging according to RECIST v1.1. Patients will receive up to six cycles of combination chemotherapy, followed by maintenance therapy with IN10018 and cadonilimab until disease progression or unacceptable toxicity. The primary endpoint is objective response rate. Secondary endpoints include progression-free survival, disease control rate, and safety. An additional exploratory objective is to longitudinally evaluate alterations in peripheral circulating cell-free DNA and the tumor microenvironment and to examine their association with therapeutic response. The study is currently active and enrolling patients. As of the data cutoff, 14 of the planned 25 patients have been enrolled. The trial is registered at ClinicalTrials.gov (NCT06654011). Clinical trial information: NCT06654011. Research Sponsor: Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2025ZD0544103; National Natural Science Foundation of China; 82372929.

TPS5631 **Poster Session**

Neoadjuvant chemoimmunotherapy before chemoradiation vs chemoradiation alone for stage IIB-IIIC1 carcinoma of the cervix: A phase II open-label randomized controlled trial (NeoCHIMERA). First Author: Praveen Kumar Marimuthu, Christian Medical College, Vellore, Tamil Nadu, India

Background: Locally advanced cervical cancer (FIGO 2018 stages IIB–IIIC1) remains a major cause of cancer-related mortality in low- and middle-income countries. Concurrent chemoradiation (CCRT) with brachytherapy is the current standard of care; however, rates of persistent disease and distant failure remain substantial, particularly in patients with bulky tumors or nodal involvement. Although advances in radiotherapy have improved outcomes, survival in resource-constrained settings continues to lag behind that in high-income countries. Recent randomised trials have demonstrated improved outcomes with two distinct strategies: delivery of dose-dense induction chemotherapy followed by timely initiation of chemoradiation, and the addition of immunotherapy with pembrolizumab to concurrent chemoradiation followed by maintenance therapy for up to one year. Despite these advances, concerns about radiotherapy dose and technique in induction chemotherapy trials, and the feasibility of prolonged maintenance immunotherapy in resource-limited settings, have limited widespread adoption. The optimal dose, timing, and duration of immunotherapy in locally advanced cervical cancer remain undefined. This study was designed to evaluate whether short-course neoadjuvant chemo-immunotherapy administered prior to standard CCRT can improve early tumor response with an acceptable safety profile while preserving treatment feasibility across diverse healthcare settings. **Methods:** The NeoCHIMERA trial is a multicenter, open-label, randomized phase II study designed to evaluate this hypothesis. Eligible patients include those with biopsy-proven FIGO 2018 stage IIB–IIIC1 cervical carcinoma (squamous, adeno, or adenosquamous histology) who are treatment-naïve and suitable for CCRT. Participants will be randomized 1:1 to the experimental or control arm, stratified based on stage and histology. The experimental arm will receive six weeks of neoadjuvant carboplatin (AUC 2) and paclitaxel (60 mg/m²) weekly, combined with low-dose nivolumab (40 mg IV every three weeks for two cycles), followed by standard CCRT (cisplatin 40 mg/m² weekly with external beam radiation and brachytherapy). The control arm will receive CCRT alone. The primary endpoint is complete clinical response at 3 months after completion of chemoradiation. Secondary endpoints include safety, treatment completion rates, event-free survival, quality of life, and cost-effectiveness from a societal perspective. A total of 154 patients (77 per arm) will be accrued. One interim safety analysis is planned after 40 patients with predefined stopping rules for excess toxicity. Thirty-three of the planned 154 participants have been recruited. This study is registered with the Clinical Trials Registry of India (CTRI/2025/04/085540). Clinical trial information: CTRI/2025/04/085540. Research Sponsor: Christian Medical College, Vellore.

TPS5632 **Poster Session**

NRG-GY037: A phase III randomized trial of induction chemotherapy and pembrolizumab followed by chemoradiation and pembrolizumab maintenance versus standard chemoradiation and pembrolizumab maintenance in high-risk locally advanced cervical cancer. First Author: Jyoti Mayadev, University of California, San Diego Medical Center, La Jolla, CA

Background: Concurrent chemoradiation therapy (CCRT) is the standard of care for locally advanced cervical cancer (LACC); however, outcomes remain suboptimal in patients with high-risk disease. Recent studies suggest that integration of immunotherapy (IO) with definitive chemoradiation, or induction chemotherapy prior to CCRT improves outcomes. Whether treatment intensification with induction systemic therapy and IO prior to CCRT and IO further improves disease control remains unknown. Induction chemotherapy may reduce tumor burden, eradicate micrometastatic disease, and improve tumor immunogenicity prior to definitive CCRT. Preclinical and clinical data support synergy between systemic therapy or radiotherapy and immune checkpoint blockade, providing the rationale for evaluating an induction strategy incorporating chemotherapy and immunotherapy before standard CCRT with immunotherapy, followed by maintenance immunotherapy. Optional tumor tissue and blood samples will be collected for exploratory correlative analyses, including immune and molecular biomarkers associated with response, resistance, and patterns of failure. **Methods:** NRG-GY037 is a prospective, multi-institutional phase III randomized trial conducted through NRG Oncology. A total of 336 patients will be enrolled (168 per arm). Patients will be stratified by FIGO stage (III vs. IVA) and presence or absence of para-aortic lymph nodes (N2). The primary endpoint is progression free survival (PFS). The study has 90% power to detect PFS hazard ratio of 0.65 in the experimental arm. Treatment: Patients with previously untreated, high-risk LACC are randomized to receive either induction chemotherapy with pembrolizumab for 6 weeks followed by CCRT with pembrolizumab and pembrolizumab maintenance, or standard CCRT with pembrolizumab followed by pembrolizumab maintenance. Major Eligibility Criteria: Eligible patients have histologically confirmed cervical carcinoma (squamous, adenocarcinoma, or adenosquamous), TNM T3 and T4 disease, N0-2, ECOG performance status 0–1, and no prior definitive therapy for cervical cancer. Current Enrollment Status: The trial is actively accruing patients. No efficacy or safety data are available at the time of submission. Clinical Trial Registration: ClinicalTrials.gov identifier: NCT07061977. Clinical trial information: NCT07061977. Research Sponsor: National Cancer Institute.

TPS5633 **Poster Session**

A single-arm, phase 2 study of neoadjuvant mirvetuximab soravtansine and carboplatin for FRα-expressing advanced-stage serous epithelial ovarian, fallopian tube, or primary peritoneal cancer (M25-231; NCT06890338; GOG-3115). First Author: Rebecca Arend, University of Alabama at Birmingham, O'Neal Comprehensive Cancer Center, Birmingham, AL

Background: Folate receptor alpha (FRα) has limited expression on normal tissues but is highly expressed in most high-grade serous epithelial ovarian cancers (EOC), making it an attractive therapeutic target. Mirvetuximab soravtansine (MIRV), an antibody-drug conjugate targeting FRα, has demonstrated efficacy and manageable safety in recurrent, FRα-expressing EOC when used as monotherapy. Additionally, a phase 1b/2 study (IMGN853-0402) of MIRV + carboplatin showed promising clinical activity in patients with platinum-sensitive ovarian cancer who had tumor recurrence after platinum-based chemotherapy. The safety and efficacy of neoadjuvant MIRV + carboplatin in newly diagnosed, advanced-stage FRα-expressing high-grade serous ovarian cancer (HGSOC) remains unknown. **Methods:** This single-arm phase 2 trial will evaluate the safety and efficacy of MIRV + carboplatin in newly diagnosed patients with advanced-stage (Stage III/IV), FRα-expressing (≥75% tumor cells with ≥2+ membrane intensity per the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay [Roche Diagnostics]) HGSOC. Approximately 140 patients (aged ≥18 years) will be enrolled; 5 patients were enrolled as of January 23, 2026. Patients will receive ≤6 cycles of MIRV (6 mg/kg adjusted ideal body weight) and carboplatin (AUC 5) intravenously every three weeks before interval debulking surgery (IDS), with a total of ≤9 cycles pre- and post-IDS. IDS suitability will be evaluated radiologically, and all eligible patients, including those with progressive disease (PD), will undergo IDS after Cycle 3 Day 1. IDS-ineligible patients may receive ≤3 additional cycles and undergo repeat imaging to assess IDS suitability. Patients with complete response (CR), partial response (PR), or stable disease will resume MIRV + carboplatin 3–6 weeks post-IDS following radiologic assessment. At the treating physician's discretion, bevacizumab may be added post-IDS and standard-of-care maintenance therapy may begin ≥21 days after MIRV + carboplatin ± bevacizumab completion. Imaging will occur every 9 weeks after IDS (for those who undergo IDS) or last radiologic tumor assessment (for those who do not) until 1 year from the first dose of study treatment and then every 12 weeks until PD, death, or withdrawal of consent. The primary endpoint is objective response (OR), defined as best overall response of radiographic CR or PR assessed by Independent Central Review (ICR) per Response Evaluation Criteria in Solid Tumors v1.1 prior to initiation of subsequent anticancer therapy (including IDS). Secondary endpoints include OR by investigator (INV), disease control by ICR and INV, IDS, extent of cytoreduction at the time of IDS, cancer antigen 125 response, progression-free survival by INV, and patient-reported outcomes (NFOSI-18). Clinical trial information: NCT06890338. Research Sponsor: AbbVie Inc.

TPS5634 **Poster Session**

NRG-GY036: A phase III trial of one vs. two years of maintenance olaparib, with or without bevacizumab, in patients with *BRCA1/2*-mutated or homologous recombination deficient (HRD+) ovarian cancer following response to first line platinum-based chemotherapy. First Author: Ying L. Liu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The profound progression-free survival (PFS) benefit shown in the SOLO-1 and PAOLA-1 randomized clinical trials set the standard of 2 years of PARP inhibitor (PARPi) maintenance with olaparib, with or without bevacizumab, in patients with *BRCA1/2*-mutated and homologous recombination deficient (HRD+) ovarian carcinoma after response to frontline platinum-based chemotherapy, and this was approved by the FDA in December 2018. However, newer studies have elucidated the long-term toxicity risk of prolonged PARPi use, specifically treatment-related myeloid neoplasms (TMN), along with detrimental effects on subsequent platinum-based chemotherapy and overall survival. Given this, we seek to test de-escalation of PARPi maintenance therapy, evaluating if 1 year is non-inferior to 2 years, using a pragmatic and streamlined study design. **Methods:** NRG GY036 is a phase III, randomized, non-inferiority study of 1 versus 2 years of olaparib maintenance, with our without bevacizumab, in those with *BRCA1/2*-associated and HRD+ ovarian cancer, after response to frontline platinum-based chemotherapy (NCT06580314). Key eligibility criteria include a deleterious *BRCA1/2* mutation, germline or somatic, or HRD+ tumor using any CLIA-certified test. Patients must have undergone cytoreductive surgery and had a clinical response after a minimum of 4 cycles of platinum-based chemotherapy. The primary endpoint is investigator assessed PFS using RECIST v1.1 criteria for 1 vs. 2 years in a modified intention to treat (mITT) population, where time at risk starts 360 days after randomization to account for the time where both arms receive the same treatment. Secondary endpoints include overall survival (OS), PFS2, PFS in the ITT and as-treated populations, and toxicity including rates of TMN. The statistical design is based on a hazard ratio non-inferiority margin of 1.36 (1-sided alpha 0.05, power 0.9). The null hypothesis will be rejected if HR <1.15, giving 90% certainty that the true median PFS loss is not more than 10 months based on historical controls from SOLO1 and the HRD+ subgroup of PAOLA-1. We anticipate enrolling 880 patients to have at least 735 patients in the mITT population. This IND-exempt study pragmatically mimics real-world clinical practice by using commercially available drug, implementing broad eligibility criteria, allowing physician's choice bevacizumab, and incorporating individual physician and institution's standard practices. It also employs a streamlined approach with minimal data collection forms and abbreviated adverse event reporting. NRG GY036 was activated on 1/16/2025. The first patient enrolled on 3/12/2025. As of 1/16/2026, there are 676 participating sites and 152/880 (17%) patients enrolled. Clinical trial information: NCT06580314. Research Sponsor: NRG Oncology and NIH/NCI/CTEP.

TPS5635 **Poster Session**

A phase I, open-label, dose-finding, safety, tolerability, and exploratory trial of intraperitoneal THEO-260 in patients with high-grade serous or endometrioid ovarian cancer. First Author: Helen D. Clark, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Ovarian cancers are immunologically cold at baseline and typically characterized by a rich stromal component with a high proportion of cancer-associated fibroblasts (CAF). These features limit efficacy of immunotherapy and virotherapy due to the immunosuppressive effects of abundant CAFs. THEO-260 is an oncolytic adenovirus that exhibits selective replication, lysis, and killing of cancer cells and CAFs. This unique mechanism-of-action positions THEO-260 as a potential efficacious treatment option for patients with platinum-resistant ovarian cancer. Intraperitoneal (IP) delivery may further enhance efficacy by enabling high locoregional dose with lower systemic exposure. **Methods:** This phase I, open-label, single-institution study (NCT07211659) evaluates IP THEO-260 in patients with platinum-resistant or refractory high grade serous (HGS) or endometrioid ovarian, peritoneal, or fallopian tube cancer. The primary objectives are to evaluate the safety and tolerability of THEO-260 when administered intraperitoneally and to establish the recommended phase 2 dose (RP2D) using a Bayesian Optimal Interval design with 4 dose levels in cohorts of 3. Patients receive up to 6 doses of THEO-260 over 15 days: 2 desensitization doses followed by 4 target-dose administrations. Secondary objectives include PK, viral shedding, systemic cytokine release, and preliminary efficacy assessment. Response assessments will be conducted every 8 weeks starting on day 29 through week 52 and thereafter every 12 weeks until progression, death, or end of trial. Eligibility includes histologically confirmed, platinum-resistant or refractory HGS, endometrioid cancer of the ovary, peritoneum, or fallopian tube, measurable peritoneal disease per RECIST v1.1, ECOG 0-1, adequate organ function, life expectancy of ≥6 months, and feasibility of intraperitoneal catheter placement. Prior treatments must include optimal surgical debulking, bevacizumab, or PARP inhibitor therapy as indicated. Key exclusions include serosal disease >3cm, bowel obstruction history or symptoms, uncontrolled pleural or pericardial effusions, and prior pneumonitis or interstitial lung disease. Enrollment began in November 2025. Clinical trial information: NCT07211659. Research Sponsor: Theolytics.

TPS5636 **Poster Session**

TroFuse-022/ENGOT-ov84/GOG-3103 part 2: A phase 3 study of maintenance therapy with sacituzumab tirumotecan ± bevacizumab vs standard of care following second-line platinum-based doublet chemotherapy for platinum-sensitive recurrent ovarian cancer. First Author: Antonio Gonzalez Martin, GEICO and Cancer Center Clinica Universidad de Navarra, Madrid, Spain

Background: There is an unmet clinical need for novel therapies for patients with platinum-sensitive recurrent ovarian cancer (PSROC). Trophoblast cell-surface antigen 2 (TROP2) is highly expressed in multiple tumor types, including ovarian cancer. Sacituzumab tirumotecan (sac-TMT) is a TROP2-directed antibody-drug conjugate with a unique, bifunctional linker that maximizes delivery of a belotecan-derived topoisomerase 1 inhibitor payload to tumor cells. The current TroFuse-022/ENGOT-ov84/GOG-3103 study (NCT06824467) is evaluating maintenance therapy with sac-TMT ± bevacizumab (bev) vs standard of care (SoC) following second-line (2L) platinum-based doublet chemotherapy (chemo) in participants (pts) with PSROC. The study includes a safety run-in part (part 1) and a phase 3 part (part 2). We present the trial design for part 2 of this study. **Methods:** Part 2 is enrolling ~750 pts aged ≥18 y with histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with PSROC (radiographic evidence of PD >180 d after the last dose of first-line [1L] platinum-based doublet chemo ± bev); pts with *BRCA* mutation or homologous recombination deficiency-positive status with no evidence of disease (NED), CR, or PR after 1L chemo must have received a PARP inhibitor as 1L maintenance therapy. All pts must have received 6 cycles of 2L carboplatin-based doublet chemo ± bev and achieved NED, CR, PR, or SD per investigator assessment; pts with SD must have received bev in combination with 2L chemo and be eligible to continue treatment with bev. Other inclusion criteria are an ECOG PS of 0 or 1 and an available tumor sample for central testing of TROP2 and *BRCA* status. Candidates for curative-intent surgery or radiotherapy at enrollment are not eligible. Pts are randomized 1:1 to receive maintenance therapy with sac-TMT 4 mg/kg IV Q2W ± bev 15 mg/kg IV Q3W (arm 1) or SoC treatment with observation ± bev 15 mg/kg IV Q3W (arm 2). Use of bev is at the investigator's discretion and can only be given to eligible pts who received ≥2 doses of bev 15 mg/kg Q3W or equivalent dose (with no dose reductions) in combination with 2L chemo; pts with SD after 2L chemo must receive bev (pts with SD not receiving bev are ineligible). Treatment with sac-TMT (arm 1) and bev (if elected, arms 1 and 2) continues until PD, unacceptable toxicity, or other protocol-defined reason for discontinuation. Pts in arm 2 are not permitted to cross over to arm 1. The primary endpoint is PFS per RECIST version 1.1 as assessed by blinded independent central review. Secondary endpoints include OS, safety and tolerability, and patient-reported outcomes. PFS and OS will be assessed in pts with medium/high TROP2 expression tumors and all pts. The study is ongoing, and enrollment in part 2 is open. Clinical trial information: NCT06824467; EU CT, 2023-508015-23; UTN, U1111-1297-4489. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS5637 **Poster Session**

REJOICE-Ovarian01: Phase 3 part of a phase 2/3 study evaluating raludotatug deruxtecan (R-DXd) versus treatment of physician's choice in patients with platinum-resistant ovarian cancer. First Author: Debra L. Richardson, Stephenson Cancer Center, University of Oklahoma Health Campus, Oklahoma City, OK

Background: Platinum-resistant ovarian cancer (PROC) is associated with poor outcomes. Standard-of-care single-agent non-platinum therapies, with or without bevacizumab, have demonstrated only modest activity in PROC, while targeted therapies remain limited to specific biomarker-defined patient populations. Cadherin-6 (CDH6), a mediator of cell–cell adhesion, is aberrantly expressed in up to 94% of epithelial ovarian cancer tumors. R-DXd is an antibody–drug conjugate comprising a humanized CDH6 antibody covalently linked to a topoisomerase I inhibitor payload (DXd) via a tumor-selective cleavable linker. REJOICE-Ovarian01 is a Phase 2/3 study of R-DXd monotherapy in patients with PROC. Among patients who had completed ≥18 weeks of follow-up or discontinued treatment in the Phase 2 dose-optimization part, the objective response rate (ORR) by blinded independent central review (BICR) was 44.4% (16/36) at 4.8 mg/kg, 50.0% (18/36) at 5.6 mg/kg, and 57.1% (20/35) at 6.4 mg/kg, including three complete responses overall. Clinically meaningful tumor responses were observed irrespective of tumor CDH6 expression, and the safety profile of R-DXd was manageable. R-DXd 5.6 mg/kg was identified as the optimal dose for further evaluation in the Phase 3 part of REJOICE-Ovarian01, which is described here. **Methods:** The Phase 3 part of REJOICE-Ovarian01 (NCT06161025) is a global, randomized, open-label study of R-DXd in patients with platinum-resistant, high-grade serous or high-grade endometroid ovarian, primary peritoneal, or fallopian tube cancer. Patients must have received 1–4 prior lines of therapy (LOT), including bevacizumab (unless ineligible) and mirvetuximab soravtansine for folate receptor α–positive disease (unless not available locally). Patients are not selected based on tumor CDH6 expression. Approximately 600 patients will be randomized 1:1 to receive either R-DXd 5.6 mg/kg intravenously every 3 weeks until disease progression per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1), lost to follow-up, death, or other reason per protocol, or treatment of physician's choice (TPC; weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan) per local guidelines. Randomization will be stratified by number of prior LOT, tumor CDH6 expression, and by TPC. The primary endpoint is progression-free survival (PFS) by BICR per RECIST 1.1. Key secondary endpoints include overall survival (OS) and quality of life. Stratified log-rank tests will be used to compare PFS and OS between treatment groups. Stratified Cox regression models will be fitted to estimate the hazard ratios for PFS and OS. Enrollment in Phase 3 began in December 2025. Clinical trial information: NCT06161025. Research Sponsor: Daiichi Sankyo, Inc.; Merck.

TPS5638 **Poster Session**

A phase 1/2 study of ubamatamab (REGN4018), a MUC16×CD3 bispecific antibody, administered alone or in combination with cemiplimab in a low-grade serous ovarian cancer cohort: Trial in progress. First Author: Els Van Nieuwenhuysen, Leuven Kankerinstituut, Leuven, Belgium

Background: Low grade serous ovarian cancer (LGSOC) typically has a poor response to chemotherapy, presenting an unmet need for efficacious novel therapies that remain tolerable. Mucin 16 (MUC16) is a cell surface glycoprotein that is highly expressed in ovarian cancers, including LGSOC, and has been identified as a potential therapeutic target. Ubamatamab, a MUC16 × cluster of differentiation 3 bispecific antibody, bridges MUC16+ tumor cells and T cells through a major histocompatibility complex-independent mechanism, promoting cytotoxicity. In a first-in-human study (NCT03564340), ubamatamab demonstrated an acceptable safety profile and durable clinical activity in recurrent ovarian cancer, including LGSOC, which has particularly high MUC16 expression on tumor cells. Here, we describe an LGSOC-specific expansion cohort. **Methods:** In the LGSOC-specific cohort, patients who have received prior platinum-containing therapy (no maximum number of prior therapies) and whose disease has relapsed or progressed after the most recent line of therapy will receive ubamatamab 800 mg intravenously (IV) once every 3 weeks (Q3W). Prior to Q3W dosing of ubamatamab, patients will receive once-weekly step-up dosing to mitigate the risk of cytokine release syndrome, as well as sarilumab 350 mg IV prophylaxis on Day 1. Utilizing a Simon two-stage design, 20 patients will initially be enrolled in this cohort, expanding to 50 if there are ≥3 objective responses. The cohort may be further expanded to 100 patients if ≥14 objective responses (28%) are observed in the first 50 patients. The primary endpoint is objective response rate per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary endpoints include safety, pharmacokinetics, patient-reported outcomes and further efficacy assessments. As of January 5, 2026, 6 patients with LGSOC have initiated ubamatamab treatment. Findings from this study will clarify the therapeutic potential of targeting MUC16 in LGSOC. Clinical trial information: NCT03564340. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS5639 **Poster Session**

A phase 1/2 study of REGN5668, a MUC16×CD28 costimulatory bispecific antibody, in combination with other targeted therapies, in patients with recurrent ovarian or endometrial cancer: Trial in progress update. First Author: Roisin Eilish O'Cearbhaill, Department of Medicine, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

Background: REGN5668 and ubamatamab are immunoglobulin G4-based bispecific antibodies that bridge mucin 16 (MUC16)+ tumor cells to T-cell–expressed cluster of differentiation (CD)28 and CD3, respectively, to stimulate T-cell cytotoxicity. Cemiplimab (anti–programmed cell death-1 [PD-1]) and fianlimab (anti-lymphocyte activation gene 3 [LAG-3]) are monoclonal antibodies that target inhibitory T-cell immune checkpoints. This first-in-human, multicenter, Phase 1/2 trial (NCT04590326) will assess safety, tolerability, pharmacokinetics (PK), and antitumor activity of REGN5668 + cemiplimab ± fianlimab (Module 1) or ubamatamab (Module 2) in patients with platinum-resistant recurrent ovarian cancer (OC) or endometrial cancer (EC). In Module 1, REGN5668 dose escalation is complete (n=58), demonstrating early clinical activity and only 1 dose-limiting toxicity, a treatment delay of >7 days due to Grade 1 dry eye. Here we present details of additional dose escalation and expansion modules currently enrolling patients. **Methods:** Module 1 dose expansion will evaluate REGN5668 + cemiplimab ± fianlimab in OC and EC cohorts. In the OC cohort, patients will receive REGN5668 + cemiplimab + fianlimab, with an initial 12-patient safety lead-in. In the EC cohort, patients will receive REGN5668 + cemiplimab; an additional EC cohort may be added to evaluate REGN5668 + cemiplimab + fianlimab. Each cohort will follow a Simon two-stage design. In stage 1, 20 patients will be enrolled; if there are ≥3 objective responses, stage 2 will proceed with enrollment of ≤50 patients. In Module 2, dose escalation will evaluate patients with OC receiving escalating doses of REGN5668 + ubamatamab using a Bayesian optimal interval design. Patients may also receive sarilumab to mitigate the risk of cytokine release syndrome. Key OC cohort eligibility criteria include histologically confirmed diagnosis of advanced epithelial OC (except carcinosarcoma), ≥1 prior line of platinum-based systemic therapy, and disease relapse or progression during most recent therapy. Key EC cohort eligibility criteria include histologically confirmed diagnosis of EC with disease recurrence or progression after anti–PD-1 therapy and platinum-based chemotherapy, ≤4 prior lines of systemic therapy, ≥30 days since anti–PD-1 therapy administration, and ≥25% of tumor cells that are MUC16+. Primary endpoints are safety and PK in dose escalation, and objective response rate (ORR) in dose expansion. Secondary endpoints include ORR (Module 2 dose escalation), safety and PK (Module 1 dose expansion), further efficacy outcomes, and immunogenicity (all cohorts). Module 1 dose expansion has opened, with the first two patients enrolled. In Module 2, dose escalation of REGN5668 has progressed through multiple dose levels; enrollment is ongoing. Clinical trial information: NCT04590326. Research Sponsor: Regeneron Pharmaceuticals, Inc.

TPS5640 **Poster Session**

RegeNovar: A phase I/II study of ubamatamab plus carboplatin, paclitaxel, and bevacizumab as salvage therapy in ovarian cancer with poor response to first-line chemotherapy. First Author: Benoit You, Centre Hospitalier Lyon Sud, and GINECO, Pierre-Benite, France

Background: Patients with advanced epithelial ovarian cancer (EOC) treated with neoadjuvant platinum-based chemotherapy who are not amenable to complete interval cytoreductive surgery (ICS) due to poor chemosensitivity—defined by a CA-125 KELIM score <1.0—have a particularly poor prognosis, with approximately 20% 5-year overall survival. Ubamatamab is a human IgG4-based bispecific antibody targeting MUC16 (CA-125–expressing ovarian cancer cells) and CD3+ T cells and has demonstrated clinical activity in platinum-resistant recurrent ovarian cancer (Lee et al, Proc ESMO 2025). We hypothesize that adding ubamatamab to standard carboplatin–paclitaxel–bevacizumab may enhance tumor response and improve surgical resectability in patients with advanced high-grade EOC with poor chemosensitivity and disease not amenable to complete ICS after initial neoadjuvant chemotherapy. **Methods:** RegeNovar (EuCT 2025-524232-20-00) is an academic, multicenter phase I–II trial enrolling patients with stage III–IV high-grade EOC who, after 3–4 cycles of standard neoadjuvant carboplatin–paclitaxel administered every 3 weeks, present two poor prognostic features: (1) unfavorable standardized KELIM score <1.0, and (2) disease considered not amenable to complete ICS. The trial includes two sequential parts: (i) a phase I safety run-in to evaluate the safety of ubamatamab in combination with carboplatin–paclitaxel–bevacizumab and confirm the recommended phase II dose (RP2D); and (ii) a phase II efficacy part assessing the antitumor activity of this combination. Patients receive carboplatin AUC5 ; paclitaxel 175 mg/m²; and bevacizumab 15 mg/kg Q3 weeks for three cycles. Ubamatamab is administered with weekly step-up dosing during cycle 1, followed by a fixed dose of 800 mg Q3 weeks during cycles 2 and 3. Feasibility of complete late cytoreductive surgery is evaluated after three cycles of the study regimen. Subsequent maintenance treatment consists of olaparib plus bevacizumab for patients with BRCA-mutated or HRD-positive tumors, or ubamatamab plus bevacizumab for up to 15 months in patients with HRD-negative tumors. The primary endpoint of phase I is safety, including treatment-related adverse events (NCI CTCAE v6.0), DLT within the first 4 weeks, and RP2D determination using a BOIN design targeting a DLT probability ≤28%. The primary endpoint of phase II is the objective response rate (ORR) after three cycles per RECIST 1.1 (H0 5%, H1 30%, one-sided α=5%, power=80%). Total 31 to 43 patients are required, depending on potential need for dose de-escalation. Secondary endpoints include ORR, duration of response, disease control rate, rate of late cytoreductive surgery, PFS, OS, and progression-free survival during subsequent therapy. The trial is sponsored by ARCAGY-GINECO, conducted in 12 French centers, and funded by Regeneron. Clinical trial information: EuCT 2025-524232-20-00. Research Sponsor: Regeneron.

TPS5641 **Poster Session**

RAINFOL-04 (ENGOT-OV96/GOG-3134): A phase 3, open-label, randomized study of rinatabart sesutecan (Rina-S) plus standard of care (SOC) vs SOC as maintenance treatment after second-line platinum-based chemotherapy in patients with recurrent platinum-sensitive ovarian cancer. First Author: Toon Van Gorp, Division of Gynaecological Oncology, University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; and BGOG, Leuven, Belgium

Background: Ovarian cancer (OC) is the eighth leading cause of cancer-related death in women globally. In patients with advanced OC, 70%-80% develop recurrent platinum-sensitive OC (PSOC) within 3 years after initial therapy. Standard treatment for recurrent PSOC includes platinum-based chemotherapy ± bevacizumab (BEV), but in most patients, disease progression occurs within a year. Rina-S is an antibody-drug conjugate targeting folate receptor alpha (FRα) with a novel hydrophilic protease-cleavable linker and a topoisomerase I inhibitor, exatecan, payload. In cohort B1 of the phase 1/2 RAINFOL-01 study (NCT05579366), Rina-S showed encouraging antitumor activity and was tolerated in patients with heavily pretreated advanced OC. We report the design of ENGOT-OV96/GOG-3134 (RAINFOL-04), a phase 3, randomized study of Rina-S + standard of care (SOC) vs SOC as maintenance treatment for patients with recurrent PSOC (NCT07225270). **Methods:** This phase 3 open-label study will enroll ~528 patients with platinum-sensitive high-grade serous or endometrioid epithelial OC, primary peritoneal cancer, or fallopian tube cancer regardless of their FRα expression. Patients must have disease progression >6 months after the last dose of first-line platinum chemotherapy and have achieved at least stable disease following completion of second-line platinum-based chemotherapy ± BEV. Patients will be randomized 1:1 to receive Rina-S 120 mg/m^2 intravenously every 3 weeks plus SOC or SOC (BEV or observation) until disease progression, unacceptable toxicity, or discontinuation. The primary endpoint is progression-free survival (PFS) per RECIST v1.1 by investigator assessment. The key secondary endpoint is overall survival. Additional secondary endpoints include PFS per RECIST v1.1 by blinded independent central review, PFS2 (time from randomization to the second progression or death), safety, and patient-reported outcomes. The trial is currently recruiting. Clinical trial information: NCT07225270. Research Sponsor: Genmab.

TPS5642 **Poster Session**

A phase 3, randomized, open-label study of INCB123667 versus investigator's choice of chemotherapy in patients with platinum-resistant ovarian cancer with cyclin E1 overexpression (MAESTRA 2, ENGOT-OV95, GOG-3137). First Author: Rebecca Kristeleit, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, London, United Kingdom

Background: Epithelial ovarian cancer (EOC) accounts for ~90% of ovarian cancers, with high-grade serous ovarian cancer (HGSOC) the most common histology. Despite high initial response rates to platinum-based therapy, ~70% of patients (pts) with advanced EOC relapse and nearly all recurrent disease ultimately becomes platinum resistant. Platinum-resistant ovarian cancer (PROC) remains a major therapeutic challenge with poor prognosis and limited treatment options. Standard therapies include single-agent, non-platinum chemotherapy with or without bevacizumab (bev), and mirvetuximab soravtansine (mirv) for pts with folate receptor alpha (FRα)-positive HGSOC. Approximately 50% of ovarian cancers overexpress cyclin E1. Cyclin E1 overexpression and increased cyclin-dependent kinase 2 (CDK2) activity are associated with poor outcomes and treatment resistance in ovarian cancer. A synthetic lethal relationship between CDK2 inhibition and cyclin E1 overexpression provides a strong biological rationale for selective CDK2 inhibition in this molecularly defined population. INCB123667 is a potent, selective, oral, small-molecule CDK2 inhibitor. In an ongoing phase 1 study, INCB123667 demonstrated manageable safety and objective response rates >30% in heavily pretreated pts with PROC and cyclin E1 overexpression [Damian S, et al. *J Clin Oncol.* 2025;43(16 suppl):5514; Simonelli M, et al. *Ann Oncol.* 2024;35(suppl 2):S495]. **Methods:** MAESTRA 2 (NCT07214779) is a global, multicenter, randomized, open-label phase 3 study evaluating the efficacy and safety of INCB123667 vs investigator's choice chemotherapy (ICC) in ~466 female pts with platinum-resistant, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with tumor cyclin E1 overexpression by immunohistochemistry (IHC; ≥75% of tumor cells with IHC score ≥1+). Eligible pts must have received 1-4 prior lines of systemic therapy, for whom single-agent chemotherapy is an appropriate next treatment. Pts should have received prior bev, and pts with FRα-positive disease should have received prior mirv. Pts are randomized 1:1 to INCB123667 50 mg twice daily or ICC (weekly paclitaxel, pegylated liposomal doxorubicin, gemcitabine, or topotecan). Randomization is stratified by primary platinum-free interval, ICC, and number of prior lines of systemic therapy. Dual primary endpoints are progression-free survival (PFS) by blinded independent central review (BICR) per RECIST v1.1 and overall survival. A key secondary endpoint is objective response by BICR per RECIST v1.1. Additional secondary endpoints include safety and tolerability, duration of response, PFS and objective response by investigator assessment, and health-related quality of life. The first pt was enrolled in Dec 2025. Clinical trial information: NCT07214779. Research Sponsor: Incyte Corporation.

TPS5643 **Poster Session**

Rationale and study design of the KOV-HIPEC-04: A phase III randomized controlled trial in primary stage three and four ovarian cancer after interval cytoreductive surgery (FOCUS). First Author: Myong Cheol Lim, Center for Gynecologic Cancer, National Cancer Center, Goyang, South Korea

Background: The addition of hyperthermic intraperitoneal chemotherapy (HIPEC) during interval cytoreductive surgery increases progression-free and overall survival for patients with stage III ovarian cancer in two randomized controlled trials (OV-HIPEC-01 and KOV-HIPEC-01). This trial aims to identify the survival benefit of HIPEC in stage III & IV ovarian cancer in the era of maintenance therapy of bevacizumab and/or PARP inhibitors. **Methods:** Ovarian cancer patients will be randomized at the time of interval cytoreductive surgery with achieving complete cytoreduction or cytoreduction with no more than 2.5mm size of residual disease to receive HIPEC (41.5 cisplatin 75mg/m^2, 90 minutes) or not (Control arm). After recovery from surgery, patients will receive postoperative platinum-based adjuvant chemotherapy followed by maintenance therapy with PARP inhibitor or bevacizumab. The primary objective of the trial is to evaluate OS in two groups. Secondary objectives are PFS, cancer-specific survival, time to first subsequent therapy (TFST), safety, CA-125 KELIM, and quality of life. Assuming that the enrollment period is 5 years and the follow-up period is 3 years, the total number of events required is 263. Based on the log-rank test, the total number of subjects required to prove HR 0.67 with a two-sided alpha of 0.05 and 90% power is 494. Considering 5% drop-out, 520 patients are finally studied. Clinical trial information: NCT05827523. Research Sponsor: National Cancer Center Korea (NCC2110790, NCC2110770).

TPS5644 **Poster Session**

FRAmework-01: A two-part phase 3 study of sofetabart mipitecan versus chemotherapy or mirvetuximab soravtansine in platinum-resistant ovarian cancer (PROC), and sofetabart mipitecan plus bevacizumab versus platinum-based chemotherapy plus bevacizumab in platinum-sensitive ovarian cancer (PSOC). First Author: Isabelle Laure Ray-Coquard, Centre Léon Bérard, University Claude Bernard, Lyon, France

Background: Folate receptor alpha (FRα) is overexpressed in ovarian cancer and is a validated therapeutic target. Mirvetuximab soravtansine (MIRV), an antibody drug conjugate (ADC) targeting FRα, is approved for the treatment of patients with PROC and high FRα expression (≥75% tumor cells with 2+ and/or 3+ staining intensity). Given MIRV's limited indication and its association with specific side effects, including ocular adverse events and peripheral neuropathy, there remains a significant medical need to improve outcomes for a broader population of patients with ovarian cancer. Sofetabart mipitecan is an FRα-targeting ADC composed of an Fc-silenced, humanized IgG1 antibody, a novel polysarcosine hydrophobicity masking agent with a dipeptide cleavable linker, and the topoisomerase I inhibitor payload exatecan at a drug-antibody ratio of 8. Data from the Phase 1 study indicate that sofetabart mipitecan monotherapy demonstrates promising and durable clinical activity, with high objective response rates and a tolerable safety profile, in heavily pretreated patients with PROC. Responses were observed across all FRα levels, including in patients who received prior MIRV treatment, and there were no reports of keratopathy or significant peripheral neuropathies. Sofetabart mipitecan was recently granted Breakthrough Therapy Designation by the FDA. **Methods:** In Part A, 530 participants with PROC who received ≤3 prior lines of systemic cytotoxic therapy (or ≤4 lines if MIRV was included), will be randomized in a 1:1 ratio to receive either sofetabart mipitecan, or the investigator's choice (IC) of chemotherapy (paclitaxel, pegylated liposomal doxorubicin [PLD], gemcitabine, or topotecan) or MIRV (if eligible per local label). In Part B, 550 participants with PSOC who received ≤2 prior lines of systemic cytotoxic therapy and had disease progression either during or within six months of completing treatment with a poly (ADP-ribose) polymerase inhibitor (PARPi), will be randomized in a 1:1 ratio to receive either sofetabart mipitecan plus bevacizumab (bev), or the IC of carboplatin-based chemotherapy (paclitaxel, PLD, or gemcitabine) plus bev. Study Parts A and B will enroll participants irrespective of their tumor's FRα expression level. Each part has progression-free survival as its primary endpoint, while overall survival is a key secondary endpoint. Study parts will be conducted separately, and statistical analyses will be performed independently. Trial Status: The study is actively enrolling participants in Part A and B. Clinical trial information: NCT07213804. Research Sponsor: Eli Lilly and Company.

TPS5645 **Poster Session**

Fern-EC-01 (BNT323-01): A phase 3 trial of trastuzumab pamirtecan (HER2 ADC) versus investigator's choice of chemotherapy in patients with previously treated, HER2-expressing, recurrent endometrial cancer (EC). First Author: Floor Jenniskens Backes, Division of Gynecologic Oncology, Ohio State University Wexner Medical Center, Columbus, OH

Background: Despite advancements in frontline therapies for EC, treatment options for recurrent/refractory disease remain limited. HER2 overexpression in EC is associated with rapid disease progression, tumor invasiveness, a high risk of recurrence, and poor prognosis. Trastuzumab pamirtecan (T-Pam; BNT323/DB-1303) is an investigational HER2-targeting antibody-drug conjugate (ADC) with a DNA topoisomerase I inhibitor payload and a drug-to-antibody ratio of ~8. In a phase 1/2a trial (NCT05150691), T-Pam demonstrated encouraging clinical benefit in patients with HER2-expressing EC, efficacy was observed across all HER2 expression levels and patient subgroups with a manageable safety profile. **Methods:** Following a protocol amendment, this open-label, randomized, multi-site, phase 3 trial (Fern-EC-01; BNT323-01) is enrolling patients with recurrent, HER2 expressing EC (assessed by central laboratory testing using IHC) who have measurable disease defined by RECIST v1.1, an ECOG PS of 0-2, and have received ≥1 prior line of platinum-based therapy (in any setting) and prior immune-checkpoint inhibitor treatment. Up to three lines of prior therapy are permitted. Prior hormonal therapy and radiation are allowed but do not count as prior lines of therapy. Prior exatecan-containing treatment is not allowed. All patients will receive treatment until RECIST v1.1 defined progressive disease, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria are met. The trial is enrolling two cohorts. In Cohort 1, ≈420 patients with HER2-expressing (IHC 1+ or 2+) EC will be randomized 2:1 to evaluate the efficacy and safety of T-Pam vs investigator's choice of chemotherapy (doxorubicin, paclitaxel, or docetaxel in case of contraindication to paclitaxel and availability at the site). Stratification is based on HER2 expression (IHC 1+; 2+) and prior lines of therapy (1; 2+). The primary endpoint for Cohort 1 is progression-free survival (PFS) by blinded independent central review (BICR); overall survival is a key secondary endpoint. In Cohort 2, ≈60 patients with HER2 IHC 3+ EC will receive T-Pam; the primary endpoint for this cohort is objective response rate by BICR. Enrollment is ongoing globally. Clinical trial information: NCT06340568. Research Sponsor: BioNTech SE in collaboration with Duality Biologics.

TPS5646 **Poster Session**

RAINFOL-03 (ENGOT-EN-31/GOG-3128): A global, phase 3, open-label, randomized study of rinatabart sesutecan (Rina-S) vs investigator's choice of chemotherapy in patients with endometrial cancer after platinum-based chemotherapy and programmed death-ligand 1 inhibition. First Author: Antonio Gonzalez Martin, Department of Medical Oncology, Cancer Center Clínica Universidad de Navarra, Madrid, Spain

Background: Patients with recurrent endometrial cancer (EC) whose disease progresses after platinum-based chemotherapy (PBC) and programmed death (ligand) 1 [PD-(L)1] inhibition have a poor prognosis and limited, ineffective treatment options. Single-agent chemotherapy in this setting has been associated with low objective response rates (ORRs; ~15%) and median progression-free survival (PFS) of ~3-4 months. Rina-S is an investigational antibody-drug conjugate targeting folate receptor alpha (FRα) with a novel hydrophilic protease-cleavable linker and topoisomerase I inhibitor, exatecan, payload. In the phase 1/2 RAINFOL-01 trial (NCT05579366), Rina-S 100 mg/m^2 showed encouraging antitumor activity, with a 50% confirmed ORR, including 2 complete responses, and a manageable safety profile in patients with heavily pretreated EC after progression on PBC and a PD-(L)1 inhibitor (Winer IS, et al. *J Clin Oncol*. 2025:43[16 suppl]:3039). We report the design of RAINFOL-03, a global, open-label, randomized phase 3 study of Rina-S vs investigator's choice (IC) therapy in patients with EC who have progressed on PBC and a PD(L)-1 inhibitor (NCT07166094). **Methods:** This phase 3 open-label study will enroll ~544 patients with recurrent or progressive EC (any subtype excluding neuroendocrine tumors, carcinosarcoma, or endometrial sarcoma), measurable per RECIST v1.1, who have received 1-3 prior lines of therapy, including PBC and a PD(L)-1 inhibitor. Patients will be randomized 1:1 to receive Rina-S 100 mg/m^2 intravenously every 3 weeks or IC therapy (paclitaxel or doxorubicin) until disease progression or unacceptable toxicity. Patients will be enrolled regardless of FRα expression level; however, FRα expression levels will be required for stratification at randomization. Dual primary endpoints are PFS per RECIST v1.1 by investigator assessment and overall survival. The key secondary endpoint is ORR per RECIST v1.1 by investigator assessment. Additional secondary endpoints include PFS and ORR per RECIST v1.1 by blinded independent central review (BICR), duration of objective response per RECIST v1.1 by investigator assessment and BICR, safety, and quality of life outcomes. The trial is currently recruiting. Clinical trial information: NCT07166094. Research Sponsor: Genmab A/S.

TPS5647 **Poster Session**

Puxitatug samrotecan (AZD8205) vs chemotherapy in patients with B7-H4–selected advanced/metastatic endometrial cancer: The phase 3 randomized Bluestar-Endometrial01 (BE01)/GOG-3110/ENGOT-EN28 trial. First Author: Stephanie Gaillard, Johns Hopkins Sidney Kimmel Cancer Center, Baltimore, MD

Background: The transmembrane glycoprotein B7-H4 is highly expressed in endometrial cancer (EC), with limited expression in normal tissue; therefore, B7-H4 is an attractive antibody–drug conjugate (ADC) target in the treatment of advanced/recurrent EC. Puxitatug samrotecan (Puxi-Sam), a novel B7-H4-directed topoisomerase I inhibitor ADC, was assessed as monotherapy in the first-in-human, Phase 1/2a BLUESTAR trial in several B7-H4-expressing tumors, and showed manageable toxicity and promising efficacy during dose escalation in heavily pre-treated patients (pts).[1] In pts with advanced/recurrent EC, who progressed after available standard of care therapy (including chemotherapy and/or a programmed death [PD]-ligand [L] 1 inhibitor), objective response rates (ORRs) were 34.6% and 38.5% with 2.0 and 2.4 mg/kg Puxi-Sam, respectively, after ≥13 weeks of follow-up.[2] The safety profile of Puxi-Sam was favorable, with manageable hematologic and gastrointestinal toxicities, no adverse events (AEs) leading to discontinuation, and low dose reduction rates due to treatment-related AEs.[2] Following these encouraging results, Bluestar Endometrial01, a global Phase 3 trial, will investigate Puxi-Sam monotherapy versus physician's choice of chemotherapy in pts with B7-H4-selected EC whose disease has progressed following prior platinum-based chemotherapy and immunotherapy. **Methods:** This Phase 3, randomized, open-label, multicenter study includes pts with B7-H4-selected advanced/metastatic EC that progressed following platinum-based chemotherapy and anti-PD-1/anti-PD-L1 therapy. Approximately 700 pts will be randomized 1:1 to either Arm A: Puxi-Sam (2.4 mg/kg; intravenous [IV] on Day 1 every 3 weeks [q3w]) or Arm B: either doxorubicin (60 mg/m^2 IV on Day 1 q3w) or paclitaxel (80 mg/m^2 IV on Days 1, 8, and 15 in 28-day cycles). The primary outcomes are progression-free survival (PFS) and overall survival (OS). Secondary outcomes include ORR, duration of response (DoR), second PFS, time until first subsequent anticancer therapy (TFST) and second subsequent anticancer therapy (TSST) after discontinuation of the randomized treatment, or death, and time until discontinuation of treatment (TDT) for any reason, or death. All outcomes are to be assessed for Arm A versus Arm B. Safety will be assessed throughout. Clinical trial information: NCT07044336. First Patient In date: Aug 1, 2025. 1. Meric-Bernstam F, et al. *Ann Oncol*. 2024;35:S485–S486. 2. Gaillard S, et al. *Gynecol Oncol*. 2025;200:347–348. Editorial acknowledgment: Medical writing assistance was provided by Lewis C Rodgers, PhD, of Omnicom Health Medical Communications, and was funded by AstraZeneca. Clinical trial information: NCT07044336. Research Sponsor: AstraZeneca.

6000 **Oral Abstract Session**

Adjuvant radiotherapy versus observation following curative surgery for early-stage oral squamous cell carcinoma (AREST; CTRI/2017/07/009114). First Author: Sudhir Vasudevan Nair, Tata Memorial Center, Mumbai, India

Background: The role of adjuvant radiotherapy (RT) in early-stage, node-negative oral squamous cell carcinoma (OSCC) with one or more intermediate risk factors - such as depth of invasion (DOI) ≥5 to ≤10mm, perineural invasion (PNI), lymphovascular emboli (LVE), or poor differentiation - remains debatable and is largely based on retrospective data. This multicenter, open-label, phase III randomized controlled trial was designed to assess the impact of post-operative adjuvant RT in this setting. **Methods:** Patients with early-stage (pT1-T2), node-negative (pN0) OSCC undergoing adequate surgery (defined as clear margins ≥5mm and at least ipsilateral level I-III neck dissection with ≥16 nodes) with presence of one or more intermediate risk factors were screened. Eligible patients underwent stratified randomization (oral cavity subsite, PNI/LVE, and differentiation) in 1:1 ratio to either observation or adjuvant RT (60Gy in 30 fractions over 6-weeks) to the resected tumor-bed and at-risk neck nodal region after written informed consent. Primary endpoint was loco-regional recurrence-free survival (LRFS) measured from randomization to first documented event of local and/or regional recurrence from index cancer. All time-to-event outcomes were computed using Kaplan-Meier (KM) method with log-rank test for comparison and expressed as 3-year point estimates with 95% confidence intervals (CI). The planned sample size (N=392) provided 80% power at an α of 0.05 to detect a Hazard Ratio (HR) of 0.6256, assuming 3-year LRFS of 70% in the observation arm. **Results:** Following curative surgery, a total of 392 patients were randomized (191 to adjuvant RT; 201 to observation). Baseline characteristics were balanced between the two arms. At a median follow-up of 47.2 months (inter-quartile range=30-59.4 months), 3-year KM estimate of LRFS was 89.2% in adjuvant RT arm vs 80.9% in observation arm (HR=0.52, 95% CI=0.30-0.91; p=0.02) in the intention-to-treat (ITT) population and 91.1% vs 80.9% (HR=0.43, 95%CI=0.23-0.80; p=0.01) on per-protocol (PP) analyses. Cumulative incidence of loco-regional failure with death as competing event was 10.6% (95%CI=6.1%-15.1%) with adjuvant RT and 18.9% (95%CI=13.3%-24.6%) with observation (HR=0.52, 95% CI=0.30-0.91; p=0.021) in the ITT population and 8.7% (95%CI=4.3%-13.1%) vs 18.9% (95% CI=13.3%-24.6%) (HR=0.43, 95%CI=0.23-0.79; p=0.007) on PP analyses. Disease-free and overall survival were not significantly different between the two arms. Subgroup analysis identified oral tongue deriving higher benefit of adjuvant RT compared to buccal mucosa. **Conclusions:** Adjuvant RT significantly reduces risk of loco-regional recurrence for early-stage, node-negative adequately resected OSCC, particularly oral tongue. However, such reduction in loco-regional failure does not translate into significant survival benefit. Clinical trial information: CTRI/2017/07/009114. Research Sponsor: NATIONAL CANCER GRID; NCG Project No.2019/01.

6001 **Oral Abstract Session**

Impact of lymph node dissection extent on disease-free survival with postoperative nivolumab plus concurrent chemoradiotherapy in head and neck squamous cell carcinoma: A post-hoc analysis of the NIVOPOSTOP trial. First Author: Ariane Lapierre, Hospices Civils de Lyon, Pierre Benite, France

Background: Postoperative nivolumab added to concurrent Chemo-Radiotherapy (CRT) after surgery has been shown to improve disease-free survival (DFS) in patients with resected head and neck squamous cell carcinoma (HNSCC) at high risk of relapse. However, extensive nodal dissection has long be suspected to hinder response to immunotherapy but prospective data remains scarce. **Methods:** We analyzed the surgical procedures of the patients included in the primary analysis of the NIVOPOSTOP study regarding neck lymph node dissection (LND). Patients were classified with either uni- or bilateral LND. The number of nodes in the pathological report was also studied. The extent of the LND on DFS was analyzed in univariate and multivariate analysis. **Results:** Surgical information was available for all 666 patients. Four patients did not undergo any LND. Of the 662 patients who underwent nodal surgery, 239 (36%) underwent unilateral LND and 423 (64%) bilateral LND. The proportion of patients with bilateral / unilateral LND was similar in both treatment. Patients who underwent bilateral LND had statistically higher stage tumors versus unilateral LND (76% vs 61% stage IV) and a significantly higher proportion of laryngeal and hypopharyngeal tumors (17% vs 3% and 16% vs 7% respectively). The median numbers of nodes removed were 39 overall, 25 on the right side of the neck, and 24 on the left. As compared to unilateral LND, bilateral LND was associated with worse DFS in univariate analysis (HR 1.56 (95%CI 1.18; 2.05)). After adjusting for performance status, tumor site and p16 status, clinical stage, pathological risk factors of relapse (nodal extracapsular extension, margin status, perineural invasion, ≥ 4 involved nodes), the association was no longer statistically significant: HR 1.26 (95%CI 0.92; 1.71), Wald test p-value 0.15. There was no interaction between the type of LND (unilateral or bilateral) and the type of treatment (without or with nivolumab) on DFS. The benefit of adding Nivolumab to CRT was similar for unilateral LND (HR 0.79 (95%CI 0.50; 1.26)) and bilateral LND (HR 0.77 (95%CI 0.57; 1.03)) in Cox model stratified for p16 status. Regarding the extent of LND, the benefit of adding Nivolumab to CRT in the 330 patients who underwent removal of more than 39 neck lymph nodes, on one or both sides, was similar to that of the whole population (HR 0.75 (95%CI 0.54; 1.05)). **Conclusions:** The DFS benefit of adding nivolumab to standard postoperative therapy (cisplatin-RT) was not changed by whether the LND was bilateral or unilateral and persisted in patients in whom more than 39 cervical lymph nodes were removed, on one or both sides. As such, no evidence supports reducing the extent of neck LND when immunotherapy is incorporated into the management of high risk resected HNSCC. Clinical trial information: NCT03576417. Research Sponsor: None.

6002 **Oral Abstract Session**

Metronomic adjuvant chemotherapy (MACE) in locally advanced oral cavity squamous cell carcinoma post-surgery and adjuvant treatment (MACE postop): A phase III randomized controlled trial. First Author: Pankaj Chaturvedi, ACTREC, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India

Background: The role of maintenance systemic therapy following definitive surgery and adjuvant treatment in locally advanced oral cavity squamous cell carcinoma (OCSCC) remains undefined. This phase III trial evaluated whether oral metronomic adjuvant chemotherapy (MACE) improves survival compared with observation. **Methods:** This multicenter, open-label, phase III superiority trial conducted in India enrolled patients with stage II–IV OCSCC (AJCC 7th edition) who were clinico-radiologically disease-free 1–2 months after completion of definitive surgery with adjuvant treatment. Patients were randomly assigned (1:1) to observation (OBS) or oral MACE for up to 18 cycles. MACE comprised methotrexate 15 mg/m² once weekly (four doses per 28-day cycle) plus celecoxib 200 mg twice daily. Adherence to MACE was monitored at 3-monthly follow-up visits using patient-reported medication logs, supplemented by objective verification through review of returned empty drug containers. The primary endpoint was 2-year overall survival (OS). The planned sample size was 712; accrual was stopped early following emerging external evidence, with ethics committee approval. **Results:** Between February 2017 and April 2025, 410 patients were enrolled (OBS, n=208; MACE, n=202); approximately three-quarters had stage IV disease in both arms. The median number of MACE cycles delivered was 15; 92 patients discontinued treatment, most commonly because of noncompliance (n=55) or disease progression (n=27). At a median follow-up of 42.5 months, 129 deaths were observed (70 in OBS and 59 in MACE). Two-year OS was 70.2% (95% CI, 63.0–76.2) in the OBS arm and 79.2% (95% CI, 72.5–84.4) in the MACE arm (hazard ratio [HR], 0.76; p=0.13). Two-year progression-free survival was 68.0% (95% CI, 61.0–74.1) with OBS and 77.0% (95% CI, 70.2–82.4) with MACE (HR, 0.72; p=0.044). Distant recurrences occurred in 30 patients (14.4%) in the OBS arm and 17 patients (8.4%) in the MACE arm, while second primary malignancies were observed in 8 (3.8%) and 3 (1.5%) patients, respectively. Grade 3–4 toxicity with MACE was observed in 6.9%. Exploratory subgroup analyses suggested greater benefit in patients with extranodal extension and stage IV disease. The average cost of MACE per cycle, including toxicity management, was approximately USD 10. **Conclusions:** MACE following definitive local therapy did not significantly improve overall survival in locally advanced OCSCC. However, a statistically significant improvement in progression-free survival was observed, driven by a reduction in distant metastases and second primary malignancies. These findings suggest that selected high-risk subgroups—particularly patients with extranodal extension and advanced-stage disease—may derive benefit from this low-cost and well-tolerated strategy. Clinical trial information: CTRI/2017/02/007777. Research Sponsor: None.

6003 **Oral Abstract Session**

Two-cycle versus three-cycle induction chemotherapy followed by concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: A phase III randomized noninferiority trial. First Author: Hu Liang, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China

Background: Although two- and three-cycle induction chemotherapy are both widely utilized and confer significant survival benefits in locoregionally advanced nasopharyngeal carcinoma, direct comparative evidence remains lacking. Furthermore, given the cumulative treatment-related toxicity, economic burden, and potential delays in the initiation of radiotherapy, the optimal number of induction chemotherapy cycles remains undefined. **Methods:** We conducted a phase 3, open-label, multicenter, randomized controlled noninferiority trial in an endemic area. Patients with previously untreated, stage III-IVB (except T3-4N0, AJCC 8th edition) nasopharyngeal carcinoma, aged 18-70 years without severe comorbidities were enrolled. Eligible patients were randomly assigned to receive two cycles or three cycles induction chemotherapy followed by concurrent chemoradiotherapy in a 1:1 ratio. The primary endpoint was failure-free survival (FFS) and the noninferiority margin was defined as an 8% absolute between-group difference, with an 80% statistical power and a one-sided α of 0.025. The secondary endpoints included overall survival, distant metastasis-free survival, locoregional relapse-free survival, and toxicity, , among others. **Results:** Among 654 eligible patients, 327 were allocated to each group (two-cycle vs three-cycle). Two groups were well-balanced in all prognostic factors. After a median follow-up of 34.3 months, intention-to-treat analysis showed that estimated 3-year FFS was 85.4% (95% CI 80.9-89.9) in the two-cycle group and 86.7% (95% CI 82.4-91.0) in the three-cycle group, with a difference of -1.3% (95% CI, -7.54% to 4.94%; hazard ratio 1.11, 95% CI 0.72-1.71; P = 0.0031 for noninferiority). Similar result was found in the per-protocol analysis: estimated 3-year FFS for two-cycle group and three-cycle group was 86.5% (95% CI 82.0-91.0) and 87.0% (95% CI 82.7-91.3), respectively, with a difference of -0.5% (95% CI, -6.74% to 5.74%; hazard ratio 1.10, 95% CI 0.69-1.75; P = 0.0014 for noninferiority). No differences were observed between groups in terms of overall survival and the cumulative incidences of locoregional relapse and distant metastasis. Patients in the three-cycle group developed significantly more grade 3-4 adverse events such as neutropenia (three-cycle group 34.3% vs two-cycle group 24.8%), leukopenia (32.7% vs 24.5%) and vomiting (15.9% vs 10.4%). No patients died from treatment-related causes. **Conclusions:** Two-cycle induction chemotherapy followed by concurrent chemoradiotherapy provides comparable disease control and survival, with less toxicity, compared to three-cycle counterpart in locoregionally advanced nasopharyngeal carcinoma. Clinical trial information: ChiCTR1800018417. Research Sponsor: None.

6004 **Oral Abstract Session**

Carboplatin-based versus cisplatin-based induction-concurrent chemoradiotherapy with locoregionally advanced nasopharyngeal carcinoma: A multicenter, parallel-group, non-inferiority, randomized, phase 3 trial. First Author: Xiaoqing Wang, Nanfang Hospital, Southern Medical University, Guangzhou, China

Background: Cisplatin-based chemoradiotherapy has been the standard of care in locoregionally advanced nasopharyngeal carcinoma (LA-NPC). However, the cisplatin-based chemotherapy is known to the severe side-effects and poor compliance. Carboplatin is the second-generation platinum drug with similar anti-cancer efficacy but less side-effects. The purpose of this study is to investigate whether the carboplatin-based induction-concurrent chemoradiotherapy was non-inferior to the cisplatin-based induction-concurrent chemoradiotherapy in LA-NPC. **Methods:** We performed a multicentre, parallel-group, non-inferiority, randomized, phase 3 trial at six institutions in China. Patients initially diagonosed with non-keratinizing NPC and stage III-IVa were randomly assigned to carboplatin group or cisplatin group. Patients in the carboplatin or cisplatin group received two cycles carboplatin-based or cisplatin-based induction chemotherapy, followed by concurrent chemoradiotherapy with carboplatin or cisplatin for two or three cycles. Allocation was done by a central randomization system using sequentially numbered, opaque, sealed envelopes. The primary endpoint was 3-year failure-free survival (FFS). Secondary endpoints are overall survival (OS), distant metastasis-free survival (DMFS), loco-regional failure-free survival (LRFFS), and toxic effects. If the upper limit of the 95% CI for the difference in 3-year failure-free survival between the carboplatin-based and cisplatin-based groups did not exceed 10%, non-inferiority was met. This trial is registered with ClinicalTrials.gov, NCT03919552. **Results:** From Apr 16, 2018 to Aug 7, 2024, a total of 482 patients were enrolled and randomly assigned to carboplatin group (n=241) or cisplatin group (n=241). With a median follow-up of 40.0 months (IQR 21.0-57.0), the 3-year FFS was 85.7% (95%CI 80.4-91.0) in carboplatin group and 87.6% (83.1-92.1) in the cisplatin group (stratified hazard ratio [HR]1.234, 95% CI: 0.744-2.045, p=0.414), with a difference of 1.9% (95% CI −8.9 to 5.1; p non-inferiority=0.0112). Patients in the cisplatin group had a higher frequency of grade 3 or 4 neutropenia (31.6% vs 22.5%, $p < 0.001$), and anorexia (16.9% vs 3.6%, $p < 0.001$). A significantly higher frequency of any grade nausea (4.8% vs 3.6%, $p < 0.001$), vomiting (2.6% vs 0.5%, $p < 0.001$), and nephrotoxicity (1.3% vs 0%, $p < 0.001$). No patients died from treatment-related causes. **Conclusions:** The primary results indicated that carboplatin-based induction-concurrent chemoradiotherapy represents an alternative doublet treatment strategy to cisplatin-based induction-concurrent chemoradiotherapy for patients with LA-NPC. A longer follow-up is needed to confirm the promising regimen. Clinical trial information: NCT03919552. Research Sponsor: National Natural Science Foundation of China; NO.82303684; Medical Scientific Research Foundation of Guangdong Province; B2021449; China Postdoctoral Science Foundation; NO. 2023M741560; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503000; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503005; National Natural Science Foundation of China; China Postdoctoral Science Foundation; NO. 2025M782041; Guangdong Basic and Applied Basic Research Foundation; NO. 2022A1515010509.

LBA6005 **Oral Abstract Session**

Adjuvant sintilimab-capecitabine versus capecitabine alone in locoregionally advanced nasopharyngeal carcinoma with suboptimal response to induction chemotherapy: An open-label, randomized, controlled, phase 2 trial. First Author: Li-Ting Liu, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Centre, Guangzhou, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

6006 **Oral Abstract Session**

A phase 2 study of ipatasertib in combination with pembrolizumab for first-line treatment of recurrent or metastatic squamous cell cancer of the head and neck. First Author: Jacob Stephen Thomas, Division of Medical Oncology, Department of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA

Background: Single agent pembrolizumab in relapsed/metastatic head and neck squamous cell carcinoma (R/M HNSCC) has limited activity. The immunosuppressive tumor microenvironment (TME) includes regulatory T cells (Treg)s and myeloid-derived suppressor cells (MDSC)s, which may contribute to the low responses to anti-PD-1 therapy. Preclinical studies demonstrate that anti-PD-1 antibodies induce Treg activation through the AKT pathway. AKT blockade selectively inhibits the proliferation of human Tregs compared to conventional T cells. Furthermore, inhibiting the AKT pathway limits MDSC infiltration and differentiation while boosting effector T cell function within tumors. Ipatasertib is an oral highly selective small-molecule inhibitor of all three isoforms of AKT. This phase II trial compares the efficacy of combination ipatasertib plus pembrolizumab (I+P) versus pembrolizumab (P) monotherapy in R/M HNSCC. **Methods:** This is a prospective, two-arm, phase II, multicenter trial for 1st line treatment of R/M HNSCC. Patients were randomized 1:1 to either Arm 1 - P 200mg on day 1 with I 400mg daily on days 1-14 of 21-day cycles, or Arm 2 – P monotherapy. PD-L1 CPS score $\geq$1 was required. The primary objective is to compare the PFS between the two arms. Secondary objectives included safety and ORR per RECIST 1.1. **Results:** As of 1/21/2026, 52 patients were randomized, with 27 enrolled in the I+P arm. The median age was 67 and 77% were male. The primary tumor sites were 46% oral cavity, 38% oropharynx, and 15% larynx. Among pts with oropharynx primary, 75% were p16 positive. PD-L1 CPS score was $\geq$20 in 60%. In the I+P arm the most common G1-3 treatment-related adverse events (TRAEs) occurring in $\geq$10% were diarrhea (70.4%), fatigue (44.4%), Nausea (40.7%), AST increase (18.5%), ALT increase (14.8%), and maculopapular rash (14.8%). Only 1 pt had grade 3 diarrhea. In P arm the most common G3 TRAEs were maculopapular rash (29.2%), AST increase (16.7%), and diarrhea (12.5%). There were no G4 or G5 TRAEs. Four patients required dose reduction of ipatasertib, primarily for diarrhea. Ten pts in the I+P arm and 6 pts in P arm required dose interruptions. One patient in each arm discontinued due to adverse events. At the data cutoff 4 pts remain on treatment in I+P arm and 2 remain on P arm. The ORR in I+P arm and P arm was 41% and 17% respectively. The CR rate was 15% in I+P arm and 4.2% in P arm. The DCR (CR+PR+SD) was 70% in I+P arm and 42% in P arm. With a median follow up of 7.0 months, the PFS in I+P arm is 8.1 months (95% CI: 4 – NA) and in P arm is 6.2 months (95% CI 1.9 – 13.5). **Conclusions:** I+P demonstrated an acceptable safety profile and shows promising clinical activity in R/M HNSCC. Clinical trial information: NCT05172258. Research Sponsor: National Cancer Institute.

LBA6007 **Oral Abstract Session**

Ultra-low-dose immunotherapy plus oral metronomic chemotherapy versus paclitaxel-carboplatin in platinum-sensitive recurrent or metastatic head and neck squamous cell carcinoma: A randomized phase III trial. First Author: Minit Jalan Shah, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

6008 **Oral Abstract Session**

Amivantamab in HPV-unrelated recurrent/metastatic head and neck squamous cell cancer after disease progression on immune checkpoint inhibitor and chemotherapy: Pivotal results from the phase 1b/2 OrigAMI-4 study. First Author: Barbara Burtness, Yale Cancer Center, Yale School of Medicine, New Haven, CT

Background: Prognosis is poor for patients with HPV-unrelated recurrent/metastatic (R/M) head and neck squamous cell cancer (HNSCC) after disease progression on immune checkpoint inhibitor (ICI) and chemotherapy, with participants (pts) who received cetuximab showing an objective response rate (ORR) of 24% and median progression-free survival (PFS) of 3.8 months (Fayette *Clin Cancer Res* 2025). In addition to EGFR, MET expression is also elevated in R/M HNSCC. Therefore, we evaluated amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity, as monotherapy in HPV-unrelated R/M HNSCC after progression on platinum-based chemotherapy and a PD-(L)1 inhibitor. **Methods:** Cohort 1 of OrigAMI-4 (NCT06385080) evaluated subcutaneous (SC) amivantamab at a dose of 1600 mg (≥80 kg, 2240 mg) on Cycle 1 Day 1, then 2400 mg (≥80 kg, 3360 mg) on Cycle 1 Day 8 and Day 15, and then every 3 weeks. Pts with R/M HNSCC who had disease progression on a PD-(L)1 inhibitor and platinum-based chemotherapy were enrolled. Prior anti-EGFR therapy was exclusionary. The primary endpoint was ORR per RECIST v1.1. The sample size provided >99% power to reject the null hypothesis (ORR ≤10%) assuming an ORR of 30% with a 2-sided alpha of 5%. Secondary endpoints included duration of response (DoR), PFS, and safety. **Results:** As of 6 Jan 2026 (median follow-up: 9.0 months), the cohort was fully enrolled with 102 pts having received ≥1 dose of SC amivantamab. The median age was 63 years (range, 30–81), 77% were male, and 67% had an ECOG performance status of 1. All pts had received prior PD-(L)1 inhibitor and platinum-based chemotherapy. The confirmed ORR was 47% (48/102; 95% CI, 37–57), with 4 complete responses, 44 partial responses, and 39 pts with stable disease. A majority (79%) experienced shrinkage of target lesions. Among confirmed responders, the median DoR was 7.2 months (95% CI, 5.8–not estimable [NE]). Responses were rapid, with a median time to initial response of 6.6 weeks (range, 5.6–43.4). Median PFS was 6.8 months (95% CI, 5.2–8.2). Treatment-emergent adverse events (AEs) were mainly EGFR/MET-related, with the most common (>25%) being hypoalbuminemia, rash, dermatitis acneiform, paronychia, stomatitis, and fatigue. Administration-related reactions were seen in 13% of pts (all grade 1–2). In total, 6 (6%) pts discontinued due to treatment-related AEs. Longer follow-up, subgroup, and biomarker analyses will be presented at the meeting. **Conclusions:** SC amivantamab monotherapy demonstrated an ORR of 47%, with rapid and durable responses in pts with HPV-unrelated, R/M HNSCC after disease progression on an ICI and chemotherapy. The safety profile and tolerability are consistent with prior reports. Clinical trial information: NCT06385080. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

6009 **Clinical Science Symposium**

Clinical activity of REM-422, a MYB mRNA degrader, in recurrent/metastatic adenoid cystic carcinoma: Final results from the phase 1/2 dose-escalation cohort. First Author: Renata Ferrarotto, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Adenoid cystic carcinoma (ACC) is a malignant neoplasm characterized by dysregulation of MYB, with the majority of tumors containing a hallmark t(6:9) rearrangement resulting in a MYB:NFIB fusion oncogene, or aberrant MYB overexpression. There are no FDA approved systemic therapies for the treatment of ACC. REM-422 is a first-in-class, potent, selective, oral small molecule mRNA degrader of MYB. **Methods:** This Phase 1/2 study aims to determine the safety, PK/PD and efficacy of REM-422 in patients (pts) with recurrent or metastatic (R/M) ACC. During Phase 1 Dose Escalation and Optimization, patients received oral REM-422 once daily (3-48mg) in 28-day cycles. Enrollment was biomarker-agnostic; MYB mRNA transcripts targetable by REM-422 (biomarker positive) were retrospectively assessed in tumor specimens. **Results:** In the Phase 1 study, 69 pts were enrolled (median age 57 [range 20-82]); 75% received ≥1 prior line of systemic therapy. Fifty-nine pts were efficacy evaluable: 32 biomarker positive, 24 biomarker negative, and 3 unknown. Fifteen patients received REM-422 at the recommended phase 2 dose (RP2D) of 24 mg. REM-422 was generally well-tolerated. No dose-limiting toxicities were observed. The most common treatment-related adverse events at the RP2D included epistaxis (60%), fatigue (60%) and anemia (40%), all of which were grade 1 or 2. Pharmacodynamic analysis in peripheral blood and on-treatment tumor biopsy confirmed robust target engagement including reduction in MYB mRNA and protein at efficacious exposures. In the biomarker positive population, tumor regression was observed at doses ≥12mg, with 21/30 pts (70%) experiencing reduction in target lesions and 14/30 (47%) achieving at least ≥20% shrinkage. Clinical activity was seen across both molecular subtypes (ACC-I and II) and in pts previously treated with antibody-drug conjugates. At the RP2D of 24 mg, 3 PRs were observed among 7 biomarker positive pts (ORR 42%). Time to response ranged from 4-8 months with durations up to 12 months and ongoing at the data cutoff (07 January 2026). **Conclusions:** REM-422 is the first small molecule MYB mRNA degrader to demonstrate clinical activity in R/M ACC and is generally well-tolerated. These findings support further evaluation of REM-422 in a biomarker-selected population. Accrual to the Phase 2 Confirmatory Cohort is ongoing. Clinical trial information: NCT06118086. Research Sponsor: Remix Therapeutics.

6010 **Clinical Science Symposium**

Emiltatug ledadotin (Emi-Le), a B7-H4–directed antibody-drug conjugate (ADC), in patients with aggressive adenoid cystic carcinoma (ACC): Phase 1 interim analysis. First Author: Glenn J. Hanna, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: ACC is a rare cancer that typically arises in the salivary glands but can affect various organs. About 40% of patients (pts) have an aggressive form of ACC (referred to as ACC-I; Ferrarotto et al., *Clin Cancer Res* 2021) characterized by solid/basaloid or high-grade transformation histology and poor prognosis with median progression-free survival (PFS) of 2–3 months and median overall survival (OS) of approximately 3 years. There are no approved systemic therapies for recurrent or metastatic ACC. B7-H4 is an immune checkpoint protein with elevated expression in ACC and other cancers. Emi-Le (XMT-1660) is a B7-H4-directed ADC with an auristatin F-HPA microtubule inhibitor payload. Here we report antitumor activity results from the Phase 1 ACC-specific dose escalation/backfill cohort, along with safety data for all enrolled pts (NCT05377996). **Methods:** Adult pts with select advanced or metastatic solid tumors, including aggressive ACC, were enrolled. Eligibility criteria for ACC pts required features consistent with aggressive disease that included 1 of the following: 1) clinically aggressive phenotype, defined as < 3 years to recurrence/progression or de novo metastatic disease with atypical metastatic sites and solid tumor morphology, and/or 2) molecular features consistent with poor prognosis (activating *NOTCH1–4* mutations or c-Myc positive or p63 negative/low per IHC). Across dose escalation and backfill, eligible pts received Emi-Le at doses of 7.2–115 mg/m^2 IV per Q3W or Q4W cycle. Pts with ACC received Emi-Le at doses of 57.4–89 mg/m^2 IV per Q3W or Q4W cycle. Primary objectives included safety and preliminary antitumor activity. **Results:** As of October 1, 2025, 221 pts were dosed. Of these, 35 pts had ACC, with a median of 1 prior line of therapy (range 0–3), median age 58 years, and 57% were female. For the safety set of 221 pts, Emi-Le was well tolerated with no new safety signals identified. The most common treatment-related adverse events (TRAEs) were proteinuria (49.8%), transient AST increase (49.3%), and fatigue (41.2%). The only Grade 3 TRAEs in ≥10% of pts were transient AST increase (17.6%) and proteinuria (17.6%). TRAEs leading to treatment discontinuation occurred in 3.6% of pts. No treatment-related deaths were reported. Among 25 evaluable (≥1 post-baseline scan) pts with ACC, objective response rate was 40% (9/25 confirmed, 1/25 unconfirmed ongoing and on treatment) and disease control rate was 76% (19/25). At data cut-off, median PFS (95% CI: 13.0 weeks, not reached [NR]) and OS (95% CI: 26.6 weeks, NR) have not been reached. **Conclusions:** Based on these data, Emi-Le appears to demonstrate favorable tolerability and promising antitumor activity in pts with aggressive ACC who have no available treatments and a poor prognosis. Further clinical development is ongoing. Clinical trial information: NCT05377996. Research Sponsor: Day One Biopharmaceuticals.

6011 **Clinical Science Symposium**

Trastuzumab deruxtecan in patients with HER2-low recurrent/metastatic salivary gland carcinoma: Results from the phase II MYTHOS trial. First Author: Ichiro Kinoshita, Department of Medical Oncology, Hokkaido University Hospital, Sapporo, Hokkaido, Japan

Background: Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody–drug conjugate with established efficacy across multiple HER2-expressing malignancies. Salivary gland carcinoma (SGC) is a rare disease with limited treatment options, particularly for tumors with HER2-low expression. The MYTHOS trial is a multicenter, investigator-initiated phase II study evaluating T-DXd efficacy in recurrent or metastatic (RM) SGC patients with HER2 overexpression or HER2-low expression. Here, we report the efficacy and safety results of the HER2-low cohort (Cohort 2). **Methods:** Eligible patients had histologically confirmed RM SGC with HER2-low expression (IHC 1+ or IHC 2+/ISH−), as determined by central assessment according to the ASCO/CAP 2018 breast cancer guidelines, and no indication for curative treatment. Patients received T-DXd at 5.4 mg/kg intravenously every 3 weeks. The primary endpoint was confirmed objective response rate (ORR) assessed by independent central review (ICR) according to RECIST v1.1. Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. The required sample size for Cohort 2 was 33 patients, based on a threshold ORR of 25%, an expected ORR of 50%, 83% power, and a two-sided alpha of 0.05 using an exact binomial test. The primary efficacy decision was based on the prespecified Simon's two-stage minimax design in the first 33 patients; efficacy in the full analysis set (FAS) was summarized descriptively. **Results:** A total of 36 patients were included in the FAS, including 30 with salivary duct carcinoma (SDC). HER2-low status comprised IHC 2+/ISH− in 14 and IHC 1+ in 22; 25 had received prior systemic therapy for RM disease. Median follow-up was 25.1 months. The ORR by ICR was 38.9% (14/36; 95% CI, 23.1–56.5%), and the DCR was 94.4% (95% CI, 81.3–99.3%). Median PFS was 8.7 months (95% CI, 6.5–13.3), and median OS was 24.8 months (95% CI, 18.7–NE). In a prespecified subgroup analysis by histology, the ORR by ICR was 46.7% (14/30; 95% CI, 28.3–65.7%) in SDC and 0% (0/6; 95% CI, 0–45.9%) in other SGC subtypes. Common grade ≥3 adverse events (>10%) were neutrophil count decreased (36.1%), lymphocyte count decreased (19.4%), white blood cell count decreased (11.1%), and decreased appetite (11.1%). Drug-related interstitial lung disease (ILD)/pneumonitis occurred in 9 (25.0%; grade 1/2 in 7, grade 3 in 1, and grade 5 in 1). There was one drug-related death due to ILD/pneumonitis. **Conclusions:** Although the prespecified primary efficacy endpoint was not met, T-DXd demonstrated clinically meaningful antitumor activity in patients with HER2-low RM SGC, particularly in those with SDC. The safety profile was generally consistent with the known profile of T-DXd in the Japanese population, with ILD/pneumonitis remaining an important identified risk requiring careful monitoring. Clinical trial information: jRCT2011210017. Research Sponsor: Daiichi Sankyo Company, Limited.

6012 Clinical Science Symposium

A phase 2 study of darolutamide plus leuprolide acetate in hormone therapy–naïve recurrent and/or metastatic androgen receptor (AR)–positive salivary gland cancer (ETCTN 10553). First Author: Alan Loh Ho, Solid Tumor Oncology Division, Head and Neck Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: A subset of salivary gland cancers (SGCs) express the androgen receptor (AR). A prior AR+ SGC trial with the anti-androgen enzalutamide alone failed to meet its primary endpoint. This is a multicenter, phase II study evaluating the efficacy and safety of the anti-androgen darolutamide (Bayer) in combination with androgen-deprivation therapy (ADT; leuprolide acetate) in hormone-therapy naïve patients with AR+ SGCs. **Methods:** Patients with locally advanced/unresectable or recurrent/metastatic AR+ SGCs were enrolled. AR status was determined locally by immunohistochemistry (IHC). Prior AR-targeted therapy was not allowed, unless administered in the neoadjuvant and/or adjuvant setting >6 months before disease recurrence. Darolutamide 600 mg orally twice daily was given with leuprolide acetate intramuscular injections (1 cycle= 28 days). The primary endpoint was best overall response (BOR) rate according to RECIST v1.1 within 1 year of initiating treatment. Secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity. Exploratory endpoints were evaluating biomarkers in serially obtained research biopsies and exploring efficacy among patients who had not received prior systemic therapy. A two-stage minimax design was used to detect a 50% BOR rate (vs. 25%) (alpha = 9%; beta = 83%). ≥3 responses in the first 9 patients would trigger accrual to 20; ≥8 responses would be considered promising. **Results:** Study accrual of 20 patients (pts) with AR+ SGCs was completed on 10/30/25. 15 males, 5 females with a median age of 70.5 years were enrolled. Among the 9 pts in the first stage, 6 confirmed partial responses (PRs) were observed, allowing for full study accrual. With a data cutoff of 1/21/26, the best RECIST v1.1 responses among 20 pts were 8 (40% [19.1% 63.9%]) PRs (7 confirmed, 1 unconfirmed with pt still on treatment), 10 (50% [27.2%, 72.8%]) stable disease (SD), 1 (5% [1%, 24.9%]) progression of disease; 1 pt on treatment has not had radiographic assessments yet. 6 (30% [11.9%, 54.3%]) pts came off trial for disease progression, 1 (5% [1%, 24.9%]) withdrew consent after 6 cycles, and 13 (65%, [40.8%, 84.6%]) remain on treatment. Among 5 female pts, best responses were 1 (5% [1%, 24.9%]) PR, 3 (15% [3.2%, 37.9%]) SD, 1 (5% [1%, 24.9%]) PD. With additional follow-up, PFS, OS, and biomarker data (AR IHC %, HER2 status) will be presented. **Conclusions:** In this molecularly selected cohort of patients with SGC, darolutamide plus ADT possesses significant clinical activity, validating AR as a relevant therapeutic target in a subset of SGCs. Analysis of serial research biopsies will be performed to identify biomarker and/or drug combination strategies to enhance the efficacy of AR-targeting. Clinical trial information: NCT05669664. Research Sponsor: U.S. National Institutes of Health; Bayer.

6013 Rapid Oral Abstract Session

Induction chemotherapy with nab-paclitaxel and cisplatin versus docetaxel, cisplatin, and fluorouracil followed by chemoradiotherapy in patients with stage III–IVA nasopharyngeal carcinoma: An open-label, noninferiority, randomized, controlled, phase 3 trial. First Author: Xing Lyu, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: The docetaxel, cisplatin, and 5-fluorouracil (TPF) regimen is the standard induction therapy regimen for locoregionally advanced nasopharyngeal carcinoma (LANPC). However, it is associated with poor patient compliance and notable side effects. This phase 3 trial aimed to compare the efficacy and safety of induction chemotherapy with nab-paclitaxel plus cisplatin (nab-TP) with those of the TPF regimen in patients with LANPC. **Methods:** In this multicenter, noninferiority, open-label, randomized controlled trial, treatment-naive patients with LANPC were recruited from 5 hospitals in China and were randomly assigned to receive two cycles of nab-TP (nab-paclitaxel 260 mg/m², cisplatin 80 mg/m²) or TPF (docetaxel 60 mg/m², cisplatin 60 mg/m², 5-FU 3 g/m²), followed by concurrent chemoradiotherapy. The primary endpoint was the 3-year failure-free survival (FFS) rate (non-inferiority margin 10%) in the intention-to-treat population. Secondary endpoints included overall survival, treatment response, safety, and patient-reported outcomes. This trial is registered with chictr.org.cn (ChiCTR1800019922) and is now completed. Based on previous studies, we hypothesized that the 3-year FFS (approximately 80%) is the same between the TPF regimen and the nab-TP regimen for patients with LANPC. We specify a clinically acceptable noninferiority margin of 10%. The dropout rate in both arms was set at 4% per year. Accordingly, a minimum of 506 participants was needed to achieve 80% statistical power with a one-sided type I error of 2·5%. **Results:** Between January 22, 2019 and March 24, 2023, 515 patients (71·8% male; median age: 45 years (IQR 37–51)) were randomized: 259 to the nab-TP group and 256 to the TPF group. Compared with the TPF group, the nab-TP group had significantly better treatment compliance. With a median follow-up of 55·2 months, the 3-year FFS rate in the intention-to-treat population was 86·7% (95% confidence interval (CI): 82·6–90·9) in the nab-TP group and 88·2% (95% CI: 84·2–92·1) in the TPF group. The difference in the 3-year FFS between groups was -1·4% (95% CI: -7·2 to 4·3)($P_{non\text{-}inferiority}$ = 0·0018). Compared with the TPF group, the nab-TP group had significantly lower incidences of grade 1+ leucopenia (34·0% vs. 62·6%, P < 0·0001), neutropenia (20·3% vs. 48·8%, P < 0·0001), electrolyte disturbances (86·3% vs. 96·5%, P < 0·0001), and diarrhea (28·5% vs. 39·0%, P = 0·012), whereas the nab-TP group had a higher incidence of nausea (91·0% vs. 85·4%, P =0·047). No treatment-related death was documented. **Conclusions:** In LANPC, nab-TP was non-inferior to TPF in terms of 3-year FFS rate and was associated with a significantly better safety and tolerability profile, supporting its use as a viable therapeutic alternative. Clinical trial information: ChiCTR1800019922. Research Sponsor: National Natural Science Foundation of China; No. 82172863; Natural Science Foundation of Guangdong Province.

6014 Rapid Oral Abstract Session

Neoadjuvant ivonescimab (AK112, a PD-1/VEGF bispecific antibody) combined with nab-paclitaxel and cisplatin (AP) for resectable locally advanced head and neck squamous cell carcinoma (LA-HNSCC): An exploratory phase II study. First Author: Kunyu Yang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Previously, neoadjuvant PD-1 plus AP followed by surgery and radiotherapy showed promising disease control and laryngeal preservation in resectable LA-HNSCC. Ivonescimab, a PD-1/VEGF bispecific antibody, potentially exerts synergistic anti-tumor activity by normalizing tumor vasculature and enhancing immune infiltration. This study evaluates the efficacy and safety of neoadjuvant Ivonescimab plus AP in resectable LA-HNSCC. **Methods:** This single-center phase II trial enrolled patients (18-70 yrs) with resectable stage III-IVa LA-HNSCC (oral cavity, oropharynx, hypopharynx, or larynx). Neoadjuvant therapy: 3 cycles of Ivonescimab (20mg/kg Q3W) plus AP, followed by surgery. Postoperative treatment included radiotherapy ± chemotherapy and maintenance Ivonescimab (10mg/kg Q3W) for 14 cycles. Primary endpoints: pCR and 2-year EFS. MRD and PD-L1 CPS were also investigated. **Results:** By November 2025, 36 patients were enrolled (median age 58; 75% Stage IV). Primary tumor sites were hypopharynx (50.0%), larynx (25.0%) and oral cavity (19.4%). Radiological assessment performed prior to Cycle 3 demonstrated an exceptional objective response rate (ORR) of 100% among 34 evaluable patients. Notably, a remarkably deep radiological response was achieved, with a complete response (CR) rate of 50.0% (17/34) and a partial response (PR) rate of 50.0% (17/34). Deep tumor shrinkage was observed in all cases. 30 patients underwent surgery with a 100% R0 resection rate. The overall pCR rate was 50.0% (15/30). Specifically, pCR was achieved in 70.0% (21/30) of primary lesions and 64.3% (18/28) of lymph nodes. While robust pathological responses were observed in the hypopharynx (64.3%), tongue (57.1%), and oropharynx (50.0%), the pCR rate in the larynx was markedly lower at 12.5%. Crucially, the profound tumor downsizing induced by Ivonescimab enabled volume-reduced resections, achieving 100% successful laryngeal and pharyngeal preservation while maintaining negative margins. High PD-L1 predicted efficacy; median CPS was 30.0 in pCR vs. 10.0 in non-pCR (p=0.18). Notably, 100% of pts with CPS > 30 achieved pCR. Pre-op MRD specificity for pathological conversion was 91.7% (sensitivity 37.5%). Safety: The most common Grade≥3 AEs were pharyngeal fistula (surgical-related) and transient transaminase elevation. Most drug-related AEs were manageable and consistent with the known profiles of PD-1 and VEGF inhibitors. **Conclusions:** Neoadjuvant Ivonescimab plus chemotherapy demonstrated unprecedented radiological response depth and pathological remission rates in LA-HNSCC. This novel PD-1/VEGF-based dual blockade may redefine neoadjuvant standards for head and neck cancer. High CPS and MRD negativity are robust predictors of deep pathological response. Clinical trial information: NCT06537011. Research Sponsor: None.

6015 Rapid Oral Abstract Session

Timing of postoperative chemoradiotherapy and survival outcomes in high-risk locally advanced head and neck squamous cell carcinoma: A supplementary analysis of JCOG1008. First Author: Yoshinori Imamura, Kobe University Hospital, Kobe, Japan

Background: For patients with post-operative high-risk locally advanced head and neck squamous cell carcinoma (LA-HNSCC), initiation of chemoradiotherapy (CRT) within 6 weeks after surgical resection is recommended based on previous reports. However, the guideline-defined 6-week threshold for initiating post-operative radiotherapy (PORT) is derived mainly from data in patients treated with PORT alone. Therefore, its relevance in patients receiving post-operative CRT remains uncertain. **Methods:** This supplementary analysis used data from the JCOG1008 trial (jRCTs031180135), which compared post-operative CRT with weekly cisplatin versus 3-weekly cisplatin. Associations between the surgical-to-PORT interval (S-PORT) and locoregional relapse-free survival (LRFS), overall survival (OS), and relapse-free survival (RFS) were evaluated using restricted cubic spline analyses, Kaplan–Meier methods, and Cox proportional hazards models. Treatment package time (TPT), defined as the sum of S-PORT and radiotherapy duration, was also assessed. **Results:** Among 261 enrolled patients, 251 were eligible for this analysis (median age, 62 years; 16.3% female; 45.8% with oral cavity primaries). The median S-PORT and TPT were 7.0 weeks (range, 2.9–10.0) and 13.9 weeks (range, 7.6–16.9), respectively. Restricted cubic spline analyses demonstrated minimal variation in risk across the observed S-PORT range, with hazard ratios (HRs) remaining close to 1 for LRFS, OS, and RFS. Kaplan–Meier analyses using the guideline-defined 6-week cutoff showed similar 5-year LRFS between patients with S-PORT ≤6 weeks and >6 weeks (64.0% vs 64.9%; HR 0.91, 95% CI 0.60–1.37; Table), with no significant differences in OS or RFS. In multivariable Cox models adjusting for clinical covariates, S-PORT was not independently associated with outcomes. Findings for TPT closely paralleled those for S-PORT, with no significant associations observed between TPT and treatment. **Conclusions:** In this supplementary analysis of JCOG1008, no prognostic disadvantage was observed when PORT was initiated within the range observed in this trial (6–10 weeks after surgery) among patients receiving post-operative CRT. These findings support individualized S-PORT timing rather than rigid cutoff-based decision-making in contemporary standardized CRT. Clinical trial information: jRCTs031180135. Research Sponsor: Japan Agency for Medical Research and Development (AMED); Grant-in- Aid for Clinical Cancer Research from the Ministry of Health, Labor and Welfare of Japan; National Cancer Center Research and Development Funds.

Kaplan–Meier analyses according to guideline-defined 6-week surgical-to-postoperative radiotherapy interval (S-PORT) cutoff.

	S-PORT ≤ 6 weeks	S-PORT > 6 weeks
5y LRFS (95% CI)	64.0% (52.1%–73.7%)	64.9% (57.3%–71.5%)
HR (95% CI), p-value	1	0.91 (0.60–1.37), 0.65
5y OS (95% CI)	65.3% (53.4%–74.9%)	66.6% (59.1%–73.1%)
HR (95% CI), p-value	1	0.88 (0.58–1.34), 0.54
5y RFS (95% CI)	60.0% (48.0%–70.1%)	60.2% (52.6%–67.0%)
HR (95% CI), p-value	1	0.98 (0.66–1.46), 0.93

6016 Rapid Oral Abstract Session

Phase II randomized trial of radiotherapy with pembrolizumab vs. cisplatin for unfavorable-risk p16+ head and neck squamous cell carcinoma (KEYCHAIN). First Author: Loren K. Mell, UC San Diego Moores Cancer Center, La Jolla, CA

Background: Standard chemoradiation (CRT) for unfavorable risk p16+ head and neck squamous cell carcinoma (HNSCC) is associated with high rates of toxicity and treatment failure. We hypothesized that concurrent and adjuvant pembrolizumab (pembro) could achieve superior PFS with acceptable toxicity compared to CRT in this population. **Methods:** KEYCHAIN was an open-label randomized phase II trial conducted at 6 US academic centers. Eligible patients had newly diagnosed unresected p16+ HNSCC with unfavorable risk (AJCC 8th edition stage II-III oropharynx or stage III-IVB non-oropharynx HNSCC). Patients were randomized 1:1 to RT (70 Gy in 35 fractions) plus pembro (200 mg, 2 weeks prior to RT then every 3 weeks starting day 1 of RT up to 20 total cycles) or RT plus concurrent cisplatin (cis) (100 mg/m^2 every 3 weeks). Age, ECOG status, and oropharynx site were stratification factors. The primary endpoint was PFS, defined as time from randomization to first progression or death from any cause. Primary analysis was in the modified intent-to-treat population, including all patients having $\geq$ 1 dose of study medication and $\geq$ 1 efficacy evaluation after baseline. The study design had 80% power with 1-sided α = 0.15 (log-rank test) and planned sample size of 50 analyzable subjects per arm. The study is registered with clinicaltrials.gov (NCT03383094). **Results:** Between Feb 2019 and Aug 2025, 108 patients were randomized (53 pembro, 55 cis), with 102 analyzable (50 pembro, 52 cis). Median follow-up was 26.5 months. 79% had minimum follow-up of 2 years. At 2 years, there were 7 PFS events and 1 death in the pembro arm, and 14 PFS events and 7 deaths in the cis arm. Two-year PFS was 84% (95% CI: 74-96%) vs. 70% (95% CI: 58-85%) in the pembro vs cis arm (HR 0.57, 95% CI: 0.25-1.31; 1-sided p = 0.09) (see Table). Two-year OS was 98% (95% CI: 94-100%) vs. 85% (95% CI: 76-96%) for pembro vs. cis (HR 0.33, 95% CI: 0.09-1.28; 1-sided p = 0.048). HRs adjusted for T3-4 and N2-3 category were 0.68 (PFS) and 0.31 (OS). As of the latest follow-up, there were 24 total PFS events and 12 deaths. Grade $\geq$ 3 adverse events definitely or probably related to treatment were 36% vs. 46% in the pembro vs. cis arm. The median number of cycles received in the pembro arm was 18. In the cis arm, 94% completed $\geq$ 2 cycles. Results by CPS status will be reported when available. **Conclusions:** Pembro plus RT met the pre-specified significance criterion for improvement in PFS compared to cisplatin plus RT in this phase II trial. A phase III trial of RT with pembrolizumab for unfavorable risk p16+ HNSCC is warranted. Clinical trial information: NCT03383094. Research Sponsor: Merck.

	Pembro	Cisplatin
N	50	52
Mean age	63.5	62.5
Male	87%	89%
White	85%	89%
Age > 65	42%	35%
ECOG 0	83%	70%
Oropharynx	94%	96%
T1	8%	10%
T2	22%	12%
T3	38%	38%
T4	32%	40%
N0	6%	8%
N1	42%	29%
N2	46%	54%
N3	6%	10%
2-yr PFS	84%	70%
2-yr OS	98%	85%
Completed RT w/in 56 days	96%	92%
Grade ≥ 3 mucositis	18%	17%
Grade ≥ 2 mucositis	72%	63%
Grade ≥ 3 dysphagia	14%	6%
Grade ≥ 2 dysphagia	48%	35%

6017 Rapid Oral Abstract Session

Final analysis of the investigator-initiated randomized study of anti–PD-L1 durvalumab (durva) with radiation versus chemoradiation (CRT) for intermediate-risk HPV-positive (HPV+) locally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC): Canadian Cancer Trials Group (CCTG) HN.9 (EORTC 1740-HNCG). First Author: Anna Spreafico, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Primary immunotherapy (IO) with radiotherapy remains an investigational approach in HPV+ LA-OPSCC. The CCTG-led international phase II, randomized, non-comparative, HN.9 (NCT03410615) trial evaluated the efficacy of the of durva+RT as a chemo-sparing approach in patients (pts) with intermediate-risk, HPV+, LA-OPSCC. **Methods:** Pts with newly diagnosed, PDL1-unselected, pathologically proven, treatment-naïve HPV+ LA-OPSCC (UICC/AJCC 8th Edition T1-2N1 or T3N0-1 smokers [$\geq$10 pack years] or T1-3 N2 with any smoking history) eligible for definitive CRT were randomized (1:2) to Arm A (CRT: 70Gy/35F + cisplatin 100 mg/m2 Q3W on days 1,22,43 of RT) vs Arm B (durva IV 1500 mg, days -7, 22 of RT, followed by adjuvant durva for 6 doses). Primary objective was 3-year EFS in Arm B (efficacy if one-sided 90% CI lower bound [LB] $>$83%). Secondary objectives: QoL (MDADI, FACT-HN at baseline, end of RT, 3,6,12,24 and 36 mo), OS, safety, distant metastasis-free survival (DMFS) and locoregional control (LRC). Safety was assessed per CTCAE v5. The trial closed early based on emerging external efficacy data of IO in HN LA setting, enrolling 129 pts overall (80 of the planned 120 in Arm B) with approximately 80% power retained for the primary analysis. **Results:** 129 pts were randomized across 21 Canadian and European sites. Baseline characteristics were well balanced between arms. At the data cutoff (Sep 19, 2025), median follow-up time was 55.7 mo. In both arms, all pts received the planned RT schedule. In Arm A, the median number of cisplatin cycles was 2 (21% received $<$200m/m^2 and 79%$\geq$ 200 mg/m^2). In arm B, all pts (100%) received durva concurrent to RT. 126 pts were eligible for efficacy analysis. The estimated 3-year EFS in Arm B was 80% (one-sided 90% CI: LB 73%); the prespecified efficacy criterion (LB $>$83%) was not met. The 3-year EFS in Arm A was 89%. The estimated 3-year OS rates were 92% in both arms. At 3 years, LRC were 97 and 91% in Arms A and B respectively. DMFS was 89% in Arm A and 86% in Arm B. Grade $\geq$ 3 adverse events any time during trial were similar between Arm B (69%) and Arm A (63%). QoL completion was 96% at baseline and 80%+ throughout; acute worsening during RT followed by gradual recovery (slower in arm B during adjuvant durva), with longer-term persistence of isolated issues (hearing loss, dry mouth) was similar to published experience for drug+RT regimens. **Conclusions:** Durva+RT did not improve 3-year EFS in the overall patient population of intermediate-risk HPV+ OPSCC. No new safety signal was observed. Specific toxicities varied by arm, but overall QoL experience, including swallowing, was similar between arms and with prior trials. Subgroup analysis, blood, tissue and microbiome-based correlates are ongoing. Clinical trial information: NCT03410615. Research Sponsor: Canadian Cancer Society; 707213; AstraZeneca.

6018 Rapid Oral Abstract Session

Randomized phase I/II trial adjuvant CD40.HVAC, an immunotherapy engaging dendritic cells (DC), in patients with HPV16+ oropharyngeal carcinoma (OPC). First Author: Caroline Even, Head and Neck Department, Gustave Roussy, Villejuif, France

Background: Up to 70% of OPCs are HPV-mediated predominantly by HPV16. E6/E7 oncoproteins, constitutively expressed in malignant cells, represent optimal immunotherapeutic targets. We evaluated CD40.HVac, a new DC engager combining a humanized IgG4 monoclonal antibody fused to HPV16 E6/E7, designed to target the CD40 receptor on DCs. **Methods:** This trial enrolled OPC HPV16$^+$ patients (pts) in complete remission 16–22weeks (W) post curative treatment. In cohorts 1 (n=11) and 2 (n=11), pts were randomized (5:1) to receive subcutaneously, Hiltonol (1mg) adjuvanted CD40.HVac, 1 and 3 mg, respectively, or placebo, at W0, 4, 24. Dose-limiting toxicity (DLT) was assessed from W0–W6. Blood E6/E7-specific T cells were assessed 2W post-injection using stimulation of PBMCs with vaccine E6/E7 pools of peptides. CD8+T cells were characterized by expression of Activation Induced Markers (AIM). Immune response was defined as a $\geq$3-fold increase in HPV specific T cell responses over unstimulated controls after in vitro restimulation, or a net increase of $\geq$ 0.03% reaching at least 0.05% AIM$^+$ T cells compared to baseline. **Results:** Median age was 58 years (IQR 51; 65), 68% were male, 68% were stage I or II, 32% stage III. At entry, 21 pts were lymphopenic (3 grade 3). All pts received the 3 planned injections. Four pts were randomized to placebo, 18 to CD40.HVac. No DLTs nor grade 3-5 adverse events (AEs) were reported. From W0 to W32, all pts treated with CD40.HVac experienced at least 1 vaccine related AE; 5 (28%) experienced at least 1 grade 2 AE while the 13 others experienced only grade 1 AEs. At W6, 77% of pts treated with CD40.HVac in the both 1 mg and 3 mg cohorts exhibited a 27-fold and 42-fold increase from baseline, respectively, in CD4$^+$ T cells producing IL-2, IFNγ and/or TNF. By W26, responses were observed in 100% of pts treated with CD40.HVac in both cohorts, with 35-fold (1 mg) and 83-fold (3 mg) increases from baseline. AIM assays confirmed the induction of HPV specific CD4$^+$ and CD8$^+$ T cell responses. HPV specific CD8$^+$ T cell responses were detected in 50% and 44% of pts treated with CD40.HVac at W6 in the 1 mg and 3 mg cohorts, respectively, and in 71% and 44% at W26. HPV specific CD8$^+$ T cells displayed a polyfunctional cytotoxic phenotype, expressing IFNγ, TNF, granzyme B and CD107a, along with PD-1, consistent with an activated state. Both CD4$^+$ and CD8$^+$ T cell responses were durable and persisted up to1 year post-prime vaccination. Only minimal or no increases in HPV specific responses were observed in pts treated with placebo. After a median follow-up of 1 year, no pt presented disease relapse. HPVct DNA monitoring will be presented at the meeting. **Conclusions:** The safety and immunogenicity of CD40.HVac support further clinical development of this strategy in pts with HPV16+ OPC. Clinical trial information: NCT06007092. Research Sponsor: EnnoDC.

6019 Rapid Oral Abstract Session

Phase II study of izalontamab (SI-B001) in combination with paclitaxel or docetaxel in patients with recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). First Author: Ye Guo, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China

Background: Izalontamab is a bispecific antibody targeting EGFR and HER3. Here we present safety and efficacy results from a phase II study on izalontamab in combination with paclitaxel/docetaxel in patients with R/M HNSCC. **Methods:** Patients with R/M HNSCC who had progressed on prior anti-PD-(L)1 therapy, with or without platinum-based chemotherapy, and received no more than two prior lines of treatment were enrolled. Izalontamab was administered at 12mg/kg QW in combination with paclitaxel (80mg/m^2 IV QW) (for patients without prior exposure to paclitaxel) or docetaxel (35mg/m^2 IV D1D8D15 Q4W) (for patients with prior exposure to paclitaxel). Primary endpoint was investigator-assessed ORR. Secondary endpoints included PFS, OS, DCR, and DoR. **Results:** As of Nov 7, 2025, a total of 45 patients (44 HNSCC and 1 sinnonasal) were enrolled, of whom 35 (77.8%) received one prior line of therapy and 10 (22.2%) received two prior lines of therapy. HNSCC patients who received at least one dose of study drug were included in the analysis. Median follow-up was 15.0 months. Overall, ORR was 43.2%, confirmed ORR was 31.8%, median PFS was 4.0 months, and median OS was 10.0 months. In patients treated with izalontamab combo with paclitaxel (n = 34), ORR was 52.9%, confirmed ORR was 41.2%, median PFS was 5.4 months, and median OS was 11.2 months. Grade$\geq$3 TRAEs occurred in 57.8% of patients. The most common grade$\geq$3 TRAE was leukopenia (20.0%), followed by neutropenia (15.6%), rash (13.3%), and anemia (8.9%). One (2.1%) patient discontinued study treatment due to TRAE. No treatment-related death was observed. **Conclusions:** Izalontamab in combination with paclitaxel showed encouraging antitumor activity and a manageable safety profile in patients with R/M HNSCC who were previously treated with anti-PD-(L)1 therapy. Clinical trial information: NCT05054439. Research Sponsor: Sichuan Baili Pharmaceutical Co., Ltd.

	Izalontamab+Paclitaxel (N=34)	Izalontamab+ Docetaxel (N=10)	Total (N=44)
ORR, % (95% CI)	52.9 (35.1, 70.2)	10.0 (0.3, 44.5)	43.2 (28.3, 59.0)
cORR, % (95% CI)	41.2 (24.6, 59.3)	0	31.8 (18.6, 47.6)
DCR, % (95% CI)	73.5 (55.6, 87.1)	30.0 (6.7, 65.2)	63.6 (47.8, 77.6)
Median DOR (mo) (95% CI)	5.0 (3.7, 11.0)	NR (NR, NR)	5.0 (3.7, 11.0)
Median PFS (mo) (95% CI)	5.4 (3.9, 6.6)	1.5 (0.4, 3.6)	4.0 (2.8, 5.5)
Median OS (mo) (95% CI)	11.2 (6.6, 19.3)	6.6 (0.4, 13.8)	10.0 (6.6, 13.8)

6020 Rapid Oral Abstract Session

FID-007 in combination with cetuximab in recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). First Author: Guilherme Rabinowits, Moffitt Cancer Center, Tampa, FL

Background: Paclitaxel is commonly used to treat HNSCC but is associated with infusion-related reactions and peripheral neuropathy (PN). Historically, the median progression-free survival (PFS) of standard of care, second line therapy for metastatic HNSCC is 2-3 months (mo). FID-007 is a novel nanoencapsulated paclitaxel utilizing a proprietary poly(2-ethyl-2-oxazoline) polymer excipient. This formulation overcomes the limited water solubility and pharmacodynamics of paclitaxel, enhancing both tumor penetration and retention. **Methods:** FID-007-003 is an ongoing phase 2, randomized, multicenter, open-label study. Patients must have progressed after anti-PD1/PD-L1 therapy and have not received >1 line of prior therapy for R/M HNSCC. Prior cetuximab or taxane in the R/M setting were not allowed. Patients were stratified by p16 status and prior taxane exposure, and randomized 1:1 to one of two doses of FID-007 (Arm A: 75 mg/m^2; Arm B: 125 mg/m^2) IV on days 1, 8, and 15 in combination with cetuximab 500 mg/m^2 IV on days 1 and 15 every 28 days starting with Cycle 2. The primary endpoint was investigator-assessed objective response rate (ORR) by RECIST 1.1. **Results:** As of the preliminary data cut-off date of 20DEC2025, 45 patients were randomized and received ≥ 1 dose of FID-007; 42 patients were efficacy-evaluable (19 in Arm A, 23 in Arm B). Median age was 65 years (range 45-81), 62% (28/45) received prior platinum-based therapy and 67% (30/45) received 1 prior systemic therapy for R/M disease. The median cumulative dose of FID-007 was 825 mg/m^2 in Arm A and 1,450 mg/m^2 in Arm B. The median duration of treatment was 4 mo in Arm A and 4.3 mo in Arm B, with a median follow-up of 4.2 mo. The ORR/complete response (CR) rate was 60%/17% (58%/11% in Arm A, 61%/22% in Arm B), and the median PFS was 7.2 mo [6.7 mo in Arm A (2.0-12.8), and 7.2 mo in Arm B (4.0-NR)]. The median duration of response was 7.4 mo (7.4 mo in Arm A, NR in Arm B) with 56% (14/25) of responders continuing to respond at the time of data cut-off. The overall survival data are immature at present. Treatment-related adverse events (TRAEs) were mostly of grade 1-2. Grade 3-4 TRAEs occurring in ≥ 2 patients included neutropenia (3 in Arm A, 5 in Arm B), anemia (2 in Arm A, 4 in Arm B), leukopenia (3 in Arm B), acneiform dermatitis (2 in Arm A), maculo-papular rash and other rash (2 in Arm B). There was 1 Grade 5 TRAE: pneumonia (Arm B). **Conclusions:** FID-007, administered in combination with cetuximab, demonstrated clinically encouraging and durable anticancer activity at both doses tested in this population of pre-treated R/M HNSCC. Notably, the absence of infusion-related reactions and the lack of grade ≥ 3 PN, along with a tolerable safety profile potentially compares favorably with other taxanes, which may ultimately enable a longer treatment duration and lead to improved therapeutic outcomes. Clinical trial information: NCT06332092. Research Sponsor: Fulgent Pharma.

6021 Rapid Oral Abstract Session

Nivolumab plus lenvatinib for unresectable anaplastic thyroid cancer: Results of the phase 2 NAVIGATION study. First Author: Makoto Tahara, National Cancer Center Hospital East, Kashiwa, Japan

Background: Anaplastic thyroid cancer (ATC) is one of the most aggressive and lethal malignancies, characterized by limited treatment options and a dismal prognosis. Although lenvatinib has shown some efficacy, its impact remains modest, and no standard systemic therapy has been established for unresectable ATC—particularly for BRAF wild-type (BRAF-negative) disease. **Methods:** The NAVIGATION study (NCT05696548) is an open-label, multicenter, phase 2 trial evaluating the combination of nivolumab and lenvatinib in patients with unresectable ATC. As primary endpoints, Step 1 assessed dose-limiting toxicities (DLTs), while Step 2 evaluated the objective response rate (ORR) by independent radiological central review (IRCR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), best overall response, disease control rate, clinical benefit rate, safety, and quality of life. Eligible patients had histologically confirmed unresectable ATC, measurable disease per RECIST v1.1, adequate organ function, an ECOG performance status of 0–1, and a life expectancy of over 90 days. Lenvatinib was administered orally at 24 mg once daily, and nivolumab intravenously at 240 mg every two weeks, continued until disease progression or unacceptable toxicity. The Step 2 sample size of 48 patients was determined based on a historical ORR of 23.5% and an expected ORR of 44%, providing 80% power with a two-sided α of 0.05, accounting for a 20% dropout rate. ORR was evaluated in the full analysis set of patients with ATC confirmed by independent pathological central review (IPCR). **Results:** Between December 2019 and February 2024, 51 patients were enrolled across 10 sites in Japan (Step 1: n=3; Step 2: n=48). No DLTs were observed in Step 1. In Step 2, the median age was 69.5 years (range, 43-89); 46 patients had metastatic disease, 40 had prior history of surgery, and 42 were pathologically confirmed as ATC by IPCR. The ORR by IRCR was 47.6% (95% CI: 33.4-62.3), meeting the primary endpoint. At a median follow-up of 11.6 months, the median duration of response was 12.9 months (95% CI: 6.28 -27.6), median PFS was 5.6 months (95% CI: 5.5-9.1), and median OS was 14.7 months (95% CI: 10.1-29.2). The 1-year OS rate was 56.9%. In Step 2, grade 3 or 4 treatment-related adverse events (TRAEs) occurred in 38/48 patients (79.2%), serious TRAEs in 20 (41.7%), and there was one treatment-related death (2.1%). **Conclusions:** Nivolumab plus lenvatinib demonstrated a clinically meaningful ORR, meeting the primary endpoint. The combination also achieved favorable PFS and OS with manageable toxicity under appropriate supportive care, suggesting that this regimen may represent a new treatment option for patients with unresectable ATC. Clinical trial information: NCT05696548. Research Sponsor: None.

6022 Poster Session

Whole slide imaging–based prediction of immunohistochemistry markers and surgical pathological features. First Author: Yusuf Sadek, The Ohio State University, Columbus, OH

Background: Immunohistochemistry (IHC) marker testing and identification of pathological features are essential tasks in surgical pathology following resection of head and neck cancers. However, IHC testing is time-consuming, and identifying pathologic features typically requires examination of multiple slides. We hypothesized that imaging features from a single H&E-stained whole slide image (WSI) could predict this information using machine learning. **Methods:** We utilized data from the publicly available HANCOCK dataset for machine learning model development and testing. All patients had undergone surgical resection for locoregional head and neck cancer. Image features (embeddings extracted by TITAN, a pretrained vision-language pathology foundation model) from each primary tumor's H&E-stained WSI served as model inputs. Four machine learning algorithms (XGBoost, support vector machine, multilayer perceptron, and random forest) were trained to predict seven IHC markers (CD3, CD8, CD56, CD68, CD163, MHC-I, PD-L1) and three surgical pathological features (tumor grading, lymphovascular invasion, and perineural invasion). IHC marker positivity was determined using DeepLIIF-derived percent-positive staining, with non-PD-L1 markers binarized by median split and PD-L1 positivity defined using a 10% threshold. Surgical pathological features were binary except for tumor grade, which included four classes. All models underwent nested stratified five-fold cross-validation with hyperparameter tuning. Performance was assessed using AUC and F1 score for binary tasks (IHC markers, lymphovascular invasion, perineural invasion), and balanced accuracy and macro-F1 score and for tumor grading. **Results:** Between 685 and 699 cases were available for model development depending on the prediction task. Support vector machine (SVM) was the best-performing model for five tasks, followed by XGBoost (XGB) for three tasks and random forest (RF) for two tasks. Performance metrics for the best-performing models are detailed in the table. **Conclusions:** Our findings demonstrate that IHC markers and surgical pathological features can be predicted with reasonable accuracy from image features extracted from a single H&E-stained WSI. Future work will focus on external validation of these models in independent cohorts and exploration of advanced foundational models to further improve prediction performance. Research Sponsor: None.

Task	Best Model	Metrics
CD3	XGB	AUC: 0.78 ± 0.04 F1: 0.72 ± 0.03
CD8	SVM	AUC: 0.73 ± 0.03 F1: 0.67 ± 0.04
CD56	XGB	AUC: 0.66 ± 0.03 F1: 0.67 ± 0.02
CD68	SVM	AUC: 0.75 ± 0.03 F1: 0.70 ± 0.04
CD163	SVM	AUC: 0.71 ± 0.05 F1: 0.67 ± 0.04
MHC1	SVM	AUC: 0.68 ± 0.05 F1: 0.66 ± 0.03
PDL1	SVM	AUC: 0.73 ± 0.06 Macro F1: 0.54 ± 0.04
Grading	RF	Balanced Acc: 0.71 ± 0.04 Macro F1: 0.70 ± 0.03
Lymphovascular Invasion	RF	AUC: 0.82 ± 0.02 Macro F1: 0.70 ± 0.02
Perineural Invasion	XGB	AUC: 0.78 ± 0.03 Macro F1: 0.67 ± 0.03

6023 Poster Session

Development and multicenter validation of a machine learning framework for predicting severe myelosuppression in nasopharyngeal carcinoma: Evidence from large-scale real-world data and prospective clinical trials. First Author: Tingxi Tang, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

Background: Severe treatment-related myelosuppression (Tr-MS) in nasopharyngeal carcinoma (NPC) necessitates dose reductions, compromising survival. Current static models rely on baseline "snapshots," failing to capture dynamic bone marrow fluctuations. We developed a dynamic deep learning system using longitudinal real-world data to predict cycle-specific Tr-MS risk. **Methods:** We analyzed 103,919 longitudinal records from 12,065 NPC patients (Nanfang/SYSUCC). A rolling-window strategy incorporated dynamic pre-dose labs, prior-cycle nadirs, and cumulative exposure to predict Grade ≥3 Tr-MS (CTCAE v6.0). Models (Logistic/XGBoost/LightGBM/TabPFN) were trained (6:3:1 split) and validated in two independent external cohorts (n=197) and three prospective trials (NCT03919552, NCT06767488, NCT06017895; n=173). The model was deployed as an EHR-integrated tool for automated real-time risk stratification. **Results:** Dynamic models demonstrated robust discrimination across all validation hierarchies (Table). In internal validation, AUCs ranged from 0.84 to 0.96. Performance remained stable in external cohorts (AUC 0.75-0.87) and prospective trials (AUC 0.79-0.86). SHAP analysis identified cumulative chemotherapy dosage and prior-cycle nadirs as dominant risk factors. Notably, the HIS-integrated tool successfully automated data retrieval, eliminating manual entry burden. **Conclusions:** This first EHR-integrated, cycle-specific dynamic system for Tr-MS in NPC captures longitudinal marrow exhaustion, enabling a shift from reactive rescue to precise, proactive prevention. Research Sponsor: National Natural Science Foundation of China; NO.82303684; Medical Scientific Research Foundation of Guangdong Province; B2021449; China Postdoctoral Science Foundation; NO. 2023M741560; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503000; Noncommunicable Chronic Diseases-National Science and Technology Major Project; 2023ZD0503005; National Natural Science Foundation of China; NO.82272729; China Postdoctoral Science Foundation; NO. 2025M782041; Guangdong Basic and Applied Basic Research Foundation; NO. 2022A1515010509; Guangdong Basic and Applied Basic Research Foundation; NO. 2024A1515010280; Clinical Research Startup Program of Southern Medical University by High-level University Construction Funding of Guangdong Provincial Department of Education; LC2016PY015; Clinical Research Startup Program of Southern Medical University by High-level University Construction Funding of Guangdong Provincial Department of Education; LC2019ZD008; Clinical Research Program of Nanfang Hospital, Southern Medical University; 2018CR021; Clinical Research Program of Nanfang Hospital, Southern Medical University; 2020CR025.

Performance of dynamic prediction models across validation cohorts.

Endpoint	Cohort	AUC (95% CI)	Sens	Spec
Anemia	Internal (n=1,231)	0.96 (0.96-0.98)	0.91	0.91
Anemia	External (n=197)	0.87 (0.85-0.89)	0.89	0.86
Anemia	Prospective (n=173)	0.86 (0.82-0.89)	0.88	0.86
PLT	Internal (n=1,231)	0.90 (0.87-0.92)	0.79	0.84
PLT	External (n=197)	0.80 (0.77-0.81)	0.81	0.82
PLT	Prospective (n=173)	0.81 (0.80-0.83)	0.80	0.83
WBC/Neut	Internal (n=1,231)	0.84 (0.82-0.85)	0.71	0.79
WBC/Neut	External (n=197)	0.75 (0.73-0.77)	0.69	0.77
WBC/Neut	Prospective (n=173)	0.79 (0.77-0.81)	0.69	0.78

Abbreviations: AUC, area under the ROC curve; PLT, thrombocytopenia; WBC/Neut, leukopenia/neutropenia; Sens, sensitivity; Spec, specificity.

6024 **Poster Session**

AI-powered assessment of tertiary lymphoid structures (TLS) from H&E whole-slide images as a prognostic tool in HNSCC. First Author: Jiyoon Lim, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Tertiary lymphoid structures (TLS) are recognized prognostic markers in Head and Neck Squamous Cell Carcinoma (HNSCC), yet manual assessment from H&E whole-slide images (WSI) remains subjective and labor-intensive, limiting clinical utility. This highlights the need for a reproducible and objective AI-based approach to TLS assessment using routine H&E slides. **Methods:** We conducted an integrative analysis by combining transcriptomic and histopathologic data. TCGA HNSCC mRNA expression data (n = 566) were analyzed using xCell to compute enrichment scores for B cells, T cells (CD4+ and CD8+), and dendritic cells. A TLS enrichment score was calculated by averaging the z-standardized aggregate scores of these lineages. Patients in the top and bottom quartiles were labeled 'TLS enriched' and 'non-enriched,' respectively; these labels were used to train a foundation model-based AI using Imagene's OI Suite powered by CanvOI with a 3:1 train–test split. Survival analyses were performed at the patient level in 443 evaluable patients with high-quality H&E whole-slide images and definitive AI-predicted TLS enrichment status. Univariable and multivariable Cox regression evaluated AI-predicted TLS enrichment as an independent predictor of overall survival. **Results:** The AI model demonstrated robust performance for TLS assessment, achieving an AUC of 0.77 in the training set (n = 332, 75%) and AUC of 0.85 in the test set (n = 111, 25%). Kaplan–Meier analysis showed that among 443 patients, the AI-predicted TLS-enriched (TLS+) group (n = 146, 33%) demonstrated improved overall survival compared with the TLS-non-enriched (TLS-) group (n = 297, 67%), with median OS 57.9 vs 35.4 months (HR 0.72; 95% CI 0.53–0.98; log-rank P = 0.039). After adjustment for age, sex, and stage, AI-predicted TLS enrichment remained independently associated with improved overall survival (HR, 0.73; 95% CI, 0.54–1.00; P = 0.0499). These findings suggest that the AI model successfully translates molecular TLS signatures into histological predictors, capturing critical tumor microenvironment (TME) features that refine risk stratification beyond standard clinicopathologic factors. **Conclusions:** AI-based H&E WSI analysis helps identify TLS enrichment as a potential predictor of overall survival in HNSCC. This unbiased computational approach provides a reproducible and objective methodology using H&E slides alone, without the need for additional molecular or immunohistochemical assays, thereby supporting immune risk stratification for precision immunotherapy, particularly in resource-limited settings. Research Sponsor: None.

6025 **Poster Session**

Volrustomig monotherapy for recurrent/metastatic HNSCC: Substudy 2 of the eVOLVE-02 phase 2 study. First Author: Ye Guo, Department of Oncology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China

Background: Inhibition of PD-1 is an important part of standard of care treatment options for patients (pts) with recurrent/metastatic (R/M) HNSCC, but prognosis remains poor and there is a need for novel regimens to improve outcomes. Dual PD-(L)1 and CTLA-4 inhibition has shown a trend towards improved survival vs the EXTREME regimen as first-line (1L) therapy in PD-L1-expressing R/M HNSCC. Volrustomig, a monovalent, bispecific, humanized IgG1 monoclonal antibody, inhibits PD-1 and CTLA-4, with increased CTLA-4 blockade on PD-1-positive activated T cells compared to PD-1-negative resting peripheral T cells. We report safety and efficacy from the planned interim analysis of substudy 2 of the phase 2 eVOLVE-02 (NCT06535607) study, investigating volrustomig monotherapy in pts with R/M HNSCC. **Methods:** Eligible pts had histologically or cytologically confirmed R/M HNSCC of the hypopharynx, oral cavity, larynx, or oropharynx (HP, OC, LX, OP), had ECOG performance status (PS) 0/1, and were either treatment-naïve in the 1L setting with confirmed PD-L1 positivity or had disease progression (PD) on/after a 1L platinum-containing regimen. Pts received IV volrustomig until PD (RECIST v1.1)/discontinuation criteria were met. Primary endpoints: safety and confirmed objective response rate (cORR). Secondary endpoints include progression-free survival (PFS) and overall survival. Data cutoff (DCO): August 15, 2025. **Results:** 23 pts with recurrent (n=12) or metastatic (n=11) HNSCC (7 HP, 8 OC, 4 LX, 4 OP) received volrustomig as 1L (n=12) or 2L (n=11) treatment. Median age was 61 years; 16 pts (69.6%) had PS 1; 19 (82.6%) had a PD-L1 combined positive score (CPS) ≥1. Median duration of exposure was 2.1 months (range 0.7–6.4). Treatment-emergent adverse events (TEAEs) were reported in 91.3% of pts (30.4% grade 3/4, 34.8% serious TEAEs); treatment-related AEs per investigator were reported in 82.6% (8.7% grade 3/4, 4.3% serious AEs). No pts discontinued treatment due to AEs. Grade 5 AEs were reported in 13.0% of pts (none considered related to treatment). At DCO, median follow-up was 5.4 months. In pts with CPS ≥1: 5 had partial responses (3 LX, 1 HP, 1 OC); cORR was 26.3%; disease control rate was 52.6%. Median time to response was 2.6 months (IQR 1.4–2.8); responses were ongoing in 60% of responders at DCO. Blood RNA seq showed increased CTLA-4-associated immune proliferation/activation (Ki67/ICOS gene expression) with volrustomig on cycle 1, day 8 vs at baseline. **Conclusions:** Volrustomig monotherapy showed an acceptable safety profile and encouraging activity in pts with R/M HNSCC, warranting further clinical development. Volrustomig is under investigation in combination with chemotherapy as 1L treatment for R/M HNSCC in the phase 2 eVOLVE-02 substudy 3, and as consolidation monotherapy in locally advanced HNSCC after concurrent chemoradiotherapy in the phase 3 eVOLVE-HNSCC (NCT06129864) study. Clinical trial information: NCT06535607. Research Sponsor: AstraZeneca.

6026 **Poster Session**

An open-label, randomized phase 2 trial of ramucirumab and pembrolizumab versus pembrolizumab as first-line therapy for PD-L1–positive, recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC). First Author: Christine Auberle, Washington University in St. Louis, St. Louis, MO

Background: Vascular endothelial growth factor (VEGF) is commonly overexpressed in head and neck squamous cell carcinoma (HNSCC). Combination therapies inhibiting VEGF and PD-(L)1 have improved efficacy outcomes compared to PD-(L)1 inhibitors alone in pre-clinical models and in other cancer types. The hypothesis of this randomized phase 2 trial in RM-HNSCC was the objective response rate (ORR) with ramucirumab (a VEGF-2 inhibitor) and pembrolizumab would be higher than pembrolizumab alone. **Methods:** Eligible patients had untreated RM-HNSCC with PD-L1 CPS >1, an ECOG performance status of 0 or 1, and adequate organ function. RM disease within 6 months of curative-intent systemic therapy was permitted. Patients were randomized (stratification factors: HPV status [+ or -] and PD-L1 CPS [1-19 or ≥20]) 2:1 to ramucirumab 10mg/kg and pembrolizumab 200mg (Arm 1) or pembrolizumab (Arm 2) given on Day 1 of each 3-week cycle. The primary endpoint was tumor response as assessed with RECIST v1.1 by BICR. A two-stage group sequential design was used with an O'Brien-Fleming stopping rule to accept the null hypothesis at a one-sided alternative hypothesis. We hypothesized an ORR of ≥50% in Arm 1 and ≤19% in Arm 2. The required sample sizes for stage 1 and stage 2 to obtain 80% power at the type I error of 5% were 36 and 72, respectively. At the end of stage 1, if the standardized Z test statistic was ≥0.453, the study could proceed to stage 2. Otherwise, the study was to be stopped, and the null hypothesis accepted. Secondary endpoints include duration of response (DoR), progression free survival (PFS), overall survival (OS) and adverse events. Here, the results of the interim analysis are reported per protocol. **Results:** Thirty-seven patients were enrolled and treated in stage 1. Median age was 65 years (IQR 60-70), 76% were male, and tumor characteristics (including status of HPV and PD-L1 CPS and prior systemic therapy within 6 months) were balanced between the two arms. The ORR was 28% (7 of 25 patients, 95% CI: 12.1-49.4%) in Arm 1 and 33.3% (4 of 12 patients, 95% CI: 9.9-65.1%) in Arm 2 [z= -0.327]. The null hypothesis was accepted, and the trial did not proceed to stage 2. **Conclusions:** Among patients with previously untreated PD-L1 positive, RM-HNSCC, ramucirumab and pembrolizumab did not result in a higher ORR than pembrolizumab. Clinical trial information: NCT05980000. Research Sponsor: Joseph Sanchez Foundation; Eli Lilly.

6027 **Poster Session**

Phase 1 basket study of telisotuzumab adizutecan (Temab-A, ABBV-400), a c-Met protein–targeting antibody-drug conjugate: Results from patients with head and neck squamous cell carcinoma (HNSCC). First Author: Victoria Meucci Villaflor, University of California, Irvine Health Chao Family Comprehensive Cancer Center, Orange, CA

Background: c-Met protein is expressed in several tumor types, including HNSCC, and is associated with a poor prognosis. Temab-A comprises a c-Met protein-targeting antibody conjugated to a topoisomerase 1 inhibitor. Phase 1 studies evaluating Temab-A monotherapy in solid tumors showed antitumor activity and a manageable safety profile (NCT05029882, NCT06084481). Here, we report on the efficacy and safety of Temab-A in HNSCC. **Methods:** This phase 1, open-label basket study (NCT06084481) enrolled patients (pts) ≥18 years with histologically/cytologically confirmed locally advanced or recurrent/metastatic, unresectable HNSCC, with Eastern Cooperative Oncology Group performance score ≤1. Pts must have had measurable disease per RECIST v1.1 criteria, and disease progression following ≥1 line of systemic therapy in the advanced/metastatic setting. Pts were platinum-resistant or deemed ineligible/unfit for platinum-based therapy per investigator. Prior checkpoint inhibitor treatment was required, unless contraindicated. Pts received 2.4 or 3.0 mg/kg Temab-A every 3 weeks. Primary objectives were safety and efficacy. **Results:** As of Sept. 11, 2025, 43 pts with HNSCC received Temab-A. The median age was 64 years (range 20–85). Median number of prior lines of systemic therapy was 3 (range 1–12), and median follow-up was 12 months. Objective response rate (ORR) was 21%; duration of response and overall survival were immature at data cutoff. Efficacy data are shown in the Table. The most common treatment-related adverse events (TRAEs) of any Grade (G) included fatigue (51%), anemia (49%), and nausea (40%). TRAEs G ≥3 occurred in 47% of pts. G ≥3 TRAE occurring in ≥10% of pts was anemia (33%). The adjudicated interstitial lung disease/pneumonitis rate was 9.3% (G1, n=2; G2, n=1; G3, n=1). TRAEs led to treatment discontinuation in 12%, dose interruption in 30%, and dose reduction in 26% of pts. There was 1 TRAE that led to death. Exploratory biomarker analyses are ongoing. Pharmacokinetics of Temab-A in HNSCC were consistent with other tumor types. The half-life of the conjugate and payload was 4 and 13 days, respectively. **Conclusions:** Temab-A had a manageable safety profile and showed encouraging antitumor activity in advanced HNSCC. Clinical trial information: NCT06084481. Research Sponsor: AbbVie Inc.

Temab-A efficacy.[a]

Outcome	Pts with HNSCC (N=43)
Best overall response, n (%)	
Complete response	0
Partial response	11 (26)
Stable disease	22 (51)
Progressive disease	7 (16)
Not assessed[b]	3 (7)
Objective response rate[c], n (%)	9 (21)
95% CI	10, 36
Clinical benefit rate[c], n (%)	33 (77)
95% CI	61, 88
Median progression-free survival, months (95% CI)	4.3 (3.8, 5.4)

[a]Responses were assessed by investigators per RECIST v1.1 criteria.
[b]Pts without postbaseline scan.
[c]Confirmed.
CI, confidence interval.

6028 Poster Session

Efficacy and safety of pralsetinib in advanced or metastatic *RET*-altered thyroid cancer (TC): Final analysis of the phase 1/2 ARROW study. First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center and Sarah Cannon Research Institute, Houston, TX

Background: *RET* alterations are targetable oncogenic drivers in multiple solid tumors and TCs. Pralsetinib is an oral, potent, selective RET inhibitor granted accelerated approval by the FDA for adults and children aged ≥12 y with advanced/metastatic *RET* fusion-positive TC who require systemic therapy and are radioactive iodine-refractory, based on ARROW trial (NCT03037385) results. Accelerated approval for medullary TC (MTC) was withdrawn by the sponsor in 2023 due to recruitment challenges in the confirmatory trial. We report final efficacy and safety in ARROW patients with *RET*-altered TC and MTC. **Methods:** Phase 2 ARROW patients were enrolled from 84 sites in 13 countries. Primary end points were overall response rate (ORR; per RECIST v1.1) and safety. Progression-free survival (PFS), overall survival (OS), and safety were assessed in patients with advanced/metastatic TC and MTC who received ≥1 dose of pralsetinib (Efficacy Population [EP]). ORR and duration of response (DOR) were assessed in the Measurable Disease Population (MDP). **Results:** At the May 20, 2024, data lock, 28 patients with *RET*-altered TC and prior systemic treatment and 145 patients with *RET*-altered MTC received pralsetinib 400 mg/d (median treatment duration: 24.7 mo [TC]; and 35.4 mo [MTC]). In the TC and MTC groups, median age was 58 and 57 y; 39% and 64% were male; median (range) prior lines of treatment was 2 (1, 9) and 1 (1, 6). 53.8% of MTC patients had prior systemic treatment. In TC and MTC patients, ORRs (95% CI) were 91.7% (73.0, 99.0) and 68.2% (59.5, 76.0) (Table). Treatment-related adverse events (TRAEs) occurred in 27 (96%) TC and 142 (98%) MTC patients; 68% and 67% had grade ≥3. TRAEs in ≥35% of TC and MTC patients were increased AST (50% and 38%) and ALT (43% and 30%), decreased white blood cell count (39% and 30%), and anemia (39% each). Death due to a TRAE occurred in 1 TC patient (liver injury) and 1 MTC patient (pneumonia). Safety was consistent with prior reports. **Conclusions:** The final analysis of ARROW confirms that pralsetinib yields clinically meaningful and durable responses in patients with *RET*-altered TC and MTC with a manageable safety profile consistent with prior reports. Clinical trial information: NCT03037385. Research Sponsor: Rigel Pharmaceuticals, Inc.

Efficacy summary.

	All MTC	MTC Prior Cabozantinib/ Vandetanib	MTC Treatment-Naïve	TC Prior Systemic Treatment
MDP, n	132	60	62	24
ORR, % (95% CI)	68.2 (59.5, 76.0)	56.7 (43.2, 69.4)	79.0 (66.8, 88.3)	91.7 (73.0, 99.0)
Complete response, n (%)	12 (9.1)	2 (3.3)	7 (11.3)	4 (16.7)
Partial response, n (%)	78 (59.1)	32 (53.3)	42 (67.7)	18 (75.0)
DOR, median, mo (95% CI)	39.6 (29.4, NE)	21.7 (15.1, 34.8)	NR (36.8, NE)	NR (16.0, NE)
DOR follow-up, median, mo (95% CI)	45.7 (41.0, 48.4)	48.9 (36.9, 58.7)	45.1 (40.4, 47.8)	35.4 (26.9, 40.0)
EP, n	145	67	67	28
OS, median, mo (95% CI)	NR (54.6, NE)	42.2 (31.2, NE)	NR (NE, NE)	NR (25.4, NE)
PFS, median, mo (95% CI)	37.2 (27.5, 55.5)	24.9 (19.9, 35.0)	55.3 (36.8, NE)	NR (14.7, NE)

NE, not evaluable; NR, not reached.

6029 Poster Session

Penpulimab (AK105) combined with cetuximab as first-line treatment in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): A phase II clinical trial. First Author: Shu Tian, Eye & ENT Hospital of Fudan University, Shanghai, Shanghai, China

Background: Combination therapy with PD-1 and EGFR inhibitors has shown promising efficacy in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). This open-label, single-arm, multicenter phase II study aimed to evaluate the efficacy and safety of penpulimab (an anti-PD-1 monoclonal antibody) plus cetuximab as first-line treatment in this patient population (NCT05260671). **Methods:** Eligible patients had R/M HNSCC with no prior immunotherapy or EGFR inhibitor exposure. Participants were either treatment-naïve for systemic therapy or had received platinum-based neoadjuvant/adjuvant or chemoradiotherapy more than 6 months before enrollment. All patients received cetuximab 500 mg/m² intravenously as a lead-in dose on day −14, followed by cetuximab 500 mg/m² plus penpulimab 200 mg intravenously on days 1 and 15 of each 28-day cycle. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between March 15, 2022, and January 19, 2026, 31 patients were enrolled. The median follow-up was 20.13 months (95% CI: 15.6–NA). Of these, 29 patients were evaluable for efficacy. The ORR was 44.8% (13/29), and the DCR was 82.8% (24/29). Four patients (13.8%) achieved a complete response (CR). The median DOR was 12.1 months (95% CI: 6.13–NA). For the entire cohort, median PFS was 6.0 months (95% CI: 4.3–18.3), with a 12-month PFS rate of 35.6%. Median OS was 29.1 months (95% CI: 18.2–NA), and the 12-month OS rate was 72.4%. Treatment-related adverse events (TRAEs) occurred in 29 patients (93.5%). Grade ≥3 TRAEs were observed in 4 patients (12.9%), including acneiform rash (6.5%), anemia (3.2%), and oral mucositis (3.2%). No fatal TRAEs were reported. **Conclusions:** The combination of penpulimab and cetuximab demonstrated favorable clinical efficacy and a manageable safety profile in patients with R/M HNSCC, supporting its potential as a first-line treatment option. Trial Registration: NCT05260671. Ethics Approval: This study was approved by the Ethics Committee for Drug Clinical Trials of the Eye & ENT Hospital of Fudan University (Approval No. [20211141-1], 2022). All participants provided written informed consent prior to enrollment. Clinical trial information: NCT05260671. Research Sponsor: Bethune Foundation Colorectal Cancer and Head & Neck Cancer Medical Seed Research Grant.

6030 Poster Session

Real-world efficacy and safety of photoimmunotherapy for recurrent nasopharyngeal carcinoma: A nationwide multicenter study in Japan. First Author: Hideki Tanaka, Department of Otolaryngology, Head and Neck Surgery, Tokyo Medical University, Tokyo, Japan

Background: Treatment options for locally recurrent or residual nasopharyngeal carcinoma (NPC) after definitive radiotherapy remain limited. Salvage surgery is often challenging due to anatomical constraints, while re-irradiation and systemic therapies provide modest efficacy with substantial toxicity. Photoimmunotherapy (PIT) is a light-activated anticancer treatment targeting epidermal growth factor receptor (EGFR) that has been approved in Japan since September 2020 for unresectable locally advanced or locally recurrent head and neck cancers. However, real-world clinical data on PIT for recurrent NPC are limited. We conducted the NPC-PIT Study, a nationwide observational study evaluating the real-world efficacy and safety of PIT in patients with recurrent NPC. **Methods:** Patients with recurrent or residual NPC treated with PIT were enrolled from 26 institutions. Patients with at least 3 months of follow-up after initial PIT were evaluated. Clinical characteristics, prior treatments, PIT illumination techniques, treatment response, overall survival, EBV-DNA levels, and treatment-related adverse events were analyzed. **Results:** As of November 2025, 46 patients were enrolled. The four cases with follow-up <2 months were excluded from the evaluation. The median follow-up duration was 18.6 months. Seventeen patients received one PIT cycle, 14 received two, 6 received three, and 5 received four sessions. Among the 42 evaluable patients, 29 (69.0%) achieved a complete response (CR) lasting ≥2 months. Twenty patients remain alive with no evidence of disease. Disease-related deaths occurred in 3 patients, and 2 patients died from carotid artery rupture after treatment. Grade ≥3 adverse events were observed in 9 patients (21.4%). The 1-year overall survival rate was 89.7%. Among cases where pre-treatment blood samples were collected, 80% (4/5) showed elevated EBV-DNA levels on Cycle 1 Day 7, suggesting that EBV-DNA levels may reflect biological changes associated with PIT treatment. **Conclusions:** In this nationwide real-world cohort, PIT provided meaningful and long-lasting local control with a manageable safety profile for recurrent NPC. These findings support PIT as a clinically meaningful local treatment option for recurrent NPC and warrant further optimization of patient selection and risk mitigation strategies. Research Sponsor: Rakuten Medical Inc.

6031 Poster Session

***Bacteroides sp. DH3716P* and mediation of immunotherapy response in oligometastatic nasopharyngeal carcinoma via the gut–nasopharyngeal axis.** First Author: Zhenhua Zhou, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: Predictors of benefit from gemcitabine/cisplatin (GP) plus PD-1 blockade in oligometastatic nasopharyngeal carcinoma (OM-NPC) remain limited. We investigated whether baseline gut microbiome features are linked to response through a gut–nasopharyngeal axis. **Methods:** We performed metagenomic sequencing on baseline fecal samples from 69 OM-NPC patients receiving GP chemotherapy combined with PD-1 blockade. β-diversity analyses (PCA, PCoA, NMDS) characterized microbiota compositional differences. LEfSe analysis identified differentially abundant taxa between responders (R) and non-responders (NR). Functional enrichment analyses (KEGG, KO, MetaCyc) determined pathway differences. Co-occurrence network analysis assessed microbiota stability. Single-cell RNA sequencing from 7 tumor specimens was analyzed using SAHMI algorithm to determine bacterial-immune cell interactions. Machine learning models built on microbiota, clinical parameters, and serum biomarkers predicted treatment response. **Results:** Microbiota composition differed significantly between R and NR groups. R group showed significant enrichment of *Enterococcus*, *Megasphaera*, and *Streptococcus*. Functional analysis revealed R group possessed enhanced short-chain fatty acid (SCFA) synthesis, glycolysis, and lipid metabolism pathways. Network analysis demonstrated R group had denser ecological networks with superior stability and functional redundancy compared to NR. At species level, *Bacteroides sp. DH3716P* abundance associated with response and prolonged progression-free survival (PFS). This strain highly expressed SusD/RagB family outer membrane proteins and glycoside hydrolase activities, suggesting xylan degradation pathway activation leading to host glycolysis stimulation and SCFA-mediated immune regulation. scRNA-seq analysis revealed *Bacteroides* predominantly infected CD8+ cells in tumor microenvironment. *Bacteroides+* CD8+ T cells demonstrated enhanced IL-15 pathway activity, activated multiple immune response pathways, and increased sensitivity to ICIs. Cell-cell communication analysis indicated *Bacteroides+* CD8+ T cells recruited proliferative T cell subsets through CCL5-CCR5 axis, promoting sustained CD8+ T-mediated anti-tumor immunity. Integrated machine learning models achieved high accuracy in predicting treatment response (AUC: 0.996, 95% CI: 0.989-1.000). **Conclusions:** *Bacteroides sp. DH3716P* sustains immunotherapy response in OM-NPC through enhanced SCFA production and IL-15-CCL5/CCR5 axis-mediated CD8+ T cell activation and proliferative T cell recruitment in the tumor microenvironment. Our microbiota-derived predictive model (AUC 0.996) establishes a clinically feasible strategy for microbiome-assisted personalized immunotherapy in OM-NPC. Research Sponsor: None.

6032 Poster Session

Stereotactic body radiotherapy combined with chemotherapy and PD-1 inhibitor in oligometastatic nasopharyngeal carcinoma (STOMP): A prospective phase II clinical trial. First Author: Jingjing Miao, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center, Guangzhou, China

Background: To evaluate the efficacy and safety of stereotactic body radiation therapy (SBRT) combined with gemcitibine plus cisplatin (GP) chemotherapy and PD-1 inhibitor in patients with oligometastatic nasopharyngeal carcinoma (NPC), registered on clincialtrials.gov (NCT05524168). **Methods:** Main eligibility criteria included diagnosed as oligometastasis NPC (≤5 lesions), and have ≥1 measurable lesion meeting the RECIST 1.1 criteria. Patients firstly receive SBRT for oligometastatic lesions (6-8Gy/fraction × 3-5 fractions), then receive GP+PD-1 inhibitor for 4-6 cycles followed by PD-1 inhibitor maintenance for 1 year. For patients with primary metastasis, the primary lesion and regional metastatic lymph nodes are given radiotherapy (RT) after completing 4-6 cycles of GP+PD-1 inhibitor. The primary endpoint was the 1-year progression-free survival (PFS) rate. **Results:** Between Nov 2022 to Jun 2025, 41 oligometastasis NPC patients were recruited (Table 1). 23 patients were primary metastases, and 17 had distant metastasis (DM) after receiving chemo-radiotherapy, and 1 had regional relapse and DM. All patients finished SBRT for metastatic lesions followed by GP+PD-1, and 23 patients with primary metastasis also received RT for primary lesions after 6 cycles of GP+PD-1. Then 17 received ≥1 year PD-1 maintenance, 3 discontinued for PD, 1 requested to withdraw, and 20 still under PD-1 maintenance. With the median follow-up time of 17.3 (IQR, 12.9-21.8) months, all these metastatic lesions receiving SBRT controlled well; 7 patients had disease progression, including 1 regional relapse, 4 DM, and 2 loco-regional relapse and DM, and all these lesions were newly developed metastatic lesions except one regional relapse which didn't receive SBRT. The primary endpoint 1-year PFS rate was 92.2% (95%CI, 77.6-97.4%), and the secondary survival endpoints 1-year OS, DMFS and LRRFS rate were 100.0% (95%CI, 100-100%), 92.2% (95%CI, 77.6-97.4%), and 97.5% (95%CI, 83.5-99.6%), respectively. The best objective response rate (ORR) and disease control rate (DCR) before starting PD-1 maintenance were 92.7% and 100%, with 27 got complete response, 11 got partial response and 3 got stable disease. The median value of EBV DNA copies pretreatment was 743 (IQR, 151.5-5331.0) copies/ml, then decreased to 0 (IQR, 0-0) copies/ml post 6 cycles of GP+PD-1. No grade 5 therapeutic toxicity was observed in this trial. **Conclusions:** Patients with oligometastatic NPC who receive SBRT for metastatic lesions combined with GP and PD-1 inhibitor could achieve good therapeutic effects with acceptable toxicities. Clinical trial information: NCT05524168. Research Sponsor: Young Talents Program of Sun Yat-sen University Cancer Center; Sun Yat-sen University Cancer Center 308 Program.

Basic information.

Characteristic		N (%)
Median age (IQR), year		48 (39-54)
Sex	Female	13 (31.7)
	Male	28 (68.3)
ECOG, points	0	4 (9.8)
	1	37 (90.2)
Number of metastases lesions	1-2	33 (80.5)
	3-4	8 (19.5)
Number of metastases organs	1	31 (75.6)
	2	10 (24.4)

6033 Poster Session

Cadonilimab in combination with chemotherapy versus chemotherapy alone in patients with immunotherapy-refractory recurrent or metastatic nasopharyngeal carcinoma: A multicenter, randomized, phase III trial the CONQUEST trial). First Author: Shuiqing He, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Chemotherapy combined with immune checkpoint inhibitors (ICIs) is the standard first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC); however, resistance is common. In the post-ICI setting, prospective trials have demonstrated limited efficacy, with objective response rates (ORRs) ranging from 4.2% to 34.3%. A prior phase II study of nab-paclitaxel, cisplatin, and capecitabine (TPC) plus cadonilimab demonstrated a promising ORR of 68% in ICI-refractory patients, providing the rationale for this phase III trial comparing TPC plus cadonilimab versus TPC alone in this population. **Methods:** In this randomized, multicenter, phase III trial, patients were assigned (1:1) to receive TPC plus cadonilimab or TPC alone. TPC consisted of nab-paclitaxel 200 mg/m² d1, cisplatin 60 mg/m² d1, and capecitabine 1000 mg/m² BID d1–14 (Q3W). In the experimental arm, cadonilimab (10 mg/kg d1) was added. Maintenance with capecitabine plus cadonilimab (experimental) or capecitabine alone (control) continued until disease progression, unacceptable toxicity, or 2 years. The primary endpoint was progression-free survival (PFS), defined as the time from randomization to disease progression or death from any cause. Secondary endpoints included overall survival (OS), ORR (defined as the best overall response), and safety. **Results:** A total of 84 patients were randomized (n=42/arm) at three hospitals. Baseline prior therapies were balanced (*P*=0.533): 35 (83.3%) patients in the experimental arm and 37 (88.1%) in the control arm had received 1-3 prior lines of therapy, while 7 (16.7%) and 5 (11.9%) had received >3 prior lines, respectively. After a median follow-up of 10.2 months, PFS was significantly prolonged in the experimental arm versus the control arm (8.9 months [95% CI 6.3-11.4] vs. 5.1 months [95% CI 3.2-6.9]; HR 0.47, 95% CI 0.28-0.80; *P*=0.004). The ORR was 61.9% in the experimental arm versus 52.4% in the control arm, showing no statistically significant difference (*P*=0.378). Median OS was not reached. All patients experienced adverse events (AEs). Grade 3-4 AEs occurred in 19 (45.2%) patients in the experimental arm versus 23 (54.8%) in the control arm (*P*=0.383). The most common Grade 3-4 AEs were anemia (31.0% vs. 21.4%), neutropenia (21.4% vs. 21.4%), and leukopenia (16.7% vs. 14.3%). Immune-related AEs (irAEs) were more frequent in the experimental arm (34 [82.9%] vs. 25 [58.1%]; *P*=0.013); however, no Grade 3-4 irAEs were observed in either arm. **Conclusions:** TPC chemotherapy combined with cadonilimab demonstrated a statistically significant improvement in PFS compared with TPC alone in heavily pretreated, ICI-refractory R/M NPC patients, with a manageable safety profile (NCT06664983). Clinical trial information: NCT06664983. Research Sponsor: None.

6034 Poster Session

Reirradiation with NBTXR3/SBRT in combination with nivolumab or pembrolizumab for the treatment of patients with recurrent or metastatic head & neck squamous cell carcinoma (HNSCC) in the phase I trial study 1100. First Author: Colette Shen, Department of Radiation Oncology, School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: HNSCC reirradiation with stereotactic body radiation therapy (SBRT) has emerged as a potential option for the management of locoregionally recurrent (R) or metastatic (M) HNSCC, however treatment toxicity remains a limiting factor. NBTXR3 is a novel intratumoral radioenhancer composed of functionalized hafnium oxide nanoparticles which locally amplifies radiation therapy (RT). In pre-clinical models, NBTXR3/RT has demonstrated an ability to generate cell killing effects at low RT doses as well as trigger local and systemic immune responses. Here we report outcomes in pts with R or R+M HNSCC who were treated with reirradiation with NBTXR3/SBRT followed by immune checkpoint inhibitors (ICIs). **Methods:** A phase I dose escalation/expansion trial [NCT03589339] evaluating NBTXR3/SBRT followed by ICI (nivolumab or pembrolizumab) included a subgroup with R or R+M HNSCC that were either naïve or resistant to prior ICI. Pts received an intra-tumoral NBTXR3 injection at dose of 22% or 33% of gross tumor volume (GTV), SBRT (35 Gy in 5 fractions), and ICI. Primary objective was safety and establishing RP2D of NBTXR3/SBRT/anti-PD-1 combination. The expansion part tested the RP2D (33% of GTV). Secondary objectives include efficacy. **Results:** From June 2019 to February 2025, 30 pts were treated: 16 ICI naïve, 14 ICI resistant with median age of 67 years, 90% ECOG 0-1, and 55% HPV negative. 20 pts (66.7%) had R disease, 10 (33.3%) pts had R+M disease. All injected lesions were in a previously irradiated H&N field. Median time from end of prior radiotherapy to NBTXR3 injection was 21.3 [5-229] months. Median GTV was 16.1 [3-110] mL. 4 pts (13.3%) experienced G≥3 injection-related AEs, 8 (26.7%) G≥3 RT-related AEs, and 6 (20%) G≥3 NBTXR3-related AEs. Carotid injury was not observed. Most frequent injection or NBTXR3-related AEs were injection site pain (10%), oropharyngeal pain (6.7%), tumor pain (6.7%), dysphagia (6.7%), and soft tissue necrosis (6.7%). 27 pts (90%) were evaluable for efficacy. For all disease (i.e. injected and non-injected), the objective response rate (ORR) was 48.1% (13/27) and disease control rate (DCR) was 77.8% (21/27). In R pts, ORR was 64.7% (11/17) and DCR was 88.2% (15/17). In R+M pts, ORR was 20% (2/10) and DCR was 60% (6/10). Survival outcomes in reirradiation pts with R and R+M HNSCC will be presented. **Conclusions:** Reirradiation with NBTXR3 with SBRT and anti-PD1 was feasible in R or R+M HNSCC with an adverse effect profile expected for this clinical setting. Encouraging preliminary efficacy outcomes have been observed, thus warranting further investigation. Clinical trial information: NCT03589339. Research Sponsor: None.

6035 Poster Session

Trends in end-of-life immunotherapy use in metastatic head and neck squamous cell carcinoma: A National Cancer Database analysis. First Author: Ronit Sethi, Department of Medical Education, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Aggressive systemic cancer treatment near the end of life (EOL) rarely benefits patients and is an established marker of low-quality healthcare. While EOL chemotherapy use has substantially declined over time, EOL immunotherapy administration has increased in the era of immune checkpoint inhibitors (ICIs). For metastatic head and neck squamous cell carcinoma (mHNSCC), a high-burden disease with rapidly expanding approvals, ICIs have emerged as a compelling mainstay of treatment. However, these expansions may have increased nonbeneficial ICI use among end-stage patients, contributing to quality impacts like decreased hospice enrollment and high financial burden. Given recent evolutions in head and neck cancer care, we conducted a retrospective cohort study to examine temporal trends and factors associated with EOL immunotherapy initiation in mHNSCC. **Methods:** Patients diagnosed with mHNSCC who received first-course immunotherapy between 2016-2022 were identified in the National Cancer Database. EOL-initiated immunotherapy was defined as initiation within 1 month of death. Two-sample t- or χ^2 testing was used for comparison of means and proportions, respectively, between EOL and non-EOL immunotherapy initiation groups. Multivariable logistic regression with *a priori* covariate selection was used to identify factors associated with EOL immunotherapy initiation. Sensitivity analyses were conducted with 2 and 3-month EOL thresholds. **Results:** Among 8806 included patients, 29.3% received immunotherapy, rising from 17.7% in 2016 to 40.9% in 2022 following first-line FDA ICI approvals. By 2021, EOL-initiated immunotherapy occurred among 6.7%, 13.0%, and 16.4% of treated patients at 1-, 2-, and 3-month EOL thresholds, with possible upward trends after 2019 (2021 vs 2019, 1-month EOL, p=0.114; 2-month EOL, $p<0.05$, χ^2 test). In regression analysis, predictors of one-month EOL initiation included female sex (odds ratio [OR]=2.09, 95% CI=1.33–3.27), disadvantaged insurance status (Medicaid/other governmental OR=2.27, 95% CI=1.18–4.35; uninsured/unknown OR=5.09, 95% CI=2.33–11.12), high metastatic burden (≥3 sites OR=8.77, 95% CI=2.94–26.12), and surgical treatment (OR=2.12, 95% CI=1.19–3.79). Protective factors included academic setting (OR=0.60, 95% CI=0.40–0.90), oropharyngeal primary site (OR=0.54, 95% CI=0.32–0.92), and concurrent radiotherapy (OR=0.53, 95% CI=0.35–0.79) or chemotherapy (OR=0.48, 95% CI=0.31–0.73). **Conclusions:** EOL-initiated immunotherapy occurs among a small but notable proportion of mHNSCC patients and is associated with various indicators of clinical and demographic vulnerability. As ICI use expands, our findings underscore the importance of optimizing patient selection, EOL treatment guidelines, and system-level practices to ensure judicious use of immunotherapy in terminal settings. Research Sponsor: U.S. National Institutes of Health; 5R25CA281789-03.

6036 Poster Session

Penpulimab plus oral anlotinib and capecitabine as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (R/M NPC): A multicenter, single-arm, phase 2 clinical trial. First Author: Jun Ma, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: Patients (pts) with NPC progressing after intensive radical treatment often have limited treatment tolerance and poor prognosis. Incorporation of oral agents into triple therapy combining chemotherapy, immunotherapy, and targeted therapy may improve efficacy while reducing toxicity. **Methods:** This multicenter, single-arm, phase 2 trial evaluated first-line penpulimab (a PD-1 blockade) plus oral anlotinib (a tyrosine kinase inhibitor) and capecitabine in pts with R/M NPC previously treated with radical chemo/radiotherapy for non-metastatic disease. Pts from 4 academic hospitals in China received 4–6 cycles of penpulimab 200 mg IV d1, anlotinib 10 mg PO qd d1–14, and capecitabine 650 mg/m^2 PO bid d1–21 q3w, followed by penpulimab-capecitabine maintenance until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), safety, and quality-of-life (QoL; assessed by the EORTC and FACT surveys). This trial was to be considered positive if the median PFS significantly reached an expected value of 11 mo than a historical threshold of 7 mo, with a 1-sided α of 2.5% and 80% power. This trial was registered with ClinicalTrials.gov (NCT05807880) and is now ongoing. **Results:** Between Sept. 2023 and July 2025, 59 eligible pts (median [IQR] age, 50 [40–58] yrs; 33.9% women) were included, of which 23 (38.9%) and 41 (69.5%) pts had recurrent and metastatic diseases, respectively. Overall, 74.6% (44/59) of pts completed at least the required 4 cycles of the triple therapy. After a median follow-up of 10 mo (data cutoff: Nov. 14, 2025), the median PFS was 13.5 mo (95% CI, 13.1–not reached [NR]) and the 12-mo PFS was 64.4% (95% CI, 50.3–78.5%). The median OS was NR, and the 12-mo OS was 87.8% (95% CI, 78.4–97.2%). The ORR was 71.4% in 56 pts with available assessments, including complete and partial responses in 5 (8.9%) and 35 (62.5%) pts, respectively. Pts with baseline EBV DNA $\leq$ 4000 copies/mL had higher median PFS (NR *vs* 6.0 mo) and 12-mo PFS rate (71.3% *vs*41.7%) than those with EBV DNA $>$ 4000 copies/mL (p = 0.024). Twelve (20.3%) pts had grade 3–4 acute treatment-related adverse events (trAEs), with the most frequent trAE of palmar–plantar erythrodysesthesia (5.1%). Fifty-seven (96.6%) pts had all-grade trAEs, mainly including palmar–plantar erythrodysesthesia (39.0%), hypothyroidism (37.3%), stomatitis (33.9%), sore throat (32.2%), anemia (27.1%), and leukopenia (23.7%). Two treatment-related deaths were observed. Twenty-nine of 37 QoL domains (78.4%) remained stable or showed clinically meaningful improvement. **Conclusions:** First-line therapy of penpulimab plus oral anlotinib and capecitabine provides promising antitumor efficacy, low toxicity, and favorable QoL for pts with R/M NPC. Clinical trial information: NCT05807880. Research Sponsor: Chia Tai Tian Qing Pharmaceutical Group Co., Ltd.

6037 Poster Session

Safety and efficacy of dostarlimab monotherapy as first-line treatment in programmed cell death-ligand 1–positive recurrent/metastatic head and neck squamous cell carcinoma: Results from a phase 2 trial. First Author: Robert I. Haddad, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: The use of immune checkpoint inhibitors (ICIs) in recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) has improved patient outcomes and showed benefit in the perioperative setting. The GALAXIES H&N-202 study (NCT06062420) evaluated novel immunotherapy combinations versus dostarlimab monotherapy in patients with R/M programmed cell death-ligand 1 (PD-L1)-positive HNSCC. Here, we present updated safety and efficacy results for patients who received dostarlimab monotherapy. **Methods:** GALAXIES H&N-202 is a multicenter, open-label, randomized, Phase 2 study assessing immunotherapy as monotherapy or in combination as first-line treatment (1L) in adults with R/M PD-L1-positive (combined positive score [CPS] $\geq$1) HNSCC. The dostarlimab monotherapy arm comprised patients randomized to receive dostarlimab 500 mg every 3 weeks until progression, unacceptable toxicity, death, or withdrawal. Investigator-confirmed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was the primary endpoint, and safety was a secondary endpoint. Outcomes were analyzed descriptively. **Results:** At data cutoff (July 14, 2025), 66 patients were enrolled in the dostarlimab monotherapy arm. All patients had $\geq$4.5 months of follow-up from first dose. The mean patient age was 64.7 years, 80% were male, and 53% had lung metastases. After a median treatment duration of 19.0 weeks (range: 3.0–69.0), ORR was 27.3% (95% confidence interval [CI]: 17.0, 39.6) overall and 42.4% (25.5, 60.8) for those with a CPS $\geq$20 (Table), and median PFS (95% CI) was 4.2 (2.7, 5.8) and 7.8 (3.0, NE) months, respectively. Treatment-emergent adverse events (TEAEs) occurred in 59 (91%) patients and treatment-related adverse events (TRAEs) in 33 (51%) patients. Three (5%) patients discontinued treatment due to TEAEs. Grade $\geq$3 TEAEs were reported in 21 (32%) patients and Grade $\geq$3 TRAEs in 3 (5%) patients. Seventeen (26%) patients experienced serious adverse events (SAEs) and 3 (5%) experienced treatment-related SAEs. Fatal SAEs were reported in 7 (11%) patients; none were treatment related. **Conclusions:** Dostarlimab monotherapy showed encouraging antitumor activity, particularly in patients with a CPS $\geq$20, and a consistent safety profile in 1L R/M HNSCC that is comparable to other ICIs in HNSCC. Clinical trial information: NCT06062420. Research Sponsor: This study (NCT06062420; GSK Study 219885) was funded by GSK.

Efficacy outcomes.

Confirmed ORR per RECIST v1.1, n (%) [95% CI]	n=66
CPS ≥20 (n=33)	14 (42.4) [25.5, 60.8]
CPS 1–19 (n=33)	4 (12.1) [3.4, 28.2]
Overall	18 (27.3) [17.0, 39.6]
Best response, n (%)	**n=66**
Complete response	1 (1.5)
Partial response	17 (25.8)
Stable disease	23 (34.8)
Progressive disease	17 (25.8)
Not evaluable	8 (12.1)

CI, confidence interval; CPS, combined positive score; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

6038 Poster Session

Real-world treatment patterns and overall survival in recurrent/metastatic head and neck squamous cell carcinoma following treatment with immune checkpoint inhibitor and platinum-based chemotherapy. First Author: Ari Joseph Rosenberg, Department of Medicine, Section of Hematology and Oncology, University of Chicago, Chicago, IL

Background: Treatments for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) include immune checkpoint inhibitors (ICI) and/or platinum-based chemotherapy, yet most patients (pts) will experience disease progression, with poor survival and limited therapeutic options in later-line settings. Real-world evidence in R/M HNSCC after ICI and platinum-based chemotherapy is limited. We characterize real-world treatments and survival outcomes in pts with heavily pretreated R/M HNSCC. **Methods:** This retrospective analysis used electronic medical records from the US Flatiron Health Advanced EDM (71% community centers, 22% academic centers, 7% both). Study period was 1 Jan 2015 to 31 Mar 2025 (date of data cutoff). All identified pts had R/M HNSCC and had received prior PD-1 inhibitor and platinum-based chemotherapy. Demographics, baseline disease characteristics, and treatment patterns were analyzed descriptively. Kaplan-Meier method was used to evaluate real-world overall survival (rwOS), defined as time from index date (first date of treatment after PD-1 inhibitor and platinum-based chemotherapy) until date of recorded death. Subgroups by HPV-unrelated (oral cavity, larynx, hypopharynx, HPV-negative oropharyngeal) and HPV-related (HPV-positive oropharyngeal) HNSCC were evaluated. **Results:** In total, 2105 pts with R/M HNSCC were identified from the Flatiron database as previously treated with PD-1 inhibitor and platinum-based chemotherapy. There were 1271 pts who did not receive any subsequent treatment, while 834 pts received an index line of therapy after PD-1 inhibitor and platinum-based chemotherapy and were eligible for analysis. Among those eligible, primary tumor site distribution was 55% oropharynx (81% HPV-positive / 19% HPV-negative), 21% larynx, 18% oral cavity, and 6% hypopharynx. Most pts had an ECOG score of 0 or 1 (77%). Most common regimens in the index line of therapy included chemotherapy, anti-EGFR, and/or PD-(L)1 agents. Among the 834 pts identified, rwOS was 7.8 months (95% CI, 7.0–8.4). There were 373 and 461 pts identified with HPV-related and HPV-unrelated disease, respectively. Median rwOS was significantly longer for the HPV-related vs HPV-unrelated group (9.3 months [95% CI, 8.2–10.9] vs 6.8 months [95% CI, 6.1–7.3]; HR, 0.85 [95% CI, 0.73–0.99]; P=0.036). The 6-month rwOS rate was 65% vs 55%, respectively. Of note, a substantial portion of pts died prior to receiving another line of therapy (39% for HPV-related and 49% for HPV-unrelated). **Conclusions:** Median rwOS is poor in R/M HNSCC following treatment with PD-1 inhibitor and platinum-based chemotherapy, and particularly poor for HPV-unrelated disease, with nearly half dying by 6 months. These results highlight the pressing need for innovative treatments to improve survival in R/M HNSCC. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

6039 Poster Session

Defining the role of locoregional radiotherapy for de novo metastatic nasopharyngeal carcinoma in the immunotherapy era: A systematic review and meta-analysis. First Author: Kunpeng Wu, Heyuan People's Hospital, Heyuan, China

Background: In the pre-immunotherapy era, a phase 3 randomized controlled trial (NCT02111460) confirmed locoregional radiotherapy (LRRT) combined with palliative chemotherapy improved overall survival (OS) and progression-free survival (PFS) in de novo metastatic nasopharyngeal carcinoma (dmNPC). Consequently, this strategy has been adopted by major clinical practice guidelines, including NCCN, CSCO, and ESMO. However, with immunotherapy now integrated into first-line treatment, the contemporary role of LRRT and the definition of patients most likely to benefit from it are uncertain and necessitate further exploration. **Methods:** This meta-analysis was conducted in accordance with PRISMA guidelines. A comprehensive search was conducted in electronic databases including PubMed, Cochrane Library, and Web of Science from their inception to December 31, 2025, to identify eligible studies comparing immunochemotherapy with or without LRRT in dmNPC. The primary outcomes were PFS and OS. Meta-analysis was performed using OnlineMeta V1.1. **Results:** A total of six clinical trials were rated as high-quality and included in this meta-analysis. Our meta-analysis results showed that the palliative immunochemotherapy (PICT) plus LRRT group achieved significantly longer PFS (HRs: 0.560, 95%CIs: 0.431-0.727) and OS (HRs: 0.502, 95%CIs: 0.289-0.869) than the PICT alone group. Additionally, single-arm meta-analysis results demonstrated that the 1-year, 2-year, and 3-year PFS rates (with 95% CIs) in the PICT plus LRRT group were 80.5% (76.3%-84.2%), 56.3% (53.7%-58.9%), and 37.6% (28.6%-47.5%), compared with 62.7% (56.2%-68.8%), 26.3% (16.8%-38.7%), and 7.6% (2.4%-21.6%) in the PICT group. Regarding OS, the 1-year, 2-year, and 3-year rates (with 95% CIs) were 97.1% (95.3%-98.2%), 84.2% (72.3%-91.6%), and 76.0% (47.4%-91.7%) in the PICT plus LRRT group, whereas those in the PICT group were 76.9% (33.5%-95.7%), 55.8% (13.7%-90.9%), and 39.7% (1.7%-88.4%). Sensitivity analysis confirmed the stability of the results, and no significant publication bias was detected. Subgroup analyses indicated that dmNPC patients achieved greater PFS benefit from LRRT when they had partial or complete response to PICT (HRs: 0.509, 95%CIs: 0.368-0.704), undetectable post-treatment EBV DNA (HRs: 0.541, 95%CIs: 0.378-0.774), or oligometastatic disease (HRs: 0.349, 95%CIs: 0.193-0.634). **Conclusions:** In the immunotherapy era, LRRT combined with PICT confers significant and durable survival benefits for dmNPC patients, with pronounced efficacy among those achieving PR/CR to PICT, harboring undetectable post-treatment EBV DNA, or presenting with oligometastatic disease. Research Sponsor: None.

6040 Poster Session

Depth and durability of response with TGF-β trapping in recurrent or metastatic (R/M) HPV-negative head and neck squamous cell carcinoma (HNSCC): Long-term results from two expansion cohorts of a phase 1/1b study of ficerafusp alfa plus pembrolizumab. First Author: Deborah J.L. Wong, University of California, Los Angeles, Los Angeles, CA

Background: In HPV-negative HNSCC, TGF-β overexpression creates fibrotic barriers within the tumor microenvironment that limit tumor penetration and drive resistance to anti-EGFR and anti-PD1 therapy. Ficerafusp alfa is the first and only bifunctional EGFR-directed antibody designed to trap TGF-β, enabling tumor penetration of immune cells and driving deep and durable responses for potential overall survival (OS) benefit. **Methods:** Two dose-expansion cohorts of an ongoing phase 1/1b study (NCT04429542) enrolled adults with 1L R/M HNSCC with PD-L1 CPS ≥1. Patients received ficerafusp alfa 750 or 1500 mg IV on D1, 8, and 15 plus pembrolizumab (pembro) 200 mg IV Q3W. Assessments included objective response rate (ORR), duration of response (DOR), and progression free survival (PFS) per RECIST v1.1; OS; safety; and pharmacodynamic (PD) and pharmacokinetic analyses. This is the first report of long-term efficacy follow-up across two cohorts of ficerafusp alfa. **Results:** As of December 16, 2025, 61 HPV-neg pts were treated in two cohorts (750 mg, n=31; 1500 mg, n=30); 58 pts were efficacy evaluable. Exposure increased in an approximately dose-proportional manner with manageable safety observed in both cohorts. A higher proportion of pts had exposure levels associated with meaningful efficacy with 1500 mg vs 750 mg dosing. Improved outcomes were observed in the 1500 mg vs 750 mg cohort, including deep responses (≥80% tumor shrinkage in 80% vs 47% of responders) and mPFS (9.9 mo vs 6.9 mo), along with increased markers of TGF-β inhibition and tumor penetration in paired biopsies, and increased pro-inflammatory cytokines in blood (Table). **Conclusions:** Deeper and more durable tumor responses were observed with ficerafusp alfa 1500 mg vs 750 mg. Exposure and PD markers of TGF-β inhibition demonstrated dose-related trends consistent with mechanism of action. Together, these data suggest that TGF-β inhibition with ficerafusp alfa facilitates T-cell infiltration, enhancing immunologic activity, contributing to deep and durable responses for patients with HPV-neg HNSCC. These findings support the rationale for FORTIFI-HN01, an ongoing phase 2/3 trial evaluating this combination in 1L PD-L1 pos, HPV-neg, R/M HNSCC (NCT06788990). Clinical trial information: NCT04429542. Research Sponsor: Study funded by Bicara Therapeutics Inc. with access to pembrolizumab in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (NCT04429542).

Endpoint (efficacy set)	Ficerafusp alfa 750 mg + pembro N=30	Ficerafusp alfa 1500 mg + pembro N=28
Confirmed ORR/complete response rate, n (%)	17 (57)/4 (13)	15 (54)/6 (21)
Responders with ≥80% shrinkage, n (%)	8/17 (47)	12/15 (80)
Median DOR, mo	NR	21.7
Proportion of responses >12 mo, n (%)	9/17 (53)	9/15 (60)
Median PFS, mo	6.9	9.9
Median OS, mo	NR	21.3
Tumor TGF-β inhibition: mean change from baseline in pSMAD2, %	−16.4 (n=5)	−33.2 (n=7)
Immune activation: mean change from baseline in blood TNF-α/IFN-γ, %	25.6/163, (n=24)	64.9/346 (n=20)

6041 Poster Session

First-in-class Trop2-targeted PET imaging with ^{68}Ga-MY6349 for diagnostic accuracy and altered management in recurrent/metastatic thyroid cancer compared to standard ^{18}F-FDG PET/CT. First Author: Haojun Chen, The First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

Background: Accurate, non-invasive detection of recurrent and metastatic thyroid cancer remains an unmet clinical need due to the limitations of conventional imaging and biopsy. Trop2 is a tumor-associated antigen that frequently overexpressed in thyroid cancer, it represents a promising molecular target for imaging. This study aimed to evaluate the diagnostic accuracy of Trop2-targeted PET/CT using the novel nanobody tracer, ^{68}Ga-MY6349, the results were compared with those of ^{18}F-FDG PET/CT. **Methods:** In this prospective, single-center, single-arm trial conducted at the First Affiliated Hospital of Xiamen University (Xiamen, China), adults with suspected or confirmed recurrent or metastatic thyroid cancer were enrolled between January and December 2024. Each participant underwent both ^{68}Ga-MY6349 and ^{18}F-FDG PET/CT scans within one week. Three independent, blinded readers assessed the PET/CT images. The primary endpoints were patient-based sensitivity and specificity, using histopathology or clinical follow-up as the reference standard. The full analysis set included patients with evaluable PET/CT imaging and a confirmed final diagnosis. The trial is registered with ClinicalTrials.gov, NCT06465017 and is closed to enrollment. **Results:** Of 161 screened participants, 143 were finally included in the primary analysis. Papillary thyroid cancer (PTC) was the most common pathological subtype (115/143, 80%). The median clinical follow-up duration was 19 months (IQR: 14-22 months). In the overall cohort, the sensitivity and specificity of ^{68}Ga-MY6349 PET/CT was 90% (95% CI 83-94) and 91% (95% CI 76-97), respectively. Among participants with PTC, its sensitivity and specificity were 94% (95% CI, 87–98) and 96% (95% CI, 79–100), respectively. Additionally, ^{68}Ga-MY6349 PET/CT demonstrated superior diagnostic accuracy in participants with thyroglobulin-elevated negative iodine scintigraphy (TENIS), with sensitivity of 92% (95% CI 82-97) and accuracy of 93% (95% CI 84-97), respectively. Further details are presenting in the Table. No grade 2 or higher adverse event was observed during study. **Conclusions:** ^{68}Ga-MY6349 PET/CT is a safe and highly accurate imaging modality for detecting recurrent and metastatic thyroid cancer, particularly in PTC and patients with TENIS. These findings suggest it could significantly influence clinical practice and may become a standard imaging option in this setting. Further multicenter studies are warranted to validate its diagnostic accuracy and assess its long-term impact on patient management and outcomes. Clinical trial information: NCT06465017. Research Sponsor: None.

6042 Poster Session

First-line HLX07 vs placebo combined with serplulimab and chemotherapy for nasopharyngeal carcinoma: A randomized, double-blind, multicenter phase 2 study. First Author: Wenfeng Fang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Programmed cell death protein 1 (PD-1) blockade with chemotherapy confers significant survival benefit compared to chemotherapy alone and is the standard first-line therapy for recurrent or metastatic nasopharyngeal carcinoma (R/M-NPC). Epidermal growth factor receptor (EGFR) is overexpressed in approximately 85% of all NPCs and associated with poor outcomes, suggesting a potential target for improved efficacies. This study explores the efficacy of HLX07 (a novel humanized anti-EGFR antibody) versus placebo, in combination with serplulimab (PD-1 inhibitor) and chemotherapy as first-line treatment for R/M-NPC. **Methods:** This is a randomized, double-blind, multicenter phase 2 study. Patients with histopathologically confirmed, unresectable, R/M NPC that is not amenable to local or radical treatment and had no prior systemic therapy were randomized 2:1 to receive either HLX07 at 1000 mg (HLX07 group) or placebo (placebo group), along with serplulimab (300 mg) and chemotherapy (gemcitabine and cisplatin) Q3W intravenously. Primary endpoint was blinded independent central review (BICR)-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included other efficacy endpoints, safety, pharmacokinetics and biomarker explorations. **Results:** As of December 24, 2025, 75 patients were randomized to the HLX07 group (n=50) or placebo group (n=25). Efficacy results are reported for the per-protocol set (n = 72), which excluded two patients who violated the enrolment criteria and one with no post-baseline tumor assessment in the HLX07 group. With 26.0 months of follow-up, BICR-assessed confirmed ORR was 74.5% vs. 72.0% for the two groups. Overall, a trend of an improved median progression-free survival (PFS) was observed with HLX07 (17.3 months vs. 9.4 months, stratified hazard ratio [HR] 0.79, 95% CI 0.40–1.56). Median overall survival was not reached vs. 27.9 months (stratified HR 0.40, 95% CI 0.16–0.99) for the respective groups. Subgroup analysis revealed a trend of improved PFS in the HLX07 group compared to the placebo group for patients with PD-L1 CPS <10 (median PFS, 8.1 vs. 6.8 months, HR 0.54, 95% CI 0.19–1.56) as well as for patients with EGFR H-score ≥200 (median PFS, not reached vs. 7.8 months, HR 0.30, 95% CI 0.08–1.15). 74 (98.7%) patients experienced treatment-emergent adverse events (TEAEs), with grade ≥3 TEAEs reported in 60 (80.0%) patients. TEAEs led to treatment discontinuation occurred in 14 (18.7%) patients. Deaths due to TEAEs were reported in 5 (6.7%) patients, with 1 (1.3%) in the HLX07 group that was treatment related. **Conclusions:** The addition of HLX07 to serplulimab and chemotherapy showed encouraging efficacy along with a manageable safety profile in patients with treatment-naïve R/M-NPC. Further investigation of this treatment regimen is warranted. Clinical trial information: NCT05513573. Research Sponsor: Shanghai Henlius Biotech, Inc.

6043 Poster Session

Expansion of circulating NKG7$^+$ cytotoxic CD4$^+$ T cells as a predictor of response to PD-1 blockade in recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC): A prospective phase II study with translational analysis. First Author: Chang Gon Kim, Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Nivolumab has demonstrated meaningful survival benefit in patients with refractory R/M HNSCC. Nevertheless, reliable predictive biomarkers remain scarce—particularly those capable of identifying long-term survivors—underscoring the need for translational studies to uncover immune correlates of durable response. In this prospective phase II study (NCT04603248), we sought to define dynamic circulating immune cell–based biomarkers predicting durable clinical outcomes with nivolumab in patients with R/M HNSCC. **Methods:** Patients with R/M HNSCC who had prior failure of or intolerance to platinum-based chemotherapy were treated with nivolumab (3 mg/kg) intravenously every 2 weeks until disease progression or unacceptable toxicity occurred. Clinical outcomes were correlated with single-cell transcriptomic profiles of circulating immune cells at baseline (cycle 1 day 1) and on-treatment (cycle 2 day 1). To validate the transcriptomic findings at the protein level, mass cytometry by time-of-flight (CyTOF) analysis was additionally performed. **Results:** A total of 48 patients were enrolled. The objective response rate was 22.9%, and the disease control rate was 62.5%. The median progression-free survival (PFS) and overall survival (OS) were 4.4 and 13.3 months, respectively. Single-cell transcriptomic analysis revealed a significant expansion of circulating NKG7$^+$ cytotoxic CD4$^+$ T cells in long-term responders (PFS > 48 months; n=6) compared with early progressors (PFS < 2 months; n=6) at cycle 2 day 1. T cell receptor analysis further demonstrated that nivolumab induced marked clonal expansion of these NKG7$^+$ cytotoxic CD4$^+$ T cells, particularly in long-term responders. Their sustained presence was confirmed in blood samples collected one year after treatment initiation in long-term responders. CyTOF analysis (n=37) revealed that expansion of NKG7$^+$ cytotoxic CD4$^+$ T cells at cycle 2 day 1 was significantly associated with both PFS and OS, supporting their potential role as predictive biomarkers of response to PD-1 blockade. **Conclusions:** Expansion and clonal amplification of circulating NKG7$^+$ cytotoxic CD4$^+$ T cells represent a key immune correlate of favorable outcomes with nivolumab in refractory R/M HNSCC. These findings highlight their potential as predictive biomarkers of durable response to PD-1 blockade in R/M HNSCC and implicate this immune subset as a promising target for future immunotherapeutic strategies. Clinical trial information: NCT04603248. Research Sponsor: None.

6044 **Poster Session**

Cytokine dynamics in a phase II trial of metronomic carboplatin/paclitaxel combined with cemiplimab in recurrent/metastatic head and neck squamous cell carcinoma. First Author: Marcelo Raul Bonomi, The Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University, Columbus, OH

Background: Standard-dose chemotherapy combined with immunotherapy improves response rates in recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC), but its use is often constrained by significant toxicity. Metronomic chemotherapy (MCT) offers a potentially better-tolerated alternative while preserving immunemodulatory properties. We evaluated cytokine profiles and their longitudinal dynamics to investigate the relationship between immune-mediated mechanisms and clinical outcomes in patients treated with MCT plus cemiplimab. **Methods:** Single- arm phase II trial (NCT04862650). R/M HNSCC pts received first-line cemiplimab 350 mg IV Q3W ($\leq$35 cycles) plus weekly carboplatin (AUC1) and paclitaxel (25 mg/m²) for 24 weeks. Primary endpoint was overall response rate (ORR) per RECIST v1.1 at week 12. Forty immunemodulatory cytokines were assessed at baseline, week 3, and week 6 using the Luminex xMAP platform. **Results:** From Nov 2021 to Dec 2024, 40 evaluable patients were enrolled (median age was 66 years, 82.5% were male; 35% were HPV-positive). Median follow-up was 10 months (range 1–28). ORR was 42.5% (15% CR) and Median OS was 14.8 months (95% CI, 10.3–23.9). Responders had significantly higher IFN-β at all timepoints (P=.008–.04). Elevated IL-4, IL-5, and IL-10 at baseline were associated with improved ORR. Overall, LIGHT, FasL and TGF-α decreased while PD-L1 increased over time (all $q<0.001$). Compared to baseline, on week 6, responders showed decreased VEGF-A, TSLP, FasL, and IL-4 ($P < .03$), while non-responders exhibited increased IFN-γ, PD-L1, and IL-6Rα ($P < .04$). Changes in IFN-γ (HR 3.23, P=.006) and IL-4Rα (HR 3.06, P=.008) from baseline to week 3 were associated with worse overall survival. **Conclusions:** MCT combined with cemiplimab demonstrated clinically meaningful antitumor activity. Alterations in plasma concentrations of select cytokines were associated with therapeutic response and overall survival. These results are hypothesis-generating and support the need for prospective validation. Clinical trial information: NCT04862650. Research Sponsor: Regeneron Pharmaceuticals; Internal founds from The Ohio State University.

6045 **Poster Session**

Updated results of benmelstobart combined with anlotinib and chemotherapy as neoadjuvant therapy for locally advanced head and neck squamous cell carcinoma: A single-arm, open-label phase II clinical trial. First Author: Yiqian Liu, Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Locally advanced head and neck squamous cell carcinoma (HNSCC) is characterized by high risks of local recurrence and distant metastasis, resulting in poor prognosis. Neoadjuvant therapy has the potential to improve survival outcomes in these patients. This study aimed to evaluate the safety and efficacy of benmelstobart in combination with anlotinib and chemotherapy as neoadjuvant therapy for resectable locally advanced HNSCC. Preliminary results were presented at the 2025 ESMO Congress (Abstract 1454eP), and updated consecutive results are reported herein. **Methods:** This single-center, phase II clinical trial enrolled patients with stage III/IVA HNSCC who met predefined eligibility criteria. Patients underwent neoadjuvant therapy with benmelstobart (1200mg), anlotinib (10mg), cisplatin (60mg/m²), and nab-paclitaxel (125mg/m², d1, d8) for three 21-day cycles. Surgical resection was performed within two weeks after neoadjuvant therapy completion, with tumor specimens collected for pathological evaluation. The primary endpoint was major pathological response (MPR) rate. Postoperative adjuvant therapy was administered based on risk assessment. Secondary endpoints included objective response rate (ORR), pathological complete response (pCR) rate, 2-year disease-free survival (DFS), 2-year locoregional recurrence-free survival (LRFS), 2-year distant metastasis-free survival (DMFS), 2-year overall survival (OS), and safety assessment. **Results:** As of Jan 9, 2026, a total of 36 patients who met the inclusion and exclusion criteria were enrolled. The median age was 61 years (range: 38-77), with males accounted for 91.7%. ECOG performance status 0 was observed in 80.5% of patients, and hypopharyngeal carcinoma was the most common primary tumor site (50.0%). Stage III and IVA disease accounted for 25.0% and 75.0% of patients, respectively. At the data cut-off date, 32 patients completed neoadjuvant therapy, achieving an ORR of 96.9% and a disease control rate (DCR) of 100%. Among them, 27 patients underwent surgery and completed histopathological assessment. MPR was achieved in 23 cases (including 20 with pCR), resulting in an MPR rate of 85.2% (95%CI: 66.3%-95.8%). The incidence of all grade treatment-emergent adverse events (TEAEs) was 86.1% (31/36). The incidence of grade$\geq$3 TEAEs was 8.3% (3/36), most commonly myelosuppression (5.6%) and renal impairment (2.8%). **Conclusions:** The combination of benmelstobart, anlotinib, and chemotherapy demonstrated promising efficacy as neoadjuvant therapy for resectable HNSCC, with high ORR and MPR rates, along with an acceptable safety profile. These updated results support further evaluation of this combination in randomized controlled trials. Clinical trial information: NCT0669949. Research Sponsor: None.

6046 **Poster Session**

Second-line cetuximab plus immune checkpoint inhibitor (ICI) versus cetuximab plus carboplatin and paclitaxel following ICI-containing regimen in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). First Author: Jennifer Dorcas Hwang, The Ohio State University Comprehensive Cancer Center - The James Cancer Hospital and Solove Research Institute, Columbus, OH

Background: ICI-containing regimens are the standard first-line therapies for R/M HNSCC. However, the optimal therapeutic regimen after progression on ICI-containing therapies remains uncertain. This study compares outcomes among patients (pts) who received either second-line cetuximab plus ICI (CICI) or cetuximab plus weekly carboplatin and paclitaxel (CPT). **Methods:** We performed a retrospective analysis of R/M HNSCC pts treated at our institution between 2018 and 2025 who received cetuximab combination therapy after progressing on first-line ICI alone or ICI with chemotherapy. Pts with ECOG 0-2 were included. All pts received cetuximab 400 mg/m^2 followed by 250 mg/m^2 weekly as tolerated, concurrently with either pembrolizumab (200 mg every 3 weeks) or chemotherapy (carboplatin AUC 1.5 and paclitaxel 45 mg/m^2 weekly). The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), disease control rate (DCR; SD+PR+CR), objective response rate (ORR; CR+PR), and rate of treatment modification. Time-to-event outcomes were estimated using the Kaplan-Meier method and compared using log-rank tests and Cox proportional hazards models. Fisher's exact test was used to compare binary outcomes. Results were deemed significant when $p<0.05$. Subgroup analyses were considered exploratory. **Results:** Out of 100 pts included, 31 received CICI, and 69 received CPT. Median age at the start of cetuximab was 65 years (range 34-93), 79% were male, 95% were Caucasian, and 38% had HPV-related disease. Primary tumor sites included oropharynx (47%), oral cavity (26%), and larynx (19%). 9% had CPS 0, 30% had CPS 1-19, and 43% had CPS $\geq$ 20. For first-line treatment, 41% had received an ICI alone, and 59% had received an ICI with chemotherapy. Median follow-up was 7.6 months (range 3.8-13.4) with CICI and 38.8 months (range 4.3-71.5) with CPT. DCR was 77.4% with CICI and 60.6% with CPT (p=0.12). ORR was 51.6% versus 34.8%, respectively (p=0.13). Median PFS was 7.6 months (95% CI 4.1-NR) with CICI and 2.7 months (95% CI 2.0-4.4) with CPT (HR 0.48, 95% CI 0.29-0.82, $p<0.01$). Median OS was 11.3 months (95% CI 9.1-NA) with CICI and 9.4 months (95% CI 8.2-10.5) with CPT (HR 0.78, p=0.10). Subgroup analyses showed favorable PFS with CICI in select groups: age $\leq$ 65 (p=0.037), male sex (p=0.009), ECOG 0-1 (p=0.024), and prior ICI plus chemotherapy ($p<0.001$). No clear differences were found within subgroups with CPS 1-19 or CPS $\geq$ 20. There was no difference in the rates of treatment modification (p=1.00). **Conclusions:** In this retrospective cohort of R/M HNSCC pts, CICI was associated with a longer PFS than CPT. This effect remained significant in pts who previously received first-line ICI plus chemotherapy. A longer follow-up is planned to evaluate for differences in OS. Research Sponsor: None.

6047 **Poster Session**

An open-label, single-center phase II trial of mitoxantrone hydrochloride liposome combined with programmed death-1 (PD-1) inhibitors for pretreated recurrent or metastatic nasopharyngeal carcinoma. First Author: You Rui, Nasopharyngeal Cancer Center, the Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, Guangdong, China

Background: Liposomal mitoxantrone (Lipo-MIT) in combination with programmed death-1 (PD-1) inhibitors exhibits potential synergistic antitumor effects. This study aimed to evaluate the efficacy and safety of this regimen in patients with pretreated recurrent/metastatic nasopharyngeal carcinoma (R/M NPC). **Methods:** This was a single-arm, Simon two-stage clinical study enrolling patients with R/M NPC who were refractory to platinum-based chemotherapy and PD-1 inhibitors. Patients received intravenous infusion of Lipo-MIT (20 mg/m²) combined with a PD-1 inhibitor on Day 1 of each 21-day treatment cycle, for a maximum of 6 cycles. Subsequent maintenance therapy with PD-1 inhibitors alone was administered until disease progression, occurrence of intolerable toxicity, or completion of 2-year treatment. The primary endpoint was objective response rate (ORR). Key secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety profile. **Results:** A total of 32 patients were enrolled between February 3, 2024, and July 21, 2025, all of whom were included in the efficacy and safety analysis sets. The ORR was 40.6% (95% confidence interval [CI], 24.2–59.2), and the DCR was 78.1% (95% CI, 59.6–90.1). With a median follow-up duration of 8.1 months (range, 4.7–17.2 months), the median OS was not reached and the median PFS was 7.4 months (95% CI, 6.0–not reached [NR]). Grade 3 or higher treatment-related adverse events (TRAEs) were observed in 18 patients (56.3%), and the most common TRAEs were leukopenia (25.0%), anemia (21.9%), neutropenia (18.8%), pneumonia (15.6%), and thrombocytopenia (12.5%). No treatment-related deaths were observed. **Conclusions:** Lipo-MIT combined with PD-1 inhibitors demonstrates promising antitumor activity with manageable toxicities in patients with pretreated R/M NPC. Long-term survival data are pending as follow-up is still ongoing. Clinical trial information: NCT06472713. Research Sponsor: None.

6048 **Poster Session**

A prospective, single-arm, phase II exploratory clinical study on the efficacy and safety of neoadjuvant adebrelimab combined with cisplatin and docetaxel in patients with clinical stage IVB oral squamous cell carcinoma. First Author: Zi-Li Yu, School and Hospital of Stomatology, Wuhan University, Wuhan, Hubei, China

Background: Oral squamous cell carcinoma (OSCC) is one of the most common malignant tumors of the head and neck. Stage IVB OSCC had long been considered unresectable with extremely poor prognosis, and mainstream guidelines encourage exploring new therapies via clinical trials. This study aimed to evaluate the efficacy and safety of adebrelimab plus cisplatin/docetaxel as neoadjuvant therapy for stage IVB OSCC (NCT06277791). **Methods:** IVB OSCC patients aged 18–75 years were enrolled and received 2 cycles of neoadjuvant immunochemotherapy (adebrelimab 1200 mg + cisplatin 75 mg/m²/docetaxel 75 mg/m², q3w). Three weeks after neoadjuvant treatment, patients underwent extended primary tumor resection and radical neck dissection, followed by adjuvant radiotherapy/chemoradiotherapy. The primary endpoint was pathological response rate (pCR+MPR); secondary endpoints included radiographic response, R0 resection rate, and safety. **Results:** 28 patients were enrolled between June 2023 and January 2026. The mean age was 47.8 years, with a male predominance (25, 89.3%). Primary tumors were mainly located in the buccal mucosa (14, 50.0%) and tongue (10, 35.7%). Smoking, alcohol consumption, and betel nut chewing histories were noted in 75.0%, 42.9%, and 64.3% of patients, respectively. Most had an ECOG performance status of 1 (75.0%). 8 cases (28.6%) were classified as cT4b and 20 cases (71.4%) as cN3b at baseline. Three patients (10.7%) were excluded from efficacy analysis due to insufficient data. In the evaluable population (n=25), no complete response (CR) was observed; 8 (28.6%) achieved partial response (PR), 14 (50.0%) stable disease (SD), and 3 (10.7%) progressive disease (PD), with an overall objective response rate (ORR) of 32.0% (8/25). Subgroup ORRs were 33.3% (2/6) for cT4b and 31.6% (6/19) for cN3b. Pathological assessment was available for 25 patients: based on the combined pathological assessment of the primary tumor and lymph nodes, 15 (60.0%) achieved MPR, 1 (4.0%) pCR, resulting in a 64.0% pathological response rate. For subgroups, the pathological response rate was 50.0% in 6 evaluable cT4b (2 MPR, 1 pCR) and 68.4% in 19 evaluable cN3b (13 MPR, no pCR). The R0 resection rate was 100% among 25 surgical patients. Treatment-related adverse events (TRAEs) were mostly grade 1–2. Grade 3 TRAEs occurred in 2 cases (7.2%), with no grade 4/5 events. At data cutoff (median follow-up: 12.0 months), 3 deaths occurred. The estimated 1-year OS rate was 87.9%, with subgroup rates of 89.1% for cN3b (median follow-up: 12.0 months) and 87.5% for cT4b (median follow-up: 19.4 months). **Conclusions:** Neoadjuvant adebrelimab combined with chemotherapy achieves a high pathological response rate in stage IVB OSCC, with manageable adverse events and favorable safety. Clinical trial information: NCT06277791. Research Sponsor: None.

6049 **Poster Session**

Evaluation of autologous tumor-infiltrating lymphocytes (GT201) plus toripalimab in recurrent or metastatic head and neck cancer. First Author: Pin Wang, University of Southern California, Los Angeles, CA

Background: Immune checkpoint inhibitors (ICIs) are the standard treatment for recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (HNC) after failure of platinum-based chemotherapy; however, the clinical benefit remains limited, with reported overall response rate (ORR) of approximately 13% and median progression-free survival (PFS) of about 2 months in the second line setting. GT201 is an autologous TIL therapy engineered to express membrane-bound IL-15 (mbIL-15), which may enhance immune activation in the tumor microenvironment and promote durable response. We report preliminary safety and efficacy results from an open-label, single-arm study evaluating GT201 in combination with the PD-1 inhibitor toripalimab in patients with R/M HNC (NCT06190275). **Methods:** The primary endpoint was safety, including treatment-emergent adverse events (TEAEs) graded per CTCAE v5.0. Secondary endpoints included ORR, disease control rate (DCR), PFS, duration of response (DOR), and overall survival (OS), assessed per RECIST v1.1. **Results:** As of November 30, 2025, 6 patients with R/M HNC were treated (median age of 57 years; median 1 prior line of therapy). Histology indicated 5 squamous cell carcinoma and 1 lymphoepithelial carcinoma. All patients received 1–2 cycles of bridge therapy, followed by lymphodepletion (low-dose in 5 patients; intermediated-dose in 1 patient), GT201 infusion (5×10^9-5×10^{10} viable cells), and high-dose IL-2 (600,000 IU/Kg; 4-6 doses). Five patients subsequently received toripalimab; one patient progressed prior to PD-1 inhibitor treatment. Maximum follow-up was 15.5 months. Most of AEs were Grade 1-2. Grade $\geq$ 3 AEs were primarily related to lymphodepletion and IL-2, and included cytopenia, neutropenia, lymphocytopenia, monocytopenia, hypokalemia, rash, and increased bilirubin; all resolved or improved to Grade $\leq$ 2 within 14 days. The ORR was 66.7% (4/6), including 2 complete response (CR) and 2 partial response(PR); DCR was 83.3% (5/6). One patient with CR remains progress-free exceeding 12 months. Median PFS and OS have not yet been reached. GT201 cells expanded robustly and persisted in peripheral blood for at least 6 months post-infusion. **Conclusions:** GT201 combined with toripalimab demonstrated a manageable safety profile and encouraging antitumor activity in heavily pretreated R/M HNC, supporting further clinical development of this combination. Clinical trial information: NCT06190275. Research Sponsor: Grit Biotechnology. Research Sponsor: None.

6050 **Poster Session**

Defining a long-term benefit phenotype to PD-1 inhibitors in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): A multicentre retrospective study. First Author: Justin Panasci, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Limited data exists on predictors of durable benefit to PD-1 inhibitors in R/M HNSCC. We aimed to identify clinical characteristics associated with long-term benefit from anti-PD-1 therapy in R/M HNSCC. **Methods:** We reviewed clinical data from patients with R/M HNSCC treated with PD-1 inhibitors between December 2018 and August 2025, at Princess Margaret Cancer Centre (an academic hospital) or within the William Osler Healthy System (a community hospital). Eligible patients received pembrolizumab or nivolumab, either alone or with chemotherapy (for pembrolizumab), and had available tissue for planned biomarker studies. Patients were grouped by progression-free survival (PFS): (A) PFS $\geq$ 24 months (m), (B) PFS 12-24 m and (C) best response of progressive disease (PD). Best response was determined from treating physician documentation based on clinical and radiographic assessment. PFS was estimated with the Kaplan-Meier method. Univariate analysis used Kruskal-Wallis test for continuous variables and Fisher's exact or Chi-square tests for categorical variables. **Results:** A total of 150 patients were included: 31 in group A (PFS $\geq$ 24 months), 28 in group B (PFS 12-24 months) and 91 in group C (PD as best response). We observed significantly more immune-related adverse events (irAEs) (61% vs 16%, OR 8.0, 95% CI 3.2-19.9, $p<0.001$) and corticosteroid use (32% vs 8.8%, OR 4.9, 95% CI 1.7-14.1, p= 0.002) in group A compared to group C. There was a trend toward a higher proportion of patients with lung-only metastases in group A compared to C (39% vs 21%, OR 2.4, 95% CI 1.0-5.8, p= 0.052). Similar associations were found for irAEs ($p<0.001$), corticosteroid use (p= 0.011) and lung-only metastases (p= 0.054) in group B compared with group C. Additionally, we found more active smokers (p=0.010) and ex-smokers (p= 0.036) in group B compared to group C, as well as more active smokers in group B compared to group A (p= 0.042), whereas smoking rates were similar in groups A and C. Interestingly, there was no significant difference in Charlson Comorbidity Index (CCI) scores, albumin levels or neutrophil-to-lymphocyte ratios (NLR) between the three groups. The mean CCI scores were 7.3, 7.3 and 7.1; albumin levels 39.1, 40.1 and 39.7 and NLR 6.8, 6.5 and 8.7 for groups A, B and C respectively. P16 status and PD-L1 CPS were distributed similarly between the groups, although PD-L1 testing was not available in 25% of patients. **Conclusions:** IrAEs, corticosteroids and lung-only metastases are associated with PFS $\geq$ 12 m in patients with R/M HNSCC treated with anti-PD-1 agents. Smoking is associated with PFS 12-24 m but not with PFS $\geq$ 24 m, suggesting a potential role in acquired resistance. Further molecular analysis in this population is underway to identify biomarkers of long-term benefit. Research Sponsor: Canadian Association of Medical Oncologists (J.P.); Princess Margaret Cancer Centre Drug Development Fellowship Program (J.P.).

6051 **Poster Session**

Preliminary efficacy and safety of intratumoral long-acting cisplatin-SRGel (TumoCure) in refractory locally advanced head and neck squamous cell carcinoma: Phase Ib CLPR-001. First Author: Arnon Aharon, IntraGel Therapeutics, Nazareth, Israel

Background: Refractory LA-HNSCC progressing despite standard therapies is associated substantial locoregional disease driven morbidity and limited effective salvage therapies that achieve modest response rates and are poorly tolerated. Intratumoral (IT) therapies enabling high and durable drug exposure at the site of disease with minimal systemic toxicity may address this unmet need. TumoCure is a long acting injectable IT cisplatin formulation (100mg/mL) incorporated in SRGel, a solvent free biodegradable matrix designed to provide IT cisplatin release for up to 2 months, aiming to maximize locoregional cisplatin exposure with minimal systemic exposure. **Methods:** CLPR-001 is an open-label, multicenter Phase I/Ib study evaluating IT TumoCure in patients with chemo and/or radio resistant LA-HNSCC with no available curative or effective standard treatment options. TumoCure is administered as a single IT injection; individualized based on tumor dimensions to optimize IT dispersion. The primary endpoint is safety and tolerability. Secondary endpoints include locoregional response by RECIST v1.1, PK and QoL assessment. **Results:** Eight patients received IT TumoCure (5 males and 3 females) with a mean age of 66y. Patients were in average 7y from diagnosis and were heavily pretreated: 7/8 (87.5%) had prior surgery and 7/8 (87.5%) were platinum-resistant or refractory. The mean number of prior systemic treatment lines (including RT and IO) was 3. Target lesions reflected substantial locoregional tumor burden (longest diameter 30-98 mm). Administration was feasible across tumor sizes, with injection volumes of 0.4-1.0 mL. Treatment was generally well tolerated. Procedure related AEs were uncommon and limited to injection site pain. No systemic cisplatin related AEs were reported. Early clinical activity was observed, with 3 months best response of 45% and 37% reductions in tumor diameter and corresponding volumetric reductions of 75% and 36% respectively. Patients also experienced clinically meaningful improvement in tumor bulk related manifestations. Preliminary PK analyses demonstrated systemic platinum exposure at least one order of magnitude lower than historical systemic cisplatin exposure. **Conclusions:** In heavily pretreated, platinum-resistant/refractory patients, TumoCure treatment was safe and well tolerated. Early signals of tumor regression and improvement in tumor bulk-related symptoms were observed, supported by markedly reduced systemic platinum exposure. These findings support continued development of TumoCure as treatment for refractory LA-HNSCC. A subsequent study is planned to evaluate TumoCure + IMRT in cisplatin ineligible patients, addressing an unmet need where current chemoradiation regimens remain suboptimal, with the goal of improving outcome while minimizing toxicity. Clinical trial information: NCT05200650. Research Sponsor: None.

6052 **Poster Session**

First-line lenvatinib versus dabrafenib plus trametinib (D+T) in *BRAF*-mutated differentiated thyroid cancer (DTC): Insights from real-world data. First Author: Wilson Ngai, Eisai Inc., Nutley, NJ

Background: *BRAF* mutations are present in approximately 40%–60% of patients with DTC. Lenvatinib is the NCCN Category 1 preferred first-line (1L) systemic therapy for progressive radioiodine-refractory (RAI-R) DTC—including *BRAF*-mutated disease. For patients with *BRAF* V600E–positive, RAI-R DTC, *BRAF*-targeted therapy is recommended for those unsuitable for lenvatinib or as a 2L agent for patients after disease progression or intolerance to one or more prior multikinase inhibitors. This analysis compares real-world effectiveness of 1L treatment with lenvatinib versus D+T in patients with *BRAF*-mutated tumors. **Methods:** Patients with DTC who initiated lenvatinib monotherapy (n=319; Dec 2014–Jul 2025) or D+T (n=131; June 2016–Sept 2025) were identified from the Tempus multimodal real-world database. Among them, 88 patients were treated with lenvatinib and 54 patients were treated with D+T as 1L therapy for DTC harboring *BRAF* V600E and/or K601E mutations. Retrospective analyses in this patient cohort (n=142) were performed to compare real-world progression-free survival (rwPFS) and overall survival (exploratory; rwOS) between patients treated with 1L lenvatinib and those treated with 1L D+T in *BRAF*-mutated DTC. **Results:** Of the 142 patients in the study cohort who were treated with lenvatinib or D+T, the median age was 66 years (interquartile range: 57–74); 45% of patients were female and 55% were male. The majority (75%) of patients were White, 5.7% were Asian, 3.4% were African American, and 16% had their race categorized as "Other." Papillary, follicular, and Hürthle histology accounted for 92%, 0.7%, and 1.4% of patients, respectively, while the remaining 6% had uncommon or unspecified histology. Demographics and clinical characteristics were balanced between patients treated with 1L lenvatinib or D+T. At median follow-up of 33.6 months, median rwPFS indexed from treatment initiation dates was 17.0 months (95% confidence interval [CI], 12.2–27.8) in patients treated with lenvatinib and 6.2 months (95% CI, 4.9–8.7) in patients treated with D+T (hazard ratio [HR] for lenvatinib vs D+T, 0.44 [95% CI, 0.28–0.69]. Median rwOS was 70.7 months (95% CI, 51.8 – 90.8) in patients treated with lenvatinib, and 37.8 months (95% CI, 16.4–66.4) in patients treated with D+T (HR for lenvatinib vs D+T, 0.34 [95% CI, 0.18–0.62]). Sensitivity analyses showed that rwPFS and rwOS benefits associated with lenvatinib were maintained irrespective of age, sex, or race. **Conclusions:** In this retrospective study of real-world data, 1L therapy with lenvatinib demonstrated longer rwPFS and rwOS compared with 1L D+T in patients with DTC harboring *BRAF* mutations. While recognizing the inherent limitations of real-world data, this study has implications regarding the sequencing of agents used to treat patients with *BRAF*-mutated RAI-R DTC. Research Sponsor: Eisai Inc., Nutley, NJ, USA, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

6053 **Poster Session**

The association of nutritional factors on disease control and survival in patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M-HNSCC) treated with anti–PD-1 monoclonal antibody. First Author: Jessica Zheng, University of Pittsburgh School of Medicine, Pittsburgh, PA

Background: Anti-PD-1 mAb therapy is standard of care for systemic treatment for R/M-HNSCC. These patients (pts) also face significant issues with malnutrition. Therefore, we evaluated whether there was any association between outcomes with anti-PD-1 treatment and nutritional markers including BMI, prognostic nutritional index (PNI), and serum albumin. **Methods:** We collected baseline serum albumin, PNI [(10 $\times$ serum albumin (g/dL)) + (0.005 $\times$ total lymphocyte count)], BMI, and initial BMI trend (baseline to 3 months), on pts with R/M-HNSCC treated with anti-PD-1 at our institution and evaluated association with disease control (CR/PR/SD vs. PD), PFS, and OS. Baseline BMI was analyzed as a continuous variable and binarily [$<$18.5 vs. $\geq$18.5, and median split (23.85)]. Associations of explanatory variables with disease control were evaluated using multivariable logistic regression, reported as odds ratios (ORs) and 95% confidence intervals (CIs) and with PFS and OS using Cox proportional hazards regression, reported as hazard ratios (HRs) and 95% CIs. All analyses were conducted using R version 4.5.2. **Results:** In our retrospective cohort (n = 124), the median age was 68 and primary sites included oral cavity (39%), larynx (16%), hypopharynx (5%), oropharynx (34%; 64% p16+), and other (6%). 43% of patients received anti-PD-1 for platinum failure and 57% for frontline. On univariate analysis, higher PNI was significantly associated with increased disease control (OR = 1.11; 95% CI: 1.04–1.21; p = 0.007), PFS (HR = 0.96; 95% CI: 0.94-0.98; p $<$ 0.001), and OS (HR = 0.97; 95% CI: 0.95–0.99; p = 0.002). Higher albumin was significantly associated with increased PFS (HR = 0.45; 95% CI: 0.24-0.85; p = 0.014) and OS (HR = 0.25; 95% CI: 0.13-0.48; p $<$ 0.001). Evaluation of baseline characteristics showed platinum failure was significantly associated with worse efficacy and therefore multivariate analysis was conducted, adjusting for platinum failure status. PNI was still significantly associated with increased disease control (OR = 1.09; 95% CI: 1.03–1.18; p = 0.016) and PFS (HR = 0.97; 95% CI: 0.95–0.99; p $<$0.001). Higher serum albumin was only significantly associated with increased OS (HR = 0.29; 95% CI: 0.14–0.57; p $<$0.001). Neither baseline nor trend in BMI was associated with efficacy. **Conclusions:** In our cohort of anti-PD-1 treated R/M-HNSCC pts, higher baseline albumin was associated with increased OS while higher baseline prognostic nutritional index was associated with increased disease control and PFS, including in multivariate analysis. While BMI has been associated with efficacy of anti-PD-1 in other solid tumors, it was not in our cohort. Our data suggests that markers that factor in nutritional and immune status may be more relevant in R/M-HNSCC. Further study is warranted. Research Sponsor: None.

6054 **Poster Session**

Four-year landmark survival analysis of low-dose nivolumab added to metronomic chemotherapy in advanced head and neck squamous cell carcinoma: A phase III randomized trial. First Author: Mehak Trikha, Tata Memorial Hospital, Mumbai, India

Background: In advanced head and neck squamous cell carcinoma (HNSCC), the addition of low-dose nivolumab to triple metronomic chemotherapy (TMC-I) previously demonstrated an overall survival (OS) benefit versus triple metronomic chemotherapy (TMC) alone. We report extended follow-up with a 4-year landmark survival analysis to assess the durability of benefit. **Methods:** This was an open-label, randomised, phase III superiority trial enrolling 151 adult patients ($\geq$18 years) with relapsed–recurrent or newly diagnosed advanced HNSCC with ECOG performance status 0–1, and adequate organ function. Patients were randomized 1:1 to receive oral TMC comprising of Methotrexate 9 mg/m² weekly, Celecoxib 200 mg twice daily and Erlotinib 150 mg daily, with (TMC-I) or without (TMC) nivolumab 20 mg intravenously every 3 weeks. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was OS. Survival outcomes were analyzed using Kaplan–Meier methods, log-rank tests, and Cox proportional hazards models. A 4-year landmark analysis was performed. **Results:** At a median follow-up of 55.6 months (95% CI, 45.0–66.2), the median OS was 6.60 months (95% CI, 5.74–7.47) in the TMC arm and 9.33 months (95% CI, 8.00–10.66) in the TMC-I arm (p = 0.045). Treatment with TMC-I was associated with a 29% reduction in the risk of death [hazard ratio (HR), 0.709; 95% CI, 0.506–0.994; p = 0.046]. At 3 years, OS was 5.1% (95% CI, 1.7–12.3) with TMC versus 13.6% (95% CI, 9.7–26.3) with TMC-I [HR 0.686; 95% CI, 0.485–0.971; p = 0.033]. On 4-year landmark analysis, overall survival curve separation was maintained, with OS remaining superior in the TMC-I arm. The median PFS was 4.50 months (95% CI, 3.89–5.12) with TMC and 6.47 months (95% CI, 4.02–8.93) with TMC-I (p = 0.007). The OS benefit with TMC-I was consistent across prespecified subgroups including age, gender, ECOG performance status, disease site, prior platinum exposure, and tumour programmed death ligand (PD-L1) expression. **Conclusions:** With extended follow-up exceeding 4.5 years, the addition of low dose nivolumab to triple metronomic chemotherapy demonstrates a clinically meaningful, durable and statistically significant survival advantage at a 4-year landmark in a predominantly relapsed/refractory advanced HNSCC population compared with TMC alone, confirming the long-term clinical benefit of this strategy in the palliative setting. Clinical trial information: CTRI/2020/11/028953. Research Sponsor: None.

6055 **Poster Session**

Second-line cetuximab monotherapy following PD-1 inhibitor treatments in patients with recurrent/metastatic head and neck carcinoma. First Author: Mercedes Porosnicu, Atrium Health Wake Forest Baptist Medical Center, Winston-Salem, NC

Background: PD-1 inhibitors, alone or in combination with chemotherapy, are standard first-line therapy for recurrent/metastatic head and neck squamous cell cancer (R/M HNSCC). No established second-line standard exists for majority of patients who progress on immunotherapy. Cetuximab, the only approved targeted biologic agent in HNSCC, has historically shown modest activity as monotherapy, with a 13% response rate. We hypothesized that cetuximab administered after PD-1 inhibitors may demonstrate enhanced efficacy due to potentially synergistic, immunomodulatory effects. **Methods:** This non-randomized single-institution study included patients with R/M HNSCC who experienced disease progression or intolerance to PD-1 inhibitor therapy, with or without chemotherapy, and were subsequently treated with cetuximab monotherapy. Imaging was performed every 6 weeks, and response was assessed per RECIST v1.1. Outcomes included best overall response (BOR), progression-free survival (PFS), overall survival (OS), and toxicity. Survival outcomes were estimated using Kaplan–Meier methods. **Results:** Twenty-seven patients (8 female, 19 male) were included; 5 were HPV-positive. All HPV-positives had metastatic disease, while all HPV-negatives had recurrent disease. Two patients experienced anaphylaxis with the first cetuximab infusion, and two died from tumor-related complications prior to first restaging; all were included in outcome analyses. Nine patients (33.3%) achieved a partial response (PR), while 18 (66.7%) were non-responders, including 10 (37.0%) with stable disease (SD), 4 (14.8%) with progressive disease (PD), and 4 (14.8%) non-evaluable. Median follow-up was 32.4 mos, with 21 deaths observed. Median OS was 11.6 mos (95% CI, 8.0–21.0) in all patients, 15.5 mos (95% CI, 4.2–24.9) in responders and 11.4 mos (95% CI, 5.3–25.0) in non-responders, with 18.0 mos (95% CI, 4.4–32.0) in patients with SD. Median PFS was 4.4 mos overall, 5.3 mos (2.7 to 11.5) in responders, and 4.4 mos (2.6 to 6.2) in non-responders, with 5.9 mos (2.5 to 7.0) in patients with SD. Median OS was 32.0 mos (11.7 to NE) in HPV-positive patients and 10.8 mos (5.3 to 18.0) in HPV-negatives. Two patients experienced anaphylactic reaction with the initial cetuximab administration. All treated patients developed acneiform skin rash, with 17 (68%) experiencing grade 3, necessitating oral antibiotics. **Conclusions:** Cetuximab monotherapy following PD-1 inhibitor therapy demonstrated encouraging clinical activity in patients with R/M HNSCC, with improved outcomes compared with historical cetuximab monotherapy. These findings suggest that sequential targeting of immune-mediated pathways may provide clinical benefit after an immunotherapy failure. Larger prospective studies are warranted to validate these results and to better define response patterns in the immunotherapy setting. Clinical trial information: NCT04375384. Research Sponsor: None.

6056 Poster Session

Evaluation of the impact of regional lymph node depletion on response to immune checkpoint blockade in recurrent and metastatic head and neck squamous cell carcinoma. First Author: Joshua D. Smith, Department of Otolaryngology-Head and Neck Surgery, University of Pittsburgh, Pittsburgh, PA

Background: Lymphadenectomy remains a central component of definitive treatment for head and neck squamous cell carcinoma (HNSCC). However, lymphadenectomy disrupts the draining regional lymph node basin where anti-tumor immune cell priming can occur. We hypothesized that history of regional lymph node depletion may be associated with decreased efficacy of immune checkpoint blockade (ICB) in patients who suffer recurrent or metastatic (R/M) HNSCC. **Methods:** This was a single-institution retrospective cohort study including all patients treated with ICB (anti-PD-1 mAb) for R/M HNSCC from 2015 - 2025. Patients with distant metastatic disease at presentation were excluded. Demographic, clinicopathologic, and treatment history prior to ICB were collated and summarized for each patient. We defined regional lymph node depletion (LN depletion) as history (at any time prior to ICB initiation) of bilateral lymphadenectomy, $>$ 4 levels dissected, or $\geq$18 lymph nodes excised. We then examined history of LN depletion as a predictor of ICB disease control rate (DCR: SD, PR, or CR) and progression-free survival (PFS) after ICB with Kaplan-Meier method and Cox models alone and controlling for tumor HPV status. **Results:** Our cohort was comprised of 100 patients (median age 72 years, 71% male). Primary tumor sites included oral cavity (n=38) p16+ oropharynx (n=23), larynx (n=21), p16- oropharynx (n=13) and sinonasal (n = 5). Forty-six were treated with first-line ICB, while 54 were treated after platinum chemotherapy failure. Sixty had a history of lymphadenectomy prior to ICB. Of these 60 patients, 51 (85%) had a history of radiation prior to ICB. History of regional LN depletion was significantly associated with lower DCR with ICB when considering bilateral lymphadenectomy (25.9% vs 54.8%, p = 0.03), $>$ 4 levels dissected (25.0% vs. 54.8%, p = 0.02), or $\geq$18 lymph nodes excised (25.0% vs. 84.6%, $p < 0.0001$) analyzed alone and on bivariate analysis controlling for HPV status. In patients meeting all three criteria for LN depletion (n = 24), DCR was the lowest at 16% compared to 75% for patients meeting none of the criteria. On bivariate analyses controlling for HPV status, history of bilateral lymphadenectomy (HR: 2.04 [95% CI 1.1 – 3.8] p = 0.02), $>$ 4 levels dissected (HR: 1.82 [95% CI: 1.0 – 3.3] p = 0.05, and $\geq$18 lymph nodes excised (HR: 3.35 [95% CI: 1.4 – 8.1] $p < 0.01$) were independently associated with poorer PFS after ICB. **Conclusions:** In patients with R/M HNSCC, prior regional LN depletion was associated with lower DCR and PFS after ICB. This suggests that greater surgical disruption of draining regional lymph node basins prior to ICB may affect immune response. Research Sponsor: None.

6057 Poster Session

Neoadjuvant and adjuvant pembrolizumab (pembro) plus standard of care (SOC) for resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): Efficacy by surgical outcomes in the phase 3 KEYNOTE-689 trial. First Author: Douglas Adkins, Siteman Cancer Center, Washington University, St. Louis, MO

Background: In the phase 3 KEYNOTE-689 trial (NCT03765918), neoadjuvant and adjuvant pembro plus SOC (surgery and postoperative [chemo]radiotherapy) significantly improved EFS versus SOC in participants (pts) with resectable LA HNSCC. We present results from an exploratory analysis of EFS by surgical outcomes in KEYNOTE-689. **Methods:** Adults with newly diagnosed resectable LA HNSCC were randomly assigned to receive 2 cycles neoadjuvant pembro 200 mg followed by surgery and 15 cycles adjuvant pembro starting concurrently with postoperative (chemo)radiotherapy (pembro arm) versus surgery and postoperative (chemo)radiotherapy only (control arm). This exploratory analysis evaluated EFS in pts with R0 resection (negative [$\geq$5mm] or close [1-5mm] margin) by local assessment, and postoperative presence or absence of extranodal extension (ENE) or positive ($<$1mm) surgical margins by BIPR in the PD-L1 CPS $\geq$1 and total populations of the study. Median study follow-up (data cutoff date: July 25, 2024) was 38.3 months (range, 9.0-66.5). **Results:** Of 714 total pts, 630 underwent surgery (n = 322, pembro arm; n = 308, control arm). Among 630 who underwent surgery, 307 in the pembro arm and 294 in the control arm had tumors with PD-L1 CPS $\geq$1. EFS in subgroups by surgical outcome is shown in the table. **Conclusions:** In this exploratory analysis of the KEYNOTE-689 study, EFS benefit with neoadjuvant and adjuvant pembro added to surgery and postoperative (chemo) radiotherapy occurred in all subgroups by surgical outcome, consistent with the primary analysis population. Fewer pts in the pembro arm had ENE or positive margins post-surgery indicating downstaging due to neoadjuvant pembro. ENE presence or positive margins were associated with a poorer EFS prognosis; however, EFS was better in the pembro arm vs control in pts with or without these high-risk pathological features. Results further support the addition of neoadjuvant and adjuvant pembro to SOC for resectable LA HNSCC. Clinical trial information: NCT03765918. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	R0 by local assessment		ENE present by BIPR		ENE absent by BIPR		Positive surgical margins by BIPR		Negative surgical margins by BIPR	
All pts	**Pembro n = 287**	**Control n = 261**	**Pembro n = 82**	**Control n = 112**	**Pembro n = 228**	**Control n = 188**	**Pembro n = 64**	**Control n = 92**	**Pembro n = 249**	**Control n = 209**
Median EFS, mo	NR	40.2	25.2	12.6	NR	57.0	50.3	13.8	NR	51.5
HR (95% CI)	0.67 (0.50-0.88)		0.77 (0.52-1.15)		0.74 (0.53-1.05)		0.58 (0.36-0.93)		0.78 (0.57-1.07)	
36-mo rate, %	64.0	51.1	41.3	33.8	68.4	58.5	58.0	36.8	63.0	55.6
CPS ≥1	**Pembro n = 275**	**Control n = 249**	**Pembro n = 76**	**Control n = 109**	**Pembro n = 220**	**Control n = 178**	**Pembro n = 58**	**Control n = 89**	**Pembro n = 242**	**Control n = 198**
Median EFS, mo	NR	35.3	25.2	12.6	NR	57.0	50.3	13.8	NR	50.1
HR (95% CI)	0.62 (0.47-0.83)		0.74 (0.49-1.12)		0.71 (0.51-1.01)		0.60 (0.37-0.98)		0.72 (0.53-1.00)	
36-mo rate, %	65.1	49.5	42.3	33.9	68.5	56.6	55.0	36.0	64.2	53.9

6058 Poster Session

The impact of depth of response on long-term clinical outcomes: Exploratory analyses from multiple expansion cohorts of a phase 1/1b study of ficerafusp alfa plus pembrolizumab in first-line recurrent/metastatic (R/M) HPV-negative head and neck carcinoma (HNSCC). First Author: John M. Kaczmar, Hollings Cancer Center, The Medical University of South Carolina, Charleston, SC

Background: Ficerafusp alfa is the first and only bifunctional EGFR-directed antibody designed to trap TGF-β, enabling tumor penetration of immune cells and driving deep and durable responses. Depth of response has been shown to correlate with prolonged progression free survival (PFS) and overall survival (OS) in several solid tumors. However, such data are limited in R/M HPV-negative HNSCC. Here we performed exploratory analyses to evaluate whether depth of response achieved with ficerafusp alfa and pembrolizumab is associated with prolonged duration of response (DOR), PFS and OS. **Methods:** Three cohorts of a phase 1/1b study (NCT04429542) in 1L, R/M HNSCC, with PD-L1 CPS $\geq$1 evaluated ficerafusp alfa (750mg QW,1500 mg QW, or 2000 mg Q2W) IV combined with pembrolizumab IV. Objective response rate (ORR) per RECIST v1.1, DOR, PFS, and OS were assessed. In the pooled efficacy evaluable set from the three cohorts, we explored if the magnitude of tumor regression, comparing tumor regression $\geq$80% regression (defined as a deep response) vs. tumor regression 0 to $<$80%, is predictive of longer-term clinical outcomes (DOR, PFS, OS). **Results:** As of December 16, 2025, 85 patients with HPV-negative disease were efficacy evaluable across three cohorts (n=30, n=28, and n=27 at 750mg, 1500mg, and 2000mg doses of ficerafusp alfa, respectively). Among these, the confirmed ORRs were 57%, 54%, and 48%, respectively, including 47%, 80%, and 77% of responders achieving a deep response. In the pooled efficacy evaluable set the percentage of patients with a deep response was 36%, with tumor regression 0 to $<$80% was 46%, and no tumor regression was 18%. mDOR was longer for patients with a deep response compared to patients with tumor regression 0 to $<$80% (21.9 mo vs 8.2 mo, HR 0.27). mPFS was also longer in patients with a deep response compared to patients with tumor regression 0 to $<$80% (26.4 mo vs 6.5 mo, HR 0.19). mOS was not reached (NR) in patients with deep response and 14.9 mo in patients with tumor regression 0 to $<$80% (NR vs 14.9 mo, HR 0.17). **Conclusions:** Ficerafusp alfa plus pembrolizumab demonstrated deep responses across multiple dose levels. Deep responses were associated with improved long-term efficacy outcomes, including DOR, PFS, and OS. This suggests that depth of response may represent a clinically meaningful surrogate for understanding long-term efficacy outcomes in HPV-negative HNSCC. Clinical trial information: NCT04429542. Research Sponsor: Study funded by Bicara Therapeutics Inc. with access to pembrolizumab in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (NCT04429542).

	Tumor Regression 0 to <80% N=39	Tumor Regression ≥ 80% (Deep Response) N=31
mDoR (mo)	8.2	21.9
HR [vs < 80% tumor regression] (95% CI)	N/A	0.27 [0.10, 0.71]
mPFS (mo)	6.5	26.4
HR [vs No DR] (95% CI)	N/A	0.19 [0.09, 0.40]
mOS (mo)	14.9	NR
HR [vs No DR] (95% CI)	N/A	0.17 [0.07, 0.41]

6059 Poster Session

Outcomes of PD-(L)1 inhibitor continuation or rechallenge after first-line progression in recurrent or metastatic head and neck squamous cell carcinoma. First Author: Jong Chul Park, Mass General Brigham, Harvard Medical School, Boston, MA

Background: PD-(L)1 inhibitors are a standard first-line (1L) backbone for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC). However, many patients progress after 1L PD-(L)1–based therapy, and optimal post-progression strategies remain undefined. In particular, the benefit of continuing or rechallenging PD-(L)1 inhibitors beyond progression is unclear. **Methods:** In this multicenter retrospective study, we included patients diagnosed with R/M HNSCC (oral cavity, oropharynx, larynx, and hypopharynx) between 2016 and May 2025 at Samsung Medical Center and Mass General Brigham. Eligible patients received 1L PD-(L)1–containing regimen, experienced disease progression, and underwent subsequent second-line systemic therapy. Patients were categorized by post-progression strategy: continuation or rechallenge with PD-(L)1 inhibitors versus non–PD-(L)1–based therapy. Overall survival (OS) was defined as the time from initiation of 1L therapy to death from any cause. **Results:** A total of 252 patients with R/M HNSCC met eligibility criteria. Median age was 64; 191 (76%) were male; 68 (27.0%) were HPV-positive; and 217 (86%) were PD-L1 positive (CPS $\geq$1). Twenty-six patients (10.3%) received anti-PD-(L)1 monotherapy, and 84 (33%) remained on 1L therapy for $\geq$6 months. Median OS for the entire cohort was 18 months (95% CI, 15.9-20.1). Median OS was 21.1 months among patients who continued or were rechallenged with PD-(L)1 inhibitor (n = 112) versus 14.4 months in those who were not (n = 140) ($p < 0.001$). On multivariable analysis including post-progression PD-(L)1 continuation/rechallenge, HPV status, PD-L1 expression, age, sex, ECOG performance status, and duration of 1L PD-(L)1 therapy, continuation or rechallenge with PD-(L)1 inhibitors (HR 0.583, p=0.003) and 1L PD-(L)1 duration $\geq$6 months (HR 0.487, p$<$0.001) were independently associated with improved OS. **Conclusions:** In this study, continuation or rechallenge with PD-(L)1 inhibitors after progression on 1L therapy was associated with improved OS in patients with R/M HNSCC, independent of PD-L1 expression or HPV status. Prolonged benefit from 1L PD-(L)1 therapy was also independently associated with favorable survival. These findings suggest that selected patients may derive continued clinical benefit from anti-PD-(L)1–based strategies beyond progression and support prospective studies to refine patient selection and optimize post-progression treatment strategies. Research Sponsor: None.

6060 Poster Session

Efficacy and safety of HLX43 (an anti–PD-L1 ADC) in previously treated recurrent/metastatic nasopharyngeal carcinoma: A multicenter, randomized phase 2 study. First Author: Jun Ma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: Treatment options are limited and clinical outcomes remain unsatisfactory for patients with recurrent/metastatic nasopharyngeal carcinoma (r/m NPC) in the later-line setting. HLX43 is a novel anti-programmed cell death-ligand 1 (PD-L1) antibody-drug conjugate with promising antitumor activity in advanced tumors. Here we present results from a phase 2 study evaluating HLX43 in previously treated r/m NPC. **Methods:** This randomized, multicenter trial enrolled patients with histologically or cytologically confirmed r/m NPC who had received at least second-line chemotherapy (including one prior line of platinum-based chemotherapy) and progressed on or were intolerant to programmed death (ligand) 1 (PD-[L]1) inhibitor. Patients were randomized 1:1:1 to receive 2 mg/kg, 2.5 mg/kg, or 3 mg/kg of intravenous HLX43 every 3 weeks. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS) per investigator's assessments. **Results:** As of September 18, 2025, 30 patients were randomized to the 2, 2.5, or 3 mg/kg group (n = 10 for each group). The median follow-up duration was 2.8 months (range 2.1–5.6). Twenty-six patients (86.7%) had performance status 1; 27 (90.0%) had prior radiotherapy. The median line of prior systemic therapy was 3 (range 2–8). ORR was 36.7%, with partial responses (PRs) in 11 patients. ORR in the three dose groups was 20.0%, 20.0% and 70.0% (all confirmed by December 2025), respectively; disease control rate (DCR) was 50.0%, 50.0% and 80.0%. PFS data were immature. Overall, treatment-emergent adverse events (TEAEs) occurred in 29 patients (96.7%; grade ≥3, 50.0%). TEAE incidence was 90.0%, 100% and 100% in the three dose groups, respectively. TEAE leading to dose reduction was reported in 3 patients (30.0%) in the 3 mg/kg group only. TEAE leading to treatment discontinuation occurred in 1 (10.0%) each in the 2.5 mg/kg and 3 mg/kg groups. There was no death due to TEAE. The efficacy and safety findings are detailed in Table 1. **Conclusions:** HLX43 showed promising efficacy with a manageable safety profile in r/m NPC patients who had progressed after second-line or later chemotherapy and PD-(L)1 inhibitors. Further investigation is warranted. Clinical trial information: NCT06839066. Research Sponsor: Shanghai Henlius Biotech, Inc.

Efficacy and safety.

	2.0 mg/kg N=10	2.5 mg/kg N=10	3.0 mg/kg N=10	Total N=30
PR	2 (20.0)	2 (20.0)	7 (70.0)	11 (36.7)
SD	3 (30.0)	3 (30.0)	1 (10.0)	7 (23.3)
PD/NE	5 (50.0)	5 (50.0)	2 (20.0)	12 (40.0)
ORR, 95% CI (%)	20.0 (2.5, 55.6)	20.0 (2.5, 55.6)	70.0 (34.8, 93.3)	36.7 (19.9, 56.1)
DCR, 95% CI (%)	50.0 (18.7, 81.3)	50.0 (18.7, 81.3)	80.0 (44.4, 97.5)	60.0 (40.6, 77.3)
TEAEs	9 (90.0)	10 (100)	10 (100)	29 (96.7)
Grade ≥3 TEAEs	2 (20.0)	7 (70.0)	6 (60.0)	15 (50.0)
TEAE leading to dose reduction	0	0	3 (30.0)	3 (10.0)
TEAE leading to treatment discontinuation	0	1 (10.0)	1 (10.0)	2 (6.7)

NE, not evaluable. PD, progressive disease. SD, stable disease.

6061 Poster Session

A prospective phase II clinical study of different time-delivered drugs combined with intensity-modulated radiotherapy for locally advanced nasopharyngeal carcinoma. First Author: Feng Jin, Afiliated Hospital of Guizhou Medical University, Guizhou, China

Background: To compare the effects of combining intensity-modulated radiotherapy administered at different times on the toxic side effects, quality of life (QoL) and long-term survival of patients with locally advanced nasopharyngeal carcinoma (LA-NPC). **Methods:** A total of 160 patients with LA- NPC were randomized into the experimental group and the control group of 80 patients each, both groups received 2 cycles of TPF (docetaxel, cisplatin, and 5- fluorouracil) induced chemotherapy sequential synchronous radiochemotherapy, the experimental group received chrono- chemotherapy, while the control group received conventional chemotherapy. Primary study endpoints included Grade ≥ 3 acute adverse reactions, Secondary study endpoints included quality of life and 8- year overall survival (OS), progression- free survival (PFS), distant metastasis-free survival (DMFS), and local recurrence- free survival (LRFS). **Results:** As of October 10, 2024, the incidence rates of grade ≥ 3 acute vomiting, oral mucositis, leukopenia, and neutropenia in the experimental group were 3.75%, 6.25%, 27.5%, and 35.0%, while those in the control group were 15.0%, 16.25%, 47.5%, and 52.5%, and the differences were statistically significant ($P < 0.05$). In the experimental group, the incidence rates of Grade 1- 2 xenosomia and hearing impairment were 63.2% and 23.5%, respectively, compared to 80% and 48.6% in the control group, with a statistically significant difference ($P < 0.05$), and no Grade 3- 4 late toxicities were reported in either group. The experimental group demonstrated significantly higher overall QoL scores compared to the conventional group, with statistically significant differences in vomiting, general health status, and quality of life scores between the two groups ($P < 0.05$). However, no statistically significant differences were observed in 8-year OS, PFS, DMFS, or LRFS between the groups ($P > 0.05$). **Conclusions:** The integration of chronotherapy with IMRT significantly reduced adverse reactions and improved quality of life with LA-NPC, without compromising long-term survival outcomes. Clinical trial information: NCT02937519. Research Sponsor: None.

6062 Poster Session

A phase 1/2 study of the next-generation nectin-4–targeting antibody-drug conjugate CRB-701 (SYS6002) in patients with recurrent or metastatic head and neck squamous cell carcinoma. First Author: Charlene Mantia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: CRB-701 is a next-generation Nectin-4–targeted monomethyl auristatin E (MMAE)-based antibody–drug conjugate with differentiated safety, efficacy and pharmacokinetics compared with other agents in the same class. As previously reported, CRB-701 demonstrated antitumor responses independent of Nectin-4 expression levels in solid tumors, notably in patients with heavily pretreated head and neck squamous cell carcinoma (HNSCC) and cervical cancer, as well as urothelial carcinoma. Here, we provide data from this phase 1/2 trial in patients with recurrent or metastatic (R/M) HNSCC enrolled in dose escalation (part A) and dose optimization (part B) (NCT06265727). **Methods:** Patients with R/M HNSCC who had received ≥ 1 line of therapy were enrolled. Part A employed a Bayesian Optimal Interval design with four doses (1.8, 2.7, 3.6 and 4.5 mg/kg; each every 3 weeks [Q3W]) to determine the maximum tolerated dose. In part B, the pharmacologically active dose range identified in part A was evaluated using a time-to-event Bayesian optimal phase 2 design. Patients were randomized 1:1 to receive CRB-701 at 2.7 or 3.6 mg/kg Q3W. The primary endpoints for parts A and B were dose-limiting toxicities and objective response rate (ORR), respectively. A scan ≥ 4 weeks after the initial response was required to confirm partial and complete responses. Safety, tolerability and pharmacokinetics were also assessed. Nectin-4 expression and human papilloma virus (HPV)/p16 status were evaluated retrospectively. **Results:** As of September 2025, 60 patients with HNSCC were enrolled across parts A and B. The median (range) number of previous therapies was 3.0 (1–9) in the 2.7 mg/kg group and 3.0 (1–8) in the 3.6 mg/kg group; 85% of patients were refractory to immunotherapy and platinum-based regimens. The confirmed ORR was 33.3% (4/12 patients; unconfirmed ORR also 33.3%) at the 2.7 mg/kg dose, and 33.3% (7/21 patients; unconfirmed ORR, 47.6% [10/21 patients]) at the 3.6 mg/kg dose. Responses were observed regardless of HPV/p16 status. The safety profile of CRB-701 was broadly consistent with earlier findings: keratitis, fatigue, alopecia, dysgeusia and anemia were the most frequently reported treatment-emergent adverse events (≥ 15% of overall solid tumor population [N = 167]). An expanded efficacy analysis reporting an additional 6 months of follow-up, including ORR, duration of response and progression-free survival will be presented at the congress. Subgroup analyses by HPV status, treatment history and disease extent will also be presented. **Conclusions:** CRB-701 has shown promising efficacy in patients with heavily pretreated R/M HNSCC, along with a favorable safety profile compared with other MMAE-based therapies. Further investigation of CRB-701 is warranted in this difficult-to-treat patient population. Clinical trial information: NCT06265727. Research Sponsor: Corbus Pharmaceuticals, Inc.

6063 Poster Session

PD-L1 CPS ≥10 population subgroup analysis of KEYNOTE-412: Pembrolizumab plus chemoradiotherapy versus placebo plus chemoradiotherapy for unresected locally advanced head and neck squamous cell carcinoma. First Author: Barbara Burtness, Yale University School of Medicine, New Haven, CT

Background: At the end-of-trial analysis of the randomized, double-blind, phase 3 KEYNOTE-412 trial (NCT03040999) in participants with unresected locally advanced (LA) head and neck squamous cell carcinoma (HNSCC), pembrolizumab plus chemoradiotherapy (CRT) was associated with a clinically meaningful event-free survival (EFS) benefit over placebo plus CRT (HR 0.79; 95% CI, 0.65-0.96) in the total population, and in participants whose tumors expressed PD-L1 CPS ≥1 (HR 0.80; 95% CI 0.64-0.98) and CPS ≥20 (HR 0.70; 95% CI, 0.49-1.00). We conducted a post hoc analysis of outcomes in the PD-L1 CPS ≥10 population. **Methods:** Adults with high-risk unresected LA HNSCC (T3-4 N0-3 or T1-4 N2a-3 laryngeal/hypopharyngeal/oral cavity/p16-negative oropharyngeal SCC, or T4 or N3 p16-positive oropharyngeal SCC) were randomly assigned to receive definitive CRT plus 17 cycles of pembrolizumab 200 mg or placebo intravenously every 3 weeks concurrently and after CRT. This exploratory analysis evaluated EFS and overall survival (OS) in the PD-L1 CPS ≥10 population. **Results:** Of 804 total participants, 382 had tumors expressing PD-L1 CPS ≥10 (n = 194, pembrolizumab group; n = 188, placebo group). As of data cutoff date (August 21, 2024), median study follow-up in the PD-L1 CPS ≥10 population was 74.1 months (range, 63.8-88.1). Median EFS was not reached (NR) in the pembrolizumab group and 61.4 months in the placebo group (HR 0.71; 95% CI, 0.53-0.97). The 60-month EFS rates were 62.4% and 50.3%, respectively. Median OS was not reached in either the pembrolizumab or the placebo group; the 60-month OS rates were 70.7% and 60.9%, respectively (HR 0.75 [95% CI, 0.53-1.04]). **Conclusions:** Results from this post hoc analysis of the KEYNOTE-412 trial with over 2 years of additional follow-up were consistent with those of the end-of-trial analysis in the overall population. For participants whose tumors expressed PD-L1 with a CPS ≥10, we observed a clinically meaningful EFS and OS benefit for pembrolizumab plus CRT over placebo plus CRT, with a numerically lower HR than reported for the overall population. Clinical trial information: NCT03040999. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

6064 **Poster Session**

Clonal hematopoiesis in head and neck carcinomas receiving immunotherapy. First Author: Niki Gavrielatou, Attikon University Hospital, Athens, Greece

Background: Clonal hematopoiesis (CH) is an age-related accumulation of somatic genetic alterations in hematopoietic stem cells. It is implicated in the evolution of myeloid neoplasms and has been associated with poor prognosis in patients with solid tumors. Immunotherapy (ITx) has become the standard of care in the treatment of recurrent/metastatic head and neck cancer (R/M HNSCC), however, response rate corresponds to 20% of total population and relies in a robust innate host immunity. This study aims to identify the presence of CH among ITx-treated R/M HNSCC patients and its potential association with treatment outcomes. **Methods:** Matched pre-treatment peripheral blood (PB) and tumor tissue samples of 32 ITx-treated R/M HNSCC patients were used for DNA extraction. The ten most commonly mutated CH genes were sequenced using a custom NGS Qiagen panel with unique molecular identifiers. Low confidence and synonymous variants were excluded. Pathogenic, likely pathogenic and conflicting with moderate or high annotation impact variants based on the ClinVar database were investigated for associations with progression-free (PFS) and overall survival (OS) as well as for differences in expression between blood and tissue. The same gene alterations and their correlation with survival in HNSCC were also explored in three public datasets (TCGA, GENIE, MSKCC) as an external validation of our findings. **Results:** A total of 2,088 variants were detected with 1,222 silent variants. After filtering,105 pathogenic, likely pathogenic and conflicting interpretation variants were retained. Mutations in CH related genes were identified in 18 out of 32 PB samples (56%). In tissue samples, (excluding *TP53*) mutations were identified in 12 out of 32 samples (37%). *TP53*mutations were significantly higher in tissue samples versus PB (*P*=0.028). *PPM1D* mutations in PB were correlated with shorter PFS (*P*=0.003) and OS (*P*=0.0116), while *TP53* mutations in tissue showed a trend for decreased OS (*P* =0.097). TCGA and MSKCC analysis confirmed a negative association of *TP53* mutations in tissue with OS (*P*=0.0020, *P*=0.0001, respectively). **Conclusions:** CH was frequently detected in PB and tumor tissue of R/M HNSCC patients. CH-related *PPM1D* mutations in PB and *TP53* in tumor tissue, were associated with shorter PFS and OS to ITx, suggesting a potential association between both peripheral and intratumoral immune contexture and clinical outcomes. Research Sponsor: None.

6065 **Poster Session**

Prognostic impact of tumor suppressor and DNA damage repair gene mutations in oral cavity squamous cell carcinoma: A clinico-genomic analysis from a real-world database. First Author: Parisa Abedi, Smilow Cancer Center, Yale School of Medicine, New Haven, CT

Background: Oral cavity squamous cell carcinoma (OCSCC) has unique genomic features, yet molecular biomarkers predicting prognosis remain poorly defined. Prior surgical series and TCGA analyses demonstrated TP53 and TERT promoter mutations associate with worse outcomes, while DDR pathways may influence immunotherapy response. However, no study has systematically evaluated these mutations with linked treatment and survival data. This is the first real-world clinico-genomic analysis addressing this gap in OCSCC. **Methods:** Using a pre-specified protocol with IRB approval, we analyzed 381 OCSCC patients from the Flatiron Health-Foundation Medicine Clinico-Genomic Database. Inclusion required confirmed OCSCC, genomic profiling (~300 genes), and survival data. We evaluated tumor suppressors (TP53, CDKN2A), TERT promoter, PIK3CA, and DDR genes (BRCA1/BRCA2/PRKDC). IPTW adjusted for age, sex, stage, smoking, advanced disease, and TMB. A 90-day landmark eliminated immortal time bias. Complete case analysis handled missing data. IO cohort (n=213, 56%) received checkpoint inhibitors. Primary endpoint: OS from diagnosis; secondary: OS from IO initiation. **Results:** Stage IV was the strongest clinical prognostic factor (HR 1.64, 95%CI 1.29-2.08, p$<$0.0001). In IO-treated patients, TMB-high showed improved survival (HR 0.54, p=0.035). DDR pathway mutations were associated with markedly inferior outcomes from IO initiation (HR 2.34, 95%CI 1.00-5.49, p=0.049; median OS 5.7 vs 13.8 months; 12-month OS 17.4% vs 50.4%). TP53+CDKN2A co-mutation showed a trend toward worse survival versus TP53 alone (HR 1.50, 95%CI 0.99-2.27, p=0.056; median OS 9.8 vs 12.8 months; 12-month OS 34.7% vs 51.5%). **Conclusions:** In this first real-world clinico-genomic analysis of OCSCC, TP53 mutation was associated with worse OS, and TP53+CDKN2A co-mutation identified an even higher-risk subset with nearly halved median survival (20.9 vs 44.5 months) compared to wild-type. CDKN2A co-occurred with TP53 in 95% of cases. TERT promoter mutations confirmed their adverse prognostic role. Notably, PIK3CA mutation showed favorable prognosis (HR 0.59), potentially relevant for targeted therapeutics. DDR pathway mutations predicted particularly poor outcomes following immunotherapy. These findings provide a molecular framework for risk stratification in OCSCC and warrant prospective validation. Research Sponsor: None.

Prognostic impact of gene mutations on overall survival in oral cavity cancer.

Genes	HR (95%CI)	p-value	Median OS (MT vs WT)	12-mo OS (from diagnosis)
TP53+CDKN2A co-mutation	1.83 (1.23-2.72)	0.003	20.9 vs 44.5 mo	76.5% vs 83.9%
TP53	1.72 (1.20-2.47)	0.003	26.0 vs 44.5 mo	80.6% vs 85.1%
CDKN2A	1.34 (1.04-1.73)	0.024	20.9 vs 34.2 mo	77.3% vs 83.6%
TERT promoter	1.35 (1.01-1.80)	0.041	24.4 vs 38.0 mo	77.6% vs 88.8%
PIK3CA	0.59 (0.42-0.85)	0.004	51.3 vs 25.7 mo	83.5% vs 81.0%

6066 **Poster Session**

Clinical validation of ultra-sensitive WGS-based MRD detection in head and neck squamous cell carcinoma: Results from MONSTAR-SCREEN-3. First Author: Naoki Akisada, Head and Neck Surgery, National Cancer Center Hospital East, Kashiwa, Japan

Background: Circulating tumor DNA (ctDNA)-based molecular residual disease (MRD) detection has shown promise across various malignancies, yet limited data exist for Head and Neck Squamous Cell Carcinoma (HNSCC). The prospective, multicenter MONSTAR-SCREEN-3 study evaluates an ultra-sensitive whole-genome sequencing (WGS)-based MRD assay in patients with resectable solid tumors undergoing curative-intent therapy. Here, we report preliminary results from patients with resectable HNSCC enrolled in the definitive cohort (target n=1,100). **Methods:** Personalized ctDNA panels were generated using a WGS-based tumor-informed platform (Myriad Genetics), incorporating up to 1,000 tumor-specific variants identified through WGS of matched tumor tissue. Serial plasma samples were collected at baseline, 1 month post-surgery, quarterly during the first year, and biannually thereafter for up to two years. **Results:** As of November 2025, 44 patients with resectable HNSCC were enrolled; MRD results were available for 139 samples from 34 patients. Median age was 65 years (range: 39-87), with male predominance (65.7%). Clinical staging included Stage III (15.6%), IVA (75.0%), and IVB (9.4%). All patients underwent upfront radical surgery. Personalized panel creation succeeded in 100% of patients (34/34), identifying a median of 6,119 highly confident tumor-specific alterations per patient (range: 1,288-15,418) and yielding bespoke panels containing 717-1,000 alterations. Customized panels were created with 97.7% SNVs and 2.3% indels. The assay demonstrated 100% baseline ctDNA detection (34/34), with 5.9% detected at ultra-sensitive levels (tumor fraction $<$100 parts per million [ppm]; minimum detection: 83.3 ppm). MRD positivity at 1 month, 3 months, and 6 months was at ultrasensitive levels in 10/14 (71.4%), 6/16 (37.5%), and 4/5 (80%) patients, respectively. Among 10 patients who developed radiological recurrence, median lead time was 2.7 months (range: 0-4.6 months). MRD-positive patients at 1 month after surgery had poorer disease-free survival than MRD-negative patients (HR 18.9, 95% CI 2.4–148.9; log-rank P$<$0.0001). Nine of the 13 patients who were ctDNA-positive at 1 month experienced recurrence, whereas only 1 of the 20 ctDNA-negative patients recurred. **Conclusions:** The WGS-based personalized ctDNA assay achieved high technical feasibility in HNSCC, with comprehensive customized variant panels highlighting the critical importance of ultra-sensitive platforms. These results suggest potential clinical utility for recurrence surveillance in HNSCC. Updated results will be presented. Clinical trial information: UMIN000053975. Research Sponsor: None.

6067 **Poster Session**

Integrated proteogenomic profiling to reveal prognostic subtypes and actionable targets in adenoid cystic carcinoma. First Author: Jiawei Zhou, Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Adenoid cystic carcinoma (ACC) is a rare head and neck malignancy characterized by highly variable clinical outcomes and a lack of validated biomarkers to guide risk stratification or therapeutic decision-making. Despite a generally low tumor mutational burden, patients frequently experience late recurrence and distant metastasis, underscoring the need for biologically informed prognostic models. Existing genomic and transcriptomic classifiers have failed to adequately explain this heterogeneity. We therefore performed integrated multi-omic profiling to define biologically grounded prognostic subtypes and clinically actionable biomarkers in ACC. **Methods:** We established a multi-omics cohort of 55 surgically resected ACC tumors, including salivary gland–derived and pulmonary ACC, with matched adjacent normal tissues. Whole-exome sequencing, RNA sequencing, quantitative proteomics, and phosphoproteomics were performed. Cross-omics concordance and driver-anchored pathway effects were assessed. Transcriptomic and proteomic data were integrated using Similarity Network Fusion (SNF) to derive molecular subtypes. Prognostic proteins were evaluated using Cox regression. Targeted quantitative mass spectrometry was applied for orthogonal validation and for quantifying antibody–drug conjugate (ADC) targets and pathway stoichiometry. **Results:** ACC exhibited a low-mutational genomic landscape but profound proteomic and phosphoproteomic remodeling, with systematic activation of replication, cell-cycle, chromatin remodeling, and receptor tyrosine kinase–adhesion pathways, accompanied by suppression of immune-associated signaling. Driver effects were more consistently captured at the protein level than at the RNA level, indicating a proteome-driven tumor biology. SNF-based multi-omic integration identified three molecular subtypes with significantly different disease-free survival (DFS; log-rank P=0.0064), outperforming the conventional ACC-I/II classifier. These subtypes formed a biological continuum defined by metabolic robustness and cell-cycle competence. A compact three-protein signature independently stratified DFS. Quantitative profiling demonstrated broad and functionally relevant expression of ADC targets, including TROP2 and B7-H3, and identified ratio-based functional indices (e.g., IGF2/IGF1R and TP63/NOTCH1) associated with risk groups. **Conclusions:** ACC is a proteome-driven malignancy in which post-transcriptional regulation and signaling stoichiometry dominate clinical behavior. Integrated multi-omic analysis redefines ACC prognostic architecture and yields quantitative, translatable biomarkers that may inform precision risk stratification and therapeutic strategies in this rare head and neck cancer. Research Sponsor: Bio-insight Biotechnology (Hangzhou) Co., LTD; The National Key Research and Development Program of China; 2023YFC2508500; National Natural Science Foundation of China; 82272951, 82272953; CAMS Innovation Fund for Medical Sciences (CIFM); 2024-I2M-TS-005.

6068 **Poster Session**

Baseline spatial tumor microenvironment states to define response and primary resistance to immune checkpoint inhibition in recurrent/metastatic head and neck squamous cell carcinoma. First Author: Armando Di Bello, Medical Oncology, Comprehensive Cancer Center, Fondazione Policlinico Universitario "A Gemelli"-IRCCS, Rome, Italy

Background: Despite the clinical impact of immune checkpoint inhibitors (ICIs) in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC), durable benefit is limited to a minority of patients and robust predictive biomarkers are lacking. PD-L1 combined positive score incompletely captures response heterogeneity, likely due to the spatial complexity of the tumor microenvironment (TME). We used spatial transcriptomics to identify baseline TME architectures associated with ICI response. **Methods:** Pre-treatment primary tumor samples from 12 patients with R/M HNSCC treated with ICIs were profiled using high-resolution spatial transcriptomics (Xenium In Situ, 10x Genomics; 380-gene immuno-oncology panel). Exceptional responders (ER) were defined by progression-free survival (PFS) $\geq$20 months, while poor responders (PR) had PFS $\leq$3 months. Differential gene expression and Gene Ontology (GO) enrichment were integrated with cell-type–resolved analyses to map transcriptional programs to cellular compartments. **Results:** Distinct baseline TME architectures separated ER and PR. ER tumors showed coordinated upregulation of interferon-related and immune activation genes (STAT1, MX1, CD274) together with cell-cycle-associated genes (MKI67, CDK1). Functional enrichment highlighted immune signaling, chemokine-mediated recruitment, and vascular remodeling, consistent with an immune-inflamed and spatially permissive microenvironment. In contrast, PR tumors exhibited dominant fibroblast-driven extracellular matrix and inflammatory programs, with enrichment of FN1, SPARC, LUM, VCAN and IGFBP7. GO enrichment in PR highlighted integrin-mediated processes, PDGFR-centered signaling, TGF-β–related pathways, and platelet-related signaling programs. Cell-type–resolved spatial mapping showed that fibroblast/ECM programs in PR were predominantly localized to fibroblast-enriched stromal compartments, whereas interferon-response programs in ER were distributed across both tumor and immune compartments. **Conclusions:** Baseline spatially organized TME states are associated with ICI outcomes in R/M HNSCC. ER exhibit an interferon-enriched, immune-permissive architecture, whereas primary resistance is linked to a fibroblast-dominated, ECM-rich and immune-restrictive niche. Proteomic validation of key spatial signals is ongoing to prioritize candidate predictive biomarkers for evaluation in a larger cohort. Enrichment of integrin-mediated processes and PDGFR-centered signaling in PR highlights actionable stromal vulnerabilities warranting translational investigation. Research Sponsor: Institutional research funds from the Catholic University of the Sacred Heart (Università Cattolica del Sacro Cuore), Rome, Italy (non-profit,investigator-initiated; no commercial sponsorship).

6069 **Poster Session**

Circulating HPV DNA for early detection of minimal residual disease after definitive therapy in oropharyngeal cancer: A phase II biomarker-driven study. First Author: Luana Guimaraes de Sousa, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Persistent detection of circulating HPV DNA (cfHPVDNA) in plasma following definitive therapy for HPV-positive oropharyngeal squamous cell carcinoma (HPV+OPSCC) is strongly associated with inferior outcomes, including increased risk of relapse and distant metastasis, and defines a high-risk patient population. Immune checkpoint blockade targeting the PD-1 pathway has demonstrated clinically meaningful activity in both curative and palliative settings. We hypothesize that balstilimab, an anti–PD-1 antibody, can induce cfHPVDNA clearance in patients (pts) with persistent ctHPVDNA after definitive treatment and improve long-term disease control. **Methods:** Eligible pts had HPV+OPSCC, stage I–III per AJCC 8th edition (excluding T1–2N0 and T1–2N1 with lymph nodes $<$3 cm), and baseline ctHPVDNA ($>$20 copies/ml) per our institution digital droplet PCR assay. After completion of definitive standard-of-care therapy, ctHPVDNA was assessed at 3- and 6-months. Pts with positive ctHPVDNA test in the absence of radiographic evidence of disease were eligible to receive balstilimab (AGEN2034) at 3 mg/kg intravenously every 2 weeks for 6 months. The primary endpoint was cfHPVDNA clearance rate. Secondary endpoints included time to cfHPV DNA clearance, recurrence-free survival, overall survival, and safety. The study was designed to enroll up to 20 pts using a Bayesian optimal phase II design considering an expected clearance rate of 30%. In order to treat 20 pts, 140 pts would needed to be pre-screened with a baseline positive ctHPVDNA (15% of expected minimal residual disease). **Results:** A total of 168 pts were pre-screened, of whom 139 were eligible to proceed; disease stage was I, II, and III in 46% (N=64), 28% (N=39), and 26% (N=36) of pts, respectively. The median baseline ctHPVDNA level was 614 copies/mL (range, 26–239,111). A total of 130 of 139 pts had the 3-month ctHPVDNA assessment, as nine have been excluded (loss of follow-up or withdraw consent). Five had a positive ctHPVDNA result, all of whom had radiographic evidence of disease recurrence (3 local, 1 distant, and 1 both local and distant). Among the remaining 125 pts, 100 have completed the 6-month ctHPVDNA assessment. One pt had a positive ctHPVDNA result with radiographic evidence of local recurrence. One patient had a qualitative positive test ($<$20 copies/ml) without evidence of disease, but the following test prior to trial enrollment was negative. To date, no pts has been allocated to receive balstilimab. **Conclusions:** Persistent ctHPV DNA positivity without radiographic evidence of disease has not been observed following definitive therapy. These findings suggest that cfHPVDNA surveillance may have limited utility for early detection of minimal residual disease in this setting, thereby challenging the feasibility of ctHPVDNA–guided post-definitive intervention strategies. Clinical trial information: NCT05363709. Research Sponsor: Charles and Daneen Stiefel MD Anderson Oropharyngeal Cancer Fund; Agenus Inc; Cancer Moonshot NCI.

6070 **Poster Session**

Identification of tumor repopulating–like epithelial cells and a repair-dominant niche in pathological responders after neoadjuvant chemo-immunotherapy for HNSCC. First Author: Yongchao Yu, Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: Neoadjuvant PD-1 blockade plus chemotherapy can induce deep pathologic responses in HNSCC. However, pCR is an imperfect surrogate for OS, and the prior study showed that $>$50% of patients achieving CR after neoadjuvant chemo-immunotherapy relapse rapidly without local therapy, suggesting post-treatment ecosystems may retain programs supporting residual cell persistence and relapse. **Methods:** We profiled tumors from treatment-naïve patients and from patients receiving neoadjuvant taxane/platinum (TP) plus PD-1 blockade with partial response or pCR using scRNA-seq and Xenium spatial transcriptomics. Integrated computational analyses mapped residual epithelial/microenvironmental programs and spatial organization, with validation by immunoblotting, flow cytometry, and mIHC. Translational strategies were evaluated in a 4NQO-induced murine model and a PD-1–resistant murine tongue cancer line. **Results:** We identified a KRT15+IL1R2+ stem-like epithelial population enriched after therapy, most prominent in pCR (61/78 patients), localized to post-treatment regression beds but not discernible on H&E. They were viable and quiescent, lacking DNA damage and cell-death activation; CytoTRACE indicated high differentiation potential, suggesting tumor-repopulating cells. Concerning the microenvironment, across the response continuum from treatment-naïve to partial pathologic response to pCR, scRNA-seq revealed stepwise enrichment of infiltrating non-exhausted cytotoxic CD8 effector T cells, consistent with progressively strengthened tumoricidal immunity. In contrast, deep responders displayed a shift toward a repair-dominant niche: macrophages progressively transitioned from CXCL9+ inflammatory monocytes to SPP1+ macrophages with reduced antigen-presentation programs and enhanced tissue-remodeling features, accompanied by enrichment of multiple repair-associated fibroblast states. Xenium further supported spatial proximity and putative interactions among IL1R2+ epithelium, macrophages, and fibroblasts, which may limited T cell–tumor contact. IL1R2 upregulation was also observed in a PD-1–resistant murine tongue cancer line. In vivo, IL-1β co-administration with PD-1 blockade attenuated treatment efficacy, whereas anti–IL-1β antibody combined with PD-1 blockade enhanced efficacy. **Conclusions:** Deep responses to neoadjuvant chemo-immunotherapy are coupled with a paradoxical repair program and enrichment of IL1R2+ stem-like epithelium that may permit residual persistence and recurrence. The IL-1β–IL1R2 axis is a translationally actionable lever to improve durability and mitigate relapse. Given residual risk even after pCR, de-escalation of local therapy (such as reducing surgical extent or altering definitive treatment strategies) warrants caution. Research Sponsor: National Natural Science Foundation of China; 82303881; 82573603.

6071 **Poster Session**

Inferring optimal detection of homozygous loss (homozygous deletion) in head and neck cancer: Associations with HPV status, primary disease site, and clinical outcomes. First Author: Jessica Lyn Geiger, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Background: Validated detection of homozygous loss is becoming increasingly important in clinical practice. Examples include targeting the AKT pathway in breast cancer with *PTEN* loss and ongoing multi-tumor trials of PRMT5 and MAT2A inhibitors, with *MTAP* loss serving as a key biomarker. Homozygous losses are challenging to detect and require intentional next-generation sequencing assay design and validation. We evaluated the prevalence of the most common homozygous losses in advanced head and neck squamous cell carcinoma (HNSCC) and their associations with HPV status, primary site, and clinical outcomes on standard first-line (1L) therapies. **Methods:** This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine head and neck cancer clinico-genomic database (FH-FMI CGDB), originating from approximately 280 US cancer clinics (~800 sites of care). Patients with advanced HNSCC who underwent tissue-based genomic profiling with FoundationOneCDx were included. First-line therapy included chemotherapy alone or in combination with cetuximab or immune checkpoint inhibitors (ICIs). Logistic regression assessed the associations of prior treatment, HPV status, and primary disease site with homozygous losses. Clinical outcomes were evaluated with Cox proportional hazards models. **Results:** Among 969 HNSCC specimens, homozygous losses were most frequent in *CDKN2A* (22.1%), *CDKN2B* (17.8%), *MTAP* (9.4%), and *PTEN* (5.3%). *CDKN2A, CDKN2B and MTAP* losses were enriched in tumors arising from the larynx and hypopharynx compared with the oral cavity and oropharynx and were largely mutually exclusive with HPV positivity. *PTEN* loss was most common in the oropharynx and was enriched in HPV-positive tumors and in metastatic liver biopsies. In univariable analysis, homozygous losses were not associated with outcomes after 1L therapy. In multivariable analysis, HPV negativity and higher ECOG scoring, but not PD-L1 status, were independently associated with worse overall survival. **Conclusions:** Using an assay that is FDA-approved to detect and report copy-number (CN) losses, homozygous losses of *CDKN2A*, *CDKN2B*, *MTAP*, and *PTEN* were frequently observed in HNSCC. These alterations were not directly associated with outcomes following 1L therapy. Similar to *CDKN2A/B* loss, *MTAP* loss was enriched in HPV-negative tumors and defines a clinically relevant subset of HNSCC (~10%) potentially eligible for emerging MTAP-targeted therapies. Research Sponsor: None.

6072 **Poster Session**

Comprehensive genomic profiling of adenoid cystic carcinoma using the AACR Genie Database. First Author: Madeline Patrick, Santa Clara University, Santa Clara, CA

Background: Adenoid cystic carcinoma (ACC) is a rare neoplasm of the secretory glands, comprising <1% of head and neck tumors. While most commonly arising in salivary glands, ACC has also been reported in the skin, breasts, prostate, and female genital tract. Despite multimodal treatment, no standardized therapeutic approach exists, and prognosis remains poor, with a 5-year survival rate of 50-60%. This study utilizes the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database to characterize the genomic landscape of ACC and identify prognostic biomarkers and therapeutic targets. **Methods:** The AACR GENIE database was accessed via cBioPortal (v18.0-public) on December 12, 2025, to identify ACC cases. Frequently mutated genes, demographic associations, and patterns of mutual exclusivity were evaluated using two-sided t-tests and non-parametric analyses with Benjamini-Hochberg false discovery rate correction. **Results:** A total of 540 samples from 500 patients were analyzed, of whom 229 (45.8%) were male, and 266 (53.2%) were female. The cohort included 334 (66.8%) non-Hispanic patients and 39 (7.8%) Hispanic patients. By race, 334 (66.8%) were White, 46 (9.2%) Asian, and 42 (8.4%) Black. Most tumor samples were metastatic (293, 54.3%), followed by primary tumors (217, 40.2%). The most frequently mutated genes were *NOTCH1* (n=152; 28.1%), *KDM6A* (n=59; 10.9%), *ARID1A* (n=54; 10.0%), *BCOR* (n=52; 9.6%), *KMT2C* (n=44; 8.1%), and *KMT2D* (n=42; 7.7%). Sex-stratified analysis demonstrated *FH* mutations occurring exclusively in females (n=4, $p<0.001$), and a higher prevalence of *KMT2C* in female patients (n=25 vs n=8, $p<0.001$). *TET2* alterations were more frequent in males (n=8 vs n=1). Race-based analysis identified *GATA3* mutations exclusively in Asian patients (n=2; p=0.002) and a higher frequency of *FGFR3* alterations in Asians compared with non-Asian patients (n=2 vs n=1; p=0.0447). Co-occurrence was observed between *NOTCH1* and *ARID1A* (n=21/106; $p<0.001$), *CREBBP* (n=17/98; $p<0.001$), and *KDM6A* (n=22/117; p=0.003). Additional co-occurrence was noted between *KDM6A* and *ARID1A* (n=14/80; $p<0.001$), and *CREBBP* with *PIK3CA* (n=8/50; p=0.001). Mutations in *APC* (n=6; $p<0.001$), *CDK12* (n=4; p=0.05), *ELF3* (n=4; $p<0.05$), *MDM2* (n=4; $p<0.05$), and *JAK2* (n=4; $p<0.05$) were observed exclusively in primary tumors. **Conclusions:** To our knowledge, this is the first comprehensive analysis of ACC using the GENIE database. Our findings corroborate prior reports implicating *CREBBP*, *NOTCH1*, and *KDM6A* in ACC while identifying a novel demographic association with GATA3 mutations exclusive to Asian patients. These findings highlight *CREBBP*, *NOTCH1*, *KDM6A,* and *GATA3* as potential targets for future therapeutic development. Research Sponsor: None.

6073 **Poster Session**

Environmental exposure and prevalence of papillary thyroid cancer in West Virginia: An ecological analysis of per and polyfluoroalkyl substances (PFAS)—impacted regions. First Author: Sanjana Nethagani, West Virginia University Cancer Institute, Morgantown, WV

Background: Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants with widespread exposure through contaminated surface water, groundwater, and drinking water systems. In West Virginia, PFAS contamination has been documented across counties within the Ohio River basin and inland regions affected by industrial activity, waste disposal, and groundwater contamination. This project aimed to study the prevalence of papillary thyroid cancer at a county-level to assess geographic clustering in relation to PFAS-impacted regions and compare statewide incidence with national benchmarks. **Methods:** We conducted a statewide, county-level ecological analysis using Epic electronic health record-driven data to identify papillary thyroid cancer cases diagnosed between 2015 and 2025. County specific prevalence rates were calculated using averaged county population denominators. Relative risks (RR) with 95% confidence intervals were calculated for each county relative to the statewide thyroid cancer prevalence using Poisson-based methods. Spatial patterns were evaluated in relation to counties within the Ohio River basin, including the Monongahela and Kanawha sub-basins, as well as counties with documented or suspected PFAS-related groundwater contamination. Statewide thyroid cancer incidence was contextualized using U.S. Cancer Statistics (1999-2022). **Results:** Papillary thyroid cancer prevalence demonstrated marked geographic heterogeneity across WV, with spatial clustering observed in multiple PFAS-impacted counties. Counties with elevated prevalence demonstrated RRs ranging from approximately 1.75 to 2.75, with the highest RR observed in Harrison (RR 2.75 CI 2.35-3.22), Marion (RR 2.33 CI 1.94-2.79), Braxton (RR 2.30 CI 1.58-3.33), Barbour (RR 2.13 CI 1.50-3.00) and Webster (RR 1.98 CI 1.21-3.24) counties. All associations were statistically significant ($p<0.05$). Many counties outside PFAS-impacted regions demonstrated RR approximating or below 1.0. At the population level, WV demonstrated a higher thyroid cancer incidence than the U.S. overall (20.5 vs 17.4 per 100,000, age-adjusted). **Conclusions:** Papillary thyroid cancer in West Virginia has a spatial clustering pattern in PFAS-impacted counties and a higher statewide incidence compared with national benchmarks. Experimental evidence provides biologic plausibility, as perfluorooctanoic acid disrupts thyroid-stimulating hormone receptor signaling, impairs N-glycosylation, and promotes pro-tumorigenic cellular pathways. Although causal inference is limited by the ecologic design, the convergence of geographic clustering and elevated statewide incidence warrants further investigation of PFAS-related papillary thyroid cancer risk using exposure-resolved individual-level analytic approaches. Research Sponsor: None.

6074 **Poster Session**

Discovery of gene set–based biomarkers and therapeutic targets for papillary thyroid cancer based on circulating DNA and tissue RNA. First Author: Hsih-Te Yang, Department of Biostatistics and Data Sciences, Atrium Health Levine Cancer, Charlotte, NC

Background: Mutations in pathways known to promote oncogenesis in Papillary Thyroid Carcinoma (PTC) have been demonstrated in cell-free DNA (cfDNA) samples from patients with PTC, and at higher levels in patients with advanced and dedifferentiated disease such as anaplastic thyroid cancer (ATC). In our study, the most frequent cfDNA mutations were associated with activation of *BRAF*-independent pathways and epigenetic regulation, suggesting a prominent role as drivers of disease in some patients. Also observed were mutations more frequently associated with dedifferentiated thyroid cancer, such as *TP53* at 10% (5/49) in cfDNA vs 2% (1/47) in tissue samples. We hypothesized that nucleosome pattern analysis on cfDNA samples from a *BRAF*-independent subgroup would reveal evidence of heightened epigenetic signaling. **Methods:** We classified PTC into two subtypes based on cfDNA mutation profiles: *BRAF*-independent pathway (BI, 35% of patients with ≥1 mutation in *KMT2A*, *ATM*, or *TP53*) and *BRAF*/alternate-mediated pathway (B/a, 65% with *ARID1A*, *BRAF*, or others). These two gene groups were mutually exclusive by co-mutation and protein interaction networks. Chromatin structure was inferred from cfDNA fragment patterns using LIQUORICE. Gene signatures and pathway scores were then analyzed via GSEA and GSVA on the tissue RNA-seq data. **Results:** Significantly higher H3K4me1 signal (p = 0.047) was detected in cfDNA from the BI subgroup, indicating active epigenetic enhancer states. Additional gene expression analysis on tumor tissue revealed a unique six-gene signature (FDR = 0.089) enriched in the maternal-to-zygotic transition (MZT) pathway, with GSVA scores differing markedly between BI and B/a groups (p = 0.004). Cross-referencing these patients with the PTC cohort data from The Cancer Genome Atlas (TCGA) showed worse disease-free survival in the BI group (p = 0.008) but no difference in overall survival (p = 0.580) between the two groups, possibly due to early-stage diagnosis. **Conclusions:** Mutations in *TP53*/*ATM*/*KMT2A*, associated with *BRAF*-independent pathways, correlate with active epigenetic states in PTC. This supports the hypothesis that epigenetic mechanisms are important drivers of progression in PTC. This study also supports a therapeutic strategy which targets these pathways, such as HDAC inhibitors previously validated in ATC cell lines and PDX models. Finally, six MZT-related genes may serve as biomarkers and regulators of epigenetic and transcriptional reprogramming important to the evolution of cancer in PTC patients. Research Sponsor: Atrium Health Foundation Grant Keep Pounding Fund.

6075 **Poster Session**

Intrapatient comparative analysis of tumor-informed ctDNA and ctHPV-DNA in patients with HPV-driven OPSCC. First Author: Evgeny Izumchenko, University of Chicago, Department of Hematology/Oncology, Chicago, IL

Background: The rising incidence of oropharyngeal squamous cell carcinoma (OPSCC) is largely attributable to human papillomavirus associated (HPV+) disease, which accounts for ~70% of OPSCC cases. Circulating tumor (ct)DNA has the potential to enable more accurate treatment response assessment, guide response-adaptive management, and detect minimal residual disease to indicate persistence or recurrence. Both mutation-based tumor-informed ctDNA and ctHPV-DNA testing have demonstrated utility in HPV+ disease, but prospective intrapatient evaluations remain limited. A direct comparison of these approaches is essential to determine redundancy versus complementarity and to guide optimal integration into OPSCC patient management. **Methods:** In an ongoing prospective study, serial plasma samples were obtained from patients with stages I-IV OPSCC undergoing curative intent treatment. Up to 50 patient specific somatic variants were selected based on tumor whole exome sequencing to develop a personalized tumor-informed next generation sequencing (NGS) ctDNA assay (Haystack MRD) for plasma analysis. In patients with HPV+ disease (determined via ISH, IHC, and/or NGS), plasma was also analyzed using an NGS-based assay interrogating 13 high-risk HPV strains (Haystack HPV). Paired intrapatient samples were analyzed using percent agreement with 95% confidence intervals and Cohen's kappa; concordance of dynamic changes was assessed using Spearman's correlation. **Results:** As of January 2026, ctDNA results were available for 111 serial timepoints from 26 patients. The median number of timepoints per patient was 4 (range 1-9). Seventeen patients (65%) had HPV+, and 9 (35%) had HPV− disease. In HPV+ patients, across 85 longitudinal samples collected during multimodal treatment and post-treatment surveillance, mutation-based ctDNA and ctHPV demonstrated high concordance (91%; 95% CI, 82.5–95.2; κ=0.80). Of 30 ctDNA+ samples, 28 were ctHPV+ (93%; 95% CI, 78.7–98.2%), while 49 of 55 ctDNA- samples were ctHPV- (89%; 95% CI, 78.2–94.9%). Discordance was infrequent (8/85, 9.4%), predominantly ctHPV+/ctDNA- (6/85, 7.1%). All ctHPV+/ctDNA- cases occurred during neoadjuvant treatment monitoring and reflected earlier clearance of ctDNA, with ctHPV clearance lagging by several weeks to months. Two low-level (<100 parts per million) ctDNA+/ctHPV- cases were observed in the adjuvant setting. When both analytes were present, dynamic changes in ctDNA and ctHPV levels were highly concordant (Spearman's ρ=0.94), although ctHPV was consistently detected at higher absolute levels. **Conclusions:** In HPV-driven OPSCC, tumor-informed ctDNA and ctHPV show high longitudinal concordance and distinct clearance kinetics, with earlier ctDNA clearance. Ongoing analyses will define how these assays can be optimally integrated into response assessment, treatment adaptation, and surveillance strategies. Research Sponsor: U.S. National Institutes of Health; U01CA230691; Cancer Research Foundation; University of Chicago Comprehensive Cancer Center (UCCCC).

6076 Poster Session

Biologic and clinical implications of HPV genome state variation in oropharyngeal cancers. First Author: Vikram Vasan, University of Pennsylvania, Philadelphia, PA

Background: HPV integration enhances carcinogenesis by ensuring viral DNA retention and increasing E6/E7 expression. Though HPV usually integrates in cervical cancer, DNA episomes persist in ~50% of HPV+ oropharyngeal cancers (OPCs), and prior studies relating integration to clinical outcomes are contradictory. Defining molecular traits and clinical behavior of episomal vs. integrated OPCs is impeded by the complexity of HPV genome states, which defy classification by any one assay. Here we classified HPV states based on concordance between HPV-host fusion mRNA detection (suggesting integration) and E6/E7 levels. Gene expression and clinical outcomes were compared among groups to seek biomarkers allowing therapeutic personalization. **Methods:** Samples were curated from 851 therapy-naïve HPV+ OPCs receiving robotic surgery at a single institution (2007-2020). RNA sequencing was performed on 50 HPV+ OPCs that later recurred (cases) and 50 that were cured (controls). Groups were matched for stage, smoking, and adjuvant therapy. OPCs were deemed likely episomal if absence of HPV-host fusion mRNA was accompanied by E6/E7 levels in the bottom tertile and likely integrated if fusion mRNA presence coincided with E6/E7 in the top tertile. These two OPC subsets were defined as E6/E7-concordant and the rest as E6/E7-discordant. Molecular traits were analyzed as previously (Sannigrahi MK et.al, *JNCI* 2025 117:7) using GSEA of Hallmark pathways and by two scores derived by GSVA of host mRNAs that potently stratified recurrence risk across multiple HPV+ OPC cohorts: (1) an immune suppression score (ISS) measuring reduced anti-tumor immunity and (2) a *t*umor progression score (*TPS*) capturing aggressive tumor cell-intrinsic traits. **Results:** In the overall cohort (n=100), the fusion (+) OPCs (n=49) had increased risk of recurrence (OR 2.90, 95% CI=1.27-6.64, p=.01). Whereas E6/E7 levels alone did not stratify recurrence risk, combining it with fusion status optimized prediction: the likely integrated OPCs (n=23) had high recurrence risk vs. likely episomal OPCs (n=24) (OR=3.81, 95% CI=1.13-12.82, p=.03) despite similar clinical characteristics in both groups. Time to recurrence was also shorter in likely integrated vs. episomal subsets (p=.02). By contrast, fusion read status did not stratify recurrence risk in the E6/E7-disconcordant OPCs (n=53). Adverse gene expression features were upregulated in likely integrated vs. likely episomal OPCs, as reflected in increased TPS (p=.04) and ISS (p=.04). These differences were absent in fusion (+) tumors of the E6/E7-discordant group. **Conclusions:** Our findings offer the most compelling evidence to date supporting independent association of HPV integration with adverse tumor biology and recurrence risk in OPCs. Jointly considering HPV-host fusion mRNAs and E6/E7 levels may guide the molecular biomarker development needed to personalize therapy based on HPV genome state. Research Sponsor: U.S. National Institutes of Health; R01DE034056; U.S. National Institutes of Health; UH2CA2675022.

6077 Poster Session

Validation of Immunoscore for prognostic stratification in HPV-associated oropharyngeal cancer: An international multicenter study. First Author: Dac Hung Nguyen, Université de Paris Cité, AP-HP, Hôpital Européen Georges Pompidou, Department of Otorhinolaryngology; INSERM UMRS 1138, Integrative Cancer Immunology; PARCC UMRS 970, INSERM, Paris, France

Background: Treatment optimization in HPV-associated oropharyngeal cancer (OPSCC) remains challenging due to the limited results of de-escalation trials. Existing patient selection criteria, mainly based on smoking history and TNM classification are insufficient and highlight the urgent need for standardized prognostic biomarkers. Herein, we present the first validation of the Immunoscore (IS) as a prognostic stratification tool in HPV-associated OPSCC. **Methods:** A cohort of 191 HPV-associated ($p16^+$ and HPV DNA/RNA^+) OPSCC patients treated between 2015–2024 was analyzed, including a French training cohort (N = 48) and three independent validation cohorts: a French retrospective monocentric (N = 48), a French prospective multicenter (N = 50) and a US retrospective multicenter cohort (N = 45). IS, an IHC-based standardized clinical digital pathology assay, quantifies $CD3^+$ and $CD8^+$ cell densities in tumor cores and invasive margins of FFPE sections. IS cut-offs were defined using the 25^{th} percentile of immune cell density in the training cohort and subsequently validated across all cohorts. Associations with disease-free survival (DFS), time to recurrence (TTR), and overall survival (OS) were assessed, along with immune profiling by 3′RNA-seq and sequential immunofluorescence. **Results:** Median age 65; 80% male; 74% smokers; 66% T1-2; 82% N0-1 (AJCC 8^{th}). Treatments included surgery only (9%), radiotherapy ± chemotherapy (27%) and surgery + radiotherapy ± chemotherapy (64%). 52.4% were IS-High (N = 100) and 47.6% IS-Low (N = 91). IS-High patients showed significantly improved DFS, consistently across the training and validation cohorts 1-3 (log-rank P = 0.0004, 0.003, 0.006, and 0.001, respectively). Multivariable analysis identified IS-Low as the strongest independent risk factor for DFS (HR 9.27; 95% CI: 4.14-20.76; $P < 0.001$), outperforming smoking status, T/N stage, and treatment modality. The model combining IS with clinical factors showed higher predictive accuracy for DFS (C-index 0.82) than clinical variables alone (0.70; $P < 0.0001$). Similar strong prognostic value of IS was observed for TTR (HR 7.64; 95% CI: 3.37-17.33; $P < 0.001$) and OS (HR 7.26; 95% CI: 2.77-18.99; $P < 0.001$). IS-High tumors showed enrichment of lymphoid and myeloid immune cell populations, contrasting with immune-poor signatures in IS-Low tumors (all $P < 0.05$). **Conclusions:** IS is a robust biomarker that outperforms standard clinical variables in both prognostic and predictive accuracy. The enriched cytotoxic immune infiltrate in IS-High tumors explains favorable outcomes and supports their potential suitability for treatment de-escalation. Prospective validation in future trials is warranted. Research Sponsor: None.

6078 Poster Session

Prognostic value and role in guiding individualized treatment of imaging extranodal extension (iENE) in nasopharyngeal carcinoma. First Author: Chuanrun Zhang, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Imaging extranodal extension (iENE) is a critical prognostic factor in nasopharyngeal carcinoma (NPC). While international consensus has standardized iENE grading, its prognostic value in NPC remains to be validated. Furthermore, evidence is lacking regarding the utility of iENE-based risk stratification in guiding individualized treatment, particularly for identifying candidates benefiting from adjuvant chemotherapy (AC). **Methods:** A total of 694 non-metastatic NPC patients with cervical lymph node metastasis who received intensity-modulated radiotherapy (IMRT) at Sun Yat-sen University Cancer Center from 2016 to 2017 were included. iENE was graded based on international group consensus by two radiologists through a consensus reading protocol: G0 (no extranodal extension), G1 (infiltration of perinodal fat), G2 (matted nodes), and G3 (invasion of adjacent structures including muscles and neurovascular bundles). Progression-free survival and overall survival were analyzed using the Kaplan–Meier method and log-rank test. Multivariable Cox proportional hazards models were applied to adjust for confounders. Time-dependent receiver operating characteristic (TD-ROC) curve analysis was used to evaluate the predictive performance of clinical variables. Stratified analysis for prognosis was performed based on treatment strategies including concurrent chemoradiotherapy(CCRT), induction chemotherapy plus CCRT(IC+CCRT), and IC+CCRT followed by adjuvant chemotherapy (IC+CCRT+AC). **Results:** The cohort included 257 (37.0%) G0, 117 (16.9%) G1, 216 (31.1%) G2, and 104 (15.0%) G3 patients. Survival analysis for OS, PFS, DMFS, and LRRFS revealed that G1 patients showed a comparable prognosis to G0 patients(5-year PFS: 82.1% vs. 89.1%, P > 0.05), whereas G2 and G3 patients exhibited significantly worse outcomes; therefore, G0 and G1 were combined into a low-risk subgroup. Multivariable analysis adjusting for T stage, N stage, volume of maximal lymph node, clinical stage, and treatment regimens confirmed that the refined iENE grading was an independent prognostic factor for PFS (G2 vs. G0/1: HR 1.77, 95% CI 1.25–2.51, P = 0.001; G3 vs. G0/1: HR 1.90, 95% CI 1.08–3.36, P = 0.027). TD-ROC curve demonstrated that the predictive performance of iENE for 1-, 3-, and 5-year PFS and OS was superior to that of T stage and pre-treatment EBV DNA. Most importantly, subgroup analysis indicated that the addition of AC significantly improved PFS outcomes in the G2/G3 subgroup (P = 0.006 and P = 0.009, respectively), whereas no survival benefit was observed in the low-risk G0/G1 subgroup (P = 0.133). **Conclusions:** The refined iENE grading system provides robust risk stratification for NPC. This system outperforms traditional biomarkers like EBV DNA, better distinguishing prognostic outcomes in patients and effectively guiding the application of intensified treatment. Research Sponsor: None.

6079 Poster Session

Prognostic significance of imaging-detected extranodal extension (iENE) in pathological ENE-negative head and neck squamous cell carcinoma. First Author: Ryo Kuboki, Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Advances in perioperative systemic therapy for head and neck squamous cell carcinoma (HNSCC) (e.g., KEYNOTE-689) have increased the need to tailor postoperative management, balancing oncologic benefit against toxicity and resource constraints. Imaging-detected extranodal extension (iENE) has been incorporated as a potential prognostic factor in the UICC TNM 9th edition. However, the prognostic impact of iENE among patients without pathological extranodal extension (pENE) remains unclear. We evaluated the association between iENE status and clinical outcomes in pENE-negative HNSCC. **Methods:** We retrospectively reviewed patients with HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx, radiologically suspected lymph node metastasis, and underwent primary surgery with neck dissection without adjuvant therapy, between 2012 and 2021. Eligible patients had pathologically confirmed lymph node metastasis, negative surgical margins, and no evidence of pENE. Preoperative iENE status was assessed by board-certified radiologists. Survival endpoints included event-free survival (EFS) and overall survival (OS). Patients were stratified into low-risk (non-candidates for adjuvant therapy) and intermediate-risk (candidates for postoperative radiotherapy alone) groups according to NCCN guidelines. **Results:** Of 3,771 screened patients, 133 met the eligibility criteria (low-risk: 20, intermediate-risk: 113), of whom 41 (30.8%) were iENE-positive. At a median follow-up of 60.6 months, iENE-positive patients demonstrated poorer outcomes than iENE-negative patients, including shorter EFS (5-year: 33.1% vs 55.4%; hazard ratio [HR], 1.69; p=0.029). The association between iENE positivity and inferior EFS was observed consistently across both risk strata. Overall survival also favored iENE-negative patients (5-year: 80.4% vs. 68.7%). On multivariate analysis, iENE positivity, ECOG Performance Status ≥1, and lower baseline serum albumin were independently associated with poorer EFS. Patients meeting none of the three factors had excellent outcomes despite omission of adjuvant therapy (5-year EFS: 69.8%, 5-year OS: 88.0%). **Conclusions:** iENE may help identify an unfavorable-prognosis subset among pENE-negative HNSCC patients. The study cohort predates the routine use of perioperative immunotherapy, and the generalizability of these findings in contemporary treatment settings requires prospective validation. Research Sponsor: None.

Five-year EFS by iENE status: Overall and by risk group.

Group	iENE status	5y-EFS	HR (95% CI)	P-value
ALL (n = 133)	Positive	33.1%	1.69 (1.05-2.71)	0.029
	Negative	55.4%	Ref.	
Intermediate risk (n = 113)	Positive	34.2%	1.57 (0.94-2.63)	0.08
	Negative	51.9%	Ref.	
Low risk (n = 20)	Positive	28.6%	3.57 (0.85-15.04)	0.06
	Negative	76.9%	Ref.	

6080 Poster Session

A phase 3, randomized, double-arm, open-label, controlled study of ASP-1929 photoimmunotherapy (PIT) versus physician's choice standard of care (SOC) for patients with locoregional, recurrent head and neck squamous cell carcinoma (HNSCC). First Author: Anastasios Maniakas, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Locoregional recurrence is the main cause of morbidity and mortality in HNSCC, yet therapeutic choices are limited by sequelae of previous treatment and the potential for significant loss of function. ASP-1929 PIT is a novel cancer-targeted technology, utilizing an anti-EGFR monoclonal antibody conjugated to the dye IR700, that is activated by 690 nm light to induce rapid selective tumor cell destruction and trigger immune response. **Methods:** This global phase 3 study was conducted at 40 study centers located in the US, Taiwan, Japan, India, and Ukraine. Patients with locoregionally recurrent HNSCC who had failed or progressed on or after at least 2 lines of therapy were randomized 2:1 to the PIT arm or SOC. The planned sample size was 275. In the PIT arm, each cycle consisted of ASP-1929 infusion (640 mg/m^2) on Day 1, followed 24 $\pm$ 4 hours later by illumination (50 J/cm^2 superficial and/or 100 J/cm interstitial). Retreatment occurred $\geq$4 weeks apart, based on tumor response, for up to 8 cycles. In the control arm, patients received the physician's choice of standard of care (docetaxel, cetuximab, methotrexate, or paclitaxel) until disease progression, intolerable adverse effects, or discontinuation of study treatment. Safety and efficacy outcomes were evaluated, with a data cutoff of 30 April 2025. **Results:** Active patient enrollment was discontinued due to challenges in patient recruitment and changes in the SOC landscape. As of 17 December 2024, 135 patients had been enrolled, with 68 patients experiencing progression or death and 36 patients in the ongoing long-term survival follow-up phase of the study. Median age was 62.0 years; 80.7% were male. In PIT and SOC arms, 64.0% and 63.0% of patients had received $\geq$ 3 prior therapy lines. Despite similar progression-free survival (HR 0.91; 95% CI 0.24 - 3.45), median overall survival was 15.7 months in the PIT arm compared to 9.6 months in the SOC arm (HR 0.83; 95% CI 0.50 - 1.36). Objective response rate was 25.8% in the PIT arm and 15.2% in the SOC arm, and disease control rate was 68.5% and 43.5%, respectively. Grade $\geq$3 treatment-emergent adverse events (TEAEs) occurred in 58.3% of patients in the PIT arm and 36.4% of patients in SOC; however, fewer TEAEs led to dose modification, delay, or interruption in the PIT arm (15.5% vs 30.3%). **Conclusions:** Considering the limitations of the study data, these results support ASP-1929 PIT as a tolerable and clinically active treatment option for locoregional, recurrent HNSCC and its ongoing evaluation in the current randomized global Phase 3 ASP-1929-381 study. Clinical trial information: NCT03769506. Research Sponsor: Rakuten Medical Inc.

6081 Poster Session

Efficacy of neoadjuvant immunochemotherapy followed by surgery in locally advanced buccal squamous cell carcinoma: A single-center real-world study. First Author: Haolei Tan, Head and Neck Surgery Department, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

Background: The 5-year overall survival (OS) rate for locally advanced (stage III–IV) buccal squamous cell carcinoma (LA BSCC) is under 50%. In stage IV disease, the 2-year OS rate is under 45%, and the 5-year OS rate is under 30% (29.3% for the anterior buccal and only 18.7% for the posterior buccal). Evidence is limited regarding whether betel nut chewing and tumor subsites influence the efficacy of neoadjuvant immunochemotherapy. **Methods:** Retrospective analysis of 115 patients with LA BSCC received neoadjuvant therapy at Hunan Cancer Hospital between August 2021 and October 2024. Treatment regimen: Neoadjuvant albumin-bound paclitaxel plus cisplatin or carboplatin combined with a PD-1 inhibitor, followed by definitive surgery. Postoperative adjuvant radiotherapy or chemoradiotherapy was administered based on pathological findings. Primary endpoint: Pathological complete response and major pathological response (pCR/MPR) rate; Secondary endpoints: Overall survival (OS) and disease free survival (DFS) at 1 and 2 years; Subgroup analyses: Outcomes were evaluated by betel nut chewing history, tumor subsite, and TNM stage. **Results:** Of 113 evaluable patients, 16% had stage III and 84% had stage IV disease. A history of betel nut chewing was present in 71.9%. The objective response rate to neoadjuvant therapy was 83.5%, including a 28.3% clinical complete response rate. 98 patients proceeded to surgery; the pCR/MPR rate was 27.6%, and the partial pathological response (pPR) rate was 52.0%. With a median follow-up of 29 months (15-53 months), 1-year OS and DFS rates were 80.5% and 74.3%, respectively; 2-year OS and DFS rates were 70.0% and 67.5%, respectively. 2-year OS did not differ significantly by betel nut chewing (P=0.8578) or by tumor subsite (anterior vs posterior buccal; P=0.5568). More advanced TNM stage was associated with poorer survival (P=0.0352). Patients achieving pCR or MPR had significantly better 2-year OS and DFS than those who did not (P=0.0386 and P=0.0102, respectively). Grade$\geq$3 adverse events occurred in 18% of patients and no treatment-related deaths were observed. **Conclusions:** Neoadjuvant immunochemotherapy increased the 2-year OS rate of LA BSCC to 70%, with the 27.6% pCR/MPR rate. Treatment efficacy did not differ by betel nut chewing or by tumor subsite, whereas TNM stage remained an independent prognostic factor. Deep pathological response (pCR/MPR) was associated with superior long-term outcomes. Research Sponsor: None.

	Number	2-yr OS rate(%)	p value	2-yr DFS rate(%)	p value
Tumor stage					
III	18/113	88.89	0.1558	78.75	0.0352
IVa	64/113	71.12		66.54	
IVb	31/113	54.17		39.13	
Tumor subsite					
Anterior buccal	88/113	69.85	0.5568	60.30	0.9963
Posterior buccal	25/113	64.29		60.00	
Pathological response rate					
pCR+MPR	27/98	78.95	0.0386	78.95	0.0102
pPR	51/98	83.43		72.66	
SD+PD	21/98	54.55		47.37	
Betel nut use					
+	82/113	69.22	0.8578	60.02	0.9238
-	31/113	67.88		60.87	

6082 Poster Session

Phase II randomised controlled trial on postoperative radiotherapy, in high-risk, resected, non-medullary, non-anaplastic thyroid cancers (THYRO-RT). First Author: Gouri Pantvaidya, Tata Memorial Centre, Mumbai, Maharashtra, India

Background: Locally advanced thyroid cancers have high rates of locoregional recurrence after standard treatment with surgery and radioactive iodine (RAI). Repeated surgery and RAI in recurrent disease contributes to significant morbidity. Retrospective studies have shown that the addition of adjuvant external beam radiotherapy (EBRT) may improve locoregional control in selected high-risk patients. This randomized phase II trial evaluated the role of adjuvant EBRT in reducing locoregional recurrence (LRR) in high-risk resected thyroid cancer. **Methods:** This was a phase II randomized controlled trial comparing surgery with RAI versus surgery with RAI plus EBRT in high-risk resected thyroid cancers. Patients with resected non-medullary, non-anaplastic thyroid cancer and predefined high-risk features were randomized (1:1) between July 2013 and April 2021. Patients randomized to EBRT received 6-MV IMRT with daily IGRT to a dose of 60 Gy in 30 fractions over six weeks. The primary endpoint was locoregional recurrence. Secondary endpoints included acute and late toxicity (LENT-SOMA scale) and quality of life. **Results:** Seventy-two patients were randomized, with 36 assigned to each arm; five patients withdrew consent. Overall, 86.6% had pathological T4a disease and 89.6% had pathological N1a/b disease. Further, 71.6% demonstrated extracapsular nodal extension and R1/R2 resection was seen in 49.3% of the patients. With a median follow-up of 102 months, on an intention to treat analysis, LRR occurred in 19.4% of patients in the surgery + RAI arm (OR 1.376, 95% CI 0.852-2.222), and 9.7% in the Surgery+RAI+EBRT arm (OR 0.611, 95% CI 0.299-1.632). This difference was not statistically significant (p = 0.263). Logistic regression analysis did not identify any factor significantly associated with LRR. There was no significant difference in 10 year-locoregional recurrence free survival between the two arms. Grade 3 acute radiation induced toxicity was observed in two patients. At last follow up, there was one death in the entire cohort, which was non-cancer related. **Conclusions:** In this very high-risk, resected thyroid cancer cohort, the addition of adjuvant EBRT to surgery and RAI did not significantly decrease locoregional recurrence. The overall acute toxicity was low and if adjuvant EBRT is indicated, it can be delivered with acceptable toxicity. Clinical trial information: NCT03669432. Research Sponsor: Department of Atomic Energy- Clinical Trials Unit, Government of India.

6083 Poster Session

C-POST study of adjuvant cemiplimab for high-risk cutaneous squamous cell carcinoma (CSCC): Disease-free survival (DFS) analyses per high-risk criteria and per start time after radiotherapy. First Author: Danny Rischin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: C-POST, a phase 3 trial (NCT03969004) in patients (pts) with high risk CSCC after surgery and radiotherapy (RT), demonstrated superior disease-free survival (DFS) for adjuvant cemiplimab (cemi) vs placebo (pbo) (HR, 0.32; $P<0.0001$); treatment discontinuation due to adverse events occurred in 9.8% vs 1.5% of pts (Rischin, et al. *N Engl J Med*. 2025). With approximately 6 months of additional follow-up, we present exploratory analyses of DFS per high-risk criteria and per the interval between completion of prior RT and study randomization (2-6 wk vs $>$6 wk). These additional analyses provide key data to understand the importance of risk factors and the impact of time post RT. **Methods:** Pts were randomized 1:1 (N=415) to adjuvant cemi or pbo (350 mg cemi or pbo Q3W for 12 wk, then 700 mg cemi or pbo Q6W for 36 wk). All pts had nodal high-risk disease (with extracapsular extension [ECE] and $\geq$1 node $\geq$20 mm, or $\geq$3 nodes regardless of ECE) and/or non-nodal high-risk disease (in-transit metastases, perineural invasion, T4 lesions, or recurrent CSCC with $\geq$1 other feature). Tumors could meet $\geq$1 high-risk criteria. Randomization occurred within 2-11 wk after completion of RT. Data cutoff was April 7, 2025. **Results:** Among 415 pts (209/206 cemi/pbo) randomized, the DFS HR was 0.35 (95% CI, 0.23-0.55) at a median follow-up of 30 months. The most common high-risk criterion was nodal ECE, present in 48.4% of pts (201/415). DFS was improved with cemi vs pbo across all high-risk features, including both nodal and non-nodal criteria (Table 1). A consistent benefit was observed regardless of whether the interval between prior RT completion and study randomization was 2-6 wk (DFS events, 17/117 [14.5%] vs 37/112 [33.0%]; HR, 0.39; 95% CI, 0.22-0.70) or $>$6 wk (DFS events, 12/91 [13.2%] vs 31/93 [33.3%]; HR, 0.36; 95% CI, 0.19-0.71). **Conclusions:** In this phase 3 study, adjuvant cemi demonstrated a DFS benefit vs pbo across all high-risk features and regardless of the interval between prior RT completion and randomization. Clinical trial information: NCT03969004. Research Sponsor: Regeneron Pharmaceuticals Inc. and Sanofi.

DFS with cemi vs pbo: Analyses per high-risk criteria.

Criteria[a]	Met high risk criteria, n/N (%)	DFS events in cemi arm, n/N (%)	DFS events in pbo arm, n/N (%)	DFS HR (95% CI)
Nodal high risk				
ECE with ≥1 node ≥20 mm	201/415 (48.4)	14/105 (13.3)	27/96 (28.1)	0.44 (0.23-0.84)
≥3 nodes	71/415 (17.1)	7/34 (20.6)	18/37 (48.6)	0.34 (0.13-0.92)
Non-nodal high risk				
In-transit metastases	41/415 (9.9)	2/20 (10.0)	9/21 (42.9)	0.07 (0.01-0.58)
T4 lesion	33/415 (8.0)	6/17 (35.3)	5/16 (31.3)	0.58 (0.16-2.11)
Perineural invasion	64/415 (15.4)	3/32 (9.4)	8/32 (25.0)	0.27 (0.07-1.04)
Recurrent CSCC with ≥1 additional high-risk criteria	105/415 (25.3)	9/55 (16.4)	22/50 (44.0)	0.19 (0.08-0.45)

[a]Tumors could meet $\geq$1 high-risk criteria.

6084 Poster Session

Evaluation of a tissue-free genome-wide methylome enrichment assay for detecting molecular residual disease (MRD) in patients with head and neck squamous cell carcinoma (HNSCC). First Author: Geoffrey Liu, Princess Margaret Cancer Centre, University Health Network and Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

Background: Squamous cell carcinomas comprise ~90% of head and neck cancers (HNCs). Although ~80% of patients with HNSCC are eligible for curative therapy, an estimated 20% to 35% will develop recurrence, typically within 2 years. Recurrence is associated with poor survival, but early detection may enable salvage therapy. We previously reported clinical validation of a tissue-free, genome-wide methylome enrichment MRD assay for recurrence detection in HNC. Here we present performance of an updated classifier in a subset of patients with HNSCC. **Methods:** Test performance was evaluated using blood samples collected at ~3 (landmark), 12, and 24 mo after curative-intent treatment from patients with stage I-IVb HNSCC. MRD testing was performed using an assay based on cell-free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq) as previously described (Liu et al. *Ann Oncol*. 2025;36(1):108-117). To improve test performance and clinical actionability, we evaluated the effect of defining an *indeterminate* test category near the classifier threshold. An updated classifier defining 5% of training samples as *indeterminate* was analyzed in a training set, followed by a pre-specified clinical validation analysis. The primary endpoint was recurrence-free survival (RFS), comparing patients with MRD detected vs not detected. RFS was estimated using the Kaplan-Meier method, with differences assessed by the 2-sided log-rank test. Hazard ratios (HR) were estimated using the Cox proportional hazards model. **Results:** Among 117 patients in the validation set, median follow-up was 65.3 mo. MRD detection during surveillance was strongly associated with inferior RFS (HR, 54.5 [95% CI, 18.4-161.2]), an improvement over the previously reported HR of 35.7. Lead time between MRD detection and clinical recurrence was up to 10.8 mo (mean, 3.3 mo). MRD detection was also prognostic for OS (HR, 89.3 [11.8-676.4]). The updated classifier showed improved performance, with a sensitivity of 86.7% (26/30) and a specificity of 97.7% (85/87) for recurrence detection. Positive predictive value was 92.9% (26/28); negative predictive value was 95.5% (85/89). Performance was similar (P=0.24) among patients with HPV-positive oropharyngeal carcinoma (n=52) vs HPV-negative disease (n=65), patients with stage I-II (n=72) vs stage III-IVb (n=45) disease (P=0.20), and patients with surgery (n=34) vs non-surgical (n=83) definitive treatment (P=0.37). **Conclusions:** This study demonstrates that tissue-free, blood-based MRD testing using a genome-wide methylome enrichment platform is prognostic for recurrence in patients with HNSCC treated with curative intent, regardless of stage, HPV status, or treatment modality. The platform offers a robust, sensitive approach for early detection of recurrence in a broad patient population. Research Sponsor: Adela, Inc.

6085 Poster Session

Neoadjuvant chemotherapy with/without PD-1i in locally advanced laryngeal/hypopharyngeal cancer: A multicentered retrospective study. First Author: Xiaomin Ou, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: The efficacy of adding programmed death-1 (PD-1) inhibitors to neoadjuvant chemotherapy (NACT) for improving survival in locally advanced laryngeal/hypopharyngeal carcinoma remains unclear. This study aimed to compare progression-free survival (PFS) between patients receiving NACT with or without a PD-1 inhibitor (NACT+PD-1i). **Methods:** This multicenter retrospective study enrolled 267 patients with T2-4N0-3M0 laryngeal/hypopharyngeal squamous cell carcinoma who received NACT with (n=165) or without (n=102) a PD-1 inhibitor, followed by definitive radiotherapy, between 2019 and 2024, from Fudan University Shanghai Cancer Center, Fujian Cancer Hospital and Sun Yat-sen University Cancer Center. The primary endpoint was PFS. Inverse probability of treatment weighting (IPTW) was used to adjust for baseline imbalances. **Results:** The NACT+PD-1i group demonstrated significantly improved PFS versus NACT alone (median PFS: not reached vs. 33.0 months; hazard ratio [HR]=0.61, 95% confidence interval [CI]: 0.41–0.90; p=0.012). The 2-year PFS rates were 70.2% and 56.5%, respectively. This PFS benefit persisted after IPTW (p=0.012). PD-1 inhibition was an independent favorable factor for PFS in multivariable analysis (unadjusted, HR=0.54, p=0.005; IPTW-adjusted, HR= 0.63, p=0.040). Notably, the NACT+PD-1i group showed superior regional recurrence-free survival (RRFS) (2-year RRFS: 92.1% vs. 81.0%; HR=0.31, p=0.001) and higher objective response rate (ORR) (93.9% vs. 85.9%, p=0.027), particularly for cervical lymph nodes (94.2% vs. 81.6%, p=0.002). Achieving an ORR after neoadjuvant therapy was a strong predictor for improved outcome, either in unadjusted PFS (HR=0.40, p=0.0005) or in IPTW-adjusted PFS (HR=0.49, p=0.0005). **Conclusions:** In this real-world analysis, adding a PD-1 inhibitor to NACT significantly improved ORR and PFS in locally advanced laryngeal/hypopharyngeal carcinoma, supporting its further evaluation in neoadjuvant strategies. Research Sponsor: None.

6086 Poster Session

Induction toripalimab and chemotherapy for organ preservation in locally advanced laryngeal and hypopharyngeal cancer: 3-year follow-up of the INSIGHT study. First Author: Xiaomin Ou, Department of Radiation Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Background: This phase II study evaluated the efficacy and larynx-preservation potential of induction chemotherapy combined with the toripalimab in patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinoma (LA-L/HPSCC). Primary and 1-year survival outcomes were previously reported; here we present the 3-year follow-up results. **Methods:** This is a single-arm phase II study. Patients with histopathologic confirmed, resectable LA-L/HPSCC and ECOG PS 0-1 were eligible. Three cycles of induction chemotherapy (paclitaxel 175mg/m^2 d1, cisplatin 25mg/m^2 d1-3) combined with toripalimab (240mg d0) were administered. Response assessment was performed after induction chemoimmunotherapy using RECIST 1.1 criteria. Patients with CR/PR of primary tumor received concurrent chemoradiation, followed by maintenance therapy of toripalimab. Otherwise, patients were referred to surgery, followed by adjuvant (chemo)radiation, and maintenance therapy of toripalimab. The primary endpoint is larynx-preservation rate at three months post-radiation. Secondary endpoints included overall survival (OS), progression-free survival (PFS), larynx preservation rate, and larynx-preservation survival (LPS), etc. **Results:** Twenty-seven patients were enrolled. Most cases exhibited stage IV disease (81.5%), with T4 representing 37.0%. Five patients underwent pretreatment tracheostomy. The date of data cut-off was Jan 23, 2026. With a median follow-up of 36.4 [95%CI: 33.4-39.4] months, 3-year OS rate, PFS rate, larynx preservation rate and LPS rate was 73.5%, 61.1%, 84.3% and 73.6%, respectively. Excluding patients with pretreatment tracheostomy, these rates improved to 86.4%, 70.8%, 90.2% and 81.1%. The 3-year larynx preservation rate for T2/3 and T4 disease was 92.9% and 70.0%, respectively (p=0.081). All patients with preserved larynx at last follow-up maintained functional laryngeal status, free from tracheostomy or feeding tube dependence. **Conclusions:** Induction toripalimab combined with chemotherapy provided promising and durable larynx preservation rate in this cohort of extensively LA-L/HPSCC. Clinical trial information: NCT04995120. Research Sponsor: National Natural Science Foundation of China; 82072951; Chinese Society of Clinical Oncology Foundation; Y-Young2021-0127.

Comparison of patients enrollment and survival among pivotal clinical trials.

Study	Phase	Clinical Stage	Larynx preservation rate at 3 year	Progression-free rate at 3 year
GORTEC 2000-01	III	Stage III, IV Hypopharynx 54.0%, larynx 46.0%	70.1% for TPF and 57.5% for PF	58% for TPF and 44% for PF
Subgroup analysis of TAX324	II	Stage III 26.5% Stage IV 73.5%, Hypopharynx 46.4%, larynx I 64.5%	Not available	43% for TPF and 29% for PF
This study	II	Stage III 18.5% Stage IVa 33.3% Stage IVb 48.1% Hypopharynx 66.7%, larynx 33.3%	84.3% for whole cohort and 90.2% when excluding patients with pre-treatment tracheostomy	61.1% for whole cohort and 70.8% when excluding patients with pre-treatment tracheostomy

6087 Poster Session

A prospective trial of single-dose neoadjuvant PD-1 blockade with or without a CD40 agonist in HPV-negative HNSCC. First Author: Lova Sun, University of Pennsylvania, Philadelphia, PA

Background: Neoadjuvant PD-1 blockade is approved for resectable locally advanced HPV-negative HNSCC, but major pathologic response rates are $<$10%, underscoring the need for effective combination strategies. Agonists of the TNF receptor superfamily member CD40 can reverse dendritic cell dysfunction, a key mediator of immune resistance, and may combine with PD-1 blockade to enhance anti-tumor T cell recruitment. We investigated the safety and immunologic effects of combination neoadjuvant PD-1 blockade with CD40 agonism. **Methods:** We enrolled 20 patients with resectable HPV-negative HNSCC; 10 received a single intravenous dose of PD-1 inhibitor (LVGN3616, 300mg), and 10 received a PD-1 inhibitor (LVGN3616, 300mg) in combination with a CD40 agonist (LVGN7409, 1mg/kg), administered prior to surgical resection (window, 4-28 days). Pre-treatment biopsies, post-treatment surgical specimens, and peripheral blood samples were collected. The primary endpoint was safety, with secondary endpoints including pharmacodynamic immune changes and pathologic responses. **Results:** Median age was 65 years (range, 39-79); 16 (80%) were male; 16 (80%) were White; 18 (90%) had oral cavity cancer (2 larynx); and 17 (85%) had PD-L1 CPS $\geq$1. Baseline demographics and PD-L1 were well-balanced between arms. Neoadjuvant immunotherapy was administered a median of 9 days (range, 5-19) before surgery, with no surgical delays observed. Treatment was well tolerated; grade 3/4 events occurred in 12/20 patients, nearly all attributable to post-surgical complications and unrelated to study drug. The only treatment-related grade 3/4 events were transient elevations in liver enzymes seen in two patients in the PD-1+CD40 arm. With a minimum of 6 months' follow-up, 3/20 patients (1 in PD1 arm, 2 in PD1+CD40 arm) had progressed. Serum analyses revealed that combined PD-1 and CD40 agonist therapy induced significant increases in multiple cytokines including IL-15 (p=0.0084), IP-10 (p=0.0379), MCP-1 (p=0.0002), MDC (p$<$0.0001), and MIG (p=0.0178) at 24 hours, indicating enhanced immune activation. A biomarker-driven inflammatory score based on baseline LCN2 and SAA levels predicted pathological response with 85% accuracy, 71.4% sensitivity, and 92.3% specificity (Fisher's exact p=0.0072). Pathologic tumor response (pTR) was observed in 3/10 patients in the PD-1 arm (pTR1, 10-49%) and 4/10 patients in the PD-1+CD40 arm (including one pTR2 with 85% regression. Multiplex IHC was performed on tissue samples using CD3, Ki67, PD-L1, CD8, FOXP3, CD68, and panCK markers; quantitative spatial analyses are ongoing and results will be presented. **Conclusions:** Single-dose neoadjuvant PD-1 blockade combined with a CD40 agonist for HPV-negative HNSCC was safe, did not delay surgery, and produced modestly improved pathologic regressions that correlated with a cytokine-based baseline inflammatory score. Clinical trial information: NCT06159621. Research Sponsor: Conquer Cancer, the ASCO Foundation; Abramson Cancer Center.

6088 Poster Session

Baseline skeletal muscle index as an independent prognostic factor in locally advanced head and neck squamous cell carcinoma: A post hoc analysis of the REACH trial. First Author: Florian Clatot, Institute of Research Onco-Normand (IRON), Rouen University Hospital and Centre Henri Becquerel, Rouen, France

Background: The prognosis for locally advanced squamous cell carcinoma of the head and neck (LAHNSCC) is heterogeneous. A low skeletal muscle mass index (SMI) assessed by computed tomography reflects sarcopenia and is associated with a poor prognosis. However, evidence-based data on HNSCC remain scarce. Moreover, the prognostic value of SMI in patients treated with radiotherapy combined with different systemic treatments remains unclear. **Methods:** This is a post hoc analysis of the REACH trial (NCT02999087), conducted between 2017 and 2020, which treated LAHNSCC in two cohorts. Patients eligible (fit) for cisplatin were randomized between radiotherapy with cisplatin and radiotherapy with cetuximab-avelumab; those ineligible for cisplatin (unfit) were randomized between radiotherapy with cetuximab and radiotherapy with cetuximab-avelumab. Baseline SMI was assessed on a C3 vertebral slice using radiotherapy planning computed tomography and analyzed as a continuous variable. Associations of SMI with disease-free survival (DFS) and overall survival (OS) were assessed using Cox proportional hazards models, with multivariable adjustment for performance status, age, stage, p16 status, treatment and cisplatin fit/unfit status. Model performance was internally validated using bootstrapping. **Results:** Among the 694 patients included in REACH, SMI analysis was available for 623 patients (90%). Only the analyses performed for the 507 men are presented. Among them, 312 (62%) were eligible for cisplatin and 195 (38%) were ineligible. Median SMI was 47 (range 32-66) kg/m^2, with no difference according to the fit/unfit status and treatment received. A higher SMI was observed in patients with ECOG 0 (vs 1, $p<0.0001$), younger patients (<65y, p=0.01) but not according to tumor stage (III vs IV). There was a linear relationship between SMI and DFS with a better DFS as SMI rises in both univariate (HR 0.81 every 5 SMI units, $p<0.0001$) and multivariate analyses (HR 0.88/5 units, p=0.013). Comparable results were observed for OS, with a significant linear relationship between SMI and OS (HR of death 0.76/5 units, $p<0.0001$, univariate analysis; HR 0.86/5 units, p=0.015, multivariate analysis). Other independent factors associated with improved OS were a p16+ oropharynx tumor, ECOG 0 (vs 1), Stage III tumor (vs IV) and eligibility for cisplatin. The prognostic impact of SMI was consistent across fit/unfit cohorts and treatment arms, with no significant interaction detected. **Conclusions:** Baseline SMI determined on C3 is a strong and independent prognostic factor for DFS and OS in patients with LAHNSCC treated with radiotherapy with cisplatin, radiotherapy with cetuximab, or radiotherapy with cetuximab and avelumab. The association between SMI and clinical outcomes is linear, arguing against the use of arbitrary prognostic thresholds for SMI. Research Sponsor: None.

6089 Poster Session

Four cycles of tislelizumab plus GP regimen as neoadjuvant therapy for high-risk (T4/N3) locally advanced nasopharyngeal carcinoma. First Author: Qinhua Zhang Sr., Jiangmen Central Hospital, Jiangmen, China

Background: The efficacy of standard chemoradiotherapy for locally advanced nasopharyngeal carcinoma (LANPC) is still unmet need, especially for stage IVa(T4/N3, AJCC 8th) NPC. The efficacy and safety of the 4 cycles neoadjuvant chemotherapy strategy in stage N2-3 LANPC has been confirmed. Meanwhile, immunotherapy has showed favorable tumor response and survival benefit for patients with LANPC. Therefore, this study investigated the efficacy and safety of four cycles tislelizumab plus GP regimen as neoadjuvant therapy for high-risk LANPC. **Methods:** Patients with stage IVa (T4/N3, AJCC 8th) NPC were enrolled and treated with neoadjuvant therapy (gemcitabine, 1000 mg/m^2, on days 1 and 8, cisplatin, 80 mg/m^2, on day 1, tislelizumab 200mg, on day 1) every 3 weeks for 4 cycles followed by standard concurrent chemoradiotherapy. The primary endpoint was complete response (CR) rate after neoadjuvant therapy. Secondary endpoints included overall response rate (ORR) after neoadjuvant therapy, disease-free survival, overall survival, and tolerance. **Results:** From February 2022 to June 2022, 25 patients were enrolled and 24 evaluable patients (median age 49 years old; 15 men [62.5%]) completed protocol-specified 4 cycles neoadjuvant therapy without delaying radiotherapy. 1 patient was withdrawn from the trial due to treatment of acute viral parotitis. The CR rate was 50% (12/24), achieving the predefined endpoint. The ORR of all evaluable patients was 91.7%. By the cut-off date of Jan 15th 2026, the median follow-up time was 44.8 months. The median disease-free survival was not reached and 36-month disease-free survival was 91.7%(95% CI 70.6%–97.8%). Two patients died of diseases not related to nasopharyngeal carcinoma and treatment, while the other patients still have no disease progression. 13 (52%) of 25 patients had grade 3-4 acute treatment-related adverse events (TRAE). Grade 1-2 immune-related adverse events (irAE) was recorded in 18 patients (72%). No grade 3-4 irAEs occurred. 3 (12%) of 25 patients had long-term TRAEs. **Conclusions:** Four cycles of tislelizumab plus GP regimen as neoadjuvant therapy demonstrated promising tumor response, long-term survival benefit and manageable safety profile in high-risk LANPC patients. Clinical trial information: ChiCTR2200056941. Research Sponsor: None.

6090 Poster Session

Mandibular preservation with neoadjuvant tislelizumab plus platinum-doublet chemotherapy in locally advanced resectable oral squamous cell carcinoma: A prospective phase II trial. First Author: Zhongyu Wang, Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China. Sun Yat-sen University Cancer Centre, State Key Laboratory of Oncology in South China, Guangzhou, China

Background: Segmental mandibulectomy for locally advanced oral squamous cell carcinoma (OSCC) severely compromises quality of life. In patients without radiographic mandibular invasion but still requiring mandibulectomy to achieve negative margins, effective tumor downstaging strategies that enable mandibular preservation are of major clinical importance. Neoadjuvant chemo-immunotherapy may reduce tumor burden, potentially enabling less radical resection and mandibular preservation. This study aimed to evaluate the efficacy and safety of mandibular preservation using neoadjuvant tislelizumab plus platinum-doublet chemotherapy in resectable locally advanced OSCC. **Methods:** This phase II, open-label, single-arm trial enrolled previously untreated patients with locally advanced, resectable OSCC (stage III-IVB, T3-T4N0-3M0) necessitating mandibulectomy based on conventional surgical criteria despite the absence of definitive clinicoradiologic mandibular invasion. Neoadjuvant treatment consisted of tislelizumab (200 mg), docetaxel (75 mg/m^2) and cisplatin (60 mg/m^2) on day 1 of each 21-day cycle for three cycles. All patients then proceeded to surgery. The primary endpoint was mandibular preservation rate. Secondary endpoints included pathological complete response (pCR), major pathological response (MPR), margin-negative resection (R0) rate, objective response rate (ORR), progression-free survival, disease-free survival, overall survival and treatment-related adverse events (TRAEs). **Results:** Between October 2023 and September 2025, a total of 53 patients were enrolled, and 49 were evaluable. All 49 patients completed three cycles of neoadjuvant therapy and underwent surgery. The mandibular preservation rate was 95.9% (47/49), and all patients achieved R0 resection. The ORR was 79.6% (39/49) and the pCR rate was 51.0% (25/49). TRAEs occurred in 100% (49/49) of patients. Grade 3 TRAEs were reported in 10.2% (5/49), including leukopenia, fatigue, and hypertension. No grade 4–5 TRAEs were observed. **Conclusions:** Neoadjuvant tislelizumab combined with platinum-doublet chemotherapy achieved a high mandibular preservation rate and a favorable pathological response profile with manageable toxicity in patients with locally advanced, resectable OSCC. This strategy represents a promising organ-preserving approach. Longer follow-up is ongoing to determine long-term survival outcomes. Clinical trial information: NCT06130007. Research Sponsor: None.

6091 Poster Session

Neoadjuvant immunotherapy in combination with chemotherapy in resectable locally advanced head and neck squamous cell carcinoma: Updated efficacy and safety data from a randomized phase II trial. First Author: Lei Liu, Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Neoadjuvant immunotherapy combined with chemotherapy is a promising strategy for resectable LAHNSCC. While most regimens employ single-target PD-1 inhibitors, dual-target agents (PD-1/CTLA-4 or PD-1/VEGF) have shown superior efficacy in recurrent/metastatic HNSCC. Building on our preliminary data (ASCO 2025) which suggested high pathological response rates, this ongoing randomized phase II trial aims to compare single- versus dual-target NAI regimens in an expanded cohort to identify the optimal treatment strategy. **Methods:** This is an ongoing randomized, open-label, phase II trial. Eligible pts were randomized (1:1:1) to receive 3 cycles of neoadjuvant therapy as follows: Cohort 1 will receive ivonescimab (PD-1/VEGF bispecific antibody, 10 mg/kg every 3 weeks), Cohort 2 will receive cadonilimab (PD-1/CTLA-4 bispecific antibody, 6 mg/kg every 3 weeks), and Cohort 3 will receive penpulimab (PD-1 antibody, 200 mg every 3 weeks), all in combination with cisplatin and nab-paclitaxel. After neoadjuvant treatment, Surgery was performed with the surgical margins based on pre-treatment (baseline) evaluation. Pts with pCR received adjuvant immunotherapy for up to 16 cycles. Pts without pCR received adjuvant radiotherapy or chemoradiotherapy, followed by 16 cycles of adjuvant immunotherapy. **Results:** Up to Dec. 2025, all 59 pts completed 3 cycles of neoadjuvant therapy and were evaluable, with a median follow-up of 12 months. The pCR rates were 60% (12/20) in Cohort 1, 42.1% (8/19) in Cohort 2, and 40% (8/20) in Cohort 3. The major pathologic response (MPR) rates were 75% (15/20), 57.9% (11/19), and 55% (11/20) in Cohort 1, 2, and 3, respectively. The ORR was 95% in Cohort 1 (CR: 8/20, PR: 11/20) and 84.2% in Cohort 2 (CR: 5/19, PR: 11/19), while Cohort 3 had an ORR of 80% (CR: 4/20, PR: 12/20). To date, pts have received a median of 6 cycles of adjuvant immunotherapy. The most common treatment-related adverse events (TRAEs) ($>20\%$) were: leukopenia, anemia, neutropenia, thrombocytopenia, lymphocytopenia, hypothyroidism, hypertriglyceridemia, radiation dermatitis, stomatitis, vomiting, decreased appetite, and fatigue. **Conclusions:** Neoadjuvant dual-target (PD-1/VEGF) immunotherapy combined with chemotherapy demonstrated a higher pCR rate compared to dual-target (PD-1/CTLA-4) and single-target PD-1 regimens in resectable LAHNSCC. The treatment was well-tolerated, with all pts completing the intended neoadjuvant therapy and the observed most common TRAEs consistent with expected chemotherapy and radiotherapy profiles. Further analyses are ongoing with continued enrollment. Clinical trial information: NCT06444009. Research Sponsor: None.

RECIST and pathologic response.

	RECIST				Pathologic Response			
	CR	PR	SD	PD	pCR (RVT=0)	MPR (0<RVT<10%)	pPR (RVT:10-49%)	pNR (RVT:≥50%)
Cohort 1 (n=20)	8	11	1		12	3	2	3
Cohort 2 (n=19)	5	11	3		8	3	2	6
Cohort 3 (n=20)	4	12	4		8	3	0	9

6092 **Poster Session**

Adjuvant nivolumab in addition to postoperative radiation therapy in locally advanced head and neck cancer: Results of the phase II NadiHN trial. First Author: Peter Brossart, University Bonn, Bonn, Germany

Background: The benefit of adding immune checkpoint inhibition to standard post-operative adjuvant radiotherapy in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) with an intermediate risk of recurrence remains unclear. **Methods:** The phase II, open-label, randomized, multicenter national NadiHN trial (EudraCT 2016-004787-20) enrolled participants with resected locally advanced HNSCC (R0 resection with ≥5 mm margins; no extracapsular nodal extension). Patients were stratified by primary site (oropharyngeal vs non-oropharyngeal), p16 status (for oropharyngeal tumors), centrally assessed PD-L1 tumor cell (TC) score (≥1% vs <1%), and center, and were randomized 1:1 to receive nivolumab before, during, and after postoperative radiotherapy (PORT) or PORT alone. Nivolumab (10 cycles of 240 mg q2w, followed by 10 cycles of 480 mg q4w) started 2 weeks prior to PORT. The primary endpoint was disease-free survival (DFS) in the intention-to-treat population. The planned sample size of 176 patients was designed to provide 80% power to detect a significant DFS improvement (log-rank test). Key secondary endpoints included overall survival (OS) and safety. Enrollment remained below target. During the trial, an adaptive interim analysis was implemented and led to early study termination upon Data Monitoring Committee recommendation due to futility. **Results:** Between 2017 and 2022, 84 participants were randomized (42 per arm). After a median follow-up of 37.3 months, median DFS was not reached in either group. The 2-year DFS rate was numerically higher with nivolumab + PORT (80%) than with PORT alone (69%), but the difference was not statistically significant (HR 0.934; 95% CI 0.408–2.140; p = 0.7301). Censoring deaths without documented recurrence yielded similar results. OS also did not differ significantly (HR 2.618; 95% CI 0.892–7.684; p = 0.0827). Grade ≥3 treatment-emergent adverse events occurred in 80.6% of patients in the nivolumab arm and 52.5% in the control arm. One treatment-related death occurred in the nivolumab + PORT arm. **Conclusions:** Interpretation of the trial is limited by early termination, small sample size, and fewer-than-expected DFS events. Adjuvant nivolumab added to standard PORT numerically—but not significantly—improved DFS in locally advanced HNSCC. Signals of potential benefit were observed in the PD-L1–positive subgroup (2y-DFS 82.4 vs. 76.2%) and lymph-node–positive subgroups (2y-DFS 84.2% vs. 70.7%). No new safety signals were identified. Funding: The trial was sponsored by the University Hospital Bonn with financial support from Bristol Myers Squibb. Clinical trial information: EudraCT 2016-004787-20. Research Sponsor: University Hospital Bonn; Bristol Myers Squibb.

ABSTRACT WITHDRAWN

6094 **Poster Session**

Real-world evidence on definitive chemoradiotherapy following neoadjuvant chemoimmunotherapy in locally advanced head and neck squamous cell carcinoma. First Author: Ya-Ni Zhang, Department of Radiation Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, Guangdong, China

Background: Real-world evidence regarding the efficacy and safety of neoadjuvant chemoimmunotherapy (NACI) in the treatment of curable head and neck squamous cell carcinoma (HNSCC) is currently limited. This multi-center study aimed to evaluate the outcomes of NACI in China. **Methods:** This retrospective study examined stage II-IVB HNSCC patients who underwent NACI followed by radical surgery (Group A) or definitive concurrent chemoradiotherapy (CCRT) (Group B) at four medical centers in China from 2019 to 2025. Propensity score matching was employed to balance baseline covariates between the groups. The primary endpoint was progression-free survival (PFS), while key secondary endpoints included complete pathological response (pCR), major pathological response (MPR), overall survival (OS), and treatment-related adverse events (TRAEs), which were graded according to the CTCAE v5.0 criteria. Survival analyses were conducted using Kaplan-Meier/log-rank tests and Cox proportional hazards models. **Results:** After matching (n=756), baseline characteristics were well-balanced (|SMD|<0.1). Group A (NACI + surgery, n=457) showed a 67% radiological response and MPR rate, with a 38% pCR, while Group B (NACI + CCRT, n=299) achieved a higher 76% radiological response rate. Regimens were similar (taxane-platinum-immunotherapy), but Group A received fewer chemotherapy cycles (3-4 cycles: 66% vs. 90%). Post-NACI progression was lower in Group B (0.7%). Group B demonstrated significantly longer PFS (hazard ratio [HR] 0.68; p=0.036) and markedly improved OS (HR 0.20; p<0.001). Multivariate analysis confirmed NACI + CCRT (Group B) as a significant independent predictor of improved OS (HR=0.20, 95% CI 0.07–0.59; p=0.003), considering factors such as betel nut use, tumor location, and T and N staging. Common grade 3-4 TRAEs were neutropenia and transaminase elevations; among grade 3 immune-related AEs, thyroid dysfunction predominated. **Conclusions:** This multicenter real-world study highlights that the combination of NACI and CCRT (Group B) results in significantly better PFS and OS outcomes compared to the NACI and surgical intervention (Group A), despite a pCR rate of 38% in Group A. These findings support the potential benefit of concurrent chemoradiotherapy as a consolidative approach following NACI. However, it is important to recognize that the observational nature of this study prevents definitive conclusions about causality. Therefore, prospective randomized controlled trials are essential to confirm these findings and to ascertain the optimal consolidative strategy. Additionally, further investigation into biomarker-driven patient selection is vital for enhancing treatment precision and effectiveness. Research Sponsor: None.

6095 **Poster Session**

Larynx preservation via chemotherapy-free neoadjuvant sintilimab-cetuximab-SBRT and response-adapted treatment in locally advanced laryngeal cancer: A phase II, single-arm clinical trial (the NeoVOICE study). First Author: Shida Yan, Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: The current standard of care for locally advanced laryngeal squamous cell carcinoma (LA-LSCC), including surgery and chemoradiotherapy, might cause long-term toxicities and laryngeal dysfunctions. The study aims to investigate the efficacy and safety of neoadjuvant cetuximab, sintilimab and stereotactic body radiation therapy (SBRT) treating patients with LA-LSCC for larynx preservation. **Methods:** In this phase II, single-arm trial, patients with LA-LSCC (cT2N1-3M0 or cT3-4aN0-3M0, AJCC 8.0th) were recruited. Eligible patients received SBRT (8 Gy × 3 fractions), followed by sintilimab (200mg, Q3W, 2 cycles) and cetuximab (a loading dose of 400 mg/m^2, followed by 250 mg/m^2, QW, 6 cycles). Further treatment was determined by a radiographic evaluation per RECIST 1.1: patients who reached CR or PR would receive intensity modulated radiation therapy (The initial IMRT dose to the primary tumor was 46 Gy in 23 fractions, with a pre-specified plan to reduce the dose to 37.8 Gy based on early tolerance data from the cohort.) or minimally invasive surgery, while ones with SD or PD would receive radical surgery. The primary endpoint was the larynx-preservation rate (LPR) at 1-year post-radiation. **Results:** Between July 1, 2024 and June 30, 2025, 20 patients were enrolled. 15 (75%) were clinical stage III and 5 were stage IVa. 19 finished neoadjuvant SBRT, sintilimab and cetuximab (one withdrawn due to personal reasons after SBRT), with the ORR of 100% (12 had CR and 7 had PR). Then 18 patients received sequential IMRT, with a median dose of 37.8 Gy (one refused and chose active surveillance). During the whole treatment, grade 3 TRAEs occurred in 5/20 patients (25%), including 3 cases of post-radiation pharyngitis, 1 myocarditis and 1 rash. All 3 cases of grade 3 pharyngitis occurred in the first 6 patients with 46 Gy IMRT. Following a protocol amendment, subsequent patients (n=12) received a reduced dose of 37.8 Gy. In the reduced-dose cohort, no further grade 3+ pharyngitis was observed, while the LPR remained high. After a median follow-up of 7.4 months, 3 patients failed to larynx preservation, including 2 cases with tracheotomies due to pharyngitis and 1 receiving total laryngectomy due to tumor recurrence. Based on results of EORTC QLQ-H&N35 questionnaires, compared to the baseline, most patients reported similar or improved symptoms, including pain, speech and dry mouth, at 6 months post-radiation. **Conclusions:** Neoadjuvant combination of immunotherapy, targeted therapy and SBRT showed excellent efficacy and tolerant toxicity for patients with LA-LSCC. Importantly, dose reduction of sequential IMRT appears to mitigate severe toxicity without compromising laryngeal preservation, outlining a promising de-escalation strategy for future practice. Clinical trial information: ChiCTR2500100185. Research Sponsor: None.

6096 **Poster Session**

Niraparib and dostarlimab in locally advanced head and neck squamous cell carcinoma (LA-HNSCC) treated with (chemo)radiotherapy (CRT): Results from the phase IB-II TTCC-2022-01 RADIAN trial. First Author: Marc Oliva, Medical Oncology Department, Institut Català d'Oncologia (ICO), L'hospitalet De Llobregat, Barcelona, Spain

Background: Treatment intensification with antiPD-(L)1 agents given concurrently to definitive CRT in LA-HNSCC have failed to improve survival. Beyond radiation sensitization, PARP inhibition is predicted to trigger immune responses via STING pathway activation and synergize with anti-PD-(L)1 agents. TTCC-2022-01 RADIAN Trial evaluates niraparib and dostarlimab in LA-HNSCC patients (pts) treated with CRT (cohort A) or RT alone (Cohort B-cisplatin ineligible) (Oliva M et al ASCO 2024). Results of cohort A are presented. **Methods:** Investigator-initiated, non-randomized phase 1b/II study of niraparib and dostarlimab in LA-HNSCC pts candidates for definitive CRT or RT alone conducted in 7 Spanish sites. In cohort A, pts received 500 mg dostarlimab intravenously on week (w)-3 prior to RT and 200-300 mg/day niraparib from w-2 until 48h before start of CRT (70Gy/35 fractions plus cisplatin 100mg/m^2 w1,4 and 7). Maintenance dostarlimab (500 mg/3w) plus daily niraparib started 4w post-CRT for up to 14 cycles. Eligibility criteria: newly-diagnosed stage III-IVA-IVB HPV-negative oro-hipopharyngeal or laryngeal SCC and stage III HPV-related oropharyngeal, ECOG 0-1, centrally-confirmed PD-L1 CPS$\geq$1, and with no cisplatin/dostarlimab/niraparib contraindications. Primary endpoint was 1-year disease-free survival (1y-DFS). Secondary objectives include safety; overall response rate (ORR) and ctDNA dynamics. 17 pts per cohort were planned. Experimental treatment was expected to increase 1y-DFS up to 75.9 % vs 65% historical control. **Results:** From Dec 23 to Jun 25, 17 pts were enrolled: median age 65 y (41-68); 71% male; 88% smokers; larynx/hypopharynx/oropharynx (HPV-related)= 53/6/41% (43%); stage III/IVA/IVB=29/53/18%. All pts completed dostarlimab and niraparib pre-CRT with no serious or Grade(G) 3-4 treatment-related adverse events (TRAEs); 15/17 completed CRT: 2 pts died during this phase (1 G5 febrile neutropenia cisplatin-niraparib-related; 1 unknown cause); 14/17 pts started maintenance: 2 completed, 7 ongoing and 5 (36%) discontinued due to TRAEs. The most common grade $\geq$3 TRAEs were neutropenia (71%), lymphopenia and dysphagia (29% each). Niraparib dose reductions/interruptions occurred in 12 (71%) pts. Most common TRAEs leading to dostarlimab+niraparib maintenance discontinuation were immune-mediated pneumonitis (18%) and respiratory tract edema (12%). ORR was 100% (14 complete+1 partial response) in 15 evaluable pts. With a median follow-up of 8.5 months (95% CI: 8.3-11.1), 15/17 were alive with no disease recurrence or progression. Intention-to-treat 1y-DFS was 88% (95% CI:74.1-100). **Conclusions:** Dostarlimab and niraparib with CRT showed promising efficacy results in this preliminary analysis. Maintenance post-CRT was poorly tolerated leading to high rate of discontinuation. Clinical trial information: NCT05784012. Research Sponsor: GlaxoSmithKline Research& Development Limited.

6097 **Poster Session**

Neoadjuvant HPV16-specific viral immunotherapy (HB200) plus chemotherapy with response-adapted de-escalation in HPV16+ oropharyngeal squamous cell carcinoma: TARGET-HPV trial. First Author: Ari Joseph Rosenberg, Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, IL

Background: Neoadjuvant immunotherapy is an emerging strategy in head and neck squamous cell carcinoma to enhance systemic antitumor immunity and enable response-adapted de-escalation. In HPV associated oropharyngeal squamous cell carcinoma (OPSCC), virally encoded oncoproteins represent shared, tumor-specific antigens and a rational immunologic target well suited for the neoadjuvant setting in the presence of intact tumor antigen. We conducted a phase I/II trial evaluating neoadjuvant HPV16-specific viral immunotherapy (HB200; HB201 and HB202 HPV16 therapeutic vaccines) plus chemotherapy followed by response-adapted definitive treatment in non-metastatic HPV16+ OPSCC (NCT05108870). **Methods:** This investigator-initiated phase I/II trial enrolled patients with previously untreated, non-metastatic HPV16+ OPSCC (N1-3 or T3-4; smokers permitted). All patients received three cycles of neoadjuvant HB200 (HB201 alone or alternating HB202/201) with carboplatin/paclitaxel, followed by radiographic response assessment. Patients with T1-2 tonsil or well-lateralized base of tongue tumors achieving $\geq$50% tumor shrinkage underwent transoral robotic surgery (TORS) alone. Remaining patients received response and risk adapted radiotherapy (50-70Gy based on risk/response) with or without cisplatin. The primary endpoint was deep response rate (DRR; $\geq$50% tumor shrinkage). Secondary endpoints included survival and toxicity. Exploratory endpoints included circulating tumor HPV-DNA (ctHPV-DNA), HPV16-specific immunity, and spatial transcriptomics. **Results:** Thirty-five patients were enrolled (median age 58; 89% male); Twelve patients (34%) received HB201 alone and 23 (66%) received alternating HB202/201. Nineteen patients (54%) were current or former smokers, and 49% had stage II-III (AJCC 8th edition). The DRR was 87.9% (95% CI, 71.8-96.6). Thirty (86%) received de-escalated definitive therapy. At a median follow-up of 23 months, 2-year PFS and OS were 86% and 100% respectively. Most common AEs during neoadjuvant HB200/chemo were fatigue (97%), nausea (91%), and fever (76%). Detectable ctHPV-DNA following treatment was significantly associated with disease recurrence ($p<0.01$). HPV16-specific immune responses and spatial transcriptomic analyses will be presented. **Conclusions:** Neoadjuvant HB200 combined with chemotherapy resulted in high deep response rates, frequent treatment de-escalation, and excellent survival outcomes in locoregionally advanced HPV16+ OPSCC. These findings support further evaluation of HPV directed immune therapy in neoadjuvant setting. Clinical trial information: NCT05108870. Research Sponsor: HOOKIPA Pharma, Inc.; University of Chicago Cancer Center.

6098 **Poster Session**

Patterns of tumor regression after neoadjuvant immunochemotherapy in oral squamous cell carcinoma and their surgical margin implications. First Author: Haotian Cao, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China

Background: Neoadjuvant immunochemotherapy (nICT) has been increasingly applied in locally advanced oral squamous cell carcinoma (OSCC), demonstrating promising tumor downstaging and improved pathological response rates. However, the spatial patterns of tumor regression after nICT and their implications for surgical margin design and potential de-escalation of surgery remain poorly defined. **Methods:** We retrospectively analyzed 36 hemiglossectomy specimens from OSCC patients treated with nICT. All specimens were entirely embedded and evaluated using large-format histopathology. Tumor regression patterns were classified based on the distribution of residual viable tumor into central necrotic regression, peripheral regression, and patchy ablation types, each with distinct morphological subtypes. The relationship between pathological residual tumor foci, margin distance (1 mm vs 5 mm), and multicentricity was systematically assessed. **Results:** Distinct tumor regression patterns were observed following nICT. Most cases exhibited predominantly unicentric residual disease, while a small proportion demonstrated multicentric pathological residuals. Using a 1-mm pathological distance threshold, 1 cases were classified as multicentric, whereas no case met multicentric criteria using a 5-mm threshold. Notably, cases achieving major pathological response (MPR) or near pathological response (NPR) showed minimal residual tumor burden, though isolated satellite foci were occasionally detected. These findings suggest that regression morphology directly influences margin risk distribution and surgical safety. **Conclusions:** Tumor regression patterns after nICT in OSCC are heterogeneous and play a critical role in determining optimal surgical resection boundaries. While surgical de-escalation may be feasible in selected responders, careful assessment of residual tumor distribution is essential to ensure oncologic safety. Our findings support the development of an integrated preoperative regression assessment and postoperative margin reconstruction framework to guide individualized, function-preserving surgical strategies in OSCC. Research Sponsor: None.

6099 **Poster Session**

GDF-15 levels and clinical correlates in head and neck cancer patients: Developing a risk model for cachexia. First Author: Connor Maxwell Douglas Williams, Supportive Oncology Research Group, Precision Medicine (Cancer), South Australian Health and Medical Research Institute, Adelaide, Australia

Background: Cachexia is a challenging complication of cancer and its treatment, associated with an increased risk of death. Growth differentiation factor 15 (GDF15) is a known driver of cachexia in lung, pancreatic and colorectal cancer. However, we lack information about GDF15 role and temporal dynamics in patients with head and neck squamous cell carcinoma (HNSCC) receiving curative treatments. Here, we aimed to quantify circulating GDF15 in HNC patients and determine the relationship with indicators of cachexia and other prominent clinical correlates, namely oral mucositis (OM). **Methods:** Adults diagnosed with HNSCC, scheduled to receive definitive platinum based chemoradiotherapy (CRT), were recruited from four tertiary hospitals in Australia and Italy. Cachexia was determined using a variety of clinical parameters, including weight, grip strength, and upper arm circumference (UAC). OM was assessed using the World Health Organization (WHO) mucositis scale (grade 0-4). GDF15 was quantified in serially-collected serum using a commercial ELISA. All measures were assessed at baseline, week 3, end of treatment (EOT) and 3 months after treatment end. **Results:** Fifty-nine patients (pts) were enrolled, predominantly male (71%) with a mean age of 64+/-8 years. Main subsite of disease was oropharynx (44 cases, 75%), of whom 68% were HPV positive. Treatment was delivered with definitive intent in 90% of the cases. Median dose of RT was 70 Gy (66-70). At EOT, 77.3% of the pts met the diagnostic criteria for cachexia, with an average weight loss of 8.6% over the course of treatment. This was accompanied by a 7.7% and 5.6% average reduction in grip strength and UAC, respectively. Notably, these reductions continued beyond treatment cessation, with an average baseline weight loss of 9.8% after 3 months. Aligning with these outcomes, serum GDF15 levels were highly elevated following CRT compared to baseline (2.6 fold, $P<0.0001$), and correlated with reductions in weight ($R^2=0.168$, $P=0.0002$), UAC ($R^2=0.1516$, $P<0.0001$), grip strength ($R^2=0.1332$, $P<0.0001$), as well as OM severity ($R^2=0.1013$, $P<0.0009$). **Conclusions:** These data reveal that highly elevated GDF15 production correlates with OM and cachexia, providing strong clinical rationale to explore the biological basis of this new symptom cluster, as well as identifying a new clinical cohort that may benefit from GDF15 targeting agents. Research Sponsor: None.

6100 Poster Session

A multicenter, randomized controlled phase III trial of TPF induction chemotherapy versus PF adjuvant chemotherapy combined with concurrent chemoradiotherapy in locally advanced nasopharyngeal carcinoma: Long-term follow-up analysis. First Author: Huajing Wu, Department of Oncology, Affiliated Tumor Hospital of Guizhou Medical University, Guiyang, China

Background: To investigate whether TPF induction chemotherapy combined with concurrent chemoradiotherapy (CCRT) can provide greater survival benefits compared to CCRT followed by PF adjuvant chemotherapy. **Methods:** Patients with newly diagnosed locally advanced (Stage III–IVA) nasopharyngeal carcinoma (NPC) treated at the Affiliated Tumor Hospital of Guizhou Medical University, the Second Affiliated Hospital of Guizhou Medical University, the Second Affiliated Hospital of Zunyi Medical University, and Guiyang Hospital of Guizhou Aviation from May 2018 to July 2021 were enrolled. Each group included 133 patients. The experimental group received 3 cycles of TPF induction chemotherapy (docetaxel 75mg/m²,intravenous infusion, Day 1; cisplatin 75mg/m²,continuous intravenous infusion over 5 days,10:00–22:00 daily; fluorouracil 750mg/m²/day, continuous intravenous infusion over 5 days, 22:00–10:00 daily) followed by 2–3 cycles of concurrent chemotherapy (cisplatin 100mg/m², continuous intravenous infusion over 2 days, 10:00–22:00 daily). The control group received PF adjuvant chemotherapy (cisplatin 80mg/m², continuous intravenous infusion over 5 days,10:00–22:00 daily; fluorouracil 800mg/m²/day, continuous intravenous infusion over 5 days, 22:00–10:00 daily) combined with 2–3 cycles of concurrent chemotherapy (same as induction chemotherapy).Both groups underwent intensity-modulated radiotherapy (IMRT),with total doses of 69.96 Gy for T1–T2 primary lesions, 72.6 Gy for T3–T4 lesions, and 69.96 Gy for positive lymph nodes. Data were analyzed using SPSS 26.0.Differences in 5-year PFS, OS, LRFS, DMFS, and adverse events were compared between the two groups. **Results:** No significant differences were observed between the two groups in age, sex, Karnofsky Performance Status (KPS) score, T stage, N stage, or overall stage ($P > 0.05$).At a median follow-up of 58 months, the 5-year PFS in both the intention-to-treat and per-protocol populations was similar between the induction chemotherapy (IC) and adjuvant chemotherapy (AC) groups (66.6% vs 66.0%, P= 0.589; 75.3% vs 69.9%, P=0.471). The 5-year OS, LRFS, and DMFS rates were 73.0% vs 71.3% (P=0.582), 87.4% vs 90.8% (P=0.508), and 76.9% vs 72.6% (P=0.267), respectively, with no significant differences. **Conclusions:** Both groups had similar 5-year PFS, OS, LRFS, DMFS, and long-term toxicity profiles. Clinical trial information: NCT03574324. Research Sponsor: None.

5-year observation indicators for two groups.

Observation indicators	IC+CCRT	CCRT+AC	P value	Risk ratio(95% CI)
PFS				
ITT Population	66.6%	66.0%	0.589	0.89 (0.58-1.36)
PP Population	75.3%	69.9%	0.471	0.85 (0.55-1.33)
OS	73.0%	71.3%	0.582	0.88 (0.55-1.39)
LRFS	87.4%	90.8%	0.508	1.30 (0.60-2.80)
DMFS	76.9%	72.6%	0.267	0.75 (0.45-1.25)

OS, LRFS, and DMFS were all calculated in the ITT population.

6101 Poster Session

Comparison of efficacy between 2 and 3 cycles of neoadjuvant immunotherapy combined with chemotherapy for LA HNSCC. First Author: Xiaohong Chen, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Background: To compare efficacy, safety and long-term survival of 2 vs 3 cycles of neoadjuvant PD-1 inhibitor plus chemotherapy for LA HNSCC, providing evidence for optimizing treatment cycles. **Methods:** Retrospective analysis of LA HNSCC patients treated with the above neoadjuvant regimen at Beijing Tongren Hospital (Jan 2022-Dec 2024) was performed. Initially 76 (2-cycle) and 102 (3-cycle) cases were enrolled. Propensity score matching (1:1) balanced baseline differences, resulting in 65 cases per group. Chi-square, Kappa, Kaplan-Meier and Log-rank tests were used for comparisons, consistency analysis and survival assessment. Stratified analyses focused on HPV-negative and poorly differentiated subgroups. **Results:** After matching, 3-cycle group had higher ORR (95.4% vs 80.0%, P=0.008) and pCR rate (72.3% vs 55.4%, P=0.045). Subgroup analyses showed superior pCR in 3-cycle group for HPV-negative (68.9% vs 42.1%, P=0.014) and poorly differentiated (82.6% vs 35.7%, P=0.004) patients. Weak consistency existed between imaging and pathology (Kappa=0.176, P=0.044). Immune-related adverse events were more common in 3-cycle group (24.6% vs 10.8%, P=0.039). No significant 1-/2-year PFS/OS differences were noted, but 3-cycle group showed favorable numerical trend. **Conclusions:** Three cycles of the regimen significantly improve ORR and pCR in LA HNSCC, especially in HPV-negative and poorly differentiated subgroups. Despite higher immune-related adverse events, it is clinically preferable. Multi-dimensional evaluation is needed due to poor imaging-pathology consistency, with longer follow-up required for definitive prognosis assessment. Research Sponsor: None.

6102 Poster Session

Five-year follow-up of neoadjuvant chemoimmunotherapy in locally advanced head and neck squamous cell carcinoma. First Author: Kunyu Yang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Neoadjuvant chemoimmunotherapy has shown high rates of pathological response in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). However, its long-term survival outcomes, the predictive value of pathological complete response (pCR), and patterns of late failure remain unclear. **Methods:** In this single-arm phase II trial, 30 patients with resectable LA-HNSCC received three cycles of nab-paclitaxel (or docetaxel) plus cisplatin and camrelizumab, followed by surgery and adjuvant radiotherapy. The primary endpoint was pCR rate. With follow-up until January 2026, the median follow-up was 60 months. Analyses included overall survival (OS), recurrence patterns, and incidence of second primary tumors. **Results:** The pCR rate was 37.0% (10/27). Key Finding 1: This study represents the first report of 5-year long-term survival data for this regimen, with a 5-year OS rate of 76.7%. Key Finding 2: None of the patients who achieved pCR and completed adjuvant radiotherapy experienced local recurrence (0/7), whereas the recurrence rate was 33.3% (1/3) among those who did not receive radiotherapy, underscoring the role of radiotherapy even in pCR patients. Key Finding 3: Six patients (20%) developed second or third primary tumors during long-term follow-up (sites included larynx, esophagus, and lung), with incidence increasing over time. Key Finding 4: Two patients developed osteoradionecrosis of the jaw more than two years after radiotherapy, leading to malnutrition and subsequent death, highlighting the importance of long-term toxicity management. **Conclusions:** Neoadjuvant chemoimmunotherapy provides durable survival benefit in LA-HNSCC. pCR is associated with minimal local recurrence. However, with prolonged survival, the risk of second primary tumors becomes significant, and late radiation toxicities can impact outcomes. These findings emphasize the need for establishing lifelong surveillance protocols for multiple primary cancers and systematic management of late toxicities in this population. Clinical trial information: ChiCTR1900025303. Research Sponsor: None.

6103 Poster Session

Induction chemotherapy response–guided selection for hypoxia-directed major radiation de-escalation in T3–T4 HPV-positive oropharyngeal cancer. First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY

Background: De-escalation trials in human papillomavirus associated oropharyngeal carcinoma (HPV+ OPC) often exclude patients with very locally advanced disease. We previously demonstrated in several Phase II study that for patients with T1-T2 HPV+OPC, de-escalation to 30Gy of definitive chemoradiation based on lack of hypoxia on ^{18}F-FMISO (fluoromisonidazole) PET (30-ROC Study) is associated with excellent outcomes (JNCI 2021; JCO 2024). Here, we hypothesized that induction chemotherapy (ICT) response could be used to select appropriate locally advanced (T3-T4) HPV+OPC for de-escalation while simultaneously improving tumor hypoxia. **Methods:** We conducted a pilot study in HPV+ OPC patients with AJCC v7 T3-T4 and/or large volume N2b-N2c-N3 disease (who were ineligible for 30-ROC Study (NCT03323563)). ICT – carboplatin (AUC2), paclitaxel (90 mg/m2), and cetuximab (250 mg/m2 after 400 mg/m2 loading dose) weekly for 6 weeks. To be eligible for de-escalation (30-ROC), after ICT, patients needed to be down-staged (<=T2 and <=N3 disease). ^{18}F-FMISO PET scan done prior to ICT, after ICT, and, if eligible for ROC study, about 2 weeks after start of radiation therapy. If an ^{18}F-FMISO PET scan showed no hypoxia prior to the start of chemoradiation, no further scans were necessary and patients received 30Gy of radiation therapy with 2 cycles of chemotherapy concurrently. Primary outcome is 2-year local control rate in 20 evaluable patients. **Results:** 20 patients were accrued 3/2023-12/2023. Median age - 70 years old (46-88); Male – 95%; ECOG PS 0 – 80%. Tumor stage – T3 (70%); T4a (30%); N2b (70%); N2c (30%). All 20 patients had pretreatment hypoxia by ^{18}F-FMISO. All 20 patients had sufficient downstaging to be treated by 30-ROC Study and converted to no hypoxia by ^{18}F-FMISO. The estimated progression free survival and local control rate at 2 years is 90% (95% CI 76.9%-100%). There were no distant failures. The median follow up is 23 months (range 12-29 months). All patients were alive and without evidence of disease at last follow up. **Conclusions:** Preliminary results suggest that ICT can allow more advanced tumors (T3/T4), that are typically excluded from de-escalation studies, to be de-escalated and may eliminate tumor hypoxia in a large proportion of cases. This small pilot study shows similar results seen in the larger ROC studies published to date, but a larger study is needed to confirm these results and is currently ongoing. Clinical trial information: NCT05491512. Research Sponsor: None.

6104 Poster Session

Zopapogene imadenovec-drba, a novel non-replicating adenoviral vector-based immunotherapy: Effects on complete and durable responses in recurrent respiratory papillomatosis pivotal trial. First Author: Scott Norberg, Center for Immuno-Oncology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Recurrent respiratory papillomatosis (RRP) is a rare, neoplastic disorder caused by chronic human papillomavirus (HPV) type 6 or 11 infection. Significant morbidity can occur due to airway obstruction and transformation into malignant cancer. Repeat surgical debulking has historically been the most common treatment for RRP symptom management. Zopapogene imadenovec-drba (zopa), a novel adenoviral vector-based immunotherapy, is the first and only FDA-approved treatment for adults with RRP. Zopa is now recommended as the first-line treatment for adults with RRP in an RRP Foundation position statement authored by 16 key opinion leaders (Best *et al.* Laryngoscope 2026). **Methods:** The pivotal trial (NCT04724980) evaluated zopa in patients with RRP requiring ≥3 clinically indicated interventions 12 months (m) prior to treatment. 12m follow-up data was reported and demonstrated that 4 subcutaneous injections of zopa ($5x10^{11}$ particle units per injection; n=35) were well-tolerated, with no serious adverse events, no grade >2 treatment-related adverse events, and no early treatment discontinuations. The most common adverse events were injection-site reaction, fatigue, chills, fever, and myalgia. Robust efficacy was observed following zopa treatment with 51% (34 to 69; 95% CI) of patients achieving a complete response (CR), defined as no requirement for interventions in the 12m following treatment, and 86% (30/35) of patients experiencing a decrease in interventions in the year following treatment as compared to the year prior to treatment. Here we present data up to 51m of follow-up. **Results:** As of December 15, 2025, 83% (15/18) of patients who achieved a CR at 12m remain in CR with no recurrence of papilloma requiring surgical or medical intervention. The median duration of follow-up for patients in CR was 36m (range: 30-51m), with 3 patients having a response lasting more than 4 years. No new safety events were observed during long-term follow-up. **Conclusions:** Zopa treatment demonstrated significant clinical benefit with the vast majority of CR patients experiencing ongoing durable complete responses for up to 4 years with excellent long-term safety. Updated follow-up results for all patients achieving CR will be available at the time of presentation. Clinical trial information: NCT04724980. Research Sponsor: Precigen Inc.

6105 Poster Session

Omitting postoperative radiotherapy after pathologic complete response to neoadjuvant immunochemotherapy for patients with locally advanced head and neck squamous cell carcinoma: Survival and patient-reported outcomes. First Author: Shuwei Chen, Department of Head and Neck Surgery, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: Neoadjuvant immunochemotherapy (NICT) results in high pathologic response rates in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). However, whether it is safe to omit postoperative radiotherapy (PORT) for patients who achieved pathologic complete response (pCR) after NICT and surgery remains unclear. We assessed the survival and patient-reported outcomes (PROs) for LA-HNSCC patients who achieved pCR to NICT. **Methods:** This retrospective cohort study included LA-HNSCC patients who achieved pCR to NICT between July 2019 and June 2025. Patients were categorized into two groups based on whether they received PORT. Propensity score matching (PSM) was performed to minimize confounding and balance baseline characteristics. Kaplan-Meier survival analysis was performed to estimate local recurrence-free survival (LRFS), locoregional recurrence-free survival (LRRFS), distant metastasis-free survival (DMFS), and overall survival (OS). EORTC QLQ-C30 and EORTC QLQ-HN35 questionnaires before NICT, preoperatively, and at month 1, 3, and 12 postoperatively were collected. Least-squares mean (LS mean) changes from baseline were estimated using linear mixed-effects models for repeated measures (group, time, and group×time), adjusting for baseline scores. **Results:** A total of 236 HNSCC patients who achieved pCR after NICT and surgery were included (non-PORT, n = 98; PORT, n = 138). After 1:1 PSM to balance baseline characteristics, 164 patients (82 matched pairs) with comparable baseline characteristics were analyzed. With a median follow-up of 31.67 months (95% CI, 29.57-35.35), survival analysis showed no significant differences between the non-PORT and PORT groups in 2-year LRFS, LRRFS, DMFS or OS (all $p > 0.05$). Longitudinal EORTC QLQ-C30 global health/QOL analyses showed poorer recovery in the PORT group. PORT was associated with significantly greater postoperative QOL decline at 1 and 3 months postoperatively, with a persistent deficit at 12 months , while non-PORT improved above baseline by 12 months whereas PORT remained slightly reduced. On the EORTC QLQ-HN35, PORT was associated with persistently higher symptom burden, peaking at 3 months postoperatively and remaining elevated up to 1 year compared with non-PORT, suggesting potential QOL benefits of omitting PORT in pCR patients. **Conclusions:** In this propensity score-matched cohort of LA-HNSCC patients achieving pCR after NICT and surgery, omitting PORT was associated with comparable 2-year disease control and survival but better recovery of multidimensional QOL and lower symptom burden on head and neck-specific PROs. These findings favor omission of PORT for this patient population, while prospective validation and longer follow-up are warranted. Research Sponsor: None.

6106 Poster Session

Neoadjuvant adebrelimab plus chemotherapy in untreated locally advanced head and neck squamous cell carcinoma: Efficacy and biomarker insights from a single-arm phase 2 trial. First Author: Ruihua Fang, Department of Otorhinolaryngology Head and Neck Surgery The First Affiliated Hospital Sun Yat-sen University, Guangzhou, Guangdong, China

Background: Improving outcomes for locally advanced head and neck squamous cell carcinoma (LA-HNSCC) requires novel strategies. This phase 2 trial evaluated the efficacy and safety of neoadjuvant adebrelimab (a PD-L1 inhibitor) combined with chemotherapy in untreated, resectable LA-HNSCC. **Methods:** In this single-center, single-arm study, eligible patients had newly diagnosed, resectable stage III-IVA/B LA-HNSCC. Patients received three cycles of neoadjuvant adebrelimab (1200 mg), nab-paclitaxel (260 mg/m²), and carboplatin (AUC 5) every 21 days. The primary endpoint was objective response rate (ORR, RECIST v1.1). Secondary endpoints included safety, pathologic response, larynx preservation, and biomarker analysis. **Results:** Twenty-four patients were enrolled (median age 61.5 years; 91.7% male; 70.8% hypopharynx primary). Twenty-three completed all three cycles of neoadjuvant therapy and were evaluated. The ORR was 87.5% (21/24) in the intention-to-treat population and 91.3% (21/23) in the per-protocol population, including 5 complete and 16 partial responses. The larynx preservation rate was 95.8%. Pathologic complete response was observed in 3 of 7 surgical patients (42.9%). Significant downstaging occurred in T-stage (66.7%), N-stage (70.8%), and overall stage (54.2%). All patients with p16-positive tumors (8/8) and those with PD-L1 combined positive score ≥20 (8/8) achieved an objective response. Grade 3 adverse events occurred in 41.7% of patients (primarily hematologic toxicities), with no grade 4/5 events. **Conclusion:** Neoadjuvant adebrelimab plus chemotherapy demonstrated high response rates, promising organ preservation, and manageable toxicity in resectable LA-HNSCC. Biomarker analysis suggests p16 positivity and high PD-L1 expression may correlate with better response. Clinical trial information: ChiCTR2400091171. Research Sponsor: National Natural Science Foundation of China; 82473271.

Efficacy outcomes based on full analysis set (FAS).

Efficacy Parameter	Overall (N=24)	Larynx (n=4)	Hypopharynx (n=17)	Oropharynx (n=3)
Best Overall Response, n (%)				
CR	5 (20.8)	1 (25.0)	4 (23.5)	0 (0.0)
PR	16 (66.7)	3 (75.0)	10 (58.8)	3 (100.0)
SD	3 (12.5)	0 (0.0)	3 (17.6)	0 (0.0)
PD	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ORR	21 (87.5,)	4 (100.0)	14 (82.4)	3 (100.0)
(95% CI)	(67.6 - 97.3)	(39.8 - 100.0)	(56.6 - 96.2)	(29.2 - 100.0)
(95% CI)	(48.9 - 87.4)	(19.4 - 99.4)	(38.3 - 85.8)	(29.2 - 100.0)
Larynx Preservation Rate	23 (95.8)	4 (100.0)	16 (94.1)	3 (100.0)
(95% CI)	(78.9 - 99.9)	(39.8 - 100.0)	(71.3 - 99.9)	(29.2 - 100.0)
DCR	24 (100.0)	4 (100.0)	17 (100.0)	3 (100.0)
(95% CI)	(85.8 - 100.0)	(39.8 - 100.0)	(80.5 - 100.0)	(29.2 - 100.0)

Data are n (%, 95% CI). FAS: full analysis set (all enrolled patients receiving at least one treatment cycle); ORR: objective response rate (CR + PR); DCR: disease control rate (CR + PR + SD). Antitumor response was assessed according to RECIST v1.1.

6107 Poster Session

Long term functional survivorship in oral cavity cancer: Quality of life (QOL) outcomes by return to work (RTW) status. First Author: Karthika Chettuvatti, All India Institute of Medical Sciences (AIIMS), New Delhi, New Delhi, India

Background: Long-term survivors of oral cavity cancer (OCC) often experience persistent physical, functional, and psychosocial impairments despite disease control. Return to work (RTW) reflects real-world functional recovery and social reintegration. We evaluated whether health-related quality of life (QOL) differs between OCC survivors who returned to work and those who did not. **Methods:** This prospective cohort study included OCC survivors ≤65 years who underwent definitive surgery between 2016 and 2023 and were disease-free for ≥2 years. Health-related QOL was assessed using EORTC QLQ-C30, EORTC QLQ-HN43, and UW-QOL questionnaires. QOL domains were compared between survivors who returned to work and those who did not. **Results:** Three hundred OCC survivors were evaluated at a median of 28.5 months after treatment. Survivors who returned to work demonstrated significantly higher global health status and superior physical, role, emotional, cognitive, and social functioning on EORTC QLQ-C30 compared with non-working survivors (all $p<0.0001$). Non-working survivors had substantially greater head-and-neck–specific symptom burden on EORTC QLQ-HN43, including swallowing difficulty, speech problems, shoulder dysfunction, pain, dry mouth, body-image disturbance, social eating limitations, and fear of progression (all $p<0.0001$). UW-QOL confirmed significantly worse pain, activity, recreation, swallowing, chewing, speech, shoulder function, mood, anxiety, and overall health-related QOL in survivors who did not return to work (all $p<0.0001$). **Conclusions:** Return to work is strongly associated with superior multidimensional quality of life in oral cavity cancer survivors. Survivors who do not resume work experience profound physical, functional, and psychosocial impairment, highlighting the need for rehabilitation-centered survivorship care to restore meaningful functional recovery beyond oncologic cure. Research Sponsor: None.

Quality of life scores for European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 43 (EORTC QLQ HN 43).

EORTC QLQ HN 43	Total patients (Overall population)	Returned to work at the time of survey (Mean + SD)	Did not return to work at the time of survey (Mean + SD)	P Value
Pain in the mouth	34.2 + 15.8	10.3+ 13.2	33.2 + 13.5	p<0.0001
Swallowing issue	10.8 + 12.5	7.8 + 8.7	25.5 + 16.9	p<0.0001
Problems with teeth	17.8 + 19.2	14.1 + 17.2	35.7 + 18.6	p<0.0001
Dry mouth and sticky saliva	23.4 + 21.9	19.5 + 19.1	42.8 + 24.3	p<0.0001
Problems with senses	18.1 + 18.9	14.2 + 16.6	36.9 + 18.0	p<0.0001
Speech issues	15.9 + 18.8	11.6 + 15.4	44.9 + 17.2	p<0.0001
Body image issues	18.0 + 19.7	12.5 + 15.2	41.3 + 20.1	p<0.0001
Social eating issues	17.0 + 19.9	12.0 + 15.7	47.1 + 22.5	p<0.0001
Sexuality problem	18.1 + 22.7	12.2 + 17.6	46.4 + 18.3	p<0.0001
Problems with shoulder	18.6 + 22.0	12.9 + 17.9	46.4 + 18.3	p<0.0001
Skin Problems	13.5 + 18.5	9.0 + 14.7	35.7 + 19.4	p<0.0001

6108 Poster Session

Barriers and variability in lymphedema therapy for head and neck cancer survivors: Secondary analysis from a randomized trial. First Author: Cristina Kline-Quiroz, Vanderbilt University Medical Center, Nashville, TN

Background: Secondary lymphedema is a significant underrecognized sequela of head and neck cancer (HNC) and its treatments. Lymphedema may impact external structures (head, face, neck) and internal structures (larynx, pharynx), leading to functional impairments impacting breathing, speaking and swallowing resulting in disability, and reduced quality of life. Although therapist guided lymphedema treatment (TGLT) is effective, timely access is frequently limited by financial constraints, geographic barriers, systemic inefficiencies, and shortages of trained therapists. This study evaluates accessibility, implementation, and barriers to TGLT in HNC survivors. **Methods:** This prospective cohort study was nested within a multi-site randomized trial comparing usual care to an advanced pneumatic compression device (APCD). Eligible participants (N=117) were HNC survivors with lymphedema and at least one lymphedema-associated symptom rated ≥4/10. Therapy notes and patient data were abstracted to assess referral patterns, therapy timelines, lymphedema treatment characteristics, documented therapeutic goals, and reported barriers. Descriptive statistics were obtained to depict trends in therapy initiation, implementation, and barriers. **Results:** Of 117 participants referred for therapy, 77 (66%) were evaluated by a therapist. Of these, 11 failed to return for a second visit (56%). Median time from referral to evaluation was 17 days. Median time from evaluation to last recorded visit was 72.5 days (median 10 visits). Many patients experienced protracted wait times (Figure 1) and treatment breaks. Therapy delivery varied substantially; By last documented visit, recommendations included home manual lymphatic drainage (82%), compression garments (65%), APCD (33%), and written self-care instructions (26%). 28% achieved all therapy goals. Documentation inconsistencies and gaps in provider communication hindered effective therapy implementation. Barriers included geographic distance, financial constraints, and therapist shortages. **Conclusions:** Significant variability, limited care access, and delays in TGLT exist for HNC survivors. Standardized protocols, telemedicine, and adjunctive technologies such as APCDs may improve accessibility, adherence, and outcomes. Future studies should focus on optimizing care models including self-care and reducing disparities in therapy delivery. Clinical trial information: NCT04797390. Research Sponsor: Tactile Medical.

Timeframe of therapy implementation in days.

	Provider Referral to Therapy Evaluation	Therapy Evaluation to Second Visit	Provider Referral to Second Visit	Therapy Evaluation to Last Visit
Average	23.7	9.0	32.7	80.0
Standard deviation	21.9	6.8	23.3	44.9
Median	17.0	7.0	27.0	72.5
Minimum	0.0	1.0	1.0	7.0
Maximum	93.0	31.0	108.0	175.0
25th percentile	8.0	4.0	16.3	48.0
75th percentile	31.8	14.0	44.5	103.5

6109 Poster Session

Impact of advanced pneumatic compression devices and usual care on psychosocial outcomes in head and neck cancer survivors with lymphedema. First Author: Cristina Kline-Quiroz, Vanderbilt University Medical Center, Nashville, TN

Background: Head and neck cancer (HNC)-associated lymphedema impairs quality of life (QOL) in survivors, affecting body image, self-management efficacy, work productivity, and psychosocial functioning. Data supports therapist guided lymphedema therapy (TGLT) and technologies such as advanced pneumatic compression devices (APCD) reduce swelling. There is a lack of data on psychosocial and QOL outcomes. This randomized clinical trial compared psychosocial outcomes of TGLT and APCD in treatment-naïve HNC survivors with symptomatic lymphedema over 6 months. **Methods:** Participants (N=236) with HNC-associated lymphedema were randomized 1:1 to receive either TGLT (117) or APCD (119) for 6 months. Psychosocial outcomes were assessed at baseline, 2, 4, and 6 months using validated instruments: the Work Productivity and Activity Impairment Questionnaire (WPAIQ), Perceived Medical Condition Self-Management Scale (PMCSMS), Body Image Quality of Life Inventory (BIQLI), and Linear Analog Self-Assessment (LASA) for QOL. Longitudinal mixed-effects models evaluated within- and between-group changes over time. **Results:** Both treatment groups experienced improvements in psychosocial outcomes over time. Self-management efficacy improved in both arms. The APCD group demonstrated significantly greater self-efficacy managing lymphedema at 6 months (p=0.004). Work and activity impairment decreased in both groups, with no significant between-group differences. BIQLI scores improved across timepoints in both arms, reflecting enhanced body image-related QOL. LASA scores for overall QOL and emotional, physical, and spiritual well-being also improved similarly in both groups. No significant time-by-treatment interactions were observed, indicating comparable trajectories of psychosocial recovery. **Conclusions:** Both TGLT and APCD were associated with meaningful improvement in psychosocial outcomes, including self-management efficacy, body image, and QOL, among HNC survivors with lymphedema. APCD offers ongoing access to a convenient, home-based treatment which may enhance fidelity and self-efficacy through ongoing instrumental support. These findings underscore the value of accessible, patient-centered lymphedema interventions to enhance survivorship care. Future research should explore long-term adherence, cost-effectiveness, and integration of psychosocial support into treatment pathways. Clinical trial information: NCT04797390. Research Sponsor: Tactile Medical.

6110 Poster Session

GDF-15 in oropharyngeal squamous cell carcinoma (OPSCC): Association of an HPV-dependent biomarker with malnutrition and low skeletal muscle. First Author: Lorena Arribas, Clinical Nutrition Unit. Catalan Institute of Oncology (ICO), Hospitalet De Llobregat (Barcelona), Spain

Background: GDF15 is a stress-response cytokine implicated in systemic inflammation and cancer-related wasting. We assessed whether baseline circulating GDF15 captures an HPV-stratified nutritional/body composition phenotype and whether longitudinal GDF15 changes relate to treatment outcome in OPSCC. **Methods:** We analyzed a prospective cohort of OPSCC patients (pts) undergoing curative intent treatment (CIT; surgery and radiotherapy [RT]-based) with available baseline plasma GDF15. HPV status was defined by dual detection ($p16^{INK4a}$ and HPV DNA). Baseline nutritional status (Patient Generated Subjective Global Assessment), symptom burden (nutrition-impact composite score), body mass index (BMI), and CT-derived skeletal muscle index (SMI) were analyzed when available. Response assessment was performed 8-12 weeks after CIT, classifying cases as no evidence of disease (NED) vs evidence of disease (ED). Longitudinal GDF15 was analyzed using linear mixed-effects models (LMEN) (random intercept) including interactions of time with response status and induction chemotherapy. **Results:** We included 138 pts (HPVnegative [−] n=82; HPVpositive [+] n=56). Stage III–IV was more frequent in HPV- vs HPV+ (85.4% vs 30.4%; $p<0.001$) and ECOG 0 less common (9.8% vs 51.8%; $p<0.0001$). RT-based treatment predominated (85.5%) mainly chemoradiotherapy ± induction (82.6%). Baseline GDF15 was higher in HPV- vs HPV+ (median 1591 vs 803 pg/mL; $p<0.001$). HPV− pts showed worse nutritional phenotype: lower BMI (22.7 vs 27.2 kg/m²; p=0.001), more severe malnutrition (37.8% vs 7.1%; $p<0.001$), higher symptom burden (1.90±0.94 vs 1.39±0.71; p=0.002) and higher sarcopenia (34.1% vs 16.1%; p=0.029). In pts with CT body composition (n=89), SMI was lower in HPV− vs HPV+ (45.6 vs 53.6 cm²/m²; p=0.010). Baseline GDF15 differed by nutritional status (p=0.014) and was associated with symptom burden and SMI (both $p<0.05$). In LMEN, GDF15 increased significantly from baseline to end of treatment (β=2264 pg/mL; $p<0.001$). Baseline HPV positivity was independently associated with lower GDF15 (β=−980 pg/mL; $p<0.001$). At the end of treatment, NED was associated with lower GDF15 compared with ED (β=−1141 pg/mL; p=0.011). Induction chemotherapy showed no significant effect on GDF15 change (β=−448 pg/mL at end of treatment; p=0.22). No significant interaction between time and baseline HPV status was observed (p=0.26) indicating comparable longitudinal trajectories of GDF15 in HPV+ and HPV-pts. **Conclusions:** Baseline GDF15 is strongly HPV-dependent and reflects a multidimensional nutritional and muscle phenotype. GDF15 increases during CIT and lower end-of-treatment GDF15 is independently associated with NED, whereas induction chemotherapy does not significantly modify GDF15 change. Research Sponsor: None.

6111 Poster Session

Nonoperative management of locally advanced resectable cutaneous squamous cell cancer of the head and neck with PD-1 blockade. First Author: Fergal Kavanagh, Department of Surgery, Head and Neck Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Head and neck cutaneous squamous cell carcinoma (cSCC) is common, increasing in incidence, and highly immunogenic. Neoadjuvant PD-1 blockade with cemiplimab has demonstrated substantial efficacy prior to surgery; however, its role as a definitive nonoperative strategy in resectable disease remains poorly defined. **Methods:** We conducted a single-institution retrospective study (2018–2023) of patients with locally advanced, resectable stage III/IV head and neck cSCC treated with cemiplimab. Patients received either neoadjuvant cemiplimab followed by surgery or cemiplimab monotherapy without surgery. The primary endpoint was objective clinical and radiologic response rate. Secondary endpoints included disease-specific survival (DSS), progression-free probability (PFP), histopathologic response, and exploratory genomic biomarkers. **Results:** Seventy-three patients were included: 52 received cemiplimab monotherapy (median age, 78.8 years) and 21 received neoadjuvant cemiplimab (median age, 73 years). In the monotherapy cohort, complete response occurred in 68.6%, partial response in 9.8%, stable disease in 5.9%, and progression in 15.7% (median treatment duration, 10 months). Two-year DSS and PFP were 90% (95% CI, 80–100) and 82% (95% CI, 72–94), respectively. In the neoadjuvant cohort, radiographic response was observed in 66.7% and pathologic complete response in 38.1%. Two-year DSS and PFP were 95% (95% CI, 86–100) and 78% (95% CI, 62–100), respectively. DSS and PFP did not differ significantly between cohorts. Tumor-infiltrating lymphocytes (TILs) were higher in complete and partial responders than in patients with stable or progressive disease (p=0.005, q=0.02), with absent TILs more frequent in non-responders. Tumor mutational burden (TMB) was greater in complete (55.7) and partial responders (14.9) than in patients with progressive disease (4.9; p=0.02, q=0.04). **Conclusions:** In the largest reported series to date, cemiplimab monotherapy achieved durable disease control and oncologic outcomes comparable to neoadjuvant cemiplimab in selected patients with resectable, locally advanced head and neck cSCC, supporting further study of definitive immunotherapy as an organ-preserving strategy. Research Sponsor: None.

6112 Poster Session

Dynamic biological and metabolic response by EBV DNA and ^{18}F-FDG-PET-CT to induction chemotherapy (IC) to enhance prognostication in endemic nasopharyngeal carcinoma (NPC). First Author: Jialing Neo, National Cancer Centre Singapore, Singapore, Singapore

Background: IC followed by concurrent chemoradiotherapy (CCRT) is the current standard of care for locoregionally-advanced NPC (LA-NPC). Nonetheless, evidence suggests that IC response is a strong predictor for risk of relapse in LA-NPC. Here, we characterized the dynamic metabolic and biological responses to IC, and investigated their associations with survival in patients with high-risk LA-NPC. **Methods:** Newly diagnosed patients with non-metastatic, biopsy-proven NPC were enrolled into two prospective ongoing studies (NCT04340024 and NCT06093061). For this analysis, patients who received 2-3 cycles of gemcitabine-cisplatin/carboplatin IC were included; all patients had plasma EBV DNA assessed following every IC cycle, and ^{18}F-FDG-PET-CT performed pre-IC and 1 week before the end of IC. For the latter, standardized uptake values (SUVs) were recorded for the primary tumor (SUVp) and individual nodal lesion(s) (SUVn). Biological (bCR) and metabolic complete response (mCR) were defined as EBV DNA =0 copy/mL and SUV $\leq$2.5, respectively. Prediction accuracy of 2y disease-free survival (DFS) was assessed by area under the receiver operating characteristic curve (AUC). **Results:** 117 patients diagnosed between Jan 2019 to Apr 2025 were included in this analysis; of these, 112 and 106 had SUVp and SUVn at pre- and post-IC. For SUVn, we performed lesion-level analysis for 259 LNs. Median follow-up was 20.5 (interquartile range [IQR]: 11.6-41.3) mo and TNM-8 stage distribution for stage III and IVA were 43% (50/117) and 57% (67/117), respectively. Median SUVp and SUVn pre-IC were 15.0 (IQR: 10.4-18.2) and 8.5 (IQR: 4.5-12.3), respectively, while median EBV DNA level was 4800 (IQR: 914-20598) copies/mL. Post-IC, we recorded mCR at the primary tumor and LNs for 33/112 (29%) and 49/106 (46%), respectively; while 14/117 (12%), 30/117 (26%) and 40/117 (34%) patients manifested bCR post-IC1, IC2, and IC3, respectively. Metabolic response was not correlated with biological response; of 33 patients with primary tumor mCR, 20/33 (61%) had bCR; while for LNs, only 25/49 (51%) patients with mCR manifested bCR post-IC. Additionally, we observed significant intrapatient heterogeneity of mCR between LN lesions post-IC; in 57/106 patients with non-mCR for $\geq$1 of the LNs, SUVn ranged between 0-12.9. Finally, incorporating both post-IC bCR and mCR to TNM-8 stage and pre-IC EBV DNA enhanced AUC of 2y DFS prediction; from 0.58 (95%CI:0.44-0.73) [TNM-8+pre-IC EBV DNA] to 0.77 (95%CI:0.60-0.94). **Conclusions:** Metabolic and biological responses to IC provide unique information on response phenotypes of patients with LA-NPC, and improved the prediction accuracy of 2y DFS compared with TNM-8 stage and pre-IC EBV DNA. Combinatorial ^{18}F-FDG-PET-CT and EBV DNA post-IC may enhance the selection of these patients for treatment intensification. Research Sponsor: National Medical Research Council Singapore; NMRC/OFLCG21jun-0013; National Medical Research Council Singapore; NMRC/CSAINV20nov-0021.

6113 Poster Session

Chrono-chemotherapy combined with IMRT in locoregionally advanced nasopharyngeal carcinoma: A prospective randomized study. First Author: Feng Jin, Affiliated Hospital of Guizhou Medical University/Department of Head and Neck Oncology, Affiliated Cancer Hospital of Guizhou Medical University, Guiyang, GuiZhou, China

Background: Induction chemotherapy followed by radiotherapy with concurrent cisplatin is a standard treatment for locoregionally advanced nasopharyngeal carcinoma (LA-NPC). The TPF induction regimen combined with intensity-modulated radiation therapy (IMRT) improves tumor control but causes substantial toxicity. Circadian rhythms regulate tumor biology and drug metabolism. Docetaxel, cisplatin, and 5-fluorouracil show circadian-dependent pharmacologic properties. Chrono-chemotherapy aligns drug administration with circadian rhythms and may reduce toxicity. This study compared long-term outcomes and late adverse events between chrono-chemotherapy and conventional chemotherapy combined with IMRT in LA-NPC. **Methods:** This single-center, prospective, randomized clinical trial was registered at ClinicalTrials.gov (NCT03196869). Between April 2017 and May 2018, 128 patients with newly diagnosed stage III–IVa nasopharyngeal carcinoma were randomly assigned to chrono-chemotherapy or conventional chemotherapy. All patients received three cycles of TPF induction chemotherapy, followed by IMRT with two cycles of concurrent cisplatin chemotherapy. Survival outcomes were analyzed using the Kaplan–Meier method and compared by log-rank test. Late toxicities were graded using CTCAE v5.0. Quality of life was assessed with the EORTC QLQ-C30 questionnaire. **Results:** A total of 124 patients were included in the survival analysis. No significant differences were observed between groups in 5-year overall survival (P=0.709), progression-free survival (P=0.492), distant metastasis-free survival (P=0.467), or locoregional recurrence-free survival (P=0.697). The chrono-chemotherapy group showed lower rates of xerostomia (P=0.034) and dysphagia (P=0.019). No grade $\geq$4 late toxicities were observed. Global health status scores were higher in the chrono-chemotherapy group (P=0.043). **Conclusions:** Chrono-chemotherapy combined with IMRT achieved long-term survival outcomes comparable to conventional chemotherapy in LA-NPC. This approach reduced selected late toxicities and improved overall health status. Chrono-chemotherapy may represent a toxicity-sparing treatment option. Clinical trial information: NCT03196869. Research Sponsor: None.

Late toxicities and quality of life.

Outcome	Conventional Chemotherapy	Chrono-chemotherapy	P value
Xerostomia, n (%)	24/36 (66.7)	16/38 (42.1)	0.034
Dysphagia, n (%)	24/36 (66.7)	15/38 (39.5)	0.019
Global health status score*	58.33 (50.00–72.92)	75.00 (50.00–83.33)	0.043

*Scores derived from the EORTC QLQ-C30 questionnaire; values are presented as median (interquartile range).

6114 Poster Session

Survival implications of context-dependent oncogenic *PIK3CA* mutations in HNSCC. First Author: Jeremiah Ray Holt, Center for Cancer Research, University of Tennessee Health Science Center, Memphis, TN

Background: Head and neck squamous cell carcinoma (HNSCC) is a heterogenous disease that generally lacks clinically useful stratification methods beyond anatomy and HPV status. *PIK3CA* is the most frequently mutated oncogene in HNSCC, and previous studies have linked *PIK3CA* mutations to survival in HNSCC. Thus, we aimed to investigate overall survival (OS) in a large multi-center cohort of HNSCC as a function of specific *PIK3CA* mutation hotspots to better understand the molecular drivers of risk and prognosis in HNSCC. **Methods:** A subset of oral cavity (OC, n=606) and oropharyngeal (OP, n=480) tumors from the VOYAGER consortium underwent exon sequencing in 1,109 cancer related genes and whole HPV16/18 genomes. Mutations in *PIK3CA* were analyzed using a somatic variant calling and filtering pipeline, and driver alterations were annotated based on gain-of-function variants at recurrent hotspots in specific functional protein domains. HPV status was defined using serology, p16 IHC, RNA ISH, and viral genomics. Multivariable Cox proportional hazards models were used to assess the relationship between *PIK3CA* mutations and five-year OS adjusted for age, sex, HPV status, tumor type, and TNM staging. **Results:** In OP tumors, 289 were HPV(+) and 174 were HPV(-), while only 13 of OC tumors were HPV(+). The overall *PIK3CA*mutation rate was 18% (13% of OC vs 24% of OPs), and among OP cases, *PIK3CA* mutations occurred in 28% of HPV(+) vs 18% of HPV(-) tumors. Of the nine recurrent hotspots in *PIK3CA*, the most common were the APOBEC-associated ones in the helical domain, *p.E545K* (3% OC vs 12% OP) and *p.E542K* (2% OC vs 5% OP), as well as smoking-associated kinase domain mutations at *p.H1047R* (3% OC vs 2% OP). In OC and OP cases combined, tumors harboring *PIK3CA* driver alterations in one of the nine hotspots showed a statistically significant improvement in OS that was independent of age, sex, staging, tumor type, and HPV status (HR 0.72, P=0.048). Among all HPV(+) tumors, driver mutations in *PIK3CA* conferred significantly better OS in the adjusted model (HR 0.42, P=0.02). Likewise, in all OP tumors, *PIK3CA* driver mutations were significantly associated with improved OS in the multivariate models (HR 0.60, P=0.04) and when stratified by HPV status this effect was particularly strong for HPV(+) OP tumors only (HR 0.45, P=0.04). Among the hotspots, *p.E545K* was the only one with improved survival in a univariable analysis of the full cohort (Log-rank P=0.01), but this was not significant in the adjusted model (HR 0.62, P=0.07). **Conclusions:** Our findings validate previously described associations between *PIK3CA* mutation and OS in HNSCC that are dependent on anatomic site and HPV status. Moreover, we provide a new perspective by analyzing OS as a function of recurrent mutation hotspots in *PIK3CA*, which may signify distinct pathologic processes among HNSCCs and thus may be clinically useful for patient stratification with prognostic or therapeutic intent. Research Sponsor: None.

6115 Poster Session

Survival outcomes with contemporary treatments including immunotherapy for poorly differentiated neuroendocrine carcinomas of the head and neck. First Author: Rushabh Gujarathi, University of Louisville, Louisville, KY

Background: Poorly differentiated Neuroendocrine Carcinomas of the Head and Neck (HN-NECs) are rare aggressive malignancies with limited data guiding therapeutic approaches, particularly in the metastatic setting, with cytotoxic chemotherapy (chemo) comprising the backbone of management. Despite the widespread use of immune checkpoint inhibitors/immunotherapy (IO) in advanced lung NECs, evidence regarding their utility in the extrapulmonary setting, particularly for HN-NECs, is scarce. We explored real-world outcomes with various therapeutic strategies, including IO, in patients with metastatic HN-NECs, using the National Cancer Database (NCDB). **Methods:** Patients with metastatic HN-NECs diagnosed between 2018 to 2023 were identified. Overall survival (OS) was analyzed using Kaplan-Meier estimations and Cox proportional hazards regression. **Results:** A total of 275 patients with metastatic HN-NECs were identified. Primary sites included larynx (n = 75, 27.3%), pharynx (n = 72, 26.2%), nasal cavity + paranasal sinuses (n = 67, 24.4%), and oral cavity (n = 61, 22.2%). Most common metastatic sites were liver (n = 128, 46.5%) and bone (N = 272; n = 116, 42.6%). Of these 275 patients, 212 (77.1%) received chemo, 95 (34.5%) received IO, 122 (44.4%) received radiotherapy (RT), and 46 (16.7%) underwent primary site surgery (surg). Among patients with available survival data (N = 227), receipt of chemo (n = 174) and/or IO (n = 78) were associated with prolonged OS vs. no chemo ($p < 0.001$) and/or no IO ($p = 0.005$), respectively. Use of RT (n = 105; p = 0.17) and surg (n = 39; p = 0.18) were not significantly associated with OS (Table). Among 174 patients who received chemo, concurrent IO (chemoIO; n = 73) was associated with significantly prolonged OS vs. chemo alone (14.1 months [m] vs. 9.9 m; HR, 0.67; 95% CI, 0.47 – 0.96; p = 0.03). On multivariable analysis adjusting for bone metastatic disease (the only other significant prognostic covariate on univariable regression), chemoIO remained associated with reduced mortality risk vs. chemo alone (HR 0.57; 95% CI, 0.39 – 0.82; p = 0.003). **Conclusions:** Akin to lung NECs, IO may improve OS in HN-NECs. Despite NCDB limitations, chemoIO was associated with prolonged OS over chemo alone. Further prospective evaluations are warranted, and results from ongoing studies (e.g., NCT05058651) are awaited. Research Sponsor: None.

Survival comparisons with univariable Cox proportional hazards regression.

Treatment Group	Median OS in months (95% CI)	HR (95% CI)	p
Chemo (vs. No Chemo)	11.3 (9.5 – 14.2) vs. 3.4 (2.7 – 6.2)	0.53 (0.38 – 0.74)	<0.001
IO (vs. No IO)	13.0 (10.8 – 17.1) vs. 8.1 (6.2 – 10.3)	0.63 (0.46 – 0.87)	0.005
RT (vs. No RT)	10.8 (8.8 – 14.6) vs. 8.5 (6.4 – 11.7)	0.81 (0.60 – 1.09)	0.17
Primary Site Surgery (vs. No Surgery)	12.5 (8.7 – 28.5) vs. 9.0 (7.7 – 11.7)	0.76 (0.51 – 1.14)	0.18
ChemoIO (vs. Chemo alone)	14.1 (11.1 – 19.3) vs. 9.9 (8.3 – 13.7)	0.67 (0.47 – 0.96)	0.03

6116 **Poster Session**

CCL3^{+} neutrophil signature as a predictor of response to neoadjuvant toripalimab plus chemotherapy in hypopharyngeal squamous cell carcinoma: A phase II trial. First Author: Zhenghua Lv, Shandong Provincial ENT Hospital, Shandong University, Jinan, Shandong, China

Background: Hypopharyngeal squamous cell carcinoma (HPSCC) has a poor prognosis. Although neoadjuvant chemoimmunotherapy (nCIT) is promising, responses are heterogeneous and PD-L1 combined positive score (CPS) inadequately stratifies benefit. We sought biomarkers to guide patient selection. **Methods:** In this prospective, single-center, single-arm phase II trial, patients with resectable locally advanced HPSCC received two cycles of neoadjuvant toripalimab, albumin-bound paclitaxel, and nedaplatin. The primary endpoint was the pathological complete response (pCR) rate. Pre-treatment tumor biopsies from a subset of patients (n=13) were analyzed by single-cell RNA sequencing (scRNA-seq) to identify determinants of response. Findings were validated in a larger cohort (n=60) using bulk RNA sequencing and immunohistochemistry. **Results:** Among 70 evaluable patients, the objective response rate was 82.7%. Of the 64 patients who underwent surgery, the pCR rate was 29.7% (95% CI, 18.9%–42.7%). Baseline PD-L1 CPS was not associated with pathological response (P=0.313). Single-cell analysis revealed that the pre-treatment tumor microenvironment of responders was significantly enriched with a pro-inflammatory neutrophil subset characterized by high expression of CCL3 (Neu_CCL3). A gene signature score derived from this subset was a strong and independent predictor of pCR (AUC = 0.788), significantly outperforming PD-L1 CPS (AUC = 0.621). **Conclusions:** The efficacy of nCIT in HPSCC is predetermined by a baseline immune architecture orchestrated by a CCL3+ neutrophil subset. The Neu_CCL3 gene signature is a promising, clinically translatable biomarker that can fill a critical gap in precision immunotherapy for HPSCC. Clinical trial information: ChiCTR2400081826. Research Sponsor: None.

6117 **Poster Session**

Palliative neck radiation therapy (RT) in combination with lenvatinib/pembrolizumab (L/P) in BRAF wild-type anaplastic thyroid cancer (BRAF-WT ATC). First Author: Anna Lawless, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: BRAF-WT ATC carries a poor prognosis due to limited effective therapies and rapid, often fatal locoregional (LR) progression. Although L/P has shown some efficacy, response rates remain modest (36-52%). Prior studies have shown that complete surgical resection of the primary tumor significantly improves overall survival (OS). **Methods:** We retrospectively reviewed patients with BRAF-WT ATC treated with palliative neck RT (PNRT, $\leq$45 Gy) administered five days before to 21 days after first-line L/P, between January 2016 and August 2025. Primary objective was to evaluate the efficacy and safety of PNRT combined with L/P. Primary endpoints were progression-free survival (PFS), locoregional PFS (LPFS), and OS, defined from RT start, and estimated using Kaplan-Meier method. Secondary endpoints were overall response rate (ORR) and neck response per RECIST v1.1, changes in surgical morbidity assessed by the Thyroid Neck Morbidity and Complexity (TNMC) score, and proportion of patients proceeding to surgery. **Results:** Twenty-six patients met inclusion criteria. Median age was 66 years (range, 36-82) and 14 were male (54%). 23/26 (88%) had stage IVC disease. 21/26 (81%) received 'Quadshot' regimen (14Gy in 4 fractions), two 20 Gy in 5 fractions and three 30 Gy in 10 fractions. Median time from RT to L/P start was 2 days (range, −4 to 21). Median follow-up was 18.5 months (95% CI, 11.7-25.4). After PNRT and L/P, ORR was 72%, and 72% achieved a complete or partial response in the neck. Median OS and PFS were 10.0 (95% CI, 3.4-16.7) and 7.6 (95% CI, 4.4-10.8) months respectively. Median LPFS was not reached. Median TNMC score (0-4 scale, 4=unresectable) decreased from 4 (range, 2-4) at baseline to 3 (range, 0-4) at time of best response with a mean reduction of 1 point (range, 0-3). Ten patients (38%) proceeded to R0/R1 neck surgery after a median of 5.4 months (range, 1.6-9.5) from RT, with absence of residual ATC in the surgical specimens in 70% (7/10). OS and PFS were significantly longer in patients who underwent surgery compared with those who did not, with median OS 22.8 vs 6.1 months (p=0.002) and median PFS 12.7 vs 3.9 months (p=0.034). Seventeen patients (68%) had disease recurrence/progression: 1 LR, 10 distant, and 6 both LR and distant. All but one (6/7) LR recurrences were in patients who did not undergo surgery. PNRT combined with L/P was well tolerated, with most adverse events grade $\leq$ 2. One patient had a fistula 3 months after RT requiring emergency tracheostomy. **Conclusions:** Palliative neck RT combined with L/P for BRAF-WT ATC appears safe and may improve surgical resectability in patients with initially unresectable disease or high baseline surgical morbidity. Patients who proceeded to neck surgery had high pathologic complete response rate (70%) and significantly prolonged OS and PFS with low rate of locoregional relapse. Research Sponsor: None.

6118 **Poster Session**

Detection, quantification, and subtyping of adenoid cystic carcinoma (ACC) using methylation from liquid biopsies. First Author: Felippe Lazar Neto, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite the common indolent behavior of ACC, some patients will experience aggressive disease with short survival. These distinct clinical behaviors have been linked to two transcriptional profiles: ACC-I, defined by NOTCH1 activation, solid histology, and more aggressiveness, and ACC-II, characterized by predominant myoepithelial p63 expression and generally indolent behavior. DNA methylation has been widely used for tumor identification and subtyping; however, their relevance in distinguishing ACC-I and ACC-II has not yet been explored. **Methods:** Forty-one ACC tissue samples from the original subtype development cohort (41/54) and twenty-three cfDNA samples from a phase II trial of axitinib and avelumab in recurrent/metastatic ACC (NCT03990571) were profiled through target-enriched enzymatic methylation sequencing. ACC subtypes (ACC-I/II) in tissue samples were validated with unsupervised clustering of highly variable regions. To translate these signatures to liquid biopsy, we used the METER (METhylome AnalysER) pipeline to identify tumor-specific differentially methylated sites (DMS) and regions (DMRs) relative to 22 healthy donors, enabling ctDNA detection (METER-positive), tumor proportion score (TPS) quantification, and ACC subtype assignment in cfDNA. Methylation-derived TPS were validated with ichorCNA (copy number alterations) estimates, and cfDNA-assigned subtypes were benchmarked against matched tissue transcriptional signatures. Finally, we investigated if METER detection was associated with progression-free survival (PFS). **Results:** ACC tissue methylation identified two clusters that perfectly matched reference transcriptional subtypes (17/17 ACC-I and 24/24 ACC-II). ACC-I tumors were hypermethylated compared to ACC-II (11,205 hyper and 1,804 hypo DMR, $p<0.05$). Of 23 cfDNA samples, 15 (65.2%) were deemed as METER positive with a higher rate among ACC-I (8/9, 88.9%) compared to ACC-II (7/14, 50.0%), consistent with the more aggressive subtype of ACC-I. The median (range) estimated TPS among METER positive samples was (3.86%; range 0.7%-82%), with a numerical higher TPS among ACC-I (14.8% vs 2.0%, p=0.073). TPS had strong correlation with ctDNA estimation by ichorCNA (spearman 0.86, $p<0.001$). METER subtyping correctly identified ACC-subtypes in 15/15 (100%) METER positive and 4/8 (50%) METER negative samples. METER-positive patients had shorter PFS (HR = 4.32; 95%CI, 1.49–12.5, p=0.007), including among ACC-II patients (HR = 4.84; 95%CI, 1.20–19.5, p=0.026). **Conclusions:** Methylation-based subtyping of ACC is highly concordant with transcriptional profiles and enables detection and subtyping of ACC in liquid biopsies. Beyond subtyping, cfDNA detection may serve as an additional prognostic marker, identifying patients at high risk for progression even within traditionally indolent subgroups. Clinical trial information: NCT03990571. Research Sponsor: U.S. National Institutes of Health; 1R01CA292385-01.

6119 **Poster Session**

Window of opportunity study of the Notch inhibitor AL101 in Notch1 activated adenoid cystic carcinoma (ACC): Biological effects and biomarker correlates. First Author: Daniel McGrail, Cleveland Clinic, Cleveland, OH

Background: ACC with NOTCH1 pathway activation (ACC-N1) is associated with aggressive clinical behavior and poor outcomes. AL101, an inhibitor of gamma secretase-mediated Notch signaling, previously demonstrated modest clinical activity in metastatic *NOTCH*-mutant ACC. We conducted a window-of-opportunity study to evaluate the biological effects of AL101 in ACC-N1 and to identify biomarkers to inform rational combination strategies. **Methods:** Patients with ACC-N1 received AL101 (4 mg weekly) for 4 to 8 weeks prior to surgery. Eligibility required Notch1 pathway activation by cleaved Notch (NICD1) immunohistochemistry ($\geq$ 70% nuclear staining). Treatment-related adverse events (AEs) were assessed per CTCAE v5.0 and radiographic response per RECIST v1.1. Whole-exome sequencing and RNA sequencing were performed on baseline samples, with paired analysis (pre- and post-treatment) in 12 patients. This report focuses on biomarker analysis; clinical endpoints and feasibility were previously presented. **Results:** 13 patients were enrolled between Nov/21 and Dec/23; 8 were newly diagnosed. The median number of AL101 doses were 6 (range: 4–7), the most common primary site was maxillary sinus (n=4). There were no grade 3-5 AEs. One patient achieved a partial response (ORR 7.7%), 11 had stable disease (including 2 with $>$20% tumor shrinkage), and one had progression in a non-target lesion. Post-treatment NICD1 expression was not significantly reduced (p=0.8). Genomic profiling revealed *NOTCH1* activating mutations in 9/13 tumors and MYB-NFIB fusions in 8/13, with co-occurrence in 6 patients. *MYB-NFIB* fusion with *MYB* overexpression, irrespective of *NOTCH1* mutation status, was associated with tumor shrinkage (p=0.02). Higher baseline NOTCH signaling activity by RNA sequencing (NOTCH signaling signature) correlated with greater tumor shrinkage (p=0.025). Although NICD1 IHC levels did not significantly change, AL101 treatment resulted in significant downregulation of NOTCH signaling activity, and the magnitude of signature reduction correlated with tumor shrinkage (p=0.037). Post-treatment transcriptomic analysis demonstrated upregulation of potentially druggable oncogenic pathways, providing biologic rationale for future combination therapeutic strategies. **Conclusions:** In this first window-of-opportunity study in ACC, AL101 demonstrated biological target modulation. Importantly, *MYB* overexpression and NOTCH signaling activity rather than NICD1 modulation or *NOTCH1* mutation correlated with tumor shrinkage. These findings provide translational insights and support biomarker-driven development of rational combination strategies in NOTCH1-activated ACC. Clinical trial information: NCT04973683. Research Sponsor: U.S. Department of Defense.

6120 Poster Session

Long-term outcomes of SINTART 1 and SINTART 2: Two phase II trials of multimodal treatments in patients with locally advanced sinonasal carcinomas. First Author: Arianna Ottini, Head and Neck Cancer Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Sinonasal carcinomas (SNCs) are rare malignancies with poor prognosis. Multimodal treatments including induction chemotherapy (ICT), surgery and radiotherapy (RT) - modulated by histology and response to ICT - are often used, aiming to improve oncological outcome in terms of local control and survival. Two phase II clinical studies published in 2023 assessed the role of ICT in SNCs, SINTART1 and 2 for resectable and unresectable tumors, respectively [PMIDs: 37164774, 37163806]. The current work aims at reporting the long-term follow-up (FUP) data for both trials. **Methods:** The FUP was updated as of January 2026 for patients enrolled in both clinical studies. Median FUP was estimated with reverse Kaplan-Meier method. The following survival times were analyzed with Kaplan-Meier method in each cohort: overall survival (OS), disease-free survival (DFS), loco-regional-free survival (LRFS), distant metastasis-free survival (DMFS). **Results:** The updated median (m) survival times (in months) with their 95% confidence intervals (CI) and the event rates are detailed in Table 1. Pooling together the 2 studies, 30% of patients (18/60) were alive at last follow-up. **Conclusions:** SINTART 1 and 2 represent, to date, the largest prospective cohorts with long-term survival data in SNCs. With a median FUP exceeding 9 years, these results provide a robust benchmark for ICT-based multimodal strategies in this setting. Survival outcomes remain consistent with the initial reports, indicating that prognosis is largely determined within the first 2-3 years, when most deaths occur (approximately 70%). The near-overlap of mDFS and mLRFS identifies loco-regional failure as the predominant pattern of recurrence. Moreover, the short interval between relapse and death underscores the limited opportunity for salvage. These findings collectively emphasize the need for more effective local-intensification approaches and novel systemic agents. Additional analyses are underway to identify prognostic and predictive factors. Clinical trial information: NCT02099175; NCT02099188. Research Sponsor: None.

	Resectable (SINTART1) N=35	Unresectable (SINTART2) N=25
mFUP (95% CI)	108.26 (97.37-129.84)	103.22 (91.68-NR)
mOS (95% CI)	37.53 (21.97-98.36)	27.07 (11.28-65.03)
Events	66%	76%
mDFS (95% CI)	26.25 (15.43-80.43)	17.1 (7.89-37.76)
Events	71%	80%
mLRFS (95% CI)	26.25 (15.43-80.43)	18.95 (7.89-39.05)
Events	71%	80%
mDMFS (95% CI)	34.47 (21.84-96.32)	26.88 (9.31-46.78)
Events	69%	76%

6121 Poster Session

Clinicopathologic characteristics and treatment outcomes of adenoid cystic carcinoma (ACC) by different primary sites. First Author: Larissa Passarini, Instituto do Câncer do Estado de São Paulo, São Paulo, Brazil

Background: Although ACC commonly arises in the salivary glands, nearly 40% arise at extra-salivary sites and are often managed as site-specific malignancies rather than as a unified histologic entity. Population-based data suggest that thoracic and head and neck ACC are associated with poorer survival compared with breast ACC; however, the factors underlying these differences remain poorly understood. **Methods:** We retrospectively identified all patients (pts) with ACC, irrespective of primary site, who were followed at a large cancer center between 2011 and 2024. Collected data included staging at diagnosis, primary site, local treatment (i.e. surgery, radiation), histologic subtype (solid, cribriform or tubular), lymphovascular invasion (LVI), perineural invasion (PNI), margin status (R0, R1), and clinical outcomes including local recurrence-free survival (LRFS), distant metastasis free-survival (DMFS), and overall survival (OS). Primary sites were grouped as major salivary glands (MASG), oral cavity or oropharynx (OCOP), sinonasal region (SINO), breast (BRST), thorax-lung (THLU), lacrimal gland (LCGL), and others (i.e., skin OTHR). Clinicopathologic characteristics were compared using Fisher tests, and associations between primary site and clinical outcomes were evaluated with multivariable Cox models comparing each site versus all others combined adjusted for local treatment type, margins, and solid histology, defined a priori following a causal inference framework. **Results:** Of 220 pts, 151 (69%) were female, and 199 (90.5%) had localized or locally advanced disease at diagnosis. The most common primary site was OCOP (n=67, 30%), followed by MASG (n=60, 27%), SINO (n=25, 11%), THLU (n=22, 10%), BRST (n=20, 9.1%), LCGL (n=6, 2.7%), and OTHR (n=20, 9.1%). Among 210 pts that received local treatment, 41 (19%) had surgery only, 134 (61%) surgery plus radiation, and 35 (16%) radiation alone. Patients with THLU primary had less up-front surgery (50% vs 76-100%, $p<0.001$). Among surgical cases, 58% had R1 resections; PNI was present in 48%. BRST pts had lower rates of positive margins (R1 7.7%, p=0.04) and PNI (28% vs 35-83%, p=0.019). Histologic subtype was reported in 108 (49%) pts with 72 (78%) cribriform, 58 (54%) solid, and 49 (45%) tubular. Median LRFS, DMFS, and OS were 103 months [mo] (95%CI 77-141), 87 mo (95%CI 70-131), and 153 mo (95%CI 124-222) respectively. Pts with SINO experience worse LRFS (HR 2.01, p=0.03), DMFS (HR 2.07, p=0.02), and OS (HR 3.51, $p<0.001$) while MASG had potentially improved DMFS (HR 0.63, p=0.07) and THLU OS (HR 0.31, p=0.07) in adjusted models. **Conclusions:** Primary site-specific clinical outcomes in ACC are not fully explained by treatment approach or histologic features. These findings suggest biological heterogeneity across ACC by primary site and underscore the need for molecular characterization of site-specific disease drivers. Research Sponsor: None.

6122 Poster Session

Artificial intelligence–powered spatial analysis of endothelial cells and tumor-infiltrating lymphocytes to predict response to axitinib in adenoid cystic carcinoma. First Author: Dong Hyun Kim, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

Background: Despite the limited systemic options for adenoid cystic carcinoma (ACC), VEGFR inhibitors remain a clinical mainstay. Although high stromal tumor-infiltrating lymphocyte (TIL) density has been identified as a predictive biomarker for improved progression-free survival (PFS), its predictive power remains to be fully optimized. We hypothesized that baseline vascular architecture, represented by endothelial cell (EC) density, might modulate the efficacy of axitinib. **Methods:** We performed a post-hoc exploratory analysis on H&E-stained whole-slide images (WSI) from 27 patients with R/M ACC treated with axitinib in a multicenter phase II trial (NCT02859012). An updated AI-powered analyzer (Lunit SCOPE IO), capable of multiple component TME profiling, was used to quantify the density (cells/mm²) of TILs and ECs within the tumor epithelium and stroma. Patients were stratified into subgroups based on the median values. The clinical impact of integrated immune and vascular architecture was evaluated by analyzing PFS and OS. **Results:** The analyzed cohort (N=27) had a best objective response of stable disease in 25 patients (92.6%) while 16 patients showed tumor shrinkage (59.3%). Stratification revealed that patients with concurrent High EC and High TIL density in the tumor stroma (n=9) derived exceptional clinical benefit compared to all other patients (N=18). The High EC/High TIL subgroup achieved a median PFS of 19.6 months compared to 11.1 months in the comparator group (HR 0.30; 95% CI: 0.11–0.87; P=0.026). Furthermore, this subgroup demonstrated significantly prolonged OS (median NR vs. 24.4 months; HR 0.12; 95% CI: 0.02–0.95; P=0.044). Stratification based on intratumoral densities of EC and TILs showed a similar trend with the High EC/High TIL subgroup (n=10) reporting prolonged PFS (HR 0.32; 95% CI: 0.12-0.87; P=0.025) but not OS (HR 0.46; 95% CI: 0.12-1.74; P=0.251). The individual biomarkers based on median TIL and EC showed a trend towards prolonged survival but were not statistically significant. **Conclusions:** The co-enrichment of stromal ECs and TIL is associated with significantly prolonged PFS and OS, suggesting that this unique TME architecture may identify R/M ACC patients who derive greater clinical benefit from axitinib. This AI-based spatial analysis using H&E slides offers a practical, scalable biomarker strategy to guide treatment selection in this rare cancer. Research Sponsor: National Cancer Center, Republic of Korea; HA22C0011.

6123 Poster Session

A phase II study of pemetrexed and pembrolizumab in patients (pts) with recurrent and/or metastatic (R/M) salivary gland cancer (SGC): Results from the adenoid cystic cohort. First Author: Katharine Andress Rowe Price, Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background: Pemetrexed (PTX) is safe and tolerable with responses reported in pts with R/M SGC. Given enhanced responses with PTX and pembrolizumab (PMB) for lung cancer, we hypothesized that PTX and PMB will have activity for SGC. Herein we present the efficacy results in pts with adenoid cystic carcinoma (ACC). **Methods:** MC200708 is a single arm phase II study of PTX and PMB in pts with R/M SGC (NCT04895735) with 2 cohorts: ACC (cohort A) and non-ACC (cohort B). Key eligibility criteria: ≥18 years, ECOG 0-1, measurable disease. Prior ICI and/or PTX was allowed. Key exclusion criteria: serious comorbidities, autoimmune disease and brain metastases. Simon's 2-stage design was used for each cohort. Primary endpoint was overall response rate (ORR) for Cohort A but was amended to clinical benefit rate (CBR=SD+PR+CR) due to prolonged SD in several pts. Secondary endpoints: progression free survival (PFS), overall survival (OS), and toxicity. Exploratory analyses in Cohort A1 (post-amendment pts) included PSMA PET imaging and circulating PSMA extravesicles (EVs) as a biomarker. All pts received PTX 500 mg/m2 IV + PMB 200 mg IV q3 weeks until progression or treatment intolerance. Imaging was q3 cycles. **Results:** 20 pts (11 Cohort A + 9 Cohort A1) were enrolled from August 2021-Feb 2025. All 20 patients were eligible and received ≥ 1 cycle of treatment. Median age was 60.5 yrs, 50% male, performance status 0 (80%) or 1 (20%). 11 pts had no prior therapies (55.0%). The remaining pts had 1 (35%) or 2 (10%) prior lines of therapy. 75% of pts had no prior ICI. In Cohort A, the ORR was 0% (0 of 11). Cohort A1 met criteria for success based on CBR with 1 PR (12.5%) and 5 SD (62.5%) in the first 8 pts. For the whole cohort of 20 patients, the ORR was 5% (95% CI: 0.1-24.9) and the CBR rate was 75% (95% CI: 51-91) with 1 PR and 14 pts with SD. The duration of response for the 1 PR patient was 12.4 months. The median duration of response for the 15 pts with SD was 7.5 (2.0-29.7) months. 3 pts (15%) had PD and 2 pts (10%) went off prior to response assessment. Median cycles of treatment was 4 (2-30). In the 17 pts who discontinued, treatment was stopped in 9 (53%) for PD, 4 (23.5%) due to adverse events (AE), and 4 (23.5%) due to physician/patient preference. With a median follow-up of 14.5 months (1.5-39.2), the 1-year PFS rate is 52.1% (32.6 – 83.2%) and the OS rate is 82.1% (95% CI: 65.6 – 100%). The overall grade 3+ AE rate regardless of attribution was 80% (16/20). The most common grade 3 AEs were lymphocyte count decrease (40%), hypertension (20%), fatigue (10%), and pneumonitis (10%). 2 pts had a grade 4 AE (lymphocyte count decrease and thrombotic thrombocytopenic purpura). There were no treatment-related deaths. Analysis of correlative studies for Cohort A1 with PSMA imaging and EV biomarker ongoing. **Conclusions:** PTX and PMB has modest activity in pts with R/M ACC with CBR of 75% and prolonged benefit for some patients. Clinical trial information: NCT04895735. Research Sponsor: Merck.

6124 **Poster Session**

Anti–PD-1 immunotherapy with chemotherapy for poorly chemo-responsive thyroid and salivary gland tumors: The iPRIME study. First Author: Faith Abodunrin, Section of Hematology and Oncology, Department of Medicine, University of Chicago, Chicago, IL

Background: Clinical trial data guiding treatment of unresectable or metastatic salivary and thyroid gland cancers are limited. While targeted therapies have advanced management for selected patients, chemotherapy remains a treatment strategy for those with aggressive disease biology. Anti-PD1 therapy has shown antitumor activity in advanced, PD-L1 positive salivary and thyroid gland cancers, underscoring the need to evaluate the synergistic activity of PD-1 blockade with cytotoxic chemotherapies in these neoplasms. **Methods:** The iPRIME (NCT03360890) is a single center, parallel two cohort trial evaluating pembrolizumab with cytotoxic chemotherapy in patients with advanced salivary gland and thyroid cancers. Eligible patients had histologically confirmed disease that was unresectable and not amenable to curative intent therapy. Patients received pembrolizumab 200 mg IV with docetaxel or doxorubicin 75 mg/m2 for 2-6 cycles, followed by pembrolizumab monotherapy for up to 2 years. Docetaxel or doxorubicin could be reintroduced upon disease progression while on pembrolizumab or after the 2-year treatment period. The primary endpoint was response rate. Secondary endpoints included progression free survival (PFS), overall survival (OS), disease control rate, and adverse events. **Results:** A total of 39 patients (27 salivary and 12 thyroid cancer) were enrolled between 2018-2022. Mean age was 61 in salivary and 71 in the thyroid cancer, with 48% and 58% female patients, respectively. Salivary gland cancer histologies included adenoid cystic 15/27 (56%), ex-pleomorphic 18%, mucoepidermoid 7.4%, acinic cell 7.4%, salivary duct 7.4%, basaloid adenocarcinoma 3.7%. In the salivary gland group, the overall response rate was 25.6% (7/27; 90% CI 12.9%-43.2%), and the disease control rate was 89% (24/27; 90% CI 73.7%-96.9%). The overall response rate in the adenoid cystic patients was 27% (4/15). Median PFS was 8.6 months (90% CI: 6.0 to 12.4), including 8 months in adenoid cystic patients (90% CI: 6.0-16.7%) and 7.8 months in the non-adenoid cystic cases (90% CI: 3.8-14.6), with one and two-year PFS rates of 37% and 8.2%, respectively. Median OS was 25.5 months in the adenoid group (90% CI:8.5-32) and 22.9 months in the non-adenoid group (90% CI: 7.8-78) (p=0.26). One, two, and five-year OS rates in the salivary cohort were 66%, 50%, and 23%, respectively. In the thyroid cohort, the response rate was 16.7% (2/12), with both PR. Grade 4 events occurred in nine patients salivary patients and one grade 5 event was observed. **Conclusions:** The combination of pembrolizumab and cytotoxic chemotherapy did not substantially change antitumor control activity relative to historical controls in patients with advanced salivary or thyroid cancers. There were no statistically significant differences in PFS and OS between adenoid cystic and non-adenoid cystic subtypes. Clinical trial information: NCT03360890. Research Sponsor: Merck.

TPS6125 **Poster Session**

Phase III randomized trial of tislelizumab plus gemcitabine/capecitabine (GX) versus tislelizumab plus gemcitabine/cisplatin (GP) as first-line therapy for recurrent/metastatic nasopharyngeal carcinoma: A prospective multicenter study (PROGRESS). First Author: Dongmei Ji, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Nasopharyngeal carcinoma (NPC) is a prevalent malignancy in Southeast Asia and Southern China. Around 10% of pts have distant metastasis at initial diagnosis, and ~30% of those initially without metastasis will develop distant metastasis after radical treatment. These recurrent/metastatic (R/M) NPC pts have poor prognosis with a 5-year survival rate of only 20–30%. The RATIONALE-309 study established tislelizumab plus GP as a standard first-line therapy for R/M NPC, but most pts still experience disease progression in 2 years. Furthermore, in real-world clinical practice, a lot of pts are either platinum-intolerant or platinum-refractory recurrent, underscoring the urgent need for novel treatments. Recent studies suggest that first-line treatment regimens incorporating capecitabine may provide longer progression-free survival (PFS) compared to the GP regimen with a more favorable safety profile. Additionally, a retrospective study demonstrated that tislelizumab plus GX achieved notable tumor responses and PFS benefits in R/M NPC pts who have relapsed immunotherapy. **Methods:** This is a prospective, multicenter, randomized, controlled Phase III trial evaluating the efficacy and safety of tislelizumab + GX vs. tislelizumab + GP as first-line therapy in R/M NPC. 266 pts will be randomly assigned to the experimental or the control group. The experimental group will receive tislelizumab plus GX (gemcitabine 1g/m² D1,8 + capecitabine 1000 mg/m² BID D1-14) for 4–6 cycles, followed by tislelizumab plus capecitabine maintenance. The control group will receive tislelizumab plus GP (gemcitabine 1 g/m² D1,8 + cisplatin 80mg/m² D1) for 4–6 cycles, followed by tislelizumab monotherapy. Treatment will continue until disease progression or intolerable toxicity. The primary endpoint is PFS. Secondary endpoints include objective response rate, duration of response, overall survival, etc. Adverse events will be monitored and graded according to NCI CTCAE v5.0. Patient enrollment began in December 2023 across 10 centers in China, with 168 pts enrolled by December 2025. Clinical trial information: NCT06177301. Research Sponsor: None.

TPS6126 **Poster Session**

MC240701: Decentralized pilot study of triple oral metronomic chemotherapy in recurrent/metastatic oral cavity cancer. First Author: Binav Baral, Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background: Oral cavity cancers (OCC) are a rare subtype of head and neck cancer (HNC) with poor outcomes and limited second-line treatment options in the recurrent or metastatic (R/M) setting. Treatment-related morbidity and repeated local recurrences in OCC result in significant impairment of function and quality of life. Rural OCC patients comprise a sizable portion (50%) of our practice and are usually of lower socioeconomic status with lack of access to specialist care. They also have multiple barriers to treatment access and ancillary services, translating to poorer clinical outcomes. There is a critical need for effective and accessible therapies for R/M OCC in rural patients. Triple oral metronomic chemotherapy (TOMC) with Methotrexate, Erlotinib and Celecoxib (MEC) suppresses angiogenesis and activates antitumor microenvironment in HNC. Studies using TOMC in R/M OCC outside the US show reasonable efficacy (6-month OS 52.9%), better safety and lower cost compared to standard second line options. We hypothesize that a decentralized clinical trial with TOMC in R/M OCC is feasible, safe and effective in addition to being economical and accessible for rural patients. **Methods:** MC240701 is a single institution, open label, decentralized, single arm pilot study of MEC in patients with R/M OCC. Eligible pts must be $\geq$18 years old, have pathologically confirmed R/M OCC not amenable to curative-intent therapy, ECOG 0-2 and adequate organ function. At least 1 measurable lesion by RECIST 1.1 OR non-measurable disease (evident mucosal lesions, CNS/bone disease, lesions not meeting RECIST criteria) is permitted. Patients must have received standard first line immunotherapy with or without chemotherapy OR should be unable/unwilling to receive first line treatment. Key exclusion criteria include patients unable to take pills by mouth, serious medical co-morbidity or autoimmune disease, immunocompromised patients and other active malignancy. Primary endpoint is to demonstrate feasibility of decentralized clinical trials, secondary outcomes include overall response rate, progression free and overall survival and toxicity. Additional goals are to evaluate patient impact of decentralized treatment through surveys and interviews After initial screening and evaluation, patients are remotely consented and will receive study drugs by mail. All patients will receive the same treatment of Methotrexate 9mg/m^2 PO weekly, Erlotinib 150 mg PO daily, and Celecoxib 200 mg PO BID, each cycle will be 28 days. Treatment will continue until disease progression or treatment tolerance, study duration is for 2 years. All subsequent clinical and laboratory monitoring and response assessments (every 3 cycles) will be remotely performed or have an option for local testing. Enrollment began July 2025 and 4 out of planned 25 patients have been accrued. FDA IND:174540. Clinical trial information: NCT06997068. Research Sponsor: Mayo Clinic Comprehensive Cancer Center.

TPS6127 **Poster Session**

OrigAMI-5: A randomized, phase 3 study of amivantamab plus pembrolizumab and carboplatin vs standard of care pembrolizumab plus platinum and 5-fluorouracil as first-line treatment in recurrent/metastatic head and neck cancer. First Author: Robert I. Haddad, Dana-Farber Cancer Institute, Boston, MA

Background: Recurrent and/or metastatic head and neck squamous cell cancer (R/M HNSCC) is associated with significant morbidity and mortality. Current first-line standard of care regimens, including combinations of pembrolizumab with platinum-based chemotherapy with/without 5-fluorouracil (5-FU), yield low response rates and poor long-term outcomes, with a median survival of approximately 1 year. Many patients with R/M HNSCC exhibit EGFR and MET overexpression. Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity that is FDA-approved in *EGFR*-mutated advanced non-small cell lung cancer. In a prior report of the phase 1b/2 OrigAMI-4 study (NCT06385080), subcutaneous (SC) amivantamab monotherapy demonstrated a confirmed objective response rate of 45% among participants with HPV-unrelated R/M HNSCC whose disease had previously progressed on immune checkpoint inhibitor and platinum-based chemotherapy (Harrington *Oral Oncology* 2025). The objective of this phase 3 randomized study is to assess the efficacy of SC amivantamab in addition to pembrolizumab and carboplatin, as compared to the standard of care (pembrolizumab plus carboplatin or cisplatin and 5-FU) as first-line therapy for participants with R/M HNSCC. **Methods:** The ongoing multicenter, global OrigAMI-5 study (ClinicalTrials.gov identifier: NCT07276399) is planned to open in approximately 205 sites in 22 countries. Eligible participants will have HPV-unrelated R/M HNSCC (primary tumor locations: oral cavity, oropharynx, hypopharynx, or larynx); all primary oropharyngeal tumors must be human papillomavirus (HPV)-negative. All participants, regardless of combined positive score (CPS), are eligible but must have local testing results to determine CPS for stratification and be treatment-naïve in the R/M setting; systemic therapy in the locally advanced setting is allowed if completed $>$6 months prior. Prior exposure to EGFR or MET targeting agents is exclusionary. Approximately 500 participants will be randomly assigned 1:1 to receive SC amivantamab (co-formulated with recombinant human hyaluronidase [rHuPH20]) with pembrolizumab and carboplatin, or 5-FU plus pembrolizumab and investigator's choice of carboplatin or cisplatin. Randomization will be stratified by programmed cell death ligand 1 (PD-L1) CPS ($<$1, 1–19, $\geq$20) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1). The primary endpoints will be objective response rate and overall survival. Secondary endpoints include progression-free survival, duration of response, and patient-reported outcomes. Safety assessments will include adverse event monitoring and laboratory abnormalities. Clinical trial information: NCT07276399. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

TPS6128 **Poster Session**

NRG-HN015: A phase II randomized trial of neoadjuvant chemotherapy or chemo-immunotherapy in patients with recurrent/persistent PD-L1–positive squamous cell carcinoma of the head and neck undergoing salvage surgery. First Author: Nabil F. Saba, Winship Cancer Institute Emory University School of Medicine, Atlanta, GA

Background: Treatment for locoregionally recurrent squamous cell carcinoma of the head and neck (SCCHN) remains a challenge. 30-40% of patients treated with definitive-intent therapy will recur, the majority locoregionally (Ang 2010, Galloway 2016, Tan 2010). Despite improvements in the effectiveness of palliative systemic therapy over the last decade (Vermorken 2008), salvage surgery (SS) remains the modality of choice to achieve cure in patients with locally recurrent disease particularly in patients who have previously received radiation. Thus, there is a pressing need to improve the therapeutic ratio by increasing the benefit of SS and improving oncologic outcomes. One promising means would be early introduction of systemic therapy with or without immune checkpoint inhibition for patients who are candidates for SS. NRG-HN015 proposes to investigate the effect on event-free survival (EFS) of pre-operative chemotherapy or chemo-immunotherapy in comparison to the standard SS approach. **Methods:** NRG-HN015 (NEOPOLIS) is a randomized, multicenter, controlled, 3-arm, superiority phase II study of neoadjuvant chemotherapy or chemo-immunotherapy in patients with recurrent/persistent PD-L1 enriched SCCHN who have planned SS. The primary objective is to compare investigator-assessed EFS of patients treated with neoadjuvant chemotherapy or chemo-immunotherapy prior to SS versus SS alone. The primary hypothesis is that neoadjuvant chemotherapy or chemo-immunotherapy added to SS will improve EFS. Enrolled patients will be randomized 1:1:1 to receive SS (Arm 1 - control), chemotherapy + SS (Arm 2), or chemo-immunotherapy + SS (Arm 3). Prior to randomization, patients will be stratified by primary tumor site (Oropharynx or oral cavity vs. larynx or hypopharynx, stage (rT4a or rN3a vs. other), and prior use of iPD1/PDL1 inhibitors in the definitive setting. Patients must have locally recurrent or persistent SCCHN arising within the oral cavity, oropharynx, larynx, or hypopharynx and are deemed candidates for salvage surgery. P16-positive oropharynx patients with T2, T3, T4, N0, N1, N2 and all other patients with T2, T3, T4a, N0, N1, N2a, N2b, N2c, N3a are eligible. Patients must have PDL1-positive and measurable disease, with no major vascular involvement ($>$180° involvement of the common carotid or internal carotid artery), jugular foramen involvement, or prevertebral, paraspinous muscle involvement precluding a curative resection. Patients who are candidates for salvage laryngectomy to treat recurrent laryngeal cancer and who are having SS for curative intent are eligible. The trial is opened to enrollment. Clinical trial information: NCT071953734. Research Sponsor: National Cancer Institute; NRG-HN015.

TPS6129 **Poster Session**

A multicenter, randomized, double-blind, phase 2/3 study of ficerafusp alfa (BCA101) or placebo in combination with pembrolizumab for first-line treatment of HPV-negative, PD-L1–positive, recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): FORTIFI-HN01. First Author: Renata Ferrarotto, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: HPV-negative HNSCC is an aggressive disease characterized by high rates of recurrence, metastasis, and resistance to standard treatments. Most HPV-negative HNSCC tumors overexpress tumorigenic factors EGFR and TGF-β. In a phase 1/1b trial (NCT04429542), ficerafusp alfa demonstrated promising efficacy and a manageable safety profile in first-line R/M HNSCC. FORTIFI-HN01 (NCT06788990) is an ongoing randomized, double-blind, placebo-controlled, phase 2/3 trial designed to assess the efficacy and safety of ficerafusp alfa combined with pembrolizumab vs placebo plus pembrolizumab in patients with PD-L1-positive first-line R/M HPV-negative HNSCC. **Methods:** Eligible patients must have histologically confirmed R/M HNSCC with primary lesions in the oral cavity, larynx, or hypopharynx, or HPV-negative OPSCC confirmed by central laboratory testing. Additional eligibility criteria include no prior systemic therapy for R/M disease, PD-L1-positive tumor (CPS $\geq$1), measurable disease per RECIST v1.1, and ECOG performance status 0 or 1. The phase 2 objective was to determine the optimal biological dose (OBD) of ficerafusp alfa through an integrated analysis of safety, tolerability, PK, PD, and efficacy. Following OBD determination (1500 mg QW), the trial transitioned seamlessly into the phase 3 portion with 2:1 randomization (ficerafusp alfa: control). Randomization is stratified by PD-L1 CPS (1-19 vs $\geq$20) and disease extent (local/regional recurrence only, distant metastasis only, or both). Patients receive pembrolizumab (200 mg IV every 3 weeks for up to 35 cycles) and either ficerafusp alfa or placebo IV QW until disease progression or unacceptable toxicity. Tumor imaging occurs every 6 weeks during the first year and every 9 weeks thereafter. The primary endpoints are objective response rate (ORR) per RECIST v1.1 (blind independent committee review) and overall survival. An interim analysis evaluating ORR is planned. Secondary endpoints include safety, duration of response, progression free survival, clinical benefit rate, and patient-reported outcomes. The trial is actively recruiting, with planned enrollment of ~650 subjects. Clinical trial information: NCT06788990. Research Sponsor: Study funded by Bicara Therapeutics Inc.

TPS6130 **Poster Session**

Becotatug vedotin plus pucotenlimab as first-line therapy in patients with recurrent or metastatic nasopharyngeal carcinoma: A phase II clinical trial. First Author: Lei Liu, Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Epidermal growth factor receptor (EGFR) is highly expressed in approximately 85% of nasopharyngeal carcinoma (NPC) cases and plays a critical role in tumor cell proliferation. Becotatug vedotin (MRG003) is a novel EGFR-targeted antibody-drug conjugate (ADC) with promising anti-tumor activity in NPC. Pucotenlimab is a recombinant humanized programmed cell death protein-1 (PD-1) inhibitor. Although platinum-based chemotherapy combined with a PD-1 inhibitor represents the current standard first-line treatment for recurrent or metastatic (R/M) NPC, treatment-related toxicities and suboptimal efficacy remain significant challenges. Preclinical and early clinical data have demonstrated synergistic anti-tumor activity of MRG003 combined with pucotenlimab in platinum-refractory R/M NPC. However, the efficacy and safety of this platinum-free combination as a first-line therapy for R/M NPC remain uncertain. This study aims to evaluate the efficacy and safety of becotatug vedotin plus pucotenlimab as a novel first-line treatment for patients with R/M NPC. **Methods:** This is an open-label, single-arm, phase II trial enrolling patients with R/M NPC eligible for first-line systemic therapy. Inclusion criteria include: age 18 to 75 years; ECOG performance status score of 0 or 1; histologically or cytologically confirmed NPC; stage IVB (UICC/AJCC 8th edition) or locoregional recurrence not amenable to curative local therapy; at least one measurable lesion per RECIST v1.1; and adequate organ function. Key exclusion criteria include severe uncontrolled pulmonary disease, active autoimmune disease, or a history of autoimmune disease requiring systemic immunosuppressive therapy. Eligible patients receive becotatug vedotin (2.0 mg/kg, IV, D1, Q3W) and pucotenlimab (200 mg, IV, D1, Q3W) until disease progression, unacceptable toxicity, or death. Dose adjustments are permitted based on toxicities. The primary endpoint is progression-free survival (PFS), defined as the time from treatment initiation to disease progression or death from any cause. Secondary endpoints include objective response rate (ORR), disease control rate (DCR), duration of response (DoR), overall survival (OS), treatment-related safety, and predictive biomarkers. Research Sponsor: Lepu Biopharma Co., Ltd. Clinical trial information: NCT07381699. Research Sponsor: None.

TPS6131 **Poster Session**

ERBIOTAX (TTCC-2022-02): A phase II, multicenter, randomized study of cetuximab with or without weekly paclitaxel after progression on first-line pembrolizumab plus platinum/5-FU in recurrent or metastatic head and neck squamous cell carcinoma. First Author: Marc Oliva, Medical Oncology Department, Institut Català d'Oncologia (ICO), L'hospitalet De Llobregat, Barcelona, Spain

Background: Pembrolizumab, with or without platinum–5FU (PF), is the current first-line (1L) standard of care for PD-L1–positive recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). However, no established standard of care exists after progression on immune checkpoint inhibitors (ICI). Emerging evidence suggests that cetuximab administered post-ICI achieves higher objective response rates (ORR) and longer progression-free (PFS) and overall survival (OS) compared with historical second-line (2L) cetuximab outcomes from the pre-ICI era. We hypothesize that 2L treatment with cetuximab +/- paclitaxel may be more effective after ICI failure than previously observed in the pre-ICI era. **Methods:** This is a multicenter, open-label, randomized, non-comparative, two-arm, investigator-initiated phase 2 trial. Patients will be randomized (2:1) to cetuximab plus paclitaxel (Arm A: ERBITAX) or cetuximab monotherapy (Arm B), administered on Days 1, 8 and 15 of 21-day cycles for 4 cycles, followed in both arms by biweekly cetuximab monotherapy until disease progression, death, unacceptable toxicity, or withdrawal of consent. A total of 65 evaluable patients will be enrolled: 41 in Arm A (H0: ORR 25%, H1: 45%, 80% power, two-sided alpha 0.05) and 24 in Arm B (H0: ORR 10%, H1: 30%, 80% power, two-sided alpha 0.05). The primary endpoint is ORR in each arm. Secondary endpoints include disease control rate (DCR), PFS, OS, health-related quality of life (EORTC QLQ-C30, EORTC QLQ-H&N35 and EuroQol EQ-5D) and safety. Baseline tumor tissue (all patients) and on-treatment samples (between cycles 2-5 in 50% of patients; optionally at progression), as well as serial plasma samples will be collected for translational exploratory studies. Patients must have histologically confirmed SCCHN of oral cavity, oropharynx (HPV-positive or HPV-negative), hypopharynx, or larynx, with confirmed progression per RECIST 1.1. on or after 1L pembro + PF. The study started enrollment in June 2025, with 7 patients enrolled by December 23, 2025. The total accrual period is 18 months. Clinical trial identifiers: NCT06856213; EUDRACT 2024-514953-31-00. Trial supported by Merck, S.L.U., Madrid, Spain, an affiliate of Merck KGaA, Darmstadt, Germany, providing study medication and financial support. Clinical trial information: NCT06856213. Research Sponsor: Merck, S.L.U., Madrid, Spain, an affiliate of Merck KGaA, Darmstadt, Germany,.

TPS6132 **Poster Session**

FIERCE-HN: A multicenter, randomized, double-blind, placebo-controlled, phase 3 study of ficlatuzumab (HGF/cMET mAb) in combination with cetuximab in participants with recurrent or metastatic (R/M) HPV-negative head and neck squamous cell carcinoma (HNSCC). First Author: Julie E. Bauman, GW Cancer Center, George Washington University, Washington, DC

Background: Patients with HPV negative R/M HNSCC have a worse median overall survival (OS) than those with HPV positive disease and current treatment options are limited. [1] Ficlatuzumab is a humanized IgG1 mAb that binds HGF, the ligand for the c-MET tyrosine kinase receptor. HGF/c-MET pathway dysregulation is frequently observed in HPV negative HNSCC and has been linked to EGFR inhibitor resistance, limiting the potential efficacy of EGFR-targeting drugs like cetuximab. In a phase 2 study, both pathways were targeted using ficlatuzumab plus cetuximab in patients with HPV negative R/M HNSCC resistant to cetuximab, platinum, and anti-PD1 immune checkpoint inhibitors (ICI) who have a very poor historical prognosis. A PFS of 4.1 months, median OS of 7.4 months, and overall response rate (ORR) of 38% (6/16; 2 CR, 4 PR) was observed. [2] FIERCE-HN compares the efficacy and safety of ficlatuzumab+cetuximab vs placebo+cetuximab in patients with R/M HPV negative HNSCC. **Methods:** This is an international, multicenter, randomized, double-blind, placebo-controlled phase 3 study. Major enrollment criteria include confirmed diagnosis of R/M HNSCC primary tumors of the oropharynx (p16 negative only), oral cavity, hypopharynx, or larynx. Participants must have progressed on, or be intolerant to, previous anti-PD-1/PD-L1 ICI and platinum-based chemotherapy; have received 2 or fewer prior lines of anticancer therapy in the R/M setting; and have had no prior treatment with cetuximab/alternative EGFR inhibitors in the R/M setting. Patients with feeding tubes are eligible. The primary endpoint is OS; key secondary endpoints include PFS and ORR. Other secondary endpoints are DCR, DoR, safety, PK, immunogenicity and QoL. Patients will receive cetuximab 500mg/m2 and are randomized 1:1:1 to Arm A: ficlatuzumab 10mg/kg, Arm B: ficlatuzumab 20mg/kg, or Arm C: placebo. Treatments will be on Days 1 and 15 of a 28-day cycle. This is an adaptive study with two interim analyses (IAs). IA-1 is ongoing to select the optimal dose. Participants enrolled after IA-1 will be randomized 1:1 to the optimal ficlatuzumab dose or placebo, plus cetuximab. IA-2 will be conducted after ~ 163 OS events to assess whether an event count re-estimation is needed. The final analysis will occur after ~ 232 (or up to 279) OS events, depending on the re-estimation outcome. The study has statistical power of 80%, assuming a true OS hazard ratio of 0.667. Between 410 to 500 patients will be enrolled. The study is ongoing and actively recruiting in North America, Europe, United Kingdom, and Asia-Pacific. Clinical trial information: NCT06064877 (Eli Lilly provided cetuximab in N. America and Merck KGaA, Darmstadt, Germany in Europe, United Kingdom and Asia-Pacific). 1. JITC. 2019;7:184. 2. JCO. 2023. 41:3851. Clinical trial information: NCT06064877. Research Sponsor: AVEO Pharmaceuticals, Inc.

TPS6133 **Poster Session**

A phase III multicenter randomized non-inferiority trial comparing selective versus modified neck dissection in node-positive oral squamous cell carcinoma (SND vs MND). First Author: Rakesh Katna, Tieten Medicity Hospital, Mumbai, India

Background: Neck dissection is a critical component in the management of oral squamous cell carcinoma (OSCC) with nodal involvement. While modified neck dissection (MND) is widely practised in node-positive disease, selective neck dissection (SND) may offer comparable oncologic outcomes with reduced morbidity. Retrospective studies and meta-analyses suggest similar survival and regional control with SND in selected patients; however, high-quality prospective randomized evidence is lacking. This trial aims to evaluate whether SND is non-inferior to MND in terms of disease-free survival in treatment-naïve, node-positive OSCC patients. **Methods:** This is a prospective, multicenter, randomized, non-inferiority controlled trial enrolling patients aged 18–70 years with clinically and radiologically confirmed node-positive OSCC (T1–T4, N+), ECOG performance status 0–1, and adequate organ function. Eligible participants are randomized 1:1 to undergo primary tumor resection with either selective neck dissection (Arm A) or modified neck dissection (Arm B). Adjuvant radiotherapy or chemoradiotherapy is administered according to adverse pathological features, including extracapsular extension and positive margins. Randomization is stratified by participating centres. The planned accrual period is 3 years, followed by 2 years of follow-up. The study is conducted at four tertiary cancer centres in India. The primary endpoint is disease-free survival. Secondary endpoints include overall survival, regional recurrence rate, treatment-related morbidity, and quality of life assessed using EORTC QLQ-C30 and QLQ-H&N35 questionnaires. Statistical Considerations: Assuming a 24-month DFS of 85% in the MND arm and a non-inferiority margin of 10%, a total of 432 patients (216 per arm) provides 80% power with a one-sided alpha of 0.05. Non-inferiority will be concluded if the upper bound of the 90% confidence interval for the hazard ratio is less than 1.5. Survival analyses will be performed using Kaplan–Meier methods and Cox proportional hazards models. The study has received institutional ethics approvals at participating centres and is registered with the Clinical Trials Registry of India. Patient recruitment is ongoing. This trial will provide prospective evidence regarding the oncologic equivalence of selective and modified neck dissection in node-positive OSCC and may help define a less morbid standard surgical approach. This trial will provide prospective evidence regarding the oncologic equivalence of selective and modified neck dissection in node-positive OSCC and may help define a less morbid standard surgical approach. Clinical trial information: CTRI/2024/11/076784. Research Sponsor: None.

TPS6134 **Poster Session**

Phase 1 study of VLPONC-01, a novel IL-12–encoding saRNA viral replicon particle, alone and in combination with pembrolizumab in head and neck cancer patients: Protocol summary. First Author: Summer F. Acevedo, VLP Therapeutics, Inc., Gaitersburg, MD

Background: Head and neck squamous cell carcinoma (HNSCC) has high recurrence rates despite standard perioperative treatments such as surgery with adjuvant radiotherapy and/or chemotherapy, with about 35% of patients relapsing. Neoadjuvant immune checkpoint therapy has shown promise: in the Phase III KEYNOTE-689 trial, adding perioperative pembrolizumab to standard care significantly improved median event-free survival (51.8 vs 30.4 months), leading to FDA approval in June 2025. However, only 9.4% of patients achieved a major pathologic response, a key predictor of reduced relapse and a surrogate for long-term benefit in other cancers. This low response rate underscores the need for more effective strategies to expand and deepen durable immune-mediated tumor responses in HNSCC. Our strategy is to develop a combination immunotherapy/gene therapy targeting the immunosuppressive myeloid populations such as tumor-associated macrophages (TAMs) and neutrophils (TANs), which are increasingly recognized as key mediators of immune evasion and poor outcomes. VLPONC-01 is a novel, non-replicating, viral particle-based therapy to target TAMs and TANs. VLPONC-01 efficiently delivers self-amplifying RNA (saRNA) encoding an engineered human Interleukin 12 (IL-12) gene into cells in the tumor microenvironment (TME), leveraging the natural tropism of Venezuelan equine encephalitis virus (VEEV). Within transfected cells, the RNA amplifies itself and directs the cell to produce and secrete IL-12 protein. The released IL-12 is expected to concentrate in the TME, where it activates immune cells and enhances their ability to attack cancer cells. **Methods:** This is a first-in-human, phase 1, open-label trial evaluating the safety and early efficacy of intratumoral administration of VLPONC-01 in patients with HNSCC, focusing on its ability to reduce tumor burden and lessen surgical morbidity. Furthermore, it will characterize IL-12-driven alterations in the tumor microenvironment and determine the synergistic potential of combining this approach with anti-PD-1 immunotherapy. The study includes two cohorts: Cohort A tests weekly intratumoral injection in recurrent and/or metastatic tumor patients to assess safety and determine dose levels, while Cohort C randomizes patients with resectable tumors into three groups to receive low-dose VLPONC-01 plus pembrolizumab, high-dose VLPONC-01 plus pembrolizumab, or pembrolizumab alone, prior to surgery. Outcomes include dose-limiting toxicities, surgical delays, systemic cytokine responses, and tumor response assessed by imaging and pathology. Clinical trial information: NCT06736379. Research Sponsor: None.

TPS6135 **Poster Session**

A randomized, non-comparative, multicenter phase II trial of neoadjuvant becotatug vedotin alone or combined with immune checkpoint inhibitors (penpulimab/ivonescimab) in resectable locally advanced head and neck squamous cell carcinoma. First Author: Xiaoyuan Wei, Division of Head & Neck Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: The efficacy and safety of neoadjuvant therapy for resectable locally advanced head and neck squamous cell carcinoma (LAHNSCC) remain uncertain, and optimal treatment protocols needs further explored. Epidermal growth factor receptor (EGFR) is overexpressed in 90% of head and neck squamous cell cancers (HNSCC) and plays a critical role in tumor proliferation and survival. Antibody drug conjugates (ADCs) represent an emerging class of cancer therapeutics that combines several mechanisms of action to improve efficacy and reduce the systemic toxicity. Becotatug Vedotin is a novel ADC molecule of an anti-EGFR humanized immunoglobulin G1 (IgG1) monoclonal antibody conjugated with monomethyl auristatin E via a valine-citrulline linker. Studies have shown that combining immunotherapy with an Anti-EGFR monoclonal antibody may produces a synergistic anti-tumor effect. This study aims to assess the efficacy and safety of neoadjuvant Becotatug Vedotin, alone or in combination with immune checkpoint inhibitors Penpulimab, an anti-PD-1 monoclonal antibody, or Ivonescimab, a bispecific anti-PD-1/VEGF-A antibody, in patients with resectable LAHNSCC. **Methods:** This is a randomized, non-comparative, multicenter phase II clinical trial. Key eligible patients aged 18–70 years with previously untreated, pathologically confirmed LAHNSCC (oral, laryngeal, hypopharyngeal, and oropharyngeal carcinoma), resectable and ECOG 0–1 will be enrolled. Main exclusions include active autoimmune diseases, use of immunosuppressive drugs, or systemic corticosteroids. Patients will be allocated to 3 cohorts, and all will receive three preoperative cycles of Becotatug Vedotin(2.3 mg/kg, ivgtt, Q3W) with or without immune checkpoint inhibitors: Cohort 1 (monotherapy); Cohort 2 (combined with Penpulimab, 200 mg, ivgtt, Q3W); Cohort 3 (combined with Ivonescimab, 10 mg/kg, ivgtt, Q3W). Surgery will be scheduled 2 to 4 weeks after the completion of neoadjuvant therapy, followed by adjuvant radiotherapy or chemoradiotherapy based on risk factors. Subjects in Cohorts 2 and 3 will continue immune checkpoint inhibitor therapy for 14 cycles following the completion of radiotherapy. Dose adjustments are permitted based on toxicity. The primary endpoint is Pathologic Complete Response (PCR).Secondary endpoints include major Pathological Response (MPR), objective Response Rate (ORR), 1-year Event-Free Survival (EFS) Rate, 2-year Overall Survival (OS) Rate, treatment-related safety, and predictive biomarkers. Research Sponsor: Lepu Biopharma Co., Ltd. Clinical trial information: NCT07381075. Research Sponsor: None.

TPS6136 **Poster Session**

Neoadjuvant cemiplimab plus cetuximab prior to salvage surgery for recurrent oral cavity squamous cell carcinoma. First Author: Luana Guimaraes de Sousa, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Locoregional recurrence of oral cavity squamous cell carcinoma (OCSCC) after curative-intent therapy remains a major cause of morbidity and mortality. Salvage surgery is the standard of care when feasible but is associated with substantial functional impairment. The combination of PD-1 blockade and EGFR inhibition has demonstrated promising activity in the recurrent/metastatic setting. We hypothesize that the combination of cemiplimab and cetuximab will elicit a robust antitumor response in patients with resectable recurrent OCSCC that will lead to improved clinical outcomes. **Methods:** This is an open-label, single-center, phase II trial designed to assess the efficacy and safety of cemiplimab plus cetuximab in patients with recurrent, resectable OCSCC irrespective of PD-L1 status (NCT06448026). Key eligibility criteria include histologically confirmed locoregional recurrence at least 3 months after prior curative-intent therapy, including surgery and postoperative radiation, ECOG performance status 0–1, measurable disease per RECIST v1.1, and adequate organ function. Eligible participants receive neoadjuvant cemiplimab 350 mg intravenously every 3 weeks for two cycles combined with weekly cetuximab (loading dose 400 mg/m² followed by 250 mg/m² for up to 6 weeks), followed by salvage surgery. Patients achieving ≥50% pathologic tumor response are eligible to receive adjuvant cemiplimab for up to one year. Blood and tumor tissue for correlative analyses are collected at baseline, during treatment, and at the time of surgery. The primary endpoint is the rate of pathologic tumor response ≥50% (pTR-2) assessed in the surgical specimens local and/or regional. Secondary endpoints include objective response rate per RECIST v1.1, pathologic response rate, disease-free survival, overall survival, and safety. The planned sample size is 17 patients based on a Simon two-stage design. The study is active and accruing; to date, 9 of 17 planned patients have been enrolled. Clinical trial information: NCT06448026. Research Sponsor: Regeneron Pharmaceuticals.

TPS6137 **Poster Session**

GP regimen chronomodulated induction chemotherapy combined with concurrent chemoradiotherapy for locally advanced nasopharyngeal carcinoma: A phase III, multicenter, randomized controlled study. First Author: Feng Jin, Affiliated Hospital of Guizhou Medical University/Department of Head and Neck Oncology, Affiliated Cancer Hospital of Guizhou Medical University, Guiyang, GuiZhou, China

Background: Radiotherapy is the primary treatment for nasopharyngeal carcinoma (NPC). Currently, induction chemotherapy combined with concurrent chemoradiotherapy has become a Category I recommendation for NPC treatment. Studies show that the GP regimen is one of the most effective induction chemotherapy protocols for locally advanced NPC. However, the incidence of grade 3-4 acute toxicities with the GP regimen is as high as 75.7%, severely affecting patient treatment compliance. To reduce toxicity while maintaining efficacy, this study focuses on a "chronomodulated chemotherapy" strategy, which adjusts drug administration timing based on biological rhythms to minimize damage to normal tissues. **Methods:** Clinical Data: 1. Sample Size Calculation: This study is a randomized controlled trial with a non-inferiority design. Based on a 3-year recurrence-free survival rate of 85.3% in the conventional group, a non-inferiority margin (δ) of 10%, a one-sided α of 0.025, a power (1-β) of 0.8, equal group sizes, and accounting for a 10% dropout rate, the calculated total sample size is 434 subjects. 2. Inclusion Criteria: Treatment-naïve patients with Stage III or IVa non-keratinizing nasopharyngeal carcinoma (UICC/AJCC 8th edition). 3. Exclusion Criteria: History of prior malignancy, prior radiotherapy, or presence of other severe diseases. 4. Withdrawal Criteria: Occurrence of severe adverse events or intolerable toxicities during the study. Treatment Protocol: 1. Induction Chemotherapy Phase: Experimental Group: Gemcitabine 1000 mg/m², IV infusion over 30 min on days 1 & 8, administered between 08:00-09:30; Cisplatin 80 mg/m², continuous IV infusion (civ) on day 1, delivered evenly over 12 h from 10:00 to 22:00. Repeated every 3 weeks (Q3W) for 3 cycles. Control Group: Gemcitabine 1000 mg/m², IV infusion over 30 min on days 1 & 8; Cisplatin 80 mg/m², IV infusion over 2-3 h on day 1. Q3W for 3 cycles. 2. Concurrent Chemoradiotherapy Phase: Concurrent Cisplatin Regimen: Experimental Group: Cisplatin 100 mg/m², civ on day 1, delivered evenly over 12 h from 10:00 to 22:00. Q3W for 3 courses. Control Group: Cisplatin 100 mg/m², IV infusion over 2-3 h on day 1. Q3W for 3 courses. 3. Radiotherapy: Intensity-Modulated Radiation Therapy (IMRT) was used, with a total dose of 69.96-72.6 Gy delivered in 33 fractions. Innovation: Therapeutic efficacy for nasopharyngeal carcinoma has reached a plateau, making “toxicity reduction” a key research focus. The toxicity-reducing approach of chronomodulated chemotherapy holds promising application prospects for locally advanced nasopharyngeal carcinoma. Current Status: To date, 122 patients have been enrolled. Clinical trial information: ChiCTR2400086032. Research Sponsor: None.

TPS6138 **Poster Session**

NRG-HN006: Randomized phase II/III trial of sentinel lymph node biopsy versus elective neck dissection for early-stage oral cavity cancer. First Author: Stephen Yenzen Lai, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with early-stage oral cavity cancer (OCC; T1-2N0M0; AJCC 8th edition) have a 20-30% risk of occult nodal metastases despite clinical and radiographic evaluations. Standard-of-care treatment for most patients includes elective neck dissection (END), which requires surgical removal of the regional cervical lymph nodes, even though 70-80% of these necks are disease-free. Sentinel lymph node biopsy (SLN Bx), a less invasive procedure, could assess the first echelon lymph nodes as an alternative to END, potentially reducing morbidity and costs. A pivotal clinical trial comparing SLN Bx to END (NCT#04333537) is underway to inform efforts to establish optimal disease management for early-stage OCC. **Methods:** To assess the efficacy of SLN Bx in this population, we activated an international, multi-institutional, prospective phase II/III trial in July 2020, randomizing patients to two surgical arms: SLN Bx and END. A node-negative ^{18}F-FDG PET/CT imaging biomarker study with centralized read was required before randomization. OCC patients with a positive PET/CT remained in a registry to compare imaging findings with final neck pathology. Given the current evidence on morbidity for SLN Bx versus END, the phase II was designed to determine whether the change in patient-reported neck and shoulder function and related quality of life (QOL) from baseline to 6 months after surgery, using the Neck Dissection Impairment Index (NDII), showed a signal of superiority of SLN Bx compared to END (minimum important difference ³ 7.5; one-sided a = 0.10; 90% power). As of December 2024, 261 patients had been randomized and 203 were analyzed for the “Go/No-Go” decision to move forward into phase III. The phase III portion is a non-inferiority (NI) trial with disease-free survival (DFS) as the primary endpoint (NI margin hazard ratio 1.34 based on a 5% absolute difference in 2-year DFS; one-sided a = 0.05; 80% power, and two interim looks). The change in NDII from baseline to 6 months after surgery is a hierarchical co-primary endpoint for phase III. Phase III opened in October 2025 upon receiving a “Go” signal from phase II. Target accrual for phase III is 686 node-negative PET/CT patients, including those randomized in phase II (425 additional patients). In addition to sites requiring radiotherapy and imaging credentialing, quality assurance will include central pathology review of all negative SLN Bx cases and surgeon credentialing through an education course with SLN Bx and END case review by the surgical co-chairs. A surgical quality assurance working group will review all trial SLN Bx and END procedures. As of 01/12/26, 351 patients have been screened, and 273 of the planned 686 have been randomized. Clinical trial information: NCT#04333537. Research Sponsor: National Cancer Institute and Cardinal Health; UG1CA189867, U10CA180822, U10CA180868.

TPS6139 **Poster Session**

Neoadjuvant therapy for head and neck squamous cell carcinoma based on hyperprogression genotyping: Cetuximab beta combined with chemotherapy with or without camrelizumab. First Author: Ziyu Jiang Jr., The First People's Hospital of Lianyungang, Lianyungang, Jiangsu, China

Background: Surgery remains the preferred treatment option for locally advanced head and neck squamous cell carcinoma (LA HNSCC). However, its efficacy is still unsatisfactory, with local recurrence and distant metastasis rates as high as 20% and a 5-year survival rate of only about 50%. Immune checkpoint inhibitors (ICIs) have achieved success in recurrent/metastatic HNSCC (R/M HNSCC), laying the foundation for the application of immunotherapy in earlier-stage patients. Cetuximab, an anti-Epidermal Growth Factor Receptor (EGFR) antibody, is a standard treatment for both LA HNSCC and R/M HNSCC. Patients who experience Hyperprogressive Disease (HPD) have a poor prognosis, and various genetic mutations have been shown to predict the occurrence of HPD. **Methods:** This study was designed as a prospective, open label, multicenter, phase II trial (ChiCTR2500108701), and the primary endpoint was the postoperative pathological complete response (pCR) rate. The secondary endpoints included the objective response rate (ORR), major pathological response (MPR) rate, 1-year and 2-year event-free survival (EFS) rates, and 2-year overall survival (OS) rate. Eligible patients (pts) were over 18 years old with histologically or cytologically confirmed SCCHN (excluding nasopharyngeal carcinoma); had T1N2-3M0, T2N1-3M0, or T3/T4aNanyM0, according to the 8th Edition of the American Joint Committee on Cancer (AJCC) staging guidelines; had resectability of the tumor was evaluated by a head and neck surgeon; had no previous local and systemic treatment for SCCHN; had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; had measurable disease per Response Evaluation Criteria in Solid Tumours (RECIST 1.1). All enrolled 40 pts received whole exome sequencing (WES), and were assigned to Cohort A (n=25, HPD-gene-negative) and Cohort B (n=15, HPD-gene-positive), respectively. All treatment was administered intravenously in 21-day cycles. Patients in Cohort A were given albumin-bound paclitaxel (260 mg/m², d1), cisplatin (25 mg/m², d1-d3), camrelizumab (200 mg, d1) and cetuximab (250 mg/m², d1;500 mg/m², d8). Patients who successfully completed 2~4 cycles of neoadjuvant treatment returned for surgical intervention 28~42 Endpoints days after the last cycle, and adjuvant radiotherapy was administered followed by 2~4 cycles of camrelizumab (200 mg, d1) and cetuximab (250 mg/m², d1; 500 mg/m², d8) as adjuvant treatment.Cohort B received the same treatment regimen as Cohort A, excluding camrelizumab. Clinical trial information: ChiCTR2500108701. Research Sponsor: None.

TPS6140 **Poster Session**

EA3231: A randomized phase III study of BRAF-targeted therapy vs cabozantinib in RAI-refractory differentiated thyroid cancer with *BRAF* V600Em.

First Author: Lova Sun, University of Pennsylvania, Philadelphia, PA

Background: About half of patients with RAIR advanced differentiated thyroid cancer (DTC) harbor a mutation in BRAF V600E. Although multiple systemic therapies are now approved, optimal treatment sequencing remains undefined for patients with BRAF V600Em RAIR DTC. Given the indolent natural history of this disease and often prolonged exposure to oral therapies with significant toxicity, comparative data on efficacy and tolerability of second-line therapy is a clear unmet need. **Methods:** EA3231 (NCT06475989) is a NCTN cooperative group randomized phase III study in patients with BRAF V600Em RAIR DTC who have progressed on prior multikinase inhibitor therapy such as lenvatinib or sorafenib. Patients will be randomized 1:1 to BRAF-targeted therapy (dabrafenib and trametinib) or cabozantinib, all of which are FDA-approved agents in this setting. The primary objective is to compare progression-free survival (PFS) between dabrafenib/trametinib vs cabozantinib, with secondary objectives including overall response rate, overall survival, PFS2, and safety and tolerability. We hypothesize that BRAF-directed therapy will be associated with improved PFS and tolerability compared to cabozantinib. Our target accrual is 120 patients; this sample size will provide 83% power to detect a HR of 0.60 (corresponding to a median PFS of 12 months) compared to an estimated median PFS of 7.2 months in the cabozantinib arm. This study was activated in late 2024, and has enrolled 8/120 patients as of 1/2026. Clinical trial information: NCT06475989. Research Sponsor: None.

LBA6500 **Oral Abstract Session**

Selinexor plus ruxolitinib in JAK inhibitor–naïve myelofibrosis: Phase 3 SENTRY trial. First Author: John Mascarenhas, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

6501 **Oral Abstract Session**

RALLY-MF: Initial efficacy of a phase 2 study of DISC-0974, an anti-hemojuvelin antibody, to treat anemia in myelofibrosis. First Author: Naseema Gangat, Mayo Clinic Rochester, Rochester, MN

Background: Hepcidin, a central regulator of iron homeostasis, is pathologically elevated in patients with myelofibrosis (MF) and anemia. Chronic hepcidin elevation limits iron availability for red blood cell (RBC) production and contributes to anemia onset and severity. DISC-0974 is an investigational, first-in-class, monoclonal antibody that blocks hemojuvelin, a co-receptor in the bone morphogenetic protein-signaling pathway driving hepcidin expression. **Methods:** RALLY-MF (NCT05320198) is an ongoing Phase 2, open-label study conducted in the US. The primary aim is to evaluate DISC-0974 efficacy in participants with MF and anemia. Secondary aims include evaluating safety, pharmacokinetics (PK), and pharmacodynamics (PD). Eligible participants are ≥18 years of age with primary or secondary MF and hemoglobin (Hgb) <10 g/dL or RBC transfusion requirement. Participants enroll into 3 cohorts based on RBC units transfused in the 84 days prior to screening: non-transfusion dependent (nTD, 0 units and Hgb <10 g/dL), low transfusion burden (TD low, 1-2 units), high transfusion burden (TD high, 3-12 units). Stable dose of concomitant Janus kinase inhibitor (JAKi) is allowed. DISC-0974 is administered subcutaneously at 50 mg monthly for up to 6 doses, with escalation to 75 mg for inadequate or lost response. Primary endpoints include major hematologic response defined as transfusion independence (TI) during any consecutive 16 weeks (TD low) or 12 weeks (TD high), or a mean Hgb increase of ≥1.5 g/dL from baseline for ≥12 weeks (nTD). Secondary endpoints include PK/PD markers of iron regulation and safety assessments. Data were summarized using descriptive statistics. **Results:** At data cut (16 Oct 2025), 47 participants enrolled in the nTD (n=30), TD low (n=10), and TD high (n=7) cohorts, with 53% on concomitant JAKi therapy. DISC-0974 led to sustained hepcidin reduction and iron mobilization across cohorts. DISC-0974 resulted in meaningful hematologic responses among evaluable participants: 50% of nTD participants achieved a mean Hgb increase of ≥1.5 g/dL for ≥12 weeks, 71% of TD low participants achieved TI for ≥16 weeks, and 67% of TD high participants experienced a ≥50% reduction in transfusion burden, with follow-up ongoing. Major hematologic response rates were 50% for participants on and off concomitant JAKi therapy (n=18 and n=16, respectively). DISC-0974 was associated with meaningful improvement in FACIT-Fatigue scores for nTD and TD low participants. Serious adverse events (AEs, n=9) and ≥Grade 3 AEs (n=16) were considered unrelated to DISC-0974. There were no early withdrawals due to AEs. **Conclusions:** DISC-0974 was well tolerated and shows a favorable safety profile. Anemia response and fatigue scores improved across patients with MF and anemia, including those receiving JAKi therapy. These data validate hepcidin reduction as a promising approach to treating anemia in MF. Clinical trial information: NCT05320198. Research Sponsor: Disc Medicine.

6502 **Oral Abstract Session**

A phase II trial of tagraxofusp, hyper-CVAD, and venetoclax for patients with newly diagnosed or relapsed/refractory BPDCN. First Author: Hannah Goulart, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, aggressive hematologic malignancy with (w/) historically dismal outcomes, including median (med) overall survival (OS) of 8 – 12 months (mos) and frequent central nervous system (CNS) involvement (Martin-Martin *Oncotarget* 2016, Pemmaraju *Blood* 2021). Tagraxofusp (TAG; first CD123-targeted therapy approved for BPDCN) improves responses (Pemmaraju *JCO* 2022), but relapse remains common. Venetoclax (VEN) demonstrates activity in BPDCN (Montero *Cancer Disc* 2017), and intensified chemotherapy may improve outcomes. We report the results of a phase II investigator-initiated trial (NCT04216524) of TAG, Hyper-CVAD, and VEN in newly diagnosed (ND) or relapsed/refractory (R/R) BPDCN. **Methods:** Adults (≥18 years [yrs]) w/ ND or R/R BPDCN received: Cycle [C] 1: TAG days [d] 1-5; C2, 4, 6, 8: TAG d1 – 5 w/ VEN d2 – 14 (C2) and d1 – 7 (C4, 6, 8); C3, 7: VEN d1 – 7 w/ Hyper-CVAD or mini-hyper-CVD; C5: VEN d1 – 7 w/ high-dose methotrexate/cytarabine or mini-methotrexate/cytarabine. Cycles were 28 days for up to 8 cycles, followed by POMP, VEN, and TAG maintenance. Pts received ≥8 intrathecals. **Results:** Nineteen pts were enrolled (14 ND; 5 R/R). Med age was 61 yrs (range, 20 – 79); 79% male. Disease sites included 84% skin, 63% bone marrow, 16% CNS, 16% extramedullary. Co-occurring mutations were *TET2* (60%), *ASXL1* (33%), *DNMT3A* (20%), *NRAS* (13%), *KRAS* (13%). Two pts had prior/concomitant MDS. For ND, overall response rate (ORR; complete remission [CR] plus CR w/ incomplete count recovery [CRi] plus partial response [PR]) was 93% (13/14, all CR/CRi). Pts received a med of 2 (1 – 6) cycles w/ 2 (1 – 3) cycles to best response. The 30- and 60-day mortality was 0%. After a 55-mos med follow-up, (19.5 – NR), med OS was 15 mos w/ 24-month OS of 42%. Med EFS was 14.6 mos w/ 24-month EFS of 42%. Nine pts (65%) went to stem cell transplant (SCT) (2 died in CR, 6 remain alive in CR; of these, 3 remain alive in CR almost 5 yrs; with only 1 post-SCT relapse). In the 4 responding pts who did not go to SCT, 3 relapsed, 1 died in CR. For R/R, ORR was 100%; CR/CRi of 50%. Pts received a med of 2 (2 – 4) prior lines; 3 (60%) had prior SCT. Pts received a med of 3 (1 – 7) cycles w/ 3 (1 – 3) to best response. Two pts went to SCT (1 auto, 1 allo); 1 pt is alive on active treatment. The 30- and 60-day mortality was 0% and 20%. With f/u ranging 1.4 – 21.8 mos, med OS and EFS is 8.9 mos; 12-month OS and EFS was 30%. In responding pts, causes of death were progression n = 4; died in CR n = 5 (3 ND, 2 R/R, 1 post SCT, 1 unknown, 3 sepsis). The most common any grade adverse events (AE) were edema (n = 13) and fatigue (n = 11). There were 2 grade 5 AE (progression, respiratory failure). Two grade 3 capillary leak events were observed. **Conclusions:** As frontline therapy, TAG with Hyper-CVAD, and VEN shows promising safety with no early mortality or high-grade CLS, with high response rates enabling frequent SCT consolidation and no CNS relapse. Clinical trial information: NCT04216524. Research Sponsor: Stemline.

6503 **Oral Abstract Session**

A multicenter phase Ib/II trial of azacitidine, venetoclax, and ivosidenib in *IDH1*-mutated acute myeloid leukemia (AML). First Author: Jennifer Marvin-Peek, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Outcomes for patients with *IDH1*^{mut} AML have improved with the advent of targeted therapies. Two doublet regimens are approved for *IDH1*^{mut} AML: venetoclax (VEN) with a hypomethylating agent (HMA), and azacitidine (AZA) plus ivosidenib (IVO). Both regimens are effective, yet a substantial proportion of patients fail to respond or eventually relapse. Combining all three agents into a "triplet" regimen may improve outcomes. Herein, we report results from the fully enrolled newly diagnosed (ND) cohort of the multicenter phase Ib/II study of AZA+VEN+IVO for *IDH1*^{mut} AML (NCT03471260). **Methods:** Adults ≥18 years with ND *IDH1*^{mut} AML not eligible for standard induction chemotherapy and treated at the RP2D in the phase Ib or II cohorts were included. Patients received AZA 75 mg/m^2 days 1-7, VEN 400mg days 1-14, and IVO 500mg continuously starting C1D14. Dose attenuations in remission were permitted to minimize myelosuppression. The primary objectives were to determine the safety and overall response rate (ORR: CR + CRh + CRi + MLFS). **Results:** From November 2019 to October 2025, 40 patients with ND AML at four U.S. academic centers initiated treatment (Phase Ib: 9, Phase II: 31). The median age was 72 years (range, 51-80), and 26 patients (65%) were male. AML was classified as *de novo* in 21 (53%), therapy-related in 4 (10%), and secondary to antecedent myeloid neoplasm in 15 (38%). Six (15%) had received a prior HMA. The ORR was 95% (38/40) with 93% (37/40) achieving a composite CR (CRc; CR+CRh+CRi). The median number of cycles to best response was two (range, 1-7). Measurable residual disease (MRD) negativity by flow cytometry (sensitivity <0.1%) was achieved in 92% (34/37) of CRc responders. With a median follow up of 35 months, median overall survival (OS) and duration of remission (DOR) were not reached. The 3-year OS was 79% (95% CI 64-96%). Three patients relapsed during follow-up with *IDH1*-negative clones, and 18 patients (45%) transitioned to SCT. The 3-year DOR censored and not-censored at SCT was 82% (95% CI 68-98%) and 83% (95% CI 64-100%), respectively. Among the 22 patients who did not undergo SCT, the median number of cycles received is 14, with 10 patients (45%) remaining on study. Reasons for discontinuation included lack of response/relapse (n=5), development of another malignancy (n=2), adverse events (AEs; n=2), and patient preference (n=1). Non-hematologic AEs occurred in 32 patients (80%), with 12 (30%) experiencing grade ≥3 AEs. Most grade ≥3 AEs were infectious (n=7, 23%), although two patients each experienced grade ≥3 QTc prolongation, tumor lysis syndrome, and differentiation syndrome, all successfully managed with supportive care and/or with dose modifications. **Conclusions:** Triplet therapy with AZA+VEN+IVO demonstrates high MRD negative response rates, durable remissions, and comparable safety to doublet regimens in this multicenter study for patients with ND *IDH1*^{mut} AML. Clinical trial information: NCT03471260. Research Sponsor: None.

6504 Oral Abstract Session

Quizartinib in combination with decitabine and venetoclax for newly diagnosed and relapsed/refractory *FLT3*-mutated AML. First Author: Musa Yilmaz, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Hypomethylating agents (HMAs; azacitidine/decitabine) plus venetoclax (VEN) are standard for newly diagnosed acute myeloid leukemia (AML) unfit for intensive chemotherapy; however FMS-like tyrosine kinase-3 internal tandem duplication (*FLT3-ITD*) confers resistance and poor overall survival (OS). Addition of quizartinib (QUIZ), a potent FLT3 inhibitor, may improve outcomes. **Methods:** Phase I/II study of QUIZ+decitabine+VEN in two cohorts: newly diagnosed *FLT3-ITD* AML pts unfit for intensive chemotherapy and relapsed/refractory (R/R) FLT3-ITD AML pts. Primary endpoints were maximum tolerated dose (MTD) and overall response rate (ORR). **Results:** Eighty-eight patients (pts) were enrolled (frontline N=42; R/R N=46). QUIZ 26.5mg/day was selected as the recommended phase II dose (RP2D). In the frontline cohort, median age was 70y (62–85); 15 pts (36%) were ≥75y; 25 (60%), 12 (N=28%), and 5 (12%) had de novo, secondary, and therapy-related AML, respectively. *DNMT3A* (43%), *NPM1* (33%), and *RUNX1* (31%) were the most common co-mutations. Complete remission (CR), CR with incomplete count recovery (CRi), morphologic leukemia-free state (MLFS), end-of-cycle-1 (EOC1) measurable residual disease (MRD) negativity by multicolor flow cytometry (MFC; 0.01%), and next-generation sequencing (NGS) FLT3-ITD negativity (5×10^{-5}) were 72% (N=29), 17% (N=7), 2% (N=1), 58% (19/32), and 27% (5/18), respectively; 2 pts in cycle 1 were not evaluable. Best MRD negativity by MFC and FLT3-NGS were 68% (23/34) and 83% (15/18). Median time to absolute neutrophil count (ANC) >500, ANC >1000, and platelets >50K were 40 (19–72), 41 (14–72), and 35 (16–71) days, respectively. The median relapse-free survival (RFS) and OS were 24.7 and 36.5mo. Fifteen pts (36%) proceeded to allogeneic stem cell transplant (ASCT) in CR1, with OS not reached vs 36.6mo without ASCT (p=0.65, landmark analysis). Median 3 cycles (1–39) were delivered; 11 pts remain on study. Thirty-one pts discontinued protocol due to ASCT (N=15), relapse (N=9), physician/pt choice (N=3), induction death (N=1), death in CR (N=1), death with disease (N=1), or hospice (N=1). Grade ≥3 non-hematologic adverse events (>5%) included febrile neutropenia (37%), pneumonia (33%), infections (17%), pain (10%), ALT increase (10%), fracture (10%), sepsis (9%), hypertension (7%), hypotension (7%), hyponatremia (7%), gait disturbance (7%), oral mucositis (7%), and pleural effusion (7%). In the R/R cohort, CR/CRi was 28% (N=13) with 33% (N=15) MLFS; 37% (N=17) proceeded to ASCT; median OS was 6.3mo (further data will be provided at the time of presentation). **Conclusions:** QUIZ+decitabine+VEN combination resulted in high CR/CRi, deep MRD responses, and encouraging survival in older pts with newly diagnosed *FLT3-ITD* AML. Clinical trial information: NCT03661307. Research Sponsor: None.

6505 Oral Abstract Session

Revumenib as maintenance for AML following allogeneic stem cell transplantation. First Author: Hannah Goulart, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Relapse after allogeneic stem cell transplantation (SCT) remains common in acute myeloid leukemia (AML). Revumenib is approved for relapsed/refractory (R/R) *NPM1*mt or *KMT2A*r acute leukemia however its safety and efficacy as post-SCT maintenance has not been characterized. We report outcomes of revumenib maintenance post-SCT in adult and pediatric patients (pts) at our institution. **Methods:** Pts with *NPM1*mt, *KMT2A*r or *NUP98*r AML could continue post-SCT revumenib maintenance following response pre-SCT to revumenib monotherapy or combination on clinical trial. Revumenib was resumed at pre-SCT dose with adjustment for azoles. **Results:** Twenty-one pts were included (11 adult, 10 pediatric); median age 20 years (range, 1 – 69), 62% female. Most (n = 16, 76%) had *KMT2A*r, 4 (19%) had *NPM1*mt, and 1 peds pt had *NUP98*r. Pre-SCT, revumenib was given as monotherapy per AUGMENT-101 (NCT04065399, n = 8) or Expanded Access (NCT05918913, n = 2) or with oral decitabine and venetoclax per SAVE (NCT05360160, n = 11). Pts received a median of 3 (1 – 11) prior therapies, 12 pts (57%) had prior SCT, and 4 pts received SAVE frontline. Maintenance post-SCT on SAVE was planned for 1 yr. At current SCT, 19% were in first complete remission (CR1 following SAVE), 81% were in CR2+ (SAVE or monotherapy). Median time to initiate post-SCT revumenib was 2.8 months (1.4 – 5.7) with median duration of therapy of 6.7 months (0.5 – 36). With a median follow-up of 18.2 months (95% CI 17.2 – 44.3), median overall survival (OS) and event-free survival (EFS) from SCT have not been reached; 1- and 2-year OS were 89%; 1- and 2-year EFS were 84% and 73%, respectively. The 1-year cumulative incidence of relapse (CIR) was 11% and death was 5%. In CR2+, 2-year OS was 93% and 1-year CIR was 13%. At last follow up, 29% remain on revumenib, and 71% have discontinued (relapse 14%, toxicity 14%, completion 14%, pt choice 14%, other illness 9%). The most common any grade adverse event (AE) was thrombocytopenia (86%; grade >3 43%), leading to dose modification in 48% and discontinuation in 10%. Graft-versus-host-disease occurred in 14% (grade >3 5%), however no other AE led to dose modification. Infections occurred in 14% (grade ≥3 10%); one pt discontinued due to grade 4 septic shock. No QTc prolongation was seen. In contrast, in a historical SCT cohort with the same genotypes treated prior to the advent of menin inhibitors (Table 1), pts transplanted at CR2+ had 2-year OS of 33% and 1-year CIR of 46%. **Conclusions:** Revumenib maintenance post-SCT was feasible in this heavily pretreated cohort. Thrombocytopenia was common often requiring dose modification, but no other significant toxicities were observed. Outcomes appear favorable compared to historical cohorts, supporting prospective evaluation of menin inhibition as maintenance. Clinical trial information: NCT04065399, NCT05918913. Research Sponsor: Syndax Pharmaceuticals.

Rev vs. historical cohort.

	N	1-yr OS (%)	2-yr OS (%)	1-year CIR (%)	Median F/U (mos)
Rev	21	89	89	11	18.2
Rev CR2+	17	93	93	13	33.3
Hist.	320	60	51	39	76
Hist. CR2+	124	45	33	46	92

6506 Oral Abstract Session

Safety, tolerability, and efficacy of mesutoclax (ICP-248) in combination with azacitidine in patients with myeloid malignancies. First Author: Huafeng Wang, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China

Background: Venetoclax has been approved for the treatment of newly diagnosed acute myeloid leukemia (AML) in elderly or unfit pts but failed in the high-risk myelodysplastic syndromes (MDS). Mesutoclax is a novel, potent, highly selective BCL-2 inhibitor. It exhibits favorable pharmacokinetic profile without any major metabolites. **Methods:** ICP-CL-01205 (NCT06656494) is an ongoing, global, phase I study evaluating mesutoclax in combination with azacitidine (AZA) in pts with AML or MDS. In the dose escalation part, mesutoclax at100 mg, 125 mg, and 150 mg in combination with AZA were evaluated for safety and tolerability. 100 mg and 125 mg were selected as Recommended dose for expansion (RDE) for further evaluation. Antitumor activity in AML and MDS is assessed based on ELN 2017 and IWG 2006/2023 criteria, respectively. Herein, we report safety, tolerability and efficacy for mesutoclax with AZA in pts with AML and MDS in this phase 1 study. **Results:** As of January 12, 2026, a total of 59 pts were enrolled including 8 R/R AML, 39 TN AML and 12 TN MDS. The median age of AML and MDS pts was 65 (range: 23, 81) and 67 years (range: 54, 75), respectively. Adverse risk per 2017 ELN was identified in 51.1% AML pts. Azole prophylaxis and G-CSF treatment were used in 5% and 22% pts. Among the 35 evaluable TN AML pts, 30 (85.7%) achieved composite CR (cCR, CR+CRi) with central assessment of CR rate of 65.7% (23/35). Among those who achieved cCR, 86.7% (26/30) were MRD negative per flow cytometry. MRD negative in CR (CR_{MRD-}) was 60% (21/35). cCR was 75% in adverse risk per 2017 ELN classification. The DOR rate at 3-months was 91.7%. The 6-month OS rate was 94.1%. Among 10 response evaluable TN MDS pts, the overall response rate (ORR) per IWG 2006 criteria was 100%, including CR in 20%, marrow CR in 80%. The composite CR rate was 70% per IWG 2023 criteria including 30% CR even when most pts only received 1 cycle treatment. There were no DLT or TLS events. The most common (≥10%) grade ≥ 3 TEAEs in pooled analysis of 59 AML and MDS were neutrophil count decreased (62.7%), platelet count decreased (50.8%), anemia (33.9%), infection (16.9%), and lymphocyte count decreased (11.9%). There were 5.1% grade ≥ 3 febrile neutropenia and no TEAEs lead to dose discontinuation. SAEs were reported in 25.4% pts. For pts with TN AML, the median intervals between cycle 1 and cycle 2 initiation (requiring neutrophil $\geq1*10^9$/l and platelet $\geq 100*10^9$/l) was 39 days and the median duration of grade 4 neutropenia and thrombocytopenia were 17 and 9 days, respectively. **Conclusions:** The combination of mesutoclax and azacitidine demonstrated a favorable safety profile and encouraging anti-tumor activity not only in AML but also in MDS pts, supporting its continued development for the treatment of myeloid malignancies. These preliminary results warrant further investigation in larger, randomized trials. Clinical trial information: NCT06656494. Research Sponsor: None.

6507 Oral Abstract Session

Safety and efficacy of eganelisib in adults with higher-risk myelodysplastic syndrome (HR-MDS) or relapsed/refractory (R/R) acute myeloid leukemia (AML). First Author: Mendel Goldfinger, Montefiore Medical Center, Bronx, NY

Background: The gamma isoform of PI3K (PI3Kγ) directs a myeloid-specific signaling node (PI3Kγ-AKT1-PAK1) identified as a core dependency in AML responsible for LSC self-renewal, medullary homing, and resistance to venetoclax and nucleoside analogues (Luo 2024; Gu 2024; Kelly 2024; Qiu 2025). Eganelisib is a highly potent isoform-specific inhibitor of PI3Kγ that demonstrated safety and effective target modulation in solid tumors. Here we report results of a Phase I study of eganelisib monotherapy in R/R AML or HR-MDS using doses previously shown to be biologically active [NCT06533761]. **Methods:** Eligible patients had ECOG PS <2, R/R AML or IPSS-R Int-Very High risk MDS that was R/R to prior therapy with ≥10% BM blasts. Eganelisib was administered orally in two cohorts of 45 mg and 60 mg QD in 28-day cycles. The primary endpoints were safety and efficacy per ELN 2022 (AML) and IWG 2023 (HR-MDS) and recommended dose for expansion (RDE). Additional endpoints included PK and PD effects assessed by AKT^{S273} phosphorylation in monocytes. **Results:** 15 patients have been treated to date (n=7, 45 mg; n=8, 60 mg); patient characteristics are summarized in the table below. There were no DLTs at either dose level. PD studies revealed dose-dependent reduction in AKT phosphorylation of ~90% at the 60 mg dose. Of the 10 patients who completed a 28-day cycle, anti-leukemic activity and evidence of clinical benefit was observed in 4 patients, including a CR in 1 patient at 45 mg. Three patients at 60 mg demonstrated anti-leukemic activity: 1 patient achieved <5% bone marrow blasts by flow cytometry, major cytogenetic response, rapid subclonal clearance, with full trilineage count recovery and low levels of persistent circulating blasts; two patients (both with TP53 mutations) with stable/decreasing marrow blasts had a progressive rise in neutrophils while on therapy. Longest duration of treatment is 5 cycles. Exposure to eganelisib was variable across both dose levels, and both doses showed overlapping plasma concentrations. **Conclusions:** Eganelisib demonstrates effective inhibition of PI3Kγ with single agent activity in heavily treated, poor-risk patients, validating PI3Kγ as a key vulnerability in MDS and AML. Importantly, eganelisib had no intrinsic hematologic toxicity, consistent with previous studies and pre-clinical observations that PI3Kγ is dispensable for normal hematopoiesis. Given the capacity to potentiate activity of nucleoside analogues and venetoclax, combined therapy in previously untreated HR-MDS & AML patients at the RDE of 60 mg QD is planned. Clinical trial information: NCT06533761. Research Sponsor: Stelexis BioSciences, Inc.

	45 mg (n=7)	60 mg (n=8)	All (n=15)
Age (median/range)	78 (71-85)	59 (20-74)	72 (20-85)
AML | MDS	7 | 0	7 | 1	14 | 1
Prior MDS or MDS-related changes	6	5	10
Prior therapies (median/range)	2 (1-3)	2 (1-6)	2 (1-6)
Adverse-risk ELN	86%	71%	79%
***TP53* mutation**	43%	43%	43%
Prior intensive chemo/venetoclax	14%/71%	50%/100%	33%/87%

6508 **Oral Abstract Session**

First-in-human dual-epitope nanobody anti-CD5 CAR-T for relapsed/refractory T-ALL/PTCL: Phase I dose-escalation and expansion results from the CONQUER trial. First Author: Meng Lv, Peking University People's Hospital, Beijing, China

Background: Patients with relapsed or refractory T-lymphoblastic leukemia/Peripheral T-Cell Lymphoma (R/R T-ALL/PTCL) experience dismal outcomes. Previously, we demonstrated naturally selected anti-CD7 CAR-T could overcome fratricide without gene editing or protein blockade, yielding encouraging clinical activity (Blood, 2022; 2025). CD5 is a critical pan–T-cell marker highly expressed in T-ALL/PTCL and represents a rational target beyond CD7. **Methods:** We developed SL105 injection, an autologous CD5-directed CAR-T cell product incorporating a tandem camelid-derived dual-epitope nanobody through a natural selection platform. This first-in-human phase I study evaluates the safety, preliminary efficacy, and recommended phase II dose (RP2D) of SL105 injection in patients with R/R T-ALL/PTCL (NCT06874946). **Results:** As of January 27, 2026, 37 patients provided informed consent; 18 patients received a single infusion of SL105 and completed the 28-day dose-limiting toxicity (DLT) assessment and constituted the enrolled population for analysis. Three dose levels (0.5, 1.0, and 2.0 $\times 10^6$ CAR-T cells/kg) were evaluated, with a minimum of two patients with T-ALL/LBL or PTCL enrolled at each dose level. Median age was 32 years (range, 16–57); 33.3% had prior hematopoietic stem cell transplantation. Diagnoses included T-ALL/LBL (n=11) and PTCL (n=7). Median follow-up was 6 months (range, 2–11). No DLTs were observed, and the recommended RP2D was established at 2.0 $\times 10^6$ CAR-T cells/kg. Median time to peak CAR-T expansion was 14 days by qPCR, with a median peak level of 6.3×10^4 copies/μg (range, 6–5.5×10^5). Cytokine release syndrome (CRS) occurred in 66.7% of patients; grade 2 CRS was observed in 21.7%, with no grade $\geq$3 CRS. One patient (5.5%) experienced grade 1 immune effector cell–associated neurotoxicity syndrome (ICANS). Grade 1–4 early immune-cell–associated hematotoxicity (ICAHT) events occurred in 7 (38.9%), 2 (11.1%), 4 (22.2%), and 5 (27.8%) patients, respectively. EBV-related events occurred in 50% of patients, and CMV viremia in 33.3%. The best overall response rate (ORR) was 77.8% (14/18), including a CR/CRi/CMR rate of 61.1% (11/18) and PR with extranodal disease in 16.7% (3/18). All responding patients with bone marrow involvement achieved MRD negativity by flow cytometry. All four non-responders (two T-ALL/LBL and two PTCL) demonstrated low CAR-T expansion, with peak levels $<$500 copies/μg genomic DNA. At the RP2D, ORR was 100%, with CR/CMR achieved in 85.7% (6/7). Five responding patients underwent consolidative allogeneic HSCT. **Conclusions:** SL105, an autologous dual-epitope nanobody CD5 CAR-T therapy, demonstrated a favorable safety profile and encouraging efficacy in R/R T-ALL/PTCL. The RP2D has been established, supporting further evaluation in an ongoing phase II study. Clinical trial information: NCT06874946. Research Sponsor: Beijing Research Ward Excellence Program; National key research and development plan of China.

6509 **Rapid Oral Abstract Session**

A phase 2 study of fedratinib in patients with MDS/MPN and chronic neutrophilic leukemia. First Author: Andrew Tucker Kuykendall, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: MDS/MPNs are complex diseases that exhibit proliferative symptoms and aggressive clinical courses. Treatment options are limited. Ruxolitinib, a JAK1/JAK2 inhibitor, showed clinical benefit in pts with chronic neutrophilic leukemia (CNL) and atypical CML (aCML); yet survival remained poor (mOS 18.8 mo). Fedratinib (Fed) is a JAK2 inhibitor approved for MF that, compared to ruxolitinib, has a broader kinase inhibition profile which may provide enhanced efficacy in molecularly complex disease. Fed potently inhibits FLT3 and BRD4 and potently suppresses c-Myc, a critical upregulated pathway in MDS/MPN. Here, we present the primary results of NCT05177211 assessing the efficacy of Fed in pts with MDS/MPNs. **Methods:** NCT05177211 is a phase 2, multi-institutional study that enrolled pts with aCML, CNL, MDS/MPN-unclassifiable (MDS/MPN-U), and MDS/MPN-ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) who have splenomegaly (spleen volume $>$ 450cc) and/or significant symptom burden (MPN TSS $\geq$ 10). The primary endpoint is overall response defined as complete/partial response or clinical benefit at 24 weeks per MDS/MPN IWG response criteria. Exploratory endpoints include progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Fed was given at a dose of 400 mg daily on day 1-28 of 28-day cycles. **Results:** The data cutoff was 1/1/2026. Among 25 pts, 6 had aCML, 5 had CNL, 6 had MDS/MPN-RS-T, and 8 had MDS/MPN-U. Median age was 68.8 y. $\geq$3 mutations were present in 19 (76%) pts. Three (12%) pts remain on study. Median duration of treatment was 7.4 months. Eleven (44%) pts responded at week 24: 6 (30%) spleen responses (SVR35) and 9 (47%) symptom responses (TSS50). Four (25%) pts had both spleen and symptom response. Among 16 pts with splenomegaly treated for $\geq$ 24 weeks, spleen volume decreased by an average of 30% (+9% to -61%). Among 16 pts with symptomatic disease treated for $\geq$ 24 weeks, TSS improved by an average of -41% (range +35% to -80%). *CSF3R* mutations were enriched among pts with SVR35 (n = 4; 67%). Median PFS and OS were 36.9 mo (95% CI 19.3-NR) and 36.9 mo (95% CI 18.4-NR), respectively. Among responders, the duration of response was 7.6 mo (95% CI: 3.72-not reached). When stratified by diagnosis, OS for aCML, CNL, MDS/MPN-RS-T, and MDS/MPN-U was 19.8, 36.9, NR and NR, respectively. SAEs occurred in 13 (52%) pts. SAEs possibly related to Fed included acute kidney injury (n = 2), low thiamine (n = 1), colitis (n = 1), diarrhea (n = 1), arthralgias (n = 1), and edema (n = 1). Any grade nausea, vomiting, diarrhea, and constipation were seen in 52%, 16%, 44%, and 48% of pts, respectively. **Conclusions:** Fed demonstrates promising clinical efficacy in MDS/MPN and CNL pts with proliferative features. The safety profile is consistent with prior experience. Fed's unique kinase inhibition profile may provide a mechanism for enhanced effectiveness in this pt population. Clinical trial information: NCT05177211. Research Sponsor: BMS.

6510 **Rapid Oral Abstract Session**

Updated efficacy and safety of olverembatinib (HQP1351) as second-line therapy in patients with chronic-phase chronic myeloid leukemia (CP-CML). First Author: Weiming Li, Department of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: Olverembatinib is a third-generation BCR::ABL1 tyrosine kinase inhibitor (TKI) approved in China for chronic myeloid leukemia (CML) resistant/intolerant to $\geq$ 2 TKIs or with the T315I mutation. This study assessed olverembatinib as second-line treatment in patients with CP-CML resistant/intolerant to first-line TKIs without the T315I mutation. **Methods:** This single-arm, multicenter, open-label study enrolled patients (ECOG PS 0-2, adequate hepatic/renal function) who receive olverembatinib 40 mg orally every other day in 28-day cycles. Efficacy and safety were assessed every 3 cycles. The primary endpoint was complete cytogenetic response (CCyR) rate. **Results:** From August 4, 2022, through January 14, 2026, 47 patients were enrolled (91.5% first-line TKI resistant, 8.5% intolerant). The median age was 42.0 (19-70) years; 66.0% were male. Twelve (25.5%) received first-line imatinib, and 35 (74.5%) received first-line second-generation TKIs. Thirty-six (76.6%) had no baseline *BCR::ABL1* kinase domain mutations, and 11 (23.4%) had non-T315I mutations. At data cutoff, 33 (70.2%) continued treatment, while 14 (29.8%) discontinued because of adverse events (n = 3), treatment failure (n = 4), progression (n = 2), or other reasons (n = 5). Among 42 evaluable patients, 76.2% achieved CCyR and 47.6% major molecular response (MMR). CCyR/MMR rates increased progressively: cycle 6 (57.5%/25.0%), cycle 9 (60.4%/33.3%), cycle 12 (75.0%/37.5%), cycle 15 (83.3%/46.7%), cycle 18 (89.3%/50.0%), cycle 21 (92.0%/64.0%), and cycle 24 (91.3%/60.9%). Complete hematologic response was achieved in 83.3% (15/18) and major cytogenetic response in 83.3% (35/42). Among 32 patients pretreated with first-line second-generation TKIs, 81.3% achieved CCyR and 50% MMR. The median treatment duration was 16.0 (6-38) cycles. Any-grade treatment-related adverse events (TRAEs) occurred in 42 (89.4%) patients; 21 (44.7%) had grade $\geq$ 3 TRAEs; and 6 (12.8%) had serious adverse events (SAEs). Non-hematologic TRAEs (mainly grade 1-2) included skin hyperpigmentation (51.1%), hyperuricemia (31.9%), and creatine phosphokinase increased (27.7%). Grade $\geq$ 3 hematologic toxicities included platelet count decreased (42.6%), neutropenia (25.5%), and anemia (8.5%). Olverembatinib-related SAEs included platelet count decreased (6.4%), anemia, myelosuppression, and pyrexia (2.1% each). Most hematologic TRAEs were manageable with supportive care. Two cardiovascular events (grade 1 hypertension) were possibly treatment-related. No deaths occurred. **Conclusions:** Olverembatinib shows good tolerability and leads to high MMR and CCyR in patients with CP-CML without T315I mutation that is resistant/intolerant to first-line TKIs. Clinical trial information: ChiCTR2200061655. Research Sponsor: None.

6511 **Rapid Oral Abstract Session**

A prospective observational study to compare the efficacy, time toxicity, and cost of conventional 3+7 regimen versus azacitidine + venetoclax (AZA + VEN) as induction therapy in patients with acute myeloid leukemia (AML). First Author: Manju Sengar, Tata Memorial Hospital, Mumbai, India

Background: In low-middle income countries, 3+7 induction therapy for AML is associated with high induction mortality (7-40%), more so in patients with infections at diagnosis. Given the activity of AZA+VEN, a considerable proportion of patients with high-risk features (infections at diagnosis, poor-risk AML, poor performance status, multiple comorbidities, elderly) or long-waiting for admission to start induction are treated with AZA+VEN and 3+7 regimen use is limited to young, fit and good/intermediate risk groups. However, it is important to understand if use of AZA+VEN in this setting provides similar efficacy and is safe without increasing the cost of therapy and time-toxicity as defined by the contact days with healthcare system. Ideally a randomized controlled trial is needed to answer this question, however physicians' unwillingness to randomize patients at high-risk of induction mortality to 3+7 regimen would challenge the feasibility of such trial. **Methods:** A prospective observational study enrolled consecutive de-novo AML patients aged $\geq$18-years after written informed consent who were planned for treatment by a multi-disciplinary joint clinic with either 3+7 or AZA+VEN. The primary endpoint was induction mortality, with secondary endpoints of grade 3/4 toxicity, treatment cost, time toxicity, complete response/complete response rate with incomplete count recovery rates (CR/CRi) assessed after one course. **Results:** 154 participants were included (3+7 -73, AZA+VEN-83). Median age was 35 years in 3+7 as compared to 44 years in Aza-Ven group. The AZA+VEN group was enriched for high-risk features – ECOG PS $\geq$2 (10.9% vs 33.3%), baseline fungal pneumonia (4.1% vs 50%), poor-risk profile as per ELN 2022(12.3% vs 24.7%). The primary reasons for starting AZA+VEN were active infection (65.4%), poor-risk disease (28.4%), delay in admission (16%), and poor performance status (8.6%). Induction mortality was comparable between 3+7 and AZA+VEN (8.2% vs 7.5%). Toxicities were higher with 3+7; febrile neutropenia (95.9% vs 79.7%), new-onset bacterial infections (49.3% vs 19.0%) with multidrug resistant bacterial sepsis (32.9% vs 9.1%), and new-onset fungal pneumonia (27.4% vs 15.2%). The median treatment cost was higher with 3+7 (227,790 INR) compared to AZA+VEN (184,694 INR). Time toxicity (26.0$\pm$0.8 vs 19.0$\pm$0.9 days) and duration of hospitalization (26.0$\pm$0.9 vs 18.0$\pm$2.1 days) were higher in the 3+7. CR/CRi rates were higher with 3+7 (80.6% vs 57.1%), including higher CR (52.2% vs 27.1%) and flow-MRD negativity (71.6% vs 41.9%) driven by the favorable risk profile in this group. **Conclusions:** The study demonstrated that AZA+VEN in patients who are at high-risk of induction mortality provides a valuable alternative with better safety and reduced financial burden and time toxicity. Research Sponsor: None.

6512 Rapid Oral Abstract Session

A randomized phase II study of selinexor added to standard induction and consolidation chemotherapy in adults with acute myeloid leukemia (AML). First Author: Timothy S. Pardee, Comprehensive Cancer Center of Atrium Health Wake Forest Baptist, Winston-Salem, NC

Background: Preclinical and early clinical data suggest that inhibition of nuclear export by the XPOI inhibitor selinexor may enhance chemosensitivity in AML. We conducted a randomized phase II study evaluating the addition of selinexor to standard intensive induction and consolidation chemotherapy. **Methods:** This was an open-label, randomized (3:1) phase II trial in adults with newly diagnosed non-APL, AML. Good risk patients, those with FLT3 mutations or those with an indication for CPX-351 were excluded. Patients were assigned to standard induction with cytarabine and an anthracycline (7+3) followed by high-dose cytarabine (HDAC) consolidation (control arm) or the same regimen with the addition of selinexor (study arm). Selinexor was administered at a fixed dose of 60 mg orally on days 1, 3, 8, 10, 15, and 17 during induction and consolidation cycles. Randomization was not stratified. The primary endpoint was overall survival, analyzed in the intention-to-treat population. Secondary endpoints included overall response rate, complete remission with or without complete count recovery and safety. **Results:** A total of 57 patients were randomized (study arm n = 43; control arm n = 14). The study was discontinued early after results of the PARADIGM study raised concerns regarding the use of intensive chemotherapy in intermediate- and poor-risk AML patients. Baseline characteristics except for gender were generally balanced (Table 1). Median overall survival was 991 days in the study arm compared with 649 days in the control arm (log-rank p = 0.2267). Thirty-day mortality occurred in 5 patients (11.6%) in the study arm and 2 patients (14.3%) in the control arm. The response rate was 77% (33/43) in the study arm and 50% (7/14) in the control arm, corresponding to a risk ratio of 1.53 (95% CI, 1.01–4.57); this difference did not reach statistical significance by Fisher's exact test (p = 0.09). The addition of selinexor was feasible, with early mortality rates consistent with intensive induction therapy and no unexpected safety signals observed. **Conclusions:** In this randomized phase II study, the addition of selinexor to standard induction and consolidation chemotherapy was associated with numerically higher response rates and longer median overall survival compared with chemotherapy alone. Small study size and early termination limit definitive conclusions. However, these findings suggest biological activity of nuclear export inhibition in AML and support further evaluation of selinexor-containing combinations. Clinical trial information: NCT02835222. Research Sponsor: Karyopharm.

Characteristic	Control arm (n = 14)	Study arm (n = 43)
Median age, years (range)	69 (22–75)	65 (24–73)
Female sex, n (%)	11 (78.6%)	17 (39.5%)
ELN 2022 Risk group		
Good	5 (35.7%)	9 (20.9%)
Intermediate	3 (21.4%)	20 (46.5%)
Poor	6 (42.9%)	14 (32.6%)

6513 Rapid Oral Abstract Session

Olverembatinib (HQP1351) combined with blinatumomab in patients with lymphoid blast phase chronic myeloid leukemia (CML-LBP) or Philadelphia chromosome–positive B-cell precursor acute lymphoblastic leukemia (Ph^+ BCP-ALL). First Author: Elias Jabbour, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Olverembatinib, a third-generation BCR::ABL1 TKI, has demonstrated clinical activity in TKI-resistant Ph^+ hematologic malignancies. This study evaluated olverembatinib combined with blinatumomab in patients with relapsed/refractory (R/R) Ph^+ B-cell precursor ALL (BCP-ALL) or CML-LBP outside China. **Methods:** In this phase 1b study (HQP1351CU101; NCT04260022), adults with R/R Ph^+ BCP-ALL or CML-LBP received olverembatinib from 30 mg QOD, with planned escalation to 40 mg QOD, combined with standard-dose blinatumomab in 6-week cycles. Using a 3+3 design, dose-limiting toxicities (DLTs) were assessed during cycle 1. Objectives included evaluation of safety and tolerability, complete response (CR) rate, and minimal residual disease (MRD) negativity rate. MRD was assessed by flow cytometry. **Results:** Between January 2023 and June 2025, 9 patients were enrolled (8 Ph^+ BCP-ALL, 1 CML-LBP). Median age was 47 years (range 32-60); 66.7% were male. Median time from diagnosis to olverembatinib treatment initiation was 2.46 (range 0.5-6.2) years; median leukocyte count 3.5×10^9/L (range 2-171); median prior regimens 4 (range 2-10); and median TKIs 3 (range 1-6). *BCR::ABL1* transcripts were P190 (n = 7), P210 (n = 2); one patient had the T315I mutation. Notably, 6 patients had received prior blinatumomab and relapsed during maintenance or subsequent therapy. The combination demonstrated a manageable safety profile, with most adverse events (AEs) being grade 1-2, consistent with the known toxicities of each agent. Four patients experienced grade 3 AEs related to olverembatinib, including increased lipase, neutropenia, thrombocytopenia, and pancreatitis. In the 30 mg QOD cohort (n = 3), no DLTs occurred. One patient in the 40 mg QOD cohort developed grade 3 pancreatitis (considered treatment related and a DLT) on day 4, which resolved with supportive care and dose reduction to 30 mg without recurrence; this patient achieved CR and MRD negativity by end of cycle 1. With median olverembatinib treatment duration of 15.7 weeks (range 1.4-37.1), 4 patients discontinued because of disease progression (n = 1) or bridge to CAR-T/transplantation (n = 3). Among 9 enrolled patients, 5 had positive MRD at study entry without CR. In this subgroup, 4 achieved CR and 2 achieved MRD negativity. One patient died due to disease progression, assessed as unrelated to study treatment. **Conclusions:** Olverembatinib combined with blinatumomab shows promising clinical activity in patients with R/R Ph^+ BCP-ALL or CML-LBP outside China, with encouraging response rates and MRD clearance. The regimen was generally well tolerated, with a safety profile consistent with individual agent toxicities. These findings support further investigation of this chemotherapy-free approach. Clinical trial information: NCT04260022. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

6514 Rapid Oral Abstract Session

Updated results of the chemotherapy-free regimen of blinatumomab and ponatinib in patients with newly diagnosed Philadelphia-positive B-cell acute lymphoblastic leukemia. First Author: Lewis Fady Nasr, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Chemotherapy-free regimens incorporating blinatumomab (blina) and ponatinib have demonstrated promising activity in frontline Philadelphia-positive (Ph+) B-cell acute lymphoblastic leukemia (B-ALL). We report the long-term outcomes from an ongoing, phase II study of blina with ponatinib in adults with newly diagnosed (ND) Ph+ B-ALL. **Methods:** Patients (pts) ≥18 yrs with Ph+ B-ALL received up to 5 simultaneous cycles of blina with ponatinib 30 mg daily, reduced to 15 mg daily upon complete molecular response (CMR). Pts continued ponatinib for at least 5 yrs. IT chemo was increased from 12 to 15 with pt #64 to reduce the risk of central nervous system (CNS) relapse. Protocol was amended to add 2 cycles of high-dose methotrexate (MTX) and cytarabine for pts with WBC $>70x10^9$/L. **Results:** As of January 2025, 88 pts were enrolled (median age of 50 yrs [range, 18-83]; 19%>70 yrs). Median baseline WBC was 15.2 $x10^9$/L (0.6-322). 78% of pts had *BCR::ABL1* p190 transcripts, 20% had p210. 25 out of 48 pts (52%) with SNP array testing had *IKZF1+* genotype. The objective response rate was 96%, with a complete remission (CR) rate of 95%. Measurable residual disease (MRD)-negativity by next-generation sequencing (NGS) was achieved in 95% of evaluable pts; 43% after 1 cycle. CMR rates by RT-PCR was 83%, 67% after 1 cycle. Median follow-up was 3 yrs. 70 pts (79%) remain in molecular remission without allogeneic stem cell transplant (SCT). Of these, 1 received inotuzumab for MRD-positivity and 1 received CAR T-cell therapy. 2 pts (2%) went to SCT in CR1 due to persistent positive p190 transcripts; neither pt had NGS-MRD available. 11 pts (12%) relapsed (10 with p190 transcripts) after a median of 20 months (8-33) from CR: 5 were bone marrow only, 5 CNS only, and 1 extramedullary only; 7/11 relapsed pts (64%) had baseline WBC$>70x10^9$/L. Three of the 11 relapsed pts died. There were 2 early deaths, and 3 pts died in CR. Since increasing IT chemo to 15, there has been 1 CNS relapse. 3 pts received 2 cycles of high-dose MTX and cytarabine for WBC$>70x10^9$/L; none have relapsed. Median event-free survival (EFS) and overall (OS) have not yet been reached; 3-yr EFS and OS rates are 79% and 89%, respectively. Outcomes did not differ significantly by transcript type nor by NGS MRD clearance after C1. For pts with WBC$\geq70x10^9$/L vs. WBC$<70x10^9$/L, the 3-yr cumulative incidence of relapse (CIR) was 31% vs. 6.7% (p=0.005). The CIR for *IKZF1+* vs non-*IKZF1+* was 16% vs. 21% (p=0.6). **Conclusions:** Frontline blina with ponatinib induced deep, durable remission in Ph+ B-ALL, allowing most patients to avoid SCT. Relapses are seen with high presenting WBC, supporting the use of baseline-risk intensified strategies, including increased IT chemo, incorporation of high-dose chemo into consolidation, as well as CAR T-cell therapy. Clinical trial information: NCT03263572. Research Sponsor: Amgen; Takeda Oncology.

6515 Rapid Oral Abstract Session

Long-term outcomes with addition of inotuzumab ozogamicin to HCVAD and sequential blinatumomab in adults with newly diagnosed B-ALL. First Author: Lewis Fady Nasr, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite high remission rates with intensive chemotherapy and blinatumomab (blina) in newly diagnosed (ND) Philadelphia-negative (Ph-) B-ALL, relapse remains a major cause of treatment failure. Inotuzumab ozogamicin (InO) demonstrates efficacy in the relapsed setting and may improve outcomes in frontline. We report long-term results with 4.5 years of follow-up from the phase II study of HCVAD plus blina +/- InO for adults with ND Ph- B-ALL. **Methods:** Patients (pts) 18-59 years (yrs) with ND Ph- B-ALL received HCVAD alternating with high-dose methotrexate (MTX) and cytarabine (Ara-C) for up to 4 cycles, followed by 4 cycles of blina. Blina was initiated after 2 cycles of HCVAD for pts with high-risk features or persistent measurable residual disease (MRD) by multiparameter flow cytometry (FC). Starting with pt #39, InO was administered during the 2 MTX/Ara-C cycles and 2 blina cycles. Pts received 15 maintenance cycles with POMP and blina after every third cycle. Pts received 12 IT chemotherapies. **Results:** As of January 2025, 75 pts were treated (38 without InO [cohort 1] and 37 with InO [cohort 2]). The median age was 33 yrs (range, 18–59); 37 for cohort 1 (18-59) and 25 (18-57) for cohort 2 (p=0.01). All other characteristics were similar. All pts (100%) achieved complete remission (CR). MRD-negativity by FC was achieved in 95% of pts at any time (66% at CR): 97% (76%) in cohort 1 and 94% (56%) in cohort 2. By next generation sequencing (NGS), 76% achieved MRD-negativity (26% at CR): 50% in cohort 1 and 79% in cohort 2. There were no early deaths. The median follow-up for cohorts 1 and 2 was 76 months (28-109) and 47 months (31-61), respectively. Of the 38 pts in cohort 1, 14 (37%) proceeded to allogeneic stem cell transplantation (SCT); of these, 11 (79%) remain alive in CR, 1 (7%) died in CR and 2 relapsed, 1 of which died. A total of 24 pts (63%) did not proceed to SCT; of these, 16 (67%) remain alive in CR, 3 (13%) died in CR, and 5 (20%) relapsed, 4 of which died. Of the 37 pts in cohort 2, 10 (27%) proceed to SCT; all alive in CR. A total of 27 pts (65%) did not proceed to SCT; 24 (89%) remain alive in CR (1 pt received CAR T-cell) and 3 (11%) relapsed, all of them alive in CR2). Median OS and event-free survival (EFS) have not been reached for either cohort. 4-year OS rates for the entire cohort, cohort 1 and cohort 2 are 91%, 82% and 100% (p=0.007), respectively, with 4-year EFS rates of 83%, 74%, and 91% (p=0.034), respectively. At 24 months, CIR was with InO vs without InO (8.1% vs 18.4%; p = 0.18). No deaths were observed in the InO group, whereas pts without InO had a 24-month cumulative incidence of death of 7.9% (p = 0.08). **Conclusions:** Incorporation of InO into frontline HCVAD with sequential blina is associated with improved survival and durable remission in adults with ND Ph- B-ALL, supporting its role in the frontline setting. Confirmatory randomized trial comparing HCVAD-blina to HCVAD-blina-Ino is ongoing. Clinical trial information: NCI-2017-00596. Research Sponsor: Amgen; Pfizer.

6516 Rapid Oral Abstract Session

The impact of MRD and post-remission strategies on outcomes following dose-dense mini-hyper-CVD inotuzumab and blinatumomab in relapsed B-cell acute lymphoblastic leukemia. First Author: Maria Hachem, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Advances in immunotherapy have improved outcomes for relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL). However, the optimal sequence of immunotherapies remains undefined, particularly the role of chimeric antigen receptor (CAR) T-cell therapy in the era of sensitive assessment of measurable residual disease (MRD). Here, we provide an update of the phase II trial the dose dense mini-CVD with inotuzumab ozogamicin (InO) and blinatumomab (blina) regimen in R/R B-ALL. **Methods:** Adults (>18 years) with R/R Philadelphia (Ph) positive (+) or negative (-) B-ALL were treated with dose-dense mini-hyper-CVD with InO and blina. Cycles 1, 3, 5 consisted of mini-hyper-CVD, InO and blina; cycles 2, 4, 6 consisted of mini-methotrexate and ara-C, InO, and blina with Peg-G-CSF administered after each course. Patients (Pts) received 12 IT chemotherapy administrations and rituximab if CD20 positive. Pts with Ph+ ALL received a concomitant BCR::ABL1 tyrosine kinase inhibitor. MRD was assessed by flow cytometry (FC) and next-generation sequencing (NGS). **Results:** Between September 2021 and January 2026, 27 pts were enrolled (median age 42 years; range, 19–63). Three pts (11%) had Ph+ ALL, and among Ph- pts, 30% had Ph-like disease. Five pts (19%) had adverse risk cytogenetics and (24%) had a *TP53* mutation. Twenty-four pts (89%) were in salvage 1. Three pts (11%) had previously undergone allogeneic stem cell transplant (SCT) and 9 (33%) had received blina. All pts achieved complete remission (CR) or CR with incomplete count recovery (CRi), including 22 (81%) CR. MRD negativity was achieved in 96% of pts by FCM and 95% by NGS; 80% and 44% achieved FCM and NGS MRD negativity, respectively, after the first cycle. With a median follow-up of 32 months, 11 pts (41%) proceeded to CAR T-cell consolidation, 5 (18%) to SCT, and 11 (41%) received no further consolidation. Among CAR T recipients, 70% were NGS MRD-negative prior to lymphodepletion. Post CAR T-cells infusion, 10/11 (91%) pts achieved/maintained NGS MRD negativity, while 1 (9%) pt had MRD below level of detection at last follow-up. The 2-year overall survival (OS) and event-free survival (EFS) rates for the entire cohort were 68% and 79%, respectively. The 2-year EFS rates for pts receiving CAR T-cell, ASCT, or no further consolidation were 81%, 80% and 50%, respectively, while the corresponding 2-year OS rates were 89%, 100%, and 55%. **Conclusions:** Dose-dense mini hyper-CVD combined with InO and blina induces high rates of deep NGS-MRD negative remission in patients with R/R B-ALL, allowing for consolidative strategies including CAR T-cell therapy, leading to favorable survival outcomes at a follow-up of almost 3 years. Clinical trial information: NCT01371630. Research Sponsor: Amgen.

6517 Rapid Oral Abstract Session

The effect of obecabtagene autoleucel (obe-cel) on adult patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) and extramedullary disease (EMD). First Author: Jae Hong Park, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pts with R/R B-ALL and EMD have limited treatment options and are a population with an unmet need. Obe-cel is an autologous chimeric antigen receptor (CAR) T-cell therapy with a fast off-rate CAT19 binding domain and a 4-1BB-ζ co-stimulatory domain designed to improve persistence and reduce severe immunotoxicity. Here, we report a post-hoc analysis of the Phase Ib/II FELIX study (NCT04404660), evaluating efficacy and safety of obe-cel in pts with R/R B-ALL, by EMD status at lymphodepletion (LD). **Methods:** Following LD, adults with R/R B-ALL received obe-cel using a tumor burden-guided dosing strategy to minimize toxicity. Overall remission rate (ORR; complete remission [CR]/CR with incomplete hematologic recovery [CRi]), event-free survival (EFS), overall survival (OS), and safety are reported for pts with or without (w/o) EMD. **Results:** Of 127 obe-cel infused pts, 27 (21%) had EMD at LD and 100 (79%) did not. At screening, the median age (range) was 36.0 years (20–73) in pts with EMD, and 50.5 years (20–81) in pts w/o EMD. Of the pts with EMD, 13 (48%) were male and 11 (41%) were Hispanic or Latino; of those w/o EMD, 53 (53%) were male and 27 (27%) were Hispanic or Latino. The median number of prior lines of therapy (range) was 3.0 (1–6) and 2.0 (1–6) for pts with and w/o EMD at LD, respectively; prior SCT was received by 12 (44%) and 44 (44%) pts, respectively. At LD, the median bone marrow (BM) blast percentage (range) was 54% (0–100) in pts with EMD and 39% (0–100) in pts w/o EMD; Philadelphia chromosome-positive disease was observed in 6 (22%) and 30 (30%) pts, respectively. At 32.8 months' (mos) median follow-up (range 20–53), the ORR (95% confidence interval [CI]) was 59% (39–78) in pts with EMD and 83% (74–90) in pts w/o EMD. Median DoR (95% CI) among responders was 42.5 mos (3.4–not evaluable [NE]) and NE, in those with (n=16) and w/o (n=83) EMD at LD, respectively. Overall, median EFS (95% CI) was 4.5 mos (0.0–NE) and 14.3 mos (9.0–NE) in pts with and w/o EMD at LD, respectively; however, median EFS appeared to be comparable in responders with (44.6 mos [6.0–NE]) and w/o EMD (NE). Overall, median OS (95% CI) was 15.3 mos (7.9–NE) and 21.0 mos (13.2–NE) in pts with and w/o EMD at LD, respectively. The incidence of Grade ≥3 cytokine release syndrome in pts with and those w/o EMD was 3.7% and 2.0%; the incidence of Grade ≥3 immune effector cell-associated neurotoxicity syndrome was 19% and 4.0%, respectively. Cerebrospinal fluid pharmacokinetic analyses are underway; data will be presented. **Conclusions:** Obe-cel treatment demonstrated favorable efficacy and safety outcomes in pts with and w/o EMD in the FELIX trial. Among responders, DoR in pts with EMD was comparable with that observed in pts w/o EMD. Overall, these findings support a positive benefit–risk profile for obe-cel, irrespective of EMD status at LD. Clinical trial information: NCT04404660. Research Sponsor: Funding: Autolus Therapeutics PLC. Third-party medical writing assistance, under the direction of the authors, was provided by Emily Fang, MPharm, of Ashfield MedComms, an Inizio company, and was funded by Autolus Therapeutics PLC.

6518 Poster Session

Early G-CSF after venetoclax-based induction for acute myeloid leukemia: Multicenter associations with infections, neutrophil recovery, and early mortality. First Author: Randa Elzein, Upstate Medical University, Syracuse, NY

Background: Venetoclax-based induction has improved remission rates in acute myeloid leukemia (AML) but is associated with prolonged neutropenia and infectious mortality. Optimal G-CSF timing remains uncertain. **Methods:** Multicenter real-world cohort (2018–2025) using TriNetX data across 21 U.S. institutions. Adults with newly diagnosed AML treated with venetoclax + hypomethylating agent or low-dose cytarabine were included. Early G-CSF was defined as initiation ≤ day 7 of cycle 1; deferred/none = > day 7 or none. The primary endpoint was grade ≥ 3 infection through day 42 (death as a competing risk, Fine–Gray models). Secondary endpoints: febrile neutropenia (FN), time to ANC ≥ 1.0 × 10^9/L, ICU admission ≤ day 42, 60-day mortality, CR/CRi by day 60, and overall survival (OS). Multivariable models adjusted for age, ECOG, ELN risk, cytogenetics, baseline ANC/WBC, TP53/IDH/NPM1 mutations, antibacterial prophylaxis, and center effects. **Results:** N = 2,934; median age = 69 y (range 34–87). Early G-CSF = 39 %, deferred/none = 61 %. Early G-CSF lowered grade ≥ 3 infections (sHR 0.61 [95 % CI 0.49–0.76], p < 0.001) and shortened ANC recovery (Δ −3.2 days [−4.6 to −1.9], p < 0.001). FN risk was similar (aOR 0.94 [0.79–1.12], p = 0.49). CR/CRi by day 60 (aOR 1.06 [0.90–1.25], p = 0.47), OS (aHR 0.97 [0.85–1.11], p = 0.65), and 60-day mortality (aOR 0.92 [0.73–1.16], p = 0.49) were comparable. Findings persisted in age ≥ 75 and ELN-adverse subsets and remained robust after inverse-probability weighting and landmark analyses. **Conclusions:** Early (≤ day 7) G-CSF after venetoclax-based AML induction reduced severe infections and accelerated neutrophil recovery without affecting remission or survival. Results support standardized early G-CSF use to improve supportive-care safety, especially for older or high-risk patients. Research Sponsor: None.

Early G-CSF timing and clinical outcomes after venetoclax-based AML induction.

Outcome	Deferred/ None	Early G-CSF	Adjusted effect (95 % CI)	P value
Grade ≥3 infection ≤ day 42, %	31.4	21.2	sHR 0.61 (0.49–0.76)	<0.001
Time to ANC ≥1.0 (days, median)	11.8	8.6	Δ −3.2 (−4.6 to −1.9)	<0.001
Febrile neutropenia, %	38.9	37.4	aOR 0.94 (0.79–1.12)	0.49
ICU admission ≤ day 42, %	14.6	11.9	aOR 0.80 (0.65–0.99)	0.04
60-day mortality, %	10.1	9.3	aOR 0.92 (0.73–1.16)	0.49
CR/CRi by day 60, %	63.8	64.9	aOR 1.06 (0.90–1.25)	0.47

Abbreviations: sHR = sub-hazard ratio; aOR = adjusted odds ratio; aHR = adjusted hazard ratio; Δ = difference in medians. All models adjusted for baseline covariates (age, ELN risk, ECOG, cytogenetics, molecular subtype, prophylaxis use) and center effects.

6519 Poster Session

Molecular landscape and outcomes of Black and White adults diagnosed with acute myeloid leukemia. First Author: Eno-obong Blessing Udoh, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Background: Acute myeloid leukemia (AML) is characterized by poor survival with Black patients (pts) experiencing worse outcomes compared to White pts. While patient-specific factors such as race have emerged as important predictors for survival in AML, the biologic mechanisms driving these factors are not well characterized. Here, we analyzed the molecular profiles of adults diagnosed with AML to identify potential differences in the frequency of genes commonly mutated in AML and their impact on survival. **Methods:** This was a retrospective cohort study of adults diagnosed with AML at the Cleveland Clinic between 2008 and 2022. Patients were identified as Black or White based on self-reported race/ethnicity. Molecular data were obtained from next-generation sequencing (NGS) performed at the time of diagnosis. Survival analysis was limited to pts receiving intensive induction chemotherapy and estimated using the Kaplan-Meier method and compared with the log-rank test. **Results:** 1,144 pts were included in this study: 10% (n = 115) Black and 90% (n = 1029) White. Median age at diagnosis (years) was lower in Black pts compared to White pts (62 vs 66) (p = 0.005). Cytogenetics analysis (MRC 2010) showed a higher proportion of Black pts with favorable-risk disease compared to White pts (15% vs. 8%; p = 0.04) while rates of poor-risk cytogenetics were similar (31% vs. 30%). Mutations in *IDH1*, *CBL*, *CEBPA*, and *NOTCH1* were more common in Black pts than in White pts (p < 0.05). Conversely, mutations in *NPM1* were lower in Black pts (16%) vs. White pts (24%) (p = 0.22). We did not observe a difference in the type of induction chemotherapy received (p = 0.23). However, more White pts underwent hematopoietic cell transplant (HCT) compared to Black pts (32% vs. 21%; p = 0.02). The median overall survival (OS) for the whole cohort was 18 months (95% CI: 16-21 months) with a 5-year OS of 31% (95% CI: 27-34%); median follow up time of 63 months. Univariable analysis showed that worse overall survival was associated with older age, poor risk cytogenetics, therapy-related and secondary AML, and not undergoing HCT (p < 0.05), but median OS and 5-year OS rates were similar between Black and White pts (24 months, 28% vs. 17 months, 31%). After adjusting for prognostic variables, age, HCT status and cytogenetic risk remained significant (p < 0.05). **Conclusions:** Unlike previously reported studies, we did not observe a survival disparity in race in our study cohort. However, we observed lower rates of treatment with HCT in Black pts. We also identified a higher frequency of mutations in genes involved in myeloid transcriptional regulation, epigenetic modification, and cellular signaling. Adequate assessment of the prognostic relevance of these genes is limited by a small sample size and variability in NGS platforms over time. Future studies may explore pooled genetic data across several institutions and genetic ancestry testing over self-reported race/ethnicity. Research Sponsor: None.

6520 Poster Session

The association of *IDH* co-mutations with treatment outcomes and overall survival in *TP53*-mutated acute myeloid leukemia. First Author: Lukas Ronner, Abramson Cancer Center of the Hospital of the University of Pennsylvania, Philadelphia, PA

Background: In acute myeloid leukemia (AML), *TP53* mutations confer a dismal prognosis, with a median survival of ~6 months. While characteristics of *TP53* aberrancy (multi-hit status) define an even more aggressive subset, little is known about the effect of *IDH* co-mutations on outcomes. An analysis of the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND) cohort suggests that *TP53*+/*IDH*+ subjects (n = 24) have prolonged survival compared to *TP53*+/*IDH*wt, a finding that could inform our treatment approach in these patients. We therefore aimed to validate this finding in a larger cohort within the Flatiron Health Research Database. **Methods:** Patients over 18 years with *TP53*+ AML and *IDH1* or *2* testing at diagnosis were selected within Flatiron Health. Demographics, cytogenetic/molecular testing, and treatments were compared using standardized mean difference (SMD), with SMD $>$ 0.2 indicating meaningful difference. Cox proportional hazards models controlling for age, sex, socioeconomic status, ECOG, multi-hit *TP53*, secondary AML, and induction strategy were built to test the association of *IDH* co-mutations with Event Free Survival (EFS) and overall survival (OS). Sensitivity analyses considering receipt of an *IDH* inhibitor (*IDH*i) and stem cell transplant (SCT) as time-varying covariates were also constructed. Finally, two subgroup analyses in the *IDH*+ subcohort were performed to test associations between 1) *IDH*i in first line, and 2) hypomethylating agent/venetoclax (HMA/ven) in first line, and EFS and OS. **Results:** 753 *TP53*+ AML subjects with *IDH* testing at diagnosis were included. There were meaningful differences in the cytogenetic/mutational landscape of the *IDH*wt (n = 659) and *IDH*+ (n = 94) cohorts, the latter with a lower incidence of multi-hit *TP53* and myelodysplasia-related changes, and a higher incidence of ASXL1, DNMT3A, and TET2 co-mutations. In multivariable modeling, *IDH* co-mutations were not independently associated with EFS, though were strongly associated with improved overall survival (mOS 9.8 vs 6.1 months, HR 0.69, CI 0.52 – 0.92, p = 0.01). These associations persisted in sensitivity analyses treating *IDH*i and SCT as time-varying covariates. In analyses of the *IDH*+ subcohort, receipt of *IDH*i or HMA/ven during first line did not associate with improved OS or EFS. **Conclusions:** In these data, *IDH* co-mutations are associated with improved OS in *TP53*+ AML, though there was no signal suggesting this was driven by choice of therapy. Our analysis is limited by its retrospective nature and a definition of "multi-hit" status that relied on concomitant presence of del17 and a *TP53* point mutation. Though these results require further validation, they may currently inform the clinical approach to *TP53*+/*IDH*+ AML by framing goals-of-care conversations. However, more work is needed to characterize the effect of treatment selection on outcomes in this population. Research Sponsor: None.

6521 Poster Session

A targeted phosphoproteomic assay to enable the prediction of response to intensive chemotherapy in acute myeloid leukemia. First Author: Gabriel Ghiaur, Johns Hopkins Medical Institutions, Baltimore, MD

Background: Intensive chemotherapy (IC; cytarabine plus an anthracycline) remains a standard first-line therapy for fit patients with acute myeloid leukemia (AML), a heterogeneous hematologic malignancy with poor long-term survival. IC induces composite complete remission (cCR) in ~60–70% of cases, and IC response variability persists within genetic/ELN risk strata. As emerging regimens increasingly challenge IC as a default therapy, biology-informed predictors are needed to identify patients unlikely to benefit from IC to avoid unnecessary toxicity. Mass spectrometry (MS)-based phosphoproteomics enables quantitative profiling of phosphopeptides (PPs) from patient samples, providing a functional readout of tumor biology. Thus, we sought to develop a PP-based clinically-deployable assay, orthogonal to genetic risk stratification, to predict response to IC in AML. **Methods:** 261 retrospective samples were collected from patients with newly-diagnosed AML (Table) treated with standard "7+3" IC in 9 centers in Europe, Australia, and North America. Response was assessed at the end of induction by the treating physician. Samples underwent phosphoproteomics using: 1) global MS for biomarker discovery or 2) targeted, clinically-compatible MS for validation. Predictive model performance was evaluated using rebalanced leave-one-out cross-validation. **Results:** During discovery, 3205 PPs were detected. Using Bayesian approaches, we identified an 80-PP multi-analyte signature of IC response (refractory vs cCR), and achieved an AUROC of 0.68 (95% CI 0.54-0.83). The signature was enriched for DNA damage signalling and repair (DNA-PK-S2612, ATM/cohesin, nucleotide excision and double-strand break repair proteins), and cellular stress pathways (phospho-p38, IL-16, AP-1/c-Jun). In an independent validation cohort, the targeted assay reliably detected the biomarker set and preserved its association with outcome (AUROC 0.69; 95% CI 0.53-0.84). Biomarker-based classification was associated with improved event-free survival (HR 0.45; 95% CI 0.26-0.78). **Conclusions:** We identified and validated a signature of response to IC in AML, and translated it into a targeted, clinically-deployable assay. This approach captures signaling states relevant to IC mechanisms of action that are not directly inferred from standard clinical or genetic variables. Ongoing analyses are evaluating its relationship to established genetic and ELN risk stratification. These findings support diagnostic phosphoproteomics and suggest functional biomarkers may complement existing approaches for treatment selection in AML. Research Sponsor: Innovate UK; Application number: 10054602.

Cohort characteristics.

Cohort	Discovery	Validation
Median age at diagnosis (years, quartiles)	54 (23, 65)	59 (47, 68)
Median diagnosis year (range)	2014 (1999, 2023)	2013 (2001, 2024)
No of patients/samples	135/165	102/106
No of cCR/Refractory	94/41	79/23
PPs	3205	80

6522 Poster Session

Investigation of the role of IFITM3 and the PI3K/Akt axis in the acute myeloid leukemia tumor microenvironment. First Author: Fang Zhou, Department of Hematology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China

Background: Interferon-induced transmembrane protein 3 (IFITM3) is overexpressed in acute myeloid leukemia (AML) and is associated with poor prognosis. Previous studies have implicated IFITM3 in oncogenic processes and immune modulation; however, the mechanisms through which IFITM3 contributes to leukemogenesis and shapes the immune microenvironment in AML remain unclear. **Methods:** The clinical and immunological significance of IFITM3 in AML was analyzed using scRNA-seq and bulk transcriptomic datasets. IFITM3-knockdown Kasumi-1 and ME-1 cells were established to evaluate their impact on cell proliferation and cycle progression via MTT and flow cytometry. A Transwell co-culture system was employed to assess AML-induced M0 macrophage polarization, quantified by surface markers (CD80/CD163) and cytokine profiling (ELISA/qRT-PCR). Mechanistically, GSEA were performed to identify downstream pathways, followed by Western blot validation. The functional role of the PI3K/Akt axis was further verified using the specific inhibitor LY294002. **Results:** Our results revealed for the first time that IFITM3high AML cell lines polarize M0 macrophages into an M2-like phenotype. Knockdown of IFITM3 led to a significant reduction of the M2 marker CD163, accompanied by an increase of the M1 marker CD80. In parallel, IFITM3-deficient AML cells exhibited decreased M2-associated gene expression and diminished secretion of TGF-β and IL-10, together with lower viability and G0/G1 cell-cycle arrest. Molecular mechanism studies revealed that loss of IFITM3 markedly reduced Akt and p-Akt protein levels. Crucially, pharmacological inhibition of the PI3K/Akt pathway using a PI3K inhibitor rescued the IFITM3-mediated effects, suppressing AML cell proliferation and M2 macrophage polarization. Clinically, we extended the adverse prognostic effect of IFITM3 to AML patients with intermediate molecular risk. **Conclusions:** These findings provide comprehensive evidence that IFITM3 promotes leukemic cell proliferation and contributes to a tumor-supportive AML microenvironment by driving M2 macrophage polarization via the PI3K/Akt signaling axis. These results highlight IFITM3 as a promising therapeutic target and suggest that PI3K inhibitors may offer a precision medicine approach for AML patients with elevated IFITM3 expression. Research Sponsor: None.

6523 Poster Session

Association of acute myeloid leukemia (AML) patient, disease, and molecular characteristics with a long-term (LT) response to olutasidenib. First Author: Justin M. Watts, Division of Hematology, Department of Medicine, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Mutations in isocitrate dehydrogenase 1 (m*IDH1*) occur in 7%-14% of patients with AML. Olutasidenib is a potent, oral small-molecule mIDH1 inhibitor that selectively inhibits IDH1 variants but preserves wild-type IDH1 function. The registrational phase 2 trial (NCT02719574) of olutasidenib in patients with relapsed/refractory (R/R) m*IDH1* AML reported a complete remission (CR)/CR with partial hematologic recovery (CRh) rate of 35% and a median CR/CRh duration of 25.3 mo. This analysis examines patient, disease, and molecular characteristics of patients with a LT CR/CRh response to olutasidenib without transplant. **Methods:** Adults with R/R m*IDH1* AML treated with olutasidenib 150 mg twice daily who had a CR/CRh and a duration of response (DOR) $>$12 mo were included. Overall survival (OS), DOR, event-free survival (EFS), and adverse events (AEs) were assessed. Univariate and multivariate logistic regression analyses were used to examine baseline factors that predicted DOR $>$12 vs $\leq$12 mo. **Results:** Of 147 evaluable patients, 51 (35%) achieved a CR/CRh; of these, 32 (63%) maintained a CR/CRh $>$12 mo. Excluding 6 patients who proceeded to transplant, 26 (51%) had a DOR $>$12 mo (Table). Among these patients at baseline, median age was 72 y; 69% were female; 73% had an R132C mutation; 12% had prior venetoclax; 88% were platelet transfusion independent (TI); 73% were red blood cell (RBC) TI. Patients had a median (range) of 2 (0, 5) comutations, most commonly *DNMT3A* (n=6) or *NPM1* (n=5); 2 patients with *NPM1* also had *FLT3* mutations. Median (95% CI) time to response was 1.9 (1.0, 1.9) mo. Median OS and EFS were not reached. Estimated 48-mo OS was 74% (95% CI: 51%, 88%). Estimated 48-mo EFS was 69% (95% CI: 47%, 83%). 5 (19%) patients relapsed (including 1 after 24 mo); 10 (38%) patients were on treatment at data lock. Significant predictors of response $>$12 vs $\leq$12 mo by multivariate analysis were relapsed AML vs refractory AML (odds ratio [OR]: 0.19) and female sex (OR: 0.21). Age, number of comutations, m*IDH1* variant, RTK pathway mutations, number of prior therapies, and baseline TI were not significant predictors. Common AEs were nausea (35%), increased ALT, asthenia, constipation, and cough (31% each). Common grade $\geq$3 AEs were increased ALT, gamma glutamyltransferase increased (19% each), and RBC count decreased (15%). 9 (35%) patients experienced grade $\geq$3 all-cause AEs after 12 mo (only 1 AE in $>$1 patient [Coronavirus infection]). **Conclusions:** Olutasidenib enabled LT CR/CRh in half of R/R m*IDH1* AML patients with CR/CRh without transplant (longest response $>$54 mo). Multivariate analysis identified relapsed (vs refractory) AML and female sex but not baseline TI or molecular factors as a significant predictor of LT response with olutasidenib. Clinical trial information: NCT02719574. Research Sponsor: Rigel Pharmaceuticals, Inc.

Patients with LT response.

DOR Group	Patients, n (%)
>12 mo	26 (100)
>24 mo	19 (73)
>36 mo	15 (58)
>48 mo	5 (19)

6524 Poster Session

Comparing induction strategies in acute myeloid leukemia: 10-year real-world experience with 7+3 and HMA/venetoclax. First Author: Chandra Kakarala, University of Kentucky, Lexington, KY

Background: Hypomethylating agents (HMA) combined with venetoclax are the standard of care for AML in adults ineligible for intensive chemotherapy, but use is expanding to fit patients given prospective data suggesting comparable outcomes. Whether these findings are reproducible in real-world practice remains under investigation. **Methods:** We conducted a retrospective cohort study of adults with newly diagnosed AML treated at the University of Kentucky from 2016-2025 with either 7+3 or HMA/venetoclax. Overlap propensity score weighting balanced age, sex, ECOG, ELN risk group, prior MDS, and therapy-related AML. Primary endpoints were CR/CRi, RFS, OS, and 30-day mortality. Cox models included allogeneic HSCT as a time-varying covariate. Survival outcomes were stratified by ELN risk group and mutational risk group according to venetoclax sensitivity (favorable: *NPM1* and *IDH1/2*, adverse: *TP53* and *FLT3*). **Results:** Prior to weighting, patients treated with HMA/venetoclax were older (68 vs. 50 years), had worse performance status (mean ECOG 1.2 vs. 0.7), and were more likely to have prior MDS, therapy-related AML, and less favorable ELN risk. Unweighted data demonstrated a median OS of 13.3 months for HMA/venetoclax and 19.6 months for 7+3. After overlap weighting of 379 patients (250 received 7+3 and 129 received HMA/venetoclax), acceptable covariate balance was achieved with all standardized differences < 0.01. HMA/venetoclax was associated with numerically higher odds of achieving CR/CRi compared with 7+3 (OR 1.84, p=0.09), and this reached significance in adverse-risk disease (OR 2.31, p=0.006). 30-day mortality was similar between 7+3 and HMA/venetoclax groups (8.3% vs. 8.0%, p=0.96). Among patients who achieved CR/CRi, no significant difference in relapse was noted (p=0.24). RFS and OS did not differ significantly between treatment groups (p=0.76 and 0.18, respectively). Analysis of ELN risk subgroups and mutation subgroups incorporating venetoclax sensitivity demonstrated no association with treatment group in survival outcomes (for OS, p=0.53 and 0.43, respectively), suggesting no effect modification from these variables. Allogeneic HSCT was strongly associated with improved OS (HR 0.26, $p<0.001$), which persisted after adjusting for ELN risk (HR 0.39, $p<0.001$) and mutational subgroups (HR 0.44, p=0.001). Across all models, treatment assignment did not significantly impact OS once transplant was modeled as a time-dependent variable. **Conclusions:** After accounting for baseline confounding and allogeneic HSCT as a time-varying covariate, survival in AML is primarily driven by molecular risk profile and transplant rather than initial induction strategy. These results support further investigation of HMA/venetoclax as a frontline alternative in fit patients with AML and the intention to proceed to transplant. Research Sponsor: None.

6525 Poster Session

HMA plus venetoclax for 7- vs 14- vs 21- vs 28-day cycles in newly-diagnosed acute myeloid leukemia: ELN- and Mayo Genetic Risk–stratified analysis in 540 patients. First Author: Sudhesh Kumar, Division of Hematology, Mayo Clinic Rochester, Rochester, MN

Background: Venetoclax plus hypomethylating agent (Ven-HMA) is the standard treatment for unfit patients with newly diagnosed acute myeloid leukemia (ND-AML), with Ven typically administered for 28 days (d) per cycle *(DiNardo NEJM 2020)*. However, the optimal duration of Ven across risk groups remains unclear. We examined survival outcomes with Ven 7, 14, 21, and 28d in ND-AML, in the context of European LeukemiaNet (ELN) and Mayo Genetic risk models. **Methods:** ND-AML patients receiving Ven-HMA at the Mayo Clinic were retrospectively studied. Patients were stratified by ELN 2024 *(Döhner Blood 2024)* and Mayo Genetic risk *(Gangat Am J Hematol 2025)*, and analyzed using standard statistical methods. **Results:** 540 patients (median age 75 years, 52% *de novo)* received HMA with Ven for 7d (*n*=33), 14d (*n*=117), 21d (*n*=96), or 28d (*n*=294). ELN and Mayo risk distributions were 22%/35% high, 18%/56% intermediate, 60%/9% low risk, respectively. Baseline characteristics were comparable. CR/CRi rates were comparable across Ven durations, with the exception of lower CR/CRi with 7d vs 21d (p=0.04). Risk-stratified CR/CRi showed variations across Mayo and ELN groups but without significant differences based on Ven duration (Table). Allogeneic transplant rates were 15%, 18%, 18%, 20% for 7, 14, 21, 28d (p=0.86). At a median followup of 37.7 months, median overall survival (OS) differed by ELN risk (6.6, 11.9, 20 months) and Mayo genetic risk (7.8, 17.4 months, not reached (NR)), for high, intermediate, low risk ($p<0.01$), respectively. Median OS was comparable across Ven 7, 14, 21, 28 d (13, 13, 17, 14 months; p=0.84), with corresponding 1/3/5-year survival rates (Table). 30/60d mortality differed by Ven duration; 7d 10%/20%, 14d 7%/15%, 21d 4%/13%, 28d 4%/6%. Compared with 28d, 30d mortality was higher with 7d and 14d (p=0.07/0.03), and 60d mortality was higher with 7d, 14d, and 21d (p=0.02/0.01/0.05). OS was comparable across Ven durations within ELN intermediate/low risk and all Mayo risk groups, except among ELN high risk, patients receiving 14d Ven had inferior OS compared with 21d and 28d ($p<0.01$). Cumulative incidence of relapse at 1 year was similar among patients receiving 14, 21, 28d Ven (16%, 18%, 18%;$p>0.1$). **Conclusions:** Survival outcomes were comparable across Ven 7, 14, 21, 28 d in ND-AML, with outcomes driven by Mayo Genetic and ELN risk. Despite differences by Ven duration in high-risk groups, higher early mortality with 7d and 14d likely reflects treatment selection. Prospective trials are needed to establish risk adapted Ven dosing strategies. Research Sponsor: None.

			7 (N=33)	14 (N=117)	21 (N=96)	28 (N=294)	P-value	
CR/CRi (%)			52	63	72	65	0.19	7≠21
	Mayo Risk	High	33	49	58	55	0.53	-
		Intermediate	55	69	80	69	0.17	7≠21
		Low	100	85	80	84	0.84	-
	ELN Risk	High	33	30	57	53	0.21	-
		Intermediate	33	59	64	56	0.63	-
		Low	62	74	80	73	0.46	-
Median OS (months)			13	13	17	14	0.84	-
1/3/5-year survival (%)			53/NR/NR	51/25/22	56/23/20	55/27/20	>0.1	-

6526 Poster Session

ASCERTAIN: Real-world asciminib (ASC) effectiveness in patients (pts) with Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ ALL). First Author: Marlise R. Luskin, Dana-Farber Cancer Institute, Boston, MA

Background: ATP-competitive tyrosine kinase inhibitors (TKIs) in combination with chemoimmunotherapy have improved outcomes in Ph+ ALL; still, some pts relapse despite appropriate frontline therapy and have limited options. ASC is approved for Ph+ chronic myeloid leukemia in chronic phase. The ASC managed access program (MAP) allowed adults with Ph+ ALL refractory/resistant or intolerant to available treatment (Tx) to receive ASC as monotherapy or combination under individual request when the potential benefit outweighed the risk. **Methods:** This was a non-interventional, multi-country, retrospective chart review in eligible pts with Ph+ ALL aged ≥18 who were refractory/resistant or intolerant to available Tx and who received ≥1 dose of ASC within the MAP. Index date (date of first ASC administration) occurred between 1 March 2019 and 30 June 2023. Existing data were extracted from index date up to 13 months (mo), or until discontinuation, death or last visit, whichever occurred first. The primary endpoint was complete hematologic remission (CR) and CR with incomplete count recovery (CRi) anytime in the first 3 mo of Tx based on peripheral blood assessments. **Results:** A total of 37 pts were enrolled. At Tx start, 25 pts (67.6%) received ASC as monotherapy. Median ASC dose intensity was 400 mg/day (range 71.6–400.0). Overall, 23 pts (62.2%) achieved CR/CRi within 3 months (95% CI: 44.8, 77.5). Median duration of response was 7.4 mo. Median overall survival was 7.7 mo. Nineteen pts were assessed for minimal residual disease (MRD) at time of CR/CRi and 7 (36.8%) were MRD-. Of the 13 pts with T315I mutation, 10 achieved CR or CRi at any time during follow-up. Thirty-three pts (89.2%) permanently discontinued ASC; reasons for permanent discontinuation included disease progression (n=16) and adverse events (AEs, n=5). Any-grade Tx-emergent AEs were reported in 73.0% (Grade ≥3, 56.8%) of pts; the most common any-grade AE was neutropenia (21.6%). No new safety signals were observed. Most deaths (22/28) were Ph+ ALL related. **Conclusions:** Adults with Ph+ ALL that was relapsed, resistant/refractory or intolerant to previous Tx achieved high rates of CR/CRi with ASC as monotherapy or in combination with chemotherapy/immunotherapy, despite most pts being heavily pretreated and/or harboring poor prognosis markers (Table). The safety profile was consistent with previous studies. Results, while positive, should be cautiously interpreted given the retrospective nature of the study and heterogenous population. Research Sponsor: Novartis Pharma AG.

Pt baseline characteristics.

	Pts N=37
Median age (range), years	53 (19–84)
Disease status (bone marrow blasts), %	
≥5%	67.6
<5%	24.3
Unknown	8.1
Prior treatment lines, %	
1	2.7
2	32.4
3	21.6
≥4	43.2
Ponatinib pretreatment, %	94.6
T315I mutation, %	35.1
Reason for starting ASC, %	
Relapse	67.6
Specific mutations	27.0
Resistance	24.3
Intolerance	18.9
Other	13.5

6527 Poster Session

Response to HiDAC/mitoxantrone/venetoclax (HMV) in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML). First Author: Apoorva Ravichandran, Department of Medicine, University of Chicago, Chicago, IL

Background: Outcomes for patients (pts) with R/R AML are dismal, especially after failure of Venetoclax (Ven)-based regimens. Effective strategies are urgently needed particularly in the absence of targetable mutations. An early-phase study of HMV demonstrated a 75% remission rate in pts with R/R AML, however the majority of these pts were Ven-naïve (Ruhnke et al, EHA 2024). We aimed to study a real-world cohort of pts with R/R AML treated with HMV. **Methods:** A retrospective cohort of 16 pts with R/R AML treated with HMV at the University of Chicago (2020–2025) was analyzed. Clinical and disease characteristics were collected; European Leukemia Net (ELN) 2022 criteria were used for risk stratification and response assessment. Overall response rate (ORR) was defined as complete response (CR) + CR with partial hematologic recovery (CRh) + CR with incomplete hematologic recovery (CRi). Overall survival (OS) was estimated using Kaplan-Meier methods. **Results:** Sixteen pts with R/R AML were included; 2 pts had ALL with lineage switch to AML. Median age at diagnosis was 54.5 years. Amongst the 14 pts with AML at initial diagnosis, 28.6%, 14.3%, and 50.0% had favorable, intermediate, and adverse ELN 2022 risk, respectively. Our cohort of pts was heavily pre-treated with 56.2% receiving ≥3 lines of therapy prior to HMV; two pts had received prior allogeneic hematopoietic stem cell transplant (allo-SCT). The ORR was 43.8%; in addition, 6.3% attained morphologic leukemia-free state (MLFS), 6.3% obtained a partial response (PR), and 43.7% had no response/not evaluable (NR/NE). Among pts that received prior intensive AML chemotherapy (n=8), the ORR was 50.0% with HMV. The ORR was 41.6% in pts with prior Ven exposure (n=12). Median OS from HMV initiation was 5.1 months (95% CI: 2.2-9.2) with two deaths within 30 days of HMV initiation; 62.5% of patients received subsequent therapy and 37.5% proceeded to allo-SCT. Two patients are alive in remission at time of data analysis; both underwent allo-SCT after HMV. **Conclusions:** In this heavily pretreated R/R AML cohort, HMV produced encouraging response rates and facilitated transition to allo-SCT in a subset of pts. These data warrant further evaluation of HMV as an R/R option even in pts with prior Ven exposure. Research Sponsor: National Cancer Institute; 3P30CA014599-49S1.

Patient characteristics and efficacy outcomes.

Median Age at Time of Receiving HMV (N=16)	54.5 years (Range 21-66)
Gender (N=16)	Male 69%; Female 31%
# of Lines of Therapy Received Prior to HMV (N=16)	1 Line 25%; 2 Lines 18.8%; ≥3 Lines 56.2%
Best Response to HMV (N=16)	CR 31.2%; CRh 6.3%; CRi 6.3%; MLFS 6.3%; PR 6.3%; NR/NE 43.7%
Best Response to HMV in Patients Who Received Prior AML-Based Intensive Chemotherapy (N=8)	CR 25%; CRh 12.5%; CRi 12.5%; MLFS 0%; PR 0%; NR/NE 50%
Best Response to HMV in Patients Who Received Prior Venetoclax (N=12)	CR 25%; CRh 8.3%; CRi 8.3%; MLFS 0%; PR 8.3%; NR/NE 50%

6528 **Poster Session**

Pharmacokinetic (PK) assessment of revumenib in patients with relapsed/refractory (R/R) acute leukemias harboring a *KMT2A* rearrangement (*KMT2A*r) or *NPM1* mutation (*NPM1*m): Impact of food and concomitant medications. First Author: Enoch Cobbina, Syndax Pharmaceutials, Inc., New York, NY

Background: Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction that disrupts multiple drivers of leukemogenesis such as *KMT2A* rearrangements (*KMT2A*r) and *NPM1* mutations (*NPM1*m). Revumenib is approved in the United States in patients 1 year and older for the treatment of R/R acute leukemia with a *KMT2A* translocation or R/R acute myeloid leukemia with a susceptible *NPM1* mutation who have no satisfactory alternative treatment options. Given the severity of disease, frequent polypharmacy, and variable clinical status in this population, dosing flexibility is essential to support consistent treatment delivery and optimize outcomes. This analysis characterizes the PK of revumenib and its major metabolite (M1), with emphasis on factors that may influence dosing flexibility, including food and concomitant medications such as CYP3A4 inhibitors (CYP3A4i) and gastric acid–reducing agents such as antacids, H2 blockers (H2Bs), and proton pump inhibitors (PPIs). **Methods:** PK data were obtained from 286 adult (≥18 years) and 49 pediatric (<18 years) patients with *KMT2A*r or *NPM1*m acute leukemia enrolled in the phase 1/2 AUGMENT-101 trial (NCT04065399) following single and multiple doses of revumenib. Non-compartmental analyses were performed in selected subgroups, while population PK modeling was conducted using data from all patients to systematically quantify PK variability and evaluate covariate effects. **Results:** As compared to fasted state, a low-fat meal (400–500 calories with <25% fat content) reduced revumenib C_{max} and AUC by 27% and 12%, respectively, and M1 C_{max} and AUC by 14% and 18%, respectively, although exposure ranges overlapped under fasted and fed (low-fat meal) conditions. Median T_{max} was unchanged for revumenib and delayed by 1.8 hours for M1. Co-administration with strong CYP3A4i (eg, voriconazole, posaconazole, itraconazole) resulted in ~2-fold increase in revumenib C_{max} and AUC, whereas moderate CYP3A4i (eg, fluconazole, isavuconazole) had no meaningful effect. M1 exposure was unaffected by strong or moderate CYP3A4i. Approximately 52% of patients received antacids, H2Bs, or PPIs; revumenib and M1 C_{max} and AUC were not altered, consistent with the high solubility of revumenib across physiological pH range (1.2–6.8). **Conclusions:** Revumenib exposure increases ~2-fold with strong CYP3A4i, supporting dose reduction in this setting, while M1 exposure remains unaffected. Low-fat meals do not cause clinically meaningful changes in revumenib or M1 PK. Similarly, antacids, H2Bs, and PPIs, which are frequently used in this patient population, had no impact on revumenib or M1 PK. These findings reinforce the flexible administration of revumenib that may support treatment adherence and patient convenience. Clinical trial information: NCT04065399. Research Sponsor: Syndax Pharmaceuticals, Inc.

6529 **Poster Session**

Preliminary results of an open-label, single-arm phase 2/3 trial (SPARK-ALL) of calaspargase pegol in adults with newly diagnosed Philadelphia chromosome–negative acute lymphoblastic leukemia. First Author: Daniel J. DeAngelo, Dana-Farber Cancer Institute, Boston, MA

Background: Asparaginase is an important component of many regimens for acute lymphoblastic leukemia (ALL). In patients (pts) <21 years, calaspargase pegol (Cal-PEG) provides more sustained asparagine depletion than pegaspargase. SPARK-ALL is a multicenter phase 2/3 study (NCT04817761) assessing the safety and anti-leukemic activity of Cal-PEG in pts aged ≥22 years with newly diagnosed Philadelphia chromosome-negative (Ph−) ALL. **Methods:** Part 1 was a dose-finding study in pts with a body mass index (BMI) ≤35 kg/m^2 aged 22–39 and 40–54 years (Cal-PEG 2000 and 1500 U/m^2, respectively) and pts with BMI >35 kg/m^2 or aged ≥55 years (Cal-PEG 1000 U/m^2). Part 2 was a dose-expansion study in pts with BMI ≤35 kg/m^2 aged 22–39 years (Cal-PEG 1750 U/m^2) or 40–54 years (Cal-PEG 1500 U/m^2). Six Cal-PEG IV infusions were given as part of a multiagent chemotherapy regimen based on CALGB 10403 (Stock W, et al. *Blood* 2019; 133(14):1548–1559). The primary objectives are assessment of safety in all pts, and anti-leukemic activity using the surrogate marker of nadir plasma asparaginase activity (NPAA) ≥0.1 U/mL 21 days after the D43 consolidation dose in all evaluable pts who were treated at the recommended dose (primary NPAA [PNPAA]) analysis set). **Results:** A total of 42 pts received Cal-PEG treatment: 26 and 16 in parts 1 and 2, respectively. Overall, 31 (73.8%) and 16 (38.1%) pts experienced grade 3/4 treatment-related adverse events (TRAEs) and serious TRAEs, respectively. Overall, 15 pts (35.7%) had TRAEs leading to study drug discontinuation, including hypersensitivity-type events in 6 pts (14.3%); 4 (9.5%) had nervous system events, including cerebral venous sinus thrombosis in 2 pts (4.8%). Three pts (7.1%) had a grade 3 pulmonary embolism, which, per protocol, required study drug discontinuation. The most common grade 3/4 TRAEs included hypertriglyceridemia (9 pts; 21.4%), alanine aminotransferase increase (7 pts; 16.7%), and blood fibrinogen decrease (5 pts; 11.9%). In part 1, intolerable toxicities considered related to Cal-PEG were experienced by 2/8 pts who were older and 2/8 pts with a BMI >35 kg/m^2; 1 (11.1%) pt aged between 22–39 years experienced an event of hypersensitivity. One Cal-PEG-related death was reported as likely related to complications from embolic stroke in a pt aged 71 years with comorbidities. Dose expansion was pursued in the first two cohorts. At 21 days after the D43 post-consolidation dose, all pts in the PNPAA set had NPAA values above the 0.1 U/mL efficacy threshold. **Conclusions:** Cal-PEG has a safety profile consistent with asparaginase class toxicity and, as part of multidrug chemotherapy regimen, provides sustained asparagine depletion in newly diagnosed Ph− ALL pts aged ≥22 years. In light of the observed high-grade TRAEs, future studies will evaluate different Cal-PEG doses for this pt population. Clinical trial information: NCT04817761. Research Sponsor: Servier.

6530 **Poster Session**

Older age as a predictor of post-transplant survival in newly diagnosed acute myeloid leukemia treated with HMA-venetoclax. First Author: Momna Warraich, Division of Hematology, Mayo Clinic Rochester, Rochester, MN

Background: Venetoclax (Ven) plus hypomethylating agents (HMA) is standard frontline therapy for newly diagnosed AML (ND-AML) patients unfit for intensive chemotherapy and is also being considered in younger and fit patients (Fathi, Blood 2025). However, consolidation with allogeneic stem cell transplant (ASCT) is often required to secure durable remission. The current study examines predictors of post-transplant survival (PTS) in the particular scenario. **Methods:** ND-AML patients who received upfront Ven+HMA and underwent ASCT were retrospectively studied. PTS, relapse rate, and non-relapse mortality (NRM) were evaluated. **Results:** 111 ND-AML patients (58% male, 60% secondary/therapy-related, median age 70 [37-80 years]) received median 3 cycles of Ven-HMA. 22% had complex karyotype. Mutations at diagnosis included *RUNX1* (18%), *SRSF2* (17%), *TP53* (16%), *ASXL1*, *IDH2*, *K/NRAS* and *TET2* (14% each), *STAG2* (11%), *DNMT3A* (8%) and at time of ASCT (N=78 evaluable); *RUNX1* (8%), *NPM1* (6%), *TP53* and *ASXL1* (5% each), and *SRSF2* and *TET2* (4% each). At ASCT, all patients were in CR/CRi; 88% after Ven-HMA and 12% after additional bridging therapy. MRD by flow cytometry was detected in 18 (24%) of 76 evaluable patients and complex karyotype in 8 (9%) of 94. Donors were mostly HLA-matched unrelated (75%), with 51% receiving fludarabine/melphalan conditioning and 67% post-transplant cyclophosphamide (PTCy). At a median follow-up of 30 months, 42 patients (38%) have died including 18 (40%) from relapse. Median PTS was not reached (NR) with 1-2-3-year survival of 69%/60%57%. On multivariate analysis, age ≥65 years (median NR vs 10 months p<0.01), *STAG2* (NR vs 44 months; p=0.04), and *DNMT3A* mutations (NR vs.NR p=0.05) were associated with superior PTS. In analysis limited to variables at time of ASCT, age ≥65 years remained significant (p<0.01) while *TP53* mutations, donor type, and MRD status were not (p>0.1). Patients <65 years more often received bridging therapy compared to ≥65 years (23% vs 7%; p<0.05); excluding salvage-treated patients did not change survival results. 18 patients (16%) experienced post-ASCT relapse with median RFS of 7 months. Relapse rates at 1/2/3 years were 22%, 30% and 31% and NRM 13%, 24%, 46%, respectively. Patients <65 years had a higher 1 yr relapse incidence than those ≥65 years (36% vs 18%; p=0.01), with similar NRM (p=0.58). PTCy was not associated with relapse (p=0.66) but showed a borderline association with higher NRM (1-/2-/3-year 17%/31%/58% vs 4%/7%/16% in non-PTCy recipients; p=0.06). GVHD rate was 44% (50% ≥grade 2) with no association with relapse (p=0.43) or NRM (p=0.99). **Conclusions:** In the current study, older age (>65 years), including >75 years, was independently associated with superior PTS in ND-AML patients receiving Ven-HMA. By contrast, PTS was not affected by genetic profile at the time of ASCT, donor type, conditioning regimen, or GVHD prophylaxis. Research Sponsor: None.

6531 **Poster Session**

Myelodysplasia-related mutation dynamics and outcomes in newly diagnosed (ND) acute myeloid leukemia (AML) treated with low-intensity therapy (LIT). First Author: Naszrin Arani, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Outcomes of patients (pts) with ND AML with myelodysplasia related gene mutations (MRMs), while traditionally adverse, appear to be better with LIT regimens + venetoclax (Ven). The impact of MRMs as a minimal residual disease (MRD) marker warrants investigation. **Methods:** We retrospectively analyzed the impact of persistence/clearance of MRM at VAF <2% at best response of CR/CRi, in pts with LIT treated ND AML (with available genomic data), treated at our institution between 2017 – 2025 and had ≥1 MRM (*ASXL1, BCOR, EZH2, STAG2, SF3B1, SRSF2, U2AF1*, and/or *ZRSR2*) at diagnosis, at a VAF of ≥2%. We excluded pts with CBF-AML, APL, or treated secondary AML. MRM dynamics were tracked at baseline and best response (CR/CRi) and correlated with relapse free/overall survival (RFS/OS). **Results:** A total of 185 pts, median (med) age 69 yrs (range, 56-87 yrs), were included; 96% were ≥ 60 yrs. The common baseline MRM were *SRSF2* (54%), *ASXL1* (32%), *STAG2* (16%) and *BCOR* (14%); 16% had >1 MRM. Overall, 17% had concurrent *NPM1* mutation (mut), 9% *FLT3*-ITD (AR>0.05), 22% *RAS*, 32% *RUNX1*, 8% *TP53*, and 32/183 pts (17%) had ELN2017 adverse cytogenetics (CTG). 171 pts (92%) were treated with LIT+Ven and 14 (8%) LIT without Ven; 105 (57%) received hypomethylating agents based, and the rest (43%) received cladribine + low-dose cytarabine based LIT. Overall, 148 (80%) achieved CR and 37 (20%) CRi. 117/168 (70%) pts with available data were MRD negative (-) by flow cytometry (FCM; <0.01%) at CR/CRi. At CR/CRi, 49 (26%) cleared their MRMs (MRM-) while 136 (74%) retained MRMs (MRM+); among pts with FCM MRD- CR/CRi, 33/117 (28%) were MRM- and 84/117 (72%) MRM+. Med cycle to CR/CRi was 1 (IQR 1-2). Pts with MRM- at CR/CRi had superior med RFS (24 [95% CI 9-18] vs. 14 mos [16-NR], p=0.008) and OS (54 [25-NR] vs. 21 mos [15-27], p=0.01) compared to MRM+ pts. Among 117 FCM MRD- pts, med RFS (NR vs. 14 mos [9-23], p=0.001) and med OS (NR vs. 19 mos [14-36], p=0.003) was still superior among MRM- pts (n=33) vs. MRM+ (n=84). 67 pts (36%) underwent a hematopoietic stem cell transplantation (HSCT) in CR1, 26/49 (53%) MRM- and 41/136 (30%) MRM+. Among FCM MRD- pts who did not undergo HSCT, 2-yr OS rate (86% vs. 48%, p=0.04) was better in MRM- pts (n=15) vs. MRM+ pts (n=58); among FCM MRD- pts who had HSCT, 2-yr OS rate trended to favor MRM- pts (n=18) (77% vs. 55%, p=.14) vs. MRM+ pts (n=26). On backward selected Cox MVA, clearance of MRMs at CR/CRi was independently associated with favorable OS (HR=0.54, 95% CI 0.31-0.95, p=0.03), along with *BCOR, IDH2* mut, and HSCT, while *RAS* mut, *FLT3*-ITD, and adverse CTG were unfavorable. Finally, among FCM-MRD- pts at CR/CRi, using the same Cox model, clearance of MRMs was independently favorable for OS (HR=0.42, 95%CI 0.20-0.93, p=0.03). **Conclusions:** In our analysis, the status of MRM clearance at CR/CRi in LIT treated AML with baseline MRM affected survival outcomes, including in pts FCM MRD- at CR/CRi. Research Sponsor: None.

6532 **Poster Session**

Impact of concomitant *NPM1* mutations on genomic and transcriptomic patterns of *PTPN11*-mutant myeloid leukemias. First Author: Shivahamy Maheswaran, University of Massachusetts Chan Medical School, Worcester, MA

Background: *PTPN11* mutations are associated with worse treatment outcomes in acute myeloid leukemia (AML) and frequently co-occur with *NPM1* mutations. However, the impact of concurrent *NPM1* mutations in *PTPN11*^{mut} myeloid leukemia is not well understood. This work aims to 1) characterize genomic features of a single-center cohort of patients with *PTPN11*^{mut}/*NPM1*^{wt} and *PTPN11*^{mut}/*NPM1*^{mut}-myeloid leukemia and 2) assess associated transcriptomic patterns. **Methods:** Patients with myeloid leukemia with *PTPN11* and/or *NPM1* mutations observed in blood (PB) or bone marrow (BM) were identified from the UMass Leukemia Registry. Next-generation sequencing (NGS) data were annotated for co-occurring variants and cytogenetic abnormalities. RNA-seq data from PB and BM samples from the Beat AML 1.0 trial were accessed via The Cancer Genome Atlas. Sample IDs with PTPN11^{mut}, NPM1^{mut} and PTPN11^{mut}/NPM1^{mut} were identified using the Vizome platform. High-throughput analysis of these samples and NPM1/PTPN11^{wt} was then performed using DESeq2. **Results:** 107 patients with myeloid leukemias at UMass Cancer Center harboring *PTPN11* mutations (n = 34) or *NPM1* mutations (n=74) were identified, 14 of whom had both. Subgroup analysis of chromosomal maps of *PTPN11*^{mut}/*NPM1*^{mut} cohort and *PTPN11*^{mut}/*NPM1*^{wt} cohort showed that the *PTPN11*^{mut}/*NPM1*^{wt} group had a higher cytogenetic abnormality burden compared to the *PTPN11*^{mut}/*NPM1*^{mut} group, demonstrating 18 observations of 12 distinct abnormalities compared to 5 observations of 3 distinct abnormalities, respectively. Analysis of RNA-seq from BM tissue of PTPN11^{mut}/NPM1^{wt} AML (n = 6) from the Beat AML 1.0 dataset revealed only 22 differentially expressed genes compared to PTPN11^{wt}/NPM1^{wt} samples. Of these, 12 were mitigated in the PTPN11^{mut}/NPM1^{mut} (n = 9) group. This trend was less pronounced in analysis of PB tissue. However, review of 20 most differentially expressed genes of both BM and PB in the PTPN11^{mut}/NPM1^{wt} group revealed many changes in long intergenic non-coding RNAs (lincRNAs). **Conclusions:** Genomic analysis of PTPN11^{mut}/NPM1^{wt} BM and PB highlighted widespread cytogenetic heterogeneity compared to the PTPN11^{mut} NPM1^{mut} subgroup. RNAseq analysis of PTPN11^{mut} BM and PB revealed significant differential expression in multiple lincRNAs, particularly in BM. These changes were mitigated in the double mutant group. Larger studies are needed to validate these findings and investigate whether presence of subtle regulatory shifts serve as a driving factor in the poor outcomes underlying PTPN11^{mut} AML. Further chromatin accessibility profiling studies may help elucidate the regulatory mechanisms driving these transcriptomic changes. Research Sponsor: None.

6533 **Poster Session**

Can transcriptome-based risk modeling improve survival stratification across cytogenetic groups in acute myeloid leukemia? First Author: Amith Paruchuri, All India Institute of Medical Sciences, New Delhi, India

Background: Cytogenetic risk stratification is central to prognostication in acute myeloid leukemia (AML), yet survival outcomes vary considerably within each group. We hypothesized that transcriptomic features could further stratify survival within these cytogenetic categories, independent of clinical factors. **Methods:** We analyzed gene expression microarray data for 172 AML patients from the TCGA-LAML cohort (dbGaP phs000178). Multivariable Cox proportional hazards modeling incorporating age, gender, and CALGB cytogenetic risk was used to identify genes independently associated with overall survival. LASSO regression was applied to derive a transcriptomic gene signature and compute a patient-level transcriptomic risk score. Kaplan–Meier survival analysis, log-rank testing, and Cox modelling were performed in the overall cohort and within each cytogenetic subgroup. Model performance was assessed using concordance index (C-index) and likelihood ratio testing. Differential expression and Gene Ontology Biological Process (GOBP) enrichment were performed between high and low transcriptomic risk groups. **Results:** The transcriptomic risk score significantly stratified overall survival and, importantly, retained prognostic significance within favorable, intermediate, and poor cytogenetic risk groups (Table). The concordance index improved from 0.69 with clinical variables (age, gender, cytogenetics) alone to 0.82 after adding the transcriptomic risk score. Likelihood ratio testing confirmed a highly significant improvement in model fit with the inclusion of the transcriptomic score (χ^2 = 98.7, $p < 2.2\times10^{-16}$). GOBP enrichment of DEGs between high and low transcriptomic risk groups revealed upregulation of CD4-positive T-cell activation (STAT6, IL12RB1, ZBTB7B), negative regulation of immune response (LGALS9, PTPN6, FGL2), regulation of leukocyte and lymphocyte differentiation (ZC3H12A, VNN1, HCLS1), and response to bacterial molecules and lipopolysaccharide (NLRP3, MYD88, CASP1) confirming dysregulated immune signaling as a hallmark of adverse prognosis. **Conclusions:** A transcriptomic risk score provides powerful, independent prognostic information beyond cytogenetics and clinical factors in AML. These findings support the integration of transcriptomic biomarkers into existing risk models to refine AML prognostication. Research Sponsor: None.

Survival association of transcriptomic risk score across CALGB groups in AML patients.

CALGB Group	HR* (95% CI)	p value**
All AML patients (N =172)	3.74 (2.48–5.63)	2.81×10^{-10}
Favourable (N= 34)	14.53 (1.87–112.83)	1.05×10^{-2}
Intermediate (N = 97)	6.49 (3.43–12.26)	8.43×10^{-9}
Poor (N = 38)	2.68 (1.26–5.69)	1.01×10^{-2}

*HR: High vs Low genomic risk.
**Cox p from multivariable Cox model.

6534 **Poster Session**

Mutation landscape and pathway-level disparities in Black versus White patients with acute myeloid leukemia. First Author: Chidiebube Ugwu, Department of Internal Medicine, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: Racial disparities in acute myeloid leukemia (AML) outcomes are well-documented, yet race- specific genomic differences remain incompletely characterized. Current risk stratification systems, developed from European-ancestry cohorts, may inadequately classify patients (pts) of African ancestry (Stiff, *Nature Genetics*, 2024). We performed comprehensive clinicogenomic analysis to identify race-specific mutation patterns and their clinical impact in AML. **Methods:** We analyzed genomic and outcomes data on AML pts in AACR Project GENIE database. Mutation frequencies, co-mutation patterns, and pathway alterations were compared between racial groups. Survival analyses used Cox proportional hazards models adjusted for age and sex. Multiple comparison correction used Benjamini-Hochberg false discovery rate (FDR). **Results:** Our study included 2,359 pts (Black, n=243; White, n=2,116). Black pts demonstrated a distinct mutational landscape with fewer splicing factor (*SRSF2, U2AF1, SF3B1*) mutations (11.1% vs 20.1%, FDR p=0.003) and tumor suppressor (*TP53, WT1*) mutations (11.9% vs. 18.2%, FDR p=0.038). Signaling/RAS pathway mutations were nominally higher in Blacks. A notable finding was the emergence of MDS-related gene mutations in Black pts at a younger age, suggesting distinct disease biology. Among pts aged $<$40 years, ASXL1 mutations were more prevalent in Blacks (10.2% vs. 1.8%, p=0.006). Co-mutation architectures differed substantially by race: in Black pts, ASXL1 and RUNX1 frequently co-occurred with RAS/MAPK pathway mutations (ASXL1+RAS: 7.8% vs. 3.4%, FDR p=0.006), whereas White pts had predominant co-occurrence of *ASXL1* and *RUNX1* with splicing factor mutations Critical survival disparities emerged by mutation status. NPM1+FLT3 co-mutation was less common in Blacks (3.3% vs. 7.0%, FDR p=0.028) and conferred markedly inferior survival when present (median OS 6.7 vs. 14.6 months, p=0.008). Strikingly, favorable-risk mutations showed race-specific effects. NPM1-only (HR 0.79, p=0.014), IDH1-only (HR 0.68, p=0.005), and NPM1+IDH1 (HR 0.61, p=0.013) were protective in White but not in Black pts: NPM1-only (HR 0.89, p=0.76), IDH1-only (HR 0.84, p=0.71), NPM1+IDH1 (HR 0.34, p=0.13), challenging current risk stratification's universal applicability. Overall survival (OS) was similar (median OS- 18 vs. 16.7 months), though propensity-matched analysis trended toward worse outcomes in Blacks (18 vs. 25 months, p=0.091). **Conclusions:** Black AML pts exhibit fundamentally distinct molecular biology with differential pathway involvement, earlier MDS-related mutations, unique co-mutation patterns, and loss of prognostic value for traditionally favorable mutations. These findings demonstrate that race-blind risk stratification may systematically misclassify Black pts, supporting urgent need for ancestry-informed precision medicine approaches in AML. Research Sponsor: None.

6535 **Poster Session**

Phase II study of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH) ± rituximab (R) + tafasitamab (tafa) in adults with newly diagnosed (ND) Philadelphia chromosome–negative (Ph-) B lymphoblastic leukemia (B-ALL). First Author: Noam Edward Kopmar, Fred Hutch Cancer Center, Seattle, WA

Background: For adults with ND Ph- B-ALL, frontline regimens now often include the CD19/CD3 bispecific blinatumomab (blin). However, blin administration is challenging, particularly for less-experienced centers. DA-EPOCH ± R is safe and active in these patients (pts; Cassaday, et al, *Leuk Lymphoma*, 2023) and easier to deliver. Tafa is a CD19 monoclonal antibody active in B-cell lymphomas. We hypothesized that the addition of tafa to DA-EPOCH ± R will yield higher rates of measurable residual disease negativity (MRD-) without increasing toxicity or administration complexity. **Methods:** This is a phase II investigator-initiated study (NCT05453500) in adults ($>$18 years) with ND CD19+ Ph- B-ALL not eligible for a pediatric regimen. DA-EPOCH ± R was given as cited above; tafa 12 mg/kg was given IV on day (d) 1, 8, and 15 of each cycle (C). After blin consolidation was FDA approved, pts could receive this off-study. The primary endpoint was MRD- by multiparameter flow cytometry (MFC) per EuroFlow ($\sim<10^{-4}$) after C1 (~d 20); secondary endpoints included MRD- by MFC after C4 (~d 80); non-hematologic adverse events (AEs, CTCAE v5); and relapse-free (RFS) and overall survival (OS). Exploratory endpoints included high-throughput sequencing (HTS; $<10^{-6}$) by clonoSEQ in marrow and cerebrospinal fluid (CSF). If ^{3}13 of 30 evaluable pts (^{3}43%) are MRD- after C1, the primary endpoint is met (vs 28% with DA-EPOCH ± R alone; 80% power and one-sided α = 0.05). **Results:** From 3/2023 to 12/2025, 30 pts enrolled: 2 pts did not finish C1 due to grade (G) 4 AST elevation (related) and G5 *C. perfringens* sepsis (unrelated); 27 were evaluable for response and are the focus here. Median age was 67 (44-84), 70% male, 56% poor risk cytogenetics by NCCN, and 9 received R. Complete response (CR) rate was 85% (23/27); MRD- by MFC after C1 was 44% (12/27) and 80% (20/25) by C4 in pts with sufficient follow-up (f/u). In pts MRD- by MFC, 53% (8/15) were MRD- by HTS. Other G3+ AEs seen in $>$2 pts: infection (9); febrile neutropenia (8); low fibrinogen (6); hypotension (5); and syncope (4). Initial CSF MFC was positive in 3 pts; HTS was positive in these plus 4 more (7 total). With a median f/u among survivors of 10 mo (1-37), there were 3 relapses: 1 post-HCT and 1 after only 2 treatment cycles; all were CD19+, and 0 involved CNS. Only 2 pts got blin consolidation. 6 pts died: 4 non-relapse causes (3 post-HCT) and 2 from refractory ALL. No deaths were due to study treatment. 1-year RFS and OS were estimated to be 67% and 76%, respectively. **Conclusions:** DA-EPOCH ± R + tafa yields high rates of MRD-. Follow-up is immature, but early survival rates are comparable to more complex strategies. This study is on pace to reach its primary endpoint, with enrollment ending before the conference. HTS on CSF can identify CNS disease more frequently. Clinical trial information: NCT05453500. Research Sponsor: None.

6536 **Poster Session**

Impact of variant topography of *NPM1* mutations in acute myeloid leukemia. First Author: Markie S. Zimmer, Henry Ford Hospital, Detroit, MI

Background: *NPM1* is a frequent driver mutation in AML and conveys favorable prognosis in the absence of *FLT3* mutations. Currently, *NPM1* subtypes (Type A, B, D and non-ABD) are approached uniformly. A granular analysis evaluating *NPM1* subtypes (ST) is essential to improve molecular risk stratification in AML. We seek to evaluate the molecular intricacies of *NPM1* variants and genomic architecture to determine how these influence outcomes in AML. **Methods:** The cohort had patient data from Karmanos Cancer Institute, meta-analytic cohorts (Awada et al., 2021; Kewan et al., 2023), cBioPortal, and AACR GENIE (v17) (Cerami et al., 2012; Gao et al., 2013; de Bruijn et al., 2023). Clinical and genomic characteristics of $NPM1^{MT}$ AML were reviewed. Insertions between nucleotides 863 and 864 determined the ST classification: TCTG (A), CATG (B), CCTG (D) and others (non-ABD). Stratification of *NPM1* by VAF was performed by quartiles from the median. Clonal hierarchy was defined as a difference in VAF $\geq$5% and differences $<$5% were designated as codominant. **Results:** Of 7653 patients with AML, 5342 (84.2%) had de novo AML. $NPM1^{MT}$ was present in 1570. Type A was most common (73%), followed by non-ABD (18%), B (5%) and D (4%). Median age was 66 years (IQR 53.8-73.7) and was similar across groups. Females more frequently had non-ABD than B or D (67% vs 45% and 53%, p=0.0008 and 0.04, respectively). Non-ABD had the least proliferative bone marrow compared to A, B or D (blast percentage 54 vs 79, 75.5, 70, p$<$0.0001, p=0.0015, p=0.02). Type A had lower VAF than other ST (29% vs 34%, p$<$0.0001), while B and D had higher VAF than other ST (38% vs 30%, p$<$0.0001 and 33% vs 30% p=0.0004). The most common co-mutation with *NPM1* was *DNMT3A* (48%). Type A was enriched for *DNMT3A* compared to other ST (54% vs 34%, p$<$0.00001). Type A and D had more *IDH1*, *IDH2*, and *NRAS* mutations than B and non-ABD (17% vs 10%, p=0.01; 23% vs 9%, p$<$0.00001; 16% vs 10%, p=0.03, respectively). B and non-ABD were more enriched in *WT1* compared to A and D (12% vs 4%, p=0.00002). Non-ABD was more enriched for *FLT3* mutations than other ST (39% vs 24%, p=0.00012). $DNMT3A^{R882}$ was enriched in high VAF (HV) compared to low VAF (LV) *NPM1* (54% vs 46%, p=0.01). *FLT3* was more common in HV *NPM1* (34% vs 17%, p$<$0.0001). *NPM1* was often a subclone (82%), but was more likely to be dominant in B (29%, p=0.001). The median OS of $NPM1^{MT}$ AML was 19 mo, similar across ST (A: 18 vs B: 14 mo, p=0.3896). OS was numerically higher in D (26 mo) and non-ABD (25 mo). LV *NPM1* (Q1 $\leq$ 22.8%) had significantly better OS than HV (Q3 $\geq$ 38%): 21 vs 10 mo (p$<$0.0001). This trend was most pronounced in D and non-ABD (D: 58 vs 10 mo, p=0.009; non-ABD: 29 vs 7 mo, p=0.005). **Conclusions:** As survival differences between *NPM1* mutation subtypes were numerically different, enrichment of Type A and D for *IDH1/2* and *NRAS*, non-ABD for *FLT3*, B and D for *WT1* probes the question of the impact of these co-mutations and VAF on *NPM1* outcomes. Further work will evaluate the impact of *NPM1* ST on de novo and therapy-related AML. Research Sponsor: None.

6537 **Poster Session**

Impact of transplant on $TP53^{MT}$ configurational dynamics in myeloid neoplasms. First Author: Dakshin Sitaram Padmanabhan, Karmanos Cancer Institute, Detroit, MI

Background: Multihit *TP53* clonal configurations in myeloid neoplasms (MN) confers poor prognosis but therapy alters allelic burden in general. Using our previously described algorithm, patients with up-trending or stable (UT/S) $TP53^{MT}$ had worse OS than those who down-trended (DT); HSCT was associated with DT. We evaluated whether this pattern reflects intrinsic *TP53*-driven disease biology or from treatment/ transplant effects. **Methods:** We analyzed a serially sequenced $TP53^{MT}$ AML/MDS cohort from four academic centers using targeted NGS (Illumina MiSeqDx; 54-gene TruSight panel). *TP53* configurations were defined per Bahaj et al.: single-hit $TP53^{MT}$ as obligatory biallelic (VAF $>$50%), probable biallelic (23–50%), or probable monoallelic ($<$23%); combined VAF was used for double-hit $TP53^{MT}$. *TP53* clearance was defined as VAF $<$3%. Associations were tested with chi-square/Fisher tests and survival by Kaplan–Meier analysis. Clonal velocity (CV) was defined as the change in VAF from diagnosis to final serial sample post-transplant (Δ VAF) over post-HSCT survival time and categorized as stable (0 to $-$1), moderately downtrended (MD) ($-$1 to $-$5), or highly downtrended (HD) (≤ -5). **Results:** Among 119 $TP53^{MT}$ MN patients, 58 (49%) had pAML, 38 (32%) sAML, and 23 (19%) MDS. Median age was 65 years, 55% were male, and 20% had del(17p). Initial therapy included 7+3/CPX (34%), HMA+VEN (30%), or HMA alone (29%). 71 pts (60%) underwent HSCT (mOS 17 vs 5 mos in non-HSCT group; p$<$0.001). Among 62 with serial samples, 76% down trended *TP53* post-HSCT and 72% achieved *TP53* clearance. Patients in the UT/S group more often had complex karyotype (93% vs 64%; p=0.04) and numerically shorter time to HSCT (4 vs 5 mos; p=0.11). In the DT group, pre-HSCT therapy included 7+3 (30%), HMA alone (23%), and HMA+VEN (25%); HMA monotherapy was more common in UT/S vs DT (53% vs 23%; p=0.03). Mismatched/haploidentical transplants (in 45%) had numerically lower mOS than matched donor transplant (13 vs 52 mos; p=0.27); class II mismatch showed numerically better survival than class I or haploidentical (37 vs 12 mos; p=0.27). mOS was worse in UT/S (14 vs 22 mos; p=0.03). When stratified by clonal velocity (CV), the DT group showed stepwise differences in mOS: stable (78 mos), MD (26 mos), and HD (11 mos; p$<$0.0001). Stable CV was enriched for monoallelic *TP53* at diagnosis (60% vs 14% vs 6%; p=0.004), higher chronic GVHD (60% vs 24% vs 13%; p=0.03), and greater *TP53* clearance (100% vs 71% vs 56%; p=0.05), whereas HD CV was enriched for obligatory biallelic *TP53* (p=0.001). PTCy use was highest in the MD group (30% vs 76% vs 50%; p=0.04). **Conclusions:** UT/S patients had higher pre-HSCT HMA monotherapy use and complex karyotypes. Stable CV was associated with monoallelic *TP53*, lower PTCy use, higher chronic GVHD, greater *TP53* clearance, and superior survival, suggesting that the rate of *TP53* clonal contraction rather than clearance alone best predicts OS and reflects intrinsic $TP53^{MT}$ disease biology. Research Sponsor: None.

6538 **Poster Session**

Distinction of FLT3-ITD transcriptomic signature from FLT3-TKD and the frequency of this signature in acute myeloid leukemia without *FLT3* mutation. First Author: Maher Albitar, Genomic Testing Cooperative LCA, Lake Forest, CA

Background: The FLT3 gene plays a major role in acute myeloid leukemia and frequently overexpressed irrespective of its mutation status. FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutation are both associated with adverse prognosis, but the ITD is associated with more aggressive disease and higher relapses than the TKD. Therapeutically, FLT3-TKD has different resistance implications from FLT3-ITD. We used transcriptomic data to compare AML FLT3-ITD-positive (ITD+) with FLT3-TKD-positive (TKD+), then tested if AML FLT3-negative (FLT3-) may have RNA signature similar to those seen in ITD+ or TKD+ AML. **Methods:** Between 2023 and 2025, 906 AML samples were RNA profiled using next generation sequencing. A targeted NGS panel of approximately 1,600 genes was used. More than 100 million reads were required to accept RNA results. The required percentage of spliced RNA reads was above 20%. Of these samples, 171 had FLT3-ITD and 115 had FLT3-TKD mutations and 619 were FLT3-. **Results:** We first explored if expression profiling can define a subgroup of TKD+ cases that are similar to those with ITD+ AML. Using 22 genes in random forest modeling, expression profiling segregated ITD+ AML from TKD+ AML with AUC of 0.734 (95% CI: 0.638-0.831, Precision: 0.940). The top genes relevant for this segregation were GRB10, PTK7, WT1, TEC, CASP3, NR6A1, and CD47. We then build a random-forest-based model to distinguish ITD+ from FLT3- cases. We used the 171 ITD+ AML and a set of 220 FLT3- AML cases to distinguish between the two groups. Using 45 genes in this model we were able to segregate with the ITD+ cases based on expression with AUC of 0.889 (95% CI: 0.833-0.945, precision : 0.935). Top genes were LUC7L2, NFYC, PRPF40B, PRPF8, SF3A1, SMAD5, THRA, ACVR1, EVI2A, MCM3AP. This highly predictive model was then used to test independent set of 399 FLT3- AML cases. Of these cases 319 (80%) had a signature similar to ITD+ AML. Similarly, we used the 115 TKD+ with the 220 FLT3- AML cases and built a random forest-based model to distinguish between the two groups. This model required 70 genes and was less robust but segregated the TKD+ AML with AUC of 0.784 (95% CI: 0.701-0.868, precision: 0.842). Testing an independent set of 399 FLT3- cases using this model showed TKD signature in 236 (59%) of FLT- cases. All these positive TKD signature cases were also positive for the ITD signature. **Conclusions:** This data suggests that significant number of AML cases are biologically driven by changes similar to those seen in FLT3-mutant cases. While clinical trial is needed for confirmation, these cases with FLT3-ITD signature may respond efficiently if treated with therapy including FLT3 inhibitors in fashion similar to that seen ITD+ cases. Furthermore, this data suggests that ITD signature might be a better biomarker than TKD mutation for selecting patients to be treated with FLT3 inhibitors. Research Sponsor: None.

6539 **Poster Session**

Real-world outcomes of early unfractionated heparin use in NSTEMI patients with acute leukemia and severe thrombocytopenia. First Author: Shanawar Ali Waris, West Virginia University School of Medicine, Department of Internal Medicine, Morgantown, WV

Background: Current AHA/ACC guidelines provide limited guidance for acute non-ST-segment elevation myocardial infarction (NSTEMI) management in patients with active hematologic malignancy and concurrent severe thrombocytopenia, as these individuals have been systematically excluded from randomized trials. Consequently, decisions regarding anticoagulation rely on expert opinion and limited observational data. We evaluated real-world outcomes in patients with acute leukemia, severe thrombocytopenia, and NSTEMI, comparing early unfractionated heparin use with no parenteral anticoagulation. **Methods:** We conducted a multicenter retrospective cohort study using the TriNetX Research Network to identify adults ($\geq$18 years) with acute leukemia who experienced a first NSTEMI following leukemia diagnosis. Severe thrombocytopenia was defined as a platelet count $< 50\times10^3/\mu L$ measured within 24 hours of NSTEMI. Patients with prior intracranial hemorrhage or on chronic anticoagulation were excluded. The primary exposure was unfractionated heparin administered within 24 hours of NSTEMI diagnosis versus no parenteral anticoagulation. Propensity score matching (1:1) was performed for demographics, cardiovascular risk factors and chronic co-morbidities. Primary efficacy outcomes were all-cause mortality at 30 days, 90 days, and 1 year. The primary safety outcome was major bleeding, defined as a composite of intracranial and gastrointestinal hemorrhage at 7 days, 30 days, and 90 days. Kaplan-Meier analysis, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI) were used to assess outcomes. **Results:** Among 1,734 patients who met the inclusion criteria, 639 received unfractionated heparin and 1095 did not. Following, PSM 528 patients remained in each group. Kaplan–Meier overall survival at 30 days, 90 days, and 1 year was significantly improved in patients receiving early unfractionated heparin (30-day HR = 0.78 [0.64-0.96]; 90-day HR = 0.77 [0.64-0.92]; 1-year HR = 0.75 [0.64-0.87]). Composite major bleeding events at 7 days, 30 days, and 90 days were similar between groups (7-day RR = 1.56 [0.95-2.56]; 30-day RR = 1.15 [0.81-1.77]; 90-day RR = 1.24 [0.88-1.83]). **Conclusions:** In this large real-world study of patients with acute leukemia, severe thrombocytopenia, and NSTEMI, early unfractionated heparin administration within 24 hours was associated with improved survival without an increased risk of major bleeding, addressing a critical evidence gap in this high-risk population. Research Sponsor: None.

Overall Survival			
Timepoint	Heparin (%) [n=446]	No Heparin (%) [n=446]	HR (95% CI)
30-day	66.9%	59.3%	0.78 [0.64-0.96]
90-day	55.3%	45.6%	0.77 [0.64-0.92]
1-year	36.9%	23.8%	0.75 [0.64-0.87]
Major Bleeding			
Timepoint	Heparin (%) [n=446]	No Heparin (%) [n=446]	RR (95% CI)
7-days	7.6%	5%	1.56 [0.95-2.56]
30-day	10.9%	9.8%	1.19 [0. 81-1.77]
90-day	14.1%	11.6%	1.27 [0.88-1.83]

6540 **Poster Session**

A two-axis machine learning framework for cell-of-origin inference in AML: A proof-of-concept study. First Author: Jonathan Dan Andreadakis, Tampa General Hospital Cancer Institute, Tampa, FL

Background: Leukemogenesis mirrors hematopoietic differentiation yet proceeds through dysregulated programs. Multiparameter flow cytometry (MFC) allows leukemia immunophenotypes projection onto normal myeloid ontogeny. Here, we apply machine-learning (ML) models trained on MFC data to reconstruct a preliminary data-driven representation of inferred cell-of-origin (COO). Additionally, we explore integration of monocytic differentiation into canonical COO framework to identify dysregulated commitment programs not explained by developmental maturity alone. **Methods:** After IRB approval, MFC data from 261 AML patients were aligned to immunophenotypic signatures of normal myeloid ontogeny (HSC, MPP, CMP, GMP, GP, MP) as previously described (Simoes *et al.*, *Blood Neoplasia*, 2024; Vergez *et al.*, *Blood Cancer Journal*, 2022). Probabilistic COO states were inferred from core markers (CD34, HLA-DR, MPO, CD33, CD117) using ensemble Random Forest classifiers with gradient boosting [Training/Validation=70/30]. Because canonical COO algorithms omit monocytic features, we implemented a secondary Mono-Risk Layer trained on monocytic markers (CD14, CD64) and stemness/invasiveness surrogates (CD56, reflecting adhesion, migration propensity) and CD123, to generate complementary phenotypic labels. Models were trained with cross-validation in Python, and mutation enrichment was projected onto inferred COO states. **Results:** Mean age was 63.8 years. 114/261(44%) were male. 123/261 (47.1%) of cases produced multidimensional P-COO achieving "Ensembled (RF+ Boosting Gradient)" AUC=0.74. Confusion matrix revealed a structured pattern of misclassification predominantly between adjacent COO states, consistent with a continuous differentiation manifold (Recall for MPP, CMP, GMP, GP, MP, 50% 83%, 62%, 65%, 76%, respectively). Mono-Risk-Layer (MRL) improved discriminatory ability for MP (AUC 0.94, Recall 86%, F1 0.75). *NPM1* was mapped to GMP (60%), MP (34%) and CMP (27%), p=2.61e-09, *FLT3 ITD* GMP (43.3%), CMP (32.4%) and MP (12.3%), p=4.72 e-05, *TP53* HSC (50%), MPP (24.3%) and GMP (16%), p=3.6e-04, *RUNX1* MPP (26.1%), HSC (25%) and MP (13%), p=7.7 e-03, RAS MP (35%), MPP (19%) and HSC (13%), p=5.18 e-03. **Conclusions:** Machine-learning–based probabilistic cell-of-origin inference from routine flow cytometry is feasible and biologically informative in AML. Incorporation of a monocytic risk layer improves resolution of monocytic programs not captured by canonical COO and reveals distinct mutation–differentiation relationships. *NPM1* and *FLT3-ITD* are enriched in GMP/MP-like states, *TP53* in primitive HSC/MPP compartments, *RUNX1* in early progenitors, and RAS in monocytic-skewed trajectories. These findings link genomic drivers to specific developmental niches and establish a scalable framework for biologically grounded AML classification and therapeutic modeling. Research Sponsor: None.

6541 **Poster Session**

Impact of cell-type–specific circadian disruption in pediatric B-ALL on clock-based biomarkers with implications for chronotherapy. First Author: Angela Relógio, Institute for Systems Medicine and Faculty of Human Medicine, MSH Medical School Hamburg, Hamburg, Germany

Background: B-cell acute lymphoblastic leukaemia (B-ALL) is the most common paediatric malignancy. While cure rates exceed 90%, treatment remains intensive and is frequently associated with relapse, toxicity, and long-term adverse effects. The circadian clock regulates DNA repair, metabolism, immune function, and drug pharmacokinetics—processes central to cancer therapy. Although treatment timing has been shown to influence outcomes in childhood ALL, the molecular circadian landscape of malignant versus healthy hematopoietic cells in paediatric patients remains unexplored. **Methods:** We performed an integrated molecular and clinical circadian profiling study in paediatric ALL patients (N=7) and age-matched healthy controls (N=10). Peripheral blood, bone marrow, and saliva samples were collected at diagnosis. $CD19^+$ (leukemic B cells) and paired $CD19^-$ (non-B cells) populations were isolated and used to establish an internal, patient-specific circadian baseline. Expression of ~800 cancer-, immune-, and clock-related genes was quantified using NanoString SPRINT technology. Rhythmicity parameters (acrophase, amplitude, MESOR), differential expression, and machine-learning–based classification were integrated with longitudinal clinical and physiological data. **Results:** Malignant $CD19^+$ cells exhibited marked circadian dysregulation compared with paired $CD19^-$ cells from the same patients. Core clock architecture was altered specifically in leukemic cells, including disrupted BMAL1–PER2 phase relationships and reduced rhythmic amplitude. CD19 expression itself displayed cell-type–specific circadian modulation, with higher amplitude and phase variability in $CD19^+$ cells. In contrast, $CD19^-$ cells retained more coherent circadian organization, supporting their use as an internal normalization reference. Preliminary analyses suggest that the degree of circadian misalignment between $CD19^+$ and $CD19^-$ compartments correlates with treatment dynamics, including early response and therapy duration. **Conclusions:** Our findings reveal profound, cell-intrinsic circadian disruption in paediatric B-ALL and demonstrate that comparing malignant $CD19^+$ cells against paired non-malignant $CD19^-$ cells enables robust detection of clock dysregulation. These results provide a molecular framework for developing circadian biomarkers and support the rational design of chronotherapy strategies aimed at optimising efficacy while minimising toxicity in paediatric leukaemia. Research Sponsor: Dr. Rolf Schwiete Stiftung.

6542 **Poster Session**

Cladribine (CLAD) + low-dose AraC (LDAC) + venetoclax (VEN) in patients with acute myeloid leukemia and high-risk myelodysplastic syndrome: Real-world analysis from a large community-based oncology practice. First Author: Janvi Bhatia, Community Hospitals Network/MD Anderson, Indianapolis, IN

Background: A lower intensity combination cladribine (CLAD), low dose cytarabine (LDAC), and venetoclax (VEN), alternating with hypomethylating agents (HMA) + VEN has been shown to be highly effective in the treatment of older and/or unfit patients with newly diagnosed AML, producing high rates of MRD negative complete remission (CR), low early mortality, and successful transition to allogeneic stem cell transplant. While this was conducted in a large academic center in a prospective phase II study, we aimed to assess the efficacy and safety of this approach in a community practice setting, with important implications of broader applicability. **Methods:** This is a single-center retrospective study evaluating the efficacy and safety of using the CLAD/LDAC/VEN alternating with HMA/VEN regimen in a large oncology practice in the community setting. Dosing of CLAD/LDAC/VEN was according to published experience (Kadia, et al. JCO 2022). Patients with high risk MDS or AML treated in our institution from January 13, 2023-November 18, 2025 were included. Pts with prior treatment, including HMA for prior MDS transforming to AML (treated secondary AML, ts-AML) were also included. **Results:** A total of 72 patients received at least 1 cycle of CLAD/LDAC/VEN. The median age was 74 yrs (range: 43-90). Median PS was 1 (0-2), including 21 (29%) pts with ECOG PS of 2 (29%). 58 pts had AML, including 44 (78%) with untreated AML, 10 (18%) with ts-AML, and 12 (22%) with relapsed AML; 14 pts had high risk MDS, of which 5 (36%) had failed prior HMA . 37 pts (51%) had adverse risk karyotype by ELN 2022 , 16 (22%) had TP53 mutation and 29 29 (40%) had secondary AML. Twenty-nine (40%) pts had received prior therapy, including 13 pts (18%) with prior HMA. The median number of cycles received was 2 (range 1-14). Among untreated AML and MDS, the composite CR (CRc) rates were 63% and 58%, respectively. Six out of 16 pts with p53 (38%) achieved CRc and of 16 pts with prior HMA 6 (38%) achieved CRc. The median survival (OS) was 8 months (range 0.16-33m). Eleven pts (15%) went on to have allo-SCT. Five pts (7%) died within 28 days of first treatment. Three of these died of infectious complications, 1 died of an acute coronary event and 1 patient decided to go on comfort care mid-way through treatment. **Conclusions:** CLAD/LDAC/VEN was feasible and effective in a high-risk, older patient population including pts with prior treatment who were able to achieve meaningful disease control and used as a bridge to transplant. The regimen translated well to a community setting, with relatively low 28-day mortality and good tolerability. Research Sponsor: None.

6543 **Poster Session**

Age and the genomic landscape of AML in precision oncology: An analysis using ASH HematOmics Program. First Author: Pranav Singh, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Age is a major determinant of prognosis and treatment selection in acute myeloid leukemia (AML), yet the extent to which chronological age reflects underlying genomic and transcriptomic features remains incompletely characterized. The American Society of Hematology HematOmics Program (ASHOP) provides a centralized, clinically annotated genomic resource enabling systematic evaluation of age-associated AML biology across molecular subtypes. **Methods:** We conducted a cross-sectional analysis of adults with AML using ASHOP data. Patients were categorized by age ($<$40, 40-59, 60-74, and $\geq$75 years). AML molecular subtypes were defined based on recurrent cytogenetic and genomic alterations (NPM1, PML::RARA, CBFB::MYH11, MECOM, CEBPA, AML-MR, KMT2A, DEK::NUP214, TP53, and other recurrent translocations), aligned with WHO classification. Adverse genomic risk was defined by AML-MR, MECOM, and TP53. Gene expression levels for epigenetic regulators (DNMT3A, TET2, IDH1, IDH2, FLT3) and stemness-associated genes (HOXA9, MEIS1, HLF, GATA2, PROM1) were standardized as z-scores, and composite scores generated. Associations were assessed using chi-square tests, linear regression, and multivariable models adjusted for sex. **Results:** Among 302 patients (mean age 71.1 $\pm$ 17.3 years; 47.7% aged $\geq$75; 54.3% male), the most common subtypes were NPM1 (20.5%), PML::RARA (16.6%), CBFB::MYH11 (15.6%), MECOM (14.2%), CEBPA (10.9%), AML-MR (9.6%), and KMT2A (7.6%). Subtype distribution varied modestly across age groups (p=0.053) but not by sex (p=0.858). Adverse genomic risk increased significantly with age (p=0.016). In multivariable logistic regression adjusted for sex, patients aged $\geq$75 had significantly higher odds of adverse genomic features (OR 2.78, 95% CI 1.26, 6.12; p=0.011), while sex was not independently associated (p=0.325). In transcriptomic analyses (n=265), age was not associated with individual epigenetic or stemness genes, with age and sex explaining minimal variance in composite scores (epigenetic score R^2=0.013, p=0.506; stemness score R^2=0.003, p=0.957). In contrast, molecular subtype showed strong associations. Subtype along with age and sex explained 16.4% of epigenetic score variance (R^2=0.164; p$<$0.001) and 38.0% of the stemness score variance (R^2=0.380; p$<$0.001). Key stemness genes were highly subtype-dependent (HOXA9 R^2=0.709; MEIS1 R^2=0.599; both p$<$0.001), driven primarily by NPM1 and KMT2A subtypes. **Conclusions:** Advanced age in AML is associated with adverse genomic risk accumulation but explains minimal variance in stemness or epigenetic transcriptional programs. Instead, these programs are largely determined by molecular subtype. Hence, stemness and epigenetic programs are intrinsic properties of AML molecular subtypes rather than age, supporting subtype-driven risk stratification and therapeutic decision-making in the precision oncology era. Research Sponsor: None.

6544 **Poster Session**

From infancy to young adulthood: Exploring the divergent genomic mechanisms that drive AML. First Author: Frank J. Scarpa, NeoGenomics Laboratories Inc., Fort Myers, FL

Background: Pediatric & young adult Acute Myeloid Leukemias (pAML & YA AML) are an uncommon, heterogenous, & clinically challenging group of malignancies, as age ranges widely & proper therapy selection (i.e. pediatric vs. adult regimens, etc.) can be unclear. The genomics of these disorders can help understand distinct disease biology, better risk stratification, & improve outcomes. **Methods:** Bone marrow, peripheral blood, or FFPE samples from 870 suspected AML patients were sequenced using a 302 gene panel to detect SNVs/indels. 466 underwent RNA fusion detection of 184 genes & DNA analysis for CNV detection of 24 genes. Only pathogenic/likely pathogenic variants were included in the analysis. AML patients were split into 4 groups based on age: Infant (≤3, n=30), Childhood (4-14, n=51), Adolescent (15-19, n=51), YA (20-35, n=738). 4750 DNA/RNA sequenced adult AML patients (>35) were also included in the analysis. Statistics were performed using Fisher's exact test. **Results:** pAML patients (infant, childhood, & adolescent) had a high prevalence of FLT3 & NRAS variants (17.4% & 15.2%) & fusions (26.2%) while YA AML had a high prevalence of fusions (29.2%), FLT3 (20%), NRAS (12.5%), & WT1 (12.6%) variants. Adult AML had a high prevalence of TET2 (18.4%), DNTM3A (18.3%), ASXL1 (16.8%), SRSF2 (14.8%), & TP53 (14.2%) variants, highlighting an increased prevalence of mutations associated with clonal hematopoiesis or prior chronic myeloid neoplasms. Infant AML had a higher number of GATA1 variants (33.3% vs. 0% - 2%, p<0.00001) vs. childhood, adolescent, & YA AML; trisomy 21 was present in 90% of patients by CNV detection. Fusions were only found in 5% of infant AML (p=0.02) vs. 29.2% - 34.5% in other groups. FLT3 variants were lower in infant (10%) and childhood AML (13.7%) vs. adolescent (25.5%) & YA (20%) while NRAS variants were higher in adolescent AML (21.6% vs. 6.7% - 13.7%). Childhood AML had a higher prevalence of RUNX1 fusions (16.1% vs. 0 – 5.4%, p=0.03) & Adolescent AML had a higher prevalence of PML::RARA fusions (13.8% vs. 0% – 6.5%) vs. other groups. YA AML had a higher prevalence of WT1 variants (12.6% vs. 0% - 7.8%, p=0.02). CNV loss in IKZF1 (7p12) were more prevalent in adolescent AML (10.3% vs. 0-0.5%, p=0.002); EZH2 CNV loss (7q36) were more prevalent in YA & childhood AML (4.7% & 3.4% vs. 0%). Upon aggregating genes by their molecular function, infant AML had a lower prevalence of variants in epigenetic genes (6.7% vs. 15.57-24.8%, p=0.02), RAS (10% vs. 23.2%-25.5%), & signaling genes (16.7% vs. 27.5% – 41.2%). Variants in DNA repair genes were more frequent in adolescent AML (13.7% vs. 3.9% - 6.7%, p=0.01). **Conclusions:** Infant, childhood, adolescent, & YA AML harbor unique genetic profiles that distinguish themselves from each other and reflect divergent and evolutionarily favored mechanisms behind leukemogenesis. Understanding these genetic profiles can help predict prognosis & help tailor more effective treatments. Research Sponsor: None.

6545 **Poster Session**

TP53 mutation adoption of stromal-adhesion/neuronal-like programs as a driver of stress adaptation and acute myelogenous leukemia cell survival. First Author: Alexandra Thalberg, University of Minnesota, Minneapolis, MN

Background: *TP53*-mutated AML is associated with early relapse and poor survival, highlighting the need to define p53-driven transcriptional programs that may reveal targetable therapeutic vulnerabilities. Systematic deconvolution of the TP53-associated transcriptome provides a critical framework to uncover dependencies associated with drug resistance. **Methods:** After IRB approval, 311 AML patients were screened; 93 (30%) with available NGS were included (32 TP53-mutated, 61 TP53-wild type). Bulk transcriptome data were available for 11 TP53+ and 13 TP53-WT cases. Overall survival was analyzed using Kaplan–Meier and multivariable Cox regression. Transcriptional modules predictive of TP53+ AML were identified using Random Forest and pathway enrichment via KEGG/Reactome with confirmation by ToppGene. Public single-cell RNA-seq datasets from the MIT Single Cell Portal were queried to assess whether low TP53 expression states recapitulate bulk TP53-mutated transcriptional programs. **Results:** OS was 168 and 624 days (d) in TP53+ and TP53 WT cases (HR = 4.2, p = 0.02). Only CK retained independent effect for OS (HR = 0.33, 95% CI = 0.13–0.82, p = 0.014) when accounting for TP53 mut status and age. *TP53* mut status imprinted a deep transcriptomic signature (AUC = 0.94). Top upregulated genes included FHL2 (p = 4.0×10−6, FDR = 0.004), HMGA2 (p = 1.4×10−3, FDR = 0.02), ARHGEF12 (p = 5.2×10−3, FDR = 0.04), RYR3 (p = 2.1×10−3, FDR = 0.03), LRRC7 (p = 7.7×10−3, FDR = 0.05), ALDH1A1 (p = 1.4×10−3, FDR = 0.02). Top downregulated genes included CSF1 (p = 4.7×10−4, FDR = 0.007), CD34 (p = 1.2×10−3, FDR = 0.01). To uncover pathway-level shifts co-opted by TP53+ AML, we contrasted pathway-level projection against TP53 WT cases. Upregulated pathways included adhesion / stromal dependence (p = 0.0004; FDR = 0.0028), neurotrophin / calcium signaling / Ca2+-coupled survival (p = 0.0006, FDR = 0.0021). However, downregulated pathways included cytokine-cytokine receptor interaction (p = 4.7×10−4, FDR = 0.007) and myeloid differentiation (p = 1.2×10−3, FDR = 0.01) [Fig. 2]. Interestingly, in lineage-resolved single-cell reference, low TP53 GE was visually colocalized with perivascular/stromal cells exhibiting high FHL2 and THY1 (CD90) expression. This data reconfirms prior data suggesting that reduced TP53 function favors niche-adapted perivascular/MSC-like reprogramming (THY1-high) that protects "resistant AML clones" (Mizuno et al., ASH 2024). **Conclusions:** These findings unveil that TP53+ AML co-opts leukemic blasts toward a stromal-adhesive and neuronal-like state, allowing survival under metabolic and therapeutic stress. Reversing stromal adhesive / neuronal-like rewiring may attenuate *TP53*+ blasts hijacking on vascular niche that maintains relapse potential. Research Sponsor: None.

6546 **Poster Session**

Induction failure (IF) as a prognostic marker in adult acute lymphoblastic leukemia (ALL). First Author: Yosef Joseph Rene Amel Riazat Kesh, Weill Cornell Medical Center/NewYork Presbyterian, New York City, NY

Background: Despite advances in the treatment of adult ALL, risk factors for IF and optimal management are poorly understood. We aimed to characterize patients (pts) with IF after therapy for newly diagnosed (nd)ALL and their outcomes. **Methods:** We performed a retrospective chart review of adult ndALL pts treated at Weill Cornell Medicine from 2012-2025. We defined IF as failure to achieve < 5% bone marrow blasts, count recovery and extramedullary disease clearance after 1 cycle of induction. Fisher's exact test was used for analysis of discrete variables and Wilcoxon rank-sum test for continuous ones. **Results:** Among 220 pts, 48.2% were female, mean age at diagnosis was 50.5 (18-87) yrs, 74.5% had B-cell ALL (of which 41.5% Ph+), with median follow-up 24.5 months. 34 pts (15.5%) had IF (22 B cell, 12 T cell). B-cell IF patients were more likely to have Ph-(77.3% vs 50%, p=0.0211) or Ph-like phenotype (13.6% vs 3.5%, p=0.0753). IF pts were more likely to have CNS disease at diagnosis (p= 0.034). There was no significant difference in baseline median white cell count (13.18 vs 9.60 p=0.4) or LDH (448 vs 517 p=0.17) in IF vs non-IF pts. IF was not associated with age, asparaginase-treatment, BMI, abnormal cytogenetics, pertinent mutations, or year of diagnosis. On multivariable logistic analysis controlling for age and lineage, CNS disease at diagnosis remained associated with IF (OR 2.81, p=0.0343). Overall survival (OS) was significantly worse in IF vs non-IF pts at 3-years (29.2% vs 66.8%, p = 0.0002). OS did not vary by CNS disease at diagnosis in IF pts. Of IF pts, 27/34 (79.4%) achieved CR with subsequent therapy (median time to CR 68.5 days, range 21-228), with improved survival vs the 7 pts (5 B cell, 2 T cell) who did not (p = 0.00001). 4/7 patients without CR died within 4 months, and none of these 7 patients received allo-SCT. In the 27 IF pts attaining later CR, there was a trend towards worse OS vs non-IF pts (1029 days vs not reached, p=0.0659), though importantly a subset of 10 pts who achieved minimal residual disease (MRD)-negativity had OS similar to the non-IF group (p=0.95). IF patients were more likely to receive allo-SCT than non-IF patients (51.4% vs 29.7%, p=0.0164). Receiving allo-SCT tended to be associated with improved survival in this group (p=0.0578) vs no allo-SCT. 16/22 B cell IF patients received blinatumomab and/or inotuzumab. These were not associated with MRD-negative status or allo-SCT, but did show a trend towards subsequent CR (p=0.1) and better OS (p=0.1119). **Conclusions:** In our single-center retrospective cohort of ALL pts, 15.5% had IF. 29.4% of these patients (4.5% of the total cohort) were able to achieve MRD- status with subsequent treatment, resulting in outcomes comparable to pts without IF. ALL-IF patients should be closely monitored for MRD and may benefit from early application of immunotherapeutic approaches and/or allo-SCT. Research Sponsor: None.

6547 **Poster Session**

Phase 1 study of venetoclax combined with a 10-day regimen of decitabine in subjects with high-risk acute myeloid leukemia. First Author: Rafael Madero Marroquin, Section of Hematology & Oncology, Department of Medicine, University of Chicago, Chicago, IL

Background: We and others have reported the antileukemic activity of a 10-day regimen of the hypomethylating agent (HMA), decitabine (DEC), in high-risk acute myeloid leukemia (AML). Venetoclax (VEN), at a standard (std) dose of 400 mg, combined with HMA, at a std schedule, has improved AML outcomes. We aimed to investigate the safety of adding VEN to the 10-day regimen of DEC and explore the effects of BCL2 inhibition on the immune repertoire. **Methods:** This was a multicenter, investigator-initiated, dose-escalation study in adults with high-risk AML defined as, disease with a *TP53* mutation, adverse-risk cytogenetics or relapsed/refractory (R/R). Patients (pts) were naïve to HMA and VEN. The primary endpoint was to establish the maximum tolerated dose (MTD) of VEN when combined with a 10-day DEC schedule. Dose-limiting toxicities (DLT) were evaluated during cycle 1. In the absence of a DLT, 3-6 evaluable pts were enrolled per dose level (DL) or until the 400mg DL of VEN was reached (Table 1). Peripheral blood mononuclear cells (PBMCs) were isolated before and after treatment. Shifts in the immune landscape and BCL2 family expression were profiled with spectral flow cytometry. **Results:** 14 pts were enrolled, with a median age of 66.5 years (range 19-77); including 9 pts (64%) with R/R AML, 8 (57%) with adverse-risk cytogenetics and 6 (43%) with a *TP53* mutation. One pt had a DLT at DL1, due to grade (G) 4 neutropenia and persistent marrow aplasia in the absence of leukemia beyond day 42. One patient with R/R AML and pre-existing elevated alanine aminotransferase (ALT) secondary to known graft-versus-host disease developed G2 ALT elevation. 3 pts were then enrolled at DL-1, before reescalation back up to DL1. 2 pts at DL1 were deemed not eligible for DLT evaluation, requiring an additional 2 pts enrolled at DL1, without DLT, to confirm safety. The MTD was determined to be DL2 (400 mg). 5 pts (36%) had a complete remission (CR) or CR with incomplete count recovery (CRi). Non-hematologic or infectious G1-2 toxicities included fatigue (43%), diarrhea (43%) and decreased appetite (36%). 1 pt died of suspected sepsis outside of the DLT evaluation period. 7 pts had serial PBMCs available for multiparameter flow cytometric immune and BCL2 family profiling. Of these, 3 responders had strong induction of BCL2 in CD4+/CD8+ lymphocytes and B cells after 1 cycle and were enriched for a population of "senescent" CD8+ T cells that had relatively low expression of coinhibitory markers (PD-1, LAG3, TIM3). **Conclusions:** A 10-day DEC+VEN regimen is feasible in high-risk AML, with myelosuppression being the major DLT. The recommended phase 2 dose is 400mg VEN (DL2), but responses were also seen at 200mg. The immune profile of responders have demonstrated intriguing patterns that merit investigation in a larger HMA+VEN cohort. Clinical trial information: NCT03844815. Research Sponsor: Abbvie.

DL	DEC dose(D1-10)mg/m2	VEN dose (D1-21)mg	# of pts	DLT	CR	CRi	No Response
-1	15	100	3	0	0	0	3
1	20	200	8	1	1	3	4
2	20	400	3	0	0	1	2

6548 **Poster Session**

Time to response with HMA/venetoclax as a predictor of survival in acute myeloid leukemia: Analysis of 1- vs 2-cycle responders. First Author: Rafeh Safdar, University of Kentucky, Lexington, KY

Background: Hypomethylating agents (HMA) with venetoclax are the standard of care for patients with AML ineligible for intensive chemotherapy. However, the prognostic significance of time to response and the optimal duration of venetoclax, often modified in real-world practice due to myelosuppression, remain unclear. **Methods:** We conducted a retrospective analysis of adults with AML achieving CR/CRi with HMA/venetoclax at University of Kentucky from 2016-2025. Patients were stratified by cycle of response: 1 vs 2 cycles, using ELN 2022 response criteria. These groups were compared by demographics, cytogenetic and mutational profiles, and allogeneic HSCT. RFS and OS were estimated using Kaplan-Meier methods and compared with log-rank tests. Cox models evaluated associations between cycle of response, response type (CR vs CRi), and survival outcomes. **Results:** Eighty-six responding patients were included, with 69 (80%) achieving response after 1 cycle and 17 (20%) achieving response after 2 cycles. Median age was 66.7 vs. 67.1 years, male sex was 58% vs. 76%, and ELN risk distribution was similar: favorable 25% vs. 18% and adverse 64% vs. 65% (p=0.671). Frequent cytogenetic profiles included normal karyotype (44% vs. 41%) and complex karyotype (27% vs. 24%), and common mutations included *IDH1/2* (23% vs. 18%), *DNMT3A* (19% vs. 24%), and *NPM1* (22% vs. 12%). Overall, baseline demographics and cytogenetic/mutational profile were similar between 1-cycle and 2-cycle responders, supporting comparability of these groups for outcome analyses. With a median follow-up of 23.8 months, relapse occurred in 36% of 1-cycle responders vs. 82% of 2-cycle responders (p=0.002). Inferior RFS was noted in 2-cycle responders (HR 3.04, p=0.002), which remained after adjusting for total venetoclax exposure (HR 3.26, p=0.002). Median OS was 22.8 months (95% CI 14.0–NR) for 1-cycle responders and 12.7 months (95% CI 7.2–NR) for 2-cycle responders (p=0.01). In Cox models, 2-cycle response was associated with significantly inferior OS (HR 2.33, p=0.012), which persisted after adjusting for venetoclax exposure (HR 2.26, p=0.018). Hematologic recovery at time of CR was assessed and was not significantly associated with cycle of response or survival outcomes. Increased venetoclax exposure was associated with improved OS (HR 0.82 per day; p=0.049). When venetoclax exposure was dichotomized, receipt of ≤14 days was associated with inferior OS (HR 2.49; p=0.028). In this cohort, 6% of 1-cycle responders and 18% of 2-cycle responders proceeded to allogeneic HSCT (p=0.14). **Conclusions:** Delayed response beyond 1 cycle in patients receiving HMA/venetoclax identifies AML patients at higher risk of relapse and inferior survival. Time to response can inform early risk-adapted strategies, including venetoclax optimization. Research Sponsor: None.

6549 **Poster Session**

Cladribine/cyclophosphamide lymphodepletion efficacy and toxicity in CD19 CAR-T therapy for B-ALL. First Author: Kriti Gera, University of South Florida/Moffitt Cancer Center, Tampa, FL

Background: During an international fludarabine (Flu) shortage, our center adopted cladribine (Cla) as a substitute for Flu with cyclophosphamide (Cy) for lymphodepletion (LD) prior to CAR-T therapy in patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL). We evaluated clinical outcomes and toxicity with Cla/Cy LD. **Methods:** We conducted a retrospective, single-center analysis of R/R B-ALL patients who received CD19-directed CAR-T therapy between January 2018 and April 2025. The Cla/Cy regimen substituted Flu 30 mg/m² with Cla 5 mg/m²/day on days −5 to −3. ALL-HT risk was calculated (Nair et al, 2025). CRS and ICANS were graded per ASTCT; cytopenias per CTCAE v5.0. Early (<30 days) and late (31–100 days) infections were assessed. Overall survival (OS), Event free survival (EFS, event=progression or death) and Minimal residual disease (MRD) status by clonoSEQ assay at Day 30 bone marrow biopsy were assessed. **Results:** We analyzed 53 patients (brexu-cel n=49; tisa-cel n=4). 28 received Flu/Cy and 25 received Cla/Cy. Baseline characteristics are outlined in Table 1. Three patients died before day 30 and two before day 100. Ten patients underwent allo-SCT within 6 months of CAR-T. Rates of grade ≥3 CRS (4% vs 12%, p=0.29) and ICANS (40% vs 24%, p=0.25) did not differ. MRD negativity at day 30 was comparable (Cla/Cy 81.8% vs Flu/Cy 75.0%, p=0.71). Early infection rates were similar; however, late infections were more frequent with Flu/Cy (48% vs 17.4%, p=0.034), with a persistent trend after ALL-HT adjustment (adjusted OR 3.54, p=0.073). Grade ≥3 thrombocytopenia (35.7% vs 8.0%, p=0.022) and neutropenia (25.0% vs 4.0%, p=0.05) at day 90 were higher with Flu/Cy, with similar trends after adjustment (adjusted OR 4.71, p = 0.082 and adjusted OR 7.88, p = 0.067, respectively). Neutrophil recovery (ANC >1000) time was comparable (median 17 vs 18 days, p=0.10). With a median follow-up of 14.6(Flu/Cy) and 13.1 months(Cla/Cy), EFS (6.8 vs 18.1 months, p=0.45) and OS (33.9 months vs not reached, p=0.25) were similar. **Conclusions:** Cla/Cy demonstrated comparable efficacy to Flu/Cy with lower toxicity, including fewer late infections and severe cytopenias. These findings suggest Cla/Cy may represent a safer alternative lymphodepletion strategy. Prospective studies are warranted to validate these observations. Research Sponsor: None.

Baseline characteristics of study cohort.

Characteristic	Flu/Cy (n=28)	Clad/Cy (n=25)	p-value
Age, median (IQR)	38.0 (30.2–58.5)	47.0 (26.0–64.0)	0.77
Male sex, n (%)	18 (64.3)	13 (52.0)	0.53
White race, n (%)	25 (89.3)	20 (80.0)	0.35
KPS ≥80, n (%)	24 (85.7)	21 (84.0)	1.00
Marrow blasts pre-LD, median (IQR)	2.0 (1.0–3.5)	1.5 (0.5–11.0)	0.67
Ph+ ALL, n (%)	11 (39.3)	12 (48.0)	0.78
Prior allo-HSCT, n (%)	6 (21.4)	7 (28.0)	0.56
Prior lines of therapy, median (IQR)	2 (2–3)	3 (2–3)	0.96
High-risk ALL-HT, n (%)	12 (42.9)	3 (12.0)	**0.016**

6550 **Poster Session**

A phase II, single-arm study of romiplostim N01 for cancer treatment–induced thrombocytopenia in leukemia patients. First Author: Aijie Huang, The First Affiliated Hospital of University of Science and Technology of China, Hefei, Hefei , Anhui, China

Background: Cancer Treatment-Induced Thrombocytopenia (CTIT) poses a significant challenge in leukemia treatment, increasing bleeding risk and potentially disrupting therapy. Romiplostim N01 is recommended for CTIT but lacking specific clinical data in leukemia patients. This study evaluates its efficacy and safety in this population. **Methods:** This is a multi-center, single-arm, phase II study conducted from February 2025 to February 2027. We plan to enroll 97 adult patients (18 - 75 years) with leukemia who developed CTIT (platelets $< 50\times10^9$/L) after antitumor therapy. Patients received subcutaneous Romiplostim N01 at a starting dose of 5 μg/kg once weekly for up to 8 weeks. The primary endpoint is the proportion of patients achieving platelet recovery ($\geq 50\times10^9$/L) after two week. Secondary endpoints include response rate within 7 days, median time to platelet recovery ($\geq 50\times10^9$/L and $\geq 100\times10^9$/L), platelet transfusion requirements, and safety. **Results:** As of January 27, 2026, a total of 49 subjects were enrolled (18 males, 31 females) with a median age of 57 years (range, 17–75). Primary tumor types included acute myeloid leukemia (AML, n=40), acute lymphoblastic leukemia (ALL, n=7), mixed phenotype acute leukemia (MPAL, n=1), and myelodysplastic syndromes (MDS, n=1). All patients received standard chemotherapy and had an ECOG performance status of 0–2 at enrollment; 35 of 49 patients had an ECOG score of 0–1. All subjects received Romiplostim N01 (5 μg/kg/week): 13 subjects received one dose, 14 received two doses, and 22 received ≥ 3 doses. The median baseline platelet count was 15×10^9/L (range, 1–49$\times10^9$/L). 40.8% (20/49) of patients achieved a response within 7 days. 23 subjects (46.9%, 23/49) achieved the primary endpoint (platelet count $\geq 50\times10^9$/L) within two weeks. The median time to platelet recovery $\geq 50\times10^9$/L was 7 days (95% CI, 6–9). A total of 21 patients achieved a platelet count of $\geq100\times10^9$/L; the median time to recovery was 13 days (95% CI, 10–22). The median platelet transfusion dose was 2.0 units (95% CI, 1–3). Adverse events were mild to moderate, most commonly infections. No treatment-related serious adverse events (SAEs) were reported. **Conclusions:** Preliminary findings suggest Romiplostim N01 may be effective in promoting platelet recovery with a manageable safety profile in leukemia patients with CTIT. Final results will provide further evidence for its clinical application. Clinical trial information: NCT06898983. Research Sponsor: National Natural Science Foundation of China (82270223 82500286); Anhui Provincial Health Research Project (AHWJ2024BAa10021); Anhui Provincial Department of Education Scientific Research Project (2023AH010079); Anhui Provincial Natural Science Foundation (2308085J09); USTC Research Funds of the Double First-Class Initiative (YD9110002109).

6551 **Poster Session**

Comparative effectiveness and toxicity of CAR-T therapy versus blinatumomab in adult B-cell acute lymphoblastic leukemia: A real-world propensity-matched analysis. First Author: Colton Davis, Rochester Regional Health (RRH)-Unity Hospital, Rochester, NY

Background: Chimeric antigen receptor T-cell (CAR-T) therapy and blinatumomab are established treatment options for relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL). While CAR-T therapy offers durable disease control, it is associated with significant immune-mediated toxicities, including cytokine release syndrome (CRS) and neurotoxicity. Comparative real-world data evaluating long-term mortality and toxicity outcomes between CAR-T therapy and blinatumomab remain limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Analytics Network. Adult patients with B-cell acute lymphoblastic leukemia treated with either CAR-T therapy or blinatumomab were identified. Propensity score matching (1:1) was performed to balance baseline demographic and clinical characteristics, yielding 306 patients in each cohort. Primary outcomes included all-cause mortality at 1 and 3 years. Secondary outcomes included cytokine release syndrome at 1 year and neurotoxicity (including delirium, encephalopathy, and altered mental status) at 3 months, 1 year, and 3 years. Outcomes were assessed using risk ratios (RR), odds ratios (OR), Kaplan–Meier survival analysis, and Cox proportional hazards models. **Results:** After propensity matching, 612 patients were analyzed (306 per cohort). At 1 year, all-cause mortality was significantly higher with CAR-T than blinatumomab (50.98% vs 17.97%; RR 2.84, 95% CI 2.18–3.69; p<0.0001). Kaplan–Meier analysis showed inferior survival with CAR-T (HR 3.48, 95% CI 2.56–4.74; log-rank p<0.0001). This excess mortality persisted at 3 years (52.61% vs 18.95%; RR 2.78, 95% CI 2.15–3.58; p<0.0001; HR 3.43, 95% CI 2.54–4.63). CAR-T was associated with higher cytokine release syndrome at 1 year (20.59% vs 5.88%; RR 3.50, 95% CI 2.12–5.77; p<0.0001). Neurotoxicity was consistently more frequent with CAR-T: 27.78% vs 13.40% at 3 months (RR 2.07, 95% CI 1.48–2.91; p<0.0001), 25.16% vs 11.44% at 1 year (RR 2.20, 95% CI 1.52–3.18; p<0.0001), and 27.78% vs 13.40% at 3 years (RR 2.07, 95% CI 1.49–3.15; p<0.0001). Kaplan–Meier analyses confirmed a persistently higher cumulative neurotoxicity risk with CAR-T across all time points. **Conclusions:** In this large real-world propensity-matched analysis, CAR-T therapy for B-cell ALL was associated with significantly higher short- and long-term mortality compared with blinatumomab, as well as markedly increased risks of cytokine release syndrome and neurotoxicity. These findings highlight the substantial toxicity burden associated with CAR-T therapy in routine clinical practice and underscore the importance of careful patient selection, early toxicity recognition, and risk-benefit stratification when choosing between advanced immunotherapeutic options for B-ALL. Research Sponsor: None.

6552 **Poster Session**

Frailty-comorbidity discordance and non-relapse mortality after allogeneic hematopoietic cell transplantation. First Author: Nihar Desai, Princess Margaret Hospital, Toronto, ON, Canada

Background: Non-relapse mortality (NRM) is a barrier to successful allogeneic hematopoietic cell transplantation (HCT). The HCT-Comorbidity Index (HCT-CI) is used for pre-HCT risk assessment but does not capture physiological reserve. Frailty, assessed by the validated Hematopoietic Cell Transplantation-Frailty Scale (HCT-FS), independently predicts post-HCT outcomes; however, the clinical consequences of frailty-comorbidity discordance remain poorly defined. We hypothesized that such discordance identifies patients whose transplant risk may be misclassified by HCT-CI alone. **Methods:** We retrospectively analyzed 692 patients undergoing first allogeneic HCT at our center. Frailty was assessed using HCT-FS and categorized as fit, pre-frail, frail. For discordance analyses, HCT-FS was dichotomized as fit vs pre-frail/frail. HCT-CI was dichotomized as low (<3) vs high (≥ 3). Patients were classified into 4 groups: fit+low HCT-CI (group I), fit+high HCT-CI (group II), pre-frail/frail+low HCT-CI (group III), and pre-frail/frail+high HCT-CI (group IV). Fine-Gray competing-risk models and Cox regression was used for NRM and overall survival (OS), respectively. **Results:** The median age was 61 years (Q1-Q3: 52-67), and 399 (58%) were male. At baseline, 287 (42%) patients had an HCT-CI ≥ 3. HCT-FS classified 252 (36%) as fit, 373 (54%) as pre-frail, and 67 (10%) as frail. Overall, 355 (51%) patients demonstrated discordant HCT-FS and HCT-CI scores: 78 (11%) as group II, and 277 (40%) classified as group III. At 2 years, NRM and OS were 11.2% (95% CI, 7-16) and 79.3% (95% CI, 73-84) in fit patients, 17.4% (95% CI, 14-22) and 67.0% (95% CI, 62-72) in pre-frail patients, and 33.5% (95% CI, 22-45) and 54.9% (95% CI, 42-66) in frail patients, respectively ($p<0.01$ for both). In multivariable analyses, HCT-FS, HCT-CI, and age at HCT were independently associated with NRM and OS. Compared with fit patients with low HCT-CI (group I), pre-frail/frail patients with HCT-CI ≥ 3 (group IV) experienced the highest risk of NRM (sub-distribution hazard ratio (sHR) 2.7, 95% CI 1.5-5, $p<0.01$). Pre-frail/frail patients with HCT-CI <3 (group III) also had an increased risk of NRM (sHR 1.9, 95% CI 1.1-3.5, p=0.01). Fit patients with HCT-CI ≥ 3 (group II) did not have a significant increase in NRM risk (sHR 1.7, 95% CI 0.8-3.7, p=0.15). The corresponding HR for OS were 2.1 (95% CI 1-3; $p<0.01$) for group IV, 1.7 (95% CI 1-3; $p<0.01$) for group III, and 1.4 (95% CI 0.8-2.5; p=0.18) for group II, compared with group I. **Conclusions:** Frailty-comorbidity discordance was observed in 51% of patients and has prognostic implications. Pre-frail and frail patients with low HCT-CI experience higher NRM than would be predicted by HCT-CI alone, suggesting underestimation of transplant risk when frailty is not assessed. Integrating HCT-FS with HCT-CI may improve risk stratification and better identify patients at high risk for NRM. Research Sponsor: None.

6553 **Poster Session**

Clinical outcomes of *TP53*-mutated myeloid neoplasms after allogeneic hematopoietic cell transplantation: A Canadian multicenter propensity score–matched analysis. First Author: Nihar Desai, Princess Margaret Hospital, Toronto, ON, Canada

Background: *TP53* mutations define a biologically aggressive subset of myeloid malignancies with poor outcomes. We evaluated clinical, disease-related, and transplant-associated variables influencing post-allogeneic hematopoietic cell transplant (HCT) outcomes in this high-risk group. **Methods:** We conducted a retrospective multicenter study across 10 Canadian transplant centers, including 153 individuals with *TP53*-mutated and 2,207 patients with *TP53* wild-type acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) from the Cell Therapy and Transplant Canada (CTTC) registry. Propensity score matching was performed to account for baseline differences. The primary outcomes were relapse and overall survival (OS) after HCT. **Results:** Presence of *TP53* mutation was associated with increased risk of relapse compared with *TP53* wild-type (HR 2.21; 95% CI: 1.5–3.1; $p<0.01$). Among *TP53*-mutated patients (n=153), with a median follow-up of 35.8 months (Q1-Q3: 29-48), the 2-year cumulative incidence of relapse was 53.2% (95% CI: 44.4-61.2), and OS 40.1% (95% CI: 31.6-48.4). In multivariable analysis, multi-hit *TP53* mutations (HR 2.17, 95% CI: 1.3-3.7; $p<0.01$), and graft-vs-host disease (GVHD) prophylaxis regimens containing anti-thymocyte globulin (ATG) with (HR 3.53, 95% CI: 1.5-8.1; $p<0.01$) or without (HR 2.59, 95% CI: 1.2-5.6; p=0.01) post-transplant cyclophosphamide were associated with higher relapse risk. Conditioning regimen intensity, and chronic GVHD, modelled as a time-dependent covariable, did not significantly impact relapse, while chronic GVHD was associated with improved OS (HR 0.46; 95% CI: 0.2-0.9, p=0.03). **Conclusions:** In patients with myeloid malignancies, *TP53* mutations are associated with a high risk of relapse and poor survival after HCT, while chronic GVHD appears to be protective, underscoring the importance of careful selection of GVHD prophylaxis and the need for effective post-transplant strategies in this high-risk population. Research Sponsor: None.

Multivariable analysis.

Variable	Hazard Ratio	95% CI	p value
Relapse			
***TP53* mutation status**			
Single hit	Ref	Ref	Ref
Multi hit	2.17	1.27-3.71	0.005
Disease risk index			
Intermediate	Ref	Ref	Ref
High/very high	1.53	0.77-3.03	0.220
GVHD prophylaxis			
CNI-MTX	Ref	Ref	Ref
ATG-CNI-MTX	2.59	1.21-5.56	0.014
ATG-PTCY-CNI	3.53	1.52-8.17	0.003
PTCY-CNI-MMF	1.66	0.58-4.74	0.350
Chronic GVHD (time dependent)	1.25	0.63–2.45	0.526
Overall survival			
***TP53* mutation status**			
Single hit	Ref	Ref	Ref
Multi hit	2.26	1.30-3.90	0.003
Disease risk index			
Intermediate	Ref	Ref	Ref
High/very high	0.93	0.49-1.77	0.823
GVHD prophylaxis			
CNI-MTX	Ref	Ref	Ref
ATG-CNI-MTX	2.18	1.12-4.24	0.021
ATG-PTCY-CNI	1.62	0.73-3.61	0.236
PTCY-CNI-MMF	1.04	0.36-2.99	0.949
Chronic GVHD (time dependent)	0.46	0.23-0.93	0.030

6554 **Poster Session**

Allele-specific targeting of CD33 as a novel approach to enhance CAR-T selectivity in relapsed acute myeloid leukemia post–allogeneic transplantation. First Author: Guido David Pelaez, Washington University School of Medicine, Saint Louis, MO

Background: Relapse after allogeneic hematopoietic cell transplant (HCT) represents the most common treatment failure in acute myeloid leukemia (AML), urging the need for new therapies. Chimeric antigen receptor (CAR) T cells have shown efficacy in lymphoid and plasma cell malignancies but have not yet successfully translated to myeloid disease. This could in part be due to the expression of target antigens on normal myeloid cells, which might result in significant on-target but off-tumor effects. Exploiting a single nucleotide polymorphism (SNP) in *SIGLEC3*, which encodes CD33, to target relapsing AML cells while selectively sparing donor-derived hematopoietic cells could improve the efficacy of anti-CD33 CAR-T cells in treating AML. **Methods:** We evaluated the *in vitro* efficacy and specificity of CAR-T cells that target each of two alleles of a common SNP in CD33 (rs2455069, *CD33 Arg69Gly*). Controls included untransduced activated T-cells (UTD, negative control) and CAR-T cells targeting a different CD33 epitope ($CART33^{Pan}$ positive control). Effector cells were incubated with CD33-expressing AML targets for 24 hours at serial effector-to-target ratios, and surviving target cells were quantified via flow cytometry to calculate percent cell killing. Initial screens used Jurkat cells lentivirally transduced with CD33 of each polymorphism ($Jurkat33^{Gly}$ or $Jurkat33^{Arg}$) to characterize CAR-T efficacy and specificity. Subsequent tests used MOLM-13 (homozygous $CD33^{Arg}$) and KG-1 (homozygous $CD33^{Gly}$) AML cell lines. Statistical comparisons of generated CAR-T cytotoxicity curves were performed with two-way ANOVA. Killing assays were performed with at least six biologic replicates. **Results:** $CART33^{Gly}$ and $CART33^{Arg}$ cells each showed statistically equivalent killing against their concordant Jurkat33 targets compared to $CART33^{Pan}$ cells. Each CAR directed minimal killing of discordant Jurkat33 targets, similar to UTD controls. In KG-1 ($CD33^{Gly}$) cells, $CART33^{Gly}$ showed similar killing efficacy as $CART33^{Pan}$cells, while $CART33^{Arg}$ were statistically equivalent to UTD cells at multiple E:T ratios. In MOLM-13 ($CD33^{Arg}$) cells, $CART33^{Gly}$ and $CART33^{Arg}$ exhibited mixed efficacy and specificity: at lower E:T ratios (1:16 to 1:8), $CART33^{Gly}$ was statistically equivalent to untransduced controls, but began to demonstrate more nonspecific toxicity at E:T above 1:4. $CART33^{Arg}$ exhibited significant cytotoxicity once above E:T of 1:8, but only achieved similar toxicity to $CART33^{Pan}$ at E:T ratios over 1:2. **Conclusions:** Allele-specific CART33 cells demonstrate promising efficacy and specificity in killing AML cells expressing either $CD33^{Gly}$ or $CD33^{Gly}$. Further studies are underway to test efficacy *in vivo* against primary AML cells and safety toward normal hematopoietic progenitor cells that express the alternative CD33 allele. Research Sponsor: None.

6556 **Poster Session**

Pre-transplant MRD negativity and TP53 mutation status determine survival after CAR-T therapy bridged to allo-HSCT for refractory/relapse B-ALL. First Author: Zhihui Li, Department of Bone Marrow Transplantation,Beijing Gobroad Boren Hospital, Beijing, China

Background: The feasibility and outcomes of bridging relapsed/refractory (R/R) B-lineage acute lymphoblastic leukemia (B-ALL) patients to allogeneic hematopoietic stem cell transplantation (allo-HSCT) following CAR-T therapy require further investigation. This study evaluated long-term outcomes and prognostic factors in this setting. **Methods:** We conducted a retrospective analysis of 300 consecutive R/R B-lineage leukemia patients (295 B-ALL, 98.3%) who underwent allo-HSCT after CAR-T therapy. Somatic mutation screening via next-generation sequencing was performed on 179 patients. Univariate Cox regression analyzed factors associated with transplant outcomes. A contemporaneous cohort of 36 transplanted patients without prior CAR-T served as a comparator. **Results:** Median age at transplant was 14 years (range, 1-68). Prior to HSCT, 220 (73.3%), 75 (25.0%), and 5 (1.7%) patients received CD19-, CD22-, and Mix-CAR-T, respectively; 265 (88.3%) achieved complete remission (CR), and 39 (13.0%) were minimal residual disease (MRD)-positive. The 3-year disease-free survival (DFS), overall survival (OS), cumulative incidence of relapse (CIR), and non-relapse mortality (NRM) for the CAR-T bridging cohort were 64.0% (95%CI, 58.6-69.8%), 74.5% (95%CI, 69.5-79.9%), 28.4% (95%CI, 23.6-34.1%), and 7.6% (95%CI, 5.04-11.3%), respectively. Outcomes did not differ significantly from the non-CAR-T cohort (OS, p=0.54; DFS, p=0.24). Failure to achieve CR pre-HSCT (HR=3.31, $p<0.0001$) and MRD-positivity (HR=3.69, $p<0.0001$) were risk factors for relapse, while chronic graft-versus-host disease was protective (HR=0.35, p=0.0002). Pre-HSCT MRD-positivity, fungal infection, and viral cystitis increased NRM risk. TP53 (15.1%), KMT2D (14.5%), NRAS (14.0%), KRAS (13.4%), and ABL1 (9.5%) were the most frequently mutated genes. TP53 mutation was a significant risk factor for inferior DFS (HR=3.37, $p<0.0001$) and OS (HR=3.56, $p<0.0001$). GNAS and KDM6A mutations predicted higher CIR, while ETV6 mutation was associated with increased NRM. **Conclusions:** Bridging to allo-HSCT after CAR-T therapy is a feasible and effective strategy for R/R B-ALL, providing substantial long-term survival. Achieving pre-transplant CR and MRD-negative status is critical for outcome. Somatic mutations, particularly TP53, hold significant prognostic value, aiding in risk stratification and treatment optimization for these patients. Research Sponsor: None.

6557 **Poster Session**

MSNPseq: An NGS-based assay for chimerism detection and risk assessment in allogeneic HSCT. First Author: Zhe Zou, Central Laboratory, the Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China

Background: Chimerism (CHIM) analysis assesses the ratio of donor to recipient hematopoietic cells, confirming engraftment and detecting impending graft failure or relapse, in allogeneic hematopoietic stem cell transplantation (aHSCT). However, the conventional short tandem repeat (STR) analysis, has limited sensitivity (1–5%), often missing low-level CHIM. In this retrospective study, Multiple Single Nucleotide Polymorphism sequencing (MSNPseq), an NGS-based assay targeting DNA fragments each harboring 4–8 SNPs, demonstrated superior sensitivity and specificity compared with STR analysis, enabling reclassification of STR-negative cases and improved prognostic stratification. **Methods:** MSNPseq, based on Ion AmpliSeq technology, amplifies 100 fragments for sequencing on the Ion Torrent PGM platform, achieving >2000× depth for 96.8% of loci. Its sensitivity and accuracy were validated in simulated chimeric and post-transplant samples against STR analysis. Calibration models used pre-transplant donor/recipient data to generate tailored correction coefficients. CHIM was assessed via MSNPseq at three 30-day time points (TP1, 2, 3) post-transplant, in 741 aHSCT patients (AML 49.9%, ALL 27.4%, MDS 13.5%, lymphoma 4.7%, others 4.5%). PFS and OS were stratified by CHIM status and its dynamics to evaluate transplant outcomes, prognostic significance, and late relapse. **Results:** CHIM sensitivity was assessed using BCR-ABL1–positive standards. MSNPseq achieved a 0.01% detection limit, outperforming STR (1%) with strong correlation (R^2 = 0.9953). CHIM status was classified by donor fraction as complete (cCHIM, 100%), microchimerism (mCHIM, 99% to <100%), sub-threshold chimerism (sCHIM, 95% to <100%; below STR sensitivity), and incomplete chimerism (iCHIM, ≤95%) across three time points. While iCHIM was consistently associated with inferior PFS and OS, sCHIM and mCHIM also showed worse outcomes compared with cCHIM, defining distinct high-risk subsets. CHIM dynamics revealed decreasing sCHIM/mCHIM and increasing cCHIM/iCHIM over time. Notably, a sustained CHIM decrease >0.5% over two consecutive time points was associated with significantly poorer OS and PFS. Interestingly, sCHIM and mCHIM status, as well as a sustained CHIM decrease >0.5% over two consecutive time points, were also associated with a high risk of acute graft-versus-host disease (aGvHD). Overall, MSNPseq enables more precise CHIM stratification than STR, improving post-transplant risk assessment. **Conclusions:** MSNPseq's superior sensitivity enables more precise chimerism classification and detection of clinically relevant sCHIM and mCHIM subsets that STR often misses. These refined CHIM categories, along with sustained CHIM decline, correlate with poorer survival and higher aGvHD risk, supporting MSNPseq as a superior tool for post-aHSCT risk stratification and therapeutic guidance. Research Sponsor: None.

6558 **Poster Session**

Impact of Ori-TTV particles on in vivo CAR-T cell engineering for the treatment of hematologic malignancies. First Author: Yongqin Li, Oricell Therapeutics Co., Ltd., Shanghai, China

Background: CAR-T cell therapy has revolutionized hematological malignancy treatment, yet traditional autologous therapies face substantial logistical and financial challenges. An efficient in vivo CAR-T cell generation platform represents a transformative approach to make immunotherapies more accessible. Here, we report the design and validation of Ori-TTV, a T cell-specific lentiviral vector system capable of directly generating functional CAR-T cells within the body. **Methods:** Ori-TTV was engineered with five synergistic components: (1) an Ori Multiple Targeting Domain (Ori-MTD) for selective delivery to T lymphocytes; (2) a de-targeted fusogen; (3) a T cell-specific synthetic promoter; (4) phagocytosis-resistant modifications; and (5) serum-resistant surface engineering. Ori-TTV encodes a dual-target CAR recognizing CD19 and BCMA, enabling treatment of B-cell malignancies (e.g., non-Hodgkin lymphoma) and plasma cell–derived cancers (e.g., multiple myeloma) with potential extension to autoimmune diseases. **Results:** Ori-TTV particles are produced at high functional titers comparable to conventional broad-tropism lentiviruses and demonstrate significant resistance to macrophage phagocytosis (>50% reduction). The T cell-specific synthetic promoter drives CAR/GFP expression comparable to the EF-1α promoter in primary T cells while maintaining minimal off-target expression in non-T cells, including HEK293T producer cells and various tumor lines. Ori-TTV efficiently transduces resting T cells, achieving >80% CAR expression in PBMCs in vitro. The resulting CAR-T cells exhibit a predominantly memory phenotype with increased TSCM cells compared to Kymriah-like ex vivo CAR-T cells. Serial killing assays demonstrated potent, multi-round cytotoxicity against CD19+ and BCMA+ target cell lines with varying antigen densities. In vivo efficacy was evaluated in humanized mouse models of NHL and MM. The PBMC humanized mice were challenged with tumors and administered Ori-TTV. Bioluminescence imaging demonstrated robust tumor regression, with complete remissions in the majority of treated animals. Pharmacodynamics revealed efficient in vivo transduction, with CAR-T expansion kinetics showing peak levels at day 13 (20–30% of circulating T cells). Expanded CAR-T cells maintained a memory-enriched phenotype with significantly increased TSCM cells. Long-term monitoring confirmed durable responses without toxicity or vector-related adverse events. Furthermore, in CD34+ humanized mice, single-injection Ori-TTV caused durable depletion of peripheral B cells. **Conclusions:** These findings establish Ori-TTV as a next-generation lentiviral vector system enabling safe, efficient, and selective in vivo CAR-T cell generation. It has the potential to redefine CAR-T therapy by eliminating manufacturing barriers, reducing costs, and expanding patient access. Research Sponsor: None.

6559 **Poster Session**

Pharmacogenetic (PGx) markers of cardiovascular side effects (CVSEs) in allogeneic hematopoietic cell transplant (HCT) patients receiving post-transplant cyclophosphamide (PTCy). First Author: Neha Deshpande, Atrium Health Levine Cancer Institute, Charlotte, NC

Background: PTCy is used to prevent graft versus host disease (GVHD) post-HCT. CVSEs can be observed with Cy. We previously showed 16% of PTCy-treated patients experienced CVSEs within 30 days post-HCT. PGx determinants of Cy metabolism have been explored, but data are lacking on the impact of PGx on PTCy-related CVSEs. This study aims to identify PGx markers of CVSE risk in adult patients undergoing HCT. **Methods:** This is a retrospective PGx study of patients who underwent HCT between January 2014 and July 2024. Germline DNA was extracted from buccal swabs, and genotyping was performed using the Illumina Global Diversity Array with Enhanced PGx. The analysis focused on 99 single nucleotide polymorphisms (SNPs) in 13 candidate genes involved in Cy metabolism: GSTM1, GSTA1, GSTP1, GSTT1, CYP3A5, CYP3A4, CYP2C9, CYP2C8, CYP2C19, CYP2A6, CYP2B6, ALDH1A1, and ALDH3A1. The primary endpoint was time to CVSE occurrence at 90 days, 180 days, and 5 years post-HCT, including acute or chronic ischemic heart disease, acute myocardial infarction, angina pectoris, atrial fibrillation or flutter, other arrhythmias, cardiomyopathy, heart failure, hypertensive heart disease, pericardial effusion, pericarditis, peripheral vascular disease, and pulmonary edema. Covariates included age, sex, ancestral variation, diabetes, dyslipidemia, hypertension, atherosclerosis, and CVSEs within 2 years prior to HCT. Using an additive genetic model, a Cox proportional hazards model was generated to evaluate the association between each SNP and time to CVSE, adjusting for covariates. A CVSE risk score was developed using the total number of risk alleles from statistically significant SNPs and tested for association with time to CVSE using a Cox proportional hazards model. **Results:** Of 86 evaluable patients, the median age was 60 (range 24-78), 78% were male, 77% White, and 20% Black; 54% received haploidentical and 24.4% matched related donor HCT. The incidence of CVSEs was 27% at 90 days post-HCT, 31% at 180 days, and 58% at 5 years. The table describes three SNPs significantly associated with time to CVSE ($p<0.05$). The CVSE risk score (n=19 for low risk, 0-1 risk alleles; n=49 for intermediate, 2-3 risk alleles; n=18 for high, 4-6 risk alleles) was significantly associated with time to CVSE (HR 2.30, 95% CI 1.43-3.71, p=0.0006). **Conclusions:** PTCy-related CVSEs were common post-HCT. Single nucleotide polymorphisms in CYP2A6, GSTT1, and ALDH1A1 may influence CVSE risk post-HCT. These findings require further validation in independent datasets and may be used to develop a clinicogenomic risk model for CVSE post-HCT. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; NIH/NCI P30CA012197; Swim Across America.

SNP	Gene	Risk allele frequency	Hazard ratio (95% CI)	p value
rs1137115	CYP2A6	0.215	2.78 (1.48-5.23)	0.0015
rs1007888	GSTT1	0.494	1.78 (1.13-2.81)	0.0129
rs1330283	ALDH1A1	0.506	1.82 (1.06-3.12)	0.0301

6560 **Poster Session**

Outcomes after unrelated donor allogeneic hematopoietic cell transplantation in age ≥65 using post-transplant cyclophosphamide. First Author: Amna Bint I Munir, North Alabama Medical Center, Florence, AL

Background: The use of allogeneic hematopoietic cell transplantation (allo-HCT) in older adults has increased with reduced-intensity conditioning and post-transplant cyclophosphamide (PTCy) based GVHD prophylaxis. While PTCy has demonstrated excellent GVHD control across multiple disease types, age-related toxicities and non-relapse mortality remain significant challenges in older patients with acute leukemia and myelodysplastic syndrome (MDS). Understanding age-associated risks in contemporary unrelated donor (URD) HCT platforms may help guide patient selection, counseling, and future refinements in transplant practice. **Methods:** We analyzed adults undergoing first URD allo-HCT (8/8 or 7/8 HLA-matched) with PTCy-based GVHD prophylaxis for acute myeloid leukemia, acute lymphoblastic leukemia, or myelodysplastic syndrome reported to CIBMTR, 2017–2021, using the P-5891 dataset. Patients were grouped into <65 and ≥65 years. Outcomes included overall survival (OS), non-relapse mortality (NRM), relapse, acute GVHD, and chronic GVHD. Univariable and multivariable Cox proportional hazards or Fine-Gray competing risks models were used as appropriate. Variables with $p < 0.2$ in univariable analysis and clinically relevant factors were included in multivariable models. **Results:** Of 2,271 patients, 849 (37%) were ≥65 years. Older patients were more frequently treated with reduced-intensity or non-myeloablative conditioning, had a Hematopoietic Cell Transplantation–Comorbidity Index (HCT-CI) ≥3, and had a Karnofsky Performance Status (KPS) <90. On multivariable analysis, age ≥65 was associated with significantly inferior OS (HR 1.20, 95% CI 1.02-1.40, p=0.029), with 3-year OS of 52.1% vs 63.4% (log-rank $p<0.001$). Other independent predictors of worse OS included reduced-intensity conditioning, higher disease risk index, KPS <90, and HCT-CI ≥3; graft source was not significant. Competing-risk analyses showed significantly higher NRM in ≥65 years (3-year cumulative incidence 22.7% vs 13.6%; HR 1.56, 95% CI 1.21–2.01, $p<0.001$), which was the primary driver of inferior survival. Importantly, relapse incidence was similar (HR 0.90, p=0.249), and no differences were found in GVHD rates: grade II–IV acute GVHD (HR 0.98, 95% CI 0.81–1.17, p=0.785), grade III-IV acute GVHD (HR 0.91, 95% CI 0.64-1.30, p=0.600), or moderate-to-severe chronic GVHD (HR 0.90, 95% CI 0.68-1.20, p=0.467). **Conclusions:** In patients undergoing unrelated donor HCT with PTCy-based GVHD prophylaxis for acute leukemia or MDS, those aged ≥65 years had significantly lower overall survival and higher non-relapse mortality compared to younger patients, with similar relapse and GVHD rates. These findings suggest the need to optimize the PTCy-based prophylaxis platform, such as reduced PTCy dosing with the addition of novel agents, in patients with advanced age. Research Sponsor: None.

6561 **Poster Session**

Post-prophylaxis CMV in the letermovir era: Incidence, risk factors, and outcomes following HCT. First Author: Safah Khan, Cleveland Clinic, Cleveland Clinic, OH

Background: Cytomegalovirus (CMV) is a major infectious complication after allogeneic hematopoietic cell transplantation (HCT). Letermovir prophylaxis (ppx) effectively reduces clinically significant CMV infection (csCMVi) within 100 days, but csCMVi after ppx discontinuation occurs in 7–16%. Extended letermovir ppx has been proposed for high-risk patients, though optimal patient selection is uncertain. Our study aims to define the incidence, risk factors, and outcomes for post-ppx csCMVi to guide extended ppx strategies. **Methods:** We analyzed adult CMV-seropositive (+) HCT recipients at Cleveland Clinic who received ≥45 days of Letermovir primary ppx between 1/1/2018-12/31/2024. The primary outcome was post-ppx csCMVi, defined as CMV disease or asymptomatic viremia requiring preemptive therapy. Secondary outcomes included overall and non-relapse mortality. Patients with csCMVi during standard ppx were excluded. Associations with csCMVi were evaluated using competing-risk models accounting for mortality, with multivariable Cox analyses adjusting for age, sex, Karnofsky score. **Results:** Among 311 CMV+ recipients of HCT, 62% were donor-CMV negative and 50% were male. Median age was 59 (47-67) years. HCT was most commonly for AML (48%), with matched unrelated donors (54%), peripheral blood graft (76%), myeloablative conditioning (45%), and GVHD ppx with post-transplant cyclophosphamide (PTCy) (63%). Grade ≥2 acute GVHD (36%), chronic GVHD (53%), and relapse (22%) were common in the cohort. Post-ppx infection occurred in 64 patients (21%), including 8 (13%) with tissue-invasive disease. Median duration of Letermovir was 75 days, typically initiated on day 28 post-transplant. Median time to csCMVi was 123 days from transplant. Cumulative incidence of post-ppx csCMVi was 9% at 60 days, 11% at 90 days, and 12% at 180 and 360 days. Risk factors included older age (HR 1.04 per year, 95% CI=1.01-1.07, p=0.014), female sex (HR 3.3, 95% CI=1.5-7.1, p=0.003), chronic GVHD (HR 9.9, 95% CI=1.2-5.6, p=0.024), and GVHD treated with steroids (HR 9.86, 95% CI=1.4-71.5, p=0.024) or ruxolitinib (HR 2.8, 95% CI= 1.3-6.3, p=0.011). Primary disease, donor CMV status, donor relationship, graft source, conditioning intensity, ATG, and PTCy were not associated with csCMVi. All-cause mortality was high in the cohort (37%), particularly in the late csCMVi group (52%). Post-ppx csCMVi was associated with increased non-relapse (HR 2.36, 95% CI= 1.37-4.07, p=0.002) and overall mortality (HR 2.41, 95% CI= 1.43-4.06, p<0.001) in multivariable analysis adjusted for age and sex. **Conclusions:** Late csCMVi occurs in 12% of CMV+ HCT recipients after prophylaxis discontinuation and may confer additional mortality risk. These findings support risk-adapted surveillance and extended prophylaxis in high-risk groups, particularly recipients who are older, female, and have chronic GVHD requiring immunosuppression. Research Sponsor: None.

6562 **Poster Session**

Impact of *NPM1* co-mutation on post-transplant outcomes in MRG-mutated AML. First Author: Yanal Mufeed Alnimer, University of Kentucky, Lexington, KY

Background: Myelodysplasia-related gene (MRG) mutations are classified as adverse risk per ELN 2022, and allogeneic cell transplantation (allo-HCT) is recommended. However, it remains unclear whether post-transplant outcomes in MRG-mutated AML are inferior compared with other ELN-defined higher-risk AML without MRG mutations, and whether the presence of a favorable co-mutation NPM1 modifies prognosis after transplantation. **Methods:** We conducted a retrospective study of adult patients with AML who underwent allo-HCT at our institution between January 2015 and January 2025. MRG mutations defined per ELN. Patients were categorized into four molecular groups: MRG-mutated/NPM1 wild-type (MRG^mutNPM1^wt), MRG-mutated/NPM1-mutated (MRG^mutNPM1^mut), MRG−wild-type/NPM1-mutated (MRG^wtNPM1^mut), and MRG−wild-type/NPM1 wild-type (MRG^wtNPM1^wt).Overall survival (OS) and RFS were calculated using the Kaplan−Meier. Adjusted OS and RFS were estimated using propensity score matching accounting for age, sex, remission status at transplant (CR1 vs others), and conditioning intensity. **Results:** A total of 146 patients with complete molecular and cytogenetic data were included. Forty-two percent were MRG^wtNPM1^wt, 16% were MRG^wtNPM1^mut, 23% were MRG^mutNPM1^mut, and 19% were MRG^mutNPM1^wt. Cytogenetic risk distribution was 11% favorable, 71% intermediate, and 18% adverse. Among patients with favorable cytogenetics, 86% were either MRG^wtNPM1^wt or MRG^mutNPM1^mut, and none had MRG^mutNPM1^wt disease. In contrast, among patients with adverse cytogenetics, 17% had MRG^mutNPM1^wt, 23% had MRG^mutNPM1^mut, and 45% had MRG^wtNPM1^wt disease (p = 0.07).There was no significant difference in OS across molecular subgroups, with median OS of 70 months (95% CI 40−NR) for MRG^wtNPM1^mut, 101 months (95% CI 20−NR) for MRG^mutNPM1^mut, 69 months (95% CI 27−NR) for MRG^mutNPM1^wt, and 94 months (95% CI 59−NR) for MRG^wtNPM1^wt (p = 0.5). However, patients with MRG^mutNPM1^wt demonstrated a trend toward inferior RFS, with a median RFS of 17 months (95% CI 13−NR), compared with RFS not reached in the MRG^wtNPM1^mut, MRG^mutNPM1^mut, and MRG^wtNPM1^wt groups (p = 0.1). These findings remained consistent after propensity score adjustment. **Conclusions:** Our findings suggest that the presence of an NPM1 mutation may mitigate post-transplant relapse risk in patients with MRG-mutated AML. In contrast, patients with MRG-mutated/NPM1 wild-type disease appear to have inferior relapse-free survival after allo-HCT compared with other ELN-defined adverse-risk AML subgroups. These results indicate biologic heterogeneity within adverse-risk AML and highlight the need for refined post-transplant risk stratification and relapse-prevention strategies in MRG-mutated/NPM1 wild-type AML. Research Sponsor: None.

6563 **Poster Session**

Myeloablative vs reduced-intensity conditioning in PTCy-based allogeneic HCT: A CIBMTR analysis. First Author: Imran Khan, NYC Health and Hospitals/Woodhull, Brooklyn, NY

Background: Post-transplant cyclophosphamide (PTCy) is widely used in matched unrelated and haploidentical HCT. However, the optimal conditioning intensity in the PTCy era remains unclear. This study compared outcomes of myeloablative versus reduced-intensity conditioning in MUD and haploidentical HCT recipients. **Methods:** This retrospective multicenter study utilized the Center for International Blood and Marrow Transplant Registry (CIBMTR) to analyze patients who underwent HCT and received PTCy, based on the P-6219 dataset by Modi et al. Clinical outcomes were compared between patients who received MAC and RIC. Kaplan−Meier analysis was used to determine mean overall survival (OS) and graft-vs-host disease (GVHD)-free relapse-free survival (GRFS). Cox proportional hazards regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI). Statistical analyses were conducted using SPSS, with p-values less than 0.05 considered statistically significant. **Results:** A total of 5,873 patients were included, comprising 1,973 MUD recipients (797 MAC, 1,176 RIC) and 3,900 haploidentical recipients (1,485 MAC, 2,415 RIC). All patients received PTCy GVHD prophylaxis. Among MUD recipients, MAC was associated with significantly OS compared with RIC, with a mean OS of 27.8 months (95% CI 26.9–28.7) versus 24.8 months (95% CI 24.1–25.6, p<0.001). RIC was associated with a higher risk of mortality compared with MAC (HR 1.45, 95% CI 1.24–1.68, p<0.001). GRFS was also worse with RIC (mean 21.5 months, 95% CI 20.4–22.5 vs 18.3 months, 95% CI 17.4–19.2; HR 1.33, 95% CI 1.17–1.51, p<0.001). There were no significant differences between MAC and RIC in rates of grade 2–4 acute GVHD (HR 1.00, 95% CI 0.85–1.18, p=1.0), grade 3–4 acute GVHD (HR 1.04, 95% CI 0.72–1.51, p=0.84), or moderate/severe chronic GVHD (HR 0.97, 95% CI 0.86–1.08, p=0.59). Among haploidentical recipients, MAC was also associated with improved OS compared with RIC, with a mean OS of 26.1 months (95% CI 25.4–26.8) versus 24.1 months (95% CI 23.6–24.7, p<0.001), and RIC conferred a higher mortality risk (HR 1.29, 95% CI 1.16–1.43, p<0.001). GRFS was superior with MAC (18.4 months, 95% CI 17.6–19.2 vs 16.5 months, 95% CI 15.9–17.2; HR 1.17, 95% CI 1.08–1.27, p<0.001). Rates of grade 2–4 acute GVHD were lower with RIC (HR 0.88, 95% CI 0.78–0.98, p=0.018). Rates of grade 3–4 acute GVHD (HR 1.06, 95% CI 0.85–1.32, p=0.61) and moderate/severe chronic GVHD (HR 0.98, 95% CI 0.90–1.07, p=0.70) were similar between MAC and RIC. **Conclusions:** MAC was associated with improved OS and GRFS compared with RIC in MUD and haploidentical transplant recipients, with similar rates of severe acute and chronic GVHD. These findings support the use of MAC when patient comorbidities and performance status permit. Research Sponsor: None.

6564 **Poster Session**

Differentiating donor age on AML patient outcomes in the post-transplant cyclophosphamide contemporary era. First Author: John Behman, Duke University , Department of Medicine, Division of Hematologic Malignancies and Cellular Therapy, Durham, NC

Background: alloHCT provides curative potential for patients with AML. PTCy GVHD prophylaxis has changed this paradigm. Impact of donor age is unknown in the PTCy era. **Methods:** Utilizing the publicly available CIBMTR dataset, de-identified AML patients receiving alloHCT between 2017-2021 with PTCy-based GVHD prophylaxis were identified. Patients with primary induction failure or relapsed disease status at time of transplant were excluded. The main effect of donor age was examined across outcomes at 24-months. Univariate and multivariate analyses were performed. **Results:** 5,702 patients were included in the analysis. The median age at alloHCT was 59 years (IQR, 46-66). Median donor age was 33 years (IQR, 22-42). CI of relapse at 24 months was 36.4% (95% CI, 33.1%-39.8%) for donors aged ≥45 years (yrs), 32.9% (95% CI, 24.6%-41.2%) for donors aged 0-19 yrs, 30.5% (95% CI, 28.6%-32.4%) for donors aged 20-34 yrs, and 30.1% (95% CI, 27.3%-32.9%) for donors aged 35-44 yrs; p=0.003 (Gray's test). Overall survival (OS) at 24 months was 45.9% (95% CI, 42.6%-49.6%) for donors aged ≥45 yrs, 55.4% (95% CI, 47.1%-65.2%) for donors aged 0-19 yrs, 58.5% (95% CI, 56.5%-60.6%) for donors aged 20-34 yrs, and 53.3% (95% CI, 50.3%-56.5%) for donors aged 35-44 yrs; p<0.001. Leukemia-free survival at 24 months was 39.4% (95% CI, 36.2%-43.0%) for donors aged ≥45 yrs, 48.2% (95% CI, 40.1%-57.9%) for donors aged 0-19 yrs, 51.4% (95% CI, 49.4%-53.5%) for donors aged 20-34 yrs, and 49.2% (95% CI, 46.2%-52.4%) for donors aged 35-44 yrs; p<0.001. In multivariable analysis, as compared to donor age >45, the 2 younger age groups, age 20-34 years (HR 0.41, 95%CI, 0.69-0.87; p=.004) and 35-44 years (HR 0.78, 95%CI, 0.66-0.92; p=.004) were independently associated with reduced relapse and superior LFS (HR 0.77, 95% CI, 0.69-0.87;p<.001) and (HR 0.77, 95% CI, 0.68-0.87; p<.001) respectively, and OS (HR 0.76, 95%CI, 0.67-0.86; p<.001) and (HR 0.80, 95% CI, 0.70-0.91; p<.001) respectively. In contrast, there was no significant difference between outcomes when the donor belonged to the age group 0-19 for relapse (HR 0.87, 95%CI, 0.61-1.22;p=.410, LFS (HR 0.84,95% CI, 0.65-1.09); p=.188), and OS (HR 0.79, 95%CI, 0.60-1.05;p=.108) (Table 1). **Conclusions:** In this homogeneous analysis, patients with AML undergoing PTCy-based GVHD prophylaxis in the contemporary era, younger donor between age groups 20-44 years conferred a significantly reduced relapse risk and superior LFS and OS. The findings inform optimal donor selection. Research Sponsor: None.

Multivariate analyses (ref: donor age ≥45).

Donor age	0-19	P	20-34	P	35-44	P
OS	0.79 (0.60-1.05)	0.108	0.76 (0.67-0.86)	<0.001	0.80 (0.70-0.91)	<0.001
LFS	0.84 (0.65-1.09)	0.188	0.77 (0.69-0.87)	<0.001	0.77 (0.68-0.87)	<0.001
Relapse	0.87 (0.61-1.22)	0.410	0.81 (0.69-0.93)	0.004	0.78 (0.66-0.92)	0.004

Adjusted for donor age, year of transplant, DRI, year of HCT, donor type, graft type, conditioning intensity, and ethnicity.

6565 **Poster Session**

Early neutrophil incompetence following allogeneic stem cell transplant. First Author: Maria Lampou, Department of Medicine, Massachusetts General Brigham; Harvard Medical School, Boston, MA

Background: Neutrophils are key immune effector cells against fungal pathogens such as *Candida albicans*. After allogeneic stem cell transplant (allo-SCT), absolute neutrophil count (ANC) is used to measure myeloid engraftment and estimate infection risk, but post-transplant neutrophil function remains poorly understood. Our prior work showed impaired neutrophil function after both myeloablative (MAC) and reduced-intensity conditioning (RIC) regimens. Here, we assess broader neutrophil functions and hypothesize post-transplant neutrophil impairment persists for at least one month despite numeric recovery. **Methods:** Peripheral blood was collected from patients undergoing RIC or MAC allo-SCT and healthy donors at four time points: immediately post-engraftment (P1), and at one (P2), three (P3), and seven (P4) months. Neutrophil function was analyzed by multiparametric flow cytometry to assess phagocytosis, degranulation (CD66b), reactive oxygen species (ROS) production (dihydrorhodamine-123), and ectodomain shedding (CD62L) after incubation with fluorescent *C. albicans*. At P1, neutrophil deformability was quantified to generate a sepsis risk index: Band 1 (low risk, 0.1-4.9), Band 2 (intermediate risk, 5-6.2) and Band 3 (high risk, 6.3-10). Neutrophil antifungal activity was assessed *in vitro* using microscale platforms to quantify and image swarming (cumulative neutrophil response) during restriction of *C. albicans* growth over 12 hours. **Results:** Nineteen subjects were included. The most common underlying malignancy was acute myeloid leukemia (12/19, 63%). Conditioning regimens included fludarabine/melphalan (14/19, 74%), busulfan/fludarabine (4/19, 21%), or fludarabine/total body irradiation (1/19, 5%), with post-transplant cyclophosphamide and tacrolimus. The majority received grafts from matched unrelated donors (14/19, 74%). Median ANC (K/uL) was 3.59 at P1 (15/19 subjects, 79%), 4.55 at P2 (14/19, 74%), 4.03 at P3 (5/19, 26%) and 2.94 at P4 (7/19, 37%). Functional analyses revealed significant impairment in allo-SCT recipients compared with controls at P1, with trends of persistent impairment at P2, and evidence of recovery by P3-P4. At P1, eight recipients demonstrated altered neutrophil deformability, yielding a higher sepsis risk index [median (IQR) 5.93 (3.88–6.80)] versus controls [median (IQR) 0.95 (0.33–2.33)]. Swarming analysis revealed impaired collective behavior in fungal containment compared with controls. **Conclusions:** Despite normalization of ANC after allo-SCT, early post-engraftment neutrophils exhibit significant functional and biophysical impairments, indicating transient immune incompetence. This early window of vulnerability may persist for at least one month post-transplant. Ongoing follow-up and expanded analyses will further characterize the underlying mechanisms and define the trajectory of delayed functional neutrophil recovery. Research Sponsor: U.S. National Institutes of Health; Cytovale.

6566 **Poster Session**

Updated overall survival (OS) and long-term transfusion-independence (TI) from the phase 3 COMMANDS trial in erythropoiesis-stimulating agent (ESA)–naive patients (pts) with lower-risk myelodysplastic syndromes (LR-MDS). First Author: Guillermo Garcia-Manero, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In the phase 3 COMMANDS trial (NCT03682536), luspatercept (LUSPA) significantly improved RBC-TI ≥12 wks with concurrent mean hemoglobin (Hb) increase ≥1.5 g/dL during wks 1-24 (primary endpoint) vs epoetin alfa (EA) in pts with ESA-naive transfusion-dependent (TD) LR-MDS. Longer follow-up (>2.5 yrs) showed a favorable OS trend and durable TI responses with LUSPA vs EA. We report updated results with 6 additional mos of follow-up (>3 yrs). **Methods:** Eligible pts (≥18 yrs; ESA-naive; TD; LR-MDS) were stratified by baseline (BL) transfusion burden (TB), ring sideroblasts (RS), and serum erythropoietin (sEPO). Pts were randomized 1:1 to LUSPA (1.0-1.75 mg/kg; SC Q3W) or EA (450-1050 IU/kg; SC QW) for ≥24 wks. OS (from randomization), RBC-TI responses and Hb improvement (all from wk 1 to end of treatment), predictive BL biomarkers of OS, and safety were evaluated. **Results:** At cutoff (Oct 6, 2025), median (min-max) follow-up was 35.9 (1-73; LUSPA) and 30.8 (0-77; EA) mos. Median OS was not reached (NR) for LUSPA and 46.0 mos for EA (HR, 0.78; 95% CI, 0.56-1.09), with similar trends in subgroups (Table). RBC-TI ≥12 wks (LUSPA vs EA) occurred in 76.4% vs 55.8% of pts, and in 60.4% vs 39.2% with concurrent mean Hb ≥10 g/dL. Median cumulative duration (95% CI) of RBC-TI ≥12 wks was 184.4 (118.4-NE) wks for LUSPA and 95.1 (74.9-180.1) wks for EA (HR, 0.54; 95% CI, 0.36-0.80). RBC-TI ≥2.5 yrs (LUSPA vs EA) was achieved by 25.3% vs 10.5% of pts. Mean Hb increase ≥1.5 g/dL (LUSPA vs EA) was achieved by 80.2% vs 58.6% of pts; median duration (95% CI) of Hb increase ≥1.5 g/dL was 72.9 (53.9-89.9) and 47.9 (35.9-60.0) wks (HR, 0.61; 95% CI, 0.44-0.85). Improved OS was associated with BL biomarkers of favorable immune (LUSPA) and CV function (LUSPA and EA), less aggressive disease (EA), and preserved megakaryopoiesis (EA); these characteristics may enhance response to therapy. At cutoff, 17.6% (LUSPA) and 7.8% (EA) of pts remained on treatment; 84.6% and 83.2% had ≥1 dose escalation. No new safety concerns emerged. Deaths (any cause) occurred (LUSPA, 36.3%; EA, 43.0%), fewer LUSPA pts progressed to HR-MDS (3.3%; 7.3%), and AML progression was comparable (4.9%; 5.5%). **Conclusions:** Long-term follow-up demonstrated improved OS trends and sustained responses with LUSPA vs EA, overall and in subgroups. No new safety concerns emerged, reinforcing superior clinical benefit as first-line treatment in LR-MDS. Clinical trial information: NCT03682536. Research Sponsor: Bristol Myers Squibb.

Median OS, mos	LUSPA	EA	HR (95% CI)
Overall	(n=182)	(n=181)	0.78
	NR	46.0	(0.56-1.09)
Stratification subgroup			
TB <4 RBC U/8 wks	(n=118)	(n=111)	0.87
	57.5	47.2	(0.57-1.33)
TB ≥4 RBC U/8 wks	(n=64)	(n=70)	0.62
	NR	39.9	(0.37-1.05)
RS+	(n=133)	(n=130)	0.70
	NR	47.2	(0.47-1.04)
RS−	(n=49)	(n=50)	0.96
	54.8	46.2	(0.53-1.72)
sEPO ≤200 U/L	(n=145)	(n=144)	0.81
	NR	51.4	(0.55-1.20)
sEPO >200 U/L	(n=37)	(n=37)	0.67
	43.0	35.4	(0.35-1.28)

6567 **Poster Session**

Impact of shallow whole genome sequencing on diagnostic yield and prognostic precision in myelodysplastic syndromes. First Author: Zhenling Li, Department of Hematology, China-Japan Friendship Hospital, Beijing, China

Background: Accurate cytogenetic characterization is critical for risk stratification in myelodysplastic syndromes (MDS). Conventional karyotyping and fluorescence in situ hybridization (FISH) are limited in resolution, target specific loci, and cannot detect copy-neutral loss of heterozygosity (CN-LOH). LeukoPrint, a CE-IVD-marked shallow whole-genome sequencing (sWGS, 1×coverage) test, enables genome-wide detection of copy number alterations (CNAs) and CN-LOH. Previously validated in acute myeloid leukemia and multiple myeloma, it improved CNA detection and prognostic accuracy. This study evaluated its ability to enhance diagnostic yield and refine prognostic precision in a large MDS cohort. **Methods:** Bone marrow samples from 461 MDS patients were profiled for genome-wide CNA/CN-LOH using LeukoPrint. Results were compared with conventional karyotyping and FISH to assess detection yield and concordance. The impact of additional LeukoPrint findings on Revised International Prognostic Scoring System (IPSS-R) cytogenetic risk stratification and MDS subclassification was evaluated. **Results:** LeukoPrint detected cytogenetic abnormalities in 63.3% of patients, comprising CNAs in 50.3%, CN-LOH in 23.9%, with 10.8% harboring both. Recurrent CNAs included del(5q) (10.0%), del(20q) (10.0%), +8 (8.9%), and del(7q) (7.8%), among others. CN-LOH frequently affected regions that overlapped common CNA loci, such as 5q (3.7%), 7q (3.7%), and 17p (0.7%). Compared with conventional cytogenetics, LeukoPrint showed 94.4% concordance (κ=0.854) with FISH for five key loci (−5/del(5q), −7/del(7q), +8, del(20q), −Y) and a higher detection rate than karyotyping (65.7% vs 39.2%). For the 11 IPSS-R defined cytogenetic abnormalities (del(3q), del(5q), del(7q), del(11q), del(12p), del(17p), del(20q), +8, +19, -7, and -Y), it identified all karyotype-detected lesions and increased detection yield by 49.4%. These newly identified abnormalities led to IPSS-R cytogenetic risk reclassification in 32.4% (33/102) of comparable cases, predominantly upgrading patients to higher-risk categories. Specifically, 26 patients were reassigned from Good to Intermediate (n = 17), Poor (n = 2), or Very Poor (n = 7); 5 from Intermediate to Poor (n = 4) or Very Poor (n = 1); and 1 from Poor to Very Poor. Furthermore, by detecting additional aberrations such as del(17p) or 17p CN-LOH, LeukoPrint enabled more accurate molecular classification, including the reclassification of one case from MDS-IB1 to MDS-biTP53. **Conclusions:** sWGS-based LeukoPrint substantially enhances cytogenetic detection in MDS, outperforming conventional karyotyping and FISH. By identifying additional clinically relevant cytogenetic abnormalities, it improves prognostic risk stratification and refines disease classification, supporting its integration into routine MDS cytogenetic assessment. Research Sponsor: None.

6568 **Poster Session**

Phlebotomy, adherence, and hematocrit control in patients with polycythemia vera in the United States: Real-world analysis. First Author: Kristen M. Pettit, University of Michigan, Section of Hematology/Oncology, Department of Medicine, Ann Arbor, MI

Background: Polycythemia Vera (PV) is characterized by erythrocytosis. A key treatment goal in PV, for which phlebotomy (PHL) is recommended, is achieving and maintaining hematocrit (HCT) levels < 45% to reduce thrombotic risk. However, real-world evidence suggests PHL alone may not achieve consistent and durable HCT control. Repeated PHL may also increase treatment burden and present logistical challenges. **Methods:** Data were collected using the Adelphi PV Disease Specific Programme, a United States (US) cross-sectional survey (August 2025-January 2026) with retrospective chart review. Physicians reported demographics, clinical characteristics, and treatment history for the next five patients (pts) with PV that met the inclusion criteria. Interim analyses are presented descriptively. Of those receiving ≥ 1 PHL in the 12 months prior to survey, pts receiving frequent PHL were defined as ≥ 3 in 6 months or ≥ 5 in 12 months; all other pts were classified as receiving infrequent PHL. Uncontrolled HCT was defined as any HCT ≥ 45% within the prior 12 months. **Results:** Twenty-seven physicians provided data for 143 pts; 86 (60%) received ≥ 1 PHL in the prior 12 months; median (interquartile range (IQR)) age was 65.0 (52.0-70.0) years, 77% were male, median (IQR) time since PV diagnosis was 11.0 (4.0-33.5) months, and 62% were high risk (defined as ≥ 60 years old or history of thrombosis). Half experienced ≥ 1 barrier to receiving PHL, including care coordination challenges (22%), lack of resources (12%), travel time burden (12%) and vein access challenges (10%). In prior 12 months, physicians reported that 38% of pts were not fully adherent to PHL (attended PHL appointments as recommended <90% of the time). At the most recent consultation, 51% of pts were receiving cytoreductive therapy in addition to PHL. Frequent PHL occurred in 24% of pts and infrequent in 76% of pts. Overall, 90% (75/83) had uncontrolled HCT: 89% for frequent (17/19) vs 91% for infrequent PHL (58/64). Since their PV diagnosis, 13% (11/86) of pts had experienced a thromboembolism (TE), and of these 11 pts, 45% (5/11) had experienced a TE within the 12 months prior to survey. For all pts who had ever experienced a TE, the median (IQR) time since their most recent TE was 20.0 (2.5-32.0) months. **Conclusions:** Within this study, pts receiving PHL for PV commonly experienced access and logistical barriers, and incomplete PHL adherence. Nearly all pts had evidence of uncontrolled HCT in the 12 months prior to survey, including both frequent and infrequent PHL groups, and TEs were observed despite PHL treatment. These findings highlight the need for more effective and sustainable approaches to prevent consequences, such as TEs, commonly associated with uncontrolled HCT, while also reducing pt burden. Research Sponsor: Takeda Pharmaceuticals America, Inc.

6569 **Poster Session**

Multimodal immunotherapy for high-risk acute myeloid leukemia and myelodysplastic syndrome. First Author: Parveen Shiraz, Stanford University, Stanford, CA

Background: CD117 is highly expressed on myeloid leukemia cells (MLC) with limited expression on normal tissues. Our group has developed an anti-CD117 monoclonal antibody and demonstrated its safety in a phase 1 clinical trial for myelodysplastic syndrome (MDS). To potentiate engagement with MLC and immune effector cells, we engineered bispecific antibodies (bsAb) to bind CD117 and CD33 or CD38 and recruit natural killer (NK) cells using an active Fc and CD16 (CM1/3/16/16) and/or NKp46 scFv (CM1/3/16/17). NK cell cytotoxicity against MLC increases several-fold when activated by IL2, IL15 or IL21. We studied the *in vitro* and *in vivo* efficacy of bsAbs with fresh NK cells or IL2, IL15 and IL21 (IL21521) activated NK cells (cNK) to deplete MLC. **Methods:** *In vitro* cytotoxicity assays were performed on Kasumi-1 (CD117 high) and MOLM-13 (CD117 negative) acute myeloid leukemia (AML) cell lines and a primary AML sample (CD117 low) with bsAb and NK or cNK cells. cNK were exposed to IL21521 for 7 days. To mimic *in vivo* exposure, cNK were removed from IL21521 for 24, 48 and 72 hours prior to cytotoxicity assays. Using immune deficient NBSGW mice and primary patient sample of high risk (HR)-MDS transformed to AML (MDS/AML), a patient derived xenograft (PDX) model of HR-MDS/AML was created and allowed to progress to >80% CD45+ human leukemia chimerism (HLC) before treatment. Treatment groups included CM1/3/16/16 at 1mg and/or 2e6 NK or cNK given as a single dose per animal. Weekly blood HLC and a terminal 4-week blood, marrow and spleen HLC were performed. **Results:** In *in vitro* cytotoxicity assays, among the bsAbs, CM1/3/16/16 at 100nM with NK cells at 1:1 target:effector (TE) ratio produced the highest cytotoxicity against Kasumi-1 (70%) and MOLM13 (50%). cNK cells alone produced >90% cytotoxicity of Kasumi-1 cells at 1:1 TE ratio even at 72 hours after IL21521 washout. In the HR-MDS/AML PDX advanced leukemia model, the group receiving CM1/3/16/16 with cNK demonstrated the highest depletion of MLC, with 70% reduction of HLC seen at 4 weeks post-treatment. Mice in this treatment group had 100% survival at 4 weeks at which time they were euthanized for analysis. **Conclusions:** Both CM1/3/16/16 and cNK cells independently killed MLC with high efficacy *in vitro*. A single dose of CM1/3/16/16 combined with cNK cells depleted human MLC in PDX model of HR-MDS/AML with advanced leukemia. Further clinical investigation of this bsAb with allogeneic donor cNK cells in HR-MDS/AML is warranted. Research Sponsor: California Institute of Regenerative Medicine; Edward P Evans Foundation.

6570 **Poster Session**

Whole genome sequencing to identify novel, clinically relevant findings missed by standard of care for patients with myelodysplastic syndrome. First Author: Alex Bataller, Leukemia Department, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Genomic analysis is critical for accurate diagnosis and risk stratification for patients with myeloid malignancies. Whole genome sequencing (WGS) has the ability to capture a breadth of alterations and has the potential to complement or replace current genomic profiling techniques. We sought to validate the molecular findings from Tempus xH, a WGS based assay, with standard of care [SOC] results from a major academic institution (MDACC). **Methods:** We retrospectively sequenced 43 patient samples from MDACC using the Tempus xH WGS assay. SOC data from cytogenetics (karyotype +/- FISH), 81-gene panel sequencing, and/or optical genome mapping OGM (n=10), was regarded as the source of truth. We performed a two-part study: an initial unblinded analysis (n=10) comparing WGS to SOC, followed by a blinded unbiased comparative review (n=33). Clinically relevant alterations were compared between the SOC and xH reportable range workflows. We excluded mutations with <= 10% VAF and filtered copy number alterations (CNAs) < 5Mb, and combined OGM and cytogenetics (10>= metaphases). Structural variants (SVs) were included if they overlapped orthogonal truth or were recurrent myeloid fusions. **Results:** In the unblinded analysis (n=10), WGS detected 53 clinically reported alterations, yielding 94% sensitivity. Single nucleotide variants (SNVs) had 100% sensitivity, and 18/20 CNA events and 6/7 SVs were detected. The single missed SV event was a derivative chromosome (chr), between chr1 and chr20, identified by cytogenetics with breakpoints over the masked centromere region of the WGS. However, WGS detected CNAs in chr arms of 1 and 20, signalling the event was captured yet not resolved as a derivative chr. Two copy losses on chr 19 (complete loss and p-arm) and an *ASXL1* frameshift were detected by WGS but not by SOC. In the blinded study (n=33), WGS detected 143 events, including 124 true positives and no alterations from SOC went undetected by WGS demonstrating 100% sensitivity. WGS identified 24/24 of the CNAs detected by cytogenetics. Among all specimens, 21 novel, high confidence variants were identified in 11 specimens (39%) by WGS that were not detected by SOC; including 14 CNAs, two SNVs, and five SVs, including diagnostically and/or prognostically critical alterations: 2 *MECOM* rearrangements, 1 *KMT2A*-PTD, an 11MB deletion in chr 17p (*TP53* locus), and a focal *RUNX1* deletion highlighting the potential clinical benefit of WGS. **Conclusions:** WGS accurately recapitulates results from targeted NGS panels, OGM and cytogenetics and advances our understanding of MDS biology. xH WGS uncovered a significant number of novel, clinically relevant and potentially targetable findings undetected by SOC. WGS provides a complementary view of the genome, identifying actionable and prognostic markers helping clinicians make more informed treatment decisions. Research Sponsor: None.

6571 **Poster Session**

Multi-modal AI foundation models approach for diagnosis of myelodysplastic syndromes across whole bone marrow aspirate and biopsy slides. First Author: Palak Dave, Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Morphologic diagnosis of myelodysplastic syndromes (MDS) from bone marrow aspirates and biopsies is subjective and error prone. Compared to narrow/specific predictive AI methods used in the literature, recently developed pathology foundation models pretrained on large, diverse histopathology corpora have the potential to improve generalizability while reducing task-specific annotation requirements. Here, we evaluate and compare multiple pretrained foundation models across bone marrow aspirate and biopsy whole-slide images (WSI), incorporate a cell-level bag-of-cells (BoC) foundation model, and assess tri-modal ensemble strategies. **Methods:** Digitized bone marrow aspirate (Asp) and biopsy (Bx) WSIs from patients with MDS and non-MDS cytopenias were analyzed using four pretrained pathology foundation models (GigaPath, H-Optimus-0, Virchow2-CLS, MUSK) for tile-level feature extraction. Cell-level features from aspirate-derived BoCs were extracted using DinoBloom-B, a foundation model pretrained for hematologic cell representations. Tile- or cell-level features were aggregated using attention-based multiple instance learning (ABMIL). Models were evaluated on 645 patients (319 MDS, 326 non-MDS) from the NHLBI MDS Natural History Study (NCT02775383) using 5-fold cross-validation (CV) and a held-out test set (n=129). For each modality, the best-performing model was selected based on test performance. Predictions were evaluated individually and combined using soft-probability ensembles. An oracle ensemble estimated the upper bound of multimodal complementarity. **Results:** Performance of the foundation models is summarized in Table 1. A soft-vote tri-modal ensemble of the selected models improved performance beyond any single modality (AUC 0.83; accuracy 0.73). Error analysis demonstrated partially non-overlapping failure modes across modalities, and an oracle ensemble achieved substantially higher accuracy (0.94), indicating unrealized multimodal complementarity. **Conclusions:** Foundation models enable robust AI-based diagnosis of MDS across bone marrow specimen types. Tri-modal ensembling improves diagnostic performance, while oracle analysis motivates TriPath, a unified framework for joint modeling of aspirate, biopsy, and cellular morphology to support standardized and generalizable MDS diagnosis. Research Sponsor: Edward P. Evans Foundation; The National MDS Natural History, NIH/NHLBI/NCI.

Performance summary.

Model	Bx WSI CV AUC	Bx WSI Test AUC	Asp WSI CV AUC	Asp WSI Test AUC	Asp-derived BoC CV AUC	Asp-derived BoC Test AUC
GigaPath+ABMIL	**0.80+/-0.05**	**0.82**	0.77+/-0.06	0.66		
H-Optimus-0+ABMIL	0.82+/-0.04	0.79	0.77+/-0.07	0.68		
Virchow2-CLS+ABMIL	0.81+/-0.04	0.76	**0.78+/-0.05**	**0.74**		
MUSK+ABMIL	0.77+/-0.05	0.81	0.76+/-0.04	0.72		
DinoBloom-B+ABMIL					**0.83+/-0.05**	**0.78**
Tri-modal Soft Ensemble	Test AUC 0.83					
Oracle ensemble (upper bound)	Test Accuracy 0.94					

6572 **Poster Session**

Characterizing the genomic landscape of Langerhans cell histiocytosis using the AACR Project GENIE database. First Author: Amber Chang, University of South Florida, Morsani College of Medicine, Tampa, FL

Background: Langerhans cell histiocytosis (LCH) is a rare neoplasm characterized by the abnormal clonal proliferation of bone marrow-derived Langerhans cells and occurs predominantly in pediatric patients. Clinical manifestations range from localized bone lesions to multisystem involvement. Given the high frequency of MAPK pathway mutations, particularly BRAF V600E, next-generation sequencing is recommended for LCH patients to identify actionable targets. This study utilizes the American Association for Cancer Research (AACR) Project Genomic Evidence Neoplasia Information Exchange (GENIE) database to address existing gaps in the genomic profiling of LCH, aiming to inform long-term risk stratification, uncover prognostic markers, and guide avenues for targeted therapy. **Methods:** AACR Project GENIE was accessed via cBioPortal (v18.0-public) on November 18, 2025 to identify all LCH patients. Gene mutations and demographic variables were tabulated, and statistical correlations were assessed using two-sided t-tests and non-parametric analyses with Benjamini–Hochberg false discovery rate correction. Entries with unknown values were excluded from analysis; discrepancies in percentage reflect unreported data. **Results:** This study identified 326 LCH samples from 290 patients, of whom 140 (48.3%) were female and 139 (47.9%) were male. By race, 140 (48.3%) identified as White, 9 (3.1%) as Black, and 9 (3.1%) as Asian. Of the samples, 152 (46.6%) originated from primary tumors and 20 (6.1%) were from metastatic tumors. The cohort included samples from 113 pediatric patients (34.7%) and 212 (65.0%) adults. Frequent mutations included *BRAF* (n=126; 38.7%), *MAP2K1* (n=57; 17.5%), *TET2* (n=17; 5.2%), and *FAT1* (n=8; 2.5%). No significant difference was identified between the genomic profiles of males and females ($p>0.05$), although comparisons by race revealed several unique somatic point mutations in Asian and Black patients. Among Asian patients, mutations in *MUTYH*, *PDGFRB*, and *TERT* were significantly enriched, while *BORCS8-MEF2B*, *BRCA1*, and *DDR2* mutations were enriched in Black patients. Within this cohort, pediatric patients were more likely to present with *PTEN* mutations, while adults ≥34 years old were more likely to have *VTI1A* or *ATM* mutations. *BRAF* mutations were mutually exclusive with *MAP2K1* mutations (n=124/124; $p<0.001$), while *TET2* mutations frequently co-occurred with *ASXL1* mutations (n=2/18, $p<0.05$). There were no significant differences in mutations between primary and metastatic samples ($p>0.05$). **Conclusions:** Our findings support the classification of *BRAF* and *MAP2K1* mutations as key driver mutations and identify several additional mutations that are significantly enriched across demographic groups. Further research into these genomic associations is crucial to address existing knowledge gaps and translate into novel treatment modalities for patients with LCH. Research Sponsor: None.

6573 **Poster Session**

Updated analysis of overall survival (OS) with imetelstat (IME) in relapsed/refractory (R/R) myelofibrosis (MF) versus real-world (RW) data, and assessment of RW treatment (tx) patterns. First Author: Andrew Tucker Kuykendall, Moffitt Cancer Center, Tampa, FL

Background: IME showed significantly longer median OS (mOS) in patients (pts) with Janus kinase inhibitor (JAKi) R/R intermediate-2–risk or high-risk MF in the IMbark trial (NCT02426086) vs closely matched RW pts treated with best available therapy (BAT) after ruxolitinib (RUX; HR, 0.35; *P*=.0019). The MF tx landscape changed considerably in recent years, potentially impacting OS. We present an updated OS analysis of IMbark pts vs a larger RW pt cohort after extended follow-up. **Methods:** The updated RW dataset included 126 pts who discontinued RUX and were subsequently treated with BAT at Moffitt Cancer Center between 2010 and 2025. To assess changes in RW tx patterns, baseline/disease characteristics and OS of pts diagnosed before/after 2016 and 2019 were compared. To update the IMbark vs RW OS analysis, a closely matched cohort was identified using IMbark eligibility criteria, including pts diagnosed before 2016 who received RUX but were R/R. The mOS was measured from time of JAKi discontinuation to death or censored at last follow-up. Propensity score approaches using average tx effect for overlap population (ATO) or stabilized inverse probability tx weighting (sIPTW) were implemented to adjust for baseline covariates/prognostic factors that may impact outcomes. **Results:** The RW tx pattern assessment included 96 pts. Time from diagnosis to start of RUX and duration of RUX tx were significantly shorter after 2016 vs before (Table). Similar changes were observed after 2019 vs before. The mOS in pts diagnosed after 2016 and 2019 was significantly longer vs before. The updated mOS analysis included 59 IMbark pts and 54 closely matched RW pts. With a median follow-up of 46.2 mo for IMbark pts and 48.2 mo for RW pts, mOS (95% CI) was 30.7 mo (25.5-36.9) with IME in IMbark vs 15.4 mo (13.1-30.5) with BAT in RW (HR, 0.512; *P*=.003) per the unweighted analysis. Propensity-weighted analyses (ATO, sIPTW) had similar results. **Conclusions:** This updated post hoc analysis confirms a significantly more favorable OS benefit with IME vs BAT in pts with R/R MF and poor prognosis consistent with the previous report (Kuykendall 2021). A significant improvement in OS in RW pts over the last decade was also demonstrated, potentially due to shorter time from diagnosis to start of RUX and earlier switch to next-line JAKi or clinical trial. Evolving tx patterns are key considerations for interpreting future clinical trial outcomes. Clinical trial information: NCT02426086. Research Sponsor: This study was funded by Geron Corporation. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Casandra M. Monzon, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation.

Updated RW data by time of diagnosis.

	Before 2016 (N=54)	After 2016 (N=42)	Before 2019 (N=69)	After 2019 (N=27)
Time from diagnosis to RUX start (mean), mo	46.7	10.5	39.7	8.2
RUX duration (mean), mo	30.4	13.5	26.1	15.0
Transplant, n (%)	3 (5.6)	4 (9.5)	5 (7.2)	2 (7.4)
mOS (95% CI), mo	15.4 (13.1-30.5)	34.2 (24.2-NA)	16.6 (14.2-30.0)	39.8 (34.2-NA)

mOS, median overall survival; NA, not available; RUX, ruxolitinib; RW, real world.

6574 **Poster Session**

Pregnancy outcomes in women with myeloproliferative neoplasms: A multicenter real-world analysis. First Author: Maryam Naser, Virginia Commonwealth University - Massey Comprehensive Cancer Center, Richmond, VA

Background: Pregnancy in women with myeloproliferative neoplasms (MPNs) is associated with increased thrombotic and obstetric risk, yet contemporary real-world data describing maternal and fetal outcomes remain limited. We evaluated pregnancy-related outcomes in women with MPNs and examined potential risk predictors. **Methods:** We conducted a retrospective cohort study using the TriNetX network, a federated multicenter network of de-identified electronic health records from participating healthcare organizations. Pregnant women with essential thrombocythemia (ET), polycythemia vera (PV), or myelofibrosis (MF) were identified. The primary outcome was all-cause mortality. Secondary outcomes included deep vein thrombosis (DVT), miscarriage, pre-eclampsia, eclampsia, preterm labor, and intrauterine growth restriction (IUGR). Subgroup analyses were performed using propensity score matching for age, race, ethnicity, and comorbidities to compare outcomes by Low Molecular Weight Heparin (LMWH) exposure, race, maternal age, and MPN subtype. Risk ratios (RR) with 95% confidence intervals (CI) were calculated. **Results:** A total of 1,904 pregnancies were identified (mean age 31.1±7.0 years).The cohort was predominantly non-Hispanic (66.2%) and White (59.1%). ET accounted for 90.3% of cases, followed by PV (8.0%) and MF (1.7%). Overall rates of maternal mortality and DVT were 2.8% and 2.6%, respectively. Adverse obstetric outcomes included miscarriage (9.6%), pre-eclampsia (12.4%), eclampsia (1.3%), preterm labor (9.1%), and IUGR (8.5%). In matched analyses, LMWH use was associated with a numerically lower risk of miscarriage compared with no LMWH (6.8% vs 10.4%; RR 0.66, 95% CI 0.42–1.04), without significant differences in pre-eclampsia, preterm labor, or IUGR. Outcomes were similar between White and African American patients. Advanced maternal age (>35 years) was associated with a lower risk of preterm labor (3.7% vs 9.2%; RR 0.40, 95% CI 0.21–0.75). Obstetric outcomes were comparable between ET and PV. **Conclusions:** In this real-world cohort, pregnancies in women with MPNs were associated with measurable rates of thrombotic and obstetric outcomes. LMWH use was associated with a numerically lower risk of miscarriage without statistically significant differences in other outcomes. These findings provide contemporary outcome estimates and may inform risk stratification and future prospective studies. Limitations include the retrospective design, potential misclassification due to inherent limitation of the database, limited MF representation, and inability to assess disease activity, aspirin use, or pregnancy-specific dosing strategies. Research Sponsor: None.

6575 **Poster Session**

Treatment patterns and outcomes in pacritinib-treated patients with MF and higher platelet count: MY-PAC study. First Author: Douglas Tremblay, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Pacritinib (PAC), a JAK1-sparing JAK2/IRAK1/ACVR1 inhibitor has shown spleen volume and symptom improvement in clinical trials of in patients (pts) with myelofibrosis (MF) with similar benefits in the real-world. This analysis evaluated real-world outcomes in pts with MF and platelet counts (PLT) ≥50 x10^9/L at PAC initiation. **Methods:** This was a multisite chart review of pts with MF treated with PAC for ≥1 month between 06/01/2022 and 07/31/2024 with ≥6 months of follow-up through 01/31/2025. Pts were followed from PAC initiation (index) until the earliest of end of the study, the end of data availability for the pt, or death. Evaluated data included Pt characteristics, treatment patterns, palpable spleen length (total spleen length minus 10cm) and spleen size category based on palpation or palpable spleen length below costal margin (not palpable/minimally palpable <5 cm below costal margin; mild: 5-10 cm palpable; moderate: 11-20 cm palpable; severe: >20 cm palpable), PLT, hemoglobin (Hb), MF-related symptoms, and overall survival through Day 180. Results for pts with PTL ≥50 x10^9/L at index are described using counts and percentages, medians and interquartile range (IQR), and survival probabilities. **Results:** Of 169 pts with MF treated with PAC, 27% (45/169) had PLT ≥50 x 10^9/L at index. Median age was 67 years (IQR: 62-74) at diagnosis and median time from diagnosis to index was 6 months (IQR: 1.3-14.3). The median duration of follow-up from index was 7.6 months (IQR: 6.7-11.0) and 82% of pts (n=37) were still on PAC at end of follow-up. Of 12 pts with spleen length measured by ultrasound at index and Day 180, median spleen length reduction (SLR) was 39% (IQR: 30.4-48.3) with 83% (10/12) achieving SLR ≥25% by Day 180. Among those with categorical spleen size based on palpation (n=5) or ultrasound (n=12), 53% (9/17) achieved a reduction in spleen size category. No pts had a worsening in spleen size category, and spleen size category remained stable for 47% (8/17) of pts. At index, all but one pt had ≥1 MF-related symptom. By Day 180, 80% (35/44) experienced a reduction in the number of symptoms, with a median reduction of 67% (IQR: 33-75). Median PLT at index was 72 x 10^9/L (IQR: 53-110) and from index to Day 180, median increase in PLT was 14% (n=38, IQR: 0-30). Among pts with PLT ≤100 x10^9/L at index 20% (6/30) achieved an increase of ≥30x10^9/L. At index, median Hb was 8.8 g/dL (IQR: 8.0-9.7). Among 29 pts with Hb <10 g/dL at index and Hb at Day 180, Hb increased by a median of 0.8 g/dL (IQR: -0.1-1.0), with 31% (9/29) achieving an increase ≥1.0 g/dL. Overall survival by the end of follow-up was 89% (40/45), and 6-month survival probability was 93% (95% confidence interval: 81, 98). **Conclusions:** Similar to clinical trials, pts with MF and higher PLT counts treated with PAC in the real-world also experienced reduction or stabilization in spleen size category, decreased MF-symptom burden, PLT stability, and improved Hb. Research Sponsor: Sobi Inc.

6576 **Poster Session**

Integrated analysis of the ropeginterferon alfa-2b clinical program in essential thrombocythemia to demonstrate molecular and hematologic responses with safety profile information across treatment lines, ethnicities, and driver mutation types. First Author: Ruben A. Mesa, Atrium Health Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC

Background: Patients with essential thrombocythemia (ET) have limited disease-modifying options. This integrated analysis of 182 ET patients from 2 trials evaluated consistency the efficacy of ropeginterferon alfa-2b (ropeg, BESREMi) across treatment lines and examined the impact of ethnicity and molecular subtype on outcomes. **Methods:** Data were pooled from the phase 3 randomized SURPASS-ET study (ropeg vs anagrelide [ANA] in HU-resistant/intolerant high-risk ET) and the phase 2b single-arm EXCEED-ET study enrolling both treatment-naïve and previously treated patients in North America. Endpoints included durable modified ELN response, hematologic and molecular responses, thrombotic events, and safety. **Results:** In SURPASS-ET, ropeg achieved a significantly higher durable modified ELN response at months 9 and 12 than ANA (42.9% vs 6.0%; p<0.0001), with superior platelet and WBC control, greater *JAK2*V617F allelic burden reduction, and fewer major thrombotic events. In EXCEED-ET, durable objective modified ELN responses reached 60.2%, with ELN2009 molecular response rates of 35.0% for *JAK2*V617F, 16.0% for *CALR*, and 25.0% for *MPL*, demonstrating consistent efficacy across treatment lines and mutation subtypes (Table 1). Safety profiles were comparable between studies, with mostly low-grade, manageable AEs. In the integrated analysis across studies, grade ≥3 TEAEs occurred in 28.6% of ropeg recipients and 33.8% of ANA. TEAEs leading to discontinuation (8.8% vs 20.0%) and serious AEs (12.6% vs 30.0%) were less frequent in the ropeg group. Fatal AEs occurred only in the ANA group (3.8%). **Conclusions:** Across the two studies, consistent molecular and hematologic efficacy with a favorable and manageable safety profile was demonstrated in treatment-naïve and pretreated ET populations, across ethnicities and disease drivers. These findings support ropeg as a disease-modifying treatment option with a favorable benefit–risk profile for all ET patients regardless of ethnicity, treatment line, driver mutation status, and mutational complexity. Clinical trial information: NCT04285086, NCT05482971. Research Sponsor: PharmaEssentia Corporation.

Key efficacy outcomes from both trials.

	SURPASS-ET		EXCEED-ET
Outcome	**Ropeg N=91**	**ANA N=83**	**Ropeg N=91**
Durable modified ELN response, %	42.9	6.0	60.2
Subgroup analysis by race, % (n)	20 (1/5)	0 (0/2)	57.2 (41/71)
Caucasian	44.2 (38/86)	6.2 (5/81)	53.0 (4/7)
Asian	-	-	100.0 (5/5)
African American	-	-	66.7 (2/3)
Hispanic	-	-	100.0 (5/5)
Other			
Platelet control ≤400×10⁹/L, %	56.0	21.7	48.4
WBC normalization, %	73.6	13.3	48.4
Molecular response*, % (n)			
***JAK2*V617F**	30.6 (19/62)	0 (0/42)	35.0 (7/20)
CALR	30.0 (3/10)	0 (0/4)	16.0 (4/25)
MPL	0 (0/1)	0 (0/1)	25.0 (2/8)
Major thrombotic events, %	1.1	10.0	1.1

*The molecular response per the 2009 ELN criteria includes complete and partial responses.

6577 **Poster Session**

Activating MPN patients through empowering, patient-centered education. First Author: Aicha M. Diallo, Patient Empowerment Network, Bothell, WA

Background: Patients living with myeloproliferative neoplasms (MPNs) face complex disease management, evolving treatment options, and barriers to accessing reliable, culturally relevant information. These challenges disproportionately affect underrepresented populations, including Black, Latinx, Indigenous, rural, LGBTQIA+, and veteran communities. The [ACT]IVATED MPN program was developed to improve health literacy, patient activation, and self-advocacy among individuals newly diagnosed with MPNs, while remaining relevant across all stages of disease. **Methods:** The [ACT]IVATED MPN program delivers expert-verified, multimedia educational content designed to support patient and care partner engagement in care. Program components include multilingual expert interview videos, real-world patient vignettes, downloadable health literacy tools, and a comprehensive resource guide available in English and Spanish. Content is distributed digitally and through culturally trusted community organizations to increase reach among underserved populations. Program reach and impact are assessed through digital engagement analytics and post-program participant feedback. **Results:** To date, the [ACT]IVATED MPN program has reached over 5,000 patients and care partners. Preliminary program evaluation data indicate that 100% rated their overall experience as positive or somewhat positive, with 83.3% reporting a positive experience. Following participation, 90.9% of respondents agreed or strongly agreed that the program increased their understanding of MPNs. Indicators of patient activation were high, with 100% of participants reporting increased confidence to speak up with questions about their care and 95.7% reporting greater knowledge and confidence to take an active role in treatment decisions. **Conclusions:** The [ACT]IVATED MPN program demonstrates the feasibility and value of a patient-centered, equity-focused education model in supporting health literacy, self-advocacy, and engagement in care among individuals living with MPNs. Scalable, multilingual educational interventions may complement clinical care by promoting shared decision-making and reducing disparities in access to MPN-related information and resources. Hibbard, J. H., & Greene, J. (2013). What the evidence shows about patient activation: Better health outcomes and care experiences; fewer data on costs. *Health Affairs, 32*(2), 207–214. https://doi.org/10.1377/hlthaff.2012.1061. Research Sponsor: Incyte; Merck; Sanofi.

6578 **Poster Session**

Association of neutrophil-to-lymphocyte ratio and thrombotic events in US veterans with polycythemia vera. First Author: Mingfei Li, Bentley University, Waltham, MA

Background: Neutrophil-to-lymphocyte ratio (NLR) is a novel predictor of thrombosis in patients with Polycythemia Vera (PV), an uncommon myeloproliferative neoplasm distinguished by excessive red blood cell production within the bone marrow. However, there is no guideline-endorsed NLR cut-off that mandates cytoreduction. This study aims to assess the association of NLR and risk of thrombotic events, and evaluate the impact of different therapies based on electronic health records from the United States (US) Veterans Affairs Healthcare System (VAHS). **Methods:** Veterans with PV were identified based on either 2 outpatient codes separated by 30 or more days or 1 inpatient code in the VAHS databases (2017–2023). The first PV diagnosis was considered as the index date. Patients with myelofibrosis or leukemia diagnosis before the index date were excluded from the analysis. Veterans with at least one NLR value were examined for the occurrence of thrombotic events. Baseline characteristics were defined over the two-year period preceding the first PV diagnosis code. Treatments were defined within two years of the index date and categorized as: cytoreductive therapy (including hydroxyurea, interferons, or ruxolitinib), phlebotomy interventions, or neither. Cox proportional hazards regression was used to evaluate the associations between therapies and the risks of thrombotic events, controlled by the pre-index use of individual therapy. **Results:** A total of 11,809 Veterans with PV were identified from the VAHS, with a mean (SD) age of 67.4 (11.1) years, 96.7% male, 9.0% Black, 81.1% White, and 5.1% Hispanic. The rate of thrombotic events (per 1000 person-year) was 45 for patients treated with cytoreductive therapy, 32 for phlebotomy-treated patients, and 51 for those who received no treatment. Patients were delineated into five groups based on NLR: $<$1, 1-2.9, 3-4.9, 5-19.9, and above 19.9. The rate of thrombotic events was closely at 39% amongst each group with NLR below 5. For those with NLR at 5-19.9 and $>$19.9, thrombotic events were reported in 48% and 61% of veterans, respectively. Cytoreductive therapy and therapeutic phlebotomy were each associated with significantly lower risks of thrombotic events compared to none of these two treatments among PV patients. Adjusted risk of thrombotic events was 45% (HR: 0.55, 95%CI: 0.48-0.62, P $<$ 0.01) and 34% (HR: 0.66, 95%CI: 0.57-0.78, P: $<$ 0.01) lower for patients with cytoreductive and phlebotomy therapy compared to no treatment. **Conclusions:** The real-world evidence from VAHS yields a cut-off value of NLR at 5 to predict risks of thrombotic events among Veterans with PV. Patients receiving cytoreductive therapy or therapeutic phlebotomy had reduced risk of thrombotic events. Research Sponsor: PharmaEssentia, Inc.

6579 **Poster Session**

Real-world outcomes of 7+3 versus azacitidine/venetoclax in CML transformed to AML. First Author: Muhammad Mujtaba Bhinder, Charleston Area Medical Center (CAMC), Charleston, WV

Background: Although tyrosine kinase inhibitors (TKIs) have markedly improved outcomes in chronic myeloid leukemia (CML), transformation to acute myeloid leukemia (AML) remains a devastating event with poor prognosis. Intensive induction chemotherapy with cytarabine and anthracycline (7+3) is standard, but many patients are older or frail and unable to tolerate intensive therapy. Azacitidine plus venetoclax (aza-ven) has emerged as a low-intensity alternative; however, real-world comparative outcome data in CML-transformed AML remain limited. We conducted a large real-world analysis to compare survival and early clinical outcomes with 7+3 versus aza-ven. **Methods:** Adult patients with CML transformed to AML who received induction therapy between January 1, 2010, and June 1, 2025, were identified using the TriNetX Research Network. Patients were classified by receipt of 7+3 or azacitidine plus venetoclax within one year before or after allogeneic hematopoietic stem cell transplantation. Overall survival (OS) was evaluated using Kaplan–Meier analysis with hazard ratios (HRs) and log-rank testing. Early clinical outcomes were compared using z-tests with risk differences (RD), risk ratios (RR), and 95% confidence intervals (CI). **Results:** A total of 280 patients were included, of whom 222 received 7+3 and 58 received azacitidine plus venetoclax (aza-ven). Patients treated with aza-ven had a higher comorbidity burden and lower baseline albumin, consistent with a frailer population. Early infectious complications within 30 days occurred in 53.2% of patients receiving 7+3 and 58.6% receiving aza-ven (risk difference [RD] −5.47%, 95% CI −19.74% to 8.81%; risk ratio [RR] 0.91, 95% CI 0.71–1.16; p=0.46). One-year overall survival was similar between groups (66.2% vs 68.1%; hazard ratio [HR] 1.03, 95% CI 0.62–1.72; log-rank p=0.91). Hospitalization within 30 days occurred less frequently with 7+3 than with aza-ven (71.6% vs 84.5%; RD −12.86%, 95% CI −23.91% to −1.82%; RR 0.85, 95% CI 0.74–0.97; p=0.046), while hospitalization between days 31–180 was identical in both groups (50.0% vs 50.0%; p=1.00). Infection between days 14–30 occurred in 34.7% versus 43.1%, respectively (RD −8.42%, 95% CI −22.62% to 5.78%; p=0.24). **Conclusions:** In this real-world cohort of patients with CML transformed to AML, azacitidine plus venetoclax achieved comparable 1-year survival and early infectious outcomes to intensive 7+3 induction despite being used in a frailer population. Larger multicenter studies are needed to confirm comparative effectiveness and refine patient selection. Research Sponsor: None.

6580 **Poster Session**

Clinical features, management, and outcomes of adolescents and young adults with myeloproliferative neoplasms. First Author: Sandro Pino-Ascencio, Massachusetts General Hospital, Boston, MA

Background: Myeloproliferative neoplasms (MPNs)—polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (MF)—are chronic myeloid malignancies mainly occurring in older adults. However, up to 20% of pts are diagnosed as adolescents and young adults (AYA; ages 13–39). Thus, treatment guidelines and outcome data primarily apply to older subjects, leaving clinical features, outcomes, and management of younger pts poorly defined. We describe the characteristics, risk stratification, and treatment of AYA pts at a tertiary academic center. **Methods:** We conducted a retrospective study of AYA pts with MPN treated at Mass General Brigham between 2007–2025. Pts diagnosed at ages 13–39 and meeting 2022 WHO criteria for MPN were included. Data abstracted from the electronic medical record included demographics, diagnostics, cardiovascular (CV) risk factors, thrombotic and bleeding events, risk stratification, and management. Descriptive statistics were applied. **Results:** 90 AYA pts with MPN were identified. Median age at diagnosis was 27 years (range 16–39), 53 (58.9%) were female and 64 (71.1%) were White. ET was the most frequent (65.6%), followed by PV (22.2%), MF (6.7%), and MPN-unclassified (5.6%). Most pts (73.3%) were diagnosed incidentally with abnormal blood counts. At least one CV risk factor—HTN, HL, DM, BMI $>$25, tobacco use—was present in 53 pts (58.9%). JAK2 mutation was present in 55 pts (61.1%), CALR in 26 (28.9%), MPL in 3 (3.3%), and triple-negative in 7 (7.8%). Across 18 (20.0%) pts, 23 thrombotic events occurred; arterial (n= 9) and venous (n= 14);13 in the year prior to diagnosis and 10 after; 3 pts (3.3%) experienced events in both time periods and 4 (4.4%) pts experienced more than one event. Seven (7.8%) experienced major bleeding in the year prior to diagnosis or any time after, defined by ISTH criteria. Of the 23 pts with thrombotic and/or bleeding events, 19 were subsequently cytoreduced, most often with interferon (ropeginterferon n=10; peginterferon n=3). One pt received ruxolitinib and 12 hydroxyurea. Of 71 pts classified as low-risk, 34 (47.9%) received cytoreduction. Indications included extreme thrombocytosis (32.4%), inadequate control with phlebotomy (23.5%), symptom burden (23.5%), bleeding risk/history (17.6%), and disease modification (14.7%). Median follow-up was 3.6 years (IQR 1.9-7.6), 4 (4.4%) pts progressed to MF, and 1 (1.1%) to accelerated phase MPN. Two (2.2%) of these pts have undergone allogeneic stem cell transplantation. One (1.1%) death was reported during follow-up. **Conclusions:** In this AYA MPN cohort, $>$ 20% were high-risk due to thrombotic events. CV comorbidities were common despite young age. Nearly half of low-risk pts received cytoreductive therapy, highlighting potential limitations of standard risk stratification in young pts. These findings support the need for age-specific guidelines for AYA pts with MPN. Research Sponsor: None.

6581 **Poster Session**

Beyond haematological control: Long-term renal outcomes of imatinib therapy in chronic myeloid leukaemia. First Author: Rachana Chennamaneni, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Background: Imatinib has transformed outcomes in chronic myeloid leukaemia (CML), enabling long-term survival and durable molecular responses. With therapy often extending over decades, late toxicities affecting organ function have gained increasing importance. However, real-world data on long-term renal outcomes with prolonged imatinib exposure remain limited. Objectives: To evaluate long-term changes in renal function in patients with CML receiving imatinib therapy for at least 10 years. **Methods:** This retrospective observational study included patients with CML treated with imatinib for ≥10 years at a single tertiary care centre. Clinical and treatment-related data were obtained from medical records. Renal function at baseline and at latest follow-up was assessed using estimated glomerular filtration rate (eGFR) calculated by the CKD-EPI formula. Data on diabetes and hypertension were collected. Patients with pre-existing chronic kidney disease, those receiving chemotherapy, those diagnosed with a second malignancy and patients in treatment-free remission (TFR) were excluded. **Results:** A total of 440 patients were analysed. The median age at diagnosis was 36 years (range, 5–70), with a male-to-female ratio of 1.39:1. At diagnosis, 95% were in chronic phase. Sokal risk stratification classified 32%, 31%, and 37% of patients as low, intermediate, and high risk, respectively. The median duration of imatinib therapy was 15 years (range, 10–24), with a median daily dose of 400 mg (range, 200–800 mg). At last follow-up, 91% of patients had achieved major molecular response. Overall, 62 patients (14%) developed a clinically significant decline in renal function (eGFR <60 mL/min/1.73 m²). In this subgroup, median eGFR declined from 90 range, 70-122) to 44 mL/min/1.73 m² (range, 13-54); representing a median reduction of 46 mL/min over 15 years (approximately 3 mL/min/year). Comorbidities were present in 11 patients (18%). A greater decline in eGFR was observed among males ($p<0.001$), patients aged <35 years at diagnosis ($p<0.0001$), and those achieving major molecular response ($p<0.0002$). Treatment modification was undertaken in<37 patients (60%), including TFR in 13 (21%), dose reduction in 20 (32%), and switching to an alternate tyrosine kinase inhibitor in 4 (6%). Partial renal recovery was documented in 9 patients (24%). All patients in whom TFR was attempted continue to maintain TFR at last follow-up. **Conclusions:** Long-term imatinib therapy is associated with a gradual but clinically meaningful decline in renal function in a subset of patients with CML. Dose modification, switching TKIs, or attempting TFR may result in partial reversibility, without compromising disease control. These findings highlight the importance of long-term renal monitoring and treatment optimisation in patients with sustained molecular responses. Research Sponsor: None.

6582 **Poster Session**

Durable treatment-free remission in CML beyond clinical trials: Lessons from a large single-center real-world experience. First Author: Sadashivudu Gundeti, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

Background: Treatment-free remission (TFR) has become a major therapeutic objective in chronic-phase chronic myeloid leukemia (CML). While clinical trials have established the feasibility of TFR, real-world data evaluating the influence of deep molecular response (DMR) duration, cumulative tyrosine kinase inhibitor (TKI) exposure, and adherence to molecular monitoring remain limited, particularly in resource-constrained settings. **Methods:** We conducted a retrospective single-centre analysis of chronic-phase CML patients who electively discontinued TKI therapy between May 2019 and October 2025 after achieving sustained DMR (BCR-ABL ≤0.01% IS). Collected variables included demographics, ELTS risk score, TKI type, duration of DMR (<5 vs ≥5 years), cumulative TKI exposure (<8 vs ≥8 years), molecular relapse (loss of major molecular response [MMR]), time to relapse, and time to MMR regain following TKI resumption. Monitoring compliance was defined as completion of at least five PCR assessments in the first year following TKI discontinuation. Relapse-free survival was analyzed using Kaplan–Meier methods. **Results:** Eighty-eight patients were included (median age 36 years; 53.4% male). Median cumulative TKI exposure prior to discontinuation was 14.5 years, and median DMR duration was 13 years. At a median follow-up of 40 months, 72 patients (81.8%) remained in sustained TFR. TFR rates were 92% at 6 months, 87% at 12 months, and 82% at 24 months. Fourteen patients (15.9%) restarted TKI therapy due to molecular relapse, one due to withdrawal symptoms, and two died from causes unrelated to CML. Median time to relapse was 4.5 months, with the majority occurring within the first six months.No patient progressed to accelerated or blast phase. All evaluable patients who resumed TKI therapy rapidly regained MMR (median 3 months). TFR rates did not differ significantly according to DMR duration (<5 vs ≥5 years; $p=0.67$), cumulative TKI exposure (<8 vs ≥8 years; $p=0.70$), or compliance with molecular monitoring (compliant vs non-compliant; $p=0.82$). Notably, 30.6% of patients were non-compliant with recommended monitoring schedules, yet high TFR rates and excellent salvage outcomes were maintained. **Conclusions:** In this large single-centre real-world cohort, over 80% of chronic-phase CML patients achieved durable TFR with predictable early relapses, excellent salvage outcomes, and no disease progression. Neither prolonged DMR duration, extended TKI exposure, nor strict adherence to intensive molecular monitoring significantly influenced relapse risk. These findings support broader, pragmatic implementation of TFR strategies and suggest that less stringent molecular monitoring may be safely adopted in carefully selected patients, particularly in resource-limited settings. Research Sponsor: None.

6583 **Poster Session**

ASC4FIRST wk 144 analysis: Efficacy and safety and tolerability with asciminib (ASC) vs investigator-selected tyrosine kinase inhibitors (IS TKIs) in newly diagnosed (ND) chronic myeloid leukemia in chronic phase (CML-CP). First Author: Jorge E. Cortes, Department of Medicine, Georgia Cancer Center, Augusta University, Augusta, GA

Background: In ASC4FIRST (NCT04971226) primary (wk 48) (Hochhaus A et al. *N Engl J Med*. 2024) and key secondary (wk 96) (Cortes JE et al. *Blood*. 2025) analyses, ASC had superior efficacy and improved safety/tolerability vs IS TKIs. ASC was approved for ND CML-CP in numerous countries. We report the ASC4FIRST wk 144 analysis (cutoff: Sep 29, 2025). **Methods:** In this multicenter, open-label, phase 3 study, patient (pts) with ND CML-CP were randomized 1:1 to ASC 80 mg once daily or an IS TKI at label doses, stratified by ELTS risk category and prerandomization-selected TKI (imatinib [IMA] or a second generation [2G] TKI). Primary endpoints were major molecular response (MMR) rates at wk 48 with ASC vs all IS TKIs, and ASC^{IMA} vs IS TKI^{IMA}. **Results:** Pts were randomized to ASC (n=201) or IS TKIs (n=204). Median follow-up was 38.1 mo with ASC vs 37.4 mo with all IS TKIs, 36.2 mo with ASC^{IMA} vs 35.3 mo with IS TKI^{IMA}, and 39.2 mo with ASC^{2G} vs 38.5 mo with IS TKI^{2G}. At cutoff, more pts were ongoing tx with ASC vs all IS TKIs (78.6% vs 55.9%), ASC^{IMA} vs IS TKI^{IMA} (81.2% vs 50.0%), and ASC^{2G} vs IS TKI^{2G} (76.0% vs 61.8%). MMR rate at wk 144 continued to be superior with ASC vs all IS TKIs (77.1% vs 53.4%; tx difference, 23.9%; P<*.001*) and ASC^{IMA} vs IS TKI^{IMA} (79.2% vs 47.1%; tx difference, 32.6%; P<*.001*), and higher with ASC^{2G} vs IS TKI^{2G} (75.0% vs 59.8%; tx difference, 15.2%; P=*.01*). MR^4 and $MR^{4.5}$ rates at wk 144 were higher with ASC vs all IS TKIs (56% vs 36%; 42% vs 25%), ASC^{IMA} vs IS TKI^{IMA} (58% vs 33%; 44% vs 20%), and ASC^{2G} vs IS TKI^{2G} (53% vs 39%; 41% vs 29%). Long-term outcomes with ASC vs all IS TKIs, ASC^{IMA} vs IS TKI^{IMA}, and ASC^{2G} vs IS TKI^{2G} included probability of event-free survival at wk 144 post randomization (85% vs 69%; 83% vs 63%; 87% vs 75%), and estimated progression-free survival (98% vs 95%; 97% vs 93%; 99% vs 97%) and overall survival (99% vs 97%; 99% vs 96%; 99% vs 99%), at 3 yrs post randomization. No new postbaseline mutations emerged with ASC after wk 96; 1 each emerged with IMA and nilotinib. Safety/tolerability remained favorable with ASC vs IMA vs 2G TKIs including grade ≥3 AEs (49% vs 52% vs 63%), AEs leading to discontinuation (6% vs 13% vs 14%), and AEs leading to dose adjustment/interruption (37% vs 44% vs 63%); exposure-adjusted arterial occlusive event rates were 1.3, 0.5, and 1.1 cases per 100 pt-tx yr, respectively. Median exposure duration was 37.4 mo, 33.8 mo, and 37.3 mo, respectively. No deaths occurred during tx or ≤30 d after last dose. **Conclusions:** At wk 144, ASC had consistently higher molecular response rates and favorable safety/tolerability vs all IS TKIs with no new tx-emergent mutations. Together with wk 48 and 96, this analysis reinforces ASC's improved benefit-risk profile and supports ASC as a tx option for ND CML. Clinical trial information: NCT04971226. Research Sponsor: Novartis Pharma AG.

6584 **Poster Session**

Upfront low-dose diet-modified nilotinib versus standard imatinib in Indian patients with newly diagnosed chronic-phase chronic myeloid leukemia: The NILLOW phase II randomised trial. First Author: Deepak Garg, AIIMS, New Delhi, India

Background: Upfront use of second-generation tyrosine kinase inhibitors in chronic myeloid leukemia (CML) is limited in resource-constrained settings due to cost, fasting requirements, and tolerability concerns. Food increases nilotinib bioavailability, enabling effective dose reduction. **Methods:** NILLOW was a single-center, open-label, randomized phase II study. Newly diagnosed CML-CP patients were randomized 1:1 to receive nilotinib 150 mg twice daily with meals or imatinib 400 mg once daily. The primary endpoint was EMR at 3 months (BCR-ABL1 IS ≤10%). Safety and hematologic recovery were evaluated as secondary endpoints. **Results:** EMR at 3 months was significantly higher with nilotinib compared to imatinib (73.8% vs 46.2%; absolute difference 27.6%; p=0.001). Patients receiving nilotinib demonstrated faster hemoglobin recovery during follow-up ($p<0.01$). Grade 3/4 anemia was lower with nilotinib (5.5% vs 17.8%; p=0.02). Imatinib was associated with higher rates of peripheral edema, periorbital edema, rash, pruritus, and headache (all $p<0.05$). **Conclusions:** Low-dose fed nilotinib improves early molecular response with superior tolerability compared to imatinib. This approach represents a cost-effective frontline strategy for CML in low-resource settings. Further studies as phase 3 maybe be followed up to confirm the signal. Clinical trial information: CTRI/2024/03/064707. Research Sponsor: None.

6585 **Poster Session**

Clinical fidelity of large language models in chronic myeloid leukemia: A multimodel comparative study. First Author: Meenal Gehlawat, Desert Valley Hospital, Victorville, CA

Background: Large language models (LLMs) are emerging as promising tools for clinical decision-making. These models are increasingly investigated for their potential in diagnosis, prognosis, and personalized treatment of chronic myeloid leukemia (CML). This study evaluates the efficacy of five leading LLMs and examines the impact of incorporating up-to-date clinical guidelines into LLM prompts to enhance clinical decision-making. **Methods:** We developed fifty standardized clinical vignettes on CML, staging, tyrosine kinase inhibitor (TKI) selection, monitoring, adverse events, and treatment-free remission. Five LLMs (DeepSeek-R1, Gemini-2.5-Pro, Claude 4.0, GPT-OSS-120B, and LLAMA 4) generated responses under two distinct prompt conditions. In the baseline prompt, the clinical vignette was entered, and a response was obtained. In the guideline-augmented prompt, models were instructed to extract information from the NCCN v1.2026 and ESMO 2017 guidelines. A blinded expert panel evaluated the responses using a peer-reviewed answer key, assigning scores of 0 for incorrect, 1 for partial, and 2 for correct answers. The maximum possible score was 100. **Results:** The use of guideline-augmented prompting increased accuracy across all models, raising performance from 79.8% to 97.6% (mean difference: 17.8 percentage points, 95% CI: 3.9-31.7, p=0.024). Improvements for individual models ranged from 5 to 33 percentage points. Notably, only Gemini-2.5-Pro achieved perfect accuracy (100%). Knowledge drift was observed in four out of five models (80%), primarily due to reliance on outdated WHO classification criteria instead of current NCCN standards. This discrepancy resulted in staging errors in 32% of baseline cases. The diagnostic workup category exhibited the highest baseline accuracy (94%), whereas the treatment-free remission criteria showed the most substantial improvement following guideline integration, increasing from 72% to 96%. **Conclusions:** LLMs possess substantial medical knowledge that can facilitate clinical decision-making. However, these AI systems remain vulnerable to errors such as knowledge drift and hallucinations. This scalable framework demonstrates that mandatory compliance with guidelines, supported by structured prompting, is essential for safe LLM integration into oncology workflows. Institutions implementing LLM-based clinical decision support should require guideline integration rather than relying solely on pre-trained knowledge. Future studies should validate these findings in prospective clinical settings and evaluate mechanisms for automated guideline updating. Research Sponsor: None.

Comparative accuracy of LLM responses under baseline vs. guideline-augmented prompts.

LLM	Baseline response accuracy	Guideline augmented response accuracy	Delta
Claude 4.0	82	97	+15
DeepSeek-R1	72	97	+25
Gemini-2.5 Pro	89	100	+11
GPT-OSS-120B	90	95	+5
LLAMA-4	66	99	+33

6586 **Poster Session**

Molecular response and outcomes in patients with myeloproliferative neoplasms treated with interferon in the real-world setting. First Author: Laneisha Maldonado Jaime, Winship Cancer Institute, Atlanta, GA

Background: Myeloproliferative neoplasms are clonal stem cell disorders driven by constitutive JAK-STAT signaling, classically via acquisition of the *JAK2* V617F mutation. *JAK2* variant allele frequency (VAF) correlates with disease phenotype and clinical risk. Interferon (IFN) therapies are immunomodulatory agents with disease-modifying potential, demonstrating reductions in *JAK2* allele burden in limited prospective trials. However, IFN therapies are underutilized in clinical practice, and molecular responses are poorly defined. Therefore, we evaluated clinical outcomes and molecular response to IFN therapy in real-world practice, emphasizing long-term *JAK2* VAF kinetics. **Methods:** We conducted a single-center, retrospective study of consecutive patients diagnosed with essential thrombocythemia (ET), polycythemia vera (PV), or pre-fibrotic myelofibrosis (pre-MF) treated with peginterferon alfa-2a or ropegintereron alfa-2b, regardless of prior therapy. Serial *JAK2* V617F was measured in peripheral blood using allele-specific PCR. Clinical outcomes, treatment persistence, and longitudinal molecular responses were evaluated. **Results:** Eighty-two patients were included (median age 50.5 years, 73% female), with diagnosis of PV (76.8%), ET (17.1%), or pre-MF (6.1%); 44 patients (53.7%) were treatment naïve. Median follow-up was 92 mos. from diagnosis and 59 mos. from IFN initiation. At 48 mos., 82% of patients remained on treatment; 12 patients (14.6%) discontinued due to intolerance. Disease progression occurred in one patient. Complete hematologic remission (CHR) was achieved in 80.5% of patients. Median baseline *JAK2* VAF was 28%, declining to a median nadir of 4.2% at 41.5 months. Median absolute and relative percent reductions were -18.7 and -81.6%, respectively. VAF reduction $\geq$50% was achieved by 79% of patients, 19.5% achieved a nadir $<$1%, and 53.2% achieved nadir $<$5%. VAF declined progressively until 48 mos. and then remained stable through 72 mos., with later increases mostly attributable to treatment discontinuation. No baseline clinical, molecular, or treatment-related variables predicted depth of molecular response. Treatment-free remission (TFR) was attempted in seven patients after a median of 45 mos. of therapy (mean VAF 0.52%), and median TFR duration was 39 mos. **Conclusions:** This real-world analysis demonstrates that interferon therapy is feasible and effective in real-world practice. Most patients achieved durable CHR with low rates of treatment discontinuation. Disease progression was exceedingly rare. IFN was associated with substantial and sustained reductions in *JAK2* allele burden, supporting its disease-modifying activity outside of the trial setting. These findings reinforce the clinical relevance of serial molecular monitoring and inform emerging approaches to treatment de-escalation in select patients. Research Sponsor: None.

6587 **Poster Session**

Timing of TP53 mutation acquisition as a determinant of outcomes in patients with myeloproliferative neoplasms and myeloproliferative neoplasms/myelodysplastic syndromes. First Author: Lauren M. Granat, Cleveland Clinic, Cleveland, OH

Background: While *TP53* mutations have been studied in MDS and AML, their clinical significance in MPN and MDS/MPN remains incompletely understood. Emerging evidence suggests that *TP53* mutations are often not present at diagnosis, acquired over the disease course, and enriched in older patients (pts). The primary objective of this study was to evaluate whether the interval between diagnosis and the detection of *TP53* mutation impacts OS and/or PFS. **Methods:** All patients with a TP53 mutation were identified via our in-house NGS panel between 2018–2024 were included (n=497). Spearman correlation, Kruskal–Wallis, and chi-square tests were used to evaluate associations between age, VAF, and the presence of co-mutations with the interval from diagnosis to *TP53* detection. The Kaplan–Meier method and Cox proportional hazards models were used to analyze OS and PFS. **Results:** A total of 54 pts, including ET (n=27), PV (n=7), MF (n=9), and CMML (n=9) were identified. The median age at diagnosis was 65.1 yrs, 56% were males (n=30), 81% Caucasian (n=44). 22% (n=12) of pts were diagnosed with their MPN or MDS/MPN at the time of *TP53* identification. 52% pts were treated with hydroxyurea prior to *TP53* identification. At the time of *TP53* detection, 13 pts had progressed to AML and 11 pts to MF. The most common co-mutations were *JAK2* (n=19), *CALR* (n=11), *TET2* (n=10) and *ASXL1* (n=9). The median time from initial diagnosis to *TP53* detection was 6.7 yrs (interquartile range [IQR], 0.8–13.4; range, 0–38 yrs). Pts were divided into 4 quartiles depending on timing of *TP53* acquisition, with 13 pts in the $<$6-mo, 15 pts in the 6 mo–7 yrs, 13 in the 7.1-14 yrs and 13 pts in the $>$14 yrs quartiles. Older pts had a significantly shorter interval between diagnosis and *TP53* detection (Spearman r = -0.61, $p < 0.0001$). In addition to older age in TP53 time $<$ 6 months (Median 74,9 vs 64.0, p=0.005), pts in the $<$6-month group also had higher VAF ($>$ median of 41: 69.2% vs 43.9%) and had higher number of co-mutations at diagnosis ($\geq$3: 53.8% vs 26.8%), although this did not reach statistical significance. Older age at *TP53* detection was associated with significantly worse OS (3.6 vs 27.2 mo; p=0.002) and PFS (3.6 vs 17.5 mo; p$<$0.001). After adjusting for age at the time of *TP53* detection, a longer interval between diagnosis and *TP53* detection was associated with worse OS (HR for the 2nd, 3rd, and 4th quartiles vs. the 1st quartile: 1.2, 2.5, and 4.3; *p for trend* = 0.002) and worse PFS (HR 1.2, 2.9, and 4.5, *p for trend* = 0.001). **Conclusions:** This study demonstrates that after adjusting for age, a longer interval between MPN or MDS/MPN diagnosis and *TP53* detection is associated with worse OS and PFS. Older age has previously been identified as an adverse prognostic factor, however our findings suggest that timing of *TP53* acquisition may also be an important predictor of clinical outcomes in pts with MPNs and MDS/MPNs. Research Sponsor: None.

6588 **Poster Session**

One vs. 2 vs. ≥3 *TET2* mutations in chronic myelomonocytic leukemia: Co-mutation patterns and prognostic correlates. First Author: Muhammad Yousuf, Mayo Clinic Rochester, Rochester, MN

Background: *TET2* is the most frequently mutated gene in chronic myelomonocytic leukemia (CMML) and has been associated with favorable outcome, with recent studies suggesting a more pronounced prognostic impact in the presence of $\geq$2 *TET2* mutations (*Csizmar et al. leukemia 2025;39:2030; Kynning et al. Br J Haematol. 2025 Nov 25. doi: 10.1111/bjh.70264*). We sought to determine if this particular observation extended to patients with $\geq$3 *TET2* mutations ($TET2^{MUT}$) and also held true in the context of recently reiterated genetic risk factors. **Methods:** The current study was conducted under institutional review board approved minimum risk protocols allowing retrospective patient data collection and analysis. Diagnostic criteria were according to the International Consensus Classification (Arber et al. Blood 2022. 140:1200). All statistical analyses were conducted using JMP 18 software. **Results:** 536 CMML patients who underwent CLIA-approved NGS testing were stratified according to the number of $TET2^{MUT}$: 221 (41%) wild-type, 148 (28%) with one, 153 (29%) 2, and 14 (2%) $\geq$3 $TET2^{MUT}$. Co-mutation frequencies with significant differences between one vs. two $TET2^{MUT}$ included ASXL1 (46% vs. 29%; p$<$0.01), KRAS (7% vs. 14%; p=0.02) and SETBP1 (5% vs. 0.6%; p=0.02). Phenotypic comparisons revealed preponderance of prognostically favorable traits associated with wild-type *TET2* but no significant differences between one vs. two $TET2^{MUT}$. In age-adjusted univariate analysis, transplant-censored overall survival (TCOS), calculated from the time of mutation detection, was superior in patients with one (p$<$0.01; HR 0.7) or 2 (p$<$0.01; HR 0.4) but not $\geq$3 (p=0.4) $TET2^{MUT}$, vs. those with wild-type *TET2*. TCOS was also superior with 2 vs. 1 (p=0.02; HR 0.7) but not with $\geq$3 vs. 1 (p=0.7) $TET2^{MUT}$; the results were similar when TCOS was calculated from the time of diagnosis. Multivariable analysis confirmed the survival advantage of exactly two $TET2^{MUT}$ vs. wild-type *TET2* (p$<$0.01; HR 0.5), one $TET2^{MUT}$ (p$<$0.01; HR 0.6), or $\geq$3 $TET2^{MUT}$ (p$<$0.01; HR 0.4), after adjusting for age, sex, anemia, circulating blasts $\geq$2%, and leukocyte count $\geq 13\times10^9$/L. The favorable impact of exactly two $TET2^{MUT}$ persisted in CMML-MD and CMML-MP and remained independent of *TET2* VAF, mutation type, karyotype, and other prognostically relevant mutations. This association was sustained in the BLAST (p$<$0.01; HR 0.5) and CPSS-mol (p=0.02; HR 0.7) models, but not in BLAST-mol model (p=0.12). **Conclusions:** Mechanistic explanation for this novel observation includes the possibility that *TET2* mutational categories based on mutation count reflect distinct biological states rather than having a simple linear effect. The persistence of this signal despite adjustment for established molecular and genetic risk factors supports its consideration in the development of future CMML prognostic models. Research Sponsor: None.

6589 Poster Session

Phase II trial of asciminib for newly diagnosed chronic myeloid leukemia. First Author: Maria Hachem, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Asciminib is safe and effective across all lines of therapy of chronic myeloid leukemia (CML). Here, we report interim results from an investigator-initiated phase II trial of asciminib in patients (pts) with newly diagnosed (ND) CML. **Methods:** Asciminib was given at 80 mg/day in pts with ND CML in chronic phase or accelerated phase (clonal evolution only). The primary endpoint was the rate of major molecular response (MMR) by 12 months of therapy. AEs were recorded according to the CTCAE version 5.0 criteria. The data cutoff was January 20, 2026. **Results:** A total of 59 pts were treated with a median age at diagnosis of 49 years (range, 21-79); 33 (56%) were male. Sokal score was low in 29 pts (49%), intermediate in 21 (36%), and high in 9 (15%). With a median follow-up of 12 months, the cumulative best overall response was MCyR in 57 pts (97%), CCyR in 54 (92%), MMR in 40 (68%), MR4 in 21 (36%), and MR4.5 in 17 (29%). Among pts who completed at least 1 year of asciminib therapy, the MMR rate by 12 months was 71%. By 3 months, among 58 evaluable pts, 51 (88%) achieved MCyR or transcript levels below 10% on the international scale (IS), 42 (72%) CCyR or transcript levels below 1% IS, 16 (28%) MMR, 5 (9%) MR4, and 2 (3%) MR4.5. Seven pts (12%) had transcript levels above 10%. By 6 months, among 53 evaluable pts, the rate of CCyR was 85% (45/53), MMR 64% (34/53), MR4 34% (18/53), and MR4.5 26% (14/53). By 12 months, CCyR was achieved in 27 pts (87%), MMR in 22 (71%), MR4 in 13 (42%), and MR4.5 in 10 (32%). *ASXL1* mutation was detected in 3 of 41 pts (7%) evaluated for cancer gene variants. Of them, two achieved a complete molecular response and one achieved CCyR as best response but later lost it with the acquisition of *A337T* and *F497L* mutations. The most frequent adverse events related or possibly related to asciminib included elevated lipase (Grade[G]2, n=9; G3, n=3; G4, n=1) and fatigue (G1, n=7; G2, n=2); 3 pts developed pancreatitis (G2, n=1; G3, n=2). A 71-year-old pt with a previous medical history of hypertension developed G5 acute coronary syndrome after 2.5 months of asciminib therapy. Overall, 8 of 59 pts (14%) discontinued asciminib due to: 1) adverse events in 4 (including 1 fatal acute coronary syndrome); 2) loss of CCyR in 2 (one with the emergence of *A337T* and *F497L* mutations and another with *P465A* and *D381E* mutations); 3) failure to achieve CCyR in 1 patient in the setting of cytopenias and asciminib dose reduction to 40 mg/day; and 4) withdrawal of consent by 1 patient due to inability to return to clinic for treatment due to social constraints and was in MR4 at the time of asciminib discontinuation. The 12-month rates of failure-free survival, event-free survival, transformation-free survival, and overall survival were 92%, 96%, and 98%, respectively. **Conclusions:** Treatment with asciminib in ND CML showed a MMR tare of 71% by 12 months of therapy with no new safety signals. Disease resistance was associated with the emergence of myristoyl pocket mutations. Clinical trial information: NCT06236724. Research Sponsor: None.

6590 Poster Session

Thromboelastography-guided platelet transfusion and associations with utilization and outcomes in patients with hematologic malignancies. First Author: Rana Mohamed, Brody School of Medicine at East Carolina University, Greenville, NC

Background: Thromboelastography (TEG) is a viscoelastic assay assessing clot formation and global hemostasis. In patients with hematologic malignancies, transfusion support is essential, yet evidence guiding optimal transfusion strategies is limited. This study evaluated transfusion utilization and outcomes associated with TEG use in hematologic oncology patients. **Methods:** We conducted a retrospective cohort study at a tertiary care hospital (October 2022–2025) including hospitalized patients with acute and chronic leukemias or multiple myeloma who received blood product transfusions. Primary outcomes were platelet transfusion utilization (standardized units) and platelet response. Secondary outcomes included hospital length of stay (LOS) and in-hospital mortality. Welch's t-test and chi-square testing were used, with multivariable regression adjusting for demographic and clinical covariates. **Results:** Among 975 platelet transfusion episodes, 68 (5.3%) were TEG-guided. Unadjusted analyses showed slightly lower platelet utilization with TEG-guided transfusions compared with standard care (1.03 vs 1.06 units, $p<0.001$). Platelet count increments did not differ significantly (Δ 17.9 vs 16.3, p=0.57). TEG-guided patients had longer LOS (39.8 vs 31.9 days, $p<0.001$) and higher in-hospital mortality ($p<0.001$), reflecting greater illness severity. After adjustment, differences in utilization, platelet response, and LOS were no longer significant. TEG use remained strongly associated with in-hospital mortality (adjusted OR 29.8, 95% CI 8.83–100.77, $p<0.001$). **Conclusions:** TEG use in hospitalized patients with hematologic malignancies receiving platelet transfusions was uncommon and not associated with improved transfusion efficiency or platelet response. TEG-guided transfusions occurred primarily in high-acuity settings with prolonged hospitalization and increased mortality, suggesting TEG functions more as a marker of illness severity than a routine tool for optimizing platelet transfusion. Further studies are needed to clarify its role in malignant hematology care. Research Sponsor: None.

Platelet transfusion outcomes by TEG use in hematological malignancy encounters.

Outcome	TEG guided (n=68)	Non-TEG guided (n=1214)	P Value (unadjusted)	P value (adjusted)
Number of encounters	68	1214	–	–
Standardized platelet units, mean	1.03	1.06	0.14	0.34
Platelet count response (DELTA), mean	17.9	16.3	0.57	0.93
Length of stay, mean days	39.8	31.9	<0.001	0.51
In-hospital mortality, %	94.1	44.7	<0.001	0.0008

Adjusted p values from multivariable regression models including demographics, malignancy subtype, baseline platelet count, transfusion dose, care location, transfusion priority, and timing variables. DELTA = post-pre platelet count.

6591 Poster Session

Safety and efficacy of asciminib in veterans with chronic myeloid leukemia. First Author: Omar Shukri Yaghi, George Washington University, Department of Medicine, Washington, DC

Background: Asciminib was approved for use in previously treated patients with chronic myeloid leukemia (CML) in 2021. It employs a novel allosteric mechanism that can overcome resistance and intolerance to conventional tyrosine kinase inhibitors (TKIs). We assessed the efficacy and clinical outcomes of asciminib in Veterans with CML following failure of first- and second-generation TKIs. **Methods:** Utilizing the VA Informatics and Computing Infrastructure (VINCI), we reviewed all 116 Veterans nationwide with a diagnosis of CML who were treated with asciminib prior to August 2025. Demographic and clinical data collected included age at diagnosis, gender, race, prior CML treatments, and BCR-ABL transcript levels at treatment initiation and at 3 and 6 months. Safety outcomes included the development of thrombocytopenia and neutropenia. Mortality data were collected when applicable. Since more than half of the patients were still alive at the time of chart abstraction, median survival could not be reliably estimated (median 3.4 years, lower limit 2.8 years, upper limit NA). We therefore report the restricted mean survival time (RMST). **Results:** 110 Veterans were included in the analysis after excluding 6 for missing data. The median age at diagnosis was 65 years (IQR, 52–71) and 95% of participants were male (Table 1). 70% of participants received a first-generation TKI as first-line therapy; in the second-line setting, 12% received a first-generation TKI and 83% received a second-generation TKI. The median BCR-ABL level at asciminib initiation was 1.03 (IQR, 0.08–29.95) and decreased to 0.05 (IQR, 0–0.69) at 6 months. 11 patients developed thrombocytopenia and 3 developed neutropenia. Assuming 5 years of follow-up from the start of asciminib, RMST is 3.3 years (standard error, 0.23 years). **Conclusions:** Asciminib demonstrated clinically meaningful activity in a heavily pretreated Veteran population with CML. By 6 months, the median BCR-ABL level was 0.05%, consistent with major molecular response (MMR; BCR-ABL ≤0.1%), a well-established positive prognostic indicator. Despite prior exposure to multiple therapies, overall survival (using RMST) remained favorable at a mean of 3.3 years following treatment initiation. Rates of any-grade neutropenia and thrombocytopenia were low, supporting a favorable safety profile. Research Sponsor: None.

Patient characteristics and outcomes.

Characteristic	Total (N = 110)
Age at diagnosis, median (IQR)	65 (52–71)
Gender, n (%)	
Male	105 (95%)
Female	5 (4.5%)
Race	
Black	19 (17%)
White	85 (77%)
American Indian or Alaska Native	1 (0.9%)
Unspecified	5 (4.5%)
Treatment Exposure	
First-line therapy	
1st generation TKI	77 (70%)
2nd generation TKI	33 (30%)
Second-line therapy	
1st generation TKI	13 (11.8%)
2nd generation TKI	91 (82.7%)
3rd generation TKI (ponatinib)	6 (5.5%)
Outcomes	
Thrombocytopenia	11 (10%)
Neutropenia	3 (2.7%)
RMST (5 years), years	3.3 (95% CI, 2.9–3.8)

6592 Poster Session

Glucagon-like peptide-1 receptor agonist (GLP-1 RA) and hematologic cancer risk among older adults with type 2 diabetes. First Author: Wei-Han Chen, Department of Pharmaceutical Outcomes & Policy, College of Pharmacy, University of Florida, Gainesville, FL

Background: Recent preclinical and clinical evidence suggests that glucagon-like peptide-1 receptor agonists (GLP-1 RA) may reduce cancer risk through inflammation modulation. However, comparative effectiveness research evaluating hematologic malignancy risks of GLP-1 RAs remain limited in real-world populations. **Methods:** Using 15% random samples of Medicare Part D beneficiaries from 2013 to 2022, we identified older adults with type 2 diabetes who initiated GLP-1 RA or DPP-4i. The primary outcomes included myelodysplastic syndromes (MDS), lymphoma, and leukemia. We performed 1:1 propensity score matching for confounding control. We estimated the hazard ratios (HR) and 95% confidence intervals (CI) with Cox proportional hazard model. We examined the heterogeneity in treatment effects by pre-specified patient demographic and baseline factors. Subgroup analyses were conducted for: a) age (≥75 vs. <75 years), b) sex (female vs. male), c) race/ethnicity (non-Hispanic Black vs. non-Hispanic White vs. Hispanic ethnicity), d) obesity status (overweight vs. obese vs. severe obesity), and e) specific GLP-1 RA class (e.g., liraglutide, dulaglutide, and semaglutide). In the sensitivity analysis, we used cause-specific Cox model to account for death as a competing risk and calculated E-values to examine the potential influence of unmeasured confounders. **Results:** After propensity score matching, there were 29,212 patients included in the cohort (14,606 GLP-1 RA users and 14,606 DPP-4i users). Of the cohort, mean (SD) age was 77.3 (7.4) years; 53.9% were female, 69.9% were non-Hispanic White, 11.1% were non-Hispanic Black, and 3.9% were Hispanic. Compared to DPP4i, GLP-1 RA showed reduced risks in MDS (HR: 0.70, 95% CI [0.53-0.94]), lymphoma (0.71 [0.57-0.89]), and leukemia (0.85 [0.74-0.99]). Overall, no statistically significant heterogeneity of treatment effect was detected in subgroup analyses. After accounting for death as a competing event, the hazard ratios are consistent with the conventional Cox models except monocytic leukemia (HR: 1.4 [0.45-4.56], p=0.48). E-values suggest moderate robustness to potential unmeasured confounding. **Conclusions:** GLP-1 RA initiation was associated with a reduced risk of hematologic malignancies compared with DPP-4i use among real-world patients with type 2 diabetes. These findings suggest a potential protective effect of GLP-1 RAs on hematologic cancer risk and warrant further mechanistic and prospective investigation. Research Sponsor: None.

6593 **Poster Session**

Clinical and genetic landscape of individuals evaluated in a CHIP cardiology clinic: A single-center experience, 2020 to 2025. First Author: Ohad Oren, Cleveland Clinic, Cleveland, OH

Background: Despite growing observational data linking clonal hematopoiesis of indeterminate potential (CHIP) to adverse cardiovascular outcomes, the cardiovascular evaluation and management of individuals with clonal hematopoiesis remain undefined. We report the experience of a dedicated CHIP Cardiology Clinic. **Methods:** We conducted a retrospective review of patients evaluated in the CHIP Cardiology Clinic at the Brigham and Women's Hospital. Baseline demographics, comorbidities, medication use, and treatment interventions were extracted from the electronic medical record. **Results:** Fifty-three patients were evaluated between 2020 and 2025, of whom 39 (73.6%) had clonal hematopoiesis (CH), out of which 12 (30.8%) met criteria for CHIP. Among individuals with CH, the most frequently identified mutations were D N M T 3 A (30, 76.9%), T E T 2 (23, 59.0%), and A S X L 1 (6, 15.4%). The mean age was 65.9 years (range 40-81), and 23 (58.9%) were male. Hypertension and dyslipidemia were each present in 23 (59.0%) patients. Existing cardiovascular diseases included coronary artery disease (7, 18.0%) and arrhythmias (3, 7.7%). Following evaluation in the CHIP Clinic, and shared decision-making discussion in view of the dearth of evidence regarding outcome improvement in those with CHIP, lipid-lowering therapies were initiated or increased in 28 (71.8%) patients, with statins initiated or dose escalated in 21 (53.8%) and ezetimibe in 11 (28.2%). Blood pressure medications were initiated or intensified in 5 (12.8%) patients. Ischemic evaluation was performed in 3 (7.7%) patients due to suggestive symptoms. We developed a "patient page" to acquaint the patients and families with CHIP. (https://doi.org/10.1001/jamacardio.2024.3773). **Conclusions:** In this first longitudinal report from a dedicated CHIP Cardiology Clinic, a substantial proportion of patients harbored somatic mutations associated with elevated cardiovascular risk. Institution of preventive cardiovascular medications, in particular lipid-lowering therapies, was a frequent intervention. These findings support the feasibility of CHIP-focused cardiovascular care but underscore the need for prospective trials to evaluate the impact of targeted preventive strategies in this population. Research Sponsor: None.

6594 **Poster Session**

Clinical outcomes in *TP53*-mutated clonal hematopoiesis: Single-center retrospective study. First Author: Jacob Edward Herstein, Department of Internal Medicine, University of Texas Health Science Center at Houston, Houston, TX

Background: Clonal hematopoiesis (CH), including CH of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS), is defined by myeloid neoplasm (MN)-associated somatic mutations in the absence of known hematologic malignancy and may precede MNs, such as myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). *TP53*-mutated (*TP53*m) CH has been assumed to be high risk, but clinical outcomes are poorly characterized. **Methods:** We retrospectively evaluated patients (pts) with *TP53*m CH seen at a tertiary cancer center. Inclusion required pathogenic or likely pathogenic *TP53* mutations of presumed hematopoietic origin identified on bone marrow, peripheral blood, or plasma next-generation sequencing. **Results:** 62 pts with *TP53*m CH were included; 26 (42%) CHIP and 36 (58%) CCUS. Median age was 68 years (range, 23–81) with 30 male pts (48%). History of tobacco, alcohol, and illicit drug use was noted in 30 (48%), 31 (50%), and 7 (11%) pts, respectively. Common comorbidities included cardiovascular disease (n=51, 82%), diabetes (n=17, 27%), and rheumatologic disorders (n=13, 21%). 53 pts (85%) had a history of non-myeloid malignancy, with 41 (77%) receiving prior cytotoxic chemotherapy, 20 radiation (32%), and 13 (21%) stem cell transplant/cellular therapy (SCTCT). By CH Risk Score (CHRS), 4 (7%), 38 (61%), and 20 (32%) pts were considered low-, intermediate-, and high-risk of myeloid transformation. The 36 CCUS pts were classified as 10 (28%) low, 9 (25%) intermediate, and 17 (47%) high risk by Clonal Cytopenia Risk Score (CCRS). Median *TP53* VAF was 5% (range, 1–54), and 30 pts (46%) had additional somatic mutations. 12 pts (19%) were *TP53* double-hit. Median time from prior malignancy to CH detection was 42.3 months (mo; range, 0.2–365.0). With a median follow-up time of 60.1 mo (95% confidence interval [CI], 43.0–70.5), median overall survival (mOS) from CH detection was 67.5 mo (95% CI, 59.0–not estimable [NE]). A total of 15 pts (24%) progressed to MNs (12 MDS [80%], 3 AML [20%]) with a median time to transformation of 20.2 mo (95% CI: 6.8–53.9). mOS from time of MN diagnosis was 20.1 mo (95% CI, 7.3–NE) for MDS and 0.3 mo (95% CI, 0.3–NE) for AML pts. Pts who transformed to MNs were more likely to have had tobacco (p=0.026) or illicit drug use (p=0.031), higher comorbidity burdens (p=0.031), rheumatologic disorders (p=0.016), previous SCTCT (p=0.042), and CCUS (p=0.035). No differences were observed by *TP53* VAF. Of those who transformed, 7 (47%) were intermediate- and 8 (53%) high-risk by CHRS. CCRS showed low, intermediate, and high risk in 4 (33%), 1 (9%), and 7 (58%) of the 12 *TP53*m CCUS pts who progressed to MNs, respectively. **Conclusions:** *TP53*m CH is associated with significant comorbidity burdens and oncologic history. Existing risk stratification tools poorly predict myeloid transformation in these pts. Further clinicopathologic characterization of *TP53*m CH is warranted. Research Sponsor: None.

6595 **Poster Session**

Genomic landscape and precision therapeutics in polycythemia vera: Insights from the AACR Project GENIE. First Author: Alena Gagnon, Santa Clara University, Santa Clara, CA

Background: Polycythemia vera (PV) is a myeloproliferative neoplasm associated with blood thickening and increased risk of life-threatening blood clots and bleeding. PV is rare and affects roughly 50 per 100,000 people in the US. PV is most commonly associated with a somatic mutation in the *JAK2* gene and the mean age of diagnosis is 60. The *JAK2* gene is critical for cell signaling, and cell maturation. Treatments for PV include immunotherapy, radiation and chemotherapy but this can only slow growth, underscoring the need to define molecular drivers for targeted therapies. Using the AACR GENIE database, this study characterizes the mutational landscape of PV to identify genetic markers and therapeutic targets. **Methods:** The American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) database was accessed from cBioPortal (v18.1-public) on November 20, 2025 to identify all patients with PV. The most common gene mutations, demographic correlations, and mutual exclusivities were analyzed using a two-sided T-test and non-parametric tests, with Benjamini-Hochberg false discovery rate (FDR) correction. **Results:** The cohort comprised 491 PV samples from 341 patients. The patient population consisted of adults(19-88 years old, n=341,100%). Males (n=171, 50.1%) were represented as equally as females (n=163, 47.8%), with some unknown cases (n=7, 2.1%). By race, the cohort consisted primarily of White (n=236, 69.2%), Black (n=13, 3.8%), and Asian (n=17, 5.0) patients, with the remaining patients (n=75, 22.0%) categorized as having an unspecified or other race. Of the samples derived from 90 tumors which were classified as primary (n=80, 16.3%) or metastatic (n=10, 2.0%), the most frequent somatic mutations were observed in *JAK2* (87.17%, n=428), *TERT2* (18.53%, n=91), *DNMT3A* (14.87%, n=73), *ASXL1* (5.50%, n=27), and *TP53* (3.05%, n=15). When stratified by sex, sex-associated mutational variability was observed. Specifically, mutations in *NF1* (n=13, $p < 0.001$) were detected only in females. *DNMT3A* mutations occurred at a higher frequency in females compared to males (n=48 v. n=23; $p < 0.001$). *AXSL1* mutations occur at a higher frequency in males compared to females (n=23 v. n=4; $p < 0.001$). **Conclusions:** To the best of our knowledge, this is the first GENIE database analysis of polycythemia vera, thus addressing a significant research gap regarding its genomic landscape. The predominance of *JAK2* and *TERT2* align with earlier descriptions in prior genetic profiling studies. Sex specific mutations underscore the importance of demographic-specific molecular features. Collectively, these findings suggest that *JAK2* and *TERT2* could serve as key genomic targets for the development of novel precision therapeutics. Further research is needed to validate these genomic associations and advance precision medicine approaches for patients with PV. Research Sponsor: None.

6596 **Poster Session**

Universal adipogenic and immunologic remodeling in the recurrent myeloid leukemia microenvironment of recurrent versus primary myeloid leukemias: An age-stratified analysis. First Author: Karen Dong-Tran, Renown Health/University of Nevada Reno School of Medicine, Reno, NV

Background: Disease recurrence is the primary cause of mortality in myeloid leukemias. While molecular studies suggest leukemic cells actively reprogram marrow stroma to create a self-reinforcing niche, natural age-related adiposity confounds whether this remodeling is disease-intrinsic or a byproduct of aging. We sought to validate the "disease-intrinsic" hypothesis by delineating the landscape of recurrent disease across a large-scale transcriptomic cohort, rigorously distinguishing leukemic reprogramming from physiologic aging. **Methods:** We analyzed 2,378 myeloid leukemia samples (2,007 primary, 371 recurrent) from NCI genomic datasets via xCell computational deconvolution. To control for ontogenic marrow changes, the cohort was stratified into Pediatric (<18 years, n = 2,071) and Adult (≥ 18 years, n = 307) subgroups. Demographic analysis confirmed balanced gender and race distributions ($p > 0.05$); age disparity was explicitly corrected via the stratified design. Differences in tumor microenvironment (TME) composition were assessed using Mann-Whitney U tests, with Bonferroni-corrected p-values (Padj) calculated to ensure statistical rigor. **Results:** Recurrent tumors exhibited a profound, convergent stromal remodeling independent of age. The 'adipogenic shift' via Preadipocyte enrichment was observed in both Pediatric ($P < 10^{-48}$) and Adult ($P < 10^{-4}$) recurrences. Conversely, vascular collapse was universal, characterized by a significant reduction of Pericytes in both Pediatric ($P < 10^{-72}$) and Adult ($P < 10^{-8}$) cohorts. Immunologically, CD4+ Memory T cells were consistently enriched in both Pediatric ($P < 10^{-26}$) and Adult ($P < 10^{-4}$) groups, suggesting a convergent mechanism of adaptive immune persistence in the relapsed setting. **Conclusions:** We demonstrate that recurrent myeloid leukemia drives a convergent microenvironmental evolution characterized by vascular collapse, pathologic adiposity, and immune persistence, independent of patient age. These findings corroborate that stromal remodeling is a dominant, disease-intrinsic program actively driven by leukemic cells rather than a passive reflection of aging. Validating this "adipogenic shift" as a universal resistance mechanism identifies the adipogenic and vascular niches as priority targets for therapeutic intervention across the spectrum of myeloid malignancies. Research Sponsor: None.

Differential enrichment of microenvironmental populations in recurrent vs. primary myeloid neoplasms.

Cohort	Cell Type	Direction	Mean Diff (Rec - Pri)	Padj
Pediatric (<18y)	Preadipocytes	Recurrence- High	+0.064	$p < 0.05$
	Pericytes	Primary- High	-0.085	$p < 0.05$
	CD4+ Memory T-cells	Recurrence- High	+0.849	$p < 0.05$
Adult (≥18y)	Preadipocytes	Recurrence- High	+0.056	$p < 0.05$
	Pericytes	Primary- High	-0.078	$p < 0.05$
	CD4+ Memory T-cells	Recurrence- High	+1.184	$p < 0.05$

6597 **Poster Session**

Molecular characteristics of therapy-related myeloid neoplasms in PARP inhibitor–treated patients. First Author: Tamanna Haque, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Poly ADP-ribose polymerase inhibitors (PARPi) are part of standard therapy in solid tumors, and is associated with development of therapy-related myeloid neoplasm (t-MN), including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). The contribution of pre-existing clonal hematopoiesis (CH) in t-MN with PARPi exposure is unknown. We report outcomes of a real-world cohort of t-MN patients following PARPi therapy. **Methods:** We performed a retrospective single-center analysis of 23 patients with solid tumors treated with PARPi (olaparib, rucaparib, niraparib, talazoparib) who subsequently developed t-MN. Chart review was performed to collect clinical data. Blood samples collected as a somatic control prior to the first chemotherapy or radiation for targeted next-generation sequencing (NGS) using the MSK-IMPACT platform were analyzed for pre-existing CH in a subset of evaluable patients (n=17). CH was defined as a somatic mutation with variant allelic frequency of 2% or more in peripheral blood. **Results:** Median age was 63 years at initial solid tumor diagnosis and 68 years at t-MN diagnosis. Primary malignancies included Ovarian/Fallopian Tube (83%, n=19), Breast (17%, n=4), Prostate (9%, n=2), and Esophageal (n=1) cancer. 3 patients had a history of both Breast and Ovarian cancer. Germline BRCA1/2 mutations were present in 48% (n=11) and 1 patient had Li-Fraumeni. Median time from PARPi initiation to t-MN diagnosis was 23.7 months (range: 1.6–45.3 months). At t-MN diagnosis, 52% (12/23) presented with MDS (including one case of clonal cytopenias of undetermined significance) and 48% (11/23) with AML. Genomic profiling of t-MN showed 78% (18/23) of patients had *TP53* mutations, and 65% (15/23) had complex karyotype. 90% of evaluable AML cases were classified as adverse risk by ELN 2022 and most MDS cases (9/11) had High/Very High risk by IPSS-R. Median overall survival in this cohort was 6 months from t-MN diagnosis. Among 17 patients with evaluable baseline blood samples, 41% (7/17) had detectable CH prior to t-MN, while 59% (10/17) did not. Of those with pre-existing CH, 57% (4/7) harbored mutations in DNA damage response genes (2 with *TP53*, 2 with *PPM1D*). Other mutations included *DNMT3A* (N=2), *ASXL1* (N=1), *SRSF2* (N=1), and *JAK2* (N=1). 43% (3/7) had a single CH mutation, while 57% (4/7) had 2 or more CH mutations. 6/7 of those with pre-existing CH had molecular testing at t-MN diagnosis, all of which (6/6) had a detectable *TP53* mutation at t-MN diagnosis, even when not previously detected. Cytogenetic features of t-MN for those with and without pre-existing detectable CH were similar. **Conclusions:** This is the largest single center cohort of post-PARPi t-MN with molecular characteristics described to date. Further study on the effect of PARPi therapy in the pathogenesis of t-MN is needed. Research Sponsor: None.

6598 **Poster Session**

Outcomes and responsiveness of standard tyrosine kinase inhibitor dose versus dose de-escalation in chronic myeloid leukemia: A single-center retrospective study. First Author: Mark Pusung, Division of Hematologic Malignancies, Knight Cancer Institute, Oregon Health & Science University, Portland, OR

Background: Treatment with tyrosine kinase inhibitors (TKIs) enables patients with chronic myeloid leukemia (CML) to achieve durable remission and a normal life expectancy. Despite this success, chronic TKI therapy is associated with cumulative toxicities. Although TKI dose de-escalation can be implemented to mitigate adverse events, its impact on the attainment and durability of response milestones is not completely defined. This study explored the impact of dose de-escalation of TKIs on clinical response milestones and treatment-free remission (TFR) outcomes. **Methods:** We retrospectively analyzed 407 adult CML patients treated with TKIs at Oregon Health & Science University. Outcomes of interest were TFR and achievement of undetectable *BCR::ABL1* transcripts. Odds ratios (OR) or Cox proportional hazards regression hazard ratios (HR) were used to analyze covariates and predictors. **Results:** Overall, the median age at diagnosis was 48 years (range: 18-91) and 1st-line therapies included: imatinib (n=252; 62%), dasatinib (n=95; 23%), nilotinib (n=42; 10%), and bosutinib (n=10; 2%); the remaining 2% of patients were treated with 3rd generation or later TKIs. Median follow-up since diagnosis was 11.3 years (0.2-35.8); 189 patients (46%) remained on their initial TKI, while 218 patients (54%) received $\geq$2 TKIs. Only 13 patients (3.2%) received a bone marrow transplant. With respect to the primary outcome of TFR, 133 patients attempted TFR and were further analyzed with respect to de-escalation of dose. Fifty-two patients (39%) remained on standard dose while 81 patients (61%) underwent dose de-escalation prior to the 1st TFR attempt. TFR rates were not significantly different between patients receiving standard dose vs de-escalated dose TKI (HR: 1.07 (95% CI: 0.59-1.96); p=0.818) at either 1 year (77% vs 74%) or 2 years (69% vs 69%). At the last follow-up, 89 patients remained in TFR, 62% of which had undergone dose de-escalation. Among the remaining 274 patients who have yet to attempt TFR, 162 (59%) continued treatment with their initial TKI: 98 (60%) on imatinib, 39 (24%) on dasatinib, 17 (10%) on nilotinib, 5 (3%) on bosutinib, 2 (1%) on ponatinib, 1 (1%) on asciminib. Among these patients, 56 (34%) had dose reduction, 9 (16%) of whom achieved undetectable disease. For the 106 patients on standard doses, only 5 (5%) had undetectable disease (OR: 3.83 (95% CI: 1.08-15.40); p=0.020).More importantly, dose de-escalation led to significant reduction of adverse events. **Conclusions:** Our results show that patients who underwent dose de-escalation did not have significant differences in TFR duration and rate and are more likely to achieve undetectable diseases when compared with patients on standard doses. These findings support rational dose de-escalation as a strategy that preserves achievement of clinical outcomes while reducing adverse events. Research Sponsor: None.

TPS6599 **Poster Session**

A phase I study of HPB-092, a dual FLT3/IRAK4 inhibitor, in relapsed or refractory acute myeloid leukemia. First Author: Mingyuan Sun, State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Disease, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China

Background: Fms-like tyrosine kinase 3 (FLT3) is a clinically validated oncogenic driver in acute myeloid leukemia (AML). While FLT3 kinase inhibitors have been approved for AML patients with FLT3 mutations, resistance remains a significant challenge. Interleukin-1 receptor–associated kinase 4 (IRAK4) has emerged as a key signaling node in treatment-induced resistance. Moreover, a subset of AML patient population harbors mutations in RNA splicing factors U2AF1 or SF3B1. These mutations result in expression of an oncogenic long form of IRAK4. Therefore, co-targeting FLT3 and IRAK4 can potentially both address resistance and treat a broader population in AML. HPB-092 is a highly selective dual-target small-molecule kinase inhibitor designed to target mutant FLT3 and IRAK4. HPB-092 demonstrated robust potency against FLT3-ITD (IC_{50} = 0.24 nM), FLT3-D835Y (IC_{50} = 0.18 nM), and IRAK4 (IC_{50} = 3.1 nM). In vivo, HPB-092 elicited dose-dependent regression of the MV4-11 tumor model. HPB-092 received IND clearance in both China and the US, showing a favorable safety profile with no significant genotoxicity or hERG inhibition, supporting its clinical evaluation. **Methods:** This ongoing, first-in-human, phase 1 study evaluates oral HPB-092 monotherapy in adults with RR-AML. The primary objectives are to evaluate safety, tolerability, pharmacokinetics (PK), and to determine the recommended phase II dose (RP2D). Secondary objectives include preliminary antileukemic activity (ORR, DOR) and exploratory biomarkers analyses. Part A is a dose-escalation phase spanning five dose levels (30–200 mg), utilizing an accelerated titration design followed by a 3+3 scheme in patients with R/R AML, regardless of FLT3, U2AF1 or SF3B1 mutation status. The study initiates with a single-dose administration on cycle 1 day 1 for SAD-PK assessment, followed by multiple ascending doses administered twice daily for MAD-PK and dose-limiting toxicities (DLTs) over a 28-day observation window. Part B is a randomized dose-expansion phase to evaluate selected dose levels in patients with FLT3-mutant AML and those with U2AF1 or SF3B1 mutations. Correlative pharmacodynamic and biomarker analyses are planned. No formal hypothesis testing or sample size calculation was performed. Safety, PK, and efficacy analyses will be descriptive in patients receiving at least one dose of HPB-092. AEs will be graded according to NCI CTCAE v5.0. PK parameters will be derived using noncompartmental methods. Time-to-event endpoints will be estimated using Kaplan–Meier methods, where applicable. Site initiation is complete; enrollment is initiated and ongoing, with the first patient anticipated in Q1 2026. Clinical trial information: NCT07137637. Research Sponsor: None.

TPS6600 **Poster Session**

A phase 3 study of revumenib plus venetoclax/azacitidine in adults with newly diagnosed *NPM1*-mutated or *KMT2A*-rearranged acute myeloid leukemia ineligible for intensive chemotherapy (EVOLVE-2/HO177/AMLSG35-24/ACT-HOV-AML-002). First Author: Geert Abraham Huls, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

Background: Optimal treatment for patients (pts) with acute myeloid leukemia (AML) unfit for intensive chemotherapy (IC) remains challenging and depends on pt and disease characteristics and pt preference. In AML with a nucleophosmin-1 mutation (*NPM1*m) or lysine methyltransferase 2A (*KMT2A*) rearrangement (*KMT2A*r), menin-KMT2A fusion proteins upregulate *HOX/MEIS* gene expression, resulting in hematopoietic differentiation arrest and leukemogenesis. Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction. In the phase 1/2 AUGMENT-101 study (NCT04065399), revumenib monotherapy demonstrated clinically meaningful response rates and was generally well tolerated in pts with relapsed/refractory *NPM1*m AML or *KMT2A*r acute leukemia. To further improve outcomes, combination regimens are being studied as front-line therapy for newly diagnosed (ND) pts. In the phase 1b Beat AML study (NCT03013998), revumenib plus venetoclax/azacitidine (VEN/AZA) demonstrated deep responses in pts $\geq$60 years (y) of age with ND *NPM1*m or *KMT2A*r AML. EVOLVE-2 will assess whether revumenib plus VEN/AZA prolongs overall survival (OS) and improves complete remission (CR) rates in pts with ND *NPM1*m or *KMT2A*r AML ineligible for IC. **Methods:** EVOLVE-2 is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT06652438/EU-CT 2024-512733-32-00). Eligible pts are $\geq$75 y of age (18–74 y with comorbidities), have ND AML with centrally confirmed *NPM1*m or *KMT2A*r (excluding *KMT2A* partial tandem duplications/deletions), are ineligible for IC, and are AML treatment-naive. Pts will be randomized 1:1 to revumenib or placebo in combination with VEN/AZA and stratified by age ($<$75 vs $\geq$75 y), genotype (*NPM1*m vs *KMT2A*r), and region (Europe vs Australia vs United States). In Cycle (C) 1, VEN is given daily on Days (D) 1–28 and AZA daily on D1–7, $\pm$ revumenib twice daily on D1–28. In C2+, responders (per 2022 European LeukemiaNet criteria) may adjust VEN based on remission status/count recovery. Treatment continues until disease progression, unacceptable toxicity, pt withdrawal, or death. The dual primary endpoints are OS and CR rate. Key secondary endpoints include event-free survival and rate of CR/CR with partial hematologic recovery (CRh). Other endpoints include rates of CRh and CR/CR with incomplete hematologic recovery (CRi), measurable residual disease (MRD) negativity (CR, CR/CRh, CR/CRi with MRD negativity), time to/duration of response, adverse events, time to hematopoietic recovery, and incidence of platelet and red blood cell transfusions. Overall, 448 pts will be enrolled. As of January 27, 2026, the study is open to enrollment. Clinical trial information: NCT06652438. Research Sponsor: Syndax Pharmaceuticals, Inc.

TPS6601 **Poster Session**

Phase 1, open-label, multi-center trial of RPT1G in patients with relapsed/refractory acute myeloid leukemia and higher-risk myelodysplastic syndromes/neoplasms. First Author: Dennise De Jesus Diaz, Remedy Plan Therapeutics, Gaithersburg, MD

Background: Nicotinamide phosphoribosyltransferase (NAMPT), the rate limiting enzyme in the NAD salvage pathway, regulates cellular energy metabolism and is overexpressed in blood cancers. Because cancer cells depend on elevated NAD-flux, they are highly sensitive to NAMPT inhibition. Since normal cells also require NAD for survival, prior clinical trials of complete NAMPT inhibitors lead to dose-limiting toxicities. We developed RPT1G, a novel hyperbolic inhibitor with an improved therapeutic window that enables therapeutically effective NAD depletion in malignant cells while sparing normal tissues (Crimmins, ASH 2023). A first-in-human, Phase 1, randomized, double-blind, placebo-controlled, SAD and MAD study in healthy volunteers of RPT1G showed that oral administration of RPT1G is safe and well-tolerated with a favorable pharmacokinetics (PK) profile. Target engagement results showed that RPT1G inhibits NAMPT at doses predicted to be therapeutically relevant. **Methods:** RPT1G is being investigated in a Phase 1, multi-center, open-label clinical trial (NCT07107126) for treatment of Relapsed/Refractory Acute Myeloid Leukemia (R/R AML) and Higher-Risk Myelodysplastic Syndromes/Neoplasms (HR-MDS). It is the first NAMPT hyperbolic inhibitor to be studied for the treatment of R/R-AML and HR-MDS patients. With a standard 3+3 design, this study explores escalating oral doses of RPT1G, given twice daily in 28-day cycles. Other dosing schedules will be studied based on observed PK, PK/pharmacodynamic relationships, safety, and tolerability to identify the maximum tolerated dose or presumptive biologically effective dose and select the recommended phase 2 dose (RP2D). The starting dose of 120 mg BID was active in healthy adults. Primary objectives include: 1) defining safety and tolerability; 2) determining the RP2D, optimal schedule and/or BED. Key secondary objectives include: 1) evaluating PK; 2) assessing preliminary efficacy by European LeukemiaNet 2022, including overall response rate, duration of response, and hematologic improvement, and clinical benefit by transfusion independence and the International Working Group 2023 HR-MDS response criteria. Enrollment criteria: adults $\geq$ 18 years old, with a histological confirmation of R/R-AML (ELN 2022 criteria) or HR-MDS (International Consortium for MDS 2023 criteria) that have received appropriate standard of care therapy(s) or declined receipt of these. Adequate organ function is required. Exclusion criteria: ongoing AEs from prior therapies; received radiation $<$ 14 days from the first RPT1G dose; known active infections; or have uncontrolled cardiac issues, or other medical comorbidities that preclude safety evaluation. Clinical trial information: NCT07107126. Research Sponsor: None.

TPS6602 **Poster Session**

A phase 3 study of revumenib in combination with intensive chemotherapy in patients with newly diagnosed *NPM1*-mutated acute myeloid leukemia (REVEAL-ND NPM1). First Author: Eytan Stein, Memorial Sloan Kettering Cancer Center, New York, NY

Background: There are currently no approved targeted therapies for newly diagnosed (ND) acute myeloid leukemia (AML) harboring a nucleophosmin-1 mutation (*NPM1*m), which occurs in ~30% of ND adult AML cases. In *NPM1*m AML, the NPM1m/XPO1 protein complex binds to DNA to sustain the interaction of menin and wild-type KMT2A that drives upregulation of *HOX*/*MEIS* gene expression, resulting in hematopoietic differentiation arrest and leukemogenesis. Revumenib is a first-in-class, oral, potent, and selective inhibitor of the menin-KMT2A interaction. In the phase 1/2 AUGMENT-101 study (NCT04065399), revumenib monotherapy demonstrated clinically meaningful response rates and was generally well tolerated in relapsed/refractory *NPM1*m AML, leading to US Food and Drug Administration approval for that patient population on October 24, 2025. Standard AML treatment for younger, non-frail adults is based on intensive chemotherapy (IC) regimens and hematopoietic stem cell transplant (HSCT). The addition of revumenib to standard IC may further improve treatment responses specifically in the ND setting. This study is designed to assess the safety and efficacy of revumenib in combination with IC in patients with ND *NPM1*m AML. **Methods:** REVEAL-ND NPM1 is a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT07211958). Eligible patients are $\geq$12 years of age, weigh $\geq$40 kg, and have treatment-naive ND AML with locally determined (centrally confirmed) *NPM1*m. Patients will be randomized 1:1 to revumenib or placebo in combination with IC. Induction consists of 1 to 2 cycles of revumenib or placebo (dosed orally) alongside IC with cytarabine and daunorubicin or idarubicin (dosed intravenously). Consolidation consists of 1 to 3 cycles of revumenib or placebo plus cytarabine. HSCT may be performed after initial induction or consolidation. Treatment with revumenib or placebo monotherapy will continue for up to 2 years, with long-term follow-up until death, withdrawal of consent, or study closure. The dual primary endpoints are event-free survival and measurable residual disease-negative complete remission (CR) in the bone marrow, both assessed by independent reviewers. A key secondary endpoint is overall survival. Additional investigator-assessed endpoints include CR rate, composite complete remission (CRc) rate, overall response rate, duration of response (CR, CRc), safety, and quality of life. Overall, ~468 patients will be enrolled. As of January 27, 2026, the study is open to enrollment. Clinical trial information: NCT07211958. Research Sponsor: Syndax Pharmaceuticals, Inc.

TPS6603 **Poster Session**

A phase 2 study of olutasidenib in combination with azacitidine followed by olutasidenib maintenance after venetoclax plus a hypomethylating agent regimen for *IDH1*-mutated acute myeloid leukemia (University of California Hematologic Malignancies Consortium Study 2441). First Author: Brian Andrew Jonas, Division of Malignant Hematology/Cellular Therapy and Transplantation, Department of Internal Medicine, University of California Davis School of Medicine, Sacramento, CA

Background: Acute myeloid leukemia (AML) with isocitrate dehydrogenase-1 (IDH1) mutations represents a subset of up to approximately 7-14% of patients. For patients with IDH1m AML ineligible for first line intensive induction, the combination of a hypomethylating agent (HMA) and venetoclax (VEN) is a standard of care based on the VIALE-A study. In patients with IDH1m, the HMA azacitidine (AZA) plus VEN regimen leads to a complete remission (CR) plus CR with incomplete count recovery (CRi) rate of 66.7%, duration of remission (DoR) 21.9 months, and median overall survival (OS) of 15.2 months. However, one of the limiting features of HMA-VEN is myelosuppression, leading to dose delays and reductions, and adverse events (AEs) led to discontinuation in up to 30% of patients on the VIALE-A study. Approaches to increase tolerability and improve outcomes are of interest. Olutasidenib (OLU) is a potent, oral and selective small-molecule IDH1m inhibitor currently approved for relapsed/refractory AML patients with an IDH1 mutation, based on the pivotal cohort of a Phase 1/2 study. Overall, this study showed that OLU alone or in combination with AZA in patients with IDH1m AML was well-tolerated and showed meaningful clinical activity, including in those with prior VEN treatment. We hypothesize that, after achieving a response on HMA-VEN, de-escalating and switching maintenance from HMA-VEN to OLU-AZA followed by OLU monotherapy will lead to improved outcomes for patients with IDH1m AML. **Methods:** This multicenter investigator-initiated study through the University of California Hematologic Malignancies Consortium (UCHMC) is a phase II single-arm study evaluating the combination of OLU in combination with AZA followed by OLU monotherapy as a switch maintenance approach after HMA-VEN for patients with IDH1m AML. Key eligibility criteria include a diagnosis of IDH1m AML, achievement of CR or CRi to first-line HMA-VEN with no more than 4 cycles of HMA-VEN at the time of enrollment, IDH1m inhibitor naïve, age 18+, and performance status 0-2. The primary endpoint is treatment failure, defined as AML-related death, relapse, or treatment discontinuation due to AE within 12 months from the time of CR/CRi. Secondary endpoints include treatment-related AE, time to treatment failure, relapse-free survival, DoR, OS, and rate of allotransplant. Patients will receive OLU 150mg BID in combination with standard AZA during the first 4 cycles followed by OLU 150mg BID monotherapy until any discontinuation criteria are met. Disease assessments will be performed at baseline, following cycles 4, 8, and 12, and then as clinically indicated. The trial will enroll up to 28 patients across the UCHMC. The trial is currently enrolling. Clinicaltrials.gov ID is NCT07304011. Clinical trial information: NCT07304011. Research Sponsor: Rigel.

TPS6604 **Poster Session**

Updated protocol: IMPROVEMF, a phase 1b trial of imetelstat (IME)+ ruxolitinib (RUX) in patients (pts) with intermediate (INT)-1/2 or high-risk (HR) myelofibrosis (MF). First Author: John Mascarenhas, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY

Background: In preclinical evaluations, sequential treatment (tx) with RUX, a Janus kinase inhibitor (JAKi), and IME, a telomerase inhibitor, selectively reduced MF hematopoietic stem cells (HSC) and progenitor cells. In the Phase 2 IMbark trial (NCT02426086), IME monotherapy showed clinical activity and disease-modifying potential in pts with INT-2 or HR MF relapsed/refractory to JAKi. These findings, and the nonoverlapping mechanisms of action, supported the evaluation of IME+RUX in frontline MF. IMproveMF (NCT05371964) is an open-label study of IME+RUX in pts with INT-1/INT-2/HR MF. In Phase 1 (dose finding), IME+RUX was generally well tolerated, with no dose-limiting toxicities at any dose, and a safety profile consistent with reports from other IME trials. Notably, a dose-dependent signal of clinical activity was observed. The pharmacokinetics for the combination were similar to those of previous monotherapy studies. Thus, the recommended Phase 1b dose of 8.9 mg/kg IME active dose (equivalent to 9.4 mg/kg IME sodium) was chosen. **Methods:** Phase 1b (dose confirmation and expansion) will enroll adult pts with INT-1/INT-2/HR MF with an Eastern Cooperative Oncology Group performance status $\leq$2 and peripheral blood and bone marrow blasts $<$10%, $\geq$2 active symptoms with a score of $\geq$3, or a total score of $\geq$10 on the MF Symptom Assessment Form v4.0, an absolute neutrophil count of $\geq 1.5\times10^9$/L independent of growth factor support and platelets of $\geq 75\times10^9$/L (updated criterion), no active systemic hepatitis infection, acute or chronic liver disease unrelated to underlying MF, and no prior history of HSC transplantation. The study was planned to evaluate 2 cohorts. In cohort A (JAKi-naive pts), upon enrollment, pts will start RUX for $\geq$12 weeks (24 weeks max); once the RUX dose is stable for 4 weeks, 8.9 mg/kg IME intravenously (IV) every 4 weeks will be added. Per the updated protocol (November 2025), the study will no longer recruit pts into cohort A. Existing enrollees will continue in the study per schedule. In cohort B, ~15 pts will be enrolled who are currently on first-line RUX per standard of care for $\geq$12 weeks, with $\geq$4 weeks at a stable dose, and will begin 8.9 mg/kg IME IV every 4 weeks after enrollment. Tx will continue until toxicity, disease progression, or withdrawal. The primary endpoint includes safety and symptom response rate at week 24 (proportion of pts with $\geq$50% reduction in total symptom score [TSS] at week 24 from start of IME+RUX tx). Secondary endpoints include absolute change in TSS at week 24, average absolute change in TSS over 24 weeks, spleen response ($\geq$35% spleen volume reduction) at week 24, and progression-free survival. The primary analysis is planned ~6 months after the last pt's first dose of IME+RUX; the final analysis will occur after the study ends. Cohort B is actively enrolling. Clinical trial information: NCT05371964. Research Sponsor: This study was funded by Geron Corporation. All authors contributed to and approved the abstract; writing and editorial assistance were provided by Mohamed Abdelmegeed, MD, PhD, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation.

TPS6605 **Poster Session**

A phase 2 study to assess the safety and efficacy of bomedemstat (IMG-7289) in combination with momelotinib in patients with myelofibrosis. First Author: Ciro Roberto Rinaldi, United Lincolnshire Teaching Hospital and University of Lincoln, Lincoln, United Kingdom

Background: Myelofibrosis (MF) is a chronic myeloproliferative neoplasm characterized by splenomegaly, cytopenias, inflammatory symptoms, and progressive marrow fibrosis. Momelotinib, a JAK1/JAK2 and ACVR1 inhibitor, improves splenomegaly and anemia; however, a substantial proportion of patients experience inadequate spleen, symptom, or hematologic responses. Bomedemstat (IMG-7289), an oral irreversible inhibitor of lysine-specific demethylase 1 (LSD1), has demonstrated disease-modifying activity in MF, including effects on megakaryopoiesis, inflammatory signaling, and fibrosis. Preclinical and clinical data support complementary mechanisms between JAK inhibition and LSD1 inhibition. **Methods:** This is an open-label, single-arm, multicenter phase 2 study enrolling approximately 50–60 adults with primary or secondary MF (post–polycythemia vera or post–essential thrombocythemia) with intermediate-2 or high-risk disease. All patients receive momelotinib 200 mg orally once daily. After 12 weeks of momelotinib monotherapy, patients with protocol-defined suboptimal response—based on spleen volume reduction, symptom improvement, hematologic parameters, or transfusion requirements—initiate combination therapy with bomedemstat 50 mg orally once daily, with dose titration per MF-specific guidelines, through week 24. Two cohorts are included: (1) patients previously treated with momelotinib who demonstrate suboptimal response after ≥12 weeks of therapy, and (2) patients with baseline cytopenias initiating momelotinib within the study who demonstrate suboptimal response at week 12. The primary endpoint is the proportion of patients achieving ≥35% spleen volume reduction at week 24 by MRI or CT. Secondary endpoints include ≥50% reduction in total symptom score, changes in symptom burden, transfusion independence, hematologic responses, overall response rate, duration of response, progression-free survival, overall survival, and safety and tolerability. Exploratory endpoints include molecular and biomarker analyses assessing changes in driver mutation allele burden, inflammatory cytokines, and markers of differentiation and fibrosis. The study will run in 5 Countries (UK, France, Spain, Dubai, USA), for a total of 20 Sites. Enrollment expected to start in September 2026. Clinical trial information: ISRCTN98283910. Research Sponsor: MSD; MISP 103465.

TPS6606 **Poster Session**

ASC4Kids-2: Asciminib in pediatric chronic myeloid leukemia with or without T315I. First Author: Nobuko Hijiya, Columbia University Irving Medical Center, New York, NY

Background: Adenosine triphosphate (ATP)-competitive tyrosine kinase inhibitors (TKIs), including imatinib, dasatinib, nilotinib, and bosutinib, are the standard of care for pediatric patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP), with efficacy and safety profiles generally comparable to those observed in adults. However, TKIs can cause long-term adverse effects in pediatric pts, including delayed growth and development. Effective therapies that minimize long-term adverse effects in pediatric pts are needed. No TKI is approved for pediatric pts with the T315I mutation, which is linked with lower progression-free and overall survival. Asciminib represents an alternative to ATP-competitive TKIs that works by Specifically Targeting the ABL Myristoyl Pocket (STAMP). Asciminib is approved for adults with newly diagnosed and previously treated CML-CP (at 80 mg daily), and those harboring T315I (at 200 mg twice daily). In ASC4Kids (NCT04925479), asciminib was well-tolerated and efficacious in pediatric pts resistant or intolerant (R/I) to 1 prior TKI without T315I. Here, we describe ASC4Kids-2 (NCT07354074), a phase 2 study evaluating asciminib in pediatric pts with CML-CP. **Methods:** Approximately 50 pediatric pts aged 1 to <18 years with Philadelphia chromosome positive (Ph+) CML-CP who are (1) newly diagnosed without known T315I, (2) R/I to ≥1 prior TKI without known T315I, or (3) with T315I irrespective of prior TKIs, will be enrolled in this multicenter, open-label, single-arm study. Asciminib will be administered at 80 mg once daily, or at 200 mg twice daily for pts with T315I using the adult formulation under fasting conditions, or as a body weight–based pediatric formulation (2.6 mg/kg once daily or 6.5 mg/kg twice daily for pts with T315I, rounded to the nearest 5 mg) in the fed state. ASC4Kids-2 consists of a 22-day screening period followed by a treatment period with visits at weeks 1, 2, 4, 8, 12, 24, 36, and 48, then every 12 weeks. A posttreatment follow-up period includes a 30-day safety follow-up call and survival assessments every 12 weeks until study end, which is 240 weeks after the last pt receives the first dose. The primary objective is to assess treatment efficacy via MMR at week 48 (defined as the proportion of pts who meet MMR criteria at week 48, excluding those who discontinued earlier or lost response at/before week 48). Secondary endpoints include MMR at week 96; hematologic, cytogenetic, and molecular responses at and by scheduled time points; time to response, progression, or treatment failure; duration of response; event-free and overall survival; growth and sexual maturation (assessed via height, weight, bone age measured by x-ray, and Tanner staging); safety; and pharmacokinetic parameters. Clinical trial information: NCT04925479. Research Sponsor: Novartis Pharma AG.

TPS6607 **Poster Session**

Phase Ib study of momelotinib during and following hematopoietic stem cell transplantation for patients with primary or secondary myelofibrosis. First Author: Gabriela Hobbs, Massachusetts General Hospital, Boston, MA

Background: Despite progress in the treatment of myelofibrosis (MF) with multiple approved JAK inhibitors (JAKi), the only curative therapy is allogeneic hematopoietic cell transplantation (HCT). Discontinuation of JAKi's before HCT is challenging as patients experience return of symptoms, moreover, hematopoietic recovery post-HCT is challenging as fibrosis takes many months to resolve. Although we have shown that ruxolitinib can be safely used during and after HCT with excellent survival, low rates of GVHD, and no adverse impact on engraftment (Hobbs et al., JCO Advances 2025), important unmet needs persist: better prevention of GVHD and improved management of post-transplant anemia and residual symptoms. Momelotinib is a JAK1/JAK2, ROCK2 and ACVR1 inhibitor that may help prevent GVHD via JAK1 and ROCK2 inhibition, which play key roles in immune cell function and inflammatory signaling. Moreover, in addition to momelotinib's efficacy in spleen and symptom control, this agent improves anemia through ACVR1 inhibition. Thus, we aim to conduct a phase Ib study to determine the safety and tolerability of momelotinib in the peri/post-HCT period along with its impact on reducing transfusion needs. **Methods:** This is a phase Ib, single institution study investigating momelotinib given pre-, during- and for 1-year post-HCT for patients with primary or secondary MF (NCT 07104799). The primary endpoint is 1-year GVHD-free, relapse-free survival (GRFS). Secondary endpoints include overall (OS) and progression free survival (PFS), engraftment, and incidence of acute and chronic GVHD. Patients will be treated with reduced intensity conditioning with fludarabine (30mg/m^2/d x 5 days) and melphalan (100 or 140mg/m^2 x 1). Patients will receive peripheral blood stem cell grafts from either 7/8 or 8/8 HLA-matched donors. GVHD prophylaxis will consist of standard tacrolimus and methotrexate. We will conduct a 3+3 dose escalation of momelotinib starting on day -7 of HCT through engraftment to test the safety of momelotinib at 100 mg, 150 mg and 200 mg during the peri and early post-HCT period. Once patients achieve engraftment, dose escalation to the approved dose of 200 mg daily will be allowed and continued for one-year post-HCT. We will collect samples for correlative analysis at baseline, day +100 and 1 year post-HCT. This study is the first to test momelotinib use pre-, during- and post-HCT in patients with MF. We have demonstrated that ruxolitinib use during and after-HCT leads to excellent GRFS and OS, however, post-HCT cytopenias remain an issue. Moreover, as more JAKi become available, it is important to evaluate the safety and efficacy of different JAKi during the time of HCT. This trial is open to accrual as of January of 2026. Funding and Product for this study is provided by GSK. Clinical trial information: NCT 07104799. Clinical trial information: NCT 07104799. Research Sponsor: GlaxoSmithKline LLC.

TPS6608 **Poster Session**

A phase 3 study of olverembatinib (HQP1351) in patients with chronic-phase chronic myeloid leukemia: POLARIS-2 trial in progress. First Author: Elias Jabbour, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Chronic myeloid leukemia (CML) is driven by the BCR::ABL1 oncogenic fusion protein. Although tyrosine kinase inhibitors (TKIs) have transformed CML management, normalizing life expectancy for many patients, treatment resistance and intolerance remain significant clinical challenges. Olverembatinib is a novel third-generation BCR::ABL1 TKI with activity against wild-type BCR::ABL1, multiple resistance-conferring mutations including T315I, and challenging compound mutations. The POLARIS-2 study evaluates olverembatinib efficacy and safety in patients with relapsed/refractory chronic phase CML (CP-CML). **Methods:** This global, multicenter, open-label, randomized phase 3 registrational study includes two patient cohorts based on T315I mutation status (ClinicalTrials.gov identifier: NCT06423911; internal study number: HQP1351CG301). Part A randomly allocates patients with CP-CML previously treated with at least two approved TKIs to receive either olverembatinib or bosutinib (2:1 randomization). The primary endpoint is major molecular response (MMR) rate at 24 weeks. Part B is a single-arm study evaluating olverembatinib in patients with CP-CML with the T315I mutation at screening, and the primary endpoint is MMR rate by 24 weeks. Key inclusion criteria include age ≥18 years, diagnosis of CP-CML, Eastern Cooperative Oncology Group performance status ≤ 2, and adequate organ function. Key exclusion criteria include prior hypersensitivity to study drugs and pregnancy or lactation. Patients in Part A receiving bosutinib who do not achieve MMR by 24 weeks are eligible to cross over to olverembatinib. The study hypothesis posits that olverembatinib will demonstrate superior MMR compared to bosutinib in Part A and provide clinical benefit in T315I-positive patients in Part B. Clinical trial information: NCT06423911. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

LBA7000 **Oral Abstract Session**

frontMIND: Phase 3 study of tafasitamab (Tafa) plus lenalidomide (Len) and R-CHOP for patients (pts) with newly diagnosed diffuse large B-cell lymphoma (DLBCL). First Author: Georg Lenz, University Hospital Münster, Department of Medicine A for Hematology, Oncology and Pneumology, Münster, Germany

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

7001 **Oral Abstract Session**

Integrating BTK inhibition into R-da-EPOCH for HIV-related DLBCL. First Author: Ida Wong-Sefidan, University of California, San Diego, San Diego, CA

Background: Human immunodeficiency virus (HIV)-related diffuse large B-cell lymphomas (DLBCL) are heterogeneous in nature, clinically, & molecularly. R-da-EPOCH is accepted as a standard of care in HIV+DLBCL. Classifying tumors with respect to immunophenotype & genomic features may facilitate personalized therapy to improve outcomes in this diverse disease. The Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib (ibr), also inhibits inducible T cell kinase (ITK). As HIV hijacks host ITK during replication, ibr may have additional clinical benefits in HIV+DLBCL. This trial added ibr to R-da-EPOCH in HIV+DLBCL, with an attempt to enrich for non-germinal center B-cell (non-GCB) subtype, to evaluate safety, feasibility & activity, impact on T cells, & correlate lymphoma cell of origin (COO) with response. **Methods:** This multi-center study included a 3+3 dose de-escalation cohort followed by dose-expansion at recommended phase 2 dose (RP2D). Participants (pts) age 18-64 years (y) with stage II-IV HIV-DLBCL were untreated or received 1 cycle (cy) R-da-EPOCH/CHOP off-study. CD4 $<$100 & asymptomatic leptomeningeal disease were allowed. Ibr was dosed daily days 1-21 & R-da-EPOCH administered as previously published (PMID 32430507) for 6 total cy. Moderate/strong CYP3A4 inhibitors were excluded, due to effects on ibr and chemotherapy. **Results:** 43 pts were evaluable for toxicity & 37 evaluable for response. 41/43 (95%) pts tolerated $\geq$2 cy; median cy of study therapy (tx) received = 5. At baseline median age was 52y (24-64) & CD4 count 204 (21-757); 9 pts had CD4 $<$100. 81% were male, 42% White & 49% Black. 86% were stage III/IV, 40% non-GCB, & 88% had ECOG 0-1. Ibr RP2D was 560mg daily. Noting PET was optional, overall response rate was 100% with 57% (21/37) complete (CR) & 43% (16/37) partial responses (PR). Relapse/progression occurred in 16% (6/37; 1CR, 5PR) during a median follow-up of 4.2y (95%CI = 2.3 to 4.87); median duration of response = 2.8y. 3y event-free (EFS) & overall survival (OS) were 83 & 81% respectively (GCB: 88 & 87%, non-GCB: 76 & 63%). Among 679 treatment-related adverse events (TRAE), the most frequent were (total, % grade (gr) 3+) anemia (105, 50%), thrombocytopenia (81, 41%), neutropenia (60, 88%) & lymphopenia (60, 68%). Non-hematologic AEs (total TRAE, # max gr) included diarrhea (22, 2 gr3), nausea (21, 1 g3), hypokalemia (20, 4 gr3), fatigue (17, 17 gr1), & sepsis (1 gr4). Reasons for tx discontinuation: 1 progression, 4 withdrawal, 4 TRAE, 1 lost to follow up. **Conclusions:** Incorporating ibrutinib 560mg daily with R-da-EPOCH in HIV-related DLBCL treatment resulted in manageable toxicities typical of R-da-EPOCH. Although lower confirmed CR, 3y EFS & OS are comparable or higher than prior studies of HIV+DLBCL R-da-EPOCH. Ongoing studies to be updated at the meeting include impact on T cell subsets, & correlations of response & survival with circulating tumor DNA & lymphoma features (EBV, MYC, BCL2, BCL6 & genomic determinations of COO). Clinical trial information: NCI-2017-01240. Research Sponsor: None.

7002 **Oral Abstract Session**

Phase 2 trial of epcoritamab in combination with rituximab-mini CVP for older unfit/frail or anthracycline-ineligible adult patients with newly diagnosed diffuse large B-cell lymphoma: Interim futility analysis. First Author: Dai Chihara, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The median age at diagnosis of diffuse large B-cell lymphoma (DLBCL) is approximately 65 years, with nearly one third of patients in the US diagnosed at age $>$75 years. This older unfit/frail population is particularly vulnerable to treatment-related toxicity due to comorbidities and limited cardiac reserve, frequently leading to treatment discontinuation, and outcomes with standard attenuated anthracycline-based chemo-immunotherapy remain suboptimal. There is therefore a critical unmet need for effective, better-tolerated non-anthracycline treatments. We hypothesize that epcoritamab combined with non-anthracycline chemotherapy (R-miniCVP) can achieve high and durable CR rates. **Methods:** This is an open-label, single-arm phase 2 trial conducted at MD Anderson Cancer Center (NCT06045247). Eligible patients have histologically confirmed DLBCL and are unfit/frail per FIL simplified geriatric assessment, or not eligible for anthracycline due to reduced ejection function ($<$50%), or prior anthracycline exposure therapy. Patients receive one cycle of R-miniCVP for debulking, followed by epcoritamab added from cycle 2 using step-up dosing, then 48 mg on day 1 of each subsequent cycle. After 6 cycles, patients achieving CR complete treatment, while patients with PR continue epcoritamab to 12 cycles. The primary endpoint is CR rate after 6 cycles. **Results:** We plan to enroll 40 patients. At the data cutoff, 22 patients have completed six cycles of therapy. The median age of 22 patients was 80 years (range, 71-87); 27% had PS 2, and 86% had an IPI $\geq$3. All patients completed planned treatment. The CR rate after 6 cycles was 86% (95% CI, 65-97%). Two patients achieved PR and continue on epcoritamab. One patient achieved PR after cycle 3 but progressed after cycle 6 and subsequently died of progressive lymphoma following 2 additional lines of therapy. With a median follow-up of 11 months (range: 5-23 months), the 1-year progression-free survival was 94.7% (95% CI, 68-99%). Cytokine release syndrome occurred in 12 patients (55%), all grade 1 and occurred around C2D15, which fully resolved in 1-2 days in all patients. Four of them received tocilizumab. One patient developed grade 2 neurotoxicity after C2D15, which resolved within 24 hours after switching prednisone to dexamethasone. The trial protocol was amended to change prophylactic steroid from prednisone to dexamethasone, after which no further neurotoxicity was observed. **Conclusions:** The combination of epcoritamab with R-mini-CVP demonstrated encouraging efficacy with a favorable tolerability profile in older, unfit or frail patients who may be unable to tolerate full-dose chemotherapy. Based on these promising early-phase results, the study is planned for expansion into a multicenter trial with a larger patient cohort. Clinical trial information: NCT06045247. Research Sponsor: None.

7003 **Oral Abstract Session**

A phase 1 study of the PRMT5 inhibitor AZD3470 in patients with relapsed/refractory classic Hodgkin lymphoma (PRIMAVERA). First Author: Enrico Derenzini, Instituto Europeo Di Oncologia SRL, Milano, Italy

Background: The epigenetic enzyme protein arginine methyltransferase 5 (PRMT5) plays a critical role in cell proliferation and differentiation; PRMT5 dysregulation is associated with cancer development. Methylthioadenosine (MTA) is an endogenous partial inhibitor of PRMT5 that accumulates in cancer cells deficient in MTA phosphorylase (MTAP). In classic Hodgkin lymphoma (cHL), we previously reported that $>$80% of primary patient (pt) tumor samples are MTAP deficient (Urosevic J, ASH 2023). The MTA-cooperative PRMT5 inhibitor AZD3470 preferentially binds to the MTA-bound state of PRMT5, increasing its target engagement to MTAP-deficient cancer cells. Here, we present safety and preliminary efficacy of AZD3470 from a first-in-human Phase 1 study in relapsed/refractory (r/r) cHL (NCT06137144). **Methods:** Eligible pts were $\geq$18 years with r/r cHL after $\geq$3 prior lines of therapy (including brentuximab vedotin (BV) and anti-PD-1). In dose escalation, pts received oral AZD3470 monotherapy QD in ascending dose levels (DLs) using an mTPI-2 design. Primary endpoints were incidence and severity of treatment-emergent adverse events (TEAEs) and dose-limiting toxicity (DLT). Secondary endpoints were overall response rate (ORR) and complete response rate (CRR) per Lugano 2014 criteria. **Results:** As of Nov 25, 2025, 39 pts had received AZD3470 at DLs ranging from 1 to 8. Most pts were male (62%) with stage IV disease (77%) and a median age of 42 (range 25–78) years. Pts had received a median of 6 prior lines of anticancer therapy (range 3–14); all had had prior BV and anti-PD1 treatments, and 20 (51%) and 5 (13%) pts had had prior autologous and allogeneic hematopoietic stem cell transplantation, respectively. All patients evaluable for MTAP protein expression were MTAP deficient. Median duration of exposure was 15 weeks (range 0.1–45.1), with treatment ongoing in 16 pts (41%). TEAEs occurred in 85% of pts, predominantly grades 1 or 2. The most common TEAEs (any grade) were anemia (28%) and nausea (15%), followed by asthenia, constipation, fatigue, and neutropenia (13% each). Grade $\geq$3 TEAEs occurred in 28% of pts, most commonly neutropenia (related) and hypokalemia (n=2 each). Serious TEAEs occurred in 5 (13%) pts. Two pts had dose reductions due to TEAEs (grade 4 hypertriglyceridemia and grade 3 esophagitis). No DLTs, treatment discontinuations nor deaths due to TEAEs were reported. Of the 31 pts evaluable for efficacy, 14 had an objective response, with responses at doses $\geq$DL4. The highest response rate was observed at doses $\geq$DL7 (n=10) with an ORR of 80% and CRR of 50%. **Conclusions:** AZD3470 monotherapy was well tolerated up to DL8, with no DLTs and mainly low-grade AEs. Incidences of grade $\geq$3 AEs and SAEs were low. Importantly, both the ORR and CRR were dose-dependent and notably high in this heavily pretreated cHL population. Dose optimization is ongoing and further safety and efficacy will be reported. Clinical trial information: NCT06137144. Research Sponsor: AstraZeneca.

7004 Oral Abstract Session

Linperlisib plus CHOP for newly diagnosed peripheral T-cell lymphoma: A single-arm, phase Ib/II study (LINCH trial). First Author: Qingqing Cai, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Peripheral T-cell lymphoma (PTCL) is a heterogeneous type of aggressive non-Hodgkin lymphoma with poor prognosis. CHOP-based regimens are most widely used for PTCL yet response rates and long-term survival remain unsatisfactory. Linperlisib, a selective PI3Kδ inhibitor, has shown encouraging antitumor activity with manageable safety profile in relapsed or refractory PTCL. This study aimed to evaluate the efficacy and safety of linperlisib plus CHOP (L-CHOP) as first-line treatment for newly diagnosed PTCL. **Methods:** The LINCH trial (NCT05949944), a multi-center, single-arm phase Ib/II study, enrolled patients aged ≥ 18 years with newly diagnosed PTCL. In phase Ib, 6 patients received 6 cycles of L-CHOP to determine the recommended phase II dose (RP2D). In phase II, patients received L-CHOP at the RP2D. Following 6 cycles, patients achieving complete response (CR) or partial response (PR) continued linperlisib maintenance until progression or intolerable toxicity or up to 24 months. The primary endpoints were the DLTs incidence (phase Ib) and the CR rate after 6 cycles of L-CHOP (phase II). Preliminary results were reported. **Results:** From August 15, 2023 to November 15, 2025, 44 patients were enrolled, including 6 patients in phase Ib. The median age was 57 years (range 18–77); 28 patients were males (63.6%). Most patients (n = 35, 79.5%) had stage III-IV disease, and 17 (38.6%) had an IPI score of 3–5. In phase Ib, one DLT (grade 3 febrile neutropenia) occurred in cycle 1, confirming linperlisib 80 mg once daily as RP2D. At the data cutoff on December 30, 2025, efficacy was evaluable in 34 patients (26 completed six cycles; 8 discontinued early), with 10 still receiving induction therapy. After six cycles of combination therapy, 19 patients (55.9%) achieved CR and four achieved PR, resulting in an objective response rate (ORR) of 67.6%. Treatment-emergent adverse events (TEAEs) occurred in 32 patients (94.1%); hematologic toxicity were common: neutropenia (n = 24, 70.6%), leukopenia (n = 21, 61.8%), anemia (n =14, 41.2%). Grade ≥ 3 TEAEs occurred in 19 patients (55.9%), most frequently neutropenia (n = 13, 38.2%), leukopenia (n = 10, 29.4%) and pneumonia (n = 4, 11.8%). **Conclusions:** Preliminary results from LINCH study suggest that linperlisib combined with CHOP as first-line treatment for PTCL achieved promising efficacy and manageable safety. A randomized controlled trial evaluating linperlisib plus CHOP versus CHOP in patients with newly diagnosed PTCL has been initiated (NCT06548347). Clinical trial information: NCT05949944. Research Sponsor: None.

Baseline characteristics.

Characteristics	Patients (n=44)
Age, years (median [IQR])	57 (18-77)
Sex	
Male	28 (63.6%)
Female	16 (36.4%)
ECOG PS	
0-1	39 (88.6%)
2	5 (11.4%)
Lugano stage	
I-II	9 (20.5%)
III-IV	35 (79.5%)
Pathological types	
AITL	23 (52.3%)
PTCL-NOS	14 (31.8%)
ALCL	3 (6.8%)
TFHL-NOS	2 (4.5%)
MEITL	1 (2.3%)
SPTCL	1 (2.3%)

7005 Oral Abstract Session

Impact of VT-EBV-N on disease-free survival as post-remission therapy in EBV-positive extranodal NK/T-cell lymphoma: A randomized, double-blind, placebo-controlled phase 2 study. First Author: Youngwoo Jeon, Yeouido St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea

Background: Extranodal NK/T-cell lymphoma (ENKL) is an aggressive EBV-associated malignancy. Although complete remission (CR) can be achieved with intensive therapy, patients with high-risk features remain at substantial risk of relapse, and no standard post-remission therapy exists. VT-EBV-N is an autologous EBV-specific cytotoxic T lymphocyte (EBV-CTL) therapy designed to eliminate residual EBV-infected malignant cells. This phase 2 study evaluated the efficacy and safety of VT-EBV-N as post-remission therapy in patients with EBV-positive ENKL. **Methods:** This randomized, double-blind, placebo-controlled phase 2 trial enrolled patients with EBV-positive ENKL who had achieved CR within 6 months prior to enrollment and had at least one predefined high-risk factor for relapse. Patients were randomly assigned (1:1) to receive VT-EBV-N or autologous peripheral blood mononuclear cells (PBMC) as control. Treatment was administered IV weekly for 4 weeks, followed by a 4-week rest, and then once weekly for an additional 4 weeks (total 8 doses). The primary endpoint was 2-year disease-free survival (DFS). Secondary endpoints included overall survival (OS) and safety. Efficacy was analyzed in the full analysis set (FAS), and safety was assessed in the safety set. **Results:** A total of 50 patients were randomized, and 46 patients (VT-EBV-N, n=21; control, n=25) were included in the FAS. Baseline characteristics and distributions of high-risk features were generally balanced between groups. At 2 years, VT-EBV-N demonstrated a clinically meaningful and significant improvement in DFS compared with control (95.0% vs 77.6%). DFS events occurred in 1/21 patients (4.8%) in the VT-EBV-N group and 8/25 patients (32.0%) in the control group. Stratified log-rank analysis confirmed a significant DFS benefit with VT-EBV-N (p=0.0347). No deaths occurred in the VT-EBV-N group, whereas 4 deaths (16.0%) were observed in the control group; the difference in OS did not reach statistical significance (p=0.0580). VT-EBV-N was generally well tolerated. Most adverse events (AEs) were grade 1–2. Grade ≥3 AEs (CTCAE) occurred in 2/21 patients (9.52%) in the VT-EBV-N group and 4/25 patients (16.00%) in the control group. No treatment-related deaths were reported. **Conclusions:** VT-EBV-N demonstrated a clinically meaningful improvement in disease-free survival with a favorable safety profile in patients with EBV-positive ENKL in complete remission and at high risk of relapse. These findings support VT-EBV-N as a promising post-remission therapeutic option for this rare and aggressive lymphoma. Clinical trial information: KCT0003592. Research Sponsor: ViGenCell Inc.

Key efficacy and safety outcomes.

Outcome	VT-EBV-N	Control (PBMC)
Patients analyzed (FAS), n	21	25
2-year DFS, %	95.0	77.6
DFS events, n (%)	1 (4.8)	8 (32.0)
Deaths, n (%)	0 (0.0)	4 (16.0)
Grade ≥3 AEs, n (%)	2 (9.52)	4 (16.00)

7006 Oral Abstract Session

Fixed-duration glofitamab monotherapy in relapsed/refractory (R/R) mantle cell lymphoma (MCL) with/without prior Bruton's tyrosine kinase inhibitor (BTKi) exposure: Updated data after a 3.5-year follow-up. First Author: Yasmin Karimi, Division of Hematology/Oncology, University of Michigan, Ann Arbor, MN

Background: Patients (pts) with advanced R/R MCL have poor outcomes, especially pts with high-risk features or those progressing after BTKi therapies. Glofitamab is a CD20xCD3 2:1 bispecific antibody that redirects T cells to eliminate malignant B cells. A Phase 1/2 trial (NCT03075696) evaluated glofitamab monotherapy, given with step-up dosing (SUD) after obinutuzumab pretreatment (Gpt), in pts with R/R MCL. Prior analyses showed high response rates and manageable safety, regardless of prior BTKi exposure (Phillips, et al. ASCO 2024). We report longer follow-up data from this MCL cohort. **Methods:** Pts with R/R MCL after ≥1 prior line of systemic therapy received Gpt (single 1000 mg dose or 2000 mg split over 2 days, as needed) on cycle (C)1 day (D)1. Glofitamab SUD was given on C1D8 (2.5 mg) and C1D15 (10 mg), then the target dose of 16 or 30 mg every 3 weeks on D1 of C2–12. Efficacy endpoints included investigator-assessed complete response (CR) rate, overall response rate (ORR), duration of CR (DoCR), duration of response (DoR), progression free survival (PFS), and overall survival (OS). **Results:** As of Sept 8, 2025, 61 pts with R/R MCL were enrolled (Gpt: 1000 mg, n=17; 2000 mg, n=44); 60 pts were treated. The median number of prior lines of therapy was 2 (range 1–5), median age was 72.0 years (range 41–86), 86.9% of pts had Ann Arbor stage III/IV, and 26.3% had a simplified MCL International Prognostic Index score of ≧6. Pts had high-risk disease features such as Ki-67 proliferation index ≥30% (62.3%), blastoid/pleomorphic variants (9.8%), and *TP53* mutation (19.7%). The median number of glofitamab cycles received was 12 (range 1–13). With a median OS follow-up of 41.5 months (mo; 95% CI: 37.4–48.7), the ORR and CR rate were 82% and 77%, respectively. Median DoCR was 40.8 mo (95% CI: 14.1–NE); 48.9% of pts had ongoing CRs at the data cut-off. Estimated 33-mo DoCR and DoR rates were 50.5% and 47.4%, respectively. Median (95% CI) PFS was 18 mo (11.3–42.8) and OS was NE (26.9–NE). For pts who received prior BTKi therapy (n=34 [55.7%]), the ORR and CR rate were 73.5% and 70.6%, respectively. Median (95% CI) DoCR was 15.4 mo (8.3–NE), PFS was 11.3 mo (5.1–32.6), and OS was 29.9 mo (11.3–NE). Estimated 33-mo DoCR and DoR rates were 42.7% and 41.0%, respectively. No new safety signals were observed. Cytokine release syndrome remained the most common adverse event (n=42/60, 70%; Grade 1–2, 58.3%; Grade 3–4, 11.6%), with lower rates in the 2000 mg (n=28/44, 63.6%) vs 1000 mg (n=14/16, 87.5%) Gpt cohorts. **Conclusions:** Updated data on fixed-duration glofitamab monotherapy in heavily pretreated pts with R/R MCL show robust efficacy and manageable safety, including in BTKi-exposed pts. Glofitamab monotherapy is a suitable treatment for pts with R/R MCL in need of rapid disease control and is under investigation in the Phase 3 GLOBRYTE trial. Clinical trial information: NCT03075696. Research Sponsor: F. Hoffmann-La Roche Ltd.

7007 Oral Abstract Session

Mosunetuzumab plus polatuzumab vedotin (Mosun-Pola) versus rituximab, gemcitabine and oxaliplatin (R-GemOx) in patients with relapsed/refractory large B-cell lymphoma (R/R LBCL): Updated efficacy and safety from the phase 3 SUNMO study including in second-line (2L) versus third-line plus (3L+) patient subgroups. First Author: Wonseog Kim, Samsung Medical Center, Seoul, South Korea

Background: At the primary analysis, Mosun-Pola demonstrated superior efficacy versus R-GemOx, with infrequent cytokine release syndrome (CRS) events and manageable safety in patients (pts) with R/R LBCL in the Phase 3 SUNMO trial (NCT05171647; Budde et al. 2025). We report updated efficacy and safety, including in the 2L setting. **Methods:** Pts with R/R LBCL ineligible for autologous stem-cell transplant (ASCT) were randomized 2:1 to Mosun (subcutaneous)-Pola or R-GemOx. Dual primary endpoints were IRC-assessed progression-free survival (PFS) and objective response rate (ORR); secondary endpoints included complete response (CR) rate, duration of response (DOR), duration of CR (DOCR), and safety. Overall survival (OS) was not assessed as the data cut-off was prior to the pre-defined final OS analysis. **Results:** At data cut-off (August 8, 2025), 138 and 70 pts were assigned to Mosun-Pola or R-GemOx, respectively. Overall, 91 pts had 1 prior line of therapy (LOT; 2L; Mosun-Pola, n=61; R-GemOx, n=30) and 117 had ≥2 prior LOT (3L+; Mosun-Pola, n=77; R-GemOx, n=40). With a median follow-up of 28.3 months (mos), Mosun-Pola continued to demonstrate superior PFS benefits over R-GemOx (HR, 0.41; 95% CI: 0.28–0.60; Table). ORRs with Mosun-Pola were 70.3% vs 40.0% with R-GemOx. The observed PFS benefit of Mosun-Pola over R-GemOx was similar in 2L (HR, 0.38; 95% CI: 0.22–0.67) and 3L+ (HR, 0.48; 95% CI: 0.29–0.81) subgroups. With Mosun-Pola vs R-GemOx in 2L, the 2-year PFS rates were 40.3% vs 20.1%, and the 2-year DOCR estimates were 60.8% vs 37.5%, respectively. Median DOCR was not reached with Mosun-Pola in 2L and 3L+ subgroups. ORRs with Mosun-Pola vs R-GemOx were 75.4% vs 36.7% in 2L pts, and 66.2% vs 42.5% in 3L+ pts, respectively. The safety profile was unchanged since the primary analysis. Grade (Gr) ≥2 CRS occurred in 4% of Mosun-Pola-treated pts and no ICANS events occurred. The safety profile was consistent in 2L pts: Gr 2 CRS occurred in 3% of Mosun-Pola-treated pts, with no Gr ≥3 CRS events. **Conclusions:** Mosun-Pola continues to show notable efficacy with manageable safety in pts with ASCT-ineligible R/R LBCL, particularly in the 2L setting. Clinical trial information: NCT05171647. Research Sponsor: F. Hoffmann-La Roche Ltd.

Mos (95% CI), unless stated	Mosun-Pola (n=138)	R-GemOx (n=70)	2L Mosun-Pola (n=61)	2L R-GemOx (n=30)	3L+ Mosun-Pola (n=77)	3L+ R-GemOx (n=40)
Median PFS	11.6 (5.6–17.6)	3.8 (2.9–4.1)	17.6 (5.6–NE)	3.6 (2.1–5.3)	8.6 (4.0–16.2)	3.9 (2.1–5.6)
Median DOR	18.8 (11.5–NE)	6.0 (3.7–23.9)	18.8 (11.3–NE)	6.0 (3.9–NE)	21.5 (9.5–NE)	5.4 (2.3–18.3)
CR, % (95% CI)	51.4 (42.8–60.0)	24.3 (14.8–36.0)	60.7 (47.3–72.9)	20.0 (7.7–38.6)	44.2 (32.8–55.9)	27.5 (14.6–43.9)
Median DOCR	NE	18.3 (3.9–NE)	NE (15.6–NE)	21.4 (3.9–NE)	NE (21.5–NE)	7.5 (2.3–NE)

NE, not estimable.

7008 **Oral Abstract Session**

Mediterranean CD19 genetic variations and potential influence on CAR T-cell therapy efficacy: Implications for population-tailored immunotherapy. First Author: Osama Alsmadi, King Hussein Cancer Center, Amman, Jordan

Background: CAR T-cell therapy has transformed the treatment of B-cell malignancies. However, relapse due to CD19 antigen escape remain a major challenge, often driven by genetic variants affecting CD19 structure, leading to CAR-T resistance. Mediterranean populations including Arabs, remain underrepresented in genomic studies. The Arabian prevalence and functional impact of CD19 variants is unknown. **Methods:** We analyzed and annotated *CD19* NGS data from a Mediterranean cohort comprised of 1,305 Arabian individuals. The overall allele frequencies were compared to global databases. Clinically reported resistance mutations were prioritized based on published CAR T-cell studies. Hardy-Weinberg Equilibrium (HWE) was also assessed. **Results:** This study characterizes functionally significant CD19 polymorphisms in a Mediterranean population, with particular focus on the clinically relevant L174V (rs2904880) variant known to associate with CAR-T therapy resistance. 174V was seen in this cohort with a Minor Allele Frequency (MAF) of 76.3%., and a variant allele homozygosity (V/V) of 65.2%. **Conclusions:** Our cohort displayed elevated V174 homozygosity compared to other populations, including Europeans, Americans, and South Asians, potentially predisposing to diminished CAR-T efficacy. These findings indorse population-adjusted CAR-T product development, and implementation of pre-therapy CD19 genotyping protocols to identify at-risk patients. Development of CARs targeting conserved CD19-epitopes, or combinatorial antigen approaches is warranted to mitigate resistance. Research Sponsor: None.

7009 **Rapid Oral Abstract Session**

First-line odronextamab (Odro) plus chemotherapy (CHOP) in diffuse large B-cell lymphoma (DLBCL): OLYMPIA-3 Part 1B results. First Author: Matthew Matasar, Rutgers Cancer Institute, New Brunswick, NJ

Background: Approximately 25% of patients (pts) treated with rituximab + CHOP do not have a complete response (CR), and those with refractory/relapsed disease or high-risk features have poor outcomes. To address this unmet need, bispecific antibody combinations are being evaluated. In Part 1A (dose escalation) of the Phase 3 OLYMPIA-3 study (NCT06091865), odronextamab (Odro)-CHOP demonstrated generally manageable safety (most common treatment-emergent adverse events [TEAE] were neutropenia [81.8%] and cytokine release syndrome [CRS; 54.5%]) and encouraging preliminary efficacy in pts with previously untreated DLBCL, with CR rates of 100% on PET/CT (160 mg dose level, selected for Part 1B dose optimization). Here, we report Part 1B results. **Methods:** Part 1B included pts aged ≥18 years with untreated CD20+ DLBCL not otherwise specified or high-grade B-cell lymphoma with at least 1 high-risk feature. Odro-CHOP was administered in 6 × 21-day cycles, with Odro 0.7/4/20 mg step-up dosing from Cycle 1 Day 8. Pts were randomized 1:1 to receive Odro 160 mg QW/320 mg Q2W (Regimen [R] 1) or Odro 160 mg QW/160 mg Q3W (R2) with CHOP. Primary endpoint was safety. Secondary endpoints included investigator-assessed objective response rate (ORR) and CR rate per 2014 Lugano criteria. **Results:** At data cut-off (August 19, 2025), 40 pts were enrolled in Part 1B (20 per regimen). Median age was 67.5 years, 60.0% of pts were male, and 75.0% had an IPI score of 3–5. Median duration of treatment exposure was 18.1 weeks (R1) and 16.6 weeks (R2); 67.5% of pts completed 6 treatment cycles. Median relative dose intensity ranged from 90.1 to 100% for Odro and 92.7 to 100% for CHOP. The safety profile of Odro-CHOP was similar across regimens. TEAEs led to dose interruption/delay in 70.0% vs 50.0% of pts and to CHOP dose reduction in 10.0% vs 5.0% of pts with R1 vs R2, respectively. No TEAEs led to Odro dose reduction and 1 led to treatment discontinuation (Grade 4 neutropenic sepsis, R2). The most common TEAEs were neutropenia (57.5%), CRS (55.0%), and anemia (42.5%). CRS rates were consistent with Part 1A, predominantly Grade 1 (42.5% of pts). ICANS occurred in 3 pts (all Grade 1) and resolved completely. All enrolled pts were analyzed including 3 pts who discontinued treatment prior to tumor imaging assessment. With a median follow-up of 2.3 months in both regimens, ORRs were 95.0% (R1) and 90.0% (R2), and CR rates were 85.0% (both regimens). **Conclusions:** In Part 1B of OLYMPIA-3, the safety profile of Odro-CHOP was generally manageable and preliminary efficacy was encouraging with no meaningful differences between regimens, and combination with Odro did not impact the delivery of CHOP. Given these results, the less frequent Odro dosing regimen (R2) with CHOP was selected as the recommended Phase 3 dose for Part 2 (randomized controlled trial). Biomarker data will be presented. Clinical trial information: NCT06091865. Research Sponsor: Regeneron Pharmaceuticals, Inc.

7010 **Rapid Oral Abstract Session**

Real-world outcomes of bispecific antibodies in relapsed/refractory (R/R) follicular lymphoma (FL). First Author: Jessica Allen, University of Utah/Huntsman Cancer Institute, Salt Lake City, UT

Background: Mosunetuzumab (mosun) and epcoritamab (epco) are bispecific antibodies (BsAbs) approved for R/R FL, with pivotal trials (n=90-128) initially demonstrating 60-63% complete response rate (CRR), 80-82% overall response rate (ORR), and 1-year progression-free survival (PFS) rate of 58-66%. Real-world outcomes remain limited. We report the real-world efficacy and safety outcomes of BsAbs for patients (pts) with R/R FL treated in the Collaborative United States Bispecifics Consortium (CUBIC). **Methods:** This is a multicenter retrospective study of adult pts with R/R FL treated with standard of care mosun or epco between 2/2023 and 9/2025 at eight CUBIC centers. Efficacy outcomes included ORR, CRR, PFS, and overall survival (OS). PFS and OS were estimated using the Kaplan-Meier method. Safety outcomes included incidence and grade (G) of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). **Results:** A total of 99 pts with R/R FL were treated with BsAb, with 92% receiving mosun (n=91) and 8% (n=8) receiving epco. Median age was 68 years (range 33-101), 61% were ≥65 years (n=60), 63% were male (n=62), 8% Hispanic (n=8), 92% (n=79) had ECOG performance status (PS) of 0-1, 51% (n=42) had FLIPI ≥3, and 31% (n=30) had elevated LDH. Median prior lines of therapy were 3 (range 1-14), and 15% (n=15) had prior CAR-T. Among 96 pts with complete response data, the ORR was 87% and CRR was 72%. Median time to best response was 2.9 months (mo) (range 1.2-12.7). Response rates were not significantly associated with BsAb, ECOG PS, FLIPI, elevated LDH, or prior CAR-T. At median follow-up of 16.9 mo, the one-yr and 18 mo PFS rates were 72% (95%CI 62-83%) and 56% (95%CI 45-70%). One-yr and 18 mo OS rates were 94% (95%CI 90-99%) and 92% (95%CI 86-99%), respectively. Hispanic pts had better PFS than non-Hispanic pts (2-yr PFS 100% vs 42%, p=0.02). PFS was not significantly influenced by BsAb product, elevated LDH, ECOG PS, FLIPI, or prior CAR-T. Patients with ECOG of 2 had inferior OS than pts with ECOG of 0-1 (2-yr OS 43% vs 89%, p=0.02). Male sex was associated with inferior OS compared to female sex (2-yr OS 76% vs 100%, p=0.02). No differences in ORR, CRR, PFS, or OS were observed between pts <65 vs ≥65 yrs or <80 vs ≥80 yrs. Of 96 pts with complete safety data, CRS occurred in 34% of pts (G1 26%; G2 6%), with no ≥G3 events. ICANS occurred in 3% of pts (n=3), all G1 events. The incidence of CRS or ICANS was not significantly associated with age, LDH, ECOG, FLIPI, or prior CAR-T. **Conclusions:** In this diverse, heavily pretreated real-world cohort, 61% of patients were aged ≥65 years. Bispecific antibodies for R/R FL demonstrated high response rates, favorable survival outcomes, lower rates of cytokine release syndrome—primarily due to fewer grade ≥2 events—and ICANS rates comparable to those observed in pivotal clinical trials, supporting their use across heterogeneous populations, including very elderly patients. Research Sponsor: None.

7011 **Rapid Oral Abstract Session**

Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD, + Pola-RCHP in patients (pts) with newly diagnosed aggressive B-cell lymphoma (a-BCL): Safety and 12-month (mo) efficacy results. First Author: Marc S. Hoffmann, The University of Kansas Cancer Center, Kansas City, KS

Background: Up to 40% of pts with diffuse large B-cell lymphoma (DLBCL) will relapse or have refractory disease following 1L treatment (Tx) with SOC chemoimmunotherapy regimens R-CHOP or Pola-RCHP. High risk (HR) populations include those with International Prognostic Index (IPI) score 3–5 and IPI 1–2 with either ≥1 lesion ≥7 cm or baseline LDH >1.3×ULN. GOLCA is a potential, first-in-class, oral CELMoD designed for the Tx of lymphoma, with preferential distribution to lymphoid organs and enhanced activity in lymphoma cell lines. GOLCA induces rapid and deep degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity. GOLCA 0.4 mg + R-CHOP has shown promising safety, a ≥90% minimal residual disease (MRD) negativity rate, and durable efficacy (24-mo PFS, 79%) in 1L a-BCL (Nowakowski et al, ASH 2025, 476) and is being evaluated in the Phase (Ph) 3 study GOLSEEK-1 (NCT06356129). We report initial Ph1b results with GOLCA + Pola-RCHP in 1L a-BCL. **Methods:** Pts aged ≥18 y with ECOG PS ≤2, IPI 0–5 (Part 2A) or 2–5 (Part 2B), and newly diagnosed a-BCL with measurable tumorous disease were included. Pts were treated with GOLCA + Pola-RCHP for six 21-day (D) cycles or until disease progression/unacceptable toxicity/study withdrawal. In dose escalation, GOLCA was dosed at 0.2 and 0.4 mg D1–7. In dose expansion, pts were randomized 1:1 to Pola-RCHP + GOLCA 0.2 or 0.4 mg. Primary endpoint: safety; efficacy was a secondary endpoint. **Results:** At data cutoff, 57 pts were treated with GOLCA + Pola-RCHP (0.2 mg, n=28; 0.4 mg, n=29). Median age was 63 y. Most pts had HR disease (86%) and DLBCL not otherwise specified histology (84%). For known cell of origin (COO), 47% were germinal center B cell (GCB) and 39% non-GCB by Hans algorithm. Forty-seven pts (83%) completed Tx and 52 (91%) entered the follow-up (f/u) period. Grade 3/4 Tx-emergent adverse events occurred in 95% of pts, most frequently neutropenia (86%; an on-target side effect of GOLCA) and anemia (39%). Median relative dose intensity for GOLCA and Pola-RCHP components was >95%. At 15.5 mo median f/u, end of Tx (EOT) complete metabolic response (CMR) rate was 69% at 0.2 mg, 82% at 0.4 mg, and similar across COO subtypes. EOT CMR was consistent in HR pts (65% at 0.2 mg, 83% at 0.4 mg). The 12-mo DOR and PFS rates were 92% and 88% at 0.2 mg, and 96% and 96% at 0.4 mg. In pts with both pre-Tx and EOT ctDNA analysis, 65% and 83% at 0.2 and 0.4 mg achieved MRD negativity (PhasED-Seq) at EOT. **Conclusions:** GOLCA + Pola-RCHP demonstrated a predictable and manageable safety profile, and addition of GOLCA did not compromise median dose intensity of Pola-RCHP. GOLCA 0.4 mg + Pola-RCHP resulted in a high rate of durable CMRs, high rate of MRD negativity, and a promising 12-mo PFS rate. These data continue to show that GOLCA + SOC regimens R-CHOP and Pola-RCHP has potential to improve outcomes in 1L HR a-BCL. Clinical trial information: NCT04884035. Research Sponsor: Bristol Myers Squibb.

7012 **Rapid Oral Abstract Session**

Safety and efficacy of Azer-cel, an allogeneic CD19 CAR T for the treatment of patients with relapsed/refractory non-Hodgkin lymphoma and chronic lymphocytic leukemia not previously exposed to autologous CAR T therapy. First Author: Danielle Nicole Blunt, Royal Adelaide Hospital, Department of Radiation Oncology, Adelaide, SA, Australia

Background: Azer-cel (azercabtagene zapreleucel) is an allogeneic, off-the-shelf, CD19-directed, chimeric antigen receptor (CAR) T-cell therapy derived from healthy donor T cells. We report the outcomes of patients treated with azer-cel plus low-dose interleukin-2 (IL-2) who enrolled in a Phase 1b dose expansion cohort for patients with r/r NHL and CLL and were naive to prior autologous CAR T-cell therapy (NCT03666000). **Methods:** Eligible patients with an aggressive B-cell CD19+ disease included those with diffuse large B-cell lymphoma (DLBCL, not otherwise specified or transformed), high-grade B-cell lymphoma, follicular lymphoma (FL, Grade1-3a), marginal zone lymphoma (MZL), Waldenstrom macroglobulinemia (WM), primary central nervous system lymphoma (PCNSL), and CLL/small lymphocytic lymphoma. Patients must have had at least 1-2 prior lines of therapy, depending on histological subtype, and no prior treatment with an autologous CAR T-cell therapy. Prior autologous stem cell transplant (ASCT) and bispecific antibodies were allowed. Patients received lymphodepletion with fludarabine (30 mg/m^2/day) and cyclophosphamide (750 mg/m^2/day) (Aug/Cy) for 3 days, followed by azer-cel infusion (500×10^6 cells) on Day 0 and subcutaneous low-dose IL-2 (1 million IU daily) for 14 days. Peripheral blood was collected at multiple timepoints, and levels of azer-cel transgene were quantified using qPCR. **Results:** Nineteen patients received azer-cel with low-dose IL-2. Median age was 59 years (range: 56-73). Disease subtypes included: DLBCL (5), MZL (5), CLL (4), PCNSL (3), FL (1), and WM (1). Of these, 4 (21%) had received ≥4 prior therapies, 3 (16%) had prior bispecific antibodies, and 2 (11%) had prior ASCT. Primary refractory disease was present in 6 (32%) patients. Median tumor burden was 36 cm^2 (range: 5.5-125). The overall response rate was 81% (13/16), with a complete response (CR) rate of 31% (5/16). Objective response by subtype included: DLBCL, 60% (1 CR, 2 partial responses [PRs]); MZL, 100% (3 CRs, 1 PR); CLL, 100% (3 PRs); PCNSL, 50% (1 PR); FL, 100% (1 CR); and WM, 100% (1 PR). Pharmacokinetic analysis (n=16) showed a mean CAR T-cell peak expansion of 1.7×10^5 copies/μg genomic DNA (SEM: 0.6×10^5), AUC_{0-28} of 9.5×10^5 copies/μg genomic DNA (SEM: 3.4×10^5), and time to peak expansion 5.9 days (SEM: 0.63). ICANS occurred in 7 patients (37%), with 3 Grade 1-2 events, 3 Grade 3 events, and 1 Grade 4 event. CRS was observed in 15 patients (79%), with no Grade ≥3 events. **Conclusions:** Azer-cel in autologous CAR T-naïve patients demonstrates promising clinical activity across a broad range of CD19+ B-cell malignancies, including MZL and CLL. Encouraging response rates, robust CAR T-cell expansion, and a manageable safety profile support further investigation. Clinical trial information: NCT03666000. Research Sponsor: None.

7013 **Rapid Oral Abstract Session**

REVO-U: A next-generation, gene-editing–free universal CAR-T platform to enable ultra–high-yield manufacturing and identification of early clinical activity in relapsed/refractory DLBCL. First Author: Di Wu, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Background: We previously invented autologous CAR-T product ciltacabtagene autoleucel (Carvykti) for multiple myeloma, with robust efficacy. However, its personalized nature incurs high costs and limits scalability. Conventional universal CAR-Ts rely on complex gene editing, yielding 50-100 doses/batch, yet to be commercially approved. We created REVO-U, a gene-editing-free universal CAR-T platform using proprietary technologies, initiating explorations in hematologic and solid tumors. It enables >3,000 doses/single batch from healthy donor cells, reducing costs and potentially eliminating capacity constraints in cell therapy. **Methods:** REVO-U uses protein-directed degradation to mitigate GvHD without gene editing. In a single-arm, open-label exploratory study, CD19-targeted REVO-UWD19 was given post-lymphodepletion (fludarabine/cyclophosphamide) with short-term oral mycophenolate sodium (EC-MPS) in relapsed/refractory DLBCL patients. **Results:** Four subjects treated (see Table for details). Subject 1 (Flu 30/Cy 300 mg/m² + 100e6 cells; EC-MPS 1440 mg BID x5 days, MPA average AUC 22.12 mg·h/L): PK Cmax 4.3k copies/mL, Transient fever (38.5°C, grade 0 CRS); ≥PR ongoing >10 months. Subject 2 (Flu 30/Cy 400 mg/m² + 200e6 cells; EC-MPS 1440 mg BID x11 days, MPA average AUC 71.44 mg·h/L): Cmax 173.9 k copies/mL, grade 1 CRS, CMR by PET-CT (PFS 4 months). Subject 3 (73y, high burden; Flu 30/Cy 500 mg/m² + 200e6 cells; EC-MPS x14 days, MPA average AUC 71.23 mg·h/L): REVO-U CAR-T expansion was highly significant. Cmax reached 19,057.6 k copies/mL, grade 3 CRS/HLH (controlled), followed by prolonged neutropenia and a fatal infection; PR, unconfirmed CR. Subject 4 (post-DLT: Flu 30/Cy 400 mg/m² + 50e6 cells; EC-MPS x22 days, MPA average AUC 15.21 mg·h/L): Cmax 2.01 k copies/mL, No CRS, PD. No GvHD in any patient. The target effective MPA AUC is >30 mg·h/L. Only Subjects 2 and 3 achieved this threshold on average MPA exposure. **Conclusions:** REVO-U enables ultra-scalable manufacturing like biologic drugs. Early DLBCL data show no GvHD, with expansion, CRS and responses influenced by lymphodepletion, dose & MPA exposure. Timely EC-MPS adjustment per MPA AUC may be needed for efficacy assurance. Promising PK expansion, persistence post-EC-MPS withdrawal, and efficacy signals have also emerged in solid tumor target explorations. We will report updated data on this innovative universal platform across malignancies at future conferences. Clinical trial information: NCT06662227. Research Sponsor: Wondercel Therapeutics; The First Affiliated Hospital of Xi'an Jiaotong University.

Summary of lymphodepletion, cell dosing, MPA exposure, pharmacokinetic, safety, and efficacy.

Subject #	Flu/CTX (mg/m^2)	Dose (million cells)	EC-MPS (Day used)	MPA-mAUC (mg*h/L)	PK Cmax (k Copies/mL)	CRS (Grade)	DLT	Efficacy (30 days)	PFS (months)
1	30/300	100	5	22.12	4.3	0	-	PR (CR?)	>10
2	30/400	200	11	71.44	173.9	1	-	CMR	3
3	30/500	200	14	71.23	19057.6	3	+	PR (CR?)	
4	30/400	50	22	15.21	2.01	0	-	PD	

7014 **Rapid Oral Abstract Session**

First-in-human in vivo CAR T-cell generation using a CD8-targeted lipid nanoparticle platform in relapsed/refractory B-cell lymphoma. First Author: Xi Zhang, Xinqiao Hospital of Army Medical University, Chongqing, China

Background: R/R B-cell lymphomas remain challenging despite advances in ex vivo CAR T-cell therapies, which are limited by complex logistics, manufacturing delays, and cost. In vivo CAR T-cell generation using targeted delivery offers a paradigm shift. We report the first-in-human study of a CD8-targeted lipid nanoparticle (CD8-tLNP) platform to generate functional CD19 CAR T cells *in vivo*. **Methods:** The CD8-tLNP was constructed by conjugating an anti-CD8 VHH to the surface of LNP encapsulating mRNA coding a CD19-directed chimeric antigen receptor, Safety, pharmacodynamics, and tolerability were first evaluated in non-human primates following intravenous administration. Subsequently, 4 patients with R/R CD19$^+$ B-cell lymphoma received four intravenous doses of CD19-CD8-tLNPs. Peripheral blood was collected at serial time points to assess CAR$^+$ CD8$^+$ T cells, B-cell depletion, cytokine levels, and clinical laboratory parameters. Antitumor activity was evaluated by PET-CT imaging, and adverse events were graded according to standard criteria. **Results:** The platform showed favorable safety and PD in monkeys. To date, seven patients with relapsed or refractory CD19$^+$ B-cell lymphoma have been treated. Among the evaluable patients, two patients achieved PR with decreased tumor lesions, one maintained SD by day 28; four patient remains pending efficacy evaluation. Following *i.v.* administration, CAR gene and surface expression in peripheral blood CD8$^+$ T cells peaked within 4–6 hours and declined thereafter, consistent with transient in vivo CAR T-cell generation. This was accompanied by rapid and near-complete peripheral B-cell clearance, with complete depletion (<1 B cell/μL) observed between 12 hours and day 3. Three booster doses administered at 3-day intervals sustained complete B-cell depletion and CAR T-cell activity. The treatment was generally well tolerated. No cytokine release syndrome of grade ≥2 was observed. Transient increases in CRP and ferritin were observed and were clinically manageable, without significant elevations in liver enzymes or prolonged cytopenias. Two patients showed naïve B-cell reconstitution by day 32 or 47. **Conclusions:** This first-in-human study demonstrates the feasibility and early clinical activity of in vivo CAR T-cell generation using a CD8-targeted LNP platform in patients with relapsed or refractory B-cell lymphoma. The approach enables rapid, transient CAR T-cell expression, repeatable dosing, and a favorable safety profile without lymphocyte clearance and complex manufacturing in *ex vivo* CAR T-cell. These findings provide clinical proof of concept for a scalable, off-the-shelf CAR T-cell therapy and support further clinical evaluation in hematologic malignancies. Clinical trial information: 2025-02-02. Research Sponsor: None.

7015 **Rapid Oral Abstract Session**

First-in-human novel bispecific epitope anti-CD5 nanobody CAR-T cells for refractory or relapsed T-cell malignancies. First Author: Lu Haiyang, Ruijin Hospital, Shanghai, China

Background: Refractory/relapse (r/r) aggressive T-cell lymphomas have poor prognosis with 5-year PFS of 20~30%, meanwhile CAR-T therapy brings new hope to this progressive disease. We previously reported allogeneic humanized CD5 CAR-T (huCD5 CAR) therapy achieved 100% ORR in r/r acute T lymphoblastic leukemia/lymphoma (T-ALL) patients. However, huCD5 CAR-T exhibit insufficient expansion activity, necessitating the optimization of CAR-T structure. Here, we developed a llama-derived nanobody-based bispecific epitope anti-CD5 CAR (NbCD5 CAR) construct, and evaluated its efficacy and safety in r/r T-ALL and T-cell non-Hodgkin's Lymphoma (T-NHL). **Methods:** llama-derived nanobody library was utilized to screen for CD5-specific nanobodies. The efficacy was then examined in NSG mice inoculated with Jurkat cell line. Tumor burden was assessed by flow cytometry and bioluminescent imaging. Finally, the efficacy and safety of the NbCAR vector were evaluated in the trials of r/r T-ALL (NCT07070323) and r/r T-NHL (NCT07022964). **Results:** We selected the NbCD5 CAR-T cells with superior cytotoxicity against T-cell lines compared to huCD5 CAR-T constructs. Then we determined its efficacy in NSG mice inoculated with Jurkat cell line. On day 7 post-tumor inoculation, mice received either Mock-T, huCD5 CAR-T or NbCD5 CAR-T cells. We observed that the NbCD5 CAR completely controlled tumor burden in mice and showed superior efficacy compared to huCD5 CAR. Then we proceed to the clinical trials containing 5 cases of T-ALL and 9 cases of T-NHL. In the T-ALL cohort, 3 patients have history of allo SCT, 4 patients received prior CD7 CAR-T therapy. All patients have infused 1.0×10^6/kg NbCD5 CAR-T cells. The adverse events (AEs) included grade 1 CRS (5/5), grade 2 ICANS (1/5), and grade 1~2 GVHD (2/5). All patients achieved CR at day 30 evaluation. In the median follow-up time of 80 days, 2 patients bridged to allo SCT, 1 patient relapsed at day 45 and died shortly thereafter. In the T-NHL cohort, 9 patients aged 30 to 64 have failed of at least 2 lines of chemotherapy, and 1 patient had history of auto SCT. The patients have received 1.0×10^6/kg NbCD5 CAR-T cells. All patients had grade 1-2 CRS, no ICANS was reported. Notably, EBV reactivation (5/9) was observed, including Grade 3-5 EBV reactivation (3/9). The ORR was 66.7% at day 30, 2 patients failed to respond for CAR-T expansion failure or weak CD5 expression. The CAR-T expansion was reached its peak at day 12 (range: 11-17), with the clearance of CD5$^+$ T cells in blood. In the median follow-up time of 94 days, 5 patients bridged to allo SCT. **Conclusions:** We optimized the nanobody NbCD5 CAR construct and showed superior cytotoxicity *in vitro* and *in vivo*. We also got preliminary safety and efficacy profiles in r/r T-ALL and T-NHL. This clinical trial is still ongoing, and long-term efficacy and clinical complication of CD5 CAR-T cell therapy still require further investigation. Clinical trial information: NCT07070323, NCT07022964. Research Sponsor: None.

7016 **Rapid Oral Abstract Session**

Genetic signatures of CNS relapse in DLBCL patients profiled with next-generation sequencing (NGS). First Author: Jackson Thomas Bowers, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

Background: CNS relapse of DLBCL is a devastating event with median survival <6 months. While the overall incidence is low (~5%), various factors impact the risk of CNS relapse including CNS-IPI, cell-of-origin (COO), and *MYC* rearrangement. Recent studies using NGS have defined DLBCL genetic subgroups with distinct biology. The MCD and C5 subgroups, defined by LymphGen and DLBc*lass*, respectively, have a shared genetic signature characterized by MYD88 L265P and CD79B mutations, immune evasion, and extranodal tropism with enrichment in CNS lymphomas. We investigated the impact of MCD/C5 signature on the risk of CNS relapse in a large cohort of DLBCL patients (pts) profiled with NGS. **Methods:** We performed a retrospective analysis of 155 DLBCL pts treated with chemoimmunotherapy and profiled with the UCSF500 NGS panel, which includes 529 genes and copy number data. FISH was performed to evaluate for *MYC*, *BCL2* and *BCL6* rearrangements. Pts with CNS involvement at diagnosis were excluded. Data were extracted from medical records including demographics, WHO-HAEM5 diagnosis, COO per Hans algorithm, CNS-IPI, and treatment history. LymphGen and DLBc*lass* subtypes were determined using online classifiers incorporating NGS and FISH data. We identified LymphGen and DLBc*lass* subtypes enriched in pts with CNS relapse. We performed univariable and multivariable analysis (MVA) (Cox proportional hazards model) to assess the impact of COO, CNS-IPI, and genetic signature on the cumulative incidence (CI) of CNS relapse. **Results:** The median age was 61. 60% were male, 57% non-Hispanic white, 21% Asian, 16% Hispanic, and 3% Black. DLBCL subgroups included DLBCL-NOS (60%), transformed DLBCL (15%), Richter transformation (8%), high-grade B-cell lymphoma (HGBCL)-double hit (5%), primary mediastinal LBCL (4%), DLBCL, post-transplant (3%), HGBCL-NOS (3%), and T-cell histiocyte-rich LBCL (2%). 67% were stage III-IV, 51% non-GCB type, and 21% high-risk CNS-IPI. LymphGen subtypes included EZB-MYC- (26%), ST2 (12%), MCD (9%), EZB-MYC+ (7%), BN2 (7%), N1 (3%), and composite cases (3%); 34% were unclassifiable. DLBc*lass* subtypes included C1 (13%), C2 (3%), C3 (52%), C4 (8%), and C5 (11%); 14% were not classified given <50% confidence in assignment. Median follow-up was 30 months. 18 pts experienced CNS relapse; these cases were enriched for MCD and C5 subtypes (28% each). The 2-year CI of CNS relapse in pts with MCD and/or C5 subtypes (N=21) was 20.4% vs. 6.4% in non-MCD/C5 cases (HR 3.46, p=0.007). Notably, 3 MCD/C5 pts had late CNS relapse (>3 years from diagnosis). In MVA, MCD/C5 signature was an independent risk factor for CNS relapse (HR 4.51, 95% CI 1.42-14.32, p=0.011) along with *MYC* rearrangement (p=0.036) and non-GCB COO (p=0.028). **Conclusions:** In this heterogeneous DLBCL cohort, MCD/C5 genetic signature was an independent risk factor for CNS relapse. Incorporation of CNS-active agents should be prioritized for this subgroup. Research Sponsor: UCSF Clinical and Translational Science Institute.

7017 **Rapid Oral Abstract Session**

Outcomes by LymphoMAP archetypes in untreated diffuse large B-cell lymphoma from the POLARIX trial. First Author: R. Andrew Harkins, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Single cell multiomics helped identify three tumor microenvironment archetypes: FMAC, high tumor-associated fibroblasts and macrophages; LN, high naive and memory T cells; TEX, high exhausted $CD8^+$ T cells (Li, et al, Cancer Cell 2025) with FMAC associated with inferior outcomes with 1L R-CHOP. The POLARIX study showed sustained and significant 5-year PFS/DFS benefits favoring Pola-R-CHP (Morschhauser et al, JCO 2025) supporting use as a standard of care for pts with untreated intermediate/high-risk LBCL. In this post hoc exploratory analysis, we investigated the clinical outcomes of LymphoMAP subtypes in POLARIX. **Methods:** LymphoMAP subtypes were determined from global gene expression patterns (GEP) using the LymphoMapR classifier. Cell of origin (COO) status was determined by NanoString. Hazard ratios (HR) were adjusted for IPI score (2 vs 3–5), age (≤ 60 vs > 60 years) and COO. All statistics are descriptive. **Results:** GEP data were available for 669 pts (Pola-R-CHP, n=331; R-CHOP, n=338; baseline characteristics comparable with ITT); among which 244 (33.5%), 229 (34.2%), 196 (29.3%) were FMAC, LN, and TEX respectively (Table). Balanced baseline clinical characteristics seen across subtypes, except lower proportion of LN with high IPI (3–5) and higher proportion of TEX as ABC-DLBCL (Table). With a median follow-up 61 months, the adjusted HRs for PFS favored Pola-R-CHP compared with R-CHOP in all subtypes and were 0.66 (95% CI: 0.43–1.01) for FMAC, 0.79 (95% CI: 0.51–1.23) for LN, and 0.81 (95% CI: 0.50–1.32) for TEX. The 5-yr PFS estimates (95% CI) were 66.0 (57.1–76.2)%, 64.6 (55.4–75.4)%, 68.8 (59.7–79.4)% for FMAC, LN, and TEX respectively in the Pola-R-CHP arm, and 56.9 (47.6-68.0)%, 61.2 (52.8–70.9)%, 56.6 (45.8–69.9)% for FMAC, LN, and TEX respectively in the R-CHOP arm. A similar trend of OS improvement was observed in the FMAC subtype with 5-yr OS estimates of 82.5 (76.3–89.3)% vs 72.0 (63.8–81.2)% with Pola-R-CHP vs R-CHOP (HR 0.64; 95% CI: 0.37–1.10). Trends of PFS and OS improvements of Pola-R-CHP over R-CHOP were observed in ABC-DLBCL pts across all LymphoMAP subtypes. For GCB-DLBCL pts, no benefit was observed with Pola-R-CHP vs R-CHOP in the TEX subtype. **Conclusions:** In this exploratory analysis, Pola-R-CHP demonstrated PFS/OS improvement trends over R-CHOP in all three LymphoMAP subtypes, especially for the FMAC subtype. Future prospective validation is required. Research Sponsor: F. Hoffmann-La Roche Ltd.

	FMAC (N = 244)	LN (N = 229)	TEX (N = 196)	BEP (N = 669)
Pola-R-CHP	134 (55%)	105 (46%)	92 (47%)	331 (50%)
R-CHOP	110 (45%)	124 (54%)	104 (53%)	338 (50%)
Age Median [Min, Max]	65 [22, 80]	66 [19, 80]	64 [22, 80]	65 [19, 80]
IPI 3–5	157 (64%)	125 (55%)	133 (68%)	415 (62%)
Bulky	109 (45%)	99 (43%)	87 (44%)	295 (44%)
Extranodal	174 (71%)	146 (64%)	143 (73%)	463 (69%)
COO ABC	68 (28%)	56 (24%)	90 (46%)	214 (32%)
GCB	138 (57%)	135 (59%)	65 (33%)	338 (50%)
Unclassified	20 (8%)	34 (15%)	38 (19%)	92 (14%)
Unknown	18 (7%)	4 (2%)	3 (2%)	25 (4%)

7018 **Poster Session**

Epigenetic profiling to identify aggressiveness markers in non-Hodgkin lymphoma via a targeted methylation-based multi-cancer early detection (MCED) blood test. First Author: Xiang-Yu Zhao, Peking University People's Hospital, Peking University Institute of Hematology, Beijing, China

Background: Non-Hodgkin lymphoma (NHL) encompasses a broad spectrum of malignancies, ranging from highly indolent to highly aggressive subtypes, each requiring distinct clinical management strategies. We developed a targeted methylation-based MCED test, and our prior work showed aggressive solid tumors exhibit elevated cell-free DNA (cfDNA) tumor fractions and distinct methylation signatures characterized by high methylated-to-unmethylated (M/U) ratios. This study focused on NHL subtypes to systematically compare epigenetic biomarkers (cfDNA tumor fraction and methylation signatures) for reliable differentiation of indolent and aggressive NHL. **Methods:** Pretreatment blood samples from NHL patients enrolled in a MCED study were analyzed using the targeted methylation assay. Patients were stratified into aggressive (diffuse large B-cell lymphoma [DLBCL], n=134; mantle cell lymphoma [MCL], n=18; other aggressive NHL, n=2) and indolent subgroups (follicular lymphoma [FL], n=58; marginal zone lymphoma [MZL], n=38; other indolent NHL, n=16). cfDNA tumor fraction was quantified via a zero-inflated negative binomial model, based on the distribution of methylation signal intensities. Methylation profiles were assessed by computing M/U ratios between subgroups. Intergroup comparisons of these biomarkers were conducted using the Mann-Whitney *U* test, with adjustments for multiple testing. Additional subgroup analyses were stratified by clinical stage to mitigate confounding factors. **Results:** MCED testing showed higher sensitivity in identifying aggressive NHL subtypes (78.06% vs 67.54% in indolent subtypes), even in stage I-II cases (62.50% vs 46.34% in indolent subtypes). Aggressive subtypes exhibited significantly higher cfDNA tumor fractions than indolent subtypes (Wilcoxon rank-sum test, $p=1.27e^{-06}$). A total of 31,075 methylation markers (71.66% hypomethylated) showed elevated M/U ratios in aggressive subtypes. These differences in cfDNA tumor fractions and M/U ratios persisted after clinical stage stratification. **Conclusions:** The MCED assay's superior sensitivity for aggressive NHL suggests preferential detection of aggressive NHL while minimizing indolent NHL overdiagnosis. Aggressive NHL is characterized by elevated cfDNA tumor fractions and distinct methylation profiles with high M/U ratios. These findings demonstrate cfDNA methylation patterns are promising epigenetic biomarkers, enabling aggressiveness differentiation in both solid tumors and NHL. Collectively, this study establishes a potential non-invasive strategy for NHL risk stratification and optimized clinical management. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co. Ltd.

7019 **Poster Session**

Fragmentia AI—Lymphoma: A cfDNA language model for lymphoma detection using ultra-low-pass WGS. First Author: Rui Liu, Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China

Background: Despite the potential of cfDNA liquid biopsy for non-invasive cancer monitoring, its clinical utility is often limited by high sequencing costs and a reliance on detectable driver mutations. To address these barriers, we introduce Fragmentia AI – Lymphoma, a novel transformer-based cfDNA language model designed for lymphoma detection using cost-effective ultra-low-pass whole genome sequencing (ULP-WGS). **Methods:** Trained on a cohort of 389 samples (189 lymphoma and 200 healthy), the architecture integrates genomic language model backbone with gated attention-based multiple instance learning. Fragmentia AI – lymphoma learned to identify malignancy-associated, mutation-independent signals directly from raw cfDNA sequences. We validated performance on an independent test cohort of 190 lymphoma patients and 200 healthy controls. Additionally, to evaluate clinical scalability, we conducted a read-depth titration analysis to test the minimum input requirements for sustained model performance. **Results:** Fragmentia AI – lymphoma achieved an AUC of 0.943 in the training cohort and 0.944 in the testing cohort. At 95% specificity, the model demonstrated a sensitivity of 0.889 (F1 score: 0.913). Notably, diagnostic performance remained robust even with a threefold reduction in sequencing reads (AUC > 0.94), significantly lowering the required depth compared to standard somatic mutation calling. Feature attribution analysis revealed that model's decision-making was predominantly anchored in pathognomonic fragmentomic signatures, specifically GC-content biases and aberrant fragment-size distributions characteristic of malignant cfDNA. **Conclusions:** Our model effectively identified mutation-independent diagnostic signals from low coverage sequencing data, providing a scalable and cost-effective approach for lymphoma screening and monitoring. Research Sponsor: National Natural Science Foundation of China; 82370192; 1.3.5 Project of Center for High Altitude Medicine, West China Hospital, Sichuan University; GYYX24003; Natural Science Foundation of Sichuan Province; 2026NSFSC1696; Qimingxing" Research Fund for Young Talents, West China Hospital, Sichuan University; HXQMX0101; National Natural Science Foundation of China; 82500245; National Natural Science Foundation of China; 82400248; Natural Science Foundation of Sichuan Province; 2026NSFSC0677.

7020 Poster Session

Early corticosteroid dosing after anti-CD19 CAR-T therapy for large B-cell lymphoma: Multicenter associations with neurotoxicity, cytokine release syndrome, and survival. First Author: Randa Elzein, Upstate Medical University, Syracuse, NY

Background: Corticosteroids are key to CAR-T toxicity management, but the impact of early dosing remains unclear. Over-treatment may blunt efficacy; under-treatment risks severe neurotoxicity. We evaluated early corticosteroid strategies after anti-CD19 CAR-T for large B-cell lymphoma (LBCL). **Methods:** Multicenter retrospective cohort across 22 U.S. programs (2019–2024). Adults receiving commercial anti-CD19 CAR-T for LBCL were included. Early steroid strategies: (1) Moderate (≤48 h from first fever or grade 1–2 ICANS; 0.5–1 mg/kg for ≤3 days, taper ≤5 days); (2) High-dose (≥1.5 mg/kg or ≥5 days); (3) None within 48 h. Primary endpoint: 12-month overall survival (OS). Secondary endpoints: grade ≥3 ICANS/CRS (Fine-Gray models), ICU admission, hospital stay (LOS), 6-month relapse, and day-30 response. Multivariable Cox/logistic models adjusted for key clinical covariates and center effects. Sensitivity analyses used inverse-probability weighting and time-dependent exposure. **Results:** N = 2,186; median age 62. Strategies: Moderate 34 %, High-dose 22 %, None 44 %. Versus None, Moderate dosing reduced grade ≥3 ICANS (sub-hazard ratio [sHR] 0.62, 95 % CI 0.50–0.78; p < 0.001) with no OS change (adjusted hazard ratio [aHR] 0.96, 0.84–1.10; p = 0.55). High-dose was linked to worse OS (aHR 1.22, 1.05–1.41) and more early relapse (aHR 1.28, 1.06–1.54) despite similar CRS rates. ICU admission was lower with Moderate vs None (adjusted odds ratio [aOR] 0.78, 0.64–0.95) and LOS shorter (−1.2 days, 95 % CI −2.0 to −0.4). Findings were consistent across age ≥65 and high-risk groups. **Conclusions:** A moderate, time-limited early steroid approach after anti-CD19 CAR-T reduced severe ICANS without loss of efficacy, whereas high-dose/prolonged use correlated with poorer survival and earlier relapse. Results support adopting standardized moderate early dosing and avoiding routine high-dose regimens. Research Sponsor: None.

Clinical outcomes by early corticosteroid strategy after anti-CD19 CAR-T.

Outcome	None (n=963)	Moderate (n=742)	High-dose (n=481)	Adjusted effect vs None (95 % CI)	P value
12-mo OS (%)	61	62	55	aHR 0.96 (0.84–1.10); 1.22 (1.05–1.41)	0.55; 0.009
Grade ≥3 ICANS (%)	13.4	8.7	12.9	sHR 0.62 (0.50–0.78); 0.96 (0.75–1.23)	<0.001; 0.77
Grade ≥3 CRS (%)	6.1	5.4	5.8	sHR 0.89 (0.67–1.19); 0.94 (0.72–1.23)	0.43; 0.65
ICU admission (%)	18.9	15.4	19.6	aOR 0.78 (0.64–0.95); 1.03 (0.83–1.29)	0.013; 0.77
Hospital LOS (days)	10.1	8.9	10.6	Δ −1.2 (−2.0 to −0.4); Δ +0.3 (−0.5 to +1.1)	0.003; 0.48
Early relapse (6 mo %)	23.7	24.1	29.8	aHR 1.01 (0.87–1.18); 1.28 (1.06–1.54)	0.88; 0.009
Day-30 response (%)	68.2	69.5	66.9	aOR 1.05 (0.90–1.22); 0.94 (0.79–1.12)	0.54; 0.49

Abbreviations: aHR = adjusted hazard ratio; sHR = sub-hazard ratio; aOR = adjusted odds ratio; Δ = adjusted difference in medians.

7021 Poster Session

Overcoming resistance to prior CAR-T therapy: Efficacy and safety of a sequential, multi-antigen targeted CAR T-cell strategy in B-cell NHL. First Author: Guoai Su, Beijing GoBroad Boren Hospital, Beijing, China

Background: Relapse following CAR T-cell therapy is a significant unmet need for patients with B-cell non-Hodgkin lymphoma (B-NHL). Strategies to effectively salvage these patients are urgently required. We report the results of a prospective study evaluating a novel approach of sequential CAR T-cell administration, often with alternative antigen targeting, in this heavily pre-treated population. **Methods:** In this single-center, Phase I/II investigator-initiated trial, we enrolled patients with R/R B-NHL who had progressed after at least one prior CAR T-cell infusion. Patients received a second autologous CAR T-cell product targeting a different (e.g., CD20, CD22, CD79b) or re-challenging the same antigen with a different construct. The primary endpoints were safety and overall response rate (ORR). The cohort included high-risk subtypes such as primary central nervous system lymphoma (PCNSL). **Results:** As of the data cut-off, 26 patients with R/R B-NHL (DLBCL, n=18; PCNSL, n=6; Burkitt, n=2) were infused. The median number of prior therapies was 5 (range 3-8). All patients had failed a prior CAR-T therapy. With a median follow-up of 10.2 months, the ORR was 88.5% (23/26), with an outstanding CR rate of 73.1% (19/26). Efficacy was profound even in the most challenging histologies; in the cohort of 6 patients with R/R PCNSL, the CR rate was an unprecedented 83.3% (5/6). The safety profile was highly encouraging. Cytokine release syndrome (CRS) occurred in 92.3% (24/26) of patients, with the majority being Grade 1 (61.5%) or Grade 2 (30.8%). No Grade ≥3 CRS was observed. Immune effector cell-associated neurotoxicity syndrome (ICANS) was rare and mild, with only Grade 1 events reported in 19.2% (5/26) of patients; no Grade ≥2 ICANS occurred. Hematologic toxicities were manageable and reversible. **Conclusions:** Sequential CAR T-cell therapy is a highly effective and safe strategy that can induce high rates of durable complete responses in B-NHL patients who have relapsed after initial CAR-T treatment. The exceptional activity observed in PCNSL suggests this approach can overcome the blood-brain barrier and address a critical unmet need. These results support the integration of sequential CAR T-cell therapy as a new standard of care for this patient population. Clinical trial information: ChiCTR1900025419. Research Sponsor: None.

7022 Poster Session

Late infectious complications after CD19-directed chimeric antigen receptor T-cell (CAR-T) therapy for large B-cell lymphomas (LCBL): Real-world predictors and outcomes. First Author: Daniel E. Goyco Vera, UT Southwestern Medical Center, Dallas, TX

Background: CD19-directed CAR-T therapy is a curative option for patients (pts) with relapsed/refractory (R/R) LBCL. Infectious complications are a major source of morbidity and non-relapse mortality (NRM). While early infections are attributed to lymphodepleting chemotherapy and management of immune-related toxicities, real-world data defining predictors of late infections after CAR-T remain limited. **Methods:** We performed a single-center retrospective study of adult pts with R/R LBCL, including transformed indolent lymphomas, treated with anti-CD19 CAR-T. Infectious events were defined by compatible clinical features supported by laboratory, microbiologic, or radiographic evidence. Early infections were defined as ≤30 days post-infusion and late infections as >30 days. Logistic regression assessed associations with late infection risk. Multivariable models included a priori selected clinically relevant covariates. Stepwise logistic regression was performed as a sensitivity analysis. **Results:** Ninety-five pts were included (median age 65 years; median follow-up 32 months). Most pts received axi-cel (88%); 10% received liso-cel and 2% tisa-cel. Salvage and/or bridging therapy prior to CAR-T was administered in 59% of pts. Early infections occurred in 16% of pts, while 63% experienced late infectious complications. Among patients with late infections, 53% were in remission post CAR-T; 43% had both viral and bacterial infections over time, 33% viral only, 22% bacterial only, and 2% fungal overall. Hypogammaglobulinemia (IgG <400 mg/dL at day +30 and/or +90) occurred in 48%, and grade 4 neutropenia between days +30 and +90 in 31%. Five-year NRM was 12%, with infections contributing to 80% of deaths. On univariate analysis, hypogammaglobulinemia was associated with higher infection risk (OR 2.38, 95% CI 1.00–5.85; p=0.053). After adjustment for prespecified covariates, the association was attenuated but directionally consistent (p=0.082) and remained the only variable retained on stepwise regression. **Conclusions:** Infectious complications are common following anti-CD19 CAR-T therapy for R/R LBCL and occur predominantly beyond 30 days post-infusion. Hypogammaglobulinemia showed a consistent association with infection risk across multiple modeling strategies. Ongoing prospective studies will clarify the role of immunoglobulin replacement in mitigating late infectious complications in CAR-T recipients. Research Sponsor: None.

7023 Poster Session

Real-world patient characteristics, outcomes, and resource utilization of chimeric antigen receptor (CAR) T cell therapy across Foundation for the Accreditation of Cellular Therapy (FACT) and non-FACT treatment centers in large B-cell lymphoma (LBCL). First Author: Renju V. Raj, University of Tennessee Knoxville Medical Center, Knoxville, TN

Background: CAR T cell therapy has transformed the LBCL treatment landscape and is now being offered in some non-FACT accredited centers. We evaluated clinical characteristics, AEs, time to next treatment (TTNT), and health care resource utilization (HCRU) of patients with LBCL who received CAR T cell therapy from FACT versus non-FACT centers. **Methods:** This retrospective cohort study used the Komodo Health Claims Database (01/2015–08/2025). Adults with LBCL receiving CAR T cell therapy were identified via International Classification of Diseases, Ninth/Tenth Revision, diagnosis and procedure codes. Centers were classified as FACT or non-FACT based on public records. Cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and infections were assessed within 15 and 30 days after infusion. TTNT was estimated using KM methods. All-cause HCRU was reported as per patient per month (PPPM) to adjust for variation in follow-up duration; inpatient utilization was assessed by length of stay (LOS). Comparisons used chi-square test. **Results:** Among 6857 CAR T cell therapy—treated eligible patients with LBCL (FACT, n = 6748; non-FACT, n = 109), demographics and characteristics were comparable between cohorts; mean Charlson Comorbidity Index score was 4.6 versus 4.9, respectively. Significantly more patients treated at FACT sites traveled > 50 miles compared with those treated at non-FACT sites (43% vs 31%; $P < 0.05$); median distance traveled was 34 versus 17 miles, respectively. Rates of CRS (44% vs 40%), ICANS (21% vs 24%), and infections (39% vs 36%) within 15 days after infusion were similar between cohorts (FACT vs non-FACT, respectively); rates were also comparable within 30 days. Median (95% CI) TTNT was numerically lower in the FACT-treated (23 months [21–25]) versus non-FACT–treated cohort but not statistically significant (42 months [18–not estimable]; $P = 0.20$; estimates limited by small sample size); 12-month TTNT rates were 58% versus 67%, respectively. Excluding infusion visits, FACT-treated patients had marginally higher post-infusion HCRU (PPPM) over 1 year, including inpatient (0.93 vs 0.61; $P = 0.52$), outpatient (3.84 vs 3.16; $P < 0.05$), and ICU visits (0.13 vs 0.07; $P < 0.05$). Standardized 1-year inpatient LOS was 18.4 versus 15.9 days, respectively ($P = 0.58$). Among patients treated in an inpatient setting, HCRU including infusion visit exhibited a similar trend. **Conclusions:** In this real-world LBCL cohort, clinical characteristics, safety, TTNT, and HCRU were generally comparable between FACT- and non-FACT– accredited centers. Despite the non-FACT sample size and claims-based limitations, these findings suggest patients have similar outcomes across both types of authorized treatment centers. Research Sponsor: This study was funded by Bristol Myers Squibb.

7024 **Poster Session**

Real-world outcomes of lisocabtagene maraleucel (liso-cel) in patients (pt) with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL): First results from CIBMTR. First Author: Emily Tomasulo, University of Pennsylvania, Philadelphia, PA

Background: Liso-cel is an autologous, CD19-directed CAR T cell product with established efficacy and safety across B-cell malignancies. In TRANSCEND CLL 004 (NCT03331198), liso-cel demonstrated promising efficacy and manageable safety in pts with R/R CLL, including those previously exposed to Bruton tyrosine kinase inhibitor (BTKi) and B-cell lymphoma 2 inhibitor (BCL2i). Here, we report real-world effectiveness and safety of liso-cel in pts with R/R CLL. **Methods:** This observational study evaluated US pts with R/R CLL who received commercial liso-cel (05/2024–09/2025) and had ≥ 1 postinfusion assessment reported to CIBMTR. Effectiveness outcomes were ORR, CR rate, duration of response (DOR), PFS and OS; safety outcomes included AEs of special interest, nonrelapse mortality (NRM) and death. Results are descriptive. **Results:** Of 45 eligible pts, 64% were male; median age was 62 y (range, 44–83; ≥ 65 y, 44%). In pts with available data, all had ECOG PS 0–1 (43/43) and 57% (21/37) had ≥ 1 comorbidity, most commonly (> 10%) cardiac (24%) or pulmonary (16%). Elevated LDH was observed in 35% (15/43) and unmutated IGHV in 91%. Pts had a median of 6 (range, 1–10) prior therapies and 71% received liso-cel as fifth-line or later treatment (tx). Most pts (84%) were previously exposed to covalent BTKi and BCL2i, and nearly half (47%) had prior pirtobrutinib tx. Bridging therapy was used in 48% (21/44) of pts. At a median (95% CI) follow-up of 6.0 mo (5.4–7.1), ORR was 84% (70–93), and CR rate was 55% (39–70); 81% (13/16) of pts in CR with available data were MRD negative. Median (95% CI) DOR, PFS, and OS were not reached. Among responders (n = 36), 6-mo DOR was 89% (70–96.5); 6-mo PFS and OS were 77% (60–87) and 87% (72–95), respectively. Among pts with any-grade (gr) cytokine release syndrome (80%; gr ≥ 3, 4%) or immune effector cell–associated neurotoxicity syndrome (36%; gr ≥ 3, 13%), no gr 5 events occurred. Clinically significant infections were reported in 40% of pts, and at 30 d after infusion, 18% had persistent gr 4 thrombocytopenia and/or neutropenia. Rates were low of HLH/MAS (7%), second primary malignancies (2%; 1 case of basal cell carcinoma 34 d postinfusion), tumor lysis syndrome (7%), and gr 3/4 organ toxicity (9%). Of the 5 deaths, 2 each were due to relapse/progression or infection, and 1 pt had multiple causes reported; 6-mo NRM was 5% (95% CI, 0.8–14). Among the 49% of pts intended for outpatient infusion, 55% (12/22) were hospitalized postinfusion, with a median (range) time to hospitalization of 5.5 d (1–20) and a stay of 5.5 d (1–26). **Conclusions:** In routine clinical practice, liso-cel demonstrated response rates higher than in clinical trials, with a consistent safety profile. These real-world data support liso-cel as an effective option for pts with R/R CLL, including heavily pretreated or high-risk pts, and the potential for outpatient administration. Research Sponsor: This study was funded by Bristol Myers Squibb.

7025 **Poster Session**

Measurable residual disease (MRD) by circulating tumor (ct) DNA in patients (pt) with R/R follicular lymphoma (FL) treated with lisocabtagene maraleucel (liso-cel) in TRANSCEND FL. First Author: Ariel Avilion, Bristol Myers Squibb, Seattle, WA

Background: ctDNA is a minimally invasive method for detecting MRD in various malignancies. MRD negativity (MRD^{neg}) has been linked to improved PFS and durable disease control, including after liso-cel treatment in R/R large B-cell lymphoma. The prognostic value of MRD after chimeric antigen receptor (CAR) T cell therapy in R/R FL has not been established. We report an exploratory MRD analysis from TRANSCEND FL (NCT04245839), in which pts had high rates of deep and durable responses after liso-cel. **Methods:** Of 103 efficacy-evaluable pts with third-line or later (3L+) FL, 89 (86%) had ctDNA samples, of whom 90% (80/89) had evaluable ctDNA and efficacy data after liso-cel infusion. Tumor-derived phased variants were primarily identified from screening (baseline) plasma or tumor tissue when plasma was insufficient, using PhasED-Seq. Post-treatment ctDNA-MRD was assessed at months (M) 1 and 3 after infusion for all pts, and at M24 for ongoing responders. MRD positivity (MRD^{pos}) was defined as ctDNA above the assay detection threshold (lower limit of detection of 0.7 parts per million, with sample-specific sensitivity dependent on DNA input). **Results:** MRD^{neg} was achieved by 89% (71/80) of evaluable pts from TRANSCEND FL. Among pts with a best overall response of CR, 93% (71/76) of them achieved MRD^{neg}. ctDNA clearance increased over time, with MRD^{neg} rates of 68% (52/76) at M1, 83% (63/67) at M3, and 97% (57/59) at M24. In contrast, pts with PR, SD, or PD (n=4) never achieved MRD^{neg}. Baseline ctDNA levels were not associated with PFS after liso-cel treatment. MRD^{neg} after infusion was associated with longer PFS compared with MRD^{pos} ($P<0.001$). In addition, MRD status at M3 (HR, 7.0 [95% CI, 3.0–16.2]) showed a stronger correlation with PFS than at M1 (HR, 3.0 [95% CI, 1.3–6.8]), with 36-M PFS rates of 80% for MRD^{neg} (n=63) versus 38% for MRD^{pos} (n=13) pts. Multivariate analysis controlling for PET findings confirmed the independent prognostic value of MRD for PFS. Importantly, PFS was longer for pts with both CR by PET and MRD^{neg} at M3 (n=62) compared to pts with CR and MRD^{pos} (n=9; HR, 5.0, [95% CI, 1.8-13.4]), with 36-M PFS rates of 81% versus 56%, respectively, suggesting that combining MRD with PET may provide additional prognostic information for long-term outcomes. **Conclusions:** Liso-cel induced deep molecular responses in pts with 3L+ FL with most pts (89%) achieving MRD^{neg} after infusion. Although baseline ctDNA levels were not associated with PFS, MRD^{neg} after infusion was significantly associated with improved PFS, highlighting the therapeutic benefit of liso-cel regardless of tumor burden before treatment. These findings support the potential of ctDNA-based MRD as a prognostic biomarker in FL and underscore that liso-cel is a key treatment option capable of inducing MRD^{neg} and durable clinical outcomes in pts with 3L+ R/R FL. Clinical trial information: NCT04245839. Research Sponsor: This study was funded by Bristol Myers Squibb.

7026 **Poster Session**

Outcomes of lisocabtagene maraleucel (liso-cel) in patients (pt) with relapsed or refractory (R/R) mantle cell lymphoma (MCL): First real-world data from the CIBMTR. First Author: Jennifer Jing Huang, Fred Hutchinson Cancer Center, University of Washington, Seattle, WA

Background: Liso-cel, an autologous, CD19-directed CAR T cell product, demonstrated deep, durable responses with manageable safety in pts with R/R MCL in the MCL cohort of TRANSCEND NHL 001 (NCT02631044). In this study, we present the first report of real-world outcomes for pts with R/R MCL who received liso-cel, using data from CIBMTR. **Methods:** This retrospective study included pts in the US with R/R MCL who received commercial liso-cel from 05/2024 to 09/2025 with ≥ 1 postinfusion assessment reported to CIBMTR. Effectiveness outcomes included ORR, CR rate, duration of response (DOR), PFS, and OS. Safety outcomes included AEs of special interest, nonrelapse mortality (NRM), and death. Results are descriptive. **Results:** A total of 94 pts were eligible. Median age was 73 y (range, 46–85), 74% were male, 4% (4/92) had ECOG PS ≥ 2, and 65% (53/81) had ≥ 1 clinically significant comorbidity, with cardiac (31%), pulmonary (31%), and obesity (17%) being most common (> 10%). Largest nodal mass > 10 cm, indicative of bulky disease, was observed in 15% of pts (9/60), 31% had ≥ 2 extranodal involvement, and 5% had CNS involvement. Data on *TP53* mutation status and Ki-67 score were limited. Median number of prior lines of therapy (including HSCT/cell therapy) was 4 (range, 2–12); 69% of pts (62/90) had refractory disease and 72% (67/93) received bridging therapy. At a median follow-up of 6.0 mo (95% CI, 5.9–6.2), ORR was 88% (95% CI, 80–94) with CR rate of 80% (95% CI, 70–87). Median DOR, PFS, and OS were not reached; 6-month DOR, PFS, and OS rates were 79% (95% CI, 55–91), 79% (95% CI, 68–87), and 92% (95% CI, 83–96.5), respectively. Any-grade (gr) cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome were reported in 65% (gr ≥ 3, 2%) and 37% (gr ≥ 3, 12%) of pts, respectively, with no gr 5 events. Clinically significant infections were reported in 23% of pts, gr 4 thrombocytopenia and/or neutropenia persistent at 30 days after infusion in 18%, and second primary malignancies in 5%, with skin malignancies being the most common. Gr 3/4 organ toxicity occurred in 1 (1%) pt, and none had tumor lysis syndrome. Nine (10%) pts died, including 6 (6%) due to PD. The NRM rate at 6 mo was 1% (95% CI, 0.1–5.4). Of the 36% of pts planned for outpatient infusion, 59% (20/34) were reported as being hospitalized postinfusion with a median (range) time to hospitalization and stay of 5.5 days (1–35) and 4.5 days (2–32), respectively. **Conclusions:** These results show that liso-cel is associated with high response rates in a broad population of heavily pretreated pts with R/R MCL with early signs of durable benefit and safety profile consistent with TRANSCEND NHL 001. While longer follow-up is needed, this supports the potential of liso-cel to address critical gaps for pts with limited treatment options, providing strong effectiveness and manageable safety. Research Sponsor: This study was funded by Bristol Myers Squibb.

7027 **Poster Session**

Efficacy of tocilizumab in resolving chimeric antigen receptor T-cell (CAR T)–induced cytokine release syndrome (CRS): A pooled clinical trial (CT) analysis of patients (pts) with B-cell lymphoma (BCL). First Author: Soon Jye Kho, Medidata Solutions, a Dassault Systèmes Company, New York, NY

Background: CAR T therapy offers significant efficacy in the treatment of relapsed/refractory hematologic malignancies but is also associated with developing immune-mediated toxicity, such as CRS. Tocilizumab, an interleukin-6 receptor antagonist, is the only FDA-approved treatment for CAR T-induced CRS, but its efficacy in large pt populations remains limited. This study aims to evaluate the efficacy of tocilizumab by assessing complete response (CR) rates and median time-to-CR in pts with BCL experiencing CAR T-induced CRS, using pooled clinical trial data. **Methods:** We pooled aggregated, anonymized data made available through Medidata Clinical Cloud across <10 multinational CTs, comprising 2,304 patients. Inclusion criteria required a BCL diagnosis, who developed CAR T-induced CRS and were treated with tocilizumab. The index date was defined as the initiation of tocilizumab. CR was defined as CRS resolution within 14 days of the index date without meeting any failure to respond criteria. Non-response was defined as requiring>2 doses of tocilizumab, rescue therapy with siltuximab, CRS grade escalation after 2 tocilizumab doses, or CRS recurrence after 2 tocilizumab doses. The CRS events were graded using Lee's Criteria 2014. CR rate was described as a proportion, and time-to-CR was estimated using the Kaplan-Meier method. **Results:** Of the 2,304 pts included in the database, 680 met the inclusion criteria (37% aged ≥ 65 yrs; 63% male; 80% white; 47% Diffuse Large BCL, 14% Follicular Lymphoma & 13% Mantle Cell Lymphoma; 49% Eastern Cooperative Oncology Group (ECOG) performance score=0 & 49% ECOG=1; 48% Ann Arbor Stage IV; 27% had bulky disease; 65% without bridging therapy; 73% received CD28 costimulatory domain-targeted CAR T-infusion, 27% received 41bb costimulatory domain-targeted CAR T-infusion; 72% with grade 1 CRS at the time of onset). The median time from CAR-T infusion to CRS onset was 2 days (IQR: 1 - 4), and the median time from CRS onset to the first dose of tocilizumab was 2 days (IQR: 1 - 3). The CR rate was 66% (95% CI: 62.5% - 69.6%) and the median time to CR was 4 days (95% CI: 3 - 4), with 35% achieving CR in ≤ 2 days and 80% in ≤ 7 days. **Conclusions:** This large-sample pt-level study of pooled CT data showed significant efficacy of tocilizumab in resolving CAR T-induced CRS among pts with BCL, with two-thirds of pts achieving CR. The rapid median time-to-CR (4 days) underscores the role of tocilizumab as a first-line intervention. However, the 34% of pts who did not meet the CR criteria suggest a need for further investigation into other treatment strategies. Research Sponsor: None.

7028 **Poster Session**

Long-term real-world outcomes of axicabtagene ciloleucel (axi-cel) in relapsed/refractory (R/R) large B-cell lymphoma (LBCL). First Author: Caron Alyce Jacobson, Dana-Farber Cancer Institute, Boston, MA

Background: Axi-cel, autologous anti-CD19 CAR T-cell therapy, showed long-term survival and curative potential in R/R LBCL (ZUMA-1; Neelapu et al. *Blood*. 2023). Few studies have examined long-term outcomes beyond clinical trials. Here we report long-term real-world outcomes of axi-cel in R/R LBCL using large-sample CIBMTR data. **Methods:** A total of 1500 adults from 79 US centers receiving commercial axi-cel after ≥2 LOT for LBCL from Oct 2017-Aug 2020 were enrolled in a post-marketing requirement study. A protocol was developed prior to the study's implementation, reviewed by Kite and CIBMTR. This is a secondary analysis of said study. Key outcomes were progression-free survival (PFS), overall survival (OS), time to next therapy (TTNT), disease-specific mortality (competing risks were non-relapse deaths), subsequent malignancies, and non-relapse mortality (NRM). Outcomes were analyzed descriptively. Cases with missing data were excluded separately for each endpoint. **Results:** As of Aug 2025, 1446 patients (pts) were included in the analysis. Median age at infusion was 62.2 y (range, 19.6-90.8: 38% of pts ≥65 y); 65% were male. Five percent of pts had ECOG PS ≥2 and 16% had high-grade lymphoma. Pts had a median of 3 (range, 2-4) prior LOT, 28% had prior autologous hematopoietic cell transplantation, and 50% received bridging therapy. At 59.7 mo median follow-up, median PFS (95% CI) was 7.9 mo (6.3-10.9) and 5-y PFS was 30% (27-32). The median OS was 25.7 mo (21.6-30.2); 5-y OS was 38% (35-41). The 5-y cumulative incidence of disease-specific mortality was 51%. Among pts who were progression-free at 2, 3, 4, or 5 y post-infusion, the OS at 6 y (95% CI) was 73% (68-78), 81% (76-86), 90% (84-94), and 94% (89-97), respectively. The median duration of response (DOR) was 25.3 mo (95% CI, 20.7-32.8) and 5-y DOR was 38% (35-41). The median TTNT was 12.2 mo and 30% did not need additional LOT at 5 y. Of pts who received subsequent salvage therapy, 12 (2%) received cell therapy, 39 (7%) received hematopoietic cell transplant, and 475 (90%) received other therapy. The 1, 2, 3, 4, and 5-y cumulative incidence of relapse (95% CI) was 49% (46-51), 52% (50-55), 54% (52-57), 55% (53-58), and 56% (53-59), respectively. No new safety signals were observed. The primary causes of death (n=864; 60%) were primary disease (540; 63%), infection (111; 13%), and organ failure (57; 7%). The 5-y cumulative incidence of NRM was 16% (95% CI, 14-18). At 5 y, 11% (95% CI, 10-13) had subsequent malignancies, mostly therapy-related myeloid neoplasms (6%) and non-melanoma skin cancer (3%); none were directly attributed to axi-cel. **Conclusions:** This real-world study showed sustained survival at 5 y among pts with R/R LBCL treated with axi-cel after ≥2 LOT, consistent with ZUMA-1. Infection and organ failure were common causes of NRM. These results continue to support the use of axi-cel with curative intent in R/R LBCL. Research Sponsor: Kite, a Gilead Company.

7029 **Poster Session**

Fixed-duration subcutaneous (SC) mosunetuzumab (Mosun) in elderly/unfit patients with previously untreated diffuse large B-cell lymphoma (DLBCL): Interim analysis and patient-reported outcomes (PROs) from the phase 2 MorningSun study. First Author: Ian W. Flinn, Tennessee Oncology and OneOncology, Nashville, TN

Background: Mosun, a CD20xCD3 T-cell engaging bispecific antibody, is approved for relapsed/refractory follicular lymphoma after ≥2 prior lines of therapy. We report an interim analysis and PROs with Mosun SC in elderly/unfit patients with previously untreated DLBCL. **Methods:** MorningSun (NCT05207670) is a Phase 2, basket study of Mosun SC in patients with B-cell non-Hodgkin lymphoma. In the DLBCL cohort, eligible patients (aged ≥80 years, or 65–79 years and ineligible for chemoimmunotherapy) received outpatient Mosun SC: Day (D) 1 (5 mg), D8 (45 mg) and D15 (45 mg) of Cycle (C) 1, then 45 mg on D1 for up to 17 21-day cycles. Primary endpoint was progression-free survival (PFS) rate at 24 months. Other endpoints included overall survival (OS), objective response rate (ORR), complete response (CR) rate, change from baseline (CfB) in lymphoma symptoms as assessed by the Functional Assessment of Cancer Therapy-Lymphoma subscale (FACT-Lym LYMS; higher scores indicate improvement, a ≥3-point increase is considered clinically meaningful) and safety. **Results:** Forty-nine patients were enrolled, primarily from community sites (n=34). Median age was 83 years (range: 71–101). International Prognostic Index was 3–5 in 53.1% patients and 18.4% of patients had bulky disease. As of February 10, 2025, the median duration of follow-up was 12.5 months (range: 1.4–30.8). PFS and OS rates at 12 months were 71.3% (95% confidence interval [CI]: 54.8–82.7) and 74.7% (95% CI: 58.5–85.4), respectively. ORR was 73.5% and CR rate was 59.2%. Completion rates for FACT-Lym LYMS were ≥95% at baseline and remained ≥87% at each subsequent timepoint. Patients reported improvement in health-related quality of life (HRQoL) over time, demonstrated by increased mean CfB (standard deviation [SD]) in FACT-Lym LYMS scores: C4D1, 5.1 (9.8); C9D1, 5.6 (11.8); C17D1, 9.8 (11.4). Clinically meaningful improvements in lymphoma symptoms were observed in 53.1% (95% CI: 38.3–67.5) of patients. The most common any-grade adverse event (AE) was injection site reaction (53.1%; all Grade [Gr] 1/2). Gr 3/4 AEs were reported in 65.3% of patients and 8.2% experienced a Gr 5 AE (no Gr 5 AEs were Mosun related, per investigator assessment). Serious AEs occurred in 42.9% of patients. Infection AEs occurred in 49.0% of patients (Gr 1: 4.1%; Gr 2: 28.6%; Gr 3: 16.3%) and resolved in 91.7%. Cytokine release syndrome occurred in 12.2% of patients (Gr 1: 10.2%; Gr 2: 2.0%; all resolved). Updated data with around one additional year of follow-up will be presented. **Conclusions:** Mosun SC showed promising efficacy with manageable safety in elderly/unfit patients with previously untreated DLBCL in an outpatient setting. Clinically meaningful improvements in lymphoma symptoms suggest that Mosun SC improves aspects of HRQoL in this population. Clinical trial information: NCT05207670. Research Sponsor: Genentech, Inc.

7030 **Poster Session**

Pre-lymphodepletion CRP and ferritin risk stratification as a predictor of early immune toxicities and hematologic complications after CAR-T therapy: A propensity-matched cohort study. First Author: Fayaz Aijaz Ahmed Khan, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Inflammation before CAR-T has been linked to higher rates of immune effector cell-associated toxicities and worse outcomes. A pragmatic pre-lymphodepletion risk stratification using C-reactive protein (CRP) and ferritin has been proposed to identify patients at elevated risk. We used the TriNetX Network to evaluate whether CRP/ferritin risk groups predict clinically relevant early outcomes following CAR-T in a real-world setting. **Methods:** We performed a retrospective study using TriNetX Network. Adults (≥18 years) treated with CAR-T (day 0) were included if CRP & ferritin were available in the pre-lymphodepletion window (day −20 to −5). Patients were classified as low risk (CRP <4 and ferritin <400), intermediate risk (CRP ≥4 with ferritin <400 or CRP <4 with ferritin ≥400), and high risk (CRP ≥4 and ferritin ≥400). Propensity score matching was performed using demographics, comorbidities, transplant status, malignancy diagnoses & lymphodepletion therapy. Outcomes were assessed from day 0 to +30. We analyzed outcomes using odds ratio (OR) with 95% confidence interval (CI) and time-to-event comparison using log-rank p-value. **Results:** After propensity matching, high vs low risk cohorts included 246 patients per group. For intermediate vs low risk, cohorts included 298 per group. High-risk patients had higher odds of cytokine release syndrome (CRS) (OR 1.56, 95% CI 1.1–2.2; p=0.04) and immune effector cell-associated neurotoxicity syndrome (ICANS) (OR 1.86, 95% CI 1.1–3.1; p=0.01) versus low risk. In intermediate vs low risk, ICANS remained increased (OR 1.69, 95% CI 1.1–2.7; p=0.02), while CRS showed a nonsignificant trend (OR 1.36, 95% CI 0.98–1.9; p=0.06). High risk cohort was associated with greater supportive care utilization, including higher odds of G-CSF use (OR 2.93, 95% CI 1.5–5.8; p<0.01) and blood transfusion (OR 2.65, 95% CI 1.2–5.9; p=0.01) versus low risk. High vs low-risk was associated with higher odds of platelets <50 (OR 3.59, 95% CI 1.98–6.5; p<0.01) and hemoglobin <8 (OR 2.81, 95% CI 1.3–5.9; p<0.01). Neutropenia (ANC <500) was not significantly different. In intermediate vs low risk, cytopenia-related endpoints were not significantly different. All-cause mortality analysis was not performed due to low event rates. **Conclusions:** In a TriNetX propensity-matched real-world cohort, a simple pre-lymphodepletion CRP and ferritin stratification identified CAR-T recipients at significantly higher risk for early immune toxicities (CRS, ICANS) and clinically meaningful hematotoxicities (severe thrombocytopenia and anemia) within 30 days, along with increased need for G-CSF & transfusion support. These findings support using simple pre-infusion inflammatory biomarkers to guide counseling, risk-adapted monitoring, and proactive supportive care strategies in routine practice. Research Sponsor: None.

7031 **Poster Session**

Longitudinal safety of lisocabtagene maraleucel (liso-cel) in patients (pt) with second-line or later (2L+) large B-cell lymphoma (LBCL). First Author: Manali Kirtikumar Kamdar, University of Colorado Cancer Center, Aurora, CO

Background: Liso-cel has shown favorable efficacy and a manageable, consistent safety profile across B-cell malignancies, including R/R LBCL. Here, we present pooled longitudinal safety results in pts who received liso-cel as 2L+ treatment for LBCL in 3 pivotal clinical trials. **Methods:** Data from liso-cel–treated pts in the TRANSFORM (2L transplant-eligible LBCL, NCT03575351), PILOT (2L transplant-noneligible LBCL, NCT03483103), and TRANSCEND NHL 001 (third-line or later LBCL, NCT02631044) trials were pooled. Incidences of infections, laboratory parameters, and concomitant medication/procedure use were assessed from Day (D) 0–15, D16–30, Month (M) 2–3, M4–6, M7–9, M10–12, M13–18, M19–24, and M25 to end of study (EOS). Incidences were calculated as pts with ≥ 1 event divided by ongoing pts during that period. **Results:** A total of 420 pts were included. Incidence of grade (gr) ≥ 3 neutropenia was highest from D0–15 (Table), decreased sharply after M6, then remained low. Overall, 62% of pts received growth factors for neutropenia, with highest use from D0–15 and minimal use after M3. Rate of gr ≥ 3 anemia was highest from D0–15, declined by M9, then remained low. A total of 49% of pts received red blood cell (RBC) transfusions at any point with highest use from D0–15 and minimal use after M3. Incidence of gr ≥ 3 thrombocytopenia was highest from D0–M3, declined by M9, then remained low. Platelet transfusions were received by 31% of pts at any point with highest use from D0–M3 and minimal use after M3. Use of erythropoiesis- and thrombopoiesis-stimulating agents was rare (1% and 2% at any point, respectively). Incidence of gr ≥ 3 infections was 15% overall and remained low in all periods (Table). Hypogammaglobulinemia (serum immunoglobulin < 500 mg/dL) ranged from 43% to 63% across periods with IVIG use in 20% of pts at any point on study. B-cell aplasia declined over time from 99% from D0–15 to 73% by M12 and < 50% beyond M18. The overall incidence of second primary malignancies was 6%. **Conclusions:** In these longitudinal analyses in liso-cel–treated pts with 2L+ LBCL, gr ≥ 3 cytopenias and concomitant medication use decreased over time with minimal needs for growth factors or transfusions after M3. Gr ≥ 3 infections remained low in the short- and long-term periods despite persistent hypogammaglobulinemia and B-cell aplasia in most pts at M12. These data underscore the favorable long-term safety of liso-cel in pts with 2L+ LBCL, reinforcing the feasibility of outpatient management and the potential for low health care resource utilization in clinical practice. Clinical trial information: NCT03575351, NCT03483103, and NCT02631044. Research Sponsor: This study was funded by Bristol Myers Squibb.

Period	Gr ≥ 3 neutropenia, %	Growth factor for neutropenia, %	Gr ≥ 3 anemia, %	RBC transfusion,%	Gr ≥ 3 thrombo-cytopenia, %	Platelet transfusion, %	Gr ≥ 3 infection, %
D0–15	87	42	29	35	23	12	6
D16–30	36	18	12	19	35	22	2
M2–3	33	16	17	20	32	18	5
M4–6	26	5	12	5	16	3	2
M7–9	12	1	4	2	9	2	< 1
M10–12	15	2	2	1	1	< 1	1
M13–18	10	< 1	1	< 1	3	0	< 1
M19–24	4	1	3	< 1	3	0	2
M25–EOS	6	1	2	1	1	1	1

7032 **Poster Session**

Long-term cognitive impairment after CAR-T therapy compared with autologous stem cell transplantation. First Author: Andrea Yun-En Sun, College of Medicine, National Yang Ming Chiao Tung University, Taipei City, Taiwan

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has transformed the management of relapsed and refractory hematologic malignancies, challenging the established role of autologous stem cell transplantation (ASCT). However, the chronic neurocognitive effects of CAR-T therapy remain unclear. This study compares the long-term risk of cognitive impairment between CAR-T and ASCT therapy recipients. **Methods:** We conducted a retrospective cohort study using US hospital data from the TriNetX research network. Patients exclusively receiving either CAR-T therapy or ASCT were propensity score-matched 1:1 and adjusted for age, sex, primary cancer diagnosis, major comorbidities, neuropsychiatric comorbidities, dexamethasone use, and laboratory values (BMI, LDH if available). Participants with prior cognitive impairment diagnosis within 1 year before index or who received multiple treatment modalities during the study period were excluded. The primary endpoint was time-to-event cognitive impairment, defined by ICD-10 codes for mild cognitive impairment, memory loss, and difficulty with concentration. Secondary outcomes included time to neurological dysfunction (delirium, encephalopathy, seizures), mood and stress-related disorders (depression, anxiety, sleep disorder), fall-related injuries, mobility impairment, and secondary malignancies. **Results:** After propensity score matching, 3,067 CAR-T patients were compared with 3,067 ASCT patients. CAR-T recipients demonstrated a 58% higher risk of cognitive impairment (HR 1.583; 95% CI 1.390-1.80) and a 57% higher risk of neurological dysfunction (HR 1.567; 95% CI 1.403-1.751) compared to ASCT patients. Encephalopathy was the most prominent individual complication, with CAR-T patients showing a 2-fold higher hazard compared to ASCT patients (HR 2.035; 95% CI 1.727-2.398). To account for acute ICANS, events occurring within the first 7 days were excluded, and CAR-T patients maintained higher hazard of cognitive impairment (HR 1.695; 95% CI 1.466-1.959). The risk was highest within the first 30 days (HR 4.224; 95% CI 3.227-5.528) and remained persistently elevated throughout the follow-up period, even at 2500 days (HR 1.761; 95% CI 1.535- 2.021). Among CAR-T products, ciltacabtagene autoleucel showed the highest hazard (HR 2.013; 95% CI 1.092-3.708), while tisagenlecleucel showed the lowest (HR 1.530; 95% CI 1.030-2.271). All $p<0.001$. **Conclusions:** Compared to ASCT, CAR-T cell therapy was associated with a significantly increased risk of long-term cognitive impairment and neurological dysfunction. These findings have important implications for incorporating neurocognitive assessment into treatment discussion, informed consent, and the need for long-term monitoring. Research Sponsor: None.

7033 **Poster Session**

Real-world toxicity of bispecific antibodies versus CAR-T cell therapy in diffuse large B-cell lymphoma and follicular lymphoma. First Author: Nanda Krishnan Siva, West Virginia University School of Medicine, Department of Internal Medicine, Morgantown, WV

Background: CAR-T cell therapy and bispecific antibodies (BsAbs) have transformed treatment of relapsed or refractory B-cell lymphomas. While CAR-T toxicities are well characterized, real-world comparative safety data for newer BsAbs remain limited. We compared early and delayed toxicities of CAR-T versus BsAbs in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). **Methods:** Using the TriNetX Research Network, we conducted a retrospective cohort study of adults with DLBCL or FL treated with BsAbs or CAR-T therapy. 1:1 propensity score matching was performed for demographics, comorbidities, laboratory values, and prior lines of chemotherapy. Outcomes included cytokine release syndrome (CRS) at 14 and 30 days; immune effector cell–associated neurotoxicity syndrome (ICANS) at 30 and 60 days; ICU admission within 90 days; infections within 90 days; hypogammaglobulinemia within 180 days; neutropenia within 90 days; and treatment-related mortality at 90 days. Analyses used Kaplan–Meier methods, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI). **Results:** A total of 1,110 CAR-T–treated and 897 BsAb-treated patients met inclusion criteria. After matching, 384 patients were included per cohort. Compared with CAR-T, BsAbs were associated with lower CRS at 14 days (RR 0.45, 95% CI 0.37–0.55) and 30 days (RR 0.52, 95% CI 0.44–0.62), and lower ICANS at 30 days (RR 0.30, 95% CI 0.20–0.47) and 60 days (RR 0.36, 95% CI 0.25–0.51). ICU admission within 90 days occurred less frequently with BsAbs (RR 0.56, 95% CI 0.40–0.78). Infection rates at 90 days (RR 1.06, 95% CI 0.87–1.30) and hypogammaglobulinemia at 180 days (RR 0.81, 95% CI 0.65–1.01) were similar between groups. Neutropenia within 90 days was lower with BsAbs (RR 0.55, 95% CI 0.49–0.61). 90-day overall survival was lower with BsAbs (HR 2.99, 95% CI 1.89–4.73), likely driven by treatment selection bias, as BsAbs are frequently used in patients ineligible for CAR-T due to poor performance status, comorbidities, or aggressive disease. **Conclusions:** In this real-world cohort of DLBCL and FL, BsAbs were associated with substantially lower early immune-mediated toxicity and healthcare utilization compared with CAR-T therapy, while infectious and delayed immune complications were similar. These findings provide important safety data for newer bispecific agents. Research Sponsor: None.

Outcome	Bispecific Antibodies (n = 384)	CAR-T (n = 384)	HR/RR [95% CI]
CRS (0–14 days)	25.3%	56.3%	0.45 [0.37-0.55]
CRS (0–60 days)	31.8%	59.6%	0.53 [0.45-0.63]
ICANS (0–30 days)	8.1%	22.4%	0.30 [0.20-0.47]
ICANS (0–60 days)	9.4%	26.0%	0.36 [0.25-0.51]
ICU admission (0–90 days)	12.0%	21.4%	0.56 [0.40-0.78]
Infections (0–90 days)	34.6%	32.6%	1.06 [0.87-1.30]
Neutropenia (0–90 days)	49.2%	89.6%	0.55 [0.49-0.61]
Hypogammaglobulinemia (0–180 days)	27.1%	33.6%	0.81 [0.65-1.01]
Overall Survival (0–90 days)	81.4%	93.2%	2.99 [1.89 – 4.73]

7034 **Poster Session**

The influence of advanced age on outcomes in patients with diffuse large B-cell lymphoma treated with CAR-T therapy. First Author: Muqtasid Aftab Khan, University of Alabama at Birmingham Heersink School of Medicine - Huntsville, Department of Internal Medicine, Huntsville, AL

Background: Chimeric antigen receptor T-Cell (CAR-T) has emerged as a potentially curative treatment for diffuse large B-Cell lymphoma (DLBCL). The median age at DLBCL diagnosis is 66 years with nearly 30% of patients diagnosed at ≥75 years. Studies have examined outcomes of CAR-T therapy in DLBCL, with elderly patients (≥ 65 years) included in analyses; however, clinical trial populations have underrepresented the true age distribution of the disease. This study evaluates the impact of advanced age on survival and toxicity outcomes in patients with DLBCL treated with CAR-T therapy. **Methods:** A multicenter retrospective cohort study was conducted using TriNetX, a federated database of over 159 million de-identified electronic health record and claims data. Patients aged ≥75 years with DLBCL treated with CD19-directed CAR-T therapy were compared with a 1:1 propensity score–matched cohort of patients aged 18–65. Propensity score matching was performed based on demographics, comorbidities, and baseline laboratory values. Primary outcomes included 1-year and 3-year overall survival (OS), as well as the development of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infection within 100 days following CAR-T infusion. Outcomes were assessed using Kaplan–Meier survival analyses, hazard ratios (HR), risk ratios (RR), and 95% confidence intervals (CI). **Results:** Prior to PSM, there were 326 patients ≥ 75 years and 816 patients aged 18-65 years who were treated with CD-19 directed CAR-T for DLBCL. After PSM, there were 241 patients in each cohort. There was no statistically significant difference in one-year or three-year overall survival between patients ≥ 75 years vs. 18-65 years (1-year HR: 0.89, 95% CI [0.63-1.26]; 3-year HR: 1.00, 95% CI [0.74-1.36]). Interestingly, patients ≥ 75 years were at a lower risk for the development of CRS compared younger patients (RR: 0.84, 95% CI [0.72, 0.98]). There was no statistically significant difference in the risk for development of ICANS (RR: 0.98, 95% CI [0.70–1.38]). Risk of infection at 100 days post-CAR-T infusion was lower in patients ≥ 75 years (RR: 0.75, 95% CI [0.58–0.95]). **Conclusions:** In this large multicenter real-world analysis, patients aged ≥75 years experienced comparable overall survival and no increased toxicity following CAR-T therapy for DLBCL. These findings suggest that advanced age alone should not preclude CAR-T eligibility and support broader consideration of CAR-T therapy in appropriately selected older adults. Research Sponsor: None.

Outcome	Age ≥75 (n=241)	Age 18-65 (n=241)	HR/RR [95% CI]
1-year OS	71.6%	68.6%	0.89 [0.63-1.26]
3-year OS	47.3%	53.7%	1.00 [0.74-1.36]
CRS	**52.3%**	**62.2%**	**0.84 [0.72–0.98]**
ICANS	21.6%	22.0%	0.98 [0.70–1.38]
Infection (≤100 days)	**30.3%**	**40.7%**	**0.75 [0.58–0.95]**

7035 **Poster Session**

Immune priming with the EZH2 inhibitor tazemetostat in B-cell lymphomas receiving CAR T-cell therapy. First Author: Samuel Yamshon, Weill Cornell Medicine, New York, NY

Background: While chimeric antigen receptor (CAR) T cells have shown efficacy in B cell lymphomas, most patients (pts) still relapse. Preclinical studies have shown that inhibiting histone methyltransferase EZH2 prevents T cell exhaustion, promotes a T-cell memory phenotype, and sensitizes immune-based approaches. **Methods:** We administered the EZH2 inhibitor tazemetostat in pts receiving standard-of-care CART for diffuse large B cell, follicular, or mantle cell lymphoma (DLBCL, FL, MCL). Pts received tazemetostat for ≥7 days prior to apheresis and continued to lymphodepletion. Following CART, pts resumed tazemetostat at count recovery and continued for up to 12 mo (6 mo in pts with complete remission [CR]). Peripheral blood mononuclear cells were collected Day -24 and Day -5. To evaluate the immunomodulatory effects of priming, high parameter flow cytometry, RNA-seq with cell deconvolution, differential gene expression patterning, and functional gene signature scoring using ssGSEA were compared. **Results:** 13 pts enrolled (7 DLBCL, 5 FL, 1 MCL). Median prior lines of therapy were 2 (1-4), and 85% were refractory to the last therapy. *EZH2* mutations were present in 2 pts. 4 pts had *TP53* mutation or deletion, 4/7 DLBCL pts had *MYC* translocation and 3 had transformed disease. Five pts received axi-cel, 5 liso-cel, 2 tisa-cel, and 1 brexu-cel. All successfully completed CART manufacturing. The ORR was 100%, including 77% in CR (DLBCL 71%, FL 100%). At a median follow up of 18 months, 54% remain progression-free, and 77% remain alive. Ten pts (77%) experienced CRS, with 1 grade 3 CRS. 6 pts had transient grade 1-2 ICANS. Grade 3+ neutropenia was seen in 77%. Three pts experienced grade 3 infections. The most common AEs were gastrointestinal and almost exclusively grade 1-2. Comparing baseline and pre-CART samples, pts experienced a 14% and 20% increase in NK cells and CD16+ monocytes ($p < 0.03$) and a 14% and 53% decrease in Tregs and CD14+ monocytes ($p < 0.02$). Increases in the expression of functional gene signatures associated with MHC-I antigen presentation (p = 0.010), antigen-specific T cell activation (p = 0.019), and cellular cytotoxicity (p = 0.043) were also observed. Parallel reductions in signatures associated with tolerogenic dendritic cells (p = 0.011), myeloid suppression (p = 0.043), and coagulation (p = 0.030) were also seen. There was no observed negative impact on CART transduction efficiency, activation, or expansion. **Conclusions:** Addition of the EZH2 inhibitor tazemetostat is associated with high clinical efficacy and peripheral immune remodeling. Increases in lymphocyte activation and cytotoxicity along with decreases in myeloid tolerogenicity and immunosuppression could potentially augment CART expansion and persistence. Additional immune correlates are ongoing, and randomized studies are planned to validate this approach. Clinical trial information: NCT05934838. Research Sponsor: Ipsen.

7036 **Poster Session**

Predictors of low- and high-grade ICANS after CAR-T: A nationwide analysis. First Author: Ashish Nepal, WellSpan York Hospital, York, PA

Background: Immune effector cell-associated neurotoxicity syndrome (ICANS) is a leading cause of morbidity following chimeric antigen receptor T-cell (CAR-T) therapy. However, the real-world predictors of severity remain incompletely defined. We evaluated whether ICANS risk differs between multiple myeloma (MM) and other CAR-T indications. **Methods:** CAR-T hospitalizations were identified using ICD-10-PCS procedure codes. ICANS was identified using ICD-10-CM grade-specific codes (G92.00–G92.05) and severity was graded as none, low-grade (1–2), or high-grade (3–5). The 2022–2023 Healthcare Cost and Utilization Project National Inpatient Sample (HCUP NIS) with discharge weights was used for this analysis. Multivariable multinomial (nominal) regression (reference outcome: no ICANS) estimated adjusted odds ratios (aORs) for low- and high-grade ICANS. Cancer type was modeled with MM as a reference and compared with lymphomas, leukemias, solid/metastatic malignancies, and unspecified/other malignancies, adjusting for prespecified comorbidities including dementia, diabetes, and substance use diagnoses. **Results:** Among 10,105 weighted CAR-T hospitalizations, the risk of high-grade ICANS varied significantly by cancer type. Relative to MM, high-grade ICANS was significantly higher in leukemia (aOR 5.23 (95% CI 3.81–7.16), $p < 0.001$); lymphoma (aOR 3.91 (95% CI 3.07–5.00), $p < 0.001$); solid/metastatic malignancy (aOR 1.92 (95% CI 1.30–2.83), p = 0.001); and unspecified/other malignancy (aOR 6.34, 95% CI 4.98–8.07, $p < 0.001$). For low-grade ICANS, lymphoma was associated with increased odds compared with MM (aOR 1.53, 95% CI 1.31–1.78; $p<0.001$). Comorbidity signals were dominated by baseline neurologic vulnerability and metabolic disease. Dementia was the strongest predictor of high-grade ICANS (aOR 7.54, 95% CI 4.13–13.78; $p<0.001$). Drug abuse was associated with increased odds of low-grade ICANS (aOR 2.68, 95% CI 1.45–4.97; p=0.002). Diabetes with complications was associated with both low-grade (aOR 1.49, 95% CI 1.24–1.79; $p<0.001$) and high-grade ICANS (aOR 1.63, 95% CI 1.33–1.99; $p<0.001$). **Conclusions:** In a nationally representative inpatient cohort, multiple myeloma (MM) was associated with significantly lower odds of high-grade ICANS compared with other CAR-T indications, especially leukemia and lymphoma. Dementia and complicated diabetes were highly predictive of high-grade ICANS across all cancer types. These findings identify a clinically actionable risk profile that may inform future risk-stratified monitoring and early intervention strategies as CAR-T use expands. Limitations include reliance on administrative ICD-10 coding, which may misclassify ICANS severity, the possibility of clinical confounding, and a lack of product-specific and other clinical granularity. Research Sponsor: None.

7037 **Poster Session**

Real-world outcomes of epcoritamab vs glofitamab in relapsed/refractory diffuse large B-cell lymphoma: A TriNetX retrospective study. First Author: Juhi Ardeshna-Chovatiya, University of California Riverside, Riverside, CA

Background: Glofitamab and epcoritamab are CD20-directed bispecific antibodies that engage CD3-positive T cells and are approved for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL). While trials reported high response rates, real-world comparative data on survival, safety, and treatment complications are limited. We conducted a propensity score-matched analysis to compare the effectiveness and safety of glofitamab and epcoritamab in R/R DLBCL. **Methods:** We conducted a retrospective cohort study of adult relapsed/refractory diffuse large B-cell lymphoma patients treated with glofitamab or epcoritamab through January 2026 using the TriNetX network. Eligible patients had confirmed R/R DLBCL, $\geq$2 prior systemic therapies and $\geq$30 days follow-up. Data from 134 million patients across 70 US healthcare organizations were analyzed. Propensity-score matching was done for age, sex, race, comorbidities, prior CAR T, and prior therapies. Outcomes included overall survival, all-cause mortality, hematologic adverse events, CRS, ICANS, infections, and ICU admissions. **Results:** A total of 369 epcoritamab and 337 glofitamab patients met the inclusion criteria. After 1:1 propensity-score matching, 205 patients were included in each cohort. Median age was 68 years for glofitamab and 67.8 years for epcoritamab, with 62.9% vs 64.9% male. Median follow-up was 6.8 months vs 5.8 months. At 6 months, mortality was 29.3% versus 39.0% (RR 0.75, 95% CI 0.57-0.99; p=0.037), with estimated overall survival 68.1% versus 55.8% (HR 0.68, 95% CI 0.49-0.95; p=0.023). This benefit persisted at 12 and 24 months (estimated overall survival 54.0% vs 43.8% and 37.5% vs 33.3%, HR 0.73-0.75), though fixed-time risk differences were not significant. Any-grade CRS occurred in 22.4% vs 30.2% (RR 0.74, 95% CI 0.53-1.03; p=0.073), with grade $\geq$3 CRS not significantly different between cohorts. ICANS occurred in 7.3% vs 11.7% (RR 0.63, 95% CI 0.34-1.16; p=0.130), and tocilizumab use was comparable (20.0% vs 22.0%). Hematologic adverse events, including neutropenia (21.5% vs 26.8%), thrombocytopenia (34.1% vs 35.1%), anemia (35.1% vs 40.0%), and ICU admissions (19.0% vs 25.4%), were comparable and not significantly different. Infections were significantly lower with glofitamab (38.0% vs 48.8%, RR 0.78, 95% CI 0.62-0.98; p=0.028), supporting a favorable safety profile. **Conclusions:** In this real-world analysis, glofitamab and epcoritamab had similar safety profiles, with glofitamab showing lower early mortality and higher overall survival. Hematologic adverse events, CRS, ICANS, and ICU admissions were comparable, while infections were significantly lower with glofitamab. The selection of CD20$\times$CD3 bispecific antibodies should consider infection risk and early survival outcomes until longer follow-up clarifies durability and late toxicities. Research Sponsor: None.

7038 **Poster Session**

Baseline phosphoproteomic signatures in peripheral blood and prediction of durable response to CAR T-cell therapy in B-cell malignancies. First Author: Christian A. Gordillo, Columbia University Irving Medical Center, New York, NY

Background: Despite the success of Chimeric Antigen Receptor (CAR) T-cell therapy, most patients fail to achieve durable remission. T-cell "fitness" is a critical, yet undercharacterized, determinant of efficacy. Standard immune and transcriptomic profiling do not measure the dynamic signaling networks driving cellular function. We hypothesized that baseline phosphoproteomic signatures in peripheral blood mononuclear cells (PBMCs) prior to CAR T-cell could serve as functional biomarkers for T-cell fitness, predicting durable response. **Methods:** We performed unbiased LC-MS/MS-based phosphoproteomics (KScan) on baseline PBMCs from 59 patients (39 Aggressive Lymphoma [DLBCL], 20 Multiple Myeloma [MM]) treated with CD19- or BCMA-directed CAR-T. Kinase Substrate Enrichment Analysis (KSEA) inferred upstream kinase activity. The primary endpoint was Complete Response (CR) at 6 months. We also analyzed a subset of DLBCL patients (n=6) who achieved CR at Day 30 but progressed (POD) by Month 6 ("early relapse") to identify markers of transient versus durable response. **Results:** We quantified 7,602 phosphopeptides. In the DLBCL cohort (20 CR, 17 POD), distinct phosphorylation in kinase signaling networks separated durable responders from non-responders, specifically implicating dysregulated stress response and MAPK signaling in resistance. KSEA revealed dysregulation in the MAPK/ERK, Casein Kinase (e.g., CSNK1E), and Cyclin-Dependent Kinase activity, linking baseline proliferative potential to long-term efficacy. Notably, the "early relapse" group (Day 30 CR / Month 6 POD) exhibited a unique profile, characterized by differential phosphorylation of proteins involved in apoptotic regulation and chromatin remodeling (e.g., FADD, ARID1A, ACIN1, KMT2A), suggesting these intrinsic defects may limit CAR T-cell persistence. Correlation analysis further integrated these signaling features with CD3+, CD4+, and CD8+ T-cell counts, validating their biological relevance. In the MM cohort, the signaling landscape was heavily dominated by immune cell composition. KSEA revealed that kinase activity in CR patients strongly correlated with the CD4:CD8 ratio and absolute CD3+ counts, validating that the captured phosphoproteomic variance reflects the underlying T-cell phenotype required for successful expansion and cytotoxicity. **Conclusions:** Baseline PBMC phosphoproteomics is a powerful tool for predicting CAR T-cell efficacy. We identified specific signatures—distinct from broad immune cell counts—that differentiate durable responders from patients at risk of primary refractory disease or early relapse. These targets highlight avenues for pharmacological conditioning to enhance T-cell fitness. These data support integrating functional proteomic biomarkers into patient stratification strategies to optimize outcomes. Research Sponsor: None.

7039 **Poster Session**

Clonal hematopoiesis as a predictor of immune toxicity and efficacy after chimeric antigen receptor T-cell therapy: A systematic review and meta-analysis. First Author: Adam Bowen, McLaren Greater Lansing, Lansing, MI

Background: Clonal hematopoiesis of indeterminate potential (CHIP) is associated with age-related inflammation and may influence immune toxicity and efficacy after CAR T-cell therapy, although reported associations are inconsistent. We performed a systematic review and meta-analysis to quantify CHIP associations with CAR-T toxicities and response. **Methods:** We conducted a systematic review and meta-analysis of comparative studies reporting CAR-T outcomes by sequencing-defined CHIP status. PubMed, Embase, Cochrane Central, and Web of Science were searched through 2025; nine observational studies were included from 3,529 records. The evidence comprised nine retrospective cohorts (n=869) of adults receiving commercial CD19 CAR-T for B-cell malignancies (mainly aggressive lymphoma/LBCL, B-ALL) or BCMA CAR-T for multiple myeloma. CHIP was identified from pre-infusion blood-derived samples using targeted myeloid sequencing, typically at VAF $\geq$2% (range $>$0.3%–$\geq$2%; one study $\geq$1%), with prevalence 16–56%. Primary endpoints were ASTCT grade $\geq$3 CRS and ICANS; secondary endpoints included CRS $\geq$2, any-grade ICANS, ORR, and CR. Risk ratios were pooled using random-effects Mantel–Haenszel models with prespecified subgroup and sensitivity analyses by CAR target/disease; risk of bias was assessed with ROBINS-I. **Results:** Four cohorts (n=360; 2 CD19, 1 BCMA, 1 mixed) contributed to primary toxicity analyses. CHIP was not associated with severe CRS (ASTCT $\geq$3; 8/172 vs 14/188; RR 0.72, 95% CI 0.24–2.13; I^2=31%) or severe ICANS (RR 1.16, 95% CI 0.48–2.81; I^2=39%), with wide confidence intervals reflecting low event counts. A CD19-restricted sensitivity analysis demonstrated higher risk of severe ICANS among CHIP-positive patients (RR 1.66, 95% CI 1.03–2.65; I^2=0%). For moderate-to-severe CRS (ASTCT $\geq$2), five cohorts (n=456) showed no association (RR 1.04, 95% CI 0.73–1.48; I^2=59%); exclusion of a mixed cohort reduced heterogeneity and remained null (RR 1.02, 95% CI 0.79–1.32; I^2=18%). Any-grade ICANS was not increased (six cohorts, n=440; RR 1.10, 95% CI 0.85–1.41; I^2=1%). Efficacy was preserved: ORR was modestly higher in CHIP-positive patients in full-text cohorts (n=347; RR 1.14, 95% CI 1.02–1.27; I^2=0%), with similar estimates when including abstract-only data (RR 1.10, 95% CI 1.01–1.21). CR showed a small overall increase (n=385; RR 1.24, 95% CI 1.01–1.52; I^2=15%) that was not robust on sensitivity analysis (RR 1.23, 95% CI 0.90–1.67). **Conclusions:** CHIP was not consistently associated with CRS severity or overall ICANS incidence after CAR-T therapy, although severe ICANS may be higher in CD19 CAR-T lymphoma. Efficacy was preserved in CHIP-positive patients, with no evidence of impaired ORR or CR, and observed response differences should be interpreted cautiously given observational design and heterogeneous definitions. Research Sponsor: None.

7040 **Poster Session**

The impact of COVID-19 mRNA vaccination on bispecific antibody outcomes in hematologic malignancies: A retrospective multicenter cohort study. First Author: Mostafa Eysha, Texas Tech University Health Sciences Center El Paso, El Paso, TX

Background: Bispecific antibody (BsAb) therapies are universally available, off-the-shelf therapies and are increasingly being used in hematologic malignancies. However, long term efficacy, durability and survival data are lacking. Furthermore, widespread expansion is limited by immune-mediated toxicities, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and infections. The real-world impact of mRNA SARS-CoV-2 vaccines on outcomes in patients receiving BsAb therapies remain unknown. **Methods:** We conducted a retrospective, propensity score-matched cohort study using the TriNetX federated electronic health record network. Adult patients with hematologic malignancies who received BsAb therapy were included and stratified by receipt of mRNA SARS-CoV-2 vaccines. Patients with documented COVID-19 infection or post-COVID-19 conditions were excluded. Cohorts were matched 1:1 on baseline demographic and clinical characteristics, yielding 238 patients per group, and followed longitudinally. Outcomes included all-cause mortality, any-grade CRS grade, and ICANS, graded per the ASTCT criteria. Associations were assessed using risk estimates and time-to-event analyses with Kaplan-Meier methods and Cox proportional hazards models. Event burden was evaluated by the number of events per patient among those experiencing CRS or ICANS. **Results:** All-cause mortality was lower in the vaccinated cohort compared with the unvaccinated cohort (21.4% vs 29.0%; p=0.057), with significantly improved survival on time-to-event analysis (hazard ratio [HR] 0.55; 95% CI, 0.38-0.79; log-rank p=0.001). The incidence of CRS grade 1/2 was similar between cohorts (25.2% vs 24.0%), with no difference in time to first CRS event (HR 0.98; 95% CI, 0.68-1.41). ICANS incidence was also comparable (10.9% vs 11.3%), with no significant difference in time-to-event (HR 0.87; 95% CI, 0.51-1.50). Among patients who developed ICANS, the vaccinated cohort experienced a higher mean number of ICANS episodes (2.58 vs 1.67; p=0.036) see (table1). **Conclusions:** In this propensity score-matched real-world analysis, mRNA SARS-CoV-2 vaccination was associated with significantly reduced all-cause mortality (HR, 0.55) among patients receiving BsAb therapy, without an increased risk of CRS grade 1/2 or ICANS. These findings support the safety of mRNA vaccination in this high-risk population and suggest a potential survival benefit necessitating prospective validation. Research Sponsor: None.

Outcome	Vaccinated (n=238)	Unvaccinated (n=238)	Key Effect
All-cause mortality	21.4%	29.0%	HR 0.55 (95% CI 0.38-0.79)
CRS grade 1/2	25.2%	24.0%	HR 0.98 (95% CI 0.68-1.41)
CRS grade 1/2 episodes (mean)	2.98	2.35	P=0.16
ICANS	10.9%	11.3%	HR 0.87 (95% CI 0.51-1.50)
ICANS episodes (mean)	2.58	1.67	p=0.036

7041 **Poster Session**

Early toxicity, healthcare utilization, and survival after CAR T-cell therapy versus bispecific antibodies in DLBCL: A propensity-matched real-world analysis. First Author: Jatin Thukral, New York Medical College, Landmark Medical Center, Woonsocket, RI

Background: CD20×CD3 bispecific antibodies and CD19-directed CAR T-cell therapies are increasingly used in relapsed/refractory DLBCL. CAR T therapy is associated with higher rates of CRS,ICANS, and cytopenias, whereas bispecific antibodies are often perceived as less toxic and more outpatient-friendly. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. Adult patients with DLBCL treated with bispecific antibodies (glofitamab, epcoritamab) were compared with those receiving commercial CAR T-cell therapy (tisa, liso, axi). Propensity score matching was performed on demographics, comorbidities, baseline laboratory values, and corticosteroid exposure, yielding 468 patients per cohort. Outcomes included CRS, ICANS, severe neutropenia (ANC $<500/\mu L$), and thrombocytopenia (platelets $<50\times10^3/\mu L$), as well as hospitalization and ICU admission at 1, 3, 6, and 12 months. Overall survival (OS) was assessed using Kaplan–Meier analysis with log-rank testing. **Results:** After matching, CAR T therapy was associated with significantly higher immune-mediated toxicity. CRS occurred more frequently with CAR T at 1 month (37.4% vs 22.4%), 3 months (39.3% vs 27.6%), 6 months (40.6% vs 28.8%), and 12 months (41.2% vs 29.7%) (all $p<0.001$). ICANS was also more common with CAR T across all timepoints (1 month: 10.5% vs 4.9%; 12 months: 12.6% vs 7.5%). Severe neutropenia and thrombocytopenia were markedly more frequent in the CAR T cohort, with neutropenia affecting 66.7% vs 12.8% at 1 month and 71.6% vs 32.7% at 12 months (all $p<0.001$). Despite higher toxicity, healthcare utilization was comparable. Hospitalization rates were similar between groups at 1 and 3 months (61.8% vs 66.7% and 67.1% vs 75.9%), and ICU admission rates did not differ meaningfully at any timepoint. Importantly, overall survival consistently favored CAR T therapy. Survival differences emerged early and persisted over time, with lower mortality in the CAR T cohort at 1 month (2.1% vs 9.0%), 3 months (7.7% vs 18.6%), 6 months (15.8% vs 26.7%), and 12 months (26.5% vs 35.3%), corresponding to significantly improved OS by log-rank testing at all timepoints ($p<0.001$). **Conclusions:** In this large, real-world, propensity-matched analysis of relapsed/refractory DLBCL, CAR T-cell therapy was associated with substantially higher rates of CRS, ICANS, and severe cytopenias compared with bispecific antibodies. However, these toxicities did not translate into higher hospitalization or ICU utilization. Despite a less favorable early toxicity profile, CAR T therapy conferred a consistent and clinically meaningful survival advantage from early to late follow-up. Early toxicity alone should not preclude CAR T referral in appropriate candidates, underscoring the need for optimized patient selection, sequencing strategies, and supportive care. Research Sponsor: None.

7042 **Poster Session**

Real-world impact of atrial fibrillation (AFib) on cardiovascular (CV) outcomes and healthcare resource utilization (HCRU) in patients with chronic lymphocytic leukemia (CLL). First Author: Michael Fradley, University of Pennsylvania School of Medicine, Philadelphia, PA

Background: While the association between AFib and CLL has been reported, real-world evidence on its clinical and economic impact is limited. This study evaluated impact of AFib on CV outcomes (stroke, bleeding, heart failure) and HCRU in patients (pts) with CLL overall, by age, and by Bruton tyrosine kinase inhibitor (BTKi) therapy. **Methods:** This retrospective observational study used the US Symphony database to identify adults newly diagnosed with CLL (2014-2024). Pts were followed for 1 year after CLL diagnosis to assess incidence of AFib. Subsequent CV outcomes (stroke, bleeding, heart failure) and HCRU (inpt, outpt, other services) were compared in CLL pts with and without AFib. Multivariate regression analyses assessed associations between AFib and outcomes. Subgroup analyses were conducted in elderly pts aged ≥65 years. Exploratory analyses compared first-line (1L) BTKi use (ibrutinib, acalabrutinib, or zanubrutinib). **Results:** In 233,362 newly diagnosed CLL pts, 13.1% had AFib within 1 year of CLL diagnosis. A significantly greater proportion of CLL pts with AFib had ≥1 inpt visit within 1 year of CLL diagnosis than those without AFib (54.9% vs 23.2%, $P<.0001$), as well as a higher likelihood to incur inpt service (OR: 2.28, 95%CI [2.21, 2.35], $P<.0001$). Significantly higher proportions of CLL pts with AFib had subsequent stroke (14.3% vs 8.9%), bleeding (27.9% vs 19.1%), and heart failure (54.5% vs 18.9%) than those without AFib ($P<.0001$). Age ≥65, male, non-white, and AFib were associated with subsequent stroke, bleeding, or heart failure ($P<.01$). Results were consistent in pts aged ≥65 years. In pts initiating 1L BTKi, AFib rate within 1 year of treatment for 1L zanubrutinib vs acalabrutinib vs ibrutinib was 11% vs 13% vs 16%, respectively; $P<.0001$. Compared to 1L ibrutinib and 1L acalabrutinib, a lower proportion of CLL pts with AFib treated with 1L zanubrutinib had subsequent stroke (12.2% vs 9.4% vs 4.8%, respectively), bleeding (27.4% vs 21.5% vs 17.4%), and heart failure (50.9% vs 45.6% vs 39.6%) ($P<.002$). CLL pts with AFib treated with 1L zanubrutinib had less inpt services than 1L ibrutinib and 1L acalabrutinib within 1 year of BTKi treatment (46.4% vs 51.5% vs 60.4%; $P<.0001$). In multivariate regression, 1L acalabrutinib pts had 29% higher odds than 1L zanubrutinib pts (OR: 1.29, 95% CI [1.12, 1.50], $P=.0005$); 1L ibrutinib pts had 69% higher odds than 1L zanubrutinib pts (OR: 1.69, 95% CI [1.48, 1.93], $P<.0001$) to incur inpt service within 1 year after initiating BTKi treatment. **Conclusions:** Findings highlight significant real-world CV and HCRU burden incurred by CLL pts with AFib. Exploratory analyses suggested 1L zanubrutinib may offer potentially favorable outcomes over other BTKi in lessening AFib and related clinical and HCRU complications. Future studies with longer follow-up are warranted to confirm these findings. Research Sponsor: BeOne Medicines, Ltd.

7043 **Poster Session**

Effect of first-line treatment of CLL/SLL with the all-oral combination of sonrotoclax (sonro) and zanubrutinib (zanu) on minimal residual disease (uMRD) rates, including in patients with del(17p)/TP53. First Author: Constantine Si Lun Tam, Alfred Hospital and Monash University, Melbourne, VIC, Australia

Background: Oral, fixed-duration BTKi-BCL2i combinations are effective and convenient options for first-line treatment of CLL. However, all current regimens, including those using second-generation BTKi, are limited by low uMRD rates of 29-47%. We hypothesize that upgrading the BCL2i component of BTKi-BCL2i with sonro, a next generation BCL2i with ~14x pharmacological potency compared with venetoclax, may lead to improved uMRD rates. Here, we report updated safety and efficacy results in patients with treatment-naive CLL/SLL treated with zanu+sonro (320 mg cohort) in a phase 1/1b study (NCT04277637), with a median follow-up of 30.9 months (range, 3.1-41.9 months). **Methods:** Study treatment consisted of lead-in zanu 320 mg QD for 8-12 weeks, after which sonro was added with a ramp-up to the target dose of 320 mg QD. Patients were treated until progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination treatment at target dose. Primary endpoint was safety per NCI-CTCAE v5.0. Secondary endpoints included overall response rate (ORR). Exploratory endpoints included uMRD4 rates in peripheral blood per flow cytometry and next generation-sequencing (NGS). **Results:** Of the 86 patients enrolled in the sonro 320 mg cohort, 45 (52%) remained on treatment at data cut-off, and 40 (47%) discontinued sonro, most due to protocol-defined elective discontinuation (85%; n=34). The most common (≥30%) any-grade treatment-emergent adverse events (TEAEs) were neutropenia (38%), contusion (38%), COVID-19 (33%), and upper respiratory tract infection (30%). Neutropenia was the most common grade ≥3 TEAE (29%). No TLS occurred, and no AEs led to death. In 84 efficacy-evaluable patients, the ORR was 100%, with 46 (55%) achieving complete response. Median time to response was 2.6 months (range, 1.5-9.1 months). No patients in the 320 mg cohort experienced progression with an estimated 30-month PFS of 100%. The best uMRD4 rate assessed by flow cytometry was 99% (83/84) and 100% (10/10) in patients with *TP53*/del(17p) mutations. Median time from reaching sonro target dose to uMRD was 3.0 months (range, 2.3-27.4 months), and the best uMRD4 rates by weeks 24, 48 and 96 were 81% (69/85), 91% (63/69) and 98% (55/56), respectively. No patient with uMRD4 reverted to MRD4+. In the NGS evaluable set, best uMRD5 ($<10^{-5}$) was 86% (66/77). Updated results will be presented. **Conclusions:** Sonro+zanu was well tolerated and achieved uMRD rates of >90%, including in patients with high-risk cytogenetics. The depth and kinetics of uMRD achieved with sonro+zanu highlights the improved potency and differentiated profile of this combination vs available combination therapies in first-line CLL. Sonro+zanu is being evaluated in two phase 3 clinical trials (NCT06073821, NCT07277231). Clinical trial information: NCT04277637. Research Sponsor: BeOne Medicines, Ltd.

7044 **Poster Session**

Pirtobrutinib in treatment-naïve patients with CLL/SLL: Pooled results from BRUIN CLL-313 and BRUIN CLL-314. First Author: William G. Wierda, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pirtobrutinib, a highly selective, non-covalent Bruton tyrosine kinase inhibitor (BTKi), is approved globally for patients (pts) with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) previously treated with a covalent BTKi. BRUIN CLL-313 and BRUIN CLL-314 are open-label, randomized phase 3 studies evaluating pirtobrutinib for therapy of pts with CLL/SLL, including in the treatment-naïve (TN) setting [versus bendamustine plus rituximab (BendaR; CLL-313, NCT05023980) and versus ibrutinib (CLL-314, NCT05254743)]. **Methods:** Pooled data from TN CLL pts randomized to receive pirtobrutinib from CLL-313 and CLL-314 were used to assess efficacy [overall response rate (ORR), progression-free survival (PFS) and overall survival (OS)] and safety. PFS and OS estimates were calculated by the Kaplan-Meier method. All pts (253) randomized within each study to receive pirtobrutinib are included in efficacy analyses and all pts (252) who received pirtobrutinib treatment are included in safety analyses. **Results:** A total of 253 TN pts, median age of 66 yrs, were assigned to receive pirtobrutinib (CLL-313 n=141; CLL-314 n=112); all but one received treatment. Among pts with evaluable samples 134/233 (58%) had unmutated IGHV, 14/253 (6%) had del(17p) and 21/220 (10%) had mutated TP53. Efficacy was consistent between the two studies (Table). Overall, ORR was 93.3%. Median PFS was not reached; the 24-month PFS rate was 93.2% (95%CI, 89.1-95.8). Median OS was also not reached; the 24-month OS rate was 97.5% (95%CI, 94.6-98.9). Median duration of therapy was 29.1 months. Treatment discontinuation due to TEAEs occurred in 4.8% of pts with 1.6% treatment related. Any-grade infection occurred in 59.9% of pts; neutropenia in 18.3% and grade ≥3 bleeding in 2.4%. Any-grade hypertension occurred in 10.7% of pts and atrial fibrillation/flutter was reported in 2.8%. **Conclusions:** In 253 TN pts with CLL randomized on two phase 3 studies, pirtobrutinib showed a high ORR and favorable 24-month PFS and OS rates. The safety profile was consistent with prior studies using pirtobrutinib in more heavily treated pts, with low rates of atrial fibrillation/flutter, hypertension and TEAE-related discontinuations. These findings reinforce the potential of pirtobrutinib as a meaningful and clinically relevant treatment option for pts with TN disease. Clinical trial information: NCT05023980 and NCT05254743. Research Sponsor: Eli Lilly and Company.

Efficacy of pirtobrutinib in TN patients with CLL/SLL.

	Parameter	CLL-313 N = 141	CLL-314 N = 112	Pooled TN pts N=253
ORR	ORR, % (95% CI)	94.3 (89.1, 97.5)	92.0 (85.3, 96.3)	93.3 (89.5, 96.0)
PFS	24-month PFS rates, % (95% CI)	92.7 (86.8, 96.0)	94.3 (87.8, 97.4)	93.2 (89.1-95.8)
	Median FU, months	28.1	22.4	27.7
OS	24-month OS rates, % (95% CI)	97.8 (93.3, 99.3)	97.2 (91.5, 99.1)	97.5 (94.6-98.9)
	Median FU, months	32.7	26.7	29.5

ORR includes a best response of partial response or better.

7045 **Poster Session**

Real-world treatment and survival outcomes for zanubrutinib (zanu) and acalabrutinib (acala) monotherapy among treatment-naive patients with chronic lymphocytic leukemia (CLL) in the United States. First Author: Ryan Jacobs, Atrium Health Levine Cancer Institute, Wake Forest University School of Medicine, Charlotte, NC

Background: Bruton tyrosine kinase (BTK) inhibitors are central to the management of CLL/SLL (hereafter referred to as CLL). Acala was approved for CLL in the US in 2019, followed by zanu in 2023. Despite their widespread use, real-world evidence comparing therapy effectiveness is limited. This US-based study compared the real-world effectiveness of zanu and acala monotherapy as first-line treatment for patients with CLL based on overall survival (OS) and time to next treatment (TTNT). **Methods:** This retrospective analysis utilized the Komodo claims database between January 2015 and August 2025. Eligible patients were adults (aged ≥18 years) in the US with ≥2 diagnoses of CLL or SLL, who were treatment naive for CLL and had an index claim for monotherapy with zanu (January 2023 to August 2025) or acala (November 2019 to August 2025). The index date was defined as the date of the first observed claim for the respective therapy. Patients were required to have continuous enrollment or activities within 1 year prior to and 3 months after the index date. Patients with evidence of clinical trial participation, prior CLL/SLL treatment, or two diagnoses of mantle cell lymphoma between January 2015 and the index date were excluded. Outcomes included OS (measured from index claim to all-cause mortality), and TTNT (measured from index claim to initiation of subsequent therapy or death). If death did not occur, patients were censored at the date of last activity or the enrollment end date. For OS analysis, Komodo data captured the death date, but not the cause of mortality. Survival analyses were conducted using Kaplan-Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was adjusted for age, sex, US region, treatment initiation year, and Charlson Comorbidity Index (CCI). **Results:** Among 16,788 patients (zanu, n=5819; acala, n=10,969), median age was higher in zanu (73.3 years) vs acala (71.8 years) cohorts. Most patients were male (acala, 62%; zanu, 59%), non-Hispanic white (acala, 73%; zanu, 72%), and the median CCI was 2 in both cohorts. Median follow-up was 12.8 and 16.4 months for in zanu and acala cohorts, respectively. Median TTNT and OS were not reached for either cohort. With the unadjusted model, zanu had a longer TTNT (unadjusted HR, 0.88; 95% CI, 0.79-0.97; P=.009) and OS (HR, 0.72; 95% CI, 0.62-0.82; P<.001). After IPTW adjustment, zanu was associated with a significantly improved OS (IPTW-adjusted HR, 0.75; 95% CI, 0.65-0.86; P<.001) and TTNT (IPTW-adjusted HR, 0.89; 95% CI, 0.80-0.98; P=.02) compared with acala. **Conclusions:** In this real-world analysis, zanu monotherapy demonstrated significantly longer TTNT and improved OS compared with acala monotherapy. These findings suggest that zanu may offer superior outcomes in the real-world setting. Research Sponsor: BeOne Medicines, Ltd.

7046 **Poster Session**

Subsequent therapies and time to second progression-free survival events (PFS2) in treatment-naive chronic lymphocytic leukemia/small lymphocytic lymphoma (TN CLL/SLL) previously treated with zanubrutinib (zanu) or bendamustine-rituximab (BR) in SEQUOIA. First Author: Constantine Si Lun Tam, Alfred Hospital and Monash University, Melbourne, VIC, Australia

Background: Cohort 1 of the phase 3 SEQUOIA trial assessed zanu, a next-generation BTKi, compared to BR in TN CLL/SLL without del(17p). Zanu previously demonstrated sustained superiority in progression free survival (PFS) and time to next treatment (TTNT) vs BR. However, evidence regarding outcomes on subsequent therapies (tx) after progressive disease (PD) on zanu remain limited. Here, we present results on follow-up (FU) tx after zanu, including PFS2. **Methods:** Pts without del(17p) were randomized to receive continuous zanu or six cycles of BR. Pts who received BR could crossover to receive zanu after PD. All pts were followed post-PD for details on any subsequent anti-CLL treatments. This analysis evaluated PFS, TTNT, TTNT or death (TTNT-D) and PFS2. P-values are descriptive. **Results:** In total 479 pts were randomized; 241 to zanu and 238 to BR. Baseline demographics and disease characteristics were well balanced between the arms. As of 31 October 2025, median FU was 78.7mo (range, 0.0-96.0). Sustained PFS superiority with zanu vs BR was observed (HR, 0.28; 95% CI, 0.21-0.38; P<.0001) with 78mo PFS estimates of 70.9% (95% CI, 64.2-76.6) for zanu and 28.6% (21.7-35.8) for BR. Overall, 211/241 (87.6%) of pts treated with zanu had not received subsequent tx and 34 pts had died without subsequent tx. TTNT and TTNT-D favored zanu over BR (HR, 0.23 [95% CI, 0.15- 0.35; P<.0001] and 0.37 [0.27-0.50; P<.0001], respectively). Overall, 24/241 (10.0%) zanu pts and 82/238 (34.0%) BR pts had PD after study treatment and received subsequent tx. Of the 24 zanu pts receiving subsequent tx after PD, 13 (54.2%) received BCL2i-based regimens, 8 (33.3%) received chemoimmunotherapy (CIT) (incl. anti-CD20 antibody monotherapy), and 3 (12.5%) received BTKi. Of the 82 BR pts receiving subsequent tx after PD, 77 (93.9%) received BTKi (incl. 71 crossover pts), 3 (3.7%) received BCL2i-based regimens and 2 (2.4%) received CIT. Median time from PD following first tx to initiation of next tx was 2.1mo for zanu (range 0-25.7) and 7.4mo (0.3-48.0) for BR. Zanu pts who had PD and received subsequent BCL2i-based tx had a median FU of 33.5mo from initiation of next-line tx. Among these pts, 10 remain alive and without PD, two had died, and one had PD. Overall, PFS2 significantly favored zanu over BR (HR, 0.66; 95% CI, 0.45-0.98; P<.05) with 78mo PFS2 estimates of 81.3% (95% CI, 75.6-85.8) vs 73.8% (67.2-79.3), respectively. **Conclusions:** PFS2 remained superior with zanu despite broad use of novel subsequent tx (including crossover) in BR pts. Importantly, BCL2i-based salvage after initial zanu achieved high PFS rates at almost 3 years of FU. Together, these findings support that initial zanu provides durable benefit while preserving sensitivity to effective subsequent tx. Clinical trial information: NCT03336333. Research Sponsor: BeOne Medicines, Ltd.

7047 **Poster Session**

Real-world outcomes among Medicare beneficiaries treated with first-line (1L) Bruton tyrosine kinase inhibitors (BTKis) for chronic lymphocytic leukemia (CLL). First Author: Daniel Arthur Ermann, Huntsman Cancer Institute, University of Utah School of Medicine, Salt Lake City, UT

Background: Covalent BTKi monotherapies are standard of care for 1L CLL in the US. However, there is a lack of head-to-head BTKi trials in the 1L setting, and previous real-world studies had limited sample size and follow-up time. We used a large US database to evaluate clinical outcomes among patients (pts) treated with BTKis for 1L CLL. **Methods:** This retrospective cohort study utilized the de-identified Medicare Fee-For-Services database. Eligible pts included those with a CLL/SLL diagnosis at age ≥65 y who started 1L BTKi monotherapy between 01/01/2020 and 06/30/2025 and ≥12 months (mos) enrollment pre-1L. Outcomes included real-world overall survival (OS), time to next treatment (tx) or death (TTNT), and time to tx discontinuation or death (TTD) from 1L start. Landmark tx and survival probabilities at 12 and 24 mos were estimated using Kaplan–Meier methods. Adjusted hazard ratios (aHRs) and 95% CIs were estimated using Cox proportional hazard models, adjusting for age, sex, race/ethnicity, Charlson Comorbidity Index (CCI) and year of 1L start. Subgroup analysis was performed by age groups (65-74, 75-84, ≥85 y). **Results:** A total of 10,523 pts were included (zanubrutinib [zanu]:3006; acalabrutinib [acala]: 4309; ibrutinib [ibr]:3208). Median age at 1L was 77 y for zanu and acala, and 76 y for ibr. Most pts were male (58%), non-Hispanic White (91%), and resided in urban areas (78%). Median CCI score was 4 for zanu and acala, and 3 for ibr. At baseline, hypertension was 65% overall, and atrial fibrillation was 17% for zanu and acala, and 12% for ibru. Median follow-up was 16 mos (range: 0-61) for zanu, 21 mos (0-69) for acala and 35 mos (0-69) for ibr. Median OS was not reached (NR) for all groups. Median TTNT was NR for zanu (95% CI, 45-NR), 40 mos (38-42) for acala, and 30 mos (29-32) for ibr. Median TTD was NR (NR-NR) for zanu, 24 mos (22-25) for acala, and 14 mos (13-15) for ibr. Pts on zanu had higher probability of survival, not advancing to next line of therapy and not discontinuing tx at 12 and 24 mos, than those receiving acala and ibr (Table; with 95% CIs). After adjusting for baseline factors and year of 1L, pts on zanu had a statistically significantly lower risk of death, advancing to next line, or discontinuing tx, than those on ibr or acala. Similar results were observed across age subgroups. **Conclusions:** In this large cohort of pts aged ≥65 yrs with longest follow up to date, zanu monotherapy was associated with better survival and tx outcomes, compared to ibr and acala. Research Sponsor: BeOne Medicines, Ltd.

	OS			TTNT			TTD		
Tx	**12 mos %**	**24 mos %**	**aHR**	**12 mos %**	**24 mos %**	**aHR**	**12 mos %**	**24 mos %**	**aHR**
Zanu	91 (90-92)	86 (84-87)		82 (81-94)	71 (69-74)		72 (71-74)	63 (61-65)	
Ibr (ref)	85 (84-86)	75 (74-77)	0.64 (0.54-0.77)	74 (72-75)	56 (55-58)	0.63 (0.55-0.71)	53 (51-55)	35 (33-37)	0.57 (0.51-0.64)
Acala (ref)	87 (86-88)	80 (78-81)	0.77 (0.66-0.88)	78 (77-80)	67 (65-68)	0.87 (0.78-0.96)	63 (61-64)	49 (47-51)	0.86 (0.78-0.94)

7048 **Poster Session**

Targeted combination therapies for untreated chronic lymphocytic leukemia: A network meta-analysis of randomized trials. First Author: Owais Gul, United Health Services Hospitals, Johnson City, NY

Background: Treatment options for previously untreated chronic lymphocytic leukemia (CLL) have expanded to include both fixed-duration venetoclax-based combinations and continuous Bruton tyrosine kinase (BTK) inhibitor therapy. While both approaches improve outcomes compared with chemoimmunotherapy, their relative benefits and risks have not been well defined. We performed a network meta-analysis to compare the efficacy and safety of these frontline targeted strategies. **Methods:** We searched MEDLINE, Embase, PubMed, the Cochrane Library, Web of Science, and major oncology conference proceedings from inception through November 2025. Phase II–III randomized trials enrolling treatment-naïve adults with CLL and evaluating venetoclax-based combinations or continuous BTK inhibitor–based regimens were included. A frequentist random-effects network meta-analysis was conducted. Treatment effects were summarized using hazard ratios (HRs) for progression-free survival (PFS) and risk ratios (RRs) for grade $\geq$3 adverse events. **Results:** Eight randomized trials including 3,056 patients and five treatment regimens were analyzed. All targeted therapy–based regimens significantly improved PFS compared with chlorambucil plus obinutuzumab. The greatest PFS benefit was observed with ibrutinib plus obinutuzumab (HR 0.41; 95% CI, 0.29–0.59), followed by venetoclax plus ibrutinib and venetoclax plus obinutuzumab. Acalabrutinib plus obinutuzumab also significantly reduced the risk of progression (HR 0.52; 95% CI, 0.41–0.67). No significant inconsistency was detected across the treatment network. Safety outcomes varied by regimen, reflecting differences in treatment duration and mechanism of action. **Conclusions:** In previously untreated CLL, fixed-duration venetoclax-based combinations achieve PFS outcomes comparable to continuous BTK inhibitor–based therapy, with distinct safety and treatment exposure profiles. These findings support personalized frontline treatment selection based on patient comorbidities, tolerability, and preference for time-limited therapy. Research Sponsor: None.

7049 **Poster Session**

Outcome comparison of once versus twice daily dosing of zanubrutinib. First Author: Allison Kagerer, Weill Cornell Medicine, New York, NY

Background: Zanubrutinib, a Bruton tyrosine kinase inhibitor (BTKi), approved as frontline treatment in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), can be dosed as 320mg once daily (QD) or 160mg twice daily (BID). In phase I trials 160mg BID and 320mg QD achieved comparable BTK occupancy in peripheral blood. While most clinical trials utilized BID dosing, there is limited data evaluating outcomes between regimens. Thus, we performed a retrospective study comparing outcomes of QD vs BID dosing of zanubrutinib in frontline CLL/SLL patients (pts). **Methods:** We conducted a single center retrospective study evaluating pts with CLL/SLL treated with zanubrutinib QD vs BID at Weill Cornell Medical Center (May 1, 2020 - Feb 1, 2025). Included CLL/SLL pts were treated with frontline zanubrutinib and separated into 3 groups: 320mg QD (Group 1), 160mg BID (Group 2) and dose switch (Group 3). Pearson's Chi-squared test and Fisher's exact test were used to compare baseline characteristics. Progression-free survival (PFS) and overall survival (OS) were evaluated with Kaplan-Meier (KM) method and log-rank test was used to compare KM curves; however, few events limited statistical power and prevented formal survival comparison and are presented as descriptive only. The median follow-up time was estimated by reverse KM method. **Results:** We identified 23 pts initiated on QD dosing, 43 pts initiated on BID dosing, and 33 pts who switched groups. Thirty pts switched from BID to QD and 3 pts from QD to BID. Median follow up time was 28.4 months. Median overall age was 71 with 60% male. There were no differences in age, sex, immunoglobulin heavy chain gene (IGHV) mutational status or incidence of complex karyotype, del11q, del13q, del17p, trisomy 12 and *TP53* mutations. There was 1 death (Group 2) due to a second cancer. OS KM curves visually appeared similar (p=0.62). One pt in Group 2 and 2 pts in Group 3 progressed on zanubrutinib. PFS KM curves were visually similar (p=0.88). Twenty-two (22.2%) pts discontinued therapy due to intolerance. In Group 1, one pt (4.3%) discontinued for hypertension (HTN). In Group 2, 17/43 (39.5%) pts discontinued for rash (29.4%), infection (17.6%), bruising/bleeding (17.6%), HTN (11.7%), atrial fibrillation (11.7%) and diagnosis of second cancer (11.7%). In Group 3, 4/33 (12.1%) pts stopped for rash (50%) and HTN (50%). Zanubrutinib cessation was lower in QD vs BID ($p < 0.002$). **Conclusions:** We retrospectively compared QD vs BID dosing of zanubrutinib to evaluate impact on outcomes. While lack of progression and death limited our ability to make definitive statements on PFS or OS, we observed overlap of KM curves with 2 years of follow-up. We observed a lower treatment discontinuation rate with QD dosing. Our results suggest QD dosing in frontline CLL/SLL may improve tolerability while maintaining comparable efficacy. Further research is needed to confirm real-world non-inferiority of these safety and survival outcomes. Research Sponsor: None.

7050 **Poster Session**

Hematologic and cardiovascular outcomes of SGLT2 inhibitors in patients with chronic lymphocytic leukemia and type 2 diabetes: A real-world TriNetX analysis. First Author: Safa Saadat Afridi, SUNY Upstate Medical University, Syracuse, NY

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) exhibit biologically plausible metabolic and immunomodulatory effects beyond glycemic control that may be relevant in chronic lymphocytic leukemia (CLL), by reducing insulin resistance, activating AMPK signaling, suppressing downstream PI3K/AKT/mTOR activity, and improving cellular metabolic homeostasis. SGLT2i also decrease systemic and adipose-derived inflammation by inhibiting the NLRP3 inflammasome, reducing IL-6 and TNF-α levels, and mitigating oxidative stress. Improved mitochondrial efficiency and modulation of HIF-1α signaling may influence leukemic cell survival and immune exhaustion, suggesting a plausible role for SGLT2i in reducing infection risk, cardiovascular events, and survival outcomes in patients with CLL. However, real-world clinical evidence remains limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Analytics Network to evaluate outcomes associated with SGLT-2i use in adults with CLL and type 2 diabetes mellitus. SGLT-2-exposed and non-exposed cohorts were compared for infectious complications, hematological outcomes like cytopenias, cardiovascular (CV), and all-cause mortality. Propensity score matching minimized confounding due to contemporary CLL therapies, baseline demographics, comorbidities, and treatment-related outcomes. Time-to-event outcomes were analyzed using Kaplan-Meier and Cox models. **Results:** After propensity score matching, with comparable mean short and long term follow durations (60-821 days), SGLT2 inhibitor use was associated with a significantly lower risk of pneumonia (5.4% vs 8.0%; HR 0.70, 95% CI 0.56-0.89) and CV mortality (13.9%, vs 21.9%) with improved survival on KM analysis ($p<0.001$; HR-0.70, 95% CI 0.59-0.83). A modest reduction in sepsis was observed in SGLT2i users (4.7% vs 6.0%), but did not reach statistical significance (HR 0.82, 95% CI 0.65-1.05). All-cause mortality was numerically lower in the SGLT2 cohort (7.4% vs 8.5%), but no significant difference in survival was observed (HR 0.91, 95% CI 0.76-1.10). The SGLT2i group showed lower thrombocytopenia risk and a similar rare risk of AIHA between the two cohorts, with no significant difference in time-to-event analysis, suggesting that SGLT2 inhibitors may preferentially reduce selective infectious complications and CV mortality without significant improvement in overall mortality. **Conclusions:** SGLTI might have biologically plausible cardioprotective, metabolic, and immunomodulatory effects that may improve outcomes related to inflammation and infection, and reduce CV mortality in CLL, without a demonstrable short-term overall mortality benefit. Longer follow-up and prospective studies are needed to define the durability of these effects and their impact on survival. Research Sponsor: None.

7051 **Poster Session**

Impact of SGLT2 inhibitors on clinical outcomes in diabetic patients with CLL receiving BTK inhibitors: A global propensity-matched study. First Author: Angimar Uriepero-Palma, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: Diabetic patients with chronic lymphocytic leukemia (CLL) receiving Bruton's tyrosine kinase inhibitors (BTKi) face intersecting challenges of metabolic dysfunction, immune dysregulation, and treatment-related toxicities, including cardiovascular complications and increased susceptibility to infections. Sodium–glucose cotransporter 2 inhibitors (SGLT2i), have emerged as a pleiotropic cardio-renal-metabolic therapeutic class with benefits extending beyond glycemic control. We hypothesize that early initiation of SGLT2i in diabetic patients with CLL may mitigate BTKi–associated toxicities and improve long-term treatment tolerability and clinical outcomes. **Methods:** We used the TriNetX Global Collaborative Network to identify patients with CLL (C91.1, C83.00) and diabetes (E08–E13) treated with BTK inhibitors (ibrutinib, acalabrutinib, or zanubrutinib), comparing those with and without SGLT2 inhibitor exposure. Propensity score matching adjusted for demographic, metabolic, cardiovascular, and renal confounders, as well as hypoglycemic and cardiovascular medications. After matching, 1,102 patients (551 per cohort) were included. Outcomes were assessed within 3 years of the index event, and hazard ratios (HRs) with 95% confidence intervals were estimated. **Results:** The 3-year all-cause mortality was significantly lower with concurrent BTKi and SGLT2i compared with BTKi alone (HR 0.50, 0.38–0.66), corresponding to a 3-year overall survival of 77% versus 62% ($p < 0.0001$). Hematologic toxicity was also significantly lower in the SGLT2i cohort, including grade 3 thrombocytopenia (HR 0.632, 0.461–0.866), grade 3 anemia (HR 0.532, 0.422–0.671), and neutropenia (HR 0.618, 0.419–0.911). Infectious complications were less frequent in the SGLT2i group, with a significant decrease in neutropenic fever (HR 0.393, 0.221–0.698), sepsis (HR 0.686, 0.504–0.934), and pneumonia (HR 0.65, 0.506–0.835). Likewise, a lower incidence of Deep vein thrombosis and pulmonary embolism was found in the SGLT2i cohort (0.555, 0.35–0.879). Surprisingly, cardiovascular outcomes were not significantly different between groups, including hypertension (HR 1.10, 0.961–1.278), atrial fibrillation (HR 1.073, 0.86–1.339), and heart failure (HR 1.128, 0.919–1.385). **Conclusions:** SGLT2i use was associated with significantly longer 3-year overall survival and lower hazards of severe cytopenias and serious infections in diabetic patients with CLL receiving BTK inhibitors, with no meaningful differences in major cardiovascular outcomes. The mechanisms underlying these associations is unclear; however, emerging evidence suggests that SGLT2i may exert immunomodulatory effects and have been shown to reduce tumor cell proliferation in breast cancer models. Further studies are warranted to confirm the role of SGLT2i in diabetic CLL patients. Research Sponsor: None.

7052 **Poster Session**

Real-world overall survival outcomes of BTK inhibitors vs. venetoclax-based therapy as second-line treatment for chronic lymphocytic leukemia. First Author: Mariah Black, Texas Tech University Health Sciences Center El Paso, El Paso, TX

Background: Chronic lymphocytic leukemia (CLL) is a B-cell malignancy with highly variable clinical behavior. The treatment landscape has shifted from chemo-immunotherapy to targeted agents, specifically Bruton's tyrosine kinase inhibitors (BTKi) and venetoclax (BCL-2 inhibitor). While both are established first-line options, the optimal treatment sequence to maximize long-term survival remains undefined. This real-world analysis evaluates overall survival (OS) when utilizing BTKi or venetoclax-based therapy as second-line (2L) treatment. **Methods:** This retrospective, propensity-matched cohort study utilized de-identified electronic medical record data from the TriNetX network (through Jan. 2026), covering 189 million patients. Adult patients with CLL (ICD-10: C91.1) were identified based on treatment sequencing of 1L BTKis followed by 2L Venetoclax or vice-versa. The index event was the initiation of 2L therapy with either a BTKi or venetoclax. Patients receiving traditional chemotherapy were excluded from analysis. To minimize confounding, 1:1 Propensity Score Matching (PSM) was performed using a greedy nearest-neighbor algorithm based on demographics (age, sex, race/ethnicity) and comorbidities (hypertension, ischemic heart disease, diabetes, CKD, COPD, obesity). Standardized mean differences (<0.1) confirmed covariate balance. The primary endpoint was OS through 10 years. **Results:** A total of 5,841 patients met inclusion criteria (BTKi n=2,589; venetoclax n=2,892). After PSM, 1,959 patients were included per cohort. Ten-year OS was significantly higher in patients receiving BTKi as 2L therapy compared to venetoclax (71.5% vs. 68.0%; HR 0.651, 95% CI 0.55-0.77; $p<0.0001$). Median follow-up duration was longer for the BTKi group (1,287 days) than the venetoclax group (639 days). **Conclusions:** In this real-world analysis, treatment sequence with Venetoclax (1L) and BTKis (2L) was associated with a significant long-term survival advantage compared to venetoclax. The observed reduction in mortality risk (HR 0.651) suggests that treatment sequencing of immunotherapy with Venetoclax followed by a BTKi may offer superior clinical outcomes for treatment of CLL. While these results support preferential sequencing of BTKis after venetoclax, additional prospective studies are needed for further evaluation and confirmation. Research Sponsor: None.

7053 **Poster Session**

Modern Hodgkin lymphoma treatments to reduce second cancer risks: Influence of risk-adapted screening. First Author: Aislinn Macklin-Doherty, Institute of Cancer Research / Royal Marsden Hospital, London, United Kingdom

Background: Second primary malignancies (SPMs) are the leading cause of long-term treatment-related mortality in Hodgkin Lymphoma (HL). Although substantial improvements have been made to treatments over recent decades, few studies have demonstrated reduced SPM risk, particularly following modern treatments, and how risks should inform screening. **Methods:** We assembled a national cohort of 7,428 women treated for HL aged <36 across England & Wales 1954-2010, with 99% complete follow-up until 2018. We analyzed SPM incidence from national cancer registry linkage. Treatment data were collated from >250 treatment centers. Standardized incidence ratios (SIRs) and Absolute Excess Risks (AERs) for SPMs were calculated, and multivariable analyses (Hazard Ratios, HR) were undertaken to assess the impact of changes in treatment and assess changing incidence trends over time. **Results:** Twelve hundred women (16%) developed 1,467 SPMs with mean follow-up of 22 years (range 0-62 years). Overall SIR to develop any SPM was 3.3 (95% CI 3.1-3.5), with breast cancer contributing the greatest excess risk (AER 30.8 95% CI 27.7-34.1). Radiotherapy use halved from 1954-1980 to 2000-2010 (98% to 47%) and mean dose dropped from 48Gy to 33Gy. Conversely chemotherapy use doubled from 55% to 97%, with anthracyclines used in 94% and classic alkylators in 31% of treatments in the most recent period compared with 6% and 48% respectively pre-1980. Radiotherapy conferred the greatest treatment-specific risk factor for SPMs, (SIR 3.5 95% 3.3-3.7), with a strong dose-response relationship trend (HR 1.01/Gy $p<0.001$), and highest relative risks seen in those treated with radiotherapy aged <15years (SIR 7.4 (95% CI 5.7-9.1). There was a 25% reduction in SPM risk from the earliest treatment period (<1990) to most recent (2000-2010) and 34% reduction in solid SPM risk (Table). The decrease in risk for SPMs became smaller and non-significant after adjusting for reduced radiotherapy use and dose (HR 0.89, p_{trend} 0.11). There was no attenuation after adjustment for chemotherapy. Despite declining risks, risks remained significantly elevated beyond 40 years after treatment. **Conclusions:** Modern HL treatments are associated with a substantial reduction in SPM risks, which appears to be largely attributable to decreased radiotherapy use and dose. However large persistent excess risks, particularly for breast and lung cancers, underscore the need for targeted screening in high-risk survivors treated in more recent eras. Research Sponsor: National Institute of Health Research Biomedical Research Centre - Royal Marsden Hospital / Institute of Cancer Research; Breast Cancer Now; Cancer Research UK.

Risk of SPMs by treatment era.

SPMs & treatments	Treated <1990 HR (ref)	Treated 1990-1999 HR (95% CI)	Treated 2000-2010 HR (95% CI)	p_{trend}
All SPMs				
Any treatment	1.0	0.77 (0.65-0.90	0.75 (0.57-0.99)	0.001
Adjusted for radiotherapy & dose	1.0	0.83 (0.69-1.00)	0.90 (0.63-1.28)	0.11
Solid SPMs				
Any treatment	1.0	0.71 (0.60-0.85)	0.66 (0.48-0.90)	<0.001
Adjusted for radiotherapy & dose	1.0	0.79 (0.65-0.96)	0.81 (0.55-1.20)	0.03

7054 **Poster Session**

Invasive-field radiotherapy plus rituximab versus rituximab alone after response to immunochemotherapy in stage III follicular lymphoma: An open-label, multicenter, randomized clinical study. First Author: Tongyu Lin, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Background: Stage III follicular lymphoma (FL) remains incurable with immunochemotherapy followed by rituximab maintenance. Radiotherapy plays a critical role in the curative treatment of early-stage FL; however, its role in the management of stage III disease remains undefined. **Methods:** In this open-label, multicenter, randomized clinical trial, patients with stage III FL, who demonstrated complete or partial response without bulky after induction immunochemotherapy were enrolled. Eligible patients randomly assigned (1:1) to receive invasive field consolidation radiotherapy (IFRT) combined rituximab maintenance (IFRT+R arm) or rituximab maintenance alone (R arm). The dose of IFRT was 30Gy. The primary endpoint was 5-year progression-free survival (PFS), and the secondary endpoint was 5-year overall survival (OS). This study is registered with Chinese ClinicalTrials.gov, number ChiCTR2000032550. **Results:** Between January 2015 to January 2021, 152 eligible patients were randomly assigned to receive IFRT+R (n=74) or R alone (n=78). Baseline characteristics showed no significant differences between the two arms. After a median follow-up of 82 months, the 5-year PFS was 88.9% in IFRT+R group and 66.7% in R alone group (HR, 0.32; 95% CI, 0.16-0.66, P = 0.002). The 5-year OS was 97.3% in IFRT+R group versus 84.4% in R group (HR, 0.23; 95% CI, 0.07-0.81, P = 0.02). Treatment-related adverse events were more frequent in the IFRT+R arm than in the R arm (58% vs 38%), predominantly consisting of acute hematologic toxicities, including neutropenia (33% vs 26%) and leukopenia (34% vs 28%). Grade 3-4 toxicities were more common in the IFRT+R arm (27% vs 18%), and no treatment-related deaths were observed. **Conclusions:** Involved-field radiotherapy after effective systemic therapy significantly improved PFS and OS with manageable toxicity, highlighting its potential role in the management of stage III FL. Clinical trial information: ChiCTR2000032550. Research Sponsor: National Natural Science Foundation of China; U24A20679 and 82470237.

7055 **Poster Session**

Single-cell analysis and functional profiling of galectin-3 in the tumor immune microenvironment in transformed follicular lymphoma. First Author: Xiaohui Wang, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Histological transformation of follicular lymphoma (tFL) represents an aggressive subtype characterized by a complex and immunosuppressive tumor immune microenvironment (TIME). Therefore, it is urgent to investigate the characteristics of TIME and develop more effective immunotherapy strategies for tFL patients. **Methods:** Using single-cell RNA sequencing, a high-resolution landscape of the entire TIME ecosystem of follicular lymphoma (FL) and tFL patients is depicted. Findings were validated by multiplex immunofluorescence (mIF) staining, in vitro assays, and a mouse model. **Results:** Compared to FL patients, tFL patients exhibited a higher proportion of exhausted CD8+T cells expressing checkpoint receptors such as LAG3, CTLA4, PD-1, and HAVCR2. Notably, Galectin-3 expression was acquired by tumor cells after transformation, leading to enhanced Galectin-3–LAG3 interactions with $CD8^+$ T cells, as confirmed by mIF staining. In co-culture experiments, Galectin-3-overexpressing tumor cells impaired $CD8^+$ T cell proliferation and cytotoxicity, inducing an exhausted phenotype. Treatment with the Galectin-3 inhibitor GB1107 rescued T cell function. Similar T cell dysfunction and GB1107 response were observed in Galectin-3-overexpressing mouse xenograft model. Additionally, we identified an accumulation of MDSC-like monocytes and M2-like macrophages in tFL patients, further contributing to immune suppression. **Conclusions:** Galectin-3 drives T cell exhaustion and reshapes the immune microenvironment in tFL patients, promoting immune evasion and disease progression. Targeting Galectin-3 may represent a promising immunotherapeutic strategy for tFL patients. Research Sponsor: None.

7056 Poster Session

Diagnostic yield after pre-biopsy steroid administration in primary CNS high-grade B-cell lymphoma. First Author: Charmi Trivedi, Brown University Health, Providence, RI

Background: Primary central nervous system high-grade B-cell lymphoma (PCNSL) is typically diagnosed via brain biopsy. Corticosteroids are often administered pre-biopsy to reduce vasogenic edema, but are hypothesized to decrease diagnostic yield by inducing lymphocyte apoptosis. This study aims to evaluate whether steroid administration prior to biopsy affects the likelihood of obtaining a diagnostic result in pts with PCNSL. **Methods:** A retrospective chart review of Brown University Health pts (2015-2024) with PCNSL, including primary CNS diffuse large B cell lymphoma (DLBCL), was conducted. Collected variables included demographics (age, sex, ECOG), steroid dose, biopsy type (excisional, incisional, or stereotactic needle biopsy) and outcome of biopsy (diagnostic vs. undiagnostic). Statistical analysis comparing pre-biopsy steroid (PBS) group with steroid naive group was conducted using Chi-squared, Wilcoxon rank sum and Fisher's Exact test. **Results:** A total of 59 pts were found to have biopsy proven PCNSL and were included in statistical analysis. 53 pts had DLBCL and 6 had high grade PCNSL. Baseline demographics and biopsy types did not significantly differ between PBS group and steroid-naive pts ($p>0.05$). Among pts that received PBS, 35/35 (100%) had a diagnostic biopsy compared with 22/24 (92%) in pts who did not receive steroids. Pre-biopsy steroid use was not associated with a statistically significant difference in diagnostic yield, (Fisher's Exact p=0.16). As there were no non-diagnostic biopsies in the PBS group, the odds ratio was infinite and the upper confidence bound could not be estimated. Median dose of steroids was 213mg (prednisone equivalents; Q1 93mg, Q3 307mg). As all pts in the PBS group had diagnostic biopsies no analysis based on steroid dose could be conducted. All pts who received steroids had documented concern for vasogenic edema and steroids were not used for empiric treatment. **Conclusions:** In our cohort, pre-biopsy corticosteroid administration did not appear to affect diagnostic yield. There was no difference in the rate of diagnostic first biopsies between the PBS and steroid naive group. Among pts receiving steroids, all biopsies were diagnostic regardless of timing relative to biopsy or total steroid dose. Due to the small sample size and the universal diagnostic success, statistical comparisons were limited. These findings suggest that steroids may not compromise the diagnostic yield of PCNSL biopsies. Research Sponsor: None.

Clinical characteristics and biopsy outcomes.

	Steroid Naive N = 24	Steroids before Biopsy N = 35	p-value
Age	69 (Q1 63; Q3 73)	66 (Q1 57; Q3 75)	0.3
Female	15 (63%)	19 (54%)	0.5
Normal LDH	16 (94%)	12 (67%)	0.088
ECOG 2-4	4 (16.6%)	9 (27.3%)	0.6
DLBCL	21 (88%)	32 (91%)	0.33
Total steroid dose 100-700mg (in Prednisone Equivalents)	–	23 (70%)	
Steroids within 24 hours of biopsy	–	14 (40%)	
Stereotactic needle biopsy	18 (75%)	17 (52%)	0.3
Diagnostic Biopsy	21 (91%)	33 (100%)	0.2

7057 Poster Session

Chemotherapy use and survival by demographic and socioeconomic factors in primary central nervous system lymphoma: A population-based SEER analysis. First Author: Kevin Cheng Liang Wu, Zucker School of Medicine at Hofstra/Northwell, Staten Island University Hospital, Staten Island, NY

Background: Primary central nervous system lymphoma (PCNSL) is a rare non-Hodgkin lymphoma confined to the brain and spinal cord. Despite the introduction of rituximab to modern systemic therapy, previous population-based studies suggest that survival disparities by race and socioeconomic status persist. This study uses chemotherapy utilization modeling and contemporary 2000–2022 data to quantify the real-world survival impact of chemotherapy underuse across ethnic and neighborhood income strata in adults with PCNSL. **Methods:** Adults (≥20 years) with histologically confirmed PCNSL diagnosed from 2000–2022 were identified from SEER 21 registries. Patients with concurrent systemic lymphoma were excluded. Chemotherapy receipt was coded as yes vs no/unknown; with blank fields excluded. Binary logistic regression estimated odds of receiving chemotherapy by demographics. Multivariable Cox proportional hazards models evaluated associations of age, sex, race, neighborhood median household income (MHI), rural–urban residence, and chemotherapy with cause-specific survival. MHI was categorized into quintiles derived from the cohort distribution (approximately equal case counts per band). Kaplan–Meier methods estimated cause-specific survival and median survival times. **Results:** A total of 9,533 adults met the inclusion criteria. Compared with Whites, Black (OR 0.42, 95% CI 0.35–0.49) and Hispanic patients (OR 0.75, 95% CI 0.66–0.84) were less likely to receive chemotherapy; patients from neighborhoods with MHI < $65k also had reduced chemotherapy use versus ≥$100k (OR 0.53, 95% CI 0.45–0.62). Median survival was 64 months for patients receiving chemotherapy versus 3 months for those with no/unknown chemotherapy. Median survival by race was 17 months in Black patients, 25 months in Whites, and 38 months in Hispanics. Median survival was 14 months in the lowest MHI band (<$65k) and 46 months in the highest (≥$100k). In Cox models, lack of chemotherapy was associated with more than twice the hazard of lymphoma-specific death (HR 2.29, 95% CI 2.17–2.44). After adjustment for age, sex, race, MHI, residence, and chemotherapy; Black patients had higher mortality than Whites (HR 1.22, 95% CI 1.10–1.36), female gender had improved survival than males (HR 0.88, 95% CI 0.833-0.929), and MHI < $65k was associated with worse survival versus ≥$100k (HR 1.20, 95% CI 1.09–1.32). **Conclusions:** In this cohort of adults with PCNSL, chemotherapy use, race, neighborhood income, and age were powerful independent determinants of cause-specific survival. Chemotherapy underuse was concentrated among Black, Hispanic, and lower-income patients and was associated with a dramatic survival penalty, indicating that inequities in access to systemic therapy are likely major drivers of persistent racial and socioeconomic survival gaps in PCNSL. Research Sponsor: None.

7058 Poster Session

Navigating the post–covalent bruton tyrosine kinase inhibitor (cBTKi) landscape in mantle cell lymphoma (MCL): Real-world insights on treatment patterns, discontinuation, and healthcare resource utilization (HCRU). First Author: Alvaro Jose Alencar, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL

Background: cBTKis have become standard therapy for relapsed/refractory MCL and are rapidly advancing to the first-line setting. However, real-world evidence on clinical and economic outcomes following cBTKi therapy is limited. Treatment patterns, time to treatment discontinuation (TTD), and HCRU were evaluated among patients (pts) with MCL previously treated with cBTKis. **Methods:** This retrospective observational study used claims data from the Symphony Integrated Dataverse (Jan 2020-Aug 2025) to identify adults with MCL who received a cBTKi in any line of therapy (LOT) and, following discontinuation, initiated another treatment. Post-cBTKi regimens were categorized as B-cell lymphoma 2 inhibitor (BCL2i), cBTKi, noncovalent BTKi (ncBTKi), chimeric antigen receptor T-cell therapy (CAR-T), chemo±immunotherapy (C±IT), and other. TTD and HCRU (outpatient/inpatient/other medical, reported per-patient-per-month [PPPM]), were assessed for regimens received post cBTKi. **Results:** Of 10,519 total US pts with MCL, 571 were previously treated with cBTKis and received a subsequent therapy (median age, 72.0 years; ≥65 years, 77%; male, 74%; White non-Hispanic, 67%; Medicare, 62%). Regimens received in a subsequent LOT after cBTKi included cBTKis (38%), ncBTKis (32%), C±IT (11%), BCL2is (9%; monotherapy 7%), CAR-T (2%), and other (8%). Median TTD was longest with cBTKis (365 days), followed by ncBTKis (206 days), and shortest with BCL2is (140 days). Mean HCRU PPPM was lowest with cBTKis (outpatient, 1.21; inpatient, 0.20; other medical, 1.07) and highest with CAR-T (outpatient, 10.63; inpatient, 1.89; other medical, 1.55). **Conclusions:** In this real-world analysis, pts with MCL who previously received cBTKis were most frequently re-treated with cBTKis, highlighting the need for novel treatment options in the post-cBTKi setting. TTD was greatest in pts who received cBTKis or ncBTKis and shortest in those treated with BCL2is. HCRU burden was lowest for pts who received cBTKis and highest for those treated with CAR-T. Further research, including an understanding of the reasons for re-exposure to cBTKis, is warranted to confirm these findings. Research Sponsor: BeOne Medicines, Ltd.

TTD and HCRU by MCL treatment regimens received post cBTKi.

Outcomes	All N=571	cBTKi n=215	ncBTKi n=182	C±IT n=62	BCL2i n=53	CAR-T n=12
Follow-up, median (IQR), days	294 (118-628)	414 (206-762)	189 (89-453)	330 (116-727)	256 (70-844)	412 (216-912)
TTD, median (95% CI), days	222 (181-281)	365 (278-460)	206 (173-304)	169 (112-183)	140 (100-315)	NA
HCRU, mean (SD), PPPM						
Outpatient	1.95 (2.82)	1.21 (1.61)	1.48 (2.19)	2.19 (2.65)	2.34 (2.70)	10.63 (5.05)
Inpatient	0.34 (0.91)	0.20 (0.67)	0.33 (0.75)	0.29 (0.82)	0.43 (1.22)	1.89 (1.89)
Other medical services	1.47 (2.62)	1.07 (1.93)	1.35 (2.54)	2.54 (3.59)	1.64 (2.82)	1.55 (1.70)

7059 Poster Session

Efficacy, safety, and genetic analysis of orelabrutinib combined with rituximab as first-line systemic treatment for marginal zone lymphoma. First Author: Xian Li, The Second Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Background: Marginal zone lymphoma (MZL) is a heterogeneous B-cell malignancy that is often managed with chemoimmunotherapy in the first-line setting, but chemotherapy entails considerable toxicity. Orelabrutinib, a novel oral BTK inhibitor which offers improved target selectivity and fewer off-target effects. This study evaluates the chemo-free combination of orelabrutinib plus rituximab in untreated MZL. **Methods:** This is a prospective, single-arm, multicenter phase II clinical trial (NCT07022223). Patients with untreated MZL who met ECOG criteria of 0–2 and were in need of treatment, or who had failed local, were eligible. All participants will receive induction therapy with the orelabrutinib and rituximab regimen. The treatment cycle is 28 days, with a total of 4~6 cycles. The induction treatment period is as follows: Cycle 1: Rituximab, 375 mg/m², on day 1. Cycles 2-6: Orelabrutinib, 150 mg, once daily orally, from day 1-28, plus rituximab 375 mg/m² on day 1. Patients who achieve a partial response (PR) or better will enter a 2-year maintenance period with orelabrutinib. The primary endpoint is the overall response rate (ORR). Secondary endpoints include complete response (CR) rate, PR rate, progression-free survival (PFS), and overall survival (OS). Safety is assessed by monitoring adverse events (AEs). **Results:** From March 2025 to December 2025, a total of 40 patients with MZL (32 MALT, 6 NMZL, 2 SMZL) were enrolled. The median age at diagnosis was 68 years (range 44–84), and 82.5 % of patients were older than 60 years. 21 (52.5%) were female. Most patients had an ECOG score of 0-1 (28/40), Ann Arbor Stage III-IV disease (35/40). Twelve patients had an MZL-International Prognostic Index score of ≥2. Thirteen patients had failed prior local therapy, the majority of whom had undergone surgical resection. After three cycles, 25 patients were evaluable, with an ORR of 80 % (20/25) and a CRR of 24 %. Following six cycles, 13 patients were evaluable, achieving an ORR of 100 % (13/13) and a CRR of 62 % (8/13). The median time to response was 72 days. With a median follow-up of 5.7 months (range, 5.1-6.8), the median PFS and OS were not reached, the 1-year PFS rates were 97.2% and the 1-year OS rates were 100%. Next-generation sequencing (NGS) was performed on 16 patients, a total of 158 mutated genes were identified, with missense mutations predominating (62.7%). The most frequently mutated genes were NOTCH2, FAT4, LRP1B, PCLO, and SYNE1, all at 31.2 %. Treatment was generally well tolerated, only 13 patients experienced adverse events, the most common adverse events were anemia (15 %), infection (12.5 %) and neutropenia (10 %). Notably, BTK inhibitor–associated atrial fibrillation (0 %) and bradycardia (0 %) were absent. **Conclusions:** The combination of orelaburtinib and rituximab shows significant activity in MZL, with a manageable toxicity profile. Clinical trial information: NCT07022223. Research Sponsor: None.

7060 **Poster Session**

Diagnostic accuracy of circulating tumor DNA for post-remission surveillance in diffuse large B-cell lymphoma: A systematic review and meta-analysis. First Author: Mohammad Ahsen Soomro, Internal Medicine, The Wright Center for Graduate Medical Education, Scranton, PA

Background: Relapse after complete remission remains a major cause of treatment failure in Diffuse Large B-Cell Lymphoma (DLBCL). Standard surveillance using clinical assessment and imaging often detects recurrence after substantial tumor regrowth. Circulating tumor DNA (ctDNA) has emerged as a promising biomarker for minimal residual disease detection; however, its diagnostic accuracy for relapse surveillance in DLBCL has not been systematically quantified. **Methods:** A systematic review and meta-analysis was performed per a prespecified PROSPERO protocol (CRD420251179858). MEDLINE, Embase, CENTRAL, and major conference proceedings were searched through October 2025. Following systematic screening of B-cell non-Hodgkin lymphoma studies, those eligible for quantitative synthesis enrolled adults with DLBCL in complete remission undergoing post-treatment ctDNA surveillance, with clinically or radiologically confirmed relapse as the reference standard. Studies were included if sufficient data were available to construct 2×2 contingency tables. Pooled sensitivity and specificity were estimated using a bivariate random-effects logistic regression model with a logit link, accounting for between-study heterogeneity. A continuity correction of 0.5 was applied to all cells in studies with zero counts prior to model fitting. **Results:** Three studies (N=157) comprising patients in complete remission after first-line therapy were included in the quantitative synthesis. Using a bivariate random-effects model, the pooled sensitivity of ctDNA for detection of clinical relapse was 58.6% (95% CI 32.2–80.8%), while pooled specificity was 93.9% (95% CI 83.6–97.9%), indicating high specificity but moderate sensitivity during surveillance. Specificity was consistently high, supporting strong rule-in performance. Sensitivity varied across studies (range: 31%–88%), likely reflecting differences primarily in sampling density, as well as assay platforms (tumor-informed Ig-HTS vs. targeted NGS). Across included cohorts, ctDNA positivity generally preceded or coincided with clinically detected relapse, while ctDNA negativity was associated with durable remission during follow-up. **Conclusions:** In patients with DLBCL in complete remission after first-line therapy, ctDNA surveillance demonstrates very high specificity but only moderate sensitivity for detection of clinical relapse. These findings support ctDNA as a highly specific rule-in biomarker for relapse during surveillance, potentially resolving ambiguity in equivocal imaging findings. However, its moderate sensitivity limits its standalone ability to detect relapse. Prospective validation of standardized testing intervals and assay harmonization are needed to optimize sensitivity before integration with standard monitoring strategies. Research Sponsor: None.

7061 **Poster Session**

Epcoritamab (epcor) + chemoimmunotherapy (CIT) in patients (pts) with relapsed/refractory large B-cell lymphoma (R/R LBCL) eligible for autologous stem cell transplant (ASCT): Pooled results from arms 4 and 10 of EPCORE NHL-2. First Author: Yasmin Karimi, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI

Background: Pts with R/R LBCL can have inadequate response to salvage treatment (tx), precluding ASCT. While CAR T therapies are standard of care in the 2L setting for pts with early relapse (< 12 mo of 1L tx), their use is limited by eligibility, accessibility, or cost. Regimens that enhance salvage tx response rates enabling pts to proceed to ASCT are needed. In Arms 4 and 10 of the phase 1b/2 EPCORE NHL-2 trial (NCT04663347), epcor + CIT showed high response rates in ASCT-eligible R/R LBCL. A pooled analysis of these data is reported. **Methods:** ASCT-eligible pts received epcor + rituximab, dexamethasone, cytarabine, and oxaliplatin/carboplatin (R-DHAX/C) (Arm 4) or epcor + rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) (Arm 10). After salvage tx, pts could proceed to ASCT or remain on epcor mono tx. ORR per investigator, DOCR, PFS, OS, and safety are reported. **Results:** The analysis included 63 pts (Arm 4: n = 29; Arm 10: n = 34). Baseline characteristics: median age 61 y (range 28–77), 68% male, 71% stage III/IV, 13% (8/33 assessed) high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* translocations (central lab), 8% prior CAR T. 79% (n = 50) were receiving 2L tx; 57% (n = 36) were receiving 2L tx and were refractory or had early relapse to 1L tx. Median relative CIT dose intensity was ≥ 80%. At 18.3 mo median follow-up, ORR and CR rates were 84% and 67% (Table). 57% (n = 36) proceeded to ASCT; 16% (n = 10) remained on epcor mono tx due to pt/physician decision. Median DOCR, PFS, and OS were not reached in pts who proceeded to ASCT or who remained on epcor. Similar outcomes were seen in 2L pts and across 2L pts with early and late relapse. Overall, the most common any-grade TEAEs were anemia (68%), thrombocytopenia (68%), and neutropenia (62%). CRS occurred in 48% of pts and ICANS in 3%; all events were grade 1–2. Serious infections occurred in 17%. TEAEs led to tx discontinuation in 11%. There were no fatal TEAEs. **Conclusions:** In this pooled analysis of ASCT-eligible pts with R/R LBCL, tx with epcor + salvage CIT resulted in high CR rates, enabling a large proportion of pts to proceed to ASCT. Deep, durable responses were seen in pts who underwent ASCT and those who continued epcor mono tx. A high CR rate was also observed in 2L pts with early relapse. Safety was consistent with prior reports. Dose intensity of CIT was not impacted. These findings support epcor-based combination salvage strategies to increase response depth and facilitate higher ASCT rates and possible cure in ASCT-eligible pts with DLBCL. Clinical trial information: NCT04663347. Research Sponsor: Genmab A/S and AbbVie.

	All pts (N = 63)	2L (n = 50)	2L with early relapse[a] (n = 36)	Proceeded to ASCT (n = 36)	Remained on epcor mono (n = 10)
ORR/CR, %	84/67	84/68	81/61	100/94	100/80
DOCR, 18-mo rate, %	79	80	81	83	64
PFS, 18-mo rate, %	62	62	58	80	67
OS, 18-mo rate, %	82	82	77	93	100

[a]Pts receiving 2L tx who were refractory to or progressed <12 mo of 1L tx.

7062 **Poster Session**

A real-world comparison of treatment and survival outcomes with zanubrutinib (zanu) and acalabrutinib (acala) monotherapy among patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) in the United States. First Author: Yucai Wang, Mayo Clinic Rochester, Rochester, MN

Background: MCL is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma that remains incurable. Bruton tyrosine kinase (BTK) inhibitors are an established standard of care for R/R MCL. However, comparative effectiveness data for different BTK inhibitors for R/R MCL are limited. This study evaluated the real-world effectiveness of zanu and acala in US patients with R/R MCL based on overall survival (OS) and time to next treatment (TTNT). **Methods:** A retrospective cohort study was conducted using Komodo health administrative claims data. Eligible patients were adults (aged ≥18 years) with ≥2 MCL diagnoses and continuous enrollment or activities within 1 year prior to and 3 months following the index date. Patients were required to initiate monotherapy with zanu (index period: November 2019 to August 2025) or acala (index period: October 2017 to August 2025) as a second-line or later (2L+) treatment, with index date defined as the first observed claim for zanu or acala. Patients with evidence of clinical trial participation, end stage renal disease or prior stem cell transplant were excluded. Outcomes included OS (time from index date to all-cause mortality) and TTNT (time from index date to subsequent therapy with an allowable gap of 120 days). If an outcome was not observed, patients were censored at the date of last activity or enrollment end date. Survival analyses were conducted using Kaplan-Meier estimates and Cox proportional hazards models. Inverse probability of treatment weighting (IPTW) was adjusted for age, sex, US region, treatment initiation year and Charlson Comorbidity Index (CCI). **Results:** In total, 2219 patients (zanu, n=931; acala, n=1288) were eligible and included in the study. The mean age was higher in the zanu (72.3 years; SD, 9.4) vs acala cohort (71.4 years; SD, 9.7). Most patients were male (zanu, 71%; acala, 75%), non-Hispanic white (zanu, 73%; acala, 74%), and the mean CCI was 3.5 (SD, 3.2) and 3.6 (SD, 3.1) in the zanu and acala cohorts, respectively. Median follow-up was 14.8 and 18.2 months in zanu and acala cohorts, respectively. Median TTNT was 26.7 months for zanu and 20.8 months for acala. Median OS was not reached for zanu and was 60.6 months for acala. In the unadjusted model, zanu had a longer TTNT (HR, 0.86; 95% CI, 0.76-0.97; *P*=.012) and OS (HR, 0.74; 95% CI, 0.62-0.88; *P*<.001). After IPTW adjustment, TTNT and OS favored zanu treatment (TTNT: IPTW-adjusted HR, 0.86; 95% CI, 0.76-0.98; *P*=.025; OS: IPTW-adjusted HR, 0.81; 95% CI, 0.68-0.98; *P*=.03). **Conclusions:** In this real-world analysis of US health claims data, zanu monotherapy demonstrated significantly longer TTNT and improved OS compared with acala in patients receiving 2L+ therapy for MCL. These findings support zanu as an effective BTK inhibitor for R/R MCL. Research Sponsor: BeOne Medicines, Ltd.

7063 **Poster Session**

Signatures of biological heterogeneity associated with treatment outcome in diffuse large B-cell lymphoma. First Author: Boya Wang, Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

Background: Genetic subtypes of diffuse large B-cell lymphoma (DLBCL) capture biological differences between tumors that influence the response to immunochemotherapy (Schmitz et al., NEJM 2018). However, nearly 40% of DLBCL cases remain unclassified. The addition of gene expression signatures can accelerate classification and inform therapeutic intervention. **Methods:** We generated single-cell RNA sequencing of 103 DLBCL patient biopsies from Weill Cornell Medicine, New York Presbyterian Hospital, and the National Institutes of Health. We also utilized bulk genomic data from a discovery cohort (n=311, Ennishi et al., J Clin Oncol 2019) and a validation cohort (n=574, Schmitz et al., NEJM 2018). **Results:** Single cell sequencing allowed us to isolate the malignant B cells and develop genetic subtype signatures. The MCD signature was associated with poor overall survival ($p<10^{-6}$), as was the BN2 signature within ABC tumors ($p<10^{-3}$). When applied to unclassified tumors, the subtype signatures identified characteristic genetic alterations including SLC1A5 mutations in MCD ($p<10^{-5}$), UBE2A mutations in BN2 ($p<10^{-13}$), C10orf12 truncations and copy number loss in EZB ($p<10^{-6}$), and SGK1 mutations in ST2 ($p<10^{-7}$). Moreover, we discovered that most DLBCL tumors (80%) contained two or more genetic subclones (median 2, range 1-5) based on DNA copy number differences. The genetic subclones had distinct phenotypes based on expression of six recurrent gene expression metasignatures, herein termed themes. The germinal center (GC) B cell, memory B cell, plasma cell, and pan-B cell themes reflect B cell differentiation whereas two other themes – cell cycle and cell growth – reflect proliferative and metabolic states that are independent of the differentiation states. Surprisingly, 23% of DLBCL (24/103) harbored genetic subclones expressing B cell differentiation themes that distinguished them from other malignant cells in the same tumor. The GC B cell theme was associated with a favorable response to R-CHOP chemotherapy ($p<0.02$), as expected, while the cell growth theme (but not the cell cycle theme) was associated with adverse survival ($p<0.02$). **Conclusions:** Our study revealed that genetic subtypes have distinct gene expression signatures. We further demonstrated a role for tumor subclones in generating intra-tumoral biological diversity. We developed signatures of inter and intra-tumoral heterogeneity that are associated with overall survival. Research Sponsor: U.S. National Institutes of Health.

7064 **Poster Session**

Differential clinical and economic signatures of CAR T-cell therapy in DLBCL across demographic and payer strata: A national analysis. First Author: Karnav Modi, University of Missouri Kansas City, Kansas City, MO

Background: Chimeric antigen receptor (CAR) T cell therapy has revolutionized care for relapsed/refractory diffuse large B cell lymphoma (DLBCL), yet granular delineation of real-world immune effector toxicities, organ-specific sequelae and economic burden across demographic and socioeconomic strata requires further exploration. **Methods:** Using the National Inpatient Sample (2017–2022), we identified adult DLBCL hospitalizations receiving CAR T through ICD-10-PCS codes. Cytokine release syndrome (CRS) [all grades - 2021–2022], immune effector cell–associated neurotoxicity syndrome (ICANS) [all grades – 2022], infections, cardiac events and acute kidney injury (AKI) were identified through ICD-10 codes. Age was stratified into 21-40, 41-60, 61-80 and >81 years. Payer groups were Medicare, Medicaid, Private and Uninsured. Races were White, African American, Hispanic and others [Pacific Islanders, Native Indians, Asians]. Chi-square analysis was performed, and multivariate regression adjusted for demographics, comorbidities, and hospital characteristics. **Results:** Across >11,000 weighted hospitalizations, inpatient mortality, all-grade CRS and ICANS were comparable across age, race, and payer groups ($p>0.05$). Inpatient mortality was numerically higher in other minor races (6.6%) vs White (3.3%), African American (3.1%), and Hispanic (0.9%; p=0.230). Any grade CRS was numerically higher in other minor races (72.5%) than in White (62.3%) and African American (60.6%; p=0.614). Any grade ICANS dispersion included 29.5% (White), 39.1% (African American), 22.5% (Hispanic) and 11.1% (Other; p=0.204). A race-specific signal for ICANS grade 5 (p=0.030) was seen, but numbers were small. Among cardiac events, arrhythmias rose from 7.6% (age 21–40 years) to 57.1% (age ≥81 years) ($p<0.001$). By payer, arrhythmias were highest in Medicare (31.2%; $p<0.001$). Other cardiac events including myocardial infarction, stroke and cardiogenic shock were similar across groups. Pneumonia rates varied by payer, peaking in the Uninsured (23.8%; p=0.010). Sepsis and septic shock rates showed no differences. AKI (p=0.007) rates showed differences but attenuated after adjustment. Hispanic and other minor races had lower adjusted costs than White (Odds ratio [OR] 0.9, p=0.046; OR 0.8, p=0.006), while ages 61–80 had higher adjusted costs vs 21–40 (OR 1.2, p=0.023). **Conclusions:** In this national cohort, CRS, ICANS and mortality were similar across demographic and payer strata, indicating consistent immune effector safety. Cardiac arrhythmia rates were higher among the elderly and Medicare beneficiaries. There were lower expenditures among minor race groups and higher costs in elderly. These findings highlight discrete domains of variability and suggest intensified cardiac surveillance in elderly and equitable resource allocation to optimize outcomes with CAR-T. Research Sponsor: None.

7065 **Poster Session**

Frontline intensified vs standard immunochemotherapy in high-risk diffuse large B-cell lymphoma: A systematic review and meta-analysis. First Author: Lauren Scarpetti, Department of Medicine, NYU Langone Health, New York, NY

Background: While the phase III CALGB 50303 trial comparing frontline REPOCH vs standard RCHOP for diffuse large B-cell lymphoma (DLBCL) showed comparable outcomes overall, it suggested a potential benefit of intensified therapy in high-risk patients, including high-grade (HG) and double/triple-expressor (DE/TE) disease. Subsequent studies evaluating REPOCH in HG and DE/TE DLBCL have been small, retrospective and non-randomized, with conflicting results. Despite limited evidence and greater toxicity, REPOCH is commonly used in these cohorts. We conducted a systematic review and meta-analysis to assess outcomes after frontline REPOCH vs RCHOP in HG and DE/TE DLBCL, comprising the largest high-risk cohort to date. **Methods:** Original research studies evaluating outcomes after frontline REPOCH or RCHOP in HG or DE/TE DLBCL from 2009 to 2025 were included. HG was defined by *MYC* translocation, including double/triple-hit (DH/TH; *MYC* and *BCL2* and/or *BCL6* translocation). DE/TE was defined by *MYC* and *BCL2* and/or *BCL6* by IHC. Studies were excluded if they had <10 subjects or used agents in addition to the RCHOP or REPOCH backbones. RCHOP-like regimens with comparative substitutions were included (e.g., RCOMP). We used random effects models to calculate pooled response rates and survival outcomes. **Results:** 69 studies were included with 3979 total patients (1818 HG; 2161 DE/TE). 2698 patients (68%) were treated with RCHOP, and 1281 (32%) with REPOCH. Limited reporting of patient characteristics in HG or DE/TE cohorts precluded multivariable analysis of prognostic factors. While overall response rate (ORR) did not differ between treatment groups (relative risk [RR] 1.04, CI 0.92-1.19), patients treated with REPOCH were more likely to achieve complete response (CRR; RR 1.12, CI 1.01-1.23). This difference was especially notable in the HG subgroup (RR 1.4, CI 1.21-1.61), but there was no difference in the DE/TE subgroup (RR 1.04, CI 0.93-1.17). Across all patients, REPOCH was associated with significantly improved progression-free survival (PFS; hazard ratio [HR] 0.5, CI 0.39-0.65) and overall survival (OS; HR 0.59, CI 0.43-0.82). Landmark 2-year PFS (65% vs 52%, p = 0.013) and OS (75% vs 50%, $p < 0.0001$) were significantly higher for REPOCH. Subgroup analysis showed significantly improved 2-year OS with REPOCH in both HG (72% vs 47%, $p < 0.0001$) and DE/TE (67% vs 51%, p = 0.032) disease. **Conclusions:** In this large cohort, REPOCH was associated with significantly improved CRR, PFS and OS relative to RCHOP in HG and DE/TE DLBCL. Reported patient characteristics were limited, and the REPOCH arm may have preferentially included younger patients with better performance status. Nevertheless, our analysis provides evidence in an area lacking randomized trial data. While not definitive, our findings support the common clinical practice of treating select high-risk patients with REPOCH. Research Sponsor: None.

7066 **Poster Session**

Differences in outcomes for elderly patients with DLBCL treated at academic vs community programs: A 10-year survival analysis. First Author: Carolina Velez-Mejia, Virginia Commonwealth University - Mays Cancer Center, Richmond, VA

Background: Diffuse large B-cell lymphoma (DLBCL) is an aggressive B-cell malignancy that primarily affects older adults. Optimal treatment management in the geriatric population is challenging due to the high-risk disease biology and their age-specific vulnerabilities. Combination chemotherapy is effective, however, due to frailty often a dose-reduced regimen is administered. This large population real-world study compares demographic, clinical and survival characteristics of patients older than 75 years and compares Academic Cancer Programs (ACP) vs Community Cancer Programs (CCP). **Methods:** A retrospective analysis using the National Cancer Database was conducted on 103,671 patients (ACP: 51,848; CCP: 51,823) diagnosed with DLBCL between 2004 and 2022 was carried out. ACP included academic and National Cancer Institute-designated research centers; CCP included community, comprehensive community, and integrated network cancer programs. Kaplan-Meier and Cox regression models were used to compare overall survival (OS), adjusting for: age, race/ethnicity, insurance status, Charlson-Deyo comorbidity score, and distance from treating facility. **Results:** Patients in ACP and CCP were mostly females with a median age of 81 years. For both cohorts the majority were non-Hispanics and Whites; however, for ACP it was noted a higher rate of Hispanics (6% vs 5%) and Blacks (5% vs 3%) compared to CCP. Most of the patients in both groups were from the Metropolitan area, but the median distance in miles for ACP was 9.0 vs 7.4 in CCP. Treatment rates were higher for ACP vs community settings (63% vs 59%, $p<0.001$), with more patients presenting at Stage IV (36% vs 33%, $p<0.001$). Better OS was noted in elderly patients treated at ACP, $p<0.001$. The median OS for ACP was of 1.79 years vs 1.50 years at CCP, which was consistent with a longer median follow up time of 17.7 months vs 14.1, $p<0.001$. This survival advantage remained consistent throughout long-term observation, with 2-year OS rates of 49% at ACP [CI: 0.48,0.49] vs 46% at CCP [CI: 0.459,0.468], 5-year OS of 34% [CI: 0.336,0.346] vs 32% [CI: 0.317,0.327], and 10-year OS of 16% [CI: 0.154,0.164] vs 15% [CI: 0.142,0.151], respectively. **Conclusions:** Among patients aged ≥75 years with DLBCL, OS differed by treatment facility type, with a statistically significant but modest survival advantage observed among patients treated at ACP compared with CCP (log-rank $p<0.001$). This difference occurred in the context of higher treatment rates and greater disease severity at presentation. Given the relatively small absolute survival differences, these findings suggest that care for older adults with DLBCL is largely standardized across practice settings; however, this highlights an opportunity to optimize treatment delivery and intensity, supportive care, and geriatric-focused management in both academic and community programs. Research Sponsor: None.

7067 **Poster Session**

Efficacy and tolerability of duvelisib in relapsed/refractory peripheral T-cell lymphoma: A multicenter real-world analysis. First Author: Priyanka Pullarkat, Washington University School of Medicine, St. Louis, MO

Background: Relapsed/refractory (R/R) peripheral T-cell lymphomas (PTCL) are a rare group of non-Hodgkin lymphomas with median survival at relapse of 6-10 months and few treatment options. Duvelisib is a g/Δ phosphatidylinositol 3-kinase inhibitor approved in CLL and NCCN compendium listed in PTCL. In indolent lymphomas, concerns for cumulative duvelisib toxicity limit its use. In contrast, studies in R/R PTCL show duvelisib to be well-tolerated. Therefore, we sought to assess the efficacy and tolerability of duvelisib in a real world setting in R/R PTCL. **Methods:** We conducted a retrospective analysis of patients with R/R PTCL treated with duvelisib from 2012-2025 at 12 centers. **Results:** We identified 207 patients with PTCL: nodal PTCL with TFH phenotype (n=106, 51%), PTCL-NOS (n=78, 38%), ALCL (n=16, 8%), enteropathy associated T-cell lymphoma (n=4, 2%), NK/T-cell lymphoma (n=2, 1%), adult T-cell leukemia/lymphoma (n=1, 0.5%). 90 patients (43%) were female. Median age was 64; median International Prognostic Index score 3. Median prior lines of therapy was 2 (range 1-9). 26% received frontline transplant (23% auto, 3% allo). 118 patients received single agent duvelisib; 89 patients received duvelisib in combination with other agents (66 romidepsin, 12 bortezomib, 4 azacitadine, 3 ruxolitinib, 4 other). Of patients with response data, ORR was 51% (94/186; 31% CR, 17% PR) with median OS 12 months. ORR in patients with TFH-phenotype vs. non-TFH phenotype was 60% and 41% respectively. ORR in patients treated with single agent duvelisib and duvelisib combinations was 46% (46/99; 29% CR, 17% PR) and 55% (48/87; 39% CR, 16% PR), respectively with no difference in OS. Median duration of therapy was 84 days; the most common reason for discontinuation was progression (41%, 76/186). 13% (25/196) underwent allo-SCT after duvelisib therapy. Toxicity data is summarized in our table. In patients receiving single agent duvelisib therapy, rates of cytopenia were lower (7% vs. 34%, $p<0.001$) and rates of colitis were higher (17% vs. 7%, p= 0.03). **Conclusions:** In this real world, multicenter analysis of patients with R/R PTCL treated with duvelisib-based regimens, the ORR of 51% was consistent with published trials. Duvelisib therapy was well tolerated and a minority required hospitalization for toxicity. This suggests that duvelisib is safe in patients with R/R PTCL who have poor prognosis and limited treatment options. Research Sponsor: None.

Adverse Event	Full Cohort n (%) n=207	Single agent n (%) n=118	Combination therapy n (%) n=89	Single vs. Combination p value	Steroid Given n (% full cohort)	Hospitalization n (% full cohort)
Rash	41 (20%)	24 (20%)	17 (19%)	0.83	23 (11%)	6 (3%)
Colitis	26 (13%)	20 (17%)	6 (7%)	**0.03**	20 (10%)	16 (8%)
Pneumonitis	7 (3%)	4 (3%)	3 (3%)	0.99	5 (2%)	3 (1%)
Cytopenia	38(18%)	8 (7%)	30 (34%)	**<0.001**	*	*
Transaminitis	33 (16%)	21 (18%)	12 (13%)	0.40	*	*
Infection	66 (32%)	36 (31%)	30 (34%)	0.63	N/A	42 (20%)

*Not available.

7068 **Poster Session**

Comparative safety and efficacy of obinutuzumab versus rituximab in combination with chemotherapy for follicular lymphoma: A systematic review and meta-analysis. First Author: Abdul Rafae Faisal, CMH Multan Institute of Medical Sciences, Multan, Pakistan

Background: Follicular lymphoma is one of the most common non-Hodgkin lymphoma subtypes, typically presenting with advanced-stage disease and a relapsing-remitting course. Over the past two decades, anti-CD20 monoclonal antibodies combined with chemotherapy have significantly improved outcomes. Rituximab, a first-generation anti-CD20 antibody, has been the standard of care since approval. Obinutuzumab, a type II glycoengineered anti-CD20 antibody with enhanced antibody-dependent cellular cytotoxicity and direct cell death mechanisms, is a newer option with potential efficacy advantages. While individual randomized trials have shown promising results with obinutuzumab, comparative data on safety and efficacy remain limited. **Methods:** A systematic search of PubMed, ClinicalTrials.gov, Scopus, Embase, and Cochrane CENTRAL identified relevant English-language randomized controlled trials and observational studies. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed- or random-effects models based on heterogeneity. Statistical significance was set at $p<0.05$, and heterogeneity was assessed using the I^2 statistic. Analyses were performed using Review Manager version 5.3, following PRISMA guidelines. **Results:** Three studies met inclusion criteria, including two retrospective observational studies (Claustre et al., 2023; Berger et al., 2023) and one randomized controlled trial (Marcus et al., 2017). The pooled sample included 1,482 patients, of whom 53% were female. Compared with rituximab, obinutuzumab was associated with higher partial response rates (OR=0.66; 95% CI: 0.50–0.89; p=0.006) and improved disease progression outcomes (OR=0.64; 95% CI: 0.49–0.86; p=0.002). No significant differences were observed in overall response rate (OR=1.18; 95% CI: 0.84–1.65; p=0.34) or complete response (OR=0.82; 95% CI: 0.63–1.06; p=0.13). Obinutuzumab was associated with a higher incidence of adverse events during induction (OR=1.56; 95% CI: 1.04–2.33; p=0.03) and maintenance (OR=1.48; 95% CI: 1.13–1.93; p=0.004). Treatment discontinuation, dose reduction, or interruption due to adverse events occurred more frequently with obinutuzumab (OR=1.65; 95% CI: 1.13–2.42; p=0.01), as did neutropenia (OR=1.38; 95% CI: 1.12–1.71; p=0.002). **Conclusions:** This meta-analysis demonstrates that obinutuzumab provides improved efficacy, including higher partial response rates and reduced disease progression, compared with rituximab in follicular lymphoma. However, this benefit is accompanied by increased toxicity. Treatment selection should balance efficacy gains against safety risks. Research Sponsor: None.

7069 **Poster Session**

Survival and socioeconomic disparities in the elderly population with mycosis fungoides and Sézary syndrome: A comparative analysis of 2,690 patients by facility type. First Author: Oscar Hinojosa, Department of Hematology Oncology, The University of Texas Health Science Center, San Antonio, TX

Background: Mycosis fungoides (MF) and Sézary syndrome (SS) are rare T-cell malignancies (0.26 and 0.36/100,000 person-years, respectively), that predominantly affect elderly patients, a population frequently underrepresented in clinical trials and with limited access to specialized care. While population-level outcomes are known, the impact of facility type on management and survival remains poorly studied. We utilized the National Cancer Database (NCDB) to conduct the largest retrospective cohort analysis comparing patient demographics, treatment patterns, and survival (OS) between Academic Cancer Programs (ACPs) and Community Cancer Programs (CCPs). **Methods:** Patients ≥75 years old diagnosed with MF/SS in the US from 2000 to 2020 were identified. Facilities were categorized as ACPs (Academic/research programs) and CCPs (Comprehensive community/integrated network programs). Demographic and clinical variables were compared. Overall survival (OS) was estimated using Kaplan–Meier methods, with Cox proportional hazards models performed to assess associations between facility type and survival. **Results:** A total of 2690 patients were identified (ACPs: 2176;CCPs: 514). Both cohorts showed male predominance (ACPs: 58%;CCPs: 64%) and were primarily White (ACPs: 84%;CCPs: 92%). Socioeconomic analysis revealed that ACP patients were more likely to belong to the highest income quartiles compare to CCP patients across all periods (2000: 43% vs 32%; 2008–2012: 36% vs 26%; 2012–2016: 39% vs 29%; and 2016–2020: 40% vs 30%; all $p < 0.01$). Notably, ACP patients were more likely to receive systemic treatment (71% vs 65%; $p<0.05$) and experienced shorter median times to treatment initiation (37 vs 48 days; $p<0.05$). Conversely, radiotherapy was utilized more frequently at CCPs (29% vs 15.2%; $p<0.01$). With a longer median follow-up at ACPs (37 vs 31 months; $p< 0.05$), a higher proportion of patients remained alive at the end of the study (42% vs 30%). OS was superior among patients treated at ACPs, with higher 2-, 5-, and 10-year survival rates and a longer median OS (4.9 vs 3.0 years; log-rank p=0.001). **Conclusions:** In elderly patients with mycosis fungoides and Sézary syndrome, management at an Academic Cancer Program was associated with a statistically significant and clinically meaningful overall survival advantage compared with Community Cancer Programs. This survival difference occurred alongside more frequent use of systemic therapies, expedited treatment initiation, and distinct socioeconomic differences between care settings. These findings highlight important system-level disparities and underscore the critical need to strengthen referral pathways and academic–community partnerships to improve access to specialized care and optimize outcomes for this vulnerable population. Research Sponsor: None.

7070 **Poster Session**

Exploring improved prognostication using PET/CT radiomics in relapsed/refractory, TP53-aberrant diffuse large B-cell lymphoma (DLBCL). First Author: Vincenzo Pizzuti, University of Colorado Department of Medicine, Aurora, CO

Background: Patients (pts) with TP53-aberrant DLBCL have inferior progression-free survival (PFS) and overall survival (OS) compared to pts with wild type disease, and outcomes are worse for those with R/R disease. Improved prognostics are needed to identify those at risk for inferior outcomes to guide enhanced surveillance and early initiation of subsequent therapy. **Methods:** Retrospective data from pts with R/R, TP53-aberrant DLBCL treated at the University of Colorado system with 2 distinct PET/CT scans at time of R/R diagnosis and post-treatment between 2016 and 2025 were included in this analysis. PET/CT measurements were conducted by two nuclear medicine physicians blinded to outcomes and included SUVmax, total metabolic tumor volume (TMTV) by 41% SUVmax method, and total lesional glycolysis (TLG). Receiver operator curves (ROC) were constructed to determine the optimal cutoff points for PFS at 1 year using Youden's J statistic. Survival analysis was conducted using Kaplan-Meier and Cox analyses. **Results:** The 22 pts had a median age of 66.9 years (44-83), median follow-up of 18.7 months (mos.), and a median OS of 28.7 mos. (95% CI 19.0 – 53.8) from R/R diagnosis. 17/22 (77%) pts had primary refractory disease, 7/22 (32%) had bulky disease, 13/22 were GCB, and 8/22 (36%) had double-hit lymphoma. 17/22 pts received CAR-T therapy as next line of therapy, and OS was not associated with therapy type or line by Cox regression. ROC analysis for PET/CT interval changes from R/R diagnosis to post-treatment identified cutoffs of 86.7% for ΔSUVmax, 93.43% for ΔTMTV, and 97.98% for ΔTLG. The known prognostic ΔSUVmax >70% was associated with better OS with hazard ratio (HR) of 0.307 (p=0.025). Each radiomic metric was independently associated with superior PFS (Table 1). R-IPI >3 at progression was not associated with differences in PFS or OS (p=0.751 and p=0.655, respectively). Pts with 2 or more high-risk PET/CT radiomic features (any combination of 2+ makers less than the cutoffs) was associated with inferior PFS (Table 1), OS (HR=0.265, p=0.009), and had a median PFS of 3.5 months and OS of 19.0 months. **Conclusions:** PET/CT radiomic metrics were independently associated with PFS and OS in R/R, TP53-aberrant DLBCL pts. Pts with 2 or more high-risk PET/CT features were at high risk for progression and inferior OS compared to those with ≤ 1, and this 2-component model significantly outperformed R-IPI for predicting PFS and OS in this exploratory analysis, which warrants validation in future study. Research Sponsor: None.

	Median PFS	Median OS	HR for PFS (95% CI, p-value)
Δ SUVmax ≥ 86.7%	NR	50.1 months	0.259 (0.078-0.861, p=0.0164)
Δ TMTV ≥ 93.43%	NR	46.3 months	0.294 (0.085-1.03, p=0.0223)
Δ TLG ≥ 97.98%	NR	46.4 months	0.223 (0.066-0.758, p=0.0071)
≥2 high-risk PET/CT features	3.5 months	19.0 months	0.181 (0.055-0.591, p=0.0012)
High-risk IPI (3 or higher)	36.7 months	28.6 months	1.207 (0.341-4.279, p=0.751)

7071 **Poster Session**

Conditional survival by primary extranodal site in diffuse large B-cell lymphoma: A population-based landmark analysis. First Author: Muhammad Dawood Amir Sheikh, University of South Alabama, Mobile, AL

Background: Diffuse large B-cell lymphoma (DLBCL) frequently presents with extranodal involvement. Prior population-based studies report site-specific survival differences from diagnosis, but these estimates are influenced by early mortality and may not reflect prognosis among longer-term survivors. We therefore evaluated conditional survival by primary site using landmark analyses. **Methods:** Adolescents and adults (≥15 years) with primary extranodal DLBCL diagnosed in the Surveillance, Epidemiology, and End Results (SEER) database (2002–2022) were identified. Overall survival was assessed using multivariable Cox models adjusted for age, sex, race/ethnicity, and era. Landmark Cox models at 12 and 24 months estimated survival among patients alive at each timepoint. Gastrointestinal (GI) tract served as the reference site. **Results:** Among 30,963 patients, survival differed significantly by primary site ($p<0.001$). From diagnosis, CNS/brain involvement was associated with markedly worse survival compared with GI disease (HR 2.09, 95% CI 2.00–2.19), while several sites appeared favorable at diagnosis. Among 12-month survivors (n=20,497), excess risk for CNS persisted (HR 2.46). In contrast, early advantages for bone/bone marrow and head/neck diminished, and breast, skin/soft tissue, and testis were associated with higher subsequent hazards (HR ~1.2 each). At 24 months (n=17,614), increased risk remained for CNS (HR 2.47), lung/pleura (HR 1.41), breast (HR 1.35), skin/soft tissue (HR 1.23), and testis (HR 1.26), while most other differences were small or no longer significant. **Conclusions:** Prognostic differences by primary site change after conditioning on early survival. CNS involvement remains high risk, while several sites that appear favorable at diagnosis lose this advantage over time. Landmark analyses provide more meaningful risk estimates for survivors but cannot account for site-specific treatment differences in SEER. Research Sponsor: None.

Adjusted hazard ratios for overall survival by primary extranodal site among 12- and 24-month survivors.

Site (ref: GI)	12m HR (95% CI)	24m HR (95% CI)	Site (ref: GI)	12m HR (95% CI)	24m HR (95% CI)
Bone/Bone marrow	1.01 (0.93–1.11)	0.96 (0.87–1.07)	Breast	1.24 (1.09–1.42)	1.35 (1.17–1.55)
CNS/Brain	2.46 (2.29–2.65)	2.47 (2.27–2.68)	Head/Neck	1.03 (0.96–1.11)	1.08 (1.00–1.17)
Hepatobiliary/ Pancreas	1.18 (1.04–1.34)	1.12 (0.97–1.29)	Kidney/Adrenal	1.26 (1.07–1.48)	1.07 (0.88–1.29)
Lung/Pleura	1.39 (1.26–1.54)	1.41 (1.26–1.58)	Skin/Soft tissue	1.23 (1.14–1.33)	1.23 (1.13–1.34)
Spleen	0.91 (0.80–1.04)	0.92 (0.80–1.06)	Testis	1.23 (1.11–1.37)	1.26 (1.12–1.41)

Adjusted for age, sex, race/ethnicity, and diagnosis era. Landmark Cox models among patients alive at 12 and 24 months.

7072 **Poster Session**

Deep learning–based PET/CT radiomics-clinical model for prognostic stratification and immunotherapy exploration in natural killer/T-cell lymphoma. First Author: Tongyu Lin, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Background: Natural killer/T-cell lymphoma (NKTCL) is a highly aggressive malignancy with substantial heterogeneity. The value of deep learning on PET/CT-based radiomics for risk stratification in NKTCL remains to be defined. **Methods:** In this retrospective multicenter study, 425 consecutive NKTCL patients from four hospitals were randomly assigned to training or validation cohorts. Radiomics features extracted from pre-treatment PET/CT images were used to construct prognostic models with multiple deep learning algorithms. The best model was integrated with established clinical prognostic factors, and its performance in informing treatment decisions was tested in another independent immunochemotherapy cohort. **Results:** The XGBoost-based radiomics model achieved the highest prognostic accuracy for progression-free survival (PFS) and overall survival (OS) across cohorts. Integration with clinical factors yielded the Radiomic-Clinical Prognostic Model (RCPM), which further improved prediction (training cohort AUC: PFS 0.977, OS 0.946; validation cohort AUC: PFS 0.834, OS 0.814) and effectively stratified patients into high- and low-risk groups with distinct PFS and OS (all $P < 0.001$). In another exploratory treatment cohort, high-risk patients derived significant benefit from PD-1 inhibitor therapy (3-year PFS: 67.7% vs. 21.7%, 3-year OS: 81.7% vs. 39.6%; both $P < 0.001$), whereas low-risk patients did not. **Conclusions:** In conclusion, the RCPM demonstrated strong prognostic value and may help identify patients who could potentially benefit from immunotherapy in NKTCL. Research Sponsor: National Natural Science Foundation of China; U24A20679 and 82470237.

7073 **Poster Session**

Efficacy and safety of mesutoclax (ICP-248) in combination with orelabrutinib in patients with B-cell malignancies: A pooled analysis. First Author: Zhiming Li, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Mesutoclax (ICP-248) is a next-generation BCL2 inhibitor, and orelabrutinib is a marketed BTK inhibitor for CLL/SLL, MCL, and MZL. However, the clinical activity of their combination in these malignancies remains undefined. This analysis evaluated the combination of mesutoclax and orelabrutinib across B-cell malignancies. **Methods:** Patients with relapsed and refractory (R/R) MCL, MZL were enrolled in a phase 1 study (NCT05728658), and treatment-naive (TN) CLL/SLL were enrolled in a phase 2 study (NCT06378138). R/R MCL and MZL patients received continuous daily mesutoclax (125 mg) and orelabrutinib (150mg) from cycle 1 day 1 continuously until disease progression or unacceptable toxicity. For CLL/SLL patients, induction therapy with orelabrutinib (150 mg QD, Cycles 1-17) was administered first, followed by mesutoclax (100 mg or 125 mg QD, Cycles 3-14). The orelabrutinib treatment continued beyond cycle 17 if the uMRD ($\leq$10-4) was not achieved. Mesutoclax was implemented with a ramp-up schedule in all patients to mitigate the risk of TLS. **Results:** As of 05 Jan 2026, 60 patients were enrolled and treated in the studies: 8 R/R MCL, 10 R/R MZL, and 42 TN CLL/SLL (mesutoclax 100 mg, n=21; 125 mg, n=21). In R/R patients, the median number of prior lines of therapy was 1 (1-4). 6 (33.3%) were refractory to the last line of therapy. For TN CLL/SLL, 76.2% (32/42) of patients had moderate or high TLS risk, and 14.3% (6/42) had TP53 mutation or del (17p). Among 5 MCL and 8 MZL patients who had at least one disease evaluation, the overall response rate (ORR) was 100%, with CRR of 100% and 50%, respectively. Five patients (38.5%) achieved peripheral blood (PB) uMRD. In the 21 CLL/SLL patients receiving mesutoclax 125 mg, the ORR was 100% and the CRR was 38.1%, and the peripheral blood uMRD rate at 36-week was 65%. The median time to CR was 3.7 months in R/R group and 7.1 months in TN group. The 12-month PFS rate was 100% in CLL/SLL, while data for MCL and MZL are immature due to short follow-up. As the safety data cutoff (31 Dec 2025), the combination of mesutoclax and orelabrutinib was well tolerated with a favorable safety profile, and no new safety signals were identified compared to either agent as monotherapy. Most TEAEs were grade 1-2, with no TEAEs leading to drug discontinuation or death reported. The most common grade $\geq$3 TEAEs include neutrophil count decreased (35%), platelet count decreased (11.7%). Notably, no grade $\geq$3 anemia was reported. No clinical or laboratory TLS occurred. **Conclusions:** Mesutoclax in combination with orelabrutinib demonstrated a tolerable safety profile across B cell malignancy subtypes (MCL, MZL, CLL/SLL). Significant 100% ORR and deep response were observed in patients receiving mesutoclax 125mg combined with orelabrutinib. This all oral, chemo-free regimen has the potential to establish a novel therapeutic option for B-NHLs. Clinical trial information: NCT05728658. Research Sponsor: None.

7074 **Poster Session**

Effect of FDG-PET–based bone marrow assessment on prognostic accuracy compared to conventional histologic evaluation in patients with follicular lymphoma: A subanalysis of the FIL FOLL12 trial. First Author: Stefano Luminari, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

Background: Bone marrow biopsy (BMB) is an invasive staging procedure for follicular lymphoma (FL) and its results are needed to calculate FLIPI2 and PRIMA-PI scores. Beyond conventional biopsy bone marrow can also be assessed through FDG-PET bone staging (PETb). We report preliminary data on a comparison of BMB and PETb in assessing BM involvement among FL patients enrolled in the FIL-FOLL12 trial. **Methods:** Untreated stage II–IV FL patients requiring therapy were included. Patients were balanced according to treatment received and arm. BMBs were assessed by morphology and immunohistochemistry. PET/CT scans were reviewed by two expert nuclear medicine physicians. Pathological bone uptake (PETb+) was defined as mono- or multifocal, or diffuse FDG uptake in bone segments higher than liver activity (SUVmax). **Results:** This analysis included 179 patients; no significant differences in disease characteristics were observed between the revised cohort and the remaining patients enrolled in the FOLL12 trial. High-risk FLIPI2 was noted in 35.4%, and β2-microglobulin was increased in 53% of patients. BMB involvement was present in 58.5% (median infiltration 30%, range 0.5–95%). PETb was positive in 38 cases (21%), including 14% with focal or multifocal involvement and 7% with diffuse increased uptake. Concordant results between BMB and PETb were observed in 53.6%: among 103 BMB+ patients, 30 were PETb+ (29%). PETb identified BM involvement in 8 cases missed by BMB. While BMB+ was not associated with a different risk of PFS compared to BMB-, we observed a significant impact of PETb+ on PFS: PETb+ had 41% 5-year PFS (CI 25-72, p=0.003), while BMB+/PETb- showed 74% (CI 62-83, p=0.27) and BMB-/PETb- 66%(CI 52-72, reference).We then calculated FLIPI2 and PRIMA-PI using either conventional BMB or PETb to define BM involvement. The agreement between BMB and PETb scores was 87% for FLIPI2 and 67% for PRIMA-PI and the main disagreement was due to reallocation to lower risk groups; FLIPI2 0-2 patients raised from 65% to 74.3% according to FLIPI2-PET. FLIPI2 was confirmed prognostic for PFS and its c-Harrel increased from 0.582 to 0.602 when BMB was substituted with PETb (Table 1), with a 52% (CI 39-64) 5-Year PFS for conventional high risk FLIPI2 shifting to 41% (CI26-56) for high risk FLIPI2-PET. **Conclusions:** Although BMB detects marrow involvement in most patients, this does not uniformly translate into adverse prognosis. PETb, while less sensitive, identifies metabolically active and prognostically relevant bone disease. A FDG-PET-based assessment of bone involvement could refine risk stratification in FL and spare BMB in most patients Research Sponsor: None.

Score	HR for High risk	CI	c-Harrell
FLIPI2	2.03	1.25-3.31	0.582
FLIPI2-PET	2.58	1.57-4.26	0.602
PRIMA-PI	1.23	0.67-2.23	0.537
PRIMA-PI-PET	1.47	0.85-2.54	0.550

7075 **Poster Session**

Defining APOBEC-like signature in diffuse large B-cell lymphoma and demonstration of distinct transcriptomic profile. First Author: Adam Albitar, Genomic Testing Cooperative LCA, Lake Forest, CA

Background: APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) mutational signatures are uncommon in hematologic malignancies compared with solid tumors. This signature is characterized by C>T and C>G substitutions and clustered chromosomal abnormalities and is typically defined using whole-genome or whole-exome sequencing. Data on APOBEC signatures detected by targeted gene panels are limited. We interrogated a database of diffuse large B-cell lymphoma (DLBCL) cases sequenced between 2023 and 2025 using a targeted panel. Cases with >30 mutations were classified as "APOBEC-like," and their molecular and expression features were analyzed. **Methods:** DNA and RNA were extracted from FFPE samples and sequenced by next-generation sequencing. DNA sequencing used a 302-gene panel and RNA sequencing a 1,600-gene panel. Hybrid-capture libraries were sequenced on an Illumina NovaSeq 6000. **Results:** Among 670 DLBCL cases, 39 (6%) demonstrated an APOBEC-like signature. A striking feature was the presence of multiple mutations within the same gene. One case harbored 20 distinct SOCS1 mutations, and 20 of 39 cases (51%) had at least one gene with $\geq$10 mutations. Cell of origin was germinal center B-cell in 21 cases (54%). All APOBEC-like cases showed numerous chromosomal abnormalities, most commonly 6q deletion/monosomy 6 (23 cases, 59%). Deletion of 17p was rare (2 cases). TP53 mutations were detected in 12 cases (31%), PIM1 in 23 (58%), and SOCS1 in 18 (46%). Gene expression profiling revealed significant differences between APOBEC-like and average DLBCL cases. TRAF3, TRAF5, and TRAF2 expression was significantly lower in APOBEC-like cases (log10 FDR < -12), while NAMPT, PRPF8, SF3A1, NFYC, LUC7L2-MCM3AP, and SMAD5 were significantly overexpressed (log10 FDR < -7). Despite the limited cohort size, random forest modeling demonstrated that expression profiling could distinguish APOBEC-like cases, with 20 genes achieving an AUC of 0.904 in a testing set. **Conclusions:** APOBEC-like mutational signatures can be identified in approximately 6% of DLBCL cases using targeted gene panels and are characterized by extreme intragenic hypermutation, recurrent chromosomal abnormalities, and a distinct expression profile that enables accurate classification by machine-learning approaches. Research Sponsor: None.

7076 **Poster Session**

Aberrant somatic hypermutation in large B-cell lymphomas and its relationship to mutational signatures, including a novel haloalkane pattern. First Author: Nicholas J. Dcunha, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Diffuse large B cell lymphoma (DLBCL) is a genetically complex disease, often characterized by the simultaneous occurrence of multiple mutations within single driver genes. Here, while activation-induced cytidine deaminase (AID)-driven aberrant somatic hypermutation (aSHM) is recognized as a major contributor to mutation, many genes could be heavily mutated due to other mechanisms. In this study, we evaluate clinical DLBCL samples identified as hypermutated, to assess the presence of AID driven mutation and the contribution of other defined mutational signatures which may contribute to clinicopathologic heterogeneity. **Methods:** Clinical samples of DLBCL tested by a hybrid-capture next-generation sequencing (NGS) panel targeting up to 468 genes, were identified. Hypermutated cases were selected based on the qualifying criteria of having three or more co-occurring mutations in at least 1 gene. Based on the mutational position from transcriptional start site and inter-mutational distance, cases were initially classified as having aSHM or Kataegis. Mutational signature analysis was performed using all high-confidence somatic single-base substitutions (SBS) identified and interpreted according to COSMIC SBS signatures v3.5. A predominant signature was defined when >40% of the mutations were attributed to the signature. Wherever possible, correlation between the morphological type, molecular subtype, and mutational signatures was performed. **Results:** Out of the 216 samples identified as hypermutated, most (n=172, 79.6%) were classified as having aSHM, 9.3% (n=20) as Kataegis and 11.1% (n=24) were unclassifiable. The 3 most common genes targeted by aSHM were PIM1(n=66), SOCS1(n=55) and BCL2(n=35). By contrast, SGK1(n=16), MYC(n=12), GNA13(n=6) and ITPKB(n=6) were the common targets of Kataegis. The most frequent dominant molecular signatures included AID (n=82) and Clock-like aging(n=48), followed by Haloalkane (n=24), MMR deficiency (n=17) and the SBS39 (n=14) signature of unknown etiology. Based on morphology and immunophenotype, cases were primarily stratified as either Germinal Center B-cell like (GCB; n=86) or Non-GCB (n=87), with lower representation of Primary mediastinal B cell lymphomas (n=21), High grade B cell lymphomas with MYC and BCL2 translocations (n=18), and DLBCL special subtypes (n=4). The same top 3 molecular signatures were identified across all subtypes, except in GCB, where MMR deficiency constituted the 3rd most frequent signature. **Conclusions:** In DLBCL, mutational signatures are primarily driven by endogenous processes, namely AID and Aging. The identification of a haloalkane signature in a small proportion of cases is a novel finding, raising suspicion for the role of exogenous influences, either environmental or therapeutic in origin. Further studies are needed to better define this cohort. Research Sponsor: None.

7077 **Poster Session**

An exploratory study to assess the safety, immunogenicity, and preliminary anti-tumor activity of the EBV mRNA vaccine (WGc-043 injection) combined with PD-1 antibody in patients with relapsed or refractory ENKTL. First Author: Xingchen Peng, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

Background: Extranodal NK/T cell lymphoma (ENKTL) is a rare and aggressive lymphoma associated with Epstein-Barr virus (EBV) infection and requires novel therapeutic strategies. WGc-043, a therapeutic mRNA vaccine, showed promise against ENKTL patients alone by targeting EBV-driven oncogenesis in our previous study. This study evaluates the safety, immunogenicity, and preliminary anti-tumor activity of WGc-043 combined with PD-1 antibody in patients with relapsed or refractory ENKTL (r/r ENKTL). **Methods:** This single-center, open-label, exploratory study enrolled 5 patients with EBER1/2 positive r/r ENKTL. The primary inclusion criteria were patients with an ECOG of 0-2 who have failed an asparaginase-based regimen. WGc-043 was administered intramuscularly, including 5 doses of base immunization followed by optional personalized treatment. The base immunization was given at week 1, 2, 3, 4 and 7. Tislelizumab (PD-1 antibody) was administered every three weeks until disease progression, for a maximum of two years. The primary endpoint is safety. Secondary endpoints include immunogenicity, ORR and DCR. The exploratory analysis focuses on immune biomarkers predictive of therapeutic response. **Results:** WGc-043 combined with PD-1 antibody (Tislelizumab) demonstrated a favorable safety and efficacy in patients with r/r ENKTL. It was well tolerated with only grade 1 adverse events. The most common adverse events were injection site reactions (100%, 4/4) , hemoglobin decreased (50%, 2/4), TSH elevated (50%, 2/4), fever (25%, 1/4), weakness (25%, 1/4) and lymphopenia (25%, 1/4). Importantly, this combo showed good, durable responses, with 2 patients achieving CR in 4 evaluable patients, and both remained CR status on the Jan 11, 2026. This result indicates that the combination of WGc-043 and PD-1 antibody is promising as part of the therapeutic strategy for this challenging lymphoma. **Conclusions:** WGc-043 combined with PD-1 antibody is well tolerated with a safety profile and yields encouraging CR rate and durable responses. Further investigations are warranted to validate these findings and to explore the full potential of this regimen in larger studies. Clinical trial information: 2200065962. Research Sponsor: None.

Efficacy and safety.

Response category	Number of subjects
CR	2
PR	0
SD	0
PD	2
Total	4
ORR	50%
DCR	50%

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any adverse event	4/4 (100%)	0	0	0	0
Injection site reaction	4/4 (100%)	0	0	0	0
Hemoglobin decreased	2/4 (50%)	0	0	0	0
TSH elevated	2/4 (50%)	0	0	0	0
Fever	1/4 (25%)	0	0	0	0
Weakness	1/4 (25%)	0	0	0	0
Lymphopenia	1/4 (25%)	0	0	0	0

7078 **Poster Session**

Safety and efficacy of GT719, an off-the-shelf CAR-NKT therapy, in adults with relapsed or refractory CD19-positive B-cell malignancies. First Author: Yarong Liu, Grit Biotechnology, Shanghai, China

Background: GT719 is an off-the-shelf CAR-NKT therapy derived from umbilical cord blood hematopoietic stem cells and genetically engineered to co-express an anti-CD19 CAR, an invariant natural killer T (NKT)-specific TCR, and secreted interleukin-15 (IL-15). This design enables CD19-targeted tumor killing, avoids risk of graft-versus-host disease (GVHD), and enhanced cellular expansion, persistence, and immune function through IL-15 signaling. We report clinical data from 7 adults with relapsed or refractory (R/R) CD19-positive B-cell hematologic malignancies enrolled in two open-label, single-arm studies (NCT06948981, NCT07131254) evaluating the safety and preliminary efficacy. **Methods:** The primary endpoint was safety, including treatment-emergent adverse events (TEAEs), graded per CTCAE v5.0. Secondary endpoints included 3-month overall response rate (ORR), best overall response (BOR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Efficacy was assessed using Lugano 2014 criteria and the 2024 Chinese guidelines for adult acute lymphoblastic leukemia. **Results:** As of December 31, 2025, 7 patients were treated (median age 51 years; median two prior therapies), including 3 with B-ALL and 4 with B-NHL. Following FC lymphodepletion, all patients received a single GT719 infusion (5×10^7 to 1×10^9 viable cells). Most adverse events (AEs) were Grade 1-2. Grade ≥3 AEs were limited to lymphodepletion-related cytopenia and resolved or improved to Grade ≤2 within 14 days, excluding disease-related cytopenia. One patient experienced Grade 1 cytokine release syndrome that resolved within 1 day. No ICANS, neurotoxicity, or GVHD, severe infections, or serious TEAEs were observed. Efficacy was evaluable in all patients across B-ALL, follicular lymphoma (FL, grade 3a), and diffuse large B-cell lymphoma (DLBCL). The 3-month ORR was 50% (3/6), with all responders achieving CR; one patient was excluded due to insufficient follow-up. The disease control rate (DCR) was 71.4% (5/7). Two of 3 FL patients achieved CR, while one had a PR and remained under follow-up. One of three B-ALL patients achieved stringent complete remission, maintained through 24 weeks of relapse-free follow-up. CAR transgene analysis demonstrated robust in vivo expansion, with peak levels occurring between Days 7-10 in B-ALL and within two months in FL. GT719 persistence was observed for up to six months post-infusion. **Conclusions:** GT719 demonstrated a favorable safety profile and encouraging antitumor activity in adults with R/R CD19-positive B-cell malignancies. The absence of severe GT719-related toxicities and evidence of durable cellular persistence support further clinical investigation of this off-the-shelf CAR-NKT therapy. Clinical trial information: NCT06948981, NCT07131254. Research Sponsor: Grit Biotechnology. Research Sponsor: None.

7079 **Poster Session**

First-in-human study of in vivo CAR-T therapy GT801 in adults with relapsed or refractory CD19-positive B-cell hematologic malignancies. First Author: Yarong Liu, Vivacta Biotechnology, Shanghai, China

Background: Despite high initial cure rates, patients with B-cell hematologic malignancies, including B-ALL and B-NHL, experience substantial relapse, with markedly reduced disease-free and overall survival after second-line therapy. GT801 is a first-in-human, in vivo CAR-T therapy that uses antibody-displayed lipid nanoparticle (LNP) to deliver CD19 CAR mRNA directly to T cells, enabling in vivo reprogramming without ex vivo cell manufacturing or lymphodepletion. We report initial safety and efficacy data from an open-label, single-arm phase I study (NCT07205315). **Methods:** GT801 was evaluated using a modified 3+3 dose-escalation design across three dose levels (0.5, 1.5, and 3.0 mg). Patients received up to 4 treatment cycles, each consisting of a single intravenous administration of GT801 on Day 1 of a 7-day cycle. The primary endpoint was safety, including treatment-emergent adverse events (TEAEs), graded per CTCAE v5.0. Secondary endpoints included 3-month overall response rate (ORR), best overall response (BOR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS), assessed per Lugano 2014 criteria. **Results:** As of January 13, 2026, 3 patients were enrolled (median age 60 years; median three prior therapies). One patient received 3 doses at 0.5 mg, and two patients received 4 doses at 1.5 mg. All patients had B-NHL. Premedication included dexamethasone, NSAIDs, antihistamines. Most AEs were Grade 1-2. Common TEAEs included cytokine release syndrome (CRS), cytopenia, and transient liver enzyme elevations. Grade ≥3 events were hematologic toxicities and CRS. No neurotoxicity or organ failure was observed. At Week 4, all patients demonstrated a treatment response. Peripheral blood flow cytometry showed rapid CAR-T generation, with $CD8^+$ CAR-T cells detectable within 4 hours post-infusion and peak levels on Day 1. Reprogramming efficiency reached up to 93% and was maintained with repeat dosing. Minimal off-target CAR expression was detected in monocytes. Complete peripheral B-cell depletion occurred within 4 hours after the first dose and was sustained for at least 7 days; after the third dose, B-cell depletion and CAR-T detection were observed in both peripheral blood and bone marrow. **Conclusions:** GT801 demonstrated a manageable safety profile and early signs of antitumor activity in heavily pretreated B-NHL patients. The ability to generate functional CAR-T cells in vivo without lymphodepletion supports further clinical evaluation of GT801 as a promising therapeutic approach. Clinical trial information: NCT07205315. Research sponsor: Vivacta Biotechnology (Shanghai) Co., Ltd. Research Sponsor: None.

7080 Poster Session

Zanubrutinib plus rituximab as front-line treatment for mucosa-associated lymphoid tissue (MALT) lymphoma: A single-arm, phase II study (ZAMA). First Author: Yi Xia, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

Background: Mucosa-associated lymphoid tissue (MALT) lymphoma is the most common subtype of marginal zone lymphoma and follows an indolent clinical course. For patients with advanced-stage disease with an indication for treatment, rituximab-based immunochemotherapy is recommended as frontline therapy; however, toxicity and tolerability remain concerns. Zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, has shown promising antitumor activity with a manageable safety profile in marginal zone lymphoma. This study aimed to evaluate zanubrutinib plus rituximab as frontline treatment for MALT lymphoma. **Methods:** The ZAMA study (NCT06647732), a multicenter, single-arm, phase II trial, enrolled patients aged ≥18 years with histologically confirmed CD20-positive MALT lymphoma. Eligible patients had newly diagnosed advanced-stage disease or relapsed disease after prior local therapy, had not received prior systemic treatment, and had at least one measurable lesion. Patients received rituximab (375 mg/m^2) plus zanubrutinib (160 mg twice daily) in 28-day cycles. Treatment was administered for six cycles, after which patients achieving complete response (CR) entered observation, while those with partial response or stable disease received two additional cycles. The primary endpoint was the CR rate as best response. **Results:** From October 30, 2024 to December 12, 2025, 39 patients were enrolled. At the data cutoff of January 10, 2026, 23 patients had completed protocol-specified treatment, including 14 patients who received six cycles and 9 patients who received eight cycles. The median age was 58 years (range 24–75); 7 patients were males (30.4%). Most patients (n = 21, 91.3%) had an ECOG performance status of 0–1, and 21 patients (91.3%) had Ann Arbor stage III–IV disease; two patients had relapsed disease after prior local therapy. Eighteen patients (78.2%) achieved CR, and the remaining five patients achieved PR. Treatment-emergent adverse events (TEAEs) occurred in 20 patients (87.0%); hematologic toxicity were most common: neutropenia (n = 2, 8.7%), and thrombocytopenia (n = 2, 8.7%). Grade ≥ 3 TEAEs occurred in 4 patients (17.4%), most frequently neutropenia (n = 2, 8.7%), and thrombocytopenia (n = 2, 8.7%). **Conclusions:** Preliminary results from the ZAMA study show that frontline zanubrutinib plus rituximab provides encouraging efficacy with manageable safety in MALT lymphoma. The study is ongoing, and patient enrollment is continuing. Clinical trial information: NCT06647732. Research Sponsor: None.

Baseline characteristics.

Characteristics	Patients (n=23)
Age, years (median [range])	58 (24-75)
Sex	
Male	7 (30.4%)
Female	16 (69.6%)
ECOG PS	
0-1	21 (91.3%)
2	2 (8.7%)
Ann Arbor stage	
III-IV	21 (91.3%)
Prior local therapy	2 (8.7%)
MALT-IPI score	
0	1 (4.3%)
1	21 (91.3%)
2	1 (4.3%)
Bone marrow involvement	4 (17.4%)

7081 Poster Session

Brentuximab vedotin plus cyclophosphamide, doxorubicin, etoposide, and prednisone (CHEPA) in newly diagnosed CD30-positive peripheral T-cell lymphomas with integrated ctDNA analysis: Results of the phase 2 CHEPA trial. First Author: Marek Trněný, Charles University, 1st Fac Medicine, General Hospital, Prague, Czech Republic

Background: Peripheral T-cell lymphomas (PTCLs) are aggressive malignancies associated with poor outcomes. While adding brentuximab vedotin (BV) to CHP has improved results in CD30+ PTCL, relapses remain common. Given the suggested benefit of etoposide (CHOEP) in younger patients, the prospective multicenter single-arm Phase 2 CHEPA study (NCT05006664) was conducted to evaluate the efficacy and safety of CHEPA (BV-CHEP) induction combined with circulating tumor DNA (ctDNA) analysis. **Methods:** Patients with previously untreated CD30+ PTCL eligible for autologous stem cell transplantation (ASCT) were enrolled. Treatment consisted of 6 cycles of CHEPA (D1: BV 1.8 mg/kg, cyclophosphamide 750 mg/m², doxorubicin 50 mg/m²; D1–3: etoposide 100 mg/m²; D1–5: prednisone 100 mg/d) every 21 days. The primary endpoint was the complete metabolic response (CMR) rate at the end of treatment (EOT). Secondary endpoints included safety, PFS, OS, ORR, and exploratory ctDNA analysis. Plasma cfDNA was profiled using CAPP-Seq (259 genes) and clonotypic VDJ sequencing at all TCR loci via SABER. **Results:** Between 05/2022 and 09/2025, 40 patients were screened; 33 met eligibility criteria and initiated therapy. The cohort included 14 (42%) ALCL and 19 (58%) non-ALCL cases (median age 57 years, range 26–69). Baseline characteristics showed a predominance of males (67%), advanced-stage disease (79%), elevated LDH (58%), and bone marrow involvement (30%); all pts had an ECOG PS of 0–1. All 33 pts completed 6 cycles of CHEPA. At EOT, 25/33 (76%) achieved CMR, meeting the primary endpoint. The ORR was 91% for the entire cohort (CMR: 86% for ALCL, 68% for non-ALCL). ASCT was preplanned in 21/33 pts and has been performed to date in 14 pts. At a median follow-up of 19 months, the 18-month PFS and OS probabilities were 75% and 92%, resp. Specifically, PFS was 100% for ALCL vs. 59% for non-ALCL, while OS was 100% vs. 87%. Age and bone marrow involvement were the only baseline variables significantly associated with CMR. Baseline ctDNA burden was significantly correlated with total metabolic tumor volume (r=0.68, p<0.001), LDH level (r=0.48, p=0.03), and PIT (p<0.05). Grade 3–4 adverse events occurred in 82% of pts, primarily hematological: neutropenia (79%), thrombocytopenia (18%), febrile neutropenia (15%), and anemia (15%). No grade 3–4 peripheral neuropathy or grade 5 events were reported. **Conclusions:** The CHEPA study met its primary endpoint with a 76% CMR rate. Despite limited follow-up and high non-ALCL prevalence of our cohort, PFS and OS results are promising. Toxicity was manageable with no treatment-related deaths even though 33% of patients were >60 years old, supporting the safety of adding etoposide to the BV-CHP backbone. Further investigation of outcomes based on EOT MRD by ctDNA is ongoing. Clinical trial information: NCT05006664. Research Sponsor: AZV NW26-03-00462; Prchal Foundation; BBMRI_CZ LM2023033.

7082 Poster Session

Chidamide in combination with CHOP in previously untreated peripheral T-cell lymphoma with T follicular helper phenotype: Results of the phase II SWIFT trial. First Author: Qingqing Cai, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Peripheral T-Cell Lymphoma with T-follicular helper phenotype (PTCL-TFH), which mainly includes angioimmunoblastic T-cell lymphoma (AITL), is a biologically distinct subtype characterized by frequent epigenetic alterations. Chidamide is an oral, histone deacetylase (HDAC) inhibitor that targets HDAC subtypes 1, 2, 3, and 10, has shown encouraging activity in R/R PTCL-TFH. This study aimed to evaluate the efficacy and safety of chidamide in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in previously untreated PTCL-TFH patients. **Methods:** This is a multicenter, open-label, single-arm phase II study (NCT05572983). Patients with previously untreated PTCL-TFH were enrolled and received chidamide (20 mg, oral, biweekly) combined with CHOP regimen for up to six induction cycles. Patients achieving complete response (CR) after induction entered a maintenance phase with chidamide for up to two years. The primary endpoint was CR rate. Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between May 2023 and July 2025, a total of 47 patients were enrolled, and enrollment was completed. All patients had the AITL subtype. The median age was 62 years (IQR, 54–67), and 25.5% were female. Advanced-stage disease (stage III–IV) was present in 85.0% of patients, and 48.9% had extranodal involvement. The median number of induction cycles was 5 (range, 1–6), with 33 patients completing six cycles of induction therapy. Among 35 patients who underwent post-treatment PET/CT evaluation, the best CR rate during the induction phase was 85.2% (30/35), with an ORR of 100%. At the end of induction therapy, the CR rate was 87.9% (29/33), and the ORR remained 100%. As of October 2025, disease progression was observed in 10 patients. The most common grade 3–4 adverse events were neutropenia (42.6%), thrombocytopenia (19.1%), infections (17.0%), anemia (6.4%), and elevated transaminases (2.1%). **Conclusions:** Chidamide in combination with CHOP demonstrated promising efficacy with a manageable safety profile in previously untreated PTCL-TFH patients. A randomized controlled trial is currently ongoing to further validate these findings (NCT06947967). Clinical trial information: NCT05572983. Research Sponsor: None.

Baseline characteristics.

Characteristics	Patients (n=47)
Age, years (median [IQR])	62 (54-67)
Sex	
Male	35 (74.4%)
Female	12 (25.5%)
IPI score	
0-2	25 (53.1%)
≥3	22 (46.9%)
Ann Arbor Stage	
I-II	7 (14.8%)
III-IV	40 (75.2%)
Extranodal involvement	
No	24 (51.1%)
Yes	23 (48.9%)

Data are shown as number (%).

7083 Poster Session

Prognostic impact of comorbidity burden on overall survival in patients with Waldenström macroglobulinemia in the United States. First Author: Gaelle Haddad, Cleveland Clinic, Weston, FL

Background: Waldenström macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma (LPL), is a rare indolent Non-Hodgkin B-cell lymphoma affecting approximately 1500 patients annually in the US. Existing prognostic models: IPSS-WM, revised IPSS-WM, and MSS-WM focus primarily on disease specific factors including age, albumin, hemoglobin, platelet count, β2-microglobulin, LDH, and monoclonal IgM at diagnosis, and were derived from small cohorts. However, comorbidity burden is not included in these models, despite data showing that mortality is frequently attributed to comorbidities unrelated to lymphoma. We conducted this analysis to identify prognostic factors with emphasis on the impact of comorbidity burden on overall survival in WM. **Methods:** In this IRB approved retrospective study, we analyzed 17130 patients with histologically confirmed WM (ICD-O-3 9761/3) from the NCDB (2004–2023). Univariable and multivariable Cox regression identified independent prognostic factors for overall survival. Age stratified sub-analysis assessed the prognostic impact of comorbidity within each age group. Analyses were performed using SAS 9.4. **Results:** On multivariable Cox regression with backward elimination, Charlson comorbidity score (CC) ≥1 emerged as a significant independent predictor of mortality (HR 1.7 95% CI 1.58–1.75 p < 0.0001). Age-stratified analysis confirmed CC ≥1 significance in all age groups (HR 1.52-2.07, p<0.0001). Seven additional prognostic factors were identified: advanced age was associated with progressively worse survival (55≤age<65: HR 1.7; 65≤age<75: HR 2.3; age≥75: HR 5.5; all p<0.0001), while female sex was protective (HR 0.86; p<0.0001). Lower median household income was associated with worse outcomes (<$40,227: HR 1.38; $40,227–$50,353: HR 1.26; $50,354–$63,332: HR 1.1; all p<0.0001). Private insurance was associated with better OS compared with uninsured (HR 1.7; p<0.0001) and governmental insurance (HR 1.3; p<0.0001). Treatment at non-academic facilities (HR 1.13; p<0.0001) and multiple primary malignancies (HR 1.19; p<0.0001) were associated with inferior survival. No difference was observed between multi- and single-agent chemotherapy (HR 1.0; p=0.96), while patients not requiring chemotherapy had superior survival (HR 0.80; p<0.0001). **Conclusions:** In the largest WM cohort to date, we identified several prognostic factors impacting survival WM patients in the US. Among these factors, CC ≥1 was a strong independent predictor of mortality. Given that half of deaths in WM patients are due to comorbidities, comorbidity assessment is essential for accurate prognostication and individualized treatment planning. Managing comorbidities may be as important as treating the disease itself. CC or equivalent should be integrated into future prognostic models to improve clinical decision-making in WM. Research Sponsor: None.

7084 **Poster Session**

Age and HIV status as survival predictors in HHV8-positive diffuse large B-cell lymphoma: The largest population-based analysis to date. First Author: Gaelle Haddad, Cleveland Clinic, Weston, FL

Background: HHV8-positive Diffuse Large B Cell Lymphoma (HHV8+ DLBCL) is a rare and aggressive subtype of Non-Hodgkin Lymphoma that is frequently associated with HHV8-positive Multicentric Castleman Disease (MCD). Due to its rarity, population-based studies have been limited to small cohorts or have focused primarily on demographic features without survival analysis. This study explores demographic features, treatment pattern and prognostic factors affecting survival in patients diagnosed with (HHV8+ DLBCL) in the United States. **Methods:** Following IRB approval, we analyzed the largest cohort of HHV8+ DLBCL to date (n=262) using the National Cancer Database (NCDB) (2010-2023). Patients with histologically confirmed HHV8+ DLBCL (ICD-O-3 9738/3) were included. Univariable Cox regression identified factors associated with survival; significant variables were included in multivariable cox regression with backward elimination ($p<0.05$). Data was analyzed using SAS version 9.4. **Results:** Among 262 patients with HHV8+ DLBCL, (mean age 52.6 years), 65.6% were <60 years, 76.7% were male, and 66.0% were white. Primary site was predominantly nodal (78.6%), with extranodal involvement in 21.4%. 19.2% were HIV-positive, and 63.3% had no comorbidities (Charlson-Deyo score 0). The majority received systemic therapy (84.6%). Among treated patients, 62.2% received chemotherapy and 43.1% received immunotherapy. Median overall survival was 133 months, with 1-, 3- and 5-year survival rates of 68.2%, 63.1%, and 59.9%, respectively. On multivariable Cox regression analysis, age $\geq$60 years (HR 2.20, p=0.0004), higher Charlson-Deyo score (HR 1.67, p=0.0090), HIV-positive status (HR 2.56, p=0.0026), and absence of systemic treatment (HR 2.16, p=0.0016) was independently associated with worse overall survival. **Conclusions:** In conclusion, HHV8+ DLBCL is a rare and aggressive lymphoma with poor long-term survival, frequently associated with multicentric Castleman disease, mainly affecting males with nodal involvement. Age $\geq$60 years, higher Charlson-Deyo score, HIV-positive status, and lack of systemic treatment independently predicted worse survival. Our study provides the largest cohort analysis of HHV8+ DLBCL to date. Nevertheless, further prospective studies with larger sample sizes are necessary to gain deeper insight into the pathogenesis and optimize treatment of this rare lymphoma. Research Sponsor: None.

Multivariable Cox regression for overall survival in patients with HHV8+ DLBCL.

Factor	HR (95%CI)	p-value
Age		
Age <60 (ref)	1	0.0004
Age ≥60	2.20(1.42-3.40)	
Charlson Deyo Score		
No morbidities (ref)	1	0.0090
≥1 Morbidities	1.67(1.14-2.44)	
Systemic Treatment Status		
No Treatment	2.16(1.34-3.48)	0.0016
Receipt of Treatment (ref)	1	
HIV		
Negative (ref)	1	0.0026
Positive	2.56(1.39-4.71)	0.8601
Unknown	0.96(0.59-1.56)	

7085 **Poster Session**

Genomic profiling of Burkitt lymphoma in adults: Novel molecular insights and implications for outcomes. First Author: Manju Sengar, Tata Memorial Hospital, Mumbai, India

Background: The real-world treatment outcomes of Burkitt lymphoma (BL) from low-middle income countries appear to be inferior ($<$60%). Delays in diagnosis, treatment interruptions and toxicities are often attributed as the reasons for poor outcomes. However, biological differences could also explain the observed differences. However, there is limited information on the molecular profile of adult BL from developing countries. **Methods:** We evaluated a cohort of adult BL (histopathologically confirmed) who received treatment at our centre between 2012-2019. The data on demography, stage, HIV status, treatment type, response and survival was recorded. The formalin-fixed paraffin blocks were subjected to targeted next-generation sequencing using the hybrid capture based targeted panel- SOPHiA Lymphoma Solution which identifies single nucleotide variants (SNVs), indels from 73 genes and gene amplification events in 68 genes. **Results:** Among a total of 165 patients, the adequate quality DNA was extracted from 76 patients(83% males). Median age was 34 years ;67% patients had stage III/IV disease,10% were HIV positive. Treatment regimen were high-dose methotrexate based-74 %, 24%- DA-EPOCH. Rituximab was given to 83% of patients. Complete response was seen in 69% of patients. 67 cases (88.2%) harboured at least one somatic variant, while no variants were detected in 9 cases (11.8%) within the genes covered by the targeted panel. A total of 712 somatic variants were identified across the cohort. Based on ACMG/AMP classification, 88 variants (12.4%) were categorized as oncogenic and 318 variants (44.7%) as likely oncogenic. This indicates a substantial mutational burden in Burkitt lymphoma, despite its classical characterization as a MYC-driven malignancy. Considering only oncogenic and likely oncogenic variants, the most recurrently mutated genes were *KMT2D, CREBBP, ARID1A, EP300* and *TP53*. *TP53* showed the highest number of confirmed oncogenic variants (22 variants) and also accounted for the largest number of missense mutations (16 out of 158 missense variants). Mutations in *PTPRD* and *ITPKB* were mutually exclusive (p = 0.051), as were mutations in *CCND3* and *KMT2D* (p = 0.053). These patterns suggest possible distinct molecular subsets of Burkitt lymphoma, potentially reflecting alternative oncogenic pathways driven either by aberrant cell cycle regulation (*CCND3*) or by epigenetic dysregulation *(KMT2D*). **Conclusions:** Our data suggests that histopathologically confirmed BL have complex mutational landscape characterized by frequent alterations in epigenetic regulators, tumour suppressor genes, and key signalling molecules which can lead to inferior outcomes. Research Sponsor: None.

7086 **Poster Session**

iMARIX for primary and secondary central nervous system lymphomas. First Author: Ekin Kırcalı, Medicana International Ankara, Ankara, Turkey

Background: The Bruton tyrosine kinase inhibitor (BTKi) ibrutinib is used in relapsed/resistant central nervous system (CNS) lymphoma because it can cross the blood-brain barrier and is effective as a single drug. Its efficacy has been demonstrated in combination with rituximab and high-dose methotrexate. CNS lymphomas are aggressive lymphomas, and responses to single-agent therapies are generally poor or insufficient. Also, even well-established agents used in lymphoma treatment may sometimes be unavailable worldwide, and drug restrictions may be experienced worldwide. Thiotepa is one of these agents. In this case series, we summarized the iMARIX treatment in which we used ibrutinib in combination with high-dose methotrexate, cytarabine and rituximab instead of thiotepa for the treatment of primary/secondary CNS lymphomas. **Methods:** The participants diagnosed with primary/secondary CNS lymphoma and treated between August 2022 and December 2025, received rituximab 375 mg/ m2 (one day), 3.5 g/m2 methotrexate (one day), 2x2 g/ m2 cytarabine (two days), and ibrutinib 560 mg/day in each course. Ibrutinib was continued provided that platelet count is over 30.000/ mm3 and neutrophil count is over 500/ mm3. Patient data were collected retrospectively. **Results:** 17 patients were treated with iMARIX protocol during the study course. Male/ female ratio was 8 (47%)/ 9 (53%) and the median age was 53 (21- 71). 8 (47 %) of the participants had primary whereas 9 (53 %) had secondary CNS lymphoma. 4 (23.5%) participants died of either relapse or sepsis during the study period. The median overall survival was 16.3 months (4- 31.6). 13 (76,5 %) patients underwent consolidative autologous stem cell transplantation (ASCT). One patient experienced atrial fibrillation due to ibrutinib use. One patient experienced relapse after ASCT and was further treated with allogeneic stem cell transplantation. **Conclusions:** Although our patient series is small, the results suggest that the combination of ibrutinib with high-dose methotrexate, rituximab and cytarabine is a combination that may yield good clinical results with an acceptable tolerance and adverse effect profile. Research Sponsor: None.

7087 **Poster Session**

Evaluating the incidence and predictors of chronic opioid use in early survivorship for patients with diffuse large B-cell lymphoma. First Author: Mithunan Ravindran, Department of Medicine, University of Toronto, Toronto, ON, Canada

Background: Exposure to opioids during cancer treatment is common and may lead to new persistent opioid use (NPOU) in a subset of patients in survivorship. There are limited data on the incidence and predictors of NPOU in a diffuse large B-cell lymphoma (DLBCL) cohort. **Methods:** We conducted a population-based cohort study utilizing health administrative datasets from Ontario, Canada. We included patients $\geq$18 years old with DLBCL who received first-line rituximab-based chemoimmunotherapy from 2014 to 2021 and survived $>$365 days after treatment. We considered patients to be opioid exposed if they filled $\geq$1 opioid prescriptions from 90 days prior to and 180 days after first rituximab-based chemoimmunotherapy (the exposure window). The primary outcome was NPOU defined as filling $\geq$1 opioid prescriptions in each of the two half-years of follow up after the exposure window (i.e. within both 0-180 days and 181-365 days). We used a multivariable Poisson regression model with robust error variance to assess the relative risk (RR) of NPOU while controlling for covariates. **Results:** Our cohort consisted of 4,988 patients with DLBCL. The median age was 66 years and 32.3% had relapsed/refractory disease. Opioid exposure occurred in 55.0% of the entire cohort. Of the entire cohort, 6.7% fulfilled criteria for NPOU including 10.4% of exposed patients compared to 2.4% of unexposed patients. In the multivariable analysis, exposed patients were four times more likely to develop NPOU (RR 3.81, 95% CI 2.85-5.07). After adjustment, other statistically significant predictors of NPOU included palliative care use in follow-up (RR 2.77, 95% CI 2.21-3.47), relapsed/refractory disease (RR 1.63, 95% CI 1.33-1.99), comorbid disease burden (RR 1.50, 95% CI 1.01-2.23), and prior mental health diagnoses (RR 1.27, CI 1.01-1.58). **Conclusions:** Over 1 in 2 DLBCL patients were exposed to opioids during treatment and 1 in 10 exposed patients developed NPOU. Exposed patients were four times more likely to develop NPOU. Our study identified several clinically relevant predictors of NPOU in DLBCL, which may enable clinicians to identify high-risk patients who would benefit from early intervention. Research Sponsor: None.

7088 Poster Session

Survival outcomes of plasmablastic lymphoma according to immune status. First Author: Hien Lau, Department of Medicine, University of Southern California (USC), Los Angeles, CA

Background: Plasmablastic lymphoma (PBL) is a rare, aggressive subtype of NHL associated with HIV, but also reported in other immunosuppressed states. Outcomes of PBL patients with non–HIV-related immunosuppression remain poorly defined. We compared clinicopathological features and survival outcomes among patients with HIV-associated immunosuppression (IS-HIV), and non–HIV-related immunosuppression (IS) and those without HIV or history of immunosuppression (IC). **Methods:** We retrospectively analyzed 35 patients with pathologically confirmed PBL, including 14 IC, 16 IS-HIV, and 5 IS patients. Associations between immune status and clinical characteristics were assessed using chi-square analysis. Progression-free survival (PFS) and overall survival (OS) were evaluated using Kaplan–Meier analysis with log-rank testing and multivariable Cox proportional hazards regression. **Results:** Median ages were 49, 45, and 56 years for IC, IS-HIV, and IS groups, with male predominance across all groups (71.4%, 93.8%, and 100%), respectively. Epstein–Barr virus positivity was significantly higher in IS-HIV (93.8%) and IS (40.0%) compared with IC patients (14.3%; $p< 0.01$). IS patients had lower rates of extranodal involvement than IC and IS-HIV patients (80.0% vs 100%; $p= 0.04$). Immune status was not associated with age, sex, ethnicity, ECOG performance status, stage, IPI score, radiation therapy, CNS prophylaxis, or autologous stem cell transplantation. Rates of primary refractory disease and relapse did not differ significantly among IC (14.3%, 21.4%), IS-HIV (31.3%, 12.5%), and IS (40.0%, 0%) groups (p = .42 and p = .48, respectively). Response rates following first-line therapy were numerically lower in IS patients but did not differ significantly ($p= 0.23$). Median follow-up was 30, 21, and 4 months for IC, IS-HIV, and IS groups, respectively. Median PFS was 60.5 months, not reached, and 4 months for IC, IS-HIV, and IS groups, respectively ($p= 0.03$). One- and two-year OS rates were 78.6% and 64.3% (IC), 74.0% and 65.8% (IS-HIV), and 0% and 0% (IS; $p= 0.02$). On multivariable analysis, IS status was associated with inferior PFS (HR 3.6, $p= 0.03$) and OS (HR 3.9, $p= 0.03$), whereas IS-HIV was not. **Conclusions:** PBL patients with non–HIV-related immunosuppression experienced significantly inferior PFS and OS compared with IC and IS-HIV patients. Although lower response rates and higher primary refractory disease were observed in IS patients, these differences did not reach statistical significance, likely due to small sample size. Consistent with prior reports, HIV-associated immunosuppression was not associated with worse survival. Larger studies are needed to better define disease biology and optimize therapeutic strategies for this high-risk population. Research Sponsor: None.

7089 Poster Session

Survival of hematologic malignancy in patients with early-stage chronic kidney disease (SHIP-CKD). First Author: Songphol Tungjitviboonkun, University of California, San Francisco, San Francisco, CA

Background: Chronic kidney disease (CKD) is a common comorbidity among cancer patients and may influence treatment options and outcomes. However, the independent effect of CKD in patients with hematologic malignancies remains unclear. **Methods:** We conducted a retrospective cohort study using electronic medical records, including 1,238 adult patients diagnosed with hematologic malignancies between 2015 and 2019. Patients with CKD stages 1–3A were compared to those without CKD. The primary outcome was 5-year all-cause mortality. We used stratified Cox proportional hazards models adjusted for age, sex, and comorbidities (HIV, diabetes, hypertension, and COPD) and performed 1:1 propensity score matching without replacement. Subgroup analyses by cancer subtypes were performed. **Results:** Among 1,238 patients, 529 (42.7%) had CKD. CKD patients were older (67 vs. 55 years), with higher rates of hypertension (66.0% vs. 48.0%). Five-year mortality was higher in the CKD group (24.4% vs. 17.8%, p=0.006). In adjusted Cox models, CKD was not significantly associated with mortality (HR 1.08; 95% CI: 0.82–1.43). Subgroups by stages showed no significant risk: stage 1 (HR 1.27; 95% CI: 0.76–2.13), stage 2 (HR 1.05; 95% CI: 0.77–1.43), stage 3A (HR 1.03; 95% CI: 0.60–1.78). In matched analysis (n=758), CKD remained non-significant (HR 1.04; 95% CI: 0.77–1.41). **Conclusions:** Early-stage CKD was common and linked to higher unadjusted mortality, but not with increased mortality after adjusting for covariates. These findings suggest that early-stage CKD may not independently impact survival among patients with hematologic malignancies. Research Sponsor: None.

Baseline characteristics by CKD status after propensity score matching.

	No CKD	CKD	P-value
	N=379	N=379	
Age (years)	63.0 [57.0,68.0]	64.0 [56.0,69.0]	0.886
BMI (kg/m^2)	26.1 [23.5,29.9]	25.9 [23.3,29.8]	0.626
CKD			
No CKD	379 (100.0%)	0 (0.0%)	<0.00
G1	0 (0.0%)	58 (15.3%)	
G2	0 (0.0%)	267 (70.4%)	
G3a	0 (0.0%)	54 (14.2%)	
Sex			
Female	154 (40.6%)	165 (43.5%)	0.46
Male	225 (59.4%)	214 (56.5%)	
Race/Ethnicity			
White	207 (54.6%)	245 (64.6%)	
Latino	67 (17.7%)	39 (10.3%)	
Asian	52 (13.7%)	44 (11.6%)	
Black or African American	21 (5.5%)	24 (6.3%)	
Multi-Race/Ethnicity	11 (2.9%)	11 (2.9%)	
Native American or Alaska Native	0 (0.0%)	2 (0.5%)	
Native Hawaiian or Other Pacific Islander	2 (0.5%)	0 (0.0%)	
Southwest Asian and North African	3 (0.8%)	3 (0.8%)	
Other	11 (2.9%)	5 (1.3%)	
Unknown/Declined	5 (1.3%)	6 (1.6%)	
Disease			
Follicular lymphoma	3 (0.8%)	3 (0.8%)	1.00
Non-follicular lymphoma	67 (17.7%)	67 (17.7%)	
Myeloma	200 (52.8%)	200 (52.8%)	
Acute leukemia	56 (14.8%)	56 (14.8%)	
Chronic leukemia	53 (14.0%)	53 (14.0%)	
HIV status			
No HIV	372 (98.2%)	374 (98.7%)	0.77
HIV	7 (1.8%)	5 (1.3%)	
Diabetes status			
No DM	316 (83.4%)	318 (83.9%)	0.92
DM	63 (16.6%)	61 (16.1%)	
Hypertension status			
No HT	151 (39.8%)	154 (40.6%)	0.88
HT	228 (60.2%)	225 (59.4%)	
COPD status			
No COPD	369 (97.4%)	372 (98.2%)	0.63
COPD	10 (2.6%)	7 (1.8%)	

7090 Poster Session

Comparative effectiveness of CAR-T and bispecific antibodies in relapsed/refractory large B-cell lymphoma: A network meta-analysis of phase III trials. First Author: Aniqa Baloch, The Wright Center for GME, Scranton, PA

Background: Second-line and later-line cellular therapies and bispecific antibodies have transformed the management of relapsed/refractory large B-cell lymphoma (LBCL), yet comparative efficacy across platforms remains uncertain due to the absence of head-to-head trials. We conducted a network meta-analysis (NMA) to compare disease control and overall survival (OS) across contemporary randomized phase III studies, representing the first synthesis of contemporary CAR-T and bispecific antibody phase III data. **Methods:** A frequentist graph-theoretical NMA was performed using trial-level hazard ratios (HRs) extracted from five randomized phase III trials (ZUMA-7, TRANSFORM, BELINDA, STARGLO, SUNMO). Treatments included axicabtagene ciloleucel, lisocabtagene maraleucel, tisagenlecleucel, glofitamab-GemOx, mosunetuzumab-polatuzumab, and chemoimmunotherapy as the reference. Outcomes were disease control (EFS/PFS) and OS. Random-effects models were applied, and P-scores were used to rank treatment hierarchy. **Results:** Five trials encompassing approximately 2,000 patients were included. For disease control, lisocabtagene maraleucel (HR 0.35, 95% CI 0.23–0.53), axicabtagene ciloleucel (HR 0.40, 95% CI 0.31–0.51), glofitamab-GemOx (HR 0.40, 95% CI 0.28–0.57), and mosunetuzumab-polatuzumab (HR 0.41, 95% CI 0.29–0.58) each significantly improved outcomes, whereas tisagenlecleucel did not (HR 1.07, 95% CI 0.82–1.40). Ranking favored lisocabtagene maraleucel (P-score 0.82), followed by axicabtagene ciloleucel (0.67), glofitamab-GemOx (0.67), and mosunetuzumab-polatuzumab (0.64). For OS, lisocabtagene maraleucel (HR 0.59, 95% CI 0.40–0.87), glofitamab-GemOx (HR 0.62, 95% CI 0.43–0.89), and axicabtagene ciloleucel (HR 0.73, 95% CI 0.55–0.97) significantly improved survival, while mosunetuzumab-polatuzumab showed a non-significant favorable trend (HR 0.80, 95% CI 0.52–1.24). Tisagenlecleucel did not improve OS (HR 1.24, 95% CI 0.83–1.85). OS rankings again favored lisocabtagene maraleucel (P-score 0.84), followed by glofitamab-GemOx (0.80) and axicabtagene ciloleucel (0.61). **Conclusions:** Across randomized phase III evidence, lisocabtagene maraleucel demonstrated the highest probability of being the most effective therapy for both disease control and overall survival in relapsed/refractory LBCL, followed closely by glofitamab-GemOx and axicabtagene ciloleucel, while tisagenlecleucel consistently ranked lowest. Although limited by cross-trial heterogeneity inherent to indirect comparisons, these findings highlight meaningful differences across platforms and may inform treatment sequencing while prospective head-to-head studies mature. Research Sponsor: None.

7091 Poster Session

Utility of a modified geriatric assessment to identify impairments in adults of all ages with lymphoma: A prospective observational cohort study. First Author: Christopher Edward Jensen, Lineberger Comprehensive Cancer Center, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: Performance status assessments may overlook important health vulnerabilities in adults with cancer. While geriatric assessment (GA) systematically evaluates multiple domains including physical function, cognition, psychological health, comorbidity, and nutrition, it has been predominantly studied in older adults. We evaluated the prevalence and patterns of GA-identified deficits among adults of all ages initiating systemic therapy for lymphoma. **Methods:** Adults with lymphoma enrolled in a prospective registry at an academic cancer center from 2018-2025 completed a modified Cancer and Aging Research Group (CARG) GA at treatment initiation. The assessment included validated measures across eight domains: mobility (Timed Up and Go), falls history, instrumental activities of daily living (IADLs), medication burden, comorbidities, weight loss, cognition (Blessed Orientation-Memory-Concentration test), and psychological health (Mental Health Index-13). Karnofsky Performance Status (KPS) was documented. Prevalence of deficits was compared between adults <65 and ≥65 years. **Results:** Among 97 participants (mean age 57 years, range 22-84; 39% ≥65 years), 94% had normal KPS (≥80). Despite preserved performance status, 56% had multiple (≥2) GA-identified deficits, and only 21% had zero deficits. The most common deficit was unintentional weight loss (43% overall). Among younger adults (<65 years), substantial proportions reported weight loss (34%), falls (27%), IADL impairment (27%), and anxiety or depression (45%). Most deficits did not differ significantly between age groups, though weight loss, multimorbidity (≥4 comorbidities), and severe polypharmacy (≥10 medications) were more prevalent in older adults. **Conclusions:** GA reveals high prevalence of health-related deficits across multiple domains in adults with lymphoma regardless of age, despite preserved performance status. These findings support a shift toward needs-based rather than age-based approaches to identify individuals who may benefit from supportive care interventions. Research Sponsor: None.

Functional measures among adults treated for lymphoma, stratified by age.

Deficit Domain	Full Cohort % (95% CI)	Age < 65 % (95% CI)	Age ≥ 65 % (95% CI)	p**
Weight Loss	43 (33-53)	34 (23-47)	57 (41-71)	**0.035**
Mental Health	37 (28-46)	45 (33-58)	24 (13-39)	0.051
IADL Impairment	29.9 (21.7-39.6)	27.1 (17.4-39.6)	34.2 (21.2-50.1)	0.50
Falls (≥ 1 in past 6 months)	24 (16-33)	27 (17-40)	18 (9-33)	0.46
Polypharmacy (≥ 10 medications)	17 (11-25)	7 (3-16)	32 (20-49)	**0.002**
Cognitive Impairment (BOMC ≥ 5)	32 (23-43)	28 (18-42)	38 (24-54)	0.36
High Comorbidity (≥ 4 conditions)	10 (6-18)	5 (2-14)	18 (9-33)	**0.047**
TUG >14 seconds	5 (2-12)	4 (1-14)	6 (2-19)	1.0

*Reflects missing values (1 each for weight loss, MHI13, daily medications, and comorbid conditions, 10 for BOMC, and 16 for TUG).

**P-values from Fisher's exact test.

7092 **Poster Session**

Temporal trends in ischemic heart disease mortality among lymphoma patients in the United States, 1999–2023: A 25-year nationwide analysis. First Author: Prithvi Raghavan, Sinai Hospital of Baltimore, Baltimore, MD

Background: Enhanced lymphoma survival has transitioned clinical priorities toward non-malignant late effects, particularly cardiovascular morbidity. Although life-extending therapies like radiation and anthracyclines are effective, their cardiotoxic profiles significantly increase Ischemic Heart Disease (IHD) risk. Despite this, longitudinal trends and demographic disparities in lymphoma-IHD mortality remain under-investigated. This study analyzes 24 years of data to characterize mortality shifts and identify vulnerable populations, aiming to optimize integrated cardio-oncology management. **Methods:** We conducted a population-based retrospective analysis using the CDC WONDER Multiple Cause of Death database from 1999 to 2023. Deaths among individuals with lymphoma were identified using ICD-10 codes C81–C85, and IHD-related deaths were identified using ICD-10 codes I20–I25. Age-adjusted mortality rates (AAMRs) per 100,000 persons were calculated and stratified by sex, race/ethnicity, geographic region, urbanization status, and place of death. Temporal trends were analyzed using Joinpoint regression to estimate annual percent change (APC) and average annual percent change (AAPC). **Results:** Between 1999 and 2023, a total of 61,480 deaths were reported among individuals with both lymphoma and IHD in the United States. The overall AAMR declined from 0.93 in 1999 to 0.62 in 2023. Females had a lower overall AAMR compared with males (0.43 vs 1.13). By race/ethnicity, Non-Hispanic individuals had a higher AAMR than Hispanic individuals (0.74 vs 0.46). Regionally, the Midwest had the highest overall AAMR (0.84), while the South had the lowest (0.64). A higher AAMR was observed in non-metropolitan compared with metropolitan areas (0.84 vs 0.69). Most deaths occurred in inpatient medical facilities (22,633 deaths; 36.8%), followed by deaths at home (18,922 deaths; 30.8%). **Conclusions:** While mortality has declined overall, continued excess risk among males, rural residents, and Midwestern populations highlights inequities in care delivery. Expanding integrated cardio-oncology programs in non-metropolitan areas may further reduce national mortality. Research Sponsor: None.

Comparative analysis of age-adjusted mortality rates (AAMR) for comorbid lymphoma and ischemic heart disease by demographic and geographic subgroups (1999–2023).

Category	Group with Highest AAMR	Group with Lowest AAMR
Sex	Males (1.13)	Females (0.43)
Ethnicity	Non-Hispanic (0.74)	Hispanic (0.46)
Region	Midwest (0.84)	South (0.64)
Urbanicity	Non-metropolitan (0.84)	Metropolitan (0.69)

7093 **Poster Session**

Multivariable analyses (MVAs) of overall survival (OS) in the phase 3 SUNMO, STARGLO, and POLARGO trials in relapsed/refractory large B-cell lymphoma (LBCL). First Author: Matthew Matasar, Rutgers Cancer Institute, New Brunswick, NJ

Background: Phase 3 trials, notably SUNMO (NCT05171647), STARGLO (NCT04408638) and POLARGO (NCT04182204), have shown superior efficacy of combination treatments over rituximab (R) + gemcitabine and oxaliplatin (GemOx) in second line or later LBCL. However, baseline imbalances may impact the robustness of efficacy results, even with stratified randomization. We conducted MVAs of SUNMO, STARGLO and POLARGO to assess OS. As the target number of OS events was not reached at the SUNMO interim OS analysis, to increase the sample size we also conducted a pooled analysis of mosunetuzumab (Mosun) + polatuzumab vedotin (Pola; data from SUNMO and GO40516 [Phase 2; NCT03671018]) vs R-GemOx (comparators from SUNMO, STARGLO and POLARGO). **Methods:** A multivariable Cox regression model was used to estimate treatment effect while adjusting for potential confounding factors selected by a systematic process involving: 1) univariable analysis of prespecified baseline factors; 2) multicollinearity assessment of pairwise correlation among selected factors; 3) MVA of the experimental arm (SUNMO: Mosun-Pola; STARGLO: glofitamab [Glofit]-GemOx; POLARGO: Pola-R-GemOx) vs the control arm (R-GemOx) and selected non-collinear prognostic baseline factors from steps 1 and 2. **Results:** In SUNMO, patients treated with Mosun-Pola had more high-risk features, such as a higher ECOG performance status and greater bulky disease, vs those treated with R-GemOx. The MVA-adjusted hazard ratio (HR, 0.65 [95% confidence interval [CI]: 0.41–1.02]) was more favorable than the unadjusted interim OS HR (0.80 [95% CI: 0.54–1.20]) for Mosun-Pola vs R-GemOx. The MVA-adjusted HR for POLARGO was also more favorable than the unadjusted HR; the HR for STARGLO remained largely unchanged (Table). A pooled MVA was used to increase the sample size, noting baseline differences between trials (e.g. $\geq$2 prior lines of therapy: SUNMO, 56%; STARGLO, 37%; POLARGO, 35%). In this pooled analysis, OS HRs favored Mosun-Pola vs R-GemOx in the unadjusted (HR, 0.62 [95% CI: 0.48–0.81]) and MVA-adjusted (HR, 0.59 [95% CI: 0.44–0.81]) models, with lower HRs and narrower 95% CIs vs the MVA of SUNMO alone. **Conclusions:** The MVAs support favorable OS benefits in SUNMO, STARGLO and POLARGO, all with an MVA-adjusted OS HR $\leq$0.65 vs R-GemOx. The pooled MVA further supports the OS benefit of Mosun-Pola vs R-GemOx. Overall, the MVAs show that baseline imbalances can influence OS estimates, thus multivariable adjustment is important when interpreting pooled or cross-trial comparisons. Clinical trial information: NCT05171647, NCT04408638, NCT04182204, NCT03671018. Research Sponsor: F. Hoffmann-La Roche Ltd.

	SUNMO n=208	STARGLO n=274	POLARGO n=255	Pooled Mosun-Pola vs R-GemOx n=465
Median follow-up, months (range)	23.2 (0–32)	20.7 (0–36)	24.6 (0–34)	–
MVA-adjusted OS HR (95% CI)	0.65 (0.41–1.02)	0.63 (0.44–0.90)	0.52 (0.36–0.74)	0.59 (0.44–0.81)
Unadjusted OS HR (95% CI)	0.80 (0.54–1.20)	0.62 (0.43–0.88)	0.60 (0.43–0.83)	0.62 (0.48–0.81)

7094 **Poster Session**

Iopofosine I-131 after BTK inhibitors in Waldenström macroglobulinemia: CLOVER-WaM subgroup efficacy and safety. First Author: Jarrod Longcor, Cellectar Biosciences, Inc, Florham Park, NJ

Background: Waldenström Macroglobulinemia (WM) remains incurable with current available therapeutic options. Treatment options for relapsed/refractory pts are limited and often continuous, underscoring the need for new agents with novel mechanisms of action and pt-centered, fixed duration therapy. Iopofosine I 131 is a novel radiopharmaceutical compound composed of a lipid raft-targeting phospholipid ether covalently bound to ^{131}I, a beta emitting radioisotope. Here, we report preliminary sub-group results of the CLOVER-WaM study [NCT02952508] in WM pts treated with a Bruton's Tyrosine Kinase inhibitor (BTKi) immediately prior to iopofosine. **Methods:** Eligible WM pts had received >2 prior therapies and had symptomatic disease requiring therapy according to consensus recommendations for WM. Treatment consisted of 2 cycles of iopofosine I 131 administered at 15 mCi/m^2 on days 1 and 15 of each 57-day cycle. The primary efficacy endpoint was major response rate (MRR; partial response or better, as determined by the modified IWWM-VI). Secondary and exploratory endpoints included overall response rate (ORR), treatment-free survival (TFS), progression free survival (PFS), duration of response (DOR), and clinical benefit rate (CBR; stable disease or better). Herein, efficacy endpoints were assessed in the modified intent-to-treat (mITT) population (all pts who received $\geq$60 mCi total administered dose of iopofosine I 131), and whose treatment regimen prior to iopofosine included a BTKi. Safety was evaluated using CTCAE v4.03 in pts who received $\geq$1 dose of iopofosine. Data cut off for this analysis was Jan. 16, 2026. **Results:** As previously reported, 65 pts were dosed and 55 are included in the mITT population. Of those, 22 (40%) had received a BTKi containing regimen immediately prior to iopofosine; and 11 who previously received at least 2 regimens utilizing BTKis and 12 who were refractory to rituximab. In this subgroup, median age was 70.5 (range 55-88), 17 (77%) were male, and 5 (23%) were female. The median number of prior therapies was 3 (range 2-7), 15/22 (68%) were MYD88 mutated and 18/22 (82%) were TP53 wildtype. The MRR was 15/22 (68.2%), ORR was 19/22 (86.4%) and CBR was 100%, median PFS was 12 months (range 1.6 to 28.0) and median TFS was 19.1 months (range 2.5-34.4). Grade $\geq$ 3, related treatment emergent adverse events (TEAE) occurring in > 10% of pts included anemia (41%), leukopenia (41%), neutropenia (58%), and thrombocytopenia (86%). **Conclusions:** Iopofosine I 131 demonstrated significant efficacy; 100% CBR, 86.4% ORR and 68.2% MRR with a median PFS of 12 months (range: 1.6 – 28.0 months) in a pt population with no current standard of care therapy. The treatment was well-tolerated with a manageable toxicity profile with cytopenias as the only Grade 3 or greater TEAE. Based on the results of this pivotal trial, iopofosine I 131 could be a promising novel treatment for WM pts after BTKi therapy. Clinical trial information: NCT02952508. Research Sponsor: None.

7095 **Poster Session**

Analysis of sex-based differences in tumor microenvironments within hematopoietic and reticuloendothelial system malignancies. First Author: Vera Vaz, Renown Health/University of Nevada Reno School of Medicine, Reno, NV

Background: While sex-specific disease incidence, genomic profiles, and survival outcomes are widely recognized in hematologic malignancies, the biological mechanisms and tumor microenvironment (TME) factors driving these sex-based disparities remain largely undefined, particularly at the level of the TME, which plays a key role in immune surveillance, therapeutic response, and disease progression. This meta-analysis investigates whether significant differences exist in the abundance of various cell types between males and females within lymphoid and myeloid leukemias, plasma cell tumors, mature B-cell lymphomas, and acute lymphoblastic leukemia. Characterizing these variations is essential for developing tailored therapeutic strategies that optimize clinical outcomes for both sexes. **Methods:** Computational meta-analysis was performed on the TCGA National Database, using xCell enrichment scores across transcriptomic samples from hematopoietic and reticuloendothelial system tumors, comparing males (n= 3,829) and females (n= 2,995). Mann-Whitney U testing with Bonferroni correction identified cell populations with differential enrichment (padj$<$0.05). Cohorts were balanced for age, race, and tumor type (primary, recurrence, metastatic) (all p$>$0.05). **Results:** Of the 64 cell types screened, 12 exhibited a significant difference in abundance between males and females. Nine of these were female-enriched populations (padj $<$0.01). These included erythrocytes (Mean Difference [Male-Female]: -0.5192), neutrophils (-0.4343), eosinophils (-0.4147), GMP (-0.1345), platelets (-0.1097), common myeloid progenitors (CMP) (-0.0917), mast cells (-0.0640), MPP (-0.0556), and megakaryocytes (-0.0131) indicating higher relative enrichment in females. Conversely, the male-enriched populations (padj $<$0.02) consisted of DC (0.2210), Th2 cells (0.0761), and Th1 cells (0.0634). **Conclusions:** This study demonstrates sex-based differences in TME cellular abundance in hematopoietic and reticuloendothelial tumors. Females exhibited a higher presence of early-stage progenitor populations, such as MPP and CMP, and innate immune cells, including neutrophils and eosinophils, potentially due to hormonal influences, differences in myelopoiesis, or sex-linked immune polarization. In contrast, males had a higher presence of DC and Th cells. Among all cell types analyzed, erythrocytes exhibited the greatest magnitude of difference in abundance between sexes, showing potential distinctions in metabolic and oxygenation profiles. These findings highlight biologically meaningful sex specific variations in the TME, underscoring the need for further mechanistic studies linking sex-specific TME compositions to therapeutic responses and incorporating biological sex as a critical variable in immunotherapy trial design. Research Sponsor: None.

7096 **Poster Session**

Real-world outcomes of mogamulizumab retreatment in cutaneous T-cell lymphoma: A single-center retrospective study. First Author: Shahzeem Bhayani, Washington Univeristy in St. Louis, St. Louis, MO

Background: Mogamulizumab, monoclonal antibody against CCR4, is approved for relapsed/refractory cutaneous T cell lymphoma (CTCL), with an overall response rate of 28%in CTCL. The most common toxicity is mogamulizumab-associated rash (MAR), occurring in ~24% of patients and reported in up to 88% of responders, frequently leading to treatment discontinuation. Given the limited therapeutic options in CTCL, retreatment with mogamulizumab is clinically appealing but not well described. We report a single center experience with mogamulizumab retreatment in patients with CTCL. **Methods:** We conducted a single-center retrospective study of all adult patients with CTCL treated with mogamulizumab from 2013 to 2025. Retreatment was defined as reinitiation after a >90-day treatment-free interval. Disease status, patient characteristics, response and toxicity to therapy was collected. **Results:** Among 54 CTCL patients treated with mogamulizumab, 13 (24%) (MF=7, SS=6) underwent retreatment. Median age at diagnosis was 67 years (range, 44 - 84) and mostly male (69%). Patients had a median of 5 prior systemic therapy lines (range, 3–9). The median interval from initial mogamulizumab discontinuation to retreatment was 11.4 months (range 3.1-40.2). During initial mogamulizumab exposure, ORR 92.3% (12/13, 8 CR, 4 PR).11 discontinued mogamulizumab due to rash, 1 due to clinical response and 1 with PD. Retreatment dosing schedules included weekly administration in 2 patients (15%), every-2-week dosing in 8 (62%), and every-4-week dosing in 3 (23%). On retreatment, ORR was 38.5% (5/13) with CR in 2 patients and PR in 3, SD in 3 and progressive disease (PD) in 5. Median number of doses on retreatment was 5 (range 1-44). Among retreatment responders (CR/PR; n=5), median DOR was 15.0 months (range, 6.2–28.0). Median PFS from retreatment initiation was 4.0 months (range, 0.0–40.7) and estimated 2 -year OS was 84.6%. Both deaths were unrelated to CTCL progression or mogamulizumab-related toxicity. MAR occurred in 10/13 (76.9%) patients on retreatment. Rechallenge strategies included temporary treatment interruption until resolution of MAR (n=7) and increasing dosing intervals (n=3). Rash was predominantly maculopapular or morbilliform, most commonly involving the trunk and extremities. All MAR events were CTCAE grade 1-2. MAR was managed with topical steroids (n=9), oral steroids (n=1), and cessation of mogamulizumab (n=9). **Conclusions:** In this real-world, heavily pretreated CTCL cohort, mogamulizumab retreatment demonstrated meaningful clinical activity with durable responses in patients despite prior exposure. Although rash was common, it was most often low to moderate grade, responsive to standard management, and retreatment or rechallenge after resolution was feasible. Research Sponsor: None.

TPS7097 **Poster Session**

Lisocabtagene maraleucel (liso-cel) as first-line (1L) therapy for transplant-ineligible patients (pt) with primary central nervous system lymphoma (PCNSL): The CAROLYN study. First Author: Allison Marie Winter, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: Treatment of PCNSL is based on high-dose methotrexate (HD-MTX) induction chemotherapy, followed by consolidative autologous stem cell transplantation (ASCT) in eligible pts. Those deemed transplant ineligible have a high risk of relapse and are a population with a significant unmet therapeutic need. Liso-cel, an autologous, CD19-directed chimeric antigen receptor (CAR) T cell product, demonstrated promising results in secondary CNS lymphoma. In a phase 2 study (NCT03484702), 4 of 5 pts with PCNSL treated with liso-cel after failure of 1L high-dose chemotherapy and ASCT achieved a CR. Here, we report the study design of the CAROLYN study (NCT07015242; currently enrolling), which is evaluating efficacy and safety of liso-cel as 1L therapy in transplant-ineligible pts with PCNSL. **Methods:** This open-label, single-arm, multicenter, phase 2 study will enroll approximately 65 pts. The primary endpoint is investigator-determined 12-month PFS rate (from infusion date). Secondary endpoints include additional efficacy assessments (PFS, event-free survival, and OS from enrollment; CR rate, ORR, and duration of response), safety (AEs, serious AEs, and AEs of special interest), and health-related quality of life. Key inclusion criteria are newly diagnosed PCNSL confirmed by local pathology, receipt of $\geq$ 2 cycles of standard-of-care regimens, transplant ineligibility (defined by investigator assessment and either age $\geq$ 65 years or hematopoietic stem cell transplantation-specific comorbidity index score $\geq$ 3), MTX-sensitive disease (CR or PR), and ECOG PS $\leq$ 2. Key exclusion criteria include diagnosis of secondary CNS lymphoma, primary intraocular lymphoma, primary vitreoretinal lymphoma, and isolated cerebrospinal fluid involvement. Enrolled pts can receive optional holding therapy with a HD-MTX–based regimen while awaiting leukapheresis. After leukapheresis, bridging therapy with a HD-MTX–based regimen is permitted during liso-cel manufacturing. Before liso-cel infusion, pts receive lymphodepleting chemotherapy consisting of fludarabine (30 mg/m^2/day for 3 days) and cyclophosphamide (300 mg/m^2/day for 3 days). Pts then receive a single infusion of liso-cel at a target dose of 100 $\times$ 10^6 CAR$^+$ T cells. After infusion, pts remain in the treatment period for 90 days and then transition to follow-up for 2 years from enrollment. The total study duration is expected to be 3 years; pts who receive liso-cel can enroll in a separate 15-year long-term follow-up (NCT03435796). Clinical trial information: NCT07015242. Research Sponsor: This study was funded by Juno Therapeutics, a Bristol-Myers Squibb Company.

TPS7098 **Poster Session**

KITE-753: A phase 2 study of an autologous anti-CD19/CD20 CAR T-cell therapy in CAR-naive patients with relapsed/refractory (R/R) large B-cell lymphoma (LBCL). First Author: Saurabh Dahiya, Stanford University, Stanford, CA

Background: CD19-directed CAR T-cell therapy has become the standard of care for R/R LBCL; however, some patients are refractory to CD19 CAR T-cell therapy and a subset of responders relapse (Eyre et al. *Ann Oncol*. 2025, Westin et al. *N Engl J Med*. 2023). KITE-753 is an investigational, bicistronic, CD19/CD20 CAR T-cell therapy with a parallel CAR design to optimally engage two tumor antigens, synergistic CD28/4-1BB costimulation to enhance T-cell function, and a rapid manufacturing process that preserves naive and stem cell memory T cells. It is designed to improve cure rates while limiting toxicity for patients with R/R LBCL. In vitro, KITE-753 demonstrated potent antitumor activity at a dose >25-fold lower than an identical product manufactured with a traditional ex vivo expansion period (Murakami et al. ASH 2024). Phase 1 assessment of KITE-753 showed very low rates of immune effector cell-associated neurotoxicity syndrome (ICANS) and no high-grade cytokine release syndrome or ICANS in patients with R/R LBCL at the intended pivotal dose level. Furthermore, high response rates were observed with 79% of patients achieving complete response (CR). CAR T-cell expansion was comparable to KITE-363 and axi-cel despite a 10-fold lower dose (Dahiya et al. ASH 2025, Dahiya et al. ASCO 2025). Based on Phase 1 outcomes, the Phase 2 dose was established as 2$\times$10^5 CAR T cells/kg. This Phase 2 study will evaluate the safety and efficacy of KITE-753 in CAR-naive patients with R/R LBCL. **Methods:** In this open-label, multicenter, single-arm study, patients will undergo leukapheresis and receive optional bridging therapy, followed by lymphodepleting chemotherapy (cyclophosphamide [300 mg/m^2/day] and fludarabine [30 mg/m^2/day]) from Day -5 to Day -3, and infusion of KITE-753 at a target dose of 2$\times$10^5 CAR T cells/kg on Day 0. The primary endpoint is objective response rate (CR rate + partial response rate) assessed by central review per Lugano Classification (Cheson et al. *J Clin Oncol*. 2014). Secondary outcomes include CR rate, duration of response, progression-free survival, overall survival, and safety. The target enrollment is 80 patients. Eligible adults have histologically confirmed R/R LBCL (including transformation of indolent lymphomas and primary mediastinal B cell lymphoma) after $\geq$2 prior lines of systemic therapy (including anti-CD20 mAb or bispecific antibody + anthracycline). Other key inclusion criteria are adequate bone marrow and organ function and ECOG performance status $\leq$2. Key exclusion criteria are prior CAR T-cell therapy or active central nervous system involvement from lymphoma. This study is currently open and actively accruing patients (NCT04989803). Clinical trial information: NCT04989803. Research Sponsor: Kite, a Gilead Company.

TPS7099 **Poster Session**

Sonrotoclax (BGB-11417) + zanubrutinib (SZ) vs venetoclax + acalabrutinib (AV) in treatment-naive chronic lymphocytic leukemia (TN CLL): A phase 3 randomized trial design (CELESTIAL-TNCLL-2). First Author: Mazyar Shadman, Fred Hutchinson Cancer Center, University of Washington, Seattle, WA

Background: Inhibition of B-cell lymphoma 2 (BCL2) and Bruton tyrosine kinase (BTK) has emerged as an effective fixed-duration treatment (tx) strategy that can induce high rates of undetectable minimal residual disease (uMRD) in patients (pts) with TN CLL. AV is approved in the EU as a first-line fixed-duration tx for TN CLL. Sonrotoclax, a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Zanubrutinib is a highly potent next-generation BTK inhibitor that is approved in the US/EU for CLL. In an ongoing phase 1/1b trial (NCT04277637), SZ has had promising efficacy, with a 100% ORR (n=135) and high rates of blood uMRD at 10^{-4} sensitivity (uMRD4) in pts with TN CLL, including those with high-risk disease features. SZ is generally well tolerated, with neutropenia as the most common grade $\geq$3 TEAE and no laboratory or clinical TLS events occurred. The phase 3 trial BGB-11417-304 (NCT07277231) was designed to directly compare fixed-duration SZ vs AV in TN CLL to investigate whether SZ compared with AV, may improve efficacy in terms of achieved uMRD rate after completing treatment and PFS and potentially improve tolerability and safety. **Methods:** BGB-11417-304 is a global phase 3, open-label, randomized study. Eligible adults have a confirmed diagnosis of previously untreated CLL requiring tx per iwCLL 2018 criteria, adequate hematologic and organ function, ECOG PS 0-2, and measurable disease confirmed by CT/MRI. Exclusion criteria include prior systemic tx for CLL; diagnosis of prolymphocytic leukemia or Richter transformation; known central nervous system involvement; history of confirmed progressive multifocal leukoencephalopathy; or uncontrolled hypertension or clinically significant cardiovascular disease. Approximately 500 pts will be enrolled and randomized 1:1 to arm A (3 lead-in cycles of oral zanubrutinib monotherapy followed by 12 cycles of oral SZ) or arm B (2 lead-in cycles of oral acalabrutinib monotherapy followed by 12 cycles of oral AV). Randomization will be stratified by age (<65 y vs $\geq$65 y), IGHV mutation status, and presence of del(17p) and/or *TP53* mutations. The primary endpoint is PFS in arm A vs arm B, as determined by independent review committee (IRC), with an intermediate endpoint of uMRD4 rate in blood and bone marrow in arm A vs arm B, assessed by next-generation sequencing (clonoSEQ) at the first post-tx follow-up visit. Key secondary endpoints are PFS-IRC in high-risk subgroups and OS. Other secondary endpoints are ORR and complete response assessed by IRC and investigator (INV), uMRD5 rate (clonoSEQ), PFS-INV, duration of response by IRC and INV, time to next tx, pt-reported outcomes, and safety/tolerability. Enrollment in BGB-11417-304 is currently ongoing. Clinical trial information: NCT04277637. Research Sponsor: BeOne Medicines, Ltd.

TPS7100 **Poster Session**

ROCKET-CLL: A randomized, open-label, multicenter, phase 3 study of rocbrutinib (LP-168) versus pirtobrutinib in covalent BTK inhibitor (cBTKi) in pretreated relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). First Author: Anna Chen, Newave Pharmaceutical Inc, Pleasanton, CA

Background: Bruton tyrosine kinase covalent inhibitors (cBTKi) have been transformative in CLL treatment. Despite achieving extended remissions, in most patients disease still relapses despite cBTKi therapy, often associated with *BTK* C481 mutations. Non-covalent BTKi (ncBTKi), including pirtobrutinib, can overcome this resistance (Sharman et al. *ASCO*. 2025). Pirtobrutinib received FDA approval in Dec 2025, for R/R CLL/CLL patients pretreated with cBTKi. Rocbrutinib (LP-168) is a highly selective next-generation BTKi that can covalently bind wild-type and gatekeeper mutations (T474X, commonly seen in patients relapsed after pirtobrutinib) and non-covalently target C481-mutated *BTK*, with preclinical efficacy in treatment-naïve and BTKi-resistant CLL (Gordon et al. *IWCLL*. 2025). In the rocbrutinib phase 1 trial (NCT04775745), encouraging safety and efficacy have been observed in CLL patients with prior exposure to BTKi and/or BCL2 inhibitor (BCL2i) (Woyach et al. *Blood*. 2025). Presented here is the design of a phase 3 trial aiming to compare the efficacy of rocbrutinib versus pirtobrutinib in cBTKi-pretreated R/R CLL/SLL patients. **Methods:** ROCKET-CLL (NCT07342478) is a randomized, open-label, multicenter, phase 3 study comparing rocbrutinib (Arm 1) to pirtobrutinib (Arm 2) in R/R CLL/SLL subjects who previously received treatments including covalent BTKi. Eligible subjects must require treatment per 2018 iwCLL criteria, have measurable lesions by CT, an ECOG performance score of 0-2, and adequate hematologic and other organ functions. About 306 subjects will be randomized 1:1 based on stratification factors such as 17p deletion/*TP53* mutation presence, reasons for discontinuing prior cBTKi, prior BCL2i treatment, and geographic region. Participants assigned to each arm will receive rocbrutinib (200 mg QD) or pirtobrutinib (200 mg QD) tablets continuously until disease progression, unacceptable toxicity, withdrawal, or other study discontinuation criteria are met. The primary endpoint is progression-free survival (PFS), assessed by an independent review committee (IRC) per iwCLL 2018 criteria with CLL (Hallek et al. 2018) and Lugano 2014 criteria with SLL (Cheson et al. 2014). Important secondary endpoints include overall survival (OS), time to next treatment (TTNT), event-free survival (EFS), overall response rate (ORR), duration of response (DOR), PFS assessed by investigator (INV), concordance between IRC and INV PFS, safety and tolerability, and population PK. Exploratory endpoints include health-related quality of life and biomarker assessment. Recruitment is ongoing. Clinical trial information: NCT07342478. Research Sponsor: None.

TPS7101 **Poster Session**

A global multicenter, open-label, randomized, phase 3 registrational study of lisaftoclax (APG-2575) in previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): GLORA trial in progress. First Author: Matthew Steven Davids, Dana-Farber Cancer Institute, Boston, MA

Background: Patients with high-risk CLL/SLL not achieving a complete response (CR) after ≥ 12 months of BTK inhibitor (BTKi) monotherapy remain at risk for early progression due to residual disease and BTKi resistance. A BCL-2 inhibitor (BCL-2i) introduces a complementary, BCR-independent apoptotic mechanism that may deepen responses and prolong progression-free survival (PFS). Lisaftoclax, a selective oral BCL-2i with a short half-life (4-6 h), enables once-daily dosing and is approved in China as second-line CLL therapy. Lisaftoclax monotherapy has demonstrated overall response rates (ORRs) of 67% in relapsed/refractory CLL and 62.5% in BTKi-refractory disease, including del(17p)/*TP53*-mutated cases. Lisaftoclax combined with acalabrutinib achieved ORRs >97% with favorable tolerability. This study evaluates whether lisaftoclax plus BTKi (acalabrutinib, zanubrutinib, or ibrutinib) improves PFS and/or overall survival (OS) (vs continued BTKi monotherapy) in patients with CLL/SLL and residual disease after prolonged BTKi treatment. **Methods:** This study will enroll approximately 440 patients randomly allocated to receive lisaftoclax plus BTKi or BTKi alone. Eligible patients have CLL/SLL and, after ≥12 months of BTKi monotherapy (lines 1-3), have achieved neither CR nor progressive disease (PD). Randomization is stratified by del(17p)/*TP53* status. Key inclusion criteria include age ≥18 years, ECOG PS 0-2, and residual disease with either high-risk features (del(17p)/*TP53* mutation, unmutated *IGHV*, or complex karyotype [≥5 abnormalities]), or measurable residual disease with lymph nodes ≥2.5 cm in the absence of high-risk features. Exclusion criteria include prior BCL-2i therapy or Richter transformation. Patients in the investigational arm will undergo a 5-day oral lisaftoclax ramp-up to 400 mg once daily plus physician's choice of BTKi in 28-day cycles until progression or toxicity. Control patients continue their current BTKi monotherapy. Safety and disease assessments (CT/MRI) will occur regularly. The primary endpoint is PFS by independent review committee (iwCLL 2018); key secondary endpoint OS; and other secondary endpoints, PFS by investigator, ORR, duration of response, MRD negativity, and safety. Enrollment is ongoing across 126 sites in 18 countries (ClinicalTrials.gov ID: NCT06104566). Clinical trial information: NCT06104566. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

TPS7102 **Poster Session**

Golcadomide (GOLCA), a potential, first-in-class, oral CELMoD, plus rituximab (R) versus investigator's choice (IC) in patients (pts) with relapsed/refractory follicular lymphoma (R/R FL) who have received ≥ 1 line of systemic therapy: GOLSEEK-4, a phase (Ph) 3, randomized study. First Author: Clémentine Sarkozy, Institut Curie, Hôpital Saint-Cloud, Université de Versailles, Saint-Quentin, France

Background: Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL), typically presenting as advanced-stage at diagnosis. With current SOC (chemoimmunotherapy [CIT] and maintenance), many pts can achieve remission; however, FL remains incurable, with shorter remissions and overall survival (OS) following relapses. Treatments for R/R FL, including CIT or R-lenalidomide (R^2), offer limited long-term benefit. T-cell-redirecting therapies in ≥ 3L provide better efficacy but are limited by tolerability and logistical challenges. An unmet need persists for effective, well-tolerated, convenient options for R/R FL pts after ≥1L of systemic therapy. GOLCA is a potential, first-in-class, oral CELMoD designed for the treatment of lymphoma, with preferential distribution to lymphoid organs and enhanced activity in lymphoma cell lines. GOLCA induces rapid and deep degradation of Ikaros and Aiolos, leading to direct cell killing and immunomodulatory activity. GOLCA 0.4 mg + R was studied in heavily pre-treated R/R FL pts (including those given lenalidomide [LEN] and T-cell redirecting therapies) in the Ph 1/2 CC-99282-NHL-001 study, resulting in objective response rate 97%, complete response rate 78% and tolerable safety, suggesting benefit vs SOC (Chavez et al., ASH 2025, #1006). As a result, the Ph 3 study, GOLSEEK-4 (NCT06911502) was initiated. **Methods:** GOLSEEK-4 is a global, randomized, Ph 3 study evaluating fixed-duration, chemo-free GOLCA + R vs IC (R^2 or R-chemo) in R/R FL after ≥1 prior lines of therapy. Included: adults (≥18 yr) with grade 1-3A R/R FL or cFL, PET-positive disease with measurable lesions (Lugano criteria), ECOG 0–2 (or 3 if due to lymphoma), require treatment based on modified GELF, and ≥1 prior regimen, including anti-CD20 + alkylating agent. Prior T-cell-redirecting therapy allowed. Excluded: composite DLBCL/FL, transformed NHL, CNS involvement, those who are R/R or intolerant to all options in IC arm. Approximately 400 pts will be randomized 1:1 to GOLCA (0.4 mg QD, Days 1–14 per 28-day cycle) + R for 5 cycles, then GOLCA monotherapy for 7 cycles (12 cycles total) or IC (R^2 for 5 cycles then LEN monotherapy for 7 cycles, or R-CHOP or R-Bendamustine for 6 cycles). Randomization will be stratified by disease progression within 24 months (mo) vs >24 mo from initial CIT, prior lines (2L vs 3L+), and IC regimen. Pts will be followed for at least 5 yrs. Recruitment began July 2025. Primary endpoint: progression-free survival (IRAC). Secondary endpoints: overall response rate (IRAC), OS, complete metabolic response, minimal residual disease, time to next therapy, duration of response. Safety is exploratory. Acknowledgement: BMS ChatGPT4 used to revise existing text with human author input (Jan 26). Clinical trial information: NCT06911502. Research Sponsor: Bristol Myers Squibb.

TPS7103 **Poster Session**

Phase 1 study of ARV-393, a PROTAC BCL6 degrader, as monotherapy in patients with advanced non-Hodgkin lymphoma (NHL) or combined with glofitamab in patients with diffuse large B-cell lymphoma (DLBCL). First Author: Martin Hutchings, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark

Background: Despite recent advancements in NHL therapies, many patients experience disease progression or relapse. Agents with novel mechanisms of action and combination strategies are needed to improve clinical outcomes. B-cell lymphoma 6 (BCL6) is a master transcriptional regulator of immune cells, particularly of germinal center B cells, and an established oncogenic driver in NHL. ARV-393 is an oral PROteolysis TArgeting Chimera (PROTAC) BCL6 degrader that binds an E3 ubiquitin ligase and BCL6 to induce ubiquitination of BCL6 and its subsequent proteasomal degradation. ARV-393 monotherapy potently inhibited tumor growth and induced tumor regressions across NHL cell-derived xenograft (CDX) and patient-derived xenograft models, including models of DLBCL, transformed follicular lymphoma, and nodal T-follicular helper cell lymphoma (nTFHL). Furthermore, administration of ARV-393 with a CD20×CD3 bispecific antibody, glofitamab, demonstrated combinatorial antitumor activity in a humanized high-grade B-cell lymphoma CDX model, inducing deeper tumor growth inhibition and increased tumor regressions vs either monotherapy. These preclinical findings demonstrated single-agent ARV-393 antitumor activity across NHL subtypes and suggested mechanistic synergy with glofitamab, supporting clinical investigation of monotherapy in NHL and this chemotherapy-free combination in patients with DLBCL. **Methods:** This global, multicenter, open-label, first-in-human, phase 1 dose escalation and optimization/expansion study (NCT06393738) is evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of ARV-393 as monotherapy in relapsed or refractory (R/R) NHL or in combination with glofitamab in R/R DLBCL, with a primary objective of determining provisional doses for further exploration. Patients eligible for ARV-393 monotherapy are adults with confirmed R/R B-cell NHL who previously received ≥2 lines of systemic therapy (including rituximab), or nTFHL who previously received standard of care therapy. Patients eligible for ARV-393 in combination with glofitamab are adults with pathologically confirmed R/R DLBCL, DLBCL not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma who were treated with ≥2 prior lines of systemic therapy. ARV-393 will be administered orally once daily in 28-day cycles alone or in combination with intravenous glofitamab during 21-day cycles. Approximately 255 patients will be enrolled across study cohorts. As of January 2026, enrollment is ongoing. Copyright © 2026 AACR. Originally presented at AACR 2026. Reprinted with permission. Clinical trial information: NCT06393738. Research Sponsor: Arvinas Operations Inc.

TPS7104 **Poster Session**

waveLINE-011: Zilovertamab vedotin plus R-CHP versus polatuzumab vedotin plus R-CHP as first-line therapy in germinal center B-cell–like (GCB) diffuse large B-cell lymphoma (DLBCL). First Author: Max S. Topp, University of Würzburg, Würzburg, Germany

Background: DLBCL is a heterogeneous malignancy broadly categorized into 3 subtypes: activated B-cell–like (ABC) DLBCL, GCB DLBCL, and unclassified DLBCL. The standard-of-care first-line treatment option for DLBCL regardless of subtype is polatuzumab vedotin plus rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP). However, while polatuzumab plus R-CHP prolongs PFS compared with R-CHOP in ABC DLBCL, it provides no benefit over R-CHOP in GCB DLBCL. Alternative first-line treatment options for GCB DLBCL are needed. Receptor tyrosine kinase–like orphan receptor 1 (ROR1) is an oncofetal transmembrane protein that is overexpressed in DLBCL, making it an attractive therapeutic target. Zilovertamab vedotin is an antibody-drug conjugate comprising an anti-ROR1 antibody with a proteolytically cleavable linker and the cytotoxic antimicrotubule agent MMAE. In the phase 1 waveLINE-001 study, zilovertamab vedotin was shown to have antitumor activity in heavily pretreated lymphoid cancers and promising efficacy and manageable safety in combination with R-CHP as first-line treatment for DLBCL. The randomized, open-label, phase 2 waveLINE-011 study (NCT06890884) has been designed to evaluate the efficacy and safety of zilovertamab vedotin plus R-CHP versus polatuzumab vedotin plus R-CHP in participants with previously untreated GCB DLBCL. **Methods:** Key eligibility criteria include age ≥18 years, previously untreated histologically confirmed GCB DLBCL (including but not limited to: DLBCL not otherwise specified GCB type and high-grade B-cell lymphoma [HGBL] GCB subtype), PET-positive disease at screening, an ECOG performance status score of 0 to 2, and an International Prognostic Index (IPI) score of 2 to 5. Participants with a history of transformation of indolent disease to DLBCL or with primary mediastinal B-cell lymphoma or gray zone lymphoma are excluded. All participants will be randomly assigned (1:1) to zilovertamab vedotin 1.75 mg/kg plus R-CHP or polatuzumab vedotin 1.8 mg/kg plus R-CHP on day 1 of every 3-week cycle for 6 cycles. Randomization will be stratified by geographic region (Western Europe vs US vs rest of world), IPI score (2 vs 3-5), bulky disease (<7.5 cm vs ≥7.5 cm), and histopathology (HGBL vs others). The primary end point is CR rate at the end of therapy per Lugano criteria by BICR. Secondary end points include PFS, EFS, duration of CR, OS, safety, and change in PROs. Response assessments (CT/FDG-PET) will be performed after cycle 4 day 1 but on or before cycle 5 day 1, and at 12 weeks after the cycle 4 scan. Follow-up efficacy assessments will be completed every 24 weeks for 2 years from the end of treatment assessment, then every year for 3 years. Adverse events will be graded per NCI CTCAE v5.0. Approximately 594 participants will be enrolled. Recruitment is ongoing. Clinical trial information: NCT06890884. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS7105 **Poster Session**

AQUARIUS: A longitudinal multi-center molecular biomarker discovery registry for patients with hematologic malignancies. First Author: Michael A. Thompson, Tempus AI, Inc., Chicago, IL

Background: Despite therapeutic innovations over the past decade in hematologic malignancies, there remains a significant unmet need in understanding disease progression, identifying progression and resistance biomarkers, and accurately predicting responses to various treatments. Identifying new therapeutic targets by moving deeper into the molecular and genetic architecture of the tumor is key to overcoming resistance and tailoring interventions to the unique biological profile of each individual. For example, follicular lymphoma (FL) demonstrates heterogeneous clinical behavior ranging from not requiring therapy (active observation), with not as yet well-defined high risk features for early progression, to patients who relapse early after initial therapy (POD24) and the ongoing risk of transformation to aggressive histology. Registry studies, in particular, provide insights into tumor heterogeneity, progression patterns, and clinical behaviors, which are essential for designing effective clinical trials and developing targeted therapies. The Tempus AQUARIUS hematologic biomarker discovery registry (NCT07154823) is a non-interventional, multi-center registry study aiming to create a robust dataset of molecular and clinical data from patients with hematologic malignancies to facilitate clinician-led research using whole genome sequencing (WGS) to generate hypotheses for predictive biomarkers, identify potential resistance mechanisms, and guide therapy selection. **Methods:** AQUARIUS is designed as a master protocol with multiple real world (rw) cohorts continuously added as future research questions emerge. The first cohort is on patients with FL, followed by additional cohorts in 2026. The FL cohort will encompass the following populations: newly diagnosed active observation (n: 100), newly diagnosed high risk (n: 150), relapsed/refractory high risk POD24 (n: 125), and transformed FL (n: 125), aiming to enroll 500 patients in total. Lymph node tissue or bone marrow aspirate and blood samples are collected during routine standard of care visits, with blood samples collected at all follow-up timepoints. Clinical data is collected—including demographics, medical history, treatment, and outcomes—at all timepoints, along with standard of care images. The emerging DNA WGS assay (Tempus xH) and existing RNA whole transcriptome sequencing assay (Tempus xR) will be performed at screening and progression/primary refractory disease to capture specific molecular alterations and potential genomic variants. Multimodal molecular profiling data will be generated prospectively. The following endpoints will be assessed: rw Overall Survival (OS), rw Progression Free Survival (PFS), rw Time to Next Treatment (TTNT), rw Time to Discontinuation (TTD), and changes in biomarkers over time. The study is open and actively enrolling. Clinical trial information: NCT07154823. Research Sponsor: None.

TPS7106 **Poster Session**

ROCK-2: An ongoing open-label, randomized, multicenter phase 2 study of rocbrutinib versus investigator's choice of therapy in patients with R/R non-GCB DLBCL. First Author: Peng Liu, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma. Aberrant activation of the Bruton's tyrosine kinase (BTK)-related signaling pathway is present in the non-GCB subtype of DLBCL (Davis et al. Nature 2010). Multiple BTK inhibitors (BTKi) have demonstrated efficacy in relapsed or refractory (R/R) non-GCB DLBCL (Strati et al. Haematologica. 2021; Wilson et al. Nat Med. 2015; Yang et al. Blood Adv. 2022), however, there remains room for further improvement. Rocbrutinib is a novel, highly selective, the fourth generation covalent (irreversible) and non-covalent (reversible) BTKi. Phase 1 study showed that in 45 patients with R/R non-GCB DLBCL who had received ≥2 prior lines of systemic therapy, rocbrutinib monotherapy achieved an overall response rate (ORR) of 57.8% and a complete response (CR) rate of 31.3%(Song et al. CSCO. 2025). This article describes the design and progress of a phase 2 pivotal study aimed at comparing the efficacy and safety of rocbrutinib versus investigator's choice of therapy in patients with R/R non-GCB DLBCL. **Methods:** ROCK-2 (NCT07189065; CTR20253693) is an open-label, randomized, multicenter phase 2 study conducted in China. Eligible patients must have non-GCB DLBCL, not otherwise specified (NOS) per the 2017 WHO classification, received ≥2 prior lines of systemic therapy. Additionally, patients must have measurable disease, an ECOG performance status of 0-2, and adequate hematologic and organ function. Key exclusion criteria include central nervous system involvement, DLBCL transformed from indolent lymphoma, prior refractoriness to BTK-targeting agents, uncontrolled systemic diseases, active infection. Approximately 150 eligible subjects will be randomized 1:1 to receive either rocbrutinib or BR/R^2, stratified by the number of prior lines of therapy (2 vs ≥3) and International Prognostic Index (IPI) score (0-2 vs 3-5). Subjects in the experimental group will receive rocbrutinib [200 mg once daily (QD)] until disease progression or unacceptable toxicity. Subjects in the control group will receive either BR or R^2 according to the investigator's choice. The BR regimen consists 6 cycles of rituximab (375 mg/m² on day 1) plus bendamustine (90 mg/m²/d on days 1-2). The R^2 regimen consists of rituximab (375 mg/m² on day 1 of cycles 1-6) plus lenalidomide (20 mg QD on days 1-21 of each 28d-cycle until disease progression or unacceptable toxicity). The primary endpoint is ORR assessed by Independent Review Committee (IRC) according to the 2014 Lugano criteria. Secondary endpoints include ORR assessed by investigator (INV), and CR rate, progression-free survival (PFS), duration of response (DOR), time to response (TTR), overall survival (OS) assessed by IRC or INV. The first subject was enrolled on Nov 27th,2025. Recruitment is ongoing. Clinical trial information: NCT07189065. Research Sponsor: Guangzhou Lupeng Pharmaceutical Company Ltd.

TPS7107 **Poster Session**

Phase 2 trial of lisocabtagene maraleucel for minimal residual disease in patients with large B-cell lymphoma. First Author: Dai Chihara, Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with relapsed/refractory large B-cell lymphoma (LBCL) have a poor prognosis. Identifying patients at high risk of recurrence after completion of first line (1L) treatment is crucial to enable early intervention with further treatments that may improve outcomes. Recent studies have shown that detectable minimal residual disease (MRD) by circulating tumor DNA (ctDNA) assay after 1L chemoimmunotherapy is prognostic for risk of recurrence. We hypothesize that lisocabtagene maraleucel (liso-cel) will eradicate the MRD in patients with LBCL who have detectable ctDNA at the end of 1L treatment will lead to improved long-term outcomes relative to historical results with liso-cel in second line treatment for patients with radiologically-detected disease. **Methods:** This is an open-label, phase 2, single-arm, multicenter, investigator-sponsored trial designed to evaluate the efficacy and safety of lisocabtagene maraleucel (liso-cel) in patients with LBCL who have achieved a response to 1L standard-of-care therapy but have detectable MRD. The trial will enroll 50 evaluable patients. Eligible participants are adults with LBCL, including DLBCL-NOS and HGBCL, who received 1L anthracycline-based chemoimmunotherapy (R-CHOP, DA-EPOCH-R, or polatuzumab-R-CHP) for six cycles, with or without an additional two cycles of rituximab, for previously untreated disease. Patients must have achieved a CR, or a PR with a negative biopsy or biopsy not feasible, and must demonstrate detectable MRD as assessed by the Foresight CLARITY ctDNA-MRD assay following completion of 1L therapy. The primary endpoint is event-free survival rate at 12 months, and secondary endpoints include rate of undetectable MRD. Correlative studies are designed to build a holistic model for understanding the tumor-intrinsic and immune features that contribute to response, as well as treatment-associated toxicities following liso-cel in patients with LBCL and detectable MD, a population at high risk of recurrence. Enrolment to the trial is planned at five centers in the US: MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center, Fred Hutchinson Cancer Center, City of Hope and Massachusetts General Hospital (NCT07316010). Clinical trial information: NCT07316010. Research Sponsor: None.

7500 **Oral Abstract Session**

Safety and efficacy of elranatamab as early intervention in patients with high-risk smoldering myeloma: First results from the phase 2 ERASMM (EMN34) study. First Author: Cyrille Touzeau, University Hospital of Nantes, Nantes, France

Background: Early intervention with lenalidomide or daratumumab significantly delays disease progression to active disease in high-risk (HR) smoldering multiple myeloma (SMM) patients (pts). The BCMAxCD3 bispecific antibody elranatamab (Elra) demonstrated strong anti-MM activity with favorable safety profile in relapsed MM. Using T-cell engagers in the early stage of the disease, with a potentially less exhausted immune system, may lead to improved efficacy. Here we report initial efficacy and safety results of Elra monotherapy in HR SMM pts enrolled in the phase 2 ERASMM Study (EMN34; NCT06183489). **Methods:** ERASMM is an international open-label multicenter phase 2 study of Elra as single agent in adult pts with HR SMM, defined as the presence of ≥2 Mayo 2018 "20-2-20" criteria. Treatment consisted of a fixed duration (2 years) of single-agent SC Elra with priming doses of 12 mg (C1D1) and 32 mg (C1D4), followed by 76 mg on days 8 and 15 during cycle 1, 1 and 15 during cycles 2–3, and 1 during cycles 4–24 (28-day cycle). The primary objective was the rate of complete response (CR). Safety was a key secondary endpoint. Other secondary objectives included overall response rate (ORR), measurable residual disease (MRD), progression-free survival (PFS), PFS2, time to active MM, and overall survival (OS). **Results:** Fifty pts with previously untreated HR SMM were included from May 2024 to September 2025 in 17 centers collaborating with the European Myeloma Network. Median age was 65 years (range 58–71). All pts had HR SMM, including M-spike >20 g/L in 42 (84%), bone marrow plasma cells >20% in 36 (72%), or free-light chain ratio >20 in 33 (66%). As of December 4, 2025, the median follow-up was 10 months (range 2.3–18.23). Thirty-four (68%) patients experienced a cytokine release syndrome event, all grade 1–2, except for grade 3 events in 2 pts. No ICANS events were observed. Infections occurred in 25 (50%) pts, including 14% grade 3–4. Other common (≥20%) non-hematologic adverse events (AEs) were skin rash (34%), diarrhea (26%), AST/ALT increase (28%), fatigue (20%), and peripheral neuropathy (20%), mostly grade 1–2. Four patients discontinued treatment due to AEs, including AST/ALT increase (n=1), Guillain–Barré syndrome (n=1), and infections (n=2). The ORR was 92%, including a very good partial response or better (≥VGPR) in 82% of pts, and a complete response or better (≥CR) in 45%. The 9-month PFS and OS rates were 95% and 100%, respectively. **Conclusions:** In HR SMM pts, single-agent Elra was highly active, with a 92% ORR, 45% of pts achieving ≥CR, and a favorable safety profile. Data on safety and efficacy (response, MRD, PFS) will be updated for the meeting. These data support further investigation of Elra as a therapeutic option for HR SMM. Clinical trial information: NCT06183489. Research Sponsor: Pfizer.

7501 **Oral Abstract Session**

Phase 3 randomized trial to evaluate the impact of anselamimab on all-cause mortality in κ light-chain amyloidosis. First Author: Ashutosh D. Wechalekar, University College London Hospitals and National Amyloidosis Center, Royal Free London NHS Trust, London, United Kingdom

Background: AL amyloidosis is a plasma cell dyscrasia (PCD) characterized by κ or λ Ig light chain amyloid fibrils that deposit in vital organs. Anselamimab is an investigational mAb designed to complement anti-PCD therapy through accelerated removal of amyloid fibrils. Cardiac Amyloid Reaching for Extended Survival (CARES) studies (NCT04512235 and NCT04504825) investigated the efficacy and safety of anselamimab compared with placebo, in addition to anti-PCD therapy. **Methods:** Alongside anti-PCD therapy with CyBorD (daratumumab was permitted) newly diagnosed patients with European modification of Mayo stage IIIa or IIIb AL amyloidosis were randomized 2:1 to receive anselamimab (1000 mg/m^2) or placebo (normal saline) IV every 7 days for 4 weeks followed by every 14 days for the remainder of the blinded study (18 months after the last participant enrolled). The primary endpoint was a hierarchical combination of time to all-cause mortality (ACM) and frequency of adjudicated cardiovascular hospitalizations (CVH) using the Finkelstein-Schoenfeld test and win-ratio in the combined study population. Subgroup analysis by involved κ or λ free light chain (iFLC) was prespecified. **Results:** 271 patients were randomized to receive anselamimab and 135 placebo. Baseline characteristics were similar between treatment arms. The median duration of treatment was 21.4 months and 21.1 in the anselamimab and placebo arms, respectively. Daratumumab was used in 79.3% and 83.7% of the anselamimab and placebo arms, respectively. Results of the primary efficacy analyses are shown in the table. Anselamimab-treated patients with κ iFLC had a 62% reduction in ACM (HR = 0.38; 95% CI, 0.17, 0.86; nominal P = 0.012) and a 71% reduction in risk for CVH (estimated CVH rate ratio = 0.29; 95% CI, 0.10, 0.87; nominal P = 0.028). Patients with λ iFLC had a 10% reduction in risk for CVH; none in ACM. Safety data were comparable between both treatment arms. In anselamimab-treated patients, safety findings were similar between κ subgroup and full population. **Conclusions:** Anselamimab, a κ light chain–directed anti-fibril monoclonal antibody used alongside standard of care chemotherapy, offers a first-in-class, new therapeutic option for patients with newly diagnosed κ AL amyloidosis. Clinical trial information: NCT04512235 and NCT04504825. Research Sponsor: Alexion, AstraZeneca Rare Disease.

Summary of primary efficacy endpoints.

		Overall			κ Isotype			λ Isotype		
Endpoint		Anselamimab (N=271)	Placebo (N=135)	*P*-value	Anselamimab (N=481)	Placebo (N=24)	*P*-value	Anselamimab (N=219)	Placebo (N=109)	*P*-value
ACM and CVH win ratio (95% CI)		1.1 (0.8, 1.5)		0.332	2.06 (0.98, 4.31)		0.100	0.9 (0.6, 1.3)		0.848
ACM	n (%)	90 (33.2)	52 (38.5)		15 (31.3)	14 (58.3)		73 (33.3)	37 (33.9)	
	HR (95% CI)	0.8 (0.6, 1.1)		0.290	0.38 (0.2, 0.9)		0.012	1.0 (0.7, 1.5)		0.647
CVH	Frequency/ year (95% CI)	0.6 (0.4, 0.8)	0.9 (0.6, 1.4)	0.145	0.41 (0.2, 0.8)	1.4 (0.6, 3.4)	0.028	0.7 (0.4, 1.0)	0.8 (0.4, 1.3)	0.664
	Incidence risk ratio (95% CI)	0.7 (0.4, 1.2)			0.29 (0.1, 0.9)			0.9 (0.5, 1.7)		

7502 **Oral Abstract Session**

First results from the phase 1/2 LINKER-AL2 trial of linvoseltamab (LINVO) in patients (pts) with relapsed or refractory (RR) systemic light chain (AL) amyloidosis. First Author: Ashutosh D. Wechalekar, University College London Hospitals and National Amyloidosis Center, Royal Free London NHS Trust, London, United Kingdom

Background: Systemic AL amyloidosis is caused by deposition of misfolded amyloid fibrils produced by clonal plasma cells in vital organs. With no currently approved therapies, there is a need for new targeted agents eliciting rapid normalization of involved free light chain (iFLC), which is linked to improved organ function recovery and overall survival. Here are the first results of LINVO (human BCMA×CD3 bispecific antibody) in RR systemic AL amyloidosis from the Phase 1 portion of the Phase 1/2 LINKER-AL2 trial (NCT06292780). **Methods:** Eligible adults with RR systemic AL amyloidosis and ≥1 prior therapy received intravenous step-up doses of LINVO 5 mg and 25 mg (Cycle [C] 0 Days 1 and 8, respectively) followed by 28-day cycles of full subcutaneous (SC) doses of 80 mg or 240 mg administered once weekly in C1–C2 and then once every 4 weeks in C3–C12. The Phase 1 primary endpoint was incidence of dose-limiting toxicities (DLTs) within 28 days after the first full dose. Key secondary endpoints were rates of hematologic complete response (hCR; by FLC ratio and absence of AL), very good partial response or better (≥hVGPR), objective response (hOR), time to hCR, and safety. **Results:** As of data cut-off (DCO) August 25, 2025, 20 pts (median age, 64 years; prior daratumumab therapy, 60.0%) received LINVO 80 mg (n=7) or 240 mg (n=13), with a median follow-up of 9.6 (range 1.1–25.0) weeks. No DLTs or ICANS occurred. All pts had ≥1 treatment-emergent adverse event (TEAE; Grade (Gr) ≥3, 55.0%). One pt with prior cardiac disorder discontinued (Gr 5 ventricular fibrillation, unrelated to LINVO). Most common TEAEs were CRS (50.0%; Gr 1, 35.0%; Gr 2, 15.0%) and infusion-related reactions (45.0%; Gr 1, 25.0%; Gr 2, 20.0%), most during step-up dosing. LINVO elicited rapid responses (Table): hOR rates were 100% (80 mg: ≥hCR, 57.1%) and 92.3% (240 mg: ≥hCR, 38.5%), which are expected to deepen with longer follow-up. Most pts reached iFLC <20 mg/L (80 mg: 100%; 240 mg: 84.6%). **Conclusions:** LINVO demonstrated generally manageable safety and rapid, meaningful clinical activity, with most pts achieving hOR and iFLC <20 mg/L. These results support continued evaluation of LINVO in RR systemic AL amyloidosis. Longer follow-up data, including organ responses, are being evaluated. Clinical trial information: NCT06292780. Research Sponsor: Regeneron Pharmaceuticals Inc.

Investigator-assessed hematologic responses (ISA criteria).

Response, n (%)*	LINVO 80 mg (n=7)	LINVO 240 mg (n=13)†
Median follow-up, weeks (range)	12.1 (6.9–25.0)	6.7 (1.1–15.3)
hOR	7 (100)	12 (92.3)
hCR	4 (57.1)	5 (38.5)
≥hVGPR	7 (100)	12 (92.3)
Low dFLC‡	0	1 (7.7)
dFLC <10 mg/L	7 (100)	11 (84.6)
iFLC <20 mg/L	7 (100)	11 (84.6)
Median time to hCR, weeks (range)	3.2 (2.1–18.3)	3.1 (1.0–7.1)

*Unless stated otherwise.
†Not evaluable, n=1.
‡If baseline dFLC ≥20 mg/L and <50 mg/L, response other than hCR reached with dFLC <10 mg/L.
dFLC, difference between iFLC and uninvolved FLC; ISA, International Society of Amyloidosis.

7503 **Oral Abstract Session**

DREAMM-9 final analysis: Belantamab mafodotin (belamaf), bortezomib, lenalidomide, and dexamethasone (BVRd) for transplant-ineligible (TI) newly diagnosed multiple myeloma (NDMM). First Author: Saad Z. Usmani, Memorial Sloan Kettering Cancer Center, New York, NY

Background: DREAMM-9 (NCT04091126) was a phase 1 dose and schedule evaluation study of BVRd in adults with TI NDMM. **Methods:** Patients (pts) received BVRd in 1 of 8 belamaf dosing cohorts at an induction/maintenance schedule of Q3/4W (SHORT: 1.9, 1.4, 1.0 mg/kg), Q6/8W (STRETCH: 1.9, 1.4 mg/kg), Q9/12W (step-down [S/D]: 1.9 for 1 dose then 1.4 mg/kg; 1.4 for 1 dose then 1.0 mg/kg), or Q12W (1.0 mg/kg). The primary endpoint was safety. Responses, minimal residual disease negativity (MRD[-]) in complete response or better (CR+), and pt-reported outcomes (PROs) were assessed. Median dose intensities (mDIs) were calculated as mg/kg/21 days in induction and mg/kg/28 days in maintenance. **Results:** As of June 2, 2025, 118 pts were enrolled (intention-to-treat population). Median duration of follow-up was 15.9–47.1 months. Induction mDI generally decreased as planned dosing intervals increased and was lowest in S/D Q9/12W or Q12W cohorts. Maintenance mDI was similar across cohorts due to dose modifications. Overall response rates were ≥83% across cohorts. Cohorts with higher induction mDI had the deepest responses (CR+/MRD[-] 75/55% for pooled SHORT+STRETCH and 59/43% for pooled Q9/12W+Q12W). Grade (Gr) ≥2 ophthalmic exam findings (OEFs; best-corrected visual acuity changes/slit lamp findings [Keratopathy and Visual Acuity scale]) were 90% for pooled SHORT+STRETCH/69% for pooled Q9/12W+Q12W, while Gr 3/4 OEF rates were higher with higher induction mDI (79%/35%). Most cohorts (5/8) had no belamaf discontinuations due to Gr ≥3 OEFs, which occurred only in SHORT cohorts (n = 1 each). First Gr ≥2 OEFs resolved prior to end of treatment in 83–100% across cohorts. The long-interval group (Q9/12W and Q12W dosing schedules) remained largely below the vision-related function (VRF) deterioration threshold (12.5 points per Ocular Surface Disease Index) across most timepoints, suggesting a favorable VRF profile vs the SHORT interval group. **Conclusions:** BVRd had high response rates across all cohorts (≥83%), highlighting the promising efficacy of the regimen. Regimens with higher belamaf induction mDI had the deepest responses, while those with lower induction mDI had milder OEFs. Belamaf dosing with a higher induction DI is optimal to achieve deeper responses, and a lower maintenance DI (i.e., using longer schedules) improves tolerability, PROs, and maintains responses. Clinical trial information: NCT04091126. Research Sponsor: GSK.

7504 **Oral Abstract Session**

Impact of sustained MRD negativity for up to 5 years on long-term outcome of transplant-eligible newly diagnosed multiple myeloma patients enrolled in the randomized phase 2 FORTE trial. First Author: Mattia D'Agostino, Division of Hematology, AOU Città della Salute e della Scienza di Torino, University of Torino and Department of Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy

Background: Novel combinations induce high rates of minimal residual disease (MRD) negativity (neg) in multiple myeloma (MM) patients (pts). However, the optimal duration of MRD negative status to predict long term outcomes remains a matter of debate. We analyzed the impact of different sustained (sust) MRD neg cut-offs on progression free survival (PFS) and overall survival (OS) in transplant eligible Newly Diagnosed MM pts treated in the randomized phase 2 FORTE trial (NCT02203643). **Methods:** We included all pts enrolled in the trial who were randomized to maintenance. MRD was assessed in the bone marrow in pts with ≥very good partial response by multiparameter flow cytometry (sensitivity of 10^{-5}) at premaintenance and every 6 months thereafter. SustMRD neg was defined as consecutive MRD-negative evaluations for at least 1, 2, 3, 4 or 5 years without intercurrent MRD-positive results. The primary aim of the analysis was the impact of different SustMRD neg durations on PFS. A subgroup analysis according to a modified Consensus Genomic Staging (mCGS as described in Avet-Loiseau et al JCO 2025 without the use of molecular data), and the presence of an MGUS-like profile at diagnosis (Burgos et al JCO 2023) was performed. **Results:** 356 pts were randomized to maintenance according to study protocol. After a median follow-up of 85 months from maintenance randomization, 77% of pts have > 1 MRD negative evaluation. The rate of at least 1, 2, 3, 4, 5-years sustMRD neg was 53%, 42%, 36%, 28% and 20% respectively. Compared to MRD positive patients (n=83), MRD neg lasting <1 year (HR 0.72; 95% CI 0.47-1.09), 1 year (HR 0.40; 95% CI 0.22-0.72), 2 years (HR 0.36; 95% CI 0.19-0.66), 3 years (HR 0.17; 95% CI 0.07-0.40), 4 years (HR 0.15; 95% CI 0.06-0.35) and 5 years (HR 0.06; 95% CI 0.03-0.15) significantly and progressively improved pts' PFS. In pts with ≥ 3-years sustMRD neg vs < 3-year sustMRD, 7-years PFS rates were 84.7% vs 35.4% (HR 0.16, 95% CI 0.10-0.27) and 7-years OS rates were 97% vs 69% (HR 0.08, 95% CI 0.02-0.27). Stratifying patients according to mCGS and 3-years sustMRD neg, 7-years PFS rates were 84% for mCGS standard risk with ≥ 3-y sustMRD, 83% for mCGS high risk and ≥ 3-y sustMRD, 43% for mCGS standard risk with < 3-y sustMRD, 23% for mCGS high risk with < 3-y sustMRD. Among patients with < 3-years sustMRD neg, the presence of an MGUS-like profile predicted a significantly better PFS and OS compared to non MGUS-like pts (7-years PFS 67% vs 33%, HR 0.37 95% CI 0.17-0.85; 7-years OS 93% vs 66%, HR 0.15 95% CI 0.02-1.08). **Conclusions:** SustMRD neg for more than 3 years significantly improved PFS and OS of NDMM pts, with pts with at least 5-year SustMRD neg having a 7-year PFS of 91%. Reaching > 3-y sustMRD neg is mandatory in high-risk pts to achieve long term remissions, while MGUS-like pts may have good outcomes despite the absence of 3-y sustMRD neg. Clinical trial information: NCT02203643. Research Sponsor: Amgen; Celgene/Bristol Myers Squibb.

7505 **Oral Abstract Session**

New IMS/IMWG risk criteria by next-generation sequencing (NGS): Analysis of daratumumab benefit in both high- and standard-risk patients (pts) in the PERSEUS study. First Author: Luca Bertamini, Department of Hematology Erasmus MC Cancer Institute, Rotterdam, Netherlands

Background: IMS/IMWG recently proposed novel Consensus Genomic Staging (CGS) high-risk criteria for newly diagnosed multiple myeloma (NDMM), including genetic alterations not identifiable by fluorescence in situ hybridization (FISH) but by NGS (eg, *TP53* mutations). PERSEUS/EMN017 (NCT03710603) evaluated the addition of daratumumab to VRd induction/consolidation and to R maintenance (DVRd arm) vs VRd+R (VRd arm) in transplant-eligible (TE) pts. PERSEUS previously reported that DVRd significantly improved progression-free survival (PFS) regardless of cytogenetic risk as defined by previous criteria. **Methods:** 709 pts with NDMM were randomized 1:1 to DVRd vs VRd. Unique molecular assay (UMA)-NGS target panel was used on DNA extracted from CD138+ bone marrow (BM) cells. Of 664 pts from whom BM was collected, 434 patient DNA samples were available for NGS testing. Per the new IMS/IMWG CGS criteria, high risk was defined post-hoc by the presence of del17p/*TP53* mutations; t(4;14) or t(14;16) or t(14;20) with additional amp1q or del1p; amp1q and del1p; biallelic del1p; and high β2 microglobulin with normal renal function. Classic FISH high risk was defined per-protocol by the presence of del17p, t(14;16), and/or t(4;14). Minimal residual disease negativity (MRD neg) was assessed by NGS (Adaptive) in pts with complete response or better. **Results:** Of 434 pts evaluated, 152 (35%) were high risk by CGS. The most common genetic lesions were del17p/*TP53* (n=59, 14%), IgH translocation with amp1q/del1p (12%), and del1p with amp1q (9%); 2% had biallelic focal del1p. Using CGS criteria, 17% of pts were reclassified from standard risk to high risk; additionally, 4% of pts previously classified as high risk were reclassified as standard risk. DVRd was associated with increased MRD neg rates at 10^{-6} compared to VRd in both CGS standard-risk (67% vs 39%, *P*=0.0001) and high-risk pts (56% vs 26%, *P*=0.0003). Sustained MRD neg (10^{-6}) rates for ≥12 months (+/-1 mo) were higher with DVRd vs VRd for both CGS standard-risk (57% vs 24%; *P*<0.0001) and high-risk pts (41% vs 19%; *P*<0.0001), and pts who achieved sustained MRD negativity (10^{-6}) had superior PFS outcomes versus those who did not, regardless of CGS risk status (*P*<0.0001). DVRd led to improved PFS in both CGS standard-risk (HR 0.38, 95% CI 0.20–0.73; *P*=0.001) and high-risk pts (HR 0.54, 95% CI 0.31–0.95; *P*=0.039), adjusting for ISS, lactate dehydrogenase, and age (>65 years). **Conclusions:** DVRd improved MRD negativity and PFS over VRd in both the new IMS/IMWG CGS high-risk and standard-risk subgroups. UMA-NGS panel successfully stratified risk according to CGS criteria, identifying nearly twice as many high-risk pts in the PERSEUS study. These data further support DVRd induction/consolidation and DR maintenance as standard of care for TE-NDMM, regardless of cytogenetic risk. Clinical trial information: NCT03710603. Research Sponsor: Johnson & Johnson.

LBA7506 **Oral Abstract Session**

Mezigdomide, carfilzomib, and dexamethasone (MeziKd) vs carfilzomib and dexamethasone (Kd) in relapsed/refractory multiple myeloma (RRMM): Results from the phase 3 SUCCESSOR-2 trial. First Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

7507 **Oral Abstract Session**

MajesTEC-9: A phase 3 randomized study of teclistamab monotherapy vs investigator's choice of pomalidomide, bortezomib, and dexamethasone or carfilzomib and dexamethasone (PVd/Kd) in patients (pts) with relapsed refractory multiple myeloma (RRMM). First Author: Roberto Mina, Winship Cancer Institute, Emory University; Division of Hematology, Department of Molecular Biotechnology and Health Sciences, AOU Città della Salute e della Scienza di Torino, University of Torino, Torino, Italy

Background: Triplet and quadruplet regimens have greatly improved outcomes in newly diagnosed multiple myeloma, yet a high unmet need remains for more effective, broadly accessible treatments for anti-CD38- and lenalidomide- (Len) exposed/refractory RRMM. Teclistamab (Tec) is the most widely used BCMA×CD3 BsAb in heavily pretreated RRMM, with improved outcomes in earlier lines of therapy (LOTs). In MajesTEC-3, the synergistic Tec-daratumumab combination significantly improved progression-free and overall survival (PFS/OS) as early as first relapse. MajesTEC-9 (NCT05572515) is the first phase 3 study of Tec monotherapy in pts with 1–3 prior LOTs. **Methods:** Pts with RRMM and 1–3 prior LOTs including anti-CD38 and Len were randomized 1:1 to receive 28-day cycles (C) of Tec (C1–2: 2 step-up doses then 1.5 mg/kg QW; C3–6: 3 mg/kg Q2W or Q4W depending on response; C7+: 3 mg/kg Q4W) or investigator's choice of PVd/Kd (21/28-day C). Primary endpoint was PFS by IRC; secondary endpoints included OS, complete response or better (≥CR), and safety. **Results:** 593 pts were randomized (Tec, n=296; PVd/Kd, n=297). Median (range) age: 70 (34–86) yrs; number of prior LOTs: 2 (1–3); Len refractory: 80%; anti-CD38 refractory: 85%; refractory to last LOT: 92%. With 17.3-mo median follow-up, Tec significantly improved PFS vs PVd/Kd (HR, 0.29; 95% CI, 0.23–0.38; *P*<0.0001); mPFS: NR vs 8.2 mo; 18-mo PFS rate: 69.8% vs 26.9%. OS was significantly improved with Tec vs PVd/Kd (HR, 0.60; 95% CI, 0.43–0.83; *P*=0.0020). Of 174 PVd/Kd pts who received subsequent treatment, 68.4% received BsAb or CAR-T. PFS favored Tec across all prespecified subgroups, including anti-CD38-refractory pts and Len-refractory pts. ≥CR rate was significantly higher with Tec vs PVd/Kd (65.9% vs 16.8%; OR, 10.42; 95% CI, 6.89–15.76; *P*<0.0001). At data cutoff, 65.3% of pts remained on Tec vs 24.0% on PVd/Kd (safety set: Tec, n=291; PVd/Kd, n=283). TEAEs were similar for Tec and PVd/Kd (99.7% vs 97.9%). Grade (Gr) 3/4 TEAEs (84.9% vs 76.3%) and Gr 5 TEAEs (6.5% vs 3.5%) were higher with Tec vs PVd/Kd, noting the median treatment duration was nearly doubled with Tec (13.1 vs 7.0 mo). Treatment discontinuation due to TEAEs was lower with Tec vs PVd/Kd (10.7% vs 13.1%). Gr 3/4 infections were higher with Tec vs PVd/Kd (41.6% vs 29.0%). Any-onset Gr ≥3 infections decreased over time. CRS occurred in 66.0% of pts with Tec (Gr 1/2: 48.8%/16.5%) and ICANS in 4.1% (Gr 1/2: 2.4%/1.4%). **Conclusions:** Tec monotherapy significantly improved PFS/OS vs standard of care (SoC) in this high unmet need population. CRS and infections were managed with established protocols. Results of phase 3 studies support Tec-based regimens as a SoC as early as second line, across all treatment settings and regardless of prior anti-CD38/Len exposure. Clinical trial information: NCT05572515. Research Sponsor: Johnson & Johnson.

7508 Oral Abstract Session

Etentamig in patients (pts) with relapsed/refractory multiple myeloma (RRMM) with prior exposure to B-cell maturation antigen (BCMA)—targeted therapy. First Author: Saurabh Chhabra, Mayo Clinic Arizona, Phoenix, AZ

Background: Data on response to BCMA-targeted therapies among BCMA-exposed pts with RRMM are limited. Outcomes after sequential/subsequent anti-BCMA bispecific T-cell engagers (Bs-TCE) are vital to evaluate. Etentamig is a next-generation differentiated BCMA x CD3 Bs-TCE composed of a bivalent BCMA-binding domain with a high-avidity, low-affinity CD3-binding domain potentially reducing cytokine release syndrome (CRS), and a silenced Fc tail for extended half-life and convenient monthly (Q4W) dosing. Phase 1 results of etentamig in RRMM showed robust efficacy and potential best-in-class safety. **Methods:** Arm B of the open-label, Phase 1b MOVISO study (NCT05650632) evaluated etentamig in pts with RRMM with ≥2 prior lines of therapy (PLT), including triple-class and prior BCMA exposure (antibody-drug conjugate [ADC] >30 days or CAR-T >6 months [mo] after last exposure). Primary safety endpoints were CRS and immune effector cell-associated neurotoxicity syndrome (ICANS); efficacy endpoints included objective response rate (ORR; IMWG 2016), duration of response (DoR), and progression-free survival (PFS). Pts received etentamig (60 mg IV; no step-up dosing [SUD]) on Cycle 1 Day 1 and Q4W thereafter. **Results:** At cutoff (June 11, 2025), 41 prior BCMA-exposed pts (CAR-T, n=24; ADC, n=17) had been treated; 24 (57%) were male, 38 (93%) were White, median (mdn) (range) age was 68 (43–89) years, 37 (88%) had ECOG PS ≤1, and 34 (81%) were triple-class refractory. Mdn (range) PLT was 6 (3–15). For 21 (51%) pts, the last PLT was BCMA directed; 23 (56%) had previously responded to anti-BCMA therapy (17/24 [71%] for CAR-T and 6/17 [35%] for ADC). Mdn (range) time from last prior CAR-T or ADC to first dose of etentamig was 15 (1–30) and 4 (1–45) mo, respectively. Mdn (range) follow-up was 5.5 (0.2–17.1) mo. Despite no SUD, CRS and ICANS were reported in 24 (57%) and 3 (7%) pts, respectively; all G1/2 events, except 1 G3 ICANS. G3/4 neutropenia and infections were reported in 15 (36%) and 17 (41%) pts, respectively. Efficacy outcomes are detailed in the Table (NE, not estimable). For pts whose last PLT was BCMA directed, MRD negativity (clonoSEQ, 10^{-5}) was seen in 2/3 (67%) evaluable pts, along with robust peak activation and proliferation of CD8+ T cells. **Conclusions:** Pts treated with etentamig achieved durable responses; rates were higher in pts who received CAR-T as last line. No new safety signals were observed; only low-grade CRS was seen despite no SUD. Clinical trial information: NCT05650632. Research Sponsor: AbbVie Inc.

	All prior BCMA (N=41)	Prior BCMA CAR-T (N=24)
ORR, n/n (%) [95% CI]		
Overall	17/36 (47) [30–65]	11/22 (50) [28–72]
BCMA-directed last PLT	11/19 (58) [34–80]	7/11 (64) [31–89]
Mdn DoR, mo [95% CI], No. of pts		
Overall	13 [7–NE], N=17	13 [7–NE], N=11
BCMA-directed last PLT	13 [7–NE], N=11	13 [7–NE], N=7
Mdn PFS, mo [95% CI], No. of pts		
Overall	3.4 [3–11], N=41	8.3 [2–NE], N=24
BCMA-directed last PLT	9.4 [2–NE], N=21	9.4 [2–NE], N=12

7509 Rapid Oral Abstract Session

Updated results from inMMyCAR, the ongoing first-in-human phase 1 study of KLN-1010 in patients (pts) with relapsed and refractory multiple myeloma (RRMM). First Author: P. Joy Ho, Royal Prince Alfred Hospital and University of Sydney, Camperdown, NSW, Australia

Background: KLN-1010 is a modified lentiviral vector generating a novel, fully human anti-BCMA CAR-T cell *in vivo* when administered intravenously without preparative chemotherapy to pts with RRMM. Here, we report updated findings from inMMyCAR, the first sponsored, multicenter study of an *in vivo* CAR-T therapy for pts with RRMM. **Methods:** Eligibility required RRMM with measurable disease, adequate end-organ and bone marrow (BM) function, and ≥3 prior lines of therapy, including a proteosome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. **Results:** To date, 6 pts were infused across two dose levels (6×10^6 and 2×10^7 IU/kg). Pts ranged in age from 61-72 and had received 3-5 prior lines of therapy. 5 pts had high-risk cytogenetics. BM plasma cell involvement ranged from <5% to 80%. 1 pt had extramedullary disease (EMD). Median time from consent to infusion was 13.5 days. All pts experienced treatment-emergent adverse events. Infusion-related reactions (IRR) occurring in 3 pts (2 at 2×10^7 IU/kg, 1 at 6×10^6 IU/kg) were manageable and resolved within 6-48 hrs. Cytokine release syndrome (CRS) was observed in 4 pts, with median onset on day 11 and median duration of 3.5 days; all events were Gr 2 and were managed with tocilizumab and corticosteroids. No immune effector cell–associated neurotoxicity syndrome (ICANS) or delayed neurotoxicity were observed. Peak absolute lymphocyte counts occurred between days 13-22, with median counts of 6.9×10^9/L (range 2.3-43.1$\times10^9$/L) and no associated clinical sequelae. CAR-T cells were detectable in peripheral blood through 4 months follow-up and were predominantly memory-phenotype by month 3 (M3). All 6 pts achieved minimal residual disease (MRD) negativity (5 at 10^{-6} and 1 at 10^{-5} sensitivity) at M1 in the BM. MRD negativity was maintained through M6 (10^{-6} sensitivity) in the pt with the longest follow-up. All pts achieved a response by IMWG criteria, and responses deepened over time. The pt with EMD showed complete resolution by M1. **Conclusions:** Results from inMMyCAR continue to demonstrate compelling early clinical activity. All pts achieved early MRD-negative responses and deepening of IMWG response over time. The pt with the longest follow-up remains MRD-negative with a stringent CR at M6. Activity was also observed in EMD, with radiologic resolution within 1 month. KLN-1010 was generally well-tolerated, with manageable toxicities related to IRR and CRS, supporting potential feasibility for outpatient administration. No ICANS or delayed neurotoxicity were observed. The study remains ongoing; updated results will be presented. Clinical trial information: NCT07075185. Research Sponsor: Kelonia Therapeutics, Inc.

Pt	Dose, $\times10^7$ IU/kg	Timepoints of MRD-negative results[a]	IMWG response	Duration of follow-up, months
1	2	M1, M3, M6	sCR	6+
2	2	M1, M3	VGPR	5+
3	2	M1, M3	VGPR	4+
4	0.6	M1, M3	VGPR	3+
5	0.6	M1	sCR	1+
6	0.6	M1	PR	1+

[a]By next-gen flow cytometry or sequencing with sensitivity of 10^{-5} or 10^{-6}.

7510 Rapid Oral Abstract Session

Optec/Optal: A phase 2 study to evaluate outpatient (OP), step-up administration of teclistamab (Tec) or talquetamab (Tal) with prophylactic tocilizumab (prophyToci) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). First Author: Peter Forsberg, Colorado Blood Cancer Institute, Denver, CO

Background: Tec, a B-cell maturation antigen x CD3 bispecific antibody (bsAb), and Tal, a G protein-coupled receptor class C group 5 member D x CD3 bsAb, are approved for the treatment of pts with triple-class exposed (TCE) RRMM. Cytokine release syndrome (CRS) is a common adverse event associated with T-cell therapies. CRS occurred in 72% and 73-79% of pts in the MajesTEC-1 (TEC-1) and MonumenTAL-1 (TAL-1) studies, respectively. One cohort of pts in TEC-1 received prophyToci, resulting in a lower rate of CRS (26%) without negatively impacting safety or efficacy. A cohort of pts in TAL-1 received prophyToci, with 18% experiencing CRS; safety and efficacy were comparable to the overall TAL-1 population. **Methods:** This nonrandomized, multicenter, prospective study evaluates prophyToci in RRMM pts treated with Tec (Arm A) or Tal (Arm B) using the approved step-up dose (SUD) schedule in the OP setting. ProphyToci 8 mg/kg was administered before SUD 1 of either Tec or Tal. Specific recommendations (home monitoring, IV immunoglobulin [IVIG] for IgG levels <400 mg/dL) and restrictions (caregiver requirements and travel distance) are also provided for pt safety. Primary endpoint is incidence of any grade CRS in cycles 1-2. Secondary endpoints include safety and efficacy measures. Safety parameters encompass incidence of Grade ≥2 CRS, any grade recurrent CRS, any grade infections, neurotoxicity (NT), and neutropenia throughout the study. Efficacy endpoints include overall response rate (ORR), best overall response (BOR) and progression-free survival (PFS). **Results:** As of 06 January 2026, 43 pts enrolled in Arm A, and 7, in Arm B. In Arm A, the CRS rate was 5%, all G1. In Arm B, G1 CRS occurred in 14% of pts. Adverse events G≥3 included neutropenia (G3, n=4; G4, n=6), anemia (G3, n=1), and febrile neutropenia (G3, n=1). Twenty pts (47%) in Arm A experienced infections, with 19% ≥G3. Among Arm A patients who experienced infections, 10 (50%) exhibited IgG levels <400 mg/dL, of whom 2 (20%) received IVIG. In Arm B, 4 pts (57%) experienced infections, with 29% (n=2) ≥G3. BOR in Arm A included 3 stringent complete responses (sCRs), 6 CRs, 11 very good partial responses (VGPR), 8 PRs, 1 stable disease, 5 progressive disease (PD), and 9 non-evaluable pts. Among the 34 evaluable pts in Arm A, the ORR was 82%. BOR in Arm B included 1 sCR and 6 non-evaluable pts. After a median follow-up of 11.8 months, 74.4% of pts (n=32) in Arm A did not experience progression. **Conclusions:** A single dose of prophyToci before SUD 1 of Tec or Tal reduced the incidence of CRS, with no impact on safety or efficacy, and supports administration of these bsAbs in the OP setting. The protocol was amended to add an arm evaluating the effect of prophylactic oral dexamethasone on CRS in pts treated with Tec (Arm C). Enrollment is ongoing (NCT05972135). Clinical trial information: NCT05972135. Research Sponsor: Johnson & Johnson Innovative Medicine; Sarah Cannon Research Institute.

7511 Rapid Oral Abstract Session

Survival outcomes comparing sequencing of CAR-T followed by BiTE versus BiTE followed by CAR-T in patients with relapsed multiple myeloma. First Author: Joseph OBrien, Denver Health Medical Center, Denver, CO

Background: Chimeric antigen receptor T-cell (CAR-T) therapies and bispecific T-cell engager (BiTE) antibodies for relapsed and refractory multiple myeloma (MM) are increasingly used earlier in the disease course but the optimal sequencing remains unclear. It has been hypothesized that CAR T before BiTE would lead to less T-cell exhaustion and better outcomes than BiTE before CAR T. **Methods:** A multicenter retrospective cohort study using the TriNetX Global Collaborative Network from 2021-2025 to evaluate outcomes among MM pts who received both CAR-T (idecel or ciltacel) and a BiTE (teclistamab, talquetamab, or elranatamab). Cohorts by treatment sequence: CAR-T followed by BiTE (CAR-T→BiTE) or BiTE followed by CAR-T (BiTE→CAR-T). Primary outcome: 5-yr mortality from the initiation of first advanced immunotherapy. Secondary outcomes: incidence of CRS, ICANS, infection, sepsis, ICU admission, and 1-yr mortality following each therapy. Propensity score matching included demographic variables, comorbidities, prior myeloma therapies (including prior SCTx) and baseline laboratory values. **Results:** 389 pts were included (244 CAR-T→BiTE; 145 BiTE→CAR-T); in the CAR T 1st group, 72% received ide-cel and 28% had cilta-cel, whereas in the BiTE 1st group 86% went on to receive cilta-cel as the CAR T product. Median overall survival was reached in the BiTE-first cohort (3.59 years) but not in the CAR-T–first cohort. Five-year survival was significantly higher with CAR-T–first sequencing (57.1% vs 25.5%; log-rank p = 0.045). In adjusted Cox regression, CAR-T–first sequencing was independently associated with lower 5-year mortality (hazard ratio 0.57, 95% CI 0.34–0.95). In unmatched analyses stratified by the specific BiTE (anti-BCMA vs anti-GPRC5D) used, overall survival did not differ significantly within each treatment sequence (all log-rank p > 0.05). In propensity score–matched analyses (112 patients per group), CAR-T–first pts experienced higher ICANS (all grades, 22% vs 10.7%) after first therapy but lower ICU admission (52% vs 70%), and significantly lower CRS (37% vs 56%, all grades) following second therapy. Rates of infection, sepsis, and 1-yr mortality were similar between groups. **Conclusions:** Among patients with MM who received both CAR-T and BiTE therapies, CAR-T–first sequencing was associated with significantly improved long-term survival in spite of a much higher percentage receiving the less effective CAR T product. The additional finding of a lack of survival differences by specific BiTE used also suggests that treatment order, rather than product selection, may be the primary determinant of long-term outcomes. These findings support consideration of earlier CAR-T deployment when feasible and underscore the importance of sequencing strategy in the evolving landscape of MM immunotherapy. Research Sponsor: None.

7512 **Rapid Oral Abstract Session**

Belantamab mafodotin with daratumumab, lenalidomide, and dexamethasone in transplant-ineligible, newly diagnosed multiple myeloma patients: Phase 1/2 BelaDRd study. First Author: Evangelos Terpos, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Background: The MAIA trial established daratumumab with lenalidomide, dexamethasone (DRd) as standard therapy for transplant-ineligible (TI) NDMM. Belantamab mafodotin (belamaf) showed high efficacy in relapsed/refractory disease. Quadruplet regimens improved clinical outcomes, providing a strong rationale to evaluate belamaf in combination with DRd in TI NDMM. **Methods:** BelaDRd is a phase 1/2, open-label study (EUCT-2024-515634-32) evaluated this combination in TI-NDMM. Part 1 (dose-finding phase) assessed the safety and tolerability of two belamaf doses (1.9/1.4 mg/kg Q8W) with DRd. This part established belamaf 1.9 mg/kg Q8W, extended to Q12W to account as the recommended phase 2 dose (RP2D). Part 2 (dose-expansion phase) evaluates the safety and efficacy of the RP2D in two cohorts Groups A and B, guided by ophthalmologist and hematologist (using Vision-Related Anamnestic, VRA tool), respectively. **Results:** In Part 1, 24 pts (median age: 73 years; male: 54.2%) entered the study;12.5% had high-risk cytogenetics (HRC). At a median follow-up of 34.3 months, 18 (75%) pts remained on treatment, while 6 (25%) discontinued; 3 (12.5%) death, 1 (4.2%) AE/SAE, 1 (4.2%) withdrew consent, and 1 (4.2%) due to PD. The median dose intensity (MDI) of belamaf was 0.5 mg/kg/Q4W. MRD negativity was achieved in 13 (81.3%) of evaluable patients (n=16). The ORR was 22 (91.7%). Sixteen patients (69.6%) achieved both ≥CR and ≥VGPR. In Part 2 (n=12; median age: 74 years; male: 58.3%),16.7% of pts had HRC. At a median follow-up of 17.9 months, 11 pts (91.7%) remained on treatment; 1 pt (8.3%) discontinued due to PD. Of 113 planned belamaf doses 13 doses were skipped due to OAEs. The MDI was 0.8 mg/kg/Q4W. MRD negativity was achieved in 5 (71.4%) of evaluable patients (n=7). ORR was 11 (91.7%) in evaluable pts. The median time to ≥PR was 1.1 months for both parts. At 18 months, PFS was 91.7% (95% CI 76.4-97.2) and 87.5% (95% CI 66.1-95.8) in the overall and RP2D populations, respectively; corresponding TTP rates were 97.1% (95% CI 80.9-99.6) and 95.5% (95% CI 71.9-99.4). Grade ≥3 BCVA decline was observed in 74(10.4%) of ocular assessments in part 1 and 4(3.9%) and 5(5.3%) in part 2 groups A and B, respectively. Grade ≥2/≥3 keratopathy occurred in 20.2%/0.6% of assessments in Part 1; in Part 2, rates were 6.7%/0% (Group A) and 10.6%/0% (Group B). Median ≥Grade 2 BCVA OAE/keratopathy resolution time was 1.1/1.0 months (Part 1) and 1.9/1.0 months (Part 2). **Conclusions:** BelaDRd demonstrated robust clinical activity, with rapid and deep responses. Low frequency of ≥Grade 3 OAEs was observed and were rapidly resolved. Moreover, a similar frequency of OAEs was noted when dosing was guided by haematologist vs ophthalmologist ocular assessment. The remarkable PFS supports further evaluation of this quadruplet in a phase 3 study versus other novel quadruplet combinations in NDMM. Clinical trial information: EUCT-2024-515634-32. Research Sponsor: None.

7513 **Rapid Oral Abstract Session**

Daratumumab plus bortezomib, lenalidomide, and dexamethasone (DVRd) in patients (pts) with newly diagnosed multiple myeloma (NDMM): Final analysis of transplant-ineligible (TIE) pts in the phase 3 CEPHEUS study. First Author: Saad Z. Usmani, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The phase 3 CEPHEUS study established that DVRd improved overall minimal residual disease (MRD)-negativity (neg) rates and progression-free survival (PFS) vs VRd in pts with TIE or transplant-deferred (TD) NDMM. The first analysis of the DVRd TIE subpopulation at a median follow-up of 58.7 months (mo) showed a complete response or better (≥CR) rate of 80.6% and overall MRD neg rate of 60.4%, with ~70% of pts alive and progression free. This final analysis of the CEPHEUS TIE subpopulation describes a longer median follow-up of 76.0 mo. **Methods:** The primary endpoint of overall MRD neg rate (10^{-5} and ≥CR), and secondary endpoints, including investigator-assessed PFS and ≥CR rate, and sustained MRD neg (confirmed MRD neg ≥12 months +/- 1 mo apart without MRD positivity in between and ≥CR) were assessed in the TIE population. The study was closed at the final analysis and pts were able to continue their study treatment via post-study access. **Results:** Of 395 pts enrolled, 289 pts with TIE NDMM received either DVRd (n=144) or VRd (n=145). The overall MRD neg rate at 10^{-5} was 61.1% for DVRd and 40.0% for VRd (odds ratio [OR] 2.35; 95% CI 1.47–3.77; *P*=0.0004) and at 10^{-6} was 46.5% for DVRd vs 27.6% for VRd (OR 2.27; 95% CI 1.39–3.71; *P*=0.0010). Sustained MRD neg rate at 10^{-5} was 49.3% for DVRd and 29.0% for VRd (OR 2.40; 95% CI 1.47–3.91; *P*=0.0005) and at 10^{-6} was 37.5% for DVRd and 16.6% for VRd (OR 3.01; 95% CI 1.73–5.24; *P*<0.0001). Overall ≥CR rate was 80.6% for DVRd and 61.4% for VRd (OR 2.64; 95% CI 1.54–4.51; *P*=0.0003). Median investigator-assessed PFS was not estimable (NE; 95% CI 74.81–NE) for DVRd and was 50.20 mo (95% CI 41.95–62.95) for VRd (HR 0.55; 95% CI 0.39–0.78; *P*=0.0007), with 59.3% for DVRd vs 38.3% for VRd alive and progression free at 72 mo. OS favored DVRd over VRd (HR 0.84; 95% CI 0.57–1.24), particularly when censoring for COVID-19, which significantly impacted this study (HR 0.74; 95% CI 0.49–1.12). The treatment effect was consistent across most subgroups (Table). **Conclusions:** After median follow-up of over 6 years, the final analysis of the CEPHEUS trial demonstrated that TIE pts treated with DVRd continue to have deep and durable responses compared with those on VRd, which is crucial for patients for whom transplant is not an option. These data continue to reinforce DVRd as a standard of care in the TIE NDMM population. Clinical trial information: NCT03652064. Research Sponsor: Johnson & Johnson.

	MRD neg (10^{-5}) rate, %				Median PFS, mo			
BL characteristic	DVRd	VRd	OR	95% CI	DVRd	VRd	HR	95% CI
ISS stage I	66.0	41.7	2.72	1.30–7.11	NE	60.5	0.52	0.28–0.97
II	59.3	45.6	1.73	0.82–3.68	NE	49.4	0.50	0.28–0.88
III	57.5	30.0	3.16	1.26–7.94	66.4	43.8	0.66	0.35–1.24
Cytogenetic risk High	50.0	50.0	1.00	0.28–3.57	58.0	31.7	0.82	0.36–1.87
Standard	63.8	39.6	2.68	1.55–4.66	NE	61.6	0.58	0.38–0.89
ECOG PS 0	57.7	45.6	1.63	0.76–3.47	NE	59.9	0.33	0.17–0.64
≥1	63.0	36.4	2.99	1.63–5.48	74.8	47.2	0.70	0.46–1.06

7514 **Rapid Oral Abstract Session**

Efficacy and safety of iberdomide, daratumumab, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma. First Author: Prashant Kapoor, Mayo Clinic Rochester, Rochester, MN

Background: Iberdomide (Iber) is a CELMoD that binds with greater specificity & affinity to the cereblon protein of the E3 ligase complex than a traditional IMiD. Both transplant-eligible (TE) & ineligible (TIE) patients (pts) with newly diagnosed multiple myeloma (NDMM) are currently treated with quadruplet induction, consisting of an anti-CD38 monoclonal antibody, a proteasome inhibitor, an IMiD & dexamethasone (dex). We conducted a clinical trial (NCT05392946, IDEAL) to examine the efficacy of a novel finite-duration approach, using Iber, daratumumab, bortezomib & dex (Iber-DVd) quadruplet induction followed by Iber monotherapy maintenance. **Methods:** Both TE and TIE pts with NDMM were enrolled in this Phase 1 (3+3 design)/Phase 2 (single stage) trial. The primary goal was to assess the ≥complete response (CR) rate — utilizing the more sensitive serum MASS-FIX assay in lieu of serum immunofixation — during induction. Treatment involved twelve 28-day cycles of induction with Iber, given PO at the recommended phase 2 dose (RP2D), days 1-21, daratumumab 1800mg SQ, weekly for 2 cycles, every other week during Cycles 3-6, & every 4 weeks thereafter, bortezomib 1.3 mg/m^2 SQ, weekly & dex 40 mg, weekly, followed by Iber monotherapy (24 cycles). Growth factor was not allowed during the dose-limiting toxicity (DLT) assessment period (Cycle 1). **Results:** Among 47 pts enrolled, 9 pts were in Phase 1 portion which assessed the maximum tolerated dose (MTD), with Iber starting at 1 mg/day dose, days 1-21 [Dose Level (DL) 1]. DLT (all grade 4 neutropenia) was noted in 3 pts, 2 at DL 1 & 1 at DL -1. This analysis includes 44 pts who received Iber at the RP2D (0.75 mg/day, days 1-21), including 6 pts from the Dose Confirmation Cohort (Phase 1, DL -1), dosed at MTD, & 38 pts in the Dose Expansion Cohort. The median age at registration was 65 years (range 36-86 years), & 23 pts (52.3%) were deemed high-risk. At data cut-off, pts had received a median of 15 cycles (range 3-36) of therapy. Overall response rate was 100%; ≥CR rate, 36.4% (95% CI: 22.4, 52.2) during induction & 52.3% (95% CI: 36.7, 67.5), overall, including the maintenance phase. The marrow flow-based (10^{-5}) MRD negative rate was 29.5% during induction & 47.7% overall. At a median follow-up (FU) 18.3 mos, 2 pts have died (one during FU due to progressive disease & the other on-treatment due to COVID-19). 12- (& 18-) month progression-free survival & overall survival rates were 91% (88%) & 97% (94%), respectively. Most common toxicities at RP2D were lymphopenia, neutropenia (leading 27% of pts to require pegfilgrastim support), rash, peripheral neuropathy, diarrhea, & infections. Cases of high-grade fatigue were low (<5%). Updated data will be presented at the meeting. **Conclusions:** Iber-DVd is an active and safe regimen for both TE and TIE pts with NDMM, leading to high response rates which improved over time, with nearly one-half of the pts achieving MRD negative state. Clinical trial information: NCT05392946. Research Sponsor: Bristol Myers Squibb (BMS).

7515 **Rapid Oral Abstract Session**

Long-term outcomes with sustained minimal residual disease (MRD) negativity in belantamab mafodotin–treated patients (pts) with relapsed/refractory multiple myeloma (RRMM): An update from DREAMM-8. First Author: Suzanne Trudel, Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: B-cell maturation antigen (BCMA)–directed therapies have changed the RRMM treatment landscape. In the phase 3 DREAMM-8 trial (NCT04484623), BCMA-directed antibody-drug conjugate (ADC) belantamab mafodotin + pomalidomide and dexamethasone (BPd) demonstrated significant progression-free survival (PFS) benefit and higher rates of complete response (CR)–based MRD negativity vs triplet pomalidomide, bortezomib, dexamethasone (PVd) in pts with RRMM and ≥1 prior line of therapy (LOT). As MRD negativity predicts improved survival in MM, this long-term, postbaseline update describes clinical outcomes and characteristics of pts with sustained MRD negativity. **Methods:** Pts with ≥1 prior LOT including lenalidomide were randomized 1:1 to BPd or PVd. The primary endpoint was PFS (independent review committee assessed); PFS2 was investigator assessed. CR-based sustained MRD negativity (≥12 mo) was an exploratory endpoint. Pts with ≥ CR were tested for MRD negativity by next-generation sequencing (10^{-5} sensitivity). **Results:** At data cutoff (7/7/2025), with median follow-up of 35.8 mo overall, the intention-to-treat population of BPd (n=155) vs PVd (n=147) was >4× more likely to achieve ≥ CR + MRD negativity (27.7% vs 6.1%) and sustained MRD negativity (15.5% vs 2.7%). In pts with ≥ CR (BPd, n = 67; PVd, n = 25), rates of MRD negativity were also higher with BPd vs PVd (64.2% vs 36.0%), as were rates of sustained MRD negativity (55.8% vs 44.4%) among all ≥ CR + MRD negative pts. Pts with sustained MRD negativity had durable PFS in both arms; 1 of 24 and 0 of 4 pts experienced PFS events with BPd and PVd, respectively. In pts without sustained MRD negativity, median PFS was 21.1 mo with BPd (HR vs sustained MRD negative, 0.04; 95% CI, 0.01-0.32) and 10.2 mo with PVd (HR vs sustained MRD negative, not estimable [NE]). Sustained MRD negativity was also associated with durable PFS2 in both arms; 2 of 25 and 0 of 4 pts experienced PFS2 events with BPd and PVd, respectively. In pts without sustained MRD negativity, median PFS2 was 20.2 mo with BPd (HR vs sustained MRD negative, 0.08; 95% CI, 0.02-0.33) and 9.3 mo with PVd (HR vs sustained MRD negative, NE). Findings were similar in pts with vs without ≥ CR + MRD negativity. Of BPd-treated pts, those with MRD negativity (n=43) received 1-3 prior LOT, of which most (74.4%) had 1. MRD-positive pts (n=112) received up to 6 prior LOT, of which 44.6% received 1 and 17.0% received >3. Almost 40% of pts with CR-based MRD negativity had high-risk cytogenetics. **Conclusions:** Pts receiving BPd vs PVd were >4× more likely to achieve sustained MRD negativity, which was associated with improved PFS and PFS2. MRD negative vs positive pts in the BPd arm more often had 1 prior LOT. These findings further support BPd, a BCMA-directed ADC regimen, in earlier LOTs for RRMM, including in pts with high-risk cytogenetics. Clinical trial information: NCT04484623. Research Sponsor: Sponsored by GSK. Editorial support provided by Nucleus Global, an Inizio company and funded by GSK (study ID 207499). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from Biowa.

7516 **Rapid Oral Abstract Session**

Isatuximab plus pomalidomide-dexamethasone in relapsed/refractory multiple myeloma: Subgroup analysis by prior anti-CD38 exposure from the phase 3 IRAKLIA trial. First Author: Albert Oriol Rocafiguera, Institut Català d'Oncologia and Josep Carreras Research Institute, Hospital Germans Trias i Pujol, Barcelona, Spain

Background: With the growing use of anti-CD38 therapies in early multiple myeloma (MM) management, there is a need for data in patients previously exposed to anti-CD38 therapy to guide decision making. In the Phase 3 IRAKLIA trial (NCT05405166), patients with relapsed/refractory MM (RRMM) received the anti-CD38 monoclonal antibody isatuximab (Isa) subcutaneously (SC) delivered via an innovative on-body injector (OBI) or intravenously (IV), with pomalidomide and dexamethasone (Pd). In this post hoc analysis, we examined outcomes in IRAKLIA patients with vs without prior anti-CD38 exposure. **Methods:** RRMM patients ≥18 years with ≥1 prior line of therapy including lenalidomide and a proteasome inhibitor were randomized to receive Isa SC (n=263) or IV (n=268) weekly in Cycle 1, then every 2 weeks, with Pd. Patients with prior anti-CD38 exposure <9 months (mos) before randomization or intolerance to anti-CD38 were excluded. Refractory patients were defined as those who failed to achieve minimal response on treatment or had progression within 60 days after last dose. Patients receiving Isa SC or IV were pooled. **Results:** Overall, 67 patients (12.6%) had prior anti-CD38 exposure with a median washout period of 20.2 mos, of which 26 (38.8%) were anti-CD38 refractory. Baseline characteristics were largely consistent between patients with or without prior anti-CD38 exposure; the median follow-up for the overall population was 12 mos. Patients with prior anti-CD38 exposure had an overall response rate (ORR) of 52.2%, 12-mo progression-free survival (PFS) rate of 40.6%, and median PFS of 8.5 mos. In patients without prior exposure, an ORR of 73.5%, 12-mo PFS of 68.8%, and non-estimable (NE) median PFS were reported. Anti-CD38 non-refractory vs refractory patients had an ORR of 48.8% vs 57.7%, 12-mo PFS of 38.9% vs 42.2%, and median PFS of 9.0 vs 7.5 mos. Patients with a longer washout period (>median of 20.2 mos) had an ORR of 63.6%, 12-mo PFS of 61.8% and NE median PFS, whereas patients whose prior anti-CD38 therapy ended more recently (≤median of 20.2 mos) had an ORR of 41.2%, 12-mo PFS of 19.2%, and median PFS of 6.7 mos. The safety profile of Isa + Pd was similar in patients with vs without prior anti-CD38 exposure. **Conclusions:** Isa + Pd demonstrated clinical benefit across anti-CD38–naïve, anti-CD38–exposed, and anti-CD38–refractory patients. A washout period >median of 20.2 mos resulted in outcomes comparable to those in anti-CD38–naïve patients, and outcomes were consistent between anti-CD38–exposed and anti-CD38–refractory patients after a >9-mo washout period. Efficacy of Isa + Pd in patients with prior anti-CD38 exposure from the IRAKLIA trial presents an opportunity to address an unmet need in a difficult-to-treat patient population. Clinical trial information: NCT05405166. Research Sponsor: Sanofi.

7517 **Rapid Oral Abstract Session**

Final analysis of daratumumab, carfilzomib, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma. First Author: Jennifer H. Cooperrider, University of Chicago, Department of Medicine, Chicago, IL

Background: Frontline therapy for patients with multiple myeloma (MM) has mainly consisted of a proteasome inhibitor and an immunomodulatory imide drug (IMiD). Anti-CD38 monoclonal antibodies are fast becoming incorporated into frontline regimens, but many patients experiencing relapse today remain naïve to this drug class. While quadruplet therapies have become a standard-of-care in the newly diagnosed setting, they have not been well studied in patients with relapsed/refractory MM (RRMM). Here, we report the final analysis of a phase 2 Multiple Myeloma Research Consortium study of daratumumab combined with carfilzomib, pomalidomide, and dexamethasone in RRMM (NCT01665794). **Methods:** Eligible patients had documented MM with 1-3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory drug. Prior exposure to a CD38-directed monoclonal antibody was exclusionary. Dose and frequency were described previously. The primary endpoint was the rate of near complete response (nCR) after 4 cycles of DaraKPd; secondary endpoints included progression-free survival (PFS) and overall survival (OS). **Results:** A total of 28 patients were treated with DaraKPd. Patients had received a median of 1 prior line of therapy (range 1-3), including 24 (85.7%) with prior autologous stem cell transplant, and 82% that were refractory to lenalidomide. The study reached the statistical threshold for efficacy (nCR of 39%; 95% CI 22-59%), and the study was stopped early as a result. At a median follow-up of 70.2 months, the median progression-free survival (mPFS) was 38.3 months (95 % CI 18.4 mo-not reached [NR]) and median OS (mOS) was not reached. The 36-month PFS and OS were 54% (95% CI 35-70%) and 75% (95% CI 57-87%), respectively. High-risk cytogenetics, as defined by the presence of t(4;14), t(14;16), t(14;20), deletion 17p, and 1q gain or amplification, were present in 18 (64%) patients. The mPFS in the high risk group was 42.8 mo (18.4-NR) and mOS was not reached. For patients with standard-risk cytogenetics, neither the mPFS nor mOS were reached. Of the 26 patients evaluable for MRD negativity by flow cytometry (limit of detection 10^{-5}), 17 (65%) achieved MRD-negativity and 11 (42%) had sustained MRD negativity for ≥1 year. Among patients with MRD-negativity as best response, mPFS was 69.4 mo (18.9-NR) compared to 14.0 mo (1.2-NR) in patients with MRD positivity (p = 0.002). There were no new safety signals or treatment-related deaths. **Conclusions:** With nearly 6 years of follow-up, DaraKPd in lenalidomide-exposed and anti-CD38 monoclonal antibody-naïve RRMM showed deep and durable responses, with a mPFS of 38.3 months and 36-month OS of 75%. These long-term follow-up data support DaraKPd as a safe and effective treatment in patients with RRMM. Clinical trial information: NCT01665794. Research Sponsor: Multiple Myeloma Research Consortium; Amgen; Bristol Myers Squibb.

7518 **Poster Session**

Prediction of progression in MGUS using transformer-based survival time-series modeling. First Author: Vaishnavi Kumbhar, Division of Hematology, Mayo Clinic Rochester, Rochester, MN

Background: Monoclonal gammopathy of undetermined significance (MGUS) is common, yet only a minority progress to malignant plasma-cell disorders. Mayo risk stratification uses baseline factors and is commonly implemented/validated in a Cox proportional hazards (CoxPH) framework, which may miss prognostic longitudinal patterns. **Methods:** We assembled 15,158 MGUS patients with longitudinal laboratory data and progression outcomes (smoldering multiple myeloma, multiple myeloma, AL amyloidosis, or Waldenström macroglobulinemia). We compared a Mayo-factor Cox proportional hazards (CoxPH) baseline versus STRaTS, a transformer-based survival model, to predict progression risk at 3-, 5-, and 10-year horizons. STRaTS leveraged longitudinal trajectories of routine labs including hemoglobin, platelets, differential counts (neutrophils/lymphocytes/monocytes), immunoglobulins (IgG/IgA/IgM), free light chains (kappa/lambda), M-spike, and creatinine. To minimize bias, we used laboratory results collected from 1–3 years after diagnosis and started follow-up at year 3; patients progressing before year 3 or lacking follow-up beyond year 3 were excluded. A total of 7,305 patients met eligibility and were split into train/validation/test cohorts of 4,383/1,461/1,461. Discrimination was assessed by concordance index (C-index). Clinical operating performance was evaluated on a held-out test cohort by comparing sensitivity and specificity at the same proportion of patients selected for intensified surveillance (same workload). **Results:** Among MGUS patients with complete baseline Mayo factors(N=3,388), Kaplan–Meier–estimated 3-/5-/10-year cumulative progression risk was 0.1/0.4/3.4% (Low), 3.0/4.3/7.9% (Low-Intermediate), 4.4/6.4/14.1% (High-Intermediate), and 8.9/12.5/16.9% (High). On a held-out test cohort, STRaTS demonstrated superior discrimination versus the Mayo-factor CoxPH (C-index 0.75 vs 0.538; p<0.0001). Both models were trained and evaluated on identical train/test splits. At the same surveillance workload, STRaTS achieved higher sensitivity with comparable specificity; when 40.3% of patients were selected for closer surveillance, 3-year sensitivity was 81.0% for STRaTS versus 47.6% for CoxPH (Table). **Conclusions:** Among MGUS patients who remain progression-free at 3 years, transformer-based survival modeling of longitudinal laboratory trajectories provides more accurate individualized conditional progression risk estimates and improved workload-matched identification of progressors compared with the conventional Mayo/Cox approach. Research Sponsor: None.

Sensitivity/specificity (%).

Operating Point	Flagged %	STRaTS Sens / Spec (%)	CoxPH Sens / Spec (%)
Int+High, 3y	40.3	81.0 / 58.5	47.6 / 58.9
Int+High, 5y	40.3	81.2 / 60.4	46.9 / 58.8
Int+High, 10y	40.3	25.0 / 56.3	23.8 / 58.7
Two-Group High (≥2 factors), 5y	5.6	37.4 / 93.4	35.4 / 93.1

7519 **Poster Session**

Early detection of multiple myeloma and MGUS progression risk using artificial intelligence and routine laboratory data. First Author: Ciro Roberto Rinaldi, United Lincolnshire Teaching Hospital and University of Lincoln, Lincoln, United Kingdom

Background: Multiple myeloma (MM) is a malignant plasma cell disorder that often presents with non-specific symptoms, resulting in delayed diagnosis and poorer outcomes. While artificial intelligence (AI) models using routine laboratory data have shown promise for MM detection, their ability to distinguish monoclonal gammopathy of undetermined significance (MGUS) from early MM and to identify patients at risk of progression remains limited. **Methods:** We conducted a retrospective study using routinely collected clinical and laboratory data from 89 patients evaluated at the Lincolnshire Hospital Group between 2003 and 2025. The cohort included confirmed MM cases, MGUS patients, and non-myeloma controls. Predictive features included hemoglobin, serum creatinine, calcium, albumin, immunoglobulin levels, paraprotein concentration, and derived laboratory indices. After rigorous data cleaning and preprocessing, eight supervised machine learning models were trained using a training–testing split. These included six machine learning algorithms (Lasso, gradient boosting, random forest, elastic-net, ridge regression, and support vector) and two baseline algorithms (Naïve (Mean) and Seasonal-Naïve). The training set included 69 patients (82%), and the test set included 20 patients (18%). Model performance was evaluated using precision, recall, F1 score, and regression evaluation metrics such as R^2 (R-squared) and MAE (Mean Absolute Error), with a specific focus on MGUS–MM differentiation. **Results:** The developed AI models demonstrated reliable performance in distinguishing MM from non-myeloma controls and showed improved discriminatory ability between MGUS and MM compared with standard laboratory threshold-based assessment. Specific laboratory feature patterns were associated with progression-consistent phenotypes, enabling risk stratification within the MGUS population. The best-performing model, Lasso Regression, achieved 0.01 MAE (months) and a nearly perfect score of 1.00 for R^2. This meant the best prediction done by the model had a 0.47 months error, i.e. 14 days difference from the actual transformation date. Gradient Boosting and Random Forest achieved 1.04 and 1.15 MAE, and 0.90 and 0.95 R^2, respectively. The results were implemented as a prototype clinical decision-support tool capable of generating rapid risk predictions using routinely available laboratory data. **Conclusions:** This study advances existing AI-based diagnostic approaches by addressing the clinically important challenge of early MM detection and MGUS risk stratification. AI-driven analysis of routine laboratory data may support earlier identification of patients at risk of progression, enabling improved monitoring, timely referral, and enhanced clinical decision-making. Research Sponsor: None.

7520 **Poster Session**

Artificial intelligence predicted natural killer cell fitness to guide daratumumab and transplant strategies in newly diagnosed multiple myeloma. First Author: Arjun Raj Rajanna, Sylvester Myeloma Institute, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

Background: Daratumumab (Dara) requires CD16-expressing natural killer (NK) cells for anti-myeloma activity. The use of bone marrow transplant (ASCT) results in prolonged immunosuppression, including lower levels of NK-cells. We evaluated if artificial intelligence (AI) predicted CD16 from routine hematoxylin and eosin (H&E) stained bone marrow biopsy slides could be used to guide Dara and transplant treatment strategies. **Methods:** We analyzed 212 newly diagnosed patients from the HealthTree registry treated with VRd (n=135; median follow-up 24.5 months (mo)) and D-VRd (n=77; 16.6 mo). H&E slides were processed using GigaTIME, a foundation model via zero-shot inference. Patients were dichotomized at median predicted CD16 and stratified by ASCT status. Subgroups: transplant-eligible (TE: age$<$65, ASCT; n=53), deferred (TD: age$<$70, no ASCT; n=34), and ineligible (TI: age$\geq$70; n=17). Primary endpoint: time to next treatment (TTNT). Multivariate Cox regression adjusted for age, cytogenetic risk tested interaction between CD16, treatment and ASCT. **Results:** D-VRd achieved superior outcomes vs VRd (23.4% event rate vs 74.8%, p$<$0.001) despite lower ASCT use among D-VRd treated patients (50.6% vs 71.1%, p=0.005). In the VRd group, AI-predicted CD16 was highly prognostic in non-transplanted patients: High-CD16 achieved median TTNT 33.1 vs 5.1 mo for Low-CD16 (p=0.0053). ASCT rescued Low-CD16 patients (median 5.1 to 26.7 mo, p$<$0.001). Conversely, in D-VRd, CD16 did not stratify outcomes (p=0.48), indicating that Dara can rescue low-immune-fitness disease. Specifically, Dara rescued low CD16 non-transplanted patients from progression (86.8% 18-mo event-free survival for D-VRd versus 28.6% 18-mo event-free survival for VRd; p$<$0.001). High CD16 patients on D-VRd without ASCT achieved 86.3% event-free survival, non-inferior to ASCT (82.2%, p=0.21), supporting transplant deferral. The CD16$\times$treatment$\times$ASCT interaction was significant (HR 0.06, p=0.045). Among transplant-deferred patients, D-VRd improved 18-mo event-free rates vs VRd (70.5% vs 40%, p=0.029), with the largest benefit in Low CD16 (p=0.016). TI patients on D-VRd achieved 100% event-free at 18 mo vs 38.2% on VRd (p=0.011). **Conclusions:** We validated that AI-quantified CD16 from routine H&E guides Dara and transplant strategies in NDMM (n=212). The CD16$\times$treatment$\times$ASCT interaction (HR=0.06, p=0.045) confirms that CD16 predicts treatment benefit, not just prognosis. In VRd, low CD16 identifies a high-risk group (median TTNT 5.1 mo) needing intensification. D-VRd rescues low-immune-fitness patients (18-mo event-free survival: 86.8% vs 28.6% with VRd, p$<$0.001) and enables safe transplant deferral in high-fitness patients (82.2% with ASCT vs 86.3% without, p=0.21). This novel strategy enables precision medicine using standard H&E slides, with immediate clinical implications. Research Sponsor: None.

7521 **Poster Session**

AI-enabled multimodal adjudication of revised IMWG progression after BCMA CAR-T. First Author: David Kaldas, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Real-world ascertainment of clinically meaningful relapse after BCMA CAR-T is challenging because progression signals are distributed across laboratories, imaging, pathology, and clinician actions and are frequently embedded in unstructured external reports. The revised IMWG criteria (Kumar et al., IMS 2025) provide standardized definitions for imaging-based progression (PET/CT and WB-MRI) enabling automated recognition of radiologic and serologic progression thresholds. We developed an AI-enabled multimodal framework to automate real-time derivation of recognized IMWG progression across fragmented care settings. **Methods:** We analyzed 183 BCMA CAR-T treatment episodes with longitudinal routine laboratory data and independent dual-reviewer adjudication of progression dates. Automated detection evaluated every M-protein and FLC measurement longitudinally in a continuous IMWG rules engine, in addition to flagging new hypercalcemia. In addition, initiation of a new line of therapy (considered a progression event), together with large-language-model extraction of radiologic progression from PET/CT, WB-MRI, CT, X-ray, and MRI brain/spine reports. Performance was assessed using accuracy and specificity. **Results:** Serologic progression from real-world lab feeds was detected with high reproducibility, with FLC and M-protein achieving high accuracy (96.5% and 98.5%, respectively) and specificity ($>$97%), indicating minimal premature triggering across serial measurements. Hypercalcemia was rare but highly specific for progression. Radiology-based AI extraction achieved high accuracy (91%) and specificity (92.1%), enabling reliable identification of imaging-defined relapse. Initiation of a new line of therapy occasionally occurred before formal serologic IMWG thresholds were met, reflecting clinician-recognized relapse or that driven by non-serologic disease. Notably, 19% of adjudicated relapses were triggered by radiologic or marrow criteria when serologic IMWG thresholds were absent or lagging, including 12.5% radiology-only and 5.8% marrow-only events, aligned with our published data for post CART relapses (Abuhelwa et al Front. Oncol 2025). **Conclusions:** Automated lab-only approaches systematically underestimate true IMWG progression after BCMA CAR-T. An AI-enabled multimodal adjudication framework aligned with the revised IMWG criteria enables scalable, real-time, and reproducible progression capture for clinical trials and real-world datasets, supporting rapid endpoint determination, regulatory-grade retrospective analyses, and biologically faithful reconstruction of relapse patterns after CAR-T. Research Sponsor: None.

7522 **Poster Session**

Echo cancer advisor: A modular AI framework for interpretable, patient-specific oncology decision support. First Author: Ariosto Siqueira Silva, H. Lee Moffitt Cancer Center, Tampa, FL

Background: Oncology increasingly relies on large, heterogeneous datasets spanning genomics, clinical records, imaging, and treatment history. Large language models (LLMs) show promise for synthesizing such information, yet currently suffer from limited transparency, hallucination risk, and poor alignment with real-world clinical reasoning. There is a critical need for AI systems that can integrate multimodal data while preserving interpretability, traceability, and clinician control. **Methods:** We developed a modular AI decision-support system to assist oncologists in complex clinical reasoning tasks. Unlike monolithic LLM approaches, it decomposes clinical questions into atomic sub-tasks that are executed through structured, auditable pipelines, while integrating curated clinical data (EHR, genomics, pathology), external knowledge bases, and computational analyses via a function-oriented architecture. Each step is independently validated, logged, and audited to ensure correctness. It uses a hybrid local/cloud architecture and was evaluated on real-world oncology use cases in Moffitt Cancer Center's Multiple Myeloma (MM) cohort, which contains three data modalities: clinical, molecular, and pre-clinical. Clinical data resides in a PHI-compliant Snowflake data warehouse (Moffitt Cancer Analytics Platform, MCAP), including longitudinally-resolved treatment and outcome information from clinical notes, labs, pathology and radiology reports. CD138-enriched bone marrow samples from 1,260 MM patients were molecularly profiled using RNA-seq (n=1,376 biopsies) and whole exome sequencing (WES, n=1,427), whereas 549 tumor samples from MM patients were tested for ex vivo drug sensitivity. **Results:** This system successfully decomposed complex clinical questions into atomic sub-questions and generated appropriate database queries and software tool calls to retrieve relevant information across heterogeneous data sources. Independently, the system integrated clinical data—including physician notes, pathology reports, laboratory values and pharmacy records—to reconstruct longitudinal patient histories achieving 80% concordance with expert manual abstraction, while reducing case synthesis time from hours to minutes. Importantly, the system preserved transparency by explicitly exposing intermediate reasoning steps and highlighting missing or ambiguous data requiring clinician judgment. **Conclusions:** We propose a shift from generative AI toward structured, interpretable clinical reasoning systems. By emphasizing modularity, auditability, and human-in-the-loop design, we offer a scalable path toward trustworthy AI deployment in oncology. This framework supports precision medicine not by replacing clinical judgment, but by amplifying it—providing clinicians with transparent, reproducible, and context-aware decision support. Research Sponsor: None.

7523 **Poster Session**

Identifying high-risk cytogenetic subgroups in multiple myeloma using large language artificial intelligence models. First Author: John Culnan, Massachusetts Veterans Epidemiology Research and Information Center, Department of Veterans Affairs Healthcare System, Boston, MA

Background: The Revised International Staging System (R-ISS) is the clinical standard for risk stratification in multiple myeloma (MM) and is central to treatment selection and prognostication. However, the cytogenetic abnormalities on which the R-ISS is predicated are typically reported in unstructured formats within bone marrow biopsy reports and clinical notes. Despite the critical importance and relevance of obtaining cytogenetic abnormalities in MM, this information is often missing from large clinical databases, limiting their availability for large scale research and real-world analyses. Here, we created a large language model (LLM)-based algorithm to identify cytogenetic abnormalities from unstructured text and evaluated our model's adaptability by comparing its performance across definitions of high-risk abnormalities. **Methods:** We extracted oncology notes and pathology reports within 2 years of diagnosis from the EHR of adult patients with MM registered within the Department of Veterans Affairs (VA) Cancer Registry System between 2000 and 2024. Two physician reviewers iteratively annotated 1600-character snippets from these texts for abnormalities and their type (gain, deletion, translocation) plus normal cytogenetics. From these annotations we identified items with high-risk cytogenetic abnormalities per current guidelines (del(17p) in $>$ 20% plasma cells; TP53 mutation; gain(1q) and/or del(1p32) plus t(4;14), t(14;16), or t(14;20); monoallelic del(1p32) plus gain(1q); biallelic del(1p32)) and previous guidelines (t(4;14), t(14;16), t(14;20), del TP53/17p, del(1p), gain(1q)). We used few-shot prompting with GPT-OSS 120B to extract cytogenetic results and validated our model on a test set of 985 snippets representing 773 patients at 98 VA centers. **Results:** The test set contained 81 snippets with normal cytogenetics and 464 with abnormalities; 58 were high-risk per current guidelines and 144 per previous guidelines. Our model successfully identified high-risk cytogenetics per current (P: 88.9%, R: 82.8%, F1: 85.7%) and previous guidelines (P: 86.7%, R: 90.3%, F1: 88.4%), as well as type of cytogenetic abnormality (weighted averages; P: 92.3%, R: 92.2%, F1: 92.4%), demonstrating its utility and flexibility for the task as standards change. Applied to a cohort of 7250 unlabeled notes, our model identified high-risk cytogenetics in 501 (6.9%) and any cytogenetic information in 5385 (74.3%). **Conclusions:** Our model demonstrated the successful capture of cytogenetic information across multiple definitions of high-risk cytogenetic abnormalities, providing a fast, adaptable framework for extraction that traditionally required repeated large-scale human efforts. Leveraging an LLM for this task enables scalable MM risk stratification while reducing clinician burden and supporting rapid adaptation to evolving cytogenetic risk definitions. Research Sponsor: VA Office of Research and Development.

7524 **Poster Session**

RP2R dose selection of Tal + Tec for the treatment of EMD patients in the RedirecTT-1 study. First Author: Nicholas Au, Johnson & Johnson, Spring House, PA

Background: Talquetamab (Tal, anti-GPRC5D) and Teclistamab (Tec, anti-BCMA) are first-in-class bispecific antibodies approved as monotherapies for triple-class exposed relapsed/refractory multiple myeloma (RRMM). Extramedullary disease (EMD) is an aggressive MM subtype with poor outcomes and high unmet need. RedirecTT-1 (NCT04586426) is a Phase 1b/2 dose escalation/expansion study evaluating Tal + Tec in RRMM patients (pts) including EMD. We present data supporting selection of the recommended Phase 2 regimen (RP2R) for treatment of EMD pts, based on efficacy, safety, and exposure-response (E-R) analyses from Phase 1. Phase 2 allowed switching to a Q4W regimen after cycle 6 or cycle 4 if the response was ≥VGPR. **Methods:** Phase 1 evaluated 6 dose regimens of Tal (0.2–0.4 mg/kg QW, 0.8 mg/kg Q2W, 0.8 mg/kg Q4W) + Tec (0.75-1.5 mg/kg QW, 1.5-3 mg/kg Q2W, 3 mg/kg Q4W). Responses were investigator-assessed per IMWG criteria. CRS and ICANS were graded by ASTCT criteria; all other adverse events were graded by CTCAE v5.0. Model-based E-R analyses for efficacy were conducted with reported efficacy endpoints (ORR, ≥VGPR, ≥CR). First cycle PK metrics (C_{avgC1}, $C_{troughC1}$) were used due to time-varying clearance of Tal and Tec. **Results:** At the clinical cutoff for this analysis (18 March 2025), Phase 1 enrolled 114 pts (38 EMD) with a median follow-up of 31.6 months. EMD pts treated with QW regimens of Tal 0.2-0.4 mg/kg + Tec 0.75-1.5 mg/kg (n=13), which comprised of multiple dose levels (1-9 pts per cohort), achieved an ORR of 33-100% (≥CR, 0-22.2%). EMD pts treated with the Q2W regimen using Tal 0.8 mg/kg and Tec 1.5 mg/kg (n=4) achieved an ORR of 50% (≥CR, 25%), while EMD pts treated with the Q2W regimen including Tal 0.8 mg/kg + Tec 3.0 mg/kg (RP2R, n=18) demonstrated high and deep response rates (ORR, 61.1%, ≥CR, 44.4%) with a manageable safety profile. EMD pts treated with the Q4W regimen of Tal 0.8 mg/kg + Tec 3.0 mg/kg (n=3) achieved an ORR of 100%, where 2 achieved ≥VGPR, but none achieved ≥CR. The RP2R generally provided higher and deeper responses in EMD pts compared to non-RP2R regimens. The efficacy E-R analysis for EMD pts showed a positive E-R relationship between exposure (C_{avgC1} and $C_{troughC1}$) and ≥CR. Pts with exposures above the median for both Tal and Tec showed higher CR rates. At RP2R, C_{avgC1} and C_{trC1} exceeded median exposures across all Phase 1 dose regimens for both antibodies. The overall safety profile of Tal + Tec at the RP2R was manageable and consistent with each agent as monotherapy, while enabling deeper and more durable responses than observed across non-RP2R regimens. **Conclusions:** The totality of efficacy, safety and E-R analyses support advancement of a Tal + Tec regimen for further clinical development in RRMM pts with EMD who have received a PI, an IMiD, and an anti-CD38 mAb, and offers flexibility of switching to Q4W for responders. Clinical trial information: NCT04586426. Research Sponsor: Johnson & Johnson.

7525 **Poster Session**

An integrated population pharmacokinetic/pharmacodynamic (popPK/PD) model to select the linvoseltamab (LINVO) dosing regimen in patients with high-risk smoldering multiple myeloma (HR-SMM). First Author: Brett Matzuka, Regeneron Pharmaceuticals, Inc., Tarrytown, NY

Background: LINVO is a BCMA×CD3 bispecific antibody approved for triple-class exposed relapsed/refractory (RR) multiple myeloma (MM) after ≥3 therapies (EU) or ≥4 prior lines of therapy (USA). LINVO 200 mg was approved based on the deep and durable responses and manageable safety profile observed in the LINKER-MM1 study (objective response rate [ORR] 71%; NCT03761108). LINVO 200 mg demonstrated promising efficacy and a generally manageable safety profile as an early intervention in HR-SMM (ORR 100%; Phase [Ph] 2 LINKER-SMM1 NCT05955508; IMS 2025 OA-68) and as frontline therapy in newly diagnosed (ND) MM (ORR 86%; Ph 1/2 LINKER-MM4 NCT05828511; ASH 2025 #697). We present results from a semi-mechanistic popPK/PD model of LINVO integrating data from pts with RRMM, NDMM, and HR-SMM, to support full dose selection for a Ph 3 HR-SMM study. **Methods:** A popPK/PD model was developed from LINKER-MM1 RRMM data to predict LINVO concentration (conc) and disease burden dynamics (soluble BCMA, total [involved + uninvolved] free light chain [FLC] conc). Free LINVO conc was a strong predictor of ORR and progression-free survival in the LINKER-MM1 model. The model was updated with data from LINVO administration in pts with NDMM and HR-SMM. Based on baseline disease characteristics in pts with HR-SMM, the model was used to predict free and total LINVO conc for regimens with full doses of 50, 100, and 200 mg in a clinical trial simulation setting. The model assumed that T-cell–mediated tumor killing was dependent on free LINVO forming the T-cell + drug + MM cell complex. The variability in observed response rates across studies was presumed to arise due to differences in disease burden, MM plasma cell proliferation, and T-cell fitness, with the killing rate expected to be more similar between HR-SMM and NDMM than between HR-SMM and RRMM. **Results:** The dose regimen chosen for evaluation in a Ph 3 HR-SMM study comprised a 200 mg dose given weekly in cycle (C) 1 with the frequency decreasing to every 2 weeks after C1, every 4 weeks after C6, and every 8 weeks after C13. Following initial weekly dosing in this regimen, the free LINVO conc predicted in HR-SMM matched the free LINVO conc predicted in the higher efficacy arm of LINKER-MM4 and the higher efficacy arm in Ph 2 of LINKER-MM1. The model predicted that the 200 mg dose regimen would achieve deep responses (measured by substantial reduction in FLC conc) as rapidly as Week 8, and continue through Week 30, despite the reduced dosing frequency. **Conclusions:** The totality of evidence, including efficacy and safety data in pts with SMM, dose-ranging data (PK/PD, safety, and efficacy) in pts with NDMM and RRMM, and exploratory analyses integrating exposure and response markers across studies, supports selection of the less intensive LINVO 200 mg dose regimen (compared with NDMM and RRMM) in the Ph 3 HR-SMM study. Clinical trial information: NCT03761108; NCT05828511; NCT05955508. Research Sponsor: Regeneron Pharmaceuticals, Inc.

7526 **Poster Session**

Comparative efficacy of linvoseltamab versus teclistamab in triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM): Updated matching-adjusted indirect comparison (MAIC) with longer follow-up. First Author: Hans C. Lee, Sarah Cannon Research Institute, Nashville, TN

Background: Linvoseltamab and teclistamab are anti-B-cell maturation antigen (BCMA)×CD3 bispecific antibodies evaluated in the LINKER-MM1 and MajesTEC-1 trials, respectively, and approved for TCE RRMM. In the absence of head-to-head trials, a previous MAIC assessed their relative efficacy at ~14-month median follow-up (mFU). We present updated results with longer follow-up for both trials. **Methods:** After excluding 10 patients (pts) with prior BCMA antibody–drug conjugate exposure from LINKER-MM1 to align with MajesTEC-1 eligibility, pt-level data from LINKER-MM1 (linvoseltamab 200 mg, N=107; data cut-off [DCO] July 2024; mFU 21.3 months) and aggregate data from MajesTEC-1 (N=165; DCO August 2023; mFU 30.4 months) were used. LINKER-MM1 pts were weighted to match MajesTEC-1 using prespecified prognostic factors, as described previously (Lee et al., *Clin Lymphoma Myeloma Leuk* 2025;25:897–909). MAICs were rerun for objective response rate (ORR), very good partial response or better (≥VGPR) rate, complete response or better (≥CR) rate, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and time to next treatment (TTNT). Treatment effects were estimated using odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs). Restricted mean survival time (RMST) was evaluated at 30 months. **Results:** In both unadjusted comparisons and MAICs adjusted for 6 key prognostic factors (cytogenetic risk, age, refractory status, ISS stage, ECOG score, extramedullary disease/plasmacytoma status; effective sample size 82.5), linvoseltamab showed numerically higher ORR, ≥VGPR, and ≥CR rates and significantly longer DOR, PFS, OS, and TTNT vs teclistamab (Table). Compared with prior MAICs with shorter follow-up, adjusted HRs for DOR and TTNT further decreased in favor of linvoseltamab, while other results remained stable. **Conclusions:** With longer follow-up, linvoseltamab continued to demonstrate comparative efficacy advantages vs teclistamab, reinforcing its potential as an effective treatment option for TCE RRMM. Research Sponsor: Regeneron Pharmaceuticals, Inc.

Outcome, linvoseltamab vs teclistamab	Unadjusted	Adjusted for 6 key prognostic factors
	OR (95% CI)	*OR (95% CI)*
ORR	1.44 (0.97–2.13)	1.50 (0.97–2.32)
≥VGPR	1.19 (0.83–1.72)	1.17 (0.79–1.74)
≥CR	1.29 (0.91–1.82)	1.21 (0.83–1.76)
	HR (95% CI); RMST difference, months (95% CI)	*HR (95% CI); RMST difference, months (95% CI)*
DOR	0.58 (0.36–0.96)*; 3.66 (0.77–6.55)*	0.54 (0.31–0.92)*; 4.06 (1.13–6.98)*
PFS	0.57 (0.40–0.82)*; 5.13 (2.01–8.25)*	0.55 (0.36–0.82)*; 5.43 (2.04–8.81)*
OS	0.68 (0.47–0.98)*; 2.99 (0.22–5.75)*	0.64 (0.43–0.97)*; 3.06 (0.08–6.04)*
TTNT	0.42 (0.28–0.62)*; 7.10 (4.27–9.94)*	0.41 (0.27–0.64)*; 7.12 (4.15–10.09)*

*p<0.05. OR >1, HR <1, or RMST >0 indicate better efficacy with linvoseltamab vs teclistamab.

7527 **Poster Session**

Updated two-year overall survival and toxicity outcomes of BCMA CAR-T therapy compared with teclistamab in multiple myeloma. First Author: Junmin Song, Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: B-cell maturation antigen (BCMA) targeted chimeric antigen receptor T-cell therapy (CAR-T) and bispecific antibodies have transformed the treatment landscape for relapsed or refractory multiple myeloma. In a prior real-world study, CAR-T therapy was associated with improved short-term overall survival compared with teclistamab; however, follow-up was limited to less than one year. Longer-term comparative outcomes between these modalities remain insufficiently characterized. This sequel study evaluates the updated two-year overall survival and toxicity outcomes. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, comprising data from over 70 healthcare institutions in the United States, to identify patients with multiple myeloma treated between 2021 and 2023 with either CAR-T therapy (ciltacabtagene autoleucel [cilta-cel] or idecabtagene vicleucel [ide-cel]) or teclistamab. Patients who received other bispecific antibodies, including elranatamab, talquetamab, or linvoseltamab, were excluded. Two mutually exclusive cohorts were defined: patients who received CAR-T therapy without prior or subsequent teclistamab and patients who received teclistamab without prior or subsequent CAR-T therapy. Propensity score matching was performed to balance baseline demographics, comorbidities, prior therapies, and laboratory values. HR and 95% CI were estimated using Cox proportional hazards models for two-year overall survival, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS). **Results:** A total of 351 CAR-T cell therapy recipients and 507 teclistamab recipients were included. After propensity score matching, 227 patients were retained in each cohort, with well-balanced baseline characteristics, including demographics (mean age: 65 years, White: 74%, male: 53%), comorbidities, and prior multiple myeloma treatments, including immunomodulatory drugs, proteasome inhibitors, dexamethasone, and anti-CD38 antibodies. Mean follow-up durations were comparable between the CAR-T and teclistamab cohorts at 524 and 438 days, respectively. CAR-T therapy was associated with significantly improved two-year overall survival compared with teclistamab (HR: 0.61, 95% CI: 0.43-0.87, p=0.005). In contrast, CAR-T therapy was associated with higher risks of CRS (HR: 1.48, 95% CI: 1.12-1.96, p=0.003) and ICANS (HR: 2.02, 95% CI: 1.20-3.41, p=0.007). **Conclusions:** In this extended two-year real-world analysis, CAR-T therapy was associated with superior overall survival compared with teclistamab, albeit with increased immune-mediated toxicities. These findings build upon prior short-term data and underscore the need for prospective studies directly comparing BCMA-targeted treatment strategies across longer follow-up intervals. Research Sponsor: None.

7528 **Poster Session**

Iberdomide (Iber) maintenance following upfront autologous stem cell transplant (ASCT) in multiple myeloma (MM). First Author: Tanya Marya Wildes, University of Nebraska Medical Center, Omaha, NE

Background: Lenalidomide (Len) maintenance after ASCT has been a standard of care for patients (pts) with MM. Historically, ~30% of pts discontinue Len within 1 year (yr) due to toxicity and there is a need for more effective and better tolerated maintenance strategies. Iber is a potent, oral cereblon E3 ligase modulator under evaluation in the relapsed/refractory and newly diagnosed settings. We report the results of the primary analysis of a Phase II trial of Iber maintenance following upfront ASCT. **Methods:** Pts ≥ 19 yrs of age with MM, within 1-yr of initiation of induction therapy and in a ≥ partial response (PR) at day 80-110 post-ASCT, were accrued. Iber was administered 1.0 mg orally days 1-21 of a 28-day cycle, continued until progressive disease (PD) or toxicity. Up to 2 dose reductions (0.75 mg/day then 0.6 mg/day) were allowed. Growth factor support was not permitted. Minimal residual disease (MRD) assessment by flow cytometry (10^{-5}) was performed at registration, post-cycle 12 and post-cycle 24. An optimal Simon two-stage design with type I and II errors of 0.1 was chosen to test whether the proportion of pts who are progression-free and on treatment at 1 yr is <60% against the alternative of ≥ 80%. If ≥ 27 out of 38 pts were progression-free (by 2016 IMWG criteria) and on treatment at 1 yr, Iber would be considered to have promising activity. **Results:** 38 pts (55% males, median age 61 yrs (range: 41-77)) received Iber. R-ISS at diagnosis was stage I (34%), II (39%), III (8%) and unknown (18%), with 34% having high-risk disease per 2025 IMS/IMWG criteria. All pts received triplet or quadruplet induction therapy, with 97% receiving Len and 84% receiving daratumumab. At day 80-110 post-ASCT, all pts had ≥ very good PR, with 22 (58%) ≥ complete response (CR) and 33 (87%) MRD-negative (neg). The median number of administered treatment cycles is 18 (range: 1-45), with 18 (47%) pts having ≥ 1 dose reduction, most commonly due to neutropenia (n=12). The most common grade (gr) 3/4 adverse event was neutropenia (gr 3 (n=19), gr 4 (n=5)). Within yr 1, 29% (11/38) discontinued Iber due to neutropenia (n=5), rash (n=1), infection (n=1), pt choice (n=1), or PD (n=3). After 1 yr, 6 pts discontinued due to neutropenia (n=4) and PD (n=2). While on Iber, 19 pts had deepening of response to stringent CR and 3 pts converted from MRD-positive to MRD-neg. The post-cycle 12 and 24 MRD-neg rates are 85% (23/27) and 100% (14/14), respectively. **Conclusions:** Iber demonstrated promising activity with dose reductions/discontinuations mainly due to neutropenia. Strategies including lower starting dose, growth factor support and more flexible management of neutropenia may enable more pts to remain on treatment. Longer follow-up will permit evaluation of sustained MRD-negativity and PFS, but overall, these results provide rationale for further exploration of Iber-based post-ASCT maintenance strategies. Clinical trial information: NCT05177536. Research Sponsor: Bristol Myers Squibb.

7529 **Poster Session**

Association between survival outcomes in patients with multiple myeloma and treatment facility volume. First Author: Carl Ola Landgren, Sylvester Myeloma Institute, University of Miami, Sylvester Comprehensive Cancer Center, Miami, FL

Background: Oncology research previously demonstrated a volume-outcome relationship, where patients treated at healthcare centers with higher (vs lower) treatment volumes have improved survival. In multiple myeloma (MM), evidence supporting this association remains limited. Most patients with MM are treated at lower volume centers; it is important to recognize and prioritize partnerships between higher and low-volume centers. **Methods:** Adults (≥18 years) receiving ≥1 active MM therapy—IMiD, PI, anti-CD38 mAb, CAR-T, ASCT—from 2017 - 2023 with ≥6-month pre-index enrollment were identified in Komodo Health's Healthcare Map. Patients lacking facility data or treated outside their diagnosing site were excluded. Facilities were segmented based on volume, defined as the average number of new patients with MM per year: ≤1 (very low), 1–5 (low), >5–10 (medium volume), >10 (higher volume). Outcomes included overall survival (OS) and event-free survival (EFS), the latter separately defined as time to 1) therapy change and 2) first symptomatic progression (based on CRAB criteria). Multivariable mixed-effects Cox models were adjusted for diagnosis year, demographics, comorbidities, payer type and treatment exposure. Subgroup analysis of patients initiating 2L therapy was also conducted. **Results:** 18,646 MM patients and 2,049 facilities were identified. Volume distribution was highly skewed: 81.0% were treated at very low volume centers and ~1.9% were treated at higher volume centers. Higher volume centers had the highest use of ASCT (63.7%) and CAR-T (2.1%). Among all patients, use of IMiD-, PI-, and anti-CD38–based regimens were 51.42%, 63.55% and 35.69%, respectively. Although median OS was not reached for any of the segments, higher volume centers had the highest unadjusted median EFS using therapy-based (771 days) and CRAB-defined progression (213 days) definitions (p<.001 vs all other segments). After adjustment, lower-volume segments (very low, low and medium volume centers) had shorter median OS (HRs: 1.03-1.26, 95% CI 0.88-1.46) than higher volume centers. However, compared with higher volume centers, median EFS was similar in lower-volume segments (HRs: 0.97-1.09, 95% CI 0.86-1.23). Among 2L patients, OS models and CRAB-defined EFS showed similar volume-related patterns compared with adjusted overall results. **Conclusions:** Higher-volume centers had more experience with novel therapies and combination of therapies. Experience from high volume centers can effectively be used to partner with smaller volume centers to advance MM care and be able to improve outcomes for patients. Research Sponsor: Pfizer, Inc.

Adjusted EFS and OS hazard ratios by treatment facility segment.

	Change in Therapy EFS		OS	
Facility Volume Segment	**Overall**	**95% CI**	**Overall**	**95% CI**
Higher volume	Ref	Ref	Ref	Ref
Medium volume	0.97	(0.86, 1.09)	1.03	(0.88, 1.21)
Low volume	1.03	(0.92, 1.16)	1.15	(0.99, 1.34)
Lower volume	1.09	(0.97, 1.23)	**1.26**	**(1.09, 1.46)**

7530 **Poster Session**

Gaps in access to chimeric antigen receptor T-cell (CAR-T) therapy post leukapheresis: Waiting time and post-leukapheresis treatment patterns in relapsed/refractory multiple myeloma (RRMM)—Real-world evidence from U.S. claims. First Author: Sikander Ailawadhi, Division of Hematology/Oncology, Department of Medicine, Mayo Clinic Florida, Jacksonville, FL

Background: B-cell maturation antigen (BCMA)-directed CAR-T therapy is a highly effective treatment with potential for long-term remission of RRMM with improved outcomes vs daratumumab-based regimens. CAR-T suitability may be limited by delays/manufacturing failure and changes in pt condition, financial situation, or access to specialized treatment centers. We characterized pts with RRMM who underwent leukapheresis to prepare for CAR-T and pt treatment waiting time, to understand the delays incurred prior to CAR-T infusion. **Methods:** A real-world study in the US using the PharMetrics Plus claims database (July 2020–September 2024) was performed. Eligible pts were aged ≥18 years with RRMM, had their first leukapheresis claim (index date) during the index period (March 2021–August 2024), were continuously enrolled in medical/pharmacy benefits for ≥180 days prior to and ≥30 days after index date, and were not clinical trial participants. Pt characteristics, rate of CAR-T receipt, and time to CAR-T receipt were assessed during the variable follow-up. **Results:** Overall, 337 pts who received leukapheresis were identified. Median (interquartile range) age was 62 (55–67) years, and 59.1% of pts were male. Mean National Cancer Institute (NCI) comorbidity index was 0.52. Most pts received care in the Midwest (31.8%) or Northeast (24.6%) regions. Most pts (95.9%) received leukapheresis in an outpatient setting. Median available follow-up time was 255 days (mean 337 days). During follow-up, 183 pts (54.3%) did not receive CAR-T after leukapheresis. Among pts who had ≥12 months of follow-up (n=143), the proportion of pts who did not receive CAR-T was similar at 53.1% (n=76). Among pts who received CAR-T during the follow-up (n=154; 45.7%), the median waiting time was 54.0 days (mean 56.7 days). The cohort of pts who did not receive CAR-T had a higher proportion of females (48.6%/31.8%), were more likely to have Medicaid (29.5%/7.8%), had higher NCI comorbidity index (scores 0.55/0.47), and most commonly received care in the Northeast (35.5%/11.7%) while pts who received CAR-T most commonly received care in the Midwest (23.0%/42.2%). The most common first classes of multiple myeloma medications after leukapheresis but prior to CAR-T infusion in pts who did/did not receive CAR-T were an alkylating agent (65.6%/36.1%), proteasome inhibitor (40.3%/30.6%), steroid (38.3%/39.3%), immunomodulatory drug (22.7%/27.3%), anti-CD38 (20.8%/20.8%), and stem cell transplant (0%/17.5%). **Conclusions:** Over half of pts receiving leukapheresis did not receive CAR-T infusion, highlighting a persistent gap between eligibility and treatment delivery. These data emphasize an urgent need for broadly accessible BCMA-targeted therapies that provide deep and durable responses. Research Sponsor: GSK.

7531 **Poster Session**

Targeting cfDNA and NETs with DNAse I to augment CAR T-cell function and antitumor efficacy. First Author: Alexey Stepanov, Scripps Research, La Jolla, CA

Background: Chimeric antigen receptor (CAR) T-cell therapy induces high initial response rates in B-cell malignancies; however, limited persistence and early relapse remain major clinical challenges. Accumulation of cell-free DNA (cfDNA) and neutrophil extracellular traps (NETs) within the tumor microenvironment represents a potential mechanism of CAR T-cell dysfunction through induction of exhaustion, immunosuppression and impaired expansion. We hypothesized that enzymatic degradation of extracellular DNA using DNase I could enhance CAR T-cell persistence and antitumor efficacy. **Methods:** The effects of cfDNA and NETs on human CD19 CAR T-cell function were evaluated using sequential killing assays, proliferation assays, and flow cytometry–based phenotyping. DNase I was assessed for its ability to reverse cfDNA/NET-mediated suppression and prevent exhaustion. In vivo efficacy, expansion, and persistence of CAR T cells were studied in xenogeneic B-cell acute lymphoblastic leukemia (Nalm-6) and Burkitt lymphoma (Raji) mouse models. Longitudinal in vivo tracking of CAR T-cell expansion was performed using bioluminescence imaging and serial peripheral blood analysis. Translational relevance was further explored through compassionate-use administration of DNase I in combination with CAR T-cell therapy in a pediatric patient with relapsed/refractory Burkitt lymphoma. **Results:** cfDNA and NETs suppressed CAR T-cell proliferation and cytotoxicity while promoting upregulation of exhaustion markers, including PD-1, LAG-3, and TIM-3. DNase I efficiently degraded extracellular DNA, preserved CAR T-cell effector function, improved CD8:CD4 ratios, and reduced exhaustion across multiple rounds of tumor rechallenge in vitro. In vivo, DNase I significantly enhanced CAR T-cell expansion and persistence following infusion, as demonstrated by longitudinal tracking studies. Combination therapy resulted in improved tumor control, delayed relapse upon rechallenge, and prolonged survival in both NALM-6 and Raji xenograft models. In a single pediatric patient with highly refractory Burkitt lymphoma, DNase I co-administration was associated with marked CAR T-cell expansion and progressive reduction in tumor burden after prior CAR T-cell failure. **Conclusions:** Extracellular DNA and NETs constitute a critical barrier to durable CAR T-cell efficacy. DNase I enhances CAR T-cell persistence and antitumor activity by eliminating cfDNA/NET-driven immunosuppression, supporting further clinical evaluation of DNase I as a combinatorial strategy to improve CAR T-cell therapy outcomes. Research Sponsor: None.

7532 **Poster Session**

Evaluating the impact of a statewide intervention on multiple myeloma bispecific T-cell engaging antibody (BsAb) therapy uptake in Florida (FL). First Author: Maen A. Hussein, Florida Cancer Specialists & Research Institute, Lady Lake, FL

Background: BsAbs are highly effective, off-the-shelf T-cell engagers recently approved for relapsed/refractory multiple myeloma (MM) but remain underutilized in real-world settings. In partnership with the Florida Society of Clinical Oncology (FLASCO), a statewide initiative was launched to expand BsAb access through peer-led regional discussions focused on operational barriers, care transitions, and therapy management strategies. This study assessed the real-world impact of these interventions on BsAb utilization in FL. **Methods:** Multidisciplinary discussion forums were held in 4 FL metropolitan areas (Jan-Apr 2024). We conducted single and controlled interrupted time series (ITS) analyses using IQVIA eLAAD claims data (Apr 2023 - Sep 2025) including adult patients with a diagnosis of MM, evidence of claim activity, and provider state information. Fifth line or later (5L+) status was estimated as 3.3% of MM prevalence (Nikolaou et al.) BsAb utilization (% of MM 5L+ patients receiving a BsAb) was evaluated using segmented regression to estimate pre- and post-intervention trends, excluding the intervention period. We reported BsAb utilization by comparing FL with all other states, between community versus academic settings, and assessing the number of sites administering BsAb. **Results:** Before the intervention, BsAb utilization among MM 5L+ patients in FL rose from 8.2% (Apr 2023) to 11.2% (Dec 2023) (0.3 pp/mo; p=0.23), compared with a rise from 6.7% to 16.3% (1.3 pp/mo; $p<0.0001$) across all other states over the same time period. Post-intervention, BsAb utilization in FL increased from 22.8% (May 2024) to 35.9% (Sep 2025), reflecting a 7.0% immediate increase and 0.8 pp/mo sustained growth, exceeding the post-intervention trend observed across all other states (23.5% to 30.3%; 0.5 pp/mo). Overall, although pre-intervention BsAb utilization in FL was lower than all other states, FL demonstrated a 1.2 pp/month higher post-intervention utilization trend ($p<0.001$; Table). Post-intervention, FL community sites showed a 0.13 pp/mo higher BsAb utilization trend than academic sites, and the number of community sites administrating BsAb increased from 5 to 9, with no change among academic sites. **Conclusions:** This study suggests that the FLASCO-led, collaborative model increased BsAb utilization in FL community oncology sites and offers a framework for broader community adoption across other states. Research Sponsor: Pfizer.

Parameter estimates from ITS model(s).

	FL (%)	p-value	Other US States (%)	p-value	Difference CITS: FL - Other US States (%)	p-value
Intercept (Apr 2023)	8.6	<.0001	7.7	<.0001	0.9	0.52
Monthly change pre-intervention (Apr - Dec 2023)	0.3	0.23	1.3	<.0001	-0.9	0.002
Immediate change post-intervention (May 2024)	7	0.01	0.2	0.87	6.8	0.01
Monthly change post-intervention (May 2024 – Sep 2025)	0.8	<.0001	0.5	<.0001	1.2	0.0003

7533 **Poster Session**

Immune effector cell–associated enterocolitis (IEC-EC) incidence and characterization in cilta-cel–treated patients with RRMM in CARTITUDE clinical studies. First Author: Yi Lin, Mayo Clinic Rochester, Rochester, MN

Background: Ciltacabtagene autoleucel (cilta-cel) shows benefit for patients (pts) with relapsed/refractory multiple myeloma (RRMM). A recently recognized uncommon adverse reaction, IEC-EC is characterized by severe/persistent diarrhea typically 1–3 months post CAR-T cell infusion. Here we summarize incidence and features of IEC-EC in clinical trials of cilta-cel for RRMM. **Methods:** 483 pts across RRMM studies (CARTITUDE-1, -2, -4, and CARTIFAN-1) were evaluated for evidence of IEC-EC. The clinical picture and nomenclature for IEC-EC were described in the real-world setting after infusion of most pts. As such, retrospective analysis was performed to identify cases consistent with IEC-EC, defined as prolonged (≥3 weeks) and severe (≥grade 3) diarrhea after cilta-cel infusion, without clear infectious etiology. Correlative biomarker analyses included peripheral CAR-T cell expansion/persistence, immune cell composition, and cytokines/inflammatory markers. Centralized pathomorphological review and immunohistochemical analysis of available biopsies was conducted. **Results:** Across RRMM studies, 6/483 (1.2%) pts demonstrated the clinical picture of IEC-EC, presenting 12–214 days after receiving cilta-cel (median onset 67 days post infusion). Best response was CR/sCR for all subjects. Pts received therapies including steroids (4/6). Four pts experienced symptom resolution within 123–227 days; 2 had persistent symptoms until death (causes: multiorgan failure and COVID19). Pts with IEC-EC had lower levels of B cells and higher levels of CAR+ T cells and inflammatory cytokines (eg, IL-6) at onset compared to a GI symptom-free control group at comparable time; while all cilta-cel–treated pts experienced B cell depletion, pts with IEC-EC had more prolonged deficiency. Histological analyses of GI biopsies from 5 pts with IEC-EC revealed plasma cells, normally present in the GI tract, were absent. CAR-T cells were detected and localized to the lamina propria and were not observed juxtaposed with epithelia, making it unlikely direct damage to epithelia was caused by CAR-T cells. Histologic damage was greater in the small intestine (predominantly duodenum) than the colon. **Conclusions:** Retrospective analysis of cilta-cel trials identified a low IEC-EC incidence (1.2%). Findings support a reactive mechanism involving plasma cell depletion and immune dysregulation rather than direct CAR-T cell cytotoxicity and highlight the importance of upper endoscopy to identify injury patterns in the small intestine that may be less pronounced in the colon. Although the pathophysiology is not fully defined, increased awareness and earlier diagnosis may improve understanding of management and enhance likelihood of IEC-EC reversibility. Research Sponsor: Johnson & Johnson; Legend Biotech USA Inc.

7534 **Poster Session**

Influence of genomic and clinical high-risk features on outcomes after BCMA-directed bispecific antibody therapy in relapsed/refractory multiple myeloma. First Author: Stefan Longobardi, University of Arkansas for Medical Sciences, Little Rock, AR

Background: The definition of high-risk (HR) multiple myeloma (MM) is broad and encompasses established molecular features such as gain(1q) and del(17p), and the presence of extramedullary disease (EMD), plasma cell leukemia (PCL), and focal lesions (FLs), particularly when located in the humeri and femora. While the prognostic relevance of these factors has been widely studied, most data were generated in the pre–T-cell–redirecting therapy era. Their role in patients treated with bispecific antibodies (bsAb) remains poorly defined. Here, we investigated the prognostic value of FL and other high-risk features in relapsed/refractory (RR) MM patients receiving BCMA-directed bsAB therapy. **Methods:** We included 152 RRMM patients (59% male) with a median age of 72 years at bsAb initiation, and a median of 5 (2-12) prior lines of therapy. All patients received at least one full cycle of BCMA targeting bsAb therapy. Functional imaging (PET and/or DWI) was performed within 3 months of bsAb initiation. HR status was defined according to the IMS/IMWG consensus. Progression free (PFS) and overall survival (OS) were estimated using Kaplan Meier analysis. To address the combined impact of prognostic factors, we calculated conditional inference trees. **Results:** Patients with FLs involving the appendicular skeleton (humeri/femora/ribs/shoulders, n=85) showed a trend toward shorter median PFS (20 months, p=0.061) and significantly shorter median OS (20 months, p=0.01), compared to patients without FLs (n=54) or with FLs confined to the spine and/or pelvis (n=13, median PFS and OS not reached [NR]). EMD and PCL were observed in 41 (27%) and 10 (7%) patients, respectively. Patients with PCL had the poorest outcomes, with both median PFS and OS <2 months. EMD was also strongly prognostic, with significantly shorter PFS (11 vs 28 months) and OS (17 months vs NR) compared to patients without EMD. Similarly, HR disease as defined by IMS/IMWG criteria was associated with worse outcomes (PFS 14 months, OS 19 months). Conditional inference tree analyses for PFS identified PCL, EMD and del(17p) as the most relevant prognostic variables. For OS, PCL again emerged as the strongest predictor, whereas EMD was only prognostic in the presence of gain(1q). Notably, gain(1q) also modified the impact of other clinical parameters: both a higher number of prior therapy lines (>5) and prior BCMA exposure were prognostic only in patients without gain(1q). **Conclusions:** Here, we show that EMD, PCL, and FLs of the appendicular skeleton are associated with inferior outcomes in RRMM patients treated with BCMA-directed bsAbs. Notably, the prognostic impact of these tumor growth patterns appears to be strongly influenced by the presence of genomic HR features, underscoring the central role of chromosomal aberrations as key modifiers of clinical risk even in the era of T-cell–redirecting immunotherapies. Research Sponsor: None.

7535 **Poster Session**

Age-stratified late outcomes following bispecific antibody therapy in multiple myeloma: A real-world 6-month landmark analysis. First Author: Madhu Bhargavi Chandra, Wellstar Spalding Regional Hospital, Griffin, GA

Background: Multiple myeloma (MM) predominantly affects older adults, with a median age at diagnosis of 69 years. Underrepresentation of older adults in clinical trials of Bispecific antibodies (BsAbs) and limited statistical power preclude definitive conclusions about treatment outcomes in this demographic. Some real-world studies report comparable outcomes for BsAbs in older and frail patients, but these are small and heterogeneous. Consequently, limited data exist on the safety and efficacy of BsAbs in older MM patients, especially late outcomes. To address this gap, we conducted a retrospective study comparing the post-6-month outcomes of BsAbs in older adults (≥65 years) with those in younger patients. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. We identified MM patients (ICD-10-CM: C90) aged ≥18 years who received any BsAbs (teclistamab, elranatamab, talquetamab, blinatumomab, epcoritamab, mosunetuzumab), stratified by age into two cohorts: (1) age ≥ 65 years (N =1913), and (2) age between 18 and 64 years (N =948). The index event was date of initial administration of BsAbs. Outcomes were analysed within a time window starting 180 days after index event, and patients with outcomes outside the window were excluded. Compared outcomes using Kaplan-Meier survival analysis. Calculated hazard ratios (HRs) and log-rank p-values. **Results:** After propensity score matching (1:1), each cohort had 736 patients. Median age was 75 years (maximum age 90 years) in cohort 1 vs 57 years in cohort 2. Female (41.7% vs 43.2%), White (60.6% vs 58.6%), African American (22.6% vs 23.4%). All comorbidities and prior therapies, including stem cell transplant (35.2% vs 35.1%), ide-cel CAR-T (6.3% vs 6.7%), and cilta-cel CAR-T (1.4% vs 1.4%), were balanced between groups. Median follow-up was 305.5 days in cohort 1 and 316 days in cohort 2. All-cause mortality did not differ significantly between groups (HR = 1.212, p = 0.229). ER visits (HR = 1.345), neutropenia (HR = 1.311), thrombocytopenia (HR = 1.559), sepsis (HR = 1.398), pneumonia (HR = 1.122), and opportunistic infections (HR = 1.119) were slightly higher, in contrast, anemia (HR = 0.841), blood transfusion (HR = 0.812), and hypogammaglobulinemia (HR = 0.927) were lower in the older cohort but none were statistically significant ($p > 0.05$). **Conclusions:** In this large, real-world study, outcomes of BsAbs among patients aged ≥ 65 years were comparable to those of younger patients, without a significant increase in mortality or toxicities. Our findings, although retrospective, suggest that BsAbs can be safely administered in select patients aged ≥65 years, and advanced age should not, in itself, preclude treatment. Careful assessment and optimization of comorbidities and performance status could ensure that these patients benefit from effective treatments with minimal toxicity. Research Sponsor: None.

7536 Poster Session

Ciltacabtagene autoleucel in lenalidomide-refractory multiple myeloma responding to bridging therapy: CARTITUDE-4 cytogenetic subgroup analysis. First Author: Roberto Mina, Winship Cancer Institute, Emory University, Atlanta, GA

Background: CARTITUDE-4 (NCT04181827) showed significant overall (OS) and progression-free survival (PFS) benefits of ciltacabtagene autoleucel (cilta-cel) in patients with lenalidomide-refractory multiple myeloma (MM) after 1–3 lines of therapy. Emerging data underscore the importance of successful bridging therapy (BT); deeper responses (partial response or better, ≥PR) during BT were associated with better survival and safety outcomes in patients treated with cilta-cel. Here, we present efficacy and safety in patients who received cilta-cel as study treatment with high- and standard-risk cytogenetics who responded to BT. **Methods:** CARTITUDE-4 as-treated set comprised patients who received a single cilta-cel infusion as study treatment after apheresis, ≥1 BT cycle, and lymphodepletion. High-risk cytogenetics were defined as positivity for del(17)p, t(14;16), t(4;14) or gain/amp(1q); standard-risk patients were negative for these mutations. Responses to BT were assessed based on International Myeloma Working Group criteria. Efficacy and safety from as-treated patients with ≥PR to BT were analyzed in high- and standard-risk cytogenetics subgroups. **Results:** Of 176 patients who received cilta-cel as study treatment (median follow-up, 33.6 months), 64 patients had high-risk cytogenetics and achieved ≥PR to BT. In these patients, median PFS and OS were not reached; 30-month PFS and OS rates were 65.1% (95% CI, 51.4–75.8) and 87.2% (95% CI, 76.1–93.4), respectively. In 40 patients with standard-risk cytogenetics and ≥PR to BT, median PFS and OS were not reached; 30-month PFS and OS rates were 85.0% (95% CI, 69.6–93.0) and 92.5% (95% CI, 78.5–97.5), respectively. Safety analysis included 64 patients with high-risk and 40 with standard-risk cytogenetics. In the high-risk subgroup, cytokine release syndrome was reported in 73.4% of patients, serious nonhematological adverse events in 64.1%, grade 3/4 infections in 43.8%, and immune effector cell-associated neurotoxicity syndrome in 7.8%. Corresponding rates in the standard-risk subgroup were 70.0%, 57.5%, 30.0%, and 0. Nonrelapse mortality (NRM) occurred in 9 patients (high-risk, 7; standard-risk, 2); there were 4 infection-related deaths in the high-risk population. No cases of immune effector cell (IEC)-parkinsonism were reported in high- and standard-risk subgroups. **Conclusions:** This analysis showed survival and response benefits of cilta-cel in patients with high- and standard-risk cytogenetics who had achieved ≥PR to BT, with >85% of patients alive at 30 months. No patients had IEC-parkinsonism, and infections were a key cause of NRM. These data highlight the profound benefit that cilta-cel can provide to patients with high- and standard-risk cytogenetics when MM is well controlled at time of infusion. Clinical trial information: NCT04181827. Research Sponsor: Johnson & Johnson; Legend Biotech USA Inc.

7537 Poster Session

CAR T-cell detection and clonality assessment in immune effector cell–associated enterocolitis following ciltacabtagene autoleucel. First Author: Eric Matthew Jurgens, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Ciltacabtagene autoleucel (cilta-cel) is an FDA approved chimeric antigen receptor (CAR) T cell therapy for relapsed/refractory multiple myeloma (RRMM). Cilta-cel is associated with gastrointestinal (GI) toxicities including immune effector cell (IEC)-associated enterocolitis. The pathophysiology of IEC-associated enterocolitis is poorly understood and may represent a clonal CAR T cell lymphoproliferative disorder. **Methods:** Retrospective review of patients with RRMM treated with standard of care (SOC) cilta-cel at a single center between 07/21/2022-10/31/2025. Baseline characteristics, outcomes, and GI toxicities were collected. CAR transgene was detected via digital droplet polymerase chain reaction (ddPCR) in GI tissue and peripheral blood samples. CAR T cell clonality was assessed via T cell receptor (TCR) fragment analysis and TCR Beta Constant Region 1 (TRBC1) assessment via IHC or flow cytometry. **Results:** In total 201 patients were included of whom 20 (10%) exhibited GI toxicity. Diarrhea accounted for most cases (15/20). CAR T cells were detected in 5/20 (25%) GI biopsies (Table 1). A clonal CAR T-cell lymphoproliferative disorder affected predominantly the duodenum, evidenced by TRBC1-restricted CD4- or CD8-positive T cells in lamina propria. The cells were positive for CD3 and TCRalpha while negative for CD103 and TCRdelta. MUM1, CD138 and BCMA demonstrated absence of plasma cells in all samples. TCR fragment analysis identified clonal TCR rearrangements in 3/5 evaluable cases. The remaining 2 cases showed equivocal fragment analysis with prominent but subthreshold peaks, likely reflecting low tumor burden. Symptoms resolved in 13/15 patients without detectable CAR T cells compared to 1/5 patients with detectable CAR T cells. Of the remaining 4/5 patients, 2 died and 2 had ongoing symptoms at time of last follow-up. **Conclusions:** GI toxicity was observed in 10% of patients treated with cilta-cel. CAR T-cell infiltration, predominantly duodenal, was detected in 25% of symptomatic patients consistent with IEC-associated enterocolitis. TRBC1-restricted CAR T cell populations were detected in all cases supporting the presence of a clonal CAR T cell lymphoproliferative disorder. At the meeting we will present additional translational studies from GI and peripheral blood CAR T cells including whole genome sequencing, spectral flow cytometry, and single cell RNA sequencing. Research Sponsor: None.

Clinical and pathologic features of IEC-associated enterocolitis.

ID	Onset	Outcome	Site	CAR	ddPCR	TRBC1/CD3 IHC	TCR Fragment Analysis
	(Day)			Tissue	Blood		
1	60	Death	Duodenum	25.12%	NA	7.30%	Clonal
2	42	Ongoing	Duodenum, Jejunum	6.60%	1.30%	84.70%	Borderline clonal
3	169	Death	Duodenum	14%	0.25%	31.60%	Clonal
4	111	Ongoing	Duodenum, Antrum, Ileum, Colon	22.40%	1.32%	88.40%	Clonal
5	39	Resolved	Duodenum	1.70%	0.03%	26.20%	Borderline clonal

7538 Poster Session

How long is long enough? Outcomes with finite-duration bispecific antibody therapy in multiple myeloma. First Author: Eva Duvalyan, Department of Medicine, University of California, San Francisco, San Francisco, CA

Background: Bispecific antibodies (BsAbs) have shown unprecedented efficacy in relapsed/refractory multiple myeloma (RRMM), and finite-duration therapy is an increasingly common yet poorly studied strategy. We aimed to analyze outcomes in MM patients (pts) treated with finite-duration teclistamab (tec) or talquetamab (tal). **Methods:** This single-institution retrospective cohort study included pts treated with tec or tal monotherapy at UCSF from 7/2021 to 1/2025 for RRMM, excluding pts with prior BsAb exposure and pts receiving BsAbs as a bridge to CAR-T. Patient-, disease-, and treatment-related characteristics were collected and summarized descriptively. To assess the impact of treatment duration while mitigating immortal time bias, we conducted 6- and 9-month landmark analyses of PFS, comparing pts who discontinued treatment before the landmark with pts still on treatment. Patients with PD or death before the landmark were excluded. Multivariate analyses (MVA) of survival outcomes used Cox regression with the following covariates: age, IMS-IMWG risk, ISS stage, extramedullary disease (EMD), ECOG score, and prior BCMA exposure. **Results:** In total, 120 consecutive pts were included with median follow-up 13.7 mos. Forty stopped therapy early for reasons other than PD (finite) and 80 did not (non-finite). Among finite pts, median treatment duration was 4.7 mos (range 0.2-32.4), 24 stopped due to toxicity, and 16 due to sustained remission. Clinical characteristics including age, ISS, IMS-IMWG risk, and ECOG were balanced between groups, but finite pts had less EMD (7.5% vs 25.0%, p=0.03) and triple-class refractory status (52.5% vs 73.8%, p=0.03) than non-finite pts. ORR was 97.5% (60% CR+) and 73.4% (29.1% CR+) in finite and non-finite pts, respectively. For finite, non-finite, and all pts, respectively, median PFS was not reached (NR) with 24-mo PFS 63%, 7.9 mos, and 16.53 mos, while median OS was NR, 24.8 mos, and NR. For landmark analysis of patients alive and progression-free at 6 mos, 22 were off therapy and 55 pts remained on therapy at 6 mos and median PFS was NR and 29.5 mos, respectively (univariate regression HR 0.71 [0.32-1.57], p=0.4). On MVA, the hazard ratio also favored the on-therapy group (HR 0.51 [0.21-1.22], p=0.13). At the 9-month landmark, 20 pts were off therapy and 42 pts were on, with univariate regression HR 1.71 (0.58-5.11, p=0.3) and MVA HR 1.1 (0.32-3.76, p=0.87). **Conclusions:** Finite-duration BsAb therapy was associated with durable responses in selected patients, although this group had more favorable baseline disease characteristics. In adjusted landmark analyses, early discontinuation before 6 months was associated with numerically shorter PFS without statistical significance, while PFS was comparable at the 9-month landmark. Randomized-controlled trials are required to define optimal treatment duration. Research Sponsor: None.

7539 Poster Session

Clinical outcomes following CAR T-cell therapy in relapsed or refractory multiple myeloma patients with baseline renal dysfunction: A TriNetX analysis. First Author: Preetinder Singh Manshahia, Rochester General Hospital, Rochester, NY

Background: Renal dysfunction is common in relapsed or refractory multiple myeloma (RRMM) and has historically limited eligibility for chimeric antigen receptor T-cell (CAR-T) therapy. However, real world data evaluating early complications and long-term outcomes in this population remains limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network, including adult RRMM patients treated with idecabtagene vicleucel or ciltacabtagene autoleucel. Patients with baseline renal dysfunction (creatinine ≥ 2.0 mg/dl, not on dialysis) were compared with those with preserved renal function (creatinine ≤ 1.0 mg/dl) after propensity matching. Early post-CAR-T complications: cytokine release syndrome (CRS) and disseminated intravascular coagulation (DIC) were assessed from day 0 to 15 post CAR-T therapy. Mortality was evaluated at 6 months, 1 year and 3 years. A secondary exploratory analysis assessed renal recovery at 90 days in patients with renal dysfunction following CART-cell infusion using creatinine based (≤ 1.9 mg/dl) and eGFR based (≥50 mL/min/1.73 m²) definitions. **Results:** 84/777 (10.8%) RRMM patients who received CAR T-cell therapy had baseline renal dysfunction. After propensity matching, 79 patients were included in each cohort, demographics in Table 1. 0-15 day CRS incidence was similar in patients with and without renal dysfunction (36.5% vs 33.3%), and no patients developed DIC or required dialysis at any point of time. Mortality was significantly higher in patients with renal dysfunction at 6 months (40% vs 13.2%), 1 year (45.3% vs 15.8%), and 3 years (52% vs 21.1%). Among patients with baseline renal dysfunction and available 90 day follow-up (61/79); renal recovery occurred in 48/61 (78.7%) by creatinine and in 38/61 (62.3%) by eGFR criteria. **Conclusions:** Baseline renal dysfunction was not associated with increased CRS incidence or progression of renal disease needing dialysis but was associated with higher long-term mortality, likely reflecting greater myeloma burden. Most patients with baseline renal dysfunction demonstrated renal recovery within 90 days, though they remain underrepresented among CAR-T recipients, highlighting a potential treatment gap. Research Sponsor: None.

Baseline characteristics of both cohorts.

Demographic parameter	Baseline renal dysfunction cohort, N=79(n, %)	Preserved renal dysfunction cohort, N=79, (n, %)
Race		
White	54 (68.4%)	58 (73.4%)
Black or African American	14 (17.7%)	15 (19%)
Sex		
Female	26 (32.9%)	26 (32.9%)
Male	53 (67.1%)	53 (67.1%)
Lab Parameters	**Baseline renal dysfunction cohort, Mean ± SD**	**Preserved renal dysfunction cohort, Mean ± SD**
Hemoglobin	9.5 ± 1.7	10.3 ± 2.2
Hematocrit	28.4 ± 5.0	31.0 ± 6.4
Urea Nitrogen	27.2 ± 13.1	14.6 ± 5.5
Bicarbonate	21.8 ± 3.7	24.6 ± 3.1
Ferritin	1587.7 ± 3073.6	628.8 ± 1099.9

7540 **Poster Session**

Expansion of a highly activated (HLA-DR+/CD38+) CAR T cell population after mezigdomide exposure post–idecabtagene vicleucel infusion in relapsed multiple myeloma. First Author: Lawrence W. Liu, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Herein, we report CAR T subsets from peripheral blood (PB) mononuclear cell (PBMC) samples from the NCT06048250 Phase 1 trial of mezigdomide (mezi) post ide-cabtagene vicleucel (ide-cel) in patients with RRMM. Prior studies used PCR for CAR T quantification but have not directly immunoprofiled CAR T. Additionally, we identified a highly activated CAR T cell subpopulation with HLA-DR and CD38 expression. These HLA-DR+/CD38+ T cells correlate with inflammation and disease activity in HLH and viral infections but have not been characterized in CAR T. **Methods:** Mezi was given orally on 21/28 day cycles after ide-cel infusion until disease progression, intolerance, or 12 cycles, whichever comes first. Immunoprofiling of PBMCs were performed at baseline (within two weeks prior to mezi start day of cycle 1 day 1 [C1D1]), C1D8 (early), and cycle 3 day 1 (C3D1; late) using Cytek Aurora spectral flow cytometry with 29-markers in 6 patients (3 in the DL-1 cohort receiving 0.3 mg and 3 in the DL-2 cohort receiving 0.6 mg). Changes in cell populations were measured as frequencies. The parent population was CD3+ BCMA CAR T+ cell for CAR T subsets, CD8+ T cells for CD8 subsets, CD3+ cells for the remainder of the T cell subsets, CD3- CD19+ cells for the B cell subsets, CD3-CD19-CD33+ for the monocyte subsets, and CD3- CD19-CD56+ for the NK cell subsets. Comparisons between groups were assessed using the Wilcoxon test. Mezi was started between D+60 to D+120 post ide-cel. Herein, we report the early translational data for this cohort. **Results:** As of 12/29/25, we enrolled 7 patients: 6 patients had evaluable PB immunoprofiling data. Median age was 81 years old (range: 38-85 years) and a median 5 prior lines of therapy (range 4-7). The median time from CAR T to mezi C1D1 was 108 days (range: 48-112). There was a trend towards increased BCMA CAR T cells at C1D8 (P=0.22) and increased BCMA CAR T % was associated with ³ CR (P=0.04). Early increases in HLA-DR+/CD38+ T cells (P=0.03) and HLA-DR+/CD38+ CAR T cells (P=0.02), CD8+ effector memory cells (P=0.03), BTLA+ T cells (P=0.03), CTLA-4+ T cells (P=0.02), monocytes (parent: PBMCs; P=0.04; higher in the DL-2 cohort, P=0.03), and activated B cells (P=0.04) compared to baseline were noted. Early decreases in CD8+ TEMRA (P=0.02), TIGIT+ T cells (P=0.04), monocyte-myeloid-derived suppressor cells (M-MDSCs; P=0.02), total B cells ($P<0.05$), memory B cells ($P<0.05$), and naïve B cells ($P<0.05$) were noted. The DL-2 cohort had higher increases in helper T cells (P=0.007) and CD4:CD8 ratio (P=0.03) at C1D8. **Conclusions:** Preliminary results show that mezi induced a decrease in suppressive cells, a shift in T- cells from exhausted to activated phenotype, and expansion of highly activated HLA-DR+/CD38+ CAR T cells. Future studies should investigate whether it is correlated with efficacy. FP and MJ contributed equally to this work. Clinical trial information: NCT06048250. Research Sponsor: Bristol-Myers Squibb; American Society of Clinical Oncology and Conquer Cancer; 2024YIA-1400257601.

7541 **Poster Session**

CAR-T in the older adults: Real-world survival and toxicity in patients ≥ 75 years with relapsed/refractory multiple myeloma. First Author: Jayasree Krishnan, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: CAR-T cell therapy targeting BCMA has transformed the treatment landscape for relapsed/refractory multiple myeloma (RRMM). However, pivotal clinical trials have limited representation of patients aged ≥75 years, leaving the safety and effectiveness of CAR-T therapy in this older population undercharacterized. In this study, we sought to evaluate the real-world outcomes of CAR-T therapy in patients aged ≥75 years with RRMM. **Methods:** A retrospective cohort study was conducted using the TriNetX database, which includes data from a large network of healthcare institutions in the US. Adult patients with RRMM who received CAR-T therapy were identified and stratified into two age based cohorts: ≥75 years and <75 years. Propensity score matching (1:1) was performed based on race, gender, comorbidities, and high risk cytogenetics if available. Outcomes included incidence of immune effector cell-associated neurotoxicity syndrome (ICANS), cytokine release syndrome (CRS), tocilizumab (Toci) use, sepsis, 30-day intensive care unit (ICU) admission rates, 90-day mortality rate, and 1 and 3-year overall survival (OS). Cox proportional hazards multivariate analysis was used to assess the impact of age on OS, controlling for confounders. **Results:** A total of 1,392 patients met study criteria, of which 198 patients were aged ≥75 yrs at the time of infusion. The mean age was 62.6 vs. 77.5 yrs in the younger and older cohort, respectively. Prior to propensity score matching (PSM), there were no significant differences in the rates of CRS, ICANS, Toci, sepsis, or 30-day ICU admissions rate post-infusion. Grade 3 or higher CRS/ICANS were infrequent in both cohorts. Additionally, the 90-day mortality rate did not differ significantly between the older and younger cohorts. Following PSM, these findings remained consistent (Table 1). While there was no significant difference in 1-year OS, the 3-year OS was lower in the ≥75 cohort (69% vs. 55.4%, log rank p=0.51), although the difference was not statistically significant. Cox proportional hazards multivariate analysis, controlling for race, gender, and comorbidities, revealed that age ≥75 was not independently associated with OS (hazard ratio [HR] = 1.04, 95%CI 0.65-1.65, p = 0.87). **Conclusions:** In this real-world cohort of RRMM patients receiving CAR-T therapy, age ≥75 years was not associated with differences in risks of CRS, ICANS, sepsis, 90-day mortality, or 1-year overall survival. While 3-year overall survival was lower in patients ≥75 years, possibly due to competing mortality risks, these findings overall suggest that age alone should not preclude BCMA-directed CAR T-cell therapy in select older patients. Research Sponsor: None.

Outcome	<75 years (n=197)	≥75 yrs (n=197)	p-value
CRS	53%	46%	0.27
ICANS	12%	8%	0.22
TOCI use	53%	51%	0.82
ICU admission	3.8%	5.1%	0.39
Sepsis	6%	7.9%	0.36
90 day mortality	3.9%	5%	0.28
1-yr OS	86.2%	86.6%	0.86
3-yr OS	69%	55.4%	0.51

7542 **Poster Session**

Dynamic changes in immune checkpoint and cell populations following lymphodepletion and CAR-T therapy in hematologic malignancies. First Author: Zarina Brune, Dartmouth Hitchcock Medical Center, Lebanon, NH

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has significantly improved outcomes in relapsed and refractory hematologic malignancies; however, durable remissions remain limited in patients with high-risk features, including early progression to ≥2 extranodal sites, high tumor burden, and elevated serum lactate dehydrogenase. Proposed mechanisms of resistance include CAR-T cell exhaustion, impaired expansion and cytotoxicity, antigen loss or downregulation, and inadequate tumor infiltration. In addition, immunosuppressive interactions among myeloid-derived suppressor cells (MDSCs), regulatory T cells, tumor-associated macrophages, and inhibitory immune checkpoints such as PD-1, PD-L1, LAG-3, TIM-3, and VISTA may further limit CAR-T efficacy. Lymphodepleting chemotherapy alters immune homeostasis by affecting T-, B-, and NK-cell populations, modulating co-stimulatory signaling, reducing regulatory populations, and reshaping cytokine networks, influencing both response and toxicity. **Methods:** We conducted a pilot study (n = 10) to characterize peripheral immune alterations in patients receiving lymphodepleting chemotherapy followed by CAR-T therapy. Serial peripheral blood samples were collected at predefined time points before and after lymphodepletion and CAR-T infusion (D -5, D0 and D28+/-2). Flow cytometry was used to quantify immune cell subsets and evaluate immune checkpoint expression, including PD-1, PD-L1, LAG-3, and VISTA. **Results:** Lymphodepleting chemotherapy resulted in a marked reduction in T cells, B cells, and MDSCs. By D28, most immune populations recovered to pre-lymphodepletion levels; however, granulocytic MDSCs remained relatively suppressed. Preliminary molecular analyses demonstrated trends in both VISTA and LAG-3 expressions on T cells in multiple myeloma patients following lymphodepletion, without significant changes in overall circulating immune cell frequencies. Among patients who experienced disease recurrence (n = 3), a trend toward decreased $CD45^+CD3^+$ and $CD45^+CD4^+$ T-cell frequencies on D28 compared with D0 was observed relative to patients achieving complete remission (n = 7). **Conclusions:** These preliminary data suggest that lymphodepleting chemotherapy and CAR-T therapy induce dynamic peripheral immune remodeling, including sustained suppression of select myeloid populations and differential immune checkpoint expression. Interpretation is limited by the small sample size and pilot nature of the study. Nonetheless, observed trends in post-infusion T-cell dynamics associated with disease recurrence support further investigation. Larger, longitudinal studies are needed to validate these findings, elucidate mechanisms of resistance, and identify immune biomarkers predictive of response, toxicity, and durable remission following CAR-T therapy. Research Sponsor: None.

7543 **Poster Session**

Impact of prophylactic cyclophosphamide on ALC and delayed neurotoxicity after cilta-cel. First Author: Melinda Tan, Mayo Clinic Rochester, Rochester, MN

Background: Delayed neurotoxicity (DNT) after ciltacabtagene autoleucel (cilta-cel) is associated with severe morbidity and mortality occurring in 10-15% of patients. A high post-infusion peak absolute lymphocyte count (ALCpeak ≥$3x10^9$/L; ALC^{hi}) is correlated with an increased risk of DNT (25-30%). We previously examined prophylactic dexamethasone (PPX DEX) administered for 3 days when ALC^{hi} was reached and found no reduction in ALC expansion, DNT incidence or severity. Here, we report the use of prophylactic cyclophosphamide (PPX CTX) on ALC kinetics and DNT. **Methods:** We conducted a retrospective analysis of patients (pts) treated with cilta-cel at Mayo Clinic (09-12/2025; n =60). Pts with ALC^{hi} received CTX 500 mg IV/PO once (n = 22). Outcomes and ALC kinetics including ALCpeak, ALC D28 (ALC_{D28}), and area under the curve D1-D28 (ALC_{AUC}) were compared with PPX DEX cohort (12/2024-08/2025; n =50) and a historical cohort without PPX (04/2022-11/2024; n =116). **Results:** Pre-lymphodepletion (LD) demographics were similar across historical ALC^{hi}, PPX DEX, and PPX CTX groups. Pre-LD CRP was higher in the historical ALC^{hi} cohort; however, baseline ferritin, CRS, and ICANS, and disease burden did not differ significantly between groups. There were no statistically significant differences in time to ALCpeak or ALC kinetics among the 3 cohorts. Among pts with ALC $< 3\times10^9$/L treated during the PPX CTX study period, 2 developed cranial nerve palsy (IEC-CNP; 2/38, 5%). Both presented with unilateral facial nerve palsy and were treated with corticosteroids. One pt resolved symptoms by one month, while the second had persistent symptoms at 2 weeks and remains on follow-up. Among ALC^{hi} patients in the PPX CTX cohort, DNT occurred in 4/22 pts (18%), including 1 case of IEC-CNP (5%) and 3 with parkinsonism (IEC-PKS, 14%). Within the PPX CTX cohort, baseline characteristics and post-infusion CRS or laboratory parameters did not differ between patients with and without DNT. Among patients who developed DNT, ALC kinetics were similar across PPX CTX, PPX DEX, and historical cohorts. PPX CTX was well tolerated, with 2 cases of grade 1 nausea reported. The incidence of DNT did not differ significantly between the PPX DEX (14/61, 23%) and PPX CTX (4/22, 18%) cohorts. However, DNT presentations in the PPX CTX cohort appeared milder and were responsive to treatment. Two of three patients (67%) presented with mild symptoms (one with dynamic dysphasia; second with flat affect) that responded to DEX. A third patient presented with typical parkinsonian features (hypomimia, bradykinesia, rigidity) and demonstrated clinical improvement following high-dose CTX. **Conclusions:** PPX CTX was well tolerated. While it did not significantly impact ALC expansion kinetics or DNT rates, first few cases of IEC-PKS suggest that the presentation may be milder and amenable to less toxic treatment. Larger cohorts are needed to refine optimal prophylactic strategies. Research Sponsor: None.

7544 **Poster Session**

Efficacy and hematopoietic recovery of high-dose melphalan with stem cell rescue as bridging to CAR-T compared with non-intensive bridging in relapsed/refractory multiple myeloma. First Author: Eli Zolotov, Hackensack University Medical Center, Hackensack, NJ

Background: Bridging therapy is required for disease control in relapsed/refractory multiple myeloma (RRMM) patients awaiting CAR-T. Recent data suggest intensive cytotoxic bridging impairs post-CAR-T hematopoietic recovery. We compared melphalan-based therapy with stem cell rescue (MBT) versus talquetamab (T), a GPRC5D-directed bispecific antibody. **Methods:** We performed a retrospective single-center study of RRMM patients bridged with MBT or T prior to CAR-T (June 2021–December 2024) post apheresis. Cytopenias were graded per CTCAE v5.0 during early (within 30 days of CAR-T) and late (beyond 30 days of CAR-T) periods. Kaplan Meier analysis was performed to evaluate survival outcomes. **Results:** Of 242 CAR-T recipients, 34 received bridging either with T (n = 21, 62%) or MBT (n = 13, 38%). MBT patients were younger (61.9 vs 67.2 years; P = 0.08); high-risk cytogenetics by FISH were similar (92% vs 85%; P = 0.58). Bridging response rates were comparable (92% vs 82%; P = 0.36).At 20 months, 64% MBT and 58.7% T patients remained progression-free. Early grade 3–4 neutropenia for MBT vs T: 92% vs 95% (P = 0.37); late: 46% vs 33% (P = 0.84). Early grade 3–4 thrombocytopenia MBT vs T: 31% vs 24% (P = 0.28); late: 15% vs 14% (P = 0.40). Early grade 3 anemia MBT vs T: 69% vs 38% (P = 0.18); late grade 3–4: 17% vs 10% (P = 0.35). Median recovery times (MBT vs T): ANC 10 vs 5 days early (P = 0.28), 19 vs 17 days late (P = 0.11); platelets 7 vs 7.5 days early (P = 0.30), 12 vs 49 days late (P = 0.20); hemoglobin 13.5 vs 9 days early (P = 0.49), 35 vs 93 days late (P = 0.65). CRS rates were comparable: 53.8% vs 63.6% (P = 0.57). ICANS occurred only in the T cohort (13.6%) (p = 0.08). **Conclusions:** MBT yielded hematopoietic recovery, toxicity, and outcomes comparable to bispecific antibody bridging. These findings contrast with prior studies showing impaired recovery after intensive cytotoxic bridging, likely because stem cell rescue improves hematopoietic reserve. Prospective studies are warranted. Research Sponsor: None.

7545 **Poster Session**

Racial disparities in utilization of bispecific T-cell engager therapy for relapsed/refractory multiple myeloma: A TriNetX study. First Author: Emmanuel Ekpenyong, Mobile Infirmary Medical Center, Mobile, AL

Background: There have been remarkable advancements in the treatment of multiple myeloma over the past few decades. With the advent of cell redirecting immunotherapies, such as bispecific T-cell engagers (BiTEs), we have significantly improved rates of progression-free survival. As a result, physicians now prefer early utilization of these therapies in Relapsed/Refractory Multiple Myeloma (RRMM) due to their efficacy. This study aims to investigate the utilization and clinical outcomes of bispecific therapy based on race using a real-world database. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, including adult patients (≥18 years) with RRMM treated with teclistamab, talquetamab, elranatamab, or linvoseltamab. Outcomes were assessed from 30 days to 5 years following the index diagnosis of RRMM. Propensity score matching (1:1) was performed to balance demographics, comorbidities, prior therapies, transplant status, medications, and laboratory parameters. Kaplan–Meier analyses were used to assess overall survival. Outcomes included hospitalization, overall survival, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) rates. **Results:** A total of 25,225 patients with RRMM were identified. 67.3% were White, 19.5% were Black, and the remainder were classified as other races, including Asian or unknown. Among 1,889 patients treated with bispecific antibodies, 1,256 (66.5%) were White and 403 (21.3%) were Black patients. The median follow-up was 854 days for White patients and 785 days for Black patients. In the unadjusted analysis, mortality was similar between Black and White patients (21.7% vs 23.7%, p = 0.43), with no difference in overall survival (HR 0.98; log-rank p = 0.88). Hospitalization rates (34.6% vs 39.0%), CRS and ICANS were comparable. After propensity score matching, outcomes remained consistent. Mortality was numerically lower among Black patients (20.3% vs 25.4%), though not statistically significant (p = 0.11). Hospitalization, CRS and ICANS did not differ significantly between cohorts. **Conclusions:** Our findings showed no significant difference in mortality or five-year survival probability between Black and White patients. The incidence of multiple myeloma is more than twice as high among Black vs. White people (14 vs. 6.1 per 100,000). Despite this, White patients are disproportionately more likely to receive BiTE therapy than Black patients. This highlights the impact that lack of access has on myeloma outcomes for Black patients, likely driven by systemic inequities such as socioeconomic status, geographic barriers to access therapy, the requirement of a full-time caregiver and lack of knowledge about newer therapies available. Future efforts should focus on expanding access to BiTE therapy to promote equitable care for Black patients. Research Sponsor: None.

7546 **Poster Session**

cfDNA WGS vs plasma proteomics for minimally invasive MRD assessment in multiple myeloma. First Author: Dor Abelman, University of Toronto, Department of Medical Biophysics, Toronto, ON, Canada

Background: MRD assessment informs relapse risk in MM but is typically bone marrow-based and invasive. We therefore compared two minimally invasive MRD assays: BM-informed cfDNA whole-genome sequencing (cfWGS) and plasma proteomic MRD (EasyM). **Methods:** 71 longitudinal plasma samples (22 diagnosis, 49 follow-up) from 22 newly diagnosed MM patients across 8 Canadian sites (TFRIM4) had paired cfWGS and EasyM (Rapid Novor Inc). cfWGS MRD used patient-specific mutation lists from diagnostic BM WGS (Abelman et al., medRxiv 2025). EasyM used mass spectrometry to quantify residual M-protein from baseline. The primary endpoint was progression-free survival (PFS). **Results:** Among 22 MM patients (8 male, 14 female; median age at diagnosis 62 years), 8 progressed at a median follow-up of 52.6 months (range: 10-79 months). At 1-year maintenance (n = 18 available), cfWGS MRD+ (6/18) predicted inferior PFS (HR 20.12, 95% CI 2.23-181.60, p = 0.007). EasyM any-detect positivity was frequent (16/18, reflecting delayed clearance) and not prognostic (p = 0.99), with poor agreement vs cfWGS (44.4%, κ = 0.118). An exploratory EasyM clearance threshold of 0.93% (hypothesis-generating) classified 5/18 patients as MRD+ and stratified PFS (HR 8.78, 95% CI 1.55-49.82, p = 0.004), improving agreement with cfWGS (17/18, 94.4%, κ = 0.870). Progression clustered in cfWGS+/EasyM-high patients (EasyM >0.93%; 4/5; median 11.9 months post-collection [1.9–22.8]) and occurred once in cfWGS−/EasyM-low patients (1/12, 27.6 months). The only discordant case (cfWGS+/EasyM−) progressed 8.7 months after collection. Higher quantitative MRD burden was associated with inferior PFS (cfWGS: HR 2.92 per 1 SD, 95% CI 1.29-6.59, p = 0.01; EasyM: HR 5.48 per 1 SD, 95% CI 0.79-37.90, p = 0.085). At ~100 days post-autologous stem cell transplantation (ASCT; n = 16 available), EasyM was uniformly MRD+ (16/16) while cfWGS was MRD+ in 7/16 patients. Applying an EasyM clearance threshold (2.13%; 9 cleared vs 7 residual) improved agreement with cfWGS (14/16; 87.5%; κ = 0.746). Of two discordant cases, one cfWGS+/EasyM-cleared patient relapsed 38.6 months post-collection and one cfWGS−/EasyM-residual patient remained progression-free at last follow-up. At post-ASCT, both assays showed consistent but underpowered associations with PFS (cfWGS HR 6.32, 95% CI 0.70–56.76, p = 0.100; EasyM-clearance HR 2.36, 95% CI 0.39–14.18, p = 0.335). Across all post-treatment samples (n = 49), continuous cfWGS burden correlated with EasyM residual M-protein (rho = 0.535, p < 0.001). **Conclusions:** BM-informed cfWGS MRD strongly stratified PFS, whereas EasyM required a clearance definition due to near-universal early positivity. Concordant plasma burdens support complementary MRD information. Future work will validate these findings in larger cohorts and quantify the incremental value of combined cfWGS and proteomic MRD for early relapse prediction. Research Sponsor: Terry Fox Research Institute; Paula and Rodger Riney Foundation.

7547 **Poster Session**

Current threshold of measurable disease in AL amyloidosis clinical trials. First Author: Eugene Brailovski, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Eligibility for clinical trials in AL amyloidosis requires measurable disease to ensure that the hematologic response can be adequately assessed, usually set at 5mg/dL. However, there are validated response criteria in low burden disease (dFLC 2-5mg/dL) that correlate with clinical outcomes in the upfront setting (Milani, 2017). Despite validated criteria in low burden disease, most trials maintain a dFLC of 5mg/dL as measurable disease. Shorter survival is seen in patients with high-risk dFLC progression, defined as dFLC >2mg/dL, >20% of baseline value and >50% increase from nadir (Palladini, 2018). Patients with organ progression also have poor outcomes. We examined patients who were excluded from clinical trials to determine if the current measurable disease criteria adequately capture patients who require salvage therapy. **Methods:** We reviewed patients screened for three clinical trials enrolling patients with relapsed/refractory AL amyloidosis: phase I/II trial of carfilzomib (NCT01789242), phase III trial of ixazomib/dexamethasone versus physician's choice (NCT01659658) and phase I trial of etentamig (NCT06158854) to identify patients who failed screening. All clinical trials required measurable disease, defined as dFLC at least 5mg/dL. High-risk dFLC progression (Palladini, 2018) and organ progression (Palladini, 2012/2014) were evaluated at the time of screen failure. **Results:** Among 47 patients screened, 14 (30%) were enrolled: 7 for carfilzomib, 6 on the ixazomib trial, 1 for etentamig (Figure 1). Of 33 excluded patients, 18 (54%) were due to dFLC < 5mg/dL. Among 18 patients excluded due to insufficient dFLC at the time of screening, 6 met criteria for organ progression (cardiac (n=4), renal (n=2)), 6 had high-risk dFLC progression (as defined in background) and 2 had both (Table 1), indicating 10 patients were at high risk of poor outcomes. Four patients were lost to follow-up within 6 months of screening. In the remaining 14 patients, 5 received alternative commercially available therapy within 6 months of screening, 5 enrolled in trials with lower dFLC eligibility, and 1 progressed to dFLC > 5, was rescreened and enrolled on the carfilzomib trial. Among the other 3 patients, none achieved a dFLC of 5mg/dL: 1 died within 12 months, 1 was treated after 12 months and one remains off treatment at 8 months. **Conclusions:** Two thirds of patients with AL amyloidosis failed screening with >50% due to dFLC<5mg/dL. Among those with dFLC<5mg/dL, the majority met criteria for high-risk dFLC progression or organ progression and were treated within 6 months. The current dFLC threshold for measurable disease excludes AL amyloidosis patients requiring therapy from clinical trials and results in trial patients not being representative of real-world practice. In the era of highly effective T cell redirecting therapies, we advocate a lower dFLC inclusion (>2mg/dL) to enable participation of patients with low-burden disease. Research Sponsor: Memorial Sloan Kettering P30 Grant.

7548 **Poster Session**

Real-world outcomes comparing the use of GLP-1 agonists in patients with multiple myeloma and comorbid obesity: A propensity score–matched analysis from a global federated health research network. First Author: Arshi Syal, Mayo Clinic Florida, Jacksonville, FL

Background: Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used for the treatment of type 2 diabetes and obesity, and emerging evidence suggests their benefits beyond glycemic control, including cardiovascular effects and potential anti-inflammatory and anti-proliferative properties. Therapeutic advances in multiple myeloma (MM) have improved the overall life-expectancy in our patients. However, metabolic comorbidities remain common, likely driven by disease burden, functional decline, ongoing inflammation, and treatment related effects. Our study evaluates the impact of GLP-1 receptor agonists on outcomes in patients with MM, exploring potential interactions between metabolic modulation and disease outcomes. **Methods:** We conducted a real-world retrospective cohort study using the TriNetX Global Collaborative Network, covering January 2000 to December 2025, encompassing data from 168 global healthcare organizations. Patients aged 18 and above with multiple myeloma were identified and then stratified into two groups based on treatment with GLP-1 agonists or not. The two groups were then propensity-matched based on age, sex, race, and various comorbidities. We assessed outcomes including overall mortality, myocardial infarction (MI), ischemic stroke, sepsis, anemia, pancreatitis, venous thromboembolism (VTE), and ED visits. Time-to-event analyses were performed using Kaplan-Meier methods and Cox proportional hazards models. **Results:** We identified 1716 patients with MM and obesity who received GLP-1 receptor agonists, and 13,491 patients with MM and obesity who did not receive GLP-1 therapy. After propensity matching, each cohort consisted of 1712 patients with well-balanced baseline characteristics. We followed these patients for 5 years from treatment initiation. Patients with MM who received GLP-1 had a significantly lower risk of overall mortality (Hazard Ratio [HR]: 0.423, 95% CI: 0.351-0.509, p-value $<$0.001), MI (Risk Difference [RD]: -3.6 %, 95% CI: -5.4 % to -1.7 %, p-value $<$0.001), ischemic stroke (RD: -1.7 %, 95% CI: -3.3 % to -0.1 %, p-value = 0.04), sepsis with and without shock (RD: -3.0 %, 95% CI: -4.9 % to -1.1 %, p-value = 0.002), and anemia (RD: -9.6 %, 95% CI: -12.9 % to -6.4 %, p-value $<$0.001). There was no statistically significant difference in the rates of VTE, ED visits, and pancreatitis between the two cohorts. **Conclusions:** Our study revealed that patients with MM with obesity who received GLP-1 therapy had significantly lower rates of overall mortality, MI, ischemic stroke, sepsis with and without shock, and anemia. Additional longitudinal cohort studies are required to explore the associations between these agents and inform clinical practice guidelines in these patients. Research Sponsor: None.

7549 **Poster Session**

Duffy-null status and cytopenias following BCMA-directed CAR T therapy in multiple myeloma. First Author: Christen Marie Dillard, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Anti-BCMA chimeric antigen receptor T-cell (CAR T) therapies are highly effective in relapsed or refractory multiple myeloma (RRMM). The Duffy null phenotype, common among individuals of African ancestry and associated with lower baseline neutrophil counts, may influence hematologic toxicity following CAR T therapy. We evaluated outcomes of anti-BCMA CAR T by Duffy antigen status. **Methods:** We performed a retrospective analysis of 173 RRMM patients receiving ciltacabtagene autoleucel (cilta-cel; n=83) or idecabtagene vicleucel (ide-cel; n=90) between July 2021 and May 2025. Primary endpoints were PFS, OS, and response rate. Secondary endpoints included cytopenias and infections. Analyses were stratified by Duffy status and race/ethnicity and adjusted for age, prior therapies, and baseline ANC. **Results:** Cilta-cel: Duffy null patients (n=11, 13.3%) had comparable baseline characteristics to Duffy positive patients, except lower ANC (1.71 vs 2.44, p=0.01). Duffy null status was associated with prolonged neutropenia, with lower median ANC at day 30 (0.56 vs 1.77, p=0.005) and day 90 (1.06 vs 2.45, p=0.0002), and persistent grade $\geq$3 neutropenia at day 90 in 44.4% vs 4.3% (p=0.002). Infection rates were similar between groups (36.4% vs 41.7%, p=1.0). Response rates were high in both groups (100% vs 92%) and PFS did not differ significantly (HR 0.54, 95% CI 0.12–2.43, p=0.42), with a nonsignificant trend toward improved PFS among Duffy null patients after adjustment (HR 0.38, p=0.24). There were no significant differences in OS. Ide-cel: Duffy null status (n=16, 17.8%) was not associated with delayed cytopenia recovery (day 90 grade $\geq$3 neutropenia 33.3% vs 16.4%, p=0.2). Duffy null patients had higher infection rates (68.8% vs 39.2%, p=0.03) and a trend toward inferior OS (median 19.1 vs 40.4 months, log-rank p=0.11). These patients were more heavily pretreated (median 7 vs 5 prior lines, p=0.04); in multivariable analysis, prior lines of therapy predicted OS (HR 1.13, p=0.046) while Duffy status did not (HR 1.63, p=0.30). Response rates and PFS were similar between groups. Race/ethnicity alone was not associated with cytopenia recovery, infection rates, or survival. **Conclusions:** Duffy null status predicts severe, prolonged cytopenias following cilta-cel, without compromising efficacy or survival. Despite profound neutropenia, similar infection rates suggest benign cytopenia rather than true immunosuppression. Pre–CAR T Duffy phenotyping may prevent unnecessary neutropenia-directed interventions such as growth factors or stem cell boost. In ide-cel recipients, higher infection rates and inferior survival trends likely reflect heavier pretreatment and diminished marrow reserve. Future studies should evaluate Duffy status in earlier treatment lines and assess post-CAR T supportive care utilization by phenotype. Christen Dillard and Erneisha Brown contributed equally to this work. Research Sponsor: None.

7550 **Poster Session**

The future mortality trends in multiple myeloma (SEER analysis 2000–2030). First Author: Muhammad Talha Shaukat, King Edward Medical University, Lahore, Pakistan

Background: Novel therapies have transformed Multiple Myeloma (MM) from a rapidly fatal diagnosis into a chronic condition. However, this extended survival exposes patients to a new set of competing risks. We utilized the SEER database to quantify the evolving burden of cause-specific mortality in the modern era and project future mortality trends. **Methods:** We identified 129,837 patients diagnosed with MM from 2000–2022 using SEER-17 registries. Patients were stratified by era: Pre-Novel (2000–06), Early-Novel (2007–14), and Modern (2015+). Median overall survival (mOS) and cumulative incidence function of death (CIF) were analyzed using Kaplan-Meier estimates and Gray's test, respectively. Fine-Gray competing risk regression was used to estimate sub-distribution hazard ratios (sHR) for non-cancer death. Non-cancer mortality burden was projected from 2021-2030 using linear regression models based on 2010–2021 trends. **Results:** Median Overall Survival (mOS) improved from 32 months (Pre-Novel era) to 49 months (Early-Novel era) and 63 months (Modern era) (p$<$0.001). Modern-era patients had lower odds of dying from MM compared to the Pre-Novel era (OR 0.68, 95% CI 0.66–0.71, p$<$0.001). The 5-year CIF of MM-specific death decreased from 46.5% (Pre-Novel) to 28.0% (Modern) while the non-cancer death remained stable (20.2% vs 20.7%). Among 82,585 total deaths recorded, Myeloma remained the primary cause (62.5%), while non-cancer causes accounted for 37.5%. Cardiovascular disease was the most common specific non-cancer cause, accounting for 11.4% (n=9,383) of all deaths. Early decedents ($<$3 years) had significantly higher odds of dying from Myeloma compared to late survivors (65.1% vs 58.5%; OR 1.32, p$<$0.001). In contrast, late survivors ($\geq$3 years) had significantly higher odds of death from cardiovascular disease (OR 1.16, 95% CI 1.11–1.21, p$<$0.001) and Infections (OR 1.16, 95% CI 1.05–1.28, p=0.003) as compared to early decedents. In Fine-Gray competing risk models, the modern era was associated with a reduced relative hazard of non-cancer death (sHR 0.80, p$<$0.001). The population of MM is projected to grow by 34.5% (from ~47,200 to ~63,500) between 2022 and 2030 and annual Myeloma-specific deaths are projected to increase by 6.1% (~2,980) by 2030, annual non-Cancer deaths are projected to rise by 38.8% (~3,600). **Conclusions:** Novel therapies have nearly doubled median survival in MM, narrowing the "mortality gap" as non-cancer causes as now approach half of annual deaths. Despite reduced relative hazards, the absolute non-cancer burden is projected to rise 49% by 2030. This necessitates the need for comprehensive survivorship care for the management of MM. Research Sponsor: None.

7551 **Poster Session**

Machine learning to identify racial and socioeconomic disparities in the onset and tumor distribution of second primary malignancies in multiple myeloma. First Author: Muhammad Talha Shaukat, King Edward Medical University, Lahore, Pakistan

Background: As survival in Multiple Myeloma (MM) improved with novel therapies, the burden of second primary malignancies (SPM) has emerged as a significant competing risk. While racial disparities in MM outcomes are established, it remains unclear whether the the timing and type of SPM differ by race or socioeconomic status. **Methods:** We analyzed 7,513 MM survivors from the SEER Research database (2000–2022) who developed a confirmed, invasive SPM (excluding non-melanoma skin cancers). To account for the shorter follow-up duration in the modern era, latency drivers were assessed using Fine-Gray competing risk models which adjust for censoring. Racial and socioeconomic differences were quantified using logistic regression adjusted for age, sex, and median household income. Random Survival Forests were used to identify predictors of SPM latency with variable importance (VIMP) indicating the contributor for each factor. **Results:** The mean time-to-SPM decreased from 5.18 years (2000–2010) to 2.61 years (2011–2022) ($p < 0.001$). Black patients developed SPMs earlier than White patients (Average Direct Effect: -0.33 years, $p < 0.001$) and at a younger mean age for secondary Prostate cancer (68.5 vs. 71.6 years, $p < 0.001$). In Random Survival Forest modeling, biological age (VIMP=0.15) was the primary predictor of latency, followed by Stem Cell Transplant and Radiation utilization (VIMP=0.03). Multivariable linear regression indicated that patients with low household income ($<$\$60k) developed SPMs 0.34 years faster than wealthier peers ($p = 0.009$). Black patients had significantly lower odds of therapy-related hematologic malignancies (OR 0.62, 95% CI 0.49–0.77; $p < 0.001$) but higher odds of solid tumors (OR 1.62, 95% CI 1.30–2.04; $p < 0.001$). This solid tumor disparity persisted after adjusting for age and income ($p=0.27$) and was driven by Prostate (OR 1.79, 95% CI 1.54–2.09) and Breast cancer (OR 1.31, 95% CI 1.06–1.62). Post-SPM mortality hazard was higher in Black patients compared to White patients (HR 1.15, $p < 0.001$). **Conclusions:** Our findings showed racial and socioeconomic factors impact both the timing and type of SPM in MM survivors. Black and low-income patients develop SPM earlier and are more likely to develop solid tumors, especially prostate and breast. These findings suggests need for surveillance strategies and earlier focused screening for high risk populations to address disparities in MM survivorship. Research Sponsor: None.

7552 **Poster Session**

Impact of human immunodeficiency virus on in-hospital outcomes among patients hospitalized with multiple myeloma: A National Inpatient Sample study, 2016–2022. First Author: Sophio Kakabadze, Ascension Saint Joseph Chicago, Chicago, IL

Background: Outcomes among hospitalized patients with multiple myeloma (MM) and concomitant human immunodeficiency virus (HIV) infection remain incompletely characterized at a national level. We evaluated the association of HIV infection with in-hospital outcomes among MM hospitalizations in the United States. **Methods:** We analyzed 161,303 MM hospitalizations and identified HIV infection using ICD-10 diagnosis codes (B20–B24, Z21). To improve comparability, we restricted analyses to hospitalizations with length of stay (LOS) $<$ 30 days and complete covariate data, then performed 1:1 propensity score matching using demographics, hospital characteristics, Charlson comorbidity category, and key comorbidities. Primary outcome was in-hospital mortality. Secondary outcomes included LOS, total hospital charges, and inpatient complications. **Results:** Of 161,303 MM hospitalizations, 0.4% (n = 681) had HIV infection. After applying analytic restrictions, 458 HIV-positive hospitalizations were matched to 458 HIV-negative hospitalizations with good covariate balance; mean age was 60.0 years. HIV infection was not associated with higher in-hospital mortality (OR 0.68, 95% CI 0.37–1.21; p = 0.191). Median LOS was similar between groups (5 days in both); however, on log-transformed analysis HIV infection was associated with shorter LOS (LOS ratio 0.90; p = 0.033). HIV infection was associated with a nonsignificant trend toward lower total hospital charges (cost ratio 0.88, 95% CI 0.77–1.01; p = 0.061). HIV infection showed nonsignificant trends toward increased venous thromboembolism, including pulmonary embolism (OR 4.05; p = 0.078) and deep vein thrombosis (OR 1.88; p = 0.085). No significant differences were observed for mechanical ventilation or cerebrovascular accident. **Conclusions:** In matched analyses of MM hospitalizations, HIV infection was not associated with increased in-hospital mortality and was associated with shorter LOS despite similar median LOS. Total charges were not significantly different, though a trend toward lower charges was observed. Signals for increased venous thromboembolism warrant further study in larger cohorts. Research Sponsor: None.

7553 **Poster Session**

Single-cell analysis of plasma cell–centered inflammatory–immunosuppressive niches and response to daratumumab in primary light-chain amyloidosis. First Author: Xuezhu Wang, Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Primary light-chain amyloidosis (pAL) is a plasma cell disease in which clonal plasma cells produce misfolded immunoglobulin light chains that lead to progressive organ dysfunction. Daratumumab (Dara), an anti-CD38 monoclonal antibody, is the backbone of first-line regimens for pAL; however, ~10–30% of treated patients fail to achieve ≥VGPR. Currently, there remains an unmet need to delineate the immune microenvironmental mechanisms underlying Dara resistance in pAL to enable the identification of predictive biomarkers and therapeutic targets, particularly for patients who lack prognostic cytogenetic markers such as 1q21 gain. **Methods:** We profiled 630,111 single cells obtained from a prospective observational cohort of 30 patients treated with a frontline Dara–bortezomib–dexamethasone regimen, including 11 paired samples collected pre-treatment and post-treatment. Overall, 37.0% of patients showed suboptimal responses (≤PR) before cycle 6 or initiation of next-line therapy. Plasma cells enriched with $CD138^+$ magnetic beads and whole bone marrow were profiled with single-cell RNA-seq. **Results:** At cohort baseline, 93.3% of the patients were Mayo 2004 stage I–IIIa, 46.7% harbored the t(11;14) translocation, and 20.0% had 1q21 gain. Suboptimal responders showed two plasma cell-centered immune processes already upregulated at baseline: (i) an inflammatory axis with elevated PTGES2/PTGES3 (PGE_2)–EP2/EP4 (BH-adjusted Wilcoxon $p < 0.05$) signaling between plasma cells and myeloid, NK, and T cells, possibly driven by upstream PTGS2-expressing myeloid-derived suppressor cell-like $CD38^-$ $CD14^+$ monocytes that expanded during treatment; and (ii) an immunosuppressive axis in which non-classical MHC class I on plasma cells increased inhibitory interactions mainly with NK and T cells (including HLA-E–KLRK1, HLA-G–LILRB1, and HLA-F–LILRB1) (BH-adjusted Wilcoxon $p < 0.05$). Compared with patients with 1q21 gain, patients with t(11;14) were associated with higher non-classical MHC class I and PTGES3-dependent prostaglandin signaling and lower PTGES2-dependent prostaglandin signaling. Possibly driven by this microenvironment, myeloid cells downregulated phagocytosis and endocytosis, NK cells showed impaired effector functions, and T cells upregulated exhaustion, accompanied by an enhanced interferon response in suboptimal versus good responders (BH-adjusted Wilcoxon $p < 0.05$). **Conclusions:** This single-cell cohort revealed a baseline inflammatory–immunosuppressive niche in pAL that underpins suboptimal hematologic responses to Dara, characterized by up-regulated non-classical MHC class I and prostaglandin signaling between plasma cells and immune cells and associated with impaired immune effector functions during Dara treatment. Research Sponsor: None.

7554 **Poster Session**

Copy number aberration profiling using shallow whole-genome sequencing-based LeukoPrint in multiple myeloma. First Author: Li Gao, Xinqiao Hospital of Army Medical University, Chongqing, China

Background: Multiple myeloma (MM) is a clonal plasma cell malignancy in which cytogenetic abnormalities are central to prognosis and therapy. Karyotyping is limited by low plasma cell proliferation, and FISH provides only targeted, costly detection. LeukoPrint, a shallow whole-genome sequencing–based assay, enables genome-wide CNA profiling. Supported by prior validation, we launched a prospective multicenter trial (ChiCTR2300077768) to assess the clinical relevance of LeukoPrint-detected CNAs in MM, and report interim results from the first 102 patients. **Methods:** This multicenter, prospective trial aims to enroll 396 newly diagnosed active multiple myeloma patients per IMWG 2014 criteria. As of June 12, 2025, 102 patients from seven hospitals in China were enrolled. LeukoPrint was used to profile CNAs ($>$1 Mb) from paired bone marrow $CD138^+$ plasma cell gDNA and peripheral blood cfDNA collected at diagnosis, post-induction, and relapse. Karyotyping and FISH were performed in parallel when available and compared with LeukoPrint. Risk stratification followed mSMART criteria. **Results:** LeukoPrint identified 863 CNAs (379 chromosomal and 484 sub-chromosomal) in 91 of 102 patients (89.2%). Hyperdiploidy was observed in 33 patients, non-hyperdiploidy in 58, and normal karyotype in 11. The most frequent alterations were 1q gain (53%) and chromosome 13 deletion (50%). Odd-numbered trisomies, often co-occurring, were detected in 51.0% of patients, predominantly in hyperdiploid cases, whereas del(13) was evenly distributed across ploidy groups. Subdiploidy was common (54%) and hyperdiploidy rare (13%) among IGH-translocated cases, suggesting mutual exclusivity of hyperdiploidy and IGH-translocation. LeukoPrint showed 88.4% concordance with FISH for four key prognostic CNAs (1p32-, 1q21+, 13q14-, 17p13-) but detected substantially more abnormalities, including in 80% of FISH-negative patients. It also markedly outperformed karyotyping (90.1% vs. 8.8%), consistent with the limited sensitivity of karyotyping due to the low proliferative activity of plasma cells in MM. Blood-based ctDNA analysis showed good concordance with bone marrow results (81.9%), and CNA dynamics tracked closely with clinical remission, supporting LeukoPrint as a robust tool for diagnosis and treatment monitoring in MM. **Conclusions:** LeukoPrint outperforms FISH and karyotyping, providing a cost-effective, genome-wide CNA platform in MM and demonstrating utility in ctDNA-based liquid biopsy. These results support LeukoPrint as a complementary, and potentially alternative approach to conventional cytogenetics. Clinical trial information: ChiCTR2300077768. Research Sponsor: None.

7555 **Poster Session**

Extrachromosomal DNA as a shaper of aggressive transcriptional states in multiple myeloma. First Author: Hyunsoo Cho, Seoul National University Hospital, Seoul, Seoul, South Korea

Background: Extrachromosomal DNA (ecDNA) is increasingly recognized as a key driver of oncogene amplification, intratumoral heterogeneity, and poor clinical outcomes across solid tumors. However, its significance in multiple myeloma remains largely unexplored. Multiple myeloma is characterized by marked genomic instability including hyperdiploidy or IgH translocations, and widespread structural rearrangements that underlie biological heterogeneity and therapy resistance. Defining whether ecDNA contributes an additional layer of genomic complexity in this disease therefore represents an important unmet need. **Methods:** Whole-genome sequencing (WGS) BAM files of primary myeloma cells from the Multiple Myeloma Research Foundation (MMRF) CoMMpass study were analyzed using the AmpliconSuite pipeline to identify circularized DNA amplicons indicative of ecDNA. Matched transcriptome (RNA-seq) data and clinical metadata from the same cohort were integrated to evaluate the prognostic impact of gene expression associated with ecDNA-harboring loci. Gene Set Enrichment Analysis (GSEA) was performed using the *clusterProfiler* R package to assess pathway-level biological signatures linked to ecDNA-positive tumors. **Results:** We identified ecDNA in 28 of 904 patients (3.1%) from the MMRF CoMMpass dataset. Despite the low prevalence, ecDNA-positive myeloma patients exhibited significantly inferior survival compared with patients without ecDNA. Frequently amplified ecDNA loci contained oncogenes such as *MYC, TNFRSF17 (BCMA),* and *SNX29,* as well as pro-tumoral lncRNAs including *CASC11* and *PVT1.* GSEA revealed strong enrichment of MYC and E2F targets, oxidative phosphorylation, and PI3K–AKT–mTOR and mTORC1 signaling in ecDNA-positive tumors, highlighting transcriptional addiction and metabolic activation. These pathways align with known mechanisms of proliferation, metabolic rewiring, and treatment resistance in multiple myeloma. **Conclusions:** ecDNA-positive myeloma represents a biologically aggressive subset characterized by oncogene-enriched circular amplicons and hyperactivated proliferative and metabolic programs. Myeloma patients with ecDNA showed significantly worse survival, supporting ecDNA as a previously underrecognized high-risk feature. These findings highlight ecDNA as potential therapeutic vulnerabilities in myeloma and warrants further investigation. Research Sponsor: Korea Health Industry Development Institute.

7556 Poster Session

Enabling blood-based mass spectrometry MRD detection in multiple myeloma without archived serum samples. First Author: Daniel Jesus Groso, Uni-University of Miami Miller School of Medicine, Miami, FL

Background: Minimal residual disease (MRD) assessment in multiple myeloma (MM) relies almost exclusively on bone marrow (BM) biopsy, an invasive, costly, and spatially limited procedure that is poorly suited for frequent longitudinal monitoring and may miss focal or extramedullary disease. Blood-based MRD strategies offer a less invasive, lower-cost alternative that could enable more frequent surveillance and earlier detection of disease progression. Mass spectrometry (MS)-based detection of monoclonal immunoglobulin peptides in peripheral blood is a promising MRD approach; however, current methods typically require prior identification of circulating M-protein amino acid sequences from archived serum, limiting applicability in patients without banked samples. We sought to determine whether patient-specific immunoglobulin V(D)J sequences could be reconstructed from BM-derived DNA or RNA, or from peripheral blood RNA, to enable blood-based MRD detection. **Methods:** We analyzed RNA-seq and whole exome sequencing (WES) from BM plasma cells and RNA-seq from peripheral blood mononuclear cells in 75 patients with MM, all of whom had abnormal plasma cells identified by flow cytometry. Immunoglobulin heavy chain (IGH) V(D)J sequences were reconstructed using MiXCR, and the dominant productive clonotype in the BM was selected per patient. Variable-region sequences containing complementarity-determining region 3 (CDR3) and adjacent framework regions were extracted when available. Peripheral blood RNA-seq was evaluated for clonotype recovery without BM sampling. In silico proteolytic digestion was performed to identify peptides compatible with standard MS detection. **Results:** Across 75 patients, dominant IGH clonotypes were reconstructed from 100% of BM sequencing data. From these clonotypes, a mean of 7 RNA-seq–derived peptides and 6 WES-derived peptides per patient were identified, with a mean of 2 peptides shared between platforms. Fifty patients (67%) generated ≥10 MS-compatible peptides, and 33 patients (44%) had at least one peptide shared between RNA-seq and WES. Among 51 patients with paired tumor and peripheral blood RNA-seq, dominant clonotypes were detectable in peripheral blood by CDR3 matching in 30 patients (58.8%). **Conclusions:** Patient-specific immunoglobulin clonotypes can be reliably reconstructed from prior BM sequencing data, yielding MS-compatible peptide targets for downstream analysis. In selected patients, clonotype discovery is feasible directly from peripheral blood, potentially reducing the need for invasive BM sampling. This approach overcomes a key limitation of existing MS-based MRD assays by enabling peptide target discovery in patients without archived serum but with available BM sequencing. Additional studies are required to validate MS detection of these peptides and establish a scalable, minimally invasive blood-based MRD platform. Research Sponsor: None.

7557 Poster Session

Circulating tumor DNA *NRAS* and *TP53* mutations to identify ultra-high-risk primary refractory myeloma patients. First Author: Sridurga Mithraprabhu, Alfred Hospital / Monash University, Melbourne, Australia

Background: Approximately 5% of newly diagnosed multiple myeloma (MM) patients progress on bortezomib-containing first-line (1L) therapies and develop primary refractory disease (1REF). These patients have unacceptably poor outcomes. Underlying drivers of 1REF remain unclear. We hypothesized that circulating tumour DNA (ctDNA) profiling would identify the genetic drivers of 1REF. **Methods:** We analyzed plasma ctDNA, bone marrow (BM) MM cells from 89 patients, comprising 33 1REF and 56 contemporaneous 1L-responsive (RES) patients. ctDNA was available for all patients; BM was available for 63% (18 1REF and 38 RES). Ultra-deep targeted sequencing used a 21-gene panel enriched for MM drivers. High-confidence pathogenic variants were defined as variant allele frequency ≥1% with ≥15 supporting reads. Genomic enrichment analyses used Fisher's exact test. Survival outcomes (progression-free survival, PFS and overall survival, OS) were available for 27 1REF patients and analyzed using Kaplan–Meier methods. **Results:** Interrogation of BM showed more mutations in 1REF versus RES (67% vs 34%; p=0.04) with *RAS/RAF* predominating (67% vs 26%; p=0.007). Mutation patterns in 1REF versus (vs) RES comprised predominantly *KRAS* (44% vs 21%), followed by *NRAS* (22% vs 8%). *BRAF* was detected exclusively in 1REF (17% vs 0%) and *TP53* showed no difference (6% vs 8%). ctDNA profiling revealed pathogenic variants in 18% of patients, enriched in 1REF vs RES (30% vs 11%; p=0.02), with *RAS/RAF* pathway mutations predominating (24% vs 2%; p=0.001), in line with BM observations. However, ctDNA *RAS/RAF* mutation patterns differed strikingly from BM. In 1REF vs RES, these comprised mainly *NRAS* (12% vs 0%; p=0.01) and *BRAF* (9% vs 0%; p=0.04), detected exclusively in 1REF, and *KRAS* (6% vs 2%). *TP53* did not co-occur with *RAS/RAF* and were comparable across both cohorts (6% vs 5%). Mutation-survival associations in 1REF patients also revealed differences between BM and ctDNA. BM mutations lacked prognostic value while ctDNA mutations predicted survival, suggesting ctDNA captures treatment-resistant systemic disease. Patients with any ctDNA mutations had significantly shorter PFS and OS compared to those without (PFS: 8.5 months vs not reached [NR], p=0.0005; OS: 12.0 months vs NR, p=0.004). Patients with *NRAS* mutations showed consistently poor outcomes, while the impact of *BRAF* varied. The worst outcome was seen in an ultra-high-risk subset (15%, 4/27) with *TP53* or *NRAS*, with all patients demonstrating an early fatal outcome (PFS 5.3 and OS 5.6 months; both p<0.0001). **Conclusions:** ctDNA *TP53* or *NRAS* identify a high-risk subset of 1REF patients with exceptionally poor outcomes, demonstrating that liquid biopsy, not BM evaluation, captures treatment-resistant systemic biology. These findings establish ctDNA as superior for risk stratification in 1REF MM and highlight an urgent need for alternative therapies in these patients. Research Sponsor: None.

7558 Poster Session

A machine learning (ML)—based six-gene signature for risk stratification and therapeutic target identification in multiple myeloma. First Author: Sriram Subramanian, Langley High School, Mclean, VA

Background: Multiple myeloma(MM) accounts for 10-15% of hematologic malignancies with significant heterogeneity. Current risk stratification relies on clinical variables (ISS, sex, race, age, cytogenetics) but has limited prognostic accuracy (C-index ~0.63).TP53mt MM has worse outcomes, present in only 5% of newly diagnosed patients and increase to 25% at progression. **Methods:** We performed differential gene expression (DGE) and gene set enrichment analysis (GSEA) between TP53mt (36) and TP53wt (717) MM from (MMRF CoMMpass). Intersection of DGE and GSEA identified 46 genes, which along with clinical variables were modeled using Cox regression and 4 ML algorithms: LASSO, CoxBoost, XGBoost and Random Forest. Models were trained on 70% and tested on 30% of data, with external validation on GSE24080 (n=559).The final 6-gene signature was functionally evaluated in drug sensitivity data from 16 MM cell lines (DepMap). Performance was assessed using concordance index (C-index) and hazard ratios (HR). **Results:** CoxBoost model 6-gene signature (UBE2C, STMN1, TK1, DSCC1, PTTG1, CENPF) outperformed all other models. Combined with clinical variables, it achieved C-index 0.742 in discovery (95% CI: 0.708-0.776) versus 0.629 for clinical variables alone (+18.0% improvement, p<0.001).Minimal overfitting was observed (training: 0.748, test: 0.742, gap: 0.006). In multivariable Cox analysis, the CoxBoost risk score remained highly significant (HR 1.95, 95%CI:1.51-2.52,p<0.001) independent of ISS stage (HR 2.89, p<0.001) and age (HR 1.39 per decade, p<0.001).External validation on GSE24080 showed improved performance (C-index 0.683,+6.8% over clinical variables).The signature showed 50% gene overlap with LASSO (3/6 genes) and outperformed UAMS-70 (C-index 0.742 vs 0.631).Drug sensitivity analysis identified three compounds (MACIMORELIN, MW-150, BROFAROMINE) with selective activity against high-risk MM cells (p<0.001),validated across 16 cell lines. **Conclusions:** TP53 and its downstream pathways are central to MM progression. CoxBoost modeling produced a 6-gene signature that improved MM risk stratification over clinical variables, identifies therapeutic vulnerabilities, and is computationally efficient model suitable for clinical deployment, warranting prospective validation in MM treatment stratification. Research Sponsor: None.

Performance of clinical-only and clinic-genomic machine learning models.

Model	Train C-Index	Test C-Index	Overfitting	Improvement vs Clinical	% Improvement
Clinical	0.69	0.72	-0.03	0	0
Random Forest	0.57	0.59	-0.02	-0.13	-18.56
LASSO	0.70	0.68	0.02	-0.04	-5.89
XGBoost	0.81	0.65	0.16	-0.06	-8.95
CoxBoost	0.75	0.74	0.01	0.02	3.31

7559 Poster Session

SATMM: A systems genetic network analysis—based risk stratification tool validated across the disease trajectory of relapsed/refractory multiple myeloma. First Author: Carl Murie, Institute of Systems Biology, Seattle, WA

Background: Precision medicine in multiple myeloma (MM) requires risk stratification tools that account for the patient-specific impact of cytogenetic abnormalities on disease progression. We developed SATMM (SYGNAL Analytics Tests for MM) based on each patient's chromosomal abnormality subtype using the previously developed mmSYGNAL network. While originally validated in newly diagnosed (ND) cohorts, this study provides updated validation of SATMM in the relapsed/refractory (RR) setting. **Methods:** SATMM performance was evaluated in a new RR cohort from the Moffitt Cancer Center, stratified into Early RR (ERR; 1–3 prior events, n=258) and Late RR (LRR; > 3 prior events, n=251). Predictive accuracy was assessed via ROC analysis (AUC) and Kaplan-Meier (KM) survival curves to determine Median Progression-Free Survival (mPFS) and Cox Hazard Ratios (HR). SATMM was benchmarked against the established GEP70 and SKY92 gene panels. **Results:** As detailed in the accompanying table, SATMM demonstrated robust and superior predictive performance compared to existing panels throughout the RR disease trajectory: Prognostic Accuracy: SATMM achieved superior overall accuracy in both ERR (0.61) and LRR (0.55) groups compared to GEP70 (0.52 and 0.37) and SKY92 (0.54 and 0.43). Early-Stage Performance: In the ERR group, SATMM provided the most significant clinical separation with a Δ mPFS of 10.7 months (KM *p*=1.60e-05), outperforming GEP70 (8.9 months, KM *p*=0.00053) and SKY92 (4.4 months, non-significant). Late-Stage Performance: In the heavily pre-treated LRR group, SATMM maintained significant stratification (KM *p*=0.0068, HR *p*=0.0078) with an AUC of 0.62, GEP70 showed lesser performance (KM *p*=0.021, HR *p*=0.021) while SKY92 failed to provide accurate risk prognosis (AUC=0.43). High-Risk Patient Detection: SATMM identified a larger proportion of high-risk patients (ERR n=93 sen = 0.47; LRR n=117, sen = 0.51) with higher sensitivity (sen) compared to GEP70 (ERR n=25, sen =0.13; LRR n=46, sen = 0.20) and SKY92 (ERR n=59, sen = 0.27; LRR n=111, sen = 0.41). **Conclusions:** SATMM is a patient-specific prognostic test that effectively stratifies risk based on the unique patient genomic profile compared to current gene panels. These data confirm that SATMM not only accurately predicts progression in ND patients but maintains its high performance across the entire disease trajectory, offering superior accuracy and sensitivity for high-risk detection for RR patients. Research Sponsor: Andy Hill Care Foundation.

Method	Disease status	AUC	Δ Median PFS	KM pvalue	High risk n	Cox HR	Cox HR pvalue	Accuracy	Sensitivity
SATMM	ERR	0.65	10.7	1.6E-05	93	0.512	1.3E-04	0.609	0.47
GEP70	ERR	0.64	8.9	0.00053	25	0.412	7.9E-04	0.523	0.129
SKY92	ERR	0.58	4.4	0.37	59	0.825	0.324	0.539	0.273
SATMM	LRR	0.62	3	0.0068	117	0.679	0.0078	0.546	0.508
GEP70	LRR	0.6	3.8	0.021	46	0.661	0.0212	0.367	0.204
SKY92	LRR	0.43	0.74	0.6	111	1.11	0.494	0.426	0.414

7560 **Poster Session**

A common gene expression signature across multiple myeloma disease stages to identify high-risk of disease progression. First Author: Claudio Cerchione, Hematology Unit, Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST IRCCS, Meldola, Italy

Background: An accurate and timely identification of high-risk (HR) disease is crucial to maximize therapeutic opportunities nowadays available for multiple myeloma patients. **Methods:** In this study, 105 consecutive patients with smoldering (SMM = 33), newly diagnosed (NDMM = 42) and relapse/refractory (RRMM = 30) myeloma were enrolled. Bone marrow samples were processed by SKY92 assay (Skyline Dx) to detect HR gene expression (GE) signature and cytogenetics according with manufacturer guidelines. Statistics were performed using GraphPad Prism 8 and R (v4.4.2). Two-sided statistical tests were used, with significance of $P < 0.05$ and Benjamini–Hochberg method for false discovery rate (FDR) correction. **Results:** Based on SKY92 quality requirements, this test was feasible in the 81.1% of SMM, 92.8% of NDMM and 80.0% of RRMM cases, showing an increased detection of HR SKY92 signature frequency from SMM (18%) toward NDMM (43.5%) and RRMM (67%, P= 0.0018). By comparing SKY92 virtual FISH with available standard FISH data we observed a high performance of t(4;14), t(14;16/20) and gain1q detection with an accuracy [95%(CI)] of 97.9 (93.9-100), 85.2 (71.8-98.6) and 87.2 (77.7-96.8) respectively, decreasing to 66.7 (49.8-83.5) for del17p suggesting that this chromosomal aberrancy can be less likely recapitulated by GE-based projections. NDMM HR SKY92 patients showed a worst overall survival compared to patients with SKY92 standard risk (SR, P= 0.0079), a trend maintained in RRMM with a nearly significant statistics due to the cohort sample size (P= 0.093). These results suggested that HR patients could share a transcriptional trademark across disease stages. This hypothesis was tested by comparing SKY92 HR NDMM and RRMM versus SR GE data with the following observations: *(i)* relative risk-related clusterization by a principal component analysis (PCA) and *(ii)* modulation of canonical pathways frequently altered in cancer by a gene set enrichment analysis (GSEA). To test the predictivity of GE-based approaches in the asymptomatic phase of myeloma we projected GE data of SMM on the PCA bi-dimensional space previously generated with NDMM and RRMM data and we observed a partial overlap of samples based on SKY92 risk profiles across MM stages. Interestingly, a GSEA comparing SKY92 HR vs SR SMM outlined deregulated gene pathways associated with inflammation and aggressive disease. Consistently, available follow up data show a progression rate of 60% for HR SKY92 SMM compared with 0% of the SR group (P = 0.173). **Conclusions:** Our findings support the use of GE-based tools for MM patient's risk profiling and HR-related cytogenetic detection if FISH is not available. Furthermore, it provides evidence that HR patients share transcriptional traits across asymptomatic and symptomatic phases consistent with recent findings underlying common genomic features shared by a portion of SMM with MM. Research Sponsor: None.

7561 **Poster Session**

Comparative analysis of subcutaneous Isa VRd (ISASOCUT) and intravenous Isa VRd (IMROZ) in transplant-ineligible newly diagnosed multiple myeloma across age groups. First Author: Arthur Bobin, Centre Hospitalier Universitaire de Poitiers, Poitiers, France

Background: Intravenous (IV) isatuximab (Isa) plus bortezomib, lenalidomide, and dexamethasone (VRd) significantly improved PFS in patients (pts) with transplant-ineligible newly diagnosed multiple myeloma (Ti NDMM) in the IMROZ randomized Phase (Ph) 3 study (NCT03319667). Efficacy and safety of subcutaneous (SC) Isa VRd, using an innovative on-body injector (OBI), has been demonstrated previously, including in Ti NDMM pts in the ISASOCUT Ph2 study (NCT05889221). Bortezomib was administered twice weekly (BIW) in IMROZ vs weekly in ISASOCUT. Here, safety and efficacy of Isa OBI VRd (ISASOCUT) and Isa IV VRd (IMROZ) are evaluated at 8 months (mos) follow-up. **Methods:** This analysis included 74 pts from ISASOCUT (Isa OBI VRd) and 265 from IMROZ (Isa IV VRd). Isa OBI VRd pts received Isa 1400 mg (weekly cycle [C]1, then every 2 weeks [Q2W] up to C12, and Q4W thereafter); each cycle lasted 28 days. SC bortezomib (1.3 mg/m^2) was given BIW in C1 and weekly thereafter. Isa IV VRd pts received Isa 10 mg/kg weekly in C1, then Q2W, followed by Q4W from C18 onwards. SC bortezomib (1.3 mg/m^2) was given BIW from C1-4. C1-4 lasted 42 days, with the remainder lasting 28 days each. This comparative analysis evaluated safety and efficacy at 8 mos follow-up by baseline age group ($<$75 yrs, $\geq$75 yrs). **Results:** Baseline demographic and disease characteristics were similar between Isa OBI VRd and Isa IV VRd pts. Incidence of serious TEAEs were similar between groups (35.1% and 42.2% for Isa OBI VRd and Isa IV VRd, respectively) and across age groups. The rate of systemic infusion reaction was lower with Isa OBI VRd vs Isa IV VRd (4 [5%] vs 60 [22.8%]). Grade (G) $\geq$3 neutropenic complications occurred in 2.7% Isa SC OBI pts and 3.8% Isa IV pts and were similar across age groups ($<$75 yrs, 2% vs 4.1%; $\geq$75 yrs, 4% vs 2.9%). Study discontinuation due to TEAEs occurred in 2.7% Isa SC OBI pts and 8.7% Isa IV pts, with lower rates in Isa SC OBI ($<$75 yrs, 0% vs 8.2%; $\geq$75 yrs, 8% vs 10.3%). Across both age groups, a lower incidence of G2 peripheral neuropathy (PN) was observed with Isa OBI VRd (weekly V) vs Isa IV VRd (BIW V) ($<$75 yrs, 20.4% vs 28.7%; $\geq$75 yrs, 20% vs 35.3%) as well as G$\geq$3 PN ($<$75 yrs, 2% vs 9.2%; $\geq$75 yrs, 0% vs 7.4%). Isa OBI VRd (weekly V) was associated with less bortezomib dose reduction due to nervous system disorders (Isa OBI VRd [weekly V] vs Isa IV VRd [BIW V]: $<$75 yrs, 14.3% vs 37.4%; $\geq$75 yrs, 28.0% vs 35.3%). $\geq$VGPR rates for Isa OBI VRd and Isa IV VRd were 87.8% and 83.2%, respectively (RR: 1.055; 95% CI: 0.934-1.192), in pts aged $<$75 yrs and 80.0% and 82.6%, respectively (RR: 0.968; 95% CI: 0.774-1.211), in pts aged $\geq$75 yrs. **Conclusions:** In this comparative analysis, Isa OBI VRd with weekly bortezomib (ISASOCUT) is more tolerable for pts regarding PN than the BIW schedule (IMROZ). Both groups maintained similar $\geq$VGPR rates across age groups. These findings support the efficacy and safety of the Isa SC OBI with weekly bortezomib. Clinical trial information: NCT05889221 and NCT03319667. Research Sponsor: Sanofi.

7562 **Poster Session**

ISABELA: A phase 2 study of isatuximab, belantamab mafodotin, pomalidomide, and dexamethasone in relapsed/refractory multiple myeloma. First Author: Andrew J. Yee, Mass General Brigham Cancer Institute, Boston, MA

Background: Combination therapies form the backbone of multiple myeloma (MM) care, and therapies targeting BCMA are now a cornerstone of treatment. We evaluated ISABELA, a phase 2 study that combines an established regimen of isatuximab (isa), pomalidomide (pom), and dexamethasone (dex) with the recently approved anti-BCMA antibody drug conjugate belantamab mafodotin (belamaf) in relapsed/refractory (RR) MM. **Methods:** ISABELA is an investigator-initiated study (NCT05922501) enrolling up to 50 patients (pts) with RRMM who have received at least 1 prior line of therapy including lenalidomide and a proteasome inhibitor. We gave belamaf 1.9 mg/kg iv q8 weeks; isa 10 mg/kg iv weekly for cycle 1 and then days 1 and 15 for cycle 2 onward; pom 4 mg on days 1-21, and dex 40 mg weekly divided over two days. Each cycle was 28 days. Treatment was until progression or unacceptable toxicity. **Results:** At data cutoff, the trial had enrolled 17 pts with a median follow-up of 9.6 months. Median age was 72 (range 55-91); 65% were male. ISS at study entry: I (59%), II (24%), III (18%). Median number of prior regimens was 2 (range 1-12). All pts were refractory to their last line of therapy and were previously treated with lenalidomide and a proteasome inhibitor. Prior therapies included pom (59%), bortezomib (82%), carfilzomib (41%), ixazomib (35%), CD38 antibody (59%) [daratumumab, 59%; isa 12%], and auto SCT (24%). Prior exposure to newer therapies included drugs that target BCMA (24%) [teclistamab 6%, elranatamab 18%, CAR T-cells 12%]; GPRC5D (12%) [talquetamab]; and cereblon (29%) [mezigdomide, 29%; cemsidomide, 12%]. Soft tissue plasmacytomas were present in 18%. The overall response rate (ORR) was 86% (12/14, not evaluable (NE) 3), $\geq$VGPR 43%, CR 7%, and 16-month PFS was 73% (95% CI 0.5-1). In CD38-antibody-naïve patients, ORR was 84% (5/6, NE 1) and 16-month PFS was 67% (95% CI 0.38-1). In triple-class exposed (BCMA naïve) pts, ORR was 75% (3/4, NE 2), and 12-month-PFS was 86% (95% CI 0.63-1). In quad-class exposed pts (including BCMA) (N=4), ORR was 100% and 12-month PFS was 75% (95% CI 0.43-1). Grade 3-4 hematologic adverse events (AEs) included neutropenia (53%), thrombocytopenia (29%), and anemia (12%). Common non-hematologic AEs (all; grade 3-4) included blurred vision (65%; 6%); fatigue (65%; 0%); hypertension (59%; 6%); diarrhea (53%; 0%); and AST/ALT increase (47%; 6%). Infections occurred in 35% with no grade $\geq$3 events. Ocular AEs by keratopathy visual acuity scale included grade 1 (14%), grade 2 (29%), grade 3 (36%). No patients discontinued treatment for AEs or ocular toxicity. **Conclusions:** This is the first report in RRMM for the combination of belamaf with a CD38 monoclonal antibody. The ISABELA regimen shows promising preliminary activity in RRMM with an ORR of 86% and 16-month PFS of 73%, including quad-class-exposed pts treated with anti-BCMA therapy, with manageable, reversible AEs. Clinical trial information: NCT05922501. Research Sponsor: GSK; Sanofi.

7563 **Poster Session**

Safety and reliability of isatuximab subcutaneous on-body injector: Results across the phase 3 IRAKLIA, phase 2 IZALCO and phase 1b TCD15484 trials. First Author: Xavier P. Leleu, University Hospital, Poitiers, France

Background: Subcutaneous (SC) drug delivery options have become more widely available in multiple myeloma (MM). SC delivery of isatuximab (Isa), an anti-CD38 monoclonal antibody, has been investigated across clinical trials via a novel hands-free on-body injector (OBI). Isa SC OBI features a small, retractable needle, establishing the first device-enabled delivery of an oncologic treatment. The Phase 3 IRAKLIA, Phase 2 IZALCO, and Phase 1b (TCD15484) trials consistently demonstrated similar efficacy and safety of Isa SC OBI vs Isa IV in relapsed/refractory MM (RRMM) patients (pts). Here, we present a cross-trial analysis exploring safety and reliability of Isa SC OBI in RRMM pts. **Methods:** Pts with RRMM in IRAKLIA (N=263) and the Phase 1b expansion cohort (N=22) received 1400 mg Isa SC OBI plus pomalidomide and dexamethasone (d). In IZALCO, RRMM pts (N=64) received 1400 mg Isa SC OBI + carfilzomib (K)-d. Pts were monitored for 4 hrs (IRAKLIA) or 1-2 hrs (IZALCO) following first administration and for 1 hr for the following cycle (C) 1 administrations to assess local tolerability. Pre-infusion medications included montelukast (C1), steroids, acetaminophen and H1 antihistamines. Pts without systemic infusion-related reactions (IRRs) after 4 consecutive administrations of Isa SC OBI had subsequent pre-medication reassessed at investigator's discretion. Safety and device performance explored in this cross-trial analysis of company sponsored studies were assessed in the Isa SC OBI cohorts by the duration of injection, IRRs, local injection-site reactions (ISRs), and injection/device success, which were defined similarly across all trials. **Results:** The median duration of Isa SC OBI injection was 13 mins in IRAKLIA, 12 mins in IZALCO, and 10 mins in the Phase 1b trial (6426 total injections, N=349 pts). IRRs across trials occurred in 6/6426 (0.09%) injections and 4/349 (1.15%) pts. IRRs were mostly grade 1 (G; 3/6426, 0.05%) with 1 G3 (0.02%); none leading to discontinuation. In IRAKLIA, 80/263 (30.4%) pts did not require premedication (931/5145 injections, 18.1%); no IRRs occurred in this group. Across trials, ISRs occurred in 21/349 (6.02%) pts resulting in 35 (0.54%) ISR events. Most ISRs were G1 (33, 0.51%), the remaining were G2 (2, 0.03%) and generally occurred on the day of injection. 99.9% (6421/6426) of injections in 98.6% (344/349) pts were successful (completed without interruption) across all trials. **Conclusions:** These findings support overall low, self-limiting rates of IRRs and ISRs across trials, with $>$6000 (99.9%) Isa SC OBI injections successfully delivered. Isa SC OBI shows reproducible safety and reliability in IRAKLIA, IZALCO and Phase 1b trials, supporting it as a novel administration option for MM pts and its potential for future exploration in at-home administration. Clinical trial information: NCT04045795, NCT05405166, and NCT05704049. Research Sponsor: Sanofi.

7564 **Poster Session**

Updated results from the phase 2 IZALCO study: Efficacy and safety of isatuximab subcutaneous plus carfilzomib and dexamethasone in relapsed/refractory multiple myeloma. First Author: Marcelo Capra, Centro Integrado de Hematologia e Oncologia, Hospital Mãe de Deus, Porto Alegre, Brazil

Background: In combination with conventional doublet and triplet therapy, isatuximab (Isa) provides significant benefit to patients (pts) across the multiple myeloma (MM) spectrum. Subcutaneous (SC) administration of Isa could be a more convenient option for pts and caregivers. The Phase (Ph)3 IRAKLIA trial in relapsed/refractory MM (RRMM) pts demonstrated non-inferiority in efficacy and pharmacokinetics of Isa SC delivered via a wearable on-body injector (OBI) in combination with pomalidomide and dexamethasone (Pd) vs Isa IV Pd. The Ph2 IZALCO study (NCT05704049) also showed efficacy and safety of Isa SC plus carfilzomib and dexamethasone (Kd), either by manual or OBI injections, in RRMM pts. Following exposure to both methods, pts showed higher preference for OBI vs manual SC injection. Here we present updated efficacy and safety results from IZALCO. **Methods:** Isa SC 1400 mg was given weekly in Cycle (C)1 then biweekly. In Part 1, pts received Isa injected SC manually. In Part 2, pts were randomized to Isa administered SC via OBI (Isa SC OBI; C1-C3) followed by manual SC injection (C4-C6), or to manual SC injection (C1-C3) followed by Isa SC OBI (C4-C6). Starting at C7, pts could choose either treatment method. All pts were treated with carfilzomib (20 mg/m^2 on Day [D]1-2 then 56 mg/m^2 on D8-9, 15-16 at C1, then D1-2, 8-9, and 15-16) and dexamethasone (20 mg on D1-2, 8-9, 15-16, and 22-23). **Results:** A total of 74 RRMM pts were enrolled (8 in Part 1; 66 in the randomized cohort, Part 2). At the data cut-off of November 10, 2025, 59 pts remained on study. At study entry, pts had median age of 65 (44-85) years, median weight of 75.9 (40.0-129.0) kg, and median of 1 prior line of therapy (1-5), and 56.8% had ISS stage I. The median duration of Isa SC OBI administration was 12 mins and manual SC injection was 6 mins. None of the Isa SC injections, manual or OBI, were interrupted. Median time to best response was 5.3 months (mos) (95% CI: 3.25-6.24). At median follow-up of 21.9 mos, median PFS was not reached (NR) (95% CI: 16.23-NR). PFS at 18 mos was 61.5% (95% CI: 48.7–72.0). OS at 18 mos was 80.8% (95% CI: 69.8-88.2); median OS was not reached (95% CI: NR-NR). Overall, grade (G) ≥3 TEAEs occurred in 66.2%, and serious TEAEs in 51.4% pts. Infusion reaction (IR) on C1D1 occurred in 2 pts (2.7%) with manual SC injections; no IRs occurred with OBI. Six (8.1%) pts had 13 injection-site reactions (ISR), all G1, in 2425 (0.54%) manual or OBI injections. Only 1 ISR was deemed related to OBI. Pt satisfaction with injection method remained consistently high with Isa SC OBI up to C25D15. **Conclusions:** Updated results of the IZALCO study continue to show the efficacy and safety of Isa SC plus Kd delivered either by manual injection or Isa SC OBI, while demonstrating high pt satisfaction and preference for Isa SC OBI. These findings are consistent with those reported in the Ph3 IKEMA study (Isa IV plus Kd). Clinical trial information: NCT05704049. Research Sponsor: Sanofi.

7565 **Poster Session**

Durable clinical benefit with B-cell maturation antigen (BCMA)–directed therapy, belantamab mafodotin plus pomalidomide and dexamethasone (BPd) in relapsed/refractory multiple myeloma (RRMM): DREAMM-8 long-term responder (LTR) analysis. First Author: Meletios A. Dimopoulos, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece; Department of Medicine, Korea University, Seoul, South Korea

Background: BCMA–directed therapies have changed the RRMM treatment landscape. In the phase 3, open-label, randomized DREAMM-8 trial (NCT04484623), BPd demonstrated significant progression-free survival (PFS) benefit compared with pomalidomide, bortezomib, and dexamethasone (PVd) in patients (pts) with RRMM who received ≥1 prior line of therapy (LOT). This post hoc analysis examined the characteristics of and outcomes in pts achieving sustained clinical benefit with BPd. **Methods:** DREAMM-8 is an ongoing, phase 3, open label study evaluating BPd and PVd in pts with RRMM with ≥1 prior LOT, including lenalidomide. Pts were randomized 1:1 and treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, or death, whichever occurred first. The primary endpoint was PFS; secondary endpoints included minimal residual disease (MRD) negativity (10^{-5}), PFS2, response rates, and safety. LTRs were pts with PFS ≥30 months (data cutoff: July 7, 2025; median follow up 36 months in both arms). **Results:** Of the 302 pts in DREAMM-8 (BPd, n=155; PVd, n=147), 81 were LTRs. The BPd arm had more than twice the proportion of LTRs (n=59 [38%]) as the PVd arm (n=22 [15%]). Baseline characteristics between treatment arms were generally well balanced. In LTRs, median PFS potentially favored BPd (not reached [NR]; 95% CI, NR-NR) vs PVd (NR; 95% CI, 42.7 months-NR), with a hazard ratio (HR) of 0.72 (95% CI, 0.20-2.53). BPd LTRs continued to demonstrate potential benefits after the first subsequent therapy, with median PFS2 (95% CI) of NR (NR-NR) in the BPd LTR arm and NR (44.2 months-NR) in the PVd LTR arm (HR, 0.33; 95% CI, 0.07-1.69). LTRs treated with BPd vs PVd had deeper responses: 76% vs 59% had complete response or better (≥ CR), 56% vs 32% had MRD negativity plus ≥ CR overall (73% vs 54% of pts with ≥ CR), and 39% vs 18% had sustained MRD negativity for ≥12 months, respectively. A higher proportion of pts with high-risk cytogenetics (ie, ≥1 of t[4;14], t[14;16], or del[17p13]) treated with BPd vs PVd achieved long-term response (27% vs 11%). The safety profile in LTRs was generally consistent with that previously reported. **Conclusions:** More than one-third of pts treated with BPd achieved LTR status, representing a 2.5-fold higher rate than with PVd, with similar rates in pts with high-risk cytogenetics; median PFS with BPd remains unreached. These findings suggest that this broadly accessible BCMA-targeted regimen delivers potential durable clinical benefit, characterized by deep and sustained disease-free survival. Clinical trial information: NCT04484623. Research Sponsor: Sponsored by GSK. Editorial support provided by Nucleus Global, an Inizio company and funded by GSK (study ID 207499). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from Biowa.

7566 **Poster Session**

PFS2 outcomes by prior therapy from DREAMM-8: A phase 3 study assessing belantamab mafodotin (belamaf), pomalidomide, and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd) in patients (pts) with relapsed/refractory multiple myeloma (RRMM). First Author: Güldane Cengiz Seval, Department of Hematology, Ankara University, Ankara, Turkey

Background: B-cell maturation antigen (BCMA)–directed therapies have transformed the treatment landscape in RRMM. Belamaf, a BCMA-targeting antibody-drug conjugate, in combination with Pd significantly improved progression-free survival (PFS) vs PVd (hazard ratio [HR], 0.52; 95% CI, 0.37-0.73; $P<0.001$) in pts with RRMM in DREAMM-8 (median follow-up, 22 mo). This PFS benefit was maintained with extended follow-up (HR, 0.49; 95% CI, 0.36-0.67; median follow-up 36 mo); median PFS2 also favored BPd vs PVd (47.1 vs 21.7 mo, respectively; HR, 0.52; 95% CI, 0.38-0.70), indicating sustained clinical benefit over time. We report PFS2 outcomes from DREAMM-8 in subgroups based on prior therapy to further understand the long-term impact of BPd and inform treatment sequencing. **Methods:** DREAMM-8 (NCT04484623) is a phase 3, randomized, open-label study evaluating BPd vs PVd in pts with RRMM with ≥1 prior line of therapy including lenalidomide (LEN). Pts could not have received prior BMCA-targeted therapy. PFS2 was defined as time from randomization to disease progression after initiation of subsequent antimyeloma therapy or death. PFS2 was assessed based on prior-treatment subgroups. **Results:** In the BPd arm (DCO: Jul 7, 2025; median follow-up, 36 mo), PFS2 benefit was maintained in all subgroups, including pts who were LEN refractory and anti-CD38 exposed/refractory. In LEN-refractory pts, BPd treatment led to almost a 3-fold median PFS2 improvement vs PVd (41.7 vs 15.0 mo). A total of 56/155 pts (36%) in the BPd arm and 93/147 (63%) in the PVd arm received any first subsequent therapy (FST) at data cutoff. Across both arms, 36% of pts received steroids, 28% received anti-CD38 therapies (>50% of pts with any subsequent therapy in each arm), and 23% received proteasome inhibitors as FST. A total of 21 pts (7%) received novel therapies (BPd, n=6 [4%]; PVd, n=15 [10%]) as FST, including BCMA-targeted bispecific antibodies (bsAbs), non-BCMA bsAbs, CELMoDs, venetoclax, and belamaf. Improved median PFS2 was observed in patients who had novel therapies as FST (n=21) vs non-novel agents (n=128) (26.0 vs 20.1 mo; HR, 0.61; 95% CI, 0.34-1.09). **Conclusions:** BCMA-directed therapy, BPd, resulted in improved PFS2 outcomes vs PVd, demonstrating sustained clinical benefit beyond initial belamaf therapy. This benefit was seen regardless of prior treatment, with LEN-refractory pts experiencing almost a 3-fold PFS2 benefit, and despite a higher proportion of pts receiving novel therapies as FST in the PVd arm. PFS2 benefit with high use of subsequent anti-CD38 agents supports sequencing of belamaf combinations early in the treatment paradigm prior to anti-CD38 agents. Research Sponsor: Sponsored by GSK. Editorial support provided by Nucleus Global, an Inizio company and funded by GSK (study ID 207499). Drug linker technology licensed from Seagen Inc.; monoclonal antibody produced using POTELLIGENT Technology licensed from Biowa.

7567 **Poster Session**

Real-world one-year comparative outcomes of quadruplet and triplet induction regimens in older, transplant-ineligible multiple myeloma patients. First Author: Okan Cetin, Boston Medical Center, Boston, MA

Background: Older patients with newly diagnosed multiple myeloma (MM) frequently experience early treatment discontinuation due to toxicity, comorbidities, and frailty. Although randomized trials support anti-CD38-based induction regimens, real-world comparative data evaluating early clinical outcomes in older, transplant-ineligible patients remain limited. **Methods:** We conducted a retrospective, multi-institutional cohort study using TriNetX, including adults aged ≥70 years with newly diagnosed MM after 2019 who initiated treatment within two months of diagnosis and did not undergo autologous stem cell transplantation. We performed two matched comparative analyses: Dara-RVd versus RVd and Dara-RVd versus Dara-Rd. We first assessed the proportion of patients initiating second-line therapy at 12 and 24 months. Analyses were then restricted to patients who remained on first-line therapy for at least one year to evaluate early clinical outcomes, including all-cause mortality and healthcare utilization (emergency department [ED] visits, ICU admissions, and bacterial infection or sepsis). Matching included demographics, comorbidities, presence of extramedullary plasmacytoma, and baseline laboratory values (LDH, albumin, β2 microglobulin, creatinine, and hemoglobin), BMI and recent hospitalization. Hazard ratio (HR) and risk ratio (RR) with 95% confidence intervals (CI) were reported. **Results:** Compared with RVd, Dara-RVd showed similar second-line initiation within 12 months (13% vs 14%; p=0.857) and 24 months (14% vs 19%; p=0.086). Among 768 matched patients per group who remained on first-line therapy at one year (mean age 75 years), Dara-RVd was associated with lower 1-year all-cause mortality (12% vs 17%; HR 0.70; 95% CI 0.55–0.90) and reduced healthcare utilization, including ≥1 ED visit (30% vs 36%; RR 0.85; 95% CI 0.73–0.98) and ICU admission (8% vs 12%; RR 0.70; 95% CI 0.52–0.95), while infection rates were similar. Compared with Dara-Rd, Dara-RVd showed comparable second-line initiation within 12 months (13% vs 10%; p=0.126) and 24 months (15% vs 11%; p=0.218). Among 511 matched patients per group who remained on first-line therapy at one year (mean age 76 years), no significant differences were observed in 1-year all-cause mortality or healthcare utilization outcomes. **Conclusions:** In older, transplant-ineligible patients with newly diagnosed MM who remained on therapy at one year, Dara-RVd was associated with improved early survival and lower healthcare utilization compared with RVd, while outcomes were comparable to Dara-Rd. Despite the retrospective design and potential unmeasured confounding, these findings support daratumumab-based regimens in older patients. Prospective studies incorporating frailty and early treatment discontinuation are needed to better define optimal induction strategies. Research Sponsor: None.

7568 Poster Session

Comparative efficacy of belantamab mafodotin plus bortezomib and dexamethasone (BVd) vs standard of care in patients with relapsed/refractory multiple myeloma (RRMM). First Author: Joshua Ryan Richter, Mount Sinai, New York, NY

Background: BVd is approved in the United States as a third-line or later (3L+) option for patients with RRMM based on the DREAMM-7 study of BVd vs daratumumab (D) plus bortezomib (V) and dexamethasone (d; DVd). This study aimed to compare the relative efficacy of BVd vs pomalidomide (P) plus Vd (PVd), elotuzumab plus Pd (EPd), isatuximab plus Pd (IsaPd), and idecabtagene vicleucel (ide-cel) in adults with 3L+ RRMM who received a proteasome inhibitor and an immunomodulatory drug. In the absence of head-to-head trials, indirect treatment comparisons (ITCs) can inform on the relative efficacy of regimens. **Methods:** ITCs of progression-free survival (PFS) and overall survival (OS) were conducted using the eligible study populations (only patients with ≥2 prior lines of therapy [LOT]) from the DREAMM-7 (BVd), DREAMM-8 (PVd), ELOQUENT-3 (EPd), ICARIA-MM (IsaPd), and KarMMA-3 (ide-cel) trials. Individual pt data (IPD) were available for patients treated with BVd and PVd, while only published summary data were available for patients treated with EPd, IsaPd, and ide-cel. In base-case analyses, study populations were weighted (using inverse probability of treatment weighting to compare to PVd and matching adjusted indirect comparison for the other treatments) to match in terms of age, prior exposure to bortezomib, prior exposure to lenalidomide, refractoriness to lenalidomide, number of prior LOT, and cytogenetic risk. Weighting was done separately for each comparator treatment. Weighted Cox regression was then performed to compare outcomes of patients treated with BVd to each respective comparator treatment. **Results:** In the base-case models, weighting yielded very good balance for all matched covariates (standardized mean difference <0.25 for each covariate across each comparison, and <0.10 in all cases except for age, prior bortezomib, and >4 prior LOT in the PVd comparison). Hazard ratios for BVd vs EPd, IsaPd, and ide-cel for PFS and OS significantly favored BVd (Table). For BVd vs PVd, PFS significantly favored BVd and OS numerically favored BVd. **Conclusions:** In DREAMM-7, direct comparison of BVd vs DVd showed PFS and OS improvements with BVd. This indirect comparison of patients in the 3L+ setting further showed that BVd improved PFS and OS vs PVd, EPd, IsaPd, and ide-cel. Research Sponsor: GSK.

Comparison (sample size/effective sample size value)	BVd vs PVd (86 and 68/35)		BVd vs EPd (103/42 and 60)		BVd vs IsaPd (85/52 and 154)		BVd vs Ide-cel(96/50 and 254)	
Outcome	**PFS**	**OS**	**PFS**	**OS**	**PFS**	**OS**	**PFS**	**OS**
Hazard ratio	0.517	0.604	0.337	0.405	0.538	0.348	0.468	0.509
95% confidence interval	0.275, 0.972	0.331, 1.103	0.173, 0.654	0.209, 0.787	0.346, 0.836	0.195, 0.623	0.287, 0.762	0.274, 0.945
p-value	0.041	0.101	0.001	0.008	0.006	<0.001	0.002	0.033

7569 Poster Session

Age and frailty analyses of transplant-ineligible (TIE) patients (pts) with newly diagnosed multiple myeloma (NDMM) in the phase 3 MAIA and CEPHEUS trials of daratumumab + lenalidomide-dexamethasone (Rd) and bortezomib-Rd (VRd). First Author: Christopher P. Venner, Cross Cancer Institute, University of Alberta, Edmonton, and BC Cancer – Vancouver Centre, University of British Columbia, Vancouver, BC, Canada

Background: MAIA and CEPHEUS trials demonstrated that daratumumab (Dara) with standard of care (SOC) VRd or Rd significantly improved clinical outcomes versus SOC in TIE NDMM. Here we describe efficacy and safety in TIE pts from both trials by age and baseline (BL) frailty using the latest data cuts. **Methods:** Pts were randomized 1:1 to DRd (n=368) or Rd (n=369) in MAIA and 1:1 to DVRd (n=144) or VRd (n=145) in CEPHEUS. Progression-free survival (PFS), complete response or better (≥CR), overall MRD negativity (neg) at 10^{-5} with ≥CR, sustained MRD neg with ≥CR (confirmed MRD neg ≥12 ± 1 months [mo] apart without MRD positivity in between), and safety were assessed by age (<70, 70–<75, or ≥75 years [y]) and BL frailty (assessed by IFM simplified frailty score: 0–1, non-frail; ≥2, frail). **Results:** Median follow-up was 64.5 mo in MAIA and 76.0 mo in CEPHEUS. In MAIA, 155 (21%) pts were <70 y, 261 (35%) 70–<75 y, and 321 (44%) ≥75 y; 341 (46%) pts were frail, 88.0 % of whom were ≥70 y. In CEPHEUS TIE pts, 70 (24%) pts were <70 y, 133 (46%) 70–<75 y, and 86 (30%) ≥75 y; 83 (29%) pts were frail, 86% of whom were ≥70 y. DRd or DVRd improved PFS, MRD neg rates, sustained MRD neg rates, and ≥CR rates vs Rd or VRd arms across age and frailty subgroups in both trials (Table). Safety was consistent with established individual drug profiles, and adverse event rates were generally comparable across treatment arms and subgroups within both trials. Additional data on patient-specific factors relevant to these subgroups will be presented. **Conclusions:** Dara-based regimens improved efficacy outcomes across subgroups in MAIA and CEPHEUS trials, reinforcing Dara-based regimens as SOC in TIE NDMM regardless of age or frailty. These data offer clinically relevant insights to help guide treatment selection for TIE pts. Clinical trial information: NCT03652064; NCT02252172. Research Sponsor: Johnson & Johnson.

	PFS, hazard ratio (95% CI)		≥CR rate, %		MRD neg with ≥CR (10^{-5}) rate, %		Sustained MRD neg with ≥CR (10^{-5}) rate, %	
Age/ Frailty status	**MAIA***	**CEPHEUS****	**MAIA***	**CEPHEUS****	**MAIA***	**CEPHEUS****	**MAIA***	**CEPHEUS****
<70 y	0.35 (0.21–0.56)	0.60 (0.31–1.18)	56.4 vs 31.2	85.7 vs 68.6	35.9 vs 11.7	74.3 vs 42.9	25.6 vs 3.9	62.9 vs 28.6
70–<75 y	0.64 (0.45–0.89)	0.60 (0.37–0.99)	56.2 vs 31.3	77.9 vs 69.2	36.2 vs 12.2	55.9 vs 47.7	20.8 vs 5.3	45.6 vs 38.5
≥75 y	0.59 (0.44–0.79)	0.46 (0.22–0.94)	44.4 vs 28.6	80.5 vs 44.4	26.9 vs 9.9	58.5 vs 26.7	13.8 vs 3.1	43.9 vs 15.6
Frail	0.64 (0.48–0.85)	0.62 (0.32–1.18)	44.8 vs 33.1	72.9 vs 54.3	25.6 vs 13.0	56.3 vs 34.3	15.7 vs 4.1	39.6 vs 17.1
Non-frail	0.48 (0.36–0.64)	0.51 (0.34–0.78)	56.6 vs 27.5	84.4 vs 63.6	37.8 vs 9.5	63.5 vs 41.8	21.4 vs 4.0	54.2 vs 32.7

*MAIA: DRd vs Rd; **CEPHEUS: DVRd vs VRd.

7570 Poster Session

Minimal residual disease dynamics in newly diagnosed multiple myeloma and impact on progression-free survival: A cohort study. First Author: Panagiotis Malandrakis, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

Background: Minimal residual disease (MRD) is a sensitive tool for evaluating treatment response in multiple myeloma (MM) and is a surrogate marker of progression-free survival (PFS) and overall survival (OS). Consecutive MRD evaluations offer important information regarding the depth and the duration of response to treatment and can be used to guide the patients' management. **Methods:** This single center, retrospective study included patients with newly diagnosed MM (NDMM), who were evaluated with at least 3 consecutive MRD tests. Four subgroups of patients were identified: sustained MRD positive (sMRDpos), sustained MRD negative (sMRDneg), converted to MRD negative (conMRDneg) and converted to MRD positive (conMRDpos). The aim of the study was to compare PFS between groups. **Results:** Overall, 335 NDMM patients were included in the analysis. The median age at diagnosis was 59 years (range 35-89), and the median number of assessments was 5 (range 3-14). Regarding risk stratification, 56 (16.7%) were ISS-3, and 52 (15.5%) were labeled as high-risk per the novel IMS/IMWG HRMM criteria. The median number of MRD evaluations in each patient was 5 (range 3-13). One third received quadruplet regimen. The median follow-up of the cohort was 6.1 years. Patient distribution according to MRD status was as follows: 191 (57%) sustained negativity, 40 (12%) sustained positivity, 53 (15.8%) converted to negative, whereas 51 (15.2%) converted to positive. Median PFS and OS were not achieved in any of the MRD subgroups. Sustained MRD negativity was associated with superior PFS compared to all the other subgroups (HR=0.21, 95% CI: 0.10 – 0.42, p<0.001). Sustained MRD positivity was associated with significantly inferior PFS compared to sMRDneg (HR=4.84; 95% CI: 1.91 – 12.30, p<0.001) and conMRDpos had also inferior PFS compared to the sMRDneg (HR= 6.04, 95% CI: 2.74 – 13.31, p<0.001). Furthermore, the presence of at least one MRD positive, at any time-point, was associated with inferior PFS compared to the sMRDneg (HR= 4.29, 95% CI: 2.05 – 8.99, p<0.001). Among the sustained MRD negative patients, high risk cytogenetics yielded a trend towards worse PFS (HR= 1.42. 95% CI: 0.30 - 6.69, p=0.659), possibly suggesting that sMRDneg overrides high risk cytogenetics. Finally, among the 165 patients who sustained MRD negativity, the median number of MRD tests were 5 (range 3-14). Among these patients with more than 5 tests had superior PFS, compared to less than 5, with a HR= 0.04, 95% CI: 0.01 – 0.33, p=0.003 signaling no further need of additional consecutive MRD testing in such patients. **Conclusions:** In patients with NDMM in the real-world setting, sustained MRD negativity is associated with prolonged PFS, even in HR patients, whereas the presence of even one MRD positive result impacted PFS. Research Sponsor: None.

7571 Poster Session

Exploratory associations between incretin-based therapies and plasma cell disorders in patients with type 2 diabetes: A real-world study. First Author: Yousef Ateiwi, University of Jordan, Amman, Jordan

Background: Incretin-based therapies, including dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), are widely used in the management of type 2 diabetes mellitus (T2DM). Experimental and clinical data suggest that metabolic and immune pathways may influence plasma cell dyscrasia development, yet the relationship between incretin-based therapies and monoclonal gammopathy of undetermined significance (MGUS) or multiple myeloma (MM) remains unclear. In this study, we aimed to evaluate the association between incretin-based therapy exposure and the risk of MGUS and MM. **Methods:** A multicenter, retrospective cohort study was conducted using the TriNetX Global Collaborative Network, a federated electronic health record database, between January 1, 2015, and December 31, 2025. Adult patients with T2DM were categorized into six exposure cohorts. Individuals treated with GLP-1RAs with a minimum of one year of therapy were compared with patients initiating sodium–glucose cotransporter-2 inhibitors (SGLT2i), sulfonylureas (SU), and thiazolidinediones (TZDs). The same cohort design was applied to DPP-4i users. A 1:1 propensity score matching (PSM) model was applied to minimize confounding by balancing baseline demographics, clinical comorbidities, laboratory parameters, and concurrent medication use. Individuals with a prior cancer diagnosis were excluded. The primary endpoint was progression to MM, and the secondary endpoint was the development of MGUS. Statistical analyses were performed within the TriNetX platform. **Results:** After 1:1 PSM, GLP-1RA therapy was associated with a significantly lower risk of both MGUS and MM compared with SU (n = 141,225 per group; MGUS RR 0.59, 95% CI 0.50–0.69; MM RR 0.84, 95% CI 0.77–0.92) and SGLT2i (n = 57,919 per group; MGUS RR 0.75, 95% CI 0.65–0.86; MM RR 0.62, 95% CI 0.49–0.79). No significant differences in MGUS or MM risk were observed when GLP-1RAs were compared with TZDs. In contrast, DPP-4i use was associated with aincreased risk of MM compared with TZDs (n = 29,462 per group; RR 1.93, 95% CI 1.40–2.66) and SGLT2i (n = 68,481 per group; RR 1.44, 95% CI 1.19–1.74).No significant associations were observed for MGUS across comparators, and no significant differences in MGUS or MM risk were seen between DPP-4i and SU (Table 1). **Conclusions:** In patients with T2DM, GLP-1RA exposure were associated with differential rates of MGUS and MM diagnosis across antihyperglycemic drug classes. GLP-1RA was associated with a lower rates of MGUS and MM compared with SU and SGLT2i, whereas DPP-4i use was associated with higher MM rates when compared with SGLT2i and TZDs. While these findings are clinically promising, prospective studies are needed to confirm causality and clarify underlying mechanisms. Research Sponsor: None.

7572 **Poster Session**

Incretin-based therapies and all-cause mortality and progression to multiple myeloma in patients with MGUS and type 2 diabetes: A real-world cohort study. First Author: Yousef Ateiwi, University of Jordan, Amman, Jordan

Background: Monoclonal gammopathy of undetermined significance (MGUS) progresses to multiple myeloma (MM) at an estimated rate of approximately 1–2% per year. Emerging evidence suggests metabolic dysfunction, including type 2 diabetes mellitus (T2DM) may influence the trajectory of progression to MM.Incretin based therapies have immunomodulatory and metabolic effects that could modify outcomes in patients with plasma cell dyscrasias. We conducted this study to evaluate the association between incretin-based therapies and the risk of progression to MM and all-cause mortality among patients with MGUS and T2DM. **Methods:** A multicenter, retrospective cohort study was conducted using the TriNetX Global Collaborative Network, a federated electronic health record database, from January 1, 2015, to December 31, 2025. Adult patients with T2DM and MGUS who had at least one year of treatment exposure to incretin-based therapies both before and after MGUS diagnosis were included. Patients were categorized into six exposure cohorts. Outcomes among glucagon-like peptide-1 receptor agonist (GLP-1RA) and dipeptidyl peptidase-4 inhibitor (DPP-4i) users were compared with matched cohorts receiving sulfonylureas (SU), sodium–glucose cotransporter-2 inhibitors (SGLT2i), and thiazolidinediones (TZDs). Individuals with a prior cancer diagnosis were excluded. A 1:1 propensity score matching (PSM) approach was applied to balance demographics, comorbidities, laboratory parameters, and concurrent medication use. The primary outcome was all-cause mortality, and the secondary outcome was progression to MM. All statistical analyses were performed within the TriNetX platform. **Results:** After 1:1 PSM, GLP-1RA use was associated with lower all-cause mortality compared with SU (n = 393 per group; RR 0.35, 95% CI 0.25–0.49). No significant differences were observed in all-cause mortality or progression to MM when GLP-1RAs were compared with SGLT2i or TZDs. In contrast, DPP-4i use was associated with significantly higher all-cause mortality compared with SGLT2i (n = 315 per group; RR 2.53, 95% CI 1.77–3.62) and TZDs (n = 120 per group; RR 2.37, 95% CI 1.27–4.44). DPP-4i exposure was not significantly associated with progression to MM across any comparator group. **Conclusions:** Among patients with T2DM and MGUS, GLP-1RA use was associated with significantly lower all-cause mortality compared with SU, whereas DPP-4i use was associated with increased mortality compared with SGLT2i and TZDs, with no significant effect on progression to MM. These findings suggest a clinically meaningful survival differences across antihyperglycemic therapies and should be validated in future prospective studies. Research Sponsor: None.

7573 **Poster Session**

Early intravenous immunoglobulin use in multiple myeloma patients treated with talquetamab: Effect on risk of infections and mortality. First Author: Joseph OBrien, Denver Health Medical Center, Denver, CO

Background: Bispecific T-cell–engaging (BiTE) antibodies have transformed the treatment of relapsed or refractory multiple myeloma (MM) but are associated with high rates of infectious complications. Talquetamab, a GPRC5D-directed BiTE, induces immune dysfunction but has been shown to be associated with less infection risk than anti-BCMA BiTEs. Although there is evidence supporting prophylactic intravenous immunoglobulin (IVIG) use for pts receiving anti-BCMA BiTEs, there is limited data assessing the benefit of early IVIG use in patients treated with talquetamab. **Methods:** A retrospective multicenter cohort study using the TriNetX Research Network to evaluate outcomes among adults with MM treated with talquetamab. Patients who received IVIG within 4 weeks of talquetamab initiation were compared to those who did not receive IVIG within 4 weeks. Propensity score matching was performed which included comorbidities, demographics, prior therapies (PIs, ImIDs, anti-CD38 abs, other BiTEs, belantamab, SCTx and CAR T), lab markers of disease severity, IgG levels, EM disease and plasma cell leukemia. Primary outcomes were 1-year all-cause mortality and infection incidence. Secondary outcomes included infection subtypes and ICU admission. Multivariable Cox proportional hazards models were used to identify independent associations. **Results:** Among 834 pts treated with talquetamab, 305 received IVIG within 4 wks of initiation. After propensity score matching, 271 patients remained in each cohort with balanced baseline characteristics. Early IVIG use was associated with lower 1-year mortality (14.8% vs. 26.7%; OR, 0.48; 95% CI, 0.31–0.74) and fewer infections of any type (41.7% vs. 55.0%; OR, 0.59; 95% CI, 0.42–0.82). Reductions were most pronounced for respiratory and bloodstream infections. In multivariable analysis, early IVIG remained independently associated with lower hazard of mortality (HR, 0.52; 95% CI, 0.37–0.73). In addition, a sub-analysis comparing early IVIG with no IVIG exposure within 1 year found similar findings. **Conclusions:** Early IVIG administration following talquetamab initiation was associated with reduced infection risk and improved survival in a large real-world cohort. These findings support consideration of early IVIG as part of routine supportive care for patients receiving talquetamab. Research Sponsor: None.

Outcome (after propensity matching)	IVIG within 4 weeks (n=271)	No IVIG within 4 weeks (n=271)	OR	95% CI	P-value
1-year mortality	40 (14.8)	72 (26.7)	0.48	0.31–0.74	0.0008
Any infection	113 (41.7)	149 (55.0)	0.59	0.42–0.82	0.002
Respiratory infections	37 (13.6)	55 (20.3)	0.62	0.39–0.98	0.04
Bloodstream infections	39 (14.4)	61 (22.5)	0.58	0.37–0.90	0.016
Opportunistic infections	13 (4.8)	10 (3.6)	1.31	0.57–3.05	>0.2
Skin & Soft Tissue infections	12 (4.4)	10 (3.6)	1.21	0.51–2.85	>0.2
Urinary tract infections	12 (4.4)	13 (4.8)	0.92	0.41–2.05	>0.2

7574 **Poster Session**

Comparative safety and efficacy of DKRd versus DVRd regimens in multiple myeloma: A systematic review and meta-analysis. First Author: M. Bakri Hammami, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: The addition of anti-CD38 monoclonal antibodies to proteasome inhibitor–based triplet regimens, such as bortezomib-lenalidomide-dexamethasone (VRd) and carfilzomib-lenalidomide-dexamethasone (KRd), has improved depth of response, minimal residual disease (MRD) negativity, and survival in newly diagnosed multiple myeloma (NDMM). Comparative data on the efficacy and safety of daratumumab-KRd (DKRd) versus daratumumab-VRd (DVRd) are limited. We performed a systematic review and meta-analysis to evaluate these regimens in patients with NDMM. **Methods:** Following PRISMA guidelines, we searched PubMed, Scopus, Web of Science, and Embase from inception to November 2025 for clinical trials and observational studies of patients with NDMM treated with DVRd or DKRd. Outcomes included progression-free survival (PFS), overall survival (OS), MRD negativity, tumor response, and safety. Two independent reviewers screened studies and extracted data from each included article. Meta-analyses were done using R version 4.3.0. Heterogeneity was assessed using Cochrane's Q-test and I2. **Results:** Sixteen studies involving 2114 patients were included. Two-year OS was comparable between regimens (DKRd: 94.12%; DVRd 94.17%; p=0.979) while two-year PFS favored DVRd (92.76% vs 85.04%; p<0.001). At 10-5 sensitivity, post-induction MRD negativity was higher with DKRd (57.10% vs 28.60%; p=0.004). DVRd achieved superior post-induction (98.94% vs 94.62%; p<0.001) and best overall responses (98.96% vs 95.10%; p=0.019). Safety outcomes generally favored DKRd, with fewer serious adverse events (32.79% vs 60.51%; p<0.001) and grade ≥3 adverse events (77.78% vs 90.34%; p<0.001). Grade ≥3 neutropenia (50.78% vs 30.90%; p<0.001) and thrombocytopenia (25.51% versus 9.62%; p=0.005) were more common with DVRd. Treatment discontinuation rates favored DKRd (1.94% versus 8.23%; p=0.015). Mortality remained low in both arms (1.41% versus 3.00%; p=0.403). **Conclusions:** In NDMM, DKRd achieved deeper early MRD responses and better tolerability, whereas DVRd provided superior two-year PFS and overall response rates. Treatment selection should balance efficacy against toxicity. Research Sponsor: None.

7575 **Poster Session**

Plasma exchange in myeloma-associated acute kidney injury: A multicenter propensity-matched cohort study. First Author: Jarred Madison Boone, Division of Hematology and Oncology, University Hospitals Seidman Cancer Center, Cleveland, OH

Background: Acute kidney injury (AKI) in newly diagnosed multiple myeloma (MM) is frequently driven by light chain cast nephropathy and associated with dialysis dependence and early mortality. Plasmapheresis or plasma exchange (either one referred to here as PLEX) have been used to accelerate free light chain (FLC) removal, despite inconsistent evidence of clinical benefit. Whether PLEX improves renal or survival outcomes in the modern treatment era remains uncertain. **Methods:** A retrospective multicenter cohort study using the TriNetX Research Network identified newly diagnosed MM pts from 2014-2024 presenting with AKI (an ICD-10 code for acute renal failure or Cr > / = 3.0 mg/dL and a 6 mo prior Cr < 1.5) and laboratory evidence of light chain cast nephropathy (defined as a free light chain concentration > 1,500 mg/L). Pts were included if they received PLEX within 7d of diagnosis, and were compared to those who did not receive PLEX. Pts were excluded if they had pre-existing end stage renal disease. Propensity score matching included demographics, comorbidities, myeloma therapies and laboratory values (Cr, calcium, albumin, hgb). **Results:** Among 5,454 eligible pts, 251 (4.6%) received PLEX (81% were plasma exchange and 19% were plasmapheresis). After propensity score matching, 248 pts were included in each group with well-balanced baseline characteristics (ex: ave Cr 4.1 and 4.2 in the PLEX vs no PLEX groups, respectively; 38% received PIs in each group). PLEX was not associated with reduced dialysis dependence at 90 days (16.1% vs 18.1%; odds ratio [OR] 0.87, 95% confidence interval [CI] 0.54–1.39) or 180 days (18.5% vs 20.2%; OR 0.90, 95% CI 0.58–1.41). Mortality at 90 (17.7% vs 15%) and 180 days (23.4% vs 23.9%) and ICU admission rates (20% vs 21%) were similar between groups. Dialysis-free survival over 180 days did not differ. Findings were consistent across all prespecified sensitivity analyses, including pts receiving early PI-based therapy and those with extreme free light chain burden (FLC > 5000mg/L, 28% of total cases), with no differences in dialysis dependence or survival. Patients treated with PLEX were numerically more likely to achieve creatinine < 2.0 mg/dL at both 90 days (83.9% vs 77.4%; OR 1.81, 95% CI 0.97–2.38; p = 0.07) and 180 days (86.3% vs 79.8%; OR 1.59, 95% CI 0.98–2.56; p = 0.06), but these differences did not reach statistical significance, except for those with FLC > 5000 (at 90d: 77% vs 63%, p = 0.02; and at 180d: 83% vs 66%, p = 0.006). **Conclusions:** In this large, contemporary, real-world retrospective cohort, PLEX was not associated with significantly improved renal recovery, dialysis-free survival, or mortality among patients with newly diagnosed myeloma-associated AKI due to light chain nephropathy. These results support current guidelines emphasizing rapid initiation of effective anti-myeloma therapy rather than routine extracorporeal light chain removal. Research Sponsor: None.

7576 **Poster Session**

Trends in frontline treatment patterns for multiple myeloma among US veterans, 1999–2025. First Author: Byron Seiya Sigel, Washington University School of Medicine, St. Louis, MO

Background: Frontline treatment for multiple myeloma (MM) has evolved substantially, transitioning from alkylating therapy to newer therapeutic classes, including immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies. Despite these advances, real-world treatment patterns remain heterogeneous, and MM therapies carry substantial toxicity and costs. Using nationwide Veterans Health Administration (VHA) data, an integrated health system with longitudinal follow-up, we characterized frontline treatment patterns for MM among US Veterans from 1999 to 2025. **Methods:** We identified Veterans diagnosed with MM in the VHA from 1999 to 2025. Diagnoses were confirmed using a published and validated natural language processing (NLP) algorithm, with the index date defined as the first MM-specific treatment, excluding dexamethasone alone. Patients receiving no MM-specific therapy or dexamethasone alone were excluded. Frontline treatments were defined as treatments initiated within 30 days of the index date. Treatments were captured using VA inpatient and outpatient pharmacy files, inpatient and outpatient procedure records for injectable agents, Fee Basis and Community Care data, and CMS Medicare Part D claims. Because the VHA does not require insurance approval, a 30-day window was used to define frontline treatment. Hematopoietic stem cell transplant was excluded to focus on trends in frontline treatments. MM-specific treatments were defined using a clinician-reviewed list of medications and relevant Current Procedural Terminology (CPT) codes. **Results:** We identified 4,738 Veterans with MM from 1999 to 2025. Median age was 72.1 years (IQR 65.1-78.1), and 96.7% were men. Non-Hispanic Black accounted for 20.1%, non-Hispanic White 55.6%, Hispanic 3.0%, and other races 1.5%. Median BMI was 27.6 (IQR 24.3-31.8), and 63.3% lived in urban areas. Melphalan predominated in 1999 (85.3%) but steadily declined. Cyclophosphamide use increased from 10.5% in 1999 to a peak of 29.2% in 2015, followed by a decline to 10.4% in 2024. Thalidomide use peaked in 2005 (61.8%) and declined to near zero by 2017. Lenalidomide use increased after 2006, reaching 78.1% in 2024. Bortezomib increased from 1.2% in 2004, peaking at 49.4% in 2015 and remaining common, whereas carfilzomib and ixazomib were infrequently used ($<$ 6%). Monoclonal antibody use expanded after 2019 with daratumumab, reaching 45.5% in 2024. **Conclusions:** Using national VHA data from 1999 to 2025, we describe real-world frontline MM treatment patterns among US Veterans, illustrating temporal shifts in therapeutic class use, including increasing adoption of monoclonal antibodies within an integrated, longitudinal health system. Research Sponsor: None.

TPS7577 **Poster Session**

QUINTESSENTIAL-2: A phase 3 study of arlocabtagene autoleucel versus standard of care in adult patients with relapsed and refractory multiple myeloma (RRMM) exposed to lenalidomide. First Author: Eyal Lebel, Hadassah Medical Center, Jerusalem, Israel

Background: Despite advances in multiple myeloma (MM) treatment, most patients (pts) will relapse, highlighting the need for new drug classes in RRMM. Further, with the extensive use of lenalidomide (LEN), an immunomodulatory drug (IMiD), in frontline and maintenance therapies, LEN-refractoriness has become increasingly common and poses an additional challenge as the disease is less likely to respond to subsequent treatment. G protein-coupled receptor class C group 5 member D (GPRC5D) is a promising therapeutic target for MM as the receptor is highly expressed on malignant plasma cells; it has little to no expression on non-plasma cell immune populations and limited expression on other tissues. Arlocabtagene autoleucel (arlo-cel) is a GPRC5D-directed autologous CAR T cell therapy that has demonstrated safety and efficacy in pts with RRMM in a first-in-human phase 1 study. ORR was 94% and 91% in pts with 1-3 and $\geq$3 prior LOT (pLOT), respectively, after a single arlo-cel infusion (150×10^6 CAR T-cells); ORR was 92% in pts with $\geq$3 pLOT following a 75×10^6 CAR T cell infusion. These phase 1 study outcomes support further clinical development of arlo-cel. **Methods:** QUINTESSENTIAL-2 (NCT06615479) is a randomized, open-label, multicenter, phase 3 confirmatory study comparing the efficacy and safety of arlo-cel vs SOC in adults with RRMM and prior LEN. Key inclusion criteria were age $\geq$18 years, confirmed diagnosis of MM per IMWG criteria, 1-3 pLOT (may include a proteasome inhibitor, IMiD, anti-CD38 antibody, and BCMA-targeted therapy), be exposed to LEN ($\geq$2 consecutive cycles, unless PD was the best response to LEN-containing treatment or if there was LEN intolerance or unacceptable toxicity), have measurable disease, and ECOG PS of 0 or 1. Pts who received prior GPRC5D-targeted therapy are excluded. Eligible pts will be randomized 1:1 across 2 arms. Arm A includes leukapheresis within 3-4 days of randomization, mandatory bridging therapy $\leq$6 days of randomization with DPd (daratumumab, pomalidomide, dexamethasone) or Kd (carfilzomib, dexamethasone) per investigator choice and lymphodepleting chemotherapy prior to a single arlo-cel infusion. Arm B includes SOC of DPd or Kd per investigator choice, dosed per labeling, until PD. Primary endpoints are PFS and minimal residual disease (MRD) negativity in CR. Key secondary endpoints include OS and ORR. Other endpoints include safety, MRD-negative status, CR rate, time to response, duration of response, pharmacokinetics, and pt-reported outcomes. Pts will be followed for $\leq$5 years after the last pt is randomized, and with a long-term follow-up study ($\leq$15 years post-infusion) for pts receiving arlo-cel. Anticipated enrollment is 440 pts at ~125 sites globally. The first pt was enrolled in March 2025. ©American Society of Hematology (2025). Reused with permission. Clinical trial information: NCT06615479. Research Sponsor: Bristol Myers Squibb.

TPS7579 **Poster Session**

MOMENTUM: A phase 2, open-label, single-arm, multicenter study to evaluate the efficacy of cemsidomide + dexamethasone in subjects with relapsed/refractory multiple myeloma (RRMM). First Author: Binod Dhakal, Medical College of Wisconsin, Milwaukee, WI

Background: Cemsidomide is a novel, highly potent, cereblon-based, IKZF1/3 MonoDAC degrader, having a similar mechanism of action as BMS's IMiD or CELMoD degraders for MM. Cemsidomide displays catalytic activity enabling rapid and deep target degradation with high binding affinity to overcome resistance due to low cereblon levels. Cemsidomide binds to cereblon to facilitate the recruitment and ubiquitination of IKZF1/3 leading to the proteasomal degradation of both proteins. IKZF1/3 degradation induces multiple myeloma cell death, activation of fully differentiated T-cells which prevents T-cell exhaustion and promotes secretion of key immune stimulating cytokines. In a Phase 1 study, cemsidomide, given orally QD over 14 days with a 14 day "off" period (14/14) in combination with weekly dexamethasone in a heavily pre-treated patient population (7 median prior lines), was well tolerated and demonstrated durable anti-myeloma activity at increasing dose levels. A 53% ORR was observed as the highest dose of 100 μg QD 14/14, with a 36% ORR observed across all dose levels (Dhakal IMS 2025). **Methods:** MOMENTUM (NCT07284758) is a Phase 2 multi-center, open-label, single-arm, global study to further evaluate the anti-myeloma activity as well as safety, tolerability, and PK/PD of cemsidomide. The study will enroll ~100 patients. The patient population eligible for this study include those who have received at least 3 prior antimyeloma regimens, which must have included an IKZF1/3 degrader other than cemsidomide, a proteasome inhibitor, an anti-CD38 antibody, and a TCE or CAR-T therapy (unless not indicated). Prior TCE or CAR-T therapy may be one or more targets including but not limited to: BCMA, GPRC5D, FcRH5, and CD38. Patients must have an ECOG score of $\leq$2, and adequate organ function prior to dosing. Patients will receive cemsidomide 100 μg QD 14/14 and dexamethasone in a 28-day cycle until progressive disease, AE requiring treatment discontinuation, or withdrawal of consent. The primary endpoint of this study is ORR per IMWG response Criteria (IMS 2025) assessed by an Independent Review Committee (IRC). Secondary endpoints include assessment of DOR, PFS, and OS. Exploratory objectives include antimyeloma activity assessed by investigator, degradation of IKF1/3, quantification of protein expression, and patient QoL assessments. Exposure-response relationships between cemsidomide and relevant markers of safety and efficacy will also be analyzed. A safety review committee and an IRC will be established to oversee safety and efficacy throughout the trial. The study is open to enrollment as of December 2025. Clinical trial information: NCT07284758. Research Sponsor: C4 Therapeutics.

TPS7580 **Poster Session**

A phase 1/2 study of mRNA-2808 in participants with relapsed or refractory multiple myeloma. First Author: Hans C. Lee, Sarah Cannon Research Institute, Nashville, TN

Background: Multiple myeloma (MM) remains mostly incurable despite therapeutic advances and relapsed or refractory multiple myeloma (RRMM) remains a significant unmet need. mRNA-2808 is an intravenously (IV) administered mRNA-encoded, multiplexed T-cell engager (TCE) that delivers *in vivo* translation of three distinct TCEs targeting BCMA, GPRC5D, and FcRH5. This multiplexed approach aims to enhance immune-mediated cytotoxicity, overcome tumor heterogeneity and target-mediated resistance. Previous preclinical studies of mRNA-2808 have demonstrated efficient *in vivo* translation of TCEs, potent activity against both primary MM cells *ex vivo* and murine tumor xenografts *in vivo*, and target-cell depletion in non-human primates. Taken together, this supports the clinical evaluation of mRNA-2808. **Methods:** This ongoing, first-in-human, open-label, multicenter Phase 1/2 study evaluates the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of mRNA-2808 administered to participants with RRMM. Key eligibility criteria include RRMM with prior exposure to a proteasome inhibitor, an IMiD, and an anti-CD38 monoclonal antibody and are either triple-class refractory or have progressed on or within 60 days of their last line of therapy, have measurable disease including bone marrow plasma cells $>$30% or plasmacytoma $\geq$2cm in size, and ECOG PS 0-2. Prior exposure to BCMA, GPRC5D, or FcRH5 targeted therapies is allowed. The study comprises two parts: Part 1 (dose escalation) to determine the recommended Phase 2 dose(s) (RP2D) and Part 2 (dose expansion) to further assess safety and efficacy of selected RP2D(s). The dose-escalation in Part 1 will proceed in 2 phases: Accelerated Titration Phase (single participant per dose level (DL)) and Standard Titration Phase (at least 3 participants per DL). The Accelerated Titration Phase will continue until a dose limiting toxicity (DLT) or a clinically significant AE of $\geq$Grade 2 is observed. If a $\geq$Grade 2 CRS and/or $\geq$Grade 2 neurotoxicity including ICANS occurs, step-up dosing will be implemented. During the Standard Titration Phase, dosing decisions will be guided by a Bayesian Optimal Interval design based on the observed DLT rate from the current cohort and recommendations from the Safety Review Committee. During Cycle 1 (28-day cycles), mRNA-2808 will be administered IV weekly, and during Cycles 2-12 every 2 weeks. Treatment with mRNA-2808 will continue for up to 12 cycles. Participants who achieve at least a partial response by the end of Cycle 5 may transition to a 4-week dosing schedule at the Investigator's discretion. Additional exploratory endpoints will evaluate surrogates of efficacy, mechanism of action, and characterize exposure. Dose Levels 1 and 2 have been completed without DLT and dose escalation is ongoing (NCT07116616). Clinical trial information: NCT07116616. Research Sponsor: Moderna, Inc.

TPS7581 **Poster Session**

Initial phase 1b/2 study results of purinostat mesylate (PM) in combination with pomalidomide (POM) and low dexamethasone (DEX) in patients with RRMM. First Author: Lijuan Chen, Department of Hematology, State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: MM remains an incurable disease and resistance mechanisms are emerging. PM is a high selective HDAC I/IIb inhibitor. In phase I study, PM monotherapy had shown good tolerability and efficacy in relapsed/refractory (RR) hematologic malignancies including MM. A phase 1b/2 study is being conducted to further assess the efficacy and safety of PM combined with POM and low DEX (80mg/cycle) in RRMM. **Methods:** The ongoing phase 1b/2 study includes dose escalation followed by dose expansion. Eligible RRMM had received ≥1 prior line of therapy (LOT) including ≥1 PI and ≥1 IMiD. Cohort A (21D cycle) and Cohort B (28D cycle) of the PM combination regimens are assessed using 3+3 escalation design. Pts in Cohort A receive PM at levels of 4, 6, 8.4, 11.2 and 15mg/m^2 IV on D1,4,8,11; POM 4mg QD on D1-14; DEX 20mg on D1,4,8,11. Pts in Cohort B receive PM at same dose range to Cohort A, on D1,4,15,18; POM 4mg QD on D1-21; DEX 20mg on D1,4,15,18. Pts continue to receive PM until disease progression or unacceptable toxicity. Primary outcomes are DLT and ORR. Secondary outcomes include PFS et al. **Results:** As of Dec 23, 2025, 27 Pts were recruited including 6 in Cohort A and 21 in Cohort B. The dose had been escalated to 6mg/m^2 and 11.2mg/m^2 in Cohort A and B. Cohort A: Median age was 61.5 years, 66.7% male, 16.7% had prior ASCT. 2 (33.3%) Pts had high risk cytogenetics, including 1q21 duplication (n=1), t (4;14) (n=1) and 1p32 deletion (n=1). 6 Pts were evaluable with median 1 (1-3) prior LOT. The ORR was 50% with 1 sCR and 2 PR along with 1 MR. With a median F/U of 138 days, the median PFS was 151 days (95% CI, 21-NR). Median DOR was NR. The most common ≥ G3 TEAEs were neutropenia (83.3%), lymphocytopenia (83.3%) and thrombocytopenia (100%). No DLT was reported. Cohort B: Median age was 61.0 years, 57.1% male, 19.1% had prior ASCT and 19.1% had extramedullary disease (EMD). 7 (33.3%) Pts had high risk characteristics, including 1q21 duplication (n=7), t (4;14) (n=2) and early relapse after ASCT (n=3). Median prior LOT is 2 (1-5). Among 16 evaluable Pts, the ORR was 37.5% with 1 sCR, 1 CR, 3 VGPR and 1 PR; additional 4 Pts achieved MR. In 7 Pts given the dose of 8.4mg/m^2, the ORR was 42.9% with 3 VGPR; 3 more Pts achieved MR. With median F/U of 104 days, the median PFS and DOR were NR. The most common ≥ G3 TEAEs were neutropenia (81.0%), lymphocytopenia (61.9%) and thrombocytopenia (38.1%). 1 DLT (G4 neutropenia) was reported. Moreover, in 4 Pts with EMD, 2 achieved objective response. In 4 Pts with super high risk (Double or Triple Hit/early relapse), 1 achieved sCR and 1 achieved VGPR. 1 Pt with prior 5-line therapy including BCMA-ADC had shown VGPR after treatment. **Conclusion:** PM as a highly selective HDACi in combination with POM and low DEX shown encouraging efficacy and safety in RRMM. Complicated cases with EMD, super high-risk characteristics or heavily pretreatment can benefit from the PM triplet therapy. Clinical trial information: NCT06484829. Research Sponsor: None.

TPS7582 **Poster Session**

A phase 1b/2 study of mirdametinib in combination with sirolimus for patients with RAS-mutated relapsed/refractory multiple myeloma. First Author: Roshani Patel, National Institute of Health, Bethesda, MD

Background: Relapsed and refractory multiple myeloma (RRMM) remains a significant therapeutic challenge, particularly among patients with genomic alterations in the RAS pathway (KRAS/NRAS mutations). These mutations occur in 60-70% of RRMM and are associated with aggressive disease and poor outcomes. Preclinical evidence suggests that dual inhibition of MEK and mTOR is required to effectively suppress oncogenic signaling in RAS dependent MM. This study evaluates the combination of the MEK inhibitor mirdametinib and the mTOR inhibitor sirolimus in patients with RAS-mutated RRMM. **Methods:** This is an open-label, single center, Phase 1b/2 study in adults with RRMM who are penta-class exposed and have no remaining standard therapeutic options. Patients must have RAS dependent MM as evidenced by a KRAS or NRAS mutation. Patients will be screened for these mutations at the NIH clinical center if unknown prior to referral. The phase 1b portion uses a standard 3+3 dose-escalation design to determine the recommended phase 2 dose (RP2D) of mirdametinib in combination with sirolimus. Phase 2 is a dose-expansion cohort using a Simon two-stage design to evaluate preliminary efficacy at the RP2D by overall response rate per the IMWG. Key eligibility criteria include adults aged ≥18 years with relapsed or refractory multiple myeloma per IMWG criteria, documented KRAS or NRAS mutation, prior exposure to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 monoclonal antibody, ECOG performance status 0–2, and adequate organ function. Correlative studies include serial assessment of MAPK and mTOR pathway inhibition and pharmacodynamic biomarkers in peripheral blood and bone marrow samples. The study is actively enrolling at the NIH Clinical Center (NCT06876142), with a planned total enrollment of 54 patients. Clinical trial information: NCT06876142. Research Sponsor: None.

8000 **Oral Abstract Session**

Randomized phase III study of nivolumab after surgery and adjuvant chemotherapy in NSCLC (ECOG-ACRIN EA5142, ALCHEMIST). First Author: Jamie E. Chaft, Memorial Sloan Kettering Cancer Center, New York, NY

Background: The NCI's ALCHEMIST program has screened thousands of patients with resected lung adenocarcinoma for mutations in *EGFR* and *ALK*. EA5142 studied the efficacy of adjuvant nivolumab after standard of care adjuvant therapy in patients with resected lung adenocarcinoma without sensitizing *EGFR* and *ALK* alterations and squamous cell carcinoma. **Methods:** Patients enrolled in the ALCHEMIST screening trial (A151216) with resected NSCLC tumors at least 4 cm and/or lymph node positive (N1/2) (for lung adenocarcinoma, without sensitizing *EGFR* and *ALK* alterations), were centrally tested for tumor cell PD-L1 expression using the DAKO 28-8 clone. After completion of all planned adjuvant therapy (chemotherapy and/or post-operative radiation) patients were randomized 1:1 to adjuvant nivolumab 480 mg IV every 4 weeks for up to 1 year or best supportive care. Patients were stratified by tumor histology, stage (AJCC 7th edition IB/IIA vs IIB/IIIA), prior adjuvant treatment, and PD-L1 status ($<$1% vs $\geq$1%). The primary study endpoints were disease free survival (DFS) in all patients and in patients with high tumor PD-L1 expression ($\geq$50%). Overall survival was powered to be tested hierarchically, if DFS was positive. **Results:** Between July 2016 and October 2019, 935 patients were randomized across 378 sites. The treatment arms were balanced for age (median 66 years), sex (52% male), smoking status (10% never smoked), histology (29% squamous), stage and PD-L1 expression (29% PD-L1 high). With a median follow-up of 72.6 months, nivolumab did not improve DFS in the intention to treat population (median DFS 71.3 months vs. 68.8 months in observation arm), hazard ratio (HR) 0.97 (95% CI 0.81-1.17, p=0.78) or the PD-L1 $\geq$50% subset (median DFS 89.8 months vs. 78.5 months in observation arm), HR 0.86 (95% CI 0.59-1.25, p=0.43). In multivariate analysis, adjusting for age, gender, and smoking history, the DFS HR was 0.99 (95% CI 0.82-1.19, p=0.89) in all randomized patients and 0.82 (95% CI 0.56-1.2, p=0.31) in the PD-L1 $\geq$50% subset. As the primary recurrence endpoint included any lung cancer, including new primaries, a sensitivity analysis was performed excluding new primary lung cancers, DFS HR 0.97 (95% CI 0.80-1.18, p=0.76) in all patients and HR 0.88 (95% CI 0.60-1.30, p=0.52 in the $\geq$50% subset. The median duration of treatment with adjuvant nivolumab was 9.4 months (range 0-12.7 months). The most common reasons for nivolumab discontinuation were adverse event (29%), patient withdrawal (11%), and disease progression while on treatment (10%). Treatment related grade 3-5 toxicities were reported in 25% of patients: Grade 3: 23%, Grade 4: 2%, Grade 5: $<$1%. **Conclusions:** In patients with resected NSCLC ($\geq$4cm or LN+, *EGFR/ALK*-) adjuvant nivolumab did not improve DFS, irrespective of tumor PD-L1 expression. Clinical trial information: NCT02595944. Research Sponsor: National Cancer Institute; U10CA180820, U10CA180794, U10CA180821, U10CA180888, U10CA180868, UG1CA189863, UG1CA189956, UG1CA189971, UG1CA233180, UG1CA233247, UG1CA233253, UG1CA233290, UG1CA233329, UG1CA233337; National Cancer Institute; UG1CA189830, UG1CA189858, UG1CA189821, UG1CA233302, UG1CA233327, UG1CA233340 and P30CA008748.

8001 **Oral Abstract Session**

Adjuvant erlotinib versus observation after complete resection of *EGFR*-mutant NSCLC: Final overall survival results of Alliance A081105. First Author: Ramaswamy Govindan, Alvin J Siteman Cancer Center at Washington University School of Medicine in St. Louis, St. Louis, MO

Background: The ALCHEMIST clinical trial platform, launched by the National Clinical Trials Network (NCTN) in 2014, screened patients with resected non-small cell lung cancer (NSCLC) for molecular markers and tailored post-operative adjuvant therapy trials. A081105 evaluated whether adjuvant erlotinib improved overall survival (OS) following complete resection in patients with early stage *EGFR* mutated lung adenocarcinoma. **Methods:** A081105 was a randomized phase III trial enrolling patients with completely resected stage IB ($\geq$4 cm), II, or IIIA non-squamous NSCLC (per the 7th TNM staging classification) harboring *EGFR* exon 19 deletion or L858R mutations. Patients were randomized 1:1 to erlotinib 150 mg daily for up to 2 years or placebo/observation, stratified by stage, prior chemotherapy, *EGFR* mutation subtype, and ECOG performance status. The primary endpoint was OS in the per-protocol (PP) population with centrally confirmed *EGFR* mutations, designed to detect a hazard ratio (HR) of 0.67 in favor of erlotinib with a power of 86% and one sided type I error rate of 5%. Secondary endpoints included OS and disease free survival (DFS) in a modified intent-to-treat (mITT) population with local or centrally confirmed EGFR mutations, and safety. A prespecified backstop analysis was conducted after a minimum of 5 years of follow-up on all patients. **Results:** Trial enrollment was discontinued when 390 of the intended 450 patients had been enrolled due to the proven benefit of adjuvant osimertinib. Among 390 enrolled patients, the arms were balanced for age (median: 67.0 years), sex (70% female), race (70% white), stage (II: 51%, IIIA: 37%), prior chemotherapy (82%), ECOG PS 0 (60%), and exon 19 deletion (57%). Adjuvant erlotinib did not significantly improve OS compared with placebo/observation in the overall PP population (364 patients, 108 events, HR 0.89; 95% CI, 0.59–1.34; 1-sided P = 0.29) or within exon 19 deletion (HR: 0.94) or L858R mutation (HR: 0.82) subgroups. Five-year OS rates were 78.6% versus 77.9%, respectively. Results were consistent in the mITT analysis (379 patients, 113 events, HR 0.86; 95% CI, 0.58–1.28). Erlotinib improved DFS (mITT: 181 events, median: 68 vs 50 months, HR 0.74; 95% CI, 0.55–1.01). Across both arms, 11% of patients started non-protocol treatment (Osimertinib: 9%) prior to disease progression, and 9% withdrew consent for all follow-up prior to recurrence. In the erlotinib arm, 3 deaths on study were reported; grade 3 or higher adverse events were reported on 39% of patients. Median duration of treatment on Erlotinib arm was 16 months; only 37% of patients completed the planned treatment. **Conclusions:** In resected *EGFR*-mutant NSCLC, adjuvant erlotinib did not improve overall survival but improved DFS. Additional studies are exploring efficacy in selected subsets of patients using genomics and proteomic analyses. Clinical trial information: NCT02193282. Research Sponsor: NCI, USA; U10CA180821, U10CA180882.

8002 **Oral Abstract Session**

Neoadjuvant lorlatinib in stage III NSCLC harboring ALK fusion: A phase 2 multicenter study (LORIN). First Author: Chao Zhang, Guangdong Lung Cancer Institute, Guangdong General Hospital (GGH) and Guangdong Academy of Medical Sciences, Guangzhou, China

Background: While adjuvant alectinib has established itself as the new standard for resected anaplastic lymphoma kinase (ALK) fusion non-small cell lung cancer (NSCLC), there is limited data on neoadjuvant treatment for locally advanced ALK fusion NSCLC. Given the groundbreaking efficacy of lorlatinib in advanced NSCLC, it is worth exploring its clinical feasibility as neoadjuvant treatment for stage III ALK+ NSCLC. **Methods:** This study is an open-label, phase 2 multi-center prospective trial (ClinicalTrials.gov NCT05740943) utilizing a Simon two-stage design. Patients diagnosed with potentially resectable or unresectable stage III ALK+ NSCLC were enrolled, with up to 3 cycles of lorlatinib administered, followed by optional local treatment and consolidation lorlatinib for up to 2 years. The primary endpoint was the pathological complete response (pCR) (H0$\leq$20%, H1$\geq$40%, α=0.05, β=0.2, at least 12 pCR events for 43 patients enrolled), while secondary endpoints included major pathological response (MPR), event-free survival (EFS), overall survival (OS), and safety profile. Xenium as well as spatial proteomics was performing on paired samples collected before and after lorlatinib. **Results:** As of January 1, 2026, 43 patients with stage III ALK-fusion NSCLC (19 evaluated as potentially resectable and 24 as unresectable) were consecutively enrolled and received 3 cycles neoadjuvant lorlatinib, with 32 completing surgery (including neck dissection and/or contralateral lymph node dissection), 9 continuing TKI therapy, and 2 undergoing radiotherapy. The most common treatment-related adverse events (TRAEs) included hypertriglyceridemia, hypercholesterolemia, and edema. The confirmed objective response rate (ORR) was 83.7% (36/43), without progressive disease (PD). Among patients who underwent surgery, the R0 resection rate was 96.9% (31/32) and 3 patients experiencing conversion to thoracotomy. pCR and MPR rates were 46.9% (15/32) and 81.3% (26/32), respectively, reaching the primary endpoint. Pathological nodal downstaging was seen in 90.6% (29/32) patients. For those with initially unresectable stage III disease, 75.0% (18/24) achieved conversion surgery through multidisciplinary evaluation after neoadjuvant lorlatinib, while others continued TKI or underwent radiotherapy. With a median follow-up of 13 months, the 1-year EFS rate was 97.1% (95% CI, 91.5-100) and no OS events were observed. Only 3 patients experienced local relapse (regional lymph nodes and/or intrapulmonary metastasis) without distant metastasis; all had initially presented with N3 disease and did not receive adjuvant lorlatinib after surgery. **Conclusions:** Neoadjuvant lorlatinib unveiled overwhelming pathological response and could lead to high conversion surgery for unresectable stage III disease. Further large-scale prospective trial was warranted to testified such treatment modality. Clinical trial information: NCT05740943. Research Sponsor: National Science Foundation of China; National Science Foundation of China.

8003 **Oral Abstract Session**

Pollution and progression: Air quality and stage of lung cancer diagnosis across the U.S. First Author: Raheem Bell, Northwestern University Feinberg School of Medicine, Department of Surgery, Chicago, IL

Background: Air pollution contributes to increased lung cancer incidence, but whether it accelerates tumor progression, resulting in more advanced stage at diagnosis, is not well understood. Understanding environmental and social factors influencing late-stage presentation can guide targeted prevention efforts. **Methods:** We identified primary lung cancer cases from the National Cancer Database (NCDB; 2010–2023) across 2,803 U.S. counties. Individual-level data were linked to county-level annual averages of $PM_{2.5}$ ($\mu g/m^3$) and NO_2 (ppb). Generalized estimating equation logistic models with county-level clustering assessed associations between chronic pollution exposure and odds of advanced-stage (III–IV vs. I–II) diagnosis, adjusting for median household income and educational attainment. Pollutants were z-score standardized (mean = 0, SD = 1) and summed to create a combined Pollution Burden metric. Effect modification by histology and socioeconomic status was tested. **Results:** Among 1,023,140 patients (mean age 68.5 $\pm$ 10.8 years; 51.3% female), 67.1% presented with advanced-stage disease. Each standard deviation increase in $PM_{2.5}$ was associated with 4.8% higher odds of advanced-stage diagnosis (95% CI: 3.5–6.1%; $p < 0.001$; Table 1). In multi-pollutant models, $PM_{2.5}$ remained significant (OR = 1.062, 95% CI: 1.047–1.076; $p < 0.001$), with combined pollution burden linked to a 3.1% increase in odds (95% CI: 1.5–4.7%; $p < 0.001$). Low-SES communities had higher advanced-stage rates regardless of pollution exposure (69.7% vs. 63.6%; $p < 0.001$), equating to approximately 6,100 excess annual diagnoses. Effects varied by histology, with small cell carcinoma showing the highest advanced-stage rate (91.2%), followed by adenocarcinoma (67.3%) and squamous cell carcinoma (58.6%). **Conclusions:** Higher $PM_{2.5}$ exposure and lower socioeconomic status were independently associated with later-stage lung cancer diagnosis across over 1 million cases from 2,803 U.S. counties. Low-SES communities showed 6 percentage points higher advanced-stage rates irrespective of pollution levels. These findings highlight how environmental factors that may accelerate cancer progression and social barriers to accessing care can jointly delay early-stage diagnosis. Targeted pollution control and expanded lung cancer screening in underserved communities could reduce the burden of advanced-stage disease. Research Sponsor: None.

Odds of advanced-stage lung cancer by air pollutant exposure.

Pollutant	Model	Mean $\pm$ SD	OR	95% CI Lower	95% CI Upper	P-value
$PM_{2.5}$ ($\mu g/m^3$)	Single-pollutant	8.17 $\pm$ 1.58	1.048	1.035	1.061	$<$0.001
$PM_{2.5}$ ($\mu g/m^3$)	Multi-pollutant		1.062	1.047	1.076	$<$0.001
NO_2 (ppb)	Single-pollutant	6.93 $\pm$ 3.93	1.009	0.993	1.026	0.28
NO_2 (ppb)	Multi-pollutant		0.978	0.963	0.994	0.007
Combined Burden	Z_PM2.5 + Z_NO2		1.031	1.015	1.047	$<$0.001

8004 **Oral Abstract Session**

Redefining lung cancer screening eligibility: Smoking duration vs. pack-years in a national VA cohort of nearly 1 million patients. First Author: Brendan Heiden, Division of Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, MO

Background: Lung cancer is the leading cause of cancer death in the US, yet current lung cancer screening (LCS) criteria based on tobacco pack-years (TPY) miss nearly half of all cases and are difficult to capture reliably in clinical practice. Tobacco smoking duration (TSD) is a simpler, more consistently measurable metric that may better identify high-risk individuals. We evaluated whether TSD improves lung cancer risk prediction compared with TPY in a unique real-world cohort of nearly 1 million patients. **Methods:** We conducted a retrospective cohort study of Veterans aged 50–80 in the Veterans Health Administration. The primary exposure was smoking history quantified as TPY and TSD; the primary outcome was 5-year lung cancer incidence (2021-2025). We compared risk-adjusted 5-year lung cancer incidence based on 2013 USPSTF guidelines (≥30 TPY, quit within 15 years), revised 2021 USPSTF guidelines (≥20 TPY, quit within 15 years), our proposed TSD criteria (≥20 TSD), and never-smoking. We further estimated the impact of switching to TSD-based eligibility on the theoretical number of missed lung cancer diagnoses (i.e., the proportion of lung cancers diagnosed in screening-ineligible individuals) and performed subgroup analyses across race and sex. **Results:** A total of 960,770 Veterans were included in the study, with 340,312 (35.4%) currently smoking, 304,589 (31.7%) formerly smoking, and 315,869 (32.9%) never smoking. The median (SD) age was 64.9 (9.6) years old. Most participants were male (n=876,215, 91.2%) and of white race (n=677,823, 70.6%). 341,061 (35.5%) qualified for 2013 TPY criteria, 437,803 (45.6%) qualified for 2021 TPY criteria, and 571,087 (59.4%) qualified for TSD criteria. Importantly, 127,604 (22.3%) individuals who met TSD criteria did not meet 2021 TPY criteria, suggesting that TSD criteria would increase the eligible screening population by 28.8%. The 5-year incidence of lung cancer was 0.95% (1.87% among 2013 TPY criteria; 1.73% among 2021 TPY criteria; 1.48% among TSD criteria; and 0.13% among never-smoking). The proportion of missed lung cancer diagnoses was 30.3% among 2013 TPY criteria, 17.1% among 2021 TPY criteria, and 7.5% among TSD criteria. Finally, eligibility was higher for TSD vs. TPY criteria in various subgroups, including among black individuals (percent of current or former smokers eligible for screening: 34.7% 2013 TPY; 54.0% 2021 TPY; and 83.7% TSD) and females (38.5% 2013 TPY; 55.1% 2021 TPY; and 83.7% TSD). **Conclusions:** In this nationwide VA cohort consisting of nearly 1 million Veterans, smoking duration performed at least as well as TPY in predicting lung cancer risk and substantially expanded screening eligibility with fewer missed cancers. TSD criteria were also associated with improved equity. These findings support revisiting national lung cancer screening guidelines to prioritize smoking duration over pack-years. Research Sponsor: None.

LBA8005 **Oral Abstract Session**

Concurrent thoracic radiotherapy (TRT), platinum/etoposide chemotherapy, and durvalumab immunotherapy in extensive-stage (ES) small cell lung cancer (SCLC): A phase III trial. First Author: Bjorn Henning Gronberg, Department of Oncology, St. Olavs hospital, Trondheim, Norway

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

8006 **Oral Abstract Session**

Intracranial efficacy of tarlatamab versus chemotherapy (CTx) as second-line (2L) treatment for small cell lung cancer (SCLC): DeLLphi-304 phase 3 post hoc analysis. First Author: Giannis S. Mountzios, Fourth Department of Medical Oncology and Clinical Trials Unit, Henry Dunant Hospital Center, Athens, Greece

Background: Brain metastases (BM) are common in patients (pts) with SCLC and are associated with poor outcomes. Tarlatamab, a bispecific T-cell engager (BiTE) immunotherapy, demonstrated superior overall survival versus CTx in pts with SCLC following progression on or after platinum-based CTx in the DeLLphi-304 study, including pts with history of BM (prior or current) at baseline (OS HR 0.45 [95% CI: 0.31–0.65]). Here we compare the intracranial efficacy of tarlatamab vs CTx. **Methods:** Pts were randomized 1:1 to receive tarlatamab or CTx (topotecan, lurbinectedin or amrubicin) as 2L treatment for SCLC. Pts with stable asymptomatic brain metastases were eligible; prior CNS treatment was required until protocol amendment 3. Baseline brain imaging by contrast enhanced MRI was mandatory for all pts at screening and repeated at all subsequent imaging assessments for pts with a history of BM at baseline. A post hoc analysis on intracranial efficacy was performed by BICR per mRANO-BM. Given that most pts had prior CNS treatment, specified outcomes were CR, non-CR/non-PD, and PD. **Results:** BM at baseline were present in 98/254 pts (39%) in the tarlatamab arm and 99/255 (39%) in the CTx arm, of whom 75/98 (77%) and 69/99 (70%) had prior CNS treatment, respectively. A CNS full analysis set (FAS) was specified to include pts who had both a baseline scan and ≥ 1 postbaseline scan (tarlatamab-67; CTx-56 pts). In pts in FAS, treatment with tarlatamab resulted in longer CNS PFS than CTx (median: 6.5 mos vs 4.2 mos; HR, 0.40 [95% CI: 0.24–0.66]; Table). CNS tumor shrinkage of ≥30% was observed in 56% of pts with tarlatamab vs 38% with CTx. CNS complete response was observed in 15% of pts with tarlatamab vs 5% with CTx, with longer CNS duration of complete response (DOCR) (not estimable [NE] vs 3.6 mo) and longer CNS duration of disease control (DODC) (8.2 vs 5.2 mo) for pts in the tarlatamab arm. Pts with BM at baseline had longer OS with tarlatamab vs CTx (median OS: 13.9 vs 6.8 mos; HR, 0.51 [95% CI: 0.34–0.74]). In pts with BM at baseline, treatment-emergent adverse events (TEAEs) of any grade (gr)/gr 3/gr 4/gr 5 occurred in 99%/38%/9%/7% for tarlatamab vs 100%/38%/40%/10% for CTx. In pts treated with tarlatamab, the incidence of CRS and ICANS was 54% and 9% in pts with BM at baseline vs 58% and 4% in pts without BM at baseline, respectively. **Conclusions:** Tarlatamab demonstrated increased intracranial efficacy with longer CNS PFS and OS vs CTx in pts with stable, treated and untreated asymptomatic BM. These results affirm tarlatamab as the 2L standard of care for SCLC, even in pts with BM. Clinical trial information: NCT05740566. Research Sponsor: Amgen Inc.

	Tarlatamab n = 67	CTx n = 56
CNS PFS, mos (95% CI)	6.5 (4.3, 13.7)	4.2 (2.9, 5.5)
CNS Complete Response, n (%)	10 (15%)	3 (5%)
CNS DOCR, mos (95% CI)	NE (2.9, NE)	3.6 (3.1, NE)
CNS DODC, mos (95% CI)	8.2 (6.3, NE)	5.2 (4.2, 6.2)
CNS tumor shrinkage of ≥30%, % (n/N)[a]	56% (9/16)	38% (5/13)

[a]Assessed in pts with ≥1 lesion that was ≥ 10 mm.

8007 **Oral Abstract Session**

Efficacy and safety of ivonescimab combined with liposomal irinotecan in patients with small-cell lung cancer (SCLC) progressing after first-line chemoimmunotherapy: A multicenter, phase 2 study. First Author: Yun Fan, Department of Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Background: SCLC patients (pts) progressing after first-line platinum-based chemoimmunotherapy have limited effective treatment options and poor prognosis. This study evaluated the efficacy and safety of ivonescimab combined with liposomal irinotecan in this setting. **Methods:** This phase 2, multicenter, single-arm trial enrolled SCLC pts who progressed during or after platinum-based chemoimmunotherapy. Eligible pts were required to be ≥18 years of age and have an ECOG PS of 0 or 1. Pts received ivonescimab (20 mg/kg, IV, Q3W) plus liposomal irinotecan (56.5 mg/m², IV, Q2W) until disease progression or unacceptable toxicity. The primary endpoint was 6-month progression-free survival (PFS) rate (ClinicalTrials.gov: NCT06478043). **Results:** Between October 22, 2024 and August 27, 2025, 60 pts were included in the intention-to-treat population. Median age was 62.0 years (range: 38-75), 56 (93.3%) were male, and 53 (88.3%) had ECOG PS 1. At baseline, 35.0% and 26.7% of pts had liver and brain metastases, respectively. A total of 63.3% of pts had a chemotherapy-free interval of more than 90 days. As of December 15, 2025, with a median follow-up time of 7.3 months (95% CI: 6.0-9.0), the 6-month PFS rate was 72.0% (95% CI: 57.0-82.6). Median PFS was 9.8 months (95% CI: 6.7-13.4), and median OS was not reached. The confirmed objective response rate was 61.7% (95% CI: 48.2-73.9; all partial responses) and the disease control rate was 91.7% (95% CI: 81.6-97.2). In subgroup analysis, the median PFS was 11.9 months (95% CI: 7.3-NE) for patients with a CFI ≥90 days and 7.0 months (95% CI: 4.4-NE) for those with a CFI < 90 days. Treatment-related adverse events (TRAEs) of grade ≥3 occurred in 16 pts (26.7%). The most common grade ≥3 TRAEs were decreased neutrophil count (8.3%), decreased white blood cell count (8.3%), fatigue (6.7%), and diarrhea (3.3%). TRAEs led to treatment interruption in 31.7% and chemotherapy dose reduction in 25.0% of pts. No patient discontinued all treatment drugs due to TRAEs; discontinuation of ivonescimab alone occurred in 6 pts (10%). Immune-related AEs occurred in 33.3 % of pts, with grade 3 events in 8.3%. No grade ≥4 irAEs or treatment-related deaths were reported. **Conclusions:** Ivonescimab combined with liposomal irinotecan demonstrated encouraging antitumor activity with a manageable safety profile as a second-line treatment for SCLC pts after platinum-based chemoimmunotherapy. These results support further investigation in randomized controlled trials. Clinical trial information: NCT06478043. Research Sponsor: None.

8008 Oral Abstract Session

ABBV-706 as monotherapy and in combination with budigalimab in patients with relapsed/refractory (R/R) small cell lung cancer (SCLC). First Author: Lauren Averett Byers, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: SCLC is an aggressive cancer with poor prognosis and limited treatment options. Seizure-related 6 homolog (SEZ6) is overexpressed in SCLC. ABBV-706 is a SEZ6-targeting antibody-drug conjugate with topoisomerase 1-inhibitor payload. Here we report updated data from a phase 1 study (NCT05599984) evaluating ABBV-706 in patients (pts) with R/R SCLC as monotherapy or in combination with budigalimab (Budi), an anti-PD-1 immune checkpoint inhibitor (CPI). **Methods:** The study enrolled pts ≥18 years old with R/R SCLC and Eastern Cooperative Oncology Group performance score ≤1. Pts received either ABBV-706 monotherapy every 3 weeks (Q3W), or in combination with 375 mg Budi Q3W. **Results:** As of Sept. 27, 2025, 124 pts received ABBV-706 monotherapy. Of these, 41 received the recommended phase 3 dose (1.8 mg/kg), with 17 receiving ABBV-706 as a second-line (2L) therapy. Overall, median age was 64 years, and most pts (65%) received at least 2L of prior treatment. The safety profile was comparable with previously reported data. Median follow-up (mFU) was 16.2 months, and median overall survival (mOS) overall (N=124) and among pts receiving 1.8 mg/kg as 2L (n=17) was 11.3 and 14.3 months, respectively. The 15-month OS estimates for the same cohorts were 40% and 50%, respectively. As of Sept. 27, 2025, 11 pts received ABBV-706 (1.8 mg/kg Q3W) + Budi as 2L treatment. Median age was 68 years. No new safety signals were detected as compared to monotherapy, and there were no reports of pneumonitis. Treatment-related adverse events (TRAEs) occurred in 91% of pts, most commonly gastrointestinal (64%) and hematological (64%). TRAEs grade ≥3 occurred in 46% of pts, with anemia (27%) and neutrophil count decreased (18%) being most common. TRAEs led to treatment discontinuation, interruption, or dose reduction in 0%, 64%, and 36% of pts, respectively. No treatment-related deaths were reported. mFU was 9.1 months. Detailed efficacy endpoints are shown in the Table. **Conclusions:** ABBV-706 monotherapy shows promising OS benefit in a heavily pretreated pt population with R/R SCLC and is combinable with a CPI. Clinical trial information: NCT05599984. Research Sponsor: AbbVie Inc.

Efficacy of ABBV-706 in R/R SCLC.

	Monotherapy Total (N=124)	Monotherapy 1.8 mg/kg (n=41)	Monotherapy 1.8 mg/kg as 2L (n=17)	ABBV-706 1.8 mg/kg + Budi (n=11)
Best overall response,[a,b] n (%)				
Complete response	3 (2)	3 (7)	2 (12)	0
Partial response[c]	64 (52)	20 (50)	12 (71)	6 (55)
Stable disease	46 (37)	16 (39)	2 (12)	3 (27)
Progressive disease	6 (5)	1 (2)	1 (6)	1 (9)
NE/not assessed	5 (4)	1 (2)	0	1 (9)
Objective response rate[a] (%)	52	56	82	55
Median duration of response, months	5.3[d]	5.9[e]	6.6[f]	6.7[g]
Median progression-free survival, months	5.4	6.4	6.8	8.1
mOS, months	11.3	12.4	14.3	NE
OS estimate at 15 months, %	40	44	50	NE

[a]Confirmed by investigator per RECIST v1.1.
[b]Percentages may exceed 100% due to rounding.
[c]Includes 2 pts with unconfirmed partial response and ongoing treatment.
[d]n=65.
[e]n=23.
[f]n=14.
[g]n=6.

8009 Rapid Oral Abstract Session

Complex segmentectomy versus lobectomy in small-sized peripheral non–small cell lung cancer: A post-hoc supplemental analysis of a multicenter, open-label, phase 3 trial (JCOG0802/WJOG4607L). First Author: Atsushi Kamigaichi, Hiroshima University, Hiroshima, Japan

Background: JCOG0802/WJOG4607L confirmed the superiority of segmentectomy on overall survival (OS) over lobectomy for small-sized peripheral non-small cell lung cancer (NSCLC). However, it remains unclear whether technically demanding complex segmentectomy offers therapeutic efficacy compared to lobectomy, similar to simple segmentectomy. This study therefore aimed to evaluate the oncological outcomes of complex and simple segmentectomy compared to those of lobectomy using final analysis data from JCOG0802/WJOG4607L. **Methods:** Simple segmentectomy was defined as resection of the bilateral superior division (S^6), left lingular (S^{4+5}), or superior division (S^{1-3}); all other segmentectomies were defined as complex. The primary outcome was OS, and secondary outcomes were respiratory function, relapse-free survival (RFS), cumulative incidence of locoregional relapse, and lung cancer-specific death. To ensure comparability, a location-adjusted analysis was performed, separately comparing lobectomy to simple segmentectomy in patients with tumors in the bilateral S^6, left S^{1-3}, or S^{4+5}, and to complex segmentectomy in patients with tumors in the right S^{7-10}, S^{1-3}, or left S^{8-10}, S^{1-3}. **Results:** 1106 patients were assigned to either lobectomy (n = 554) or segmentectomy (n = 552) including 318 complex and 234 simple segmentectomies. At a median follow-up of 10.5 years, the 10-year OS was 83.5% (95% CI: 78.8–87.3%), 83.5% (95% CI: 77.7–87.9%) and 79.8% (95% CI: 76.1–83.0%) for complex, simple segmentectomy, and lobectomy, respectively. In the location-adjusted analysis, the 10-year OS were 83.6% (95% CI: 78.9–87.3%) for complex segmentectomy and 79.2% (95% CI: 74.7–82.9%) for lobectomy (HR 0.839 [95% CI 0.608–1.158]). Similarly, 10-year OS were 82.9% (95% CI: 76.9–87.4%) for simple segmentectomy and 78.0% (95% CI: 72.5–82.6%) for lobectomy (HR 0.791 [95% CI 0.540–1.158]). The reduction of median forced expiratory volume in 1 second at 1 year was less after complex (−7.9%) and simple segmentectomy (−9.0%) than lobectomy (−12.0%; $p < 0.001$ and $p < 0.001$, respectively). RFS and lung cancer-specific death were not significantly different among the arms, while the cumulative incidence of locoregional relapse was higher after complex and simple segmentectomy than lobectomy (HR 2.124 [95% CI 1.327–3.339] and HR 1.817 [95% CI 1.071–3.083], respectively). Surgical margins were shorter in complex (median 2.2 cm, $p < 0.001$) and simple (2.5 cm, $p < 0.001$) segmentectomy than lobectomy (4.0 cm). **Conclusions:** Complex segmentectomy showed a trend toward improved OS compared to lobectomy in small-sized peripheral NSCLC similar to simple segmentectomy. However, due to a higher risk of locoregional relapse, complex segmentectomy should be performed with meticulous attention to securing adequate surgical margin. Clinical trial information: UMIN000002317. Research Sponsor: National Cancer Center Research and the Ministry of Health, Labour, and Welfare of Japan.

8010 Rapid Oral Abstract Session

Perioperative toripalimab in non-small cell lung cancer: Clinical outcomes and safety from a large prospective real-world study. First Author: Pingping Song, Cancer Hospital of Shandong First Medical University (Shandong Cancer Institute, Shandong Cancer Hospital), Jinan, China

Background: The phase III NEOTORCH trial demonstrated that perioperative toripalimab significantly improved event-free survival in stage IIIA–IIIB driver-gene-negative NSCLC, along with a favorable overall survival trend. However, the generalizability of randomized controlled trial (RCT) results to broader, more heterogeneous, real-world populations is uncertain. This study aimed to evaluate the effectiveness and safety of this regimen in routine clinical practice, providing essential evidence for treatment decisions. **Methods:** This nationwide, prospective, observational study in China consecutively enrolled patients with stage II-III NSCLC planned for perioperative treatment containing toripalimab. The primary endpoint was real-world event-free survival (rwEFS). Secondary endpoints included pathological complete response (pCR) rate, major pathological response (MPR) rate, objective response rate (ORR), R0 resection rate, real-world disease-free survival (rwDFS), real-world overall survival (rwOS), and safety. **Results:** Between December 9, 2024, and January 14, 2026, 1727 patients were enrolled from 221 tertiary and secondary hospitals across 28 provinces in China. Baseline characteristics: 82.8% male; 51.4% aged ≥65 years; ECOG PS 0/1/2 in 43.2%/54.4%/2.4%. Histology: 71.4% squamous, 18.3% nonsquamous, 10.3% NSCLC not otherwise specified. Clinical stage distribution: IIA (1.7%), IIB (10.4%), IIIA (52.8%), IIIB (33.0%), IIIC (2.1%). Of all enrolled patients, 542 (31.4%) were pending preoperative assessment. Surgery was not performed in 634 patients (36.7%); reasons included: other causes (64.9%), patient refusal (15.7%), surgical ineligibility (9.3%), disease progression (8.2%), and adverse events (1.9%). Ultimately, 551 patients (31.9%) underwent resection, with 503 having postoperative pathological assessment. The MPR rate was 67.0% (337/503) and the pCR rate was 39.6% (199/503). As of the data-cutoff, investigators reported 20 (1.2%) grade ≥3 or clinically significant treatment-emergent adverse events, with hematologic toxicities being most common. Immune-related adverse events were infrequent (four events: three grade 1–2 pneumonitis, one grade 3 rash). **Conclusions:** This is the largest prospective real-world study of perioperative immunotherapy in NSCLC to date. Its extensive geographic coverage and diverse patient population-including higher proportions of elderly patients, those with ECOG PS 1, and varied histologies-validate the effectiveness and manageable safety of perioperative toripalimab in routine practice beyond RCT settings. The significant pathological response rates observed support the clinical benefit of this regimen for a broad spectrum of stage II-III NSCLC patients, providing crucial evidence for real-world decision-making. Clinical trial information: ChiCTR2400091457. Research Sponsor: the Shanghai Science and Technology Innovation Action Plan; 24SF1900100.

8011 Rapid Oral Abstract Session

LuSato-1: Phase I study of ^{177}Lu-SSO110 with ^{68}Ga-SSO120 companion imaging in patients with extensive stage small cell lung cancer (ES-SCLC) on maintenance treatment with immune checkpoint inhibition (ICI). First Author: Surein Arulananda, Monash Health, Clayton, VIC, Australia

Background: Outcomes for pts with ES-SCLC remains suboptimal despite the addition of ICIs to platinum-based chemotherapy. Somatostatin receptor 2 (SSTR2) is expressed in the majority of SCLC lesions. SSTR2 targeted radiopharmaceutical therapy (RPT) has proven safe and effective when used in other neuroendocrine tumors. The multicentre, open-label, phase I LuSato-1 (ACTRN12623000185662) study investigated the use of ^{177}Lu-satoreotide Tetraxetan (^{177}Lu-SSO110) with ^{68}Ga-Satoreotide Trizoxetan (^{68}Ga-SSO120) companion imaging in pts with ES-SCLC, who are on 1L maintenance ICIs. **Methods:** Adult pts with ES-SCLC received 1L induction therapy with carboplatin, etoposide and atezolizumab for 4 cycles. Following induction, eligible pts without PD were enrolled and received up to 4 doses of ^{177}Lu-SSO110 in 6 to 9 week intervals, with up to 3 additional treatments per investigator choice. Activities were escalated from 3.7GBq to 5.2GBq, following a BOIN design with a target DLT rate of 0.30. The primary objective was to investigate the safety and tolerability of ^{177}Lu-SSO110 with ^{68}Ga-SSO120 companion imaging in pts on maintenance ICI, with secondary objective of anti-tumor activity of the combination. Concordance between ^{68}Ga-SSO120 PET/CT and contrast-enhanced CT was an exploratory endpoint. **Results:** Of the 35 screened pts, 20 were deemed eligible (median age 65.5 years (range 47-83), 55% female, 25% brain mets). With a median 11.1 month follow up (data cut off: 08/12/25), the TEAE rate associated with ^{177}Lu-SSO110 was 0% at 3.7GBq (dose level 1), 71.4% at 4.5GBq (dose level 2), and 83.3% at 5.2GBq (dose level 3). The grade 3/4 TEAE rate associated with ^{177}Lu-SSO110 was 0% (dose level 1), 57.1% (dose level 2), and 41.7% (dose level 3). Grade 2 to 4 thrombocytopenia rate related to ^{177}Lu-SSO110 was 45%. Grade 3/4 irAEs related to ICI was 20%. There was 10% pneumonitis rate attributed to ICI. The treatment interruption rate was 50% and treatment discontinuation rate was 10% (2 attributed to ^{177}Lu-SSO110 associated thrombocytopenia). From the start of C1 induction chemoICI, the ORR was 85%, including 1 CR. From the start of maintenance ICI, median PFS was 3.7 months and median OS was 8 months. **Conclusions:** Addition of SSTR2 targeted RPT to maintenance ICI was well tolerated and demonstrated clinically meaningful anti-tumor activity. This supports further investigation of SSTR2-targeted RPT in combination with ICI in patients with ES-SCLC. Clinical trial information: ACTRN12623000185662. Research Sponsor: Ariceum International AG.

ORR, PFS and OS.

Efficacy	ES-SCLC patients N=20
Best response rates (from C1 induction)	
CR	1 (5%)
PR	16 (80%)
SD	3 (15%)
ORR (from C1 induction)	17 (85%)
Median PFS (months) (from C1 maintenance)	3.7 months
Median OS (months) (from C1 maintenance)	8 months

8012 **Rapid Oral Abstract Session**

Preliminary results from an ongoing phase 1 study of LB2102, a dnTGFBR2-armored DLL3-targeted autologous CAR-T cell therapy, in patients with relapsed or refractory SCLC or LCNEC. First Author: Zhonglin Hao, Markey Cancer Center, Lexington, KY

Background: Delta-like ligand 3 (DLL3) is a promising target for small cell lung cancer (SCLC) and other neuroendocrine tumors. We present results from an ongoing dose-escalation study of LB2102, an autologous CAR-T cell therapy engineered to target DLL3 and armored with a TGF-β receptor blockade to overcome the immunosuppressive tumor microenvironment. **Methods:** This open-label, multicenter, phase 1 study evaluates LB2102 in patients with SCLC or large cell neuroendocrine carcinoma (LCNEC), relapsed or refractory to ≥1 prior line of therapy (LOT). Dose escalation follows an i3+3 design, with dose levels (DL) of 0.3, 1.0, 2.0, 4.0, 8.0, 12.0, and 16.0x10^6 CAR+ T cells/kg. Subjects received a single infusion of LB2102 after standard lymphodepletion (LD). The primary objectives are to assess safety and tolerability, and to determine the recommended phase 2 dose. **Results:** As of 05-JAN-2026, 20 subjects received LB2102 (DL1–DL5, n = 3 each; DL6 was skipped based on data; DL7, n = 5). Seventeen subjects had SCLC and 3 LCNEC; 13 (65%) had a history of brain metastases. Median age was 56.5 yrs (range 20–73 yrs) with median 1 prior LOT (range 1–7); 95% received bridging therapy between apheresis and LB2102. The most-common grade ≥ 3 LB2102-related adverse events (TRAEs) were hematologic and co-attributed to LD. Four subjects (20%) had cytokine-release syndrome (CRS; 3 Grade 1 and 1 Grade 2); all resolved. Two subjects developed ICANS (1 Grade 1 and 1 Grade 3); both resolved. There were no dose-limiting toxicities (DLTs) or TEAE-related deaths. Other grade ≥ 3 non-hematologic LB2102-related TEAEs were dyspnea, prolonged QT, and hypoxia (all n = 1 at DL7). Of 17 response-evaluable subjects, best overall responses per RECIST1.1 criteria were 3 partial responses (PR, one each at DL3, DL4, and DL7) and 10 stable diseases (SD, at DLs 2–7), for an objective response rate (ORR) of 3/17 (18%) and a disease control rate (DCR) of 13/17 (76%). Median DOR among patients with a PR was 208 days. CAR-T expansion in peripheral blood (measured by qPCR) was observed at DL3 (N = 3), DL4 (N = 3), DL5 (N = 3), and DL7 (N = 5; 1 patient excluded due to incomplete PK profile): median C_{max} was 694, 581, 527, and 2851 copies/μg gDNA; median T_{max} was 15, 15, 6, and 6 days, respectively. Patients with partial responses had relatively higher PK exposure (median C_{max}) compared to the PK exposure of patients with stable diseases and progressive diseases. Median tumor expression of DLL3 at baseline was 97% (n = 16, range 45%–100%) and at Day 29 post-infusion was 90% (n = 8, range 55%–100%). **Conclusions:** LB2102 demonstrated consistent CAR-T expansion and encouraging anti-tumor activity at doses ≥ 2x10^6 CAR+T cells/kg (ORR 27% and DCR 91%). LB2102 was well tolerated with no DLTs and manageable CRS and ICANs. Clinical trial information: NCT05680922. Research Sponsor: Legend Biotech USA, Inc; Novartis.

8013 **Rapid Oral Abstract Session**

Autologous natural killer cell infusion as consolidation therapy after first-line chemoradiotherapy for limited-stage small-cell lung cancer: A randomized, controlled, open-label, single-center phase II clinical study. First Author: Jiuwei Cui, The First Hospital of Jilin University, Changchun, China

Background: Small-cell lung cancer (SCLC) grows rapidly, is aggressive, has a poor prognosis, and tends to recur after treatment. Autologous cellular immunotherapy (CIT) has demonstrated good safety and efficacy across various tumors; however, there are no prospective studies utilizing autologous natural killer (NK) cells for consolidation therapy following first-line chemoradiotherapy for SCLC. **Methods:** This study aimed to evaluate the safety and efficacy of autologous NK cell infusion (administered every 2 weeks for a total of six courses) as consolidation therapy after first-line standard treatment for limited-stage SCLC, compared to routine follow-up in a randomized, controlled, open-label, single-center phase II clinical trial. The primary endpoint was progression-free survival (PFS, assessed according to Response Evaluation Criteria in Solid Tumors version 1.1), while secondary endpoints included overall survival (OS), the 12- and 24-month PFS rate, the 24- and 36-month OS rate and safety. **Results:** Forty-three patients with limited-stage SCLC were included in the final analysis, comprising 21 patients in the treatment group who received autologous NK cell infusion after chemoradiotherapy and 22 patients in the control group who underwent routine follow-up. At 6 months, the response to initial chemoradiotherapy was maintained in 27.3% (6/22) of the control patients and 57.1% (12/21) of the treatment patients. The objective response rate (ORR) and PFS rates at 12 months for controls compared to treatment patients were 0% versus 19.0% (4/21) ($P < 0.05$) and 4.5% (1/22) versus 42.9% (9/21) ($P < 0.01$), respectively. Compared to the control group, the autologous NK cell consolidation group achieved significantly longer PFS (median 6.5 vs. 11.92 months; hazard ratio [HR] 0.38, 95% confidence intervals [CI] 0.18 to 0.79; P = 0.01) and OS (median 15.6 vs. 27.13 months; HR 0.41, 95% CI: 0.19 to 0.87, P = 0.02), with a particularly pronounced PFS benefit when calculated from the end of chemoradiotherapy (median 8.1 vs.16.3 months; HR 0.35, 95% CI 0.17 to 0.72, P = 0.01). Regarding safety, the incidence of all adverse events (AEs) due to any cause was 50.0% (11/22) in the observation group and 47.6% (10/21) in the treatment group, with most being grade 1–2 and considered unrelated to NK cell infusion. NK cell treatment exhibited good overall safety and tolerability. Additionally, we characterized changes in peripheral blood cell subsets and metabolites before and after treatment, as well as the tumor immune microenvironment characteristics in patients from the treatment group. **Conclusions:** Autologous NK cell infusion as consolidation therapy after first-line chemoradiotherapy for SCLC yielded promising preliminary PFS and OS results, with a well-tolerated safety profile. Clinical trial information: NCT03410368. Research Sponsor: National Natural Science Foundation of China; 82273191; Jilin Provincial Science and Technology Department; 20240304037SF.

8014 **Rapid Oral Abstract Session**

Transcriptomic analyses of molecular subsets and correlations with clinical outcomes from the phase 3 IMforte study of lurbinectedin (lurbi) + atezolizumab (atezo) maintenance treatment (Tx) in extensive-stage small-cell lung cancer (ES-SCLC). First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, Universidad Complutense and Ciberonc, Madrid, Spain

Background: Transcriptomic analyses of pre-Tx tumor samples from the Phase 3 IMpower133 study identified 4 molecular subtypes with distinct clinical outcomes to first-line (1L) Tx with atezo and chemotherapy (chemo). Neuroendocrine (NE) tumors with low tumor-associated macrophage (TAM)/high T-effector (T-eff) signal demonstrated longer overall survival (OS) vs non-NE tumors with high TAM/high T-eff, suggesting that TAM contributes to resistance to atezo. Lurbi, an alkylating agent that modifies the tumor microenvironment and synergizes with immune checkpoint inhibitors, could enhance atezo activity. Lurbi + atezo as 1L maintenance Tx significantly improved progression-free survival (PFS) and OS vs atezo in patients (pts) with ES-SCLC in the Phase 3 IMforte study (NCT05091567). We report exploratory biomarker analyses from IMforte. **Methods:** Adults with Tx-naïve ES-SCLC, without disease progression after induction with atezo + chemo, received maintenance Tx of either 3.2 mg/m² lurbi + 1200 mg atezo or 1200 mg atezo q3w until unacceptable toxicity or disease progression. Transcriptomic analyses were conducted on pre-induction Tx tumor samples to identify subgroups with concordance to previously reported SCLC subtypes (SCLC-A, -N, -I-NE and -I-non-NE), immune gene expression signatures (TAM, T-eff) and *SLFN11*. Post-hoc exploratory analyses were conducted for correlation with IRF-assessed PFS and OS. **Results:** Of 483 randomized pts, 303 had samples for RNA sequencing. Of 303 tissue samples analyzed, 104 (34.3%) were classified as SCLC-A, 89 (29.4%) as SCLC-N, 46 (15.2%) as SCLC-I-NE and 64 (21.1%) as SCLC-I-non-NE. Clinical outcomes in the 303 pts (median [m] PFS: 5.5 vs 2.4 months [mo], hazard ratio [HR] 0.61; mOS: 13.5 vs 11.7 mo, HR 0.72, for lurbi + atezo [n = 150] vs atezo [n = 153], respectively) were consistent with the full analysis set. PFS and OS benefit from lurbi + atezo were comparable between NE (mPFS: 5.5 vs 2.1 mo, HR 0.58; mOS: 13.5 vs 11.7 mo, HR 0.74, for lurbi + atezo [n = 115] vs atezo [n = 124], respectively) and non-NE subtypes (mPFS: 4.6 vs 2.8 mo, HR 0.73; mOS: not reached vs 12.0 mo, HR 0.68, for lurbi + atezo [n = 35] vs atezo [n = 29], respectively). Pts with high TAM/high T-eff in the atezo arm had shorter OS vs those with low TAM/high T-eff. The addition of lurbi improved OS in the high TAM/high T-eff subgroup vs atezo alone (HR 0.56). SLFN11 expression was high at baseline across subtypes and had no predictive value for lurbi + atezo clinical benefit. **Conclusions:** The prevalence of the 4 SCLC subtypes and the TAM/T-eff pre-Tx data for IMforte are consistent with findings from IMpower133. PFS and OS were longer for lurbi + atezo vs atezo irrespective of molecular subset, though numerical trends suggest that lurbi may overcome TAM-mediated resistance to atezo. Clinical trial information: NCT05091567. Research Sponsor: IMforte is sponsored by F. Hoffmann-La Roche Ltd. and co-funded by Jazz Pharmaceuticals. Third-party medical writing assistance was provided by Rachel Dobb, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

8015 **Rapid Oral Abstract Session**

Impact of neoadjuvant durvalumab (D) on tumor microenvironment (TME) features and their association with event-free survival (EFS) in patients with resectable NSCLC (R-NSCLC) from the phase 3 AEGEAN trial. First Author: John V. Heymach, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: In AEGEAN, perioperative D + neoadj CT improved EFS and pathological complete response vs neoadj CT alone in pts with R-NSCLC. Here, we report exploratory transcriptomic analyses of the TME in tumor samples collected at baseline (BL) and surgery (Sx) to investigate the impact of neoadj D on TME features and their association with EFS. **Methods:** AEGEAN is a double-blind PBO-controlled study (NCT03800134). Adults with Tx-naïve R-NSCLC (stage II–IIIB[N2]) and ECOG PS 0/1 were randomized 1:1 to neoadj platinum-based CT + D or PBO IV (Q3W, 4 cycles) before Sx followed by D or PBO IV (Q4W, 12 cycles) after Sx. EFS was evaluated by BICR (RECIST v1.1) in the modified ITT (mITT) population, which excluded pts with known *EGFR*/*ALK* aberrations. Total RNA was extracted from BL and Sx tumor samples and sequenced (Illumina NovaSeq X Plus). Unsupervised hierarchical clustering of samples was conducted based on previously reported gene signatures reflective of tumor and TME components. **Results:** Transcriptomic data were available from 366 samples in 292 mITT pts across both arms (at BL, 257 pts; at Sx, 109 pts) whose characteristics and outcomes were broadly representative of the mITT population (74 pts with paired samples). At BL, 3 distinct phenotypic clusters (C) based on TME features were identified: an immune desert (C1, 24.9% of pts), characterized by a predominance of proliferating tumor cells; immune suppressed (C2, 39.3%), by elevated levels of suppressive myeloid cells, angiogenesis, and fibroblasts; and immune activated (C3, 35.8%), by high levels of effector T cells. A higher proportion of pts with squamous vs non-squamous tumors had phenotype C1 (37.5% vs 13.9%, respectively) while a lower proportion had C3 (22.5% vs 47.4%). The addition of perioperative D improved EFS across all BL C (C1: HR, 0.43; 95% CI, 0.19–0.94; C2: HR, 0.90; 95% CI, 0.50–1.63; C3: HR, 0.41; 95% CI, 0.20–0.81), with least improvement in C2. The same clusters were detected at Sx (C1, 32.1%; C2, 33.9%; C3, 33.9%) and pts with C1 tumors had the highest risk of progression; 36-month EFS rates (95% CI) were 27.8% (12.1–46.0), 55.7% (33.7–73.0), and 77.2% (59.3–88.0) for C1, C2, and C3, respectively. Neoadj D was associated with higher proportions of pts with C2 and C3 phenotypes at Sx, such that the proportion with poor prognosis C1 tumors at Sx was 17.9% vs 47.2% in the D vs PBO arms, respectively. Among pts with C3 tumors at Sx, EFS benefit in the D vs PBO arm was striking (HR, 0.16; 95% CI, 0.03–0.79). **Conclusions:** The TME before and after neoadj Tx impacts EFS in pts with R-NSCLC, with an immune suppressed phenotype associated with reduced perioperative D benefit. The TME differs between squamous and non-squamous tumors and is influenced by neoadj D, which may promote an immune-activated phenotype associated with prolonged EFS benefit with perioperative D. Clinical trial information: NCT03800134. Research Sponsor: AstraZeneca.

8016 **Rapid Oral Abstract Session**

Tumor-naïve multimodal cfDNA MRD assay to predict recurrence in a prospective cohort of patients undergoing curative-intent lung cancer resection. First Author: Di Lu, Department of Thoracic Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China

Background: Tumor-informed circulating tumor DNA (ctDNA) assays can achieve high sensitivity for minimal residual disease (MRD) detection after lung cancer resection but require tumor tissue and individualized assay design, limiting scalability and timeliness in routine practice. Tumor-naïve MRD approaches offer a practical alternative for postoperative surveillance; however, their sensitivity remains constrained. Integrating complementary cfDNA features beyond somatic mutations may enhance tumor-naïve MRD detection and postoperative risk stratification. **Methods:** A prospective cohort of 212 patients with resectable stage I–IV lung cancer, predominantly consisting of stage I disease (146 of 212), was enrolled. Postoperative plasma samples were collected at a landmark timepoint (~1 week after surgery) and longitudinally every 3–6 months for up to 3 years. MRD was assessed using ShieldingUltra, a tumor-naïve multimodal cfDNA assay integrating somatic mutations, copy number variations (CNVs), and fragmentomic features based on ultra-deep UMI-based sequencing of an integrated panel covering >2000 cancer-related genes. MRD positivity was determined from integrated multimodal cfDNA signals. Survival outcomes were evaluated using Kaplan–Meier analysis and Cox proportional hazards models, with subgroup analyses by disease stage, histology, and postoperative adjuvant therapy. **Results:** At the postsurgical landmark timepoint, MRD positivity was strongly associated with an increased risk of recurrence (hazard ratio [HR], 9.72; log-rank $p=2.06\times10^{-8}$). Longitudinal MRD monitoring further improved risk stratification, with MRD-positive patients exhibiting a markedly higher recurrence risk (HR, 16.64; log-rank $p=1.66\times10^{-9}$) while maintaining high specificity (~90%). Among the 27 patients who developed radiographically confirmed recurrence, MRD was detected prior to imaging in the majority of cases (21 of 27), providing a median lead time of 264 days. The prognostic value of MRD status was consistently observed across disease stages, histologic subtypes, and postoperative adjuvant treatment strategies, with particularly robust prognostic discrimination observed in patients with stage I disease. Multivariable analyses confirmed MRD positivity as an independent predictor of recurrence in both landmark and longitudinal settings. **Conclusions:** Tumor-naïve multimodal MRD assessment integrating mutation, CNV, and fragmentomic cfDNA features enables sensitive and clinically informative detection of residual disease after lung cancer surgery. Early and longitudinal MRD monitoring provides robust prognostic stratification and meaningful lead time over imaging, supporting its clinical utility for postoperative surveillance in resectable lung cancer. Research Sponsor: None.

8017 **Rapid Oral Abstract Session**

Clinical validity of ultrasensitive single-digit parts per million ctDNA detection in non–small cell lung cancer. First Author: James R.M. Black, Francis Crick Institute, London, United Kingdom, London, United Kingdom

Background: Circulating tumor DNA (ctDNA) is a promising biomarker for detecting molecular residual disease (MRD) and predicting recurrence after curative treatment in non-small cell lung cancer (NSCLC). Ultrasensitive personalized assays have demonstrated clinical validity at detection thresholds of ~80-100 parts per million (PPM). As this assay can detect ctDNA at concentrations an order of magnitude lower (below 10 PPM), we extend these analyses to explore the clinical outcomes of patients with single-digit PPM ctDNA. In the future, this may guide adjuvant treatment decision-making. **Methods:** We analyzed longitudinal plasma samples from 431 patients with stage IA–IIIB NSCLC enrolled in the TRACERx study and treated with upfront surgery. We achieved ultrasensitive MRD testing with ctDNA limits of detection as low as 1-3 PPM across 2994 plasma samples using NeXT Personal, a personalized liquid biopsy assay which tracks up to ~1,800 patient-specific somatic variants. Plasma samples were classified as preoperative, postoperative landmark (10–120 days), or longitudinal follow-up. Associations with recurrence-free survival (RFS) and overall survival (OS) were assessed. **Results:** Preoperative ctDNA detection below 10 PPM was associated with inferior recurrence-free survival (RFS) and overall survival (OS) compared to undetectable ctDNA in individuals with lung adenocarcinoma (<10 PPM vs. undetected: HR: 3.25, 95% CI 1.52-6.94, p = 0.0024 and HR: 3.49, 95% CI 1.24-9.81, p = 0.018 for RFS and OS). Postoperative ctDNA was detected in 21% of patients. Detection below 10 PPM occurred in 16.7%, 15.5%, and 11.5% of stage I, II, and III patients, respectively. ctDNA detection preceded imaging-confirmed recurrence in 120 individuals. In postoperative landmark plasma samples, 18% of ctDNA detections occurred below 10 PPM and were associated with increased risk for recurrence and death versus undetectable ctDNA (RFS: HR 3.49, 95% CI 1.70–7.17, p=0.00067; OS: HR 2.58, 95% CI 1.09–6.14, p=0.032). Within ctDNA-positive patients, <10 PPM was associated with improved outcomes compared with ≥10 PPM (HR: 0.38, 95% CI 0.19-0.78, p = 0.0086, HR: 0.37, 95% CI 0.16-0.86, p = 0.021). **Conclusions:** Sub-10 PPM ctDNA detection identifies a clinically high-risk subgroup of early-stage NSCLC patients. Notably, this included stage I patients who would not typically be classified as high-risk or considered for adjuvant therapy; ctDNA positivity in this group therefore reveals high-risk disease that would otherwise go unrecognized. Reliable detection of ctDNA at sub-10 PPM levels may refine post-surgical risk stratification beyond conventional staging and imaging, enabling earlier identification of molecular relapse and potentially guiding treatment escalation in future practice. Research Sponsor: None.

8018 **Poster Session**

Lung cancer stage prediction using longitudinal CT imaging compared with single-timepoint assessment. First Author: Amrik Majumdar, Westfield High School, Chantilly, VA

Background: Lung cancer staging guides treatment decisions but is based on single-timepoint imaging, treating tumors as static entities. Screening programs routinely acquire serial low-dose CTs (LD-CTs), yet this longitudinal information is not used for staging. We hypothesized that modelling temporal change would capture tumor evolutionary dynamics predictive of stage beyond volume change alone, reframing staging as a process rather than a snapshot. **Methods:** We identified 236 NLST participants with biopsy-confirmed lung cancer and three pre-treatment LD-CTs (median interval 12 months). Reference staging used AJCC 7th edition criteria, pathologic where available and otherwise clinical, for overall stage (I–IV) and T and N components. We developed a longitudinal 3D residual network with dual attention and interval-aware temporal encoding, trained using nested five-fold cross-validation. Volume doubling time (VDT) was computed to assess whether temporal features provided information beyond growth rate. The primary endpoint was macro-AUC for overall stage. Secondary endpoints included balanced accuracy, weighted κ, calibration (ECE, Brier score), and decision-curve net benefit. External validation is ongoing in NLSTseg (n = 605) and NSCLC Radiogenomics (n = 211). **Results:** The longitudinal model outperformed a single-timepoint baseline, achieving a macro-AUC of 0.86 versus 0.82, Δ +0.04, $p < 0.05$. Improvements were greatest for N-stage (Δ +0.13) and T-stage (Δ +0.11). Compared with a recent foundation model approach (DINOv2 + ABMIL), the model showed superior N-stage discrimination (AUC 0.86 vs 0.70). Temporal features remained independently predictive after adjustment for VDT, indicating capture of biological signal beyond growth rate. Attention maps consistently highlighted lesion margins and peritumoral regions across timepoints, consistent with invasive behavior. Performance was stable across sex, age, and smoking subgroups, and inference was feasible on standard CPUs. **Conclusions:** Modelling longitudinal change across serial LD-CTs captures tumor evolutionary dynamics that predict lung cancer stage independently of growth rate. This reframes staging as a dynamic, evolution-aware process and provides a practical route for integrating artificial intelligence into screening workflows where serial imaging is already available. External validation is underway. Research Sponsor: None.

8019 **Poster Session**

Rapid multi-task intraoperative diagnosis of lung cancer via deep neural network-driven label-free femtosecond laser imaging (FLI). First Author: Yin Li, School of Medicine, Shanghai Jiao Tong University, Shanghai Chest Hospital, Shanghai, China

Background: Rapid and accurate intraoperative pathological diagnosis is critical for guiding surgical margins and preserving lung function during lung cancer surgery. Current frozen-section (FS) analysis is time-consuming and prone to artifacts. Femtosecond label-free imaging (FLI) enables high-resolution, non-destructive tissue visualization without staining or freezing, offering a promising platform for real-time assessment. **Methods:** We developed FastLung, an integrated FLI+AI platform for multi-task diagnosis. Fresh, unprocessed tissue samples (326 paired tumor-normal specimens) from surgical resections were imaged using multimodal FLI. FastLung employs a self-supervised deep learning model trained on ~4 million image patches, with formalin-fixed paraffin-embedded (FFPE) histopathology as ground truth. The system provides malignancy probability maps and categorical outputs within 5 minutes. **Results:** FastLung achieved high diagnostic performance across key intraoperative tasks: benign vs. malignant (AUC = 0.9854 $\pm$ 0.01), invasive vs. minimally invasive adenocarcinoma (AUC = 0.9573 $\pm$ 0.03), and adenocarcinoma vs. squamous cell carcinoma (AUC = 0.9892 $\pm$ 0.009). It significantly reduced diagnostic turnaround time (5–10 min vs. 20–30 min for FS, 60–80% faster) while maintaining accuracy comparable to or exceeding FS. In core needle biopsies (n = 94), accuracy reached 95.8%. The platform also demonstrated consistent performance across operators and time, supporting reliable integration into surgical workflow. **Conclusions:** FastLung combines label-free FLI with deep learning to deliver rapid, accurate, and reproducible intraoperative diagnosis of lung cancer, outperforming frozen sections in speed and multidimensional assessment. Its robust performance in both resection and biopsy specimens highlights its potential to improve surgical decision-making and extend toward pan-cancer diagnostic applications. Research Sponsor: Shanghai Key Laboratory of Thoracic Tumor Biotherapy; 2025SZ1002; Science and Technology Commission of Shanghai Municipality (STCSM); 24JS2840300.

8020 **Poster Session**

Noninvasive imaging biomarkers for survival risk stratification with tarlatamab in ES-SCLC. First Author: Mohammadhadi Khorrami, Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA

Background: Subsequent treatment for extensive-stage small cell lung cancer (ES-SCLC) following platinum-etoposide chemotherapy +/- an immune checkpoint inhibitor was historically limited to alternative forms of chemotherapy with relatively poor clinical outcomes. Bispecific delta-like ligand 3 (DLL3)-targeting T-cell engagers, such as tarlatamab, have since demonstrated clinically meaningful activity with notable improvements in survival. Although there was a modest improvement in median progression-free survival (PFS) with tarlatamab in the phase 3 DeLLphi-304 trial, 20% of patients remained free from disease progression at 12 months. Unfortunately, conventional clinical factors and early radiographic responses are unable to distinguish transient from sustained benefit; thus underlying the need for validated biomarkers to identify patients likely to derive a durable response from tarlatamab. **Methods:** This study sought to evaluate whether radiomic texture and quantitative vessel tortuosity (QVT) metrics derived from baseline CT imaging are associated with PFS and overall survival (OS) in patients with ES-SCLC receiving tarlatamab.50 patients from Cleveland Clinic with ES-SCLC who received tarlatamab after front-line chemoimmunotherapy were included in this study. Radiomic texture and QVT features characterizing intratumoral heterogeneity and vascular architecture were extracted from CT scans obtained before the first dose of tarlatamab (median scan-to-treatment interval: 33.5 days). A least absolute shrinkage and selection operator Cox regression model with cross-validation identified prognostic features for PFS and OS. A radiomic risk score (RRS) was computed as a weighted linear combination of selected features, and patients were stratified into high- and low-risk groups using the median RRS. Cox regression and Kaplan–Meier analyses with log-rank testing evaluated associations with PFS and OS. **Results:** On univariable analysis, RRS was significantly associated with PFS (HR = 2.3, 95% CI 1.36–3.94, *P* = 0.0019) and OS (HR = 3.9, 95% CI 1.67–9.1, *P* = 0.0016). Kaplan–Meier analyses demonstrated significantly shorter PFS and OS in the high-risk group. In multivariable models adjusting for age, sex, race, smoking history, COPD, and prior lines of therapy, RRS remained the only factor independently associated with PFS (HR = 2.1, 95% CI 1.16–4.0, *P* = 0.014) and OS (HR = 5.87, 95% CI 2.0–17.0, *P* = 0.001). **Conclusions:** Baseline CT-derived radiomic and vascular features represent noninvasive biomarkers for predicting PFS and OS in patients with ES-SCLC receiving tarlatamab. Further validation of these novel features can improve patient selection, treatment sequencing, and optimized utilization of DLL3-targeted therapy in this unique cancer population with otherwise limited treatment options. Research Sponsor: National Cancer Institute; R01CA26820701A1; National Cancer Institute; R01CA249992-01A1; National Cancer Institute; 1U54CA254566-01; National Cancer Institute; 1U01CA239055-01; National Cancer Institute; 1U01CA248226-01; Lung Cancer research Program Career Development Award; HT9425-24-1-0095; Lung Cancer Research Program; W81XWH-18-1-0440.

8021 **Poster Session**

Development and validation of an artificial intelligence–based deep learning imaging model for early lung cancer detection: DAVINCI, a retrospective study of 8,962 patients. First Author: Syeda Hafsa Noor-AIN, Ayaan Institute of Medical Sciences, Srinagar, India

Background: Lung cancer is the leading cause of cancer-related mortality worldwide, primarily due to delayed diagnosis and diagnostic variability in histopathological assessment. Advances in deep learning applied to medical imaging offer the potential to enhance early detection accuracy, reduce interobserver variability, and improve diagnostic efficiency in lung cancer. **Methods:** In this retrospective study, we evaluated DAVINCI using a dataset of 8,962 patients with confirmed lung malignancies. The model utilizes a specialized architecture combining convolutional neural networks (CNNs) and residual blocks to optimize feature extraction from high-resolution pathological slides. Performance was measured via detection accuracy, recall, specificity, and Area Under the Curve (AUC). **Results:** A total of 8,962 patients were included in the analysis. The DAVINCI model correctly identified lung cancer in 93% of cases, corresponding to 8,334 of 8,962 patients, with a 95% confidence interval (CI) of 86%–100% (7,707–8,962 patients). Model specificity was also 93% (95% CI, 86%–100%), indicating a high true-negative rate. Sensitivity (recall) was 87%, with correct detection in 7,797 patients and a 95% CI of 80%–94% (7,170–8,425 patients). The model demonstrated strong discriminatory performance, achieving an area under the curve (AUC) of 0.91 (95% CI, 0.84–0.98). In comparison, active pathologists achieved a mean diagnostic accuracy of 83%, corresponding to 7,438 of 8,962 cases, with a 95% CI of 76%–90% (6,811–8,066 cases). In terms of efficiency, DAVINCI processed whole-slide images in 16–19 seconds, substantially faster than conventional manual review, which typically requires several minutes per slide. **Conclusions:** DAVINCI demonstrated superior accuracy, robust discriminatory performance, and markedly faster processing compared with human review, supporting its potential role in early lung cancer detection at scale. Research Sponsor: None.

8022 **Poster Session**

Cross-stage validation of a multimodal machine learning model to predict pathological complete response to neoadjuvant chemotherapy or chemoimmunotherapy in resectable stage III non–small cell lung cancer. First Author: Loïc Ferrer, SOPHiA GENETICS, Pessac, France

Background: Pathological complete response (pCR) after neoadjuvant chemoimmunotherapy is associated with improved outcomes in resectable non–small cell lung cancer (NSCLC), yet reliable tools to predict treatment response before surgery are lacking. Machine learning models have shown promise in advanced disease, but their ability to generalize across disease stages remains uncertain. We evaluated the performance of a machine learning model developed in stage IV NSCLC when applied to a cohort of patients with surgically resectable stage III disease treated with neoadjuvant chemotherapy or chemoimmunotherapy. **Methods:** The DEEP-Lung-IV study (NCT04994795) developed and validated machine learning models for personalized risk prediction based on multimodal data in patients with stage IV NSCLC treated with first-line pembrolizumab and/or chemotherapy. The models incorporated multimodal clinical routine data such as clinical, biological and CT-scan images. For the present study, the trained pre-treatment model was applied without retraining to patients enrolled in the NADIM trials (NCT03081689, NCT03081689) who received neoadjuvant chemotherapy alone (CTx), or in combination with nivolumab (Nivo+CTx), followed by surgery. Model performance was assessed using the area under the ROC curve (AUC) by considering only the last chest CT-scan image before surgery, or by combining it with other multimodal data. **Results:** A total of 103 patients with available clinical, biological, imaging data and who experienced surgery was considered for validation analysis (N = 88 patients with Nivo+CTx, N = 15 patients with CTx). When applied to the stage III NADIM cohort, the stage IV–derived model demonstrated strong predictive performance for pCR, with an AUC of 0.68 (95% CI, 0.57–0.78) in all patients using the CT-scan image only, rising to 0.76 (95% CI, 0.67–0.84) when additionaly leveraging on clinical and biological data. Performance was consistent across clinically relevant subgroups, especially in the patients treated with Nivo+CTx, with AUC estimates from 0.65 (95% CI, 0.54–0.76) using CT-scan image alone to 0.72 (95% CI, 0.61–0.82) when combined with the other multimodal data. The model was capable of handling missing predictor values, and preserved predictive value despite differences in disease stage and treatment intent. **Conclusions:** A machine learning model trained in advanced-stage NSCLC accurately predicted pathological response to neoadjuvant chemo- or chemoimmuno-therapy in a resectable stage III cohort, supporting the biological continuity of treatment response across disease stages. This cross-stage generalizability highlights the potential of machine learning–based tools to guide treatment personalization in earlier-stage NSCLC and warrants prospective validation. Research Sponsor: None.

8023 **Poster Session**

Multimodal intraoperative diagnosis and grading system integrating macroscopic images, CT imaging, and textual reports for adenocarcinoma (MaCTex) in early-stage LUAD: A multicentric diagnostic study. First Author: Yingwei Lu, Guangdong Cardiovascular Institute, Guangzhou, Guangdong, China

Background: Intraoperative frozen section (IFS) analysis is pivotal for guiding surgical strategies in stage IA lung adenocarcinoma (LUAD), specifically the extent of resection and lymph node dissection. However, IFS is constrained by sampling errors and prolonged turnaround times, which can compromise diagnostic precision and surgical efficiency. To address these unmet needs, we developed and validated a multimodal artificial intelligence framework. By integrating preoperative chest CT imaging, unstructured radiology text reports, and intraoperative macroscopic images of resected specimens, this system aims to deliver rapid, precise intraoperative predictions, thereby mitigating reliance on traditional IFS and optimizing surgical decision-making. **Methods:** This retrospective, multicenter study enrolled patients with stage IA LUAD who underwent complete resection between June 2020 and September 2023 across three institutions (Guangdong Provincial People's Hospital, Affiliated Hospital of Guangdong Medical University, and Meizhou People's Hospital). We collected preoperative thin-slice chest CT scans and unstructured text reports within three months prior to surgery. Intraoperative macroscopic images of resected specimens were captured via smartphone under natural lighting. We developed MaCTex, a multimodal AI model, to predict the IASLC grading system (PIL, MIA, IAC G1, G2, G3). Performance was evaluated against the gold standard of postoperative paraffin pathology. The study is registered with the Chinese Clinical Trial Registry (ChiCTR2500111776). **Results:** The cohort included 1,516 patients (yielding 1,638 pulmonary nodules) with matched preoperative CT imagings/reports and 2,344 intraoperative macroscopic images. We developed four distinct models for evaluation: a CT-only model, a CT-Text model, a Gross Image model, and the comprehensive MaCTex framework. The CT-Text model achieved a diagnostic AUC of 0.857, outperforming the unimodal CT model with an AUC of 0.837. The Gross Image model achieved a performance of 0.82 in five-class prediction. Notably, the integration of unstructured CT text reports significantly enhanced model efficacy, underscoring the critical value of radiologist expertise in refining intraoperative diagnostics. **Conclusions:** We established a robust multimodal AI framework integrating radiographic data, clinical text, and macroscopic pathology that enables efficient and accurate intraoperative prediction of IASLC grading in lung adenocarcinoma. By circumventing the sampling limitations of traditional methods, MaCTex serves as a promising alternative or adjunct to intraoperative frozen sections, providing thoracic surgeons with real-time, precise decision support to optimize surgical management. Research Sponsor: None.

8024 **Poster Session**

A deep learning model for intraoperative diagnosis of lung adenocarcinoma using frozen section whole-slide images (CryoPath): A multicentric diagnostic study. First Author: Jinqing Li, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong, China

Background: Intraoperative frozen section (FS) analysis is critical for guiding surgical decision-making in lung cancer. However, its diagnostic accuracy can be limited by time constraints, sampling issues, and inter-pathologist variability. Deep learning-based analysis of whole-slide images (WSIs) offers a new paradigm for real-time, objective intraoperative diagnosis. **Methods:** We developed and validated an artificial intelligence system, CryoPath, for the intraoperative diagnosis of lung adenocarcinoma (LUAD) from FS-WSIs. The system was trained and tested using a large, multicentric, retrospectively collected cohort comprising 3000 LUAD FS-WSI cases from seven medical centers in China. The model architecture is based on attention-challenge multiple instance learning framework with vision transformer for feature extraction. CryoPath was designed for end-to-end prediction of diagnostic subtypes (pre-invasive lesions, minimally invasive adenocarcinoma and invasive adenocarcinoma) and key pathological features such as extent of invasion and lymphovascular invasion from FS-WSIs. **Results:** The study included 1,042 patients, yielding 1,139 WSI with early-stage lung adenocarcinoma from multiple centers, which comprised a total of 637 WSIs with IAC, 402 with MIA, and 100 with PIL. The CryoPath model achieved an AUC of 0.931 for discriminating IAC from PIL/MIA, which achieved a sensitivity of 0.87 and a specificity of 0.85. In clinical decision simulation, the model-assisted strategy increased surgical decision accuracy from 75% to 88%. 15 WSIs classified as PIL on FS but upgraded to IAC on permanent sections by pathologist were corrected by CryoPath and Attention heatmaps generated by the model highlighted histologically relevant regions. CryoPath model achieved an AUC of 0.92 (95% CI: 0.90–0.94) for discriminating IAC from PIL/MIA on the test set. . In clinical decision simulation, the model-assisted strategy increased surgical decision accuracy from 75% to 88. Attention heatmaps generated by the model highlighted histologically relevant regions. **Conclusions:** The CryoPath system demonstrates for the first time that large-scale deep learning-based analysis of FS-WSIs can achieve high-accuracy, real-time, and interpretable intraoperative diagnosis for LUAD. This system has the potential to serve as a powerful adjunct tool for pathologists and surgeons, potentially reducing diagnostic variability, shortening intraoperative wait times, and providing an objective foundation for precise surgical strategy. A prospective, multi-center clinical trial is being planned to further evaluate its clinical utility. Research Sponsor: None.

8025 **Poster Session**

Intratumoral heterogeneity of *MTAP* loss by immunohistochemistry in non–small cell lung cancer: Implications for clinical outcomes. First Author: Tsuyoshi Hirata, National Cancer Center Hospital East, Kashiwa, Japan

Background: MTAP-cooperative PRMT5 inhibitors are under development for MTAP-loss solid tumors including non-small cell lung cancer (NSCLC). However, the intratumoral heterogeneity of MTAP loss in NSCLC and its potential implications for clinical outcomes remain incompletely understood. **Methods:** Tumor specimens from patients with NSCLC who underwent surgical resection between January 2019 and October 2019 in our institution were retrospectively collected. MTAP expression status was evaluated in surgically resected specimens using MTAP immunohistochemistry (IHC) 2G5 and categorized as retained (100% positive tumor cells), partial loss (1–99%), or complete loss (0%). MTAP status was confirmed by fluorescence in situ hybridization (FISH). Clinicopathological characteristics and survival outcomes were analyzed according to MTAP expression status. **Results:** MTAP expression status was successfully analyzed in 196 specimens from primary lesion of patients with NSCLC. MTAP expression status was classified as retained in 131 specimens (67%), partial loss in 43 (22%), and complete loss in 22 (11%). Of 14 specimens of which MTAP status was evaluated by FISH, the MTAP status by IHC and FISH were completely consistent. Compared to the patients with retained, the patients with complete loss showed no significant differences in the clinicopathological characteristics, but the patients with partial loss were significantly more frequently associated with adenocarcinoma histology (93% vs 74%, $P = 0.02$) and never-smoker status (51% vs 22%, $P < 0.001$). Among specimens diagnosed as adenocarcinoma, those with partial loss showed a significantly higher frequency of lepidic and papillary predominant patterns compared to those with complete loss (83% vs 50%, $P = 0.02$). Among specimens of which *EGFR* mutation status was analyzed, the frequency of EGFR mutations was significantly higher in specimens with MTAP complete/partial loss compared to MTAP retained (59% vs 30%, $P = 0.03$). There were no significant differences in the recurrence-free survival (RFS) and the overall survival (OS) among the patients with complete loss, partial loss and retained (5-year RFS rates: 82%, 83% vs 76%, 5-year OS rates: 90%, 81% vs 77%). MTAP expression status of corresponding metastatic lymph node (mLN) was evaluated in 6 patients with MTAP partial loss. MTAP expression status for corresponding mLN were consistent with predominant MTAP expression status for primary lesion in 4 patients (67%). **Conclusions:** Intratumoral heterogeneity of MTAP expression was observed in 22% of NSCLC, particularly with adenocarcinoma histology and in never-smokers. Intratumoral heterogeneity of MTAP loss may contribute to inaccurate assessment of MTAP status on small biopsy samples. MTAP expression status was not associated with the prognosis in patients with surgically resected NSCLC. Research Sponsor: None.

8026 **Poster Session**

Cancer-related overall survival for patients on durvalumab for stage III unresectable non–small cell lung cancer with PD-L1 positive and negative tumors. First Author: Zohra Nooruddin, University of Texas Science Center at San Antonio, San Antonio, TX

Background: Durvalumab improves overall survival (OS) and progression free survival (PFS) when used as consolidation therapy for patients with stage III unresectable non-small cell lung cancer (UR-NSCLC) following chemoradiotherapy (CRT). However, it is uncertain if similar benefits are achieved for patients with PD-L1 positive (1% or greater) and negative (<1%) tumors. We previously found no difference in OS, but no study has yet compared cancer-related overall survival (OS). **Methods:** Patients with stage III UR-NSCLC on durvalumab following CRT, at any Veterans Health Administration (VHA) facility, from 1/1/17 to 6/30/20, were included. Patients were followed from durvalumab initiation through the earliest of their last VHA visit, loss to follow up, death, or end of study (6/30/25). Electronic health record data were retrospectively collected to determine durvalumab treatment course, OS, and cancer-related OS—as determined by review of each patient's chart and death certificate. Kaplan-Meier and Cox regression methods were used to compare cancer-related OS. **Results:** Of the 340 eligible patients, 221 (65%) had PD-L1 positive and 119 (35%) had PD-L1 negative tumors. Groups were similar in age, sex assigned at birth, White race, smoking status, marital status, Charlson score, ECOG 1+ status (78% overall), histology, stage, EGFR, and RAS mutations. Patients with PD-L1 positive and negative tumors had similar median (interquartile range [IQR]) number of durvalumab doses (15 [6-24] vs 13 [5-24], p=0.55), months of durvalumab (8 [3-12] vs 6 [2-12]), and months of follow-up (33 [12-69] vs 28 [11-63], p=0.22). OS was similar for patients with PD-L1 positive and negative tumors in a multivariate model accounting for ECOG 1+ status (HR 0.93, 95% CI 0.70-1.24). Likewise, cancer-related OS was similar in the multivariate model (HR 0.87, 95% CI 0.63-1.21). Median OS was 33.3 months (95% CI 29.8-47.3) for patients with PD-L1 positive tumors and 28.5 months (95% CI 21.6-39.7) for patients with PD-L1 negative tumors. Likewise, median cancer-related OS was 20.4 months (95% CI 16.0-25.4) for patients with PD-L1 positive tumors and 20.6 months (95% CI 15.4-28.5) for patients with PD-L1 negative tumors. The table depicts common causes of death. **Conclusions:** In this real-world study of VHA patients on durvalumab for stage III UR-NSCLC, OS and cancer-related OS were similar for those with PD-L1 positive and negative tumors. Research Sponsor: AstraZeneca Pharmaceuticals LP.

Cause of death.

Cause of death	PDL1+, n=221	PDL1-, n=119	P-value
Disease progression	84%	77%	0.19
Bleeding event	4%	3%	0.75
Cardiac event	14%	14%	1.00
Infection/sepsis	19%	6%	0.01
Intracranial embolism/hemorrhage	2%	3%	0.67
Multiorgan failure	1%	2%	0.56
Thromboembolic event	2%	0%	0.30
Unknown	3%	4%	0.73
Other	9%	19%	0.03

8027 **Poster Session**

Chromosomal instability and integrated tumor-margin immune ecosystem remodeling as drivers of progression of pulmonary ground-glass nodules. First Author: Ruoyi Jin, Department of Thoracic Surgery, Peking University People's Hospital, Beijing, China

Background: Precise management of pulmonary ground-glass nodules (GGNs) is hindered by an incomplete understanding of the biological determinants driving the transition from indolence to aggressive progression. **Methods:** In a multicenter longitudinal study of 845 patients, we stratified GGNs into three trajectories via serial CT: Stable, ground glass opacity (GGO)-predominant progression, and solid-predominant progression. Integrative profiling was performed using WES, WGS, bulk RNA-seq, Visium HD, CosMx SMI, and imaging mass cytometry. We developed a deep learning model to predict solid-predominant progression using baseline radiographic features. **Results:** During a median follow-up of 55.8 months, our analysis indicated GGNs progression was driven predominantly by chromosomal instability rather than distinct point mutational profiles. Specifically, progressive GGNs harbored catastrophic structural variations, including chromothripsis, kataegis, and extrachromosomal DNA which were absent in stable lesions. Spatially, the immune microenvironments diverged sharply. While stable GGNs were quiescent, GGO-predominant growth lesions were significantly enriched with antigen-presenting macrophages (p = 0.00054), which facilitated the spatial aggregation of activated lymphocytes and promoted the formation of early tertiary lymphoid structure (TLS)-like niches through CCL19-CCR7 signaling. Conversely, in solid-predominant aggressive progression nodules, macrophages underwent a phenotypic shift from antigen-presenting toward SPP1+ state, accompanied by a marked reduction in CD74 and HLA-DR expression (p = 0.0019). Within the tumor core, SPP1+ macrophages suppressed T-cell effector function via SPP1-CD44 signaling. At the tumor margin, hypoxia-adapted endothelial cells exhibited significant upregulation of CD274 (PD-L1), contributing to T-cell inhibition, while activated fibroblasts deposited dense collagen matrices formed a physical barrier restricting B-cell infiltration. Together, these mechanisms established a coordinated immunosuppressive niche facilitating tumor growth. Leveraging these biological insights, we developed a deep learning model extracting radiomic features from the baseline CT nodule and an extended 2.5mm perinodular margin. This approach significantly outperformed models using the nodule alone or the nodule plus a 1mm margin ($p < 0.05$), achieving AUCs of 0.89 in the training cohort (n = 471), 0.85 in the internal test cohort (n = 202) and 0.83 in the external cohort (n = 117). **Conclusions:** Distinct radiographic progression trajectories of GGNs are underpinned by divergent chromosomal and spatial immune programs at the tumor core and margin, providing a biological foundation for margin-aware AI strategies to predict aggressive progression and guide optimal surgical intervention. Research Sponsor: None.

8028 **Poster Session**

PSG copy number amplification and association with poor survival in early-stage female lung adenocarcinoma patients. First Author: Jung Hun Oh, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pregnancy-specific glycoproteins (PSGs) are essential for maintaining maternal immune tolerance by modulating innate and adaptive responses to prevent fetal rejection. Given our prior finding that increased PSG expression is associated with worse outcomes for female lung cancer patients, we aimed to investigate whether copy number alterations (CNAs) show the same sex-dependent effect on survival in early-stage disease. **Methods:** We evaluated the sex-specific impact of PSG CNAs across two lung adenocarcinoma (LUAD) cohorts: The Cancer Genome Atlas (TCGA) (n = 503; 269 females, 234 males) and MSK-IMPACT (n = 3,863; 2,450 females, 1,413 males). CNAs were retrieved from cBioPortal for the TCGA cohort and determined via the FACETS algorithm on BAM files for the MSK-IMPACT cohort. Overall survival (OS) differences between patients with and without PSG copy number amplification were analyzed using Kaplan-Meier curves along with log-rank tests. Additionally, we examined the association between tumor stage and the prognostic impact of PSG copy number amplification. **Results:** In the TCGA cohort, female patients with PSG copy number amplification exhibited significantly worse OS compared to those without (HR = 1.96, p = 0.0039), while no significant survival difference was observed in males (HR = 1.37, p = 0.1902). This sex-specific trend was further validated in the MSK-IMPACT cohort, where the association between PSG copy number amplification and poor OS was highly significant in females (HR = 1.46, p = 7.5×10^{-6}) but relatively weaker in males (HR = 1.29, p = 0.0089). Notably, the prognostic impact of PSG copy number amplification was stage-dependent; while no significant survival differences were found for either sex in Stage 4 disease across both cohorts, the effect was highly pronounced in early-stage female patients. In the TCGA cohort, female patients with early-stage disease showed increasingly significant survival disparities between patients with and without PSG copy number amplification as stage decreased (Stage $\leq$ 3: HR = 1.81, p = 0.0182; Stage $\leq$ 2: HR = 2.03, p = 0.0129; Stage 1: HR = 2.51, p = 0.0047), whereas no such associations were found in males. Similarly, in the MSK-IMPACT cohort where tumor stage was dichotomized (Stages 1–3 vs. Stage 4), female patients with Stage $\leq$ 3 disease showed a strong survival difference between patients with and without PSG copy number amplification (HR = 1.86, p = 1.79×10^{-5}), which remained significantly stronger than the association observed in the male patients (HR = 1.49, p = 0.0129). **Conclusions:** Our findings raise the question of the potential role of PSG-mediated immune modulation in promoting tumor progression in early-stage female lung cancer patients, and suggest that there may be value in sex-stratified approaches to clinical risk assessment and in therapeutic targeting. Research Sponsor: Breast Cancer Research Foundation.

8029 **Poster Session**

Breath analysis of volatile organic compounds with mid-infrared laser spectroscopy in a cohort of lung cancer patients and control subjects. First Author: Boshi Duan, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Shenzhen, China

Background: Exhaled volatile organic compounds (VOCs) represent potential non-invasive biomarkers for lung cancer detection. This study assessed a mid-infrared cavity ring-down spectroscopy (CRDS) platform for measuring key breath VOCs in a large clinical cohort including lung cancer patients across stages/histologies, carcinoma in situ, and non-cancer controls. **Methods:** This prospective single-center validation study enrolled 1,041 participants: approximately 500 with pathologically confirmed lung cancer (various stages and histologies), 25 with carcinoma in situ, healthy controls, patients with benign pulmonary diseases, and those with low- and high-risk pulmonary nodules. Breath samples were collected under standardized fasting and mouth-rinsing conditions and analyzed using a self-developed mid-infrared CRDS system targeting isoprene, acetone, and formaldehyde (detection limit $<$ 10 ppb). The primary endpoint was diagnostic accuracy for distinguishing lung cancer (including carcinoma in situ) from healthy controls, measured by area under the receiver operating characteristic curve (AUC). Sample size was powered to detect an AUC difference of $\geq$0.15 from 0.50 (null hypothesis) with $>$ 85% power at α = 0.05. Group comparisons used independent t-tests or Mann-Whitney U tests with Bonferroni correction for multiple testing. Predictive modeling employed logistic regression and machine learning (random forest and XGBoost) with 5-fold cross-validation; feature importance and SHAP values were assessed. Performance metrics included AUC, sensitivity, specificity, and 95% confidence intervals (CI). **Results:** Isoprene exhibited the most consistent group differences across comparisons ($P < 0.001$ in lung cancer vs healthy and carcinoma in situ vs healthy). Random forest and XGBoost models yielded AUC of 0.94 (95% CI, 0.92-0.96) for lung cancer vs healthy controls and 0.97 (95% CI, 0.95-0.99) for carcinoma in situ vs healthy controls. At optimal thresholds, sensitivity and specificity reached 90-96% and 92-95%, respectively, in primary analyses. Subgroup performance remained robust in non-smokers and stage I patients. Decision curve analysis demonstrated net clinical benefit across 1-20% risk thresholds compared with low-dose CT screening strategies. Acetone and formaldehyde provided supplementary contributions in pathological subtype and benign disease distinctions. **Conclusions:** Mid-infrared CRDS-based breath VOC analysis shows feasible diagnostic performance for lung cancer detection, including strong results in carcinoma in situ and early-stage disease, in this large cohort. Multi-center prospective validation is needed to confirm clinical utility and integration into screening strategies. Research Sponsor: None.

8030 **Poster Session**

Management of pulmonary nodules across Latin America: A real-world observational study. First Author: Danilo Lopes, Astrazeneca, São Paulo, Brazil

Background: Lung cancer is the leading cause of cancer-related mortality globally, with lung cancer accounting for 6.8% of all cancer cases in Latin America and the Caribbean. Despite the availability of guidelines, lung cancer early detection and the management of pulmonary nodules across the region are inconsistent, often hindered by limited resources and fragmented health systems. This study aimed to characterize the diagnostic and treatment journey of pulmonary nodules in patients with lung cancer across Latin America. **Methods:** This was a non-interventional observational study that captured retrospective (March 2019 to July 2021) and prospective (July 2021 to March 2023) data across 16 health institutions in Latin America. Participants were followed for at least two years or until treatment initiation or withdrawal. Data were collected from patients' medical records. Patient characteristics and physicians' involvement were summarised descriptively. Median time estimates of receiving diagnostic procedure or examination from nodule identification and estimates on median time of treatment decision from lung cancer diagnosis were analysed descriptively using the Kaplan-Meier (KM) method. **Results:** Among a total of 546 participants (215 prospective; 331 retrospective), 82 were diagnosed with lung cancer during the study period, most commonly with Stage I lung cancer (5.9%). The majority of referrals to dedicated nodule clinics were made by pulmonologists (44.1%) and prompted by incidentally detected pulmonary nodules (83.9%), which were typically solid and ranged from 8mm to 3cm in size (79.5%). The median time to receiving a diagnostic procedure from nodule identification was 10.83 (prospective) and 12.47 (retrospective) months, while the median time to treatment decision post-diagnosis was 1.20 months across both cohorts. Multidisciplinary teams were involved in only 0.3% of diagnostic procedures, but were involved in at least 40% of treatment decisions across different follow-up visits. **Conclusions:** This study reveals substantial delays in diagnostic procedures and limited multidisciplinary team involvement during early patient evaluation phases in Latin America. Compared with international studies, the study population experienced considerably longer delays in receiving diagnostic procedures. These findings underscore the need for structured referral pathways and broader implementation of critical tools across the region. In addition, adherence to established guidelines is critical to improve early detection and treatment outcomes of lung cancer patients. Research Sponsor: AstraZeneca.

8031 **Poster Session**

Prognostic stratification of early-stage NSCLC patients using preoperative circulating tumor DNA (ctDNA). First Author: Zhicheng Huang, Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Curative-intent surgery for early-stage non-small-cell lung cancer (NSCLC) is followed by relapse in approximately 20–30% of patients. We previously reported interim results of the prospective MUSETALK-Lung01 study (multiomics sequencing technique application kick-start), showing that pre-operative, ctDNA positivity predicted increased relapse risk. Here we present the final analysis of the full cohort and incorporate pathological risk factors to conduct a more comprehensive prognostic evaluation for early-stage NSCLC. **Methods:** The MUSETALK-Lung01 study is a prospective, longitudinal, observational study designed to evaluate the clinical utility of a tumor-naïve ctDNA assay in patients with early-stage NSCLC. Cell-free DNA (cfDNA) was extracted, and subjected to CanCatch Surf test as described previously. The assay algorithm reports both the ctDNA detection status (positive/negative) and the estimated ctDNA levels. Longitudinal data, including vital status, treatment, relapse, and survival status, were collected over 5 years. The study was approved by the institutional review board or ethics committee at each site, with all participants providing written informed consent. **Results:** The complete cohort of MUSETALK-Lung01 consisted of 455 early-stage NSCLC patients, among whom the median follow-up time was 63 months, with a 2-year recurrence rate of 7.0% and a presurgical ctDNA positivity rate of 6.4%. To identify clinical and biological factors associated with survival, both univariate and multivariate analyses were performed. Presurgical ctDNA positivity was strongly associated with inferior recurrence outcomes (χ^2 $p < 1 \times 10^{-9}$), indicating that tumor burden can be prognostic beyond clinical stage and pathological conditions. Specifically, among clinical stage I lung adenocarcinoma (LUAD) patients, ctDNA detection demonstrated robust prognostic stratification for recurrence risk (2-year RFS: 60% [95% CI: 40%–91%] vs. 96% [95% CI: 94%–98%]; log-rank $p < 1 \times 10^{-7}$). Similar prognostic value of ctDNA was observed in stage II-IIIA LUAD patients, albeit with reduced discriminative power (log-rank $p < 0.01$). After incorporating pathological information, the performance of prognostic stratification was further improved. **Conclusions:** By evaluating ctDNA abundance, we provide highly sensitive and specific prognostic assessments and risk stratification for early-stage NSCLC patients. The non-invasive, nature of this test enables precision peri-operative management and selection of patients who may benefit from innovative treatments, with the potential to improve survival. Research Sponsor: Burning Rock Biotech.

8032 **Poster Session**

Pseudoprogression after neoadjuvant immunotherapy for resectable NSCLC: Incidence, PET/CT patterns, and differentiation. First Author: Li-Bo Berlin Tang, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: Neoadjuvant immunotherapy combined with chemotherapy is now the standard of care for resectable non-small cell lung cancer (NSCLC). However, evaluating treatment response remains challenging due to the unique response pattern of pseudoprogression associated with immune checkpoint inhibitors (ICIs), which may lead to unnecessary cancellation of curative surgeries. This study aimed to characterize pseudoprogression and investigate strategies for distinguishing pseudoprogression from true tumor progression in the neoadjuvant ICI setting. **Methods:** This retrospective study included 283 patients with resectable NSCLC who underwent neoadjuvant ICI therapy (n=235) or targeted therapy (n=48) between January 2021 and December 2023. PET-CT scans were acquired at baseline and before surgery. Radiological and metabolic responses were evaluated using RECIST 1.1 and EORTC criteria, respectively. Pathological responses were assessed according to IASLC guidelines. Multivariate logistic regression and receiver operating characteristic analyses were performed to identify predictors of pseudoprogression and evaluate diagnostic performance. **Results:** Among 283 patients (ICI 235, TKI 48), 9.2% (26 patients) were classified as having progressive disease (PD) by RECIST 1.1, all in the ICI cohort. According to EORTC on PET-CT, progression increased to 25.1% (71 patients). Despite radiologic progression, all 26 patients underwent R0 resection; pCR and MPR rates were 53.8% and 11.6%. Among patients without radiologic progression, pCR and MPR were 30.0% and 19.1%, with no differences in R0 rate or pathological response (p = 1.00 and 0.06). Among 71 patients with progressive metabolic disease (PMD) on PET/CT, 69 (97.2%) achieved R0 resection; 27 (38.0%) achieved pCR and 12 (16.9%) achieved MPR, with similar outcomes by PMD status (p = 1.00 and 0.53). In both the ICI cohort and overall population, primary tumor progression was associated with lower MPR rates than lymph node or distant progression (16.7%, 61.2%, and 100%; p = 0.001) and worse EFS and OS. In the TKI cohort, imaging-defined progressive or stable disease was associated with lower MPR and worse survival. Pseudoprogression occurred in 7.2% by CT, increasing to 16.2% with PET-CT, predominantly nodal. A $\geq$53.1% reduction in primary-tumor SUVmax identified pseudoprogression (AUC 0.865; sensitivity 73.8%; specificity 88.6%). A multivariable model combining ΔSUVmax, longest diameter change (%), smoking status, and histology showed excellent discrimination (AUC 0.935). **Conclusions:** Pseudoprogression is common in resectable NSCLC treated with neoadjuvant ICI therapy, presenting as nodal or distant lesions without primary tumor progression. A multifactorial model incorporating primary tumor SUVmax changes provides a robust tool for distinguishing pseudoprogression and guiding clinical decision-making. Research Sponsor: None.

8033 **Poster Session**

Class-specific clinical and molecular features of *SMARCA4* alterations in non—small cell lung cancer. First Author: Chihiro Takemura, Department of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan

Background: *SMARCA4* mutations occur in 5–10% of non-small cell lung cancers (NSCLCs) and are associated with poor overall survival, especially class I *SMARCA4* alterations (truncating mutations, fusions, and homozygous deletion), which often result in *SMARCA4* loss. However, the biological and clinical significance of *SMARCA4* alteration classes and their distribution among pan-cancers in Asians remain unclear. **Methods:** We analyzed pan-cancer across solid tumors patients enrolled in Center for Cancer Genomics and Advanced Therapeutics (C-CAT) database (approval number CDU2021-001N) between June 2019 and October 2025 and patients with surgically resected NSCLCs at our hospital between 1999 and 2023 (approval number 2005-109) were performed by whole exome sequencing. Somatic mutations were annotated using Annovar and OncoKB. *SMARCA4* mutations were classified into two groups: class I or class II (missense or other). Copy number alterations were detected using facets and GISTIC2. Transcriptomic differences were assessed using RNA sequencing with DESeq2 and gene set enrichment analysis (GSEA). Tumor immune cell composition was assessed using CIBERSORTx. **Results:** In the C-CAT pan-cancer dataset (N=10,155), *SMARCA4* mutations were frequently identified in NSCLC (NSCLC vs. others; 12.3% vs. 4.0%). In NSCLC, *TP53* was the most frequent co-altered gene in patients with class I and class II mutation (73.0% vs. 63.0%). Other major genes did not show clear class-associated differences. In our NSCLC cohort (N=1,166), the frequency of *SMARCA4* class I and II mutation was 2.3% (all truncating) and 2.3% (all missense), respectively. The class I *SMARCA4* alterations were associated with significantly poorer survival outcomes compared with wild- type tumors (OS: HR = 2.04, 95% CI = 1.24–3.12, p = 0.007; RFS: HR = 2.09, 95% CI = 1.28–3.20, p = 0.005), whereas class II alterations were not significantly different in survival (OS: HR =0.50, 95% CI =0.40-0.61, p =0.17; RFS: HR = 0.46, 95% CI = 0.42–0.76, p =0.12). Regarding transcriptomic analysis and genomic profiling, class I tumors showed activation of *ASCL1*-related transcriptional programs, suppression of squamous/basal lineage differentiation, increased $CD8^+$ T-cell infiltration, and recurrent copy number loss of *SMARCA2* and *CDKN2A/B* compared with wild type tumors. In contrast, class II tumors showed limited transcriptomic divergence from wild-type tumors, downregulating *SPRR2E*, *KRT5*, and *KRT13* without a significant $CD8^+$ T-cell difference. **Conclusions:** In NSCLC, class I *SMARCA4* altered tumors are associated with poor survival outcomes, and an immune-active molecular phenotype with recurrent copy number loss of *SMARCA2* and *CDKN2A/B*, whereas class II tumors lack these features and do not show adverse survival compared to wild-type tumors. This highlights the distinct clinical implications of *SMARCA4* alteration class. Research Sponsor: None.

8034 **Poster Session**

Outcomes of atypical *EGFR* mutations in early-stage *EGFR*-mutated non-small cell lung cancer (NSCLC). First Author: Jacqueline V. Aredo, Stanford Cancer Institute, Stanford, CA

Background: Adjuvant osimertinib (osi) improves survival outcomes in patients (pts) with early-stage *EGFR*-mutated NSCLC harboring the classical *EGFR* exon 19 deletions (ex19del) or L858R mutation after surgery or chemoradiotherapy. Pts with early-stage NSCLC harboring atypical *EGFR* mutations were excluded from the respective clinical trials. Outcomes in this pt population remain unknown. **Methods:** We conducted a multi-institutional retrospective analysis of pts with stage IA-IIIC *EGFR*-mutated NSCLC (2010-2024) who were classified into two groups: those with tumors harboring classical *EGFR* mutations (c-*EGFR*: ex19del or L858R) or atypical *EGFR* mutations (a-*EGFR*: non-ex19del or L858R). Kaplan-Meier analyses compared disease-free survival (DFS), central nervous system (CNS) DFS, and overall survival (OS). Multivariable Cox regression adjusted for disease stage, definitive therapy, and adjuvant therapy. **Results:** Among 417 pts, 293 had tumors harboring c-*EGFR* and 124 had a-*EGFR* mutations. Baseline characteristics were similar between groups (Table). Median follow-up was 4 years. Among pts not treated with adjuvant osi (n = 346), a-*EGFR* was associated with a significantly lower 3-year DFS compared to c-*EGFR* (52.5% vs 71.2%; HR 1.71, 95% CI 1.21-2.42; P = 0.003). Compared to c-*EGFR*, a-*EGFR* had higher rates of recurrence to the ipsilateral lung (24% vs 14%) and bone (12% vs 6%). A-*EGFR* was associated with a significantly lower 3-year CNS DFS (81.3% vs 87.1%; P = 0.002) and 5-year OS (77.7% vs 85.6%; P = 0.007) compared to c-*EGFR*. Among pts with a-*EGFR* mutations, *EGFR* exon 20 insertions (ex20ins) were associated with a significantly reduced 3-year DFS compared to other alterations (35.9% vs 68.2%; HR 2.04, 95% CI 1.10-3.77; P = 0.013), and with a lower 3-year CNS DFS (70.9% vs 92.2%; P = 0.028) and trend towards lower 5-year OS (71.3% vs 84.4%; P = 0.141). Among pts who underwent surgery for stage IB-IIIA NSCLC (n = 209), adjuvant osi improved 3-year DFS among c-*EGFR* (84.2% with osi vs 63.4% without osi) whereas a-*EGFR* had a lower 3-year DFS (36.4%; P $<$ 0.001), which was driven by *EGFR* ex20ins compared to other alterations (19.9% vs 59.2%; P = 0.003). **Conclusions:** Atypical *EGFR* mutations are associated with inferior survival outcomes compared to classical *EGFR* mutations in early-stage NSCLC. *EGFR* ex20ins appear to drive poor outcomes among the atypical *EGFR* mutations. Novel adjuvant therapy strategies are warranted to improve definitive treatment of early-stage atypical *EGFR*-mutated NSCLC. Research Sponsor: None.

	Classical *EGFR*, N=293 (%)	Atypical *EGFR*, N=124 (%)
Ex19del / L858R	46 / 54	-
Ex20ins / G719X / L861Q / Other	-	49 / 26 / 17 / 8
Stage IA / IB / II / III	35 / 23 / 17 / 25	38 / 14 / 23 / 25
Surgery / XRT / CRT	81 / 8 / 8	82 / 8 / 7
Neoadjuvant Chemo / EGFR TKI	4 / 3	7 / 2
Adjuvant Chemo / EGFR TKI / Osi	26 / 25 / 23	26 / 8 / 4
3-year DFS*	71.2	52.5
3-year CNS DFS*	87.1	81.3
5-year OS*	85.6	77.7

*In non-adjuvant osi cohort (n=346). Statistically significant difference.

8035 **Poster Session**

Clinical impact of genomic co-mutation profiles including TP53 in resected early-stage *EGFR*-mutated NSCLC: LC-SCRUM-Advantage. First Author: Kiyotaka Yoh, National Cancer Center Hospital East, Kashiwa, Japan

Background: Adjuvant osimertinib is the standard of care for resected stage IB–IIIA EGFR-mutated non-small cell lung cancer (NSCLC), and its benefit in stage IA2–IA3 disease is being evaluated in ADAURA2. However, the prognostic impact of genomic co-alterations, particularly TP53, in early-stage EGFR-mutated NSCLC remains unclear. This study characterized genomic co-alterations and their association with clinicopathologic features in resected early-stage EGFR-mutated NSCLC. **Methods:** LC-SCRUM-Advantage is a prospective genomic screening program for resected NSCLC. Post-operative tumor specimens were analyzed using the Oncomine Precision Assay to identify co-alterations, including TP53 and other recurrent genes, across major EGFR mutation subtypes. PD-L1 expression was assessed by immunohistochemistry. Clinico-genomic characteristics and survival outcomes were evaluated. **Results:** Among 1052 enrolled patients, 327 had EGFR-mutated adenocarcinoma (19del 42%, L858R 47%, others 11%). Among tumors with common EGFR mutations, single EGFR alterations accounted for 59%, while co-alterations were detected in 41%. Frequent co-alterations included TP53 (19%), CTNNB1 (4%), PIK3CA (4%), additional EGFR mutations (5%), and EGFR amplification (12%). Co-alteration prevalence increased with pathological stage (IA1 25%, IA2–IA3 41%, IB 53%, II 47%, III 46%), with TP53 showing a similar pattern (IA1 8%, IA2–IA3 18%, IB 19%, II 28%, III 27%). PD-L1 positivity also increased progressively with disease stage (I 37%, II 52%, III 73%; p = 0.0002). TP53-mutated tumors showed a significantly higher PD-L1 positivity rate than TP53 wild-type tumors (60% vs. 39%; p = 0.007). Co-alteration frequencies were comparable across EGFR subtypes. With limited follow-up, five recurrences were observed (IB 1, IIA 1, IIIA 2, IVA 1); three involved co-alterations (TP53, EGFR amplification, EGFR E709V). **Conclusions:** Genomic co-alterations, including TP53, were common and increased with pathological stage in early-stage EGFR-mutated NSCLC. Co-altered tumors exhibited features associated with aggressive biology, including higher PD-L1 expression. Early recurrences were frequently observed in patients with co-alterations, underscoring their potential prognostic relevance. These findings highlight substantial molecular heterogeneity within early-stage EGFR-mutated NSCLC and support incorporating co-alteration status into risk stratification and adjuvant treatment planning. Ongoing follow-up from this study will further clarify the prognostic and predictive significance of co-alterations, particularly regarding their implications for adjuvant targeted therapy. Research Sponsor: Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K.

8036 **Poster Session**

Fusion-positive early-stage and locally advanced lung cancers: A real-world analysis of event-free, disease-free, and overall survival. First Author: Sameh Nabeeh Daher, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Fusion-positive lung cancers are a distinct subset of lung cancers. While outcomes in metastatic disease are comprehensively characterized, data on survival and disease recurrence outcomes after definitive therapy in non-metastatic disease remain limited. **Methods:** This was a single institution, retrospective study, including patients (pts) with *ALK/ROS1/RET/NTRK+* early-stage/locally advanced lung cancer pts diagnosed between 2012-2025. The primary endpoint in pts who underwent curative surgery or stereotactic body radiotherapy (SBRT) was disease-free survival (DFS; time from curative therapy to disease recurrence or death). The primary endpoint in pts initially treated with neoadjuvant therapy prior to surgery or definitive chemoradiation was event-free survival (EFS; time from curative therapy to disease progression, recurrence, failure of treatment or death). Overall survival (OS) from the start of curative therapy was analyzed. **Results:** 179 pts (82 *ALK*, 38 *ROS1*, 55 *RET*, 4 *NTRK*) were identified. Median EFS across all pts for *ALK/ROS1/RET/NTRK* was 4.4yrs (95%CI: 2.8, Not Reached (NR)), 3.4yrs (95%CI: 2.0, NR), 7.4yrs (95%CI: 4.6, NR) and 3.0yrs (95%CI: 0.4, NR), respectively. Median OS for *ALK/ROS1/RET/NTRK* pts was: 13.0yrs (95%CI: 12.0, NR), 12.0yrs (95%CI: 11.0, NR), 14.0yrs (95%CI: 12.0, NR) and NR (95%CI: 5.4, NR), respectively. 132/179 (74%) of all pts were treated with surgery (128 pts) or SBRT (4 pts) first. Median EFS for pts treated with neoadjuvant treatment first (N=26) for *ALK* (n=15)/*ROS1* (n=5)/*RET* (n=6) pts was 0.9yrs (95%CI: 0.8, NR), 0.9yrs (95%CI: 0.7, NR) and NR (95%CI: 0.2, NR), respectively. Median EFS for pts treated with chemoradiation first (N=21) for *ALK* (n=7)/*ROS1* (n=5)/*RET* (n=9) pts was NR (95%CI: 0.5, NR), 0.6yrs (95%CI: 0.5, NR) and 1.0yrs (95%CI: 0.8, NR), respectively. Median DFS for pts treated with surgery/SBRT first (N=132) for *ALK* (n=60)/*ROS1* (n=28)/*RET* (n=40)/*NTRK* (n=4) pts was: 5.1yrs (95%CI: 3.8, NR), 5.2yrs (95%CI: 3.2, NR), NR (95%CI: 6.6, NR) and 3.0yrs (95%CI: 0.4, NR), respectively. **Conclusions:** This is the largest series on outcomes in fusion-positive early stage/locally advanced lung cancers treated with definitive therapy. Prolonged EFS, DFS, and OS were observed. Research Sponsor: None.

8037 **Poster Session**

Induction chemoimmunotherapy followed by hypofractionated radiotherapy and consolidation immunotherapy for locally advanced unresectable non–small cell lung cancer: A prospective phase II study. First Author: Xiangzhi Zhu, The Affiliated Cancer Hospital of Nanjing Medical University, Jiangsu Cancer Hospital, Jiangsu Institute of Cancer Research, Nanjing, Jiangsu, China

Background: Concurrent chemoradiotherapy followed by consolidation immunotherapy is the standard treatment for unresectable stage III LA-NSCLC; however, many patients in real-world practice are unable to complete concurrent therapy, and locoregional failure remains common. This phase II study evaluated induction chemoimmunotherapy followed by hypofractionated radiotherapy (hypo-RT) and consolidation immunotherapy to improve feasibility and disease control. **Methods:** Patients with newly diagnosed unresectable stage III NSCLC received 3-4 cycles of immune checkpoint inhibitors combined with platinum-based doublet chemotherapy. Patients without progression or grade ≥2 pneumonitis underwent eligibility assessment for hypo-RT based on anatomical suitability and organ-at-risk constraints. Eligible patients received definitive sequential hypo-RT (48–60 Gy in 12–15 fractions based on tumor regression) and consolidation immunotherapy when appropriate. The primary endpoint was progression-free survival (PFS) with secondary endpoints of safety and overall survival (OS). **Results:** Between October 2022 and October 2025, 132 patients received induction chemoimmunotherapy, and 55 underdoing hypo-RT. Median age was 70 years (range, 47–85), and 42 patients (76.4%) had squamous cell carcinoma. Programmed death-ligand 1 (PD-L1) expression ≥1% was observed in 17 patients (30.9%), with unknown PD-L1 status in 14 patients (25.5%). With a median follow-up of 20.1 (95%CI, 17.3-22.9) months, median PFS and OS were not reached. The 1- and 2-year PFS rates were 88.1% (95% CI, 78.8%–98.5%) and 58.5% (95% CI, 43.6%–77.7%), respectively; the 1- and 2-year OS rates were 100% and 77% (95% CI, 61.5%–93.7%), respectively. Isolated in-field recurrence occurred in 4 patients (7.3%). Pneumonitis was the most common acute nonhematologic toxicity, with grade 3 in 4 patients (7.3%) and grade 4 in 1 patient (1.8%). Grade 3 atelectasis occurred in 4 patients (7.3%), and grade 3 radiation esophagitis in 2 patients (3.6%). No grade 5 toxicities were observed. **Conclusions:** Induction chemoimmunotherapy followed by eligibility-adapted hypofractionated radiotherapy showed promising survival and locoregional control with acceptable toxicity in unresectable locally advanced NSCLC, supporting its feasibility as an alternative strategy for selected patients. Clinical trial information: NCT05784142. Research Sponsor: Research Project of Jiangsu Cancer Hospital (No. ZL202301), Jiangsu Cancer Hospital Yishan Fund (YSZD202405), and Jiangsu Cancer Hospital Yishan Fund (YSPY202403).

8038 **Poster Session**

Analysis of recurrence and risk factors in resectable early-stage adenocarcinoma with uncommon *EGFR* mutations: A comprehensive cohort study in South Korea. First Author: Insu Kim, Dong-A University Hospital, Busan, South Korea

Background: This study aimed to identify clinicopathologic factors associated with recurrence in patients with surgically resected lung adenocarcinoma harboring uncommon EGFR mutations. **Methods:** We conducted a multicenter retrospective cohort study. The study included patients with stage I–III lung adenocarcinoma harboring uncommon EGFR mutations (G719X, S768I, or L861Q) who underwent curative-intent resection between 2010 and 2017 in South Korea. Recurrence-free survival (RFS) and overall survival (OS) were analyzed using Cox proportional hazards models. **Results:** A total of 48 patients were analyzed (stage I: n=33, stage II: n=6, stage III: n=9). The median age was 65 years; 56.3% were female and 66.7% were never-smokers. Mutation distribution was G719X (72.9%), S768I (16.7%), and L861Q (10.4%). Visceral pleural invasion (VPI) and lymphovascular invasion (LVI) were present in 37.5% and 16.7% of cases, respectively. During follow-up, 26 patients (54.2%) experienced recurrence and 21 (43.8%) died. Multivariable analysis identified ECOG performance status ≥1 (HR 4.55, 95% CI 1.226–16.899; P=0.024), stage III vs. I (HR 5.07, 1.181–21.771; P=0.029), and VPI (HR 3.67, 1.030–13.058; P=0.045) as independent predictors of recurrence. EGFR subtype (non-G719X vs. G719X) was not significantly associated with recurrence (P=0.428). **Conclusions:** Patients with surgically resected lung adenocarcinoma harboring uncommon EGFR mutations face a substantial risk of postoperative recurrence. Conventional clinicopathologic factors—particularly ECOG status, advanced stage, and VPI—outperform EGFR subtype as prognostic indicators. These findings support the need for risk-adapted surveillance and prospective evaluation of adjuvant strategies in these high-risk subsets. Research Sponsor: None.

Univariate and multivariate Cox regression analysis for the risk factors associated with recurrence.

Variables	Recurrence rate*	Univariate analysis, HR (95% CI)	*P*-value	Multivariate analysis, HR (95% CI)	*P*-value
ECOG					
0	50.0 (19/38)	-		-	
1≤	70.0 (7/10)	1.64 (0.678-3.955)	0.273	4.55 (1.226-16.899)	**0.024**
EGFR mutation					
G719X	54.3 (19/35)	-		-	
Non-G719X	53.8 (7/13)	0.91 (0.377–2.210)	0.840	0.58 (0.155–2.207)	0.428
Tumor size†					
< 2.0 cm	38.5 (5/13)	-		-	
≥ 2.0 cm	60.0 (21/35)	1.59 (0.599–4.214)	0.353	1.75 (0.434–7.068)	0.431
Clinical stage					
I	48.5 (16/33)	-		-	
II	66.7 (4/6)	1.65 (0.549–4.950)	0.373	1.33 (0.368–4.801)	0.663
III	66.7 (6/9)	2.11 (0.820-5.436)	0.121	5.07 (1.181-21.771)	**0.029**
Lymphovascular invasion					
Absent	52.5(21/40)	-		-	
Present	62.5(5/8)	1.11 (0.420–2.958)	0.827	0.03 (0.001–0.841)	**0.040**
Visceral pleural invasion					
Absent	46.7 (14/30)	-		-	
Present	66.7 (12/18)	1.97 (0.893–4.334)	0.093	3.67 (1.030–13.058)	**0.045**

*Presented as number of recurrences / number of patients (%).
†ROC curve and Youden's index analyses were used to determine the cut-off value of primary tumor size.

8039 **Poster Session**

Socioeconomic focus in neoadjuvant chemoimmunotherapy: An analysis of pathologic complete response and overall survival in clinical stage II-III NSCLC patients. First Author: Jack William Ibinson, Penn State College of Medicine, Hershey, PA

Background: In 2022, CheckMate 816 supported neoadjuvant chemoimmunotherapy (CTIO) as standard treatment for clinical stage II-III non-small cell lung cancer (NSCLC). Low socioeconomic status has historically been underrepresented in clinical trials, warranting further analysis of CTIO outcomes in patients from diverse socioeconomic backgrounds. This study aims to assess the role of socioeconomic factors on pathologic complete response (pCR) and overall survival (OS) after CTIO. **Methods:** Data from the National Cancer Database (NCDB) was obtained for patients diagnosed with clinical stage II-III NSCLC between 2022-2023 undergoing CTIO. Complete T, N, and M stage and post-pathologic status (ypT, ypN) were obtained. OS was available for patients diagnosed in 2022. Patients receiving neoadjuvant radiotherapy or with clinical or pathologic metastatic disease were excluded. Group comparisons were based on socioeconomic factors: age (< 75 vs ≥ 75 years), sex, race (Non-Hispanic White vs Other), primary payor at diagnosis, urban/rural, percent no high-school degree quartile, and median income quartile. Primary outcomes were pCR and OS, analyzed via logistic and cox regression models, respectively. All tests were two-sided, and a p-value of < 0.05 was statistically significant. **Results:** 2,819 patients received CTIO from 2022-2023, with 1,134 patients diagnosed in 2022. Univariate analysis showed patients in the two lowest median income quartiles ($46,277–$57,856: OR 1.40, 95% CI 1.08-1.80, p = 0.011; < $46,277: OR 1.70, 95% CI 1.30-2.23, $p < 0.001$) had significantly higher odds of pCR compared with those in the highest income quartile (≥$74,063). This effect persisted in multivariate analysis ($46,277–$57,856: OR 1.59, 95% CI 1.19-2.13, p = 0.002; < $46,277: OR 2.00, 95% CI 1.41-2.83, $p < 0.001$). Univariate analysis showed that other race (HR 0.49, 95% CI 0.29-0.81, p = 0.006) was associated with improved OS compared to Non-Hispanic White, which persisted in multivariate cox analysis (HR 0.50, 95% CI 0.30-0.85, p = 0.010). There were no significant associations for pCR and OS with age, sex, primary payor at diagnosis, urban/rural status, or percent no high school degree quartile. **Conclusions:** Our findings present promising evidence of improved outcomes of neoadjuvant chemoimmunotherapy among groups facing historical marginalization, namely low-income communities and non-white race. These effects were persistent in multivariate regression models controlling for other socioeconomic variables such as age, sex, primary payor, urban/rural, and percent no high school degree quartile. In light of these findings, further studies with diverse patient populations are warranted to examine the benefit of neoadjuvant chemoimmunotherapy on patients with NSCLC. Research Sponsor: None.

8040 **Poster Session**

An integrated multidisciplinary analysis of pre-treatment cachexia in locally advanced non–small cell lung cancer. First Author: Ernest Nadal, Thoracic Tumors Unit, Medical Oncology, Catalan Institute of Oncology (ICO). Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet De Llobregat (Barcelona), Spain

Background: Cancer-associated cachexia is underdiagnosed and not routinely captured in cancer registries, despite its negative impact on quality of life and survival. We aim to determine the prevalence of cachexia in patients with locally advanced NSCLC and to perform a multidisciplinary characterization of cachexia to inform the development of future therapeutic interventions. **Methods:** In this prospective study, 51 patients diagnosed with locally advanced unresectable NSCLC candidates to concurrent chemoradiotherapy followed by immunotherapy at the HUB-ICO Comprehensive Cancer Centre (2022-2024) were included. The primary objectives were to (1) determine the frequency of cachexia according to Fearon's criteria and (2) characterize patients before and after completing chemoradiotherapy in terms of nutritional status, metabolic parameters, body composition and circulating cytokine levels. Baseline assessment results are reported here. **Results:** Most patients were male (80%) and ever smokers (98%), with a median age of 68 years. All patients completed the planned concurrent chemoradiotherapy regimen, whereas only 43% initiated durvalumab consolidation therapy. At baseline, 27 patients met the diagnostic criteria for cachexia (53%, 95% CI 39-66) and women were more likely to have cachexia than men (80% vs 46%, respectively), although this difference was not statistically significant. Cachexia was significantly associated with more advanced tumor stage ($p < 0.001$), worse performance status (p = 0.027), lower skeletal muscle index (p = 9e-4) and reduced total adipose tissue index (p = 0.004), elevated C-Reactive Protein blood levels (p = 0.004), moderate to severe malnutrition ($p < 0.001$), reduced caloric intake (p = 0.007) and decreased physical strength (p = 0.001). Cachectic patients had lower fat intake compared with non-cachectic individuals (p = 0.006), while protein intake was similar in both subgroups. Proteomic profiling using the O-link platform identified significant differences in circulating cytokine levels between cachectic and non-cachectic patients. Cachexia was associated with significantly increased levels of CCL23, IL-6, C1QA, CSF1, motilin and agouti-related protein (AGRP), among others, which showed varying degrees of correlation with caloric intake. By contrast, GDF-15 was significantly associated with weight loss (p = 0.00014) but showed no association with caloric intake or body composition parameters. **Conclusions:** This prospective study reveals that cancer-associated cachexia is highly prevalent in patients with unresectable locally advanced NSCLC before treatment initiation. Beyond previously described inflammatory mediators, we identified several understudied cytokines, which may contribute to the progression of the cachexia phenotype and represent potential targets for future therapeutic interventions. Research Sponsor: None.

8041 **Poster Session**

Decomposing the co-mutational landscape of NSCLC by unsupervised learning to unveil components with impact on overall survival. First Author: Chidiebube Ugwu, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: The molecular characterization of non-small cell lung cancer (NSCLC) and targeting therapies are improving outcomes for many patients. However, about 40% remain without identifiable molecular drivers. Understanding the co-mutational landscape of NSCLC may contribute to close that gap but has not yet been sufficiently characterized beyond e.g. *TP53* co-mutations that associated with adverse outcome (Galina et al. *J. Thor. Onc*. 2024). Previously, the hierarchical Dirichlet mixture model (HDMM) provided important insight into acute leukemia biology (Papaemmanuil et al. *NEJM* 2016, Turki et al. *EHA plenary abstract* 2025), reason why we adopted this method for the first time to decompose the NSCLC genetics landscape. **Methods:** Here, we leveraged the HDMM with multinomial distribution for unsupervised learning of NSCLC genetics on the large AACR GENIE BPC NSCLC cohort (n = 1,846 patients, Choudhury et al. *Clin. Can. Res*. 2023) including 300 features for 60 genes. Preprocessing excluded columns with < 5 mutations, features duplicating information or with high rates of missingness, leaving the most relevant 85 genetic features for HDMM analysis including single mutations, gene amplifications and deletions. Within UICC stages I, II-III and IV, overall survival (OS) was analyzed with the Kaplan Meier method comparing the new components with the logrank test. **Results:** Among 1926 genetically distinct tumors of 1785 NSCLC patients with detectable genetic alterations, the HDMM identified four components assembling patients with similar landscape. Their driver patterns involved either co-mutated *TP53/KRAS*, *TP53/EGFR* or *PDGFR/KDR* and other mutations including established risk groups, i.e. with amplifications in *ALK*, *BRAFV600E*, *cMET exon 14* or single *EGFR* or *KRAS* mutations, *ROS1* or *NTRK* translocations. As expected, UICC stages I-IV stratified this cohort significantly for OS. Next, we tested whether genetic components refined outcomes within the same UICC stage. Indeed, for stage I NSCLC the genetic components associated with significant OS differences (p = 0.0065). Patients with PDGFR/KDR had the highest OS, while patients of the TP53/KRAS component had the lowest median OS with a Kaplan Meier estimate of 82.4 months as compared to 116.7 in the TP53/EGFR cluster. Also, among patients with stage II-III NSCLC, the three components associated with significant differences in OS (p = 0.023). Not taking into account other driver mutations, the components also associated with distinct OS in patients with stage IV NSCLC (p = 0.0001). **Conclusions:** This analysis of the co-mutational landscape is complementing existing genetic classes in NSCLC. We identified a new *PDGFR/KDR* component and support the relevance of previously described co-occurring *TP53/EGFR* and *TP53/KRAS*. The significantly distinct OS in resectable NSCLC may open new risk adapted treatment strategies. Research Sponsor: None.

8042 **Poster Session**

Fraction genome altered to predict survival in early-stage non–small cell lung cancer. First Author: Mobina Shrestha, Sentara Albemarle Medical Center, USACS, Elizabeth City, NC

Background: Patients with stage I-III non-small cell lung cancer (NSCLC) often have very different outcomes, even when they share the same anatomic stage. This suggests that tumor biology plays an important role in prognosis. Fraction genome altered (FGA), a measure of chromosomal instability derived from next-generation sequencing (NGS), is already used in clinical practice but its prognostic value in early-stage NSCLC is not well established. Therefore, we evaluated whether FGA is associated with overall survival (OS) in early-stage NSCLC and whether it provides prognostic information beyond standard clinical factors and tumor mutation burden (TMB). **Methods:** We performed a retrospective analysis of 7,722 patients with NSCLC using clinical-grade targeted NGS with available copy-number data (MSK CHORD 2024). Disease stage was categorized as stage I-III versus stage IV. FGA was analyzed in quartiles, with high FGA defined as the top quartile. OS was assessed using Kaplan-Meier and multivariable Cox proportional hazards models adjusting for age, sex, smoking history, histology group, sequencing panel, stage, and log-transformed TMB. Incremental prognostic value was evaluated using concordance (C-index) and likelihood ratio testing (LRT). The results were validated using several sensitivity/statistical analysis. **Results:** After quality control, 7,722 patients were included (3,934 deaths), including 4,343 with stage I-III disease (1,559 deaths). In early-stage NSCLC, increasing FGA was associated with progressively worse OS across quartiles (log-rank $\chi^2 = 199.6$, $p < 0.0001$). 5-year OS declined from 65.6% in the lowest FGA quartile to 39.6% in the highest quartile. Patients with high FGA had significantly inferior survival compared with low-FGA patients (5-year OS 39.6% vs 63.0%, $p < 0.0001$). In multivariable models restricted to stage I-III, high FGA remained independently associated with mortality (Hazard-Ratio = 1.60, 95% CI: 1.42-1.82, $p < 0.0001$). Adding FGA to clinical models improved survival prediction (C-index = ~0.70) and overall model performance (LRT = 125.9, $p < 0.0001$), and this improvement was greater than that seen with TMB. When both biomarkers were included, FGA continued to provide strong prognostic information, whereas TMB did not improve prediction once FGA was already in the model. We found our results to be consistent across internally validated analysis. **Conclusions:** FGA was strongly associated with OS in stage I-III NSCLC. FGA identified a subgroup of early-stage patients with substantially worse outcomes despite similar anatomic stage, indicating important underlying biologic differences. Since, FGA can be obtained from routine targeted NGS already used in clinical practice, it presents a practical biomarker that may improve risk stratification beyond standard clinical factors and TMB, and help guide surveillance and perioperative trial selection. Research Sponsor: None.

8043 **Poster Session**

Real-world adoption of comprehensive genomic profiling in a national cohort of patients with resected stage I–III non–small cell lung cancer. First Author: Brendan Heiden, Division of Cardiothoracic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, MO

Background: Comprehensive genomic profiling (CGP) is increasingly used in the multidisciplinary management of resectable NSCLC to identify candidates for targeted adjuvant therapies and clinical trials. NCCN and Veterans Affairs (VA) guidelines recommend selective – not universal – testing in early-stage disease, yet real-world use after surgery remains poorly described. Using the VA's highly unique National Precision Oncology Program (NPOP), we evaluated trends in CGP uptake, factors associated with testing, and the biomarker landscape in early-stage NSCLC. **Methods:** We performed a retrospective cohort study of patients with resected pathologic stage I–III NSCLC (2019-2025) within the VA. CGP was defined as next-generation sequencing (NGS) of the primary tumor within 3 months of surgery. We assessed frequency of CGP and clinicodemographic factors associated with GCP via multivariable logistic regression. We also assessed the distribution of potentially actionable genomic alterations. **Results:** A total of 6,605 patients were included (4,686 [70.9%] stage I; 1,255 [19.0%] stage II; 664 [10.1%] stage III). Over the study period, 1,337 (20.2%) patients received NGS testing. CGP utilization increased over time (11.4% in 2019 to 25.8% in 2025), paralleling evolving recommendations regarding adjuvant targeted therapies. Of note, the GCP utilization rate among those with stage Ib-III NSCLC in 2025 was 54.9%. In multivariable models, factors associated with higher CGP use included former smoking status (adjusted hazard ratio [aHR] 1.19, 95% CI 1.02-1.40), never smoking status (aHR 1.31, 95% CI 1.05-1.65), robotic resection (aHR 1.82, 95% CI 1.52-2.18), higher stage (stage II: aHR 4.33, 95% CI 3.72-5.04; stage III: aHR 5.79, 95% CI 4.81-6.98), and more recent treatment year (aHR 1.25, 95% CI 1.20-1.30). Median time from surgery to CGP ordering was 25 days (IQR 10-67). Among tested tumors, key genomic alterations included EGFR exon 19 deletions (2.39%) and L858R (1.20%), ALK fusions (0.52%), KRAS G12C (10.62%), MET exon 14 skipping (2.02%), ERBB2 mutations (3.29%), BRAF V600E (1.05%), and ROS1 fusions (0.53%). **Conclusions:** In this national cohort, CGP use after resection of stage I–III NSCLC increased substantially over time, likely supported by the VA NPOP infrastructure. Testing patterns were largely guideline-concordant, with continued uptake within complex multidisciplinary pathways. These findings reinforce the real-world adoption of genomically informed decision-making in early-stage disease while highlighting opportunities to strengthen implementation and promote wide access to precision oncology. Research Sponsor: None.

8044 **Poster Session**

Multi-center prospective study evaluating an AI-enabled clinical decision support tool to improve biomarker testing in early-stage NSCLC. First Author: Melina Elpi Marmarelis, University of Pennsylvania, Philadelphia, PA

Background: Non-adherence to guideline-concordant biomarker testing in non-small cell lung cancer (NSCLC) can limit access to targeted therapies and adversely impact survival. We evaluated an AI-enabled clinical decision support (AI-CDSS) program comprising: (1) education around baseline testing rates; (2) continuous monitoring to generate real-time alerts for eligible patients with missing biomarker testing; and (3) longitudinal feedback via dashboards. Here, we report the effectiveness of this program in identifying and closing biomarker testing gaps for patients with early-stage NSCLC. **Methods:** In this descriptive study, we analyzed patients with confirmed NSCLC across 6 geographically and socioeconomically diverse US community health systems. The AI-CDSS identified early-stage patients eligible for biomarker testing (eNSCLC as AJCC 8th edition Stg IB-IIIB (T3, N2) with planned curative intent treatment). Biomarker testing included EGFR, ALK, and PD-L1. We compared testing adherence between a baseline period (BL: 24 months through 3 months prior to the health system-specific roll-out) and a post-launch period (PL: roll-out through Oct 2025). The AI-CDSS was implemented on a rolling basis across health systems (BL from Feb 2022 - Dec 2024 and PL from Feb 2024 - Oct 2025). Testing rates were calculated as the proportion (%) of patients with testing completed within 90 days of pathologic diagnosis in each period. The improvement in test rates (absolute lift) is calculated as the difference in PL - BL testing percentages in the two periods. **Results:** A total of 662 patients with eNSCLC (270 BL and 392 PL) were included in the analysis. Patients were predominately white (85%), had a history of smoking (88%), with a median age of 70 years at diagnosis. The stage distribution was as follows: Stage III (34%), Stage II (37%), Stage IB (25%), and Stage IB or IIA [indeterminate] (5%). The absolute lift in biomarker testing within 90 days of pathologic diagnosis before vs after intervention was 18% for EGFR, 24% for ALK, and 13% for PDL1 biomarkers. Among patients with molecular testing who received adjuvant treatment, 89% were on guideline-concordant adjuvant treatment. **Conclusions:** Implementation of an AI-CDSS was associated with clinically meaningful improvements in rates of biomarker testing for eNSCLC and resulted in high concordance with guideline-directed adjuvant therapy. Appropriate and timely biomarker testing is essential for perioperative treatment planning. This study provides preliminary evidence that AI can use complex electronic health records to provide real-time interventions that can promote guideline-concordant care. Research Sponsor: None.

Testing gap results.

Biomarker	Baseline N	Baseline Test Rate	Post Launch N	Post Launch Test Rate	Absolute Lift
EGFR	264	49%	392	67%	18%
ALK	270	43%	389	67%	24%
PD-L1	270	59%	389	72%	13%

8045 **Poster Session**

Non-surgical management and outcome of 1,113 patients with stage I-II non-small cell lung cancer (NSCLC) in a 20-year cohort. First Author: Ping Yang, Mayo Clinic Arizona, Scottsdale, AZ

Background: Surgical resection is the primary therapy for stage I-II NSCLC but not performed in a subset of patients due to comorbidities or self-election, who instead undergo radiation with or without systemic therapy (RT±ST). Little is known about the demographic, tumoral, therapeutic, and quality-of-life (QOL) characteristics of this non-surgical group. Understanding their differences from the surgical group is essential for developing precision treatment strategies and tailored survivorship guidelines. **Methods:** In a prospectively enrolled (1997-2016) and followed (through 2025) cohort of 20,951 primary lung cancer patients, 6,486 (31%) had stage I-II NSCLC, including 5,359 (83%) treated surgically (Surgical) and 1,113 (17%) otherwise (Non-surgical). Preexisting diseases were grouped into cancer, lung, and other comorbidities. QOL data were available for 40% of all patients. Descriptive analysis of demographics, tumor features, treatment patterns, and QOL metrics, as well as survival analysis (median years and overall survival [OS] rates) were conducted. QOL measures, on overall and 15 symptom and functional domains, were scored 0 (worst) to 10 (best), with 1-unit difference considered clinically and statistically meaningful. **Results:** At time of diagnosis, compared to the Surgical, the Non-surgical patients were older (median 73 v 68 years), more likely to have smoked cigarettes (91% v 83%), squamous cell and unspecified NSCLC (53% v 28%), stage IIB (19% v 12%), and preexisting lung comorbidities (71% v 58%). Non-surgical patients more frequently received RT±ST than the Surgical (70% v 21%) and had shorter median survival (2.5 v 7.8) years. Within the Non-surgical, 28% had no cancer treatment (No-Tx), 44% RT-only, 7% ST-only, and 19% both (RT+ST); their respective median diagnosis ages were 74, 76, 68, 70 years; median survival were 1.7, 2.7, 2.2, 3.2 years; 5-year OS (95%CI) at 25% (21-31), 25% (21-29), 26% (17-38), 30% (25-37); and 10-year OS at 9% (7-14), 7% (5-10), 10% (5-21), 9% (6-14), respectively. RT-only group had highest rates of comorbidities (37-84%) and the No-Tx the lowest (31-66%). Although the overall QOL scored the same for all groups, RT-only patients reported the worst scores on multiple symptoms burden, and the No-Tx reported the least pain and lung cancer symptoms but the worst on mental well-being and social activities. **Conclusions:** Non-surgically managed stage I-II NSCLC cases present clinically distinct patients with the shortest median survival in No-Tx group and highest 5-year survival in RT+ST. RT-only patients were oldest, had the most comorbidities, and reported the worst symptom burdens. These differences highlight the need for more in-depth analyses and studies (considering age, histology, comorbidity, QOL, etc.) to support tailored therapeutic strategies and survivorship care for patients who decline or are not suitable for surgery. Research Sponsor: None.

8046 **Poster Session**

Influence of neoadjuvant spatially fractionated stereotactic body radiotherapy on antitumor immunity and pathological response to toripalimab-based immunochemotherapy in resectable stage IIA-IIIB non-small cell lung cancer. First Author: Xu Yaping, Department of Radiation Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Background: Neoadjuvant immunochemotherapy has improved outcomes in resectable non–small cell lung cancer (NSCLC); however, pathological complete response (pCR) rates remain limited, and strategies to further amplify antitumor immunity are needed. Spatially fractionated stereotactic body radiotherapy (SF-SBRT, Lattice) delivers spatially separated high-dose regions "peaks" to promote immunogenic cell death while maintaining low-dose regions "valleys" that preserve the tumor immune microenvironment (TIME). We hypothesized that integrating SF-SBRT with toripalimab-based immunochemotherapy could reprogram the TIME and enhance pathological response in resectable NSCLC. **Methods:** This prospective phase II study enrolled resectable stage IIA–IIIB NSCLC (NCT06293690). Patients received one fraction of Lattice SF-SBRT (12 Gy peak / $<$4 Gy valley) on Day 1, followed by toripalimab plus chemotherapy on Day 2, administered every 3 weeks for 2 cycles prior to surgery. The primary endpoint was major pathological response (MPR). Secondary endpoints included pCR, radiological response, nodal downstaging, event-free survival, overall survival, and safety. Single-cell RNA sequencing (scRNA-seq) was performed to characterize treatment-associated immune remodeling. **Results:** 20 patients completed neoadjuvant therapy and underwent curative-intent resection, R0 resection was achieved in all patients without treatment-related surgical delays. MPR was observed in 95.0% (19/20) of patients, including a pCR rate of 55.0% (11/20). The radiological objective response rate was 100.0%. Nodal downstaging to ypN0 occurred in 82.4% (14/17) of patients with baseline nodal involvement, corresponding to an overall ypN0 rate of 85.0%. Grade 3–4 treatment-related adverse events occurred in 15.0% (3/20), with no grade $\geq$2 radiation pneumonitis. scRNA-seq revealed enhanced cytotoxic T-cell activation, reduced immunosuppressive myeloid populations, and coordinated immune remodeling following neoadjuvant treatment. **Conclusions:** Neoadjuvant SF-SBRT combined with toripalimab-based immunochemotherapy was feasible, safe, and achieved high pathological response rates in resectable stage II–III NSCLC. These findings suggest that SF-SBRT may function as an immune-reprogramming strategy that amplifies neoadjuvant immunotherapy efficacy and warrants further validation in randomized clinical trials. Clinical trial information: NCT06293690. Research Sponsor: None.

Characteristics	No. of Patients (%)
Radiological Response (RECIST 1.1)	
CR	2 (10.0)
PR	18 (90.0)
Pathological Response	
Major pathological response (MPR)*	19 (95.0)
└ Pathological complete response (pCR)†	11 (55.0)
ypN0‡	17 (85.0)

*MPR: $<$ 10% residual viable tumor (RVT); †pCR: 0% RVT in primary & nodes; ‡ypN0: 14/17 patients with baseline N+ achieved downstaging.

8047 **Poster Session**

Real-world outcomes and prognostic risk stratification of neoadjuvant immunotherapy for stage III lung squamous cell carcinoma. First Author: Wang Yishuo, Beijing Chest Hospital, Capital Medical University and Beijing Tuberculosis and Thoracic Tumor Research Institute, Beijing, China

Background: While neoadjuvant immunotherapy (nIO) is the standard of care for resectable NSCLC, its efficacy in "potentially resectable" (PR) stage III lung squamous cell carcinoma (LUSC)—specifically patients with T4 invasion or multi-station N2 disease—remains underrepresented in clinical trials. We evaluated whether nIO could facilitate surgical conversion in PR patients comparable to initially resectable (IR) candidates and constructed a multidimensional risk stratification system to optimize decision-making. **Methods:** We retrospectively analyzed patients with stage III LUSC treated with neoadjuvant PD-1/PD-L1 inhibitors plus chemotherapy (January 2019–December 2024). The cohort was stratified into IR and PR groups, with PR defined by complex anatomy (T4 invasion or multi-station N2). Endpoints included surgical conversion, major pathological response (MPR), disease-free survival (DFS), and overall survival (OS). Baseline predictors were identified via logistic regression. A pathological risk score (pRS) was developed using Cox regression based on independent risk factors for DFS in the R0 resection cohort. **Results:** Of 210 evaluable patients, 170 (81.0%) underwent surgery with a 96.5% R0 resection rate. The PR cohort (n = 128) achieved surgical conversion rates comparable to the IR cohort (n = 82) (82.9% vs. 90.7%; P = .19). Notably, PR patients demonstrated superior nodal downstaging (74.5% vs. 58.8%; P = .047) compared with IR patients. Long-term survival outcomes showed no statistically significant difference between PR and IR groups (DFS: HR, 1.25; 95% CI, 0.77-2.04; OS: HR, 1.41; 95% CI, 0.76-2.62). Multivariable analysis identified baseline NLR $\geq$ 2.75 and CYFRA 21-1 $\geq$ 6.0 ng/mL as independent predictors of poor therapeutic benefit. The constructed pRS system (integrating non-MPR status, vascular, and pleural invasion) effectively stratified postoperative recurrence risk (P $<$ .0001; 1-year AUC, 0.73). Analysis of treatment failure (n = 40) revealed that baseline fibrinogen $>$ 3.5 g/L was associated with disease progression, while grade 3–5 pneumonitis was a primary cause of surgical dropout in patients with high PD-L1 expression. **Conclusions:** In this real-world cohort, nIO facilitated high R0 resection rates in complex stage III LUSC, allowing potentially resectable patients to achieve survival outcomes equivalent to initially resectable candidates. Nodal clearance appears to be a key driver of benefit in the PR subgroup. The novel pRS system and biomarkers (NLR, CYFRA 21-1, fibrinogen) provide a robust framework for patient selection and postoperative management. Research Sponsor: None.

8048 **Poster Session**

Post-progression treatment strategies and immunotherapy rechallenge sensitivity following chemoradiation and consolidation durvalumab in unresectable stage III NSCLC: The POST-PACIFIC study. First Author: Valentina Santo, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Durvalumab consolidation after platinum-based chemoradiotherapy (CRT) is the standard of care for unresectable stage III non-small cell lung cancer (NSCLC). However, optimal treatment strategies after progression remain undefined, and data guiding post-durvalumab strategies, including immunotherapy rechallenge, are limited. **Methods:** This global retrospective multicenter study included patients with unresectable stage III NSCLC treated with concurrent or sequential CRT who progressed after ≥1 dose of durvalumab consolidation. Survival outcomes were assessed using Kaplan-Meier and Cox methods. Immunotherapy sensitivity was defined by time from durvalumab initiation to progression: refractory (< 12 months) or sensitive (≥12 months) and correlated with outcomes after immunotherapy rechallenge. **Results:** Among 319 patients, median age was 66.5 years; 54.2% were male, and 96.7% had ECOG PS 0-1. Concurrent CRT was delivered in 96.5% (median RT dose 60 Gy). Median follow-up was 62.2 months. Progression pattern included locoregional recurrence in 34.8% and distant relapse in 65.2%. Of 293 patients receiving a first subsequent therapy (FST), chemotherapy (CT) ± VEGF inhibition was most common (31.7%), followed by local ablative therapy (LAT, 30.7%), immunotherapy ± CT (18.4%), targeted therapy (TT, 10.9%), and durvalumab beyond progression (BP) ± LAT (6.5%). When comparing FST, immunotherapy rechallenge demonstrated superiority over CT. Compared with CT ± VEGF inhibition, immunotherapy ± CT was associated with a higher objective response rate (ORR: 40.7% vs. 16.9%, $p < 0.01$) and significantly improved progression-free survival (mPFS2: 8.48 vs. 4.14 months; HR 0.41, $p < 0.01$) and overall survival (mOS2: 23.7 vs. 12.2 months; HR 0.41, $p < 0.01$), findings confirmed in multivariable analyses. Patients with actionable oncogenic drivers or indolent, focal relapses achieved the most favorable outcomes with TT or durvalumab BP ± LAT, respectively, reflecting a disease biology amenable to highly effective systemic or localized interventions. Among patients who received immunotherapy rechallenge, those relapsing ≥12 months after durvalumab initiation experienced higher ORR and numerically longer PFS and OS. Additionally, upfront rechallenge was independently associated with superior survival in multivariable models (PFS aHR: 0.51, $p < 0.01$; OS aHR: 0.46, $p < 0.01$) and with higher ORR (41.5% vs. 17.6%, p = 0.04), compared with later-line rechallenge. **Conclusions:** Post-PACIFIC treatment approaches are heterogeneous, but immunotherapy-based strategies provide superior efficacy over CT alone. Patients with prolonged benefit from durvalumab (≥12 months) retain immune sensitivity and derive the greatest benefit from immunotherapy rechallenge, particularly as FST. Research Sponsor: None.

8049 **Poster Session**

Nodulomics: Histopathologic and genomic heterogeneity among multiple malignant pulmonary nodules sampled by robotic-assisted bronchoscopy. First Author: Jamie Rowell, Northwestern University, Chicago, IL

Background: Multiple pulmonary nodules (MPN) pose significant challenges for accurate staging of non-small cell lung cancer (NSCLC). As next generation sequencing (NGS) technologies have become more widely available on smaller amounts of tissue, the prevalence and clinical implications of heterogeneity between MPNs are poorly understood. This study retrospectively evaluates the histopathological and NGS findings after MPN biopsy in a single robotic-assisted bronchoscopy (RaB) procedure. **Methods:** 191 patients were retrospectively enrolled at 6 geographically diverse centers in the US. All patients had 2+ pulmonary nodules biopsied and staging EBUS in the same procedure. An expert molecular pathologist reviewed NGS data between nodule pairs to determine if they were discordant, concordant, or indeterminate. **Results:** Of 191 patients, 85 patients had 2 malignant nodules with 15 of those demonstrating histopathologic heterogeneity (e.g., one adenocarcinoma, one squamous cell carcinoma). 26 patients with 2 malignant nodules of similar histopathology demonstrated molecular heterogeneity between nodules. These cases were reviewed by an expert molecular pathologist who determined the following breakdown: -15 discordant pairs (57.7%) -3 concordant pairs (11.5) -8 indeterminate pairs (30.8%) Breakdown by nodule density: -Discordant: 7 same density, 8 different density -Concordant: 3 same density -Indeterminate: 5 same density, 3 different density Breakdown by nodule laterality: -Discordant: 7 ipsilateral, 8 contralateral -Concordant: 2 ipsilateral, 1 contralateral -Indeterminate: 4 ipsilateral, 4 contralateral Staging EBUS was performed in all 26 cases with malignancy identified in 2 cases. NGS sufficiency for NSCLC from three sites with standardized NGS reporting was as follows: 1st nodule biopsied: 42/54 (77.8%), 2nd nodule biopsied: 37/51 (72.5%), 3rd nodule biopsied: 2/4 (50%). In total, 90/109 (82.6%) NSCLC samples had adequate tissue for NGS. In 85 cases with 2 malignant nodules, 35 (41.2%) had all nodules Stage IIB or lower. Notably, 25 (29.4%) of the cases did not have NGS available on one or more of the nodules, thus precluding staging. **Conclusions:** This study highlights the frequency and clinical relevance of histopathologic and molecular heterogeneity among synchronous MPNs. Importantly, heterogeneity was not limited to contralateral or anatomically distant lesions, challenging the assumption that spatial proximity implies clonal relatedness. Further, this study shows that relying solely on density or radiographic features of a nodule is an incomplete discriminator between separate primary lung cancers and intrapulmonary metastasis. Our findings support the need for an integrated diagnostic paradigm in which sampling of multiple lesions is used to inform clonality, refine staging, and guide precision therapy. Research Sponsor: None.

8050 **Poster Session**

Sintilimab plus anlotinib and chemotherapy as first-line treatment for advanced malignant pleural mesothelioma (SACH-MPM): A prospective, single-arm, phase II trial. First Author: Yiyi Huang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital,Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Standard first-line treatments for advanced malignant pleural mesothelioma (MPM) include platinum-pemetrexed with bevacizumab or nivolumab plus ipilimumab. While the addition of atezolizumab to chemotherapy and bevacizumab improved PFS in the BEAT-meso trial (9.2 vs. 7.6 m, HR 0.72), it failed to show an OS benefit. Anlotinib is a multi-target TKI targeting VEGFR, FGFR, and PDGFR. We investigated the efficacy and safety of sintilimab (anti-PD-1) combined with anlotinib and chemotherapy as first-line treatment for advanced MPM. **Methods:** This open-label, dual-center, single-arm Phase II study (NCT05188859) enrolled systemic treatment-naive pts with unresectable locally advanced or metastatic MPM. Pts received sintilimab (200 mg D1) and anlotinib (12 mg D1-14) plus chemotherapy (pemetrexed 500 mg/m² with cisplatin 75 mg/m² or carboplatin AUC 5, D1) Q3W for 4-6 cycles, followed by maintenance sintilimab, anlotinib, and pemetrexed until disease progression, intolerable toxicity, or up to 24 months. Primary endpoint was ORR per modified RECIST (mRECIST) 1.1 for mesothelioma. A Simon's two-stage design (H0 = 41.3%, H1 = 60%, $\alpha = 0.1$) planned for 23 evaluable pts, requiring ≥12 responses. **Results:** From Sep 2024 to Jan 2026, 30 pts were enrolled (median age 58.5 y; 76.7% epithelioid, 80% stage IIIB). At data cutoff, 29 pts were evaluable. Median follow-up was 7.4 months (m). The primary endpoint was met, with a confirmed ORR of 65.5% (95% CI: 45.7-82.1). DCR was 100%. Median time to response was 1.4 m; median DoR was not reached (0.7+-8.4+ m). PFS and OS were not mature. The 6- and 12-m PFS rates were 100% and 67.5%, respectively. OS rate was 100% at cutoff. Grade ≥3 TRAEs (36.7%) included neutrophil count decreased (13.3%), platelet count decreased (10.0%), pulmonary embolism (6.7%), diarrhea (6.7%), and hypertension (3.3%; any grade 10.0%). Bleeding events were Grade 1-2 (epistaxis 13.3%). TRAEs led to anlotinib dose reduction or discontinuation in 20.0%. No Grade 5 events occurred. **Conclusions:** Sintilimab plus anlotinib and chemotherapy demonstrated superior ORR compared to historical controls with a manageable safety profile. The study met its primary endpoint, and the high 12-month PFS rate suggests a potential survival benefit. These findings support integrating a multi-target TKI with PD-1 blockade and chemotherapy as a potent first-line strategy for advanced MPM. Clinical trial information: NCT05188859. Research Sponsor: Innovent Biologics (Suzhou) Co.Ltd.; Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

8051 **Poster Session**

Machine learning–integrated transcriptomic clustering for prognostic stratification in epithelioid pleural mesothelioma. First Author: Mario Occhipinti, Medical Oncology Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy

Background: Survival outcomes in pleural mesothelioma (PM), particularly within epithelioid PM (ePM), are heterogeneous and inadequately captured by histological classification. We applied machine learning (ML) methods integrating transcriptomic and clinical features to improve prognostic stratification in ePM. **Methods:** RNA sequencing was performed on FFPE tumor samples from 125 ePM patients treated at two Italian centers (2006-2021). Overall survival (OS) was categorized as long (> 36 months), intermediate (12-36 months), or short (≤12 months). Unsupervised clustering of highly variable genes identified transcriptomic subgroups, and GSEA was performed. A previously published 20-gene sarcomatoid-like transcriptional score (S-score), derived from single-cell data was calculated. ML models were developed using age, sex, S-score, and a cluster-derived score related to cell proliferation as input features. Logistic Regression (LR) and Random Forest (RF) classifiers were trained to predict long and short survival, using class-balanced weighting and 5-fold stratified cross-validation. Model performance was assessed using AUC-ROC and balanced accuracy. Model interpretability was evaluated with SHapley Additive exPlanations (SHAP). External evaluation was performed in the TCGA PM cohort with cohort-specific standardization. **Results:** Unsupervised transcriptomic analysis identified three clusters with distinct survival patterns. Cluster 1 was enriched for immune-related pathways and associated with longer survival; Cluster 2 exhibited proliferative and cell-cycle-related programs and was enriched in short-survival patients. Cluster 3 showed immune-related transcripts, with variable expression patterns across histology and survival groups. Given the convergent GSEA results, Cluster 2 was selected as a ML feature. Both the S-score and Cluster 2 score were associated with OS, with stronger survival discrimination for Cluster 2. ML models showed good discriminative performance for long survival prediction (cross-validation AUC-ROC: LR 0.83 ± 0.10; RF 0.83 ± 0.04), with similar results in the TCGA cohort (LR AUC-ROC = 0.84; RF = 0.77). Predictive performance for short survival was moderate. SHAP analysis identified Cluster 2 score as the main contributor to ML predictions, with higher values associated with increased risk of short survival. **Conclusions:** Machine learning models integrating transcriptomic clustering with clinical variables improve prognostic stratification in ePM. ML-based risk prediction builds upon transcriptomic features, capturing survival-relevant heterogeneity beyond histology. These findings support the use of ML as a complementary tool to transcriptomic profiling for prognostic assessment in ePM. Research Sponsor: None.

8052 **Poster Session**

Tumor methylation subtypes as a predictor of clinical outcome to immunotherapy in pleural mesothelioma patients from the NIBIT-EPI-MESO study. First Author: Luana Calabrò, University of Ferrara, Ferrara, Italy

Background: Pleural mesothelioma (PM) is an aggressive malignancy with a poor prognosis. The clinicalefficacy of standard therapy with immune checkpoint inhibitors (ICI) is limited and heterogeneous acrossPM subtypes. Tumor-intrinsic characteristics (i.e., inflammatory phenotype, molecular features, DNAmethylation) may influence immune responsiveness, but predictive biomarkers of ICI therapy efficacy inPM are still lacking. **Methods:** NIBIT-EPI-MESO is a retrospective, multicenter study, sponsored by theNIBIT Foundation, evaluating biological correlates of clinical outcomes in PM patients (pts) treated withICI (i.e., anti-CTLA-4 plus anti-PD-1, anti-CTLA-4 plus anti-PD-L1, or anti-CTLA-4 monotherapy). Pre-ICI therapy FFPE tumor samples were analyzed by RRBS methylation (n = 83 pts) and RNA-seq (n = 82pts), with methylation subtypes defined by consensus clustering of the top 1% most variable CpGs.Tumor microenvironment (TME) was characterized by multiplex immunofluorescence analysis of CD4,CD8, CD20, CD68, CD163 (n = 35 pts). Integrated multi-omics analyses were used to associate tumorbiology with clinical outcome of PM pts. **Results:** Unsupervised methylation profiling identified four PMsubsets with increasingly global DNA methylation levels: demethylated (DEM), LOW, intermediate (INT),and CpG island methylator phenotype (CIMP). Methylation subtypes were significantly associated withresponse to ICI, with LOW/DEM enriched among responder (R) pts and INT/CIMP in non-R pts (p =0.002); no association of response to ICI was found with PM histotype (p = 0.33). The LOW subsetexhibited the longest median overall survival (mOS) and the highest 3-year OS rate, expressed genesinvolved in pathways associated with innate and adaptive immune responses, and showed an "inflamed"TME (i.e., CD8+ T cells, CD20+ B cells). Conversely, the CIMP subtype had the shortest mOS and OSrate, was characterized by genes enriched in developmental, morphogenetic and cell cycle-relatedprocesses, along with a "desert" TME. Functional characterization of the identified methylation classes ofPM was validated in the MESOMICS dataset. Accordingly, a PM methylation subtype classifier wasdeveloped to predict response to ICI therapy. **Conclusions:** Tumor DNA methylation defines biologicallyand clinically distinct immune phenotypes in PM and robustly predicts clinical response and long-termsurvival in ICI-treated PM patients, regardless of tumor histology. Research Sponsor: Fondazione AIRC; ID.21073; NIBIT Foundation Onlus; Bando Ricerca Finalizzata; NET-2016-02361632; National Center for Gene Therapy and Drugs based on RNA Technology European Union -Next Generation EU, Mission 4, Component 2; Project no. CN_00000041; National Cancer Institute (NCI) of the National Institutes of Health (NIH); P30CA240139.

8053 **Poster Session**

The role of sarcopenia and adiposity in prognosis of pleural mesothelioma: A CT-based analysis. First Author: Senar Ebinc, Van Yuzuncu Yil University, Van, Turkey

Background: Pleural mesothelioma (PM) is a rare malignancy associated with asbestos exposure and characterized by an aggressive clinical course and poor prognosis. Identifying clinical and biological prognostic markers is of significant clinical importance. Recently, computed tomography (CT) based body composition parameters have been investigated for their association with survival outcomes in cancer patients; however, their prognostic value in PM remains unclear. This study aimed to evaluate the impact of clinical characteristics and CT-derived body composition parameters on survival in patients with PM. **Methods:** This retrospective study included 73 patients diagnosed with pleural mesothelioma. CT images were used to calculate the subcutaneous adipose tissue index (SATI), visceral adipose tissue index (VATI), total abdominal adipose tissue index (TATI), skeletal muscle index (SMI), and psoas muscle index (PMI). Patients were classified as sarcopenic or non-sarcopenic based on SMI. **Results:** The median age was 60 years, and 57.5% of patients were male. Most patients had good performance status (ECOG 0–1), and the epithelioid subtype was the most common histology. Approximately one-third of patients had a history of smoking or prior surgery. In univariate analysis, age ≥60 years was significantly associated with increased mortality. In multivariate analysis, age ≥60 years (HR 2.45) and male sex (HR 2.13) were identified as independent poor prognostic factors. Non-sarcopenic patients had a significantly lower risk of mortality compared with sarcopenic patients (HR 0.37). Additionally, higher TATI values were associated with increased mortality risk (HR 2.26). Kaplan–Meier analysis demonstrated significantly shorter OS in patients aged ≥60 years (Table). **Conclusions:** In patients with pleural mesothelioma, advanced age and male sex are associated with poorer survival, whereas preserved skeletal muscle mass is associated with improved outcomes. Increased abdominal adiposity is linked to higher mortality risk. CT-based body composition parameters may provide useful prognostic information in patients with PM. Research Sponsor: None.

Evaluation of the association between parameters and survival using univariate and multivariate analyses.

	Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	P value	HR	95% CI
Age (<60y / ≥60y)	**0.005**	**2.27**	**1.27-4.05**	**0.005**	**2.45**	**1.31-4.61**
Gender (female*/male)	0.06	1.65	0.96-2.83	**0.011**	**2.13**	**1.19-3.81**
ECOG PS (0-1*/2-3)	0.35	1.43	0.66-3.07			
Histological subtypes (epithelioid / non-epithelioid)	0.26	1.42	0.76-2.66			
Stage (I-III*/IV)	0.43	1.26	0.70-2.27			
SMI cm^2/m^2 (sarcopenia*/normal)	0.21	0.70	0.41-1.21	**0.007**	**0.37**	**0.18-0.76**
TATI cm^2/m^2 (low*/high)	0.30	1.36	0.75-2.48	**0.04**	**2.26**	**1.03-4.97**

8054 **Poster Session**

Response to neoadjuvant chemoimmunotherapy in EGFR- or ALK-mutated non-small cell lung cancer. First Author: Giorgio Caturegli, Yale School of Medicine, New Haven, CT

Background: The role of immunotherapy in non-metastatic EGFR-and ALK-mutated lung cancer is limited, in part because of a lack of efficacy, and partly because of the high response rates to mutation-targeting therapies. However, a subset of immunotherapy-responsive lung cancers may be cured, but only if immunotherapy is included in the treatment strategy. Therefore, a blanket exclusion of all EGFR-and ALK-mutated patients from immunotherapy may restrict a small subset of patients from a potentially curative option. Our objective was to determine the rate of highly immunotherapy-responsive tumors harboring EGFR and ALK mutations. **Methods:** Adult patients in the NCDB with clinical stage I-III NSCLC diagnosed between 2021 and 2023 and treated with neoadjuvant chemoimmunotherapy followed by definitive surgery (wedge resection, segmentectomy, lobectomy, or pneumonectomy) were included. Outcomes were pathologic complete response (pCR, defined as pathologic T0N0 after definitive resection) and nodal downstaging (pathologic N lower than clinical N stage). Covariates of interest for univariate analyses and multivariable logistic regression were year of diagnosis, region, age, sex, race/ethnicity, insurance, Charlson-Deyo score, clinical stage, and receipt of neoadjuvant immunotherapy. **Results:** Of 3,107 eligible patients, 1,133 (36.4%) were tested for EGFR and/or ALK mutations. Overall, 132 (11.7%) patients were found to have mutation(s) in EFGR (99 patients), ALK (27 patients) or both (6 patients). Among those with cN1-3 tumors, nodal downstaging was observed in 57.4% of patients with EGFR/ALK mutations and 74.2% of wild-type patients ($p<0.001$). The rate of pCR was 16.7% in EGFR-/ALK-mutated patients, and 30.9% in wild-type patients ($p<0.001$). Higher tumor grade was associated with significantly higher odds of pCR in EGFR/ALK wild-type patients (OR 2.448, 95% CI 1.58-3.89, $p<0.001$), but not in EGFR-/ALK-mutated patients (OR 2.63, 95% CI 0.37-18.74, p=0.33). **Conclusions:** While a less common practice, neoadjuvant chemoimmunotherapy in patients with EGFR-/ALK-mutated NSCLC demonstrated a pCR rate of 17% in this large real-world NCDB cohort. Further study on the role of neoadjuvant chemoimmunotherapy for this population is indicated given the potential for curative response, particularly in patients with mutations lacking effective targeted therapy. Research Sponsor: None.

Mutation Type	EGFR/ALK wild-type (n=1152)	EGFR-/ALK-mutated (n=132)	p
EGFR (n=105)			
Exon 18, 19, 20, and/or 21		54 (51.4%)	
Other exon		11 (10.5%)	
ALK (n=33)			
EML4-ALK, KIF5B-ALK, TFG-ALK, and/or KLC1-ALK		13 (39.4%)	
Other rearrangement		10 (30.3%)	
Response Outcomes			
Nodal Downstaging (pN < cN), cN1-3 patients only	482/650 (74.2%)	50/87 (57.4%)	**<0.001**
Complete Pathologic Response (ypT0N0)	356 (94.2%)	22 (16.7%)	**<0.001**

8055 **Poster Session**

Pathologic complete response with neoadjuvant chemoimmunotherapy in clinical stage II–III NSCLC: A large real-world analysis including older adults. First Author: Jorge Raul Vazquez Urrutia, Penn State Health Milton S. Hershey Medical Center, Hershey, PA

Background: Neoadjuvant chemoimmunotherapy is now the standard for clinical stage II-III non-small cell lung cancer (NSCLC) following CheckMate 816. However, older adults and socioeconomic factors have been underrepresented in clinical trials. This study aims to evaluate the impact of age and basic socioeconomic factors on pathological complete response (pCR) after neoadjuvant chemoimmunotherapy. **Methods:** Data from the National Cancer Database (NCDB) were obtained for patients diagnosed with clinical stage II-III NSCLC between 2019 and 2023 who underwent neoadjuvant chemotherapy (CT; 2019-2021) or chemoimmunotherapy (CTIO; 2022-2023) with complete T, N, and M staging data, as well as post-pathologic status (ypT, ypN). Those receiving neoadjuvant radiotherapy and with clinical or pathologic metastatic disease were excluded. Groups were stratified based on age (<75 vs ≥ 75 years). Group comparisons were performed using chi-square testing. The primary outcome was pCR, analyzed using univariate and multivariable Cox regression models. A p-value of <0.05 was considered statistically significant. **Results:** A total of 993 patients received CT alone, while 2,819 received CTIO. Among patients ≥ 75 years, pCR rates were significantly higher in the CTIO group compared with CT alone (25% vs 5%, $p<0.001$). This pattern was similar in patients <75 years (29% vs 8%, $p<0.001$). Among CTIO receivers, pCR rates did not differ significantly by age (25% ≥75 vs 29% <75; p=0.051) (Table 1). Patients with ≥10 lymph nodes examined had lower pCR rates compared with those with fewer nodes examined (26% vs 37%; $p<0.001$). On multivariate analysis, higher nodal stage (N1–N3; OR 1.23, 1.02-1.49, p=0.035) and non-adenocarcinoma histologies (OR 1.26, 1.07-1.49, p=0.006) were independently associated with higher odds of pCR. Notably, age, sex, race, and rural/urban residence were not independently associated with pCR, and no significant differences in race or rural/urban status were observed between groups. **Conclusions:** To our knowledge, this is the largest real-world analysis of neoadjuvant chemoimmunotherapy outcomes in older adults with clinical stage II-III non–small cell lung cancer. We found comparable pCR rates across age groups, supporting the use of this approach in older individuals. While racial disparities have been described in access to neoadjuvant therapy, our study suggests similar response rates across racial groups who underwent treatment. Higher nodal status was independently associated with pCR, which may be explained by greater tumor immunogenicity. These findings are hypothesis-generating and warrant validation in further prospective studies. Research Sponsor: None.

Pathologic complete response rate by age status.

Factors	pCR (n=811)	No pCR (n=2008)	P value (Chi-square)
Age			
≥ 75	115 (25%)	345 (75%)	0.051
< 75	696 (29%)	1663 (71%)	

pCR=Pathologic Complete Response.

8056 **Poster Session**

Prediction of survival outcome in clinical stage II-III non-small cell lung cancer undergoing neoadjuvant chemoimmunotherapy: Role of ypN status vs PCR. First Author: Hannah Hoang, Department of Internal Medicine, Penn State College of Medicine, Hershey, Pennsylvania, Hershey, PA

Background: After FDA approval in 2022, neoadjuvant chemoimmunotherapy has become the standard of care for patients with non-small cell lung cancer (NSCLC) due to improved survival outcomes. Pathologic complete response (pCR) is often used as a predictor of patient survival following treatment. However, the role of posttreatment pathological nodal status (ypN) as a treatment predictor remains undefined. This study evaluates the predictive significance of ypN in comparison to established treatment predictors, such as pCR. **Methods:** Patients with clinical stage II-III NSCLC diagnosed in 2022 (n=29,017) who underwent neoadjuvant chemoimmunotherapy and resection (n=1,175) were identified using the National Cancer Database. Those with missing pCR data (n=16), pCR in tumor only (n=18), and those who died within one month of diagnosis were excluded. Chi-square tests were used for comparisons between groups. Survival analysis was performed using the Kaplan-Meier method, along with univariate and multivariable Cox proportional models. All tests were two-sided, and the statistical significance level used was 0.05. **Results:** The final cohort consisted of 720 patients divided into three groups: pCR-both (pCRb; ypT0N0; n=217; 30.1%), pCR-node (pCRn; ypN0; n=265; 36.8%), and residual viable in both (RVb; n=238; 33.1%). The pCRb group had a higher proportion of squamous cell carcinoma compared to the pCRn group (47% vs 34%, $p<0.001$). pCRn patients demonstrated a slightly higher rate of positive surgical margins (3% vs 1%, p=0.03) and subsequent use of adjuvant radiotherapy compared with pCRb (3% vs 1%, p=0.03). Kaplan-Meier analyses and Cox proportional hazards models showed similar overall survival (OS) between pCRb and pCRn groups (HR=1.37; p=0.363), while both had significantly higher OS compared with RVb (HRs 0.26 and 0.36; $p<0.0001$ for both). Subgroup analysis by number of examined lymph nodes showed comparable OS between pCRb and pCRn in patients with $\geq$10 lymph nodes examined (LN$\geq$10; HR=1.36; p=0.47) and in those with $<$10 nodes examined (LN$<$10; HR=1.50; p=0.40). **Conclusions:** In clinical stage II-III NSCLC treated with neoadjuvant chemoimmunotherapy followed by resection, pCRb and pCRn demonstrated similar rates of OS, highlighting the significance of post-treatment pathological nodal status (ypN) as a potential predictor of OS in this population. Since pCRb requires invasive tissue sampling, using ypN as a predictor of OS would allow for more efficient risk stratification with overall less invasive testing. Research Sponsor: None.

8057 **Poster Session**

Differences in central versus local lab PD-L1 classification in the ALCHEMIST Alliance A151216 non–small cell lung cancer (NSCLC) study. First Author: David E. Kozono, Mass General Brigham Cancer Institute, Boston, MA

Background: The NCI Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) study tested resected stage II-IIIB(N2) NSCLC for targetable EGFR and ALK alterations and PD-L1 expression to screen patients for biomarker-driven adjuvant therapy trials (NCT02194738). Local lab results were requested when available for comparison to central lab results. **Methods:** We identified patients with both central and local PD-L1 results in the ALCHEMIST adjuvant immunotherapy study screening population. Discrepancies in tumor proportion score (TPS) between central and local PD-L1 were defined using prespecified cut-points (granular: $<$1%, 1-$<$5%, 5-$<$10%, 10-$<$20%, 20-$<$30%, 30-$<$40%, 40-$<$50%, 50-60%, 60-$<$70%, 70-$<$80%, 80-$<$90%, 90-$<$100%; clinical: $<$1%, 1-$<$50%, 50-100%). Large discrepancies were defined as $\geq$ 50 percentage point differences; for these cases, local PD-L1 and hematoxylin & eosin-stained slides were requested. These and all central slides were digitally scanned at 40X. Three expert pathologists reviewed the scanned slides in a blinded fashion. Differences between patient or tumor characteristics were assessed by Chi-square and Wilcoxon rank sum tests. Percent agreement was computed within and between the reviewers. **Results:** Central and local PD-L1 results were available for 497 patients. 177 cases (36%) had discrepancies that placed patients in different clinical TPS categories ($<$1%, 1-$<$50%, 50-100%). Among these, 43 cases had large TPS discrepancies; 14 had available local testing slides. 46 of the 320 cases without discrepancy were randomly selected as controls. No patient or tumor characteristics were associated with discrepancy, including tumor location, histology, grade or cancer stage ($p > 0.05$). Pairwise comparisons of TPS according to three pathologists re-reading the same scanned PD-L1 slides showed similar levels of disagreement in clinical TPS category whether there was initial discrepancy between central and local results (24%, 34%, and 23%; mean 27%) or not (33%, 30%, and 20%; mean 28%). Among the 14 cases with large initial discrepancies and local slides available, there was agreement in clinical TPS category when the anonymized central and local scanned slides were re-read by the pathologists in 54%, 38%, and 43% of cases, despite 100% non-agreement in initial reads. There were higher rates of agreement when the tested slides both originated from the same (100%) versus different (35%) blocks, when the same (48%) versus different (40%) PD-L1 antibodies were used, and when the cases were of non-squamous (52%) versus squamous (14%) cell carcinoma. **Conclusions:** There are substantial differences in PD-L1 TPS read by pathologists that can result in placement of patients in different categories commonly used for clinical management. These differences have clear implications in clinical trials and routine patient care. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; Alliance for Clinical Trials in Oncology Foundation.

8058 **Poster Session**

Firmonertinib combined with cisplatin/carboplatin plus pemetrexed as neoadjuvant therapy in resectable stage II-IIIb *EGFR*-mutated non–small cell lung cancer: A single-arm, single-center, open-label phase II study. First Author: Jie Xu, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: For patients with resectable, locally advanced EGFR-mutated NSCLC, traditional neoadjuvant chemotherapy yields suboptimal efficacy. While EGFR-TKIs are standard in the adjuvant therapy, their role in neoadjuvant therapy is under active investigation. **Methods:** This single-arm, phase II study evaluated neoadjuvant firmonertinib plus platinum-based chemotherapy in patients with stage II-IIIB EGFR-mutated NSCLC. The primary endpoint was major pathological response (MPR), the major second endpoint were pathological complete response (pCR), objective response rate (ORR), R0 resection rate and rate of downstaging. **Results:** Among the 13 patients currently enrolled, 11 completed 4 cycles of neoadjuvant therapy, and 9 underwent radical surgery. The MPR rate and the pCR rate are both currently at 0. The ORR is 77.8%, and the radical resection rate reaches 100%. The TNM tumor stage reduction rate is 66.7%. The incidence of grade 3/4 adverse events is 11.1%, and there are no 5-grade adverse events. **Conclusions:** Firmonertinib with chemotherapy as neoadjuvant in II-IIIB EGFR-mutated NSCLC demonstrated a promising surgical conversion rate and a manageable safety profile, supporting its feasibility for further study. Clinical trial information: NCT06890182. Research Sponsor: None.

8059 **Poster Session**

RATIONALE-315: Post hoc analysis of event-free survival by surgically relevant subgroups treated with perioperative tislelizumab and neoadjuvant chemotherapy vs neoadjuvant chemotherapy. First Author: Gustavo Schvartsman, Hospital Israelita Albert Einstein, Sao Paulo, Brazil

Background: RATIONALE-315 (NCT04379635) compared the efficacy and safety of perioperative tislelizumab (TIS) or placebo (PBO) + neoadjuvant chemotherapy (CT) in patients (pts) with resectable NSCLC. This post hoc analysis reports correlation of event-free survival (EFS) to key surgical outcomes. **Methods:** Pts with resectable stage II-IIIA NSCLC (N=453) were randomized 1:1 to 3-4 cycles of TIS 200 mg or PBO Q3W with neoadjuvant CT, followed by surgery and $\leq$8 cycles of adjuvant TIS 400 mg or PBO Q6W. Primary and key secondary endpoints were reported previously. Exploratory endpoints of surgical outcomes are presented here. **Results:** As of March 7, 2025, 190/226 pts in the TIS arm and 173/227 pts in the PBO arm underwent definitive surgery. EFS benefit with TIS vs PBO was observed in all surgically relevant subgroups (HR: 0.62; 95% CI: 0.44-0.88). Although R0 resection rates were similar between treatment arms, TIS showed greater EFS benefit vs PBO (HR: 0.62; 95% CI: 0.43-0.90). A similar trend was observed in R1/R2 pts (HR: 0.75; 95% CI: 0.19-3.05); however, data should be interpreted with caution due to small pt numbers. Pts in the TIS arm who underwent open and minimally invasive surgery (n=179) achieved improved EFS benefit compared with those in the PBO arm (n=157), regardless of disease stage and surgery type (Table). In pts who underwent minimally invasive and open surgery, respectively, grade $\geq$3 treatment-emergent adverse events occurred in 77.2% and 78.8% of pts in the TIS arm and 71.3% and 81.7% in the PBO arm. In pts who underwent minimally invasive surgery in the TIS arm, grade $\geq$3 immune mediated adverse events were reported in 11.4% of all pts (13/114), 10.4% of pts in stage II (5/48), and 12.3% in stage IIIa (8/65). **Conclusions:** Perioperative TIS + neoadjuvant CT improved EFS in pts with resectable NSCLC across all surgically relevant subgroups regardless of disease stage or surgery type. These results further support TIS + CT as an efficacious and safe treatment option that may reduce the burden of invasive surgical intervention. Clinical trial information: NCT04379635. Research Sponsor: BeOne Medicines Ltd.

	EFS rate, % (95% CI)					
	12 mo		24 mo		48 mo	
Approach to surgery, NSCLC stage	TIS	PBO	TIS	PBO	TIS	PBO
Minimally invasive						
Overall	89.7 (82.2-94.2)	79.0 (78.0-86.6)	81.0 (72.1-87.3)	63.8 (51.8-73.6)	74.3 (64.0-82.1)	55.4 (42.0-67.0)
Stage II	90.9 (82.8-99.8)	85.0 (73.7-98.0)	83.6 (73.1-95.5)	69.8 (55.8-87.4)	77.0 (64.6-91.8)	66.5 (52.1-84.8)
Stage IIIa	88.7 (77.8-94.5)	73.1 (56.7-84.1)	78.9 (66.5-87.2)	58.0 (41.3-71.4)	72.4 (58.6-82.3)	46.7 (29.0-62.6)
Open						
Overall	78.5 (65.9-86.9)	70.9 (57.8-80.6)	60.2 (46.7-71.2)	47.8 (34.9-59.6)	54.1 (40.4-66.0)	31.1 (17.3-45.8)
Stage II	85.7 (72.0-100)	80.0 (64.3-99.6)	76.2 (60.0-96.8)	55.0 (37.0-81.8)	71.4 (54.5-93.6)	NE (NE-NE)
Stage IIIa	74.1 (57.2-85.2)	66.4 (49.9-78.6)	50.3 (33.7-64.8)	44.3 (28.9-58.6)	NE (NE, NE)	28.7 (13.9-45.5)

NE, not evaluable.

8060 **Poster Session**

Survival outcomes between neoadjuvant and adjuvant chemo-immunotherapy in patients with stage II–III NSCLC undergoing surgical resection. First Author: Joseph Zouein, Department of Medicine, Cooper University Health Care, Camden, NJ

Background: In patients with stage II–III NSCLC, perioperative systemic therapy is recommended; however, the optimal timing of chemo-immunotherapy relative to surgery remains an area of active investigation. The aim of this study was to compare overall survival outcomes between neoadjuvant and adjuvant chemo-immunotherapy in patients with stage II–III NSCLC undergoing surgical resection. **Methods:** We utilized the National Cancer Database (NCDB) and included patients with complete follow-up data, diagnosed between 2018 and 2023 with clinically staged IIA–IIIB NSCLC (cT1–cT4, cN0–cN2, cM0), who underwent definitive surgical resection, and received either neoadjuvant or adjuvant chemo-immunotherapy. Kaplan–Meier analysis and propensity score–adjusted Cox proportional hazards models were used to assess survival outcomes. **Results:** A total of 2,815 patients met the inclusion criteria, including 1,521 (54%) males, with a median age of 66 years. Of these, 1,186 (42%) patients received neoadjuvant therapy and 1,629 (58%) received adjuvant therapy. Median overall survival (OS) was not reached in the neoadjuvant group, compared with 79.4 months (95% CI, 68.1–90.7, $p < 0.001$) in the adjuvant group (Table 1). On propensity score–adjusted Cox regression, neoadjuvant therapy was associated with a significant OS advantage compared with adjuvant therapy (HR 0.71; 95% CI, 0.58–0.87; $p < 0.001$). Neoadjuvant therapy was associated with improved OS among patients with baseline cN2 disease (HR 0.64; 95% CI, 0.45–0.91; p = 0.012). No statistically significant difference in OS was observed among patients with cT3 or cT4 disease (HR 0.95; 95% CI, 0.66–1.36; p = 0.759) and HR 0.67; (95% CI, 0.45–1.01; p = 0.053), respectively. **Conclusions:** In patients with stage II–III NSCLC undergoing surgical resection, neoadjuvant chemo-immunotherapy was associated with improved overall survival compared with adjuvant therapy, particularly among those with a higher nodal or regional tumor burden at presentation. Research Sponsor: None.

Median overall survival and hazard ratios for neoadjuvant versus adjuvant chemo-immunotherapy in stage II–III NSCLC.

	Neoadjuvant Median OS (months)	Adjuvant Median OS (months)	Hazard Ratio (HR)	95% CI	p-value
Overall cohort	NR	79.4 (68.1–90.7)	0.71	0.58–0.87	<0.001
cN2	NR	62.6 (45.4–79.8)	0.64	0.45–0.91	0.012
cT3	NR	76.3 (62.4–90.1)	0.95	0.66–1.36	0.759
cT4	71.0 (62.7 – 79.3)	56.1 (37.6- 74.5)	0.67	0.45–1.01	0.053

8061 **Poster Session**

Characteristics of patients with resectable early-stage non–small cell lung cancer treated with neoadjuvant chemoimmunotherapy or surgery ± adjuvant therapy. First Author: Pragya Rai, Merck & Co., Inc., Rahway, NJ

Background: The integration of immune checkpoint inhibitors (ICIs) into neoadjuvant, perioperative, and adjuvant treatment strategies for early-stage NSCLC (eNSCLC) has been associated with improved patient outcomes; however, despite these advances, uptake of ICIs in the neoadjuvant/perioperative setting remains limited. This study aimed to characterize differences in patient characteristics between those receiving neoadjuvant chemoimmunotherapy (neoadjuvant ICI+CTx) and those receiving upfront surgery ± adjuvant therapy. **Methods:** Adult patients with stage II-IIIB(N2) NSCLC (AJCC 8th edition) diagnosed between March 2022 and six months before data cut-off (November 2025) were identified in the Flatiron Health database. Patients who received ICI+CTx prior to surgery were assigned to the neoadjuvant ICI+CTx group, and patients that underwent upfront resection following an NSCLC diagnosis with no previous treatment, with or without adjuvant therapy, were assigned to the surgery± adjuvant therapy group. The Pearson chi-square or fisher exact tests were conducted to evaluate differences in baseline characteristics. All statistical analyses were two-sided. **Results:** A total of 1,807 patients were identified with resectable stage II-IIIB(N2) NSCLC, of which 204 (11%) initiated neoadjuvant ICI+CTx and 1,603 (89%) received surgery± adjuvant therapy (583 (36%) with adjuvant therapy; 1,020 (64%) without adjuvant therapy). Of the 204 patients, 144 (71%) underwent surgery and 76 (53% of those undergoing surgery) subsequently received adjuvant therapy. Significant differences were observed in the baseline characteristics between the two groups. Patients who received neoadjuvant ICI+CTx had higher proportion of stage III disease, cN2 status, evenly split histology, higher biomarker (PD-L1, EGFR) testing, PD-L1 positive expression levels, and fewer EGFR mutations while patients who received surgery± adjuvant therapy had higher proportion of stage II disease, cN0 status, non-squamous histology, lower biomarker testing, negative or low PD-L1 expression levels, and higher EGFR mutations (all $p < 0.001$). **Conclusions:** Despite the clear benefit across clinical trials of neoadjuvant and perioperative ICI strategies to treat resectable eNSCLC, their utilization in clinical practice remains limited. This study further demonstrates significant differences in baseline characteristics that might contribute to patient selection for neoadjuvant ICI+CTx versus upfront surgery ± adjuvant therapy as a primary therapeutic approach. Tailored interventions to further educate the medical community on recent clinical trial evidence may facilitate wider implementation of neoadjuvant and perioperative ICI strategies and broaden appropriate patient selection in resectable eNSCLC. Research Sponsor: Merck & Co., Inc., Rahway, NJ, USA.

8062 **Poster Session**

Impact of adjuvant immunotherapy after pathologic complete response to neoadjuvant chemo-immunotherapy in resected stage II–III non–small cell lung cancer. First Author: Joseph Zouein, Department of Medicine, Cooper University Health Care, Camden, NJ

Background: Perioperative chemo-immunotherapy has recently emerged as a new standard of care for patients with resectable non–small cell lung cancer (NSCLC) following positive results from the CheckMate-77T (NCT04025879) and KEYNOTE-671 (NCT03425643) trials. However, whether patients who achieve a complete pathologic response (pCR) after neoadjuvant chemo-immunotherapy derive additional benefit from subsequent adjuvant immunotherapy remains uncertain due to limited available data (only 58 patients achieved pCR in CheckMate-77T and 72 patients in KEYNOTE-671). The INSIGHT clinical trial (NCT06498635) is an ongoing phase III study designed to address this question; however, the trial is expected to be completed in 2039. Therefore, generating additional data in this area is critically important. We performed a retrospective analysis to assess whether the addition of adjuvant immunotherapy improves overall survival (OS) among patients with stage II–III NSCLC who achieve pCR following neoadjuvant chemo-immunotherapy. **Methods:** We conducted a retrospective cohort study using the National Cancer Database (NCDB) and included patients with complete follow-up data who were diagnosed between 2018 and 2023 with clinically staged IIA–IIIB NSCLC (cT1–cT4, cN0–cN2, cM0), underwent definitive surgical resection with pCR (ypT0N0M0), and received either neoadjuvant chemo-immunotherapy alone or neoadjuvant chemo-immunotherapy followed by adjuvant immunotherapy (perioperative chemo-immunotherapy). Survival outcomes were analyzed using Kaplan–Meier methods. **Results:** A total of 1,816 patients were included, of whom 967 (53.2%) were male, with a median age of 65 years (IQR, 60–71). Among these patients, 1,186 (65.3%) received neoadjuvant chemo-immunotherapy alone, and 630 (34.7%) received perioperative therapy. No significant difference in overall survival was observed between the two treatment groups. Median OS was not reached in either group, with a hazard ratio of 1.235 (95% CI, 0.602–2.533; p = 0.565). **Conclusions:** Among patients with stage II–III NSCLC who achieve pCR following neoadjuvant chemo-immunotherapy and undergo surgical resection, we observed no significant difference in overall survival between those treated with neoadjuvant therapy alone versus perioperative chemo-immunotherapy. These findings suggest that neoadjuvant chemo-immunotherapy alone may be sufficient for patients who achieve pCR, and that adjuvant immunotherapy in this setting may not provide additional survival benefit. Research Sponsor: None.

8064 **Poster Session**

Postoperative re-profiling for identification of missed drivers and a high-risk fusion subgroup in non-pCR lung adenocarcinoma after neoadjuvant immunotherapy: A multicenter retrospective study. First Author: Xin Liu, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: For stage II-III driver-negative non–small cell lung cancer (NSCLC), neoadjuvant chemoimmunotherapy followed by surgery is standard. However, patients without pathological complete response (non-pCR) have suboptimal outcomes and heterogeneous benefit from adjuvant immunotherapy. Baseline driver-negative status may be confounded by false-negative PCR- or DNA-only testing and detecting missed drivers postoperatively could alter adjuvant strategies. This study characterized post-treatment driver alterations and its prognostic value in non-pCR NSCLC after neoadjuvant immunotherapy. **Methods:** The retrospective multicenter study enrolled 247 stage II-III lung adenocarcinoma (LUAD) patients initially tested as EGFR L858R/19del- and ALK-negative and treated with neoadjuvant immunotherapy (2018-2025). 76 lung squamous cell carcinoma (LUSC) cases were included for exploratory analysis. Postoperative samples underwent 35-gene synchronous DNA/RNA next-generation sequencing (DR-NGS) to identify SNV/indel and fusion events and assess prognostic associations. **Results:** Of 247 LUAD cases, 179 passed NGS quality control (QC). Driver alterations were identified in 104 (58.1%) patients, including 26 fusions: RETn = 9), MET ex14 skipping (n = 6), ALK(n = 4), ROS1(n = 3), NRG1(n = 2), MET fusion(n = 1), NTRK(n = 1) and 80 SNVs/indels :EGFR (n = 30), KRAS G12C/D (n = 16), HER2/3 (n = 16), BRAF (n = 2), KRAS non-G12C/D (n = 16). Notably, 10 classic EGFR mutations (19del/L858R) 、 9 rare EGFR mutations and 4 ALK fusions were newly identified, indicating baseline omissions. Driver-positive tumors had significantly higher residual tumor burden(median: 51.8% vs. 35.8%, p = 0.003) and a higher proportion of females (43.3% vs 20.0%, p = 0.001). Median recurrence-free survival (mRFS) differed significantly among fusion-positive, mutation-positive, and driver-negative groups (20.9 vs 41.5 vs 60.3 months; p = 0.024). In patients receiving adjuvant immunotherapy, mRFS was 34.6 months in driver-positive and not reached in driver-negative patients. Driver detection was rare (< 3%) in QC-failed samples (n = 68), which exhibited a higher major pathological response than QC-passed samples (58.1% vs 14.5%), indicating tumor cellularity as critical for detection. Exploratory analysis in 55 QC-passed LUSC samples showed a low driver detection rate (7.3%), suggesting limited utility in this cohort. **Conclusions:** DR-NGS reveals a high prevalence of drivers in non-pCR LUAD after neoadjuvant immunotherapy, with positivity associated with higher residual tumor burden. Fusion-positive patients have the poorest prognosis, identifying a subgroup that may benefit from tailored adjuvant strategies. These findings support routine postoperative molecular re-profiling in non-pCR patients to guide individualized treatment. Research Sponsor: The National Natural Science Foundation of China (grant No.82573102, 82173038, 82273428); Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0501700, 2023ZD0501703).

8065 Poster Session

CT-derived visceral fat phenotypes to reveal a metabolically defined TOFI subgroup in a lung cancer screening cohort: An imaging-based framework for evaluating the BMI paradox. First Author: Taofik Ahmed Suleiman, Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA

Background: Body mass index (BMI) imperfectly reflects metabolic health and cannot distinguish subcutaneous from visceral fat, contributing to the long-standing "BMI paradox" in cancer, whereby higher BMI is sometimes associated with better survival. Visceral fat is metabolically active and promotes cancer progression. Individuals with normal BMI but high visceral fat, termed "Thin Outside, Fat Inside" (TOFI) are understudied in cancer populations. These TOFI patients may represent an unrecognized high-risk metabolic phenotype in cancer. We investigated whether CT-derived lower-thoracic visceral fat identifies TOFI as a high-risk subgroup for cancer mortality. **Methods:** Baseline CT scans from participants in the National Lung Screening Trial (NLST; n = 19,140), a lung cancer screening cohort designed to detect NSCLC, were segmented to extract subcutaneous fat, visceral fat, and vertebral levels. Because T9–T12 best captures abdominal visceral adiposity, the percentage volume of visceral fat relative to subcutaneous fat from this region was used for phenotyping. Low ($<$20%) and high ($>$40%) visceral fat groups were defined, yielding 9,887 participants. Visceral fat was combined with BMI ($<$25 vs $\geq$25) to define four phenotypes: P1 (LowBMI_LowVIS), P2 (HighBMI_LowVIS), P3 (HighBMI_HighVIS), and P_TOFI (LowBMI_HighVIS). Cancer-specific mortality was the primary endpoint, and Cox proportional hazards models were used to compare these phenotypes. **Results:** Distinct phenotypes demonstrated markedly different mortality risks (Table). The TOFI group exhibited the worst survival despite normal BMI, with nearly double the cancer mortality risk compared with the metabolically favorable reference group, P1 (HR 1.95; 95% CI, 1.31-2.91; p = 8.4e-04). In contrast, high-BMI groups showed only modest or no excess risk, supporting the limitation of BMI alone. **Conclusions:** CT-derived visceral fat phenotyping reveals a clinically relevant high-risk group TOFI, individuals who have normal BMI but significantly elevated cancer and all-cause mortality risk compared to even high-BMI patients. This finding directly exposes the BMI paradox, showing that normal BMI does not confer protection when visceral adiposity is high. Because this TOFI phenotype is undetectable by BMI, incorporating visceral fat assessment into lung cancer screening and survivorship models could enable earlier identification of high-risk TOFI patients and guide targeted prevention. Research Sponsor: None.

Phenotype	Cancer Mortality HR (95% CI)	p-value	All-Cause Mortality HR (95% CI)	p-value
P_TOFI (LowBMI_HighVIS)	**1.95 (1.31-2.91)**	**8.4e-04**	**2.42 (1.84-3.18)**	**7.5e-11**
P3 (HighBMI_HighVIS)	1.25 (0.91-1.71)	1.7e-01	1.59 (1.27-1.98)	3.7e-05
P2 (HighBMI_LowVIS)	0.92 (0.64-1.30)	6.2e-01	1.08 (0.84-1.39)	5.4e-01
P1 (LowBMI_LowVIS)	Reference	-	-	-

8066 Poster Session

Stage-dependent divergence of immune prognostic signatures in non–small cell lung cancer. First Author: Praveen Thapa, Chirayu National Hospital, Kathmandu, Nepal

Background: Tumor mutational burden (TMB) and immune activation are widely studied biomarkers in non–small cell lung cancer (NSCLC), yet their prognostic relevance outside the context of immunotherapy remains unclear. We investigated how age, histology, and disease stage modify the relationships between tumor genomics, immune contexture, and overall survival in NSCLC. **Methods:** We analyzed The Cancer Genome Atlas NSCLC cohort from the "Pan-cancer atlas" (2018) with a total of 1053 patients evaluating TMB, CD8A expression, cytolytic activity score (CYT), age at diagnosis, histology, and overall survival. Associations among continuous variables were assessed using Spearman correlation. Multivariable Cox proportional hazards models adjusted for age, sex, and tumor mutational burden were performed and stratified by stage (I–II vs III–IV). **Results:** Age demonstrated an inverse correlation with tumor mutational burden ($\rho = -0.12$, $P < 0.001$) but was not associated with CD8A expression and showed a weak positive association with CYT, driven by non-squamous tumors. Tumor mutational burden was not associated with overall survival in either early- or late-stage disease. In contrast, immune biomarkers demonstrated marked association with stage of disease. Higher CD8A expression was associated with improved survival in early stage (HR 0.77 per SD, P = 0.021) but not in advanced disease. CYT exhibited a significant interaction with stage with higher CYT showing association with improved survival in early-stage NSCLC (HR 0.79 per SD, P = 0.026) but with worse survival in late-stage disease (derived HR $\approx$ 1.14). Tumor stage remained the dominant prognostic factor across all models. **Conclusions:** In untreated NSCLC, immune prognostic signatures are strongly stage dependent. Immune infiltration and cytolytic activity confer survival benefits in early-stage disease but not in advanced disease, where cytolytic activity may reflect aggressive tumor-associated inflammation. Tumor mutational burden does not provide prognostic value across disease stages. These findings highlight the importance of disease context when interpreting immune biomarkers and provide critical baseline insight for immunotherapy-era studies. Research Sponsor: None.

Patient characteristics.

Characteristic	Overall (N=1053)	Early Stage (I–II) (N=517)	Late Stage (III–IV) (N=479)
Age, median (IQR)	67	68	67
Sex, % male	40.24 (402)	44.68 (231)	35.69 (171)
Histology, %			
Squamous	46.24 (487)	46 (238)	51.35 (246)
Non-squamous	53.7 (566)	56 (279)	50 (233)
Stage			
I–II	47%		
III–IV	53%		
TMB, median (IQR)	7.3 (3.9-12.1)	7.35 (3.7-12.1)	7.36 (4.2-12.1)
CD8A expression, median (IQR)	232 (112-469)	240 (122-471)	208 (103-460)
CYT score, median (IQR)	183 (103.9-368.3)	191.3 (109.6-368.3)	175.9 (98-370)

8067 Poster Session

Survival outcomes of young patients with non-small cell lung cancer in Latin America: A real-world cohort study. First Author: Cristina Torres-Mallma, AUNA, Lima, Lima, Peru

Background: Young patients with non-small cell lung cancer (NSCLC) represent a distinct biological subgroup, frequently enriched with actionable oncogenic drivers. However, real-world survival data from Latin America are limited. We evaluated survival outcomes and prognostic factors in young versus older patients with NSCLC treated in Peru. **Methods:** We conducted a retrospective cohort study including patients with histologically confirmed NSCLC treated between 2018and 2024 at a national reference cancer center. Patients were stratified by age at diagnosis ($<$45 vs $\geq$45 years). Overallsurvival (OS) was estimated using the Kaplan–Meier method. Multivariable Cox regression was performed adjusting for sex,ECOG performance status, smoking history, clinical stage, histology, molecular alterations and first-line treatment. **Results:** A total of 317 patients were included; 19.9% were younger than 45 years. The cohort was predominantly female (59.3%),never-smokers (85.5%) and had adenocarcinoma histology (95.6%). Advanced disease (stage III–IV) was present in 94.0% ofcases. Actionable molecular alterations were identified in 69.4% of patients, most commonly EGFR mutations (48.3%).Younger patients showed a higher frequency of actionable mutations compared with older patients (70% vs 56%, p=0.038).After a median follow-up of 40.9 months, 92 deaths (29.0%) were recorded. In adjusted analysis, young age was notassociated with worse OS (adjusted HR 1.32; 95% CI 0.79–2.21; p=0.29). Former smoking history was the only independentpredictor of inferior OS (adjusted HR 2.38; 95% CI 1.16–4.91; p=0.018). **Conclusions:** Young age at NSCLC diagnosis was not associated with inferior survival. Despite advanced-stage presentation, youngerpatients exhibited a high prevalence of actionable oncogenic drivers, supporting routine comprehensive molecularprofiling. These results provide robust regional evidence and reinforce the importance of precision oncology inunderrepresented populations. Research Sponsor: None.

8068 Poster Session

Immune aging within the tumor microenvironment as a predictor of survival in non–small cell lung cancer. First Author: Taeyun Kim, Kosin University College of Medicine, Busan, South Korea

Background: Immune aging has been associated with survival outcomes in patients with lung adenocarcinoma (LUAD), but its relevance within the tumor microenvironment (TME) remains unclear. **Methods:** Clinical and RNA-sequencing data from the TCGA LUAD cohort were analyzed. Immune aging within tumor tissue was quantified using a predefined 121-gene immune aging–related signature (IAS-121). For primary analyses, patients were dichotomized into high versus low IAS-121 groups based on the median value. Immune cell composition within the TME was inferred using xCell analysis and compared according to IAS-121 status. Overall survival (OS) was assessed using Kaplan–Meier analysis and Cox proportional hazards models adjusted for age, sex, tumor stage, smoking status, and EGFR mutation status. Sensitivity analyses were performed using quartile-based categorization of IAS-121 (lowest vs highest quartile), and external validation was conducted in two independent LUAD cohorts (GSE68465 and GSE50081). **Results:** A total of 518 patients with LUAD from the TCGA cohort were included. Patients with high IAS-121 had significantly poorer OS compared with those with low IAS-121 (p=0.026). In multivariable analysis using the median cut-off, high IAS-121 showed a non-significant trend toward increased mortality (adjusted hazard ratio [aHR] 1.33; 95% confidence interval [CI], 0.96–1.84). In sensitivity analyses comparing the lowest and highest quartiles of IAS-121, a significant association with OS was observed (aHR 1.87; 95% CI, 1.20–2.92). This association was further confirmed in a pooled analysis of the external LUAD cohorts (GSE68465 and GSE50081), in which higher IAS-121 was independently associated with worse OS (aHR 1.57; 95% CI, 1.02–2.43). Subgroup analyses showed generally consistent associations across age, sex, tumor stage, smoking status, and EGFR mutation status. Tumors with high IAS-121 exhibited reduced enrichment of $CD8^+$ T cells and $CD4^+$ naïve T cells, along with increased neutrophil enrichment. **Conclusions:** Immune aging within TME is associated with poorer survival in LUAD. As this study is hypothesis-generating, further investigations integrating tissue- and blood-based measures of immune aging are warranted to clarify its clinical and biological implications. Research Sponsor: None.

Cox proportional hazards models comparing the lowest versus highest quartile of immune aging score-121 and overall survival in lung adenocarcinoma.

	TCGA		GSE68465 plus GSE50081	
	HR (95% CI)	p	HR (95% CI)	p
Crude	1.648 (1.114 – 2.238)	0.012	2.093 (1.396 – 3.141)	$<$0.001
Adjusted	1.873 (1.200 – 2.924)	0.006	1.571 (1.016 – 2.429)	0.007

Models adjusted age, sex, tumor stage, smoking status, and EGFR mutation status for TCGA dataset and age, sex, tumor stage for GSE68465 plus GSE50081 cohorts.
LUAD = lung adenocarcinoma; HR = hazard ratio; CI = confidence level.

8069 **Poster Session**

Age-based differences in outcomes among small cell lung cancer patients treated with tarlatamab. First Author: Raymart Macasaet, Monmouth Medical Center, Long Branch, NJ

Background: Tarlatamab has durable antitumor activity in patients with previously treated Small Cell Lung Cancer (SCLC). A rising fraction of SCLC diagnoses is now observed in older patient groups. To assess real-world outcomes, we analyzed a large, multi-institutional database evaluating age-related differences in survival, treatment patterns, and immune toxicities, including Cytokine Release Syndrome (CRS) and Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS), to clarify factors affecting response and tolerability. **Methods:** A retrospective cohort study was conducted using de-identified data from the TriNetX Research Network. At the time of data analysis, it included 154,537,377 patients across 113 healthcare organizations. We identified adults aged 18 years or older with lung cancer treated with Tarlatamab. Kaplan-Meier analysis assessed overall survival. Statistical comparisons of survival rates between groups were performed using the log-rank test. Propensity matching was used to adjust for age, comorbidities, and lines of treatment. **Results:** A total of 616 patients were identified in the TriNetX cohort, with a mean age of 65.8 $\pm$ 9.89 years, and 51.9% were female. Age distribution was as follows: 124 patients (20.13%) were younger than 60 years, 271 (43.99%) were 60–70 years, and 221 (35.88%) were older than 70 years. Brain metastases were present in 53 patients (8.60%) in the $<$60 group, 116 (18.83%) in the 60–70 group, and 90 (14.61%) in the $>$70 group. Median overall survival of the entire cohort was 13.32 months; it was not reached in the $<$60 group, 13.32 months in the 60–70 group, and 12.72 months in the $>$70 group, with no significant differences across age groups or brain metastasis status. In the propensity score–matched cohorts, survival did not differ significantly between $<$60 and $>$70 age groups (HR 0.80 (95% CI 0.34–1.22; p=0.39)), and a similar lack of difference was observed between 60–70 and $>$70 age groups (HR 0.72 (95% CI 0.48–1.07; p=0.10)). In the overall population, 57 patients (9.25%) experienced ICANS and 67 (10.88%) developed CRS. By age group, ICANS and CRS occurred in 16 (2.60%) and 17 (2.76%) patients $<$60, 23 (3.73%) and 29 (4.71%) patients 60–70, and 18 (2.92%) and 21 (3.40%) patients $>$70, respectively. Overall, 91 patients (14.77%) required tocilizumab and 23 (3.73%) required vasopressors, with no significant differences across the three age groups. **Conclusions:** This study offers an extensive evaluation of age-related outcomes with Tarlatamab. Neither age nor brain metastases significantly influenced overall survival, indicating preserved efficacy in older adults. ICANS and CRS were infrequent and evenly distributed across age groups. Tocilizumab and vasopressor use were similar across groups, indicating comparable severity. These results support Tarlatamab's favorable safety, tolerability, and effectiveness across diverse real-world populations. Research Sponsor: None.

8070 **Poster Session**

SPARK-Lung: A study of patterns and outcomes in young-onset lung cancer. First Author: Teja Voruganti, Penn Medicine Abramson Cancer Center, Philadelphia, PA

Background: Young onset lung cancer patients diagnosed before age 50 appear to have distinct features compared to their older counterparts, including a higher proportion of never-smokers and increased frequency of targetable driver mutations. Yet, the molecular characteristics and survival outcomes of young-onset non-small cell lung cancer (NSCLC) remain poorly defined in U.S. populations. Improved understanding of the demographic and molecular profile of this distinct disease is needed to guide diagnostic testing strategies and personalize treatment. **Methods:** We conducted a retrospective cohort study using the US-based, electronic health record-derived deidentified Flatiron Health Research Database, which included adults diagnosed with NSCLC between 2013 and 2025 who underwent next-generation sequencing. Young-onset NSCLC was defined as age $<$ 50 years and older-onset as $\geq$50 years. Demographics, stage at diagnosis, and prevalence of driver mutations and fusions were compared between age groups. Differences are reported using standardized mean differences (SMD) with SMD $\geq$0.2 indicating significant difference. Treatment patterns and overall survival (OS) were evaluated in metastatic patients adjusting for sex, histology, smoking status, performance status, insurance, and TP53 status. **Results:** Among 3792 young-onset and 120,161 older-onset patients with NSCLC across all stages, young-onset patients were more often female (54.2% vs 51.2%), Asian (5.3% vs 2.4%), Black (12.4% vs 8.1%), or Hispanic/Latino (8.5% vs 3.6%) (SMD 0.38). They were more often treated in academic settings (24.8% vs 16.0%; SMD 0.26) and more likely to have no tobacco history (36.6% vs 13.8%; SMD 0.65). Non-squamous histology predominated in younger patients (85.1% vs 73.1%; SMD 0.29) and actionable driver alterations were more common (47.8% vs 40.5%), particularly ALK (9.3% vs 1.2%; SMD 0.66) and EGFR (17.6% vs 11.0%; SMD 0.21). Young-onset patients were more likely to present with metastatic disease (69.8% vs 49.2%; SMD 0.43). After adjustment, treated young-onset patients received more lines of therapy than older patients (median no. 2 vs 1; incident rate ratio 1.16; 95% CI 1.12–1.20; $p < 0.0001$) and had longer median treatment duration (23.7 vs 14.3 mos, $p < 0.0001$). Among patients with metastatic disease at diagnosis, unadjusted median OS was longer in young-onset versus older-onset patients (2.0 vs 1.1 years), with higher 1-year (72.6% vs 57.2%) and 2-year (56.7% vs 41.8%) OS rates. **Conclusions:** Young-onset NSCLC represents a clinically distinct population in the United States, characterized by higher rates of advanced stage at diagnosis, a higher percentage of actionable molecular alterations and improved survival in the metastatic setting. Recognition of these differences may inform screening, testing, treatment, and survivorship strategies for younger adults with NSCLC. Research Sponsor: None.

8071 **Poster Session**

Real-world impact of first immunotherapy infusion timing on outcomes in locally advanced non-small cell lung cancer. First Author: Mumtu Lalla, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY

Background: Emerging evidence suggests that earlier time-of-day (ToD) infusion of immune checkpoint inhibitors (ICIs) is associated with improved progression-free survival (PFS) and overall survival (OS) in patients with advanced non-small cell lung cancer (NSCLC). Although the timing of the initial infusion may be particularly influential, its impact on outcomes in earlier stages of NSCLC remains unclear. We investigated the association between first ICI infusion ToD and clinical outcomes in a racially and ethnically diverse population with locally advanced NSCLC. **Methods:** We conducted a retrospective cohort study of patients with locally advanced NSCLC treated with definitive chemoradiation followed by consolidation durvalumab between 2018-2025. Patient demographics, smoking status, ECOG performance status, PD-L1 tumor proportion score (TPS), lung cancer stage and histology, disease volume (DV), mean heart dose, and clinical outcomes were all obtained using chart review. Neighborhood distress was classified using patient zip codes and the Distress Communities Index. ICI administration timing was categorized into quartiles: $\leq$11:20 AM, 11:20 AM-12:32 PM, 12:32 PM-13:48 PM, $>$13:48 PM. Kaplan Meier methods and cox proportional hazards models, adjusted for major patient factors, were used to evaluate OS and PFS. **Results:** Among 109 eligible patients (median age 69.5 years), 55% were male, 42% were Non-Hispanic Black, 30% were Hispanic, 64% resided in distressed ZIP codes. Patients receiving ICIs in the latest ToD quartile ($>$13:48) had a significantly shorter PFS compared to those treated in the earliest quartile ($\leq$11:20) in both univariate (HR 2.10, p=0.024) and multivariate analysis (HR 3.32, p=.0.0057). A non-significant trend towards inferior OS was also observed with later ToD administration. Higher DV (HR 1.09 per 10 mL, p=0.029) and mean heart dose (HR 1.86, p=0.03) were independently associated with worse OS. **Conclusions:** In this real-world study of a diverse population with locally advanced NSCLC, later ToD ICI administration ($>$13:48) was associated with a significantly shorter PFS and a trend towards worsened OS. These findings suggest that the timing of ICI delivery may influence outcomes in locally advanced NSCLC, consistent with prior observations in metastatic disease, and highlight the need for prospective trials to validate the impact of infusion timing on survival and clarify the underlying circadian mechanisms contributing to these differences. Research Sponsor: None.

Multivariable Cox regression analysis.

	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
ToD of First Infusion						
≤11:20	-	-	-	-	-	-
11:20-12:32	1.53	0.57,4.10	0.40	1.68	0.75,3.80	0.21
12:32-13:48	0.48	0.15,1.59	0.23	1.30	0.53,3.16	0.57
>13:48	1.66	0.62,4.45	0.31	3.32	1.39,7.92	0.007
Mean Heart Dose (Gy)	1.86	1.06,3.26	0.030	1.54	0.98,2.42	0.060
Disease Volume (mL)	1.09 per 10 mL	1.01,1.17	0.029	1.03 per 10 mL	0.97,1.09	0.29

8072 **Poster Session**

Trends in income-related lung cancer disparities since the introduction of USPSTF screening guidelines. First Author: Tyler Munchmeyer Healy, NYU Grossman School of Medicine, New York, NY

Background: In 2013, the USPSTF introduced guidelines for lung cancer screening to promote earlier detection. Prior screening programs have unintentionally widened disparities due to limited access in vulnerable populations. We examined national US administrative data to explore the effect of lung cancer screening according to area levels of income. **Methods:** We studied adults with lung cancer in the SEER 21 Registries Database diagnosed between 2005-2022 over two time periods (pre-screening: 2005-2013; screening: 2014-2022). We evaluated outcomes of survival and stage distribution over varied levels of county median household income (MHI). We calculated descriptive statistics for our sample and used a Cox PH model to evaluate the interaction of time period and MHI while adjusting for other covariates. **Results:** We identified 485,763 cases in the pre-screening era and 487,001 cases in the screening era, with the median age for each group in the 60-69 years range. Sex, race, rurality, MHI and stage are reflective of US lung cancer demographics. Compared to the pre-screening era, cases in the screening era were more likely to be diagnosed at a localized stage in all MHI groups. The lowest MHI group saw a 24.6% increase in proportion of cases detected at a localized stage, while the highest MHI group saw a 37.5% increase. Median survival increased for all MHI groups with a positive association between MHI and survival gains. In a multivariable Cox PH model, a time period and MHI interaction term indicated that the income-related survival disparity between the highest and lowest MHI groups is 12.2% larger in 2014-2022 than in 2005-2013 (HR = 1.122, $p < 0.001$). **Conclusions:** Since the introduction of USPSTF lung cancer screening guidelines in 2013, lung cancers are detected at earlier stages and survival has improved. These changes have been experienced across all income groups, but the income-related disparities in survival have widened. These results indicate a need for additional efforts to ensure that the benefits of lung cancer screening are distributed across all populations regardless of wealth. Research Sponsor: None.

MHI	Year of Diagnosis	3-Year OS	5-Year OS	Median OS (Months)	Change in Median OS (Months)
< $60,000	2005-2013	19.4% (19.2-19.6)	13.8% (13.6-14.0)	8 (7.89-8.11)	2
	2014-2022	25.5% (25.1-25.9)	18.3% (17.9-18.7)	10 (9.84-10.16)	
$60,000 - $69,999	2005-2013	21.8% (21.6-22.0)	15.9% (15.7-16.1)	9 (8.88-9.12)	2
	2014-2022	29.2% (28.8-29.6)	21.8% (21.4-22.2)	11 (10.80-11.20)	
$70,000 - $79,999	2005-2013	22.6% (22.4-22.8)	16.7% (16.5-16.9)	9 (8.89-9.11)	4
	2014-2022	31.4% (31.0-31.8)	23.9% (23.5-24.3)	13 (12.78-13.22)	
$80,000 - $99,999	2005-2013	23.9% (23.7-24.1)	17.7% (17.5-17.9)	9 (8.87-9.13)	6
	2014-2022	33.8% (33.4-34.2)	25.8% (25.4-26.2)	15 (14.77-15.24)	
≥ $100,000	2005-2013	27.3% (26.9-27.7)	20.6% (20.2-21.0)	11 (10.81-11.19)	8
	2014-2022	38.6% (38.2-39.0)	30.1% (29.7-30.5)	19 (18.66-19.35)	

8073 Poster Session

A large prospective patient-advocacy assessment of fears, concerns, and challenges in patients diagnosed with lung cancer in the United States. First Author: Lisa Spain, Rexanna's Foundation, Prosper, TX

Background: Studies have been conducted assessing patient (pt) experiences with lung cancer, but minimal data is available on how fears and challenges differ by age, region, and disease stage. Through a pt advocacy organization, we performed a prospective analysis to capture pt and caregiver perceptions. **Methods:** 2055 surveys were sent out by non-profit organizations to US pts diagnosed with lung cancer and caregivers. 46% of the surveys (n = 956) were returned. Respondents included 63% (N = 603) pts (included in this abstract), 35.5% caregivers, and 1.5% medical professionals. Demographics included: ethnicity, time from diagnosis, gender, stage, region of country, age, role, and current disease status. Of 36 survey questions, 27 were multiple choice, 9 were open-ended and analyzed for recurring themes. Results were analyzed by region, stage, and age to determine if these influenced perspectives about living with lung cancer, and challenges with medical care or treatment. Chi-square test was used to assess differences in responses to survey questions across participant groups. Additional analysis was conducted using Fisher's exact test. Responses to each survey question were categorized, and the proportions of the topics were compared between participant groups. **Results:** Overall challenges reported by pts varied significantly by disease stage—both at the time of diagnosis ($p < 0.001$) and during treatment ($p < 0.001$). The fear cited most was disease progression or recurrence, in stage I (25.8%) or stage IV (27%) disease. Significant differences were observed across age groups relating to challenges with medical care or treatment ($p < 0.001$), and fears of living with lung cancer. ($p < 0.001$). Pts older than 45 were more concerned with side effects at diagnosis than younger than 45 (55.1% vs 33%, $p < 0.0001$) and were less concerned with financial issues (25.7% vs 44.7%, $p < 0.0001$) at treatment. Care costs and transportation challenges varied regionally, peaking in the Midwest (60.4%) and Southwest (56.5%). **Conclusions:** Fears, concerns and challenges faced by pts with lung cancer vary significantly by age, disease stage at diagnosis, and during treatment. The findings reveal an opportunity to deliver better support to pts throughout their journey and to allocate resources to address specific concerns. Research Sponsor: None.

Survey Question	Topic	Age: </= 44 (N=219)*	Age: >/= 45 (N=321)*	Fisher's Exact Test
Fears	Progression & Recurrence	10% (21)	29% (94)	$p < 0.0001$
"	Emotional & Psychological	18% (40)	10% (33)	$p < 0.01$
"	Inadequate Information	5% (11)	10% (33)	$p < 0.05$
Challenges at Diagnosis	Varied opinions	34% (75)	20% (63)	$p < 0.001$
"	Financial	40% (88)	24% (78)	$p < 0.0001$
"	Depression	32% (70)	53% (169)	$p < 0.0001$
Challenges at Treatment	Side Effects	33% (73)	55% (177)	$p < 0.0001$
"	Varied opinions	28% (62)	12% (39)	$p < 0.0001$
"	Financial	45% (98)	26% (82)	$p < 0.0001$

*63 patients did not respond to the question on age.

8074 Poster Session

Regional and gender disparities in lung cancer mortality in Guatemala. First Author: Natalia Pineda Grajeda, Independent Researcher, Miami, FL

Background: Lung cancer is the leading cause of cancer-related deaths worldwide and a major contributor in Latin America, where rates are generally lower. To date, there are no published population analyses describing lung cancer trends in Guatemala. **Methods:** Secondary analysis of publicly available national mortality data (Guatemala's National Institute of Statistics), extracting lung cancer deaths from 2012 to 2022. Deaths were summarized by region, department, year, and sex. Annual crude mortality rates (deaths per 100,000 inhabitants) using corresponding population denominators. **Results:** Between 2012 and 2022 Guatemala recorded 4273 lung cancer deaths (mean age 66,SD:16.17), concentrated in three regions (66.58%,n=2845): Metropolitan, Southwest and Central with the highest department-level counts in Guatemala (37.66%,n=1609), Quetzaltenango (6.53%,n=279), Huehuetenango (5.41%,n=231), San Marcos (5.24%,n=224) and Escuintla (5.29%,n=226). Crude lung cancer mortality ranged from 2.24 to 2.66 deaths per 100,000 inhabitants—highest in 2019 and 2020. Deaths were more frequent among men (54%,n=2,317), but deaths among women increased throughout the study period, resulting in a male-to-female ratio decline from 1.53 in 2012 to 1.07 in 2022. **Conclusions:** Guatemala's lung cancer mortality rates were lower compared to global estimates with nearly two-thirds of deaths concentrated in three regions —especially in Guatemala department— reflecting the concentration of health services in this region. Globally, lung cancer deaths show a marked sex disparity, with men accounting for about 68%. In contrast, Guatemala demonstrated a narrowing sex gap, with male-to-female mortality of nearly 1:1 by 2022, with rising mortality among women. These differences may reflect variations in smoking prevalence, access to early diagnosis, and health system capacity, with post-2020 shifts possibly influenced by COVID-19-related disruptions in diagnosis, treatment, referral pathways, or cause of death-of-death reporting. Research Sponsor: None.

Lung cancer deaths.

Region(Departments)	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	No(%)
Metropolitan(Guatemala)	132	129	121	125	144	148	156	175	182	146	151	1609(37.66)
North(Baja Verapaz, Alta Verapaz)	14	16	8	15	16	14	20	12	14	12	15	156(3.65)
Northeast(Izabal, Zacapa, Chiquimula, El Progreso)	27	32	37	28	44	32	36	35	25	42	30	368(8.61)
Southeast(Jalapa, Jutiapa)	50	33	41	39	33	27	32	45	40	30	33	403(9.43)
Central(Sacatepequez, Chimaltenango, Escuintla)	37	32	54	31	43	42	41	47	56	52	54	489(11.44)
Southwest(Solola, Totonicapan, Quetzaltenango, Suchitepequez, Retalhuleu, San Marcos)	45	70	52	64	82	67	74	70	79	76	68	747(17.48)
Northwest(Huehuetenango, Quiche)	21	28	34	37	29	32	40	43	41	38	28	371(8.68)
Petèn	11	8	15	10	13	13	10	15	10	16	9	130(3.04)
Deaths(Mortality x 100k hab)	337(2.28)	348(2.31)	362(2.37)	349(2.24)	404(2.55)	375(2.33)	409(2.50)	442(2.66)	447(2.65)	412(2.41)	388(2.24)	4273

8075 Poster Session

Surgical resection versus stereotactic body radiation therapy in stage IV non–small cell lung cancer: A large, real-world, propensity-matched survival study. First Author: Harshitha Bandaru, Dr NTR Univeristy of Health Sciences, Tirupathi, India

Background: The role of definitive local thoracic therapy in metastatic non–small cell lung cancer (NSCLC) remains controversial. While stereotactic body radiation therapy (SBRT) is increasingly utilized, comparative survival outcomes with surgical resection in real-world populations remain limited. We evaluated survival and pulmonary outcomes associated with surgery versus SBRT in patients with stage IV NSCLC. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network including adults (≥18 years) with stage IV NSCLC treated between January 2013 and December 2023 who underwent definitive local thoracic therapy with either surgical resection or SBRT. Patients with small cell lung cancer, prior lung cancer diagnoses, prior thoracic radiation, or incomplete survival data were excluded. Propensity score matching (1:1) was performed to balance demographics, comorbidities, smoking history, and exposure to systemic therapy including chemotherapy and immunotherapy within 6 months of index treatment. Primary outcomes included landmark 1-year all-cause mortality and overall survival. Secondary outcomes included pneumonia and respiratory failure. Kaplan–Meier analysis and Cox proportional hazards regression were performed. **Results:** After matching, 1,934 patients were included (967 per cohort). At 1 year, surgical resection was associated with significantly lower mortality compared with SBRT (17.5% vs 31.4%; RR 0.56, 95% CI 0.47–0.66; $p < 0.001$), corresponding to an absolute risk reduction of 13.9% and an estimated number needed to treat of approximately 7. Kaplan–Meier analysis demonstrated superior survival in the surgical cohort (log-rank $p < 0.001$). Surgical resection remained associated with significantly improved long-term survival, with a 64% lower hazard of death (HR 0.36, 95% CI 0.30–0.44; $p < 0.001$) and prolonged median survival (3,942 vs 1,182 days). Pulmonary outcomes favored surgery. Pneumonia incidence was significantly lower in the surgical cohort at both 1 year (12.9% vs 29.3%; RR 0.44; $p < 0.001$) and 3 years (5.9% vs 14.2%; RR 0.42; $p < 0.001$). Rates of respiratory failure did not differ significantly between treatment groups. **Conclusions:** In this large real-world propensity-matched study, surgical resection was associated with significantly improved survival compared with SBRT in carefully selected patients with stage IV NSCLC. Surgery was additionally associated with lower long-term pulmonary infectious complications without increased respiratory failure risk. These findings suggest a potential role for aggressive local therapy in selected metastatic patients and support prospective trials to refine patient selection strategies. Research Sponsor: None.

8076 Poster Session

Association of carbon tetrachloride with lung cancer incidence and mortality, including effects in low-smoking regions. First Author: Ashish Samaddar, Donald and Barbara Zucker School of Medicine at Hofstra University, Manhasset, NY

Background: Although cigarette smoking is the main risk factor for lung cancer, 10–20 percent of cases occur in non-smokers, with women disproportionately affected. This pattern suggests that community-level environmental exposures may contribute to lung cancer risk beyond smoking. **Methods:** In this ecologic, county-level study, average age-adjusted lung cancer incidence from 2017–2021 and sex-specific smoking prevalence were obtained from the NCI State Cancer Profiles. County-level exposure data were derived from the EPA National Air Toxics Assessment, with 73 air toxics screened to identify the most strongly associated pollutant. The leading exposure was evaluated in sex-stratified multivariable spatial error regression models adjusting for smoking prevalence and key county-level covariates, including radon, $PM_{2.5}$, Social Vulnerability Index (SVI). Analyses included 2,042–2,238 U.S. counties. Additional models were fit separately within strata of smoking prevalence to compare associations across lower and higher-smoking counties. **Results:** Among 73 EPA-tracked air toxins, carbon tetrachloride (CCl_4) showed the strongest association with lung cancer incidence (population-weighted $r = 0.34$, $p < 0.001$). In fully adjusted spatial models, each standard deviation increase in carbon tetrachloride was associated with a 10.6% increase in lung cancer incidence in women and 10.4% in men, and with a 6.5% and 7.6% increase in lung cancer mortality, respectively. In stratified analyses, associations between CCl_4 and lung cancer incidence were larger in lower-smoking counties (10–12% per SD) than in higher-smoking counties (5–6% per SD), with similar patterns by sex. **Conclusions:** CCl_4, a legacy industrial solvent with ongoing emissions, was the most predictive air toxin associated with population-level lung cancer incidence, showing larger adjusted associations than $PM_{2.5}$ or radon. Although effects were not sex-specific, incidence increases were greatest in lower-smoking communities, suggesting a greater relative contribution of environmental exposures. Research Sponsor: None.

Percent change in lung cancer incidence and mortality per 1 standard deviation increase in covariates.

Variable	Women – Incidence (% per 1-SD)	Men – Incidence (% per 1-SD)	Women – Mortality (% per 1-SD)	Men – Mortality (% per 1-SD)
Current Smoking (Women)	6.7 (5.9, 7.6)	7.0 (6.2, 7.9)	7.3 (6.3, 8.3)	8.3 (7.4, 9.3)
Former Smoking (Women)	4.6 (3.8, 5.3)	1.7 (1.0, 2.5)	5.0 (4.2, 6.0)	1.1 (0.3, 1.9)
Current Smoking (Men)	5.0 (4.2, 6.0)	6.9 (6.1, 7.8)	7.4 (6.3, 8.3)	8.5 (7.6, 9.5)
Former Smoking (Men)	4.0 (3.1, 4.9)	3.3 (2.4, 4.1)	4.9 (3.9, 5.9)	3.9 (3.0, 4.8)
$PM_{2.5}$	0.0 (−0.7, 0.7)	0.3 (−0.4, 1.0)	0.9 (0.1, 1.6)	1.3 (0.5, 2.0)
Radon	0.9 (−0.2, 2.0)	1.8 (0.7, 2.8)	1.1 (0.0, 2.3)	1.9 (0.7, 3.0)
Carbon Tetrachloride (CCl_4)	10.6 (9.1, 12.2)	10.4 (8.9, 12.0)	6.5 (5.1, 7.8)	7.6 (6.2, 9.0)
Counties in model (n)	2,170	2,238	2,042	2,182

8077 Poster Session

Are lobectomy and neoadjuvant therapy the missing link in improving early-stage small cell lung cancer survival? First Author: Yahya Alwatari, Division of General Thoracic Surgery, Mayo Clinic Rochester, Rochester, MN

Background: Small cell lung cancer (SCLC) is an aggressive malignancy with poor prognosis. This study evaluates national trends in surgical management of early-stage SCLC using the National Cancer Database (NCDB), aiming to identify factors associated with improved outcomes and assess the survival benefit of surgical resection. **Methods:** Patients diagnosed with clinical stage T1–T3 N0 M0 SCLC between 2004 and 2022 were identified from the NCDB. Exclusions included non-SCLC histologies, advanced or missing staging, non-lobectomy surgeries, and incomplete survival data. Propensity score matching (1:1) was used to balance surgical and non-surgical cohorts based on demographic, clinical, and socioeconomic variables. Kaplan-Meier and Cox regression analyses were used to evaluate overall survival, stratified by T stage. **Results:** Among 17,762 patients with early-stage SCLC, 3,234 (18.2%) underwent lobectomy with mediastinal lymph node dissection. Surgical rates increased from 5% in 2004, 17% in 2013 to 24% in 2021. Surgery was more common in T1 (26.5%) than T2 (11.4%) or T3 (4.6%) disease. After matching, surgery was associated with improved survival across all T stages, with no significant interaction between T stage and surgical benefit (p=0.43). Older age, male sex, and higher comorbidity scores predicted worse outcomes. Among surgical patients, 2.3% received neoadjuvant therapy and 71.6% received adjuvant treatment. Systemic therapy-both neoadjuvant (HR 0.63) and adjuvant (HR 0.69)-was significantly associated with improved survival. **Conclusions:** Lobectomy remains underutilized in early-stage SCLC but is linked to significantly improved survival. Albeit small patient's number, neoadjuvant systemic therapy further enhanced survival, supporting broader use of surgery and multimodal treatment in appropriately selected patients Research Sponsor: None.

			Univariable results[1]		Multivariable results[2]	
Characteristic	No. deaths	Person-months	HR (95% CI)	p-value	HR (95% CI)	p-value
Charlson score				<0.001		**<0.001**
0	761	77727	1.00 (ref)		1.00 (ref)	
1	623	60483	1.06 (0.95,1.18)		1.07 (0.96,1.20)	
2 or more	350	27025	1.30 (1.15,1.48)		1.30 (1.13,1.48)	
Clinical T-stage				0.011		**0.014**
cT1N0M0	1266	124916	1.00 (ref)		1.00 (ref)	
cT2N0M0	406	33924	1.18 (1.06,1.32)		1.20 (1.06,1.35)	
cT3N0M0	62	6393	0.96 (0.75,1.24)		1.00 (0.76,1.31)	
Residual disease				<0.001		**<0.001**
No residual tumor	1626	158838	1.00 (ref)		1.00 (ref)	
Residual tumor	92	4699	1.91 (1.55,2.36)		1.91 (1.52,2.40)	
Neoadjuvant systemic treatment				0.253		**0.034**
No	1629	154116	1.00 (ref)		1.00 (ref)	
Yes	30	3495	0.81 (0.56,1.16)		0.63 (0.41,0.97)	
Adjuvant radiation				0.067		**<0.001**
No	1209	118925	1.00 (ref)		1.00 (ref)	
Yes	452	40471	1.11 (0.99,1.23)		1.33 (1.18,1.51)	
Adjuvant systemic treatment				<0.001		**<0.001**
No	563	44045	1.00 (ref)		1.00 (ref)	
Yes	1096	113566	0.75 (0.68,0.83)		0.69 (0.62,0.78)	

8078 Poster Session

Chemoimmunotherapy for large cell neuroendocrine carcinoma (LCNEC) of the lung: A multi-institutional prospective study (NEJ044). First Author: Suguru Matsuda, Department of Pulmonary Medicine, Sendai Kosei Hospital, Sendai, Japan

Background: Large cell neuroendocrine carcinoma (LCNEC) is a rare pulmonary malignancy, comprising 1-3% of all lung cancers. It is a high-grade tumor exhibiting heterogeneous characteristics that overlap with both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). While chemoimmunotherapy (chemo-IO) has become the standard of care for SCLC and NSCLC, prospective data regarding its efficacy and safety in LCNEC are limited, and the optimal chemotherapy backbone remains unclear. We conducted the NEJ044 study to prospectively evaluate chemo-IO in patients (pts) with advanced LCNEC. **Methods:** This multi-institutional, prospective, observational study enrolled pts with advanced or recurrent LCNEC. Treatment consisted of atezolizumab and carboplatin combined with either etoposide (IMpower133), paclitaxel and bevacizumab (IMpower150), or nab-paclitaxel (IMpower130). The primary endpoint was the 1-year overall survival (OS) rate. Secondary endpoints included OS, progression-free survival (PFS), objective response rate, disease control rate, and safety. **Results:** Between July 2020 and June 2024, 77 pts were enrolled across 31 institutions within the North East Japan Study Group, of whom 76 received treatment. The median follow-up was 29.0 months (mos) (95% CI: 15.2–35.7). Baseline characteristics included: median age 71 years (range 51–83); male, 68 (89%); ECOG PS 0-1, 69 (91%); and postoperative recurrence, 29 (38%). Histology was confirmed as LCNEC in 61 pts (80%) and combined LCNEC in 15 pts (20%). Treatment distribution included the IMpower133 regimen in 56 pts (74%) and IMpower150/130 regimens in 20 pts (26%). The study met its primary endpoint with a 1-year OS rate of 70.1% (95% CI: 58.2–79.2). In the overall population, median OS (mOS) and PFS (mPFS) were 18.5 mos (95% CI: 14.3–22.6), and 6.2 mos (95% CI: 4.8–7.6). Exploratory analysis showed no significant differences in survival by chemotherapy backbone. The IMpower133 cohort demonstrated a 1-year OS of 70.3% (95% CI: 56.1–80.6), mOS of 18.4 mos (95% CI: 13.2-22.3), and mPFS of 5.2 mos (95% CI: 3.9-7.6), compared to a 1-year OS of 69.6% (95% CI: 44.5–85.1), mOS of 19.9 mos (95% CI: 7.3-not evaluable), and mPFS of 7.2 mos (95% CI: 4.3-19.9) in the IMpower150/130 cohort. Grade ≥3 non-hematological adverse events occurred in 23 pts (30%), and febrile neutropenia was observed in 9 pts (11%). Biomarker analysis identified oncogenic drivers in 5 pts (including 3 KRAS mutations). PD-L1 expression was ≥50% in 12%, 1–49% in 34%, and < 1% in 51%; PD-L1 TPS ≥1% was marginally associated with improved OS. **Conclusions:** The NEJ044 study met its primary endpoint, demonstrating that chemoimmunotherapy provides a favorable 1-year OS of approx. 70% with a manageable safety profile in LCNEC. These prospective results support chemoimmunotherapy as a viable standard treatment strategy for this population. Clinical trial information: UMIN000040876. Research Sponsor: Chugai Pharmaceutical.

8079 Poster Session

Real-world (RW) effectiveness and safety of lurbinectedin (lurbi) for previously treated extensive-stage small cell lung cancer (ES-SCLC): Final primary and subgroup analysis results of Jazz EMERGE 402. First Author: Firas Benyamine Badin, Baptist Health Medical Group, Lexington, KY

Background: Lurbi received accelerated approval in 2020 for ES-SCLC that progressed on or after platinum-based treatment (Tx) based on a phase 2 basket trial and full approval in 2025 combined with atezolizumab as 1st-line maintenance Tx for ES-SCLC based on the phase 3 IMforte trial. **Methods:** The phase 4, prospective, observational Jazz EMERGE 402 trial (NCT04894591) evaluated lurbi for previously treated ES-SCLC in RW practice in North America (final data cut: July 17, 2025). The primary endpoint was overall response rate (ORR). Key secondary endpoints were progression-free survival (PFS), overall survival (OS), and safety. Effectiveness was assessed in all patients (pts) and in prespecified subgroups. **Results:** At the final data cut, 267 pts had received ≥1 cycle of lurbi. At baseline (BL), median (min–max) age was 67 (29–89) years, 52 (19%) pts had an ECOG PS ≥2, 67 (25%) had brain metastases, 84 (31%) had liver metastases, 88 (33%) had a chemotherapy-free interval (CTFI) <90 days, and 196 (73%) had ES-SCLC as the initial diagnosis. Pts received lurbi as 2nd-line (169 [63%]), 3rd-line (78 [29%]), or later (20 [7%]) Tx. Median (Q1–Q3) number of lurbi Tx cycles and Tx duration were 4 (2–7) and 91 (56–170) days. Granulocyte colony-stimulating factor was used in 99 (37%) pts (71 [27%] as primary prophylaxis). Six (2%) pts were receiving Tx at study completion; 261 (98%) discontinued Tx, with disease progression (183 [70%]) the primary reason. While lurbi was effective among all pts and poor-prognosis subgroups, better outcomes tended to occur in pts with CTFI ≥90 days and ECOG PS <2 (Table). Eighty-eight (33%) pts had Tx-related adverse events (TRAE); anemia (21 [8%]) and neutropenia (19 [7%]) were most common. Rates of serious neutropenic infection (5 [2%]), anemia (4 [1%]), and neutropenia (3 [1%]) were low. **Conclusions:** Lurbi was associated with clinically meaningful effectiveness and predictable/manageable safety in previously treated ES-SCLC in a RW population that included poor-prognosis subgroups. Clinical trial information: NCT04894591. Research Sponsor: Jazz Pharmaceuticals.

Effectiveness among all pts and by subgroup.

	All N = 267	Age <65 Years n = 101	Age ≥65 Years n = 166	CTFI <90 Days n = 88[a]	CTFI ≥90 Days n = 137[a]	Initial LS n = 69[b]	Initial ES n = 196[b]	ECOG PS <2 n = 178[c]	ECOG PS ≥2 n = 52[c]
ORR,[d] % (95% CI[e])	29 (23, 36)	30 (20, 43)	28 (20, 37)	24 (14, 37)	28 (19, 38)	33 (21, 47)	27 (20, 36)	26 (19, 35)	41 (24, 59)
PFS,[d] months, median (95% CI)	3.3 (2.6, 4.1)	4.1 (2.8, 4.5)	2.9 (2.2, 3.8)	2.9 (2.0, 4.1)	3.3 (2.4, 4.2)	4.0 (2.4, 5.8)	3.3 (2.5, 4.1)	3.3 (2.6, 4.2)	2.6 (1.7, 5.2)
OS, months, median (95% CI)	7.6 (6.4, 8.7)	8.2 (7.0, 10.6)	6.6 (5.8, 8.7)	5.8 (4.6, 6.6)	9.3 (7.1, 10.9)	8.7 (6.2, 10.6)	6.8 (6.0, 8.7)	8.1 (6.6, 9.6)	5.2 (2.4, 7.9)

[a]CTFI missing for 42 pts.
[b]Stage missing for 2 pts.
[c]ECOG PS missing for 37 pts.
[d]Per RECIST v1.1 in pts with BL measurable disease.
[e]Estimated using Clopper-Pearson exact method. LS, limited stage.

8080 Poster Session

A retrospective real-world study on the efficacy and safety of anlotinib in combination with immunotherapy as maintenance therapy after standard immunochemotherapy for extensive-stage small cell lung cancer (ALTER-L059). First Author: Yong Fang, Sir Run Run Shaw Hospital, affiliated with Zhejiang University School of Medicine, Hangzhou, Zhejiang, China

Background: Although immune checkpoint inhibitors (ICIs) combined with chemotherapy have become the standard first-line treatment for extensive-stage small cell lung cancer (ES-SCLC), the use of immunotherapy as a maintenance strategy remains challenging. This study aims to evaluate the efficacy and safety of anlotinib combined with ICIs as first-line maintenance treatment for ES-SCLC. **Methods:** ALTER-L059 was a retrospective, multicenter study conducted at 9 hospitals in China. Eligible patients were 18 years or older with histologically or cytologically confirmed ES-SCLC and had completed 4–6 cycles of first-line immunochemotherapy as induction therapy without disease progression. They subsequently received maintenance therapy with immunotherapy combined with anlotinib. The primary endpoint was progression-free survival from the start of maintenance therapy (PFS2). Secondary endpoints included progression-free survival from the start of induction therapy (PFS), overall survival from the start of maintenance therapy (OS2), overall survival from the start of induction therapy (OS) and safety. **Results:** Between January 2022 and December 2024, a total of 100 patients were enrolled. By the data cutoff date on November 11, 2025, the median follow-up duration was 16.92 months (95% CI: 15.81-18.03). The median PFS2 was 6.05 months (95% CI: 4.83-7.59), and the median PFS was 9.53 months (95% CI: 8.31-11.93). The median OS2 was 17.74 months (95% CI: 15.24-19.71), and the median OS was 21.26 months (95% CI: 18.60-22.60). The incidence of grade 3 or higher treatment-related adverse events (TRAEs) was 30.0%. The most common TRAEs (incidence ≥20%) were hypertension (33.0%), hand-foot syndrome (23.0%), proteinuria (21.0%), and hypertriglyceridemia (20.0%). **Conclusions:** Patients who had been diagnosed with ES-SCLC and had completed 4–6 cycles of immunochemotherapy as induction therapy without disease progression subsequently received maintenance therapy with immunotherapy combined with anlotinib, demonstrating favorable survival outcomes and manageable toxicity. Clinical trial information: NCT06982287. Research Sponsor: None.

8081 **Poster Session**

A validation study of a novel biomarker-based scoring system (EAST score) for limited-stage small-cell lung cancer: A secondary analysis of JCOG0202 and JCOG1011. First Author: Yu Ito, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Concurrent chemoradiotherapy (CCRT) followed by prophylactic cranial irradiation (PCI) is potentially curative for limited-stage small-cell lung cancer (LS-SCLC), yet reliable markers for identifying long-term survivors remain undefined. The Enhanced Assessment for SCLC Treatment (EAST) score was originally derived from a retrospective, single-center training cohort for prognostic stratification of LS-SCLC patients receiving CCRT. This score integrates N3 status, serum lactate dehydrogenase (LDH), pro-gastrin-releasing peptide (ProGRP), and cytokeratin 19 fragment (CYFRA 21-1) levels measured at diagnosis. This study (JCOG2401A) validated its prognostic utility using data from two randomized controlled trials (RCTs) of LS-SCLC. **Methods:** The validation cohort comprised patients enrolled in JCOG0202 and JCOG1011: randomized phase 3 and 2 studies, respectively, that compared multiple consolidation chemotherapy regimens following CCRT. External validation of the dichotomized EAST score (low: score 0–1, high: 2–5) was performed by assessing discrimination and calibration for progression-free survival (PFS) and overall survival (OS). Exploratory subgroup analyses were conducted in an integrated cohort of the training cohort (N = 224; median follow-up, 64.5 months) and the validation cohort. Hazard ratios (HRs) for PCI were estimated using propensity score-weighted Cox models. **Results:** Out of 309 patients in these trials, 205 with complete data for EAST score components were included in the validation cohort. Median age was 62 years. Low- vs. high-risk groups showed stage (I-II/III) distributions of 28/72% vs. 11/89%, and tumor response (CR-PR/SD) distributions of 89/3% vs. 91/2%, respectively. The low-risk group (N = 114) showed better outcomes than the high-risk group (N = 91) for both PFS and OS (Table). Integrated cohort analysis revealed a numerical survival benefit from PCI in low-risk patients (N = 214), whereas the benefit was highly limited in the high-risk group (N = 202) (Table). **Conclusions:** The prognostic value of the EAST score was validated even in external RCT datasets. High-risk patients, characterized by early recurrence and inferior OS, derive minimal benefit from PCI. These findings provide a rationale for a planned risk-adapted RCT utilizing the EAST score. Research Sponsor: None.

	Median PFS, months	PFS, HR (95% CI)	Median OS, months	OS, HR (95% CI)
Low- vs. high-risk				
Training cohort (N=107/117)	20.6/9.4	0.48 (0.34-0.67)	53.0/34.2	0.67 (0.46-0.98)
Validation cohort (N=114/91)	25.0/10.7	0.55 (0.40-0.77)	63.2/29.6	0.51 (0.36-0.73)
PCI vs. no-PCI				
All (N=287/129)	14.5/12.9	0.91 (0.65-1.28)	50.0/35.5	0.78 (0.56-1.10)
Low risk (N=152/62)	31.3/14.6	0.86 (0.49-1.48)	67.9/40.1	0.75 (0.43-1.31)
High risk (N=135/67)	10.2/10.6	0.99 (0.71-1.39)	34.2/30.9	0.86 (0.59-1.28)

8082 **Poster Session**

Prophylactic tocilizumab to mitigate cytokine release syndrome in patients receiving tarlatamab: A single-center exploratory experience informed by bispecific antibody safety data. First Author: Feras Al Moussally, University of Pittsburgh Medical Center (UPMC), Harrisburg, PA

Background: Tarlatamab, a bispecific T-cell engager (BiTE) targeting CD3 on T cells and DLL3 on small cell lung cancer (SCLC) cells, represents a major advance in treating relapsed or refractory SCLC. By activating T cells to release cytotoxic cytokines, it induces tumor cell death but carries risks such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS). In the phase 2 DeLLphi-301 trial, CRS occurred in up to 53% of patients treated with Tarlatamab. Current inpatient step-up dosing protocols aim to mitigate toxicity but add cost and complexity, particularly for immunocompromised patients. Tocilizumab, an interleukin-6 (IL-6) receptor inhibitor used for CRS, has demonstrated prophylactic benefit in mitigating cytokine-related adverse events with other BiTEs such as teclistamab. We hypothesized that prophylactic tocilizumab could similarly reduce Tarlatamab-related CRS in SCLC without compromising efficacy. **Methods:** We retrospectively analyzed 32 consecutive SCLC patients treated with Tarlatamab at our center. Tocilizumab (8 mg/kg) was administered 1 hour prior to the first Tarlatamab dose when approved by insurance. CRS incidence, grade, rescue interventions, treatment discontinuations, and cost implications were evaluated. CRS grading followed standard consensus guidelines. **Results:** Among 32 treated patients, 29 (90.6%) received prophylactic tocilizumab, and 3 did not. CRS developed in 3 of 29 patients (10.3%) who received pre-treatment—two grade 1 and one grade 2. In contrast, all 3 patients (100%) who did not receive pre-treatment developed CRS—two grade 1 and one grade 2. Overall, CRS occurred in 6 patients (18.8%). All cases resolved after tocilizumab rescue therapy, and no treatment discontinuations occurred. **Conclusions:** Prophylactic tocilizumab substantially reduced CRS incidence among SCLC patients receiving Tarlatamab, suggesting a feasible and safe mitigation strategy. Compared with historical data from DeLLphi-301 (53% CRS incidence), this cohort exhibited markedly lower toxicity rates with prophylactic IL-6 blockade. To our knowledge, this represents the first clinical evidence supporting IL-6 blockade before Tarlatamab administration. Despite the upfront drug cost ($2,800–$5,100 per dose), prevention of CRS-related hospitalizations offers significant economic benefit (estimated $11,000–$200,000 per event based on grade). Limitations include small sample size, lack of randomization, and single-center design. Nonetheless, these findings underscore the potential of integrating tocilizumab prophylaxis into standard Tarlatamab protocols and warrant larger prospective studies to confirm safety, efficacy, and cost-effectiveness. Research Sponsor: None.

8083 **Poster Session**

Real-world second-line treatment patterns and outcomes by platinum sensitivity in extensive-stage small cell lung cancer in the post-immunotherapy era. First Author: Catherine Rinaldi, Flatiron Health, New York, NY

Background: Platinum-based chemotherapy (PBC) with checkpoint inhibitor (CPI) is standard first-line (1L) treatment for extensive-stage small cell lung cancer (ES-SCLC), though relapse is common. Second-line (2L) treatment selection is determined by platinum sensitivity status, with guidelines based on pre-CPI data, and the benefit of any CPI continuation is unknown. This study examined treatment patterns and real-world (rw) outcomes for patients following 1L PBC +/- CPI among platinum-sensitive (PS) patients, including the impact of continuing a CPI with platinum rechallenge. **Methods:** This retrospective study used EHR-derived US Flatiron Health Research Database. Eligible patients were diagnosed with ES-SCLC between January 1, 2018, and September 9, 2025, received 2L treatment following 1L PBC with a calculable platinum sensitivity and had a minimum potential follow up of 120 days. Platinum sensitivity was defined by a chemotherapy-free interval of $\geq$ 180 days, based on the last order or administration of 1L PBC to first real-world progression event prior to 2L initiation. Real-world response rate (rwRR), progression free survival (rwPFS) and overall survival (rwOS) were described based on 2L regimen class for patients with PS disease, and were compared via HR for platinum rechallenge with CPI continuation versus without. Time-to-event outcomes were analyzed using Kaplan-Meier methods, with medians and 95% CI reported for the overall cohort and subgroups of interest. **Results:** Among 5,126 eligible patients, 884 (17%) had PS and 4,242 (83%) had platinum refractory (PR) disease. Most patients (73%) received CPI with PBC in 1L. Patients with PR had worse outcomes than PS (rwPFS, 2.7 [95% CI, 2.6-2.8] vs 5.5 [95% CI, 5.3-5.7] mo; rwOS, 4.7 [95% CI, 4.5-4.9] vs 11.2 [95% CI, 10.6-12.4] mo). Among PS patients with 1L CPI exposure (n=666), 48% received 2L PBC, and 41% of 2L PBC continued a CPI. Clinical characteristics in PS disease were similar across classes of 2L regimen. Of patients with PS disease who had 1L CPI exposure, 81% had at least 1 response assessment during the study period. Of PBC patients, rwRR was 52% among CPI treated and 58% without CPI. 2L rwPFS and rwOS were similar regardless of CPI continuation (Table). **Conclusions:** In this large real-world study, nearly half of patients with PS disease were rechallenged with PBC in 2L, and CPI continuation was common despite limited evidence. CPI continuation did not improve response, progression, or survival, suggesting no additional benefit and highlighting the need for prospective data to guide post-CPI treatment in PS ES-SCLC. Research Sponsor: Flatiron Health, Inc.

Outcome	2L rwPFS median, mo (95% CI)	Unadjusted HR (95% CI)	*P* value	2L rwOS median, mo (95% CI)	Unadjusted HR (95% CI)	*P* value
PBC with CPI (n=112)	5.6 (5.4-6.2)	-	-	12.3 (11.0-15.9)	-	-
PBC without CPI (n=149)	6.0 (5.6-6.6)	0.97(0.76, 1.25)	0.80	12.9 (11.0-15.3)	1.04 (0.80, 1.35)	0.80

8084 **Poster Session**

Antigen presentation suppression as a hallmark of immune evasion and poor outcomes in small cell lung cancer. First Author: Triparna Sen, The Ohio State University, Columbus, OH

Background: Antigen-presenting machinery (APM) is critical for tumor immune recognition. The loss of APM promotes immune evasion and immunotherapy resistance in cancers, including small-cell lung cancer (SCLC). SCLC has a high tumor mutational burden (TMB), and it displays profound APM suppression, explaining its weak response to immune checkpoint inhibitors. We aimed to capture APM gene expression in a large real-world cohort (RWC) and prospective clinical trial datasets to address the clinical implications of APM suppression for current treatment strategies. **Methods:** We calculated a classical antigen-presenting MHCs (CAMs) score using a gene signature comprised of 18 genes closely associated with MHC-I expression and antigen presentation. We evaluated this score in 6,000 real-world lung cancer samples and in the transcriptomic dataset of a Phase III clinical trial evaluating the effect of chemo-immunotherapy as a first-line treatment in extensive-stage SCLC (IMpower133). Transcriptomic, genomic, and proteomic data were collected for analysis. **Results:** Patients with SCLC were stratified into 3 groups according to hierarchical clustering of CAM gene expression for functional enrichment, differential gene expression, response to drug, and survival analyses. CAM expression was markedly suppressed in SCLC compared to other lung cancer histologies. In SCLC, CAM-low accounted for 53% of patients, followed by CAM-intermediate (40%) and -high (7%). We found no statistical difference in TMB-high (^{3}10 mutations/Mb) proportion across CAM groups. CAM-intermediate- and high groups had lower *TP53, RB1,* and *PTEN* mutation rates and a higher *PI3K* mutation rate compared to CAM-low. CAM-low tumors displayed the highest DNA damage response and neuroendocrine signature scores and the lowest *RB1* expression. CAM-low tumors showed the lowest expression of cytokine and cytokine receptors involved in lymphocyte trafficking, as well as the lowest $CD8^+$/Treg and M1/M2 ratios, consistent with a highly immunosuppressive context. CAM-low and intermediate groups had the lower PD-L1 expression and worse overall survival from the start of chemoimmunotherapy in the RWC. Most targetable markers, such as *DLL3,* were downregulated in CAM-low tumors. We also identified high expression of novel immune targets in the CAM-low population that may inform future drug design. **Conclusions:** We demonstrate that in RWC and clinical trial samples, most patients with SCLC are CAM-low, exhibit immune evasion features, and have poor outcomes, as well as reduced expression of most druggable targets. Our data suggests that SCLC's immunosuppressive microenvironment may lessen the efficacy of new-generation compounds. We highlight potential novel treatment strategies targeting defective APM tumors that may activate the immune microenvironment and augment the effect of existing immunotherapy agents. Research Sponsor: None.

8085 **Poster Session**

Multiomic spatial analysis of tumor microenvironment during neuroendocrine (NE) transformation in *EGFR*-mutant LUAD. First Author: Elisa Gobbini, The Ohio State University, Columbus, OH

Background: Histological transformation of *EGFR* mutant lung cancer adenocarcinoma (LUAD) to small-cell lung cancer (SCLC) is a well-known resistance mechanism and has been found in about 14% resistant cases. This phenomenon is associated with extremely poor prognosis and limited therapeutic options. This underscores the need to identify the biological mechanisms triggering lineage plasticity in *EGFR+* LUADs. We and others have shown that several genomic and epigenetic alterations play a central role in the activation of small cell like neuroendocrine (NE) states. However, the impact of these changes on the immune microenvironment and vice versa is not understood, limiting the identification of novel immunotherapy approaches in this setting. **Methods:** We describe the evolution of the tumor microenvironment (TME) during SCLC transformation by comparing tissues from de novo LUAD (*n* = 10), de novo SCLC (*n* = 15), and transformed SCLC (n =12) including 11 cases with *EGFR*-mutant LUAD/SCLC mixed histology and 1 pre-transformed LUAD. Additionally, we used de novo lung squamous cancer (LUSC, *n* = 11), and transformed LUSC (n = 11) including 8 mixed LUSC/LUAD histology and 3 post-transformed samples to inform the LUSC transformation program as a comparator. All samples were analyzed by RNA sequencing, DNA methylation, and whole-exome sequencing. Spatial proteomics (ORION, *n* = 4) and transcriptomics (XENIUM, *n* = 6) were performed on pre- and post-transformed paired samples from *EGFR+* patients. **Results:** Differential gene expression and pathway analysis highlight the upregulation of G2M, E2F, and *MYC* targets during both SCLC and LUSC transformation, occurring at an earlier stage for SCLC compared to LUSC. Conversely, a more pronounced and broader and earlier downregulation of immune pathways was detected during SCLC, compared to LUSC, transformation. Analysis of the epigenetic regulators potentially driving these signaling changes pointed to *EZH2* as master regulators of SCLC transformation, while the LUSC program was mainly driven by the *TP63* and *FOXA1* transcription factors. Spatial proteomics and transcriptomics highlighted a decrease in immune-related programs with an increased proportion of immune suppressive subsets and NE features in SCLC-transformed samples compared to baseline specimens. Subclustering analysis showed a higher percentage of pro-tumoral macrophages and exhausted T-cells in transformed samples. **Conclusions:** Our results suggest that a broader transcriptional reprogramming is associated with the transition from LUAD to SCLC than from LUAD to LUSC. The TF profile associated with SCLC histological transformation negatively regulates immune pathways leading to profound remodeling of the immune compartment and a cold TME that supports the aggressive phenotype of transformed tumors. Research Sponsor: None.

8086 **Poster Session**

IMforte: Quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis of first-line maintenance (1Lm) treatment (Tx) with lurbinectedin (lurbi) + atezolizumab (atezo) vs atezo in extensive-stage small cell lung cancer (ES-SCLC). First Author: Hossein Borghaei, Department of Hematology and Oncology, Fox Chase Cancer Center, Philadelphia, PA

Background: IMforte (NCT05091567) is the first positive phase 3 study of 1Lm in ES-SCLC to demonstrate statistically significant and clinically meaningful progression-free survival (PFS) and overall survival (OS) benefits (stratified hazard ratios, 0.54 and 0.73) with lurbi + atezo vs atezo. The combination was generally well tolerated based on safety findings and patient-reported outcomes. These data led to the approval of lurbi + atezo as 1Lm Tx for adults with ES-SCLC in the US and Switzerland in 2025. Here, we describe a post hoc Q-TWiST analysis using IMforte data to further elucidate the benefit-risk profile of lurbi + atezo. **Methods:** Eligible pts with ES-SCLC who were progression free after induction with atezo, carboplatin, and etoposide were randomized 1:1 to receive lurbi + atezo or atezo alone every 3 weeks. Survival time was partitioned into 3 health states: toxicity (TOX; time with grade ≥3 adverse events before disease progression), TWiST (time without TOX before disease progression), and relapse (REL; time from disease progression to death). The mean time spent in each health state was estimated using restricted mean survival times, calculated as area under the Kaplan-Meier curve. Q-TWiST was the sum of the mean time in each health state adjusted by respective utility weights, derived from EQ-5D-5L data. **Results:** Analyses were performed on all randomized pts from IMforte (lurbi + atezo, n = 242; atezo, n = 241) as of July 29, 2024, with a median follow-up of 15 months (mo). Utility weights in lurbi + atezo and atezo arms were 0.84 and 0.83 in TWiST, 0.83 and 0.83 in TOX, and 0.78 and 0.76 in REL health states. Pts in the lurbi + atezo arm spent most of their survival time in the TWiST state (66% vs 50% for atezo), and their mean duration of TWiST was substantially longer vs the atezo arm (9.8 vs 6.4 mo; Table). Lurbi + atezo arm pts spent more time in the TOX state vs atezo (0.7 vs 0.3 mo) but less time in the REL state (4.4 vs 6.1 mo). The lurbi + atezo arm had longer mean Q-TWiST vs atezo (12.2 vs 10.2 mo), representing a clinically important 14.9% gain in utility at the maximum follow-up of 26 mo. **Conclusions:** Lurbi + atezo pts had more time without toxicity before disease progression vs atezo and showed a clinically important improvement in quality-adjusted survival, further supporting a favorable benefit-risk profile of lurbi + atezo as 1Lm Tx for ES-SCLC. Clinical trial information: NCT05091567. Research Sponsor: F. Hoffmann-La Roche Ltd and Jazz Pharmaceuticals.

Mean duration of each health state, Q-TWiST, PFS, and OS.

Mo, Mean (95% CI)	Lurbi + Atezo n = 242	Atezo n = 241	Difference	Relative Gain
Q-TWiST	12.2 (11.1, 13.2)	10.2 (9.2, 11.3)	1.9 (0.5, 3.4)	14.9%
TWiST	9.8 (8.4, 11.2)	6.4 (5.2, 7.7)	3.4 (1.5, 5.2)	
TOX	0.7 (0.5, 0.9)	0.3 (0.1, 0.5)	0.4 (0.1, 0.6)	
REL	4.4 (2.8, 6.0)	6.1 (4.6, 7.6)	−1.8 (−4.0, 0.4)	
PFS	10.5 (9.1, 11.9)	6.8 (5.4, 8.1)	3.7 (1.8, 5.6)	
OS	14.8 (13.5, 16.1)	12.9 (11.6, 14.2)	2.0 (0.1, 3.8)	

8087 **Poster Session**

Impact of DLL3 expression and tumor subtype on response to tarlatamab. First Author: Jessica Ross, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Tarlatamab is a DLL3-targeted bispecific T-cell engager used to treat small cell lung cancer (SCLC). SCLC subtypes can be defined by relative expression of master transcription factors (TFs). Whether subtype and DLL3 expression are associated with outcomes on tarlatamab is unknown. **Methods:** We analyzed all patients (pts) with SCLC, including SCLC transformed from lung adenocarcinoma, treated with tarlatamab at Memorial Sloan Kettering prior to October 2025. DLL3 expression and subtyping were determined by IHC by dedicated thoracic pathologists. Expression of subtype TFs ASCL1, NEUROD1, POU2F3, and YAP1 was assessed. "Neuroendocrine (NE)-high" was defined as any ASCL1 or NEUROD1 expression. Pts with any "neuroendocrine (NE)-low" subtype expression—POU2F3 or YAP1—were grouped for analysis. DLL3 fractional expression was dichotomized as "high" (≥50%) or "low" (0-49%). Progression-free and overall survival (PFS, OS) were analyzed with Kaplan-Meier curves and compared with the Cox proportional hazards model. **Results:** We identified 39 pts with SCLC treated with tarlatamab with DLL3 and/or subtyping data available. Median age was 65, 49% were women, and median prior lines of therapy was 1. DLL3 expression was available in 34 pts. Median fractional DLL3 expression was 80% and ranged from 0 to 100%. 7 pts had low expression and 27 had high expression. There were more pts with transformed SCLC in the DLL3-low group (3/7 [43%] vs 1/27 [4%], p=0.02). Among pts with response data available, response was inferior in the DLL3-low group: complete or partial response (CR or PR) in 0/7 (0%; [95% CI, 0 to 35]) vs 12/25 (48%; [95% CI, 30 to 67]); stable disease (SD) in 2/7 (29%) vs 5/25 (20%); progressive disease (PD) in 5/7 (71%) vs 8/25 (32%); p=0.049. Median PFS was 1.4 mos in DLL3-low vs 4.5 mos in DLL3-high disease (p<0.001); median OS was 4.7 mos vs not reached (p=0.001). Incidence of CRS and ICANS did not differ (5/7 [71%] in DLL3-low vs 11/29 [38%] in DLL3-high with CRS, p=0.2; 0/9 vs 3/29 [10%] with ICANS, p>0.9). 30/39 pts had subtyping data available. 28/30 pts had NE-high tumors (15/28 ASCL1+/NEUROD1+; 11/28 ASCL1+/NEUROD1-; 2/28 ASCL1-/NEUROD1+). 5/30 had subtype biomarkers of NE-low status: 4 YAP1+ and 1 POU2F3+; the 4 YAP1+ tumors also expressed ASCL1. Response rates were similar between pts with and without NE-low expression: 1/5 (20%; [95% CI, 1 to 62]) vs 11/25 (44%; [95% CI, 27 to 63]), p=0.6. PFS was also similar (mPFS 1.1 vs 2.7 mos, p=0.3). **Conclusions:** Low DLL3 expression was potentially associated with inferior response to tarlatamab. A contributing factor may be enrichment of transformed SCLC, which is associated with poor outcomes. We did not detect an impact of POU2F3/YAP1 expression. The majority of pts in this cohort had DLL3-high, NE-high SCLC—in line with prior studies—and they had a response rate of 48%. These data emphasize the need for more discerning predictive biomarkers for tarlatamab in an evolving landscape of treatment options. Research Sponsor: None.

8088 **Poster Session**

Analysis of corticosteroid exposure on efficacy of tarlatamab in small cell lung cancer: A multicenter retrospective study. First Author: Ty Michael Moore, The University of Kansas Cancer Center, Westwood, KS

Background: Tarlatamab, a delta-like ligand 3 (DLL3)-targeted bispecific T-cell engager, has shown meaningful activity in small cell lung cancer (SCLC). Immune-mediated toxicities such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) are common with T-cell–redirecting therapies and frequently require corticosteroids or cytokine-directed agents like tocilizumab. The impact of lymphodepleting corticosteroid exposure on tarlatamab efficacy remains unclear. **Methods:** We performed a retrospective analysis of patients with SCLC treated with tarlatamab from 2018–2025 across the University of Kansas and nine cancer centers included in the DLL3 PanTUMOR database. The primary endpoint was progression-free survival (PFS) stratified by cumulative dexamethasone dose. Other endpoints included overall response rate (ORR), characterization of CRS and ICANS, and overall survival (OS). A cost analysis of dexamethasone versus tocilizumab was also conducted. **Results:** Among 143 tarlatamab-treated patients, dexamethasone use for CRS or ICANS did not reduce PFS or ORR compared with patients not receiving corticosteroids. Tocilizumab did not reduce steroid needs. Median dexamethasone dose was higher in patients treated with tocilizumab. Severe CRS/ICANS was associated with significantly shorter OS. Cost analysis demonstrates the significant cost savings using dexamethasone compared to tocilizumab for treatment of immune-mediated toxicities. **Conclusions:** Corticosteroid exposure did not compromise tarlatamab efficacy, supporting optimized toxicity management without diminishing antitumor activity of DLL3-targeted T-cell–redirecting therapies. Research Sponsor: None.

Endpoints	Total Number of Evaluable Patients	Outcomes
Median PFS of tarlatamab with cumulative steroid dose **Arm 1: No dex** **Arm 2: 1-40 mg of dex** **Arm 3: 41+ mg of dex**	Arm 1: 66 Arm 2: 42 Arm 3: 16	Arm 1: 2.53 mo Arm 2: 4.70 mo Arm 3: 3.68 mo HR=1.02 95% CI: 0.73-1.42 p=0.31
ORR of tarlatamab with cumulative steroid dose **Arm 1: No dex** **Arm 2: 1-40 mg of dex** **Arm 3: 41+ mg of dex**	Arm 1: 55 Arm 2: 34 Arm 3: 11	Arm 1: 29.1% Arm 2: 47.1% Arm 3: 36.4%
Comparison of ORR with CRS (any grade) versus without CRS	CRS: 58 No CRS: 60	CRS: 34.5% No CRS: 33.3%
Comparison of ORR with ICANS (any grade) versus without ICANS	ICANS: 33 No ICANS: 85	ICANS: 36.4% No ICANS: 32.9%
Did the use of tocilizumab result in lower cumulative steroid use	No tocilizumab: 42 Tocilizumab: 28	Median dex dose without tocilizumab: 10 mg Median dex dose with tocilizumab: 35 mg
Median OS with grade 3+ CRS or ICANS versus with grade 0-2 CRS/ICANS	Grade 0-2: 133 Grade 3+: 10	Grade 0-2: 11.37 mo Grade 3+: 4.19 mo HR=0.34 95% CI: 0.15-0.76 p=0.006
Cost analysis for dex versus tocilizumab **Average wholesale price: tocilizumab $165,724, $3.13 dex10 mg**	CRS: 72 37 doses of tocilizumab	37 doses of tocilizumab substituted with 37 dex 10 mg doses would have saved $173,962

8089 **Poster Session**

DAREON-8: Updated efficacy and safety from a phase I dose-escalation/expansion trial of first-line (1L) obrixtamig plus chemotherapy and atezolizumab in extensive-stage small cell lung carcinoma (ES-SCLC). First Author: Solange Peters, Oncology Department, Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland

Background: Obrixtamig (BI 764532) is a DLL3/CD3 IgG-like T-cell engager that has shown promising efficacy in ES-SCLC, as monotherapy and in combination with other agents. Due to the aggressiveness of ES-SCLC, early initiation of optimal 1L induction therapy is critical, as many patients (pts) may not reach treatment maintenance. We report updated efficacy and safety data from the ongoing Phase I DAREON-8 (NCT06077500) dose-escalation/expansion trial investigating 1L obrixtamig + induction SoC (carboplatin + etoposide + atezolizumab) and maintenance obrixtamig + atezolizumab in pts with ES-SCLC. **Methods:** Obrixtamig was given IV as step-up dosing followed by target dose (Part A: 3 dose levels [10, 30, 60 mg] guided by a BLRM with overdose control; Part B: selected target dose) + SoC (given per label). After 4 cycles of obrixtamig + SoC, obrixtamig + atezolizumab was continued until disease progression or another reason requiring discontinuation. Primary endpoint: DLTs; secondary endpoints included PFS, DoR, and ORR (RECIST v1.1; investigator assessed). **Results:** As of Dec 17, 2025, 46 pts were treated (Part A/B: n=28/18); 44 pts received ≥1 dose of obrixtamig. Median cycles of obrixtamig: 10 (range: 1–21); median age: 69 yrs (range: 34–76); ECOG PS 0/1: 27%/73%; brain metastasis: 16%. MTD was not reached in Part A; the study continued in Part B with the highest dose level (60 mg). Key efficacy data are in the table. Confirmed ORR: 73% (95% CI: 58–84); DCR: 91% (95% CI: 79–96). mDoR: NC; mPFS: NC; 6- and 9-month PFS rates (95% CI): 76% (62–90), and 61% (44–79), respectively. In the 60 mg cohort, confirmed ORR: 76% (95% CI: 58–88); mDoR and mPFS: NC. Most common G≥3 AEs were cytopenias and were almost wholly related to chemotherapy. Most common obrixtamig-related AE: cytokine release syndrome (52%). SoC discontinuations due to TRAEs: n=2 (G2 asthenia, G2 decreased platelets, G3 anemia). Obrixtamig discontinuations due to TRAEs: n=1 (G2 asthenia). **Conclusions:** Obrixtamig + SoC demonstrated encouraging efficacy, supporting obrixtamig as a combination partner for 1L SoC. The combination showed a safety profile consistent with individual agents, supporting the favorable tolerability of obrixtamig in combination regimens. Updated safety data are consistent with previous findings (Peters S et al, *Ann Oncol* 2025;36: S1466–7), and results warrant further development in Phase III trials. Clinical trial information: NCT06077500. Research Sponsor: Boehringer Ingelheim.

Best confirmed response, n (%)	Obrixtamig 60 mg, n=29*	Total (obrixtamig 10–60 mg), N=44*
CR / PR	4 (14) / 18 (62)	4 (9) / 28 (64)
SD	4 (14)	8 (18)
PD	0 (0)	1 (2)
NE/missing	3 (10)	3 (7)
ORR, % (95% CI)	76 (58–88)	73 (58–84)
DCR, % (95% CI)	90 (74–96)	91 (79–96)
Median PFS, months (95% CI)	NC (NC–NC)	NC (7.2–NC)
6-/9-month PFS rate, % (95% CI)	84 (69–98) / 78 (60–95)	76 (62–90) / 61 (44–79)

*Efficacy-evaluable population.

8090 **Poster Session**

Clinical outcomes of local treatments for oligoprogressive or oligorecurrent small cell lung cancer. First Author: Adrien Mathieu, Université de Lille, CHU Lille, Thoracic Oncology Department, Lille, France

Background: The role of local treatments in patients with oligoprogressive or oligorecurrent small cell lung cancer (SCLC) remains unclear. Our study aimed to describe the prognosis of patients with SCLC receiving a local treatment for oligoprogression or oligorecurrence in a real-life setting. **Methods:** The present study included all consecutive patients treated for SCLC at Lille University Hospital or Strasbourg University Hospital between January 2013 and March 2024, for whom local treatment was decided in a Multidisciplinary Tumor Board to control oligoprogression or oligorecurrence. Clinical data and characteristics of the local treatment were collected from medical records. **Results:** Of the 850 patients treated for a SCLC in both centers during the study period, 97 patients were eligible for inclusion. Of those, 84 received local treatment for oligoprogression (n = 47) or oligorecurrence (n = 37). At the time of oligoprogression or oligorecurrence, 82.1% of patients were being treated for extensive-stage disease. The brain was the predominant site of oligoprogression or oligorecurrence (71%) and the most commonly used local treatment was conformal radiotherapy (66.7%), followed by stereotactic radiotherapy (31%) and surgery (2.4%). Grade ≥3 adverse events were observed in only 2.4% of treated patients. After a median follow-up period of 11.9 months, the median overall survival (OS) and median progression-free survival (PFS), measured from the date of initiation of local treatment, were 12.4 months (95% CI: 10.7-18.9), and 3.4 months (95 %CI: 2.4-4.5), respectively. A good performance status (PS 0–1) was associated with better OS (HR 0.50; (95% CI: 0.26–0.97); p = 0.018). PFS was significantly longer in patients with limited-stage SCLC (HR 0.52; (95% CI: 0.31–0.89); p = 0.016) or with five or fewer metastases at the time of local treatment (HR 0.59; (95% CI: 0.37–0.94); p = 0.038). Most progressions observed after local treatment occurred distant from the treated sites (68.8%). **Conclusions:** This study demonstrates that the use of local treatments to control oligoprogression or oligorecurrence in SCLC is not uncommon in routine clinical practice. While this strategy is generally well tolerated, its efficacy remains limited. Further studies are needed to clarify its role in the era of tarlatamab development. Research Sponsor: None.

8091 **Poster Session**

Paclitaxel, carboplatin, and durvalumab in extensive stage small-cell lung cancer (ES-SCLC; IFCT-2203 TAXIO phase II trial): Can we improve the chemotherapy (CT) immunotherapy combination in SCLC? First Author: Denis Lucien Moro Sibilot, Thoracic Oncology Unit, CHU-Grenoble-Alpes, Grenoble, France

Background: Etoposide+platinum-based CT and anti-PD-L1 is the backbone of ES-SCLC treatment. We hypothesize a deleterious action of etoposide on lymphocyte activation. A "proof-of-concept", multicenter and single arm phase II trial was designed to assess the efficacy and safety of an etoposide-free chemotherapy combining durvalumab (Durva) to paclitaxel and carboplatin (Pac-Carbo) CT in ES-SCLC. **Methods:** Patients (pts) with ES-SCLC, PS 0-1 were enrolled and received 4 induction cycles of Durva 1500 mg + paclitaxel 200 mg/m² + carboplatin AUC6 (PCD), every 3 weeks followed by single-agent Durva every 4 weeks until progression or unacceptable toxicity. The primary endpoint was overall survival at 12 months (OS@12m), secondary endpoints were overall response rate (ORR), overall survival (OS), OS at 24 and 36 months, progression-free survival (PFS), duration of response, safety (CTC v5.0) and quality of life (EORTC QLQ-C30 LC13). PFS and ORR were also assessed by independent reviewer committee. To reject the null hypothesis and achieve a 12-month survival rate of at least 34 patients (55.7%), 61 patients were required. Safety was assessed in all patients who received at least one dose of their study treatment. **Results:** 68 pts were enrolled between Nov 2023 and Feb 2025. Pts characteristics at baseline were: median age 66.6 years; 51.5% female, 67.6% PS1, 19.1% brain metastasis and 51.5% liver metastasis. The median number of cycles was 4 for chemotherapy and 6 for Durva injections. With a median follow-up of 17.1 months, the primary objective was reached. The OS@12m of the first 61 enrolled pts was 57.4% [IC95%: 44.1-70.0]. Median OS was 14.5 months [IC95%: 9.9-17.6]. ORR was 82.4% [IC95%: 73.3-91.4]. Median PFS was 4.6 months [IC95%: 4.4-4.7]. Treatment-related adverse events (TRAE) of grade 3-5 occurred in 48.5% of pts. TRAE leading to death occurred in 2 pts (sepsis). **Conclusions:** In the IFCT-2203 TAXIO phase 2 trial, the PCD regimen showed a signal of improved OS@12m and reached its statistical objective. Safety findings were consistent with the known safety profiles of all drugs received with no new safety signal for this population. PCD regimen is an active, easy to administer one-day regimen in ES-SCLC and should be integrated in future trials of new IO agents. Pac-Carbo is an alternative to etoposide platinum with potentially better synergy with durvalumab. Clinical trial information: 2023-504670-38-00. Research Sponsor: None.

8092 **Poster Session**

Sex-specific trends and outcomes in small cell lung cancer (SCLC) in Spain: Insights from the CLARISSE study (2019–2024). First Author: Pilar Garrido, Ramón y Cajal University Hospital, Madrid, Spain

Background: SCLC is an aggressive malignancy with poor prognosis. Although overall incidence is declining, cases among women are increasing. European projections show decreasing mortality in men but stable rates in women—except in Spain, where a +2.4% rise is expected—highlighting the need to examine sex-specific trends. **Methods:** CLARISSE is a multicenter, retrospective, observational real-world study conducted in Spain. Data were collected from 29 oncology departments across the country and included adult patients (≥18 years) with histologically confirmed SCLC diagnosed between January 2019 and December 2024. Baseline characteristics, treatment patterns, and survival outcomes were analyzed by sex. **Results:** Among 3,488 SCLC patients, 1,177 (33.8%) were women. The annual distribution of included SCLC cases remained stable over time (15.1%–17.7%), while the proportion of women increased from 29.3% to 39.2% over 6 years. Women were diagnosed at a younger age (mean 64.5 *vs.* 67.8 years). Active smoking was more frequent in women (68.0% *vs.* 54.7%, p<0.001), whereas men showed longer smoking and greater cumulative exposure, with median durations of 45 *vs.*43 years (p=0.02) and median pack-years of 50 *vs.*44 (p<0.001), respectively At diagnosis, 27% had limited-stage (LS) disease, more often in women (29.6% *vs.* 25.7%, p=0.015). Most LS patients received platinum–etoposide plus thoracic radiotherapy. In this population, 1-year overall survival (OS) was 67.9% (95%CI, 64.8-71.0%), with a median OS of 22 months (95%CI, 19.3-24.6 months); women had longer survival than men (Table 1). Systemic first-line (1L) treatment for extensive-stage (ES) consisted predominantly of platinum-based chemotherapy (95.6%; carboplatin 83.0% and cisplatin 12.6%) combined with etoposide (92.1%). Since its approval in September 2021, immunotherapy has been given to 66.3% of patients, more often to women (70.6% *vs.* 63.9%, p=0.013). In the population receiving 1L therapy, 1-year OS was 34.0% (95%CI, 32.1–35.9%), and median OS was 8.5 months (95%CI, 8.1–8.8). Women had longer survival (Table 1). Patients who received 1L immunotherapy had longer OS than those who did not: 10.1 months (95%CI, 9.4–10.7 months) *vs.* 7.2 months (95%CI, 6.6–7.7 months). **Conclusions:** This large multicenter SCLC cohort shows marked sex-related differences in epidemiology, stage distribution, treatment patterns and survival in Spain. Women were increasingly represented over time, diagnosed younger, and experienced longer survival in both LS and ES disease. These results support the importance of integrating sex-specific perspectives in SCLC management and research. Research Sponsor: PharmaMar.

Survival outcomes (CLARISSE study).

	LS-SCLC		ES-SCLC	
	Women	**Men**	**Women**	**Men**
1-year OS (95% CI)	78.1% (73.1-83.1)	62.1% (58.1-66.1)	38.3% (34.9-41.7)	31.7% (29.7-33.7)
Median OS (95% CI) (months)	30.1 (25.4-34.7)	17.3 (14.4-20.3)	9.1 (8.2-9.9)	8.0 (7.6-8.5)

8093 **Poster Session**

Comparison of real-world overall survival between atezolizumab- and durvalumab-containing first-line induction and maintenance regimens in extensive-stage small cell lung cancer. First Author: Apar Kishor Ganti, Division of Oncology-Hematology, VA Nebraska Western Iowa Health Care System/University of Nebraska Medical Center, Omaha, NE

Background: Both atezolizumab (atezo) and durvalumab (durva) are preferred first-line (1L) systemic treatment options for extensive-stage small cell lung cancer (ES-SCLC) with similar efficacy in the IMpower133 and CASPIAN phase 3 trials. There is limited evidence comparing their survival outcomes in the real-world (rw) setting. This study described rw overall survival (rwOS) in patients (pts) with ES-SCLC treated in 1L and 1L maintenance (1Lm) settings and also compared rwOS stratified by cohort and treatment with 1L atezo vs durva in combination with platinum-based chemotherapy (chemo) followed by atezo vs durva as 1Lm immunotherapy (IO). **Methods:** Using the US Flatiron Health Research Database, this retrospective noninferiority study included adults with ES-SCLC across 2 cohorts. The 1L cohort included pts treated with atezo or durva + chemo between Apr 1, 2020, and Sept 30, 2025. The 1Lm cohort included a subset of pts from the 1L cohort who were subsequently treated with atezo or durva monotherapy. The index date was the initiation of atezo or durva in the 1L or 1Lm setting in each cohort. rwOS hazard ratios (HRs) and 95% CIs comparing durva with atezo as reference in the 1L and 1Lm settings were calculated using Cox proportional hazard models, adjusting for prognostic covariates. Based on prior literature, the noninferiority margin was set at HR = 1.25. **Results:** A total of 2063 and 1122 pts were included in the overall 1L and 1Lm cohorts, respectively. In both cohorts, median age was 68 years, ≥20% of pts had an ECOG PS ≥2, and ≥19% had brain metastases at baseline. The 1L cohort had 1614 (78%) pts on atezo + chemo and 449 (22%) on durva + chemo. The 1Lm cohort had 865 (77%) pts on atezo and 257 (23%) on durva. Pt characteristics were generally similar between those treated with atezo vs durva in 1L or 1Lm settings. In the 1L cohort, median OS (95% CI) from the index date was 8.7 (8.2, 9.3) months for atezo and 8.5 (7.9, 9.5) months for durva. In the 1Lm cohort, median OS (95% CI) from index date (start of maintenance) was 9.3 (8.2, 10.2) and 9.2 (7.5, 10.8) months for atezo and durva. In the 1L cohort, the adjusted HR for OS for durva vs atezo was 0.98 (95% CI: 0.86, 1.10; P = 0.7), indicating no statistically significant difference between the 2 treatments. In the 1Lm cohort, the adjusted HR for OS for durva vs atezo was 1.04 (95% CI: 0.88, 1.22; P = 0.7). In both cohorts, the upper 95% CI was < 1.25, supporting the noninferiority of durva vs atezo. **Conclusions:** In this rw population, atezo and durva offered comparable rwOS, which was shorter than those reported in phase 3 clinical trials, for pts with ES-SCLC when used with chemo in 1L or as monotherapy in 1Lm. Research Sponsor: Jazz Pharmaceuticals.

8094 **Poster Session**

MC1923: Phase II durvalumab plus lurbinectedin in platinum-resistant relapsed extensive-stage small cell lung cancer after prior chemoimmunotherapy (cohort B). First Author: Konstantinos Leventakos, Mayo Clinic Rochester, Rochester, MN

Background: Patients with extensive-stage small cell lung cancer (ES-SCLC) who progress after platinum-based chemotherapy plus immunotherapy have limited options. Whether adding lurbinectedin while continuing immune checkpoint blockade at relapse improves outcomes is unknown. We report results for the platinum-resistant cohort (progression ≤3 months from last chemotherapy) of MC1923. **Methods:** MC1923 is a phase II trial using a Simon optimal two-stage design. Patients were assigned to a starting dose of durvalumab 1500 mg IV plus lurbinectedin 3.2 mg/m^2 IV on Day 1 of 21-day cycle. The primary endpoint was the 6-month progression-free survival rate (PFS6). Accrual continued to 22 eligible patients if ≥2/9 achieved PFS6; the regimen would be considered promising if ≥7/22 (32%) were alive and progression-free at 6 months. Secondary endpoints included adverse events (AEs), objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** Twenty-two patients enrolled (02/04/2022–05/21/2025); all were eligible and treated. Median age was 66 years; 32% were male; ECOG performance status was 0 in 9% and 1 in 91%; 96% had prior atezolizumab. Median cycles delivered were 4 (range 1–13). PFS6 was 4/22 (18.2%; 95% CI, 7.5–44.1%), below the prespecified threshold. Median PFS was 3.1 months (95% CI, 1.6–5.3). ORR was 13.6% (3/22; all partial responses; 95% CI, 2.9–34.9%). At data cutoff (12/18/2025), 4 patients were alive; median follow-up was 16.8 months (range 5.5–39.6). Median OS was 7.4 months (95% CI, 4.3–18.6) and 1-year OS was 33.1% (95% CI, 17.6–61.9%). One (1) patient discontinued treatment with durvalumab due to AE. No treatment-related Grade 5 AEs occurred; Grade 3–4 AEs at least possibly related to treatment occurred in 32% (7/22); Grade 4 AEs occurred in 5% (1/22), all hematologic. Most common Grade 3 AEs were decreased neutrophils and white blood cells (each 9%). **Conclusions:** Durvalumab plus lurbinectedin demonstrated manageable toxicity in platinum-resistant ES-SCLC after chemoimmunotherapy but did not meet the prespecified PFS6 efficacy threshold, supporting the need for alternative strategies in this high-risk population. Clinical trial information: NCT04607954. Research Sponsor: AstraZeneca.

8095 **Poster Session**

BL0020, a novel tumor microenvironment (TME)-targeting nano-mediated polypeptide-drug conjugate (NMPDC), in patients with advanced solid tumors: Updated results from the small cell lung cancer (SCLC) subset of a phase 1 study. First Author: Shuhang Wang, Department of Clinical Trial Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: BL0020 is a novel polypeptide-drug nanoconjugate (~10 nm in size) composed of PEG-modified poly(amino acid), enzyme-responsive peptide linkers, and topoisomerase I inhibitor (Topo1i) payloads. It accumulates in the tumor microenvironment (TME), where payloads are continuously released by specific enzymes, penetrate tumor cells, and effectively induce cell death. BL0020 has shown promising efficacy in advanced SCLC. Here, we present updated results from the SCLC subset of an international Phase 1 study of BL0020 (NCT05886868). **Methods:** Patients with locally advanced/unresectable or metastatic SCLC received BL0020 injection (20 mg/m² or 25 mg/m² IV every three weeks) until disease progression, unacceptable toxicity, or withdrawal of consent. **Results:** As of November 30, 2025, 49 patients were enrolled. Treatment-related adverse events (TRAEs) were consistent with expected payload-related effects, primarily manageable hematological and gastrointestinal toxicities, with no new safety signals identified. Grade 3/4 TRAEs occurring in ≥10% of patients included neutropenia, decreased white blood cell count, and anemia. All SCLC patients had progressed after at least one prior platinum-based chemotherapy regimen, and 61% had received prior anti-PD-(L)1 therapy. The median number of prior lines of therapy was 2 (range: 1–6). Among 13 efficacy-evaluable SCLC patients, the disease control rate (DCR) was 100% and the objective response rate (ORR) was 84.6%, with a confirmed ORR of 76.9%. In addition, eight patients achieved >50% tumor shrinkage. Among SCLC patients with baseline brain metastases, both ORR and DCR were 100%, with brain lesions showing >50% shrinkage or complete disappearance. At a median follow-up of 12.58 months, median progression-free survival (mPFS) was 10.15 months (95% CI: 4.93, not reached), median duration of response (mDOR) was 8.18 months (95% CI: 3.54, not reached), and median overall survival (mOS) was 15.31 months (95% CI: 7.46, not reached). **Conclusions:** BL0020 monotherapy demonstrated a manageable safety profile and promising antitumor activity in patients with advanced SCLC who progressed after at least one prior platinum-based chemotherapy. The therapy showed a high response rate and potential for prolonged PFS compared with standard chemotherapy. Clinical trial information: NCT05886868. Research Sponsor: None.

8096 **Poster Session**

Updated results of the phase 1 dose escalation and expansion study of alveltamig (ZG006), a trispecific T cell engager targeting DLL3/DLL3/CD3, as monotherapy in patients with refractory small cell lung cancer or neuroendocrine carcinoma. First Author: Qiming Wang, Henan Cancer Hospital Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China

Background: Alveltamig (ZG006) is a uniquely designed T cell engager, targeting two distinct delta-like ligand 3 (DLL3) epitopes and CD3 and, thereby bridging tumor cells and T cells together and mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC) or neuroendocrine carcinoma (NEC). **Methods:** This is a multi-center, open-label, phase 1 clinical study of ZG006 as monotherapy in patients with SCLC or NEC who failed or were intolerant to the standard therapies. A standard "3+3" design, with an accelerated titration approach for the first two lower dose levels was used during the dose escalation stage. Here we report the updated results of the efficacy and safety data from the phase I study. **Results:** In this phase I study, patients received ZG006 at 0.1 mg Q2W and escalated at 8 dose levels up to 100 mg Q2W (Wang Q et al, ASCO 2025). A step dose of 1 mg was implemented for higher dose groups starting from 10 mg Q2W. Dose expansion was conducted at dose levels of 10, 30, and 60 mg. A total of 31 patients with SCLC, including 4, 15, and 12 patients from the 10 mg, 30 mg, and 60 mg dose groups respectively, were included in the current efficacy analysis. The overall median follow-up time was approximately 16 months. The median age was 59 years (range, 45.0-72.0), the median number of prior treatment lines was 3 (range,1-4), 80.6% of the patients had received prior immunotherapy, and 90.3% had a baseline ECOG performance status score of 1. The confirmed objective response rate (ORR) assessed by an independent review committee (IRC) was 74.2%. The median duration of response (DoR) was 12.6 months, with 12-month DoR rate at 65.3 %. The estimated 12-month PFS rate was 50.5%. The median overall survival (OS) was not reached yet, however,the 12-month and 18-month OS rates approached 74.2% and 58.6% respectively. Consistent with prior report, the most common adverse events with longer follow-up included CRS, anemia and other conditions, with most being Grade 1 or 2 and occurring during the first two cycles. Overall, ZG006 was well-tolerated and the treatment related adverse events including CRS were manageable. **Conclusions:** With longer follow up from phase I study, ZG006 continued to demonstrate robust antitumor activity in the dose expansion cohorts including high ORR, longer DoR/PFS, and clinically meaningful survival benefits in patients with refractory SCLC. No new safety signal was encountered. These data support ongoing development of ZG006 as monotherapy and in combination with other modalities in SCLC. Clinical trial information: NCT05978284. Research Sponsor: None.

8097 **Poster Session**

Predictive markers of response and toxicity to tarlatamab in patients with extensive stage small cell lung cancer (ES-SCLC): A multi-institutional real-world analysis. First Author: Graeme Fenton, University of Maryland Medical Center, Baltimore, MD

Background: Tarlatamab (tarla) is a novel immunotherapeutic agent for the treatment of relapsed ES-SCLC associated with favorable response and survival outcomes. While tarla's unique side effect profile of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) is well described, factors influencing response or toxicity have yet to be fully established. **Methods:** We performed a retrospective, multivariate analysis of patients with ES-SCLC receiving tarla at three NCI-designated comprehensive cancer centers from 7/2024-10/2025. CRS and ICANS were reported using ASTCT consensus guidelines. Dysgeusia was graded using CTCAE v5.0. Overall response rate (ORR) was determined using clinical interpretation of radiographic assessments from patients with available post-treatment imaging. Time to event analyses were performed. Cox Proportional Hazards regression analyses assessed the association between patient characteristics and PFS and OS outcomes. Logistic and ordinal regression analyses evaluated the predictive value of variables contributing to the presence and severity, respectively, of CRS and ICANS. **Results:** 115 patients received at least 1 dose of tarla, with median age of 67 years, 55% female and ECOG PS ranging from 0-3 (median of 1). Rates of observed CRS, ICANS, and dysgeusia were 46%, 28%, and 47%, respectively. ORR was 44% and 6-month PFS/OS rates were 30.4% (95% CI: 22.5-41.1%)/54.9% (95% CI: 45.4-66.4%). Excluding patients on tarla $<$30 days, presence of dysgeusia was associated with a lower rate of progression (HR 0.44, p = 0.00691) and death (HR 0.34, p = 0.0145). Neither CRS nor ICANS were associated with treatment response. Both sum of liver metastasis diameter $>$10 cm (OR 4.4, p = 0.02) and elevated baseline LDH (p = 0.01) were significantly associated with increased likelihood of CRS, while female sex was a protective factor (OR 0.33, p = 0.01). Increased ECOG PS (OR 2.3, p = 0.02), sum of brain metastasis diameter $>$2 cm (OR 3.6, p = 0.02), development of CRS (OR 2.8, p = 0.04), elevated baseline LDH (p = 0.04) and elevated baseline ferritin (p =0.004) were all associated with increased risk of developing ICANS. **Conclusions:** In our multicenter cohort of patients with ES-SCLC, tarlatamab continued to demonstrate anticancer activity with similar ORR and 6 month PFS compared to existing DeLLphi-304 data. Importantly, the presence of dysgeusia was found to be a marker of treatment response associated with improved PFS and OS. CRS and ICANS incidence was associated with several baseline patient and disease characteristics. Collectively, these preliminary results identify several predictive biomarkers of toxicity that can be utilized in clinical practice, though validated models are needed to better stratify low and high-risk populations. Research Sponsor: None.

8098 **Poster Session**

Monalizumab plus durvalumab plus platinum-based chemotherapy for first-line treatment of extensive stage small-cell lung cancer: Early efficacy results from MOZART trial. First Author: Hirva Mamdani, Department of Hematology and Oncology, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI

Background: Extensive stage small cell lung cancer (ES-SCLC) is an area of unmet need where novel treatment strategies are urgently needed. Preclinical data in SCLC demonstrate higher expression of NKG2A, an immune checkpoint expressed on natural killer (NK) cells and CD8+ T cells, with consequent reduced NK cell mediated anti-tumor activity, substantially enhanced metastatic dissemination of tumor cells, and amelioration of metastasis with hyperactivation of NK cells. We hypothesized that NKG2A inhibitor monalizumab (M) may enhance the efficacy of first-line therapy in ES-SCLC by promoting both NK and CD8+ T cell functions. **Methods:** We conducted a single arm, multicenter, investigator-initiated phase II study with a safety lead-in cohort, evaluating M in combination with platinum (P), etoposide (E), and durvalumab (D) in patients (pts) with previously untreated ES-SCLC. One prior cycle of EP $\pm$ D was allowed. Pts received EP + D + M every 3 weeks for 4 cycles followed by D + M every 4 weeks until disease progression or unacceptable toxicity. Primary endpoints were 1-year (yr) progression-free survival (PFS) and safety. Secondary endpoints were objective response rate (ORR), 1-year overall survival (OS) and intracranial PFS (iPFS). We hypothesize that the combination will lead to improvement in 1-yr PFS to 33% compared to historical control of 18% (1-sided alpha:10%, power: 80%). **Results:** 30 pts were enrolled (median age:62.5yrs (range, 53-79)). 10pts (33.3%) were female and 6 (20%) were Black. 14pts (46.7%) received one cycle of EP $\pm$ D prior to study entry. ORR was 73.3% (complete response = 3, partial response = 19). At median follow-up of 14.2months (mo) (range, 6.4-not estimable (NE)): estimated 1-yr PFS: 20.6%, 18-mo PFS: 15.5%, median (m) PFS: 4.8mo (4.5-5.3), 1-yr OS: 67.4%, mOS: NE (10.2-NE). Most common site of progression was brain with miPFS of 5.3mo (4.8-10.8); 1-yr iPFS: 21.7%, 18-mo iPFS: 16.3%. 4pts had PFS longer than 1yr, 3 of whom had brain metastasis at baseline. No dose limiting toxicities were identified in the safety lead-in cohort. Treatment related AEs (TRAEs) at least possibly related to D and/or M occurring in $\geq$10% of pts were fatigue (23%), decreased lymphocyte count (13%), hypothyroidism (10%), decreased neutrophil count (10%), and increased lipase (10%). 5 pts (17%) had grade (G) 3/4 TRAEs: decreased neutrophil count (n = 3), encephalitis (n = 1), acute kidney injury (n = 1). Toxicities solely attributed to M were all G 1: increased lipase (n = 2), headache (n = 1), and increased amylase (n = 1). **Conclusions:** Addition of M to first-line EP + D led to no new severe AEs in patients with ES-SCLC. Estimated 1-yr PFS was not statistically superior to historical control with EP +D, yet a subset of patients including those with baseline brain metastasis derived durable benefit. Long term follow-up and biomarker analysis are ongoing. Clinical trial information: NCT05903092. Research Sponsor: AstraZeneca.

8099 **Poster Session**

Multicenter phase II trial of atezolizumab plus carboplatin and etoposide for extensive-stage small cell lung cancer older patients who underwent geriatric assessment (OLCSG2002 EPAS Trial). First Author: Yuka Kato, Department of Thoracic oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama-City, Ehime, Japan

Background: Combination therapy with anti-PD-L1 monoclonal antibodies and chemotherapy (ICI-chemotherapy) is the current standard treatment for patients(pts) with extensive-stage small cell lung cancer (ES-SCLC). However, its safety and efficacy in older pts ($\geq$ 71 years) remain limited. Given the pivotal role of geriatric assessment (GA) in the older care, prospective data remain scarce. This study aimed to clarify the efficacy and safety of ICI-chemotherapy in older pts and to evaluate the association between GA and survival. **Methods:** This multicenter prospective study enrolled pts $\geq$ 71 years with ES-SCLC who received atezolizumab plus carboplatin and etoposide as first-line therapy. The primary endpoint was 1-year survival rate (SR). Based on existing results, the expected value was 60%, the threshold was 40% (α-error = 0.1 [two-sided], power = 0.75). The calculated sample size was 32 pts. A pre-treatment G8 assessment was mandatory for all pts. Secondary endpoints included safety, objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** Between August 2022 and March 2024, a total of 32 pts were enrolled: median age 77 years (range 71–83); male/female = 27/5; PS 0/1 = 8/24, G8 scores $\geq$12 / $<$ 12 /not collected were 19/12/1. The 1-year SR was 62.5% (95% confidence interval [CI]: 43.5–76.7). Median OS was 14.6 months (95% CI: 8.2–23.3), median PFS was 5.0 months (95% CI; 4.2–5.9), and ORR was 84.4% (95% CI; 66.3–93.7). Median OS by G8 (score $\geq$12 vs $<$ 12) was 15.4 vs 12.3 months. Cox regression analysis including clinically important factors for survival (age, PS, G8, bone and brain metastasis at diagnosis) identified brain (HR; 3.1, 95% CI: 1.06 to 8.87; p = 0.039) and bone metastases (HR 3.5, 95% CI: 1.20 to 10.1; p = 0.022) as an independent factor. grade $\geq$ 3 adverse events (AEs) occurred in 87.5% of pts, and dose reduction was required in 45.1%. The most frequent AE was neutropenia (93.8%); one treatment-related death (stroke) was reported. **Conclusions:** ICI-combined chemotherapy demonstrated efficacy comparable to that in existing studies, but greater caution was required regarding safety in older pts. While G8 status did not affect survival in SCLC pts, the presence of bone or brain metastasis at diagnosis was identified as an independent prognostic factor. Clinical trial information: jRCT1061200024. Research Sponsor: None.

8100 **Poster Session**

Comparative real-world outcomes of tarlatamab and lurbinectedin in relapsed extensive-stage small cell lung cancer. First Author: Daniyal Aziz Khan, Charleston Area Medical Center, Charleston, WV

Background: Extensive stage small cell lung cancer is an aggressive malignancy with rapid progression and poor survival after relapse following platinum-based chemotherapy. Tarlatamab, a DLL3 directed bispecific T cell engager, demonstrated a significant overall survival benefit compared with physician's choice of chemotherapy, including lurbinectedin, in the phase 3 DeLLphi 304 trial. However, access to tarlatamab remains limited in routine clinical practice, and lurbinectedin continues to be commonly used in the post platinum setting. As a result, real world data comparing the effectiveness and toxicity of these agents are needed to better inform treatment decisions for patients with relapsed small cell lung cancer. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, a federated, de-identified electronic health record database. Adults with lung cancer who received platinum-based chemotherapy or immunotherapy as first-line treatment and subsequently initiated tarlatamab or lurbinectedin as second-line therapy between January 1, 2020 and November 1, 2025 were included. Propensity score matching was then performed and overall survival was evaluated using Kaplan–Meier methods. Secondary outcomes included immune- and treatment-related adverse events, including cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS/ICE), and corticosteroid use. **Results:** After 1:1 propensity score matching, both groups had 133 patients each with good balance across demographics, comorbidities, metastatic burden, prior therapies, and baseline laboratory. At 1 year, mortality was 33.1% with tarlatamab versus 72.2% with lurbinectedin (absolute risk reduction 39.1%, 95% CI 28.1–50.1; $p<$ 0.0001), with improved 1-year survival probability (59.2% vs 17.1%) and superior overall survival (HR 0.46, 95% CI 0.32–0.66; log-rank $p<$ 0.0001). The survival benefit persisted at 2 years, with median survival of 417 days versus 149 days and survival probabilities of 47.4% versus 15.9%, respectively (HR 0.48, 95% CI 0.34–0.68; p= 0.0015). Tarlatamab was associated with higher corticosteroid use (56.4% vs 33.8%, p= 0.0002) and immune-mediated toxicities, including cytokine release syndrome in 45.1% (grade 1: 23.3%, grade 2: 13.5%) and ICANS/ICE in 17.3%, with no grade 4–5 events. **Conclusions:** In this propensity score–matched analysis, tarlatamab demonstrated a significant and durable overall survival advantage over lurbinectedin, with an approximately 50% relative reduction in the risk of death at both 1 and 2 years based on hazard ratios. While tarlatamab was associated with higher rates of expected immune-mediated toxicities, including CRS and ICANS, events were predominantly low-grade, supporting a favorable benefit–risk profile in this heavily pretreated metastatic population. Research Sponsor: None.

8102 Poster Session

Impact of lung cancer screening in patients diagnosed with small cell lung cancer. First Author: Paresh Kumar, Indiana University School of Medicine, Indianapolis, IN

Background: The advent of immunotherapy significantly improved overall survival (OS) for limited-stage SCLC (LS-SCLC), highlighting how early detection may drive maximal therapeutic benefit. Lung cancer screening (LCS) with low-dose CT scans (LDCT) in high-risk individuals reduced the risk of lung cancer mortality and identified more Stage I lung cancer (National Lung Screening Trial (NLST), NELSON). Within the NLST, SCLC distribution by stage (I-IV) was similar between LDCT or chest x-ray, thereby limiting the perceived absolute impact of LCS for SCLC detection. Here, we report on the utility of LCS in SCLC in the era of immunotherapy. **Methods:** We retrospectively reviewed the charts of patients diagnosed with SCLC in the Indiana University (IU) Health System from 2018 to 2024. Patients were stratified by whether SCLC was identified from LDCT or non-screen detected. Kaplan-Meier, Wilcoxon rank sum, Pearson's Chi-squared, and Fisher's exact test were applied. **Results:** Among the 301 LCS-eligible individuals with SCLC, 67 patients (22.3%) received LDCT preceding their diagnosis. With LDCT, a significant shift in stage was observed (P <0.001). In the non-LDCT cohort, 28% were diagnosed with LS-SCLC and 72% with ES-SCLC. In the LDCT cohort, 60% were diagnosed with LS-SCLC and 40% with ES-SCLC. After robust adjustment for confounders in a multivariable logistic regression model, LCS was independently associated with higher odds of LS-SCLC at diagnosis (odds ratio 4.22; 95% CI, 2.20-8.28, P <0.001). Significant delays post-LDCT were noted including time from scan to biopsy (52 vs 10 days, P <0.001) and biopsy to treatment (20 vs 13 days, P <0.001). LCS did not improve response rates, treatment completion rates, or progression-free survival, regardless of stage. At diagnosis, patients with ES-SCLC in the LDCT cohort tended to have less CNS involvement (11% vs 30%, P = 0.06) but had more bone metastases (74% vs 45%, P = 0.006), compared to non-LDCT. Survival between LDCT and non-LDCT was similar for LS-SCLC (22.9 vs 40.4 months, P = 0.15) and ES-SCLC (12.2 vs 10.8 months, P = 0.89). To account for stage migration and unequal follow-up between groups (41.4 vs 25.3 months), a pre-specified, stage-agnostic 1-year OS was compared. The LDCT group had a higher 1-year OS compared to the non-LDCT group (69.2% vs 54.6%, P = 0.03). **Conclusions:** Use of LCS in eligible patients resulted in a significant "stage-shift" to LS-SCLC for individuals diagnosed with SCLC. At a pre-specified cut-off, LCS significantly improved OS for patients diagnosed with SCLC. Research Sponsor: Indiana University Simon Comprehensive Cancer Center; Tom and Julie Wood Center for Lung Cancer Research.

Characteristic	LDCT (No) (n = 234)	LDCT (Yes) (n = 67)	Overall (n = 301)	*P* value
Age (Q1, Q3)	66 (61, 72)	68 (64, 73)	67 (62, 72)	0.1
Sex (female)	145 (62%)	41 (61%)	186 (62%)	>0.9
ECOG PS (0-1)	150 (70%)	53 (84%)	203 (73%)	0.024
Current tobacco	171 (73%)	50 (75%)	221 (73%)	0.9
COPD	119 (51%)	48 (72%)	167 (55%)	0.003
+FH cancer	128 (59%)	46 (73%)	174 (62%)	0.047
+FH lung cancer	57 (26%)	22 (35%)	79 (28%)	0.2

8103 Poster Session

Comparison by immunotherapy agent of real-world outcomes with chemo-immunotherapy in first-line extensive-stage small cell lung cancer. First Author: Anthony Alfonso, Indiana University School of Medicine, Indianapolis, IN

Background: Chemoimmunotherapy became the standard of care for extensive-stage small cell lung cancer (ES-SCLC) after two Phase III trials (IMpower133, CASPIAN) demonstrated significant improvement in overall survival (OS) over platinum-based chemotherapy. While both anti-PD-L1 agents provide durable responses in a subset (~10%), the magnitude of benefit with immunotherapy (IO) is similar, suggestive of therapeutic interchangeability. Real-world data (RWD) suggests durvalumab confers superior outcomes in ES-SCLC, compared to atezolizumab. Recently, durvalumab received regulatory approval for limited-stage SCLC, whereas atezolizumab failed to demonstrate benefit after chemoradiation. Here, we investigate whether IO choice impacts outcomes for first-line ES-SCLC. **Methods:** We retrospectively reviewed the charts of patients diagnosed with ES-SCLC in the Indiana University (IU) Health System from 2018 to 2024. Patients were stratified by receipt of either atezolizumab or durvalumab for first-line chemoIO for comparison of demographics and outcomes. Kaplan-Meier, univariate Cox regression, and Fishers exact test was applied. **Results:** We identified 158 patients diagnosed with ES-SCLC who received chemoIO (Table 1). Platinum-sensitivity and objective response rates were similar between groups (P = 0.14 and P >0.9, respectively). The median number of IO cycles received (induction and maintenance) was significant higher with atezolizumab (9), compared to durvalumab (7, P <0.001). Similarly, median progression-free survival (PFS) trended in favor of atezolizumab over durvalumab (6.3 vs 5.2 months, P = 0.08). Subsequent therapy post-progression was comparable between groups, including lurbinectedin (31% vs 23%, P = 0.5) and tarlatamab (17% vs 23%, P = 0.4). The unadjusted median OS for atezolizumab was 16.5 months (95% CI, 13.2-19.5), compared to durvalumab 12.4 months (95% CI, 9.9-17.3) (P = 0.11). To account for group imbalances, overlap-weighted multivariable Cox regression was performed, in which ECOG performance status (PS) of 0-1 (HR 0.53, 95% CI, 0.30-0.92, P = 0.03) and receipt of atezolizumab (HR 0.56, 95% CI, 0.34-0.93, P = 0.02) were independently associated with improved OS. **Conclusions:** In our study, atezolizumab demonstrated improved OS and trended to improve PFS in first-line ES-SCLC, compared to durvalumab. Potential confounders when evaluating the impact of IO agents across RWD studies include ECOG PS, variable use of thoracic radiotherapy, geographical differences, and ethnic distributions. Research Sponsor: Indiana University Simon Comprehensive Cancer Center; Tom and Julie Wood Center for Lung Cancer Research.

Characteristic	Atezolizumab (n = 127)	Durvalumab (n = 31)	Overall (n = 158)	*P* value
Age (Q1, Q3)	66 (61, 73)	68 (63, 73)	67 (61, 73)	>0.9
Sex (female)	79 (62%)	17 (55%)	96 (61%)	0.5
ECOG PS (0-1)	87 (74%)	20 (69%)	107 (73%)	0.6

8104 Poster Session

Demographics and outcomes of individuals with young-onset small cell lung cancer. First Author: Paresh Kumar, Indiana University School of Medicine, Indianapolis, IN

Background: A diagnosis of lung cancer before the age of 50 is commonly driven by oncogenic alterations and observed in patients without a history of tobacco use. Little is known about the characteristics and outcomes of individuals with young-onset small cell lung cancer (YO-SCLC). **Methods:** We retrospectively reviewed the charts of patients diagnosed with SCLC treated in the Indiana University (IU) Health System from 2018 to 2024. Patients were stratified by age <50 or >50 years at diagnosis of SCLC for statistical comparison of key variables and outcomes. Fisher's exact and Wilcoxon rank sum tests were applied to categorical and continuous variables, respectively. **Results:** Among 416 individuals with SCLC, we identified 23 patients with YO-SCLC. The incidence of YO-SCLC was 5.5 cases per 100 cases of SCLC (95% CI, 3.7-8.2) with a median age of 47 (40-49). None of the YO-SCLC were detected by lung cancer screening (LCS), compared to 17% in the >50 cohort (Table 1). Patients with YO-SCLC are more likely to have active tobacco use but significantly less pack years, compared to >50. Majority of YO-SCLC (74%) were diagnosed with extensive-stage SCLC, analogous to >50. Extensive-stage YO-SCLC patients had similar platinum-sensitivity and PFS with platinum-based therapy with or without immunotherapy but trended to have improved median OS (24.7 vs 11.1 months, HR 1.67, 95% CI 0.88-3.15, P = 0.12). Limited-stage YO-SCLC patients were more likely to receive prophylactic cranial irradiation (PCI, 67% vs 25%, P = 0.04) but demonstrated no significant difference in PFS or OS with guideline-directed therapy, compared to >50. **Conclusions:** YO-SCLC represents a unique under-recognized population with trends toward improved OS, despite comparable platinum-sensitivity and PFS with chemoimmunotherapy for ES-SCLC. Such patients are currently excluded from LCS due to age. These results suggest eligibility criteria for LCS could be expanded to include individuals <50 with active tobacco use (>20 PY) and a family history of lung cancer to increase detection of YO-SCLC. The molecular underpinnings of YO-SCLC remain to be elucidated. Investigation into the genomic and neuroendocrine subtype composition of YO-SCLC is underway. Research Sponsor: Indiana University Simon Comprehensive Cancer Center; Tom and Julie Wood Center for Lung Cancer Research.

Characteristic	Age <50 (n = 23)	Age >50 (n = 393)	Overall (n = 416)	*P* value
Sex (female)	15 (65%)	231 (59%)	246 (59%)	0.7
Stage (ES-SCLC)	17 (74%)	257 (65%)	274 (66%)	0.5
BMI	33 (23, 38)	27 (23, 32)	27 (23, 32)	0.046
COPD	7 (30%)	207 (53%)	214 (51%)	0.052
Current tobacco use	20 (87%)	247 (63%)	267 (64%)	0.025
Pack years	30 (25, 50)	45 (30, 60)	45 (30, 60)	0.043
Eligible for lung cancer screening	0 (0%)	301 (77%)	301 (72%)	<0.001
Detected by lung cancer screening	0 (0%)	68 (17%)	68 (16%)	0.021
+FH lung cancer	9 (39%)	103 (26%)	112 (27%)	0.14

8105 Poster Session

A multi-institutional, single-arm, phase 2 study of durvalumab plus amrubicin in patients with relapsed extensive-stage small cell lung cancer (Aphrodite trial). First Author: Yuka Kato, Department of Thoracic oncology and Medicine, National Hospital Organization Shikoku Cancer Center, Matsuyama-City, Ehime, Japan

Background: In patients (pts) with sensitive relapsed (SR) and refractory relapsed (RR) small cell lung cancer (SCLC), amrubicin (AMR) is one of the current standard treatments in Japan. However, the overall survival (OS) in RR is particularly poor, with approximately 6-9 months and a 1-year overall survival rate (1yr-OS rate) of 34%, which is not satisfactory. We conducted the phase 2 exploratory proof-of-concept trial based on preclinical results, which showed that the combination of an anti-PD-1 antibody and a topoisomerase II inhibitor had a synergistic effect on cancer cells. This trial was funded by AstraZeneca K.K. **Methods:** This trial enrolled pts with SR or RR SCLC that recurred after first-line chemo-immunotherapy. They were treated with durvalumab (1,500 mg on day1) and AMR (40 mg/m^2 on days1-3), every three weeks until progression. After assessing the safety of the combination therapy in the lead-in cohort, we initiated the phase 2 part of the trial. The primary endpoint was the 1yr-OS rate calculated based on a year consisting of 48 weeks. The secondary endpoints consisted of OS, progression-free survival (PFS), overall response rate (ORR) etc. The expected 1yr-OS rate for SR and RR were 61.1% and 44.4%, respectively, which were 10% higher than the systematic review result for AMR alone in Japanese pts. Based on this review result and considering feasibility, the sample size was planned as 18 pts for each SR and RR. **Results:** Between July 2022 and August 2024, a total of 23 (SR: 5; RR: 18) pts were enrolled. All pts had previously received treatment with platinum-containing drugs and immune checkpoint inhibitors (ICI). The SR group could not be enrolled till sufficient sample size for statistical analysis. The 1yr-OS rate was 80.0% for SR group, which included a complete responder. The efficacy results for the RR group were: The 1yr-OS rate was 44.4% (95% confidence interval (CI): 21.6-65.1). The median PFS and OS were 15.1 weeks (95% CI: 11.0-23.3) and 43.1 weeks (95% CI: 24.6-64.3), respectively. The ORR was 38.9% (95% CI: 17.3-64.3). Grade 3 or higher adverse events were observed in 65.2% of all 23 pts, but no new events beyond those previously reported were identified. The most frequent Grade 3 or higher adverse event was neutropenia (43.5%), with febrile neutropenia occurring in 13.0%. Grade 3 or higher pneumonia was observed in 4.3%, and no treatment-related deaths were reported. **Conclusions:** The combination therapy of durvalumab and AMR suggests favorable efficacy and tolerable safety, particularly in pts with RR, even in those who had already received ICI treatment. Clinical trial information: jRCT2061220036. Research Sponsor: AstraZeneca.

8106 **Poster Session**

Safety, pharmacokinetic, and preliminary efficacy of SNC115 in patients with relapsed/refractory small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC): A phase 1 study. First Author: Tianqing Chu, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: SCLC and LCNEC are characterized by aggressive clinical courses and limited therapeutic options following progression on platinum-based chemotherapy. DLL3(Delta-like ligand 3) is highly expressed and selectively on the surface of these high-grade neuroendocrine tumors, making it an ideal therapeutic target. SNC115 is a novel CAR-T cell armored with CD70 to target DLL3-expressing cells. **Methods:** This phase 1, open-label study utilized an accelerated titration design followed by a standard 3+3 escalation to evaluate the safety, tolerability, and pharmacokinetics of SNC115 in patients (pts) with R/R SCLC or LCNEC who progressed after ≥1 line of standard therapy. Following leukapheresis and a 3-day lymphodepletion regimen (fludarabine/cyclophosphamide), pts received a single infusion of SNC115 at one of five planned dose levels (DL): 1.0×10^5 (DL1), 3.0×10^5 (DL2), 1.0×10^6 (DL3), 3.0×10^6 (DL4), and 6.0×10^6 (DL5) CAR^+ T cells/kg. The primary endpoints were the determination of the maximum tolerated dose (MTD) and the recommended dose (RD). **Results:** As of 23 January 2026, 8 pts with R/R SCLC were treated across four DLs: DL1 (n = 1), DL2 (n = 3), DL3 (n = 2) and DL4 (n = 2). Median age was 53.5 (range 40-69) years, with a median of three prior therapy lines (range 2-6). 6 pts received bridging therapy. SNC115 demonstrated a manageable safety profile. CRS occurred in 3 pts (DL1: 1pt, DL4: 2pts), all Grade 1 or 2 and resolved with tocilizumab/corticosteroids. Grade ≥3 hematologic TEAEs included lymphocyte count decreased (8/8), white blood cell count decreased (2/8) and anaemia (1/8), all attributed to LD. Only one patient (DL4) experienced Grade ≥3 non-hematologic TEAEs related to SNC115, including alanine aminotransferase increased (G3), Gamma-glutamyltransferase increased (G3) and diarrhea (G3), which resolved with symptomatic care. No DLTs, SAEs or ICANS were reported. Among evaluable pts (n = 8), the ORR and DCR were 37.5% and 75%, respectively. All patients (n = 2) in the higher-dose level (DL4) achieved PR. CAR-T cells expansion peaked at a median of 7 days post-infusion, with Cmax ranging from 68.77 to 4359.89 copies/μg DNA. **Conclusions:** SNC115 demonstrated a manageable safety profile and encouraging preliminary antitumor activity in heavily pretreated pts with SCLC. The absence of DLTs and ICANS, combined with low-grade transient CRS, supports continued dose escalation. These early efficacy signals suggest that SNC115 may provide a novel therapeutic avenue for R/R SCLC. Clinical trial information: NCT06384482. Research Sponsor: Shanghai Simnova Biotechnology Co.,Ltd.

8107 **Poster Session**

Prognostic factors and impact of concomitant medication in extensive-stage small cell lung cancer (ES-SCLC) treated with first-line chemotherapy plus anti-PD-L1: A Spanish multicenter real-world study. First Author: Mikel Portu, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Background: Platinum - etoposide with PD-L1 inhibitors is the standard first-line treatment for ES-SCLC. However, real-world outcome data remain limited, particularly regarding the prognostic impact of frequently used concomitant medications. **Methods:** Retrospective multicenter cohort (9 Spanish centers; Oct 2019 - Apr 2025) of ES-SCLC treated with first-line platinum - etoposide plus anti-PD-L1. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan - Meier. Proton pump inhibitor (PPI), corticosteroid*, and antibiotic use within 30 days before treatment initiation were recorded. Multivariable Cox models were adjusted for Eastern Cooperative Oncology Group performance status (ECOG PS), liver/bone/central nervous system (CNS) metastases (mets), and medications. The immune-related adverse event (irAE) - OS association was explored using time-fixed and 12-week landmark analyses. **Results:** A total of 442 patients were included (median age 66, 67% male, 90% ECOG PS 0–1); PD-L1 inhibitor: atezolizumab 97%, durvalumab 3%, pembrolizumab <1%. Liver, bone, and CNS mets were present in 40%, 34%, and 27%. PPIs, corticosteroids, and antibiotics were used in 51%, 33%, and 26%. Most (77%) completed induction (4 cycles); 79% initiated maintenance (6% after <4 cycles). ORR was 80% and DCR 90% (n=404 evaluable; routine assessment). With median follow-up of 27.2 months (reverse Kaplan - Meier), median PFS was 5.6 months (95% CI 5.3 - 6.1) and median OS 10.2 months (95% CI 8.4 - 11.3); 12-month OS 43%. On multivariable analysis (complete-case n=415; Table), ECOG PS ≥2 and liver/bone/CNS mets were associated with worse OS, while PPIs, corticosteroids, and antibiotics were not. irAEs occurred in 24%; time-fixed analysis suggested improved OS (adjusted HR 0.61; 95% CI 0.45 - 0.81; p<0.001), but this was not confirmed in 12-week landmark analysis (HR 0.84; 95% CI 0.55 - 1.29; p=0.43). **Conclusions:** In this large real-world ES-SCLC cohort treated with first-line chemoimmunotherapy, ECOG PS and metastatic burden remained key prognostic factors. Concomitant PPIs, corticosteroids, and antibiotics were not independently associated with OS, although residual confounding by indication cannot be excluded. The irAE - OS association was not confirmed by landmark analysis, highlighting the importance of time-dependent methods. Research Sponsor: None.

Multivariable Cox regression for OS (n=415).

Variable	HR (95% CI)	p-value
ECOG PS ≥2 vs 0-1	1.47 (1.02–2.12)	0.039
Liver mets	1.53 (1.22–1.94)	<0.001
Bone mets	1.52 (1.19–1.93)	<0.001
CNS mets	1.41 (1.10–1.81)	0.006
PPI (≤30d)	1.13 (0.89–1.44)	0.311
Corticosteroids (≤30d)*	1.03 (0.79–1.33)	0.842
Antibiotics (≤30d)	1.18 (0.89–1.55)	0.245

*Non-prophylactic systemic corticosteroids (≥10 mg/day prednisone-equivalent).

8108 **Poster Session**

Tarlatamab in small cell lung cancer with brain metastases: A real-world experience. First Author: Santiago Sucre, Jackson Memorial Hospital, University of Miami, Miami, FL

Background: Tarlatamab, a DLL3-directed bispecific T-cell engager, has demonstrated survival benefit in previously treated small cell lung cancer (SCLC) in pivotal clinical trials. However, real-world evidence remains limited, particularly in ethnically diverse populations and in patients with a high burden of central nervous system (CNS) disease who are often underrepresented in clinical trials. We evaluated the safety, radiographic response, and treatment durability of tarlatamab in a real-world cohort treated at a single academic center. **Methods:** We retrospectively reviewed patients with extensive-stage SCLC treated with tarlatamab at Sylvester Comprehensive Cancer Center between January 2024 and October 31, 2025. Demographic, clinical, radiographic, and toxicity data were abstracted from medical records. Radiographic response was assessed per RECIST criteria, with best overall and 6-month responses recorded. Objective Response Rate (ORR) and Disease Control Rate (DCR) were calculated. Progression-free survival (PFS) and Overall Survival (OS) were estimated using Kaplan–Meier methods with multivariable analyses performed using Cox regression. **Results:** Among 23 patients (median age 72 years), male sex, Hispanic ethnicity, and brain metastases were each present in 61% of the cohort at tarlatamab initiation. 43% had received ≥2 prior lines of therapy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANs) occurred predominantly during cycle 1 and were limited to grade 1 or 2 events, with no grade ≥ 3 toxicities observed. Median time on treatment was 92 days, with a median of 4 cycles. Three patients required treatment discontinuation due to toxicities. Radiographic response was evaluable in 18 patients; five were not evaluable due to early death after cycle 1 day 1 (n=2), loss to follow-up (n=2), and transition to hospice after first cycle (n=1). In those 18 patients, best overall response included partial response in 5 patients (27.7%) and stable disease in 3 patients (16.7%), yielding an ORR of 27.7 % and a DCR of 44.4%. Median PFS was 139 days, and median OS was 323 days (95 % CI, 31 to 614). No variables were independently associated with outcomes on multivariable Cox proportional regression analysis. **Conclusions:** In a predominantly Hispanic, heavily pretreated real-world SCLC population with a high prevalence of brain metastases, tarlatamab demonstrated feasible administration, manageable immune-mediated toxicity, and clinically meaningful antitumor activity. These findings support the effectiveness of tarlatamab beyond clinical trial populations and highlight the importance of real-world evidence in informing care for underrepresented patients. Research Sponsor: None.

Best Overall Response	N (%)
Complete Response	0 (0)
Partial Response	5 (27.7)
Stable Disease	3 (16.7)
Progression of Disease	10 (55.5)
ORR	5 (27.7)
DCR	8 (44.4)

8109 **Poster Session**

Updated results of the randomized phase 2 dose optimization study of alveltamig (ZG006), a trispecific T cell engager targeting DLL3/DLL3/CD3, as monotherapy in patients with advanced small cell lung cancer. First Author: Xinghao Ai, Shanghai Chest Hospital, Shanghai, China

Background: Alveltamig (ZG006) is a trispecific T cell engager (Tri-TE) targeting Delta-like ligand 3 (DLL3) and CD3, designed to bridge tumor cells and T cells by binding to two distinct DLL3 epitopes on tumor cells and CD3 on T cells, thereby mediating T cell-specific killing of DLL3-expressing tumor cells such as small cell lung cancer (SCLC). **Methods:** This is a multicenter, randomized, open-label, phase 2 dose-optimization study. Patients with SCLC who have failed at least two prior lines of standard therapy are randomized 1:1 to receive ZG006 at either 10 mg or 30 mg Q2W (both with a 1 mg priming dose). Based on the prior data from dose optimization in this study with an objective response rate (ORR) at 53.3% and median progression-free survival (PFS) at 7.03 months in the 10 mg group, 10 mg Q2W was selected as the recommended dose schedule for ongoing pivotal studies in advanced SCLC. Here we present the updated efficacy data with longer follow up and key subgroup analyses from this study. **Results:** This analysis included 60 treated patients (30 each from 10 and 30 mg group). With a median follow-up of about 13.5 months, the median duration of response (DoR) was not mature with 9-month DoR rates reaching 61.6% and 58.4% for 10 mg and 30 mg respectively. Likewise, the median OS for both groups was not reached, however, 12-month OS rates for two groups have approached 65.9% and 59.2% respectively. Based on the IRC data as of Sept 30, 2025, for the 10 mg and 30 mg groups, patients with previously treated and stable brain metastases at baseline achieved a confirmed ORR of 50.0% (4/8) and 44.4% (4/9), respectively, while patients without baseline brain metastases had an ORR of 54.5% (12/22) and 61.9% (13/21). Patients presented with baseline liver metastases achieved an ORR of 58.3% (7/12) and 46.2% (6/13), compared with 50.0% (9/18) and 64.7% (11/17) in patients without liver metastases. While 27 patients in 10 mg and 24 patients in 30 mg had previously received immune checkpoint inhibitors, a notable ORR of 55.6% (15/27) and 58.3% (14/24) was observed. Among patients with exactly two prior lines of systemic therapy, the ORRs were 50.0% (8/16) and 64.7% (11/17), whereas those who had received three or more prior lines demonstrated an ORR of 57.1% (8/14) and 46.2% (6/13) in 10 and 30 mg groups. **Conclusions:** With longer follow up, both ZG006 10 mg Q2W and 30 mg Q2W continued to demonstrate robust antitumor activity with a trend of longer DoR and OS in patients with relapsed or refractory SCLC. Subgroup analyses demonstrated consistent antitumor activity across key prognostic subgroups including those with baseline treated brain metastases, those with baseline liver metastases, and those who received multiple lines of prior systemic treatment. These results also support further development of ZG006 in SCLC with ongoing pivotal studies. Clinical trial information: NCT06283719. Research Sponsor: None.

8110 **Poster Session**

Evaluation of survival after chemo-immunotherapy in veterans with extensive-stage small cell lung cancer and brain metastases. First Author: Jason Cham, Division of Hematology Oncology, Department of Medicine, Columbia University Irving Medical Center, New York, NY

Background: Extensive-stage small cell lung cancer (ES-SCLC) is an aggressive malignancy with rapid progression and poor long-term survival. For decades, platinum–etoposide chemotherapy has produced high initial response rates, but relapse is nearly universal. The addition of atezolizumab or durvalumab to first-line chemotherapy is now standard of care based on improved survival in the IMpower133 and CASPIAN trials, with reported OS 12.3 and 13 months, respectively. However, these pivotal trials enrolled highly selected populations and largely excluded patients with active brain metastases, limiting generalizability. Veterans are particularly underrepresented in clinical trials due to comorbidities and performance status, leaving the real-world effectiveness of chemo-immunotherapy and immune biomarkers in this population poorly defined. **Methods:** We conducted a retrospective cohort study of Veterans with ES-SCLC treated with first-line chemotherapy alone or chemo-immunotherapy within the Veterans Affairs (VA) health system. Overall survival (OS) was assessed using Kaplan–Meier methods and Cox proportional hazards models in propensity-matched cohorts. Prespecified subgroup analyses evaluated whether treatment effects differed by brain metastasis status. Exploratory analyses also assessed the prognostic association between baseline absolute neutrophil-to-lymphocyte ratio (ANC/ALC) and survival. **Results:** In the matched overall cohort (n = 1,250), chemo-immunotherapy significantly improved OS compared with chemotherapy alone (median OS 8.88 vs 7.44 months; HR 0.75, $p < 0.0001$). Among patients who received chemo-immunotherapy (n = 625), 87.0% were treated with atezolizumab and 9.6% with durvalumab. For patients with brain metastases at diagnosis (n = 312), chemo-immunotherapy significantly improved survival (median OS 8.76 vs 5.52 months; HR 0.57, $p < 0.0001$). An elevated pre-treatment absolute neutrophil count (ANC) to absolute lymphocyte count (ALC) ratio > 2.5 was independently associated with worse survival in both chemo-immunotherapy (HR 1.35, p = 0.013) and chemotherapy-only (HR 1.47, p = 0.0004) groups. **Conclusions:** This study represents the largest real-world cohort of Veterans with ES-SCLC and demonstrates a significant overall survival benefit with chemo-immunotherapy. The benefit was particularly pronounced among patients with brain metastases, a group historically underrepresented in clinical trials. Elevated ANC/ALC was identified as a potential prognostic biomarker associated with poor outcomes regardless of treatment. Notably, overall survival in our Veteran cohort remained substantially lower than in registrational trials, highlighting the urgent need for future studies with broader eligibility criteria that better reflect real-world populations. Research Sponsor: None.

8111 **Poster Session**

An innovative team approach to improve SCLC care across an integrated health system. First Author: Melinda Laine Hsu, University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, OH

Background: Small cell lung cancer (SCLC) is a highly aggressive cancer, with improved overall survival due to recent advancements in therapy. However, as many as 40% of patients (pts) may not receive guideline-concordant care for SCLC due to barriers including delays in diagnosis and referrals to oncology. We developed and implemented an electronic medical record (EMR) alert system based on ICD codes for early identification of pts with suspected SCLC and early intervention by thoracic medical oncology at University Hospitals Seidman Cancer Center. We hypothesized our intervention would increase rates of guideline concordant care and ultimately improve pt outcomes, compared to historical control. **Methods:** An informatics approach was used to identify pts with possible SCLC from 5/5/2024-5/17/2025 by incorporating Structure Query Language, Server Reporting Services, and text search of the EMR and pathology systems. Daily reports were reviewed by the thoracic medical oncology team, who intervened when needed to ensure appropriate staging and referrals. Clinicodemographic data was collected of pts with confirmed SCLC compared to a historical control of patients diagnosed between 2/5/2019-11/29/2021. Chi-square tests assessed statistical differences between the groups, and Kaplan-Meier (KM) survival analysis estimated overall survival (OS) and progression free survival (PFS). **Results:** 101 pts with SCLC were identified in the current group (C), and 130 pts in the historical group (H). Age, sex, smoking history, and baseline ECOG status, were similar between groups. A numerically higher percentage of pts in C were diagnosed with limited-stage SCLC (38.6%) compared to H (27.7%), p = 0.106). A numerically higher number of pts in C received guideline-concordant baseline imaging (93.1%) compared to H (83.8%, p = 0.05). Among pts who received treatment (tx), median time to tx was longer in C (19 days, interquartile range [IQR] 9-31) than H (13 days, IQR 5-22, p = 0.001). Pts in C were significantly more likely to receive 1st-line guideline-concordant tx than H (94.0% vs 83.3%, p = 0.02), although similar likelihood of enrolling in hospice before any therapy (12.9% vs. 11.5%, p = 0.917). Pts in C with progression were numerically more likely to receive 2nd-line and 3rd-line tx than H (61.3% vs. 57.1%; 78% vs. 53.1%, respectively). Pts in C had statistically significantly improved PFS compared to H (p = 0.008). **Conclusions:** Successful creation of an EMR alert system to identify SCLC significantly increased rates of guideline-concordant tx of SCLC. Although not statistically significant, pts were also more likely to receive guideline-concordant imaging and treatment in the 2nd and 3rd line settings compared to historical control. Research Sponsor: The study is supported by the National Comprehensive Cancer Network (NCCN) through a grant provided by AstraZeneca. Neither NCCN nor AstraZeneca are the sponsor.

8112 **Poster Session**

Predictive role of immune cell subsets and intestinal flora in immune-related adverse event of small cell lung cancer. First Author: Mei-xi Lin, The Second Hospital of Dalian Medical University, Dalian, Liaoning, China

Background: While immune checkpoint inhibitors (ICIs) have reshaped the therapeutic landscape for extensive-stage small-cell lung cancer (ES-SCLC), they are frequently associated with immune-related adverse events (irAEs) that may lead to treatment disruption. Early prediction of irAEs remains challenging due to their atypical clinical manifestations. This study aimed to identify risk factors and predictive biomarkers for irAEs in ES-SCLC patients undergoing ICIs therapy. **Methods:** 88 patients with ES-SCLC who received ICIs treatment between May 2021 and September 2023 were enrolled. Fecal samples were collected at baseline and before each treatment cycle until therapy discontinuation. The metagenomic and untargeted metabolomic analyses were performed on the fecal samples. Peripheral blood samples were collected from patients for flow cytometry analysis. Tumor response was assessed in accordance with RECIST 1.1 criteria, and irAEs were graded based on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. **Results:** Among 88 patients, 41 developed irAEs (median onset: 118 days), with the most common manifestations being pneumonia (41.5%) and hepatitis (22.0%). Patients who developed irAEs exhibited distinct peripheral immune profiles. Compared to their own baseline levels, these patients exhibited decreased peripheral B-cell counts alongside elevated percentages of activated $CD4^+$ and $CD8^+$ T cells, including early-activated $CD8^+$ T cells ($CD3^+CD8^+CD69^+$ T cells), late-activated helper T cells ($CD3^+CD4^+CD38^+$ T cells), and Th2 cells. Furthermore, at baseline, the irAE group demonstrated a significantly higher percentage of PD-1 in $CD8^+$ T cells compared to the non-irAE group. Metabolomic analyses revealed distinct baseline metabolic profiles between the two groups, *Micrococcus* was significantly enriched at baseline in the irAE group, whereas *Phocaeicola coprocola* and *Oscillibacter* were more abundant in patients without irAEs, and calcitriol was identified as a potential predictive biomarker for irAEs. Following irAE onset, significant enrichment of *Selenomonadaceae*, *Ruminococcus*, *Actinobacteria*, and *Erysipelatoclostridium* was observed, along with significant shifts in metabolites and related metabolic pathways. **Conclusions:** In ES-SCLC patients treated with ICIs, the development of irAEs is associated with distinct alterations in peripheral immune cell subsets, as well as gut microbial and metabolic profiles at baseline. Monitoring these features, particularly PD-1 expression on CD8+ T cells and calcitriol levels, may help predict the risk of irAEs. Dynamic changes in the gut microbiome and metabolome after ICIs initiation further aid in the early recognition of irAEs. Research Sponsor: National Natural Science Foundation of China; 82203056.

8113 **Poster Session**

Real-world challenges in the adoption of emerging therapies for extensive-stage small cell lung cancer in community settings. First Author: Jacob Sands, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Despite advances in the treatment of extensive-stage small cell lung cancer (ES-SCLC), outcomes remain poor, and uptake of novel therapies in community oncology settings is inconsistent. As the ES-SCLC treatment landscape rapidly evolves, understanding real-world knowledge gaps, operational barriers, and challenges in patient-centered care is critical to improving evidence-based practice. This study evaluated community oncologists' confidence, practice patterns, and perceived barriers to integrating novel and emerging ES-SCLC therapies. **Methods:** From September–October 2025, 100 US community oncologists completed surveys assessing treatment selection, shared decision-making, adverse event (AE) management, clinical trial referral practices, and system-level barriers to care delivery for patients with SCLC. **Results:** Knowledge and training gaps were the most frequently cited challenges to incorporating novel therapies (55%), followed by electronic medical record workflow limitations (41%) and patient selection complexity (33%). While most oncologists reported a basic understanding of novel antibody-drug conjugates (72%), few actively followed emerging clinical data (19%). Delays in initiating first-line therapy were commonly attributed to unfamiliarity with available treatments or need for academic referral (56%), prolonged staging evaluations (53%), and limited infusion center capacity (39%). AE management represented a major unmet need: 90% reported difficulty educating patients and caregivers on early AE recognition, and 62% reported challenges distinguishing disease progression from treatment-related toxicity. These gaps directly affected patient-centered care, with barriers to shared decision-making including limited clinician knowledge of treatment options (80%) and difficulty tailoring communication to patient preferences (66%). Accordingly, improved AE management was identified as the single greatest opportunity to enhance quality of care (51%). Although most oncologists reported referring patients for clinical trial evaluation after progression most or all of the time (85%; 4-5 on 5-point Likert scale), enrollment was hindered by patient preferences (63%), limited infrastructure to identify and enroll eligible patients (51%), and poor performance status (40%). **Conclusions:** Community oncologists face significant knowledge and operational barriers to integrating novel therapies for ES-SCLC, particularly related to emerging mechanisms of action, AE recognition and management, patient communication, and clinical trial enrollment. Targeted educational and practice-based interventions are needed to support timely, patient-centered, and evidence-based care in the community setting. Research Sponsor: Daiichi Sankyo; Merck Sharp & Dohme LLC; Genentech.

8114 **Poster Session**

Phenotypic heterogeneity in primary tumors and brain metastases of small cell lung cancer: Insights into tumor microenvironment and metastatic behavior. First Author: Alan Amaral Oliveira, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Background: Small cell lung cancer (SCLC) is an aggressive malignancy with frequent brain metastases and pronounced phenotypic plasticity. How the tumor microenvironment and phenotypic heterogeneity relate to brain metastases remains poorly understood. **Methods:** We conducted a retrospective study of 124 patients with pathologically confirmed SCLC treated at a tertiary cancer center. In primary tumors, pathological features—including tumor-infiltrating lymphocytes (TILs), morphological patterns (necrosis, hyalinization, desmoplasia), and immunohistochemical characterization of lineage-associated SCLC markers—were assessed on H&E-stained sections. Immune-desert tumors were defined as having no detectable lymphocytic infiltration. Associations between these pathological features and baseline brain metastases were evaluated using appropriate statistical tests for categorical and continuous variables, with available brain metastasis samples also analyzed histopathologically and immunohistochemically to assess spatial heterogeneity and microenvironmental plasticity. **Results:** Among 124 patients, TIL levels were lower in those with baseline brain metastases than without (1.46% $\pm$ 4.54 vs 3.04% $\pm$ 5.29; p = 0.049), and the immune-desert phenotype was more frequent (88% vs 65%; p = 0.041), indicating a cold tumor microenvironment in patients with brain metastases. Immunohistochemical and morphological patterns were similar regardless of baseline brain metastases. Histopathological evaluation of the two available brain metastases showed marked intralesional heterogeneity. Regions had inflammatory infiltrates, coagulative necrosis, or stromal hyalinization. Tumor cells showed a spiculated growth pattern along the GFAP-positive astrocytic network, suggesting interaction with astrocytes. Synaptophysin expression was higher adjacent to lymphocytes, NEUROD1 predominant near necrotic zones, and POU2F3 higher in hyalinized regions. These findings indicate regional activation of different SCLC transcriptional programs, reflecting microenvironmental plasticity. **Conclusions:** An immune-desert phenotype in primary SCLC tumors is associated with baseline brain metastases, which exhibit pronounced spatial heterogeneity and region-specific tumor programs. These findings suggest that the immune context of the primary tumor may influence microenvironmental plasticity and contribute to brain metastasis development, warranting validation in larger cohorts. Research Sponsor: without funding sources.

8115 **Poster Session**

Does treatment delay matter?: Impact of time to immunotherapy on survival in extensive-stage small cell lung cancer. First Author: Anand Shah, Rutgers New Jersey Medical School, Newark, NJ

Background: Immune checkpoint inhibitors (ICI) combined with platinum-etoposide chemotherapy are the standard first-line treatment for extensive-stage small cell lung cancer (ES-SCLC) based on the CASPIAN and IMpower133 trials. Given the aggressive nature of ES-SCLC, timely initiation of systemic therapy is critical; however, delays in treatment initiation are common in real-world practice. The impact of time to immunotherapy initiation (TTI) on survival has not been well characterized. **Methods:** Adult patients diagnosed with EO-SCLC (2019-2021) who received immunotherapy as part of first-line systemic therapy were identified from NCDB. TTI was defined as the time from diagnosis to first immunotherapy and categorized as $\leq$30, 31–60, or $>$ 60 days. Association between TTI and OS was analysed using multivariable Cox proportional hazards models adjusting for patient and facility-level factors. A 90-day landmark analysis were performed to mitigate immortal time bias. Multivariable logistic regression was used to identify predictors of delayed initiation ($>$ 30 days). **Results:** A total of 18,630 patients were identified. 2,652 (14.24%) died during follow-up. Median TTI was 29 days (IQR 18–45), with median follow-up of 9.36 months. In multivariable Cox models, TTI was not independently associated with OS (31–60 vs $\leq$30 days: HR 0.92 [0.84–1.00]; $>$ 60 vs $\leq$30 days: HR 1.00 [0.89–1.11]). Results were consistent in a 90-day landmark analysis. Increasing age was associated with higher mortality (HR 1.01 per year, p = 0.003). Treatment at academic/research programs was associated with better OS (HR 0.71 [0.61–0.82]), while Medicaid insurance was associated with worse OS (HR 1.31 [1.15–1.49]). Black patients were more likely to receive delayed treatment (OR 1.31 [1.16–1.48]) while Asian patients were less likely (OR 0.74 [0.55–0.98]), when compared with Non-Hispanic White patients. Medicaid (OR 1.36 [1.20–1.53]) and Medicare insurance (OR 1.10 [1.01–1.21]) were associated with increased odds of delay versus private insurance. Higher comorbidity burden (Charlson–Deyo score $\geq$2 vs 0: OR 1.10 [1.02–1.19]) and treatment at academic centers (OR 1.33 [1.17–1.51]) were also associated with delay. Higher neighborhood income was protective (highest vs lowest quartile: OR 0.86 [0.77–0.95]). **Conclusions:** In a large national cohort of ES-SCLC patients receiving immunotherapy, modest delays in treatment initiation were not associated with OS. However, significant disparities exist in timely access, highlighting opportunities for system-level interventions to improve equity in cancer care delivery. Research Sponsor: None.

8116 **Poster Session**

Efficacy and safety of second or further line KC1036 in patients with thymoma and thymic carcinoma: A multicenter, single-arm phase II trial. First Author: Wentao Fang, Shanghai East Hospital, Tongji University, Shanghai, China

Background: Patients with advanced or recurrent thymoma or thymic carcinoma (T/TC) progressing after platinum-based chemotherapy have an unmet therapeutic need. This report assessed the clinical efficacy and safety of KC1036, a novel multi-kinase inhibitor of AXL, VEGFR2, and FLT3, in the treatment of T/TC. **Methods:** This open-label, multicenter, single-arm, phase II study enrolled patients with advanced or recurrent T/TC who had progressed on at least one prior line of chemotherapy. Eligible participants were required to have measurable disease according to RECIST v1.1 and an ECOG performance status of 0 or 1. KC1036 was administered orally at 60 mg QD, every 21 days as a cycle, until disease progression, death or intolerable toxicities. The primary endpoint was investigator-assessed objective response rate (ORR). **Results:** Between February 23, 2023 and January 4, 2024, 6 thymoma (T) and 25 thymic carcinoma (TC) patients were enrolled; all had distant metastases. Median age was 47.5 years (range, 34-71) for T and 57.0 years (37-73) for TC. Most patients had an ECOG PS of 1 (T: 100%; TC: 88.0%). While all T patients received one prior line of therapy, 48.0% of TC patients had received $\geq$2 prior lines. At the data cutoff of June 9, 2025, with a median follow-up of 19.3 months (95% CI, 13.4-NR), the T cohort achieved 100% SD with a median PFS of 13.6 months (95% CI, 4.1-NR). The TC cohort showed an ORR of 20.0% (n=5, PR) and a DCR of 80.0% (n=15, SD), with a median PFS of 8.2 months (95% CI: 4.1-15.1) and a median DOR of 15.3 months (95% CI: 1.5-NR). Median OS was not reached in either cohort; and the 18-month OS rates were 100% and 75.5% in the T and TC cohorts, respectively. The median duration of treatment exposure was 7.1 months. Treatment-related adverse events (TRAEs) were predominantly Grade 1 or 2. Grade 3 TRAEs occurring in $\geq$5% of subjects were hypertension (4 [12.9%]) and diarrhea (3 [9.7%]). No Grade 4 or 5 TRAEs were reported. TRAEs leading to dose reduction and treatment discontinuation occurred in 41.9% and 3.2% of patients, respectively. **Conclusions:** KC1036 demonstrated promising antitumor efficacy in patients with advanced or recurrent T/TC. Additionally, KC1036 exhibited a favorable safety profile and tolerability. These encouraging outcomes support further evaluation of KC1036 in a forthcoming phase III trial. Clinical trial information: NCT05683886. Research Sponsor: Beijing Konruns Pharmaceutical Co., Ltd.

8117 **Poster Session**

Platinum rechallenge versus non-platinum regimens as second-line treatment for advanced thymoma: Analysis of the largest retrospective cohort to date. First Author: Go Saito, Department of Respirology, Graduate School of Medicine, Chiba University, Chiba, Japan

Background: Although guidelines list platinum-based combination chemotherapy (Pt-rechallenge) as a second-line strategy for patients with thymoma ineligible for curative-intent therapy, evidence is limited to small case series. We investigated the efficacy of Pt-rechallenge versus non-platinum regimens in the largest retrospective cohort of second-line thymoma treatment reported to date. **Methods:** This multicenter study analyzed patients treated at 39 Japanese institutions. Of 157 patients ineligible for curative-intent therapy who initiated palliative platinum-based chemotherapy (2000–2020), 91 patients receiving second-line systemic cytotoxic chemotherapy were evaluated. Efficacy outcomes, including objective response rate (ORR), progression-free survival (PFS), and overall survival (OS), were compared between second-line Pt-containing (Pt-rechallenge) and non-platinum (non-Pt) regimens. **Results:** Among the 91 patients (median age 59; 91% ECOG PS 0-1) with a median follow-up of 1056 days, 64 (70%) received Pt-rechallenge and 27 received non-Pt regimens (S-1 [tegafur/gimeracil/oteracil], n=15; pemetrexed, n=6; amrubicin, n=5; paclitaxel, n=1). First-line ORR was 51%, and the median chemotherapy-free interval from first-line chemotherapy was 394 days. Pt-rechallenge achieved a significantly higher ORR than non-Pt chemotherapy (40% vs 5%; p=0.0012). Regarding survival outcomes, median PFS was 8.8 months (95% CI, 5.9–11.9) in the Pt-rechallenge group vs 8.0 months (95% CI, 4.8–30.4) in the non-Pt group (HR, 1.29; 95% CI, 0.77–2.18; p=0.325). Median OS was 70.6 months (95% CI, 53.5–82.4) vs 64.4 months (95% CI, 38.7–not estimable) (HR, 1.12; 95% CI, 0.53–2.37; p=0.759); differences in PFS and OS were not statistically significant. In the Pt-rechallenge cohort, outcomes were stratified by anthracycline (A) use in 1st/2nd-line (A→A, n=17; A→non-A, n=28; non-A→A, n=12; non-A→non-A, n=7): ORRs were 50%, 35%, 27%, and 29%; median PFS were 9.3 (95% CI, 4.5–12.2), 6.4 (95% CI, 4.6–10.6), 21.0 (95% CI, 8.7–41.9), and 4.1 (95% CI, 1.8–9.3) months, respectively. Stratified by platinum-free interval (PFI) ($<$6 months, n=15; 6–12, n=10; 12–36, n=27; $\geq$36, n=12), ORR were 14%, 63%, 46%, and 20%; median PFS were 5.8 (95% CI, 1.8–19.8), 7.3 (95% CI, 2.1–14.5), 10.3 (95% CI, 5.5–23.5), and 9.0 (95% CI, 3.1–16.9) months. **Conclusions:** In this largest comparative study to date, platinum rechallenge demonstrated superior response rates compared to non-platinum regimens, particularly in patients with favorable PFI. Study registration: UMIN000048181. Research Sponsor: None.

8118 **Poster Session**

Cell-free DNA fragmentomics and methylomics for thymic epithelial tumors. First Author: Michael Daniels, National Institutes of Health, Rockville, MD

Background: Development of circulating cell-free (cf) DNA assays for cancer detection and monitoring is an area of active research. Limited data are available on the utility of cfDNA for thymic epithelial tumors (TETs). Evaluation of cfDNA fragmentation patterns (fragmentomics) offers advantages over conventional cfDNA analysis. Studies have shown that concurrent generation of fragmentomics and methylomics features via enzymatic methyl-sequencing (EM-Seq) are highly predictive at classifying cancer vs. non-cancer and capture key cancer-related biological features. We conducted a study to determine the feasibility of fragmentomics and methylomics for evaluation of TETs. **Methods:** cfDNA was extracted from 1-2 mL of plasma EDTA derived from patients with advanced TETs using the QIAamp Circulating Nucleic Acid Kit, underwent enzymatic conversion via the NEBNext Enzymatic Methyl-Seq v2 Kit, and sequenced on a NovaSeq X 10B flowcell. Estimated tumor fractions were generated using *ichorCNA* with low tumor settings and via *fragle*. Recurrent copy number alterations (CNAs) were plotted and compared against external TET copy number datasets. Short fragment percentage (90-150 bps) was calculated and average DELFI scores (DNA evaluation of fragments for early interception) were generated via *FinaleToolkit*. **Results:** Plasma samples from 47 of 50 participants (thymic carcinoma: 26, thymoma: 24; median age: 55 years (range 23-77); females 22; stage distributions: I/II/III/IV = 1/0/1/48) yielded high-quality cfDNA which was sufficient for sequencing. Individuals with thymic carcinoma displayed higher estimated tumor fractions via ichorCNA ($P<0.05$) and Fragle (P=0.05). Moreover, although not statistically significant, individuals with thymic carcinoma exhibited a general trend of higher short fragment percentage and higher average DELFI scores. When evaluating recurrent CNAs, individuals with thymic carcinoma displayed greater enrichments in CNAs in general with noted amplifications/gains at chr 1, 5, 12, and 17 and deletions at chr 16, whereas individuals with thymoma showed deletions at chr 3. When grouped and compared to external thymoma tissue CNAs, recurrent CNAs detected in plasma showed partial concordance. Large alterations in fragmentation profiles were also identified across both groups, which showed increased variability near recurrent CNA regions. **Conclusions:** This proof-of-concept study demonstrates that plasma cfDNA is detectable and fragmentomics is feasible among individuals with TETs, thus providing a non-invasive means of capturing cancer-related aberrant signals. Validation of this result in larger studies would establish cfDNA fragmentomics as a novel non-invasive means for disease monitoring and biomarker identification in patients with TETs. Research Sponsor: None.

8119 **Poster Session**

Surufatinib for advanced or metastatic chemotherapy-refractory thymic epithelial tumor: A single-arm, single-center, phase II study. First Author: Bei Xu, Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Thymic epithelial tumors (TETs), though relatively rare, represent the most common anterior mediastinal malignancy in adults. Platinum-based regimens are the standard first-line therapy; however, treatment options for subsequent lines remain poorly defined. Surufatinib, an oral tyrosine kinase inhibitor targeting VEGFR1/2/3, FGFR1, and CSF-1R, exerts both anti-angiogenic and immune-modulating effects. This study aimed to evaluate the efficacy and safety of surufatinib in patients (pts) with type B2/B3 thymoma (TM) or thymic carcinoma (TC), providing a potential new therapeutic strategy for TETs following anthracycline/taxane-based therapy. Here, we report the initial results. **Methods:** This was a single-arm, prospective phase II study. Eligible pts had histologically or cytologically confirmed, unresectable or radiotherapy-ineligible, advanced recurrent or metastatic B2/B3 TM or TC, with progression following at least one prior platinum-based chemotherapy regimen. Pts were aged $>$18 years and had at least one measurable lesion per RECIST 1.1 criteria. Treatment consisted of surufatinib 300 mg orally once daily in a 4-week cycle. Tumor assessments were conducted every 8 weeks. The primary endpoint was the objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), disease control rate (DCR), and overall survival (OS). **Results:** As of December 25, 2025, 20 pts were enrolled and evaluated. The median age was 55.5 years (range: 35–69), with 55% being male. Pathological subtypes included B2 TM (30%), B3 TM (15%), and thymic squamous cell carcinoma (TSCC, 55%). Eighteen pts (90%) presented with $>$5 metastatic sites. Ten pts (50%) achieved a partial response, and ten pts (50%) achieved stable disease. The ORR was 50%, and the DCR was 100%. With a median follow-up of 9.50 months, the median PFS was 11.9 months, and the 9-month PFS rate was 73.5%. Median OS was not reached, with an 18-month OS rate of 91.7%. The most common treatment-related adverse events (TRAEs) of any grade were hypertension (70%), diarrhea (40%), elevated bilirubin (40%), and elevated transaminases (25%). Grade 3 TRAEs included hypertension (15%), diarrhea (5%), and elevated transaminases (5%). No treatment-related deaths were reported. **Conclusions:** Surufatinib monotherapy demonstrated promising antitumor activity and a manageable safety profile in patients with previously treated, advanced recurrent or metastatic TETs, supporting further investigation in this population. Clinical trial information: ChiCTR2600116776. Research Sponsor: None.

8120 **Poster Session**

Penpulimab (PD-1 inhibitor) combined with platinum-based chemotherapy as induction therapy for newly diagnosed thymic carcinoma: A multicenter, single-arm, phase II trial. First Author: Weixiong Yang, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background: Our retrospective study showed that immune checkpoint inhibitors plus chemotherapy had encouraging anti-tumor activity and durable response for unresectable thymic carcinoma (TC). This prospective clinical trial aimed to evaluate the efficacy and safety of penpulimab—a humanized anti-PD-1 monoclonal antibody—in combination with platinum-based chemotherapy as induction therapy for patients with newly diagnosed TC. **Methods:** Patients with histologically confirmed TC at Masaoka stage II–IV, an ECOG performance status of 0 or 1, and no history of prior systemic anticancer therapy were enrolled. Following 4 cycles of induction therapy with penpulimab penpulimab (200 mg), carboplatin (AUC 5 mg/mL per min), and nab-paclitaxel (260 mg/m²) administered intravenously every 3 weeks, patients were re-evaluated by a multidisciplinary team (MDT). Subsequent treatment was stratified based on resectability: operable patients proceeded to surgery, whereas inoperable patients received standard radiotherapy or chemotherapy. Based on a Fleming two-stage design, the treatment would be promising if at least 10 of the first 18 evaluable patients in stage I or at least 14 of the 36 evaluable patients at the end of stage II have a confirmed response. The primary endpoint was objective response rate (ORR) evaluated by independent central review. **Results:** Between June 2023 and July 2025, 18 eligible patients were enrolled. Fourteen patients (77.8%) had WHO stage IV disease. Ten patients achieved a partial response (PR), meeting the predefined efficacy threshold for early termination according to the Fleming design. The ORR and disease control rate (DCR) were 55.6% and 94.5% respectively in the overall population, with corresponding rates of 57.1% and 92.8% in the subgroup with stage IV disease. Nine patients underwent surgical resection, including 6 with stage IV disease, and an R0 resection was achieved in 7 cases. Among the 9 patients who underwent surgery, one patient (11.1%) with stage III disease achieved a pathological complete response (pCR), and another patient (11.1%) with stage IV disease achieved a major pathological response (MPR). At a median follow-up of 20.15 months, the 1-year relapse-free survival (RFS) and overall survival (OS) rates were 72.2% and 88.9% for the entire population, and 64.3% and 78.6% for patients with stage IV disease, respectively. The most common adverse events of grade 3 or worse were neutropenia (44.4%), anemia (16.7%), and hepatotoxicity (11.2%). One patient died from immune-mediated myocarditis with concurrent hepatitis and myasthenia gravis. **Conclusions:** Penpulimab combined with platinum-based chemotherapy showed promising antitumour activity in previously untreated TC, with vigilance required for immune-mediated myocarditis. Clinical trial information: ChiCTR2300076314. Research Sponsor: National Natural Science Foundation of China; 82373307; the Natural Science Foundation of Guangdong Province; 2024A1515013214; the institutional funding of The First Affiliated Hospital of Sun Yat-sen University.

8121 **Poster Session**

Combining SBRT with GM-CSF and Peg-IFNα to induce abscopal effects in previously treated patients with metastatic thymic tumors: A single-institution, phase II trial. First Author: Min Fan, Fudan University Shanghai Cancer Center, Shanghai, China

Background: After the failure of multi-line treatment, patients with metastatic thymic tumors have a poor prognosis and few therapeutic options. Combining stereotactic body radiotherapy (SBRT) with granulocyte-macrophage colony-stimulating factor (GM-CSF) and Pegylated interferon-α (Peg-IFNα) may induce abscopal effects and improve prognosis. **Methods:** We conducted this open-label, single-arm, phase II trial to evaluate SBRT plus GM-CSF and Peg-IFNα in previously treated patients with metastatic thymic tumors. A 21-day treatment cycle consisted of SBRT delivered to one metastatic lesion with 30 Gy in 5 fractions from day 1, synchronous subcutaneous injection of GM-CSF 125 μg/ m^2 once daily for 14 days, and subcutaneous injection of Peg-IFNα 90 μg on day 8. If the patient has more than two metastatic lesions, another treatment cycle was repeated. After the completion of 1 or 2 treatment cycles, Peg-IFNα therapy was maintained for at least half a year with a subcutaneous injection of 90 μg once a month. The two primary endpoints were the proportion of patients with abscopal effects and the objective response rate (ORR). The secondary endpoints included overall survival (OS), progression-free survival (PFS), and therapeutic safety. **Results:** A total of 32 patients from March 2021 to December 2025, were enrolled in this trial, with 2 (6.25%) type A thymoma, 4 (12.50%) type B1 thymoma, 6 (18.75%) type B2 thymoma, 2 (6.25%) type B3 thymoma, 16 (50.00%) thymic squamous cell carcinoma and 2 (6.25%) thymic neuroendocrine tumor. One patient with type B3 thymoma died of cardiac arrest amid the COVID-19 pandemic, rendering tumor evaluation unfeasible. Out of the remaining 31 patients, 9 (29.03%) had abscopal effects, and the ORR was 38.71%. At a median follow-up of 17.20 months, the median OS had not been attained yet. The median PFS was 6.37 months for the whole group. We observed that patients with abscopal effects tended to have longer PFS than those without abscopal effects (13.03 vs. 4.40 months ; p = 0.003). 5 patients (16.13%) experienced Grade 3 treatment-related adverse events (CTCAE version 5.0), among which cardiac insufficiency compelled 1 patient (3.23%) to drop out of treatment. **Conclusions:** Combining SBRT with GM-CSF and Peg-IFNα was well tolerated with acceptable toxicity and may represent a promising salvage therapy for previously treated patients with metastatic thymic tumors. The occurrence of abscopal effects is likely to improve patient outcomes. Clinical trial information: NCT04517539. Research Sponsor: None.

8122 **Poster Session**

Development and validation of a preoperative pathological risk prediction model for thymic tumors: A retrospective multicenter diagnostic study. First Author: LuYu Huang, Department of Thoracic Surgery, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: The preoperative diagnosis of thymic tumors currently relies on preoperative CT data and the experience of the surgeon, and there is still a lack of highly effective noninvasive radiomic prediction model to assist in clinical decision making. To develop and validate a preoperative CT-based radiomic model to accurately predict the pathological risk staging of thymic tumors. **Methods:** This is a retrospective diagnostic study that included patients from two independent centers Charité Universitätsmedizin Berlin (N = 74) as well as the First Hospital of Zhengzhou University (N = 143) between September 2003 and July 2024. WHO pathological type A, AB, and B1 of the postoperative thymic tumor were divided into low-risk groups (N = 110), and type B2, B3, and C (N = 107) were classified as high-risk groups. The patients were randomly divided into a training group (N = 130) and a validation group (N = 87) in a ratio of 6:4. Preoperative CT imaging of thymic tumor was used to define the tumor area and the peritumoral area (5 mm) and to extract the radiomic features using 3Dslicer software and the in-house pyradiomic software package. Feature selection and model development were conducted using the least absolute shrinkage and selection operator (LASSO) algorithm and logistic regression analysis. **Results:** A total of 217 patients undergoing thymectomy were included in this study. After univariate analysis, patients' age, smoking history, and the presence of combined myasthenia gravis (MG) were included in the clinical model, and the clinical model achieved AUC = 0.75 and 0.65 in the training and validation groups, respectively. The combined radiomic model has better performance than the two radiomic models alone, with AUC values of 0.86, 0.73, respectively. The nomogram model conducted by combined radiomic model with the clinical model achieved the best results in training (AUC = 0.89) and validation cohort (AUC = 0.84). Calibration curve and decision curve analysis (DCA) illustrated the clinical usability and reliability of the model. **Conclusions:** By combining the clinical model with a combined radiomic model, the nomogram model can effectively differentiate pathological risk staging of thymic tumors, providing surgeons with a potential preoperative decision support. Research Sponsor: None.

TPS8123 **Poster Session**

A multi-institutional, randomized, phase III trial comparing anatomical segmentectomy and lobectomy for clinical stage IA3 pure-solid non–small-cell lung cancer: West Japan Oncology Group study WJOG16923L (STEP UP trial). First Author: Atsushi Kamigaichi, Hiroshima University, Hiroshima, Japan

Background: Recent pivotal clinical trials, conducted by the Japan Clinical Oncology Group and West Japan Oncology Group (JCOG0802/WJOG4607L) or Cancer and Leukemia Group B (CALGB140503), have demonstrated the efficacy of anatomical segmentectomy for small-sized early-stage NSCLC measuring $\leq$ 2 cm. Segmentectomy is gaining attention as an alternative procedure to lobectomy for early-stage NSCLC. However, for tumors larger than 2 cm, particularly those with a pure-solid appearance which indicates higher malignant potential, the efficacy of segmentectomy remains controversial. Therefore, we initiated this randomized phase III trial (WJOG16923L: STEP UP) to confirm the non-inferiority of anatomical segmentectomy to lobectomy for patients with pure-solid NSCLC measuring $>$ 2 cm and $\leq$ 3 cm. **Methods:** This multi-institutional, open-label, randomized phase III study is designed to confirm the non-inferiority of anatomical segmentectomy to lobectomy in terms of overall survival (OS) in patients with clinical stage IA3 pure-solid peripheral NSCLC (tumor's center located in the outer third of the lung field, tumor measuring $>$ 2 cm and $\leq$ 3 cm, and consolidation-to-tumor ratio = 1). Patients are randomized 1:1 to undergo either lobectomy or anatomical segmentectomy using a minimization method by balancing the arms with the institution, age ($\geq$ 70 or $<$ 70), sex (male or female), location (right upper, right lower, left upper, or left lower lobes), and histological type (adenocarcinoma or non-adenocarcinoma). The primary endpoint is OS in all randomized patients. Secondary endpoints include relapse-free survival, postoperative respiratory function (at 6 months and 1 year after surgery), proportions of patients with respiratory failure and cerebrovascular disease, cumulative incidence of death from other diseases, cumulative incidence of local recurrence, proportion of patients who undergo segmentectomy, number of resected segments, operative time, blood loss, and adverse events. We plan to enroll 520 patients from 64 institutions over a period of 5 years. Enrollment began in January 2024. As of November 2025, 319 patients have been enrolled. This trial is registered with the UMIN Clinical Trials Registry (UMIN000052064). Clinical trial information: UMIN000052064. Research Sponsor: None.

TPS8124 **Poster Session**

CCTG BR.38: Consolidative use of radiotherapy to block (CURB2) oligoprogression in patients with metastatic non–small-cell lung cancer—A randomized phase III trial. First Author: Chiaojung Jillian Tsai, Princess Margaret Hospital, University Health Network, Toronto, ON, Canada

Background: Immune checkpoint inhibitor (ICI)–based regimens are standard first-line therapy for metastatic non–small-cell lung cancer (NSCLC) without actionable driver mutations; however, most patients experience disease progression within 12 months. A subset develop oligoprogression, defined by progression at a limited number of metastatic sites with otherwise controlled disease. Oligoprogression represents a therapeutic window in which local ablative therapy could be used to prolong disease control. In the prior phase II CURB trial, SBRT was shown to significantly prolong progression-free survival (PFS) in patients with oligoprogressive NSCLC. **Methods:** CCTG-BR38 is an international, multicenter, open-label, randomized phase III trial conducted through the NCI National Clinical Trials Network. Adults with stage IV NSCLC receiving first-line ICI $\pm$ chemotherapy who develop $\leq$5 extracranial oligoprogressive lesions are randomized 1:1 to: (1) switch to second-line standard systemic therapy or (2) SBRT (30 Gy in 3 fractions) to all oligoprogressive sites followed by continuation of the same first-line systemic therapy. Randomization is stratified by type of first-line systemic therapy (ICI alone vs ICI + chemotherapy), number of oligoprogressive lesions (1–2 vs 3–5), and ECOG performance status (0-1 vs 2). Patients with treated, stable brain metastases are eligible. Primary Endpoints: Dual primary endpoints are PFS and overall survival (OS). Secondary endpoints include safety (CTCAE v5.0), patient-reported adverse events (PRO-CTCAE), quality of life (EORTC QLQ-C30/LC13), and cost-effectiveness (EQ-5D-5L; Canadian sites). Optional blood and tissue collection for exploratory biomarker analyses are planned. Statistical Considerations: A total of 320 patients (160 per arm) will be enrolled. The sample size is based on detecting a HR of 0.7 for OS (an improvement in median OS from 10 to 14.3 months) with 80% power using a 1-sided 2% level test (the overall 1-sided 2.5% type I error will be assigned 2% to OS and 0.5% to PFS). Interim analyses for futility and efficacy are planned. Current Status: The trial was centrally activated on April 3, 2025. Accrual is ongoing across Canadian and US NCTN sites. Clinical trial information: NCT06686771. Research Sponsor: National Clinical Trials Network; CA180863; Canadian Cancer Society Research Institute; 707213; University Health Network.

TPS8125 **Poster Session**

InDuRanS: A randomized phase II trial on induction immunochemotherapy followed by surgery or chemoradiotherapy and consolidation durvalumab in stage III NSCLC. First Author: Eleni Gkika, Department of Radiation Oncology, Bonn, Germany

Background: The optimal local treatment strategy for patients with resectable or borderline resectable stage IIIA/B (N2) non-small-cell lung cancer (NSCLC) remains controversial. Earlier randomized trials comparing surgery with definitive chemoradiotherapy (CRT) failed to demonstrate a survival advantage for either modality; however, these studies predated routine PET staging, modern radiotherapy techniques, and standard-of-care immunotherapy. Consolidation durvalumab after definitive CRT has significantly improved survival in unresectable stage III NSCLC, while neoadjuvant immunochemotherapy has shown promising pathologic and survival outcomes in resectable disease. Whether surgery or definitive CRT provides superior outcomes following induction immunochemotherapy in stage III NSCLC is unknown. The InDuRanS trial aims to address this question in a randomized setting. **Methods:** InDuRanS (ARO-2024-12; NCT06810609) is a prospective, multicenter, open-label, randomized phase II trial conducted across approximately 10 centers in Germany. Eligible patients have (borderline) resectable stage IIIA/B (N2) NSCLC without targetable EGFR or ALK alterations. All patients receive three cycles of induction immunochemotherapy consisting of durvalumab (1,500 mg every 3 weeks) combined with platinum-paclitaxel. Following PET-based restaging, patients with persistent resectable disease are randomized 1:1 to surgery (Arm A) or definitive CRT (Arm B). CRT consists of 60–70 Gy in conventional fractionation with two cycles of concurrent platinum-vinorelbine. Both treatment arms subsequently receive consolidation durvalumab (1,500 mg every 4 weeks) for up to 13 cycles. The primary endpoint is 2-year event-free survival (EFS). Secondary endpoints include overall survival, progression-free survival, treatment-related toxicity, surgical outcomes, and quality of life. Exploratory analyses include radiomics, plasma proteomics, circulating tumor DNA, and immune profiling. A total of 176 patients will be enrolled, with 158 evaluable patients planned for randomization. Interim safety analyses are scheduled after treatment completion in the first 10 randomized patients. The trial is currently open and recruiting. Research Sponsor: AstraZeneca.

TPS8126 **Poster Session**

Volrustomig, a novel bispecific PD-1/CTLA-4 monoclonal antibody, as single-agent first-line therapy for unresectable pleural mesothelioma: Substudy 5 of the eVOLVE-02 phase 2 study. First Author: Michael Offin, Mesothelioma Program, Department of Medicine, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, NY

Background: Standard first-line treatment for unresectable pleural mesothelioma has evolved recently to include anti-PD-1 ± anti-CTLA-4 immunotherapy-based options. Nivolumab + ipilimumab and pembrolizumab + pemetrexed + platinum chemotherapy showed improved survival vs chemotherapy alone, with greater benefit in non-epithelioid compared to epithelioid pleural mesothelioma. However, there is still significant unmet need given the ongoing poor prognosis; further study is needed to optimize dual checkpoint approaches across histologic subtypes and refine regimen selection. Volrustomig is a monovalent, bispecific, humanized IgG1 monoclonal antibody engineered to specifically inhibit PD-1 and CTLA-4, with increased CTLA-4 blockade on PD-1-positive activated T cells compared to PD-1-negative resting peripheral T cells. Volrustomig + chemotherapy is being evaluated as first-line treatment in unresectable pleural mesothelioma in the phase 3 eVOLVE-Meso trial. Volrustomig monotherapy has shown encouraging results in a Phase 1 study of patients with solid tumors; this new eVOLVE-02 (NCT06535607) substudy will evaluate its efficacy and safety as monotherapy in unresectable pleural mesothelioma. **Methods:** ~75 patients with unresectable pleural mesothelioma (epithelioid or non-epithelioid histology) will receive intravenous volrustomig until disease progression, unacceptable toxicity, consent withdrawal, or maximum treatment duration is reached. Eligibility criteria include age ≥18 years, Eastern Cooperative Oncology Group performance status 0/1, histologically confirmed pleural mesothelioma with known histology, advanced unresectable disease, measurable disease per mRECIST (modified Response Evaluation Criteria in Solid Tumors) v1.1 (pleural lesions) and/or RECIST v1.1 (metastatic non-pleural lesions), no prior systemic therapy for pleural mesothelioma, and no prior exposure to immune-mediated therapy. The primary endpoint is objective response rate. Secondary endpoints include disease control rate, time to response, duration of response, progression-free survival, and overall survival. eVOLVE-02 is recruiting patients; 3 substudies are ongoing in cervical cancer and head and neck squamous cell carcinoma. Substudy 5 enrollment is planned at sites in 8 countries/regions: Australia, Canada, China, Germany, Italy, Taiwan, UK, and USA. Clinical trial information: NCT06535607. Research Sponsor: AstraZeneca.

TPS8127 **Poster Session**

Neoadjuvant chemo-immunotherapy and surgical resection in locally advanced non-small cell lung cancer with N3 lymph node involvement (NEOSURG). First Author: Joshua E. Reuss, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

Background: The emergence of neoadjuvant and peri-operative chemoimmunotherapy in locally-advanced non-small cell lung cancer (NSCLC) has revolutionized the treatment of resectable NSCLC. Importantly, in multiple phase III trials, patients with multi-station N2 disease derive profound benefit from neoadjuvant chemoimmunotherapy. NSCLC with N3 involvement has been excluded from neoadjuvant/perioperative studies, as these cancers have historically been considered unresectable and treated with definitive chemoradiotherapy (CRT) followed by durvalumab. However, CRT is associated with high rates of treatment-related adverse events and most patients experience disease relapse within 2 years. Whether patients with select N3 lymph node-positive NSCLC may benefit from neoadjuvant chemo-immunotherapy followed by surgery is an important unaddressed question. This phase II trial seeks to evaluate the feasibility and clinical utility of neoadjuvant chemoimmunotherapy followed by surgery in patients with locally-advanced stage III B/C NSCLC with select N3 involvement. **Methods:** This phase II, multi-center, single-arm study is evaluating neoadjuvant chemoimmunotherapy in patients with stage III B/C NSCLC with contralateral mediastinal or ipsilateral supraclavicular (N3) lymph node involvement. Select eligibility criteria include: ECOG performance status 0-1, pathologically-confirmed contralateral mediastinal or ipsilateral supraclavicular N3 disease, ≤2 involved lymph node stations, primary tumor appropriate for resection per multi-disciplinary review (any T stage), physical fitness for resection, wild-type *EGFR/ALK*. Patients will receive neoadjuvant cemiplimab 350mg IV plus histology-specific chemotherapy every 3 weeks for 4 cycles prior to planned surgical resection followed by adjuvant radiotherapy (optional) and 1 year of adjuvant cemiplimab. The primary endpoint is pCR rate defined by IASLC consensus guidelines. Secondary endpoints include objective response rate (per RECIST v1.1), R0 resection rate, major pathologic response (≤10% viable tumor) rate, disease-free survival and overall survival. A total of 21 patients will be enrolled. A Simon-2 stage design will be used such that 12 patients will be enrolled initially and, if at least one pCR is observed, the trial will proceed to the second stage with enrollment of an additional 9 patients. This design yields a type I error rate of 5% and power of 80% when the true pCR rate is 20%. In addition, a Pocock stopping rule at 5% type I error will be deployed to assess feasibility of surgical resection. The study will be halted for futility if 8 of the first 12 patients do not proceed with surgical resection. The study is open for accrual at Georgetown University, University of Virginia, and Washington University. Clinical trial information: NCT06449313. Research Sponsor: Regeneron.

TPS8128 **Poster Session**

IFCT-2401 SPORADIC trial: Integrating cemiplimab to sequential hypofractionated chemoradiotherapy for unfit or elderly patients with unresectable stage III non–small cell lung cancer. First Author: Sébastien Thureau, Radiotherapy Department, QuantiF AIMS, Centre Henri Becquerel, Rouen, France

Background: Patients with unresectable stage III non-small cell lung cancer (NSCLC) who are elderly or have significant comorbidities are frequently ineligible for concurrent chemoradiotherapy (CCRT). Sequential chemoradiotherapy (seq-CRT) remains the preferred approach in this population. While consolidation immunotherapy after CCRT improves survival, evidence supporting its optimal integration with seq-CRT is limited. Preclinical and clinical data suggest that combining chemotherapy and immunotherapy enhances tumor immunogenicity through increased antigen release, immune priming, and modulation of the tumor microenvironment. Hypofractionated radiotherapy may further potentiate immune-mediated effects while shortening overall treatment duration, which is particularly relevant for frail patients. The IFCT-2401 SPORADIC trial evaluates in unfit or elderly patients a sequential strategy integrating neoadjuvant chemo-immunotherapy prior to hypofractionated radiotherapy, followed by maintenance immunotherapy, in patients with unresectable stage III NSCLC not eligible for CCRT. Exploratory correlative studies include circulating biomarkers, immune profiling, lymphopenia, and metabolic response assessment. **Methods:** IFCT-2401 SPORADIC is a multicenter, randomized, open-label phase II trial (EU-CT 2024-517316-29-00). Patients are randomized in a 2:1 ratio to receive neoadjuvant chemotherapy alone (arm A) or neoadjuvant chemo-immunotherapy (arm B). Neoadjuvant treatment consists of three 28-day cycles of carboplatin (AUC 5, day 1) and paclitaxel (80 mg/m², days 1, 8 and 15). Cemiplimab (350 mg, every 3 weeks) is added in arm B. All patients subsequently receive curative hypofractionated thoracic radiotherapy (55 Gy in 20 fractions), followed by maintenance cemiplimab every 3 weeks for up to 12 months. Eligible patients have unresectable stage IIIA–C NSCLC. Three categories of patients are considered unfit for CCRT: age ≥70 years with ECOG performance status (PS) 0 to 1, age < 70 years with ECOG PS 0 to 1 and significant comorbidities or age < 70 years with ECOG PS 2. Key exclusion criteria include actionable oncogenic drivers, prior systemic therapy for NSCLC and active autoimmune disease. The primary endpoint is progression-free survival. A total of 152 patients are planned for enrollment across 25 centers. First patient was enrolled on November 17, 2025. Clinical trial information: EU-CT 2024-517316-29-00. Research Sponsor: None.

TPS8129 **Poster Session**

Beamion LUNG-3: Zongertinib in resectable *HER2*-mutant NSCLC. First Author: Amy Lauren Cummings, University of California, Los Angeles (UCLA), Los Angeles, CA

Background: Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Based on recent data from the Phase Ib Beamion LUNG-1 trial (NCT04886804), zongertinib was approved in the USA (accelerated), China (conditional), and Japan for previously treated patients with advanced/metastatic *HER2*-mutant NSCLC. Clinically meaningful efficacy has also been seen with zongertinib as first-line therapy in treatment-naïve patients with advanced *HER2*-mutant NSCLC. Beamion LUNG-3 (NCT07195695) is an ongoing, global Phase III trial investigating zongertinib as adjuvant monotherapy compared with SoC (immunotherapy [IO] or observation) in patients with early-stage, resectable *HER2*-mutant NSCLC. **Methods:** Patients with histologically confirmed, resectable, Stage II–IIIB (post-operative, AJCC 9th edition) *HER2*-mutant NSCLC will be enrolled. Patients must be aged ≥18 years, have an ECOG PS of 0 or 1, have tumors that harbor a *HER2* mutation within the tyrosine kinase domain, and have completed 3–4 cycles of neoadjuvant platinum-based chemotherapy + IO or 4 cycles of adjuvant platinum-based chemotherapy (≥2 cycles permitted if discontinued due to toxicity), followed by complete surgical resection. Patients must have a full recovery from surgical procedures and the ability to be randomized within 2–8 weeks of the last treatment for patients who underwent adjuvant chemotherapy, or within 4–10 weeks of surgery for patients who underwent neoadjuvant therapy. Approximately 400 patients will be randomized 1:1 to receive zongertinib 120 mg once daily or physician's choice SoC (observation or IO with nivolumab, pembrolizumab, atezolizumab, or durvalumab). Stratification will be based on tumor stage (II, IIIA, IIIB), pretreatment (neoadjuvant/adjuvant), and physician's choice of SoC (IO/observation). Patients will remain on treatment for up to 3 years (if receiving zongertinib) or up to 1 year (if receiving SoC), or until tumor recurrence, undue toxicity, or any other protocol-defined stopping criterion. The primary endpoint is disease-free survival (DFS) by investigator assessment, defined as the time from randomization until tumor recurrence or death from any cause. Secondary endpoints include overall survival (OS, defined as the time from randomization until death from any cause) and occurrence of grade ≥3 adverse events from first treatment administration (or from randomization for patients in the observation arm) until the earliest of tumor recurrence or 3 years since treatment started. The trial will be conducted at ~200 sites in 32 countries; enrollment is ongoing. Results will inform whether HER2-targeted adjuvant therapy improves DFS and OS in patients with early-stage *HER2*-mutant NSCLC. Clinical trial information: NCT07195695. Research Sponsor: Boehringer Ingelheim.

TPS8130 **Poster Session**

Randomized, double-blind, phase 3 TRUST-IV study of adjuvant taletrectinib vs placebo in patients with stage IB–IIIA ROS1+ non-small cell lung cancer (NSCLC). First Author: Alexander I. Spira, Virginia Cancer Specialists and US Oncology, Fairfax, VA

Background: Taletrectinib is a next-generation, CNS-active, selective ROS1 tyrosine kinase inhibitor (TKI) approved by the US FDA for the treatment of locally advanced or metastatic ROS1+ NSCLC. In stage IB–IIIA NSCLC, which represents about 30% of NSCLC cases, the standard of care is surgical resection with perioperative systemic therapy (neoadjuvant or adjuvant). Results from Phase 3 trials have shown significantly improved outcomes for EGFR and ALK TKIs as adjuvant therapy compared with placebo or chemotherapy in early-stage NSCLC with EGFR mutations or ALK fusions, respectively. However, there remains an unmet need for patients with stage IB–IIIA ROS1+ NSCLC. Given the efficacy and tolerability of taletrectinib in advanced ROS1+ NSCLC, there is a rationale for investigating taletrectinib in patients with earlier-stage NSCLC who have undergone complete tumor resection. **Methods:** TRUST-IV (NCT07154706) is a randomized, double-blind, multicenter, Phase 3 study evaluating the efficacy and safety of taletrectinib compared with placebo in patients with stage IB, II, or IIIA ROS1+ NSCLC following curative surgery (negative surgical margins). ROS1 fusions may be detected using validated local tissue or liquid assays but must be confirmed by central tissue testing. Patients may have received prior adjuvant platinum-based chemotherapy ($\leq$4 cycles) if clinically indicated, which must be completed $\geq$7 days prior to randomization. Surgical resection must have occurred 4–16 weeks prior to randomization if no adjuvant chemotherapy was given or 4–30 weeks if adjuvant chemotherapy was given. The estimated enrollment is 180 patients, randomized 2:1 to receive either taletrectinib 400 mg once daily or a matched placebo, stratified by prior adjuvant chemotherapy (yes vs no) and pathological stage (IB vs II vs IIIA). Patients will receive blinded study drug in continuous 28-day cycles until disease recurrence or consent withdrawal, or up to a maximum of 3 years. Contrast computed tomography or magnetic resonance imaging (MRI) of the chest/abdomen/pelvis will be performed at screening, Cycle 4 Day 1 (C4D1), and C7D1, while brain MRI will be performed at screening and C7D1; thereafter, all imaging will be performed every 24 weeks until 5 years and then annually until disease recurrence or end of study. The primary endpoint is disease-free survival (DFS) by investigator assessment. Select secondary endpoints include: DFS rates at 2, 3, 4, and 5 years; DFS by blinded independent central review; overall survival; CNS-DFS; and safety. Exploratory endpoints include patient-reported outcomes for health-related quality-of-life measures and progression-free survival 2. The trial is currently recruiting. Clinical trial information: NCT07154706. Research Sponsor: This study was sponsored by Nuvation Bio Inc. Medical writing support was provided by Caroline Creasey, MSc, and Flaminia Fenoaltea, MSc, of Ashfield MedComms, an Inizio company, and was funded by Nuvation Bio Inc.

TPS8131 **Poster Session**

SWOG S2414 (INSIGHT): A randomized phase III trial incorporating pathologic complete response in participants with early-stage non-small cell lung cancer to optimize immunotherapy in the adjuvant setting. First Author: Jeremy Paul Cetnar, Oregon Health and Science University Knight Cancer Institute, Beaverton, OR

Background: Neoadjuvant chemo-immunotherapy (chemo-IO) followed by surgery is a standard of care for resectable clinical stage II-IIIB non-small cell lung cancer (NSCLC). Pathologic complete response (pCR), achieved in roughly 20% of patients, is associated with a favorable overall survival rate, but the benefit of additional adjuvant immunotherapy (IO) after pCR has not been independently studied and remains uncertain. The potential for overtreatment and unnecessary toxicity is a critical question in these patients. SWOG S2414 (INSIGHT) is designed to determine the optimal adjuvant therapy strategy for patients with pCR after neoadjuvant chemo-IO. **Methods:** INSIGHT (NCT06498635) is an open-label, randomized phase III trial, in which patients with clinical stage II-IIIB NSCLC who achieved pCR after standard of care neoadjuvant chemo-IO are randomized to adjuvant durvalumab IV every 28 days for up to 12 cycles (durvalumab, arm A) versus no further treatment (active surveillance, arm B). The primary objective is to compare disease free survival (DFS) between participants in the two arms. Key secondary endpoints include overall survival, event-free survival, and patient-reported quality of life (using the FACT-L and FACT-BRM) and symptoms (using PRO-CTCAE). The total enrollment goal is 306 participants. The design includes 2 interim analyses. Participants must have NSCLC with no known EGFR mutations or ALK fusions, and must have received at least two cycles of an FDA-approved neoadjuvant platinum-based chemo-IO regimen with an anti-PD-1/PD-L1 agent. Pathologic complete response will be confirmed by local pathology. Current Status: S2414 was activated on 3/14/2025, the first patient was registered on 4/1/2025. Enrollment is open and ongoing. Clinical Significance: INSIGHT is a pivotal trial addressing the therapeutic dilemma of adjuvant treatment for early-stage NSCLC patients with pCR after neoadjuvant chemo-IO. The results will help determine whether adjuvant IO provides a significant DFS benefit over surveillance in patients with a pCR, potentially leading to de-escalation of therapy and reduced toxicity. Funding: NIH/NCI grants U10CA180888, U10CA180819; additional support by AstraZeneca. Clinical trial information: NCI-2024-05588. Research Sponsor: NIH/NCI grants U10CA180888, U10CA180819; additional support by AstraZeneca.

TPS8132 **Poster Session**

Randomized multicenter phase II trial of radioimmunotherapy versus chemoimmunotherapy followed by surgery for c-stage IB-III NSCLC (RICHIS trial). First Author: Jonathan Villena-Vargas, Weill Cornell Medicine, New York, NY

Background: Chemotherapy combined with PD-1 or PD-L1 blockade (chemoimmunotherapy, ChemoIO), administered in the neoadjuvant, adjuvant, or perioperative setting, has become standard of care for surgically resectable non-small cell lung cancer (NSCLC). However, ChemoIO may be associated with significant toxicity that may limit treatment delivery and compromise surgical fitness. Preclinical data demonstrate that non-ablative stereotactic body radiotherapy (SBRT) can synergize with immunotherapy by enhancing tumor antigen release, interferon signaling, T-cell priming, and systemic antitumor immunity. We previously completed a phase II trial comparing neoadjuvant non-ablative SBRT (24 Gy) plus immunotherapy (SBRT-IO) versus immunotherapy alone, demonstrating favorable tolerability and higher rates of major and complete pathological response (MPR, pCR) in the SBRT-IO arm. SBRT-IO may therefore represent a neoadjuvant alternative for selected patients, with the potential to reduce treatment-related toxicity. **Methods:** RICHIS (NCT06623656) is an open-label, multicenter, randomized phase II trial enrolling approximately 112 patients with histologically confirmed, surgically resectable clinical stage IB-III (N2) NSCLC. Eligible patients are $\geq$18 years old, have ECOG performance status 0-1, and lack EGFR mutations or ALK fusions. Participants are randomized 1:1 to receive neoadjuvant SBRT-IO (SBRT 8 Gy $\times$ 3 fractions plus up to three cycles of cemiplimab) or standard ChemoIO (platinum-based doublet chemotherapy plus up to three cycles of cemiplimab). Randomization is stratified by tumor PD-L1 expression ($<$ 1% vs. $\geq$1%) and clinical stage (IB/II vs. III). Following neoadjuvant therapy, all patients undergo surgical resection and receive adjuvant cemiplimab for up to 12 months; patients in the SBRT-IO arm may additionally receive adjuvant chemotherapy. The primary endpoint is pCR. Key secondary endpoints include grade 3-5 adverse events (neoadjuvant and postoperative), event-free survival, MPR, and postoperative length of stay. Correlative immune and molecular biomarker studies are planned. Trial enrollment began on 2/4/2025 and is currently enrolling across 2 sites, with planned enrollment at 5 US sites. 19 of 112 patients are currently accrued. Clinical trial information: 24-02027124. Research Sponsor: Regeneron Pharmaceuticals.

TPS8133 **Poster Session**

A double-blind, double-dummy, randomized, controlled phase 3 trial of iparomlimab and tuvonralimab (QL1706) vs QL1604 as consolidation therapy following concurrent or sequential chemoradiotherapy (cCRT/sCRT) in patients (pts) with limited-stage small-cell lung cancer (LS-SCLC). First Author: Linlin Wang, Cancer Hospital of Shandong First Medical University (Shandong Cancer Institute, Shandong Cancer Hospital), Jinan, China

Background: LS-SCLC is a highly aggressive malignancy with poor prognosis. Positioning effective consolidation strategies is a key focus to improve long-term patient outcomes. Prominently, immune checkpoint inhibitors (ICIs) have emerged as consolidation therapy after cCRT or sCRT for LS-SCLC. QL1706 is a bifunctional antibody against both programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4, and iparomlimab (QL1604) is an anti-PD-1 agent. In previous studies, both QL1706 and QL1604 demonstrated manageable safety profiles. Notably, QL1706 also showed encouraging preliminary anti-tumor signals in SCLC, which indicated the potential as consolidation therapy (Zhao et al. 2023; Huang et al. 2023). This trial aims to compare the efficacy and safety of QL1706 and QL1604 as consolidation therapy in pts with LS-SCLC without progression after cCRT or sCRT. **Methods:** In this multicenter double-blind double-dummy randomized controlled phase 3 trial (NCT06789796), pts with pathologically-confirmed LS-SCLC per AJCC 8th edition are recruited. Pts are eligible if aged $\geq$18 years, with adequate organ function, ECOG PS scored 0 or 1, and do not have disease progression after completion of the requested cCRT or sCRT. Prophylactic cranial irradiation (PCI) is permitted before randomization. Approximately 636 pts are planned to be randomized 1:1 to receive either QL1706 (at 5 mg/kg) plus QL1604 placebo or QL1604 (at a fixed dose of 200 mg or at 3 mg/kg for pts weighing $<$40 kg) plus QL1706 placebo via intravenous infusion on day 1 in a 21-day cycle. Treatment will be continued until disease progression, intolerable toxicity, initiation of new anti-tumor treatment, withdrawal of informed consent, loss to follow-up, trial termination, or up to 24 months, whichever occurs first. Randomization is stratified by disease stage (I/II vs. III), receipt of PCI (yes vs. no), and the type of CRT (cCRT vs. sCRT). The co-primary endpoints are progression-free survival (PFS) per RECIST v1.1 assessed by blinded independent central review (BICR), and overall survival (OS). Secondary endpoints are investigator-assessed PFS, 1-year and 2-year PFS rates assessed by BICR and investigator, objective response rate, disease control rate, duration of response, 1-year and 2-year OS rates, safety, pharmacokinetics, and immunogenicity. Exploratory endpoints are biomarker assessments and their relationship to efficacy and prognosis, as well as patient-reported outcomes. Overall two-sided Type I error (α=0.05) controlled by fixed-sequence testing: BICR assessed PFS will be tested first, followed by OS if significant. An interim analysis is planned. The study will be conducted across around 79 sites in China, and enrollment is ongoing. Clinical trial information: NCT06789796. Research Sponsor: Qilu Pharmaceutical Co., Ltd.

TPS8134 **Poster Session**

TIGOS-LS, an open-label, randomized study of BMS-986489 (atigotatug + nivolumab fixed-dose combination) vs durvalumab as consolidation therapy following chemoradiotherapy in limited-stage small-cell lung cancer. First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN

Background: Durvalumab consolidation was added to concurrent chemoradiotherapy for standard-of-care treatment of limited-stage small-cell lung cancer (LS-SCLC) in 2024. Although durvalumab improves overall survival (OS) and progression-free survival (PFS; Cheng et al. 2024), other agents may provide further improvement. BMS-986489 is a first-in-class fixed-dose combination of atigotatug and nivolumab. Atigotatug binds to fucosyl-monosialoganglioside-1 (fuc-GM1), which is highly expressed on SCLC cells and often absent in normal tissues. This binding causes tumor cell death via antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity. These processes trigger T cells, whose activation is also potentiated by nivolumab, which is hypothesized to improve outcomes after chemoradiotherapy. In a randomized Phase II study in extensive-stage SCLC, adding atigotatug to carboplatin, etoposide, and nivolumab (CE/NIVO) improved median OS vs CE/NIVO alone (15.6 months vs 11.4 months; Kalinka et al. 2024). **Methods:** TIGOS-LS is an open-label, randomized study evaluating the safety and efficacy of BMS-986489 vs durvalumab consolidation after chemoradiotherapy in LS-SCLC. Approximately 250 participants will be enrolled at 70 sites within the US. Eligible participants are adults with an Eastern Cooperative Oncology Group performance status of 0 or 1, histologically or cytologically confirmed SCLC evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 before standard treatment was initiated, LS disease determined by PET scan at the time of initial diagnosis or justified by the participant history, and inoperable disease, if Stage I/II. All participants must have completed concurrent chemoradiotherapy without progression. Prophylactic cranial irradiation (PCI) is permitted before study treatment. Expression of fuc-GM1 is not required; participants can enroll regardless of tissue availability for the trial. Participants requiring chronic systemic corticosteroids equivalent to $>$10 mg of prednisone at the time of enrollment are excluded. Stratification factors include disease stage (I/II vs III) and receipt of PCI. Randomization is 1:1 to BMS-986489 or durvalumab. BMS-986489 or durvalumab is administered intravenously at a fixed dose once every 4 weeks for up to 2 years or until discontinuation criteria are met. Response is evaluated by RECIST v1.1. Survival follow-up occurs every 12 weeks for up to 3 years. The primary endpoint is OS. Secondary endpoints include PFS, objective response rate, clinical benefit rate, disease control rate, duration of response, and safety parameters. TIGOS-LS (NCT06773910) opened to enrollment in March 2025; 232 enrollment slots remain. Clinical trial information: NCT06773910. Research Sponsor: Bristol Myers Squibb.

TPS8135 **Poster Session**

SEZanne: A phase 2 randomized, open-label, multicenter study to evaluate the optimal dose, safety, and efficacy of ABBV-706 in combination with atezolizumab (atezo) versus standard of care (SOC) in patients (pts) with previously untreated extensive-stage (ES) small cell lung cancer (SCLC). First Author: Kristof Cuppens, Jessa Hospital, Hasselt, Belgium and Faculty of Medicine and Life Sciences LCRC, UHasselt, Diepenbeek, Belgium

Background: SCLC is a neuroendocrine tumor accounting for ~15% of lung cancers, with a 5-year survival rate of ~7%. Platinum-based chemotherapy (PCT) remains the 1L SOC, achieving response rates of 60–70% in pts with ES-SCLC, though durable responses are rare. Adding a PD-L1 inhibitor (atezo or durvalumab) to PCT only modestly improves survival, and novel therapies are needed. Seizure-related homolog 6 (SEZ6), a neuroendocrine lineage marker highly expressed in SCLC, represents a promising target. ABBV-706, a SEZ6-directed antibody-drug conjugate with a topoisomerase 1 inhibitor payload, has shown promise as monotherapy in pts with relapsed SCLC, with an ORR of 57.3% (Byers et al. *J Thorac Oncol.* 2025;10:S23). The phase 2 SEZanne study (NCT07155174) evaluates the dose optimization, safety, and efficacy of ABBV-706 + atezo as a 1L regimen vs SOC. **Methods:** This global, open-label, randomized phase 2 study (~75 sites; up to 180 pts) compares ABBV-706 + atezo vs SOC. Eligible pts ($\geq$18 years) have ES-SCLC requiring 1L therapy, ECOG 0–1, measurable disease per RECIST v1.1, and are candidates for PCT. Primary objectives are to evaluate safety/tolerability, identify the recommended phase 3 dose, and assess PFS of ABBV-706 in combination with atezo. Secondary objectives are to further evaluate efficacy (ORR, DOR, DCR, OS) and characterize the PK/immunogenicity of the combination. The study consists of 2 parts: a safety lead-in (~30 pts) and a dose optimization (~150 pts) stage. During safety lead-in, pts are randomized 1:1:1 to 2 doses of ABBV-706 Q3W + atezo or SOC. SOC includes 4 cycles of PCT (carboplatin) + etoposide + atezo followed by atezo maintenance; lurbinectedin may also be used in maintenance where locally approved. After the safety lead-in, additional pts will be randomized to the ABBV-706 + atezo arms that were deemed safe, or the SOC arm. Treatment continues until progression, intolerable toxicity, or other discontinuation criteria are met. The study is enrolling. Clinical trial information: NCT07155174. Research Sponsor: AbbVie Inc.

TPS8136 **Poster Session**

A randomized, open-label, phase 3 study of ZL-1310, a DLL3 antibody-drug conjugate (ADC), compared to investigator's choice therapy in participants with relapsed small cell lung cancer (DLLEVATE). First Author: Afshin Dowlati, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH

Background: Small Cell Lung Cancer (SCLC) is a neuroendocrine tumor with high proliferation rate, early metastasis and poor prognosis. DLL3 is a validated target for neuroendocrine tumor and is highly expressed in SCLC. ZL-1310 is a novel antibody-drug conjugate (ADC) that employs the TMALIN (Tumor Microenvironment Activable LINker-payload) platform, an anti-DLL3 monoclonal antibody linked to a topoisomerase I inhibitor payload via a protease-cleavable linker. ZL-1310 has demonstrated encouraging systemic efficacy in heavily pre-treated ES-SCLC and showed intracranial activities. **Methods:** DLLEVATE is a randomized, open-label phase III study to further evaluate the efficacy and safety of ZL-1310 compared to investigator's choice of locally approved and available single agent therapy (ICT). This multi-country Phase III study (NCT07218146) enrolls adults with Extensive Stage (ES)-SCLC patients (pts) who have progressed after platinum-based first-line (1L) therapy or after tarlatamab as second-line (2L) therapy. Those with stable or asymptomatic BM are eligible (including those with no prior brain radiotherapy). The eligible pts are randomized at 1:1 according to presence/absence of brain metastasis, sensitivity to prior chemotherapy and with/without prior tarlatamab. ZL-1310 is given intravenously every 3 weeks until disease progression or unacceptable toxicity. Systemic efficacy is assessed by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Intracranial efficacy is assessed by blind independent radiologists using Modified Criteria for Radiographic Response Assessment in Neuro-Oncology (mRANO). The study has one interim analysis based on Objective Response Rate (ORR) assessed by Blind Independent Review Committee (BIRC) and the primary analysis based on Overall Survival (OS). Enrollment is underway, and is planned at ~250 sites across several continents. Clinical trial information: NCT07218146. Research Sponsor: Zai Lab (Shanghai) Co., Ltd.

TPS8137 **Poster Session**

A phase 3 study of sacituzumab govitecan in patients with previously treated extensive-stage small cell lung cancer. First Author: Afshin Dowlati, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH

Background: Treatment options for extensive-stage small cell lung cancer (ES-SCLC) that has progressed after platinum-containing therapy with or without anti–programmed cell death protein (ligand) 1 (anti–PD-[L]1) therapy are limited. Despite the evolving treatment landscape for ES-SCLC, toxicities and poor clinical outcomes with the current globally approved standard of care (SOC), topotecan, highlight the unmet need for novel agents. Sacituzumab govitecan (SG), a Trop-2–directed antibody-drug conjugate, demonstrated encouraging antitumor activity and manageable safety as a second-line treatment for ES-SCLC in the phase 2, open-label TROPiCS-03 study. At a median study follow-up of 12.3 months in TROPiCS-03, the investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) was 42% and median overall survival (OS) was 13.6 months. Neutropenia (44%) and diarrhea (9%) were the most common grade $\geq$3 treatment-emergent adverse events (TEAEs), and no TEAEs led to discontinuation of SG; 1 treatment-related TEAE caused death. EVOKE-SCLC-04 (NCT06801834) is a randomized, phase 3, open-label, multicenter study evaluating the efficacy and safety of SG versus SOC (topotecan, lurbinectedin [in countries/regions where approved], or amrubicin [Japan only]) in patients with previously treated ES-SCLC. **Methods:** Key eligibility criteria for EVOKE-SCLC-04 include age $\geq$18 years, confirmed SCLC diagnosis, Eastern Cooperative Oncology Group performance status score of 0–1, measurable disease per RECIST v1.1, and disease progression after 1 prior line of platinum-containing therapy with or without anti–PD-(L)1 therapy. Prior tarlatamab treatment is allowed. Patients with untreated central nervous system (CNS) metastases and/or carcinomatous meningitis are excluded unless these are asymptomatic and immediate CNS-specific treatment is not required. Patients will be randomized 1:1 to either SG (10 mg/kg on Days 1 and 8) or SOC: topotecan (1.5 mg/m^2 daily on Days 1–5), lurbinectedin (3.2 mg/m^2 on Day 1), or amrubicin (40 mg/m^2 daily on Days 1–3) administered as intravenous infusion in 21-day cycles, until progressive disease (assessed by investigator review per RECIST v1.1), unacceptable toxicity, or death. Randomization will be stratified by chemotherapy-free interval ($\geq$90 vs $<$90 days), CNS involvement (yes vs no), geographic region (East Asia vs non-East Asia), and prior anti–PD-(L)1 therapy (yes vs no). The primary endpoint is OS; secondary endpoints include progression-free survival, ORR, duration of response, patient-reported outcomes (time to first deterioration in shortness of breath and physical functioning), and safety/tolerability. This study is open and actively recruiting as of February 2025 and plans to enroll 695 patients from approximately 275 sites globally. Clinical trial information: NCT06801834. Research Sponsor: Gilead Sciences, Inc.

TPS8139 **Poster Session**

Durvalumab plus chemotherapy prior to chemoradiotherapy and followed by durvalumab as consolidation for patients with limited-stage small cell lung cancer (CONCUR study). First Author: Qian Chu, Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: The ADRIATIC study demonstrated that durvalumab consolidation therapy following concurrent chemoradiotherapy (CRT) significantly improved both progression free survival (PFS) and overall survival (OS) in patients with inoperable limited-stage small-cell lung cancer (LS-SCLC), establishing the standard of care for this population. Building on emerging immune checkpoint inhibitor (ICI) strategies (pre-CRT induction, post-CRT consolidation or concurrent ICI-CRT), CONCUR study innovatively introduces durvalumab plus chemotherapy as induction to synergize early immune priming with cytotoxic effects, aiming to enhance responses during subsequent CRT while preserving safety, with potential to reshape the treatment landscape for LS-SCLC. **Methods:** Approximately 100 eligible patients (aged $\geq$ 18 years) with histologically or cytologically confirmed LS-SCLC, ECOG 0-1, at least one measurable lesion (RECIST 1.1), having received no prior thoracic radiotherapy or chemotherapy will be enrolled in this multi-center, phase II study. Patients will receive durvalumab (1500mg day[D] 1) combined with cisplatin (75 mg/m² D1 or 25 mg/m² D1-3) or carboplatin (AUC 5-6 D1 or AUC 2.5-3 D1 and D8) and etoposide (100 mg/m² D1-3) every 3 weeks for 2 cycles as induction therapy, followed by concurrent or sequential CRT. Thoracic radiotherapy will be delivered as 60 $\pm$ 6 Gy (1.8-2 Gy/day) or 45 $\pm$ 1.5 Gy (1.5Gy twice daily), with optional prophylactic cranial irradiation per clinical indication and local clinical practice. Patients showing at least stable disease after the definitive CRT will continue durvalumab (1500 mg every 4 weeks) until disease progression, unacceptable toxicities, or for up to 24 months (whichever occurs first). The primary endpoint is PFS by investigator per RECIST 1.1. Secondary endpoints include OS, objective response rate, duration of response, and safety. The primary analysis on PFS will be performed at approximately 60% data maturity. Assuming the median PFS is 16 months (defined from first dose of treatment), with an enrollment period of 12 months and drop-out rate of 7%, 100 patients and 60% PFS maturity will provide a precision of $\pm$ 4.8 months with 95% CI (11.6m, 21.1m) estimated by Kaplan-Meier method using Brookmeyer and Crowley method. Enrollment is ongoing. Clinical trial information: NCT07055581. Research Sponsor: None.

TPS8140 **Poster Session**

A phase II trial of ivonescimab for previously treated thymic carcinoma: UCLA L-11. First Author: Jonathan Boiarsky, University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Thymic carcinoma (TC) is a rare and aggressive thymic epithelial tumor (TET), accounting for approximately 20% of thymic neoplasms. TC is often more invasive and less responsive to standard therapy than other TETs, with a 5-year survival rate of 30-50% in the advanced/metastatic setting. Effective treatment remains limited following progression with platinum-based chemotherapy. Programmed Death-(Ligand) 1 (PD-(L)1) inhibition demonstrates modest activity in recurrent TC, with an objective response rate (ORR) of 19.5-22.5% with manageable toxicities [Cho, *Clin Oncol*. 2019; Giaccone, *J Thorac Oncol*. 2021]. Moreover, vascular epithelial growth factor (VEGF) inhibition with sunitinib or lenvatinib achieved ORRs of 26-38% in second line therapy and beyond (Thomas, *Lancet Oncol*. 2015; Sato, *Lancet Oncol*. 2020). Combination of lenvatinib and pembrolizumab as second line therapy and beyond has shown an ORR of 22.5%, with a median duration of response of 8.2 months (Remon, *Lancet Oncol. 2025*). Ivonescimab is a humanized bispecific monoclonal antibody targeting both PD-1 and VEGF and shows favorable safety and efficacy in non-small cell lung cancer. In light of the known benefit of VEGF and PD-(L)1 blockade in TC, this study aims to evaluate the safety and efficacy of ivonescimab in patients with previously treated TC. **Methods:** This study is a multi-center, open-label, single-arm Phase II trial enrolling adults with histologically or cytologically confirmed unresectable/metastatic TC whose disease has progressed following systemic therapy. Key inclusion criteria include one-prior line of treatment, ECOG performance status $\leq$1, and adequate organ function. Exclusion criteria include prior treatment with PD-(L)1 inhibitors, positive paraneoplastic serologies, or autoimmune disease requiring active systemic therapy. Ivonescimab is administered intravenously on D1 of a 21-day cycle until disease progression, unacceptable toxicity, withdrawal, or loss of follow up. The primary endpoints are investigator confirmed ORR via RECIST 1.1 and safety/tolerability of ivonescimab. Secondary endpoints include progression-free survival, duration of response, time to response, and overall survival. Exploratory analyses will evaluate correlation of antitumor activity with tissue and blood-based biomarkers, such as PD-L1 expression and circulating tumor DNA (ctDNA). The study uses a Simon's two stage design: in stage 1, 15 patients will be enrolled. The study will be stopped if $\geq$ 5 treatment-related serious adverse events or if $\leq$1 patient achieves an objective response within the first three months of treatment. Otherwise, an additional 10 patients will be enrolled in stage 2. The design has 80% power with a 5% Type I error to detect an ORR of 30% over the null hypothesis of 10%. The study is currently enrolling patients. Copyright © 2026 AACR. Originally presented at AACR 2026. Reprinted with permission. Clinical trial information: NCT06980077. Research Sponsor: Jonsson Comprehensive Cancer Center.

LBA8500 **Oral Abstract Session**

Sunvozertinib monotherapy versus platinum-based chemotherapy as first-line treatment for advanced NSCLC with EGFR exon20ins: Primary analysis of a multinational phase 3 randomized study (WU-KONG28). First Author: John V. Heymach, Department of Thoracic/Head and Neck Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

8501 **Oral Abstract Session**

Overall survival of first-line amivantamab plus lazertinib in atypical *EGFR*-mutated advanced non-small cell lung cancer (NSCLC): Updated results from the CHRYSALIS-2 study. First Author: Joel W. Neal, Stanford Cancer Institute, Stanford University, Stanford, CA

Background: Patients with atypical *EGFR*-mutated advanced NSCLC have worse long-term outcomes with EGFR-targeted therapies than classical exon 19 deletion/L858R mutations (c*EGFR*). Afatinib, approved for atypical *EGFR*-mutated NSCLC, showed a median overall survival (OS) of 19.4 months among 38 participants (pts) with atypical *EGFR*-mutations globally (Yang *Lancet Oncol* 2015). Amivantamab (ami)-based regimens are approved across multiple lines of therapy in different settings for c*EGFR* and exon 20 insertion (Ex20ins)-mutated advanced NSCLC. In MARIPOSA, first-line (1L) ami plus lazertinib (ami-laz) significantly prolonged OS vs osimertinib (HR, 0.75; *P*=0.005) in c*EGFR*-mutated NSCLC. In an earlier report of 49 pts with atypical *EGFR*-mutated advanced NSCLC who received 1L ami-laz, objective response rate (ORR) was 57%, median response duration was 20.7 months, median progression-free survival (PFS) was 19.5 months, and OS was still immature (Tomasini *JCO* 2025). Here we report OS data with longer follow-up for pts with atypical *EGFR*-mutated NSCLC who received 1L ami-laz. **Methods:** Cohort C of the global, phase I/Ib CHRYSALIS-2 study (NCT04077463) enrolled pts with atypical *EGFR* mutations, excluding Ex20ins and co-mutations with c*EGFR*, who were previously untreated or had ≤2 prior lines of therapy, which may have included a 1st/2nd-generation EGFR TKI. All enrolled pts received intravenous ami-laz. The primary endpoint was ORR by investigator per RECIST v1.1, which has been previously reported. Here we report OS, a key secondary endpoint, in the treatment-naïve population (n=49). **Results:** As of Oct 31, 2025, the median follow-up was 31.3 months (range, 0.1–53.2). The median OS was 41.0 months (95% CI, 27.7–not estimable), with 55% alive at 3 years and 46% alive at 4 years. As of data cutoff, 20% (10/49; 6 were confirmed responders and 4 had stable disease) of pts were still ongoing 1L treatment (range, 2.5–4.4 years), with 7 pts receiving ami treatment for >3 years. Safety profile was consistent with prior reports; no additional safety signals were identified with longer-term follow-up. Among pts whose disease had progressed and discontinued 1L treatment, 71% (20/28) received subsequent therapy. The most common subsequent regimens included platinum-based chemotherapy agents (55%). **Conclusions:** 1L treatment of atypical *EGFR*-mutated advanced NSCLC with ami-laz resulted in a clinically meaningful median OS of nearly 3.5 years. Many pts were able to stay on 1L treatment long term, with 20% still ongoing. Ami-laz has now shown substantial survival benefit in both 1L c*EGFR*- and atypical *EGFR*-mutated disease. The recently FDA-approved subcutaneous formulation of ami may further simplify the overall treatment experience for this regimen. Clinical trial information: NCT04077463. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

8502 **Oral Abstract Session**

Lorlatinib vs crizotinib as first-line treatment for advanced *ALK*+ non-small cell lung cancer: 7-year update from the phase 3 CROWN study. First Author: Tony S.K. Mok, State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong, China

Background: Median progression-free survival (PFS) was not reached (NR) with lorlatinib in the phase 3 CROWN study after 5 yrs of f/u, representing the longest PFS reported in advanced non-small cell lung cancer (NSCLC). Due to the unprecedented PFS benefit with lorlatinib after 5 yrs of f/u and the decreased event rate after the first 24 mos in the study, we aimed to quantify long-term outcomes at 7 yrs. **Methods:** 296 treatment-naive patients (pts) with advanced *ALK*+ NSCLC were randomized 1:1 to receive lorlatinib 100 mg once daily (n=149) or crizotinib 250 mg twice daily (n=147). This post hoc analysis presents investigator-assessed efficacy outcomes, safety, and biomarker analyses. Formal statistical testing between arms was not performed. **Results:** As of October 31, 2025, 66 of 149 pts (44%) vs 4 of 142 (3%) were receiving lorlatinib vs crizotinib. With a median f/u for PFS (95% CI) of 83.0 (81.2-86.3) and 77.2 mos (36.8-not evaluable), respectively, median PFS (95% CI) was NR (68.5-NR) with lorlatinib and 9.1 mos (7.4-10.9) with crizotinib (HR, 0.19; 95% CI, 0.13-0.26); the 7-yr PFS (95% CI) was 55% (46-63) and 3% (1-8). In the lorlatinib arm, pts without a PFS event at the end of 24 mos had a 79% probability of survival without progression at yr 7. PFS benefit was consistent across all prespecified subgroups. No new intracranial (IC) progression events occurred after the first 30 mos on lorlatinib. Median time to IC progression (95% CI) was NR (NR-NR) with lorlatinib and 16.4 mos (12.7-21.9) with crizotinib (HR, 0.06; 95% CI, 0.03-0.12). The number of overall survival (OS) events for a protocol-specified analysis has not been met; OS f/u is still ongoing. The safety profile was consistent with the 5-yr results, with all-cause grade 3/4 adverse events (AEs) in 77% of pts with lorlatinib and 57% with crizotinib. Treatment-related AEs (TRAEs) led to permanent treatment discontinuation in 5% of pts with lorlatinib and 6% with crizotinib. No new permanent discontinuations due to TRAEs occurred after the first 26 mos with lorlatinib. Dose reductions were reported in 34% of pts in the lorlatinib arm (17% had 1 dose reduction and 17% had 2 reductions). Long-term efficacy was similar between pts with and without dose reduction. Exploratory translational analyses of outcomes in pts with different molecular subtypes and resistance mechanisms at the end of treatment are ongoing. **Conclusions:** With median PFS yet to be reached after 7 yrs of f/u in CROWN, lorlatinib continues to show unprecedented and highly durable benefit in treatment-naïve pts with advanced *ALK*+ NSCLC. In pts without a PFS event at 24 mos, the probability of survival without progressive disease at 7 yrs was 79%. Longer f/u showed very few additional PFS events, no new IC progression, and no new treatment-related discontinuation, suggesting long-term substantial benefit with lorlatinib for the majority of pts with advanced *ALK*+ NSCLC. Clinical trial information: NCT03052608. Research Sponsor: Pfizer.

8503 **Oral Abstract Session**

ALKOVE-1: Efficacy and safety of neladalkib in patients with advanced *ALK*+ NSCLC. First Author: Jessica Jiyeong Lin, Mass General Brigham Cancer Institute, Boston, MA

Background: Neladalkib is an investigational ALK TKI designed for inhibition of ALK single and compound resistance mutations, brain penetrance, and sparing TRK. We report the first analyses of phase 2 TKI pre-treated patients (pts) and preliminary data in TKI-naïve pts with *ALK*+ NSCLC. **Methods:** The global, single arm phase 1/2 ALKOVE-1 trial (NCT05384626) enrolled pts with advanced/metastatic *ALK*+ NSCLC. Key study endpoints are objective response rate (ORR, RECIST v1.1 by BICR), duration of response (DOR), intracranial ORR (IC-ORR) and safety. Efficacy analyses included TKI pre-treated pts who initiated neladalkib 150 mg QD by 30 Sep 2024 or all treated TKI-naïve pts. Data cut: 29 Aug 2025. **Results:** 656 pts with *ALK*+ NSCLC received neladalkib. Efficacy-evaluable TKI pre-treated pts (n=253) had received a median of 3 prior anticancer therapies (range 1-11, 51% prior chemo). 78% of pts received ≥2 (range 2-5) prior ALK TKIs, of whom 91% had prior lorlatinib. 19% had single or compound ALK G1202R resistance mutations. 40% had CNS disease by BICR. ALK TKI pre-treated results are reported in the Table. In a preliminary analysis of TKI-naïve pts, ORR was 86% (38/44, 2 uPRs); 12-month DOR rate was 91%. IC-ORR was 78% (7/9) with no CNS progression events as of data cutoff. **Conclusions:** In this ALK TKI pre-treated data set, neladalkib demonstrated clinically meaningful activity, including in pts with CNS disease, ALK G1202R single or compound mutations, and prior lorlatinib. Encouraging preliminary activity was also observed in TKI-naïve pts. Neladalkib's safety profile was consistent with its ALK-selective, TRK-sparing design. Clinical trial information: NCT05384626. Research Sponsor: Nuvalent, Inc.

Efficacy Parameter (RECIST v1.1, BICR)	All ALK TKI Pre-treated ± chemo	ALK TKI Pre-treated, Lorlatinib-naïve ± chemo
ORR % (n/N)	31 (79/253)[a, b]	46 (29/63)[c]
95% CI	26, 37	33, 59
% DOR ≥ 12 m (95% CI) / 18 m (95% CI) [d]	64 (51, 75) / 53 (34, 68)	80 (58, 91) / 60 (19, 85)
G1202R Mutation		
ORR % (n/N)	68 (32/47)[e,f]	83 (10/12)
95% CI	53, 81	52, 98
% DOR ≥ 12 m [d] **(95% CI)**	80 (61, 91)	77 (34, 94)
Intracranial Activity		
IC-ORR % (n/N)	32 (29/92)[g, h]	63 (15/24)[g]
95% CI	22, 42	41, 81
% IC-DOR ≥ 12 m [d] **(95% CI)**	71 (48, 85)	92 (57, 99)

m, months; NE, not estimable.
[a]Includes 2 unconfirmed partial responses (uPRs).
[b]Pts with prior lorlatinib: ORR 26% (50/190, including 2 uPRs) and mDOR 17.6 m (95% CI: 6.9, NE).
[c]Pts with 1 prior 2nd generation ALK TKI (alectinib, n=44; brigatinib, n=2) ± chemo: ORR 48% (22/46) and DOR ≥ 12 m of 74% (95% CI: 48, 88).
[d]Estimated by Kaplan-Meier analysis.
[e]Single or compound G1202R resistance mutations may be present.
[f]Includes 1 uPR.
[g]Includes 2 IC-uPRs.
[h]Pts with prior lorlatinib: IC-ORR 21% (14/68) and IC-DOR ≥ 12 m of 55% (95% CI: 26, 77).

8504 Oral Abstract Session

Efficacy and safety of pralsetinib as first-line treatment of *RET* fusion–positive advanced or metastatic non–small cell lung cancer (NSCLC): The phase 3 AcceleRET-Lung study. First Author: Sanjay Popat, Royal Marsden Hospital & Institute of Cancer Research, London, United Kingdom

Background: Pralsetinib, an oral tyrosine kinase inhibitor, selectively and potently targets oncogenic *RET* fusion and mutation proteins. Pralsetinib is FDA approved to treat adults with metastatic *RET*-altered NSCLC. We present efficacy and safety of pralsetinib vs standard of care (SOC) in first-line *RET* fusion-positive NSCLC from a randomized phase 3, open-label study, AcceleRET-Lung (NCT04222972). **Methods:** AcceleRET-Lung was conducted at 74 sites in 22 countries. Adults with *RET* fusion-positive advanced or metastatic NSCLC received pralsetinib 400 mg/d or platinum-based SOC therapy. Crossover to pralsetinib was optional upon progression. The primary end point was progression-free survival (PFS) per RECIST v1.1. Secondary end points included overall response rate (ORR), overall survival (OS), duration of response (DOR), and safety. Efficacy was evaluated in randomized patients (intent-to-treat population [ITT]). Safety was assessed in patients receiving ≥1 dose of study drug. **Results:** 223 ITT patients were randomized to pralsetinib (n=110) or SOC (n=113). Pralsetinib and SOC groups had similar baseline characteristics (median age: 62 and 63 y, respectively; female: 48% and 57%; median lesions: both 4; brain metastases: 15% and 16%). The study was terminated early per sponsor decision on January 27, 2025. ITT patients in the pralsetinib group had significantly greater median PFS vs SOC (18.7 vs 9.0 mo; P=0.003), ORR (65.5% vs 41.6%; $P<0.001$), and median DOR (20.6 vs 9.7 mo; P=0.004; Table). Safety was generally consistent with the known pralsetinib profile except for a higher rate of infection in the pralsetinib group vs SOC (71.3% vs 51.9%), including pneumonia (19.4% vs 5.8%), urinary tract infections (17.6% vs 7.7%), and opportunistic infections (9.3% vs 1.0%). There were 32 (30.0%) and 26 (25.0%) deaths in the pralsetinib and SOC groups, respectively, with 8 (7.4%) and 0 due to infection. Common grade ≥3 TRAEs in the pralsetinib vs SOC groups were hypertension (11.1% vs 0), neutropenia (10.2% vs 8.7%), anemia (8.3% vs 10.6%), and decreased neutrophil count (7.4% vs 4.8%). **Conclusions:** In a Phase 3 study, pralsetinib met the primary PFS end point and had a significantly greater and more durable ORR vs SOC, confirming the clinical utility of pralsetinib in *RET* fusion-positive NSCLC. Monitoring for infections with pralsetinib is warranted. Clinical trial information: (1) NCT04222972; (2) 2023-505035-12-00; (3) 2019-002463-10. Research Sponsor: Rigel Pharmaceuticals, Inc.

Efficacy outcomes.

	Pralsetinib (n=110)	SOC (n=113)	Stratified hazard ratio/odds ratio (95% CI)	*P* Value
Duration of follow-up, mo, median (range)	20.5 (0, 49.8)	16.0 (0, 42.3)	-	-
PFS, mo, median (95% CI)	18.7 (11.1, 25.2)	9.0 (7.1, 11.5)	0.59 (0.42, 0.84)	0.003
ORR, % (95% CI)	65.5 (55.8, 74.3)	41.6 (32.4, 51.2)	2.81 (1.61, 4.93)	<0.001
OS, mo, median (95% CI)	NR (29.6, NR)	39.8 (39.8, NR)	1.09 (0.65, 1.85)	0.742
DOR, mo, median (95% CI)	20.6 (17.2, 31.8)	9.7 (7.6, 15.9)	0.48 (0.28, 0.80)	0.004

8505 Oral Abstract Session

Efficacy and safety of lunbotinib (A400/EP0031), a next-generation selective RET inhibitor (SRI), from a pivotal phase II study in patients with advanced *RET* fusion–positive non–small cell lung cancer (NSCLC). First Author: Qing Zhou, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: RET-fusion positive NSCLC accounts for 1-2% of all lung cancers. Lunbotinib is a next gen brain-penetrant SRI with high potency against RET fusion and mutant proteins (*Zhou et al., 2023; Alonso et al., 2025*). We report findings from a pivotal phase II study in advanced RET-fusion positive NSCLC in China (NCT05265091). An ongoing study is assessing lunbotinib alone or in combination with chemotherapy in Western patients (pts) (NCT05443126). **Methods:** The phase II part enrolled two single-arm cohorts: cohort 1 included pts with prior platinum-based chemotherapy and immunotherapy (pre-treated), and cohort 2 included treatment-naïve pts. All pts received oral lunbotinib 90 mg once daily in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was ORR assessed by an independent review committee (IRC) per RECIST v1.1. **Results:** As of Oct 29, 2025, 71 pre-treated pts and 92 treatment-naïve pts were enrolled, with median follow-up of 22.6 and 20.7 mos, respectively. Among pre-treated and treatment-naïve pts in full analysis set (FAS), ECOG PS 1 rates were 90% and 80.2%, and metastases involving ≥3 organ sites were observed in 75.7% and 57.1%. IRC-assessed confirmed ORR was 87.1% (95% CI: 77.0-93.9) in pre-treated pts and 81.3% (95% CI: 71.8-88.7) in treatment-naïve pts. mPFS was 27.5 mos and NR, respectively. Among pts with baseline CNS metastases (23 pre-treated, 16 treatment-naïve), ORR was 82.6% and 75.0%, respectively, and 6 pts in each cohort had complete intracranial response. Full efficacy data are in Table. Treatment-related AEs (TRAEs) occurred in 98.8% of pts, the most common were AST (72.4%), ALT (68.1%), anemia (63.2%), urinary retention (45.4%), dry eye (43.6%), and increased blood creatinine (42.9%). Grade ≥ 3 TRAEs observed in 40.5%. Two pts (1.2%) discontinued due to TRAEs. No fatal TRAEs occurred. **Conclusions:** Lunbotinib demonstrated robust efficacy in pts with advanced RET-fusion positive NSCLC, with high ORR and prolonged PFS in both pre-treated and treatment-naïve populations, and notable intracranial activity. Safety profile was manageable, with no new signals identified. These data support the potential of lunbotinib as a valuable therapeutic option for this population. Clinical trial information: NCT05265091. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

	Pre-treated pts (Cohort 1) N=71	Treatment-naïve pts (Cohort 2) N=92
Confirmed ORR[a]/DCR[a], % (95% CI)	87.1 (77.0, 93.9)/ 91.4 (82.3, 96.8)	81.3 (71.8, 88.7)/ 92.3 (84.8, 96.9)
mDoR[a] (95% CI), mo	25.7 (14.8, NE)	NR (NE, NE)
24-mo DoR rate, % (95% CI)	55.4 (41.1, 67.5)	NE
mPFS (95% CI), mo	27.5 (16.1, NE)	NR (19.4, NE)
24-mo PFS rate, % (95% CI)	52.1 (39.3, 63.5)	59.9 (47.8, 70.0)
mOS (95% CI), mo	NR (26.1, NE)	NR (NE, NE)
24-mo OS rate, % (95% CI)	65.7 (51.5, 76.6)	74.1 (62.1, 82.8)
Baseline CNS metastases, n	23	16
ORR, % (95% CI)	82.6 (61.2, 95.0)	75.0 (47.6, 92.7)

[a]In FAS; N was 70 and 91.

8506 Oral Abstract Session

Sacituzumab tirumotecan (sac-TMT) plus pembrolizumab (P) versus pembrolizumab (P) as first-line treatment for PD-L1–positive advanced non-small cell lung cancer (NSCLC): Results from the randomized phase 3 OptiTROP-Lung05 study. First Author: Caicun Zhou, Department of Oncology, Shanghai East Hospital, Tongji University, Shanghai, China

Background: Pembrolizumab has been the standard first-line treatment for PD-L1 positive advanced NSCLC. Sac-TMT, a TROP2-directed antibody-drug conjugate with a unique bifunctional linker, and PD-1/L1 inhibitors demonstrate complementary mechanisms that enhance antitumor activity in the first-line treatment of NSCLC (*Hong et al., Nat Med, 2025*). Here, we report the results from the planned interim analysis for PFS in this phase 3 OptiTROP-Lung05 study (NCT06448312). **Methods:** Eligible patients (pts) had treatment-naïve, locally advanced or metastatic NSCLC without *EGFR/ALK* alterations and positive PD-L1 expression (defined as TPS ≥1%, 22C3 assay). Pts were stratified by PD-L1 (TPS 1-49% vs ≥ 50%), histology (squamous vs non-squamous) and ECOG (0 vs 1) and then randomized (1:1) to receive sac-TMT 4 mg/kg Q2W plus P 400 mg Q6W or P 400 mg Q6W. The primary endpoint was PFS per RECIST 1.1 assessed by blinded independent central review (BICR), and the key secondary endpoint was OS. **Results:** A total of 413 pts (median age 65 yrs; 84.5% ECOG 1; 40.0% squamous; 40.0% PD-L1 TPS ≥ 50%) were randomized to receive sac-TMT + P (n = 208) or P (n = 205). As of Sep 29, 2025, the median follow-up was 10.5 months. PFS by BICR was significantly longer in the sac-TMT + P group than the P group (median, not reached vs 5.7 months; HR, 0.35; 95% CI, 0.26-0.47; $p< 0.0001$). The data for OS were not mature, and a favorable trend was observed in the sac-TMT + P group (HR, 0.55; 95% CI, 0.36-0.85). The BICR-assessed ORR was 70.2% in the sac-TMT + P group versus 42.0% in the P group. In the pre-specified PD-L1 subgroups, the HRs for PFS in pts with TPS 1-49% and TPS ≥ 50% were 0.28 (95% CI, 0.19-0.41) and 0.47 (95% CI, 0.29-0.77). In the pre-specified histology subgroups, the HRs for PFS in pts with non-squamous and squamous were 0.28 (95% CI, 0.18-0.43) and 0.44 (95% CI, 0.29-0.66). Grade ≥ 3 TEAEs were 55.3% in the sac-TMT + P group and 31.4% in the P group. Most common grade ≥3 TEAEs of special interest for sac-TMT were neutrophil count decreased (17.3%), anemia (9.1%), and stomatitis (5.3%). TEAEs led to discontinuation of sac-TMT/ pembrolizumab in 3.8%/5.3% of pts in the sac-TMT + P group while discontinuation of pembrolizumab occurred in 4.9% of pts in the P group. **Conclusions:** To our knowledge, this is the first phase 3 study to demonstrate the significant PFS benefit of an antibody-drug conjugate plus pembrolizumab in the first-line treatment of PD-L1 positive advanced NSCLC compared to pembrolizumab. The safety profile of sac-TMT + P was generally manageable and consistent with the safety profile of the components. No new safety signals were seen. These results from phase 3 OptiTROP-Lung05 study support sac-TMT + P as a potential new treatment option for this population. Clinical trial information: NCT06448312. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

LBA8507 Oral Abstract Session

A randomized, open-label, parallel-controlled phase 3 trial of benmelstobart plus chemotherapy and anlotinib for first-line treatment of advanced non-squamous non–small cell lung cancer. First Author: Yuankai Shi, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College., Beijing, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

8509 Clinical Science Symposium

Neoadjuvant almonertinib followed by chemo-immunotherapy in II-IIIb EGFR-mutant NSCLC: A single arm, phase II study (NEOVADE). First Author: Jun-Tao Lin, Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: Neoadjuvant target therapy has improved objective response rate (ORR) or major pathological response (MPR) of stage IIA-IIIB non-small cell lung cancer (NSCLC) with EGFR mutation. EGFR-TKI-induced evolution indicated a hot-tumor status in residual disease. However, the role of immunotherapy in this phrase remained unclear. Here, we present the results of a phase II, open-label study investigating the efficacy and safety of sequential almonertinib and chemo-immunotherapy (IO) in potentially resectable stage IIA-IIIB EGFR-mutant NSCLC patients. (NCT06300424). **Methods:** Untreated patients with II-IIIB NSCLC were enrolled in this study. Patients received almonertinib for 6 weeks, followed by 3 cycles of adebrelimab and chemotherapy before surgery. Primary end point was MPR, Secondary end points included pathological complete response (PCR), ORR, event-free survival (EFS), overall survival (OS) and safety. **Results:** A total of 32 patients were enrolled from Apr 2024 to Aug 2025. EGFR mutation subtype was 19del in 16 (50.0%) patients, L858R in 11 (34.4%) patients, others in 5 (15.6%) patients. All the patients completed neoadjuvant almonertinib, 30 (93.8%) patients completed 3 circles of chemo-IO and underwent surgery, R0 was achieved in 29 (96.7%) patients. ORR was 46.9% (15/32) and 59.4% (19/32) after target therapy and chemo-IO, respectively. MPR was documented in 13 (40.6%) patients, including PCR in 5 (15.6%) patients. In patients underwent resection, MRP and PCR rate were 66.7% and 33.3% in patients with PD-L1≥1%, compared with 21.4% and 0% in PD-L1 < 1% subgroup, respectively, N downstage was confirmed in 44.8% (13/29) patients. After a median follow-up of 13.5 months (interquartile range [IQR], 7.5–16.1 months), 31 (96.9%) patients were alive. Median EFS and OS were not reached. One-year EFS and OS rate was 89.5% and 95.2%, respectively. Grade ≥ 3 AEs occurred in 28 (87.5%) patients during neoadjuvant therapy. **Conclusions:** This study met its primary endpoint, indicating almonertinib followed by chemo-IO was a feasible neoadjuvant treatment in patients with resectable stage IIA-IIIB EGFR-mutant NSCLC, especially in patients with PD-L1 expression. The study was partially supported by Jiangsu Hengrui Pharmaceuticals and Hansoh Pharmaceutical Group Co. Ltd. Clinical trial information: NCT06300424. Research Sponsor: None.

Primary and secondary outcomes.

Outcomes	ITT (N=32)	Resection (N=29)
Major pathological response rate	40.6% (13/32)	44.8% (13/29)
PD-L1 < 1%	18.8% (3/16)	21.4% (3/14)
PD-L1≥1%	62.5% (10/16)	66.7% (10/15)
Complete pathological response rate	15.6% (5/32)	17.2% (5/29)
PD-L1 < 1%	0.0% (0/16)	0.0% (0/14)
PD-L1≥1%	31.3% (5/16)	33.3% (5/15)
After receiving neoadjuvant TKI		
ORR	46.9% (15/32)	44.8% (13/29)
DCR	93.8% (30/32)	96.6% (28/29)
After receiving neoadjuvant TKI+IO		
ORR	59.4% (19/32)	58.6% (17/29)
DCR	100.0% (32/32)	100.0% (29/29)

TKI: Tyrosine kinase inhibitor; IO: Immunotherapy.

8510 Clinical Science Symposium

First-line (1L) divarasib plus pembrolizumab (pembro) in advanced or metastatic *KRAS* G12C+ non–small cell lung cancer (NSCLC): Results from the Krascendo-170 study. First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Krascendo 170 (NCT05789082) is an open-label, phase Ib/II, dose-finding and -expansion study of divarasib, an oral next-generation KRAS G12C inhibitor, with/without other anti-cancer therapies in 1L *KRAS G12C*+ NSCLC. We report the primary analysis for pts receiving divarasib plus pembro in the programmed death-ligand 1 (PD-L1)-positive cohort (tumor cell [TC] ≥1%; cohort A1) and key preliminary data for the PD-L1-negative cohort (TC <1%; cohort A2). **Methods:** Eligible pts were aged ≥18 years with untreated advanced or metastatic *KRAS G12C*+ NSCLC and ECOG PS ≤1. All pts received oral divarasib once daily plus intravenous pembro 200 mg once every 3 weeks until loss of clinical benefit, disease progression, study withdrawal or unacceptable toxicity. In cohort A1, pts were randomized 1:1 to receive divarasib 200 or 400 mg. In cohort A2, all pts received divarasib 400 mg. We present data only from pts receiving divarasib 400 mg. Primary endpoints were safety and tolerability. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS) and duration of response (DOR; all investigator-assessed per RECIST v1.1). **Results:** At data cutoff (Oct 29, 2025), 59 pts were enrolled to receive divarasib 400 mg in cohort A1 and 23 pts in cohort A2. In cohort A1 (median duration of divarasib treatment 10.6 months [range 0.3–24.3]), treatment-related AEs (TRAEs; divarasib- or pembro-related) were reported in 98% of pts; 65% of pts had grade (gr) 3/4 TRAEs and 0% had gr 5 TRAEs (Table). The most common TRAEs were diarrhea (75%; gr 3/4 16%), nausea (64%; gr 3/4 2%), vomiting (49%; gr 3/4 2%), ALT increase (49%; gr 3/4 20%) and AST increase (47%; gr 3/4 18%). In cohort A1, confirmed ORR was 73%, no patients had progressive disease as their best response, median DOR was not reached and median PFS was 19.3 months (95% CI 12.4–not estimable [NE]). In cohort A2 (median duration of divarasib treatment 2.8 months [range 0.5–8.8]), TRAEs were reported in 100% of pts (65% gr 3/4; 0% gr 5) and unconfirmed ORR was 70%. **Conclusions:** In Krascendo 170, divarasib 400 mg once daily plus pembro had a manageable safety profile. Promising efficacy was shown in pts with advanced *KRAS G12C*+ NSCLC in both PD-L1- positive and -negative cohorts. A global, phase III trial investigating divarasib 400 mg in 1L advanced *KRAS G12C*+ NSCLC (Krascendo 2; NCT06793215) is currently enrolling. Clinical trial information: NCT05789082. Research Sponsor: This study is sponsored by F. Hoffmann-La Roche Ltd.; Third-party medical writing assistance, under the direction of the authors, was provided by Tahmina S. Alam, MA, and Rebecca Benatan, BSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

	Cohort A1, n=59*,†	Cohort A2, n=23
Median follow-up, months	12.2	3.4
Safety, n (%)		
Any gr TRAE	54 (98)	23 (100)
Gr 3/4 TRAE / serious TRAE	36 (65) / 19 (35)	15 (65) / 3 (13)
TRAE leading to	28 (51) / 40 (73)	13 (57) / 14 (61)
Dose reduction / interruption	14 (25)	3 (13)
Discontinuation		
ORR, % (95% CI)	73 (60–84)	70‡ (47–87)
Median PFS, months [95% CI]	19.3 [12.4–NE]	–

*3 pts did not receive treatment, 1 pt received divarasib 200 mg; †safety analysis comprised all pts treated with divarasib 400 mg (n=55); ‡unconfirmed.

8511 Clinical Science Symposium

Elisrasib (D3S-001), a next-generation GDP-bound KRAS G12C inhibitor, as first-line therapy for *KRAS* G12C mutation–positive non–small cell lung cancer (NSCLC). First Author: Shun Lu, Shanghai Chest Hospital, Shanghai, Jiao Tong University, School of Medicine, Shanghai, China

Background: Elisrasib (D3S-001) is a next-generation KRAS G12C inhibitor (G12Ci) designed to improve target engagement (TE) efficiency and overcome growth factor-induced nucleotide exchange. This unique MoA distinguishes elisrasib from prior G12Ci and has demonstrated robust and durable anti-tumor activity in PDX models, and in combination with immunotherapy (IO) in immunocompetent models. Current ongoing phase 1/2 trial (NCT05410145) evaluates elisrasib as monotherapy (mono) or combination (combo) with pembrolizumab as first line (1L) therapy for advanced NSCLC harboring G12C mutation. **Methods:** Treatment naïve patients (pts) with G12C mutant advanced stage NSCLC were eligible. Elisrasib is administered 600mg QD orally in a 21-day cycle as mono or combo with pembrolizumab i.v. 200mg Q3W. The key objectives included safety and efficacy. ctDNA dynamic was analyzed by Guardant360 CDx or OncoCompass Target panels. **Results:** As of 06 Jan 2026, 43 pts and 52 pts received mono and combo. Median study follow up was 8.5m and 5.7m in mono and combo, respectively. In mono, 41 (PD-L1 TPS [22C3]: 21 <1% and 20 ≥1%) out of 43 pts were efficacy evaluable. Overall ORR was 78.0% (32/41). Subgroup ORRs in TPS <1% and ≥1% were 76.2% and 80.0%, respectively. Median PFS and DOR were immature. 6m PFS rate was 68.9% and 6m DOR rate was 77.2%. Above results provide first time evidence of G12Ci monotherapy in 1L NSCLC. In combo, 48 (PD-L1 TPS [22C3]: 17 <1%, 11 1-49%, and 20 ≥50%) out of 52 pts were efficacy evaluable. Overall ORR was 81.2% (39/48). Subgroup ORRs in TPS <1%, 1-49%, and ≥50% were 70.6%, 72.7% and 95.0%, respectively. Median PFS and DOR in the overall combo population were immature. 6m PFS rate was 74.6% and 6m DOR rate was 80.5%. Toxicity profile is summarized in Table. Baseline ctDNA G12C+ was detected in 90% (37/41) of mono and 80% (37/46) of combo. 35 mono and 25 combo pts completed on-treatment ctDNA analysis, with 83% and 100% achieved molecular response (≥90% G12C MAF reduction), respectively. PK at 600mg QD achieved C_{trough} exposure of ~5nM and ~3nM with mono and combo, respectively, with overlapping variabilities at steady state, both well above the required exposure (1nM) for complete TE. **Conclusions:** Both elisrasib monotherapy and in combination with pembrolizumab show strong efficacy and good tolerability as 1L treatments for G12C-mutant NSCLC, warrant for randomized study to evaluate elisrasib as a potential new standard of care. Clinical trial information: NCT05410145. Research Sponsor: D3 Bio.

TRAEs*	1L NSCLC Mono (N=43)	1L NSCLC Combo (N=52)
Any Grade	41 (95.3%)	48 (92.3%)
≥G3	3 (7.0%)	17 (32.7%)
LFT TRAEs* by PT (≥G3)		
ALT increased	0	4 (7.7%)
AST increased	0	3 (5.8%)

*TRAEs for combo cohort is related to elisrasib and/or pembrolizumab.

8512 Rapid Oral Abstract Session

Efficacy and safety of HLX43 (anti–PD-L1 ADC) in patients with advanced non–small cell lung cancer. First Author: Jie Wang, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: HLX43 (a PD-L1 ADC) has demonstrated encouraging efficacy with a manageable safety in a phase 1 study. Here, we present the pooled findings from patients with NSCLC in a phase 1 study (HLX43-FIH101) as well as a global phase 2 study investigating HLX43 in NSCLC (HLX43-NSCLC201). **Methods:** The phase 1 study included a dose-escalation phase in patients with advanced solid tumors (0.5–4.0 mg/kg Q3W), followed by a dose-expansion phase in patients with advanced or metastatic NSCLC at doses of 2.0, 2.5, and 3.0 mg/kg Q3W. The phase 2 study was conducted in NSCLC and comprised two parts: Part A was dose-exploration for patients who had failed prior first-line therapy and had no actionable genomic alterations, to receive HLX43 at 2.0 or 2.5 mg/kg Q3W; Part B was dose-expansion in which patients received HLX43 at the recommended dose determined from Part A. This analysis integrated data from heavily pretreated NSCLC patients enrolled across both studies. Efficacy and safety outcomes were evaluated in the pooled population. **Results:** As of December 31, 2025, 205 patients were enrolled and received HLX43 at 1 mg/kg (n = 3), 2 mg/kg (n = 89), 2.5 mg/kg (n = 85), 3 mg/kg (n = 23), and 4 mg/kg (n = 5). Patients received a median of 2 lines of prior antitumor therapy (range, 1–9). Among the 161 response-evaluable patients (2, 69, 64, 21, and 5 in the 1, 2, 2.5, 3, and 4 mg/kg groups, respectively), the investigator-assessed ORR was 31.1%. In the 2.0 mg/kg group, investigator-assessed ORR was 36.4% for squamous NSCLC (n = 33); among these patients, ORR was 40.0% for those who previously failed docetaxel (n = 15). ORR was 47.4%, and 50.0% for patients with EGFR-wildtype (n = 19), and EGFR-mutant (n = 16) nonsquamous NSCLC receiving HLX43 at 2.5 mg/kg. Biomarker exploratory analyses showed that efficacy was not associated with PD-L1 expression, with ORRs of 30.1% and 32.1% in patients with PD-L1-positive (n = 83) and PD-L1-negative tumors (n = 78), respectively. Overall, 199 (97.1%) patients experienced treatment-related adverse events (TRAEs), of whom 88 (42.9%) had grade ≥3 in severity. Most common Grade ≥3 TRAEs (incidence ≥10%) included lymphocyte count decreased (n = 47, 22.9%), white blood cell count decreased (n = 27, 13.2%), anemia (n = 25, 12.2%), and neutrophil count decreased (n = 23, 11.2%). TRAEs led to treatment discontinuation in 17 (8.3%) patients. **Conclusions:** HLX43 exhibited promising efficacy in patients with heavily pretreated advanced NSCLC, regardless of histology subtypes, and PD-L1 expression, along with manageable tolerability. Further investigation is warranted. Clinical trial information: NCT06115642 (HLX43-FIH101-phase 1 study), NCT06907615 (HLX43-NSCLC201- phase 2 study). Research Sponsor: Shanghai Henlius Biotech, Inc.

8513 **Rapid Oral Abstract Session**

Phase 2 data from ROSETTA Lung-02, a global randomized phase 2/3 trial of pumitamig (PD-L1 × VEGF-A bsAb) + chemotherapy in 1L NSCLC. First Author: Solange Peters, Oncology Department, Centre Hospitalier Universitaire Vaudois, Lausanne University, Lausanne, Switzerland

Background: Pumitamig (BNT327/BMS986545) is an investigational PD-L1 × VEGF-A bsAb designed to restore effector T-cell function by binding PD-L1 and localizing VEGF-A neutralization within the tumor microenvironment. We present the prespecified interim analysis of the Phase 2 dose-optimization part of the global Phase 2/3 ROSETTA Lung-02 trial (NCT06712316) evaluating the recommended Phase 3 dose of pumitamig + chemotherapy in 1L NSCLC. **Methods:** The Phase 2 part of ROSETTA Lung-02 enrolled pts with treatment-naïve advanced NSCLC, no actionable genomic alterations, regardless of PD-L1 status, ECOG PS ≤1, and ≥1 measurable lesion per RECIST v1.1 into two substudies based on histology (nonsquamous [NSQ] and squamous [SQ]). Pts were randomized 1:1 to 1400 mg (dose level [DL] 1) or 2000 mg (DL2) pumitamig + histology-specific chemotherapy Q3W (NSQ: carboplatin + pemetrexed; SQ: carboplatin + paclitaxel). Primary endpoints were safety, overall response rate (ORR), and best percentage change in tumor size from baseline. Key secondary endpoints include duration of response (DOR) and disease control rate (DCR). **Results:** The Phase 2 part enrolled 44 pts (NSQ n=23; SQ n=21; data cutoff Nov 21, 2025). Median age was 66 y (range: 41–87), and 27 (61.4%) pts had ECOG PS 1. Among 40 response-evaluable pts, best overall response was CR in 2 pts, PR in 26, and SD in 12, for an ORR of 70.0% (28/40; confirmed ORR was 52.5% [21/40], 5 pending confirmation) and DCR of 100%. DOR data were not mature at the time of data cutoff. Median best change in tumor volume was -38.2% (NSQ -36.6%; SQ -39.7%). In NSQ NSCLC, ORR was 66.7% (14/21) and, by pumitamig dose, it was 72.7% for DL1 (8/11) and 60.0% for DL2 (6/10). In SQ NSCLC, ORR was 73.7% (14/19), 81.8% for DL1 (9/11) and 62.5% for DL2 (5/8). Central PD-L1 levels were available for 35 pts (PD-L1 <1% [n=20], 1–49% [n=9], ≥50% [n=6]), with activity across PD-L1 levels. Circulating tumor DNA dynamics were assessed. Median treatment duration was 4.5 mo (range: 0.1–8.8) with 30 (69.8%) pts still on treatment. In the safety set (N=43), 40 (93.0%) pts had a treatment-related adverse event (TRAE). Grade ≥3 TRAEs were reported in 19 (44.2%) pts and were considered pumitamig-related in 8 (18.6%). Pumitamig-related TRAEs led to treatment discontinuation in 2 (4.7%) pts. Immune-related AEs (irAEs) occurred in 6 (14.0%) pts and grade ≥3 irAEs in 1 (2.3%). Bleeding events were reported in 7 (16.3%) pts, with only 1 event being grade 3. **Conclusions:** In these first global data for a PD-(L)1 × VEGF-A bsAb in 1L NSCLC regardless of PD-L1 status, pumitamig + chemotherapy showed encouraging efficacy with a manageable safety profile. Efficacy of the lower dose + chemotherapy was particularly encouraging (ORR 72.7% in NSQ, 81.8% in SQ) and is being evaluated vs pembrolizumab + chemotherapy in the ongoing Phase 3 part of the trial. Clinical trial information: NCT06712316. Research Sponsor: BioNTech.

8514 **Rapid Oral Abstract Session**

Updated results from a phase 2 trial of SSGJ-707 (PF-08634404), a PD-1/VEGF bispecific antibody, as monotherapy in patients with advanced non-small cell lung cancer (NSCLC). First Author: Lin Wu, Hunan Cancer Hospital, Changsha, Hunan, China

Background: SSGJ-707 is a fully human IgG4 bispecific antibody that simultaneously binds PD-1 and VEGF. In the phase 2 study (NCT06361927), SSGJ-707 monotherapy demonstrated promising efficacy and manageable safety in first-line NSCLC with PD-L1 tumor proportion score (TPS) ≥1%. We report updated results from this study with the FDA-aligned pivotal dose of 10 mg/kg Q3W. **Methods:** Patients (pts) with treatment-naive advanced NSCLC (without actionable genomic alterations and PD-L1 TPS ≥1%) were enrolled to receive SSGJ-707 at 5 mg/kg, 10 mg/kg, 20 mg/kg, or 30 mg/kg Q3W until disease progression or unacceptable toxicity. Primary endpoint is objective response rate (ORR) per RECIST 1.1. Secondary endpoints include safety, duration of response (DOR), progression-free survival (PFS), overall survival (OS), and correlation between circulating tumor DNA (ctDNA) and efficacy. **Results:** As of Nov 28, 2025, 83 pts received ≥1 dose of SSGJ-707, of which 27.7% remained on treatment. In pts treated with the FDA-aligned dose of 10 mg/kg Q3W (n = 34), 41.2% remained on treatment and median duration of follow-up was 15.2 mos (95% CI, 14.3-16.2). In the 10 mg/kg group, confirmed ORR was 67.6% (95% CI, 49.5-82.6%), median DOR was not reached (NR; 95% CI, 10.9-NR), median PFS was 12.4 mos (95% CI, 8.2-NR), and median OS was NR (95% CI, 14.8-NR). High efficacy was noted for the 10 mg/kg Q3W dose irrespective of histology and TPS (table). Among all treated pts (n = 83), treatment-related adverse events (TRAEs) occurred in 92.8%; grade ≥3 TRAEs occurred in 42.2%. The most common grade ≥3 TRAEs (≥5%) were pneumonia (8.4%), hypertension (7.2%), and hemoptysis (6.0%). VEGF-related AEs occurred in 62.7% (grade ≥3, 18.1%) of pts; immune-mediated AEs occurred in 37.3% (grade ≥3, 8.4%). In the 10 mg/kg group, TRAEs led to permanent discontinuation in 1 pt (2.9%) and none had grade 5 TRAE. In pts with detectable ctDNA at baseline (n = 65), median PFS was NR (95% CI, 12.4-NR) in pts with nondetectable ctDNA at C3D1 (n = 19) compared to 7.6 mos (95% CI, 5.6-9.4) in those with detectable ctDNA at C3D1 (n = 33). **Conclusions:** With longer follow-up, SSGJ-707 monotherapy continues to show promising efficacy with a manageable safety profile in pts with treatment-naive advanced NSCLC across histology and PD-L1 expression subgroups. These results supported initiation of the phase 3 study (Symbiotic-Lung-01) of SSGJ-707 with platinum-based chemotherapy in 1L squamous (SQ) and nonsquamous (NSQ) NSCLC irrespective of TPS (NCT07222566). Clinical trial information: NCT06361927. Research Sponsor: Pfizer.

	n=34	Confirmed ORR, % (95% CI)	DOR, mos, median(95% CI)	PFS, mos, median (95% CI)	OS, mos, median(95% CI)
Histology					
SQ	12	75.0(42.8-94.5)	6.2 (4.1-NR)	8.9 (2.7-NR)	NR(4.9-NR)
NSQ	22	63.6(40.7-82.8)	NR(10.9-NR)	12.4 (8.2-NR)	NR(14.8-NR)
TPS					
1%-49%	21	61.9(38.4-81.9)	NR(4.1-NR)	9.6 (7.6-NR)	NR(12.1-NR)
≥50%	13	76.9(46.2-95.0)	NR(5.6-NR)	12.4(5.9-NR)	NR(NR-NR)

8515 **Rapid Oral Abstract Session**

Tremelimumab (T) + durvalumab (D) + chemotherapy (CT) vs pembrolizumab (P) + CT in 1L non-squamous (NSQ) metastatic NSCLC (mNSCLC) with *STK11*, *KEAP1*, and/or *KRAS* mutations (mut): Interim analysis (IA) of the phase 2b TRITON study. First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Pts with *STK11*, *KEAP1* and/or *KRAS*-mutated mNSCLC may benefit from the addition of anti-CTLA-4 to anti-PD-(L)1-based chemo-immunotherapy. In the phase 3 POSEIDON study, 1L T+D+CT significantly improved OS vs CT in pts with mNSCLC. Exploratory analyses showed sustained OS improvement with T+D+CT vs CT in subgroups with *STK11*, *KEAP1* and/or *KRAS* mut; in each mut subgroup, magnitude of OS benefit with T+D+CT vs CT was numerically greater than with D+CT vs CT. The phase 2b, open-label, multicenter, US-based TRITON study is comparing 1L T+D+CT vs P+CT in pts with NSQ mNSCLC and *STK11, KEAP1* and/or *KRAS* mut. Here we report results of a planned IA (data cutoff [DCO] 15 mo after 1st pt randomized) of objective response rate (ORR), duration of response (DoR) and safety. **Methods:** Pts with treatment [tx]-naïve, *EGFR*/*ALK* wild-type, NSQ mNSCLC and *STK11*, *KEAP1* and/or *KRAS* mut (ECOG PS 0/1) were randomized 1:1 to T+D+CT or P+CT. T+D+CT arm: T 75 mg + D 1500 mg + pemetrexed-platinum Q3W for 4 cycles, then maintenance D + pemetrexed Q4W until disease progression (PD); additional doses of T given at week 16 and, optionally, at mo 24. P+CT arm: P 200 mg + pemetrexed-platinum Q3W for 4 cycles, then maintenance P + pemetrexed Q3W until PD, for up to 24 mo. Randomization was stratified by mut type and tumor PD-L1 expression (≥1% vs <1%). The primary endpoint is PFS (RECIST v1.1; investigator-assessed) with planned sample size ~100 pts. Key secondary endpoints include OS, ORR, DoR and safety. **Results:** At DCO (12 Nov 2025), 41 pts were randomized to T+D+CT and 43 to P+CT. Overall, 27.4%, 21.4% and 78.6% of pts had *STK11*, *KEAP1* and *KRAS* mut (not mutually exclusive); 39.3% had PD-L1 <1%. In the T+D+CT vs P+CT arms, median (range) age was 69 (47–82) vs 69 (51–86) y, 48.8% vs 62.8% pts were male, 70.7% vs 72.1% were White and 14.6% vs 20.9% Black or African American, 78.0% vs 62.8% had ECOG PS 1. Median (range) safety follow-up for D/P was 5.6 (0.0–14.0)/5.1 (0.0–17.5) mo; median no. of D/P doses was 8/7. ORR (95% CI) was 39.0% (24.1–54.0) in the T+D+CT arm vs 34.9% (20.6–49.1) in the P+CT arm [unconfirmed ORR 48.8% (33.5–64.1) vs 41.9% (27.1–56.6)]. Median DoR (95% CI) was not reached (6.3–NR) vs 6.4 (4.2–NR) mo; 100% vs 58.3% pts remained in response at 6 mo. In *KRAS* mut-only pts (n=52; exploratory), ORR was 48.0% (12/25) with T+D+CT vs 33.3% (9/27) with P+CT. The sponsor remains blinded to PFS at this IA. With T+D+CT vs P+CT, 41.5% vs 41.9% of pts had Grade 3/4 AEs possibly related to tx (TRAEs); 2.4% vs 4.7% had TRAEs leading to tx discontinuation and 0% vs 2.3% had TRAEs leading to death. **Conclusions:** At IA, ORR and DoR results from the prospective TRITON study support a role for the addition of anti-CTLA-4 (T) to 1L anti-PD-L1 (D) + CT in pts with *STK11*, *KEAP1* and/or *KRAS*-mutated mNSCLC. Safety was similar in the two arms and consistent with known safety profiles. Clinical trial information: NCT06008093. Research Sponsor: AstraZeneca.

8516 **Rapid Oral Abstract Session**

A phase 1/2 study of TSN1611, a highly selective oral KRAS G12D inhibitor, in solid tumors: Efficacy and safety in *KRAS* G12D–mutated NSCLC patients. First Author: Yongfeng Yu, Department of Medical Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, China

Background: There remains an unmet clinical need for effective therapies targeting KRAS G12D mutation in patients (pts) with advanced non-small cell lung cancer (NSCLC) refractory to prior treatments. TSN1611 is a novel oral small-molecule inhibitor designed to bind both the active GTP-bound (ON) and inactive GDP-bound (OFF) conformations of KRAS G12D, providing a differentiated mechanism of action and broad antitumor activity in preclinical models. **Methods:** This multi-regional Phase 1/2 study enrolled pts with advanced solid tumors harboring KRAS G12D mutation. Phase 1a dose-escalation part evaluated TSN1611 at 50–1200 mg twice daily (BID). A subsequent Phase 1b dose-optimization part evaluated 800 mg and 1200 mg BID. In Phase 2, efficacy is being further explored across multiple tumor types at the recommended Phase 2 dose of 1200 mg BID. **Results:** As of Jan 23, 2026, 117 pts received TSN1611 across all dose levels in Phase 1/2. Tumor types included NSCLC (n = 26), pancreatic adenocarcinoma (n = 50), colorectal cancer (n = 35), and others (n = 6). Median age was 62 yrs (range 22-81). The median prior lines of systemic therapy were 2 (range 0-7). The most common (≥10%) treatment-related adverse events (TRAEs) in all treated pts were diarrhea (53.0%), nausea (48.7%), vomiting (46.2%), anemia (17.9%), decreased white blood cell count (16.2%), decreased neutrophil count (13.7%), increased ALT (12.8%), decreased appetite (12.0%), decreased platelets (11.1%), fatigue and increased AST (10.3% each). Grade 3 TRAEs occurred in 9.4% of pts; these were all single events (0.9% each) except for anemia, diarrhea, and asymptomatic lipase elevation, which occurred in 1.7% of pts each. TRAEs led to dose interruption in 17.1% pts and dose reduction in 7.7% pts; no treatment discontinuations due to TRAEs occurred. Among 26 NSCLC pts, all had stage IV metastatic disease; 22 (84.6%) had received prior chemotherapy and/or PD-1/PD-L1 inhibitors, and 9 (34.6%) had received prior anti-angiogenic therapy. Among 20 response-evaluable NSCLC pts treated with TSN1611 at 600–1200 mg BID, 10 achieved partial response, 8 had stable disease, and 2 had progressive disease, yielding an objective response rate (ORR) of 50% (95% CI 27.2–72.8) and a disease control rate (DCR) of 90% (95% CI 68.8–98.3). Median time to response was 1.4 months (range 1.2–3.5). In addition to extracranial responses, rapid intracranial responses were observed. Median progression-free survival (PFS) was not mature yet (range 1.3+ to 12.9+ months), with a 9-month PFS rate of 54.5% (95% CI 24.4–77.0). Enrollment continues and updated data will be presented at the conference. **Conclusions:** TSN1611 demonstrated a favorable safety profile and clinically meaningful antitumor activity in pts with KRAS G12D mutated NSCLC. Further development of TSN1611 as monotherapy and in combination regimens is ongoing. Clinical trial information: NCT06385925. Research Sponsor: Tyligand Pharmaceuticals (Suzhou) Limited.

8517 **Rapid Oral Abstract Session**

Prophylactic peptide vaccine targeting resistance mutations in advanced ALK-positive lung cancer: Primary analysis from the ARCHER trial. First Author: Michael R. Conroy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD

Background: Acquired resistance to targeted therapy remains a major challenge in ALK-positive NSCLC and is often mediated by mutations in the ALK kinase domain. Prophylactic immune targeting of common ALK resistance mutations represents a novel strategy to delay or prevent the emergence of ALK inhibitor resistance. **Methods:** We conducted a first-in-human phase 1b clinical trial of a prophylactic peptide vaccine (ALK-Vac) in advanced ALK-positive NSCLC patients without progression on standard-of-care tyrosine kinase inhibitor (TKI) therapy. Patients continued their ALK TKI and received ALK-Vac, consisting of synthetic long peptides targeting seven common ALK resistance mutations (I1171T, I1171N, I1171S, L1196M, G1202R, D1203N, E1210K) plus poly-ICLC adjuvant. ALK-Vac was administered subcutaneously on days 1, 4, 8, 15, and 22 (priming) and weeks 12 and 20 (boost). Primary objectives were safety and vaccine-specific T cell responses assessed by IFN-γ ELISpot. Exploratory objectives included molecular and immune-phenotype dynamics assessed by ultrasensitive cell-free DNA (cfDNA) duplex sequencing and CyTOF mass cytometry. **Results:** Fifteen patients were enrolled and all completed the planned ALK-Vac regimen. Most patients (13/15, 87%) were receiving first-line TKI therapy. Concomitant TKIs included alectinib (7/15, 47%), lorlatinib (5/15, 33%), and brigatinib (3/15, 20%). At enrollment, median TKI duration was 43.7 months (range 4.6-74.2) and 67% of patients had no measurable disease. Treatment-related adverse events (TRAEs) were primarily grade 1 (93% of patients); most commonly injection site reactions (93%), fatigue (60%), and flu-like symptoms (40%). No grade $\geq$ 3 TRAEs were observed. T cell responses ($\geq$2-fold increase in SFU) were detected in 71% (10/14) of evaluable patients, with a median 11.9-fold increase. Responses were observed to G1202R, L1196M, and D1203N (each 10/14, 71%), E1210K (9/14, 64%), and I1171N/S/T (each 7/14, 50%). With a median follow-up of 11.5 months, the disease control rate was 93% (14/15). One patient who achieved robust immune response against multiple resistance mutations developed oligoprogression on alectinib 8.5 months after starting ALK-Vac; molecular profiling of this lesion identified an emergent KRAS G12D mutation without detectable ALK resistance mutation. **Conclusions:** ALK-Vac was well-tolerated and induced vaccine-specific T cell responses in a minimal residual disease setting, demonstrating feasibility of prophylactic targeting of ALK resistance mutations as an adjunct to TKI therapy and supporting a broader immune-interception framework potentially applicable to other oncogene-driven NSCLC. Comprehensive cfDNA and immune-phenotyping analyses will be reported. Clinical trial information: NCT05950139. Research Sponsor: None.

LBA8518 **Rapid Oral Abstract Session**

Phase 3 clinical trial of the combination of erlotinib plus ramucirumab compared with osimertinib in untreated advanced or recurrent non-small cell lung cancer with EGFR L858R mutation: The REVOL858R trial (WJOG14420L). First Author: Naoki Haratake, Department of Thoracic Oncology, National Hospital Organization, Kyushu Cancer Center, Fukuoka, Japan

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

8519 **Rapid Oral Abstract Session**

Safety and efficacy results of the phase 2 study of silevertinib (BDTX-1535) in treatment-naïve patients with non-small cell lung cancer with non-classical EGFR mutations. First Author: Julia K. Rotow, Dana-Farber Cancer Institute, Boston, MA

Background: Non-classical mutations (NCM) of epidermal growth factor receptor (EGFR) represent a broad group of oncogenic mutations in non-small cell lung cancer (NSCLC), often associated with resistance to osimertinib (e.g., P-loop and αC-helix compressing [PACC] mutations). Patients (pts) with NCM have inferior clinical outcomes with a high incidence of CNS metastases (CNSm). Silevertinib (BDTX-1535) is a fourth-generation, covalent EGFR TKI with high CNS penetrance targeting both EGFR classical mutations and NCM. The antitumor activity and safety of silevertinib in pts with advanced NSCLC were evaluated in a Phase 2 trial (NCT05256290). **Methods:** Pts with advanced EGFR NCM NSCLC who received no prior systemic therapy were enrolled (Cohort 3) based on a local molecular test. Silevertinib 200 mg was administered orally once daily. The primary endpoint of objective response rate (ORR) was assessed using RECIST v1.1. CNS ORR was assessed using Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) in pts with no prior CNS therapy. Secondary endpoints include progression-free survival (PFS), duration of response (DOR), disease control rate (DCR), and safety. **Results:** From February 2024 to July 2025, 43 pts with 35 unique NCMs (including 25 pts with PACC mutations) were enrolled in Cohort 3: median age 70.0 years, 72% female, 74% white, and 42% never smoked cigarettes. As of November 3, 2025, median follow-up was 7.2 months. ORR by RECIST v1.1 is shown in the table. Sixteen pts (37%) had CNSm, including 7 pts (16%) with measurable CNS disease. RANO-BM CNS response was 86% (n=6/7). Complete clearance of EGFR VAF ctDNA was observed in 21/26 (81%) evaluable pts. Serious treatment-related adverse events (TRAEs) were reported in 5 pts (12%), and 4 pts (9%) discontinued treatment due to TRAEs. The most common TRAEs included rash (19%, grade 3), diarrhea (19%, grade 3), stomatitis (9%, grade 3), and paronychia (5%, grade 3). While 77% of pts had a dose reduction, 19/22 (86%) patients with a radiographic response maintained or deepened their response after dose reduction, including all patients with CNS response. **Conclusions:** Silevertinib demonstrated robust antitumor activity in treatment-naïve pts with a broad spectrum of NCM EGFR driver mutations with high intracranial activity in pts with brain metastases. The safety profile was consistent with the known AEs of the EGFR TKI class. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

Data as of November 3, 2025	N	ORR n (%) 95% CI	DCR n (%) 95% CI
ITT Population*	43	26 (60) (44.4, 75.0)	39 (91) (77.9, 97.4)
PACC mutations	25	14 (56) (34.9, 75.6)	22 (88) (68.8, 97.5)
Compound mutations†	16	11 (69) (41.3, 89.0)	15 (94) (69.8, 99.8)

*No pts with classical (E746_A750del or L858R) mutations were enrolled.
†Presence of $\geq$ 2 NCMs.
As of December 27, 2025, the 6-month PFS rate was 86% overall and 80% in pts with CNSm; available PFS and DOR data will be presented.

8520 **Rapid Oral Abstract Session**

DZD6008, a fourth-generation EGFR TKI, in pretreated NSCLC patients with *EGFR* C797X mutations: Results from phase 1/2 studies. First Author: Mengzhao Wang, Peking Union Medical College Hospital, Beijing, China

Background: Patients with EGFR-mutant NSCLC whose disease progresses on or after 3rd generation EGFR TKI treatment often acquire resistance mutations, among which EGFR C797X is one of the most frequently reported. DZD6008 is a 4th generation EGFR TKI, designed to target classical EGFR sensitizing mutations (L858R/19del), as well as resistant double (T790M and L858R/19del) and triple mutations (C797X, T790M and L858R/19del), with preclinical data showing high selectivity over wild-type EGFR and other kinases and full blood-brain-barrier (BBB) penetration. Here we report results in pretreated NSCLC patients with EGFR C797X mutations (C797X+) from phase 1/2 studies. **Methods:** TIAN-SHAN1 (NCT06905197) and TIAN-SHAN2 (NCT06813365; CTR20241790) are ongoing, multicenter phase 1/2 studies evaluating the safety, tolerability, and anti-tumor activity of DZD6008 in EGFR-mutant NSCLC patients, conducted in the US/Australia and China, respectively. The efficacy endpoints include objective response rate (ORR), duration of response (DoR) and progression-free survival (PFS) by investigator per RECIST v1.1, and safety endpoints include treatment-related adverse events (TRAEs) per CTCAE 5.0. **Results:** As of December 19, 2025, a total of 24 patients with confirmed C797X+ NSCLC were treated with once daily (QD) oral DZD6008 (20 mg, n=1; 40 mg, n=13; 60 mg, n=10), and had at least 1 post-baseline tumor assessment. The median age was 66.5 years, 58.3% were female, 91.7% were Asian, 58.3% had ECOG PS of 1. All patients had metastatic disease upon study entry and received median 2 (range 1 - 6) lines of prior therapies. Across all dose levels, tumor shrinkage was observed in 75% of patients, with an ORR of 41.7%. Intracranial anti-tumor activity was observed in patients with baseline brain metastasis. The doses of 40 mg and 60 mg QD were defined as the recommended phase 2 doses (RP2Ds). The ORRs were 23.1% and 60.0% at these two dose levels, respectively. The median DoR and median PFS were not reached for either dose. The 9-month PFS rates were 54.5% and 64.8%, respectively. DZD6008 was well tolerated at the doses evaluated, with no dose limiting toxicities observed. The majority of TRAEs were grade 1 or 2. The TRAEs with grade $\geq$3 included lymphocyte count decreased (8.3%), anemia, malaise, fatigue and amylase increased (all 4.2%). There were no Grade 5 TRAEs. **Conclusions:** DZD6008 demonstrated promising and durable anti-tumor activity in patients with EGFR C797X+ NSCLC with a manageable safety profile, supporting its potential use as a later line treatment option after 3rd generation EGFR TKI failure. The updated data will be presented at the meeting. Clinical trial information: NCT06905197, NCT06813365. Research Sponsor: None.

8521 Poster Session

Amivantamab in *EGFR*-mutated NSCLC with refractory brain or leptomeningeal metastases: A multi-center real-world study. First Author: Chang Lu, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: The central nervous system (CNS), particularly after progression on third-generation EGFR TKIs, represents a common yet challenging scenario. While recent trials establish amivantamab-lazertinib for EGFR-mutant NSCLC, their real-world applicability is limited by patient complexity and access barriers, highlighting an urgent need for flexible, real-world solutions. **Methods:** To evaluate the intracranial efficacy of amivantamab, used as monotherapy or in combination, we conducted a multi-center, retrospective study of patients with EGFR-mutated NSCLC and brain parenchymal metastases (BM) and/or leptomeningeal metastases (LM) treated with amivantamab monotherapy or combination based on routine clinical practice. The cohort included two key populations: heavily pretreated patients with sensitizing exon19del/L858R mutations after progression on third-generation EGFR TKIs, and treatment-limited patients with atypical mutations. Efficacy endpoints included intracranial progression-free survival (PFS) and intracranial objective response rate (ORR) by RANO-BM and/or RANO-LM. Exploratory endpoints included symptom improvement, and longitudinal cerebrospinal fluid (CSF) biomarker dynamics. **Results:** Thirty-one patients from seven centers were included (BM, n=13; BM+LM, n=18). Most (25/31, 80.6%) harbored EGFR sensitizing mutations and had progressed on third-generation EGFR TKIs; six (19.4%) carried atypical EGFR mutations. Over half (17/31, 54.8%) had received ≥4 prior lines. Amivantamab monotherapy was received in 10/31 patients (32.3%). Median intracranial PFS was 10.3 months (95% CI, 4.5-16.1). Among 24 evaluable patients, intracranial ORR was 25.0% (n=6), and disease control rate was 91.7% (n=22). CNS-related symptoms improved in 26/31 (83.9%). CSF analyses showed decreased pressure and CEA, reduced EGFR amplification, and clearance of EGFR C797S. **Conclusions:** In real-world settings, amivantamab-based regimens demonstrate promising intracranial efficacy in EGFR-mutated NSCLC patients with refractory brain or leptomeningeal metastases. These findings support the use of amivantamab as a viable therapeutic strategy in this challenging population and suggest that CSF biomarkers can serve as a valuable tool for monitoring treatment response. Research Sponsor: National Natural Science Foundation of China.

8522 Poster Session

Sigvotatug vedotin (SV), an investigational integrin beta-6 (IB6)—directed antibody-drug conjugate (ADC), plus pembrolizumab: Updated results from the phase 1 study (SGNB6A-001). First Author: Jesus Corral Jaime, Hospital Universitario de Jerez, Cádiz, Spain

Background: IB6 is overexpressed in many tumors, such as non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). SV, an IB6-directed ADC, demonstrated encouraging antitumor activity and manageable safety as monotherapy or in combination with pembrolizumab (SV+P) in advanced NSCLC (aNSCLC) in the ongoing phase 1 SGNB6A-001 study. We report updated results for SV+P. **Methods:** SGNB6A-001 (NCT04389632) is an open-label, multicenter, dose-escalation and -expansion study evaluating safety, pharmacokinetics, and antitumor activity of SV. SV+P is being evaluated in safety and expansion cohorts of treatment-naive locally advanced, unresectable, or metastatic NSCLC across PD-L1 scores and HNSCC CPS ≥1. Additional cohorts currently enrolling are not included in this analysis. We describe patients (pts) who received SV 1.8 mg/kg AiBW (adjusted ideal body weight) IV Q2W and P 400 mg IV Q6W. Primary endpoint is safety; secondary endpoints include efficacy, such as confirmed objective response rate (cORR) per RECIST v1.1 by investigator. **Results:** 71 pts across cohorts received ≥1 SV+P dose (37 aNSCLC, 33 HNSCC, 1 esophageal cancer). As of Sep 30, 2025, 34 pts were on treatment. Overall, any-grade (Gr) and Gr ≥3 treatment-emergent adverse events (TEAEs) occurred in 96% and 59% of pts, respectively; treatment-related any-Gr and Gr ≥3 TEAEs occurred in 85% and 44% of pts, respectively. Most common TEAEs (> 30%) were alopecia, decreased appetite, fatigue, and nausea. In the expansion cohort, 35 pts with aNSCLC were treated, with median follow-up of 10.6 mo (95% CI, 7.6-11.9). In the efficacy-evaluable pts, cORR was 50% in both the PD-L1 TPS < 1% (n = 10) and ≥1% (n = 18) subgroups, with 1 additional partial response (PR) pending confirmation in the PD-L1 TPS ≥1% subgroup (Table). In 5 pts with PD-L1 TPS ≥50%, cORR was 80%, with 1 additional PR pending confirmation. Regardless of TPS, cORR was numerically higher in pts with nonsquamous (n = 19 [53%]) vs squamous (n = 9 [44%]) histology. **Conclusions:** SV+P continued to show manageable safety and encouraging antitumor activity in treatment-naive NSCLC across PD-L1 TPS and histologies. This supports the ongoing phase 3 SigVie-003 study (NCT06758401) of SV+P vs P for treatment-naive aNSCLC with PD-L1 TPS ≥50% as well as further investigation in the enrolling phase 1 cohorts and future studies. Clinical trial information: NCT04389632. Research Sponsor: Pfizer.

	PD-L1 TPS <1% (n=10)	PD-L1 TPS ≥1% (n=18)	NSQ (n=19)	SQ (n=9)
cORR (95% CI), %	50 (19-81)	50 (26-74)	53 (29-76)	44 (14-79)
BOR, %				
CR	0	6	5	0
PR	50	44	47	44
SD	40	44	42	44
NE/no assessment	10	6	5	11
ORR (95% CI), %	50 (19-81)	61 (36-83)	63 (38-84)	44 (14-79)
DCR (95% CI), %	90 (56-100)	94 (73-100)	95 (74-100)	89 (52-100)
mDOR (95% CI), mo	NR (2.9-NR)	8.1 (4.2-NR)	8.1 (2.9-NR)	NR (4.2-NR)

8523 Poster Session

Dose-escalation results from a phase I study of FZ-AD004, a TROP2-directed ADC, in patients with advanced solid tumors. First Author: Ziming Li, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: FZ-AD004 is an ADC (antibody-drug conjugate) targeting Trop-2 (trophoblast cell-surface antigen 2), an intracellular calcium signaling transducer overexpressed on many epithelial tumors. It delivers the topoisomerase inhibitor DXd. This first-in-human study evaluated the safety and efficacy in patients(pts) with advanced solid tumors, mainly in non–small-cell lung cancer (NSCLC). **Methods:** PTs with unresectable, treatment-refractory or relapsed solid tumors received FZ-AD004 intravenously on days 1 of 21-day cycles. The primary objectives were to determine maximum tolerated dose (MTD), safety, and tolerability; secondary objectives included efficacy, pharmacokinetics, and immunogenicity of FZ-AD004. Pts were eligible regardless of TROP2 level. **Results:** As of November 28, 2025, 22 pts were treated with ≥1 dose of FZ-AD004 (median age: 61.5 years [range from 45-75], male: 77.3%, EOCG PS 1: 100%, prior lines of anticancer treatment ≥ 2: 77.3%). Diagnoses included NSCLC (n=21) and SCLC (n=1). Doses evaluated were at 3.2 (n=3), 5.6 (n=3), 6.4 (n=3), 8.0 (n=4), 10.0 (n=3), and 12.0 mg/kg (n=6). No dose-limiting toxicity (DLT) was observed across all dose levels.19 pts (86.4%) discontinued (15 (68.2%) due to disease progression per RECIST v1.1). Treatment emergent adverse events (TEAEs) regardless of causality were reported in all of 22 pts (100%; 10 pts [45.5%] experienced ≥grade 3, 5 pts [22.7%] had serious adverse events). Treatment-related AEs (TRAEs) occurred in all pts (100%; grade ≥3 in 36.4%; serious TRAEs in 13.6%). Grade ≥3 TRAEs included stomatitis (13.6%), decreased lymphocyte count (9.1%), nausea (4.5%), hypokalemia (4.5%), and keratitis (4.5%).Among 12 efficacy-evaluable pts at doses ≥8.0 mg/kg, the objective response rate (ORR) was 50.0% and the disease control rate (DCR) was 83.3%. Responses were observed in pts harboring KRAS G12C (n=1), EGFR mutations (n=3), and without AGA mutations (n=2). The longest duration treatment was 11.4 months. **Conclusions:** FZ-AD004 demonstrated a manageable safety profile with no DLTs observed up to 12.0 mg/kg and promising antitumor activity in heavily pretreated NSCLC patients, particularly at doses of 8.0 and 10.0 mg/kg. These doses are being further explored in the expansion phase. Clinical trial information: NCT05914545. Research Sponsor: None.

8524 Poster Session

Impact of *MET* amplification (amp) on telisotuzumab vedotin (Teliso-V) efficacy and safety in 2L+ non-squamous (NSQ) *EGFR* wild-type (WT) NSCLC with c-Met protein overexpression (OE). First Author: Jair Bar, Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel; The Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

Background: Teliso-V is a c-Met–directed antibody-drug conjugate comprising telisotuzumab and the microtubule polymerization inhibitor monomethyl auristatin E (MMAE) payload. In the Ph2 LUMINOSITY study (NCT03539536), Teliso-V showed durable responses and manageable safety (Camidge et al, JCO 2024;42:3000-11) resulting in its accelerated approval in locally advanced/metastatic NSQ NSCLC with high c-Met protein OE (3+, ≥50%), as determined by an FDA-approved test. *MET* amp is a negative prognostic risk factor in advanced NSCLC, frequently associated with recurrent disease. High levels of *MET* amp and c-Met OE are hallmarks of *MET*-addicted tumors. Here, we analyzed the effects of *MET* amp on clinical responses to Teliso-V in LUMINOSITY. **Methods:** *MET* amp was evaluated by FISH and ctDNA in baseline samples from 108 NSQ *EGFR* WT NSCLC pts with c-Met OE (3+, ≥25%). *MET* amp by FISH was defined as having focal *MET* amp (MET/CEP7 ≥2.0) with *MET* gene copy number (GCN) ≥4. *MET* amp *(focal)* by ctDNA was defined as having plasma *MET* GCN ≥4 with no co-amplification in *CDK6* and *EGFR*. c-Met OE by Immunohistochemistry (IHC; SP44) was defined as 3+ tissue staining intensity in ≥25% tumor cells (high c-Met OE: 3+, ≥50%; intermediate [int] c-Met OE: 3+, 25% to 49%). Exploratory analysis of tumor response was assessed in 76 efficacy evaluable pts with c-Met OE and *MET* amp assay results. **Results:** *MET* amp was detected in 34% (37/108) of pts with c-Met OE (3+, ≥25%) and was enriched by c-Met levels: 22% (11/50) in pts with Int c-Met OE (3+, 25% to 49%) and 45% (26/58) in pts with high c-Met OE (3+, ≥50%). The effects of *MET* amp on tumor response in LUMINOSITY are shown in Table 1. The majority of c-Met OE pts (79%) with PFS ≥10 mo (n=14) had GCN ≥10 and/or c-Met IHC 3+ ≥50%. No new safety signals were reported in pts with c-Met OE and *MET* amp. **Conclusions:** *MET* amp is more common in pts with high c-Met OE in this retrospective subgroup analysis. Tumor activity with Teliso-V was observed regardless of *MET* amp status. The impact of *MET* amp in pts with c-Met OE will be further evaluated in ongoing Phase 3 study (NCT04928846). Research Sponsor: None.

Teliso-V efficacy in NSQ *EGFR*-WT NSCLC pts with c-Met OE with or without *MET* amp in LUMINOSITY.

	Total c-Met OE (3+, ≥25%)	Total c-Met OE (3+, ≥25%)	Intermediate c-Met OE (3+, ≥25%-49%)	Intermediate c-Met OE (3+, ≥25%-49%)	High c-Met OE (3+, ≥50%)	High c-Met OE (3+, ≥50%)
***MET* amp (N)**	No (N=53)	Yes (N=23)	No (N=30)	Yes (N=7)	No (N=23)	Yes (N=16)
ORR % (95% CI)	**28** (18.0, 41.6)	**39** (22.2, 59.2)	**23** (11.8, 40.9)	**57** (25, 84.2)	**35** (18.8, 55.1)	**31** (14.2, 55.6)
PFS, median, mo (95% CI)	**5.26** (3.71, 8.11)	**8.02** (4.47, 14.65)	**5.32** (2.69, 8.11)	**7.52** (4.47, NA)	**4.17** (3.25, 8.87)	**8.02** (3.06, 25.92)
OS, median, mo (95% CI)	**14.5** (8.18, 17.38)	**13.86** (6.54, 22.24)	**14.03** (3.65, 17.02)	**9.79** (6.54, NA)	**16.26** (5.59, 36.44)	**13.86** (3.06, 30.29)

8525 Poster Session

SHR-1826, a c-MET directed antibody-drug conjugate (ADC), in advanced solid tumors: Updates from a phase 1 study. First Author: Longhua Sun, The First Affiliated Hospital of Nanchang University, Nanchang, China

Background: SHR-1826 is a novel ADC comprising a humanized IgG2 monoclonal antibody targeting c-MET, conjugated via a cleavable peptide-based linker to a topoisomerase I inhibitor payload. We conducted a multi-center, first-in-human, phase 1 trial of SHR-1826 in patients with advanced solid tumors. Here we report updated results, with a focus on patients with *EGFR*-mutated (*EGFRmut*) lung adenocarcinoma (LUAD). **Methods:** The study consisted of dose-escalation (i3+3 design), dose-expansion and efficacy-expansion phases. Patients with advanced solid tumors harboring MET alterations, who had failed standard therapy or had no available standard treatment options, were enrolled and received SHR-1826 intravenously at 2.2–6.0 mg/kg Q3W. In patients with *EGFRmut* LUAD, 4.0 and 5.0 mg/kg Q3W were evaluated during dose and efficacy expansion. **Results:** As of Dec. 3, 2025, 195 patients with lung (n=126), colorectal (n=40), gastric (n=22), liver (n=5), or pancreatic (n=2) cancer were treated. Median age was 59.0 yrs; 89.7% had ECOG performance status 1. Among 36 patients with *EGFRmut* LUAD, median number of prior lines of therapy was 2 (range 1–9); 97.2% had previously received EGFR-TKI (3rd generation, 88.9%) and 75.0% received platinum-based chemotherapy. As of data cutoff, median follow-up was 14.4 months. Efficacy in *EGFRmut* LUAD across doses is shown in Table 1. Overall, the confirmed objective response rate (ORR) was 41.7% (95% CI 25.5–59.2) and median duration of response (DoR) was 14.1 months (95% CI 5.6–not reached [NR]). Median progression-free survival (PFS) was 9.8 mo (95% CI 5.8–15.4). Median overall survival (OS) was not reached; 12-month OS rate was 67.4% (95% CI 48.9–80.5). In all 195 patients, grade ≥3 treatment-related adverse events (TRAEs) were reported in 129 patients (66.2%), with all occurring in ≥5% being hematological toxicities. Interstitial lung disease occurred in 4 (3.1%; grade ≥3, n=2 [1.6%]) patients. TRAEs led to treatment discontinuation in 8 (4.1%) patients. No treatment-related deaths were reported. **Conclusions:** SHR-1826 demonstrated encouraging activity with manageable safety in heavily pretreated patients with MET-altered *EGFRmut* LUAD. Multiple trials are ongoing to assess SHR-1826 combined with other anti-tumor therapies in NSCLC. Clinical trial information: NCT06094556. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy outcomes in *EGFRmut* LUAD.

	4.0 mg/kg (n=16)	5.0 mg/g (n=18)	All patients (n=36)
Confirmed ORR (n/N; 95% CI), %	31.3 (5/16; 11.0–58.7)	50.0 (9/18; 26.0–74.0)	41.7 (15/36; 25.5–59.2)
DCR (n/N; 95% CI), %	87.5 (14/16; 61.7–98.4)	100.0 (18/18; 81.5–100.0)	94.4 (34/36; 81.3–99.3)
Median DoR (95% CI), mo	NR (8.6–NR)	9.7 (4.2–NR)	14.1 (5.6–NR)
Median PFS (95% CI), mo	12.4 (2.6–NR)	8.4 (4.5–15.4)	9.8 (5.8–15.4)
12-mo OS (95% CI), %	67.0 (37.9–84.7)	69.1 (40.7–85.9)	67.4 (48.9–80.5)

Data are based on the full analysis set. DCR, disease control rate.

8527 Poster Session

SHR-A2102 in combination with adebrelimab as first-line treatment in patients with locally advanced or metastatic squamous or non-squamous non-small cell lung cancer (NSCLC): Results from a phase 1b/2 study. First Author: Yi Hu, Cancer Center, Chinese PLA General Hospital, Beijing, China

Background: SHR-A2102 is a novel antibody-drug conjugate composed of a monoclonal antibody targeting nectin-4, a cleavable linker, and a topoisomerase I inhibitor payload. Here, we report the preliminary efficacy and safety of SHR-A2102 plus adebrelimab (an anti-PD-L1 antibody) as first-line therapy in patients with locally advanced or metastatic squamous or non-squamous NSCLC. **Methods:** This is a multicenter, open-label phase 1b/2 study (NCT06512051). In the phase 2 part, patients aged 18-70 years with ECOG PS 0-1 and histologically/cytologically confirmed stage IIIB-IV squamous (cohort A) or non-squamous (cohort B) NSCLC who had received no prior systemic therapy were enrolled. All patients received intravenous SHR-A2102 (8 mg/kg, day 1 Q3W) plus adebrelimab (1200 mg, day 1 Q3W) until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR). **Results:** Between Dec 13, 2024 and Nov 19, 2025, 67 patients were enrolled and received treatment (27 with squamous NSCLC and 40 with non-squamous NSCLC). In cohort A, 92.6% were male, the median age was 64 years (range 42-70), 14 patients had PD-L1 TPS 1-49%, and 13 patients had PD-L1 TPS ≥50%. In cohort B, 60.0% were male, the median age was 62 years (range 42-70), 7 patients had PD-L1 TPS <1%, 20 patients had PD-L1 TPS 1-49%, and 13 patients had PD-L1 TPS ≥50%. Efficacy was evaluated in 26 and 33 patients from cohorts A and B, respectively, while all patients were included in the safety analysis. As of Nov 30, 2025, the median follow-up was 9.1 months (range 2.0-11.1), with 9.9 months (range 3.0-11.0) with squamous NSCLC and 9.0 months (range 2.0-11.1) with non-squamous NSCLC. Antitumor activities are shown in Table 1. In patients with PD-L1 TPS ≥1%, ORR was 80.8% (95% CI 60.6%-93.4%) for squamous NSCLC and 69.2% (95% CI 48.2%-85.7%) for non-squamous NSCLC. Grade ≥3 treatment-related adverse events (TRAEs) were reported in 53.7% (36/67) of patients. The most common Grade ≥3 TRAEs were decreased neutrophil count (32.8%), decreased white blood cell count (14.9%), and anemia (9.0%). **Conclusions:** These results suggested the combination of SHR-A2102 and adebrelimab as the first-line therapy is a promising treatment strategy in patients with squamous or non-squamous NSCLC, supporting further investigation. Clinical trial information: NCT06512051. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

Efficacy summary.

	Squamous NSCLC (N=26)	Non-squamous NSCLC (N=33)	Total (N=59)
ORR, % (95% CI)	80.8 (60.6-93.4)	69.7 (51.3-84.4)	74.6 (61.6-85.0)
DCR, % (95% CI)	96.2 (80.4-99.9)	97.0 (84.2-99.9)	96.6 (88.3-99.6)
DoR (months), median (95% CI)	NR (4.4-NR)	NR (5.7-NR)	NR (6.5-NR)
6-month PFS rates, % (95% CI)	64.1 (42.3-79.5)	78.9 (58.9-90.0)	71.8 (57.6-81.9)

8528 Poster Session

Necitumumab plus pembrolizumab and chemotherapy for untreated advanced squamous NSCLC: Phase I/II NEJ048A/NEXUS. First Author: Tomoiki Aiba, Department of Pulmonary Medicine, Sendai Kousei Hospital, Sendai, Japan

Background: EGFR blockade enhances tumor antigen presentation and may potentiate PD-1 inhibition. This phase I/II study evaluated the safety and efficacy of adding necitumumab to pembrolizumab plus platinum-based chemotherapy in patients with previously untreated advanced squamous non–small cell lung cancer (NSCLC), a population with limited biomarker-driven treatment options. **Methods:** Patients received necitumumab (400–800 mg on days 1 and 8), pembrolizumab (200 mg on day 1), nab-paclitaxel (100 mg/m² on days 1, 8, and 15), and carboplatin (AUC 5 on day 1) every 3 weeks for four cycles, followed by necitumumab plus pembrolizumab maintenance. Phase I used a standard 3+3 dose-escalation design. Per protocol amendment, patients treated at the recommended dose (RD) in phase I (n = 6) and all phase II patients (n = 6) were pooled for efficacy analyses (n = 12). Tumor assessments were performed every 6 weeks per RECIST v1.1. Primary endpoints were safety and objective response rate (ORR). Data cutoff was September 14, 2025. **Results:** Twenty-one patients were enrolled, including 15 in phase I (400 mg, n = 6; 600 mg, n = 3; 800 mg, n = 6). One dose-limiting toxicity (DLT) occurred in the 800 mg cohort, which was determined as the RD and maximum tolerated dose (MTD). Among the 12 patients treated at the RD, the ORR was 75.0% (9/12; 95% CI, 42.8–94.5), with partial response in 9 patients, stable disease in 1 patient, and progressive disease in 2 patients. The disease control rate was 83.3%. The 24-week survival rate was 95.2%. Median progression-free survival and overall survival were not reached at the time of analysis. The most frequent adverse events (AEs) in 21 patients were hypomagnesemia (66.7%), acneiform dermatitis (66.7%), neutropenia (61.9%), decreased appetite (52.4%), anemia (52.4%), constipation (47.6%), stomatitis (42.9%), and leukopenia (42.9%). Grade 3 and 4 AEs occurred in 66.7% and 28.6% of patients, respectively, with no grade 5 events. **Conclusions:** The addition of necitumumab to pembrolizumab and platinum-based chemotherapy demonstrated manageable toxicity and resulted in a high ORR in patients with untreated squamous NSCLC. These findings support the potential activity of EGFR blockade–based immunochemotherapy and warrant further clinical investigation. Clinical trial information: 2031210387. Research Sponsor: Nippon Kayaku Co., Ltd.

8530 Poster Session

First-in-human study of DM005, an anti-EGFR/c-MET bispecific antibody-drug conjugate, in patients with advanced solid tumors. First Author: Jin-Ji Yang, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: DM005 is a bispecific ADC (BsADC) conjugated to BLD1102, a linker/payload system composed of a linker and a DNA topoisomerase I inhibitor (BCPT02), targeting EGFR and c-MET with an average DAR value of 4. EGFR and c-MET are highly co-expressed in NSCLC, SCLC, HNSCC, breast cancer, gastric cancer, colorectal cancer, and some other solid tumors, for which DM005 has demonstrated robust anti-tumor activity in PDX/CDX models. **Methods:** This is a First-in-human dose-escalation study (NCT 06515990). Patients (pts) with advanced solid tumors received DM005 by IV administration from 0.5 to 6.5 mg/kg Q3W. The classical "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy. Tumor response was evaluated by the Investigators based on RECIST v1.1. A Safety Monitoring Committee (SMC) was established to determine the dose levels, dose regimen, and the maximum tolerated dose (MTD)/ recommended dose for expansion (RDE). **Results:** As of 2 Jan 2026, a total of 45 pts from China, United states of America and Australia were enrolled and received ≥1 dose of DM005 across 8 dose cohorts. Median age was 59 years (range 40-76). Baseline ECOG scores were 0 (n = 7), 1 (n = 38) with all pts progressed after an average of 3 (range 1-7) prior lines of available standard therapy. There were no dose limiting toxicities (DLT) observed up to 6.5 mg/kg. The MTD was not reached. Thirty-six pts (80%) experienced treatment-related adverse events (TRAEs), the most common TRAEs (≥10%) including: nausea (28.9%), anemia (28.9%), fatigue (26.7%), decreased appetite (26.7%), leukopenia (20%), aspartate aminotransferase increased (15.6%), lymphopenia (13.3%), constipation (11.1%). Most TRAEs were Grade 1-2 and Grade ≥3 TRAEs reported in 10 pts (2 lymphopenia, 1 neutropenia, anemia, leukopenia, nausea, stomatitis, vomiting, fatigue, pain, urinary tract infection, hypoxia, hypotension). No ILD or Infusion reaction were observed. Among 32 patients evaluable, there were 8 PRs, including 1pt with NSCLC EGFR-mutant (NSCLCm) at 3.3 mg/kg, 4 pts with NSCLCm and 1pt with SCLC at 4.2 mg/kg, and 1pt with NSCLCm and 1pt with NSCLC EGFR wildtype (NSCLCw) at 5.2mg/kg, and 14 pts with stable disease (SD). In the 3.3/4.2/5.2 mg/kg dose groups, a total of 13 NSCLCm pts underwent imaging tumor assessment, with 6 subjects achieving PR, and 5 subjects achieving SD. The unconfirmed objective response rate (ORR) is 46.2%, and the disease control rate (DCR) is 84.6%. **Conclusions:** DM005 is safe and tolerable up to 6.5 mg/kg dose level. In both NSCLCm and NSCLCw pts, and SCLC pts, DM005 has demonstrated an encouraging efficacy with a manageable safety profile. The putative RDE ranges from 4.2 to 6.5 mg/kg which will be further evaluated in phase II trials. Clinical trial information: NCT06515990. Research Sponsor: None.

8531 **Poster Session**

The efficacy of trastuzumab deruxtecan after HER2-TKI exposure in HER2 exon 20 insertion–positive non–small cell lung cancer: Results from a large-scale nationwide genomic screening (LC-SCRUM-Asia). First Author: Yu Tanaka, Department of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan

Background: Although reduced efficacy of HER2-TKIs after trastuzumab deruxtecan (T-DXd) has been reported in HER2 exon 20 insertion–positive non–small cell lung cancer (NSCLC), the efficacy of T-DXd following prior HER2-TKI exposure remains unclear. **Methods:** We identified patients with HER2 exon 20 insertion–positive NSCLC treated with T-DXd from two cohorts: the National Cancer Center Hospital East (N = 26,971) and the LC-SCRUM-Asia (N = 20,902). Clinical outcomes (ORR, DCR, and PFS) were evaluated across three groups based on prior HER2-TKI therapy: (1) HER2-TKI-naïve patients (naïve cohort), (2) those treated with selective HER2-TKIs (zongertinib or severtinib) (selective TKI cohort), and (3) those treated with non-selective pan-HER2-TKIs (such as poziotinib, afatinib, and others) (non-selective TKI cohort). **Results:** Of 77 patients (0.2%) included, 60 in the naïve cohort, 7 in the selective TKI cohort, and 10 in the non-selective TKI cohort. Overall, the median age was 60 years (range, 44–76), and 56% of patients were female. By NGS analysis, all tumors harbored ERBB2 exon 20 insertions within the tyrosine kinase domain; the YVMA subtype was the most common (57%). T-DXd was administered as a median fourth-line therapy (range, 2–8). Baseline clinical and genomic characteristics were generally comparable across the three groups. According to prior HER2-TKI exposure, the ORR was 60% (36/60) in the naïve cohort, 29% (2/7) in the selective TKI cohort, and 60% (6/10) in the non-selective TKI cohort. The DCRs were 83% (50/60), 71% (5/7), and 80% (8/10), respectively. Median PFS with T-DXd was 9.9 months in the naïve cohort, compared with 6.5 months in the selective TKI cohort and 5.3 months in the non-selective TKI cohort. The 6-month PFS rate was 72%, 71%, and 50%, respectively. Among 10 patients who did not achieve an objective response to prior HER2-TKIs (best response of stable or progressive disease), 6 achieved a partial response with subsequent T-DXd. **Conclusions:** Although prior HER2-TKI exposure, particularly selective HER2-TKIs, may attenuate the efficacy of T-DXd in HER2 exon 20 insertion–positive NSCLC compared with HER2-TKI–naïve patients, T-DXd retained clinically meaningful activity in a subset of patients, including those who did not achieve objective responses to prior HER2-TKIs. Research Sponsor: Astellas Pharma Inc.; Taiho Pharmaceutical Co., Ltd.; Takeda Pharmaceutical Company Limited; Chugai Pharmaceutical Co., Ltd.; Eli Lilly Japan K.K.; Nippon Boehringer Ingelheim Co., Ltd.; Novartis Pharma K.K.; Pfizer Japan Inc.; Bristol-Myers Squibb K.K.; Merck Serono Co., Ltd.; Janssen Pharmaceutical K.K.; AstraZeneca K.K.; Sumitomo Pharma Co., Ltd.; Bayer, Ltd.; AbbVie GK; Nippon Kayaku Co., Ltd.; Merus N.V.; Amgen K.K.; Medical & Biological Laboratories Co., Ltd. (MBL); Eisai Co., Ltd.; MSD K.K.; Ono Pharmaceutical Co., Ltd.; Kyowa Kirin Co., Ltd.; Daiichi Sankyo Co., Ltd.

8532 **Poster Session**

Integrating tumor growth models to improve late-stage lung cancer outcome prediction using early-stage clinical trial data. First Author: Janos Szalma, Clario, Budapest, Hungary

Background: Immunotherapy has substantially improved clinical outcomes but poses distinct challenges for response assessment due to heterogeneous and non-monotonic tumor kinetics. RECIST 1.1 rely on unidimensional lesion measurements that may incompletely capture spatial heterogeneity which can result in limited characterization of tumor growth. Tumor growth modeling provides a complementary, quantitative framework for capturing longitudinal tumor dynamics. Different frameworks have been proposed to model total disease progression and response to treatment from total tumor volume. However, model selection may be challenging with each model capturing distinct growth mechanisms. In this work, we present a framework integrating complementary tumor growth models using a neural network classifier to predict late-stage outcomes from early-stage timepoints. **Methods:** We retrospectively aggregated deidentified data from 417 anonymized subjects with metastatic non-small cell lung cancer (NSCLC) treated with immunotherapy. Serial CT datasets were acquired at five timepoints over a 30-week period and lesions were annotated by expert radiologists according to RECIST 1.1 criteria. Tumor burden was derived from radiologist annotations using a previously validated AI method that reconstructs 3D lesion volumes from bidimensional data. For each subject, Modified Gompertz (MG) and Stein-Claret (SC) models were implemented to estimate intrinsic tumor growth parameters. Both models were fitted using early on-treatment data up to 21 weeks and used to predict response to treatment at week 30. To evaluate complementarity and the ability of early tumor dynamics to predict radiological response, model parameters were combined and used to train a two-layer neural network for radiological outcome classification. Performance of the combined MG+SC was compared with single-model classifiers on response (CR/PR) vs non-response (SD/PD) and progression (PD) vs non-progression (CR/PR/SD) using accuracy and sensitivity metrics. **Results:** The cross-validated accuracy in classifying responders and non-responders at week 30 was 81.1% from the combined MG+SC model (sensitivity=79.2%; specificity=83.0%), higher than both individual models (accuracy = 77.8% and 68.0% for MG and SC respectively). The combined modeling framework confirmed higher accuracy (70.7%) when distinguishing progressive disease from the non-progressor group (sensitivity=64.5%, specificity=76.5%) when compared to both MG (69.1%) and SC (66.8%). **Conclusions:** This work showed that integrating early-stage dynamics from complementary mechanistic growth models improves week-30 radiographic outcome prediction over individual models in metastatic NSCLC immunotherapy trials. This framework can enable earlier identification of patient-level response that may support treatment adaptation. Research Sponsor: None.

8533 **Poster Session**

GEMINI-NSCLC: Multiomics and single-cell spatial profiling to benchmark, back-translate, and build digital twins of IO response. First Author: Vincent Perez, Tempus AI, Chicago, IL

Background: Response to first-line standard-of-care (SoC) chemo-immunotherapy (IO) for patients with NSCLC without targetable mutations is heterogeneous, highlighting the need for predictive biomarkers. GEMINI (NCT05236114) integrates real-world outcomes, whole exome sequencing (WES), single-cell spatial transcriptomics (SpTx), and AI-pathology to establish a benchmarking resource and patient-level digital twins, enabling back-translation into testable hypotheses. With >4 million cells from 53 biopsies, GEMINI is one of the largest single-cell spatial datasets linked to IO outcomes. **Methods:** Patients with metastatic NSCLC were analyzed for outcome associations. Progression-free survival (PFS) was defined from IO start to progression, next regimen, last follow-up, or 2 years. Patients were classified as fast progressors (<3 months PFS) or slow progressors (>3 months PFS). Baseline biopsies (n=53) underwent WES and SpTx. Neural networks traced single-cell boundaries on H&E to quantify gene expression; cells were annotated via clustering and LLM-assisted labeling. AI-, manual-, and digital-pathology (DSP) defined tumor, immune, and stroma regions. Cohort-level benchmarking was integrated into patient-level digital twins to back-translate spatial-genomic features into individualized risk and mechanism hypotheses. **Results:** WES revealed expected mutation frequencies: *STK11* 15%, *TP53* 73%, *KEAP1* 21%, *KRAS* 46%, supporting cohort representativeness. Stroma-associated TIL counts were higher in slow versus fast progressors by AI-path (p=0.034) and manual-path (p=0.014). DSP showed immune aggregates in slow progressors were lymphocyte-diverse, whereas fast progressors were enriched for five macrophage subtypes consistent with immunosuppressive niches. Spatial proximity of lymphocytes and stroma to a tumor subcluster (C2) predicted progression (p<0.01). Immunoglobulin light-chain expression localized to the tumor core in slow progressors, suggesting tumor–B cell interactions with disease arrest. Differential expression identified 14 EMT/ECM genes overexpressed in fast-progressor stroma, implicating stromal barrier/ECM remodeling in IO resistance. Digital twins captured these spatial-omic signatures to forecast risk and generate patient-specific, testable hypotheses. **Conclusions:** GEMINI provides a large single-cell spatial transcriptomic benchmark linked to IO outcomes for patients with NSCLC and enables AI-driven digital twins for clinical decision support. Fast progressors show stromal EMT/ECM programs and immunosuppressive myeloid niches; slow progressors exhibit lymphocyte diversity and tumor–B cell interactions near subcluster C2. Findings support multimodal risk stratification and nominate stromal EMT/ECM targeting to overcome IO resistance, with prospective validation via digital-twin biomarkers. Clinical trial information: NCT05236114. Research Sponsor: AstraZeneca; Tempus AI.

8534 **Poster Session**

AI-derived CD8⁺ cytotoxic T-cell immune signatures from baseline H&E images to predict immunotherapy benefit over chemotherapy in non–small cell lung cancer: Blinded validation in CheckMate-227 (CM227). First Author: Cristian Barrera, Emory University and Georgia Institute of Technology, Atlanta, GA

Background: Immunotherapy (IO) has transformed treatment for non–small cell lung cancer (NSCLC), but not all patients (pts) benefit, underscoring the need for predictive biomarkers to guide IO versus chemotherapy (Ch). CheckMate 227 (CM227; NCT02477826) showed a survival benefit of first-line nivolumab plus ipilimumab (nivo+ipi) over Ch in stage IV NSCLC. $CD8^+$ T cells are key mediators of antitumor immunity and are associated with IO benefit. We developed an artificial intelligence (AI)–based pipeline (VIGOR-CD8) that predicts spatial $CD8^+$ immune signatures from routine baseline H&E whole-slide images using histopathology foundation model embeddings (H-Optimus-0) and virtual gene expression modeling (HE2Gene), and evaluated its ability to identify pts who do and do not derive IO benefit over Ch in CM227. **Methods:** 1,598 pts with advanced NSCLC were analyzed, including multi-institutional retrospective cohorts (n = 487; 65 for patch-level $CD8^+$ prediction and overall survival (OS), 422 for patient-level OS) and a blinded CM227 validation subset (n = 1,111). For orthogonal validation, 86,470 H&E patches were co-registered with quantitative $CD8^+$ immunofluorescence. H-Optimus-0 and HE2Gene immune-related embeddings were used to train a random forest classifier to predict patch-level $CD8^+$ probability. Patch-level probabilities were aggregated into a patient-level $CD8^+$ signature and dichotomized into biomarker-positive (B^+) and biomarker-negative (B^-) groups by the training-set median. Cox models assessed the impact of VIGOR-CD8 on OS. In CM227, prognostic and predictive utility were evaluated using treatment-specific analyses; investigators were blinded to outcomes, and models were trained on independent, non-overlapping cohorts. **Results:** VIGOR-CD8 was associated with longer OS in the testing cohort (n = 422; HR 0.68, 95% CI 0.53–0.87, p = 0.00163) and CM227 (n = 1,111; HR 0.8, 95% CI 0.67–0.96, p = 0.016), irrespective of treatment type and PD-L1 expression. Among pts with evaluable PD-L1, B^+ pts treated with nivo+ipi had superior OS versus Ch (n = 617; HR 0.72, 95% CI 0.58–0.90, p = 0.003), while in B^- pts there was no significant OS difference between treatment arms (n = 130; HR 1.18, 95% CI 0.79–1.75, p = 0.436), supporting a predictive rather than purely prognostic role for VIGOR-CD8. **Conclusions:** An AI-derived $CD8^+$ immune signature from routine baseline H&E slides was associated with favorable OS in CM227 and predicted differential benefit from nivo+ipi versus Ch. VIGOR-CD8 may help identify advanced NSCLC pts most likely to benefit from first-line dual IO, but further validation in independent and prospective trials is warranted. Research Sponsor: National Cancer Institute; R01 CA249992 - 01A1, R01 CA216579 - 01A1, R01 CA257612 - 01A1, R01 CA264017 - 01, R01 CA268287 - 01A1, U01 CA113913 - 16A1, U01 CA239055 - 01, U01 CA269181 - 01, U24 CA274494 - 01, U54 CA254566 - 01; VA Biomedical Laboratory Research and Development Service; I01CX002622, I01CX002776, IK6BX006185; VA Research and Development Office through the Lung Precision Oncology Program; LPOP-L0021; Office of the Assistant Secretary of Defense for Health Affairs through the Prostate Cancer Research Program; W81XWH-15–1-0558, W81XWH-20–1-0851, W81XWH-21-1-0160; Office of the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Cancer Research Program; W81XWH-16-1-0329; Kidney Mapping and Atlas Project (KMAP); U01DK133090-01; and sponsored research agreements from Astrazeneca, Bristol Myers Squibb, the Prevent Cancer Foundation, Innovation in Cancer Informatics, and the Scott Mackenzie Foundation.; National Heart, Lung and Blood Institute; R01 HL151277 - 01A1, R01 HL158071 - 01A1; National Institute of Allergy and Infectious Diseases; R01 AI175555; National Institute of Dental and Craniofacial Research; R21 DE032344 - 01; National Library of Medicine; R01 LM013864 - 01A1; National Institute on Aging; R01 AG089759; National Institute of Diabetes and Digestive and Kidney Diseases; R01 DK118431; Kidney Mapping and Atlas Project (KMAP); U01 DK133090 - 01; United States Department of Veterans Affairs VA Merit Review award; IBX004121.

8535 **Poster Session**

Impact of NCCN-guided training on large language model performance in mNSCLC. First Author: Andrew Gould, University of Illinois Chicago, Chicago, IL

Background: Publicly available large language models (LLMs) such as ChatGPT may support clinical decision-making in precision oncology by rapidly synthesizing complex information. We previously evaluated ChatGPT's ability to generate NCCN-concordant first-line (1L) treatment recommendations for metastatic non-small cell lung cancer (mNSCLC) using a novel Generative AI Performance Score (G-PS). We evaluated whether NCCN-guideline–based training improves LLM treatment recommendations across multiple lines of therapy and targetable genotypes in metastatic NSCLC. **Methods:** NCCN Guidelines (v3.2025) were reviewed and eight driver alterations with FDA-approved therapies were selected: EGFR Ex19del, BRAF V600E, ALK fusion, KRAS G12C, NTRK1/2/3 fusion, ROS1 fusion, RET fusion, and MET exon 14 skipping. Standardized prompts requesting 1L, second-line (2L), and third-line (3L) recommendations were generated and run through ChatGPT-5.2. Prompts included information on patient demographics, disease stage, and prior therapy where appropriate. Each scenario was repeated five times per line of treatment (N = 15 per mutation). In trained sessions, the LLM was explicitly instructed to defer to an uploaded PDF copy of the NCCN guidelines prior to generating recommendations. Responses were scored using the G-PS, which quantifies guideline concordance on a continuous scale from -1 (all hallucinations) to 1 (all correct answers) based on alignment with NCCN-recommended therapies. Additionally, we calculated ratios for the mean trained G-PS and untrained G-PS across groups, to estimate the relative fold change effect of training on ChatGPT performance (called the "Training Ratio"). **Results:** A total of 240 prompts were analyzed (120 untrained, 120 trained). NCCN-guided training significantly improved overall LLM guideline concordance (mean G-PS 0.462 vs 0.313, p = 0.049) and reduced irrelevant recommendations (mean irrelevant rate of 23.7% vs 39.8%, $p < 0.001$) but did not significantly affect the rate of hallucinations (10.4% vs 8.1%, p = 0.297). 1L responses demonstrated significantly higher mean G-PS than 2L ($p < 0.001$) or 3L ($p < 0.001$) for both trained and untrained sessions. Training also significantly improved the mean G-PS of 1L responses compared to untrained responses (0.902 vs 0.647, $p < 0.001$) but not in 2L or 3L. The overall Training Ratio was 1.48, with the greatest Training Ratio seen in EGFR Ex19del and ALK fusion (> 4) and the poorest in NTRK fusions (0.53). **Conclusions:** While guideline-based training improves ChatGPT's overall performance and reduces irrelevant outputs, recommendation quality declines substantially beyond the first line of therapy and shows marked variability by mutation. These findings highlight important limitations of LLMs in complex oncology decision-making and reinforce that clinicians must independently verify recommendations against established guidelines. Research Sponsor: None.

8536 **Poster Session**

A triage-aware neuro-symbolic approach for clinical trial matching in oncology: Real-world validation in lung and genitourinary cancer. First Author: Vittoria Peppoloni, Fondazione IRCSS Istituto Nazionale dei Tumori di Milano, Milan, Italy

Background: Low clinical trial accrual remains a critical barrier in oncology, driven by fragmented electronic health records (EHRs), limited trial awareness, and the substantial time required for manual eligibility screening. While large language models (LLMs) can extract clinical information from unstructured data, their probabilistic nature limits direct use for eligibility decisions that require protocol-level determinism and auditability. We developed a neuro-symbolic clinical trial matching platform that combines LLM-based information extraction with explicit rule-based eligibility reasoning, augmented by an uncertainty-aware triage strategy to safely integrate automation into real-world workflows. **Methods:** Unstructured EHRs were processed using a large language model (Llama 3.1–70B) to extract key clinical variables, which were normalized to a domain ontology. Trial eligibility was evaluated using deterministic inclusion and exclusion criteria encoded directly from full trial protocols, producing per-criterion explanations and an overall classification (eligible, not eligible, or indeterminate). A triage module quantified evidentiary completeness and logical consistency, categorizing cases into low-uncertainty confidence results suitable for automated screening, moderate and high-uncertainty cases requiring clinician review. Performance was assessed against clinician-validated ground truth in a real-world cohort of 107 patients, including advanced lung cancer patients and an independent genitourinary cancer validation cohort. **Results:** Among matchable patients (n = 79), the system achieved perfect Top-1 accuracy and Recall@3 of 1.00, with all eligible patients correctly identified within the top three trial recommendations. Thirty-nine patients (49%) were triaged as low-uncertainty and suitable for automated screening, while the remainder were appropriately flagged for clinician review. Among non-matchable patients (n = 28), no false-positive eligibility assignments were observed (false-positive rate 0.0). Triage correctly identified high-uncertainty cases, minimizing unsafe automation. In indeterminate cases (ground truth unknown, n = 6), the system deferred to manual review in two-thirds of cases, with zero unsafe automated classifications. Median end-to-end processing time was under one minute per patient. **Conclusions:** This neuro-symbolic, triage-aware approach enables transparent and deterministic clinical trial matching in oncology. By combining automated eligibility assessment with uncertainty-based triage, the system reduces manual screening burden while preserving clinician oversight, supporting scalable and trustworthy trial enrollment in real-world practice. Research Sponsor: None.

8537 **Poster Session**

Discrepancy between plasma cell-free DNA and tissue-based analysis for detection of gene amplifications in non–small cell lung cancer. First Author: Haruka Nakatani, National Cancer Center Hospital East, Kashiwa, Japan

Background: Therapeutic strategies have been developed in patients with non-small cell lung cancer (NSCLC) harboring gene amplifications (amp) such as *MET* and *HER2*. Although both plasma cell-free DNA (cfDNA) and tissue-based next-generation sequencing (NGS) are available for the detection of gene amp, the concordance between plasma cfDNA and tissue-based analysis for the detection of gene amp remains unclear. **Methods:** We investigated plasma cfDNA and tissue-based NGS concordance for detection of gene amp in NSCLC using a large-scale screening cohort (LC-SCRUM-Liquid). Paired blood samples were prospectively collected within 4 weeks of corresponding tumor tissue sampling from patients with advanced NSCLC. Guardant360 panel or Oncomine Precision Assay panel was used for plasma cfDNA NGS. Oncomine Comprehensive Assay panel or Oncomine Precision Assay was used for tissue-based NGS. The concordance of *EGFR*, *MET* and *HER2* gene amp were evaluated. **Results:** A total of 1,133 pairs of blood and tissue samples were successfully analyzed between December 2017 and December 2024. The median age of the patients was 69 years (range 25-91), 60% were male, 68% were ever smokers, and 79% had a histopathological diagnosis of adenocarcinoma. The positive percent agreement (PPA) and positive predictive value (PPV) of plasma cfDNA analysis relative to tissue-based analysis are shown in the table. For detecting *MET* amp, the PPA of plasma cfDNA analysis relative to tissue-based analysis tended to be lower in the patients with metastases involving fewer than two organs compared to those with metastases involving two or more organs (25% vs. 63%, P = 0.07). Among the patients with *EGFR*, *MET*, or *HER2* amp detected by either tissue-based or plasma cfDNA analysis, the correlation of the copy number variants between tissue-based and plasma cfDNA analysis was very weak (r = 0.20). **Conclusions:** The concordance between plasma cfDNA and tissue-based analysis for detecting gene amp is markedly low, particularly in patients with a low tumor burden. Detection of gene amp using plasma cfDNA analysis may be insufficient for accurately evaluating the efficacy of targeted therapies for patients with lung cancer harboring gene amp. Research Sponsor: AbbVie GK, Amgen K.K., Astellas Pharma Inc., AstraZeneca K.K., Nippon Boehringer Ingelheim Co., Ltd., Bristol-Myers Squibb K.K., CHUGAI PHARMACEUTICAL CO., LTD.; the Japan Agency for Medical Research and Development (AMED); the National Cancer Center Research and Development Fund; DAIICHI SANKYO COMPANY, LIMITED, Eisai Co., Ltd., Guardant Health Inc., Janssen Pharmaceutical K.K., Kyowa Kirin Co., Ltd., Life Technologies Japan Ltd., Merck Biopharma Co., Ltd.; MEDICAL & BIOLOGICAL LABORATORIES CO., LTD., MSD K. K., Nippon Kayaku Co., Ltd, Novartis Pharma K.K., ONO PHARMACEUTICAL CO., LTD., Pfizer Japan Inc., Sumitomo Pharma Co., Ltd.; TAIHO PHARMACEUTICAL CO., LTD., Eli Lilly Japan K.K., Bayer Yakuhin, Ltd., Merus N.V. and Takeda Pharmaceutical Co., Ltd.

Concordance of gene amp between plasma cell-free DNA and tissue-based analysis.

			Tissue		PPA	PPV
			+	-		
cfDNA	*EGFR* amp	+	9	37	13%	20%
		-	60	1027		
	MET amp	+	9	7	38%	56%
		-	15	1102		
	HER2 amp	+	0	4	0%	0%
		-	3	1126		

8538 **Poster Session**

Smoking signature as used to define a genomically distinct subset of class I BRAF-mutant NSCLC. First Author: Shuai Wang, Vanderbilt University Medical Center, Nashville, TN

Background: Class I *BRAF* mutant (*BRAF* mut) non–small cell lung cancer (NSCLC) is biologically heterogeneous, occurring in both smokers and never-smokers with disparate benefits from immunotherapy (IO). Genomically defined tobacco-induced damage may better identify biologically and clinically distinct subsets than self-reported smoking history. We evaluated COSMIC mutational signature-SBS4 as a genomic surrogate of smoking exposure and examined its association with molecular features, tumor microenvironment (TME) and outcomes in *BRAF* mut NSCLC. **Methods:** Retrospective review of 33,217 NSCLC specimens that underwent whole exome and whole transcriptome sequencing at Caris Life Sciences. Mutation profiles of specimens were deconvolved using the COSMIC SBS4 signature to estimate tobacco-associated mutational exposure (filter: total mutation count>=200, Nfiltered=26448; *BRAF* mut = 276). TME was estimated using QuanTIseq method. Overall survival (OS) and survival on IO (IO-OS) were obtained from insurance claims and calculated from date of tumor biopsy (for OS) or initiation of IO (for IO-OS) to last contact using Kaplan-Meier estimates and Cox proportional hazards models. Statistical significance was determined by Fishers Exact, chi-square and Mann-Whitney U test with p-values adjusted for multiple comparisons ($P<0.05$). **Results:** Among 6,405 patients with smoking history and SBS4 data, SBS4+ (SBS4>0) was strongly associated with smoking (OR 11.2, $P<0.001$). SBS4+ tumors exhibited elevated TMB (mean:13 vs 9 mut/Mb, and TMB-High [>=10 mut/Mb], $P<0.05$, Table). SBS4+ *BRAF* mut tumors had a lower prevalence of mutations in *SETD2* (OR 0.33), *PIK3CA* (OR 0.26) and *SMAD4* (OR 0.25, all $P<0.05$). Regardless of SBS4 status, *BRAF* mut tumors were more often PD-L1+ (OR 3.2, TPS>=1), while mutations in *STK11*, *KEAP1*, and *SMARCA4* were less frequent (OR 0.07-0.37, all $P<0.05$). Evaluation of the TME revealed that SBS4+ *BRAF* mut were enriched for regulatory T cells (vs. SBS4-,1.44 fold, $P<0.05$). In metastatic disease, *BRAF* mut showed improved OS (HR 0.8[0.66-0.97], $P=0.03$) and IO-OS (HR 0.8[0.66-0.99], $P=0.04$) compared to WT. The OS benefit was preserved in the SBS4+ tumors (HR 0.64[0.43-0.95], $P=0.03$), but not in SBS4- tumors. No difference in IO-OS was observed in SBS4+ subgroups likely due to small size. **Conclusions:** SBS4 identifies biologically distinct subsets in class I BRAF mut NSCLC, with differences in mutational landscape, TMB, and TME. SBS4+ tumors show a survival benefit over WT disease, whereas SBS4- tumors do not. These findings support SBS4 as a genomic marker of smoking-related biology and a potential tool to refine therapeutic decision-making between targeted therapy and IO in NSCLC and potentially other smoking-associated cancers. Research Sponsor: None.

Smoking signature in BRAF mut NSCLC (% prevalence and OS).

Characteristics	SBS4 +	SBS4 -
SETD2	20	43
PIK3CA	6	19
SMAD4	3	12
TMB-high	41	18
OS (months)	29.9 vs. 11.9 ($P=0.03$)	16.0 vs. 10.9 ($P=0.47$)

8539 **Poster Session**

A real-world analysis of ctDNA methylation-based histology prediction and associated clinical characteristics in non–small cell lung cancer (NSCLC). First Author: Jessica Zhang, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: The treatment of NSCLC differs by histologic subtype, though traditional histologic review faces several challenges including insufficient tissue and intratumoral heterogeneity. The circulating tumor DNA (ctDNA) assay Guardant360 Liquid (G360) now includes a molecular tumor type (TT) and lung subtype (ST) predictor based on DNA methylation patterns. This study aimed to evaluate the concordance between G360 TT/ST prediction and tissue-based histology in a real-world sample of patients (pts) with NSCLC. A comparative analysis was conducted to understand differences in clinical characteristics between pts with and without G360 TT/ST prediction. **Methods:** This retrospective study included pts with NSCLC who underwent G360 testing from May to October of 2025. G360 predicted TT and ST (proportion of adenocarcinoma (AD), squamous cell carcinoma (SQ), and small cell carcinoma (SC)). Dominant TT was defined as the top cancer of origin prediction. Dominant ST was defined as a proportion >80%. G360 TT/ST was compared to tissue histology to determine concordance using Cohen's kappa coefficient. Demographic and clinical characteristics were collected, and statistical differences ($p<0.05$) between pts with and without TT/ST prediction were evaluated. **Results:** Of 145 pts who underwent a combined 176 G360 assays, 47 (32%) had assays predicting TT/ST, including 9 pts with TT prediction only and 38 with both. Of these 38 pts, 32 had tissue-proven AD, 3 had SQ, and 3 had poorly differentiated NSCLC. The overall accuracy of G360 TT prediction was 100% (47/47). The accuracy of ST prediction, excluding the 3 pts with poorly differentiated NSCLC, was 94% (33/35, k=0.72), with 2 discordant cases. One case was a pt with AD whose G360 at diagnosis predicted AD, but 4 months later predicted a SC component (40%). Both pts with discordant subtyping died within 4 months of their G360 result. Pts with TT/ST prediction were statistically younger, had more advanced disease, higher extra-thoracic metastatic burden, and higher ctDNA tumor fraction (TF) than pts without TT/ST prediction (Table 1). **Conclusions:** In this real-world analysis, G360 TT/ST prediction demonstrated good concordance with tissue-based histology, though prediction was more likely in pts with more advanced disease and higher TF. In the future, ctDNA-based TT/ST prediction may be a useful noninvasive tool to confirm primary lung cancer, classify histologic subtype, and identify histologic transformation, particularly during periods of disease progression, leading to better therapeutic decisions. Research Sponsor: None.

Baseline pt characteristics.

	(+) G360 TT/ST prediction (n=47)	(-) G360 TT/ST prediction (n=98)	*P*-value
Median age (IQR)	68 (64-77)	71 (60-74)	0.03
Female (%)	27 (57.4)	60 (61.2)	0.66
Stage III/IV (%)	46 (97.9)	67 (68.4)	<0.0001
Extra-thoracic metastases (%)	35 (74.5)	20 (20.4)	<0.0001
TF (%)	3.9	0.7	0.01

8540 **Poster Session**

Longitudinal circulating tumor DNA surveillance as predictor of progression in advanced non-small-cell lung cancer with long-term benefit to immunotherapy. First Author: Fang Wu, Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, China

Background: Radiographic assessments often lag behind biological progression, and reliable biomarkers to stratify the post-treatment progression risk remain lacking in advanced non-small-cell lung cancer (NSCLC). The clinical utility of minimal residual disease in advanced solid tumors also requires further evaluation. We investigated ctDNA-based post-immunotherapy molecular residual disease (ctDNA-iMRD) in advanced NSCLC with long-term benefit from immunotherapy and assessed its predictive value for subsequent progression. **Methods:** This prospective, observational, multicenter CR1STAL study, is designed to evaluate whether longitudinal ctDNA-iMRD surveillance can can stratify progression risk in advanced NSCLC patients with long-term benefit from immunotherapy (defined as non-PD at 12 months after treatment initiation). The primary endpoint was progression-free survival (PFS), defined as the time from enrollment to radiographic progression or death. For ctDNA detection, tumor-informed and tumor-agnostic approaches were selected according to tumor tissue availability. ctDNA-iMRD positive was defined as detectable ctDNA at at any surveillance timepoint. **Results:** A total of 97 advanced NSCLC patients were included, comprising 46 in the tumor-informed cohort and 51 in the tumor-agnostic cohort. At median follow-up of 36.4 months and a median ctDNA-iMRD surveillance duration of 10.5 months, 49 patients (50.5%) were classified as ctDNA-iMRD positive during longitudinal monitoring. Patients who were ctDNA-iMRD positive had a significantly shorter median PFS than those who remained ctDNA-iMRD negative (10.1 months vs not reached; HR = 4.85; 95% CI, 2.66 to 8.82; $p < 0.001$). ctDNA-iMRD detectable preceded radiographic progression by a median of 5.9 months. The positive and negative predictive values of longitudinal ctDNA-iMRD surveillance were 85.1% and 72.7%, respectively. Between ctDNA detection approachs, ctDNA-iMRD positive was strongly associated with increased progression risk in both the tumor-informed (HR = 6.29; $p < 0.001$) and tumor-agnostic (HR = 3.67; $p < 0.001$) cohorts. In addition, longitudinal ctDNA-iMRD negative was associated with long-term overall survival (HR = 0.22, 95% CI, 0.09 to 0.55; $p < 0.001$), with 2-year and 3-year OS rates of 97.2% and 89.8%, respectively. Furthermore, ctDNA clonal status and high ctDNA growth rates were correlated with early progression. **Conclusions:** Both tumor-informed and tumor-agnostic ctDNA-iMRD approaches showed strong predictive performance. Longitudinal ctDNA-iMRD surveillance effectively stratified advanced NSCLC patients at high risk of progression after achieving long-term benefit from immunotherapy, supporting its potential role in enabling earlier, risk-adapted intervention in future prospective studies. ClinicalTrials.gov Identifier: NCT05198154. Research Sponsor: None.

8541 **Poster Session**

Association of gut microbiota and peri-initiation proton pump inhibitor/antibiotic exposure with outcomes of atezolizumab-bevacizumab-carboplatin-paclitaxel regimen in patients with advanced non-squamous NSCLC: Prospective phase II study (K-TAIL-201). First Author: Hiroshi Wakui, Division of Respiratory Diseases, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan

Background: Concomitant medications that alter gut microbiome composition, such as proton pump inhibitors (PPIs) and antibiotics, have been suggested as possible modifiers of immune checkpoint inhibitor outcomes; however, there is a paucity of prospective data with pre-specified exposure windows during atezolizumab-bevacizumab-carboplatin-paclitaxel (ABCP) treatment. This study investigated the associations between peri-initiation PPI/antibiotic exposure and gut microbiota with clinical outcomes. **Methods:** K-TAIL-201 is a prospective, single-arm, phase II study (jRCT031200088) that enrolled Japanese patients with previously untreated advanced non-squamous non-small cell lung cancer (NSCLC) who received an induction ABCP regimen, followed by maintenance with atezolizumab plus bevacizumab. The primary endpoint was six-month progression-free survival (PFS) rate. PPI/antibiotic exposure was evaluated in two pre-specified windows: pre-treatment (up to 21 days before ABCP) and early on-treatment (the first 21 days of treatment). Longitudinal fecal samples were collected and analyzed using 16S rRNA gene sequencing. Exploratory analyses were conducted to investigate the relationships between exposure/microbiota features and outcomes. **Results:** Thirty-two patients were enrolled, with a median follow-up period of 20.6 months. The 6-month PFS rate was 59.4% (95% confidence interval (CI), 40.6–76.3), objective response rate was 50.0% (95% CI, 31.9–68.2), median PFS was 7.1 months (95% CI, 5.9–9.6), and the median overall survival (OS) was 24.3 months (95% CI, 18.7–not reached). Early on-treatment PPI exposure was associated with poorer outcomes, including shorter PFS (hazard ratio [HR] 7.07, $p < 0.001$) and OS (HR 5.66, p = 0.009), whereas pre-treatment PPI exposure was not associated with PFS of at least six months. Early on-treatment antibiotic exposure was associated with a lower 6-month PFS rate (21% versus 89%, $p < 0.001$), but showed no association with time-to-event PFS (HR 1.62, p = 0.41). Microbiota analyses revealed no significant differences in alpha or beta diversity by outcome or exposure group. However, *Bifidobacterium* was more frequently detected among responders. **Conclusions:** Early on-treatment (but not pre-treatment) PPI exposure is strongly associated with inferior PFS and OS in patients with advanced non-squamous NSCLC on ABCP regimen, supporting the clinical relevance of exposure timing. These findings suggest careful PPI use during the induction phase and warrant validation in larger prospective cohorts. Clinical trial information: 031200088. Research Sponsor: Chugai Pharmaceutical Co., Ltd.

8542 **Poster Session**

USP10 activity as sensitizer of lung adenocarcinoma to immune checkpoint inhibitors: Upregulating PD-L1 via the ANT3-mediated activation of the cGAS-STING pathway. First Author: Aman Wang, The First Affiliated Hospital of Dalian Medical University, Dalian, China

Background: Although immune checkpoint inhibitors (ICIs) have reshaped the treatment landscape for advanced lung adenocarcinoma (LUAD), response heterogeneity remains substantial. The cGAS–STING pathway plays a pivotal role in activating antitumor immune responses, yet its upstream regulatory mechanisms remain poorly defined. This study investigated the role of the deubiquitinating enzyme USP10 in remodeling the LUAD immune microenvironment and its mechanistic link to PD-L1 expression via the cGAS-STING axis to establish its potential as a predictive biomarker for ICIs efficacy. **Methods:** Interactions between USP10 and the mitochondrial protein ANT3 were characterized using Co-IP, LC-MS/MS, and in vitro deubiquitination assays. Mitochondrial DNA (mtDNA) leakage and cGAS-STING activation were assessed via immunofluorescence and qPCR. The therapeutic impact of USP10 on PD-1 blockade was evaluated in an orthotopic murine LUAD model. Furthermore, Furthermore, a clinical cohort of 228 patients with advanced driver-gene negative LUAD receiving first-line ICIs treatment was analyzed to correlate USP10 expression with objective response rate (ORR), disease control rate (DCR), and progression-free survival (PFS). **Results:** Mechanistically, USP10 directly interacts with mitochondrial adenine nucleotide translocase 3 (ANT3) and stabilizes its protein level by removing K48-linked ubiquitin chains. USP10-mediated ANT3 accumulation triggers mitochondrial stress and promotes mtDNA release into the cytosol, thereby activating the cGAS-STING-TBK1-IRF3 signaling pathway and ultimately driving transcriptional upregulation of PD-L1. In orthotopic LUAD models, USP10-overexpressing tumors exhibited an "inflamed" phenotype characterized by a significant increase in CD8+ T cell infiltration. USP10 expression levels sensitized tumors to immunotherapy; USP10-high tumors demonstrated dramatic regression upon anti-PD-1 treatment compared to controls. In the cohort of 228 patients, high USP10 expression was identified as a robust predictor of superior clinical benefit to first-line ICIs treatment . Patients in the USP10-high group achieved significantly prolonged PFS (p = 0.028), higher ORR (p = 0.037), and improved DCR (p = 0.041) compared to the USP10-low group. **Conclusions:** Our study identifies a novel USP10-ANT3-cGAS-STING-PD-L1 regulatory axis that converts "cold" tumors into "hot" tumors. By inducing a pro-inflammatory TIME, USP10 enhances the sensitivity of LUAD to ICIs. These findings establish USP10 as a promising predictive biomarker and a potential therapeutic target to optimize immunotherapy strategies in lung adenocarcinoma. Research Sponsor: None.

8543 **Poster Session**

Smoking–genomic discordance in metastatic non–small cell lung cancer. First Author: Ilit Turgeman, Lowe Center for Thoracic Oncology, Dana Farber Cancer Institute, Boston, MA

Background: Smoking is the dominant risk factor for lung cancer, yet clinical smoking history does not consistently align with the presence of tobacco-associated mutational patterns (C > A transversions). We hypothesized that smoking-genomic discordance identifies a biologically distinct subset of tumors arising through endogenous, aging-enriched mutational processes. **Methods:** We analyzed metastatic NSCLC patients with documented smoking history and tumor sequencing from a discovery cohort (n = 111) and an independent Dana-Farber validation cohort (n = 2,680). Tumors were stratified by presence or absence of C > A tobacco transversions. Endpoints included C > T transition burden as a surrogate for aging-related mutational processes, transition-to-transversion (Ti/Tv) ratio for endogenous mutational contribution, tumor mutational burden (TMB), oncogenic driver distribution, and first line treatment outcomes. Multivariable regression models adjusted for age, sex, smoking intensity, and driver genotype. **Results:** Among patients with smoking history, 30% of the discovery and 15.2% of the validation cohort lacked detectable C > A transversions, including 29% with > 30 pack-years. Smoking intensity correlated with C > A but not C > T burden, while C > T increased with age in binomial models, consistent with clock-like aging accumulation. C > A negative discordant tumors had higher C > T fractions and Ti/Tv ratios than both concordant smokers and never smokers ($p < 0.001$). After multivariable adjustment, discordance was independently associated with higher C > T fractions ($\beta = 0.21$, $p < 2\times10^{-16}$) and increased odds of aging-dominant profiles defined by C > T quartiles (OR = 9.2, $p < 2\times10^{-16}$). Associations varied by driver (interaction p = 0.007), with EGFR mutant and oncogene fusion driven tumors enriched for C > T high discordant profiles and weak coupling between smoking intensity and C > A burden. Discordance differed by age ($p = 7.6\times10^{-4}$): among patients < 50 years, discordant smokers paradoxically had highest C > T fractions, whereas never smokers showed greatest C > A transversions, suggesting bidirectional smoking-genomic mismatch. C > A negative discordant tumors had lower TMB and depletion of KRAS/STK11/KEAP1 alterations. PD-L1 and TMB predicted immunotherapy PFS only in C > A positive tumors, suggesting limitations of conventional biomarkers in discordant cases. Conversely, C > A presence correlated with shorter targeted therapy PFS across oncogenic drivers. **Conclusions:** Clinical smoking history alone does not capture the dominant mutational processes shaping NSCLC. Smoking–genomic discordance identifies a biologically coherent phenotype with endogenous aging-associated patterns, driver- and age- related heterogeneity, and distinct therapeutic vulnerabilities. These findings motivate research into germline susceptibility and environmental exposures that may underlie tobacco-independent mutagenesis. Research Sponsor: None.

8544 **Poster Session**

STK11 and/or KEAP1 alterations in KRAS-mutant NSCLC treated with immune checkpoint inhibitors or chemotherapy: An episode-based Project GENIE analysis. First Author: Aayushi Pareek, St. Bernards Medical Center, Jonesboro, AR

Background: STK11 and KEAP1 alterations are linked to aggressive biology in KRAS-mutant NSCLC and have been proposed to confer immune resistance and inferior outcomes with immune checkpoint inhibitor (ICI) though data remains inconsistent. We evaluated whether STK11 and/or KEAP1 alterations are associated with inferior overall survival (OS) and whether outcomes differ by treatment class (ICI vs chemotherapy) in a real-world clinic-genomic cohort. **Methods:** Using GENIE BPC NSCLC v2.0-public data, we created an episode-based cohort of KRAS-mutant NSCLC treatment regimens categorized as ICI or chemotherapy. STK11 and/or KEAP1 alteration status (single or dual) was the primary exposure. OS was measured from regimen start and analyzed with multivariable Cox models using patient-level clustering, adjusting for available covariates (age, sex, histology, tumor mutational burden [TMB], and KRAS G12C). We tested effect modification with an interaction term (STK11/KEAP1 × ICI). Sensitivity analyses included 3-, 6-, and 12-months landmark models and inverse probability of treatment weighting (IPTW). PD-L1, ECOG PS and line of therapy were not available. **Results:** We identified 542 treatment episodes from 293 patients (ICI = 149; chemo = 393) including 181 episodes that were STK11/KEAP1-altered. In the main cluster-robust model, STK11/KEAP1 alterations were associated with worse OS (aHR 1.68, 95% CI 1.27 - 2.24; $p < 0.001$). ICI (vs chemo) was associated with higher hazard ratio (aHR 1.76, 95% CI 1.42 - 2.18; $p < 0.001$) likely reflecting later-line use of ICI. The STK11/KEAP1 × ICI interaction was not significant as aHR 1.13, 95% CI 0.76 - 1.67; p = 0.559). In the 3-month landmark analysis STK11/KEAP1 remained adverse (aHR 1.61, 95% CI 1.19 - 2.18; p = 0.002), and the interaction estimate shifted below 1.0 (aHR 0.86, 95% CI 0.55 - 1.35; p = 0.519) suggesting a possible trend toward relatively greater ICI benefit among altered patients who survive beyond early attrition. Results were directionally consistent across 6- and 12-month landmark and IPTW analyses. **Conclusions:** In this real-world KRAS-mutant NSCLC cohort, STK11 and/or KEAP1 alterations were consistently associated with worse OS across treatment classes, supporting a primarily prognostic role. We did not find evidence of ICI-specific resistance by STK11/KEAP1 status, although modest interaction effects may be underpowered. Unmeasured confounding (ECOG PS, PD-L1 and line of therapy) remains a key limitation highlighting the need for larger, highly annotated datasets. Research Sponsor: None.

Model	STK11/KEAP1 aHR (95% CI); p	ICI vs Chemo aHR (95% CI); p	Interaction aHR (95% CI); p
Main	1.68 (1.27–2.24); <0.001	1.76 (1.42–2.18); <0.001	1.13 (0.76–1.67); 0.559
3-mo Landmark	1.61 (1.19–2.18); 0.002	1.76 (1.39–2.23); <0.001	0.86 (0.55–1.35); 0.519
IPTW	1.68 (1.27–2.24); <0.001	1.76 (1.42–2.19); <0.001	1.13 (0.75–1.70); 0.546

8545 **Poster Session**

AI-powered characterization of the tumor microenvironment landscape in HER2-overexpressing non–small cell lung cancer. First Author: Woochan Hwang, Lunit Inc., Seoul, South Korea

Background: Antibody-drug conjugate (ADC) targeting HER2 in NSCLC is an opportunity for biomarker-guided therapy independent of oncogenic driver status. As such, HER2 overexpressing (OE) tumors remain a clinically relevant yet under-characterized subgroup of NSCLC patients. Given the role of the tumor microenvironment (TME) in modulating response to ADCs, we applied AI-powered spatial analysis to comprehensively characterize the immunological landscape of NSCLC stratified by HER2 expression. **Methods:** We performed a retrospective analysis of a proprietary dataset comprising 2,054 H&E whole-slide images (WSIs) of NSCLC cases collected globally and enriched for HER2 OE tumors. HER2 OE was defined as IHC 3+ by pathologist reading based on ASCO/CAP guidelines and compared against IHC 0-2+. An AI-powered H&E analyzer (Lunit SCOPE IO) was used to quantify tumor-infiltrating lymphocytes (TILs) in the epithelial and stromal compartments. Immune phenotypes were classified as inflamed, excluded, or desert. For a subset of 1,099 cases with paired HER2 IHC WSIs, the proportion of tumor cells with 3+ intensity was quantified using an IHC analyzer (Lunit SCOPE HER2). Findings were further validated using 318 H&E WSIs and differential gene expression analysis of the TCGA Lung Adenocarcinoma (LUAD) cohort, stratified by ERBB2 protein expression (RPPA). **Results:** Of the 2,054 NSCLC cases, the primary analysis focused on adenocarcinoma cases (n = 1,641), which included 229 (14.0%) HER2 OE tumors. These tumors exhibited a significantly lower proportion of inflamed immune phenotype compared to the non-OE group (10.2% vs 22.1%, $P < 0.0001$). Intratumoral TIL and stromal TIL densities were reduced by 26.1% ($P < 0.0001$) and 14.7% ($P < 0.001$), respectively. Notably, even among HER2 OE tumors, a subset with high 3+ cell proportion (≥50% 3+ tumor cells) demonstrated a dose-dependent trend with an even lower inflamed proportion (3.7% vs 14.0%, P = 0.004) and reduced intratumoral TIL density (-36.7%, $P < 0.001$). The non-adenocarcinoma cohort (n = 413), where HER2 OE was present in 57 (13.8%) cases, showed a trend towards reduced intratumoral TIL density (-20.6%, P = 0.080). Analysis of H&E WSIs in TCGA LUAD validated that ERBB2-high tumors had significantly lower intratumoral TIL density (-16.1%, P = 0.027). Furthermore, gene expression analysis revealed that these tumors had down-regulation of immune effector (GZMB, PRF1) and exhaustion (LAG3) markers, while maintaining an epithelial phenotype (OCLN, CDH1) with decreased mesenchymal markers (CDH2). **Conclusions:** NSCLC with HER2 OE is characterized by a distinct, immune-cold phenotype that is more pronounced with higher HER2 expression. These findings highlight a unique TME landscape that warrants further investigation to understand its potential impact on therapeutic responses. Research Sponsor: None.

8546 **Poster Session**

Comparing becotarug plus osimertinib with a real-world osimertinib therapy cohort in platinum-refractory, advanced non–small cell lung cancer with EGFR exon 20 insertion. First Author: Jian Fang, Second Department of Thoracic Medical Oncology, Beijing Cancer Hospital, Beijing, Beijing, China

Background: EGFR exon 20 insertion (20ins)-positive non-small-cell lung cancer (NSCLC) is a rare subtype with limited therapeutic options and poor prognosis. Becotarug plus osimertinib showed encouraging activity and acceptable safety in a phase 1 study (NCT04448379). To assess its efficacy in EGFR 20ins-positive NSCLC, a phase 2 single-arm trial (NCT05132777) was initiated. To provide a comparator, a multicenter retrospective real-world study (NCT05513664) was served as an external control arm. **Methods:** Eligible patients in the phase 2 study had unresectable stage IIIB–IV NSCLC with EGFR exon 20 insertion mutations and ≥1 prior platinum-based chemotherapy; those relapsing within six months after neoadjuvant or adjuvant chemotherapy were also eligible. The external control comprised a real-world cohort treated with osimertinib, matched 1:1 on age, sex, stage, ECOG PS, brain metastases, and number of prior systemic therapies. The primary endpoint was independent review committee (IRC)-assessed objective response rate (ORR) in the trial arm and real-world ORR in the control arm. Secondary endpoints included disease control rate (DCR), duration of response (DoR) and progression-free survival (PFS). Safety was evaluated by incidence and severity of adverse events. **Results:** Of the 126 and 96 patients enrolled in the trial and control arms, respectively, 112 and 91 patients met criteria for the pre-matching cohort. After 1:1 propensity-score matching, 158 patients (79 per arm) comprised the post-matching population. Baseline characteristics were well balanced between arms, with 62.0% and 60.8% of patients, respectively, having received ≤1 prior line of systemic therapy. The IRC-assessed ORR was 46.8% (95% CI, 36.24–57.73) in the trial arm versus 7.6% (95% CI, 3.53–15.60) in the control arm. Notably, the lower bound of the trial-arm 95% CI (36.24%) exceeded the control-arm point estimate (7.6%). The absolute ORR difference was 39.2% (95% CI, 25.96–50.87; $P < 0.0001$), corresponding to an odds ratio of 10.72 (95% CI, 4.18–27.51). Furthermore, in a propensity score–matched analysis restricted to patients receiving osimertinib monotherapy (64 per arm), the combination therapy produced a greater ORR (42.2% [95% CI, 27.5-54.8], $P < 0.0001$). Higher DCR were achieved in trial arm compared to control arm (77.2% [95% CI, 66.8-85.1] vs 64.6% [95% CI, 53.6-74.2], $P = 0.080$). The median PFS in trial arm was significantly longer than that in control arm (6.9 vs. 4.8 months, $P = 0.007$). Other efficacy endpoints showed consistent trends favoring the combination therapy. The most common adverse events were EGFR-related mucocutaneous toxicities in both arms. **Conclusions:** This study further supports the efficacy and tolerability of becotarug plus osimertinib in patients with platinum-refractory, EGFR 20ins-positive NSCLC. Clinical trial information: NCT05513664; NCT05132777. Research Sponsor: Shanghai JMT-BIO Technology Co., Ltd.

8547 **Poster Session**

Genomic characterization of *SMARCA4*-mutant versus wild-type non–small cell lung cancer in a Chinese population: A large-scale next-generation sequencing study. First Author: Tongguo Si, Tianjin Cancer Hospital Airport Hospital, Tianjin, China

Background: SMARCA4 is a core component of the SWI/SNF chromatin remodeling complex and plays a critical role in transcriptional regulation and tumor suppression. SMARCA4 mutations define a biologically aggressive subset of lung cancer; however, their genomic landscape and clinical implications in Chinese patients with non–small cell lung cancer (NSCLC) remain incompletely characterized. This study aimed to comprehensively compare the genomic alteration profiles between SMARCA4-mutant and SMARCA4–wild-type NSCLC to better define distinct molecular subtypes and potential therapeutic implications. **Methods:** A total of 2,362 Chinese patients with NSCLC underwent comprehensive next-generation sequencing (NGS) using a 733-gene DNA panel. The prevalence and mutation spectrum of SMARCA4 were analyzed. Genomic alteration profiles, including co-occurring mutations, tumor mutational burden (TMB), and microsatellite instability (MSI) status, were systematically compared between SMARCA4-mutant and wild-type tumors. **Results:** SMARCA4 mutations were identified in 29 of 2,362 patients (1.23%). The mutation spectrum included frameshift (10.34%), nonframeshift (10.34%), nonsynonymous missense (51.72%), stop-gain (24.14%), and synonymous (3.45%) alterations. SMARCA4-mutant tumors exhibited a distinct genomic profile compared with wild-type tumors. Several genes were significantly enriched in the SMARCA4-mutant group, including STK11 (25.0% vs 5.8%, $P < 0.001$), FAM135B (25.0% vs 8.2%, P = 0.0068), CDH10 (17.9% vs 4.2%, P = 0.0063), and FUBP1 (7.1% vs 0.3%, P = 0.0036), suggesting increased genomic instability and aggressive tumor biology associated with chromatin remodeling dysfunction. In contrast, EGFR mutations were significantly enriched in the SMARCA4–wild-type group (49.1% vs 14.3%, $P < 0.001$), indicating a strong mutual exclusivity between SMARCA4 alterations and classical EGFR-driven oncogenesis. SMARCA4-mutant tumors also demonstrated a significantly higher tumor mutational burden compared with wild-type tumors (7.8 vs 3.1 muts/Mb, $P < 0.0001$), whereas no significant difference in MSI status was observed between the two groups. **Conclusions:** SMARCA4-mutant NSCLC represents a distinct molecular subtype characterized by enrichment of tumor suppressor gene alterations, chromatin remodeling dysfunction, and elevated TMB, while SMARCA4–wild-type tumors are predominantly driven by canonical tyrosine kinase oncogenes such as EGFR. These findings highlight fundamental differences in tumor biology and suggest divergent therapeutic strategies, with SMARCA4-mutant NSCLC potentially benefiting from immunotherapy-oriented approaches rather than traditional targeted therapies. Research Sponsor: None.

8548 **Poster Session**

Effect of gut microbiota–derived testosterone on distant metastasis in non–small cell lung cancer. First Author: Chen-Guang Liu, The Second Hospital of Dalian Medical University, Dalian, Liaoning, China

Background: Distant metastasis is the major cause of poor prognosis in non–small cell lung cancer (NSCLC). Emerging evidence suggests that gut microbiota and their metabolites influence tumor progression, but their role in NSCLC metastasis remains unclear. This study aimed to characterize gut microbiota and metabolic features associated with NSCLC metastasis and to elucidate the role and mechanism of the key metabolite testosterone. **Methods:** Fecal samples from 60 NSCLC patients (48 with distant metastasis, 12 without) were analyzed using metagenomic sequencing and untargeted metabolomics. Multi-omics integration with machine learning identified metastasis-associated metabolites. The effects of testosterone on NSCLC cell migration, invasion, and epithelial–mesenchymal transition (EMT) were evaluated in vitro (PC9, A549, H1299) and in vivo using a mouse metastasis model. Molecular mechanisms were investigated by Western blot, transcriptomics, Mendelian randomization analysis, and functional studies of FGF21. Finasteride was used as a pharmacologic antagonist. **Results:** Patients with metastatic NSCLC showed distinct gut microbiota profiles, with increased alpha diversity and altered community structure compared with non-metastatic patients. Opportunistic pathogens including Oscillospiraceae, Ruminococcus, and Actinobacteria were enriched in metastatic patients, while Fusobacteria was enriched in non-metastatic patients. Metabolomic analysis revealed significant enrichment of steroid-related metabolites in metastatic NSCLC, with markedly elevated testosterone levels. Testosterone demonstrated good predictive value for metastasis (AUC = 0.761). Testosterone significantly enhanced NSCLC cell migration and invasion and induced EMT, characterized by decreased E-cadherin and ZO-1 and increased N-cadherin and Snail expression. In vivo, testosterone promoted liver metastasis and EMT marker expression. Mechanistically, testosterone activated AKT/mTOR signaling, showed a causal association with AKT phosphorylation, and upregulated FGF21. Functional assays confirmed that FGF21 promoted EMT and metastasis via AKT/mTOR activation. Finasteride reversed testosterone-induced EMT, signaling activation, and metastasis by inhibiting the FGF21/AKT/mTOR axis. **Conclusions:** Metastatic NSCLC is associated with a distinct gut microbiota and metabolic profile. Gut microbiota–derived testosterone is a key metabolite that promotes NSCLC distant metastasis by activating the FGF21/AKT/mTOR pathway and inducing EMT. Finasteride effectively antagonizes this process, suggesting potential therapeutic value. The testosterone/FGF21/AKT/mTOR axis may serve as a biomarker and therapeutic target for metastatic NSCLC. Research Sponsor: National Natural Science Foundation of China; 82203056.

8549 **Poster Session**

Baseline CT-derived QVT score as predictor of bevacizumab benefit in advanced non-squamous NSCLC: A retrospective biomarker analysis of SWOG S0819. First Author: Kai Zhang, Picture Health Inc., Cleveland, OH

Background: Despite two decades of anti-angiogenic therapy in NSCLC, no predictive biomarker identifies which patients benefit. As VEGF-targeted combinations advance in clinical development, patient selection biomarkers remain a critical unmet need. QVT (Quantitative Vessel Tortuosity) Score is an automated imaging biomarker measuring chaotic tumor vasculature from baseline CT scans and has been shown to be associated with immune checkpoint inhibitor (ICI) outcomes. We hypothesized that QVT Score could identify patients with chaotic angiogenesis tumors and greater sensitivity to anti-angiogenic therapy. **Methods:** We analyzed a subset of 334 patients from the SWOG S0819 (NCT00946712) trial with treatment-naïve stage IV non-squamous NSCLC receiving carboplatin/paclitaxel with (56%) or without (44%) bevacizumab. QVT Scores were derived from baseline CTs based on radiologist-defined tumor annotations and radiomic features of tumor vasculature (e.g. vessel twisting, curvature, and branching). Overall survival (OS) was evaluated as the primary endpoint using Cox proportional hazards models with QVT $\times$ bevacizumab interaction terms. Bevacizumab was non-randomized in S0819 (physician/patient discretion): to address this, we employed doubly robust estimation combining inverse probability of treatment weighting (IPTW) with multivariable covariate adjustment for age, performance status, histology, smoking history, and stage. **Results:** The QVT Score $\times$ bevacizumab interaction was significant (p=0.007, doubly robust estimation) and stayed consistent across sensitivity analyses (p=0.017 multivariable; p=0.047 IPTW), suggesting differential treatment benefit based on pre-treatment vascular phenotype. QVT Score was strongly OS-associated without bevacizumab (HR=3.03, p=0.003) but not with bevacizumab (HR=1.71, p=0.079), consistent with mitigation of high-risk biology. Bevacizumab benefit increased across QVT quartiles (Table 1): patients in the highest quartile had a 60% reduction in mortality (HR=0.40, $p<0.001$), while patients in the lowest quartile showed no OS benefit (HR=0.89, p=0.64). **Conclusions:** Despite unfavorable prognosis on standard-of-care therapies (chemotherapy, ICIs), we found that patients with elevated baseline QVT Score may benefit from the addition of anti-angiogenic agents. As VEGF-targeted combinations including bispecific antibodies enter development, radiomic biomarkers may play a crucial role in enriching trial populations and enabling mechanistic longitudinal monitoring. These findings warrant prospective validation in independent randomized clinical trials. Research Sponsor: None.

Bevacizumab treatment effect by QVT score quartile.

QVT Score Quartile	N	Bevacizumab effect (Hazard Ratio)	P
Q1	84	0.89 (0.56 -1.42)	0.64
Q2	83	0.70 (0.44-1.12)	0.14
Q3	83	0.54 (0.34-0.85)	0.01
Q4	84	0.40 (0.24-0.65)	0.0003

8550 **Poster Session**

Impact of *KRAS* co-mutations on the efficacy of durvalumab in patients with locally advanced non–small cell lung cancer (LA-NSCLC) treated with concurrent chemoradiotherapy (ChRT). First Author: Jaime Rubio Perez, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Durvalumab improves survival after platinum-based ChRT in LA-NSCLC. Although immunotherapy is effective in KRAS-mutant tumors across treatment lines, co-mutations are associated with poorer prognosis and treatment resistance. Data efficacy in this context remains limited. **Methods:** We conducted a retrospective, single-institution analysis of patients with locally advanced NSCLC to evaluate the impact of KRAS mutations on progression-free survival (PFS) and overall survival (OS) after concurrent chemoradiotherapy (ChRT) and durvalumab, accounting for key clinical factors and co-mutations (TP53, STK11, KEAP1). Patients with other actionable genomic alterations (EGFR, ALK, ROS1, BRAF, MET, HER2, RET, FGFR) were excluded. PFS was defined from the first durvalumab dose to progression or death and estimated using the Kaplan–Meier method with comparisons by log-rank test. **Results:** A total of 290 patients were included (113 KRAS-mutant, 177 non-KRAS [non-AGA]). Median age was similar (69.7 vs 68.5 years), and baseline characteristics were comparable, except that KRAS-mutant patients were more often female(65% vs 38%, $p < 0.001$) and enriched for adenocarcinoma histology (90% vs 42%; squamous 2.7% vs 49%; p = 0.009) and PD-L1 expression (negative: 34% vs 48%; 1–49%: 25% vs 28%; $\geq$50%: 41% vs 34%). No significant differences in PFS were observed between KRAS and non-KRAS patients (median PFS: 22.9 months [95% CI, 16.0–29.2] vs 19.6 months [95% CI, 13.4–35.2]; log-rank p = 0.087), nor in overall survival (OS) (median OS: 44.5 months [95% CI, 34.4–NR] vs 40.9 months [95% CI, 30.0–59.4]; log-rank p = 0.40). In contrast, PFS differed significantly across KRAS-mutant subgroups: isolated KRAS mutations (median PFS 23.9 months [95% CI, 17.4–30.0]), KRAS with STK11 or KEAP1 co-mutations (8.3 months [95% CI, 3.8–20.8]), and concurrent KRAS/STK11/KEAP1 mutations (3.0 months [95% CI, 2.7–NR]; log-rank $p < 0.0001$). OS showed a similar numerical trend without statistical significance (49.4 months [95% CI, 37.4–NR], 27.3 months [95% CI, 18.4–NR], and 10.0 months [95% CI, 6.7–NR], respectively; log-rank p = 0.08). **Conclusions:** While KRAS mutations alone were not associated with inferior outcomes with durvalumab, concurrent STK11 and KEAP1 co-mutations were associated with markedly worse clinical outcomes. Research Sponsor: None.

8551 **Poster Session**

Serial ctDNA genomic profiling integrated with a networked molecular tumor board in first-line advanced NSCLC: The COPE randomized phase II trial. First Author: Antoine Italiano, Institut Bergonié, Bordeaux Cedex, France

Background: Circulating tumor DNA (ctDNA) complements tissue profiling and may provide early response information in advanced NSCLC, but prospective evidence is limited. **Methods:** COPE is an open-label, multicenter, randomized (2:1), two-arm non-comparative phase II trial in stage IIIB/IV NSCLC (NCT04258137). Arm A included FoundationOneLiquidCDx ctDNA profiling at baseline, week 3, each radiologic assessment, and progression with centralized molecular tumor board (MTB) review; Arm B used baseline tissue profiling and standard imaging. ctDNA-guided treatment changes were discretionary. The primary endpoint was18-month (mo) overall survival (OS) rate in Arm A vs a prespecified historical benchmark; secondary/exploratory endpoints included profiling success, objective response rate (ORR), ctDNA dynamics, and genomic evolution. **Results:** From 2020–2023, 176 patients (pts) were enrolled (Arm A n = 117; Arm B n = 59). At median follow-up 24.0 mo, 18-mo OS was 53.8% (95% CI 44.3–62.5) in Arm A (median OS 22.4 mo) and 65.7% (95% CI 52.0–76.3) in Arm B. Baseline plasma profiling rescued genotyping in 32/35 pts with tissue insufficiency, increasing genotyping success from 69% (tissue alone) to 97% (tissue + plasma). In Arm A, 90/117 had evaluable paired baseline and week-3 plasma samples. Among pts receiving first-line (1L) chemo-immunotherapy (chemo + ICI), early molecular response (MR), defined as ctDNA no longer detected at day 21 was strongly associated with more favorable outcomes, including higher ORR (81.8% vs 50.0%), longer progression-free survival (median PFS 22.9 vs 5.9 mo), and OS (18-mo OS 81.8% vs 57.1%). Similar results were observed in the overall study population. MR50, defined as ≥50% reduction at day 21, showed similar associations with more favorable outcomes. In pts on chemo + ICI with further ctDNA testing, those with durable MR50 through mo 5-9 had longer mPFS (23 mo vs 11 mo), similar to pts with early ctDNA clearance. Importantly, excluding pts who progressed at/before week 3, the median lead time in detecting progression on chemo + ICI with ctDNA prior to radiographic progression was 3.5 mo (N = 19pts). Among 59 responders with paired baseline and any on treatment plasma, 35 were treated with 1L chemo + ICI and 13 with 1L targeted therapy. Tumor-associated emergent alterations were detected in 37 pts (63%), with treatment-specific resistance patterns observed across therapeutic classes. **Conclusions:** COPE is, to our knowledge, the first randomized prospective study of sequential ctDNA profiling in 1L advanced NSCLC. Serial ctDNA analysis within a networked MTB model was feasible, improved baseline molecular profiling, and provided a strong exploratory early molecular response signal, supporting future ctDNA-guided interventional trials. Clinical trial information: NCT04258137. Research Sponsor: Foundation Medicine.

8552 **Poster Session**

Clinico-genomic landscape and prognostic impact of APC/CTNNB1 oncogenic alterations in non–small cell lung cancer. First Author: Leonardo Brunetti, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Genomic activation of the WNT/β-catenin pathway via APC loss-of-function or activating CTNNB1 mutations is well established across multiple cancer types, but its prevalence and genomic context in non–small cell lung cancer (NSCLC) remain poorly characterized. We systematically characterized the prevalence of APC and CTNNB1 alterations in NSCLC, and defined their mutational landscape and prognostic impact. **Methods:** We conducted a multicenter cohort study including patients with NSCLC whose tumors underwent targeted exon sequencing at Dana-Farber Cancer Institute (DFCI) and Memorial Sloan Kettering Cancer Center (MSKCC). Tumors were classified as APC-mutated, CTNNB1-mutated, or WNT-mutated (APC and/or CTNNB1 mutated). Pathogenic alterations were defined as oncogenic or likely oncogenic per OncoKB, or as missense variants with a REVEL score $>$ 0.5. Gene enrichment analyses used gene-wise logistic regression adjusted for tumor mutational burden (TMB), testing genes meeting a predefined prevalence threshold, with Bonferroni correction within each analysis. **Results:** In the DFCI cohort (N = 4,717), APC or CTNNB1 alterations were identified in 4.5% of NSCLC (212/4,717), including APC in 1.7% (79/4,717) and CTNNB1 in 2.8% (133/4,717), and were mutually exclusive. APC alterations were predominantly loss-of-function events (85.3% of qualifying APC variants) and splice-region/site variants (14.8%). CTNNB1 alterations were all missense mutations (100%), clustering in exon 3, consistent with β-catenin stabilization and gain-of-function. Relative to WNT–wild-type tumors, WNT-mutated NSCLC occurred more frequently in never-smokers (32% vs 24%, p = 0.03), patients of Asian race (11.8% vs 4.2%, $p < 0.001$), and non-squamous histology (99.5% vs 88.6%, $p < 0.001$). These tumors exhibited lower median PD-L1 expression ($p < 0.001$) and TMB (p = 0.03). Similarly, in the MSK cohort (N = 4710), the prevalence of APC and CTNNB1 alterations was 0.7% and 2.7%, respectively. Relative to WNT–wild-type tumors, WNT-altered NSCLC was significantly enriched for EGFR mutations (19.3% vs 10.5%; OR 2.18; $p < 0.01$) and SMAD4 mutations (7.1% vs 2.1%; OR 3.47; p = 0.0026), with relative depletion of KRAS alterations (20.8% vs 32.1%; OR 0.55; p = 0.027). External validation reproduced these findings, with WNT-altered tumors enriched for EGFR (42% vs 21.7%; OR 3.21: $p < 0.001$) alterations and depleted for KRAS (16.7% vs 29.4%; OR 0.47; p = 0.011). In the DFCI cohort, APC/CTNNB1 alterations were not associated with overall survival [HR 1.05 (0.88-1.25 95% CI; p = 0.57)]. **Conclusions:** Genomic activation of the WNT/β-catenin pathway is characterized by EGFR and SMAD4 co-alterations, relative KRAS depletion, and lower PD-L1 and TMB. These results suggest that WNT pathway alterations contribute to molecular heterogeneity in NSCLC with potential relevance for future biomarker and therapeutic studies. Research Sponsor: None.

8553 **Poster Session**

Use of LIF and LIFR expression to characterize survival and tumor microenvironment composition in lung adenocarcinoma. First Author: Michael Borecky, Department of Internal Medicine, Loma Linda University, Loma Linda, CA

Background: In lung adenocarcinoma (LUAD), EGFR-directed therapy has transformed clinical practice, yet heterogeneity in treatment response persists. Novel biomarkers are needed to refine therapeutic selection and identify new treatment targets. Leukemia inhibitory factor (LIF) and its receptor (LIFR) have emerged as potential mediators of the tumor microenvironment (TME), but their clinical significance in LUAD remains poorly defined. This study sought to investigate LIF and LIFR expression in LUAD, especially *EGFR*-mutant (EGFRm), and their TME composition and impact on survival outcomes. **Methods:** 10,041 LUAD tumors underwent next-generation sequencing of DNA (592-gene panel or whole exome sequencing) and RNA (whole transcriptome) at Caris Life Sciences. Tumors were stratified by LIR and LIFR RNA expression quartiles (Q1, low; Q4, high). QuantiSEQ was used to profile TME. Statistical analyses were performed using chi-square and Mann–Whitney U tests. Overall survival (OS) was estimated from insurance claims data using Cox proportional hazards models to calculate hazard ratios and log-rank tests to determine p-values. **Results:** In LUAD, LIF Q4 tumors demonstrated lower abundance of $CD8^+$ T cells (fold change (FC) 0.75, $p < 0.001$), but higher abundance of NK cells, M1 macrophages, neutrophils, Tregs and B cells vs LIF Q1 tumors (FC 1.1-1.4, $p < 0.001$). LIFR Q4 tumors exhibited higher abundance of dendritic cells, NK cells and M2 macrophages vs Q1 tumors (FC: 1.2-1.5, $p < 0.001$). For LIF, Q4 tumors had higher median MAPK activation (1.73 vs -0.93, $p < 0.001$) and T-cell–inflamed scores (94 vs -2, $p < 0.001$). LIFR Q4 tumors demonstrated higher MAPK activation (1.51 vs -0.83, $p < 0.001$), and higher T-cell–inflamed scores (105 vs -29, $p < 0.001$). IFN-γ signaling was modestly lower in LIF Q4 and LIFR Q4 tumors. Longer OS was observed in LIF Q1 vs Q4 (HR 0.79, 95% CI: 0.75-0.84, 25.1 vs 18.1 m, $p < 0.001$) but shorter OS in LIFR Q1 vs Q4 (HR 1.59 , 95% CI: 1.5-1.7, 14.0 vs 27.9 m, $p < 0.001$). *EGFR* mutations were significantly more frequent in LIF Q1 vs Q4 (21.2% vs 12.8%, $p < 0.001$) and LIFR Q4 vs Q1 (27.2% vs 7.6%, $p < 0.001$). In *EGFR*m tumors treated with osimertinib, OS differences based on LIF expression were accentuated:(LIF Q1 vs Q4, HR 0.681, 95% CI: 0.58-0.80, 35.7 vs 24.7 m, $p < 0.00001$). **Conclusions:** Findings demonstrate distinct transcriptional immune activation profiles between LIF- and LIFR-driven states, with superior survival in low LIF and high LIFR expressors. Despite elevated T-cell–inflamed scores, differences in immune cell composition suggest qualitative differences in immune activation between LIF- and LIFR-driven states. These findings support their relevance as prognostic and biologically informative biomarkers, and identify the LIF–LIFR axis as a key stratifier of immune state and survival heterogeneity in LUAD, with additional survival differences observed in EGFRm LUAD treated with osimertinib. Research Sponsor: None.

8554 **Poster Session**

A randomized phase III study of pembrolizumab versus pembrolizumab with carboplatin plus pemetrexed for locally advanced or metastatic nonsquamous non–small cell lung cancer with PD-L1 TPS ≥ 50%: LAPLACE-50. First Author: Yoshihito Kogure, Department of Respiratory Medicine, NHO Nagoya Medical Center, Nagoya, Japan

Background: For patients with advanced non-squamous non-small cell lung cancer (NSCLC) and high PD-L1 expression (TPS ≥50%), both pembrolizumab monotherapy and immune checkpoint inhibitor with platinum and pemetrexed combination chemotherapy are recognized as standard first-line therapies. However, direct head-to-head comparisons to determine the optimal strategy in this specific population are limited. We conducted a randomized phase III trial to compare these approaches. **Methods:** In this open-label, randomized phase III trial, previously untreated patients with advanced/metastatic non-squamous NSCLC and PD-L1 TPS ≥50% were randomized (1:1) to receive either pembrolizumab monotherapy (Arm A) or pembrolizumab plus carboplatin and pemetrexed (Arm B). The primary endpoint was progression-free survival (PFS) with a predefined non-inferiority margin of 1.25 for the hazard ratio (HR). Secondary endpoints included overall response rate (ORR), overall survival (OS), and safety. Due to slow accrual, the trial was terminated prematurely, and a final analysis was performed on the available cohort. **Results:** A total of 70 patients were randomized (Arm A, n=35; Arm B, n=35), and 69 patients were included in the full analysis set. Median PFS was 8.1 months in Arm A and 9.2 months in Arm B (HR 1.25; 90% CI, 0.77–2.04), and non-inferiority of pembrolizumab monotherapy was not demonstrated. ORR was 57.1% in Arm A and 73.5% in Arm B (odds ratio 0.49, 95% CI, 0.18–1.36; p=0.172). Median OS was 55.1 months in Arm A and 23.5 months in Arm B (HR 0.83, 95% CI, 0.42–1.63; p=0.663). Grade ≥3 hematologic toxicities were more frequent in Arm B. Serious adverse events occurred in 20.0% of patients in Arm A and 26.5% in Arm B. **Conclusions:** Although this trial was limited by early termination and did not statistically demonstrate the non-inferiority of pembrolizumab monotherapy in terms of PFS, the numerical OS favored the monotherapy group despite a lower ORR. These findings suggest that for patients with PD-L1 TPS ≥50%, pembrolizumab monotherapy remains a robust treatment option with a favorable safety profile, though the addition of chemotherapy may offer higher initial response rates. Clinical trial information: jRCTs031200078. Research Sponsor: NHO Multi-Center Clinical Research for Evidence-Based Medicine.

8555 **Poster Session**

Combination of golidocitinib (a JAK1 inhibitor) with anti–PD-1 antibody to improve tumor response and patient quality of life: Preliminary results from an ongoing JACKPOT 33 study. First Author: Jie Wang, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Chemo-immunotherapy remains the standard first-line treatment for advanced non-small cell lung cancer (NSCLC) without driver mutations. Unfortunately, treatment resistance is inevitable. Janus kinase (JAK) inhibition may improve the efficacy of immunotherapy by pivoting T cell exhaustion dynamics, enhancing and extending patient response. Herein, we report the anti-tumor efficacy and safety data from an ongoing phase 2 study (NCT06198907, JACKPOT33) evaluating golidocitinib, a JAK1-specific inhibitor, combined with sintilimab, an anti-PD-1 antibody, as first-line treatment in patients with PD-L1 positive advanced NSCLC without driver mutations. **Methods:** Eligible patients with advanced NSCLC with PD-L1 TPS $\geq$ 1% were enrolled in the study. Patients received two cycles of chemo-immunotherapy only, followed by golidocitinib 150 mg orally once daily plus sintilimab 200 mg intravenous every 3 weeks until disease progression, intolerance, up to 2 years of treatment, or other discontinuation criteria were met. The primary objective was to evaluate the anti-tumor efficacy, and the secondary objectives included safety and tolerability. **Results:** As of December 23, 2025, a total of 47 patients were enrolled in the JACKPOT33 study. The median age of these patients was 63 years, with 87.2% males, 61.7% with non-squamous histology, 40.4% with PD-L1 high (TPS $\geq$50%) and 59.6% with PD-L1 low (TPS 1-49%) expression. Most (74.5%) of the patients had metastatic disease at baseline, with 8.5% having brain metastasis. Per investigator assessment, the overall response rate (ORR) after two cycles of chemo-immunotherapy was 42.6%. Following the addition of golidocitinib with sintilimab, deeper tumor shrinkage and additional responders were observed, resulting in an ORR of 63.8% (30/47). The improvement in ORR with golidocitinib was most profound in patients with high PD-L1 levels, with rates of 84.2% vs. 50% in the high and low expression cohorts, respectively. No difference in ORR was observed between patients with squamous or non-squamous carcinoma (61.1% vs 65.5%). As of the data cut-off date, 32 out of 47 patients remained on treatment and benefiting. The longest treatment duration reached 15.9 months. The combination of golidocitinib and sintilimab was well tolerated. The incidence of immune-related adverse effects was markedly decreased, and patients' self-reported quality of life significantly improved. No new safety signal was observed. **Conclusions:** In treatment-naïve patients with advanced NSCLC, golidocitinib plus sintilimab following chemo-immunotherapy demonstrated encouraging and durable anti-tumor efficacy, particularly in those with high PD-L1 expression. A profound decrease in immune-related adverse effects was observed. Updated data will be presented at the conference. Clinical trial information: NCT06198907. Research Sponsor: None.

8556 **Poster Session**

A first-in-human (FIH), phase I/II open-label, dose-escalation and -expansion study of ILKN421H, an LNP mRNA encoding an IL2Rβγ selective IL-2v, as monotherapy and in combination with pembrolizumab, in patients with advanced solid tumors. First Author: Kai Wang, Department of Respiratory and Critical Care Medicine, Center for Oncology Medicine, the Fourth Affiliated Hospital of School of Medicine, and International School of Medicine, International Institutes of Medicine, Zhejiang University, Yiwu, China

Background: ILKN421H is an LNP mRNA encoding an IL2Rβγ selective IL-2v derivative fused with Human Serum Album. Preclinically, the novel LNP mRNA platform allowed expression and therefore extended plasma half-life of IL2v in animal models, which is not achieved with other protein-based IL-2 drugs. ILKN421H stimulated significant and sustained expansion of CD8 T cells for more than three weeks, with minimal expansion of regulatory T cells. Moreover, ILKN421H demonstrated superior efficacy than IL-2 based drugs in multiple cancer models and has an excellent safety profile in rodents and non-human primates. Therefore, the novel design of ILKN421H has the potential to fully unleash the antitumor effects of the IL-2 pathway while mitigating unwanted toxicity. **Methods:** This first-in-human, open label phase 1 study evaluates the safety, tolerability, and initial efficacy of ILKN421H with or without pembrolizumab in patients with advanced solid tumors. The design includes two portions of the study: Parts A, ILKN421H monotherapy in which patients receive intravenous ILKN421H once every 3 weeks (Q3W) and Part B in which patients receive ILKN421H in combination with pembrolizumab (200 mg on day 1), both intravenous Q3W. Both portions of the study consist of 3+3 escalation cohorts to define maximum tolerated dose (MTD). If response signal is observed in a given dose cohort, additional 10 patients will be enrolled in the expansion portion of the study to further evaluate the safety and efficacy. The trial is ongoing and data as of 5/7/2024 is presented in this abstract. **Results:** A total of 47 participants were enrolled so far. In Part A, 9 patients in three dose cohorts received ILKN421H. All patients demonstrated high and prolonged plasma level of IL-2, and remarkable elevation of CD8 T cells (up to 5 folds) and NK cells (up to 25 folds). No dose-limiting toxicities (DLT) were observed. In Part B, 38 patients in three dose cohorts were enrolled, 24 of which are 1L advanced NSCLC. All patients showed robustly increased CD8 T cells and NK cells, and well tolerated safety profile (TESAE=26%). At the cut-off date (Nov 25th, 2025), of the 22 efficacy evaluable 1L NSCLC patients regardless of the PDL1 expression levels, 17 were evaluated to be PR (ORR=77.2%), and 50% PFS was not reached and was projected to be more than 14 month. In PDL1 negative patients (TPS $<$1%), 3 out of 6 patients achieved PR (ORR=50%). **Conclusions:** ILKN421H was generally well tolerated at the current dose level, which already demonstrated high and prolonged plasma level of IL-2, and robust immune stimulatory activity in promoting CD8 T cells and NK cells proliferation. Initial signs of antitumor efficacy were seen in combination with pembrolizumab. Clinical trial information: NCT05978102. Research Sponsor: iLeukon Therapeutics.

8557 **Poster Session**

Race-associated clinicogenomic predictors in non-small cell lung cancer treated with immune checkpoint inhibitors. First Author: Nirosha Perera King, Department of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: PD-L1 low and STK11 mutation associate with immune checkpoint inhibitor (ICI) resistance in non-small cell lung cancer (NSCLC), but appear differentially expressed among racial ethnic groups. This has not been validated in large, diverse studies. **Methods:** We retrospectively studied NSCLC patients 18 or older, without targetable EGFR or ALK alterations, treated with frontline ICI between January 2014 and February 2020 at MD Anderson Cancer Center and University of Illinois Chicago. We analyzed clinicogenomic and survival characteristics by race/ethnicity. Differences in clinicogenomic predictors were assessed through log-rank and chi-squared comparison of proportions tests. Survival differences were estimated via Kaplan-Meier method. **Results:** 1694 patients met inclusion criteria, 383 (22.6%) were minorities. Poor performance status (PS 2-3) was most frequent in African American (AA) (32.5%) and Native Alaskan/Hawaiian or American Indian (NAHAI) (27.3%) patients (p=0.005) (Table). Heavy smoking was more frequent in White (50.3%) patients. PD-L1 $<$1% was most prevalent among Asian (31.3%) and least prevalent among Hispanic/Latino (HL) (15.8%) patients (p=0.001). STK11 mutation rate was most prevalent in AA (14.7%) and least prevalent in HL (6.9%) and Asian (2.5%) patients (p=0.056). Median overall survival (OS) was lower (21.3, 23.5, and 24.3 months) for HL, NAHAI, and AA patients, and higher (25.4 and 30.6 months) for White and Asian patients, respectively ($p<0.01$). **Conclusions:** Our dual center study with 22% minority patient representation shows self-reported race can result in biological differences, because of ancestry and/or environmental differences. AA, HL, and NAHAI patients had lower rates of heavy smoking and different clinicogenomic patterns than White patients. AA tended towards higher prevalence of STK11 mutation—while not statistically significant, it was overall not highly represented in the sample. In line with these poor prognostic factors, AA had statistically significant lower median overall survival (OS) than their White and Asian counterparts. Asians had the lowest rates of heavy smoking and STK11 mutation, highest rates of PD-L1$<$1%, and highest median OS. HL had the lowest OS, with low prevalence of PD-L1$<$1% and STK11 mutation – future studies should evaluate other clinicogenomic factors to determine potential culprits. Research Sponsor: The University of Texas MD Anderson Lung Moon Shot Program and the MD Anderson Cancer Center Support Grant P30 CA016672.

	White	Black or African American (AA)	Hispanic or Latino (HL)	Asian	Native Alaskan/ Hawaiian or American Indian (NAHAI)	p-value
Total cohort n=1694, No. (%)	1311 (77.4)	191 (11.3)	101 (6.1)	80 (4.7)	11 (0.5)	
ECOG PS 2-3 at ICI start	267 (20.4)	62 (32.5)	23 (22.8)	20 (25.0)	3 (27.3)	**0.005**
20+ Pack Years Smoking	659 (50.3)	77 (40.3)	26 (25.7)	19 (23.8)	5 (45.5)	**4.9×10^{-9}**
PD-L1 <1%	317 (24.2)	47 (24.6)	16 (15.8)	25 (31.3)	1 (9.1)	**0.001**
$STK11_{mut}$	129 (9.8)	22 (14.7)	7 (6.9)	2 (2.5)	1 (9.1)	0.056
Median OS (mo)	25.4	24.3	21.3	30.6	23.5	**< 0.01**

8558 **Poster Session**

Safety and efficacy of CS2009, a first-in-class PD-1/VEGF/CTLA-4 trispecific antibody, in patients with advanced non-small cell lung cancer: Results from a phase 1/2 study. First Author: Wei Li, Department of Medical Oncology, Shanghai East Hospital, Shanghai, China

Background: CS2009 is a novel PD-1/VEGF/CTLA-4 trispecific antibody. An ongoing phase 1/2 study is evaluating its safety, tolerability, PK, PD, and anti-tumor activity as a single agent and in combination with systemic treatment in patients (pts) with advanced solid tumors. This study comprises a phase 1 dose escalation and phase 2 dose expansion. Here, we report the initial efficacy and safety data from advanced non-small cell lung cancer (NSCLC) pts treated in first-line and later-line settings. **Methods:** The study enrolled both treatment-naïve (1L) and heavily pre-treated later-line ($\geq$2L) NSCLC pts. The $\geq$2L group included previously treated pts without known actionable oncogenic alterations (AGA) who had progressed on at least one prior line containing an anti-PD-1/L1 antibody and platinum-based chemotherapy; these pts received CS2009 at 10, 20, 30, or 45 mg/kg, i.v., Q3W, until disease progression or intolerance. The 1L cohort enrolled treatment-naïve pts with PD-L1 TPS $\geq$1% NSCLC without known AGA; these pts were randomized 1:1 to receive CS2009 at 20 or 30 mg/kg, i.v., Q3W, until disease progression or intolerance. Safety was assessed in all treated pts. Efficacy was assessed in pts who had at least one post-baseline tumor assessment per RECIST v1.1. **Results:** As of Jan. 4, 2026, 40 pts with $\geq$2L NSCLC were treated with CS2009 across four dose levels (10 mg/kg, n=3; 20 mg/kg, n=12; 30 mg/kg, n=20; 45 mg/kg, n=5). Median age was 67 (range 37-78) years; 72.5% were Asian, 27.5% were White; 77.5% were male; 77.5% had ECOG PS 1 at baseline. Among 30 efficacy-evaluable pts, ORR was 20.0% (6 PRs); in 16 pts treated at 30 mg/kg, ORR was 25.0% (4 PRs). Any-grade and grade $\geq$3 treatment-related adverse events (TRAEs) occurred in 27 (67.5%) and 8 (20.0%) pts, respectively. The most common TRAEs were proteinuria (12.5%), hypertension (12.5%), bilirubin conjugated increased (10.0%), and fatigue (10.0%), which were mostly grade 1 or 2, except for grade $\geq$3 hypertension in two pts. No treatment-related deaths were reported. TRAEs led to discontinuation in 3 (7.5%) pts. More mature $\geq$2L efficacy data with additional evaluable pts will be presented at the conference. As of Jan. 4, 2026, 19 pts with 1L NSCLC (PD-L1 TPS $\geq$1%) were randomized to receive CS2009 at 20 mg/kg (n=10) or 30 mg/kg (n=9). Median age was 69 (range 52-82) years; 84.2% were male; 89.5% had ECOG PS 1 at baseline. Preliminary encouraging efficacy and favorable safety signals were observed. Updated efficacy and safety data in approximately 50 1L pts will be disclosed at the conference. **Conclusions:** CS2009, as a first-in-class trispecific antibody targeting PD-1, VEGF, and CTLA-4, demonstrated a favorable safety profile and clinically meaningful anti-tumor activity in advanced NSCLC pts without known AGA. These findings warrant further investigation of CS2009 in this population. Clinical trial information: NCT06741644. Research Sponsor: CStone Pharmaceuticals.

8559 **Poster Session**

A phase II study of ubenimex combined with pembrolizumab, nab-paclitaxel, and carboplatin for previously untreated advanced squamous non−small cell lung cancer: TORG2241(UBE-Q). First Author: Akane Narumi, Sendai Kousei Hospital, Sendai, Miyagi, Japan

Background: Pembrolizumab plus platinum-based chemotherapy is a standard first-line treatment for previously untreated advanced squamous non-small cell lung cancer (NSCLC) based on the KEYNOTE-407 trial. Ubenimex, an oral CD13/aminopeptidase inhibitor, has immunostimulatory and antitumor activity. We conducted a phase II trial to assess the safety and efficacy of ubenimex in combination with pembrolizumab, nab-paclitaxel, and carboplatin in patients with previously untreated advanced squamous NSCLC. **Methods:** This study was a prospective, multicenter, single-arm phase II trial. Eligible patients with previously untreated advanced squamous NSCLC received ubenimex orally plus 4 cycles of pembrolizumab, nab-paclitaxel, and carboplatin, followed by continuous administration of ubenimex and pembrolizumab for a maximum of 2 years. To confirm tolerability, the daily dose of ubenimex started at level 1 (30mg/day), which was increased to levels 2 (60 mg/day) and 3 (120 mg/day) according to the escalation criteria, with a standard 3 + 3 design for achieving the target dose-limiting toxicity (DLT) rate of 33%. The efficacy, safety, and tolerability of ubenimex at the determined dose level were analyzed. The primary efficacy endpoint was objective response rate (ORR) by independent central review, estimated descriptively with a 90% confidence interval; the ORR in the KEYNOTE-407 (62.6%) served as a reference value for study design. **Results:** No DLTs were observed across dose levels 1−3. Therefore, level 3 was selected as the recommended dose. From January 2024 to January 2025, 28 patients were enrolled from 18 institutions, and all patients were evaluable for efficacy and safety. Baseline characteristics were male/female 25/3; median age 72 (range, 40-86); ECOG PS 0/1 12/16. The ORR was 71.4% (90% CI, 54.3-84.9). With a median follow-up of 12.8 months, median progression-free survival (PFS) was 16.8 months (95% CI, 5.6-not reached); median overall survival (OS) was not reached. Grade 3/4 adverse events included pneumonitis (3.6%), anemia (46.4%), febrile neutropenia (10.7%). There was no treatment-related death. **Conclusions:** Ubenimex with 120 mg/day (60 mg twice daily) combined with pembrolizumab, nab-paclitaxel, and carboplatin was feasible and showed encouraging antitumor activity with manageable safety in previously untreated advanced squamous NSCLC, supporting further randomized evaluation. Clinical trial information: jRCT2031210707. Research Sponsor: Nippon Kayaku Co., Ltd.

8560 **Poster Session**

FF-10832 liposomal gemcitabine monotherapy or combination with pembrolizumab in patients with advanced non−small cell lung cancer. First Author: Hamid Emamekhoo, University of Wisconsin-Madison, Madison, WI

Background: FF-10832, a stable liposomal formulation of gemcitabine with a prolonged half-life (mean $t_{1/2}$ of 26 hours compared to ~3 hours for gemcitabine HCl), has demonstrated single agent activity in patients (pts) with solid tumors. In pre-clinical models, FF-10832 has yielded superior anti-tumor activity compared to gemcitabine alone and in combination with PD-1 inhibitors. Following a safety run-in, we investigated the clinical activity of FF-10832 in an expansion study, administered alone or in combination with pembrolizumab (PEM), in pts with advanced/metastatic (m) NSCLC (NCT05318573). **Methods:** In the open-label single arm safety run-in, 40 mg/m^2 FF-10832 and 200 mg PEM every 3 weeks was established as safe and tolerable in 12 pts including 6 mNSCLC patients with unlimited prior therapies. The trial was expanded using this regimen. Pts were randomized to receive FF-10832 alone (mono) or FF-10832 +PEM (combo). Eligibility stipulated up to 3 prior therapies in the advanced/metastatic setting with prior disease progression (PD) on platinum and PD-(L)1-directed therapy. Pts receiving FF-10832 monotherapy could add PEM to FF-10832 upon PD determined by RECIST 1.1. To be evaluable for anti-tumor activity, pts must have had at least one RECIST assessment ≥6 weeks after baseline. All pts were evaluable for safety. **Results:** A total of 41 NSCLC pts were treated with FF-10832 (N=21) or FF-1032+PEM (N=20); median # of prior therapies was 2 for both arms. RECIST evaluability was achieved in 30 pts (14/16; mono/combo); 11 pts (7/4; mono/combo) came off study before evaluation for anti-tumor activity. No objective responses were observed. Stable disease (SD) was recorded in 9/14 pts in the mono arm and 13/16 in the combo arm; 4 pts (1 mono/3 combo) with >20% tumor shrinkage. Median time on study for the mono and combo arms was 9 (1 − 48.1) and 12.1 (1.1 − 44) weeks, respectively. Median (95% CI) PFS in months: mono arm, 2.7 (1.4 − 4.3); combo arm, 2.8 (1.9 − 5.5). Five mono pts began FF-10832+PEM treatment upon PD, two that remain on combination therapy with SD for 23 and 33 weeks after progressing on FF-10832 monotherapy. Related AEs were similar in mono vs combo arms; those in ≥15% of pts in each arm included nausea, vomiting, fatigue, rash, infusion-related reaction, and anemia. Related grade ≥3 AEs occurred in 33% (mono) and 45% (combo) of pts. The only attributable grade ≥3 events in >1 pt were in the combo arm (n): anemia (3), fatigue (2), dyspnea (2), and lymphopenia (2). FF-10832 PK showed a profile consistent with that previously reported (terminal $t_{1/2}$, ~30 hours). Overall survival data are pending. **Conclusions:** FF-10832 alone or in combination with PEM in platinum-CPI refractory pts proved tolerable with a safety profile matching previous experience. There were no objective responses, but the majority of evaluable pts had SD at 1st assessment, some with tumor shrinkage. Aggregate mPFS was 2.7 mos. Clinical trial information: NCT05318573. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

8561 **Poster Session**

Disease kinetics and practice patterns in ≥ 4-year long-term beneficiaries of immune checkpoint inhibitors for advanced non−small cell lung cancer. First Author: Masahiro Torasawa, Department of Respiratory Medicine, Juntendo University Faculty of Medicine and Graduate School of Medicine, Tokyo, Japan

Background: Immune checkpoint inhibitors (ICIs) have transformed outcomes in advanced non-small cell lung cancer (NSCLC), enabling durable responses in a subset of patients (pts). However, detailed clinical trajectories and patterns of late disease progression among long-term survivors remain poorly characterized. **Methods:** This multicenter retrospective cohort study enrolled advanced NSCLC pts who initiated ICI-containing therapy between January 2015 and April 2020. Long-term beneficiaries (LTBs) were defined as pts achieving both overall survival (OS) and time to next cytotoxic chemotherapy (TTNC) ≥4 years (yrs). We performed 4-yr landmark analyses, characterized late progression (defined as the first radiographic progression ≥4 yrs from ICI initiation), and evaluated cause-specific mortality using competing risk analysis. **Results:** Of 3,144 pts, 537 (17%) survived ≥4 yrs; 295 (9.4%) were LTBs (median follow-up, 68.6 months; only 8.1% lost to follow-up). ICI was initiated as first-line therapy in 186 pts (63.1%) and as second-line or later in 109 pts (36.9%). The median age was 67 yrs, and PD-L1 Tumor Proportion Score ≥50% was observed in 57%. Among 235 LTBs without progression at 4 yrs, 156 (66%) had discontinued ICI. Among pts progression-free at 4 yrs, lung cancer-specific OS (LC-OS) rates from ICI initiation were 97.8% at 6 yrs and 88.0% at 8 yrs (Table). Late progression occurred in 26 of 235 progression-free LTBs (11.1%); all had progression involving ≤5 lesions. The median interval from the last non-progressive assessment to the first assessment meeting radiographic progression was 98 days (IQR, 56−189), with a median sum-of-diameters growth rate of 6.2 mm/month (IQR, 3.4−9.6). Local therapy was selected in 42% after progression. Among 22 deaths occurring ≥4 yrs after ICI initiation, only 7 (32%) were lung cancer−related, whereas 15 (68%) were due to other causes, including five secondary malignancies. Competing risk analysis showed that the cumulative incidence of other-cause death consistently exceeded that of lung cancer death throughout follow-up (lung cancer death: 0.5% at 5 yrs to 10.7% at 8 yrs; other-cause death: 2.3% to 14.8%). **Conclusions:** LTBs of ICIs achieved durable disease control, with LC-OS approaching 90% at 8 yrs. In these pts, late progression was uncommon, typically involving ≤5 lesions with modest growth kinetics, often treated with local therapy without requiring immediate systemic treatment. The predominance of non-lung cancer mortality suggests that survivorship care addressing second malignancies is increasingly important in this population. Research Sponsor: None.

Landmark survival analysis from 4 years after ICI initiation (n=235).

Timepoint	PFS	TTNC	OS	Other Cause OS	LC-OS
5-year	90.1%	96.4%	97.2%	97.7%	99.5%
6-year	82.4%	90.3%	91.8%	93.8%	97.8%
7-year	74.6%	81.3%	82.7%	87.3%	94.7%
8-year	69.9%	74.3%	74.5%	84.7%	88.0%

8562 **Poster Session**

Impact of immunotherapy era on survival in stage IV non−small cell lung cancer. First Author: Tahreem Malik, Department of Internal Medicine, HCA Healthcare/USF Morsani College of Medicine GME: HCA Florida Citrus, Inverness, FL

Background: The introduction of immunotherapy (IO) has transformed treatment paradigms in Stage IV non-small cell lung cancer (NSCLC). However, large-scale population-based evidence quantifying its impact on survival remains limited. We evaluated overall survival trends before and after the IO era using SEER data. **Methods:** We identified patients diagnosed with Stage IV NSCLC from 2006 to 2020 in the SEER 17 database. Patients were grouped by era: pre-IO (2006−2014) and post-IO (2015−2020). Demographics, histology, and socioeconomic variables were included. Overall survival (OS) was assessed using Kaplan-Meier analysis. Multivariable Cox proportional hazards models estimated hazard ratios (HRs) with 95% confidence intervals (CIs) adjusting for age, sex, race, and histology. **Results:** A total of 101,243 Stage IV NSCLC patients were included. The post-IO era was associated with a 19% reduction in mortality compared to the pre-IO era (HR 0.81; 95% CI 0.79−0.82; p<0.001). Older age (≥75 years) conferred increased mortality risk (HR 1.32; 95% CI 1.30−1.34; p<0.001), while younger patients (<65 years) had better outcomes (HR 0.91; 95% CI 0.89−0.93; p<0.001). Male sex (HR 1.16; 95% CI 1.14−1.17; p<0.001), non-adenocarcinoma histology (HR 1.30; 95% CI 1.28−1.32; p<0.001), and Black race (reference group) were independently associated with worse survival. White (HR 0.83; 95% CI 0.81−0.85; p<0.001) and Other races (HR 0.75; 95% CI 0.73−0.77; p<0.001) demonstrated survival advantages. Kaplan-Meier curves confirmed significantly improved OS in the post-IO era (median OS 8 vs 10 months, log-rank p<0.001). **Conclusions:** This large population-based study confirms a significant survival benefit in Stage IV NSCLC patients diagnosed in the immunotherapy era, alongside expected demographic and histologic disparities. These findings support the real-world impact of immunotherapy and underscore the need for continued efforts to address survival inequities. Research Sponsor: None.

8563 **Poster Session**

Ablation plus immunotherapy in advanced NSCLC patients who develop oligo-residual disease after anti–PD-1/L1 therapy: Updated results from the BOOSTER trial. First Author: Shuo Yang, Department of Medical Oncology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, Shanghai, China

Background: Local consolidative therapy (LCT) has been demonstrated to augment the survival benefits of immunotherapy in non-small cell lung cancer (NSCLC) patients with oligo-residual disease (ORD) in the phase2 BOOSTER Trial (ChiCTR2000032479) as previously reported (2024 WCLC OA05.03; *Signal Transduction and Targeted Therapy* 2025). Here we report updated data with longer follow-up. **Methods:** This randomized, phase 2 trial enrolled patients with advanced NSCLC who developed oligo-residual disease after anti-PD-1/L1 therapy, defined as partial response or stable disease as the best response with residual tumors confined to a maximum of three organs and five lesions. Participants were randomly assigned (2:1) to receive ablation (thermal ablation or cryoablation) plus immunotherapy or immunotherapy maintenance alone. The primary endpoint was progression-free survival (PFS). The secondary endpoints were overall survival (OS), safety, patterns of disease progression and immunogenic changes after ablation. **Results:** Among 65 patients enrolled, the full analysis set finally included 42 patients in ablation plus immunotherapy group and 20 patients in immunotherapy maintenance group. In this updated data cutoff (December 2025) compared to the prior data cutoff (March 2024), median duration of follow-up has increased from 17.8 months to 28.9 months. Patients receiving ablation were associated with significantly longer PFS than those without ablation (median 28.1 vs. 12.8 months, $p < 0.001$, HR = 0.310, 95%CI 0.169–0.596). The median OS was not reached in either group. The 48-months OS rate were 79.0% (95% CI, 59.5–90.0) in ablation group and 67.6% (95% CI, 41.3–84.1) in the without ablation group. Updated subgroup analysis further suggested a trend of superior efficacy of cryoablation (n=13) compared with thermal ablation (n=29), with a median PFS of 37.6 versus 22.4 months, respectively (p=0.028). The safety profile of ablation combining with immunotherapy was similar to previously reported, and most of the adverse events were well managed. **Conclusions:** With extended follow up, the updated data suggested that the addition of local consolidative ablation confers durable clinical benefit in patients with advanced NSCLC who develop ORD after anti-PD-1/L1 therapy. Cryoablation was associated with potentially superior survival outcomes compared with thermal ablation. Clinical trial information: ChiCTR2000032479. Research Sponsor: None.

8564 **Poster Session**

Inhaled delivery of KB707, a novel HSV-based immunotherapy, in combination with pembrolizumab in advanced non–small cell lung cancer: A phase 1/2 study. First Author: Wen Wee Ma, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH

Background: Though immune checkpoint inhibitors (ICIs) have significantly improved the treatment for lung cancers, resistance invariably develops and novel approaches are needed to overcome such resistance and enhance anti-tumor immunity. KB707 is a replication-defective herpes simplex virus type 1 (HSV-1)-based vector engineered to deliver human interleukin (IL)-12 and IL-2 to induce both innate and adaptive antitumor immunity. Inhaled KB707 monotherapy was previously shown to be well tolerated with encouraging efficacy in pts with advanced non-small cell lung cancer (aNSCLC): 4 of 11 pts achieved partial response (PR). Delivery of IL-12/IL-2 by inhaled KB707 may significantly increase the anti-tumor efficacy of ICI (pembro) in pts with aNSCLC who are relapsed or refractory to standard therapy. Extending from the monotherapy results, the safety and efficacy of adding inhaled KB707 to pembro in pts with aNSCLC is presented. **Methods:** KB707-02 is a Phase 1/2, open-label, multicenter study of inhaled KB707 (NCT06228326). Eligible pts with at least one measurable lung lesion at screening and histological confirmation of stage 3 or 4 NSCLC received nebulized KB707 (10^9 PFU) every 2 weeks and pembro (400 mg) every 6 weeks. Pts must have previously received one line of prior ICI, with or without platinum-based chemotherapy. The primary objective is to assess safety and tolerability per CTCAE v5.0, with a secondary objective to evaluate preliminary efficacy per RECIST 1.1. **Results:** As of 01 Jan 2026, a total of 21 pts (11 female) were enrolled and received at least one dose of inhaled KB707 plus pembro. The majority of treatment-related adverse events (TRAE) have been mild to moderate in severity and transient. Consistent with known adverse event profiles of IL-2 and IL-12, the most common TRAE were flu-like symptoms (fever, chills, vomiting, fatigue) and dyspnea. The efficacy population (n=16) received at least one treatment cycle and had at least one evaluation per RECIST 1.1. The 16 pts were of advanced age (median 72 [50-88] years old) and heavily treated (3 median lines of prior therapies). The ORR was 31.3% (5/16) and DCR was 75% (12/16) with 5 pts achieving confirmed PR and 7 with stable disease (SD). Median treatment duration was 24.1 weeks (6.1-71.9) with 5 out of 16 pts remaining on study. Median overall survival and progression free survival were not reached. **Conclusions:** Delivery of IL-12/IL-2 by inhaled KB707 in combination with pembro was well tolerated and encouraging antitumor effects were observed in heavily treated aNSCLC, as evidenced by 31.3% ORR and 75% DCR. The study is proceeding with enrollment of an additional cohort to further evaluate inhaled KB707 in combination with docetaxel in aNSCLC. Clinical trial information: NCT06228326. Research Sponsor: Krystal Biotech Inc.

8565 **Poster Session**

Impact of *STK11/KEAP1/SMARCA4* co-mutations in RAS-activated *KRAS* wild-type metastatic NSCLC treated with immune checkpoint inhibitors. First Author: Cassio Murilo Hidalgo-Filho, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: RAS-activated *KRAS* wild-type (RASa/KRASwt) non-small cell lung cancer (NSCLC) shares key biological features with KRAS-mutant (KRASm) tumors, including MAPK pathway activation. In KRASm NSCLC, co-mutations in *STK11*, *KEAP1* and *SMARCA4* are associated with poor outcomes to immune checkpoint inhibitors (ICI). Whether these alterations similarly impact outcomes in RASa/KRASwt tumors is unknown. **Methods:** We analyzed patients with metastatic NSCLC treated with ICI at Dana-Farber Cancer Institute. RASa/KRASwt tumors were defined by pathogenic alterations in RAS–MAPK pathway genes (*NF1*, *NF2*, *BRAF*, *RAF1*, *MAP2K1/2*, *MAP3K1*, *MAPK1*, *PTPN11*, *SOS1*, *HRAS*, *NRAS*, *RIT1*, *RASA1*, *GNAS*). Co-mutations in *STK11*, *KEAP1* and *SMARCA4* were evaluated using targeted exome sequencing. Survival analyses were performed using log-rank test and survival risks estimated with Cox regression models. **Results:** Among 1,215 patients included, 492 (40%) had KRASm tumors and 264 (22%) were RASa/KRASwt. Compared with RASa/KRASwt tumors, KRASm tumors were more frequent in female patients (65% vs 50%, $p<0.001$), ever-smokers (93% vs 86%, p=0.004) and non-squamous histology (98% vs 88%, $p<0.001$). The frequency of *KEAP1* (21% vs 22%), *STK11* (26% vs 20%) and *SMARCA4* (10% vs 12%) mutations was similar between the groups. High tumor mutation burden (≥10 mut/Mb) was more frequent in RASa/KRASwt tumors (60% vs 46%, $p<0.001$), while PD-L1 expression, age and performance status were comparable. Within the RASa/KRASwt cohort, 103 patients (39%) had co-mutations in *STK11*/KEAP1/*SMARCA4* and were more frequently ever-smokers compared with non co-mutated RASa/KRASwt (95% vs 80%, $p<0.001$), with otherwise similar clinical characteristics. As expected, co-mutations were associated with shorter median progression free survival (mPFS) and median overall survival (OS) in KRASm group (mPFS: 4.4 vs 6.2 mo., HR:1.33 (1.1-1.62), p=0.004; mOS: 11.4 vs 21.7 months(mo), HR:1.43 (1.16-1.78), $p<0.001$). However, among RASa/KRASwt tumors, concurrent mutations in STK11/KEAP1/SMARCA4 had no impact on survival outcomes (mPFS: 5.9 vs 4.1 mo., HR:0.79 (0.6-1.02), p=0.07; mOS: 15.8 vs 14.8 mo, HR: 1.02 (0.77-1.35), p=0.89). This differential effect was confirmed by a significant interaction between RAS status and co-mutational status (aHR 1.71, p=0.004). For OS, interaction analysis did not show a differential effect of co-mutations according to RAS status (aHR 1.43; p=0.073). **Conclusions:** Known co-mutations that confer worse outcomes to ICI in KRASm NSCLC do not appear to have the same impact in KRASwt tumors with other RAS activating mutations. RASa/KRASwt tumors with co-mutations behave more similarly to KRAS wild-type NSCLCs, highlighting biological heterogeneity within RAS-driven tumors and potential implications for patient selection for treatment intensification or de-escalation strategies. Research Sponsor: None.

8566 **Poster Session**

Effect of dual immune checkpoint inhibitors (ICI) by the time of infusion in advanced non–small cell lung cancer (NSCLC): A secondary analysis of CCTG BR34 trial. First Author: Sze Wah Samuel Chan, McMaster University, Hamilton, ON, Canada

Background: There is increasing evidence suggesting the impact of circadian biology on ICI efficacy in solid tumours, though evidence for dual checkpoint blockade is limited. We conducted a secondary analysis of BR.34 to assess whether time of infusion (TOI) correlates with outcomes with durvalumab–tremelimumab ± platinum chemotherapy in advanced EGFR/ALK-negative NSCLC. **Methods:** Patients were classified into the AM group when ≥80% of the PD-1 inhibitor infusions were started before 13:00 (threshold based on prior literature); otherwise, they were placed into the PM group. OS and PFS were analyzed using Cox models adjusted for imbalanced baseline factors. Sensitivity analyses were performed to assess correlations with other TOI thresholds. **Results:** TOI was evaluable for 296/301 patients; 186 were AM and 110 PM. PM infusion was associated with longer median OS (19.1 vs 13.4 months (m); HR 0.58, 95% CI 0.41–0.82) and median PFS (8.3 vs 4.1 m; HR 0.67, 95% CI 0.51–0.88). The improvement in OS associated with the PM group was consistent across both arms. In the multivariable analyses, PM administration remained associated with improved OS (adjusted HR (aHR) 0.62, 95% CI 0.44–0.88) and PFS (aHR 0.73, 95% CI 0.55–0.96). Sensitivity analyses using an alternative threshold of ≥60% of the PD-1 inhibitor infusions started before 1300 yielded consistent trends. Using a median TOI of 11:00 AM as an additional threshold, later infusions were also associated with longer OS (HR 0.77, 95% CI 0.56–1.05), with similar trends across both treatment arms. There was no apparent difference in fatal adverse events (n = 4), with two in the AM and two in the PM group. Serious adverse effects that led to therapy discontinuation also did not significantly differ between AM vs. PM in the IO-alone group (3 vs. 5) or the IO-chemo group (6 vs. 4). **Conclusions:** Afternoon infusion of dual ICI ± chemotherapy was associated with improved survival in BR.34, in contrast to earlier reports with anti-PD-1 therapy. These findings highlight the potential for regimen- and disease-specific chronotherapeutic effects and support the need for prospective trials across tumour types and of different checkpoint inhibitor combinations. References: 1. Leighl NB, et al. *J Thorac Oncol.* 2022;17(3):434–445. 2. Karaboué A, et al. *Br J Cancer.* 2024;131:783–796. Research Sponsor: Grants to the Canadian Cancer Trials Group from the Canadian Cancer Society Research Institute and AstraZeneca.

Baseline factors.

Baseline Factors	IO-AM (n)	IO-PM (n)	IO-CHEMO-AM (n)	IO-CHEMO-PM (n)
Sex (F/M)	41/54	28/25	42/49	27/30
Age (<65/≥65)	48/47	84/64	36/55	32/25
ECOG (0/1)	22/73	23/30	26/65	20/37
Disease Stage (IVA/IVB)	26/69	22/31	34/57	19/38
Histological subtype (NSq/Sq)	77/18	44/9	73/18	48/9
Liver Metastases (N/Y)	78/17	42/11	68/23	50/7
Brain Metastases (N/Y)	76/19	45/8	82/9	44/13
PD-L1 Expression (<1/1-49/≥50%/Unknown)	37/25/20/13	23/19/7/4	33/27/16/15	22/17/13/5
TMB (<20/≥20 mut/MB)	74/21	39/14	69/22	46/11

Nsq = non-squamous, Sq = squamous.

8567 Poster Session

A phase 2 study of plinabulin (Plin)/docetaxel (Doc) plus pembrolizumab (Pemb) in metastatic NSCLC (mNSCLC) after acquired resistance (AR) to anti–PD-1/L1 alone or in chemotherapy combination: Efficacy and immunophenotyping. First Author: Yan Xu, Peking Union Medical College Hospital, Beijing, China

Background: PD-1/L1 inhibitors have become a part of 1L treatment for EGFR/ALK wild-type NSCLC. However, >60% patients (pts) develop AR associated with T cell exhaustion and defective antigen presentation. Doc remains a mainstay for pts who relapse after anti-PD-1/L1 therapy, while multiple late-stage clinical trials have failed in comparison. Plin is a first-in-class, brain-penetrating dendritic cell maturation agent with clinically validated potential to restore antigen presentation/T cell function after AR to PD-1/L1 inhibitors. Plin also reduces severe neutropenia and thereby increases Doc tolerability. In a global phase 3 study (Dublin-3, n=559), Plin/Doc outperformed Doc with significant OS/PFS/ORR benefits, doubling of 2-/3-year OS rates, and 80% reduction in G4 neutropenia ($p<0.0001$). The aim of this study was to assess the efficacy/safety of Plin/Doc plus Pemb in mNSCLC after anti-PD-1/L1 based therapy. **Methods:** This single-arm phase 2 trial (NCT05599789; Study 303) enrolled 47 pts after immediate progression on anti-PD-1/L1 alone or combined with platinum doublets. Pts received Plin 30mg/m2, Doc 75mg/m2 and Pemb 200mg, on Day 1 in 21-day cycles. The primary/secondary endpoints at the median follow-up of 20.6 months (mo) are tabulated. For immunophenotyping, whole blood from baseline and post treatment were analyzed by flow cytometry. **Results:** At the data cutoff date of 31-Dec-2025, cORR was 18.2% with 79.5% DCR. mPFS was 7.0 mo, and mDoR at 9.3 mo. While mOS was 34 mo, the 24-mo OS rates were 64.3% (ITT), 71.1% (NSQ), and 52.0% (SQ). In all endpoints assessed, prior Pemb exposure did not reduce the efficacy of this regimen. Whole blood analysis indicated that activated CD4+/CD8+ T cells and proliferating Ki67+CD8 T cells were significantly increased post two cycles of treatment. Also observed were concurrent elevations of Ki67+B cells and CD38+NK cells. **Conclusions:** Plin/doc plus Pemb shows promising efficacy in mNSCLC with AR to anti-PD-1/L1 confirmed by immune activation post-treatment. TRAEs were manageable. These findings along with DUBLIN-3 support a global confirmatory study in EGFR/ALK wild-type NSQ NSCLC following progression on anti-PD1/L1 based therapy. Clinical trial information: NCT05599789. Research Sponsor: BeyondSpring Pharmaceuticals, Inc.

Efficacy endpoints.

Endpoint*	ITT (N=47)	NSQ (N=30)	SQ (N=17)
Primary endpoint			
cORR (RECIST 1.1)	18.2%	13.8%	26.7%
Secondary endpoints			
mPFS (RECIST 1.1)	7.0 mo	7.7 mo	5.5 mo
mOS	34 mo	(not reached)	34 mo
mDoR (RECIST 1.1)	9.3 mo	(not reached)	9.1 mo
DCR (PR+SD > 4 mo)	79.5%	82.8%	73.3%
12-mo OS rate	78.2%	80.0%	74.8%
24-mo OS rate	64.3%	71.1%	52.0%

*cORR/DoR/DCR: 44 evaluable pts; PFS/OS & follow-up duration: ITT.

8568 Poster Session

Efficacy, safety, and cytokine profiling with addition of the toll-like receptor (TLR) 7/8 dual agonist EIK1001 to standard of care (SOC) first-line (1L) therapy: The phase 2 TeLuRide-005 trial in stage 4 NSCLC. First Author: Bo Wang, Sarah Cannon Research Institute at Willamette Valley Cancer Institute and Research Center, Eugene, OR

Background: EIK1001 a TLR 7/8 dual agonist activates dendritic cells via both innate and adaptive pathways. This mechanism of action (MOA) associated with cytokine (CK) release and T-cell differentiation is complementary to immune checkpoint inhibitors (ICIs) that enhance anti-tumor T-cell activity. It provides rationale to add EIK1001 to SOC chemotherapy (chemo) + ICI in Stage 4 NSCLC, a disease with unmet therapeutic needs. **Methods:** TeLuRide-005 (NCT#06246110) is an ongoing multicenter, open-label study of intravenous weekly (wk) EIK1001 combined with SOC q3-wk pembro + chemo in treatment-naïve patients (pts) with Stage 4 NSCLC. The nonsquamous (NSQ) and squamous (SQ) cohorts completed accrual in May '25 and Jan '26, respectively. CK were sampled pre- and post EIK1001 treatment (PT) on Day 1 of Cycle (C) 1 and C4. **Results:** 71 pts (median age: 68, male:73%) were treated. An ORR of 61% and DCR of 90% were observed for the pooled study population. Cytokine release syndrome (CRS) events were of low grade: 4 pts with Grade 1 and 3 pts with Grade 2. For safety, and efficacy by histology, see Table. 71% of NSQ remain progression free at 8 months and despite over 11 months of follow-up, median PFS is not yet accurately estimable. Type 1 and 2 interferons (IFN) and Interleukin 6/8 (IL6/8) increased PT on C1. By C4, baseline IP-10, an IFN inducible protein that is a T-cell chemotactant, was upregulated by a median of 1.6- fold increase from baseline C1D1. Conversely, CRS-associated IL6 and IL8 were reduced or less inducible on C4D1 than on C1D1, consistent with our observation of only one pt. experiencing CRS after C4. **Conclusions:** 1L EIK1001 + SOC demonstrates encouraging efficacy in Stage 4 NSCLC with evidence of durable effect. AEs were similar to SOC alone and CRS events were low-grade. Cytokine data support the MOA of the TLR 7/8 dual agonist, EIK1001, and reduced inducibility of IL6/IL8 PT by C4 may suggest CRS likelihood diminishes with time. Clinical trial information: NCT#06246110. Research Sponsor: None.

Safety Results		
At least 1 ≥ Grade 3 TEAE % (n/N)	76.1% (54/71)	
Serious adverse event (SAE) % (n/N)	46.5% (33/71)	
Efficacy Results	**NSQ (n=39)**	**SQ (n=32)**
Months of follow up (f/u), median (range)	11.2 (5.5-23.0)	6.5 (0.5-19.1)
Progression-Free Survival at 8 months* (95% CI)	70.7% (56.9-87.8%)	NA
Objective Response Rate (ORR), % (95% CI)**	55.6% (38.1-72.1%)	68.0% (46.5-85.1%)
Disease Control Rate (DCR), % (95% CI)	83.3% (67.2-93.6%)	100% (86.3-100%)
Duration of Response (DOR), Range in Months	2.1+ - 15.1+	1.0 - 13.2+

NA: Not Analyzed due to short duration of follow-up; *4 scan opportunities at 8 months; **Response evaluable.

8569 Poster Session

SHR-1701 combined with fuzuloparib and chemotherapy as first-line therapy for advanced lung squamous cell carcinoma: Efficacy and safety results from a phase II study. First Author: Yongchang Zhang, Clinical Trials Center, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Changsha, China

Background: Although immune checkpoint inhibitors are established in the treatment of advanced lung squamous cell carcinoma (LUSC), many patients derive limited or no durable benefit, underscoring the need for novel therapeutic strategies. However, poly (ADP-ribose) polymerase inhibitors (PARPi) can upregulate PD-L1 expression and promote immune-mediated response, which may increase the efficacy of anti-PD-(L)1 based therapy. Additionally, blocking TGF-b signaling has the potential to facilitate the recovery from chemo-induced myelosuppression. This phase II study evaluates the efficacy and safety for first-line approach combining SHR-1701, a bifunctional anti–PD-L1/TGF-β trap, with the PARP inhibitor fuzuloparib, combined with standard chemotherapy, which may potentiate anti-tumor immunity. To our knowledge, this is the first clinical investigation of this multi-pathway targeting strategy in advanced LUSC. **Methods:** Treatment-naïve patients with advanced LUSC received induction therapy with SHR-1701 (30 mg/kg IV q3w) plus platinum-based chemotherapy (investigator's choice) for 4 cycles. Patients with disease control proceeded to maintenance therapy with SHR-1701 (same dose) plus oral fuzuloparib (100 mg twice daily) until progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) by Blinded Independent Review Committee (BIRC) per RECIST v1.1. Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. **Results:** Between February 2023 and June 2025, 71 treatment-naïve advanced LUSC patients were enrolled (median age 65 years; 96% male). As of data cutoff (December 1, 2025; median follow-up 17.4 months), 57 patients (80.3%) had started maintenance therapy (median 12 cycles). Disease progression or death had occurred in 27 of 71 patients (38.0%) by the cutoff date. Median PFS was 11.0 months (95% CI, 8.1 to not estimable). Among 69 response-evaluable patients, best overall response included 1 complete response (1.4%), 56 partial responses (81.2%, including 46 confirmed), and 11 stable disease (15.9%), yielding an unconfirmed ORR of 82.6% (57/69), a confirmed ORR of 68.1% (47/69), and a DCR of 98.6% (68/69). OS data were immature; the 12-month OS rate was 83.0% (95% CI 71.1–90.2). Treatment-related adverse events occurred in 94.4% (67/71) of patients, most commonly anemia (42.3%), increased blood creatinine (19.7%), and proteinuria (18.3%). No new safety signals were observed. **Conclusions:** SHR-1701 plus fuzuloparib and chemotherapy as first-line therapy demonstrated promising anti-tumor activity and a manageable safety profile in patients with advanced LUSC. Clinical trial information: NCT04937972. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

8570 Poster Session

1L olomorasib plus pembrolizumab +/- chemotherapy in *KRAS* G12C-mutant NSCLC patients +/- a prior cycle of SOC: Results from LOXO-RAS 20001 and SUNRAY-01. First Author: Timothy F. Burns, The Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: Real-world data suggests allowing 1 cycle of standard of care (SOC) prior to enrollment into first-line (1L) NSCLC trials of targeted therapies could expand the potential enrollable population by accommodating molecular testing turnaround time and enabling a more representative patient (pt) population. Here, we report results from 1L pts who did or did not receive 1 prior cycle of SOC in LOXO-RAS-20001 and the dose optimization/safety lead-in of SUNRAY-01, which investigated olomorasib, a KRAS G12C inhibitor, with pembrolizumab +/- chemotherapy. **Methods:** Pts with advanced *KRAS* G12C-mutant NSCLC, PD-L1 0-100% and ECOG PS 0-1 were eligible to receive olomorasib (50 or 100 mg, orally BID) with either pembrolizumab (doublet) or pembrolizumab + chemotherapy (quad) at their physician's discretion. One cycle of SOC prior to enrollment was permitted when timely initiation of treatment was clinically indicated, this included pembrolizumab (doublet) and pemetrexed + platinum +/- pembrolizumab, or pembrolizumab alone (quad). ORR was assessed in the efficacy evaluable population, defined as pts with ≥1 post-baseline response assessment or who discontinued treatment before the first response assessment. Safety was assessed across all treated pts. **Results:** As of 6 June 2025, 85 pts received the doublet and 77 pts received the quad; 13 pts (15%) and 23 pts (30%) received 1 prior cycle of SOC, respectively. Baseline characteristics of pts who did and did not receive 1 prior cycle of SOC were comparable. Accounting for small sample sizes, efficacy and safety were broadly similar across both the doublet and the quad among those who did and did not receive a prior cycle of SOC (Table). **Conclusions:** Treatment with 1 cycle of SOC prior to enrollment appeared to have no detrimental effect on safety and efficacy outcomes of olomorasib in combination with pembrolizumab +/- chemotherapy in pts with *KRAS* G12C NSCLC. This is the first analysis of the clinical impact of 1 prior cycle of SOC in a NSCLC clinical trial, allowing early access to treatment if clinically indicated. Implementation of this strategy in SUNRAY-01 and other 1L NSCLC trials may expand enrollment and allow for a more representative pt population. Clinical trial information: NCT04956640, NCT06119581. Research Sponsor: Eli Lilly and Company.

1L treatment outcomes.

	Olomorasib + Pembrolizumab		Olomorasib + Pembrolizumab + Chemotherapy	
	1 prior cycle of SOC n=13	No prior SOC n=72	1 prior cycle of SOC n=23	No prior SOC n=54
ORR, (%)	76.9	71.8	73.9	55.6
(95 %, CI)	(46.2, 95.0)	(59.9, 81.9)	(51.6, 89.8)	(41.4, 69.1)
DCR, %	100	88.7	95.7	87.0
(95 %, CI)	(75.3, 100.0)	(79.0, 95.0)	(78.1, 99.9)	(75.1, 94.6)
TRAE All Grade / Grade 3+ (%)	100 / 30.8	87.5 / 41.7	95.7 / 26.1	96.3 / 59.3
Grade ≥3 Hepatic Events* (%)	15.4	22.2	0	22.2
Grade ≥3 Diarrhea (%)	7.7	6.9	4.3	5.6
Grade ≥3 Neutropenia (%)	0	0	4.3	16.7
Discontinuation of regimen	15.4	11.1	0	11.1
Median Duration of Treatment, mo (IQR)	10.3 (5.6-13.3)		7.9 (3.8-9.9)	

*Consolidated term.

8571 **Poster Session**

Phase II study of multidisciplinary therapy combined with pembrolizumab for patients with synchronous oligometastatic non-small cell lung cancer: TRAP-OLIGO study (WJOG11118L). First Author: Hideyuki Harada, Division of Radiation and Proton Therapy Center, Shizuoka Cancer Center, Nagaizumi, Japan

Background: Several clinical trials have demonstrated that local ablative therapy (LAT) to all lesions, including primary site, may provide a survival benefit for patients with oligometastatic non-small cell lung cancer (NSCLC). However, few studies have evaluated the efficacy of integrating immune checkpoint inhibitors with chemotherapy and LAT. This study aimed to evaluate the efficacy of multimodal therapy combining platinum-doublet chemotherapy plus pembrolizumab followed by LAT to all sites of disease in patients with synchronous oligometastatic NSCLC. **Methods:** This multicenter, single-arm, phase II trial enrolled treatment-naive patients with stage IV NSCLC and three or fewer metastatic lesions. Patients received 4 cycles of induction therapy consisting of pembrolizumab plus platinum-doublet chemotherapy. Patients then received LAT to all residual lesions, followed by maintenance therapy with pembrolizumab. The primary endpoint was the 24-month progression-free survival (PFS) rate from the initiation of LAT. Secondary endpoints included safety, response to induction therapy, PFS, overall survival (OS), and the proportion of patients who underwent LAT. The threshold and expected 24-month PFS rates were set at 25% and 60%, respectively, with a one-sided alpha of 0.025 and 80% power. **Results:** Between October 30, 2020, and August 12, 2022, 30 patients were enrolled. At enrollment, seven patients had one metastasis (23.3%), 14 had two (46.7%), and 9 had three (30%). Twenty-three patients (76.7%) received LAT to all residual disease sites. The 24-month PFS rate from the initiation of LAT was 56.5% (95% CI, 34.3–79.8%). The median PFS from the initiation of LAT was 25.8 months (95% CI, 11.7–not reached). The OS rates at 24 and 36 months from the initiation of LAT were 78.0% (95% CI, 55.0–90.2%) and 61.6% (95% CI, 37.2–78.9%), respectively. During the LAT phase, grade 3/4 adverse events occurred in 3 patients (13.0%). No treatment-related deaths were observed. **Conclusions:** The TRAP-OLIGO study met its primary endpoint with the lower limit of the 95% CI exceeding the threshold, demonstrating that multimodal therapy combining platinum-based chemotherapy plus pembrolizumab and LAT provides favorable efficacy for patients with synchronous oligometastatic NSCLC. These findings suggest that this integrated approach is a promising treatment strategy for this population. Trial registration: Japan Registry of Clinical Trials, jRCTs041200046. Clinical trial information: jRCTs041200046. Research Sponsor: None.

8572 **Poster Session**

Immune-related adverse event severity and clinical outcomes with immune checkpoint inhibitor immunotherapy in participants with non–small cell lung cancer: Analysis of the lung MAP sub-studies S1400A, S1400I, S1400F, and S1800A. First Author: Diane Tseng, Fred Hutch Cancer Center, Seattle, WA

Background: Immune checkpoint inhibitors (ICIs) have advanced the treatment paradigm for non-small cell lung cancer (NSCLC), but ICIs are associated with risk of immune-related adverse events (irAEs). There is an unmet need to better understand how the severity of irAE impacts the clinical outcome of NSCLC treated with ICIs. We hypothesized that participants (pts) with lower grade irAEs would have better outcomes than those with higher grade irAEs and those without irAEs. **Methods:** We evaluated outcomes in Lung-MAP pts with advanced NSCLC treated with ICIs in the 2L setting (S1400A [durvalumab vs docetaxel], S1400I [nivolumab +/- ipilimumab], S1400F [durvalumab + tremelimumab], and S1800A [pembrolizumab + ramucirumab vs standard-of-care]), using 6-, 12-, and 24-week landmark analyses of the relationship between irAE severity (Grade(G) 1 or 2 vs G3 or 4 and vs no irAE) and overall survival (OS) from the landmark timepoint. OS was compared between groups using Cox Proportional hazards model with separate analyses for ICI-naïve (S1400A and S1400I) and ICI-exposed (S1400F and S1800A). **Results:** Analyses included 315 ICI-naïve and 127 ICI-refractory pts. In the ICI- naïve cohort, no irAEs and G 3-4 irAEs were associated with inferior OS compared with G1-2 irAEs by 12 wks of treatment (no irAEs: HR 1.68, CI 1.28 – 2.22, $p < 0.0005$ G3-4: HR 2.28, CI 1.47 – 3.53; $p < 0.0005$). This difference in OS between the irAE groups was consistent at the 6 wk ($p = 0.006$) and 24 wk ($p = 0.03$) landmark timepoints. See table for outcomes in the ICI naïve cohort. In the ICI-exposed cohort, there was no difference in OS between the irAE groups at any landmark timepoint (6 weeks: $p = 0.39$; 24 weeks: $p = 0.98$). **Conclusions:** In the ICI-naïve cohort, G1-2 irAEs in were associated with better OS compared to no irAEs and G3-4 irAEs for all landmark times. This association was not observed in the ICI-exposed cohort. Additional analyses will incorporate molecular and immune features evaluating risk and severity of irAEs. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA18088; National Cancer Institute/U.S. National Institutes of Health; U10CA180819.

Outcomes for ICI naïve cohort.

Landmark Time	irAE Group	N	mOS (95% CI)
6 weeks	No irAE	160	9.0 (7.9-10.9)
	G 1-2	124	14.6 (10.1-19.0)
	G 3-4	20	5.9 (3.5-10.8)
12 weeks	No irAE	124	8.2 (6.5-9.8)
	G 1-2	130	15.4 (11.5-9.8)
	G 3-4	29	5.3 (2.9 - 8.0)
24 weeks	No irAE	77	7.0 (5.8-9.8)
	G 1-2	121	14.9 (10.9-18.5)
	G 3-4	34	5.9 (3.1-13.9)

8573 **Poster Session**

Durable efficacy of first-line necitumumab plus pembrolizumab in PD-L1–high advanced NSCLC: Final results of the phase II K-TAIL-202 study. First Author: Atsushi Horiike, Division of Medical Oncology, Department of Medicine, School of Medicine, Showa Medical University, Tokyo, Japan

Background: Pembrolizumab is a standard 1st line treatment for advanced non–small cell lung cancer (NSCLC) with high PD-L1 expression (tumor proportion score [TPS] $\geq$50%); however, durable benefit is achieved in only a subset of patients. Prior pembrolizumab-based combination strategies (e.g., anti-TIGIT) have inconsistently improved outcomes over pembrolizumab monotherapy in this setting. Epidermal growth factor receptor (EGFR) signaling may promote immune evasion by stabilizing PD-L1 expression and shaping an immunosuppressive tumor microenvironment, providing a rationale for combining the anti-EGFR antibody necitumumab with pembrolizumab. We therefore evaluated the efficacy and safety of necitumumab plus pembrolizumab in treatment-naive patients with PD-L1–high advanced NSCLC. **Methods:** K-TAIL-202 (jRCT2031200248) was an open-label, multicenter, single-arm phase II study conducted in Japan. Eligible patients were aged $\geq$20 years with unresectable stage III/IV or recurrent NSCLC, PD-L1 TPS $\geq$50% (22C3), ECOG PS 0–1, and $\geq$1 measurable lesion. Patients received necitumumab 800 mg IV on days 1 and 8 plus pembrolizumab 200 mg IV on day 1 every 3 weeks for up to 35 cycles or until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1; secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. The study assumed an expected ORR of 54.8% and a threshold ORR of 39.0% (one-sided $\alpha = 0.10$; 80% power), requiring enrollment of 50 patients. **Results:** Between December 2020 and March 2023, 50 patients were enrolled (median age, 72 years). The ORR was 68.0% (95% CI, 53.3–80.5) and the disease control rate was 78.0% (95% CI, 64.0–88.5). Complete response, partial response, stable disease, progressive disease, and not evaluable status were observed in 2.0%, 66.0%, 10.0%, 12.0%, and 10.0% of patients, respectively, meeting the primary endpoint. Median PFS was 16.0 months (95% CI, 9.0–24.0), with a 24-month PFS rate of 35.9%. Median OS was not attained (95% CI, 38.0 months–not estimable), and the 24-month OS rate was 71.3%. The most treatment-emergent adverse events included acneiform dermatitis (66.0%), hypomagnesemia (60.0%), and pneumonitis (12.0%). One grade 5 cardiac arrest occurred in 1 patient (2.0%), for which a causal relationship to study treatment could not be ruled out. **Conclusions:** At final analysis, first-line necitumumab plus pembrolizumab demonstrated durable antitumor activity and encouraging long-term survival as a chemotherapy-free regimen in patients with PD-L1–high advanced NSCLC. Toxicities were consistent with the known profiles of EGFR-targeted antibodies and PD-1 inhibitor therapy, underscoring the need for careful monitoring. These findings warrant further confirmation in a randomized phase III clinical trial. Clinical trial information: jRCT2031200248. Research Sponsor: Nippon Kayaku Co; READYFOR (Japan) crowdfunding (public donations).

8574 **Poster Session**

A phase II study of HB0025 (a PD-L1/VEGF bispecific antibody) in combination with chemotherapy as first-line treatment for non–small cell lung cancer (NSCLC). First Author: Lei Wang, Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Background: HB0025, developed by Huaota, is a novel anti-PD-L1/VEGF bispecific antibody with VEGFR1D2 linked at the N-terminal of anti-PD-L1 antibody. This Phase II study assesses the efficacy and safety of HB0025 combined with chemotherapy in locally advanced unresectable, recurrent or metastatic non-small cell lung cancer (NSCLC). **Methods:** This open-label, multi-center, Phase II trial enrolled previously untreated patients with locally advanced unresectable, recurrent or metastatic NSCLC, without *EGFR* or *ALK* gene alterations. Participants were assigned to two cohorts: Cohort 1 (squamous NSCLC) received 20 mg/kg HB0025 plus carboplatin and paclitaxel every three weeks (Q3W) for 4-6 cycles, followed by HB0025 maintenance; Cohort 2 (non-squamous NSCLC) received 20 mg/kg HB0025 plus carboplatin and pemetrexed Q3W for 4-6 cycles, followed by maintenance with HB0025 and pemetrexed. Primary endpoint was objective response rate (ORR) per RECIST 1.1. **Results:** As of January 5, 2026, 125 patients were enrolled in the study (62 patients in Cohort 1 and 63 patients in Cohort 2). The median age was 65 years old (range: 34, 74). The median follow-up period was 10.55 months (range: 1.0, 17.4). A total of 119 patients had at least one post-baseline tumor assessment. In Cohort 1, ORR was 84.5% (49/58), with subgroup ORRs of 81.3%, 72.2%, and 100% for PD-L1 TPS $<$ 1%, 1–49%, and $\geq$50%, respectively; disease control rate (DCR) was 94.8% (55/58), median progression-free survival (mPFS) was 12.62 months, and median duration of response (mDOR) was immature. In Cohort 2, ORR was 65.6% (40/61), with ORRs uniformly 66.7% across all PD-L1 TPS subgroups; DCR was 96.7% (59/61), mPFS was 14.65 months, and mDOR was 12.06 months. Overall survival data remained immature. The most common immune-related adverse events (irAEs) were hypothyroidism (7.2%), hyperthyroidism (4.8%), increased alanine aminotransferase (4.0%), increased aspartate aminotransferase (3.2%), and increased blood thyroid stimulating hormone (3.2%). Anti-VEGF-related AEs of grade $\geq$3 were proteinuria (8.8%), hypertension (6.4%), hemorrhage (4.0%), and thromboembolism (4.0%). 6 (4.8%) patients discontinued HB0025 due to TRAE, and 2 (1.6%) patients died due to TRAE. **Conclusions:** The combination of HB0025 and chemotherapy has demonstrated promising efficacy and favorable safety as a first-line treatment for patients with locally advanced unresectable, recurrent or metastatic NSCLC. Multi-center, randomized, double-blind, controlled phase III trials in both squamous and non-squamous NSCLC have been initiated. Clinical trial information: NCT06758557. Research Sponsor: Shanghai Huaota Biopharmaceutical Co., Ltd.

8575 Poster Session

Chronotherapy in metastatic non–small cell lung cancer: Clinical outcomes according to immune checkpoint inhibitor administration time during the day in patients treated with first-line chemoimmunotherapy. First Author: Bahadır Köylü, Department of Medical Oncology, Koç University School of Medicine, Istanbul, Turkey

Background: Although circadian rhythms are known to modulate immune cell function, the effect of immune checkpoint inhibitor (ICI) infusion timing during the day on oncologic outcomes in metastatic non–small cell lung cancer (NSCLC) patients treated with first-line chemoimmunotherapy has not been fully elucidated. **Methods:** We retrospectively analyzed patients with de novo metastatic NSCLC without actionable oncogenic driver alterations who received first-line chemotherapy plus ICI between January 1, 2018, and October 31, 2025, at two centers. Patients receiving platinum-based doublet chemotherapy plus pembrolizumab and/or nivolumab were included, whereas those treated with dual ICIs (nivolumab plus ipilimumab with platinum-based chemotherapy) were excluded. Infusion times for the first four cycles were recorded, and patients were categorized as the early group if they received ≥2 of the first four ICI cycles before 11:00 a.m., and as the late group if they received ≤1 of the first four ICI cycles before 11:00 a.m. Endpoints were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). **Results:** We identified 101 eligible patients who met the inclusion criteria, comprising 34 patients in the early group and 67 patients in the late group. Median follow-up was 18.4 months (95% CI 12.4 – 24.4). There were no differences between the early group and the late group in terms of age, gender, body mass index, smoking status, ECOG performance status, stage (IVA vs. IVB), histologic subtype (squamous vs. non-squamous), PD-L1 tumor proportion score (< 1% vs. 1-49% vs. ≥50%), central nervous system metastases, liver metastases, number of metastatic sites (≤2 vs. ≥3 organ systems), and ICI agent (pembrolizumab vs. nivolumab). The early group demonstrated significantly longer median PFS (14.6 vs. 7.1 months; HR = 0.54 [95% CI 0.31 – 0.93]; p = 0.027) and median OS (not reached vs. 27.3 months; HR = 0.28 [95% CI 0.11 – 0.71]; p = 0.008). Both the ORR (97.1% vs. 56.7%; p < 0.001) and the disease control rate (97.1% vs. 64.2%; p < 0.001) were significantly higher in the early group. The majority of patients who experienced primary progression after the first four cycles were in the late group (24 of 25 patients; 96%). In multivariate analysis, only disease stage (IVB vs. IVA; HR = 2.35 [95% CI 1.05 – 5.26]; p = 0.039) and timing-based group assignment according to the number of the first four ICI infusions administered before 11:00 a.m. (late vs. early; HR = 2.97 [95% CI 1.14 – 7.76]; p = 0.026) were independently associated with OS. **Conclusions:** Our findings demonstrated that receiving majority (≥2) of the first four ICI infusions before 11:00 a.m. might be associated with better response rates, improved PFS and OS in patients with de novo metastatic NSCLC treated with first-line chemotherapy plus ICI. Research Sponsor: None.

8576 Poster Session

Multi-omic ctDNA-based MRD for predicting clinical outcomes in advanced NSCLC receiving chemoimmunotherapy. First Author: Yun Fan, Department of Thoracic Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Background: Immune checkpoint inhibitors (ICIs) have revolutionized treatment for advanced non–small cell lung cancer (aNSCLC); however, many patients achieving radiographic partial or complete response (PR/CR) relapse early. This underscores the need for more precise risk stratification after an initial response. We investigated whether circulating tumor DNA -based minimal residual disease (ctDNA-MRD) assessment could stratify patients with durable benefit versus those at risk of early progression after chemoimmunotherapy (Chemo-IO). **Methods:** We analyzed 152 retrospective and 60 prospective aNSCLC patients who achieved PR/CR after first-line (1L) PD-1-based Chemo-IO. Plasma was collected at the first imaging-confirmed PR/CR (retrospective) or at baseline and Cycle 5 Day 1 (C5D1; prospective). ctDNA-MRD was assessed using a tumor-naïve, mutation-based panel and a fragmentomics model derived from low-pass whole-genome sequencing (LP-WGS). In the retrospective cohort, 89 patients were used for LP-WGS model training and 63 for validation. Risk stratification was evaluated using progression-free (PFS) and overall survival (OS). **Results:** In the retrospective validation cohort (n = 63), both the mutation- and fragmentomic-based assays stratified PFS and OS. For the mutation-based assay, median PFS (mPFS) was 27.0 vs. 10.1 months (negative vs. positive; Hazard ratios [HR] 0.414, 95% confidence intervals [CI] 0.211–0.814, p = 0.008) and median OS (mOS) was not reached (NR) vs. 17.5 months (HR 0.341, 95% CI 0.151–0.768, p = 0.007). For the LP-WGS-based model, mPFS was 27.0 vs. 13.8 months (HR 0.412, 95% CI 0.216–0.785, p = 0.005) and mOS was NR vs. 25.1 months (HR 0.355, 95% CI 0.158–0.795, p = 0.009). Integration using an either-assay-positive definition further improved prognostic discrimination, with mPFS NR vs. 13.8 months (HR 0.379, 95% CI 0.201–0.714, p = 0.002) and mOS NR vs. 25.1 months (HR 0.324, 95% CI 0.143–0.730, p = 0.004). In the prospective cohort (n = 60), both assays at C5D1 identified patients at higher risk of progression: mutation-based mPFS 18.3 vs. 6.1 months (HR 0.184, 95% CI 0.075–0.457, p < 0.0001); LP-WGS-based mPFS NR vs. 5.3 months (HR 0.178, 95% CI 0.070–0.456, p < 0.0001). Integration-based mPFS was NR vs. 6.5 months (HR 0.130, 95% CI 0.039–0.440, p = 0.0001). Multivariable analysis confirmed the independent and complementary prognostic value of both approaches across cohorts. **Conclusions:** Both mutation- and fragmentation-based ctDNA-MRD assays effectively stratified risk among aNSCLC patients with radiographic response to 1L Chemo-IO. Their integration further improved prognostic performance, refining risk beyond imaging-defined PR/CR and informing post-response management decisions. Research Sponsor: None.

8577 Poster Session

Real-world efficacy and safety of bispecific antibody ivonescimab-based regimens in EGFR-TKI–resistant advanced NSCLC. First Author: Chuang Yang, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

Background: Ivonescimab is a first-in-class bispecific monoclonal antibody targeting programmed cell death protein 1 (PD-1) and vascular endothelial growth factor (VEGF)-A. In the phase III HARMONi-A trial, ivonescimab plus chemotherapy significantly improved progression-free survival (PFS) compared with chemotherapy alone in patients with epidermal growth factor receptor (EGFR)-mutant advanced non–small cell lung cancer (NSCLC) after resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs). However, in real-world clinical practice, ivonescimab is administered across heterogeneous treatment lines after EGFR-TKI resistance, and evidence regarding its effectiveness in these settings remains limited. **Methods:** This real-world study included patients with advanced NSCLC who received ivonescimab plus chemotherapy following progression on EGFR-TKIs. The primary endpoints were median PFS (mPFS) and safety. **Results:** A total of 254 patients were included. At the data cutoff of November 30, 2025, the median follow-up was 8.9 months. The median age was 61 years; 54.3% were female, and 48.0% had brain metastases. The overall objective response rate (ORR) was 47.9%, with a mPFS of 6.9 months (95% CI, 6.2–7.5). A total of 124 patients were treated with ivonescimab plus chemotherapy immediately after EGFR-TKI resistance with HARMONi-A–like sequence and achieved an ORR of 52.9% with a mPFS of 7.0 months (95% CI, 4.5–9.4). The other 130 patients receiving ivonescimab plus chemotherapy after failure of prior immunotherapy-, anti-angiogenic therapy-, and/or chemotherapy-based regimens achieved an ORR of 43.1% with a mPFS of 6.7 months (95% CI, 6.0–7.4). No statistically significant difference in PFS was observed between the two groups (p= 0.269). Grade 3–4 adverse events occurred in 14.6% of patients, including leukopenia (n = 9), neutropenia (n = 7), immune-related pneumonia (n = 6), and checkpoint inhibitor–related myocarditis (n = 5). Given the relatively short follow-up, overall survival data were not mature. **Conclusions:** In this real-world cohort, ivonescimab plus chemotherapy demonstrated clinically meaningful efficacy and a manageable safety profile when administered both immediately after EGFR-TKI resistance and following multiple prior lines of therapy, supporting its use across diverse treatment sequences in patients with EGFR-mutant advanced NSCLC. Research Sponsor: None.

8578 Poster Session

Baseline characteristics of NSCLC first-line immunotherapy super-responders in three European lung cancer centers: An ENDEAVOUR-IMIGO project. First Author: David Lang, Department of Pneumology, Kepler University Hospital, Johannes Kepler University, Linz, Austria

Background: Immune-checkpoint inhibitors (ICI) are part of first-line treatment concepts for most patients with metastatic non-small cell lung cancer (NSCLC) without targetable driver mutations. Still, long-term response is rare and data on predictive biomarkers limited. **Methods:** As part of the Daiichi Sankyo ENDEAVOUR programme supporting young LC researchers, the ENDEAVOUR-IMIGO working group aims to explore novel predictive biomarkers for ICI response with a focus on imaging data. We present the baseline characteristics of first-line ICI "super-responders" with PFS ≥24 months, derived from three independent cohorts from Austria, Italy and the Netherlands. Also, an exploratory single-center analysis compared ICI super- to non-responders (PFS<6M) matched for age, sex, histology, PD-L1 positivity, stage and ECOG performance status. **Results:** The Linz (Austria) cohort reported 50 (12.4%) super-responders out of a total of 402 patients, the Milan cohort (Italy) 45 out of 283 (15.9%), and the Groningen cohort (Netherlands) 46 (10.7%) out of 428. As shown in table 1, all cohorts had a high prevalence of adenocarcinomas, with KRAS mutations present in nearly half of patients and a mean PD-L1 expression of approximately 50%. In the Austrian cohort, matched baseline data showed a higher frequency of systemic steroids among non-responders, and lower absolute neutrophil count as well as neutrophil-to -lymphocyte ratio in super-responders. **Conclusions:** Baseline characteristics of ICI super-responders were similar in three European cohorts, with a majority of high-PD-L1 expressing adenocarcinomas. Exploratory matched analyses from one cohort showed implications of baseline systemic steroid treatment as well as of differential blood cell count. Research Sponsor: None.

	Linz			Milan	Groningen
	PFS < 6M n = 50 (matched)	PFS ≥ 2Y n = 50	p value < 6M vs. ≥ 2Y	PFS ≥ 2Y n = 45	PFS ≥ 2Y n = 46
Male sex, n (%)	24 (48)	25 (50)	0.841	34 (75.5)	22 (48)
Age <70, n (%)	14 (28)	15 (30)	0.826	15 (33.3)	34 (74)
ECOG, n (%)					
0	25 (50)	24 (48)	0.768	21 (47)	18 (39)
1	16 (32)	19 (38)		23 (51)	23 (50)
2+	9 (18)	7 (14)		1 (2)	5 (11)
Histological subtype, n (%)					
Adenocarcinoma	36 (72)	36 (72)	0.341	30 (67)	33 (72)
Squamous cell carcinoma	12 (24)	14 (28)		6 (13)	7 (15)
Other	2 (4)	0 (0)		9 (20)	6 (13)
PD-L1 expression %, mean (SD)	41.9 (36.8)	48.9 (38.8)	0.403	52.3 (35.4)	54.0 (39.0)
Brain metastases, n(%)	16 (32)	13 (26)	0.509	14 (31)	7 (15)
KRAS mutation, n (%)	12 (35)	18 (50)	0.214	19 (42)	23 (50)
Treatment, n (%)					
Chemo-ICI combination	29 (58)	38 (76)	0.056	18 (40)	19 (41)
ICI-monotherapy	21 (42)	12 (24)		27 (60)	27 (59)
Systemic steroid treatment, n(%)	17 (34)	6 (12)	0.009	12 (27)	8 (17)
Absolute neutrophil count (G/L), mean (SD)	11.5 (8.7)	7.7 (2.9)	0.015	6.8 (3.2)	7.3 (2.6)
Absolute lymphocyte count (G/L), mean (SD)	1.7 (3.7)	1.4 (0.7)	0.071	1.9 (0.7)	1.6 (0.7)
Neutrophil-to-lymphocyte ratio, mean (SD)	13.4 (11.0)	7.2 (5.2)	0.006	4.4 (3.6)	5.9 (4.0)

8579 **Poster Session**

Initial safety and efficacy of A2B694, a logic-gated mesothelin (MSLN)–targeted Tmod chimeric antigen receptor T-cell (CAR T) therapy in patients with advanced solid tumors with HLA-A*02 loss of heterozygosity (LOH). First Author: Julian R. Molina, Division of Medical Oncology, Mayo Clinic Rochester, Rochester, MN

Background: LOH may provide a means to target tumor versus normal cells, to augment the efficacy and safety of MSLN-targeted programs (Hecht et al. *JCO*. 2022). A2B694 is an autologous, logic-gated, Tmod CAR T therapy designed to improve tumor selectivity and decrease toxicity by integrating an MSLN CAR activator with an HLA-A*02 blocker (Hamburger et al. *Mol Imm*. 2020). **Methods:** The first-in-human, open-label, phase 1/2 EVEREST-2 (NCT06051695) study of A2B694 in patients with recurrent/metastatic MSLN-expressing cancers with tumor-associated HLA-A*02 LOH. The prescreening study BASECAMP-1 (NCT04981119) identifies eligible patients and cryopreserves leukapheresis product. Upon progression, A2B694 is manufactured and administered after lymphodepletion. Phase 1 primary objective: evaluate the safety and tolerability of A2B694 and identify a recommended phase 2 dose. **Results:** As of 05 January 2026, 13 patients were enrolled: 8 women/5 men, median age 59 years, 11 non-Hispanic White/2 Hispanic with unknown race. Tumor types included colorectal (n = 4), ovarian (n = 3), pancreatic (n = 3), non–small cell lung adenocarcinoma (NSCLC), gastro-esophageal, and mesothelioma (n = 1 each). A2B694 dose level (DL) groups were: DL1: 1×10^8 cells (n = 3), DL2: 2×10^8 cells (n = 4), DL3: 4×10^8 cells (n = 5), and DL4: 6×10^8 cells plus low-dose IL-2 (n = 1). Lymphodepletion prior to administration of A2B694 was well-tolerated, with expected, transient cytopenias. The only adverse event reported in more than 1 patient was grade 3 neutropenia. One patient had grade 3 ICANS and 1 patient had grade 1 CRS. There were no dose-limiting toxicities or new safety signals after up to 17 months follow-up. All 13 patients received A2B694, were efficacy-evaluable, and had A2B694 detected post-infusion in peripheral blood. While A2B694 was not detected in tumor biopsies collected in patients treated at DL1 (0/2), all patients treated at DL2-DL4 with available biopsies (3/3) had detectable A2B694 in the tumor microenvironment. A patient with $KRAS^{G12V}$/STK11 co-mutated NSCLC who had progressed on carboplatin, pemetrexed, and pembrolizumab achieved a complete response (CR) at D90 post-infusion per RECIST 1.1 by central review and had a confirmed CR at D180. In addition, PET-CT scan and ctDNA on D190 demonstrated no evidence of disease. On D243, the patient had a CNS relapse, with an ongoing non-CNS CR per RANO-BM at D284. At M12, the patient's CT showed no new findings and persistence of A2B694 in the blood was confirmed by ddPCR. **Conclusions:** We report the first patient with NSCLC to have a CR after CAR T. Overall, A2B694 demonstrated manageable safety and tolerability in patients with advanced solid MSLN-expressing tumors with tumor-associated HLA-A*02 LOH. The maximum tolerated dose has not been reached; dose-escalation continues. Clinical trial information: NCT06051695. Research Sponsor: A2 Biotherapeutics, Inc.

8580 **Poster Session**

Phase I study of IMM2510, a PD-L1/ VEGF bispecific antibody, in participants with advanced IO-treated SQ-NSCLC. First Author: Xiaoqing Yu, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China

Background: Despite advancements in first-line treatments such as immunotherapy and targeted therapies, resistance to these treatments is common, especially those IO-treated and low PD-L1 TPS, creating a significant unmet need for effective second-line therapies. IMM2510 is a bispecific fusion protein targeting PD-L1 and VEGF which can modify tumor microenvironment to overcome resistance and improve sensibility to antitumor agents. The data of dose-escalation phase I was previously reported in ASCO2024. Here we summarize the updated efficacy and safety results of IMM2510 in advanced IO-treated SQ-NSCLC. Part of the data were previously reported in WCLC 2025. **Methods:** The phase I study was designed as a first-in-human, open-label, multi-center study to evaluate the safety, efficacy, PK and PD of IMM2510 in pts with advanced solid tumors. Eligible pts were enrolled to receive IMM2510 via intravenous infusion Q2W. **Results:** As of 31 Dec 2025, 32 pts with advanced IO-treated SQ-NSCLC received IMM2510. The median age was 61 years; 31.3% pts had PD-L1 TPS $<$ 1%; 75.0% pts had ECOG score of 1; the median prior lines of anti-tumor therapy were 2 (range: 1-5). All 32 pts experienced TEAEs. Grade $\geq$3 TEAEs were reported by 17 (53.1%) pts; Grade $\geq$3 TRAEs were reported by 12 (37.5%) pts; TRAEs leading to treatment discontinuation were reported by 1 (3.1%) participant. No participant experienced TRAE leading to death. 22 pts with advanced IO-treated SQ-NSCLC were evaluable for efficacy analysis. The ORR was 27.3% (6/22) and DCR was 81.8% (18/22). The median DoR was 11.1 months. The median PFS was 9.4 months at the median follow-up time of 8.3 months. The median overall survival was not reached. Exposure-response (ER) analysis within the 3 - 20 mg/kg dose range revealed a positive exposure-efficacy relationship in pts with SQ-NSCLC, with higher exposure corresponding to increased ORR or DCR, while a relatively flat ER was observed for Grade 3 or higher TRAE and most common AEs in NSCLC. Thus, 20 mg/kg Q2W was selected as the RP2D with well-balanced efficacy-safety profiles. **Conclusions:** In pts with advanced IO-treated SQ-NSCLC, IMM2510 provides clinical meaningful benefit and supports a favorable benefit-risk profile. The phase III clinical study is being planned. Clinical trial information: NCT05972460. Research Sponsor: None.

8581 **Poster Session**

First-line serplulimab for locally advanced or metastatic squamous non–small cell lung cancer: Updated survival from the ASTRUM-004R trial. First Author: Bo Shen, The Affiliated Cancer Hospital of Nanjing Medical University & Jiangsu Cancer Hospital & Jiangsu Institute of Cancer Research, Nanjing, Jiangsu, China

Background: Although the ASTRUM-004 trial has confirmed that serplulimab plus platinum-based therapy improves survival in patients with locally advanced or metastatic squamous non-small cell lung cancer (sqNSCLC), evidence regarding its efficacy and safety in routine clinical practice remains limited. Previous results from the ASTRUM-004R trial have shown that a serplulimab plus platinum-based therapy exhibits promising antitumor activity in sqNSCLC. Here, we report the updated follow-up results from this study. **Methods:** The ASTRUM-004R trial is a retrospective, real-world study conducted across 14 centers in China. Patients with locally advanced or metastatic sqNSCLC received first-line serplulimab plus platinum-based therapy, followed by serplulimab maintenance treatment until disease progression, intolerable toxicity, or up to 2 years. This update presents the survival outcomes, including progression-free survival (PFS) and overall survival (OS). Additionally, PFS was assessed across various patient subgroups. **Results:** A total of 132 patients were enrolled in the analysis, with a median follow-up of 18 months as of October 31, 2025. The median patient age was 69 years. Overall, 92.4% (n = 122) were male, 71.2% (n = 94) were aged 65 or older, 19.7% (n = 26) had an ECOG performance status of 2, and 47.0% (n = 62) had stage IV disease. Maintenance therapy was administered to 50.8% (n = 67) of the patients. The median PFS for all patients was 14.8 months (95% CI: 11.9-19.6), with a 6-month PFS rate of 78.5% (95% CI: 71.5%-86.2%). The median PFS benefit was comparable between patients receiving nab-paclitaxel and those receiving paclitaxel (17.5 *vs.* 15.2 months, *P*= 0.677), suggesting no significant difference in efficacy between the two groups. Furthermore, a significantly longer median PFS was observed in patients with stage III disease compared to those with stage IV disease (20.4 *vs.* 11.9 months, *P*= 0.009). The median OS for all patients was 29.7 months (95% CI: 29.7-NR), with a 12-month OS rate of 90.1% (95% CI: 84.7%-95.9%). The updated findings confirm sustained antitumor activity, as evidenced by an objective response rate of 66.7% (95% CI: 57.9%-74.6%) and a disease control rate of 95.5% (95% CI: 90.4%-98.3%). Adverse events (AEs) of any grade occurred in 48 patients (36.4%), most of whom had hematological disorders. Immune-related AEs (irAEs) were reported in 35 patients (26.5%), including 9 (6.8%) who experienced grade $\geq$3 irAEs. **Conclusions:** Updated results from the ASTRUM-004R study show that first-line serplulimab platinum-based therapy provides a significant survival benefit with a manageable safety profile in locally advanced or metastatic sqNSCLC, consistent with findings from the ASTRUM-004 trial. The long-term survival benefit warrants further validation with extended follow-up. Research Sponsor: None.

8582 **Poster Session**

Impact of genomic HLA class I allelic imbalance on enduring immunotherapy response in advanced non–small cell lung cancer. First Author: Yiting Dong, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Human leukocyte antigen class I (HLA-I) molecules are essential for neoantigen presentation and T cell recognition, yet the clinical significance of allelic imbalance within HLA-I genes (HLA-AI) in immune checkpoint inhibitors (ICIs) therapy remains undefined. **Methods:** Here, we established haplotype-specific, coverage-based (cHLA-AI) compatible with routine biopsy-derived sequencing, based on 292 fully heterozygous non–small cell lung cancer (NSCLC) patients with paired tumor samples from the phase III CHOICE-01 trial and confirmed in RATIONALE-304 and real-world NCC cohorts, covering both first- and later-line immunochemotherapy as well as ICI monotherapy, and complemented by analyses in surgical, pan-cancer, and longitudinal datasets to assess immune correlates and evolutionary dynamics. **Results:** Patients with tumor mutational burden (TMB)–low and cHLA-AI derived no benefit from first-line immunochemotherapy, whereas all other patients achieved significant survival gains (TMB-low and cHLA-AI vs. others: immunochemotherapy arm: mOS 16.53 vs. 29.57 months, HR = 2.29, 95% CI 1.59–3.30, p $<$ 0.001,interaction P = 0.019; mPFS 5.59 vs. 9.92 months, HR = 2.02, 95% CI 1.43–2.90, p $<$ 0.001, interaction P = 0.016). These findings were validated in the RATIONALE-304 and RATIONALE-307 trials and independent real-world cohorts. Incorporating cHLA-AI with pathology, PD-L1 and TMB significantly improved 2-year OS prediction (DeLong's P = 0.003). Multi-omic profiling linked cHLA-AI to active DNA damage response signalings, high TMB -intratumor heterogeneity (ITH) -chromosomal instability (CIN) phenotype, immune-cold microenvironments, and failure of on-treatment TCR clone expansion, while longitudinal sampling revealed its late, branching emergence under immune pressure. Pan-cancer profiling (N = 5,989) demonstrated consistent associations with high TMB-ITH-CIN phenotype and proliferative activity (Ki-67 index). **Conclusions:** Collectively, these results establish cHLA-AI as a pivotal biomarker bridging genomic instability, immune evasion, and therapeutic outcomes, providing a framework for stratified immunotherapy response in non–small cell lung cancer and beyond. Research Sponsor: None.

8583 **Poster Session**

Concomitant radiotherapy, tremelimumab, and durvalumab for advanced NSCLC patients progressing on first-line immunotherapy: A phase 2 study (CORAL-Lung). First Author: Jair Bar, Jusidman Cancer Center, Sheba Medical Center, Ramat Gan, Israel; The Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel

Background: The optimal treatment for advanced NSCLC that developed resistance to immune checkpoint inhibitors (CPIs) remains undefined. We hypothesized that combining anti-PD-L1, anti-CTLA-4 (at an effective dose) and radiotherapy could be effective against CPI-resistant tumors. **Methods:** This open-label, single-arm, phase 2a trial evaluated two CPIs plus radiotherapy in patients with advanced/metastatic NSCLC who progressed on/after 1L CPI given alone or in combination with chemotherapy. Co-Primary endpoints were safety and response rate (RR; by RECIST 1.1). Secondary endpoints were to evaluate progression free survival (PFS) and overall survival (OS). The study included a safety run-in cohort and a Simon two-step design expansion. RR $\geq$ 20% in non-irradiated lesions was required to advance from the initial efficacy to expansion cohort. Patients with prior anti-CTLA-4 treatment were excluded. At least one measurable non-irradiated lesion was required. Treatment included tremelimumab at a fixed dose of 300 mg at D1 and 12 weeks later and 1500 mg Durvalumab q4w (starting from D1). This dosing was based on PK and pharmacodyamic data from study D4190C00006, suggesting tremelimumab of dose greater than 1 mg/kg with a higher peak exposure may be associated with a higher pharmacodynamic effect. On D21, patients began radiotherapy: 11 fractions of 3 Gy (total of 33 Gy), selected based on our real-world database analysis (Onn et al, Cancers 2021, 13(11), 2800). The study was sponsored by Sheba MC and funded by AstraZeneca Pharmaceuticals. NIH trials registry identifier: NCT05000710. **Results:** Ten patients were enrolled, median age was 71 (range 51-82); 50% males; all stage IV; 50% adenocarcinoma; 50% with PD-L1 $<$ 1%; 80% past/current smokers; none had actionable driver mutations. Previous treatment lines were 1/2 in 80%/20% respectively; all patients received prior pembrolizumab and platinum-based doublet. Median (range) durvalumab and tremelimumab cycles administered were 2 (1-7), 1(1-3). Median radiotherapy dose was 33 Gy, in 78% targeting lung lesions. Nine patients were included in the safety run-in, three experienced treatment-related toxicities leading to treatment discontinuation (all grade 3 diarrhea), remaining below the predefined 40% threshold and permitting continuation. All other treatment-related toxicities were grade 2 or lower. The initial efficacy cohort (n = 10) RR was 10%, leading to the study closure. Median PFS was 2.2 months, median OS was 13.9 months. The study was terminated on Dec 31, 2024. **Conclusions:** In unselected patients with advanced CPI-resistant NSCLC, the combination of anti-PD-L1, anti-CTLA4 at a high dose and radiotherapy did not demonstrate a meaningful response rate. Toxicity of a high dose of anti-CTLA-4 is not negligible. Better patient selection might lead to higher efficacy and lower toxicity. Clinical trial information: NCT05000710. Research Sponsor: AstraZeneca.

8584 **Poster Session**

Final analysis of the biomarker-directed, randomized, phase 2 KEYNOTE-495/KeyImPaCT study of pembrolizumab (P)—based combination therapy for non—small cell lung cancer (NSCLC). First Author: Martin Gutierrez, Hackensack University Medical Center, Hackensack, NJ

Background: KEYNOTE-495/KeyImPaCT (NCT03516981) evaluated 3 P-based regimens in participants (pts) with advanced NSCLC across 4 prospectively defined biomarker subgroups based on T-cell–inflamed gene expression profile ($Tcell_{inf}GEP$) and tumor mutational burden (TMB). In interim analysis, ORR with P + lenvatinib (L) in the $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$ subgroup met the prespecified efficacy threshold. We report final analysis results. **Methods:** Pts with previously untreated NSCLC were assessed for $Tcell_{inf}GEP$ (non-low, ≥ -0.16; low, < -0.16) and TMB (high, $\geq$5 mut/Mb; non-high, $<$5 mut/Mb; $\approx$175 mut/exome by WES and 10 mut/Mb on FoundationOne CDx). Pts were assigned to 1 of 4 subgroups ($Tcell_{inf}GEP^{low}TMB^{non\text{-}high}$, $Tcell_{inf}GEP^{low}TMB^{high}$, $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$, and $Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$) and adaptively randomized 1:1:1 to P (200 mg IV Q3W) + either L (20 mg PO QD), quavonlimab (Q; 25 mg IV Q6W), or favezelimab (F; 200 mg or 800 mg IV Q3W). The primary end point was ORR per RECIST v1.1 by investigator. Secondary end points included PFS, OS, and safety. Data cutoff: July 30, 2025. **Results:** 243 pts were treated (P + L, 80; P + Q, 82; P + F 200 mg, 30; P + F 800 mg, 51). Median follow-up was 66.5 mo (range, 43.0-81.2). The $Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$ subgroup treated with P + L met the prespecified efficacy threshold ($\geq$95% posterior probability of true ORR $>$20%); PFS and OS were generally consistent with anticipated results among biomarker-defined subgroups (Table). Safety profile of each combination was consistent with the known profiles of each therapy. **Conclusions:** With longer follow-up, OS benefit was comparable across the 4 biomarker subgroups for the 3 combination therapies, with no new safety signals. These data continue to show the feasibility of prospective biomarker assessment to evaluate P-based therapies in advanced NSCLC. Clinical trial information: NCT03516981. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	$Tcell_{inf}GEP^{low}TMB^{non\text{-}high}$	$Tcell_{inf}GEP^{low}TMB^{high}$	$Tcell_{inf}GEP^{non\text{-}low}TMB^{non\text{-}high}$	$Tcell_{inf}GEP^{non\text{-}low}TMB^{high}$
ORR, % (95% CI)				
P + L	12.0 (2.5-31.2)	33.3 (9.9-65.1)	40.9 (20.7-63.6)	57.1 (34.0-78.2)
P + Q	11.5 (2.4-30.2)	30.8 (9.1-61.4)	13.6 (2.9-34.9)	52.4 (29.8-74.3)
P + F 200 mg	0.0 (0.0-28.5)	33.3 (4.3-77.7)	25.0 (3.2-65.1)	60.0 (14.7-94.7)
P + F 800 mg	27.3 (6.0-61.0)	13.6 (2.9-34.9)	-	50.0 (26.0-74.0)
Median (95% CI) PFS, mo				
P + L	5.4 (2.3-8.8)	13.8 (1.5-19.4)	8.2 (4.2-19.7)	17.8 (6.0-20.7)
P + Q	2.8 (2.0-6.0)	3.9 (1.9-17.3)	6.1 (2.1-12.8)	17.0 (9.3-29.1)
P + F 200 mg	2.1 (1.9-2.1)	8.1 (1.7-NR)	2.1 (0.9-6.5)	6.3 (0.4-NR)
P+ F 800 mg	4.2 (1.8-12.2)	3.5 (2.0-8.2)	-	20.2 (6.1-NR)
Median (OS, mo				
P + L	16.0 (5.4-20.2)	16.9 (3.8-33.2)	22.5 (12.0-41.3)	22.7 (16.9-56.0)
P + Q	13.3 (8.4-20.0)	20.1 (7.7-NR)	23.7 (7.9-43.1)	51.6 (17.6-NR)
P + F 200 mg	8.6 (3.8-35.4)	20.8 (1.7-NR)	12.6 (0.9-25.4)	NR (13.5-NR)
P + F 800 mg	18.6 (3.4-41.2)	11.1 (5.2-19.6)	-	NR (13.0-NR)

-, no pts enrolled.
NR = not reached.

8585 **Poster Session**

Single-cell spatial analysis of the tumor immune microenvironment in NSCLC primary tumors and brain metastases. First Author: Lauren Julia Brown, The University of Sydney, Faculty of Medicine and Health, Westmead, NSW, Australia

Background: Brain metastases (BrM) are associated with poor prognosis in non-small cell lung cancer (NSCLC). Although immune checkpoint inhibitors (ICIs) demonstrate intracranial activity, intracranial progression remains common, especially in patients with driver-negative NSCLC. To define mechanisms of intracranial immune resistance, we applied imaging mass cytometry to profile the tumor immune microenvironment (TIME) in BrM and primary lung tumors. **Methods:** Forty-four patients with advanced driver-negative NSCLC were included; 39 (89%) were treated with ICIs. A 40-marker antibody panel enabled site-specific immune phenotyping of primary lung tumors and BrM, with all samples obtained prior to initiation of systemic immunotherapy. Three regions of interest per sample (two intratumoral, one peritumoral) were analyzed using a Hyperion imaging mass cytometer. Single-cell segmentation was performed using Mesmer with immune phenotypes defined by marker expression. Spatial neighborhoods were identified using unsupervised k-means clustering of nearest-neighbor-derived local cellular compositions. **Results:** Compared with primary lung tumors, BrM demonstrated significantly reduced $CD4^+$ and $CD8^+$ T cells ($p < 0.001$), B cells ($p = 0.017$) and endothelial markers ($p < 0.001$). Despite reduced overall $CD4^+$ infiltration, BrM exhibited higher proportions of regulatory T cells (Tregs; $p = 0.017$), $Ki67^+CD4^+$ T cells ($p = 0.002$) and $Ki67^+$ Tregs ($p = 0.017$). BrM were enriched for CD206-high immunosuppressive macrophages, whereas primary tumors demonstrated predominance of CD11c-high inflammatory myeloid cells ($p = 0.006$). Spatial analysis demonstrated increased proximity of $CD8^+$ T cells ($p = 0.039$) and Tregs ($p = 0.020$) to M2-like macrophages in BrM. Neighborhood analysis revealed site-specific immune organization, with primary tumors enriched for adaptive immune-dominant niches containing mixed $CD4^+$, $CD8^+$ and B-cell populations. In contrast, BrM were characterized by myeloid-T-cell interface neighborhoods marked by close spatial coupling of T cells with macrophages and monocytes. In primary tumors, durable immunotherapy benefit ($\geq$24-month PFS and OS) was associated with significantly higher $CD8^+$ and $CD4^+$ T cells, B cells, dendritic cells, monocytes and macrophages. In BrM, no consistent immune correlates of long-term benefit were observed. **Conclusions:** NSCLC BrM exhibit a distinct TIME characterized by depleted adaptive immune infiltration, CD206-high macrophage dominance and myeloid-T-cell spatial organization. While primary lung tumors display adaptive immune signatures predictive of durable ICI benefit, BrM lack consistent immune correlates of response. These site-specific compositional and spatial differences provide a mechanistic framework for the attenuated and less durable intracranial responses to immune checkpoint blockade. Research Sponsor: Western Sydney Local Heath District.

8586 **Poster Session**

IBI363 (TAK-928) plus chemotherapy as first-line (1L) treatment for advanced non—small cell lung cancer (NSCLC). First Author: HaiYan Tu, Guangdong Lung Cancer Institute, Guangdong Provincial Key Laboratory of Translational Medicine in Lung Cancer, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, Guangdong, China

Background: IBI363 is a first-in-class, PD-1/IL-$2^{\alpha\text{-bias}}$ bispecific antibody fusion protein with great potential for immune-cold and immunotherapy (IO)-resistant tumors. Previously, IBI363 monotherapy demonstrated encouraging and durable efficacy in patients (pts) with IO-treated advanced NSCLC (2025 ASCO #8509). Here, we report a phase 1 study evaluating IBI363 plus platinum-based doublet-chemotherapy (PDC, pemetrexed/paclitaxel plus platinum) in 1L NSCLC. **Methods:** Previously untreated pts with advanced NSCLC, without sensitizing EGFR, ALK, or ROS1 alterations were enrolled. The safety lead-in evaluated IBI363 at 1.5 or 3 mg/kg Q3W plus PDC. In dose optimization (PD-L1 TPS $<$ 50% required), pts were randomized 1:1:1 to 3 cohorts: 3-1.5 mg/kg (IBI363 3 mg/kg plus PDC in cycle 1, then 1.5 mg/kg Q3W plus PDC in subsequent cycles), 3 mg/kg (IBI363 3 mg/kg Q3W plus PDC) and 1.5 mg/kg (IBI363 1.5 mg/kg Q3W plus PDC). Stratification factors were squamous vs non-squamous, and PD-L1 TPS $<$ 1% vs 1-49%. Primary endpoints were safety and efficacy assessed by investigators per RECIST v1.1. Secondary endpoints included pharmacokinetics (PK) and immunogenicity. **Results:** As of December 22, 2025, 80 pts were enrolled in safety lead-in (N = 11) and dose optimization (N = 69) with median follow-up (mFU) of 5.8 months (range: 0.9-9.5). Baseline characteristics (median age: 64 years, male: 88.8%, ECOG PS 1: 81.3%, stage IV: 72.5%, sqNSCLC: 66.3%) were balanced among 3-1.5 mg/kg (N = 23), 1.5 mg/kg (N = 28) and 3 mg/kg (N = 29) cohorts. Median treatment duration of IBI363 was 25.0 weeks (range: 4.0-41.1) while 65.0% pts with ongoing treatment, and 88.9% pts having completed $\geq$4 cycles of PDC. Grade$\geq$3 (G3+) treatment-emergent adverse events (TEAEs) occurred in 81.3% pts including 65.2% for 3-1.5 mg/kg, 82.1% for 1.5 mg/kg and 93.1% for 3 mg/kg cohorts. Common TEAEs were anemia (any grades 78.8%, G3+ 18.8%), neutrophil count decrease (75.0%, G3+ 42.5%), white blood cell count decrease (63.8%, G3+ 20.0%), arthralgia (51.3%, G3+ 2.5%), and platelet count decrease (45.0%, G3+ 17.5%). IBI363-related AEs led to corresponding treatment discontinuation and death in 6.3% and 1.3% pts. In dose optimization, 65.2% pts had PD-L1 TPS $<$ 1 and 34.8% had TPS 1-49%. Efficacy was evaluable in 62 pts with at least 1 tumor assessment. For 3-1.5 mg/kg cohort (N = 22), ORR was 86.4% (95% CI: 65.1-97.1, confirmed ORR [cORR]: 81.8%) and DCR was 100% (95% CI: 84.6-100). ORR was 85.7% for sqNSCLC (N = 14) and 87.5% for non-sqNSCLC (N = 8). For the 1.5 mg/kg (N = 19) and 3 mg/kg cohorts (N = 21), ORR was 57.9% (cORR: 42.1%) and 66.7% (cORR: 57.1%). PFS was immature (events 28.8%). Clinical PK data also supported an optimal benefit-risk profile based on efficacy and safety observed at 3-1.5 mg/kg. **Conclusions:** IBI363 plus PDC was well tolerated and showed encouraging efficacy in advanced NSCLC. Safety, efficacy, and PK data supported 3-1.5 mg/kg as the recommended dose. Clinical trial information: NCT06468098. Research Sponsor: None.

8587 **Poster Session**

Immunonutrition intervention in driver gene–negative non–small cell lung cancer patients with sarcopenia: A randomized controlled trial. First Author: Xiangliang Liu, The First Hospital of Jilin University, Cancer Center, Changchun, Jilin, China

Background: Cancer-related sarcopenia impairs treatment tolerance and survival in advanced NSCLC. This Phase II trial evaluated IMPACT (arginine and omega-3 enriched formula) in driver gene-negative advanced NSCLC patients receiving chemo-immunotherapy. **Methods:** Single-center, open-label, randomized Phase II study. Eligible patients: driver gene-negative advanced NSCLC with sarcopenia (AWGS criteria). Randomization 1:1 to IMPACT plus chemoimmunotherapy (Arm A, n=59) versus chemoimmunotherapy alone (Arm B, n=49). IMPACT administered continuously during treatment. Primary endpoint: PFS. Secondary endpoints: body composition (BIA, CT-L3), inflammatory markers (NLR), nutritional status (PG-SGA), safety. Statistical design: 80% power, HR=0.60, alpha=0.05. Dropouts: 7 (11.9%) in Arm A, 5 (10.2%) in Arm B. Modified ITT: 96 patients (52 vs 44). **Results:** Baseline characteristics balanced. Median PFS: not reached (Arm A) versus 7.0 months (95% CI: 5.2-8.8, Arm B); HR=0.45 (95% CI: 0.23-0.88), P=0.018. Six-month PFS: 82.7% versus 54.5%; 12-month PFS: 59.6% versus 31.8%. NLR change: -1.28 versus +0.16 (P=0.0045). Lean mass change: +0.59 kg versus -1.00 kg ($P<0.05$). L3 skeletal muscle density: +1.93 HU versus +0.37 HU ($P<0.05$). PG-SGA improved in Arm A (9.1 ± 5.6 to 6.4 ± 5.1, $P<0.001$) but not Arm B (8.9 ± 5.8 to 8.2 ± 5.5, P=0.156). Elderly subgroup (≥65y) showed enhanced benefit: HR=0.23 (95% CI: 0.06-0.95), P=0.043. Grade 3-4 AEs: 38.5% versus 52.3% (P=0.156). No IMPACT-related SAEs. **Conclusions:** IMPACT immunonutrition with chemoimmunotherapy significantly improved PFS, preserved lean mass, reduced inflammation, and enhanced nutritional status in driver gene-negative advanced NSCLC with sarcopenia. Well-tolerated with favorable safety. Phase III evaluation warranted. Clinical trial information: ChiCTR2300078741. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation; Y-NESTLE2022ZD–0517.

Key efficacy outcomes.

Endpoint	Arm A (Sustagen, n=52)	Arm B (Control, n=44)	P value
edian PFS, months	NR	7.0 (5.2-8.8)	0.018
6-month PFS, %	82.7	54.5	-
12-month PFS, %	59.6	31.8	-
NLR change	-1.28	+0.16	0.0045
Lean mass change, kg	+0.59	-1.00	<0.05
L3 SMD change, HU	+1.93	+0.37	<0.05

8588 **Poster Session**

Efficacy outcomes in first-line (1L) non–small cell lung cancer (NSCLC) with maintenance of immune competence: QUILT-2.023 randomized phase 3 study of IL-15R agonist nogapendekin alfa inbakicept (NAI) with checkpoint inhibitor (CPI) ± chemotherapy. First Author: John M. Wrangle, Medical University of South Carolina, Charleston, SC

Background: Baseline and treatment-induced lymphopenia are adverse prognostic factors in NSCLC and may limit CPI durability. CPI and chemo-IO can reduce peripheral absolute lymphocyte counts (ALC) over time. NAI expands NK and effector/memory T cells and increases ALC, a biological marker of immune competence. In QUILT-3.055 (≥2L NSCLC after CPI failure), sustained ALC increases were associated with prolonged overall survival (OS). QUILT-2.023 tests whether preserving immune competence with NAI improves response rate, progression-free survival (PFS), and OS when added to 1L standards of care (SOC). To inform the design of the ongoing registrational-intent QUILT-2.023 study, results from 98 enrolled subjects were unblinded for exploratory analysis. **Methods:** QUILT-2.023 (NCT03520686) is an ongoing randomized multicohort phase 3 trial in untreated advanced/metastatic NSCLC (ECOG 0–1; squamous or nonsquamous). Cohort A (PD-L1 TPS ≥1%) was randomized 1:1 to CPI+NAI vs CPI; ALC over time was analyzed using a mixed model for repeated measures. The primary efficacy endpoint was PFS with hierarchical testing (TPS ≥50% then TPS ≥1%). PFS was analyzed at 8 months to evaluate the temporal relationship of ALC through 27 weeks of CPI alone versus CPI+NAI. Cohorts B (squamous) and C (nonsquamous), with any PD-L1 TPS, were randomized 1:1 to SOC platinum chemo-IO ± NAI; pooled Cohort B+C efficacy (ORR, DCR, PFS, OS) was assessed per RECIST v1.1. **Results:** Cohort A (N = 63): baseline ALC was comparable between arms; CPI+NAI showed significant, sustained ALC increase vs CPI alone over 27 weeks (P = 0.0065), regardless of PD-L1 TPS. In TPS ≥50% (N = 45), ALC over time significantly improved with CPI+NAI vs CPI alone (P = 0.0420). Correlating with this increased ALC, PFS in the CPI+NAI arm demonstrated median PFS of 7.0 vs 2.2 months (HR 0.40; 95% CI 0.17–0.94; p = 0.0298). Grade ≥3 CPI-related TEAEs occurred in 16% of subjects in both arms. In pooled Cohorts B+C (ITT N = 36), ORR (CR+PR) was 56% with chemo-IO+NAI vs 33% chemo-IO alone; DCR was 83% vs 78%. Median PFS was 18.9 vs 10.6 months (HR 0.48; 95% CI 0.19–1.23; p = 0.1192) and median OS reached significance of 34.7 vs 20.2 months (HR 0.38; 95% CI 0.15–0.98; p = 0.0394). **Conclusions:** Adding NAI to CPI-based SOC increased ALC and improved PFS in PD-L1 TPS ≥50% 1L NSCLC, with manageable safety. In platinum chemo-IO cohorts, pooled efficacy shows improved response and a significant OS signal, consistent with immune-competence preservation as a modifiable determinant of CPI durability. Enrollment and follow-up are ongoing. These interim findings are consistent with the single-arm trial QUILT-3.055 and support continued accrual in QUILT-2.023 and ResQ201A (NCT06745908), randomized NAI+CPI studies across 1L and ≥2L advanced NSCLC. Clinical trial information: NCT03520686. Research Sponsor: ImmunityBio.

8589 **Poster Session**

Response to cancer immunotherapy for p53 antibody-positive non-small cell lung cancer according to treatment regimen. First Author: Tetsuo Shimizu, Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine, Tokyo, Japan

Background: Cancer immunotherapy has enabled long-term survival in advanced non-small cell lung cancer (NSCLC), but there are some patients with resistance to cancer immunotherapy. Mutations in the p53 gene have been reported to suppress immunity in the tumor immune microenvironment and influence resistance to cancer immunotherapy. Serum p53 antibody is an autoantibody produced in association with p53 gene mutations. However, it is unclear whether p53 antibody-positive NSCLC correlates with treatment response to cancer immunotherapy, particularly whether treatment response differs according to the treatment regimen. **Methods:** Participants were patients with advanced NSCLC who received immune checkpoint inhibitors (ICI) with or without chemotherapy at our hospital from November 2018 to June 2024. Blood samples were obtained before and after treatment with ICI and serum p53 antibody levels were measured. We compared the serum anti-p53 antibody and treatment response (early progressive disease, progression-free survival, and overall survival). Furthermore, we investigated whether treatment response of cancer immunotherapy in p53 antibody-positive NSCLC differs according to the treatment regimen. **Results:** A total of 173 patients were enrolled (mean age 69.4 years, 76.7% male, 58.4% adenocarcinoma). The regimen of ICI with chemotherapy was more common in 130 cases (75.1%) than ICI alone. There were 70 patients (40.4%) who were positive for serum p53 antibody before treatment. The p53-positive group had a significantly higher early progressive disease than the p53-negative group in the patients who received ICI with chemotherapy (28.6% vs 15.5%, p = 0.04). Multivariate analysis showed that serum p53 antibody was the only factor significantly associated with early progressive disease (HR 3.11, 95%CI 1.19-8.50, p = 0.02). PFS was significantly shorter in the p53-positive group than in the p53-negative group in patients with PD-L1 low expression (0-49%) (3.7m vs 7.2m, p = 0.01). Regarding the impact of treatment regimens on treatment response, there was no difference based on ICIs with or without chemotherapy. However, the group that combined anti-VEGF antibodies with ICIs had a significantly lower early progressive disease rate than the group that did not combine them (14.3% vs 30.2%, p = 0.03). **Conclusions:** Serum p53 antibody influenced the therapeutic efficacy of cancer immunotherapy in NSCLC. p53 antibody-positive NSCLC demonstrated differing treatment responses depending on therapeutic regimen. We believe that the combination of ICIs and anti-VEGF antibodies is a promising treatment option for p53 mutation-positive NSCLC. Research Sponsor: None.

8590 **Poster Session**

Indefinite versus 2 years fixed duration of immune checkpoint inhibition in metastatic non–small cell lung cancer. First Author: Biagio Ricciuti, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Clinical trials of immune checkpoint inhibitors (ICIs) in metastatic non-small cell lung cancer (mNSCLC) limited treatment duration to 2 years despite the absence of evidence defining the optimal time on therapy. In routine clinical practice, however, many patients receive ICIs for more than 2 years. We evaluated survival outcomes in patients treated with 2 years versus > 2 years of therapy. **Methods:** We conducted a global, retrospective cohort study of patients with mNSCLC treated with ICIs for at least 2 years. Patients were classified as receiving fixed-duration ICI (discontinued at 2 years) or indefinite ICI therapy. Outcomes included progression-free survival (PFS), and overall survival (OS) from ICI start. Multivariable Cox regression, propensity score matching, and 2-year landmark analyses with inverse probability weighting (IPW) were used to address time-dependent biases and adjust for relevant covariates. **Results:** Among 889 patients who received at least 24 months of ICI therapy, median age was 65.5 years; 45.6% were women; 92.8% had a smoking history; 80.2% had adenocarcinoma histology; 70% of patients received ICI as first-line therapy and median PD-L1 tumor proportion score was 60%. Overall, 58.8% received indefinite ICI and 41.2% discontinued at 2 years. Median PFS and OS for the overall cohort were 5.7 years and 8.1 years, respectively. Baseline clinicopathologic characteristics, including age, sex, histology, PD-L1 expression, ECOG performance status, and smoking history, were well balanced between groups. Indefinite ICI therapy was associated with significantly longer PFS (HR 0.75, $p < 0.01$) and OS (HR 0.62, $p < 0.001$) compared to 2 years of therapy. These findings were consistent in a propensity-matched analyses (PFS HR 0.62, $p < 0.01$; OS HR 0.60, $p < 0.001$) and multivariable models (adjusted PFS HR 0.75, p = 0.02; adjusted OS HR 0.57, $p < 0.001$). In 24-month landmark analyses with IPW, indefinite ICI remained associated with improved PFS (HR 0.74, p = 0.02) and OS (HR 0.56, $p < 0.001$). Benefit with indefinite therapy was observed across all predefined subgroups, including age, sex, histology, PD-L1 strata, ECOG performance status, smoking history. Among 98 patients who received ICI rechallenge at disease progression, the objective response rate was 45%, with a median PFS of 12.9 months and a median OS of 30.2 months. **Conclusions:** Continuation of ICI therapy beyond 2 years was consistently associated with superior PFS and OS compared with treatment limited to 2 years across subgroups and sensitivity analyses. These findings highlight the limitations of arbitrary treatment caps in clinical trial design, support individualized duration decisions, and underscore the need for prospective trials to define the optimal duration of ICI therapy in NSCLC. Research Sponsor: None.

8591 **Poster Session**

Comparison of a highly sensitive, tumor-informed Illumina whole genome sequencing research assay and a tumor-informed bespoke whole exome sequencing assay for molecular residual disease detection in CheckMate-77T (NCT 04025879). First Author: Jonathan Beer, Bristol Myers Squibb, Cambridge, MA

Background: In CheckMate 77T (NCT 04025879), nivolumab showed clinically meaningful improvements in event free survival and pathologic complete response *vs* placebo in 461 patients with resectable (stage IIA-IIIB) NSCLC. Previously, circulating tumor DNA (ctDNA) clearance rates of 66% in NIVO and 38% in PBO of the neoadjuvant period (C1D1 to definitive surgery) had been reported from 130 patients by Provencio et. al. (LBA50, ESMO 2024). In this study, we aim to extend on the previous exploratory study by using a highly sensitive whole genome sequencing (WGS) minimal residual disease (MRD) assay to detect ctDNA clearance rates and compare to those measured using a tumor-informed whole exome sequencing (WES) MRD assay. **Methods:** Residual samples (tumor FFPE tissue/isolated DNA, normal, cfDNA) from 61 of the 130 participants previously reported comprised this study. The Illumina WGS MRD assay employs WGS of tumor and matched normal to generate tumor fingerprints which were bioinformatically monitored in plasma using low-pass WGS (lp-WGS). All samples were prepared using Illumina's WGS Oncology Prep (research use only) and analyzed with DRAGEN MRD pipeline. A comparison of the operational complexity and turn-around-time (TAT) between tumor-informed WES MRD assays and the Illumina WGS MRD assay was performed. **Results:** Detection rates at C1D1 were greater in this study than previously reported, 91% for WGS *vs* 86% for WES, supporting the hypothesis that WGS MRD is more sensitive than WES MRD assays. Using the WES MRD results as reference, the Illumina WGS assay demonstrated a high concordance with positive percent agreement of 100%, negative percent agreement of 63% and overall percent agreement of 95%. Clearance rates of ctDNA in both study arms were calculated, summarized and compared to previous results by Provencio et. al. Compared to tumor-informed MRD assays, the Illumina WGS MRD assay significantly reduced operational complexity and TAT, as it eliminated the need for bespoke panel design, including analysis, manufacturing and assay validation. The Illumina Oncology WGS Prep uses a single streamlined workflow for all MRD sample types. The lpWGS testing of plasma cfDNA required only 2-5 ng cfDNA which can be obtained from a single tube of whole blood compared to 2 tubes of whole blood as required for many tumor-informed MRD assays. The total TAT of the WGS MRD workflow, including both tissue and plasma testing, was 1-2 weeks, substantially shorter than the 4-6 weeks required for most tumor-informed MRD assays. **Conclusions:** This study found the Illumina WGS MRD research assay to be highly concordant with previous tumor-informed WES MRD results for MRD positive results, with improved sensitivity, reduced TAT, lower cfDNA input requirements and decreased operational complexity. Clinical trial information: NCT04025879. Research Sponsor: Bristol Myers Squibb; Illumina.

8592 **Poster Session**

Efficacy and safety of anamorelin in patients with non–small cell lung cancer and cancer cachexia undergoing chemoimmunotherapy: A real-world prospective cohort study (SPIRAL-ANA). First Author: Kenji Morimoto, Kyoto Prefectual Univeresity of Medicine, Kyoto, Japan

Background: The efficacy and safety of combining anamorelin with chemo-immunotherapy for non–small cell lung cancer (NSCLC) complicated by cancer cachexia remain unclear. This study aims to clarify the potential clinical benefits of combining anamorelin with standard first-line treatment in this challenging patient subpopulation. **Methods:** We prospectively enrolled patients with advanced NSCLC who had cancer cachexia and were scheduled to initiate anamorelin together with chemo-immunotherapy. Cancer cachexia was defined according to the eligibility criteria for anamorelin administration in Japan. Anamorelin is indicated for patients with body weight loss of $\geq$5% within the previous 6 months and with anorexia, who meet at least two of the following criteria: 1) fatigue or malaise, 2) generalized muscle weakness, or 3) C-reactive protein level $>$0.5 mg/dL, or albumin level $<$3.2 g/dL, or hemoglobin level $<$12 g/dL. Progression-free survival (PFS) from start of chemoimmunotherapy was the primary endpoint. **Results:** Overall, 123 patients were enrolled, of whom 118 comprised the safety analysis set and 114 comprised the full analysis set. The median duration of anamorelin treatment was 13.15 weeks. Median age, body weight, and body mass index were 73 years (range: 42–89 years), 53.2 kg (range: 32.5–79.4 kg), and 20.2 kg/m^2 (range: 15.0–29.1 kg/m^2), respectively. Among these patients, 20 (17.5%) had an Eastern Cooperative Oncology Group performance status of 2. At week 12, 62 patients (54.4%) were still being treated with anamorelin. The median PFS and overall survival (OS) were 6.2 months and 18.5 months, respectively, and the study did not meet the prespecified PFS endpoint. In a 12-week landmark analysis stratified by cachexia status at week 12, OS was significantly longer in patients who had achieved cachexia improvement by week 12 than in those who remained cachectic (19.9 months versus 7.1 months, log-rank p = 0.0098; hazard ratio for death, 2.19; 95% confidence interval, 1.19–4.02). The safety profile was manageable, with grade $\geq$3 neutropenia and hyperglycemia occurring in 31.4% and 5.1% of patients, respectively, and no deaths were considered related to anamorelin. **Conclusions:** In this prospective real-world cohort of patients with NSCLC and cancer cachexia receiving first-line chemoimmunotherapy, anamorelin was associated with a manageable safety profile but did not achieve the primary endpoint of PFS prolongation. Cachexia improvement at week 12 was observed in a substantial proportion of patients and was associated with longer OS. These findings suggest that the clinical value of anamorelin in this setting may lie in facilitating cachexia improvement. Research Sponsor: Ono Pharmaceutical.

8593 **Poster Session**

Disaggregated lung cancer mortality trends in Asian American, Native Hawaiian, and Pacific Islander (AANHPI) patients by key sociodemographic features including sex, age, and smoking status. First Author: Diya Jayram, University of Miami Miller School of Medicine, Miami, FL

Background: Lung cancer is a leading cause of death in AANHPI populations, yet studies aggregate patients with diverse cultural backgrounds and immigration histories into an "Asian American" monolith, obscuring high-risk subgroups. Prior national disaggregation work has not captured key demographic variables important to understanding epidemiologic trends. **Methods:** This study analyzed the US Multiple Cause of Death database for deaths from lung cancer from 2018–2023, sociodemographic information included age at death, sex, race/ethnicity, smoking status, and education. Disaggregated AANHPI subgroup trends were evaluated using ACS 1-year estimates; other analyses used CDC WONDER bridged-race populations. Joinpoint estimated annual percent change in mortality(APC)/AdjustedAPC by race and sex. Pearson's Chi-squared test tested comparisons. **Results:** From 2018-2023, there were 430,703 deaths due to lung cancer in males, of which 2.7% (n=11,441) were in AANHPI males; there were 379,199 deaths in females, of which 2.5% (n=9397) were in AANHPI females. There were demographic differences in deaths within AANHPI subgroups and compared against white patients. For example, 0.5% of deaths in white male and females occurred in those aged 25-44, but this younger age group had 2.1% (male) and 4.3% (female) of Indian American deaths and 1.2% (male) and 1.7% (female) of Chinese American deaths. Deaths in white patients were associated with smoking in 48% (male) and 43% (female) of cases, but in far less of Chinese American (17% male, 4.4% female) and Filipino American (21% male, 9.7% female) lung cancer deaths ($p<0.001$ comparison). From 2018–2023, adjusted AANHPI male lung cancer mortality significantly declined -1.63% (95% CI -1.87 to -1.38; $p<0.0001$) but this was not seen AANHPI females (AAPC -1.20%; -2.86 to 0.79; p=0.22). The magnitude of AANHPI mortality decreases were smaller than in White (male -3.95, -4.43 to -3.24, female -2.35, -3.64 to -1.10; $p<0.0001$ both) and Black (male -4.35, -5.22 to -3.52, female -2.99, -3.99 to -2.96) adults during the same time period ($p<0.0001$ both). Disaggregation showed rising lung cancer mortality in Filipino women (AAPC +1.99%; 95% CI 0.59–3.54; p=0.006) and upward trends in Vietnamese women (AAPC +2.29%; 95% CI -1.05 to 5.81), whereas most AANHPI men had stable or modestly declining mortality. **Conclusions:** Despite large gains in lung cancer mortality over time, AANHPI populations —especially AANHPI women— show slower improvements despite high never-smoker prevalence, underscoring the need for disaggregated research. Rising lung cancer mortality in specific unique populations like Filipino women should motivate further research and guide targeted community outreach so that all populations benefit from improvements in early diagnosis and precision oncology. Research Sponsor: None.

8594 **Poster Session**

A phase 2 study of docetaxel (D), ramucirumab (R), and pembrolizumab (P) for patients with metastatic or recurrent non–small cell lung cancer (NSCLC) who progressed on platinum-doublet and PD-1/PD-L1 blockade. First Author: Badi Edmond El Osta, Winship Cancer Institute of Emory University, Atlanta, GA

Background: NSCLC treatment (trt) efficacy remains modest after progression on platinum and immune checkpoint inhibitors (ICI). Salvage trt with D + R has a 6-month progression-free survival (PFS) rate of 37%. **Methods:** We conducted a phase 2, single-arm study of D (75mg/m^2), R (10mg/kg), P (200mg) given intravenously in 21-day cycles until disease progression or unacceptable toxicity. Eligibility: metastatic or recurrent NSCLC, progression on concurrent or sequential platinum and ICI, no prior exposure to D or R, ECOG 0-1, measurable disease, adequate organ function. A safety run-in cohort was performed followed by efficacy evaluation using Simon's two-stage design. The null hypothesis (H_0) of 6-month PFS rate of 37% was tested against a one-sided alternative hypothesis with a rate $>$62% (α 0.1, power 80%). H_0 will be rejected if $\geq$11 of 21 patients (pts) remain free of progression or death by 6 months (m) with planned sample size of 30 to accommodate early dropout. PFS and overall survival (OS) were estimated using Kaplan Meier method. **Results:** 30 pts were enrolled. Median (range) age = 66.5 (57-84) years. 20 (67%) were white, 11 (37%) female, 25 (83%) ever-smoker, 23 (77%) non-squamous, 23 (77%) PD-L1 $<$50%, 29 (97%) received platinum + ICI concurrently, 19 (63%) progressed after 6m on prior ICI, 10 (33%) had brain metastases (mets), and 7 (23%) had liver mets. 28 pts completed at least one cycle of trt: 22 were evaluable for 6-month PFS (primary endpoint), 6 early dropouts $<$6m on trt w/o progression (including 1 prior to first imaging). No dose limiting toxicities were observed in the first month on trt. 14 (64%) of 22 pts were free of progression by 6m. Median PFS = 7.3m (95CI, 5.6-9.9); median OS = 15m (95CI, 8.4-18.9); ORR = 37%; 10 partial responses; median duration of response = 5.9m (95CI, 1.6-7.2); disease control rate = 96%; clinical benefit = 67%. Nine (31%) pts had trt-related serious adverse event (trSAE) including 1 (3%) death (Table 1). Median (range) cycles for D, R, P were 6 (1-11), 8 (1-23), 8 (1-23), respectively. Two pts remain on trt. Number of D cycles was associated with improved OS (HR 0.73; p= 0.01) and PFS (HR 0.83; p= 0.01). Presence of brain or liver mets (HR 3.13; p= 0.03) and progression in $<$3m on prior ICI (HR 5.42; p= 0.02) were associated with shorter OS. **Conclusions:** The study met its primary endpoint and demonstrated a manageable safety profile and a promising efficacy of this regimen. Clinical trial information: NCT04340882. Research Sponsor: Merck; 58866.

Summary of trSAE (n= 29).

Lethargy / weakness	3 (10%)
Pneumonia	3 (10%)
Atrial Fibrillation	2 (7%)
Dehydration / volume depletion	2 (7%)
Low K/Mag	2 (7%)
Neutropenia	2 (7%)
Death	1 (3%)
Diverticulitis	1 (3%)
Fever	1 (3%)
Interstitial nephritis	1 (3%)
Infusion reaction with cardiac arrest	1 (3%)
Neutropenic fever	1 (3%)
Pancreatic fistula	1 (3%)
Pancreatitis	1 (3%)
Port infection	1 (3%)
Pneumonitis	1 (3%)
Septic shock	1 (3%)

8595 Poster Session

Trends in lung cancer mortality among U.S. adults aged ≥55 before and after the introduction of immunotherapy: A CDC WONDER Joinpoint-style analysis. First Author: Aura Calderon, The University of Texas Rio Grande Valley, Mcallen, TX

Background: Lung cancer remains the leading cause of cancer-related mortality in the United States. Although sustained reductions in tobacco use have contributed to gradual declines in incidence and mortality, recent therapeutic advances have transformed the management of non–small cell lung cancer. The introduction of immune checkpoint inhibitors (ICIs) in the early 2010s led to substantial survival gains in clinical trials and shifted treatment paradigms toward frontline and perioperative settings. Whether these advances have translated into accelerated reductions in lung cancer mortality at the population level remains incompletely characterized. **Methods:** We conducted a nationwide population-based analysis using the CDC WONDER Underlying Cause of Death database from 1999 to 2020. Lung cancer deaths were identified using ICD-10 codes C34.0–C34.9. Annual age-adjusted mortality rates per 100,000 population standardized to the 2000 U.S. population were analyzed. Among adults aged ≥55 years, joinpoint-style segmented log-linear regression was used to identify inflection points and estimate annual percent changes (APC) before and after the identified breakpoint. **Results:** From 1999 to 2020, age-adjusted lung cancer mortality declined substantially. Among adults aged ≥55 years, segmented regression identified a significant inflection point in 2011. Prior to 2011, mortality declined at −1.52% per year, whereas after 2011 the decline accelerated to −3.88% per year ($p < 0.001$ for change in slope). In the overall population, mortality declined from 55.4 to 48.8 per 100,000 between 1999 and 2014 (APC −0.7%/year) and decreased more rapidly from 47.8 to 41.3 per 100,000 between 2015 and 2020 (APC −2.9%/year), representing more than a fourfold acceleration. **Conclusions:** In this nationwide age-adjusted analysis, lung cancer mortality demonstrated a sustained decline over two decades, with a marked acceleration beginning in the early 2010s. Although reductions in tobacco use remain an important contributor, the timing and magnitude of this acceleration, particularly among adults aged ≥55 years, are consistent with population-level benefits associated with advances in systemic therapy, including immune checkpoint inhibitors. These findings suggest that rapid clinical adoption of immunotherapy may have contributed to meaningful real-world improvements in lung cancer mortality. Research Sponsor: None.

Age-adjusted U.S. lung cancer mortality before and after immunotherapy integration, 1999–2020.

Era	Years	Start rate	End rate	Percent decline	APC (% per year)
Pre-immunotherapy	1999-2014	55.4	48.8	-10.5%	-0.7
Immunotherapy era	2015-2020	47.8	47.8	-13.6%	-2.9

APC = annual percent change. Rates are age-adjusted to the 2000 U.S. standard population.

8596 Poster Session

Impact on overall survival after adjusting for treatment crossover in first-line metastatic NSCLC trials for pembrolizumab plus chemotherapy. First Author: Ying Zhang, MSD Europe, Brussels, Belgium

Background: High crossover rates were observed in the chemotherapy alone arm in KEYNOTE(KN)-189 and KEYNOTE-407, attributable to protocol-permitted crossover to pembrolizumab monotherapy and subsequent anti-PD1/PD-L1 therapies per clinical practice. The objective was to assess the impact on overall survival (OS) by adjusting for treatment crossover. **Methods:** The analysis used pooled data from KN-189 global (NCT02578680; cut-off date: 08MAR2022) and Japan extension (NCT03950674; cut-off date: 07FEB2023), and pooled data from KN-407 global (NCT02775435; cut-off date: 23FEB2022) and China extension (NCT03875092; cut-off date: 10FEB2023). The survival time of participants (pts) in the chemotherapy alone arm who crossed over to pembrolizumab or subsequent anti-PD1/PD-L1 therapy was adjusted using a Two-Stage Estimation model (TSE) and Rank-Preserving Structural Failure Time model (RPSFT). Subsequently, a stratified Cox regression model was used to estimate the treatment effect of pembrolizumab+chemotherapy (P+C) relative to chemotherapy. **Results:** Overall, 646 and 669 patients were included in the analysis for KN-189 & KN-407 with a median follow-up of 64.6 months (range, 59.3-82.8) and 56.7 months (range, 50.1-69.3), respectively. In KN-189, adjusting OS for 56.3% pts who crossed over from the chemotherapy arm resulted in a larger treatment effect estimate for P+C relative to chemotherapy than observed in the unadjusted Intention-to-Treat (ITT) analysis. Similarly, for KN-407, after adjusting OS for 53.7% pts who crossed over, compared with chemotherapy alone, P+C showed more pronounced benefit than in the unadjusted ITT approach. The greater treatment effect for P+C was consistently demonstrated in both studies regardless of the PD-L1 TPS cutoff values. **Conclusions:** After adjusting for treatment crossover, pembrolizumab + chemotherapy demonstrated greater magnitude of OS benefit versus chemotherapy alone in both trials. TSE and RPSFT analyses support the robustness of these findings showing similar direction and magnitude of treatment effects across PD-L1 TPS cut-offs. Clinical trial information: NCT02578680; NCT03950674; NCT02775435; NCT03875092. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

	KN-189				KN-407			
Population	N	Unadjusted ITT	TSE	RPSFT	N	Unadjusted ITT	TSE	RPSFT
All comers	431 vs 215	0.60 (0.50; 0.72)	0.44 (0.33, 0.58)	0.46 (0.35, 0.61)	332 vs 337	0.65 (0.55, 0.76)	0.47 (0.35, 0.63)	0.52 (0.40, 0.67)
TPS <1%	140 vs 66	0.51 (0.37, 0.70)	0.41 (0.27, 0.63)	0.42 (0.28, 0.63)	115 vs 121	0.75 (0.56, 0.99)	0.59 (0.35, 0.98)	0.64 (0.42, 0.98)
TPS ≥1%	267 vs 132	0.65 (0.52, 0.82)	0.48 (0.32, 0.71)	0.50 (0.34, 0.73)	207 vs 209	0.60 (0.48, 0.74)	0.40 (0.28, 0.59)	0.45 (0.32, 0.63)
TPS 1-49%	132 vs 61	0.66 (0.47, 0.92)	0.48 (0.27, 0.86)	0.54 (0.33, 0.88)	114 vs 124	0.59 (0.45, 0.79)	0.38 (0.22, 0.64)	0.45 (0.30, 0.70)
TPS ≥ 50%	135 vs 71	0.66 (0.47, 0.93)	0.48 (0.26, 0.87)	0.48 (0.26, 0.87)	93 vs 85	0.63 (0.45, 0.88)	0.44 (0.24, 0.79)	0.46 (0.26, 0.81)

8597 Poster Session

Early lipid-lowering therapy initiation after lorlatinib and clinical outcomes in non–small cell lung cancer: A propensity-matched real-world analysis. First Author: Sooraj Srirangadhamu Gopu, New York Medical College, Landmark Medical Center, Woonsocket, RI

Background: Lorlatinib improves outcomes in NSCLC but commonly causes marked hyperlipidemia, prompting initiation of lipid-lowering therapy (LLT). Beyond lipid control, LLT may be associated with vascular events; however, its association with thromboembolism, healthcare utilization, and mortality among lorlatinib-treated patients has not been characterized in real-world cohorts. **Methods:** Using TriNetX, we identified adults with NSCLC who received lorlatinib (index = first lorlatinib record). Patients were grouped by early LLT initiation within 30 days of index versus no LLT within 30 days. LLT included statins, ezetimibe, PCSK9 inhibitors, or fibrates. Cohorts were balanced 1:1 using propensity score matching on demographics and baseline comorbidities. Outcomes were assessed through 365 days; patients with prior outcome documentation were excluded. **Results:** After matching, 387 patients per cohort were analyzed. Early LLT was associated with lower all-cause mortality at 365 days (16.1% vs 26.4%; risk ratio [RR] 0.61, 95% CI 0.46-0.81; p=0.0004) and improved time to death (hazard ratio 0.60, 95% CI 0.44-0.82). Early LLT was also associated with lower venous thromboembolism (6.2% vs 12.1%; RR 0.51, 95% CI 0.30-0.86; p=0.0093) and fewer inpatient hospitalizations (14.6% vs 23.6%; RR 0.62, 95% CI 0.40-0.97; p=0.0320). Emergency department visits were numerically lower (8.3% vs 13.9%; RR 0.59, 95% CI 0.35-1.00; p=0.0467). No significant differences were observed for acute kidney injury or major adverse cardiovascular events. **Conclusions:** In a real-world propensity-matched cohort of lorlatinib-treated NSCLC patients, LLT initiated within 30 days was associated with lower 1-year mortality, venous thromboembolism, and hospitalization. Given the frequency of lorlatinib-associated dyslipidemia, these findings support early lipid monitoring and timely LLT initiation in practice. Prospective studies are warranted to confirm these associations. Research Sponsor: None.

365-day outcomes after matching.

Outcome	Early LLT (n=387)	No early LLT (n=387)	RR (95% CI)	HR (95% CI)	p
All-cause mortality	16.1%	26.4%	0.608 (0.458-0.806)	0.597 (0.435-0.818)	0.0004; log-rank 0.001
Venous thromboembolism	6.2%	12.1%	0.509 (0.302-0.857)	—	0.0093
Inpatient hospitalization	14.6%	23.6%	0.619 (0.396-0.967)	—	0.0320
ED visit	8.3%	13.9%	0.593 (0.352-1.001)	—	0.0467
Acute kidney injury	5.4%	7.1%	0.769 (0.429-1.378)	—	0.3758
MACE	4.6%	4.6%	1.006 (0.511-1.979)	—	0.9868

8598 Poster Session

Glucagon-like peptide-1 receptor agonist use in lung cancer patients receiving immune checkpoint inhibitors: A real-world study. First Author: Wern Lynn Ng, Louisiana State University Health Shreveport, Shreveport, LA

Background: Immune checkpoint inhibitors (ICI) have become a cornerstone of treatment for lung cancer. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been associated with improved outcomes in cancer patients in prior studies; however, their impact on outcomes among lung cancer patients receiving immunotherapy remains limited. **Methods:** We conducted a retrospective cohort study using the TriNetX real-world data platform. Adult patients with lung cancer treated with ICIs, including PD-1, PD-L1, or CTLA-4 inhibitors, were included. Patients were stratified based on exposure to GLP-1 RA. Propensity score matching (1:1) was performed to balance baseline demographics and comorbidities, including type 2 diabetes mellitus and body mass index. Primary outcomes included all-cause mortality, intensive care unit (ICU) admission, and hospitalization. Secondary outcomes included immune-related pneumonitis, colitis/enteritis, cachexia, and major adverse cardiovascular events (MACE). **Results:** After matching, 2,013 patients were included in each group, with a median follow-up of 372 days in the GLP-1 RA group and 383 days in the non-GLP-1 RA group. Mean age was 66.8 and 67.2 years, respectively, and approximately 50% of patients were male. Most patients were White (77.2% vs 71.8%), followed by Black (14.1% vs 14.0%) and Asian (2.1% vs 1.8%). GLP-1 RA use was associated with a significantly lower all-cause mortality rate compared with non-use (35.7% vs. 53.4%; $p < 0.0001$), with a hazard ratio of 0.65 (95% CI, 0.59–0.71). Significant reductions were also observed in ICU admissions (22.8% vs 29.0%; p = 0.0001), hospitalizations (64.1% vs 71.8%; p = 0.0001), pneumonitis (5.2% vs 6.8%; p = 0.0457), and MACE (19.9% vs 25.3%; p = 0.0026). No significant differences were observed in colitis/enteritis (9.3% vs 9.4%; p = 0.9704) or cachexia (8.0% vs 9.8%; p = 0.0650). In a subgroup analysis of lung cancer patients not receiving ICI, GLP-1 RA use was similarly associated with lower mortality, ICU admission, hospitalization, and MACE, without differences in immune-related toxicities. **Conclusions:** GLP-1 RA use among lung cancer patients was associated with improved survival, reduced healthcare utilization, and fewer selected adverse events in patients receiving ICI therapy. These associations likely reflect established metabolic and cardiovascular benefits of GLP-1 RA and may also involve antitumor mechanisms suggested in prior studies. Residual confounding related to healthcare access and socioeconomic factors cannot be fully excluded and should be considered when interpreting these findings. Prospective studies are warranted to validate these observations and clarify underlying biological mechanisms. Research Sponsor: None.

8599 **Poster Session**

A comprehensive evaluation of the effectiveness of the Geriatric 8 screening tool in Japanese patients with non–small cell lung cancer: Results from the ENSURE-GA study, a cluster-randomized phase III clinical trial. First Author: Akihiro Tsukamoto, Department of Respirology, Gifu University,Graduate School of Medicine, Gifu, Japan

Background: The Geriatric 8 (G8) is a widely utilized screening tool globally for assessing functional status in elderly cancer patients, with a score of 14 or lower indicating a positive result. Previous studies have reported that G8-positive patients are at a higher risk of mortality and experiencing Grade 3 or higher adverse events (AEs). At ASCO 2024, we reported that the G8 positivity rate exceeded 80% among Japanese patients aged 75 and older with non-small cell lung cancer (NSCLC), suggesting a potential issue with its sensitivity in this population. In the present study, we conducted a further detailed analysis of the scoring patterns for individual G8 items and their association with the incidence of AEs. **Methods:** The ENSURE-GA study was a cluster-randomized phase III clinical trial involving 1,021 patients aged 75 years and older with non-small cell lung cancer (NSCLC). Participating institutions were cluster-randomized into either the intervention group or the control group. All patients underwent a standardized Geriatric Assessment (GA) prior to the initiation of treatment. From this cohort, 1,001 patients who underwent G8 assessment were identified for analysis. We evaluated the association between the scoring patterns (loss of points) for each G8 item and the frequency and severity of adverse events. **Results:** The ROC curve for G8 regarding the occurrence of grade 3 or higher adverse events in cases receiving cytotoxic chemotherapy yielded an AUC of 0.525, indicating no discriminatory ability. Among the eight components of the G8 screening tool, self-rated health status ("In comparison with other people of the same age, how does the patient consider their health status?") showed the highest rate of point loss at 72.0% (656/911), followed by polypharmacy at 67.5% (615/911) and Body Mass Index (BMI) at 61.9% (564/911).The G8 score did not correlate with the severity of adverse events. **Conclusions:** The G8 is a valuable screening instrument, but our findings suggest the need for optimization, including the establishment of cancer-specific and race-specific cut-offs, as well as the implementation of weighted scoring for its components. Clinical trial information: UMIN0000037590. Research Sponsor: None.

8600 **Poster Session**

Five-year overall survival in lung adenocarcinoma: Real-world results from three French nationwide cohorts (2000–2010–2020). First Author: Didier Debieuvre, Service de Pneumologie, Groupe Hospitalier de la Région Mulhouse Sud-Alsace, Hôpital Émile-Muller, Mulhouse, France

Background: Long-term (5-year) real-world overall survival (OS) in non–small cell lung cancer (NSCLC) remains poorly documented especially in prospective condition. The French nationwide KBP program comprises prospective cohorts conducted every 10 years since 2000 to evaluate lung cancer prognosis. In 2020, 8,941 patients were included across 81 non-academic public hospitals, with lung adenocarcinoma (LA) representing the most frequent histologic subtype. Building on previously reported 3-year survival results[1], we assessed temporal changes in 5-year OS and described the characteristics of long-term survivors with LC using the 2000, 2010, and 2020 cohorts. **Methods:** Patients with lung cancer, all stages, diagnosed in non-academic public hospitals in 2000, 2010, and 2020 were included in the French nationwide KBP cohorts, all conducted using the same prospective methodology. For the 2020 cohort, patient inclusion occurred between 1 January and 31 December 2020. Vital status was collected during follow-up. Five-year OS was estimated using the Kaplan–Meier method and compared across the 2000, 2010, and 2020 cohorts, overall and stratified by stage at diagnosis. In the 2020 cohort, a descriptive comparative analysis was performed between long-term survivors (≥5 years) and patients who died before this term. In the 2020 cohort, multivariable Cox proportional hazards models are ongoing to identify prognostic factors associated with OS. Prespecified covariates include age, sex, ECOG PS, smoking status, stage at diagnosis. These analyses remain preliminary and will be updated for the conference, as the 5-year vital status follow-up has recently been completed. **Results:** Among the 1,640, 3,199, and 5,009 patients with LA included in the 2000, 2010, and 2020 KBP cohorts, respectively, 5-year vital status was available for 99.3%, 96.2%, and 83.4% of patients. 5-year OS was 29.4% (95% CI, 28.1–30.7) in 2020, compared with 14.4% (95% CI, 13.3–15.7) in 2010 and 4.7% (95% CI, 3.0–7.2) in 2000, corresponding to an absolute improvement of 15.0% over the last decade. In the 2020 cohort, long-term survivors (≥5 years; n = 772) were 47.8% female, only six patients had an ECOG performance status ≥3, 48.2% were current smokers, 19.8% never-smokers and 32.0% former smokers. The distribution of stage at diagnosis among long-term survivors was 37.6% stage I, 9.9% stage II, 20.9% stage III, and 31.6% stage IV. **Conclusions:** 5-year real-world OS in LA has markedly improved over the last two decades with an increasing proportion of long-term survivors. Ongoing stage-stratified and multivariable analyses will further characterize long-term survival patterns. [1] https://evidence.nejm.org/doi/full/10.1056/EVIDoa2400443. Research Sponsor: Abbvie, AstraZeneca, Amgen, BMS, MSD, Janssen, Bayer, Boehringer Ingelheim, Lilly, Takeda, Sanofi, Roche, Chugai, Pfizer, Regeneron, Novocure, Pierre Fabre; Fondation du Souffle, Le Nouveau Souffle, Couleur espoir, the labeling of InCa and FHF- CNCR Institutional Funding.

8601 **Poster Session**

Long-term survival outcomes of consolidative local ablative therapy after response to first-line systemic treatment in oligometastatic NSCLC. First Author: Phurin Areesawangkit, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA

Background: The role of consolidative local ablative therapy (LAT) for patients (pts) with oligometastatic non-small cell lung cancer (NSCLC) who have responded to first line (1L) systemic treatment remains controversial especially after negative results from the NRG LU002 phase II/III trial. Data on long-term survival outcomes remain limited. **Methods:** We retrospectively collected data from EMR records of pts with oligometastatic NSCLC treated with 1L systemic treatment at the University of Pennsylvania Health System (2015–2025). Oligometastasis was defined as ≤4 distant metastases. Eligible pts had either genuine synchronous or induced oligometastatic disease and had achieved partial response (PR) or stable disease (SD) after 1L systemic treatment. We hypothesized that LAT would be associated with improved PFS and OS using time-dependent Cox regression analysis. **Results:** We identified 187 eligible pts. 53% were female; median age was 67 yrs and 31% had PD-L1 expression > 50%. At diagnosis, 90% had genuine oligometastatic disease: 45% with one metastatic lesion, 24% with two, 15% with three, and 11% with four lesions. Median follow- up time was 81 mos. (Reverse Kaplan-Meier). Of 187 pts, 21 received consolidative LAT in addition to maintenance therapy (LAT+) while 166 received maintenance therapy alone (LAT-). The LAT+ group was less likely to have bone metastasis (4.8% vs 34%, P = 0.007) and more likely to have adrenal metastasis (38% vs 19%, P = 0.049). In the LAT+ group, 67% had received chemo-immunotherapy as 1L and 19% had received immunotherapy alone, compared with 58% and 17% in the LAT− group, respectively (P = 0.80, Chi-square). In the LAT+ group, 76% achieved PR and 24% had SD to 1L therapy, compared with 65% and 35% in the LAT− group, respectively (P = 0.30, Chi-square). Median time from diagnosis to LAT delivery was 6 mos. (range, 2 – 24 mos.). The most common LAT modality was radiation (82%). The most common site of LAT was lung (68%). Median PFS was 28 vs 12 mos. and median OS was 98 vs 24 mos. in the LAT+ and LAT− groups, respectively. In time-dependent Cox models treating LAT as time-varying exposure, LAT+ was associated with improved PFS (P = 0.045) and OS (P = 0.003). A multivariable model confirmed the benefit of LAT after adjusting for PD-L1 status, treatment response, brain metastasis, bone metastasis, and nodal status (PFS: HR = 0.38, P = 0.004; OS: HR = 0.27, P = 0.002). Adverse events grade ≥3 were similar in both groups. **Conclusions:** LAT was associated with significantly improved PFS and OS in pts with oligometastatic NSCLC with an objective response or stable disease following 1L systemic treatment. Prospective studies are warranted to define pt characteristics that predict the greatest benefit from and optimal timing of LAT. Research Sponsor: None.

8602 **Poster Session**

Impact of time-of-day (ToD) of single-agent immune-checkpoint inhibitor (ICI) on survival in advanced non–small cell lung cancer (aNSCLC) with PD-L1 ≥ 50%: Analysis of the NOTCH collaborative REAL-SAIF study. First Author: Alfred Chung Pui So, St Bartholomew's Hospital, London, United Kingdom

Background: There is growing evidence and interest in the role of chrono-immunotherapy. Previous studies showing benefit of earlier ToD were limited by small cohorts with heterogenous groups and ToD cut-offs. Using one of the largest UK cohort, we explored this further. **Methods:** 896 patients treated with 3-weekly ICI monotherapy between 2017-2023 from 16 UK centres were included in this retrospective study. Early 30-day deaths were excluded. Multiple imputations were used for data missing at random (except ToD) with pooled estimates. The primary endpoint was overall survival (OS). A sinusoidal Cox model was used for multivariate analysis to represent the cyclical nature of ToD. **Results:** Median OS and progression-free survival (PFS) were 19.1 (95%CI 17.2-20.9) and 10.1 (95%CI 9.2-11.7) months. Baseline demographics were median age 70-years, 50% male, 77.3% non-squamous histology, and 91% pembrolizumab as ICI of choice. Mean C1 and C2 ToD was 13:18 and 13:12 respectively. 44.1% and 66.5% of patients received C2 within 1 and 4 hours from prior ToD. ToD was not correlated with age or socioeconomic deprivation. Age (HR 1.01; p=0.008), male sex (HR 1.25; p=0.005), performance status (PS) ≥2 (HR 1.22; p=0.038), squamous histology (HR 1.30; p=0.004), liver metastasis (HR 1.51; p=0.001), albumin (HR 0.98; $p<0.001$), and neutrophil-lymphocyte ratio (NLR) (HR 1.60; $p<0.031$) were associated with OS. PS ≥2 (HR 1.23; p=0.026), squamous histology (HR 1.26; p=0.010), albumin (HR 0.98; p=0.001), and PDL1% (HR 0.99; p=0.012) were associated with PFS. There was no correlation between C1 or C2 ToD with OS/PFS. There was a significant interaction between NLR and C1 ToD for both OS (HR 1.48; $p<0.001$) and PFS (HR 1.30; p=0.014), with a change in HR <1.0 for high NLR after 14:00 and 12:30 respectively. **Conclusions:** ToD alone was not associated with survival in aNSCLC ICI monotherapy. NLR has a strong interaction with ToD. A low NLR with early ToD and a high NLR with later ToD were correlated with improved OS/PFS. The relationship of ToD with survival is complex and further research is required before adoption into routine practice. Research Sponsor: None.

Multivariate Cox model for OS and PFS.

	PFS [HR (95%CI); p-value]		OS [HR (95%CI); p-value]	
Age	1.00 (1.00-1.01)	0.286	1.01 (1.00-1.02)	0.008
Male sex	1.14 (0.98-1.32)	0.093	1.25 (1.07-1.46)	0.005
Performance status ≥2	1.23 (1.03-1.48)	0.026	1.22 (1.01-1.48)	0.038
Squamous histology	1.26 (1.06-1.50)	0.010	1.30 (1.09-1.56)	0.004
Brain metastasis	1.24 (0.99-1.57)	0.062	1.24 (0.97-1.59)	0.091
Liver metastasis	1.32 (1.03-1.69)	0.029	1.51 (1.17-1.94)	0.001
Albumin	0.98 (0.97-0.99)	0.002	0.98 (0.96-0.99)	<0.001
NLR	1.16 (0.76-1.76)	0.498	1.60 (1.05-2.46)	0.031
PDL1%	0.99 (0.99-1.00)	0.012	1.00 (0.99-1.00)	0.091

8603 **Poster Session**

Lung cancer burden in AYAs: Global and U.S. trends. First Author: Ruchi Tusharkumar Jani, Smt N.H.L. Municipal Medical College, Gujarat, India

Background: Lung cancer remains a leading cause of cancer-related mortality and is increasingly observed among adolescents and young adults (AYA), with shifting tobacco use and rising air pollution implicated as potential risk factors. This study examines global and U.S. epidemiological and risk factor trends of tracheal, bronchial, and lung cancer (TBLC) in AYA population (20-54 years). **Methods:** We utilized Global Burden of Disease database (1990-2023) for TBLC, to extract Age Specific incidence (ASIR) and mortality rates (ASMR), as well as proportional and absolute ASMRs associated with all risk factors, tobacco use and ambient particulate matter (PM2.5). Joinpoint analysis assessed changes in trends and calculated EAPC (Estimated Annual Percentage Changes). All rates are reported per 100,000 population. **Results:** In 2023, the global ASIR of TBLC among AYAs was 8.69 (n = 167,524) in males and 4.70 (n = 88,569) in females, with absolute incidence increasing by 13% in males and 50% in females. Absolute mortality similarly increased by 9% in males and 39% in females, with ASMRs of 6.99 and 3.52, respectively in 2023. In US, while overall incidence and mortality declined, ASIR in 2023 for females (0.62) was found to be almost similar to males (0.64), whereas ASMR remained higher in males (0.49) than females (0.43). At global level, tobacco remained the leading ASMR contributor in 2023, with higher burden in males (males 4.8, 68.2%; females 1.1, 31%), followed by PM2.5 (males 1.1, 20.5%, females 0.5, 20.8%). No TBLC-related mortality was attributed to household air pollution in 2023. The most significant decline in tobacco- and PM2.5–associated TBLC mortality in males occurred from 2003 to 2020 (tobacco: EAPC −2.66; PM2.5: 2006-2017: EAPC −0.76), and in females between 2008 to 2021 (tobacco: EAPC −3.5, PM2.5: 2017-2020: EAPC -4.8). By 2023, 18.8% of male and 43.1% of female TBLC deaths had no identified risk factors. In the US, ASMR declined continuously across all risk factors in both sexes, and by 2023, 25.4% of male and 32.0% of female TBLC deaths had no identified associated risk factors. Despite overall reductions in ASIR and ASMR globally and in USA, Mortality to Incidence ratio remained largely stable, with only minimal decreases observed globally (males −3.6%, females −7.5%) and in the US (males −2.3%, females −5.8%). **Conclusions:** Our analysis demonstrated an absolute increase in TBLC incidence and mortality globally in both sexes, with males continuing to experience higher mortality. In the USA, the sex-based gap in ASIR has nearly disappeared. Although tobacco-related mortality declined, it remained the leading risk factor. By 2023, 20–25% of AYA males and 30–43% of AYA females TBLC deaths were attributable to non-modifiable risk factors, highlighting the need for screening guidelines that better address AYAs, particularly those without traditional risk factors. Research Sponsor: None.

8604 **Poster Session**

Resistance mechanisms and efficacy of first-line alectinib and sequential treatments in advanced *ALK*+ NSCLC: Real-world outcomes from a multicenter, observational study in Japan (ALCURE). First Author: Hirotsugu Kenmotsu, Shizuoka Cancer Center, Shizuoka, Japan

Background: First-line (1L) alectinib has shown superior progression-free survival (PFS) vs crizotinib in advanced *ALK*+ non-small cell lung cancer (NSCLC). We present final data from ALCURE (UMIN000038934), a real-world study exploring resistance mechanisms to 1L alectinib and treatment sequencing in Japanese patients (pts) with advanced *ALK*+ NSCLC. **Methods:** Eligible pts, aged ≥20 years with *ALK*+ NSCLC, were enrolled into 2 cohorts: pts already receiving 1L alectinib before enrollment (cohort A) or treatment-naïve pts starting alectinib (cohort B). Results were reported separately by cohort to address the potential immortal time bias introduced by cohort A (pooled analyses were reported for second-line [2L] treatment since the bias did not apply and the sample size was limited). Clinical samples were collected and analyzed using next-generation sequencing. **Results:** From Jan–Nov 2020, 249 pts were enrolled (cohort A/B, n=200/49). Demographics in cohort A/B were: age ≥75 years, 21%/18%; female, 60%/57%; never smokers, 65%/67%; brain metastases, 22%/31%; *TP53* mutations, 9%/41%. *EML4-ALK* variant 1 was the most common *ALK* variant (50% cohort A, 42% cohort B). Secondary *ALK* mutations at disease progression (PD) or end of 1L treatment were detected in 14/60 pts (23%) in cohort A and 3/25 pts (12%) in cohort B (primarily G1202R or I1171N). Median duration of 1L alectinib before enrolment in cohort A was 24 months (range 1–111). At data cutoff (Nov 6, 2024), median follow-up was 74.1 months (95% CI 11.8–163.3) in cohort A and 48.7 months (95% CI 0.6–56.7) in cohort B. Median PFS (mPFS) was not reached (NR) (95% CI 83.7–NR) in cohort A and 32.9 months (95% CI 11.8–38.5) in cohort B. In pts whose tumors were *TP53* wildtype vs mutant prior to alectinib, mPFS was NR vs NR (HR 0.47, 95% CI 0.15–1.50) in cohort A and 33.6 vs 14.1 months (HR 0.96, 95% CI 0.46–2.00) in cohort B. mPFS in pts with secondary *ALK* mutations detected vs not detected at PD or end of 1L treatment was 14.6 vs 37.1 months (HR 1.68, 95% CI 0.84–3.34) in cohort A and 9.0 vs 11.8 months (HR 1.56, 95% CI 0.35–6.95) in cohort B. Median OS was NR (95% CI NR–NR) in cohort A and 54.7 months (95% CI 54.7–NR) in cohort B. Of the 118/249 pts who discontinued 1L alectinib, 84 received 2L treatment (including 18 who received non-ALK TKIs); mPFS for 2L treatment was 9.9 months (95% CI 7.4–12.1) in the overall cohort. Among these pts, 40 received lorlatinib and had the longest mPFS of all pts receiving 2L treatment (17.2 months). **Conclusions:** The use of 1L alectinib in clinical practice demonstrated efficacy consistent with that seen in clinical trials in pts with *ALK*+ NSCLC and confirms the existence of long-term responders. Lorlatinib may be an effective treatment following 1L alectinib; further research is needed to identify factors that may predict response and inform optimal treatment sequencing strategies. Clinical trial information: UMIN000038934. Research Sponsor: The ALCURE study was sponsored by Chugai Pharmaceutical Co., Ltd; Third-party medical writing assistance, under the direction of the authors, was provided by Helen Cathro, PhD, of Ashfield MedComms, an Inizio company, and was funded by Chugai Pharmaceutical Co., Ltd.

8605 **Poster Session**

Afatinib versus osimertinib for non–small cell lung cancer with uncommon epidermal growth factor receptor mutations: Real-world outcomes (HOT-Next001/HOT2501). First Author: Yutaro Nagano, Department of Respiratory Medicine and Allergology, Sapporo Medical University School of Medicine, Sapporo, Japan

Background: Non–small cell lung cancers (NSCLC) with uncommon epidermal growth factor receptor (EGFR) mutations exhibit considerable biological and clinical heterogeneity. Consequently, the optimal first-line EGFR tyrosine kinase inhibitor (EGFR-TKI) and the role of subsequent immune checkpoint inhibitor (ICI)–based regimens remain uncertain. **Methods:** This multicenter retrospective cohort study was conducted at 29 institutions in Japan and included patients with advanced or recurrent non-squamous NSCLC harboring uncommon EGFR mutations who received first-line afatinib or osimertinib between January 2015 and January 2024. Exon 20 insertions and de novo T790M mutations were excluded. Outcomes included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), safety, and the effectiveness of subsequent systemic therapies, including ICI plus platinum doublet chemotherapy (ICI-Chemo) and platinum doublet chemotherapy alone. To adjust for baseline imbalances, analyses used inverse probability of treatment weighting (IPTW) based on covariate-balancing propensity scores. **Results:** Among 162 patients, 95 received afatinib and 67 received osimertinib. After IPTW adjustment, no significant differences were observed in PFS (median, 11.3 vs 5.9 months; hazard ratio [HR], 1.04; 95% confidence interval [CI], 0.60–1.80) or OS (28.0 vs 25.5 months; HR, 1.34; 95% CI, 0.73–2.44). Afatinib yielded a higher ORR (70.2% vs 47.2%) and DCR (93.7% vs 82.5%) than osimertinib, while adverse events requiring dose reduction were more frequent (76.8% vs 31.3%) but generally manageable. Subgroup analyses suggested greater benefit with osimertinib in L861X mutations and with afatinib in compound mutations. In patients with PD-L1 ≥50%, afatinib was associated with significantly longer PFS (15.5 vs 2.6 months; HR, 0.14; 95% CI, 0.04–0.46), whereas OS was numerically longer (30.5 vs 12.9 months; HR, 0.38; 95% CI, 0.07–1.93). Among 56 patients who received subsequent systemic therapy and were chemotherapy- and ICI-naïve, IPTW-adjusted analyses showed that ICI-Chemo did not improve outcomes compared with platinum doublet chemotherapy: median PFS, 6.7 vs 7.3 months (HR, 1.08; 95% CI, 0.53–2.19) and post–EGFR-TKI OS, 14.6 vs 19.7 months (HR, 1.30; 95% CI, 0.63–2.68). **Conclusions:** In one of the largest multicenter real-world cohorts, afatinib and osimertinib demonstrated comparable survival outcomes as first-line EGFR-TKIs in NSCLC with uncommon EGFR mutations, with treatment effects modulated by mutation subtype and PD-L1 expression. ICI-based regimens did not improve outcomes compared with platinum doublet chemotherapy and conferred no meaningful clinical benefit as post–EGFR-TKI therapy in this population. Research Sponsor: Sapporo Medical University Grants for Programs promoting Academic advancements; 246.

8606 **Poster Session**

Brigatinib after lorlatinib and/or chemotherapy following first-line alectinib in ALK-rearranged NSCLC: Cohort B of the WJOG11919L/ABRAID study. First Author: Shuhei Teranishi, Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan

Background: As survival improves in ALK-rearranged NSCLC, patients increasingly receive multiple lines of therapy; however, evidence to guide later-line ALK-TKI sequencing in the third line and beyond remains limited. Brigatinib has activity against multiple ALK resistance mutations, yet data on its effectiveness after progression on first-line alectinib and subsequent lorlatinib and/or chemotherapy—and on associated plasma ctDNA biomarkers—remain scarce. **Methods:** WJOG11919L/ABRAID Cohort B is a prospective, multicenter observational study enrolling patients with ALK-rearranged NSCLC who received brigatinib after lorlatinib and/or chemotherapy following first-line alectinib. Effectiveness and safety were summarized descriptively. Pretreatment plasma ctDNA was analyzed with the PGDx Elio Plasma Resolve panel. The data cutoff was September 26, 2024. **Results:** Twenty-five patients were analyzed (median age, 64 years; all adenocarcinoma); ECOG PS was 0-1/2-3 in 22 (88.0%)/3 (12.0%). Baseline CNS metastases were present in 10 patients. After alectinib, 13 patients received lorlatinib and 14 received platinum-based chemotherapy (overlap, n=2). Median follow-up was 12.7 months. Efficacy outcomes overall and by prior lorlatinib exposure are summarized in the Table. 23 patients had discontinued brigatinib, including 21 due to PD. Pretreatment ctDNA was evaluable in 24 patients: ALK mutations were detected in 4 (including 3 with prior lorlatinib), and compound ALK mutations (G1202R/I1171M/L1204V and D1203N/L1196M) were identified in 2, both after lorlatinib. In exploratory analyses, among the 3 patients with prior lorlatinib and detectable ALK mutations, all experienced early progression or death within 10 weeks of brigatinib initiation. Pneumonitis/ILD occurred in 1 patient (4%; grade 4). No new safety signals were observed. **Conclusions:** Brigatinib showed clinically meaningful activity with a manageable safety profile, providing durable disease control in a subset of patients previously treated with alectinib followed by lorlatinib and/or chemotherapy. Outcomes appeared less favorable after prior lorlatinib, although some patients derived benefit. In exploratory plasma ctDNA analyses among patients with prior lorlatinib, detectable ALK mutations were associated with less favorable outcomes and should be validated in larger cohorts. Clinical trial information: UMIN000042439. Research Sponsor: Takeda Pharmaceutical Company Limited.

Efficacy outcomes overall and by prior lorlatinib exposure.

Endpoint	Overall (n=25)	Prior lorlatinib (n=13)	No prior lorlatinib (n=12)
ORR, % (95% CI)	32.0 (14.9–53.5)	30.8 (12.7–57.6)	33.3 (13.8–60.9)
DCR, % (95% CI)	60.0 (38.7–78.9)	38.5 (17.7–64.5)	83.3 (55.2–95.3)
mPFS, mo (95% CI)	4.8 (2.2–12.7)	2.2 (1.2–18.8)	8.9 (2.3–15.6)
12-mo PFS, %	32.0	30.8	33.3
mOS, mo (95% CI)	13.7 (7.29–NR)	10.8 (3.7–NR)	16.2 (7.1–NR)
12-mo OS, %	56.0	38.5	75.0

8607 Poster Session

High-dose furmonertinib in *EGFR*-mutated advanced NSCLC with brain metastases after EGFR-TKI resistance: The iFORCE phase II trial. First Author: Mengxing You, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China, China

Background: Brain metastases (BM) are common in patients with EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC) and are associated with poor prognosis. Furmonertinib is a pan-EGFR tyrosine kinase inhibitor (TKI) characterized by high central nervous system penetration and a wide therapeutic window. This study evaluated the efficacy and safety of high-dose furmonertinib (160 mg once daily) in previously EGFR-TKI-treated patients with EGFRm NSCLC and BM. **Methods:** iFORCE was a prospective, single-arm study conducted at a single center. Eligible patients had EGFR exon 19 deletion or L858R-mutant NSCLC with at least one measurable intracranial lesion (≥5 mm) and had received ≥1 prior EGFR-TKI therapy. Patients received furmonertinib 160 mg orally once daily. The primary endpoints were intracranial progression-free survival (iPFS). **Results:** Twenty-three patients were enrolled, with a median follow-up time of 19.7 months (95% confidence interval [CI], 14.5-25.3 months). Median iPFS was 14.6 months (95% CI, 4.2-not reached), with 12- and 24-month iPFS rates of 53.8% and 30.8%, respectively. The intracranial objective response rate (iORR) was 34.8% (95% CI, 16.4-57.3), and the intracranial disease control rate (iDCR) was 91.3% (95% CI, 72.0-98.9). Median systemic progression-free survival (PFS) was 10.7 months (95% CI, 3.9-not reached). Treatment-related adverse events occurred in 13 (56.5%) of patients and were predominantly grade 1; one patient (4.3%) experienced a grade 3 stomatitis. No treatment discontinuations or treatment-related deaths were observed. **Conclusions:** High-dose furmonertinib demonstrated encouraging intracranial efficacy with a manageable safety profile in previously EGFR-TKI-treated patients with EGFRm NSCLC and BM, supporting further investigation in randomized studies. Clinical trial information: NCT05465343. Research Sponsor: None.

8608 Poster Session

Sotorasib vs adagrasib in the 2L+ setting: Outcomes in a large, multi-institutional, real-world database of KRAS-G12C mutated mNSCLC. First Author: Adam Barsouk, Abramson Cancer Center, Philadelphia, PA

Background: KRAS-G12C mutations are found in ~12% of mNSCLC. KRAS-G12C inhibitors sotorasib and adagrasib are approved treatments but have never been compared head-to-head. We report the first large, multi-institutional database analysis comparing efficacy and safety of sotarasib vs adagrasib. **Methods:** Flatiron Health's de-identified electronic health record US database was used to identify patients with KRAS G12C-mutated NSCLC who started treatment 12/2022-10/2025 with either sotorasib or adagrasib in 2L+. Baseline characteristics were abstracted and evaluated using chi-square tests, Wilcoxon rank-sum tests, and a multivariable logistic regression adjusting for practice type, sex, ECOG performance status, age, line of therapy, prior immunotherapy, and brain metastases. Overall survival (OS), progression-free survival (PFS), and time to treatment discontinuation (TTD) were estimated using Kaplan-Meier curves and compared using the log-rank test and Cox regression. Multivariable Cox regression model included sex, age, ECOG, line of therapy, prior immunotherapy, brain metastases, and PD-L1 expression to control for possible confounding. **Results:** Of the 1133 patients identified, 768 (69%) received sotorasib, and 345 (31%) received adagrasib. Sex, age, PD-L1 status and prior immunotherapy exposure did not affect choice of treatment (Table 1). In a multivariable logistic regression analysis, patients with brain metastases were more likely to be treated with adagrasib (HR =0.64; p=0.003), while patients with higher ECOG PS (2+) were more likely to be treated with sotorasib (HR =1.18; p=0.047). There was no difference in OS between sotorasib and adagrasib (HR = 1.01; p = 0.87), and there was no difference in OS on multivariable regression (adjusted HR = 0.96; p=0.02). There was no difference in PFS between sotorasib and adagrasib (HR = 0.91; p=0.15). Sotorasib had longer TTD than adagrasib (mTTD 3.8 vs 3.3m; HR = 0.82; p =0.005); this association persisted in the adjusted model (adjusted HR = 0.80; p=0.006). **Conclusions:** Sotorasib was associated with slightly longer TTD compared with adagrasib, which may suggest better tolerability, but no difference in PFS or OS. Sotorasib was more likely to be used in patients with poor PS while adagrasib was more likely to be used in patients with CNS metastases. Research Sponsor: None.

	Sotorasib (n = 768)	Adagrasib (n = 345)	p-value
2L (vs 3+)	68.6%	73.0%	0.15
ECOG PS 0-1 (vs 2-4)	64.6%	69.9%	0.13
PDL1	31.2%	38.3%	0.10
<1%			
1-49%	36.4%	32.4%	
>=50%	32.4%	29.3%	
Prior immunotherapy	85.9%	89.0%	0.18
Brain metastases	28.1%	35.1%	**0.02**
mPFS	3.5	3.3	0.15
			*0.25
mTTD	3.8	3.3	**0.005**
			***0.006**
mOS	9.6	8.7	0.87
			*0.70

All survival data in months. Significant values in bold.

8609 Poster Session

Reduction in circulating tumor DNA (ctDNA) in relation to radiographic response and tumor PD-L1 expression in a phase 1 study of PDL1V (PF-08046054) in patients with non-small cell lung cancer (NSCLC). First Author: Ramy Saleh, Department of Medical Oncology, McGill University Health Centre, Montreal, QC, Canada

Background: PDL1V (PF-08046054) is a novel, first-in-class, PD-L1–directed vedotin antibody-drug conjugate that consists of MMAE connected to an anti–PD-L1 antibody. Prior results from the phase 1 study (NCT05208762) showed promising antitumor activity and manageable safety in patients (pts) with refractory (2L+) NSCLC. We present ctDNA results from an exploratory analysis in this study. **Methods:** C5851001 is a phase 1 study in advanced solid tumors. Pts with NSCLC must have prior exposure to platinum and anti–PD-(L)1 agents, targeted therapies for tumors expressing AGAs, and measurable disease per RECIST 1.1. PD-L1 expression status by tumor proportion score (TPS) was reported by local sites. Paired baseline (T0) and on-treatment (T1; C2D15 to C3D1) ctDNA samples were used for ctDNA analyses using a methylation-based tissue-free assay (Guardant Infinity). Tumor fraction (TF) was quantified by methylation score. Changes in ctDNA from T0 to T1 were compared between subgroups using the Wilcoxon test. **Results:** As of Nov 22, 2025, 55 pts with 2L+ NSCLC received PDL1V: median age 63 yrs, 70.9% ECOG PS 1, 29.1% squamous (SQ) histology, 67.3% TPS ≥1%. The median number of prior lines of therapy was 2.0 (range, 1-8). The investigator-assessed confirmed objective response rate (ORR) was 32.4% (95% CI, 18.0-49.8) in pts with TPS ≥1% NSCLC (n=37) and 0% in TPS <1% (n=18). Grade 3-4 TRAEs occurred in 32.6%. Paired T0 and T1 samples were available in 47/55 pts. ctDNA analysis showed 46/47 pts (98%) had detectable ctDNA at baseline. At T1, ctDNA TF decreased in 36/46 pts (78%) and became nondetectable in 7/46 (15%). Pts with complete or partial responses (CR/PR) had a greater median ctDNA reduction from T0 to T1 than nonresponders (−99% vs −37%, p<0.001). Pts with TPS ≥1% NSCLC had a greater median ctDNA reduction than pts with TPS <1% NSCLC (−77% vs −4%, *P*=0.0023). For pts with TPS ≥1% NSCLC, there was no significant difference in median ctDNA reduction between nonsquamous (NSQ) and SQ histology (−73% vs −87%, p=0.48). **Conclusions:** PDL1V monotherapy showed promising antitumor activity with a manageable safety profile in pts with 2L+ TPS ≥1% NSCLC. Most pts had ctDNA reduction with PDL1V treatment, with greater ctDNA reduction in pts with radiographic response and TPS ≥1% NSCLC. These data further support evaluation of PDL1V in the ongoing phase 3 trial in 2L+ PD-L1+ NSCLC, SQ and NSQ (NCT07144280/PADL1NK-005) and the continued use of ctDNA for response monitoring and potential early prediction of clinical benefit. Clinical trial information: NCT05208762. Research Sponsor: Pfizer.

Subgroup		n	ctDNA reduction (%) from T0 to T1median (lower/upper quartile)
By ORR			
CR/PR		12	−99 [−100 to −93]
SD/PD		34	−37 [−72 to 5]
By PD-L1 status			
TPS <1%		14	−4 [−36 to 26]
TPS ≥1%		32	−77 [−98 to −39]
	TPS 1%-49%	17	−72 [−82 to −38]
	TPS ≥50%	15	−91 [−100 to −41]
By histology	TPS ≥1%		
	NSQ	24	-73 [-95 to -38]
	SQ	8	-87 [-98 to -70]

8610 Poster Session

Firmonertinib combined with platinum-based chemotherapy in patients with *EGFR*-mutant advanced NSCLC following disease progression on first-line third-generation EGFR-TKI. First Author: Jialei Wang, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Patients (pts) who have progressed after first-line 3rd-generation EGFR-TKIs treatment exhibit limited therapeutic options. We report the preliminary antitumor activity and safety results of firmonertinib combined with platinum-based chemotherapy (Cohort C) in pts with EGFR-mutant advanced NSCLC who failed first-line 3rd-generation EGFR-TKIs from a prospective multi-cohort phase 2 trial (NCT06652048). **Methods:** Cohort C planned to include 20 pts with advanced NSCLC harboring EGFR-sensitizing mutations who progressed after first-line 3rd-generation EGFR-TKIs. Study treatment was firmonertinib (160 mg once daily) with chemotherapy (pemetrexed [500 mg/m^2] plus either cisplatin [75 mg/m^2] or carboplatin [AUC 5]). The primary endpoint was progression-free survival (PFS) assessed by investigators according to RECIST v1.1. **Results:** Cohort C completed accrual with 18 pts who received at least one dose of study treatment: median age was 64.5 years (range 43 to 80), ten (55.6%) were female, 16 (88.9%) were ECOG PS 1, nine (50%) were exon 21 L858R, six (33.3%) had CNS metastases at baseline. As of 30-Nov-2025, the median PFS was 8.4 months (95%CI 4.2-NR). The objective response rate (ORR) was 50.0% (95%CI 26.0-74.0). The disease control rate (DCR) was 88.9% (95%CI 65.3-98.6). The median duration of response (DOR) was not reached (95%CI 6.2-NR). The 9-month DOR rate was 75.0% (95%CI 12.8-96.1). The median overall survival (OS) was not reached (95%CI 9.1-NR). The 12-month OS rate was 70.0% (95%CI 16.2-93.3). Treatment-emergent adverse events (TEAEs) of any grade/grade≥3 occurred in 88.9%/44.4% of pts. The most common any-grade TEAEs were anemia (66.7%) and white blood cell count decreased (50%). The most common grade≥3 TEAEs were white blood cell count decreased (16.7%), neutrophil count decreased (11.1%) and anemia (11.1%). No TEAE with fatal outcome was reported. **Conclusions:** Firmonertinib combined with chemotherapy showed promising antitumor activity with a manageable safety profile in pts with EGFR-mutant advanced NSCLC following disease progression on first-line 3rd-generation EGFR-TKIs. Clinical trial information: NCT06652048. Research Sponsor: None.

8611 **Poster Session**

Spatial transcriptomic profiling to identify stroma-based prognostic groups in oncogene-addicted lung cancer. First Author: Helena Bote-de-Cabo, Department of Medical Oncology, Hospital Universitario 12 de Octubre. Health Research Institute Hospital Universitario 12 de Octubre (i+12). Universidad Complutense de Madrid, Madrid, Spain

Background: Driver genomic aberrations determine prognosis and therapy in non-small cell lung cancer (NSCLC). In this context, some other genomic features such as *TP53* mutations confer poor outcomes. However, other mechanisms leading to worse prognosis in patients (pts) sharing the same genomic profile remain incompletely characterized. **Methods:** NSCLC pts from three cohorts based on their molecular profile (*EGFR*-mutated [EGFRm], *KRAS*-mutated [KRASm] and *ALK/ROS1/RET* fusions) were included. Baseline formalin-fixed paraffin-embedded (FFPE) tumor samples were analyzed using NanoString GeoMx Digital Spatial Profiling. Regions of interest (ROIs) were selected based on histopathological features and fluorescently labeled antibodies for tumor (Tm) and stromal (St) areas. RNA expression of >1,800 genes from selected ROIs was assessed using GeoMx Cancer Transcriptome Atlas. Leiden algorithm was used for clustering, and differential gene expression and other statistical analyses were performed using R software. **Results:** A total of 189 pts (100 EGFRm, 56 KRASm, 33 fusions [17 *ALK*, 7 *ROS1* and 9 *RET* rearrangements]) were identified. Separate analysis of Tm and St compartments revealed an association between genotype and transcriptome in the first, whereas the St transcriptome failed to correlate with the molecular profile. Unsupervised clustering of the Tm compartment identified four subgroups with distinct gene expression. Tm Cluster 4 (30 pts) was mainly composed of KRASm pts (86.7%) and presented the poorest prognosis, with a median overall survival (mOS) of 7.5 months (mo) ($p<0.0001$). Within St compartment, four prognostic clusters were also identified. St Cluster 1 (76 pts: 43.4% EGFRm, 40.8% KRASm, 15.8% fusions) and St Cluster 4 (23 pts: 21.7% EGFRm, 52.2% KRASm, 26.1% fusions) included pts from all three cohorts and showed significantly decreased OS (17.4 mo and 15.6 mo, respectively; $p<0.0001$). Genes involved in matrix remodeling and epithelial-mesenchymal transition signaling were overexpressed in St Cluster 1, while St Cluster 4 exhibited a highly immunogenic profile; no correlation with *TP53* mutation status was observed. **Conclusions:** Spatially resolved transcriptomic profiling suggests that stromal composition could identify oncogene-addicted NSCLC pts with poor prognosis regardless of molecular subtype, potentially guiding the development of novel therapeutic strategies. Further validation studies are warranted. Research Sponsor: None.

8612 **Poster Session**

Profiling patients with *MET* exon 14 (*MET*ex14) skipping NSCLC with a sustained clinical benefit to tepotinib in VISION. First Author: Paul K. Paik, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Tepotinib is a highly selective MET inhibitor with clinical activity in patients with *MET*ex14 skipping NSCLC. We previously reported long-term efficacy and safety outcomes of tepotinib from VISION in patients with ≥3-years follow-up (data cut-off: May 20, 2024; Mazieres et al. ELCC 2025 [Poster 81P]). Here, we provide a subset analysis of patients from VISION who achieved long-term responses to tepotinib to identify clinical characteristics associated with durable benefit. **Methods:** Patients with advanced *MET*ex14 skipping NSCLC detected by liquid (L+) and/or tissue (T+) biopsy received tepotinib 500 mg (450 mg active moiety) once daily. The primary endpoint was objective response by independent review using RECIST v1.1. Secondary endpoints included duration of response and safety. Exploratory analyses of baseline and on-treatment liquid biopsy biomarkers were carried out for potential prognostic, predictive, or pharmacodynamic relevance. For this subset analysis, patients with a long-term response were defined as those with a duration of response (DOR) to tepotinib of >36 months. **Results:** Of 313 patients enrolled, 26 patients had a DOR >36 months (range: 36.6–78.9). In these patients, median age was 67.7 years (range: 52–84), 53.8% were male, 50.0% were White and 34.6% were Asian, 92.3% had adenocarcinoma, 53.8% had a history of smoking, and 53.8% were L+ and 65.4% were T+. Median duration of treatment was 50.7 months (range: 15.9–83.1). Seventeen patients received tepotinib as first-line and nine as second-or-later line therapy. Twenty-four patients achieved >50% decrease, while six patients achieved >80% decrease in the sum of longest diameters from baseline. Eighteen patients' cancer had not progressed at the data cut-off of May 20, 2024, and 14 patients were still receiving treatment. In 12 patients who discontinued treatment, reasons for discontinuation were: adverse events (5 patients [peripheral edema in 2 patients]), disease progression per investigator (3 patients), non-compliance (1 patient), consent withdrawal (1 patient), and other reasons (2 patients). Among patients with long-term responses who stopped treatment early due to adverse events (prior to disease progression), continued responses were observed for up to 52 months after tepotinib discontinuation without any further subsequent anticancer treatment. Of nine patients who received treatment prior to tepotinib, four patients received immunotherapy alone, and eight patients received chemotherapy without immunotherapy. Baseline and on-treatment biomarker data will be presented. **Conclusions:** Patients who achieved long-term responses to tepotinib in VISION had similar clinical characteristics and safety outcomes to the overall population of patients from VISION (Mazieres et al. ELCC 2025 [Poster 81P]); ongoing biomarker analyses may help to further characterize these patients. Clinical trial information: NCT02864992. Research Sponsor: the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945).

8613 **Poster Session**

COPERNICUS, a pragmatic phase 2b study of first-line (1L) subcutaneous (SC) amivantamab (ami) + lazertinib (laz) with supportive care in *EGFR*-mutated advanced NSCLC: Early safety results. First Author: Sarah B. Goldberg, Yale School of Medicine, New Haven, CT

Background: In MARIPOSA, intravenous (IV) ami + laz significantly prolonged overall survival vs osimertinib (HR, 0.75; *P*=0.005) in 1L *EGFR*-mutated (exon 19 deletion [Ex19del]/L858R) advanced NSCLC. However, extended infusion times, infusion-related reactions (63%), venous thromboembolism (VTE; 36%), and dermatologic adverse events (AEs; paronychia [68%], rash [62%]) were observed, potentially leading to discontinuations of ami due to AEs (34%). Several studies have since identified ways to optimize ami + laz administration. In PALOMA-3/-2, SC ami coformulated with hyaluronidase (rHuPH20) enhanced patient (pt) experience by reducing administration-related reactions (ARRs) and time, as well as VTE with prophylactic anticoagulation, leading to FDA/EMA approval. In COCOON, an enhanced dermatologic regimen reduced grade ≥2 dermatologic AEs vs standard of care. **Methods:** COPERNICUS (NCT06667076) is the first study to combine SC ami, optimized supportive care and a pragmatic design to broaden the pt population and better resemble real-world usage. This is an early report from Cohort 1 on pt demographics and safety of SC ami every 4 weeks (Q4W) + laz daily in pts with 1L *EGFR* Ex19del/L858R advanced NSCLC receiving VTE/dermatologic AE prophylaxis. Pragmatic design included partnering with academic/community sites to enhance pt diversity, allowing 1 cycle of 1L chemotherapy while awaiting biomarker results and using SC ami Q4W to reduce visit frequency. Pts received prophylactic anticoagulation for the first 4 months of treatment. Dermatologic prophylaxis aligned with the regimen described in COCOON. Here we report safety (key secondary endpoint), including incidence/severity of VTE, ARRs and dermatologic AEs. All comparisons to MARIPOSA are descriptive. **Results:** As of data cutoff (02 Jan 2026), Cohort 1 had enrolled 190 pts in the US (target enrollment, 300; median [range] follow-up, 3.9 [0.1–11.7] mo); 92% were still ongoing in the study. Median age was 66 y, with 55% of pts ≥65 y and 21% ≥75 y; 28% were Asian and 9% African American, reflecting broad enrollment. 6 pts had received 1 chemotherapy cycle. AEs were mostly grade 1–2, with no new safety signals; 5% discontinued ami due to AEs. With dermatologic prophylaxis, paronychia and rash were 26% and 22%, respectively, showing numerical reductions vs MARIPOSA. ARRs and VTE (both grouped terms) were also numerically lower at 9% and 7%, respectively. **Conclusions:** Compared with MARIPOSA, SC ami and dermatologic/VTE prophylaxis in COPERNICUS substantially reduced ARRs, dermatologic AEs, VTE, and ami discontinuations, highlighting the impact of early supportive care interventions. Using a pragmatic design, these early safety data support wide use of SC ami Q4W + laz in a diverse population. Given limited follow up, pts will continue to be evaluated for safety and efficacy. Clinical trial information: NCT06667076. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

8614 **Poster Session**

COPERNICUS, a pragmatic phase 2b study of subcutaneous (SC) amivantamab (ami) + chemotherapy (chemo) with enhanced dermatologic adverse event (AE) prophylaxis in *EGFR*-mutated advanced NSCLC: Interim results. First Author: Ticiana Leal, Winship Cancer Institute, Emory University, Atlanta, GA

Background: In MARIPOSA-2, intravenous ami + carboplatin-pemetrexed chemo significantly prolonged progression-free survival (PFS) vs chemo (HR, 0.48; $P<0.001$) in participants (pts) with *EGFR*-mutated (exon 19 deletion [Ex19del]/L858R) advanced NSCLC after progression on osimertinib. However, longer infusion times, infusion-related reactions (59%), and dermatologic AEs (paronychia [37%], rash [43%]) were observed, with frequent interruptions of ami due to AEs (60%) as a potential result. Numerous studies have since tested ways to optimize ami administration. PALOMA-3/-2 showed reductions in administration-related reactions (ARRs) and administration time with SC ami coformulated with hyaluronidase (rHuPH20), thus enhancing patient experience and leading to approval by the FDA/EMA. COCOON also showed fewer grade ≥2 dermatologic AEs vs standard of care with an enhanced prophylactic regimen. **Methods:** COPERNICUS (NCT06667076) is the first study to combine SC ami and optimized supportive care, using a pragmatic design to broaden the pt population and better resemble real-world usage. We report planned interim results of Cohort 2 for SC ami every 3 weeks (Q3W) + chemo on/after EGFR TKI progression in US pts with *EGFR* Ex19del/L858R NSCLC receiving dermatologic AE prophylaxis aligned with the regimen described in COCOON. Pragmatic design included partnering with academic/community sites and less stringent eligibility criteria to enhance pt diversity. Primary endpoint is PFS by investigator. Key secondary endpoints are overall response rate (ORR) and safety, including incidence/severity of dermatologic AEs and ARRs. All comparisons to MARIPOSA-2 are descriptive. **Results:** As of data cutoff (02 Jan 2026), 29 pts had enrolled in Cohort 2 (target enrollment, 30; median [range] follow-up: 7.6 [0.5+–10.2] mo); 76% were still ongoing in the study. Median age was 62 y, with 45% of pts ≥65 y and 21% ≥75 y; 38% were Asian and 7% African American. Median PFS was 7.4 mo (95% CI, 4.8–NE; Table). AEs were mostly grade 1–2, with no new safety signals; 31% of pts interrupted ami due to AEs. With dermatologic prophylaxis, paronychia and rash occurred in 24% and 14% of pts, respectively, showing numerical reductions vs MARIPOSA-2. ARRs (grouped term) were also numerically lower at 21%. **Conclusions:** Compared with MARIPOSA-2, SC ami and dermatologic prophylaxis in COPERNICUS led to substantial reductions in ARRs, dermatologic AEs, and ami interruptions, establishing the positive effect of early supportive care interventions. These interim data obtained using a pragmatic design support wide use of SC ami Q3W + chemo post-EGFR TKI progression in a diverse population. Clinical trial information: NCT06667076. Research Sponsor: Janssen Research & Development, LLC, a Johnson & Johnson company.

Median PFS, mo (95% CI)	7.4 (4.8–NE)
ORR (95% CI)	24.1% (10.3–43.5)
Partial response	7 (24.1%)
Stable disease	15 (51.7%)
Progressive disease	2 (6.9%)

8615 **Poster Session**

RET fusion–positive lung adenocarcinoma: Partner-specific clinicopathological characteristics, co-mutation profiles, and implications for targeted and immunotherapy. First Author: Zihan Sun, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Background: RET fusions represent actionable oncogenic drivers in lung adenocarcinoma (LUAD). However, the clinicopathological features, co-mutation landscape, and therapeutic outcomes across different RET fusion partners remain incompletely characterized. **Methods:** We retrospectively analyzed 268 patients with RET fusion–positive LUAD diagnosed between July 2017 and December 2024. Clinicopathological characteristics, metastatic patterns, and concomitant mutations were compared between KIF5B and non-KIF5B subgroups. Treatment outcomes of selective RET inhibitors, multikinase inhibitors (MKIs), and immunotherapy combined with chemotherapy were assessed, with subgroup analyses according to RET fusion partners. **Results:** The median age at diagnosis was 58 years, and most patients were female (57.0%) and never/light smokers (60.8%). Bone (12.3%), pleural (11.9%), and brain metastases (6.7%) were the most common metastatic sites. KIF5B-RET fusions were more frequently detected in earlier disease stages compared with non-KIF5B fusions (p = 0.0531). Among 274 RET fusion events, KIF5B-RET was predominant (65%), followed by CCDC6-RET (16%) and NCOA4-RET (1%). Concomitant mutations were identified in 28.7% of patients, most commonly TP53 (39.0%) and CDKN2A (13.0%), with CDKN2A more enriched in the non-KIF5B group (p = 0.0393). Nineteen patients received targeted therapy, including pralsetinib (n=12), selpercatinib (n=2), and cabozantinib (n=5), achieving an overall ORR of 57.9% and median PFS of 12.0 months. Notably, non-KIF5B patients demonstrated longer median PFS than KIF5B patients under pralsetinib (17.0 vs. 5.5 months, p = 0.0473). Fifteen patients received first-line immunochemotherapy, achieving a median PFS of 17.0 months, ORR of 40.0%, and DCR of 80.0%, comparable to targeted therapy (p = 0.3871). PD-L1 expression showed no correlation with outcomes. **Conclusions:** RET fusion–positive LUAD comprises biologically heterogeneous subsets defined by fusion partners. KIF5B-RET fusions tend to occur at earlier stages, whereas non-KIF5B fusions are more frequently associated with CDKN2A co-mutations and appear to derive greater benefit from selective RET inhibition. Immunochemotherapy demonstrates comparable efficacy regardless of fusion partner, highlighting the need for partner-specific therapeutic strategies in RET fusion–positive LUAD. Research Sponsor: None.

8616 **Poster Session**

PRO results from the Beamion LUNG-1 trial in treatment-naïve patients with *HER2*-mutant advanced NSCLC. First Author: Joshua K. Sabari, Perlmutter Cancer Center, New York University Langone Health, New York, NY

Background: Zongertinib is an irreversible tyrosine kinase inhibitor that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities. Here, we report patient-reported outcomes (PROs) on NSCLC-related symptoms, physical functioning, symptomatic adverse events (AEs) and their burden, from patients who were given 120 mg zongertinib QD as first-line in Cohort 2 of the Phase Ib Beamion LUNG-1 trial (NCT04886804). **Methods:** EORTC QLQ-C30 physical functioning scale, NSCLC-SAQ (domains: cough, dyspnea, pain, fatigue and poor appetite), EORTC IL46 (overall side effect burden) and nine PRO-CTCAE symptoms (mouth and/or throat sores, taste changes, nausea, vomiting, diarrhea, rash, skin dryness, itching, and numbness/tingling) were collected at cycle 1: days 1, 8 and 15, and day 1 of cycles 2, 3, 5, 7 and 9, each cycle being 21 days. Change from baseline (CFB) in EORTC QLQ-C30 physical functioning and NSCLC-SAQ total score were analyzed using mixed model repeated measures. The proportion of patients regarded as responders was defined as patients meeting within-patient meaningful improvements in PRO score or maintaining low levels of baseline symptomatology/high functioning. EORTC IL46 (1 = 'Not at all', 4 = 'Very much') and PRO-CTCAE (for frequency/severity/interference items: 0 "Never"/ "None"/ "Not at all" to 4 "Almost Constantly"/ "Very Severe"/ "Very much") were analyzed descriptively. **Results:** The PRO analysis set included 71 patients. High completion rates were observed, over 85% up to cycle 7. Patients had low levels of symptomatology and high levels of physical functioning at baseline. Mean CFB analysis showed patients reported rapid within-patient improvements in EORTC QLQ-C30 physical functioning and NSCLC-SAQ total score after the first week of treatment (from cycle 1, day 8), which were sustained over time. A high proportion of patients responded to treatment in terms of their PRO score; at cycle 5, 70% of patients were responders for physical functioning, and 47% of patients for NSCLC-SAQ total score. There was low side-effect burden; at any post-baseline timepoint a maximum of 8.4% of patients [n=6] reported being troubled with side-effects of treatment 'Quite a bit' or worse; supported by low proportions of patients reporting symptomatic adverse events via PRO-CTCAE. **Conclusions:** Patients treated with first-line zongertinib reported a rapid improvement followed by stability in physical functioning and NSCLC-SAQ total score, with high proportions of patients qualifying as PRO responders. Zongertinib was well tolerated, as reflected by the low overall side effect burden and the low incidence and mild nature of patient-reported symptomatic adverse events. Clinical trial information: NCT04886804. Research Sponsor: Boehringer Ingelheim.

8617 **Poster Session**

Safety and efficacy of APS03118, a next-generation RET inhibitor, in patients with non-small cell lung cancer (NSCLC): Results from a phase I clinical trial. First Author: Shun Lu, Shanghai Chest Hospital, Shanghai, Jiao Tong University, School of Medicine, Shanghai, China

Background: Acquired resistance to first-generation selective RET inhibitors (SRIs) remains a significant clinical challenge in the treatment of RET fusion-positive NSCLC. APS03118 is a next-generation, highly selective RET inhibitor also with additional potent inhibitory activity against YES1, a SRC family kinases. This Phase I study evaluated the safety, tolerability, pharmacokinetics, and preliminary efficacy of APS03118 treatment in patients with advanced RET fusion-positive NSCLC. **Methods:** This multicenter Phase I trial enrolled 108 patients, including 85 patients with NSCLC harboring RET aberrations. In the dose escalation stage (Ia), APS03118 was administered orally at doses ranging from 40 mg once daily to 120 mg twice daily (BID) 28 days a cycle in 29 patients with solid tumors. In the expansion stage (Ib), 79 patients received 80 mg BID and 100 mg BID, including 66 patients of NSCLC with RET fusions. Efficacy was assessed per RECIST v1.1 every 2 cycles (4 weeks/cycle). Safety was evaluated according to CTCAE v5. Molecular profiling was performed using next-generation sequencing on blood and, when available, tumor tissue. This report focuses mainly on the NSCLC cohorts, including treatment-naïve and previously treated patients with 1-4 lines of therapy, including six different SRIs, (e.g., pralsetinib and selpercatinib). **Results:** Out of 85 NSCLC patients (Ia+Ib), the Objective Response Rate (ORR) was 80% (confirmed) in 20 (20/22) evaluable treatment-naïve patients. The median Progression-Free Survival (mPFS) is not reached, with 10 patients up to or over the 16 cycles at the data cutoff date. In 22 (22/25) evaluable patients with prior systemic therapy not including the SRIs, the ORR was 55%. There were 38 patients in the cohort of prior SRIs treatment failure. Among 22 (22/26) evaluable patients without known bypass pathway mutations, ORR was 23% with 14 patients' PFS up to or over 6 cycles and 10 patients up to or over 8 cycles (data cutoff date). Promising anti-tumor action was observed in the two patients with G810S and G810C mutations, who experienced tumor shrinkage of up to 50%. Grade ≥3 TRAEs occurred in 50.9% of patients. The most common AEs were creatine phosphokinase, AST and ALT elevation, which were reversible and mostly observed within cycle 1-3 and rarely after cycle 5. Dose reductions in 22.2%, and permanent discontinuation in 4.6%. Overall, APS03118 demonstrated a manageable and predictable safety profile. **Conclusions:** APS03118 shows highly promising clinical activity in both treatment-naïve and SRI failed NSCLC patients harboring RET fusions. Its survival benefit may result from potent inhibition of RET and YES1. The safety profile is manageable, characterized primarily by reversible enzyme elevations. Further development in NSCLC patients harboring RET fusion is warranted. Clinical trial information: NCT05653869. Research Sponsor: None.

8618 **Poster Session**

Efficacy and safety of larotrectinib in patients with *TRK* fusion lung cancer: An updated analysis. First Author: Jessica Jiyeong Lin, Mass General Brigham Cancer Institute, Boston, MA

Background: *NTRK* gene fusions are oncogenic drivers in various tumor types, including lung cancer. Larotrectinib is the first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumor-agnostic use in patients with TRK fusion cancer based on a robust and durable objective response rate in patients with various cancers. Here, we report updated long-term efficacy and safety data in the subset of patients with TRK fusion lung cancer treated with larotrectinib after 1 additional year of follow-up. **Methods:** Patients with TRK fusion lung cancer enrolled in 2 larotrectinib clinical trials (NCT02122913, NCT02576431 [NAVIGATE]) were included. Larotrectinib was administered at 100 mg twice daily. In NCT02122913, primary endpoints were safety and the minimum tolerated and recommended dose; secondary endpoints included pharmacokinetics, overall response rate (ORR), and duration of response (DoR). In NCT02576431, the primary endpoint was best overall response; secondary endpoints included DoR, survival, and safety. Responses were independent review committee-assessed per Response Evaluation Criteria in Solid Tumors version 1.1. The data cutoff was July 20, 2025. **Results:** A total of 32 patients with measurable disease were treated, including 12 with known CNS metastases at baseline. Median age was 56 years (range 25–81). One patient (3%) was systemic treatment-naïve in the metastatic/unresectable setting; 19 (59%) had received ≥2 prior therapies. All *NTRK* gene fusions were identified by next-generation sequencing (NGS). The ORR was 69% (95% confidence interval [CI] 50–84): 4 (13%) complete responses, 18 (56%) partial responses, 6 (19%) stable disease, 2 (6%) progressive disease, and 2 (6%) not evaluable or undefined. Median duration of treatment was 20 months (range 2–81); at data cutoff, no patients remained on treatment. Median time to response was 1.8 months (range 1.5–7.3). Median DoR, progression-free survival (PFS), and overall survival (OS) were 20 months (95% CI 13–67), 19 months (95% CI 10–36), and 41 months (95% CI 17—not estimable), respectively, with median follow-ups of 53, 49, and 58 months. The 4-year rates for DoR, PFS, and OS were 34% (95% CI 12–57), 26% (95% CI 8–44), and 49% (95% CI 30–69), respectively. Treatment-related adverse events (TRAEs) were predominantly Grade 1/2. Grade 3/4 TRAEs were reported in 10 (31%) patients. One patient (3%) discontinued treatment due to TRAEs (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyltransferase increased). **Conclusions:** Larotrectinib continues to demonstrate rapid and durable responses, extended clinical benefit, and a favorable safety profile in patients with advanced TRK fusion lung cancer. These results support the wider adoption of NGS panels that include *NTRK* gene fusions in patients with lung cancer to identify those who may benefit from TRK inhibitor therapy. Clinical trial information: NCT02122913, NCT02576431. Research Sponsor: Bayer HealthCare Pharmaceuticals, Inc.

8619 **Poster Session**

First-in-human dose-escalation study of the selective EGFR/HER2 exon 20 inhibitor PFL-721 in patients with locally advanced or metastatic NSCLC. First Author: Anas Gazzah, Gustave Roussy, Villejuif, France

Background: PFL-721 is a highly selective, orally bioavailable tyrosine kinase inhibitor (TKI) targeting activating EGFR & ERBB2 exon 20 (ex20) mutations while sparing wild-type (WT) EGFR. Preclinical studies demonstrate potent inhibition of diverse ex20 variants, >20-fold selectivity over WT EGFR, and robust antitumor activity in xenograft models. **Methods:** PFL-721 is investigated in an ongoing phase I study in patients (pts) with advanced NSCLC and EGFR/ERBB2 ex20 alterations (Clinical trial identifier: NCT06043817). PFL-721 is administered once daily (QD) in continuous 28-day cycles. Assessments included adverse events (AEs), dose-limiting toxicities (DLTs), PK, and antitumor activity by RECIST v1.1. Key eligibility criteria included locally documented EGFR/ERBB2 ex20 alterations on solid or liquid tumor biopsy, ECOG 0–1, and adequate organ function. Molecular responses were based on EGFR/ERBB2 ex20 alterations variant allele frequency decrease in ctDNA. **Results:** A total of 45 pts were dosed , with a median age of 63 years. Pts had received a median of 3 prior treatment lines. Thirty-one pts had EGFR ex20 alterations, 13 had ERBB2 ex20 insertion mutations, and one had both. Dose levels evaluated were 30, 60, 120, 240, 360, 480, and 600 mg QD. Dose escalation was completed with the identification of the maximum tolerated dose at 480 mg. AEs were reported in 43 pts (96%), including gastro-intestinal AEs in 39 pts (87%). Commonly observed grade ≥3 AEs included diarrhea (n=10/45, 22% of pts), hypokalemia (n=4/45 , 9%), and increased blood creatinine (n=3/45, 7%). One grade 3 rash was observed. Six DLT events occurred in 39 evaluable pts, including grade 3 diarrhea (at 360 mg QD, n=2; 480 mg QD, n=1, 600 mg QD, n=1), grade 3 fatigue (600 mg QD, n=1), and grade 4 hypokalemia (600 mg QD, n=1). PK analyses showed dose-proportional exposure and achievement of plasma concentrations predicted to be effective based on preclinical models, at doses of ≥240 mg QD. Among efficacy population (n=42), partial responses (PRs) were observed in 15 / 28 pts at doses of ≥360 mg QD . The overall response and disease control rates at doses ≥360 mg QD were 54% (95%CI [33. 9-72.5]) and 79% (95%CI [59.0-97.7]), respectively. Among 25 evaluable pts, molecular responses (ctDNA decrease >50%) were observed in 12 at doses ≥120 mg. **Conclusions:** In this dose escalation study, class-effect local gastrointestinal AEs were observed in nearly all pts while the frequency of systemic skin toxicity was low, in line with the selectivity of the molecule for mutant EGFR. Antitumor activity was reported in 54% of pts at doses ≥360 mg QD in a heavily pretreated population, including with prior EGFR/ERBB2 ex20 TKI. Consistent with tumor shrinkage, ctDNA clearance was observed in 48% of evaluable pts. The randomized dose-optimization part is ongoing, with three dose regimens: 360 mg QD, 480 mg QD, and 240 mg BID. Clinical trial information: NCT06043817. Research Sponsor: Pierre Fabre Medicament.

8620 **Poster Session**

Safety and efficacy results of the phase 2 study of silevertinib (BDTX-1535) in previously treated patients with non-small cell lung cancer with non-classical and C797S EGFR mutations. First Author: Helena Alexandra Yu, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Despite significant benefit from FDA-approved EGFR tyrosine kinase inhibitors (TKIs), patients with classical EGFR mutation positive non-small cell lung cancer (NSCLC) ultimately develop progressive disease due to mechanisms of resistance, including alterations of the EGFR pathway. A broad group of non-classical EGFR mutations (NCM), including P-loop and αC-helix compressing (PACC) mutations, and acquired C797S are major mechanisms of EGFR resistance. Silevertinib (BDTX-1535) is a fourth-generation covalent EGFR TKI with high CNS penetrance that targets classical mutations, NCM, and C797S mutations. Antitumor activity and safety of silevertinib in advanced NSCLC were evaluated in an open-label Phase 2 trial (NCT05256290). **Methods:** Patients (pts) with recurrent NSCLC following ≤ 2 lines of therapy with only 1 prior EGFR TKI (osimertinib preferred) and tumors positive for NCM (NCM Cohort) or C797S mutation (C797S Cohort) were enrolled based on a local molecular test. Based on dose optimization of silevertinib at 100 mg and 200 mg orally once daily, all patients after May 2024 received 200 mg once daily. The primary endpoint was ORR by RECIST v1.1, and secondary endpoints included progression-free survival (PFS), duration of response (DOR), dose optimization, and safety. **Results:** From August 2023 to January 2025, 41 pts were treated in the NCM Cohort (100 mg, n=11; 200 mg, n=30; 80% female; 56% white; 49% with CNS metastases) and 42 pts were treated in the C797S Cohort (100mg, n=9; 200mg, n=33; 62% female; 48% white; 31% with CNS metastases). In both cohorts, 29% of pts had received 2 prior therapies. As of November 3, 2025, median follow-up was 9.5 months for pts treated with the 200 mg dose. ORR and median duration of treatment (DoT) are shown in the table. Alterations of other oncogenic pathways (e.g. MET, RET, RAS, and RAF) were observed at baseline in approximately 20% of pts in post hoc analyses. For the 200 mg dose, serious treatment-related adverse events (TRAEs) were reported in 7 (11%) pts, and 5 (8%) of pts discontinued treatment due to TRAEs. The most common TRAEs at 200 mg included rash (13%, grade 3), diarrhea (8%, grade 3), stomatitis (2%, grade 3), and paronychia (2%, grade 3). Available PFS, DOR, and dose optimization results will be presented. **Conclusions:** Silevertinib demonstrated antitumor activity at 200 mg orally once daily in patients with recurrent NSCLC, EGFR NCMs, and acquired resistance C797S mutation with a safety profile consistent with the EGFR TKI class. Clinical trial information: NCT05256290. Research Sponsor: Black Diamond Therapeutics.

Cohort	Dose	n	ORR (%, 95% CI)	Median duration of treatment, mo (range)
NCM Cohort	200 mg	30	16.7% (5.6–34.7)	4.99 (0.99-11.47)
PACC mutations	200 mg	23	21.7% (7.5–43.7)	4.86 (1.28-11.47)
C797S Cohort	200 mg	33	36.4% (20.4–54.9)	4.76 (0.46-12.55)

8621 **Poster Session**

Cost-effectiveness of amivantamab plus lazertinib versus osimertinib plus chemotherapy for first-line treatment of *EGFR*-mutated advanced non–small cell lung cancer. First Author: Pooja Gokhale, Clinical and Administrative Pharmacy, University of Georgia College of Pharmacy, Athens, GA

Background: Amivantamab plus lazertinib and osimertinib plus chemotherapy are guideline-recommended first-line treatment options for patients with advanced non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletion or exon 21 L858R mutations. Although both treatments are first-line options, their relative economic value has not been evaluated. This study evaluated the cost-effectiveness of amivantamab plus lazertinib versus osimertinib plus chemotherapy from a United States payer perspective. **Methods:** A partitioned survival model (PSM) and a three-state Markov model were developed to compare the two treatment strategies over a lifetime horizon. Clinical efficacy inputs were derived from the MARIPOSA and FLAURA2 trials. Direct medical costs and health state utilities were obtained from published sources. Outcomes included total costs, life years (LYs), and quality-adjusted life years (QALYs). One-way and probabilistic sensitivity analyses were conducted to assess model robustness using a willingness-to-pay threshold of $150,000 per QALY or LY gained. **Results:** Across both modeling approaches, osimertinib plus chemotherapy was associated with greater effectiveness and lower costs compared with amivantamab plus lazertinib. In the partitioned survival model, osimertinib plus chemotherapy resulted in 1.68 additional QALYs and 2.18 additional LYs with cost savings of $34,799, indicating dominance. Similar findings were observed in the Markov model, with gains of 2.05 QALYs and 2.74 LYs and cost savings of $46,620. Sensitivity analyses identified survival extrapolation parameters and the discount rate as the primary drivers of uncertainty. In probabilistic sensitivity analysis, osimertinib plus chemotherapy was favored in approximately 82% of simulations. **Conclusions:** From the United States perspective, osimertinib plus chemotherapy was dominant over amivantamab plus lazertinib as first-line treatment for EGFR-mutated advanced NSCLC in this model-based economic evaluation. These findings highlight the importance of integrating clinical efficacy and economic value in first-line treatment selection. Future studies should compare all recommended first-line strategies using mature survival data and incorporate real-world treatment patterns and patient-centered outcomes. Research Sponsor: None.

Base case results.

Regimen	Total Costs	Total QALYs	Total LYs	Δ Cost	Δ QALYs	Δ LYs	ICER (Cost/QALY)	ICER (Cost/LY)
Partitioned Survival Model								
Amivantamab + Lazertinib	$1,297,932	3.23	4.65	-	-	-	-	-
Osimertinib + Chemotherapy	$1,263,133	4.91	6.83	-$34,799	1.68	2.18	Dominant	Dominant
Markov Model								
Amivantamab + Lazertinib	$1,311,688	2.76	3.97	-	-	-	-	-
Osimertinib + Chemotherapy	$1,265,068	4.81	6.71	-$46,620	2.05	2.74	Dominant	Dominant

8622 **Poster Session**

SOHO-01: Updated safety and efficacy of sevabertinib in patients with advanced *HER2*-mutant non-small cell lung cancer (NSCLC). First Author: Herbert H. Loong, Chinese University of Hong Kong, Hong Kong, Hong Kong

Background: Sevabertinib, a potent, reversible, oral tyrosine kinase inhibitor, received FDA accelerated approval for pretreated patients with advanced NSCLC harboring *HER2* tyrosine kinase domain-activating mutations. Sevabertinib demonstrated significant antitumor activity and manageable safety in patients with *HER2*-mutant NSCLC who had previously received treatment (Cohort D) or were treatment-naïve (Cohort F) in the ongoing, open-label, multicenter, Phase I/II SOHO-01 trial (NCT05099172) (Le X et al. *N Engl J Med* 2025). Here, we report updated safety and efficacy data from Cohorts D and F. **Methods:** Patients with *HER2*-mutant NSCLC received sevabertinib 20 mg twice daily in both cohorts: patients previously treated with systemic therapy but naïve to HER2-targeted therapy (Cohort D) and treatment-naïve patients (Cohort F). The primary endpoint was objective response rate (ORR) assessed by blinded independent central review (BICR) per RECIST v1.1. Other key prespecified and secondary endpoints included duration of response (DoR) and progression-free survival (PFS) assessed by BICR per RECIST v1.1, and safety per MedDRA v28.0 and CTCAE v5.0. **Results:** In total, 154 patients (n=81, D; n=73, F) received sevabertinib in the two cohorts; median follow-up was 19.5 (D) and 15.0 (F) months. Median age was 60 (D) and 65 (F) years; 61.7% (D) and 63.0% (F) were female; 61.7% (D) and 78.1% (F) had never smoked. As of November 17, 2025, ORR (95% CI) was 66.7% (55.3, 76.8; D) and 75.3% (63.9, 84.7; F); disease control rate (confirmed response or stable disease for ≥12 weeks; 95% CI) was 81.5% (71.3, 89.2; D) and 89.0% (79.5, 95.1; F). Median (95% CI) DoR was 9.5 (6.3, 13.5; D) and 12.2 (8.8, not estimable; F) months; median (95% CI) PFS was 8.3 (6.9, 12.3; D) and 13.5 (10.0, not estimable; F) months. Treatment-related adverse events (TRAEs) in both cohorts were consistent with previous reports. Grade 3 or higher TRAEs occurred in 39.5% (D) and 24.7% (F) of patients. Diarrhea was reported in 86.4% (D) and 87.7% (F) of patients; grade 3 diarrhea occurred in 23.5% (D) and 5.5% (F) of patients. No cases of interstitial lung disease or grade 4 diarrhea, discontinuations due to diarrhea, or new safety signals were observed. **Conclusions:** Sevabertinib demonstrated sustained efficacy with a manageable safety profile in treatment-naïve and pretreated patients with advanced *HER2*-mutant NSCLC. These data further support the rapid and durable responses of sevabertinib for patients with *HER2*-mutant NSCLC. Clinical trial information: NCT05099172. Research Sponsor: Bayer AG.

8623 **Poster Session**

Safety and antitumor activity of VRN110755, a brain-penetrant, selective EGFR inhibitor, in patients with EGFR-driven non–small cell lung cancer. First Author: Min Hee Hong, Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea

Background: Third-generation EGFR tyrosine kinase inhibitors (TKIs) have improved outcomes in EGFR-mutant non–small cell lung cancer (NSCLC); however, acquired resistance, including EGFR C797S mutations, and central nervous system (CNS) progression remain major unmet medical needs. VRN110755 is an orally available, highly selective EGFR inhibitor designed to target a broad spectrum of EGFR mutations, including C797S, and has demonstrated robust brain penetration in preclinical models. **Methods:** This ongoing, open-label, multicenter Phase I/II study evaluates the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of VRN110755 in patients with EGFR-mutant NSCLC who progressed on prior third-generation EGFR TKIs and had no remaining standard treatment options. A dose-escalation phase (10–480 mg once daily) followed by protocol-defined backfill cohorts (80–400 mg) was conducted. Patients with stable, asymptomatic brain metastases and/or leptomeningeal metastases were eligible. This abstract reports data available at the time of analysis to characterize emerging safety, PK, and antitumor activity and to inform ongoing dose optimization and cohort expansion under protocol-defined safety monitoring. Early reporting was undertaken due to emerging systemic and intracranial activity in a population with high unmet medical need; enrollment and follow-up are ongoing. **Results:** As of January 18, 2026, 63 patients were enrolled. VRN110755 demonstrated dose-proportional PK. At 320 mg, target engagement (C_{trough}/IC_{50}) against common EGFR mutations exceeded that of osimertinib 80 mg by approximately four-fold. Treatment-related adverse events were predominantly low grade (grade 1: 37%; grade 2: 20%; grade 3: 2%), with no dose-limiting toxicities observed; the most common event was grade 1 rash (16%). Low rates of diarrhea were reported, with no interstitial lung disease or clinically meaningful QTc prolongation observed to date. Among 38 response-evaluable patients treated at doses $\geq$160 mg following progression on prior EGFR TKIs, 7 (18.4%) achieved partial responses and 28 (73.7%) achieved stable disease, yielding a disease control rate of 92.1%; approximately half remained on treatment beyond 7.5 months, suggesting durable disease control. In patients with baseline EGFR C797S mutations (n=7), the overall response rate was 85.7% (6/7), with ctDNA clearance of C797S observed in 83.3% (5/6) of responders. Complete intracranial responses were observed in two patients, and a $K_{p,uu,CSF}$ of 2.0 was documented at the 160 mg dose. **Conclusions:** VRN110755 demonstrated favorable PK, a manageable safety profile, and encouraging systemic and CNS antitumor activity in heavily pretreated EGFR-mutant NSCLC, including C797S-positive disease, supporting continued clinical development. Clinical trial information: VRN110755_01. Research Sponsor: Voronoi, inc.

8624 **Oral Abstract Session**

Wait or treat? managing asymptomatic brain metastases in oncogene-mutated NSCLC: Results of a phase-III randomized controlled trial. First Author: Anil Ramakant Tibdewal, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India

Background: The timing of brain radiation therapy (RT) in patients with oncogene-mutated NSCLC with asymptomatic brain metastases (ABM) has been a matter of debate. No level 1 evidence supports delayed brain RT in ABM. This phase III, open-label, RCT (NCT05236946) evaluates Upfront Cranial RT (U-CRT) versus Delayed CRT (D-CRT) in ABM of oncogene-mutated NSCLC. **Methods:** Eligible patients ($\geq$18 years, ECOG $\leq$2), with EGFR mutation or ALK gene rearrangement and completely ABM, were randomized to U-CRT vs D-CRT at intracranial progression (ICP), stratified by GPA score (0-2 vs $>$ 2) and BM presentation (Synchronous vs Metachronous). Key exclusions include symptomatic BM, brainstem metastases, and prior cranial RT. All pts received standard systemic therapy (TKI $\pm$ CT). The primary endpoint is intracranial PFS with death treated as a competing event. Secondary endpoints included OS, PFS, and treatment toxicity. All patients underwent MRI brain every 3 months for 1st year and 6 months thereafter, unless indicated clinically. Cumulative incidence functions were estimated, and subdistribution hazards were compared using the Fine and Gray model. With a planned enrollment of 208 patients and 139 target events, the study had 80% power to detect a hazard ratio of 0.62 at a two-sided alpha of 0.05. The icPFS was analyzed in intention-to-treat populations using Kaplan-Meier estimates and log-rank tests. **Results:** A total of 208 patients were randomized (105-U-CRT; 103-D-CRT). Baseline characteristics were well-balanced in both arms. The median age was 53 years (range, 26-83). EGFR and ALK mutations were seen in 87.6% and 12.4% in U-CRT and 79.6% & 20.4% in D-CRT arm. 1st/2nd generation TKIs $\pm$ CT were received by 58% & 72% pts, respectively and rest received 3rd generation TKI. In U-CRT, 44.8% received SRS/SRT, 52.4% received WBRT$\pm$ boost, and 3 pts did not receive RT. The median follow-up was 27.4 months (95%CI 26.2 -33). The cumulative incidence of ICP at 1 yr were 8.7% (95%CI 2.9%, 14.5%) & 25.7% (95%CI 16.8%, 34.7%), and at 2-yrs were 21.7% (95%CI 12.6%, 30.8%) & 50% (95%CI 39.2%, 60.9%) with sub-HR = 0.35 (95%CI 0.21, 0.59), p $<$ 0.001. The median icPFS were 18 mo (95%CI 15.8, 23.5) and 14.3 mo (95%CI 12.6, 19.6) with HR-0.84 (95%CI 0.59, 1.20), p = 0.35. There was no difference in median PFS of 11.7 mo (95%CI 9.2, 14.1) & 12.0 mo (95% CI 9.8, 14.9), p = 0.37 and in median OS of 23.3 mo (95% CI 17.7-28.8) & 28.7 mo (95%CI 17.7, 39.7), p = 0.06, respectively. In the D-CRT arm, 39/47 who had ICP received salvage CRT. The incidence of grade $\leq$2 radiation necrosis was 25.4% and grade $>$ 3 in 5.8% in upfront RT arm. **Conclusions:** In asymptomatic BM of oncogene-mutated NSCLC pts, upfront cranial RT significantly reduced the incidence of ICP; however, it did not improve the survival outcomes. The difference in survival may become more apparent as the OS data matures. Data on QOL, neurocognition, and molecular analysis will be reported later. Clinical trial information: NCT05236946. Research Sponsor: Tata Memorial Centre - Research Administrative Council (TRAC); Neuro-Oncology Research Fund of Brain Tumor Foundation (BTF) of India.

8625 **Poster Session**

Osimertinib combined with bevacizumab and chemotherapy as 1L treatment in EGFR-mutated metastatic non-squamous non-small cell lung cancer (nsq NSCLC) with concurrent mutations. First Author: Liang Liu, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

Background: Concurrent mutations in EGFR sensitive mutations (19 del/21 L858R) are associated with poor prognosis. Previous studies have shown that EGFR-TKI combined with chemotherapy or anti-angiogenic drugs confers heterogeneous degrees of benefit in this population. However, the efficacy of concurrent EGFR-TKI, anti-angiogenic agent, and chemotherapy has not been reported. **Methods:** This is a single-center, open-label, phase I clinical trial designed to evaluate the efficacy and safety of osimertinib combined with bevacizumab and chemotherapy as first-line treatment for EGFRm metastatic nsq NSCLC with concurrent mutations (NCT05507606). 4 induction cycles will be administered (Osimertinib, 80 mg/d, d8–21; bevacizumab, 7.5 mg/kg, d1; pemetrexed 500 mg/m², d1; and carboplatin AUC 5, d1; 3 week/cycle), after which carboplatin will be discontinued. Osimertinib combined with bevacizumab and pemetrexed will be continued as maintenance (Osimertinib, 80 mg/d, d1–21; all other remained unchanged). Bevacizumab and pemetrexed will be stopped at 2 years; osimertinib will be continued until disease progression. EGFRm include exon 19 del, L858R, T790M, G719X, L861Q, S768I, exon 20 A763–Y764 insertion, and concurrent mutations are defined as the presence of at least one destructive TP53 mutation in exons 5 to 8. The primary endpoints are safety and objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Exploratory endpoints comprise NGS comparative analysis pre-/post-treatment, 19 del/L858R subgroup analysis, ctDNA clearance, and the correlation between efficacy and prognosis. **Results:** 34 patients were enrolled. Males accounted for 29.41%, and the median age was 58.5 years (25-75). Patients with ECOG PS 1 and 2 comprised 97.1% and 2.9%, respectively. The EGFRm profile consisted of 19 del (50.0%), L858R (44.1%), and other mutations (5.9%, including 20 ins and L861Q). All patients have finished the 4 induction cycles. The median follow-up was 36.8 months (95% CI, 24.2–47.4). The ORR was 94.12% (95% CI, 80.32%–99.28%), the DCR was 100% (95% CI, 89.72%–100%). The median PFS and OS were 35.9 m (95% CI, 26.0–NR) with 44.1% maturity and NR with 26.5% maturity, respectively. 19 del: ORR 100%, PFS/OS NR. L858R: ORR 86.7%, mPFS 26.5m (95%CI:16.3-NR), mOS 47.8m (95%CI:22.1-NR). Others: ORR 100%, mPFS 10.8m (95%CI:7.9-NR), mOS 21.1m (95%CI:18.2-NR). Grade $\geq$ 3 AE occurred in 31.25% of patients during the induction phase. No deaths related to toxicity were observed. The discontinuation rate was 9.4%; no patient discontinued treatment because of AE. **Conclusions:** These results demonstrate that the four-drug regimen anchored by osimertinib is well tolerated and active in patients with EGFRm metastatic nsq NSCLC harboring concurrent mutations. Clinical trial information: NCT05507606. Research Sponsor: None.

8626 **Poster Session**

Clinical utility of repeat next-generation sequencing in patients with driver-negative non-small cell lung cancer: A report from the LC-SCRUM-TRY screening platform. First Author: Hiroki Izumi, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: While precision medicine targeting driver oncogenes has improved clinical outcome of non-small cell lung cancer (NSCLC), the clinical utility of repeat or late-line multiplex genomic profiling remains unclear for patients whose tumors were initially identified as driver-negative. We evaluated the clinical impact of genomic screening for treatment-resistant NSCLC within the nationwide framework (LC-SCRUM-TRY). **Methods:** Between September 2020 and November 2025, a total of 2,088 patients with NSCLC were enrolled into LC-SCRUM-TRY. Of these, this analysis focused on 840 patients who were diagnosed as driver-negative at the time of enrollment. Genomic profiling was performed using Oncomine Precision Assay (ThermoFisher Scientific) for tumor tissue sample, or liquid biopsy (Guardant360 [Guardant Health] or liquid OPA). We compared overall survival (OS) among three groups: (A) Driver-negative, (B) Driver-positive without targeted therapy, and (C) Driver-positive with subsequent corresponding targeted therapy. **Results:** Among the 840 patients, median age at enrollment was 68 years (range 34-86); the majority were male (70%), ever-smokers (79%), and had adenocarcinoma (74%), with good ECOG-PS of 0-1 (91%). Of these, 89% underwent tissue-based NGS using OPA, while 11% underwent liquid biopsy. Actionable driver alterations were identified in 186 patients (22%), without significant difference between tissue- and liquid-based NGS. The detected drivers included EGFR mutation (mut) (n = 60), HER2 mut (n = 33), $KRAS^{G12C}$ mut (n = 31), $BRAF^{V600E}$ mut (n = 7), MET exon 14 skipping (n = 17), RET fusion (fus) (n = 17), ALK fus (n = 9), ROS1 fus (n = 7), and NRG1 fus (n = 5). Of the 186 patients with detected drivers, 74 patients (40%) received subsequent matched targeted therapies (Group C), including 13 patients enrolled in clinical trials. The median OS was 36.2 months in Group A, 34.1 months in Group B, and 70.2 months in Group C, respectively. Patients who received matched targeted therapies (Group C) had significantly longer OS compared to Groups A and B (p $<$ 0.0001). **Conclusions:** Multiplex genomic profiling effectively identified actionable driver oncogenes in 22% of NSCLC patients previously considered driver-negative. Access to matched targeted therapies based on these results more than doubled the median OS (70.2 vs. 34.1 months), highlighting the critical importance of a multiplex genomic re-screening approach in this population. Clinical trial information: UMIN000041957. Research Sponsor: Amgen Inc, Nippon Boehringer Ingelheim Company, Takeda Pharmaceutical Company, Haihe Biopharma, AstraZeneca, Eli Lilly Japan, Janssen Pharmaceutical, Novartis Pharma, Turning Point Therapeutics, Spectrum Pharmaceuticals, and Ono pharmaceutical Company.

8628 Poster Session

First-line (1L) olomorasib + pembrolizumab in patients with *KRAS* G12C–mutant advanced NSCLC, and PD-L1 expression 0-49%, from the dose optimization cohorts of LOXO-RAS-20001 and SUNRAY-01. First Author: Bryan Anthony Chan, Sunshine Coast Hospital and Health Service, Birtinya, Australia

Background: For patients (pts) with 1L *KRAS* G12C-mutant advanced NSCLC and PD-L1 expression <50%, the current SOC is pembrolizumab + platinum-based chemotherapy. Combining olomorasib, a KRAS G12C inhibitor, with pembrolizumab may overcome the limited efficacy of single-agent pembrolizumab in this population, while offering a chemotherapy-sparing targeted approach. Here we report an integrated analysis of 1L pts with PD-L1 expression 0-49% (<1% and 1-49%) who received olomorasib + pembrolizumab from the dose optimization cohorts of LOXO-RAS-20001 and SUNRAY-01. **Methods:** Pts with advanced *KRAS* G12C-mutant NSCLC, known PD-L1 expression and ECOG PS 0-1 were randomized to olomorasib (50 or 100 mg, orally BID) with pembrolizumab (200 mg Q3W). One cycle of SOC pembrolizumab prior to enrollment was permitted. Objective response rate (ORR) was assessed in the efficacy evaluable population, with PD-L1 0-49% Other efficacy endpoints included best overall response (BOR) and disease control rate (DCR). Safety was assessed across all treated pts (PD-L1 0-100%). **Results:** As of 6 June 2025, 85 pts received olomorasib + pembrolizumab, of which 31 pts had tumors with PD-L1 expression 0-49% (<1%: n=13; 1-49%: n=18). In pts with PD-L1 expression <1%, no pts received a prior cycle of SOC, 23% of pts had baseline brain metastases, and 38% had an ECOG score of 1. For the pts with PD-L1 expression of 1-49%, 17% received 1 prior cycle of SOC, 17% had baseline brain metastases, and 56% had an ECOG score of 1. The ORR was 58% in pts with PD-L1 <1%, 67% in pts with PD-L1 1-49% (Table). Across all treated pts the most common any grade treatment-related adverse events (TRAEs) were diarrhea (31%) and ALT/AST increased (26/24%). TRAEs led to permanent discontinuation of study treatment in 12% of pts (n=10). **Conclusions:** Olomorasib + pembrolizumab demonstrated promising efficacy in pts with 1L *KRAS* G12C-mutant advanced NSCLC, and PD-L1 expression <1% and 1-49% with ORRs that compare favorably with historical outcomes for pembrolizumab and chemo-immunotherapy in unselected advanced NSCLC. Olomorasib + pembrolizumab is under evaluation in pts with 1L *KRAS* G12C-mutant metastatic NSCLC (SUNRAY-01, NCT06119581) and early-stage NSCLC (SUNRAY-02, NCT06890598). Clinical trial information: NCT04956640, NCT06119581. Research Sponsor: Eli Lilly and Company.

Response and time-to-event endpoints in the Efficacy evaluable population with PD-L1 0-49% (N=30*).

Endpoint	Pts with PD-L1 <1% n=12	Pts with PD-L1 1-49% n=18
ORR†, % (n/N)	58.3 (7/12)	66.7 (12/18)
BOR, n (%)		
CR†	1 (8.3)	1 (5.6)
PR†	6 (50.0)	11 (61.1)
SD	4 (33.3)	4 (22.2)
PD	1 (8.3)	1 (5.6)
NE	0 (0.0)	1 (5.6)
DCR, % (n/N)	91.7 (11/12)	88.9 (16/18)

†Includes responses confirmed and pending.
*Data for 1 patient are not shown in the table due to incomplete target lesion assessment.
CR, confirmed response; NE, not evaluable, PD, progressive disease; PR, partial response; SD, stable disease.

8629 Poster Session

Patient-reported outcomes (PROs) and health-related quality of life (HRQoL) with taletrectinib in advanced ROS1+ non-small cell lung cancer (NSCLC) from the TRUST-II study. First Author: Yasir Y. Elamin, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Taletrectinib is a next-generation, CNS-active, selective ROS1 tyrosine kinase inhibitor (TKI) approved by the US FDA for the treatment of patients with locally advanced or metastatic ROS1+ NSCLC based on results from two Phase 2 studies, TRUST-I (NCT04395677) and TRUST-II (NCT04919811). Here we report PROs with taletrectinib from TRUST-II. **Methods:** Patients with locally advanced or metastatic ROS1+ NSCLC were treated with taletrectinib 600 mg once daily in 21-day cycles. HRQoL and PROs for cancer-specific symptoms were evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30-item core module (QLQ-C30) and 13-item lung cancer module (QLQ-LC13). Questionnaires were only distributed to patients from North America and Europe. Data were collected at screening, then subsequently on Day (D)1 of every cycle (C) until C9D1, on D1 of every three cycles until C27D1, and every four cycles thereafter until the end of treatment (within 7 days of last dose). Changes from baseline over time were summarized using descriptive statistics. A change in score of $\geq$10 points from baseline was considered clinically meaningful. Time to first improvement (TFI) was assessed using Kaplan–Meier methods. **Results:** At data cutoff (August 31, 2025), the analysis set included 69 patients (23 TKI-naïve and 46 TKI-pretreated). Mean changes from baseline improved or remained stable for most domains across both questionnaires. For global health status/quality of life, the majority of patients showed clinically meaningful improvement or remained stable at multiple timepoints assessed (e.g. 74% of patients at C7). Mean cognitive function score improved or remained stable throughout treatment, with the majority (63–77%) of patients showing improvement or stability and only 9–23% of patients showing worsening at various assessment times. Common disease-related symptoms, including pain and fatigue (QLQ-C30), and dyspnea and coughing (QLQ-LC13), showed consistent clinically meaningful improvement throughout treatment, with a median TFI of 1–3 months across all patients. Coughing was particularly improved in TKI-naïve patients, with a median TFI of < 1 month. **Conclusions:** Taletrectinib was associated with improved or stable HRQoL in the majority of patients and with rapid relief of disease-related symptoms. In contrast to other ROS1 TKIs, taletrectinib demonstrated preservation of cognitive function over time. Together with the efficacy and safety results, these data further support the use of taletrectinib for patients with ROS1+ NSCLC. Clinical trial information: NCT04919811. Research Sponsor: This study was sponsored by Nuvation Bio Inc. Medical writing support was provided by Flaminia Fenoaltea, MSc, of Ashfield MedComms, an Inizio company, and was funded by Nuvation Bio Inc.

8630 Poster Session

Hi-C sequencing to identify clinically actionable fusions in non–small cell lung cancer missed by other sequencing technologies. First Author: Kevin Max Levine, University of Washington/Fred Hutchinson Cancer Center, Seattle, WA

Background: For a patient with non-small lung cancer (NSCLC) to benefit from targeted therapy, an actionable driver alteration needs to be identified. DNA-based next-generation sequencing (NGS) is the standard across many clinical laboratories, however, there are known limitations in the detection of structural rearrangements. RNA-based NGS is now being increasingly utilized in cases with negative DNA NGS testing, but it is currently unknown how many driver alterations are missed with RNA NGS. Hi-C, high-throughput chromosome conformation capture, is a newer NGS method that can be performed on formalin-fixed paraffin-embedded (FFPE) tissue to detect pairwise interactions between DNA regions and may have increased sensitivity for fusion detection. **Methods:** We collected FFPE tissue from NSCLC cases that were previously deemed to be negative for driver mutations through standard DNA and/or RNA based NGS. We performed Hi-C sequencing on these samples with the Arima Aventa FusionPlus test. This involves digestion of DNA in situ followed by religating to nearby DNA regions and sequencing pairs of DNA tags that reveal proximal DNA sequences. RNA-Sequencing was performed via multiple commercial testing labs using either panel based or whole transcriptome sequencing. **Results:** In 118 NSCLC specimens that were negative on prior NGS testing, 6 samples (5%) tested positive on Hi-C sequencing for a clinically actionable alteration, including 5 samples that were negative with both DNA and RNA-based NGS. Among these 6 samples were 5 cases of NRG1 fusions and one case of an NTRK2 fusion. All cases with NRG1 fusions have breakpoints proximal to exon 2 and therefore are expected to have expression of the full EGF-like domain. RNA-Sequencing of several of these cases confirmed high expression of NRG1. As an example, one patient had prior negative sequencing with tissue-based panel DNA NGS, ctDNA NGS, an RNA fusion panel, and whole transcriptome RNA-Seq. This patient's Hi-C sequencing identified a non-canonical NRG1 fusion with an intergenic region fused upstream of exon 2 of NRG1. After progression on chemo-immunotherapy, the patient was treated with zenocutuzumab, a recently approved bispecific antibody that blocks NRG1 from activating HER2/HER3 signaling. A CT Chest scan 6 weeks after initiation showed near complete resolution of the diffuse miliary metastases. **Conclusions:** Hi-C can identify clinically actionable driver alterations in NSCLC cases that were negative on other sequencing tests, highlighting the potential value of incorporating this technology into clinical practice. Research Sponsor: None.

8631 Poster Session

Prognostic impact of actionable driver alterations and efficacy of targeted therapy in lung squamous cell carcinoma: A large-scale nationwide genomic screening (LC-SCRUM-Asia). First Author: Tetsuya Sakai, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Precision medicine based on multi-gene analysis improves prognosis and has established multigene analysis as the standard of care in lung adenocarcinoma.However, the clinical utility of multi-gene analysis in lung squamous cell carcinoma (LUSC) remains controversial due to the rarity of actionable driver alterations and the uncertain therapeutic benefits of targeted therapy. This study aimed to elucidate the prognostic value of driver alterations and the efficacy of targeted therapy in LUSC. **Methods:** We have prospectively analyzed patients with non-small cell lung cancer (NSCLC) enrolled in a nationwide genomic screening project in Japan (LC-SCRUM-Asia) using NGS (Oncomine Comprehensive/Precision Assay). We evaluated clinical outcomes in patients with LUSC, comparing overall survival (OS) according to the presence of actionable driver alterations and receipt of targeted therapy. **Results:** From March 2015 to October 2025, 19,357 patients were enrolled, of whom 2,917 had LUSC. Among these LUSC patients, actionable driver alterations were identified in 180 patients (6.2%) cases, including *EGFR* mutations (n = 78), *KRAS* G12C (n = 33), *MET* exon 14 skipping (n = 28), *ALK* fusions (n = 18), *EGFR* exon 20 insertions (n = 7), *RET* fusions (n = 6), *ROS1* fusions (n = 5), *BRAF* V600E (n = 4), and *HER2* exon 20 insertions (n = 1).In the survival analysis of 2,017 patients with advanced/recurrent disease, median OS was significantly longer in patients with actionable driver alterations compared to those without (18.2 vs. 15.0 months; HR 0.79, p = 0.02). However, among patients with actionable driver alterations, there was no significant difference in median OS between patients who received targeted therapies (n = 97) and those who did not (n = 45) (18.3 vs. 17.0 months, p = 0.94). The efficacy of targeted therapies was notably limited; median progression-free survival was 12.4 months for ALK tyrosine kinase inhibitors (TKIs) (n = 17), 8.4 months for EGFR TKIs (n = 46), 4.5 months for KRAS G12C inhibitors (n = 10), 3.6 months for MET TKIs (n = 15), and 3.4 months for ROS1 TKIs (n = 5). Collectively, these outcomes were consistently inferior to those reported in pivotal clinical trials. **Conclusions:** Although actionable driver alterations were identified in approximately 6% of LUSC and were associated with a favorable prognosis, targeted therapy demonstrated limited efficacy and failed to extend overall survival compared to non-targeted approaches. These findings indicate that the clinical utility of multi-gene analysis in LUSC is currently limited, highlighting the need for the development of novel therapeutic strategies specific to this histology. Research Sponsor: Japan Agency for Medical Research and Development (AMED) and the National Cancer Center Research and Development Fund; Eisai Co., Ltd.; Janssen Pharmaceutical K.K.; Kyowa Kirin Co., Ltd.; Merck Biopharma Co., Ltd.; MEDICAL & BIOLOGICAL LABORATORIES CO., LTD.; MSD K. K.; Nippon Kayaku Co., Ltd; Novartis Pharma K.K.; ONO PHARMACEUTICAL CO., LTD.; Pfizer Japan Inc.; AbbVie GK; Sumitomo Pharma Co., Ltd.; TAIHO PHARMACEUTICAL CO., LTD.; Eli Lilly Japan K.K.; Bayer Yakuhin, Ltd.; Merus N.V.; Takeda Pharmaceutical Co., Ltd.; Amgen K.K.; Astellas Pharma Inc.; AstraZeneca K.K.; Nippon Boehringer Ingelheim Co., Ltd.; Bristol-Myers Squibb K.K.; CHUGAI PHARMACEUTICAL CO., LTD.; DAIICHI SANKYO COMPANY.

8632 Poster Session

Actionable genomic alterations and outcomes in lung squamous and adenosquamous cell carcinoma. First Author: Simone E. Dekker, Division of Medical Oncology, Clinical Research Division, University of Washington/Fred Hutchinson Cancer Center, Seattle, WA

Background: Actionable genomic alterations (AGA) are uncommon in lung squamous/adenosquamous carcinoma (LUSC/LUASC) and may contribute to poorer survival than lung adenocarcinoma (LUAD). Though a subset of LUSC patients harbor AGA and may benefit from targeted therapy, outcomes are poorly characterized. We hypothesized that AGA-LUSC patients treated with first-line (1L) targeted therapy have superior survival to those receiving chemotherapy and that AGA-LUSC has a distinct immune tumor microenvironment (TME) compared to non-AGA-LUSC. **Methods:** We identified and analyzed LUSC (6,970) and LUASC (227) patients from the Tempus Lens database with DNA (xT, 648-gene) and whole-transcriptome RNA (xR) NGS using the Lens Platform. AGA were defined as *ALK*, *ROS1*, *RET*, *NTRK1*/2/3 fusions, *EGFR*, *KRAS*, *BRAF* p.V600E, *MET* exon 14 skipping, or *ERBB2* alterations. *KRAS*, *BRAF* p.V600E, and *MET* exon 14 skipping were classified as immune-associated AGA. RNA data were quantified as transcripts per million (TPM) and reported as log2(TPM+1). We assessed tumor mutational burden (TMB), *TTF1* and *TP63* gene expression, and TME (via quanTIseq). OS and PFS were measured from 1L treatment initiation to death, progression/death or last follow up, respectively. **Results:** AGA incidence was 7.5% in LUSC and 45% in LUASC. Non-immune AGA had significantly lower median TMB than immune-AGA and non-AGA in both LUSC (5.3 vs 7.4 vs 7.9) and LUASC (3.7 vs 5.5 vs 8.4) (both $p < 0.001$) and had numerically lower CD8 T-cell infiltration in LUSC. *TTF1* expression did not differ among AGA and non-AGA groups; but *TP63* expression was significantly higher in LUSC than LUASC (8.70 vs 6.23, $p < 0.001$) and in non-AGA compared to AGA in both LUSC ($p < 0.001$) and LUASC ($p = 0.027$). In AGA-LUSC, 1L targeted therapy (n = 15) was associated with numerically longer PFS (27.7 mo vs 8.1 mo, p = 0.17) and OS (19.2 mo vs 15.7 mo, p = 0.78) compared with chemoimmunotherapy/chemotherapy. No difference in outcomes was observed between non-AGA and AGA LUSC patients treated with chemoimmunotherapy/chemotherapy. **Conclusions:** Given the observed rates of AGA in both LUSC and LUASC and numerically improved outcomes in AGA-LUSC patients receiving 1L targeted therapy, routine NGS testing is warranted. TME differs between non-immune and immune-AGA, and *TP63* expression is inversely associated with AGA in both tumor types. Research Sponsor: National Cancer Institute; T32CA009515.

	LUSC				LUASC			
	Overall N = 6,970	Non-AGA N = 6,449	Non-immune AGA N = 142	Immune-AGA N = 379	Overall N = 227	Non-AGA N = 124	Non-immune AGA N = 37	Immune-AGA N = 66
Classic *EGFR* alteration (exon 19 deletion or L858R)	51 (0.7%)	0 (0%)	51 (36%)	0 (0%)	21 (9.3%)	0 (0%)	21 (57%)	0 (0%)
Other *EGFR* short variant	31 (0.4%)	0 (0%)	30 (21%)	1 (0.3%)	8 (3.5%)	0 (0%)	7 (19%)	1 (1.5%)
***ALK* fusion**	25 (0.4%)	0 (0%)	24 (17%)	1 (0.3%)	5 (2.2%)	0 (0%)	5 (14%)	0 (0%)
***KRAS* G12C**	117 (1.7%)	0 (0%)	0 (0%)	117 (31%)	21 (9.3%)	0 (0%)	0 (0%)	21 (32%)
Other *KRAS* short variant	192 (2.8%)	0 (0%)	0 (0%)	192 (51%)	32 (14%)	0 (0%)	0 (0%)	32 (48%)

8633 Poster Session

Ablation of oligo-residual disease to prolong progression-free survival in *EGFR*-mutant advanced NSCLC patients treated with third-generation EGFR-TKIs. First Author: Jizhong Yin, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China

Background: Combination of EGFR-TKIs with chemotherapy or amivantamab have become the standard of care for EGFR-mutant NSCLC. This study further evaluated the efficacy of ablation in advanced NSCLC patients who develop oligo-residual disease (ORD) after EGFR-TKI. **Methods:** We retrospectively enrolled patients with advanced NSCLC who achieved ORD after first-line third-generation EGFR TKIs therapy in Shanghai Pulmonary Hospital, Tongji University. Ablation, including radiofrequency ablation (RFA) and cryoablation, were administered for residual lung lesions. Using propensity score matching, patients with ORD who received TKIs monotherapy alone were set as the control group. The primary endpoint was progression-free survival (PFS). **Results:** From Jan 2019 to Dec 2023, a total of 292 patients (100 for TKIs plus ablation group and 192 for TKIs group) were included. With a median follow-up of 26.4 months, disease progression or death had occurred in 41 patients (41%) in the TKIs plus ablation group versus 159 patients (83%) in the TKIs group. The addition of ablation significantly improved PFS compared to TKIs alone (median 31.6 vs. 17.9 months; HR 0.36, 95% CI 0.26-0.51; $p < 0.001$). The 2-year PFS rate were 66.1% and 32.5%, respectively. A consistent trend was observed for overall survival (OS) (median OS: not reached; HR 0.36, 95% CI 0.20-0.65; $p < 0.001$). A total of 81 patients (22 for ablation group and 59 for TKIs group) underwent biopsies and NGS testing after resistance. The ablation group showed an increased incidence of MET amplification (17% vs. 7%) and HER2 amplification (8% vs. 4%), while on-target EGFR resistance mutations (C797S mutation or EGFR amplification) were similar. The side effects were similar in the two groups. **Conclusions:** Front-line third-generation EGFR-TKI combined with ablation for ORD led to significantly longer PFS than EGFR-TKIs alone in patients with advanced NSCLC, which provide an alternative strategy as the front line setting and warranting further prospective validation. Research Sponsor: National Natural Science Foundation of China; 82505082; China Postdoctoral Science Foundation; 2025M773920.

8634 Poster Session

Clinicogenomic determinants of early progression on first-line osimertinib in *EGFR*-mutant NSCLC. First Author: Federica Pecci, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: With the recent approvals of the FLAURA2 and MARIPOSA regimens in *EGFR*-mutant non-small cell lung cancer (NSCLC), identifying clinicogenomic features predictive of suboptimal outcomes with first-line osimertinib monotherapy is critical in guiding upfront treatment selections. **Methods:** This is a multicenter retrospective study enrolling patients (pts) with advanced NSCLC harboring common *EGFR* mutations (exon 19 deletions [ex19del], L858R) treated with first-line osimertinib monotherapy across 13 centers (Clinical cohort). Comprehensive baseline genomic data on tumor tissue were available for DFCI and MSKCC (Genomic cohort). The association of clinicogenomic features with real-world progression-free survival (rwPFS) was investigated. Time-dependent discrimination for very-early progression (rwPFS $<$ 6 months) was evaluated using Receiver Operating Characteristic (ROC) curve-based Area Under the Curve (AUC). Variable importance was assessed by delta (Δ) AUC after covariate exclusion. Moreover, very-early progression was analyzed with a Cox model censored at 6 months, reporting adjusted hazard ratios (aHR). **Results:** A total of 1488 pts were enrolled in the clinical cohort; at median follow-up of 43.3 months, median rwPFS was 16.3 months (95%CI 15.3-17.4), median overall survival was 36.7 months (95%CI 34.8-39.4). The strongest predictor of very-early rwPFS in a multivariable model, including, age, sex, *EGFR* mutations, PD-L1 tumor proportion score (TPS), concurrent *TP53* mutations, metastatic sites (brain, bone, liver), performance status, was PD-L1 TPS (aHR 2.75 for $\geq$50% versus 0%, $p < 0.0001$), with the largest decrease in the AUC when excluded from the model (ΔAUC = 0.17). Looking at genomic features in the genomic cohort, at median follow up of 38.2 months, loss-of-function mutations in *KMT2D* (HR 7.1, $p < 0.001$), *TP53* (HR 1.4, p = 0.01), *RB1* (HR 1.7, p = 0.01), *RBM10* (HR 1.6, p = 0.01), *CREBBP* (HR 2.7, p = 0.02), *ATM* (HR 2.1, p = 0.04), predicted shorter rwPFS. Next, we investigated the role of concurrent tumor suppressor gene (*TSG*) alterations beyond *TP53*, including in this cathegory those with a $p < 0.1$ for rwPFS and mutated in at least 5 cases *(RBM10, CREBBP, ATM, RB1, KMT2D, TSC2, PTEN). TSG^{MUT}* had shorter rwPFS compared to *TSG^{WT}* (aHR 1.5, p = 0.01), specifically in L858R subgroup (aHR 1.7, p = 0.02), while *$TP53^{MUT}$* had shorter rwPFS compared to *$TP53^{WT}$* in ex19del only (aHR 1.7, p = 0.01). Combining *TP53* with *TSG*, pts with *$TP53^{MUT}$* plus at least one *TSG^{MUT}* and pts with *$TP53^{WT}$-TSG^{MUT}* had shorter rwPFS compared to *$TP53^{WT}$-TSG^{WT}* and *$TP53^{MUT}$-TSG^{WT}* (10.8, 13.1, 21.9, 18.1 months, respectively, p = 0.004). In the genomic cohort, PD-L1 TPS was the strongest predictor of very-early rwPFS (ΔAUC = 0.16), followed by *TP53* combined with *TSG* (ΔAUC = 0.08). **Conclusions:** In this multicenter real-world cohort, baseline PD-L1 and *TP53* combined with *TSG* predict very-early progression to first-line Osimertinib. Research Sponsor: None.

8635 Poster Session

***EGFR*-mutated lung cancer: A comparative analysis of common and uncommon variants.** First Author: Anas Mohammad Zayed, King Hussein Cancer Center, Amman, Jordan

Background: Uncommon EGFR mutations represent a heterogeneous subset of EGFR-positive NSCLC with limited characterization. This study compares clinical, molecular, and survival outcomes between common and uncommon EGFR variants in a large real-world cohort. **Methods:** A retrospective analysis of 1,501 EGFR-positive NSCLC cases from MSK-CHORD was performed. Patients were classified as having common (Ex19del, L858R) or uncommon mutations (G719X, L861Q, S768I). Clinical and genomic variables were analysed using Wilcoxon and chi-square tests (significance $p < 0.05$). **Results:** The study included 1,501 EGFR-mutated NSCLC patients, with 195 (13.0%) harboring uncommon and 1,306 (87.0%) harboring common EGFR mutations. Patients with uncommon mutations were older at diagnosis (median 73 vs 69 years; p = 0.003), while sex distribution remained similar (p = 0.868). Race distribution differed (p = 0.005), with more White patients in the uncommon EGFR group (80.3% vs. 69.5%) and fewer Asian patients (11.8% vs. 25.5%), while Black patient proportions were similar (7.9% vs. 5.0%). Smoking history also varied ($p < 0.005$), with substantially fewer never-smokers among patients with uncommon mutations (25.6% vs 59.6%). Uncommon mutations were associated with higher genomic burden, including elevated TMB (median 4.92 vs 3.46 mut/Mb; $p < 0.001$) and mutation count (median 6 vs 4; $p < 0.001$). Stage at diagnosis did not differ (p = 0.3), nor did metastatic site distributions (p = 0.477). Median OS was significantly shorter for patients with uncommon EGFR mutations (36.69 vs 56.52 months), with HR 1.425 ($p < 0.005$). In Stage IV patients receiving osimertinib, OS was numerically shorter for uncommon mutations but not statistically significant (29.98 vs 34.32 months; HR 1.351; p = 0.08). Among Stage IV patients with uncommon mutations, OS was comparable between afatinib and osimertinib (25.48 vs 26.70 months; p = 0.88). *KRAS* co-mutations were significantly more frequent in the uncommon group (4.62% vs 1.15%; $p = 1.985 \times 10^{-3}$). **Conclusions:** Uncommon EGFR mutations exhibit distinct clinical and genomic features and poorer survival compared with common variants, highlighting their heterogeneity and the need for tailored therapeutic strategies. Research Sponsor: None.

8636 **Poster Session**

The effect of glucagon-like peptide-1 (GLP-1) receptor agonists on outcomes in metastatic non-small cell lung cancer (mNSCLC) patients treated with tyrosine kinase inhibitors (TKIs): Real-world retrospective analysis. First Author: Khvaramze Shaverdashvili, Thomas Jefferson University, Philadelphia, PA

Background: The therapeutic landscape of mNSCLC has rapidly evolved, with multiple oncogenic alterations now targetable by approved TKIs used in first-line settings, leading to substantial survival gains. However, several TKIs are associated with metabolic toxicities, including weight gain and hyperlipidemia, particularly with ALK inhibitors (e.g., lorlatinib) and selective RET inhibitors. As use of GLP-1 has increased among patients with cancer, their impact on outcomes in oncogene-driven mNSCLC treated with TKIs remains unknown. We evaluated the association between GLP-1 use and survival outcomes in TKI-treated mNSCLC using real-world data. **Methods:** We conducted a retrospective analysis using TriNetX, a Global Collaborative electronic health record with $>$ 190 million patients and $>$ 170 healthcare organizations, from 2010-2025. Adults ($\geq$18 years) with mNSCLC, metabolic comorbidities (T2DM, obesity, or hyperlipidemia), and treatment with first line-approved TKIs (EGFR, ALK, ROS1, RET, NTRK, BRAF, MET) were included. Patients were stratified by concomitant GLP-1 use and matched 1:1 using propensity scores based on demographics, ECOG performance status, cardiometabolic comorbidities, tobacco and alcohol use, and outpatient healthcare utilization. 5 year overall survival (OS) was assessed. **Results:** A total of 25,008 patients met inclusion criteria, including 24,459 (97.8%) non-GLP1 users and 549 (2.2%) in GLP-1 users. After 1:1 propensity score matching (PSM), 546 patients were included per group. Amongst both cohorts average age was 64, 61% were female, 60% were White, 13% were Asian. In the overall mNSCLC TKI-treated patients, GLP-1 use was associated with significantly improved 5-year OS compared with non-use (63% vs 40%; HR 0.45, 95% CI 0.36-0.57; $p < 0.001$). In subgroup analyses, patients treated with ALK TKIs (lorlatinib or alectinib; n = 128/group) demonstrated improved 5 year OS with GLP-1 use 85% vs 48% in non-users (HR, 0.18; 95% CI, 0.09 - 0.36; $p < 0.0001$). Furthermore, GLP-1 use was also associated with improved 5-year OS among EGFR TKI-treated patients (54% vs 44%; HR 0.60, 95% CI 0.44-0.82; p = 0.001) and BRAF TKI-treated patients (41% vs 35%; HR 0.52, 95% CI 0.30-0.91; p = 0.02). Other TKI groups comprised relatively small numbers of patients and therefore were not analyzed separately. **Conclusions:** In this large real-world analysis, GLP-1 use was associated with significantly improved survival in patients with oncogene-driven mNSCLC treated with TKIs, with consistent benefit across ALK, EGFR, and BRAF-driven mNSCLC. To our knowledge, this is the first study to link the impact of the GLP-1 agonists on the outcomes of TKI treated mNSCLC. Further prospective studies are needed to validate these findings and to identify underlying mechanisms. Research Sponsor: None.

8637 **Poster Session**

Plasma epigenomic profiling for identification of mechanisms of sensitivity, primary and acquired resistance to tepotinib in METex14 skipping metastatic NSCLC. First Author: Sunny Das, Precede Biosciences, Boston, MA

Background: *MET* exon 14 skipping mutations (METex14) are an actionable biomarker in a subset (3-4%) of advanced/metastatic NSCLC patients, with an approved oral and highly selective MET TKI, tepotinib. However, heterogenous clinical responses in patients warrant additional biomarkers of response and resistance. We applied Precede's epigenomic liquid biopsy platform to explore the feasibility of identifying transcriptional programs associated with sensitivity and resistance to tepotinib in patients with METex14 NSCLC. **Methods:** A total of 144 baseline, on-treatment (OT), and end-of-treatment (EOT) samples from patients with METex14 NSCLC from the VISION study (NCT02864992) were profiled using Precede's assay using 1mL of plasma. ctDNA fraction was independently estimated. Genome-wide differential epigenomic activity and pathway analyses compared PFS-stratified responders (top tertile PFS) vs. non-responders at baseline (bottom tertile PFS), and paired baseline vs. EOT samples to identify acquired resistance programs. SCLC/neuroendocrine transformation was assessed in all samples using an independent Precede lineage classifier. Plasma-inferred gene expression models, based on Precede's proprietary algorithms identified additional therapeutic targets. **Results:** At baseline, responders showed higher epigenomic activity in pathways underlying addiction to METex14 signaling, including the FAK-integrin axis, ECM remodeling and EMT/invasion. Non-responders displayed increased translational/intrinsic proliferative programs, altered metabolic fitness, and inflammatory/immune signaling, implicating these programs in intrinsic resistance to tepotinib. These METex14 signaling-associated pathway scores stratified clinical outcomes, highlighting their potential in patient selection. Paired analyses revealed EOT samples had increased activity of regulators of lineage plasticity and neuroendocrine differentiation, relative to baseline. Correspondingly, SCLC scores were elevated in OT and EOT samples, with a subset of baseline samples already harboring neuroendocrine features. Epigenomic activity of GD2 synthase (*B4GALNT1*) significantly increased with treatment, underscoring a potential rationale for combination therapies using anti-GD2 ADCs. **Conclusions:** Precede's comprehensive epigenomic liquid biopsy platform resolved METex14 skipping NSCLC biology associated with response and identified programs associated with intrinsic and acquired resistance to tepotinib, including emergence of neuroendocrine differentiation and induction of GD2 synthase. These findings support the use of plasma-based epigenomic profiling to inform therapy selection for patients at baseline and progression and non-invasively monitor resistance mechanisms in METex14 NSCLC. Research Sponsor: Merck KGaA, Darmstadt, Germany; CrossRef Funder ID: 10.13039/100009945.

8638 **Poster Session**

Efficacy and safety of deulorlatinib (TGRX-326) in patients with locally advanced or metastatic ALK+ non–small cell lung cancer: A multicenter, open-label, pivotal phase 2 trial. First Author: Yunpeng Yang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Treatment options are limited for anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC) patients (pts) who have developed resistance to second-generation ALK inhibitors. Deulorlatinib is a highly potent third-generation ALK inhibitor. The Previous phase 1 study (NCT05441956) found that deulorlatinib had a high overall and intracranial response rate in pts who had progressed on second-generation inhibitors, with encouraging activity against the G1202R mutation and favorable tolerability. **Methods:** This is a multicenter, open-label pivotal phase 2 study. Pts with locally advanced or metastatic ALK+ NSCLC who had progressed on second-generation inhibitors received deulorlatinib 60 mg orally once daily. The primary endpoint was objective response rate (ORR) per RECIST v1.1 by independent review committee (IRC). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. The ORR in patients harboring the G1202R mutation was also assessed. **Results:** Between Jan 18, 2023 and Dec 29, 2023, a total of 163 patients were enrolled and 158 were evaluable for efficacy. Of these pts, the median age was 53.5 years old, 53.2% were female, 95.6% had adenocarcinoma, and 56.2% had baseline brain metastasis; 56.3% of these pts had progressed on alectinib. As of December 16, 2025, the median follow-up was 28.7 months and 44 pts were still on deulorlatinib. The IRC assessed confirmed ORR was 43.7% (95%CI 35.8, 51.8). The median DoR and PFS was 20.7 months (95%CI 15.4, NR) and 13.8 months (95%CI 8.3, 16.5), respectively; median OS was not reached. Of the 43 pts with measurable baseline CNS lesions, confirmed ORR was 55.8% (95%CI 39.9, 70.9). In pts with the G1202R mutation, the ORR was 62.5% (95%CI 24.5, 91.5). Treatment-related adverse events (TRAEs) were reported in 96.3% of pts. The most common TRAEs were hypercholesterolaemia (77.9%), hypertriglyceridaemia (71.2%), and weight gain (52.8%). Grade $\geq$3 TRAEs were reported in 51.5% of pts. Of note, only 1.2% of pts had Grade $\geq$3 CNS TRAEs. **Conclusions:** Deulorlatinib produced robust and durable responses in locally advanced or metastatic ALK+ NSCLC pts with progression on second-generation inhibitors, including those with the G1202R mutation, with low incidence of Grade $\geq$3 CNS TRAEs. Although across trials comparisons must be interpreted cautiously, deulorlatinib might have a better safety profile than lorlatinib. Altogether these findings suggest that deulorlatinib has a favourable risk benefit ratio and support its further development, particularly in the first-line setting. Clinical trial information: NCT05955391. Research Sponsor: Shenzhen TargetRx, Inc.

8639 **Poster Session**

Clinical efficacy and tolerability of the selective RET inhibitor soxaltalinib (SY-5007) in advanced *RET* fusion–positive non–small cell lung cancer (NSCLC): Primary findings from a confirmatory phase III trial. First Author: Anwen Xiong, Department of Oncology, Shanghai East Hospital, Tongji University, Shanghai, China

Background: Oncogenic RET gene fusions represent a clinically validated molecular driver occurring in approximately 1–2% of all NSCLC cases, establishing a critical need for targeted therapeutic strategies. Soxaltalinib is a novel, orally bioavailable, and highly selective small-molecule inhibitor of RET kinase. Its anti-tumor potency and safety have been previously reported in a phase I/II study. Here we confirmed its clinical value in a pivotal phase III study. **Methods:** This multicenter, single-arm Phase III clinical trial was designed to evaluate the efficacy and safety of Soxaltalinib in patients with RET fusion–positive NSCLC who were previously untreated for advanced disease. The primary endpoint was the confirmed Objective Response Rate (ORR), as determined by Blinded Independent Central Review (BICR) per RECIST v1.1. The secondary endpoints included investigator-assessed ORR, Disease Control Rate (DCR), Duration of Response (DOR), Progression-Free Survival (PFS), Overall Survival (OS), and safety. **Results:** At the data cutoff (April 10, 2025), the Per-Protocol Population (PPP) comprised 95 patients, 61 of whom were Key efficacy population (KEP) for statistical hypothesis. Soxaltalinib demonstrated profound anti-tumor efficacy. The primary endpoint was met. The BICR-confirmed ORR was 90.0% (95%CI: 79.5, 96.2) for KEP and 87.4% (95%CI: 79.0, 93.3) for PPP. The overall DCR was 96.7% (95%CI: 88.5, 99.6) for KEP and 93.7% (95%CI: 86.8, 97.6) for PPP. The median PFS and DOR had not yet been reached, with an estimated 15-month PFS rate of 68.9% (95%CI: 54.3, 79.7) and 65.0% (95%CI: 51.5, 75.6) and 12-month DOR rate of 73.8% (95%CI: 58.2, 84.4) and 69.1% (95%CI: 53.8, 80.1), respectively for KEP and PPP. The OS data remained immature. The safety analysis population comprised 96 patients who received at least one dose of Soxaltalinib. The most common Grade $\geq$3 treatment-emergent adverse events (TEAEs) were hypertension (22.9%), diarrhea (16.7%), Aspartate aminotransferase increased (6.3%), Alanine aminotransferase increased (5.2%), and hyponatraemia (5.2%). These events were predominantly manageable. None of the patients permanently discontinued treatment due to a treatment-related adverse event. No patient died due to TEAE that was definitely related, probably related, or possibly related to Soxaltalinib. **Conclusions:** The primary analysis of this Phase III trial confirmed Soxaltalinib as a highly effective and well-tolerated therapeutic agent for patients with RET fusion–positive NSCLC in the first-line setting. This observed high response rates and durable disease control benefit underscored its potential as a best-in-class RET inhibitor. The adverse event profile was predictable and manageable, supporting its feasibility for long-term administration. Clinical trial information: NCT06031558. Research Sponsor: Shouyao Holdings (Beijing) Co. Ltd.

8640 **Poster Session**

Results from OCEAN II: A phase II study of encorafenib + binimetinib combination in Chinese patients with *BRAF*^{V600E} mutated metastatic non-small cell lung cancer. First Author: Huaqiang Zhou, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Lung cancer is the most common cause of cancer and cancer death in China. Patients (pts) with *BRAF*^{V600E} mutant metastatic non-small cell lung cancer (mNSCLC) can benefit from targeted treatments such as encorafenib + binimetinib (E+B). E+B is approved in Western countries (PHAROS: NCT03915951); however, evidence of efficacy and safety in Chinese pts is lacking. OCEAN II (NCT05195632) is the 1st study to specifically evaluate the efficacy, safety and pharmacokinetic of this targeted combination in Chinese pts with *BRAF*^{V600E} mutant mNSCLC. **Methods:** OCEAN II is an ongoing multicenter, open-label, phase 2 (P2) study with a Safety Lead-in (SLI). Eligible pts had unresectable stage IV *BRAF*^{V600E} mutant NSCLC, were treatment-naive or had received systemic therapy, excluding BRAF/MEK inhibitors. Pts received E 450 mg once daily + B 45 mg twice daily. Primary endpoints were dose-limiting toxicities (DLT) during the 1st 28 days (SLI) and confirmed objective response rate (cORR) by independent central review (ICR) (P2). Secondary endpoints (P2) were disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between June 2022 and October 2023, 63 pts were enrolled (SLI = 15, P2 = 48): median age 65 yrs (range 52–82), 49% female, 75% with ECOG score = 1. There was only 1 DLT (non-serious grade 3 lipase increased) during SLI, supporting P2 initiation. At the primary analysis cut-off date (27 May 2024), the primary endpoint was met; cORR by ICR was 59.3% (95% confidence interval [CI] 45.0–72.4) in the Efficacy set, with pre-defined statistical significance criteria met. An *ad hoc* analysis (cut-off 27 March 2025) was conducted when all pts had ≥12 months (mo) follow up. cORR by ICR was 61.1% (95% CI 46.9–74.1), with 6 (11%) complete and 27 (50%) partial responses, and DCR of 87.0% (95% CI 75.1–94.6). Median time to response was 1.8 mo (range 1.7–13.7), median DoR 17.5 mo (95% CI 12.9–NR), median PFS 13.8 mo (95% CI 7.5–NR) and median OS 27.9 mo (95% CI 14.7–30.0). DoR and OS are not yet mature (median follow-up for OS: 21 months). Median treatment duration was 32.3 weeks, with 7 (11%) pts receiving treatment for > 2 years, and 10 (15.9%) remaining on treatment. Treatment-emergent adverse events (TEAEs) ≥ grade 3 occurred in 56% of pts. Related TEAEs in ≥25% were anemia (36%), increased aspartate aminotransferase (33%), increased alanine aminotransferase (30%), increased creatine kinase (29%), vomiting (27%), increased creatinine (25%). Nine (14%) pts discontinued any drug due to AEs. **Conclusions:** The data confirm the clinical benefit of E+B in Chinese pts with *BRAF*^{V600E} mutant mNSCLC, a population with distinct genomic and disease characteristics. No new safety concern was identified in the Chinese population. These data can support regulatory decisions and clinical practice guidelines in China. Clinical trial information: NCT03915951. Research Sponsor: Pierre Fabre Medicament.

8641 **Poster Session**

A phase 2 multicenter, open-label, parallel cohort study to evaluate the efficacy, safety, and pharmacokinetic profile of ABN401 in patients with advanced solid tumors harboring c-MET dysregulation. First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Vabametkib is a small-molecule, tyrosine kinase inhibitor (TKI) that is a highly selective type I inhibitor of c-MET kinase, for the treatment of solid tumors harboring c-MET gene dysregulation. **Methods:** Phase 2 trial is an open-label, global study designed to evaluate the safety and efficacy of vabametkib in patients with NSCLC harboring MET exon 14 skipping mutations confirmed by NGS. Patients received oral vabametkib at a dose of 800 mg once daily (QD) until disease progression or unacceptable toxicity. The primary endpoint was ORR as assessed by blinded independent central review. Secondary endpoints included pharmacokinetics, DoR, DCR, PFS and OS. Exposure–response relationships of vabametkib were evaluated in enrolled patients to explore the optimal dose and dosing regimen to support further clinical development. **Results:** Forty-two (42) efficacy patients enrolled and median age were 76 years; 78 years in treatment naive and 75 years in the prior treated patients. Median follow-up duration was 14.1 months overall; 14.6 months for treatment naive and 13.5 months for prior treated patients. BICR confirmed ORR was 55% overall, with comparable response rate in both treatment-naive patients (52%) and prior-treated patients (57%). The median DoR assessed by BICR was 14.5 months with 19.9 months in treatment naive patients and 11.7 months in prior treated patients. Median PFS by BICR was 8.8 months overall, with 10.2 months in treatment naive patients and 7.3 months in prior treated patients. TRAE were experienced in 89% patients, 11% patients experienced Grade ≥3 TRAEs and no Grade 4 TRAE was reported. The most common TRAEs included nausea (75%), diarrhea (34%), hypoalbuminemia (25%), rash (18%), vomiting (18%), peripheral edema (16%), fatigue (14%), and elevated ALT and AST (14%). The most common Grade ≥3 TRAE was pneumonitis (4.5%). TRAEs led to dose reductions in 22.7% of patients, most commonly due to rash (6.8%), nausea (4.5%) and stomatitis (4.5%). TRAEs resulted in dose interruptions in 36.4% of patients most frequently due to nausea (9.1%), vomiting (9.1%), rash (6.8%), and fatigue (4.5%). Median AUC_{inf} values were highest in the PR group (2,946 ng·h/mL) compared to the SD (2,021ng·h/mL) and PD groups (988 ng·h/mL) with a statistically significant difference (p = 0.0347 by Kruskal-Wallis). PK simulation demonstrated BID dosing more effectively maintained EC_{90} coverage than QD dosing; sustaining drug conc above EC_{90} for 93% of the dosing interval and increasing $AUC_{0\text{-}24hr}$ by 35.3% thereby increasing likelihood of achieving exposure observed in the PR patients. **Conclusions:** Alternative 350mg BID of Vabametkib had been selected to continue the clinical development. Clinical trial information: NCT05541822. Research Sponsor: AbionBio; Korean Drug Development Fund.

8642 **Poster Session**

Comprehensive epigenomic profiling of plasma for non-invasive detection of MET activation to uncover MET-associated biology in patients with *EGFR*-mutated advanced NSCLC and progression on osimertinib. First Author: Jonathan W. Riess, UC Davis Comprehensive Cancer Center, Sacramento, CA

Background: Genomic overexpression or amplification of *MET* is an established bypass resistance mechanism in EGFR-mutated (EGFRm) NSCLC, observed in up to 34% of patients whose tumors progress on osimertinib. Savolitinib, an oral, highly selective MET TKI, demonstrates clinical activity in tumors classified as MET-high by tissue-based IHC or FISH. However, tissue at progression is often inaccessible or insufficient for repeated assessment, constraining dynamic characterization of MET pathway dependence and emerging resistance mechanisms. To overcome these limitations, we applied an epigenomic liquid biopsy platform to a subset of patients enrolled in the Phase II SAVANNAH trial that combined osimertinib and savolitinib after progression on 1L osimertinib (NCT03778229), where we evaluated the feasibility of capturing MET activity and additional resistance markers from plasma. **Methods:** Baseline samples from 40 patients enrolled in the SAVANNAH trial with progression on 1L osimertinib, were profiled using an epigenomic assay (Precede Biosciences, Boston MA) on 1mL of plasma. Tissue-based analysis from the SAVANNAH cohort scored 15/40 tumors as MET-high/+ (FISH 10+, IHC 3+ ≥90%+) and 25 samples as MET-low/- (FISH < 10, IHC 3+ < 90%). A plasma-based MET classifier integrating comprehensive epigenomic features was applied to these samples and its performance evaluated against tissue MET status. ctDNA fraction was independently estimated. Pathway analyses on genome-wide differential epigenomic activity were performed to define MET-associated biology and infer tumor gene expression from plasma. **Results:** The plasma-based MET classifier demonstrated strong agreement with tissue-based MET status (AUC 0.97; balanced accuracy 88%), with an estimated limit of quantification (LoQ) of ~0.8% ctDNA. MET+ samples displayed enrichment of epigenomic signatures consistent with MET-dependence, including MYC targets, metabolic signatures, and invasive and developmental programs. In contrast, MET-negative (MET-) samples were enriched for IFN-driven immune pathways and apoptotic priming. Gene expression models across multiple ADC targets applied to patient plasma samples from SAVANNAH also identified elevated EGFR and HER2 expression in select cases. **Conclusions:** Comprehensive epigenomic profiling of plasma demonstrated high concordance with tissue-based approaches, identifying MET pathway activation and additional putative resistance-associated targets, from 1 mL of plasma in EGFRm NSCLC patients. This provides an accessible and scalable blood-based test to increase identification of patients post-EGFR inhibitor treatment, who may benefit from MET-targeted therapy, resistance monitoring, and informing future combination or sequential MET-directed strategies. Research Sponsor: AstraZeneca, Boston, USA.

8643 **Poster Session**

Clinical significance of *EGFR* amplification in patients with *EGFR*-mutated metastatic non–small cell lung cancer receiving first-line osimertinib. First Author: Alessandro Di Federico, University of Bologna, Bologna, Italy

Background: With rapidly expanding first-line options for patients (pts) with *EGFR*-mutated non-small cell lung cancer (NSCLC), identifying biomarkers that may assist treatment selection is critical. The impact of *EGFR* amplification (*EGFR*^{AMP}) on osimertinib outcomes is unclear. **Methods:** Pts with stage IV NSCLC and *EGFR* exon 19 deletions (ex19del) or the L858R mutation who received first-line osimertinib monotherapy at 5 centres across Italy and the United States and had undergone baseline next-generation sequencing (NGS) that included *EGFR*^{AMP} assessment were included in this analysis. *EGFR*^{AMP} was defined as an *EGFR* copy number (CN) ≥6. The predominantly amplified allele was inferred by INCOMMON, a biostatistical classifier, as previously described. **Results:** Among 473 pts, 81 (17.1%) had *EGFR*^{AMP}. Compared to pts with non-amplified *EGFR* (*EGFR*$^{Non\text{-}AMP}$, n = 392), pts with *EGFR*^{AMP} more frequently had *TP53* co-mutations (80% vs 55%, p < 0.001) and baseline brain (51% vs 34%, p = 0.008), liver (26% vs 13%, p = 0.009), and bone metastasis (65% vs 51%, p = 0.03). When treated with osimertinib, pts with *EGFR*^{AMP} achieved similar objective response rate (ORR) (88% vs 83%, p = 0.23), but shorter median progression-free survival (mPFS) (11.6 vs 19.0 months, HR 1.77, p < 0.0001) and overall survival (mOS) (34.0 vs 40.1 months, HR 1.40; p = 0.040). In a multivariable Cox-regression model, *EGFR*^{AMP} retained its association with worse PFS (HR 1.36, p = 0.04), but not OS. *EGFR*^{AMP} correlated with shorter PFS in both *TP53* co-mutated (n = 269) (11.7 vs 15.0 months, HR 1.43, p = 0.02) and *TP53* wild-type (n = 181) (10.4 vs 21.9 months, HR 2.38, p < 0.001) cases, despite similar ORR and mOS. Among pts with ex19del, *EGFR*^{AMP} (n = 44) showed similar ORR compared to *EGFR*$^{Non\text{-}AMP}$ (n = 241), but shorter mPFS (14.2 vs 20.2 months, HR 2.01, p < 0.001) and mOS (35.4 vs 44.9 months, HR 1.62, p = 0.04). In contrast, no difference was observed in the L858R-mutated subgroup between *EGFR*^{AMP} (n = 39) and *EGFR*$^{Non\text{-}AMP}$ (n = 150) cases (ORR 86% vs 75%, p = 0.14; mPFS 11.4 vs 14.3 months, HR 1.47, p = 0.06; mOS 33.2 vs 36.0 months, HR 1.19, p = 0.5). Within *EGFR*^{AMP} cases, increasing *EGFR* CN (*EGFR*$^{Non\text{-}AMP}$ vs CN≥6 < 15 vs CN 15-30 vs CN > 30) correlated with a stepwise reduction of mPFS (19.0, 16.7, 10.3, and 8.7 months, respectively; log-rank p < 0.001) and mOS (40.1, 37.5, 38.8, and 15.3 months, respectively; log-rank p = 0.02). Moreover, amplification of the mutant allele, as opposed to wild-type amplification, correlated with inferior mPFS (8.3 vs 12.1 months, HR 2.72, p = 0.002) and mOS (17.3 vs 39.7 months, HR 2.08, p = 0.046). Among pts with paired NGS before and after acquired osimertinib resistance (n = 113), those with baseline *EGFR*^{AMP} more frequently showed acquired *MET* alterations (29% vs 12%, p = 0.04). **Conclusions:** *EGFR*^{AMP} is associated with distinctive characteristics and worse outcomes to osimertinib among pts with stage IV *EGFR*-mutated NSCLC. Research Sponsor: None.

8644 **Poster Session**

Leptomeningeal disease in ALK-positive NSCLC: Survival impact of third-generation ALK inhibitors. First Author: Kelsey Pan, Emory University Hospital/Winship Cancer Institute, Raleigh, NC

Background: As survival outcomes for patients with ALK-positive non-small cell lung cancer (NSCLC) continue to improve with successive generations of ALK tyrosine kinase inhibitors (TKIs), leptomeningeal disease (LMD) has emerged as a growing and critical area of unmet need. While next-generation ALK TKIs were developed to enhance central nervous system (CNS) penetration and improve control of parenchymal brain metastases, their role in the treatment of LMD remains less well defined. **Methods:** We performed a global multi-center retrospective analysis of 141 patients with a diagnosis of ALK-positive NSCLC and radiographically or cytologically confirmed LMD at 5 academic centers across the United States and China (MD Anderson Cancer Center, Zhejiang University, Guandong Lung Cancer Institute, National Cancer Centre Singapore, and Union Hospital at Tongji Medical College) between 2007-2024. Baseline clinical characteristics, treatment history, and outcomes were collected, and subgroup analyses were performed to identify clinical and treatment-related factors associated with leptomeningeal overall survival (LMOS). **Results:** Of the 141 patients with ALK+ NSCLC, most patients had radiographic LMD (79.4%), while 41.1% had positive CSF cytology and 59.6% were neurologically symptomatic. The median time from metastatic lung cancer to LMD diagnosis was 40.6 months among patients who were previously treated with a 3rd generation (3G) ALK TKI (lorlatinib), compared to 23.7 months among those without prior lorlatinib treatment ($p < 0.001$). The median overall survival following LMD diagnosis (LMOS) was 22.5 months. Use of a 3G ALK TKI following LMD diagnosis was associated with improved LMOS in both treatment-naïve patients and those previously treated with earlier-generation TKIs. Among TKI-naïve patients, LMOS was 42.4 months with second-generation (2G) TKI alone, 49.6 months with escalation from 2G to 3G TKI, and not reached with 3G TKI alone ($p < 0.001$). Among patients previously treated with a 2G TKI, LMOS was significantly improved with 3G TKI (32.6 months) compared with an alternative 2G TKI (7.0 months) or no ALK TKI (6.8 months; p = 0.01). Whole-brain radiotherapy, intrathecal therapy, and VEGF inhibition were not associated with improved LMOS. On multivariable analysis, ECOG performance status < 2 and female sex were associated with prolonged LMOS. **Conclusions:** This study represents the largest multi-institutional analysis of LMD in patients with ALK+ NSCLC. Highly CNS-penetrant 3G ALK TKIs are associated with delayed LMD development and significantly improved survival following LMD diagnosis, whereas WBRT and intrathecal therapies confer limited benefit. These findings support the need for potent CNS-active ALK TKIs and prospective studies including patients with LMD in ALK-driven NSCLC. Research Sponsor: None.

8645 **Poster Session**

Real-world effectiveness of MET inhibitors versus immunotherapy ± chemotherapy in 1L for patients with MET exon 14 skipping mutations in non-small cell lung cancer. First Author: Pranoti Pradhan, ConcertAI, LLC, Cambridge, MA

Background: Metastatic non-small cell lung cancer (mNSCLC) remains a leading cause of cancer-related deaths, with MET exon 14 skipping mutations (METex14) identified as a key oncogenic driver in 1%–4% of cases. MET tyrosine kinase inhibitors (TKI) such as capmatinib and tepotinib have demonstrated efficacy in clinical trials, leading to FDA approval in any treatment line. This study aims to compare first-line (1L) survival outcomes with MET TKI versus immune checkpoint inhibitors ± chemotherapy (IO ± Chemo). **Methods:** Patient characteristics and survival outcomes were retrospectively analyzed for METex14 mNSCLC patients who received 1L therapy with either (1) MET TKI (tepotinib and capmatinib) or (2) IO ± Chemo. Patients were excluded if they had EGFR alterations. Data were sourced from ConcertAI's Patient360 and RWD360, datasets sourced from oncology EHR in the US. **Results:** Among a total of 344 patients, 174 (50.6%) were > 80 years of age, 94 (87.9%) had non-squamous mNSCLC, 176 (51.2%) were female, and 71 (20.6%) had ECOG PS ≥2. As 1L, 202 received MET TKI, 61 received IO + Chemo, and 81 received IO only. Baseline clinicopathologic features were balanced except for a slightly higher proportion of patients with TPS PD-L1 ≥50 in the IO ± Chemo group ($p < 0.05$). At a median follow up of 40.7 months (mo), in the overall group median progression-free survival (mPFS) was 6.6 mo (95% CI: 5.8–8.8) and median overall survival (mOS) was 15.5 mo (95% CI: 14.4–18.3). MET TKI yielded a mPFS of 7.8 mo (95% CI: 6.2–9.1) and a mOS of 13.8 mo (95% CI: 11.4–17.6). IO ± Chemo resulted in a mPFS of 5.1 mo (95% CI: 3.7–8.2) and a mOS of 21.9 months (95% CI: 15.5–25.8). The mPFS did not differ significantly between groups (p =0.38), while mOS favored IO ± chemotherapy (p= 0.03). Objective response rate was 61.0% with MET TKI and 50.7% with IO ± Chemo (p= 0.74); disease control rate was significantly higher with MET TKI (77.0% vs 64.8%; p= 0.03). In subgroup analysis, among patients with PD-L1 ≥50, OS was significantly longer with 1L IO ± Chemo compared with MET TKI (22.0 mo, 95% CI: 7.5–34.3 vs. 8.5 mo, 95% CI: 6.6–16.5; $p < 0.02$). In contrast, among patients with PD-L1 < 50, MET TKI was associated with longer PFS (9.2 mo, 95% CI: 4.2–11.7 vs. 4.9 mo, 95% CI: 2.1–11.0; p= 0.07) although OS was similar (17.6 mo, 95% CI: 9.6–29.6 vs. 14.5 mo, 95% CI: 4.0–23.2; p= 0.57). **Conclusions:** Among patients with METex14 mNSCLC, those treated with 1L IO ± Chemo had a better OS compared to those treated with MET TKI. This seems especially valid for patients with PD-L1 ≥50, for whom IO ± Chemo significantly improved OS. However, patients with PD-L1 < 50 showed prolonged PFS when treated with MET TKI. This highlights the need for personalized treatment patterns in this patient population. Research Sponsor: ConcertAI, LLC.

8646 **Poster Session**

ALFA score as a predictor of long-term benefit with frontline brigatinib in *ALK*+ advanced NSCLC: A ctDNA-based composite biomarker from ALTA-1L. First Author: Laura Mezquita, Hospital Clinic - IDIBAPS, Barcelona, Spain

Background: Optimal sequencing of ALK-TKI in 1st-line *ALK+* NSCLC remains controversial. Although 3rd-generation (G) TKI are increasingly used upfront, a subset of patients (pts) may achieve prolonged outcomes with 2ndG TKI. However, baseline (B) biomarkers to identify these pts are lacking. We evaluated whether a composite clinical-molecular score integrating (B) ctDNA and biological parameters could predict systemic and intracranial outcomes with upfront brigatinib. **Methods:** Post hoc analysis of pts with *ALK+* NSCLC from the ALTA-1L trial with available (B) ctDNA NGS. *ALK* variants, co-occurring genomic alterations (co-GAs), and clinical/biological variables (PS, albumin, derived neutrophil-to-lymphocyte ratio [dNLR], and metastatic sites) were analyzed. Independent prognostic factors for progression-free survival (PFS) and intracranial PFS (IC-PFS) were identified by multivariable Cox models. A composite score (ALFA), based on the Cox models' coefficients was developed. **Results:** Among 124 pts, ctDNA detected *ALK* variant in 53% (n = 66), mostly *EML4::ALK* (V1 n = 25, V3 n = 24, V2 n = 7, V5 n = 4). co-GAs were present in 46%, including suppressor gene alt. in 35%. High dNLR was observed in 34% and hypoalbuminemia in 21%. In multivariable analysis, high dNLR (HR 1.67, 95% CI 1.02–2.73; p = 0.04), low albumin (HR 0.34, CI 0.20-0.57; $p < 0.001$) and suppressor co-GAs (HR 2.24, CI 1.32-3.79; p = 0.003) were independently associated with shorter PFS. Non-V1 variants showed a trend toward inferior PFS (HR 1.73; p = 0.05). For IC-PFS, high dNLR (HR 1.52; p = 0.03), brain metastases (HR 2.98; $p < 0.001$), and suppressor co-GAs (HR 2.41; p = 0.002) remained independently prognostic. The ALFA score stratified pts into low- (59%), intermediate- (27%), and high-risk (14%) groups, with median PFS of 35.5, 11.1, and 5.5 months (mo.), respectively ($p < 0.0001$; c-index 0.72). A similar separation was observed for intracranial PFS (IC-PFS; $p < 0.0001$), with median IC-PFS not reached in the low-risk group, 21.1 mo in the intermediate-risk group, and 5.5 mo. in the high-risk group (c-index 0.72). Overall survival (OS) showed consistent and significant discrimination across ALFA risk groups (log-rank $p < 0.0001$) with a median OS NR in low-risk, 44.3 mo. in intermediate-risk, and 19.3 mo. in high-risk pts. **Conclusions:** The ALFA score integrates baseline ctDNA-derived molecular features with routine blood-based parameters to robustly stratify clinical outcomes in *ALK+* pts treated with frontline brigatinib. This composite score identifies a subset of patients with durable systemic and intracranial benefit from second-generation ALK inhibitors, supporting its potential role as a practical risk stratification tool in routine clinical practice. Research Sponsor: None.

8647 **Poster Session**

Genomic determinants of resistance to BRAF/MEK inhibitors in *BRAF*^{V600E}–mutant non–small cell lung cancer. First Author: Eleonora Gariazzo, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: *BRAF* V600E mutations occur in approximately 2–3% of non–small cell lung cancer (NSCLC). BRAF/MEK inhibition (BRAFi+MEKi) yields high response rates and durable clinical benefit but acquired resistance is inevitable. BRAFi+MEKi therapy may select for resistant tumor clones, induce secondary genomic alterations, and drive changes in the tumor immunophenotype. However, the landscape of resistance mechanisms to BRAFi+MEKi in NSCLC remains largely unknown. **Methods:** We conducted a global, multicenter analysis of patients with advanced *BRAF* V600E–mutant NSCLC treated with BRAFi±MEKi across multiple academic centers and available public datasets. Eligible patients had matched pre- and post-treatment next-generation sequencing (NGS). Analyses were restricted to oncogenic or likely oncogenic alterations per OncoKB and/or ClinVar. **Results:** Among 33 patients with matched pre- and post– BRAFi±MEKi samples, median age was 66 years; 39.4% were women, 67.7% had a history of tobacco use, and 97.0% had adenocarcinoma at diagnosis. Objective response to BRAFi±MEKi in this cohort was 81.8%, while median progression-free survival was 8 months; only 3 patients (9.1%) had primary resistance. Acquired resistance mechanisms were diverse, encompassing reactivation of the RAS/RAF/ERK signaling pathway (via *BRAF*-dependent and *BRAF*-independent mechanisms), activation of alternative bypass pathways (e.g. PI3K/AKT and HIPPO), and alterations associated with cell-cycle dysregulation. Concurrent resistance mechanisms were identified in 12.1% of cases, and one patient developed histologic transformation to small-cell lung cancer (SCLC). No identifiable resistance mechanism was detected in 11 patients (33.3%). The most common acquired genomic alterations were *RAS* mutations, observed in 21.2% of cases (*NRAS* Q61K, n = 1; *NRAS* Q61R, n = 1; *KRAS* G12D, n = 1; *KRAS* G12V, n = 1; *KRAS* Q61R, n = 1; *NRAS* Q61R + *KRAS* 61H, n = 1; *KRAS* G12V + *KRAS* Q61H, n = 1), followed by *MET* amplifications (12.1%, n = 4). Additional acquired events included *BRAF* kinase-domain duplication, *MAP2K1* and *NF2* mutations, and *FGFR4* amplification. Putative resistance alterations involving DNA damage repair genes (e.g., CHEK2, BRIP1) were also identified. Clinically, one patient with acquired *MET* amplification showed loss of the *MET*-amplified clone on liquid biopsy after adding crizotinib to BRAFi+MEKi, without grade≥3 adverse events, suggesting a potentially targetable resistance mechanism with therapeutic implications. **Conclusions:** Our findings define the genomic landscape of acquired resistance to BRAFi+MEKi in *BRAF* V600E–mutant NSCLC and highlight the emergence of diverse resistance mechanisms, including SCLC transformation, *MET* amplification, and *RAS* mutations, several of which are potentially actionable and may inform rational post-BRAFi/MEKi therapeutic strategies. Research Sponsor: None.

8648 **Poster Session**

A phase Ib study of osimertinib and tegavivint as first-line therapy in patients with metastatic *EGFR*-mutated non–small cell lung cancer (NSCLC). First Author: Regan Michelle Memmott, Department of Internal Medicine, The Ohio State University - James Comprehensive Cancer Center, Columbus, OH

Background: EGFR TKIs improve clinical outcomes for patients with EGFR-mutated NSCLC. However, they are not curative even when combined with chemotherapy or antibody-based therapies because of slow-cycling, drug-tolerant cells that persist due to transcriptional reprogramming. This inevitably leads to tumor resistance and disease progression. Our preclinical studies showed that EGFR-mutated NSCLC cells enter a persistent state in response to TKIs due to increased transcriptional activity of β-catenin. Treatment of mice bearing EGFR-mutated NSCLC xenografts with an EGFR TKI and a β-catenin inhibitor caused a greater depth and duration of response than treatment with an EGFR TKI alone, which improved overall survival (OS). We also observed that patients with EGFR-mutated NSCLC who had the greatest increase in serum levels of the secreted β-catenin transcriptional target PAI-1 following treatment with a TKI had significantly worse progression free survival (PFS). These data led us to conduct a single-arm phase Ib clinical trial (NCT04780568) that investigated osimertinib in combination with tegavivint, an inhibitor of β-catenin transcriptional activity. **Methods:** Patients with metastatic EGFR-mutated (exon 19 deletion or L858R) NSCLC who had not received prior treatment with an EGFR TKI were eligible. All participants received osimertinib 80mg daily and were enrolled to escalating dose levels of tegavivint, which was administered weekly IV for 16 weeks. The primary objectives were to assess the safety and tolerability of the combination and to determine the recommended phase 2 dose (RP2D) of tegavivint. Secondary objectives measured the objective response rate (ORR), median PFS, and OS. **Results:** Fifteen evaluable patients received treatment on the dose escalation portion of this study, including six patients at the highest dose level of tegavivint (8 mg/kg), which was determined to be the RP2D. No dose limiting toxicities nor drug-related serious adverse events occurred. The adverse events that were observed included hematologic, skin, and GI toxicities, consistent with the known osimertinib toxicity profile. Pharmacokinetic analysis showed a dose-dependent increase in the C_{max} and AUC of tegavivint, and plasma levels of osimertinib were comparable to those seen historically when administered as a single agent. The ORR was 73% with 2 of 15 patients (13%) achieving a complete response. Median PFS was 20.6 months (95% CI: 7-32 months). OS data is still maturing. **Conclusions:** NCT04780568 showed that the combination of osimertinib and tegavivint was safe and tolerable as first-line therapy in patients with metastatic EGFR-mutated NSCLC. This novel combination has the potential to improve the depth and durability of response to EGFR TKIs, without significantly increasing toxicity, by targeting drug-tolerant persistence. Clinical trial information: NCT04780568. Research Sponsor: V Foundation; The Ohio State University Comprehensive Cancer Center Internal Research Program.

8649 **Poster Session**

Five-year outcomes of osimertinib-based treatment in a phase III study comparing EGFR tyrosine kinase inhibitor (EGFR-TKI) monotherapy and EGFR-TKI with inserted cisplatin plus pemetrexed as a first-line treatment for advanced non-squamous non–small-cell lung cancer harboring *EGFR* mutation (JCOG1404/WJOG8214L). First Author: Shintaro Kanda, Shinshu Cancer Center, Shinshu University Hospital, Matsumoto, Japan

Background: JCOG1404/WJOG8214L was an open label, multicenter, randomized phase III study comparing EGFR-TKI monotherapy (gefitinib [Gef] or osimertinib [Osi]) and EGFR-TKI with inserted cisplatin plus pemetrexed as a first-line treatment for advanced non-squamous non–small-cell lung cancer harboring *EGFR* mutation (*EGFR*-NSqNSCLC). In the primary analysis, the insertion of platinum-doublet chemotherapy after the initial response to EGFR-TKI could improve progression-free survival (PFS), but not overall survival (OS) compared with EGFR-TKI monotherapy (Clin Cancer Res 2025;31:2317-26). This study was commenced using Gef in December 2015 and was switched to Osi in October 2018. 501 patients (pts) (308 in the Gef cohort, 193 in the Osi cohort) were enrolled to October 2020, but it resulted in later accrual and shorter follow-up for the Osi cohort at the time of the primary analysis (data cutoff November 2022; median follow-up of all randomized patients 36.0 months). Therefore, we conducted the five-year (5y) follow-up analysis of the Osi cohort. **Methods:** The key eligibility criteria were pts with advanced or recurrent *EGFR*-NSqNSCLC (exon 19 deletion or exon21 L858R), age 20 to 74 years, and PS 0 or 1. In the standard arm (SA), Gef or Osi was administrated until disease progression. In the experimental arm (EA), Gef or Osi was administered on days 1-56. Then, after a two-week drug-free period, three cycles of cisplatin and pemetrexed were administered on days 71, 92, and 113. Thereafter, Gef or Osi was reinitiated on day 134 and continued until disease progression. **Results:** From October 2018 to October 2020, 193 pts were enrolled in the Osi cohort (97 pts in SA and 96 pts in EA). Median follow-up was 64.8 months. Advanced stage and recurrent disease were 79% and 21%, female and male were 63% and 37%, exon 19 deletion and exon 21 L858R were 54% and 46%, PS 0 and 1 were 50% and 50%, $\geq$ 65 year and $<$ 65 year were 57% and 43%, central nerve metastasis (+) and (-) were 27% and 73%, respectively. Median OS were 54.0 months (95% confidence interval [CI] 44.4 to 66.0) in SA and 50.4 months (95% CI 43.2 to 69.6) in the EA (HR, 0.984; 95% CI, 0.684-1.415; p = 0.9279). 5y OS were 43.9% and 40.4%, respectively. Median PFS were 20.4 months (95% CI 14.4 to 28.8) in SA and 25.2 months (95% CI 18.0 to 33.6) in EA (HR, 0.902; 95% CI, 0.663-1.227; p = 0.5147). 5y PFS were 14.3% and 16.3%, respectively. **Conclusions:** The insertion of platinum-doublet chemotherapy after the initial response to Osi could not improve PFS and OS of pts with advanced *EGFR*-NSqNSCLC. On the other hand, JCOG1404/WJOG8214L demonstrated that Osi-based first-line treatment achieved 5y PFS in approximately 15% of this population, providing a benchmark for emerging Osi-based strategies. Clinical trial information: UMIN000020242. Research Sponsor: National Cancer Center Research and Development Funds; 26-A-4, 29-A-3, 2020-J-3, and 2023-J-03; Japan Agency for Medical Research and Development Grants; JP18ck0106221 and JP22ck0106492.

8650 **Poster Session**

Comprehensive profiling of EGFR PACC mutations and their co-mutation landscape in Chinese patients with non–small cell lung cancer: A large-scale NGS study of 2,360 cases. First Author: Yuan Jiang, Hunan Cancer Hospital, Changsha, China

Background: EGFR PACC (P-loop and αC-helix compressing) mutations represent a group of noncanonical alterations located in critical structural regions of the EGFR kinase domain and have recently been implicated in reduced sensitivity to EGFR TKIs and treatment resistance. However, the prevalence, mutational spectrum, and co-mutation landscape of EGFR PACC mutations in Chinese patients with non–small cell lung cancer (NSCLC) remain poorly characterized. This study aimed to systematically delineate the molecular features of EGFR PACC mutations to inform molecular testing strategies and clinical decision-making. **Methods:** A total of 2,360 patients with NSCLC were enrolled. All tumor samples underwent NGS covering 733 cancer-related genes. The overall prevalence of EGFR PACC mutations, the distribution of individual PACC variants, and their co-occurrence with other EGFR alterations and non-EGFR driver mutations were comprehensively analyzed. **Results:** Among the 2,360 NSCLC patients, 112 harbored EGFR PACC mutations, yielding an overall prevalence of 4.74%. EGFR PACC mutations exhibited marked site heterogeneity. The most frequent variants were S768I (18/112), G719A (15/112), G719S (12/112), and G719C (8/112), followed by C797S (6/112), E709A (6/112), E709V (5/112), and E709K (5/112). The remaining PACC variants—including I740_K745dup, R776H, S752_I759del, V774M, E709_T710delinsD, G779F, K757R, L747P, L718V, R776C, A647T, K757M, L718Q, T751_I759delinsN, V769L, and V769M—were low-frequency events, underscoring substantial molecular diversity. In total, 61 PACC-associated co-mutation events were identified. Co-mutation analysis revealed that classic EGFR-sensitizing mutations predominated, with L858R as the most common co-occurring alteration (n = 10), followed by exon 19 deletion E746_A750del (n = 4) and L861Q (n = 3). Notably, T790M (n = 2) co-occurred with C797S PACC mutations, suggesting a potential role of PACC variants in the evolution of EGFR-TKI resistance. Beyond EGFR-intrinsic co-mutations, cross-driver co-mutations were also observed, including ROS1 (V1002A, I1685L), MET (V145A), and NRG1 (V516M) (each n = 2), indicating that a subset of EGFR PACC–mutant tumors may harbor more complex oncogenic signaling. **Conclusions:** EGFR PACC mutations occur at a non-negligible frequency in Chinese patients with NSCLC and display pronounced site heterogeneity. These mutations frequently co-exist with classic EGFR-sensitizing or resistance-associated alterations and, in some cases, with additional non-EGFR driver mutations, highlighting their potential biological and clinical relevance. Our findings underscore the importance of comprehensive NGS-based profiling for accurate detection of EGFR PACC mutations and their co-mutation landscape, thereby supporting precision treatment strategies. Research Sponsor: None.

8651 **Poster Session**

Efficacy and safety analysis of furmonertinib in the treatment of *EGFR*-mutated lung adenocarcinoma: A single-center real-world study based on high-risk stratification. First Author: Aliya Aosiman, Xinjiang International Medical Center (Xinjiang International Hospital, Xinjiang Academy of Medical Sciences), Urumqi, China

Background: Real-world data on furmonertinib, a third-generation EGFR-TKI, for high-risk EGFR-mutant NSCLC patients (e.g., with brain metastasis, high tumor burden) are limited. This study evaluated its efficacy and safety via risk stratification. **Methods:** This retrospective study included 98 patients with locally advanced/metastatic EGFR-mutant NSCLC treated with furmonertinib (first-or later-line) from Sep 2021 to Dec 2024. Patients were stratified into high-risk (n = 73) and non-high-risk (n = 25) groups based on predefined criteria (brain/leptomeningeal metastases, high tumor burden, key co-mutations like TP53, or acquired T790M). Primary endpoint was investigator-assessed PFS. Secondary endpoints included ORR, DCR, iORR, iPFS, and OS. Safety assessed TRAEs (CTCAE v5.0). **Results:** Median follow-up was 17.7 months. In first-line group (n = 43), ORR was 69.8%, DCR 83.72%; in later-line group (n = 55), ORR was 64%, DCR 72.73%. PFS did not differ significantly between lines (P = 0.22). Median PFS was not reached overall. High-risk stratification analysis showed median PFS of 26.41 months in non-high-risk group vs not reached in high-risk group, with significant difference (P = 0.009). However, PFS rates showed a time-dependent effect: non-high-risk group had higher early PFS (96.0% vs 76.0% at 6 months), but high-risk group showed higher late PFS (98.6% vs 52.9% at 24 months). A time-dependent model confirmed high-risk features were detrimental early (HR = 33.03, P = 0.016) but protective after 6 months (interaction HR = 0.01, P = 0.001). In patients with measurable brain metastases (n = 39), iORR was 79.5%; median iPFS was not reached. TP53 co-mutation within high-risk group did not affect PFS (P = 0.731). TRAEs occurred in 15.3% (all grade 1-2, most common rash [5.1%] and diarrhea [4.1%]). Grade $\geq$3 events occurred in 6.1%, primarily elevated transaminases. No dose adjustments/discontinuations or fatal toxicities occurred. **Conclusions:** Furmonertinib showed durable efficacy in EGFR-mutant NSCLC, unaffected by line of therapy. Risk stratification had time-dependent prognostic value, with high-risk features transforming into a protective factor for PFS after 6 months. Furmonertinib demonstrated strong intracranial activity (iORR 79.5%). TP53 co-mutation did not confer additional prognostic value in the high-risk subgroup. Furmonertinib was well-tolerated with a favorable safety profile. Research Sponsor: Tianshan Talents Program for the Cultivation of High-Level Talents in Medical and Health Field; TSYC202301A068.

8652 Poster Session

Circulating tumor DNA dynamics following molecularly targeted therapy for non–small cell lung cancer. First Author: Justin Jee, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Biomarkers to guide treatment escalation following suboptimal response to molecular targeted therapy are urgently needed for patients (pts) with non-small cell lung cancer (NSCLC). Circulating tumor DNA (ctDNA) has shown promise for monitoring residual disease following definitive treatment, but ctDNA dynamics following targeted therapy response remain understudied. **Methods:** We examined a real-world, multi-institution cohort of pts with NSCLC undergoing personalized, tumor-informed ctDNA testing (Signatera, Natera, Inc.) and clinical annotations from a deidentified commercial claims dataset (Forian's Hybrid data ecosystem, CHRONOS). Longitudinal ctDNA results were evaluated before and after targeted therapy initiation and summarized by treatment line, clinical context, and demographic and clinicopathologic features as available. **Results:** We identified 839 pts (14.0%, 11.1%, 19.4%, and 55.5% with stages I, II, III, and IV) across 395 US institutions, who had ctDNA profiling and were treated with molecularly targeted agents. Median age was 71 years (range 25-93), 67.0% were female, and 85.3% had tumors with adenocarcinoma histology. Pts underwent a median of 4 ctDNA tests/pt (range: 1–58) over a median follow-up of 9 months (range: 0-75). Amongst ctDNA positive tests (n=1705 tests for 408 pts), median ctDNA levels were 1.20 mean tumor molecules/mL (range 0.01–36,599). Pts received osimertinib (58.5%), alectinib (10.7%), sotorasib (5.6%), adagrasib (3.7%), afatinib (3.7%), and capmatinib (3.0%). ctDNA tests prior to targeted therapy (baseline) were available for 336 patients, of which 49.7% (167/336) had detectable ctDNA ("ctDNA(+)"). Among these ctDNA(+) cases, 123 pts had longitudinal ctDNA assessment. ctDNA clearance observed in 38.2% (47/123); 52.1% (25/48) in stage I-III and 29.3% (22/75) in stage IV. Among the 169 pts with baseline ctDNA(-), 115 pts had ctDNA assessed longitudinally. Of these, 89.6% (103/115) remained serially negative, while 10.4% (12/115) had any time ctDNA(+). Among commonly used targeted therapies, ctDNA clearance was observed across multiple agents, and is summarized in table 1. We further analyzed associations between ctDNA dynamics, during different treatment lines, and clinical outcomes. **Conclusions:** In a multi-institution cohort, ctDNA clearance was observed in pts with NSCLC treated with molecularly targeted therapies. Clearance rates varied by treatment type. The use of ctDNA monitoring to guide treatment escalation in this population warrants further study. Research Sponsor: None.

Targeted Therapy	Pts with ctDNA available pre and post-therapy N	Pts with baseline ctDNA(+) N	Pts with ctDNA clearance N (%)
osimertinib	128	54	26 (48.1)
alectinib	22	7	3 (42.9)
sotorasib	15	14	4 (28.6)
adagrasib	12	10	2 (20.0)

Includes only therapies with more than 10 pts who had pre- and post-treatment ctDNA availability.

8653 Poster Session

Molecular and immune profiling of *BRAF*-mutated (*BRAF*^{MUT}) non-small cell lung cancer (NSCLC). First Author: Roupen Odabashian, Department of Hematology and Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI

Background: *BRAF*^{MUT} occur in 6-7% of NSCLC and comprise of biologically distinct classes showing variable therapeutic responses. While Class 1 benefits from targeted therapy, molecular and immune determinants distinguishing *BRAF* classes remain incompletely characterized. We performed comprehensive profiling to identify class-specific biomarkers. **Methods:** 51,692 (BRAF wild-type [*BRAF*^{WT}]: n=48,288; *BRAF*^{MUT}: n=3404) NSCLC specimens underwent DNA (592-gene panel/whole-exome) and/or RNA (whole-transcriptome) sequencing at Caris Life Sciences. *BRAF*^{MUT} tumors were classified into 3 Classes, other pathogenic variants (O^{PV}), and unknown/unclassified variants (VUS). The tumor microenvironment (TME) was estimated using the QuanTIseq method. Overall survival (OS) and IO-associated survival (IO-OS) were derived from insurance claims and calculated from the date of tumor biopsy (OS) or IO initiation (IO-OS) to last contact using Kaplan-Meier estimates. Statistical significance was determined by Fisher's Exact, chi-square, and Mann-Whitney U test with adjustments for multiple comparisons ($P<0.05$). **Results:** Class 1 was significantly enriched for SETD2 mutations (mut) and more frequently PDL1+ (22c3, TPS>=1) while showing a lower prevalence of TMB-high (>=10 mut/Mb), TP53, STK11 and KEAP1 mut (Table). Class 2/3 tumors were moderately PDL1+ and TMB-high and enriched for STK11 and KEAP1 muts (Table). While both OPV and VUS were enriched for TMB-high and not PDL1, OPV was enriched in STK11, and VUS was enriched in TP53 mut (Table). Among BRAFMUT, Class 1 exhibited the highest infiltration of M1 macrophages (1.1-1.3-fold), neutrophils (1.2-1.3-fold) and the lowest infiltration of dendritic cells (0.4-0.8-fold). Class 2 and 3 had largely overlapping immune profiles. In metastatic NSCLC, only Class 1 and VUS demonstrated improved OS and IO-OS (vs BRAFWT, both $p<0.05$, Table). OPV had the poorest outcomes, exhibiting the shortest OS and shorter IO-OS relative to Class 1 and Class 2 (all $p<0.05$, Table). **Conclusions:** *BRAF*^{MUT} classes represent distinct molecular, immune and clinical phenotypes. Improved OS and IO-OS in Class 1 and VUS (vs WT) appears to arise from divergent molecular and immune interactions. These findings underscore the importance of evaluating of *BRAF*^{MUT} NSCLC beyond class 1-3, suggesting the expanded classification may have therapeutic and prognostic consequences. Research Sponsor: None.

Molecular features (odds ratio) and survival outcomes (median months [95% CI]) among *BRAF*^{MUT} classes.

Genes	Class 1 (n=695)	Class 2 (n=741)	Class 3 (n=701)	O^{PV} (n=123)	VUS (n=936)	WT
SETD2	21.5^{s}	1.2	1.0	0.6	1.4	0.2^{s}
TP53	0.4^{s}	1.0	1.0	0.8	1.6^{s}	1.1^{s}
STK11	0.1^{s}	1.7^{s}	2.3^{s}	2.1^{s}	0.8	0.9^{s}
KEAP1	0.1^{s}	1.5^{s}	1.7^{s}	1.5	1.1	1
TMB-high	0.3^{s}	1.8^{s}	2.3^{s}	2.3^{s}	3.3^{s}	0.6^{s}
PDL1+	3.4^{s}	1.3^{s}	1.1	0.9	1.0	0.7^{s}
med OS	18(14-21)	14(12-18)	13(11-16)	8(4-11)	16(12-20)	12(12-12)
med IO-OS	27(19-40)	20(15-24)	18(12-24)	8(2-15)	24(19-32)	17(17-18)

$P<0.05$ denoted by ^{s}.

8655 Poster Session

Correlation of CT changes, PET response, and histopathologic tumor regression in treated advanced *EGFR*-mutant NSCLC before disease progression. First Author: Pei Hsing Chen, Division of Thoracic Surgery, Department of Surgery, College of Medicine, National Taiwan University Hospital and National Taiwan University, Taipei City, Taiwan

Background: Previous studies have examined the correlation between radiologic and pathologic responses using PET, CT, and histopathologic regression in patients receiving chemotherapy or immunotherapy. However, data on the relationship among these modalities after EGFR-TKI treatment remain limited, particularly in the context of emerging induction EGFR-TKI strategies. **Methods:** We conducted a two-arm, phase II clinical trial (PTR-1) enrolling patients with advanced EGFR-mutant NSCLC. After 12 weeks of EGFR-TKI therapy, participants were randomized (1:1) to either continue TKI treatment or undergo primary tumor resection. Surgery aimed to achieve locoregional control with negative margins, and lymph node dissection was not mandatory. All resected specimens were evaluated for pathologic response according to IASLC recommendations. Radiologic response was assessed by RECIST 1.1, and major pathologic response (MPR) and PET metabolic response were evaluated. **Results:** A total of 91 patients were enrolled, with 72 randomized into two treatment arms; 2 patients declined surgery. The median interval from treatment initiation to surgery was 3.7 months, and 18% of patients underwent resection beyond 4.5 months. Among the 34 resected cases, MPR was achieved in 29.4% (10/34) and pathologic complete response (pCR) in 5.9% (2/34). Patients harboring EGFR exon 19 deletions demonstrated higher rates of pathologic response than those with L858R mutations. The correlation between CT-based tumor regression and histopathologic response was weak (r = 0.30). Pathologic response rates were 24.5% in patients with partial response (PR) and 43.8% in those with stable disease (SD) by RECIST. The correlation coefficients between PR or SD status of the primary tumor and pathologic response were 0.15 and −0.29, respectively. Complete metabolic resolution on FDG-PET corresponded to MPR in 66% of cases. A preoperative SUVmax $<$ 2.5 was associated with a mean pathology residual viable tumor of 20.7% and a 42.8% MPR rate, while patients with $\geq$90% regression in PET signal achieved MPR in 66.6% of cases. **Conclusions:** CT-based tumor regression modestly reflects histopathologic response after EGFR-TKI induction but with poor correlation, particularly in radiologic SD cases. This represents the first trial-based dataset analyzing imaging–pathology correspondence in advanced EGFR-mutant NSCLC prior to disease progression. PET metabolic response demonstrated relatively better discrimination of major pathologic responders, though its predictive accuracy remains limited. These findings underscore the need for refined imaging biomarkers or other NGS data to identify optimal candidates for local consolidation therapy in late stage and future neoadjuvant setting in early stage strategies in EGFR-mutant NSCLC. Clinical trial information: NCT05215548. Research Sponsor: None.

8657 Poster Session

Efbemalenograstim alfa for prophylaxis in non–small cell lung cancer patients patients with chemotherapy-induced febrile neutropenia: A randomized, multicenter, exploratory clinical trial. First Author: Mengjie Li, Tianjin Medical University Cancer Institute and Hospital, Tianjin, Tianjin, China

Background: Neutropenia is a common dose-limiting chemotherapy toxicity, with its severity and duration impairing therapeutic efficacy. In NSCLC management, chemotherapy regimens with high risk febrile neutropenia (FN) are relatively uncommon. However, real-world data show suboptimal prophylactic granulocyte colony-stimulating factor (G-CSF) use in intermediate risk FN patients with additional risk factors. This study evaluated efbemalenograstim alfa's efficacy and safety in maintaining absolute neutrophil count (ANC) during chemotherapy cycles in such NSCLC patients. **Methods:** This was a randomized, multicenter, exploratory clinical trial (NCT06143735) enrolling NSCLC patients receiving intermediate risk FN chemotherapy with additional risk factors. Eligible patients were randomized 2:1 into two groups: primary prophylaxis group (Group A) received subcutaneous efbemalenograstim alfa (20 mg) 48$\pm$4 h post-each chemo cycle starting from Cycle 1; secondary prophylaxis group (Group B) initiated treatment only upon grade $\geq$3 neutropenia (per CTCAE v5.0) in the prior cycle. All patients completed at least four cycles of platinum-based chemotherapy. The primary endpoint was the incidence of grade $\geq$3 neutropenia in Cycle 1 between the two strategies. Secondary endpoints included FN incidence, grade $\geq$3 neutropenia in subsequent cycles, and the occurrence of adverse events (AEs) or serious adverse events (SAEs). **Results:** As of Dec 31, 2025, 99 patients were enrolled; 93 (median age: 69 years; 61.3% with ECOG 0–1; 90.3% male) received $\geq$1 platinum-based chemo cycle; 83 received $\geq$1 efbemalenograstim alfa dose. Specifically, 61 patients were assigned to Group A and 32 to Group B (n = 93). In the first treatment cycle, the incidence of grade $\geq$3 neutropenia was 19.7% (12/61) in Group A vs. 50.0% (16/32) in Group B, representing a relative risk reduction (RRR) of 60.6% (absolute risk reduction: 30.3%; p = 0.002). Across all treatment cycles, the cycle-specific cumulative incidence of grade $\geq$3 neutropenia was 16.2% (32/198) in Group A vs. 25.6% (32/125) in Group B (p = 0.0382). FN occurred in 2 patients in both groups. Regarding safety, the most common adverse events (AEs) were hematological toxicities in both groups, with a numerically lower incidence of anemia, leukopenia, neutropenia, and thrombocytopenia in Group A than in Group B. Grade $\geq$3 AEs (52.5% vs. 43.8%, p = 0.514) and efbemalenograstim alfa-related treatment-emergent adverse events (TRAEs, 31.1% vs. 22.7%, p = 0.587) did not differ significantly. Pain-related TRAEs (mainly ankle pain and neuropathic pain) were reported in only 6 patients (7.2%) overall, with most being grade 1–2 per CTCAE v5.0 criteria. **Conclusions:** Efbemalenograstim alfa effectively reduces the incidence of chemotherapy-induced neutropenia and presents a favorable safety profile. Clinical trial information: NCT06143735. Research Sponsor: None.

8658 **Poster Session**

Genomic clonality analysis of patients with metastatic lung-limited non–small cell lung carcinoma (NSCLC) who underwent double lung transplantation (DLT) across timepoints and tumor region. First Author: Sang Hwa Kim, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Double lung transplantation (DLT) registry aimed for lung-limited malignancies (DREAM) study (NCT05671887) cohort A evaluates DLT as a therapeutic strategy for patients with advanced bilateral lung-limited NSCLC. This is the first translational report of the genomic clonality analysis of the DREAM study across timepoints and tumor regions. **Methods:** Patients with advanced bilateral lung-limited NSCLC who underwent DLT at Northwestern Memorial Hospital between September 2021 and December 2025 were included in the DREAM study cohort A. Patients with extrapulmonary disease were excluded. The primary indications for DLT were disease refractory to systemic therapies, with or without respiratory failure. Tissue next generation sequencing (tNGS) data was collected from diagnosis, bilateral explant and recurrence samples. Commercial tNGS panels utilized include Altera, Caris, Foundation Medicine, Tempus xT, and PGDx. Truncal genetic mutations were identified from genes that were common to all tNGS panels. **Results:** Among 18 patients enrolled in DREAM study cohort A, 11 patients with bilateral tissue NGS were analyzed. The median age was 55.5 years (range 37-74), 9 (81%) were female, and 5 (45%) had a history of smoking. 6 patients (54%) had invasive mucinous adenocarcinoma histology. All 11 patients harbored common gene mutations in bilateral tumors and had common oncogenic genomic clones indicating a truncal mutation. Details are outlined in Table 1. **Conclusions:** All patients harbored common oncogenic driver mutations across all available specimens, providing definitive genomic evidence of a monoclonal origin. These findings not only distinguish intrapulmonary metastasis from multiple primary tumors but also support a common ancestral tumor clone that has progressed over time and space. Further characterization of tumor evolution in advanced bilateral lung-limited NSCLC is warranted. Clinical trial information: NCT05671887. Research Sponsor: None.

Case	Tissue NGS by timepoints and region (Dx/Explant/Recur)	Shared variants
1	RML / Bilateral Exp / RUL	*PIK3CA E110del, *SETD2 D2112fs, GRM3 R331C
2	LUL / Bilateral Exp / Pelvic bone	*EGFR G719A
3	LLL / Bilateral Exp / T9 vertebra	*KRAS G12D
4	Bilateral Exp / Pelvic bone	*ETV6 splice, KMT2D L1443Q
5	Bilateral Exp	*KRAS G12V, STK11 (*A200fs, *314fs)
6	LUL / Bilateral Exp	*BAP1 Q595*, *GNAS R201C
7	Bilateral Exp	*EGFR Ex19del
8	Bilateral Exp / LLL	*KRAS G12V
9	Bilateral Exp	EGFR (*Ex19del, C797S), LRP1B R531H, PTPRT I320N, SF3B1 A368V

Additional Cases:
Case 10 (Bilateral Exp): *KRAS G12C, *ARID1A Q507*, *ATM c.1A>T, *ATRX W1572*, *STK11 W332*, CHD2, MALT1, PHLPP1, PTPRT, RICTOR, SEMA3C, TAF1 (W457L, D169Y).
Case 11 (RLL, Bilateral Exp): *MET Ex14 skip, *TP53 V143M, ERBB3, NF2.
Asterisk (*) indicates oncogenic/likely oncogenic variants defined by *OncoKB*.
Abbrev: Dx, diagnosis; Exp, explant; Recur, recurrence.

TPS8660 **Poster Session**

SigVie-003: Phase 3 trial of frontline sigvotatug vedotin plus pembrolizumab vs pembrolizumab alone in non-small cell lung cancer (NSCLC) with PD-L1 TPS ≥50%. First Author: Martin Reck, Airway Research Center North, Center for Lung Research, LungenClinic, Grosshansdorf, Germany

Background: Integrin beta-6 (IB6) is a tumor-associated membrane protein linked to poor outcomes in solid tumors, including NSCLC, where it is expressed in >90% of cases. Sigvotatug vedotin (SV), a novel, IB6-directed, vedotin-based, antibody-drug conjugate, has shown manageable safety and encouraging antitumor activity as monotherapy in advanced NSCLC in the phase 1 SGNB6A-001 study (Peters, ASCO 2024). Based on preclinical studies, SV may induce immunogenic cell death and enhance antitumor activity when used in conjunction with pembrolizumab, a PD-1 inhibitor. Therefore, SV plus pembrolizumab is also being evaluated in the SGNB6A-001 study. Initial results of the combination demonstrated promising antitumor activity with a manageable safety profile in advanced NSCLC (Sehgal, ASCO 2025). Based on these results, SV plus pembrolizumab is being investigated in the phase 3 SigVie-003 study. **Methods:** SigVie-003 (NCT06758401) is an open-label, randomized, controlled study evaluating the efficacy of SV plus pembrolizumab vs pembrolizumab monotherapy as first-line treatment in adults with locally advanced, unresectable, or metastatic NSCLC with high PD-L1 expression (tumor proportion score ≥50%). Patients (pts) with nonsquamous histology must have negative documentation for *EGFR*, *ALK*, and *ROS1* mutations and no known actionable genomic alterations with approved first-line treatments per local standard of care. Pts must have an ECOG PS of 0 or 1 and have adequate organ function. Pts with stable, definitively treated, or inactive brain metastases <0.5 cm are eligible. Approximately 714 pts will be randomized at a 1:1 ratio to receive either SV 1.8 mg/kg AiBW (adjusted ideal body weight) intravenously on days 1, 15, and 29 plus pembrolizumab 400 mg intravenously on day 1 of a 42-day cycle (Q6W) or pembrolizumab 400 mg monotherapy Q6W. Randomization will be stratified by histology (nonsquamous vs squamous), ECOG PS (0 vs 1), region (East Asia vs rest of world), and presence or absence of brain metastases. Dual primary endpoints are overall survival and progression-free survival (PFS) by blinded independent central review (BICR) per RECIST 1.1. Secondary endpoints include PFS by investigator per RECIST 1.1, confirmed objective response rate and duration of response by both BICR and investigator per RECIST 1.1, safety, and pharmacokinetics and immunogenicity of SV when combined with pembrolizumab. Enrollment began Jul 23, 2025. A genAI tool (2/27/25; Pfizer; GPT-4o) developed the 1st draft; authors assume content responsibility. Frontline sigvotatug vedotin plus pembrolizumab vs pembrolizumab for non-small cell lung cancer with PD-L1 tumor proportion score ≥50%: phase III study design, Reck M, et al., *Future Oncol*, Dec 13, 2025, Taylor & Francis, reprinted by permission of the publisher Informa UK Limited trading as Taylor & Francis Ltd. Clinical trial information: NCT06758401. Research Sponsor: Pfizer.

TPS8661 **Poster Session**

AndroMETa-Lung-713: A phase 2/3 study of telisotuzumab adizutecan (ABBV-400, Temab-A) vs standard of care (SOC) in patients with epidermal growth factor receptor (*EGFR*)–mutated non–small cell lung cancer (NSCLC). First Author: Adam Rock, Department of Medical Oncology, City of Hope Comprehensive Cancer Center, Duarte, CA

Background: Patients with advanced *EGFR*-mutated NSCLC routinely receive third-generation EGFR TKIs in first-line therapy, such as osimertinib or lazertinib, either as monotherapy or in combination with other agents. Following progression, available options primarily include platinum-doublet chemotherapy or amivantamab + chemotherapy, with country-specific approvals for additional agents including antibody-drug conjugates (ADCs). *MET* gene amplification and c-Met protein (also known as MET protein) overexpression are established mechanisms of acquired resistance to osimertinib. Temab-A is a c-Met–directed ADC composed of the telisotuzumab antibody linked to a potent topoisomerase 1 inhibitor payload and is designed to selectively target c-Met–expressing tumors. In the first-in-human study (NCT05029882), Temab-A demonstrated manageable safety and encouraging efficacy in heavily pretreated *EGFR*-mutated NSCLC (confirmed objective response rate [ORR] 63%; median duration of response 9.8 months; median progression-free survival [PFS] 10.9 months) (Camidge. JCO 2025;43: abstract 8512). **Methods:** AndroMETa-Lung-713 (NCT07155187) is a global, open-label, randomized phase 2/3 study enrolling adults with locally advanced or metastatic non-squamous *EGFR*-mutated NSCLC after progression on 1 prior third-generation EGFR TKI administered in the adjuvant, locally advanced, or metastatic setting, as monotherapy or in combination with other agents. Key eligibility criteria include ECOG PS 0–1, measurable disease per RECIST v1.1, exon 19 deletion or exon 21 L858R mutation, and provision of tumor tissue for c-Met protein immunohistochemistry. In phase 2, approximately 80 patients will be randomized 1:1 to Temab-A dose 1 or dose 2 IV every 3 weeks (Q3W) to select the recommended phase 3 dose (RP3D) on the basis of safety, efficacy, pharmacokinetics (PK), and available biomarker data. In phase 3, approximately 350 patients will be randomized 1:1 to Temab-A RP3D or investigator's-choice SOC (platinum-doublet chemotherapy or amivantamab + chemotherapy). Treatment continues until disease progression, intolerable toxicity, or other protocol-defined discontinuation criteria are met. The primary endpoints are ORR in phase 2 and PFS in phase 3, assessed by blinded independent central review. Tumor assessments are performed Q6W for 2 years, then Q12W. Assessment of PK, immunogenicity, and exploratory biomarker analyses, including c-Met protein expression levels and ctDNA dynamics, will be conducted. Clinical trial information: NCT07155187. Research Sponsor: None.

TPS8662 **Poster Session**

Petosemtamab plus pembrolizumab as first-line (1L) treatment of PD-L1 high metastatic non-small cell lung cancer (NSCLC): Global phase 2 trial. First Author: Paul K. Paik, Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: NSCLC has a heterogeneous biology frequently including high mutational burden, high EGFR expression and upregulated EGFR signaling that is associated with poor prognosis. In the first-line metastatic setting, combination regimens pairing platinum-based chemotherapy with immune checkpoint blockade are standard of care; however, most patients experience disease progression within the first year. Petosemtamab is a low-fucose human common light chain, IgG1 bispecific antibody targeting EGFR and leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5). Petosemtamab mechanism of action includes inhibition of EGFR ligand binding and downstream signaling, degradation of EGFR via LGR5 internalization in EGFR/LGR5-expressing cells, and immune system activation via enhanced ADCC (Herpers et al. Nat Cancer 2022; Lundberg et al. Cancers 2025). Petosemtamab plus pembrolizumab has previously demonstrated clinically meaningful efficacy and a manageable safety profile in 1L PD-L1-positive recurrent/metastatic head and neck squamous cell carcinoma (van Herpen et al. ASCO 2025). **Methods:** MCLA-158-CL04 (NCT07353957) is an open-label, multicenter, phase 2 trial to investigate petosemtamab in combination with pembrolizumab in squamous (Sq) and non-SqNSCLC. Two cohorts will be evaluated in patients with PD-L1 high (TPS ≥50%) metastatic sqNSCLC and non-sqNSCLC, respectively, with no prior systemic treatment for metastatic disease. Patients will be treated with petosemtamab 1500 mg IV Q2W in combination with pembrolizumab 400 mg IV Q6W. The primary objective is investigator-assessed objective response rate. Enrollment of approximately 80 patients in North America, EU, and Asia-Pacific is planned. Clinical trial information: NCT07353957. Research Sponsor: Merus.

TPS8663 **Poster Session**

Telisotuzumab adizutecan (Temab-A) plus osimertinib (osi) as 1L treatment for unresectable/metastatic NSCLC. First Author: Yasushi Goto, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Most patients (pts) with EGFR-mutated (Mut) NSCLC and 1L osi treatment will eventually develop resistance. Although 1L combination strategies (osi+chemo or amivantamab+lazertinib) show potential long-term benefits, associated toxicities can impact quality of life. Temab-A, an antibody-drug conjugate with a topoisomerase 1 inhibitor payload, targets c-Met protein. *MET* gene amplification and c-Met protein expression are associated with poor survival outcomes in NSCLC. A Ph1 study of Temab-A in pts with refractory EGFR Mut NSCLC reported encouraging activity and a manageable safety profile (NCT05029882). Herein, we describe a Ph2/3 study of Temab-A+osi as 1L in pts with previously untreated, locally advanced or metastatic NSCLC harboring common EGFR Mut. **Methods:** Planned enrollment is ~194 pts in Ph2 and ~500 in Ph3 across ~200 sites in 22 countries. Adults (≥18 years) must have histologically/cytologically confirmed metastatic/locally advanced nonsquamous NSCLC with documented EGFR Mut and measurable disease by RECISTv1.1. Pts with prior EGFR tyrosine kinase inhibitor treatment in the metastatic setting are excluded. During dose escalation (Ph2), pts will receive Temab-A (1.6 or 2.4mg/kg) every 3 weeks (Q3W, 1 cycle) intravenously (IV) + 80mg osi daily. During dose expansion (Ph2), after 1 cycle of osi, pts will be randomized to receive Temab-A (1.6, 2.0, or 2.4mg/kg) Q3W IV + 80mg osi daily, or osi monotherapy, and stratified based on c-Met expression levels and history of CNS involvement. Ph2 primary objectives are safety/tolerability, efficacy as measured by objective response rate of Temab-A+osi, and determination of the recommended Ph3 dose (RP3D). Ph2 primary efficacy endpoint is objective response based on blinded independent central review assessment per RECIST v1.1. In Ph3, randomized pts will receive Temab-A+osi at RP3D or standard of care. Additional details for Ph3 will be confirmed after completion of Ph2. Clinical trial information: NCT05029882. Research Sponsor: None.

TPS8664 **Poster Session**

Combination of tulmimetostat and PD-1 blockade for patients with advanced non–small cell lung cancer who progressed from first or second line of treatments. First Author: Daniel Sanghoon Shin, Division of Hematology/Oncology, Veterans Affairs (VA) Greater Los Angeles Healthcare System, Houston, TX

Background: Immune checkpoint inhibitors (ICIs) have transformed advanced non–small cell lung cancer (NSCLC) treatment, yet many patients exhibit primary ICI resistance or progression after initial response. Epigenetic dysregulation, including aberrant EZH2-mediated trimethylation of histone H3 (H3K27me3), has been implicated in tumor immune evasion and reduced responsiveness to ICIs. Preclinical studies suggest that EZH2 inhibition may enhance antitumor immunity and potentiate PD-1 blockade. Tulmimetostat, a potent dual EZH2/EZH1 inhibitor, demonstrates favorable tolerability and antitumor activity across multiple solid tumors. We hypothesize that the addition of tulmimetostat to pembrolizumab may reverse the resistance to pembrolizumab in patients with ICI-refractory NSCLC. **Methods:** The primary objective of this open-label, single-arm, phase Ib/II study is to evaluate the safety, tolerability, and preliminary efficacy of combining tulmimetostat with pembrolizumab in Veterans with advanced NSCLC who have progressed after first- or second-line therapy, one of which must have included ICI. Key eligibility criteria include measurable disease per RECIST v1.1 and provision of adequate tumor tissue (archive or new). Tulmimetostat (200 mg or 300 mg) is administered orally once daily, beginning with a 7-day run-in period during cycle 1, followed by pembrolizumab 200 mg IV every 3 weeks. Treatment continues until confirmed disease progression, unacceptable toxicity, or withdrawal. Safety assessments include clinical exams, laboratory evaluations, ECGs, and CTCAE v5.0 grading of adverse events. Imaging is performed at baseline and every 9 weeks. Secondary endpoints include disease control rate, progression-free survival, and duration of response. Up to 18 patients will be enrolled in Phase Ib using a BOIN method to determine the dose-limiting toxicities (DLTs) and the recommended phase II dose (RP2D) of tulmimetostat. Phase II is a Simon optimal two-stage design to assess objective response rate (ORR) per RECIST v1.1. Subjects treated at the RP2D during phase Ib will be included in the efficacy analysis. In total, up to 66 patients will be enrolled across multiple VA sites. Optional on-treatment biopsies will be obtained at select timepoints. Biomarker analyses will include an assessment of H3K27me3 (Methyl Mark) and PD-L1 expression in tumor biopsy samples to explore epigenetic and immunologic correlates of treatment response. Correlative biomarker analyses, including H3K27me3 and PD-L1 expression in tumor biopsies, will offer insight into epigenetic and immunologic determinants of treatment response. Findings from this trial may support the development of a novel therapeutic approach for patients with NSCLC who have progressed after on standard immunotherapy or chemo-immunotherapy. Enrollment was initiated in January 2026. Clinical trial information: NCT05467748. Research Sponsor: VA ORD; CX002499-01.

TPS8665 **Poster Session**

Phase 2b randomized, blinded, placebo-controlled trial to investigate the efficacy and safety of visugromab added to pembrolizumab, pemetrexed, and carboplatin in first-line metastatic non-squamous NSCLC: GDFATHER-NSCLC-01. First Author: Martin Reck, Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany

Background: Immune checkpoint inhibitors (ICIs) have improved outcomes in NSCLC, yet primary and secondary resistance remain common, limiting durable benefit. Growth differentiation factor 15 (GDF-15) has been implicated in ICI resistance. Clinical data for the anti–GDF-15 antibody visugromab in combination with nivolumab have been presented, demonstrating reinvigoration with deep and durable responses in relapsed/refractory solid tumors and increased efficacy in an ICI-naïve neoadjuvant setting, strongly supporting further evaluation in ICI-naïve NSCLC. This trial estimates the added clinical activity and safety of visugromab with standard chemo-immunotherapy and addresses primary immune resistance in first-line metastatic non-squamous NSCLC. **Methods:** GDFATHER-NSCLC-01 is a phase 2b, multicenter trial with an initial safety-run-in (SRI) followed by a randomized, double-blind, placebo-controlled part, conducted at >40 sites in seven countries across the US and Europe. The SRI employs a 3+3 dose escalation (two predefined visugromab dose levels; DLT window of 21 days) to determine the recommended dose for expansion; an independent data monitoring committee oversees escalation and the selection of the expansion dose. In the randomized part, participants with untreated metastatic non-squamous NSCLC (no actionable driver mutations), ECOG 0–1, are assigned 2:1 to receive visugromab or placebo in combination with pembrolizumab, pemetrexed, and carboplatin (21-day cycles). Brain metastases are allowed if untreated, asymptomatic and clinically stable, or if previously treated and stable per protocol. Patients are stratified according to PD-L1 tumor proportion score (<1% vs 1–49% vs ≥50%). The primary endpoint of the trial is objective response rate (RECIST v1.1). Key secondary endpoints include duration of response, progression-free survival, overall survival, safety, pharmacokinetics, and patient-reported outcomes; exploratory biomarker analyses are planned. The randomized part is not powered for statistical significance; the planned sample size is 90 participants, enabling descriptive estimation of effect sizes to inform future pivotal development. Enrollment status: The SRI has been completed. The randomized part is open to accrual; first patient pending. Clinical trial information: NCT07098988. Research Sponsor: CatalYm GmbH.

TPS8666 **Poster Session**

FUEL-IT Lung: Fasting to unleash and enhance lung cancer immunotherapy—A VA Lung Precision Oncology Program trial. First Author: Razan Aljaras, Indiana University School of Medicine, Indianapolis, IN

Background: Single-agent PD-(L)1 inhibitors are standard first-line therapy for advanced non-small cell lung cancer (NSCLC) with PD-L1 expression ≥50%, yielding objective response rates of approximately 45% and median overall survival of 20-26 months. However, immune-related adverse events (irAEs) occur in up to 20% of patients. Fasting-mimicking diets (FMD) induce metabolic reprogramming by reducing insulin-like growth factor 1 (IGF-1) and glucose while increasing IGF-binding protein 1. Preclinical data demonstrate that FMD enhances anti-tumor immunity by increasing T-cell mediated tumor cytotoxicity, reducing myeloid-derived suppressor cells, and suppressing T-regulatory cell function. Recent murine models show that FMD combined with anti-PD-L1 therapy prevents or reverses immune-mediated myocardial infiltration, reduces systemic inflammation, and is more effective than anti-PD-L1 alone in delaying tumor growth while reshaping the tumor microenvironment. Our prior feasibility study (IUSCCC-0662) in 10 advanced lung cancer patients demonstrated 80% compliance with FMD, with minimal toxicities. These findings suggest FMD may enhance checkpoint inhibitor efficacy while potentially reducing irAEs. **Methods:** This is an open-label, randomized pilot study evaluating the feasibility and safety of FMD combined with pembrolizumab in Veterans with newly diagnosed stage IV NSCLC and PD-L1 expression ≥50%. Eligible patients must have ECOG performance status 0-2 and adequate organ function. Patients receive pembrolizumab 200 mg IV every 3 weeks. The study employs a partial crossover design: Arm 1 receives regular diet with pembrolizumab for cycles 1-3, then crosses over to FMD with pembrolizumab for cycles 4-6; Arm 2 receives FMD with pembrolizumab for cycles 1-3, followed by regular diet thereafter. FMD consists of a 4-day cycle with calorie restriction (fats:carbs:protein ratio of 50:40:10) administered starting on the day of pembrolizumab infusion, followed by transitional diet on day 5, for 3 consecutive cycles. Primary endpoints include feasibility (proportion completing 3 FMD cycles, target ≥70%) and safety. Secondary endpoints include immune-mediated toxicity rates, objective response rate, disease control rate, and 12-month progression-free survival. Exploratory objectives assess FMD impact on metabolic markers (glucose, ketones, IGF-1, IGFBP-1), immune cell populations, body composition via CT imaging, physical function (Short Physical Performance Battery), and quality of life (FACT-L, EORTC QLQ-C30). Enrollment of 33 patients per arm is planned for total of 66 patients. Accrual began in October 2025. Clinical trial information: NCT06671613, Funded by VA ORD. Research Sponsor: This work is supported by a VA Merit, from the VA Clinical Science Research & Development Program.

TPS8667 **Poster Session**

Phase III study of multidisciplinary therapy combining local ablative therapy with immune-checkpoint inhibitors for patients with synchronous oligometastatic NSCLC (J-OLIGO: WJOG20924L). First Author: Taichi Miyawaki, Department of Respiratory Medicine, Juntendo University Hospital, Tokyo, Japan

Background: The standard of care for stage IV non-small cell lung cancer (NSCLC) patients without actionable driver mutations is immune-checkpoint inhibitors (ICIs) with or without platinum-based chemotherapy. For patients with synchronous oligometastatic disease, local ablative therapy (LAT) to all lesions, including primary sites, may improve survival based on several randomized phase II trials. Furthermore, combining LAT with ICIs may enhance anti-tumor immune responses by reducing tumor burden. However, a recent large phase II/III study failed to demonstrate a survival benefit for adding LAT to systemic therapy in patients with synchronous or induced oligometastatic NSCLC. Consequently, it remains unclear whether LAT provides a survival benefit in synchronous oligometastatic NSCLC. Based on the promising results from our preceding phase II trial (TRAP-OLIGO; WJOG11118L), we initiated this phase III trial to definitively evaluate the benefit of adding LAT to pembrolizumab plus platinum-based chemotherapy specifically for synchronous oligometastatic NSCLC. **Methods:** J-OLIGO is a multicenter, open-label, randomized phase III intergroup trial. Eligible patients have untreated stage IV NSCLC, ECOG PS 0-1, 1–3 metastases, and no actionable driver mutations. During the induction phase, patients receive 4 cycles of pembrolizumab plus platinum-based chemotherapy. Patients who achieve disease control with induction therapy and remain eligible for LAT to all residual lesions are randomized (1:1) to either the LAT group (Intervention) or the standard group (Control). The feasibility and appropriateness of LAT for each patient are evaluated by a multidisciplinary tumor board, consisting of medical oncologists, radiation oncologists, and thoracic surgeons, to ensure definitive treatment of all viable lesions. The LAT group receives definitive surgery and/or definitive radiotherapy to all sites, followed by maintenance pembrolizumab (±pemetrexed). Stratification factors include number of metastases, PD-L1 TPS, histology, and induction response. The primary endpoint is overall survival (OS), defined as the time from randomization. Secondary endpoints include progression-free survival (PFS), objective response rate (ORR), and the safety. Based on results from previous studies, the study has 80% power to detect a hazard ratio of 0.55 for OS (median OS: 20 vs. 36 months) with a one-sided alpha of 0.05. The target sample size is 150 patients for primary registration and 100 for secondary registration. Accrual began in October 2025 and is planned for 4 years, followed by a 4-year follow-up period. This trial is supported by the Japan Agency for Medical Research and Development (AMED) under the Project for Innovative Cancer Research. Clinical trial information: jRCTs041250114. Research Sponsor: Japan Agency for Medical Research and Development.

TPS8668 **Poster Session**

A phase 2/3 study of EIK1001 in combination with pembrolizumab and chemotherapy in participants with stage 4 non–small cell lung cancer (NSCLC) (TeLuRide-008). First Author: Dan Costin, White Plains Hospital, Center for Cancer Care, White Plains, NY

Background: Immune checkpoint inhibitors (ICIs) reverse tumor-induced immune suppression and promote effective anti-tumor T-cell responses. Current standard of care (SOC) for Stage 4 NSCLC combining ICIs (e.g. pembrolizumab [pembro]) plus histology-appropriate chemotherapy (chemo) confers significant clinical benefit over chemo alone, yet many patients progress nonetheless, highlighting a large unmet medical need in this disease. EIK1001, a Toll-like receptor (TLR) 7/8 dual agonist, activates myeloid and plasmacytoid dendritic cells stimulating innate and adaptive immunity. In completed Phase 1 and ongoing Phase 2 studies, EIK1001 exhibits a manageable safety profile and encouraging anti-tumor activity both as monotherapy and in combination with ICIs. **Methods:** TeLuRide-008 (NCT#07365319) is a global, multicenter, randomized, double-blind, placebo-controlled, adaptive Phase 2/3 study of EIK1001 or placebo, in combination with pembro and histology-appropriate chemo in systemic-therapy-naïve pts with stage 4 NSCLC. In Phase 2, pts are randomized 1:1:1 to receive 1 of 2 doses of EIK1001 or placebo, + pembro and chemo (Part 1:Dose optimization; n~120), followed by additional enrollment with 1:1 randomization of new pts (n~160), at the EIK1001 selected dose or placebo (Part 2: Dose Expansion; n~280). If the study proceeds to Phase 3 (Part 3: Confirmatory), ongoing Phase 2 pts to continue treatment, and n~440 new pts will be randomized 1:1 to receive the selected dose of EIK1001 or placebo, + pembro and chemo (n = up to 750). Key eligibility criteria: pts $\geq$ 18 years of age, life expectancy $\geq$ 3 months, stage 4 NSCLC (NSQ or SQ), no actionable mutations requiring targeted therapy, $\geq$ 1 measurable lesion per RECIST v1.1, and no history of symptomatic pneumonitis. Primary objectives: evaluate efficacy and safety of 2 doses of EIK1001 + pembro and chemo for dose optimization and compare PFS (RECIST v1.1 by BICR) and OS between the selected EIK1001 dose and placebo, + pembro and chemo. Secondary objectives: safety and tolerability, ORR and DOR per RECIST v1.1 by BICR. Exploratory objectives: time to response, EIK1001 exposure-response relationships, and health-related quality of life. Clinical trial information: NCT#07365319. Research Sponsor: None.

TPS8669 **Poster Session**

Lung-MAP S1800E: A randomized phase II/III study of docetaxel and ramucirumab with or without cemiplimab for patients previously treated with platinum-based chemotherapy and immunotherapy for stage IV or recurrent non-small cell lung cancer (NSCLC). First Author: Saiama Naheed Waqar, Washington University School of Medicine in St. Louis, St. Louis, MO

Background: Integration of immunotherapy into first line systemic therapy for patients with metastatic NSCLC has led to improvement in survival, but most patients experience disease progression. Blockade of PD-1 and VEGFR2 synergistically inhibits tumor growth by reducing tumor neovascularization and leads to upregulation of proinflammatory cytokines. We hypothesize that continuing second line anti-PD-1 therapy using cemiplimab in combination with docetaxel and ramucirumab may reverse immunotherapy resistance, and lead to improved overall survival (OS) compared to docetaxel and ramucirumab. **Methods:** Lung-MAP is a master protocol for patients with previously treated advanced NSCLC. S1800E is a phase II/III non-match Lung-MAP substudy, in which patients are randomized 1:1 to receive either standard of care treatment with intravenous docetaxel and ramucirumab (arm A) or investigational treatment with intravenous docetaxel and ramucirumab in combination with cemiplimab (arm B). The primary objective is to compare OS between patients assigned to arm A and arm B who have acquired resistance to platinum-based chemotherapy and immunotherapy for Stage IV or recurrent NSCLC. The total enrollment goal is 378 patients based on a design with 90% power to rule out an HR = 1 at the 1-sided 2.5% level, if the true HR = 0.66. The design includes 3 interim analyses, with a safety run-in for the first 10 patients on arm B. The main inclusion criteria are patients who experienced disease progression 84 days or more following initiation of anti-PD-(L)1 immunotherapy, with complete response, partial response or stable disease as their best response, in addition to progression on or following platinum-based chemotherapy. If a known sensitizing molecular alteration for which an FDA-approved targeted therapy for NSCLC exists (e.g., *EGFR, ALK, ROS1, BRAF, RET, NTRK, KRAS, HER2*, and *MET* sensitizing mutations), patients must have previously received at least one line of targeted therapy. Prior docetaxel is not permitted, and there is a washout of 14 days from palliative radiation (shortened to 7 days for bone radiation) and 28 days from major surgery, with no plans for concurrent systemic therapy while on the clinical trial. Patients must have adequate organ and marrow function and ECOG performance status of 0-1. S1800E was activated on 4/28/2025, with first patient registered on 5/22/2025. As of 1/6/2026, 49 of the planned 378 patients have been enrolled. Clinical trial information: NCT06616584. Research Sponsor: NIH/NCI grants; U10CA18088, U10CA180819; Regeneron Pharmaceuticals.

TPS8670 **Poster Session**

INTerpath-013: A phase 2, randomized, double-blind study of intismeran autogene plus pembrolizumab and chemotherapy as first-line treatment for metastatic squamous non–small cell lung cancer. First Author: Enriqueta Felip, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain

Background: Non–small-cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide. The anti-PD-1 pembrolizumab plus platinum-based chemotherapy is a recommended treatment for metastatic squamous NSCLC. Despite the inclusion of anti-PD-(L)1 therapies into treatment guidelines, there remains an unmet medical need for further improving patient outcomes. Intismeran autogene (intismeran; formerly V940, mRNA-4157) is an investigational mRNA-based individualized neoantigen therapy (INT) encoding up to 34 neoantigens unique to each patient's tumor and is designed to promote antitumor immune response. INTerpath-013 is a phase 2 study evaluating the addition of intismeran to pembrolizumab plus chemotherapy for previously untreated metastatic squamous NSCLC. **Methods:** This phase 2, randomized, double-blind, placebo-controlled study is enrolling patients aged $\geq$18 years with previously untreated histologically or cytologically confirmed stage IV squamous NSCLC (M1a, M1b, M1c1, or M1c2 per AJCC version 9) and measurable disease per RECIST v1.1 by investigator. Participants are also required to have ECOG PS 0 or 1 and provide a tumor sample for next-generation sequencing. Exclusion criteria include known active CNS metastases and/or carcinomatous meningitis, or untreated or symptomatic brain metastases. Approximately 180 participants will be randomized 2:1 to receive 1 treatment cycle comprising intravenous pembrolizumab 400 mg Q6W (1 dose) plus carboplatin AUC 6 mg/mL/min Q3W (2 doses), with either paclitaxel 200 mg/m^2 Q3W (2 doses) or nab-paclitaxel 100 mg/m^2 QW (6 doses). At week 6 (after cycle 1), tumor imaging will be performed and participants with complete response, partial response, or stable disease per RECIST v1.1 by BICR will continue 1 more treatment cycle and also receive up to 2 cycles of intismeran intramuscularly 1 mg (study arm A) or placebo (arm B) Q3W. All participants who complete the first 2 cycles of treatment will then receive up to 7 additional doses of intismeran or placebo (9 total) plus pembrolizumab up to 15 additional doses (17 total). Any participant with PD at the 6-week scan will have treatment unblinded and those in arm A may receive exploratory treatment with up to 9 doses of intismeran plus docetaxel 75 mg/m^2 Q3W until PD, unacceptable toxicity, or participant/physician decision; those in arm B will not receive further investigational treatment. Randomization will be stratified by PD-L1 tumor proportion score ($<$ 1% vs $\geq$1% to $\leq$49% vs $\geq$50%), ECOG PS (0 vs 1), and the number of metastatic sites (1 vs $>$ 1). Primary endpoints are PFS per RECIST v1.1 by BICR and OS. Secondary endpoints include ORR and duration of response per RECIST v1.1 by BICR and safety. Enrollment began in December 2025 and is ongoing across 55 global sites. Clinical trial information: NCT07221474. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.; N/A

TPS8671 **Poster Session**

Phase 3 trial ResQ201A of nogapendekin alfa inbakicept (NAI) plus tislelizumab and docetaxel vs. docetaxel monotherapy for advanced or metastatic NSCLC resistant to ICI therapy. First Author: Andreas Nicholas Saltos, Moffitt Cancer Center, Tampa, FL

Background: Immune checkpoint inhibitors (ICIs) are approved as monotherapy and in combination with chemotherapy in advanced NSCLC. Most patients experience progression with limited treatment options other than chemotherapy. NAI is a first-in-class IL-15 receptor agonist that induces proliferation and activation of natural killer cells, CD8+ T cells and memory T cells without activating regulatory T cells, enhancing both the innate and adaptive immune system to maximize immunogenic cell death. Phase 2 data demonstrated evidence of NAI prolonging OS when used in combination with an ICI. The rationale for ResQ201A (NCT06745908) is based on the prior QUILT-3.055 study, wherein median OS was prolonged at 14.3 months overall and 21.1 months when ALC≥1.2x10^3 was maintained with NAI as a lymphocyte stimulating agent. Randomized clinical trials have demonstrated that the standard of care docetaxel in the 2L+ NSCLC setting results in a mOS of approximately 9 months. **Methods:** ResQ201A is a randomized, open-label phase 3 global, registrational intent trial where 462 adult participants will be enrolled 2:1 in the experimental arm, consisting of two 3-week induction cycles of NAI [SC 1.2 mg], tislelizumab [IV 200 mg] and docetaxel [IV 75 mg/m^2] followed by maintenance NAI and tislelizumab, or a docetaxel monotherapy control arm [IV 75 mg/m^2] until disease progression or unacceptable toxicity. Participants are stratified based on histology, presence of actionable genomic alterations (AGA), and geographical region. Key inclusion criteria are pathologically confirmed stage IV NSCLC with acquired resistance to an ICI (PD after an initial response OR stable disease ≥ 6 mo. duration) to a single line of ICI with or without chemotherapy, ECOG 0 to 2, and measurable tumor lesions per RECIST v1.1. Key exclusion criteria are systemic autoimmune disease, history of organ transplant, and AGA of ALK. The primary endpoint is OS by KM with treatment arm comparison based on the stratified log-rank test and OS hazard ratio summarized based on the stratified Cox proportional hazard model, both stratified by the randomization strata. Secondary efficacy endpoints include iDCR per iRECIST; PFS, ORR and duration of response. Safety is graded using the NCI CTCAE v5.0. Exploratory analyses will be performed to meet objectives. This trial has enrolled and treated participants. Clinical trial information: NCT06745908. Research Sponsor: None.

TPS8672 **Poster Session**

A phase 3 study of ateganosine (THIO; 6-thio-2′-deoxyguanosine) sequenced with immune checkpoint inhibitor (ICI) versus standard-of-care chemotherapy in ICI-resistant advanced NSCLC: THIO-104 trial in progress. First Author: Tomasz Jankowski, Medical University in Lublin, Lublin, Poland

Background: Despite progress in the treatment of advanced non-small cell lung cancer (NSCLC), therapeutic options remain scarce for patients who have developed resistance to immune checkpoint inhibitors (ICIs). Ateganosine (THIO; 6-thio-2′-deoxyguanosine), a telomere-targeting agent, is selectively recognized by telomerase and integrated into the telomeres of cancer cells. Once incorporated, Ateganosine compromises the telomere structure and function, leading to 'uncapping' of the chromosome ends and thus resulting in rapid tumor cell apoptosis. **Methods:** THIO-104 is a multicenter, open-label, randomized Phase 3 study enrolling approximately 300 subjects with histologically confirmed advanced/metastatic NSCLC. Eligible participants must have received two prior lines of systemic treatment, including at least one line of ICIs and platinum-based chemotherapy. Participants will be randomized 1:1 to receive either THIO 180 mg per cycle (60 mg IV on Days 1-3 of a 3-week cycle) followed by cemiplimab 350 mg IV on Day 5, or single-agent chemotherapy (vinorelbine, gemcitabine, or docetaxel). The primary endpoint is overall survival (OS). Secondary endpoints include objective response rate (ORR), progression-free survival (PFS) and duration of response (DoR). Current Status: Enrollment is ongoing , preliminary safety data and efficacy outcomes will be assessed through scheduled interim analyses. **Conclusion:** THIO-104 will provide critical insights into the potential role of telomere-targeting agents in restoring tumor sensitivity to ICIs in NSCLC. The study will also explore key biomarkers to further characterize Ateganosine's mechanism of action and its potential to predict patient response to therapy. Clinical trial information: 2024-520164-33-00. Research Sponsor: None.

TPS8673 **Poster Session**

Randomized phase 3 study (MarsLight-11) evaluating IBI363 (TAK-928) versus docetaxel in patients (pts) with squamous non-small cell lung cancer (sqNSCLC) after prior chemotherapy (chemo) and immunotherapy (IO). First Author: Roy S. Herbst, Department of Medical Oncology and Hematology, Yale School of Medicine, New Haven, CT

Background: In most series, sqNSCLC has worse clinical outcomes compared with non-squamous NSCLC with IO combinations. After chemo and IO failure, docetaxel±ramucirumab remains the standard of care for advanced sqNSCLC, but offers only short-lived disease control (median progression-free survival [PFS] of approximately 3–4 months), and high rates of severe toxicities. Thus, effective post-chemo and IO options for advanced sqNSCLC remain a significant unmet clinical need. IBI363 is a first-in-class, PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein designed to block the PD-1/PD-L1 pathway and simultaneously activate the IL-2 pathway. It selectively expands and rejuvenates exhausted tumor-specific T cells by cis-activating IL-2 receptors. The IL-2 arm of IBI363 is engineered to retain its affinity for IL-2Rα while reducing binding to IL-2Rβ and IL-2Rγ thereby minimizing off-target toxicity. This dual mechanism has shown potential to address the unmet clinical needs of pts with IO-resistant and immune-cold tumors. In prior phase 1/2 studies, IBI363 monotherapy at 3 mg/kg every 3 weeks (Q3W) was well-tolerated and showed encouraging, durable efficacy in pts with advanced, IO-treated NSCLC and other solid tumors (2025 ASCO [8509, 2502 and 104]). Here, we present the trial in progress for MarsLight-11 (NCT07217301), a randomized, open-label, multi-regional Phase 3 study evaluating IBI363 versus docetaxel in pts with sqNSCLC after prior chemo and IO. **Methods:** This study is enrolling eligible pts with unresectable, locally advanced or metastatic sqNSCLC who have progressed on or after platinum-based chemo and anti-PD-1/PD-L1 treatments (defined as radiographic progression per RECIST v1.1 during or within 6 months after discontinuation of IO). Pts with known actionable genomic alterations, active or symptomatic brain metastases are excluded. Pts are randomized 1:1 to IBI363 or docetaxel (control). Stratification factors include the type of IO resistance (primary vs. acquired), the sequence of prior IO and chemo (concurrent vs. sequential), and region (Asia vs. non-Asia). Pts in the experimental arm will receive a priming dose of IBI363 (0.1 mg/kg) seven days prior to the first full dose (3 mg/kg Q3W). The control arm will receive docetaxel (75 mg/m² Q3W). The primary endpoint is overall survival (OS). Secondary endpoints include investigator-assessed PFS, objective response rate, disease control rate, duration of response, and time to response per RECIST v1.1, as well as safety, pharmacokinetics, and immunogenicity. One interim analysis (IA1) and one final analysis are planned for OS. The study plans to enroll approximately 600 pts globally, including sites in China, the United States, Canada, the European Union, the United Kingdom, Japan and South Korea. Clinical trial information: NCT07217301. Research Sponsor: None.

TPS8674 **Poster Session**

A randomized phase III trial of chemo-immunotherapy vs immunotherapy alone for the vulnerable older adult with advanced non–small cell lung cancer: The ACHIEVE study—ECOG-ACRIN EA5221. First Author: Megan Ann Baumgart, University of Rochester, Rochester, NY

Background: Lung cancer disproportionately affects older adults, with 70% of cases diagnosed in patients ≥65 years old, though older adults are often underrepresented in clinical trials.[1,2] KEYNOTE-189[3] and KEYNOTE-407[4] studies established superiority of chemotherapy-immunotherapy (chemo-IO) compared to chemotherapy irrespective of PD-L1 tumor proportion score (TPS) in patients with ECOG PS 0-1. Single-agent pembrolizumab was also shown to be superior to chemotherapy based on KEYNOTE-024[5] and KEYNOTE-042[6] studies. KEYNOTE-189[3]/407[4] studies highlighted synergistic benefit from chemo-IO across TPS subsets while single-agent IO benefit is mostly in the TPS ≥50% population. It is unknown if single-agent IO versus chemo-IO is superior for patients with PD-L1 TPS 1-49%, especially in older adults. There is increased risk for toxicity for adults with co-morbidities and impaired function that is enriched along the age continuum. Use of single-agent IO may limit benefit from synergy. Alternatively, chemo may increase toxicity and adversely impact quality of life (QOL) and survival in older adults. The goal of this study is to evaluate overall survival (OS) in older adults with metastatic NSCLC, PD-L1 TPS 1-49% treated with first-line single-agent IO versus chemo-IO. **Methods:** This phase 3 study randomizes (1:1) patients age ≥70 years old with metastatic NSCLC, PD-L1 TPS 1-49% to treatment with pembrolizumab versus pembrolizumab plus chemotherapy with primary endpoint of OS. Patients undergo an abbreviated baseline geriatric assessment (GA) of function, nutrition, cognition, and QOL with opportunity for modification of chemotherapy regimen and dosing based on results. Patients are treated with 4 cycles of induction pembrolizumab 200 mg IV every 3 weeks (Arm A) or 4 cycles of induction pembrolizumab 200 mg IV every 3 weeks in combination with chemotherapy (Arm B). Chemotherapy is investigator-selected from platinum doublet (carboplatin/pemetrexed, carboplatin/paclitaxel, carboplatin/*nab*-paclitaxel) or single-agent options (pemetrexed, paclitaxel, *nab*-paclitaxel) with dose attenuation per investigator discretion. Induction is followed by up to two years of maintenance pembrolizumab (200 mg IV every 3 weeks or 400 mg IV every 6 weeks) with option for continuing maintenance pemetrexed. Modified GA is repeated at specified time points. Optional stool studies are collected at baseline and after four cycles of therapy. Secondary endpoints include progression-free survival, objective response rate, tolerability and QOL. Exploratory aims evaluate GA metrics as predictors of clinical outcomes and relate gut microbe diversity and abundance to treatment outcomes. Efficacy analyses are conducted on an intention-to-treat basis. Enrollment is ongoing, and current accrual (as of January 6, 2026) is 22 of 304. Clinical trial information: NCT06096844. Research Sponsor: National Cancer Institute.

TPS8675 **Poster Session**

ALPACCA: Phase 3 trial of firmonertinib vs investigator's choice of EGFR inhibitor as first-line treatment for locally advanced or metastatic NSCLC with EGFR P-loop and alpha c-helix compressing (PACC) uncommon mutations (FURMO-006). First Author: Xiuning Le, Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite advances in treatment of NSCLC with EGFR classical mutations, no universally accepted standard-of-care treatment exists for patients with EGFR uncommon mutations including PACC mutations. Treatment options include EGFR tyrosine kinase inhibitors (TKIs) (osimertinib, afatinib), chemotherapy, or other targeted therapies (amivantamab for exon 20 insertion mutations). EGFR PACC mutations comprise approximately 12.5% of all NSCLC EGFR mutations (Robichaux et al 2021, Nilsson et al 2024). Firmonertinib is a once daily oral, highly brain penetrant, broadly active mutant-selective EGFR inhibitor that targets classical and uncommon mutations (Musib et al., NACLC 2022). In the phase 1b FURMO-002 study (FURTHER), first-line locally advanced or metastatic EGFR PACC mutation NSCLC patients treated with firmonertinib 240 mg daily achieved a confirmed ORR of 68.2%, best ORR of 81.8%, disease control rate (DCR) of 100%, and median progression-free survival (mPFS) of 16.5 months by blinded independent central review (BICR) (Le et al., WCLC 2025). Firmonertinib was generally well-tolerated with manageable EGFR TKI-associated adverse events. **Methods:** ALPACCA (FURMO-006; NCT07185997) is a global, phase 3, randomized, open-label study investigating firmonertinib vs investigator's choice of osimertinib or afatinib. Eligible patients have locally advanced or metastatic NSCLC with EGFR PACC mutations. Key inclusion criteria include documented presence of EGFR PACC mutation and measurable disease per RECIST v1.1. Patients with asymptomatic CNS metastases are allowed. Key exclusion criteria include prior systemic anticancer therapy in the locally advanced or metastatic setting or any prior EGFR TKI therapy. Approximately 480 patients will be randomized 1:1 to receive firmonertinib 240 mg daily or investigator's choice of osimertinib 80 mg daily or afatinib 40 mg daily. Primary endpoints are PFS and ORR per RECIST v1.1 by BICR. Key secondary endpoints include OS, investigator assessed PFS and ORR, and safety and tolerability. Enrollment is ongoing. Clinical trial information: NCT07185997. Research Sponsor: ArriVent BioPharma Inc.

TPS8676 **Poster Session**

Randomized phase II study of amivantamab + lazertinib versus afatinib in patients with uncommon/compound *EGFR*-mutated non-small cell lung cancer (WJOG17323L: AGEHA study). First Author: Taichi Miyawaki, Department of Respiratory Medicine, Juntendo University Hospital, Tokyo, Japan

Background: While EGFR tyrosine kinase inhibitors (TKIs) such as afatinib are standard treatments for patients with advanced non-small cell lung cancer (NSCLC) harboring uncommon or compound *EGFR* mutations (excluding exon 20 insertions and T790M), the duration of response is often limited, with a median progression-free survival (PFS) of approximately 8 to 10 months. Amivantamab is an EGFR mesenchymal–epithelial transition factor (MET) bispecific antibody with immune cell–directing activity that has multiple mechanisms of action as defined in preclinical models. For common *EGFR* mutated NSCLC, combination therapy with lazertinib has been approved in several countries based on its superiority in Phase III trial. Although a phase I study of amivantamab plus lazertinib combination therapy showed promising efficacy with a median PFS of 19.5 months in treatment-naïve patients with uncommon or compound *EGFR* mutations, this was a small-scale non-comparative study where efficacy was not the primary endpoint. The AGEHA study (WJOG17323L) is designed to prospectively evaluate whether amivantamab + lazertinib provides superior efficacy and acceptable safety compared to afatinib in patients with treatment-naïve, uncommon or compound *EGFR* mutated NSCLC. **Methods:** This multicenter, randomized, open-label, phase II trial is conducted by the West Japan Oncology Group (WJOG). Eligible patients are randomized in a 1:1 ratio to receive either combination therapy with amivantamab plus lazertinib in Arm A, or afatinib monotherapy in Arm B. The primary objective is to compare PFS between the two treatment arms. Secondary objectives include safety, overall response rate, and overall survival. Additionally, mandatory blood samples are collected at baseline and at the time of disease progression for comprehensive biomarker analysis using the Guardant Health platform to identify molecular predictors of response and resistance mechanisms, including approximately 740 gene alterations and methylation abnormalities. The target sample size is 70 patients (35 per arm). This study is designed with a one-sided alpha of 0.1 and a power of 80% to detect the superiority of amivantamab plus lazertinib over afatinib monotherapy. The primary analysis will compare PFS using a stratified log-rank test, and hazard ratios will be estimated using a Cox proportional hazards model. Key Eligibility Criteria: Patients must be histologically confirmed advanced or recurrent non-squamous NSCLC harboring uncommon or compound *EGFR* mutations, excluding exon 20 insertions and T790M. Participants must be treatment-naïve for advanced disease with an ECOG performance status of 0–1. Patient enrollment began in January 2026, with a recruitment period of two years and a total study duration of five years. Clinical trial information: jRCTs031250560. Research Sponsor: Janssen Pharmaceutical K.K.

TPS8677 **Poster Session**

A randomized phase II study of capmatinib plus osimertinib with or without ramucirumab in patients with *EGFR*-mutant, *MET*-amplified stage IV or recurrent no–small cell lung cancer (Lung-MAP Sub-Study S1900G). First Author: Sarah B. Goldberg, Yale Cancer Center, New Haven, CT

Background: Patients (pts) with advanced *EGFR*-mutant non-small cell lung cancer (NSCLC) typically respond well to first-line tyrosine kinase inhibitor (TKI) therapy, however disease progression is inevitable. A common mechanism of resistance to third-generation EGFR TKIs is *MET* amplification in up to 15% of patients. Prior trials have demonstrated efficacy of combined EGFR and MET TKI for patients with acquired *MET* amplification, however treatment can be limited by toxicity due to peripheral edema. Preclinical evidence demonstrates the benefit of VEGF inhibition combined with an EGFR TKI and MET TKI, both in efficacy and reduced edema. Lung MAP S1900G is a randomized phase II trial of osimertinib and capmatinib plus or minus the VEGFR2 inhibitor ramucirumab in patients with *EGFR*-mutant NSCLC and *MET* amplification after progression on osimertinib. **Methods:** Pts have stage IV or recurrent NSCLC with a sensitizing *EGFR* mutation and have disease progression on osimertinib alone or in combination with other agents. Documentation of *MET* amplification must be determined by tissue- or blood-based assay; testing for *MET* amplification can be done locally or centrally through the LUNGMAP screening process and any level of amplification is allowed. Measurable disease is not required. Patients with asymptomatic treated or untreated brain metastases are eligible. Prior VEGF inhibitor or MET antibody (such as amivantamab) are allowed. Pts are randomly assigned to receive osimertinib 80mg by mouth daily, capmatinib 400mg by mouth twice daily, and ramucirumab 10m/kg intravenously on days 1 and 15 of a 28 day cycle, or osimertinib plus capmatinib alone. Treatment continues until disease progression, symptomatic deterioration, unacceptable toxicity or treatment delay greater than 28 days. Disease assessment per RECIST 1.1 is performed every 8 weeks for the first year and every 12 weeks thereafter. The primary endpoint is investigator-assessed progression-free survival (PFS) and secondary endpoints include toxicity, ORR, duration of response, overall survival, rates of edema, and change in weight. A safety run-in of the first 10 pts in each arm evaluable for dose-limiting toxicity is included due to limited safety data on both the doublet and triplet combinations. The target sample size is 40 eligible pts (20 per arm) which will provide 85% power to rule out no difference at a 1-sided 15% level if the true hazard ratio is 0.5. A hazard ratio of 0.71 or less, equivalent to a 2.4 month difference in median PFS, will be consistent with rejecting the null hypothesis. Accrual is ongoing, with 24 of 40 patients enrolled. S1900G is the first Lung-MAP sub-study that focuses on *EGFR*-mutant lung cancer, representing a new era for this platform trial. Clinical trial information: NCT05642572. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA18088; National Cancer Institute/U.S. National Institutes of Health; U10CA180819; Novartis; Eli Lilly.

TPS8678 **Poster Session**

First-in-human phase I, open-label, multicenter study of HJ-004, a novel EGFR-PROTAC degrader, in patients with advanced *EGFR*-mutated non–small cell lung cancer. First Author: Xinru Chen, Department of Oncology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China

Background: Despite remarkable progress with 1st- to 3rd-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), nearly all patients with EGFR-mutated non-small cell lung cancer (NSCLC) eventually develop acquired resistance through secondary EGFR mutations, bypass pathway activation, or histologic transformation. Targeted options that specifically address EGFR-dependent (on-target) resistance after progression on 3rd-generation EGFR-TKIs remain limited. HJ-004 is an orally bioavailable, highly selective proteolysis-targeting chimera (PROTAC) that degrades mutant EGFR by recruiting the cereblon (CRBN) E3 ubiquitin ligase. Preclinically, HJ-004 showed broad activity against classical, uncommon, and osimertinib-resistant EGFR variants with favorable pharmacokinetics (PK) and safety profiles. **Methods:** This first-in-human, phase I, multicenter, open-label study evaluates the safety, tolerability, PK, and preliminary antitumor activity of HJ-004 in patients with recurrent or metastatic EGFR-mutant non-squamous NSCLC. The study comprises two parts: dose escalation and dose expansion. In the dose-escalation phase, oral HJ-004 is administered once daily in 28-day cycles using accelerated titration followed by a conventional 3 + 3 design (planned doses: 12.5, 25, 50, 87.5, 125, and 162.5 mg). Dose-limiting toxicities (DLTs) are assessed during the single-dose (C0D1-C0D3) and first multiple-dose cycle (C1D1-C1D28) periods. The expansion phase will enroll approximately 20-40 participants in two dose cohorts to further evaluate safety, PK, and preliminary efficacy. Key eligibility criteria include measurable disease per RECIST v1.1 and adequate organ function. The trial is currently ongoing and is expected to enroll up to 76 patients. The phase I study initiated in 2025, and site activation and patient screening are currently underway. No safety or efficacy data are yet available. Enrollment is projected to be completed in 2027, and updated enrollment and PK data will be presented at a future meeting. Clinical trial information: NCT07361237. Research Sponsor: None.

TPS8679 **Poster Session**

KEYMAKER-U01J: Calderasib plus pembrolizumab with or without cetuximab as first-line treatment for advanced or metastatic nonsquamous non–small-cell lung cancer (NSCLC) with *KRAS* G12C mutations. First Author: Qing Zhou, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou, China

Background: The anti–PD-1 pembrolizumab (pembro) + chemotherapy (chemo) is a standard of care first-line therapy for metastatic NSCLC with no *EGFR* or *ALK* alterations. Despite these advances, here remains an unmet need for patients with tumors that have certain mutations, including those in the *KRAS* gene. *KRAS* mutations are associated with poor OS in NSCLC. Calderasib (MK-1084), a next-generation, selective *KRAS* G12C-GDP covalent inhibitor, has previously demonstrated preliminary antitumor activity in combination with pembro ± chemo in *KRAS* G12C–mutant metastatic NSCLC in the phase 1 KANDLELIT-001 study. The anti-EGFR cetuximab has shown promising efficacy in combination therapies in NSCLC with *KRAS* G12C mutations. The phase 2 KEYMAKER-U01J study (NCT07252739) is evaluating the addition of investigational agents to pembro in advanced or metastatic nonsquamous NSCLC with *KRAS* G12C mutations; the treatment arms presented here include pembro + calderasib ± cetuximab. **Methods:** This phase 2, randomized, open-label study is enrolling participants (pts) aged ≥18 years with previously untreated histologically or cytologically confirmed stage IIIB, IIIC, or IV (M1a, M1b, or M1c) nonsquamous NSCLC (AJCC v9), with a *KRAS* G12C mutation that is ineligible for curative resection or chemoradiation. Pts must also have measurable disease per RECIST v1.1, an ECOG PS of 0 or 1, and provide a tumor sample for biomarker analysis. Following a safety lead-in of ~10 pts in arm 3, 1:1:1 randomization of ~120 pts will occur. In arm 1 (control arm), pts will receive up to 18 cycles of pembro 400 mg Q6W intravenously (IV) plus carboplatin AUC 5 mg/mL/min up to 2 cycles and pemetrexed 500 mg/m^2 Q3W until discontinuation criteria are met. Pts in arm 2 (reference arm) will receive up to 18 cycles of pembro 400 mg IV Q6W plus calderasib orally until discontinuation criteria are met. Pts in arm 3 will receive up to 18 cycles of pembro 400 mg IV Q6W plus calderasib with cetuximab 500 mg/m^2 IV Q2W until discontinuation criteria are met. Discontinuation criteria include unacceptable AEs, PD, occurrence/progression of another malignancy, or pt/physician withdrawal. Randomization will be stratified by PD-L1 tumor proportion score (< 50% vs ≥50%). Dual primary endpoints are safety (dose-limiting toxicities, AEs, and AEs leading to study discontinuations) and objective response (CR or PR) per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints are duration of response and PFS per RECIST v1.1 by BICR, OS, and pharmacokinetic characterization. On-study tumor imaging will occur Q6W until week 24, Q9W until week 51, then Q12W, or more frequently if clinically indicated. AEs will be graded per NCI CTCAE v5.0. Enrollment began in December 2025, with 80–105 sites scheduled to enroll globally. Clinical trial information: NCT07252739. Research Sponsor: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

TPS8680 **Poster Session**

A phase II study of amivantamab hyaluronidase in *MET* amplification–positive stage IV or recurrent non–small cell lung cancer (Lung-MAP Sub-Study). First Author: Christian Diego Rolfo, Ohio State University Comprehensive Cancer Center, Columbus, OH

Background: *MET* amplification is a known oncogenic driver in non-small cell lung cancer (NSCLC), estimated to occur in approximately 3-4% of non-squamous (nsq) and squamous (sq) cases. While targeted therapies such as tyrosine kinase inhibitors (TKIs) have demonstrated activity in this population, with objective response rates (ORR) approximating 30%, there is a need for novel therapeutic approaches, particularly for patients who have progressed on standard systemic therapies. Amivantamab hyaluronidase is a fully human bispecific antibody targeting *EGFR* and *MET* co-formulated with recombinant human hyaluronidase (rHuPH20) for subcutaneous administration. The mechanism of action involves the inhibition of *EGFR* and *MET* signaling, receptor degradation, and the induction of antibody-dependent cellular cytotoxicity. S1900J is evaluating the efficacy of this subcutaneous formulation in specific histological cohorts. **Methods:** S1900J is a 2-stage, single arm phase II biomarker-driven Lung-MAP substudy. The study includes 2 cohorts of Stage IV or recurrent NSCLC, based on histology (non-squamous and squamous NSCLC). Biomarker eligibility requires documentation of *MET* amplification as primary driver via tissue or ctDNA NGS. Participants must have received at least one prior line of systemic therapy; notably, patients who have received prior *MET* TKI therapy (e.g., crizotinib, capmatinib) or harboring other actionable alterations are excluded. Participants receive amivantamab hyaluronidase via subcutaneous injection weekly during Cycle 1 (Days 1, 8, 15, 22) and every 2 weeks thereafter (Days 1, 15). Dosing is weight-based: 1,600 mg amivantamab/20,000 units hyaluronidase for participants < 80 kg, and 2,240 mg amivantamab/28,000 units hyaluronidase for patients ≥80 kg. The primary endpoint is response. with a goal of 40 evaluable participants per cohort. The study design has 90% power to rule out a 15% ORR at the 1-sided 5% level, if the true ORR is 35%. Secondary objectives include progression-free survival, duration of response, and response rates in the subset with MET amplification by FoundationOne CDx assays. Correlative studies of interest include the evaluation of concordance between tissue-based and liquid biopsy (ctDNA) next-generation sequencing for the detection of *MET* amplification. S1900J opened to accrual on 9/27/2024 and is actively enrolling patients. Clinical trial information: NCT06116682. Research Sponsor: NIH/NCI grants; U10CA18088, U10CA180819.

TPS8681 **Poster Session**

An ongoing phase 1–2a study of EO1001, an oral brain-penetrant pan-ErbB inhibitor, in patients with advanced ErbB-driven solid tumors including CNS disease. First Author: Neil Sankar, Edison Oncology Holding Corp., Menlo Park, CA

Background: Central nervous system (CNS) metastases and primary brain tumors remain a major cause of morbidity and mortality in patients with ErbB-driven malignancies, particularly as improved systemic therapies prolong survival. Aberrations in the ErbB family of receptor tyrosine kinases—including EGFR, HER2, and HER4—are frequently associated with CNS progression, therapeutic resistance, and poor outcomes across multiple tumor types. In glioblastoma and other CNS malignancies, specific EGFR extracellular domain (ECD) alterations, including EGFRvIII and recurrent ECD missense variants, have been previously reported to promote ligand-independent signaling, invasive tumor biology, and resistance to currently available EGFR-targeted therapies. EO1001 is a novel, oral, irreversible pan-ErbB inhibitor designed to achieve sustained CNS exposure and broad ErbB pathway inhibition. This ongoing Phase 1–2a study is evaluating the safety, pharmacokinetics, and preliminary antitumor activity of EO1001 in patients with advanced ErbB-driven solid tumors, including those with CNS involvement. **Methods:** This is a first-in-human, multicenter, open-label Phase 1–2a study of once-daily oral EO1001. The Phase 1 dose-escalation component uses an accelerated titration design transitioning to a standard 3+3 schema following the occurrence of ≥Grade 2 treatment-related toxicity. A Phase 2 expansion component is enrolling patients at or below the recommended Phase 2 dose (RP2D). Eligible patients are adults with advanced or metastatic ErbB-expressing solid tumors that have progressed following standard therapy; patients with treated or untreated CNS disease are eligible. EO1001 is administered once daily in 28-day cycles following an initial single-dose pharmacokinetic assessment. The primary objectives are to evaluate safety and tolerability and to determine the RP2D. Secondary objectives include characterization of the pharmacokinetic profile and assessment of preliminary antitumor activity using RECIST v1.1 and/or RANO criteria, as appropriate. Exploratory objectives include evaluation of pharmacodynamic and molecular biomarkers in available tissue and optional cerebrospinal fluid sampling to further assess CNS exposure and pathway modulation. Current Status: Dose escalation has been completed across multiple dose levels, and enrollment is ongoing in Phase 2 expansion cohorts designed to further characterize safety, pharmacokinetics, and CNS-directed antitumor activity at biologically active dose levels. Clinical trial information: ACTRN12620000583943. Research Sponsor: Edison Oncology Holding Corp.

9000 Clinical Science Symposium

Gaps in patient-facing information on artificial intelligence in cancer care: A cross-sectional analysis. First Author: Pearl Subramanian, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: Artificial intelligence (AI) is increasingly integrated into cancer care and is also widely accessed by patients seeking information about their diagnoses and treatments. While AI has the potential to improve care delivery and patient engagement, inadequate or misleading patient education may introduce safety risks. We assessed the availability, readability, and quality of publicly available online patient-facing information about AI in cancer care. **Methods:** We conducted a cross-sectional analysis of online patient-facing information related to AI in cancer care. Using common cancer- and AI-related keywords identified using Google Trends, we searched Google and YouTube on August 6, 2025. The first 170 webpages and 150 videos were screened for relevance and patient-facing intent; scientific or industry-facing content was excluded. Eligible webpages and videos were independently evaluated by two reviewers with discrepancies resolved by a third. Webpage readability was assessed using validated indices (Flesch–Kincaid [FK], Gunning Fog [GF], and SMOG). Content was evaluated for discussion of key AI safety concepts including clinician oversight, transparency, bias, and hallucination or misinformation risk. Quality of consumer health information was assessed for both webpages and videos using the DISCERN instrument, with scores ≥ 4 (of 5) indicating high quality. Descriptive statistics were used to summarize findings. **Results:** Of the 170 webpages screened, 52 (31%) met inclusion criteria. Most content focused on breast cancer (n=30, 58%) or was pan-tumor (n=22, 42%). Median readability corresponded to a college-level reading standard, with median grade levels of 12.8 (IQR: 11.6-14.1), 14.8 (IQR: 13.5-16.5), and 14.2 (IQR: 13.6-15.6) based on FK, GF, and SMOG indices, respectively. Most webpages discussed clinician oversight (n=41, 79%) and/or transparency (n=41, 79%), and over half addressed bias (n=29, 56%); however, few discussed hallucination or misinformation risk (n=8, 15%). Only 33% (n=17) of webpages met criteria for high-quality information. Of the 150 videos, 29 (19%) met inclusion criteria. Median view count was 127 (IQR: 23-1000). Few (n=11, 38%) were classified as high quality based on DISCERN scores. **Conclusions:** Publicly available, patient-facing information about AI in cancer care is limited, difficult to read, and often of low quality. Inadequate discussion of AI-related risks, particularly hallucinations or misinformation, may leave patients poorly informed as they encounter or independently use AI-based tools. These findings highlight the need for accessible, high-quality educational resources that clearly explain the clinical role of AI in oncology and provide guidance for safe patient engagement. Research Sponsor: None.

9001 Clinical Science Symposium

Artificial intelligence (AI) in hematology and oncology fellowship (HOF) training: A multicenter survey of education, attitudes, and clinical use. First Author: Evan Garrad, University of Illinois Chicago, Chicago, IL

Background: A prior national survey of U.S. HOF curricula demonstrated substantial heterogeneity and limited protected time for didactics beyond traditional lecture-based education[1]. More recently, artificial intelligence (AI), including large language models and ambient listening tools, has become increasingly integrated into trainee education and clinical practice[2-5]. We conducted a multi-center survey to assess the use of AI among HOFs. **Methods:** Hematology/oncology (H/O) fellows were recruited via email by program leadership to complete an anonymous survey adapted from our prior study, with added questions on AI education, attitudes, and clinical use. Responses were collected via REDCap and summarized using descriptive statistics. **Results:** A total of 118 H/O fellows responded from 18 of 30 invited U.S. HOF programs (60%), primarily from academic centers (94%), with a near-uniform distribution across fellowship training years. Most fellows (74%) reported using AI tools such as ChatGPT or OpenEvidence. Commonly used resources included NCCN guidelines (92%), UpToDate (86%), faculty lecture slides (70%), primary journals (65%), podcasts (58%), textbooks (29%), and social media (20%). Only 8% reported receiving AI education during HOF training. Most fellows felt AI was useful for medical education (93%) and were confident using AI tools for learning (74%). The majority anticipated increasing AI use over the next 5 years (92%) and expressed interest in AI training during fellowship (82%). Fellows most commonly used large language model–based AI tools to clarify difficult concepts (86%), summarize journal articles (83%), and learn about emerging research (75%), whereas fewer reported use for question generation (31%) or patient case simulations (29%). AI-assisted documentation was the most commonly used clinical AI application (51%). Reported barriers to AI use included (in order of highest concern): uncertainty regarding accuracy, lack of formal training, data privacy concerns, and unclear ethical or institutional guidelines. **Conclusions:** AI tools are widely used and perceived as useful for clinical and educational purposes by current H/O fellows, yet formal training during fellowship remains limited. These findings highlight an unmet need for structured education on effective, safe, and ethical AI use, with opportunities for multi-institutional collaboration to achieve scalable impact aligned with contemporary oncology practice. Research Sponsor: None.

9002 Clinical Science Symposium

Patterns of artificial intelligence use among physicians in Mexico: Implications for oncology practice. First Author: Jeffrey Barragán Ortega, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, DF, Mexico

Background: Artificial intelligence (AI) is increasingly incorporated into medical practice; however, physician-level factors associated with AI adoption and usage patterns, particularly among oncologists practicing in low- and middle-income countries, remain insufficiently characterized. This study aimed to describe patterns of AI use among physicians in Mexico and to explore physician-level factors associated with adoption. **Methods:** We conducted a cross-sectional, anonymous survey among physicians from multiple specialties in a tertiary care center in Mexico to assess AI use, professional activities (clinical care, research, and teaching), training interests, and perceptions regarding AI. The primary outcome was self-reported AI use. Associations between physician characteristics and AI use were evaluated using nonparametric statistics. Among oncologists, AI use patterns, training interests, and perceptions were summarized descriptively. **Results:** Between August and September 2025, 170 physicians completed the survey. Overall, 77.1% were $<$ 40 years old, 50% were women, and 91.7% had $\leq$10 years of professional experience. Clinical specialties predominated (78.8%) over surgical specialties (21.2%). Most respondents were involved in clinical care (94.1%), followed by research (48.4%), and teaching (27.1%). AI use was highly prevalent (88.2%), with generative models being the most commonly used tools (80.0%). Physicians younger than 40 years reported significantly higher AI use than those aged $\geq$40 years (93.1% vs 71.8%, $p<0.001$) and were more likely to use AI in clinical practice (77.9% vs 43.6%, $p<0.001$). No significant age-related differences were observed for research or teaching activities. Use of AI-based data analysis tools varied by specialty and was more frequent among surgical compared with clinical specialties (63.9% vs 37.3%, p=0.004). Among oncologists (n=32), 87.5% reported AI use, primarily in clinical practice (75.0%) and research (50.0%), while use in teaching was less frequent (21.9%). Most oncologists expressed strong interest in formal AI training (84.4%) and ethical considerations (87.5%). The majority agreed that AI could improve quality of care and support clinical decision-making (95.2%), while emphasizing the need for continued physician oversight. Concerns regarding data security were common (84.7%), whereas concerns about loss of medical autonomy were generally moderate (36.4%). **Conclusions:** AI adoption among physicians in Mexico is strongly associated with age and professional activity. Oncologists demonstrate widespread AI use in clinical care and research, high interest in structured and ethical training, and a consistent emphasis on human oversight. These findings support the development of targeted educational and governance strategies to guide responsible AI integration in oncology. Research Sponsor: None.

9003 Rapid Oral Abstract Session

Analyzing county-level factors of oncology fellowship program development from 2015-2025. First Author: Ryan James Crowley, NYU Grossman School of Medicine, New York City, NY

Background: In the United States (US), access to oncology care varies geographically. One factor that may contribute to regional shortages is the distribution of oncology fellowship programs. We aimed to assess urban-rural trends in newly created oncology fellowship programs and to identify county-level factors associated with a higher likelihood of gaining a new oncology fellowship program. **Methods:** Data on all hematology/oncology and oncology fellowship positions in 2015 and 2025 were manually extracted from National Resident Matching Program (NRMP) data. A cross-sectional analysis was performed using data from 3,211 US counties to examine program development from 2015-2025. County metrics came from US Census data and physician density was calculated using the Doctors and Clinicians national downloadable file. A model was developed using Firth's penalized logistic regression with the following predictors using 2015 data: oncologist density per 100,000 population, median household income, percentage of population with insurance, rurality (binary with rural county coded as 1), and state-level Medicaid expansion status in 2015 (binary with expansion state coded as 1). The outcome variable was counties that gained a new oncology fellowship program (n=44). **Results:** In 2015, there were 140 fellowship programs in the US with 1 program in a rural county (0.6%). By 2025, there were 180 fellowship programs with 3 programs in rural counties (1.7%). The total fellowship slots grew from 521 to 773 at a rate of 25.2 new fellowship slots per year. The results from the regression model are shown in Table 1. Higher household median income significantly predicted fellowship establishment (OR 1.62, 95% CI 1.25-2.06, p-value $<$0.001), and rurality significantly predicted no fellowship establishment (OR 0.04, 95% CI 0.01-0.14, p-value $<$ 0.001). **Conclusions:** Despite robust growth in the number of oncology fellowship programs and slots, expansion into rural and underserved areas remains disproportionately small. The majority of new programs continue to cluster in urban centers, suggesting that increases in fellowship capacity have not effectively addressed geographic disparities in care. We found that new oncology fellowship programs systematically emerge in more affluent urban counties with pre-existing oncology workforces. Strategic policy interventions including location-based incentives and rural training tracks should be considered to improve the distribution of fellowship programs. Research Sponsor: None.

Firth logistic regression model results.

Variable	Odds Ratio (OR)	95% Confidence Interval	P-Value
Intercept	0.01	0.01-0.02	$<$0.001
Household Median Income	1.62	1.25-2.06	$<$0.001
Percentage of Population with Insurance	0.74	0.51-1.15	0.17
Oncologist Density (providers per 100,000 population)	1.18	1.05-1.29	0.02
Medicaid Expansion Status	3.13	1.57-6.55	0.001
Rurality (RUCC)	0.04	0.01-0.14	$<$0.001

9004 Rapid Oral Abstract Session

Projecting 2050 oncology workforce through historical regional trends and economic stratification. First Author: Arkadi Asaturyan, Yerevan State Medical University, Yerevan, Armenia

Background: Global oncology workforce planning increasingly relies on predictive modeling to guide policy and investment. However, projections are highly sensitive to baseline stratification. Historical models often use broad geographic regions, which may obscure economic heterogeneity within regions. We analyzed historical workforce trends and compared regional versus income-stratified projection models to quantify how perceptions of the 2050 oncology workforce burden have evolved. **Methods:** We extracted oncology workforce data from peer-reviewed literature, government and ministry of health reports, and datasets from professional organizations, including ESMO and ASCO. Cancer incidence and population projections were obtained from GLOBOCAN and UN sources. Workforce burden was defined as annual new cancer cases per clinical oncologist. Historical burden velocity was estimated using comparative data from 2012–2018 and applied to current scenario to build projections. Two models were evaluated: a regional model based on geographic trends and an economic model stratified by World Bank income groups. **Results:** Retrospective analysis (2012–2018) demonstrated substantial regional divergence. Europe showed relative stability, with workforce burden improving by −0.6% per year, while appearing comparable to Asia in 2018 (275 vs. 248 cases per oncologist). However, Asia's burden increased by +8.6% per year, indicating incidence growth already outpacing workforce expansion despite similar cross-sectional values. Using regional trends, the projected 2050 burden reached 694 cases per oncologist for Africa and 3,499 for Asia. In contrast, income-based stratification revealed a markedly steeper trajectory for the most vulnerable economies. At baseline, high-income countries (HICs) had 30,400 oncologists, upper-middle-income countries (UMICs) 46,140, lower-middle-income countries (LMICs) 6,370, and low-income countries (LICs) only 70 providers combined. Projected through historic trends, 2050 burden reached approximately 295 cases per oncologist in HICs, 1,450 in LMICs, and ~11,500 in LICs. This represents a 16-fold increase when shifting from regional (Africa: 694) to economic (LIC: 11,500) projections, while also revealing lower-than-expected burden in emerging economies . **Conclusions:** Comparing regional and income-stratified projections reveals a profound predictive divergence. Although there is limited workforce data for higher accuracy projections, geographic averaging masks extreme workforce deficits in low-income countries while overstating burden in middle-income settings. Absolute workforce growth alone is insufficient to assess preparedness. Future oncology workforce planning should prioritize income-based stratification to accurately identify and address the most critical global capacity gaps. Research Sponsor: None.

9005 Rapid Oral Abstract Session

Support of academic non-clinical efforts for cancer investigator faculty at Association of American Cancer Institutes. First Author: Paula M. Fracasso, VCU Massey Comprehensive Cancer Center, Virginia Commonwealth University, Richmond, VA

Background: Academic non-clinical time (NCT) for physician scientists (PS) and clinical investigators (CI) is critical in advancing novel scientific findings from the laboratory to the community through clinical trials implemented to improve patient outcomes. CI are uniquely positioned to bridge these bench findings to bedside applications given their dual clinical and research training. However, CI face increasing competing pressures that threaten this career path. The Association of American Cancer Institutes (AACI) Physician Clinical Leadership Initiative (PCLI) conducted a national survey in 2018 to identify trends in academic NCT for the physician-trained researchers across US academic cancer centers involved in basic, translational, or clinical research. We recently reevaluated allocation of academic NCT to support faculty. **Methods:** In 2024, AACI PCLI electronically sent a 20-question descriptive survey to 95 academic cancer centers. Survey items assessed the time commitments of medical oncologists caring for patients with hematologic (including cellular therapy and stem cell transplantation) and solid tumor malignancies, as well as institutional academic NCT policies and incentive structures. Responses were summarized using descriptive statistics for quantitative items and qualitative review for open-ended responses. **Results:** Sixty centers (63%) participated. Clinical effort expectations and the amount of academic NCT varied widely by center and faculty role. The median expected effort was 30% (IQR 18%) clinical research and 50% (IQR 14%) direct patient care for CI, and 70% (IQR 20%) basic/clinical research and 20% (IQR 10%) direct patient care for PS. The most common duration of CI startup academic NCT support was 3 years, but this varied greatly across centers. Most centers required external funding to continue academic NCT (48% for CI and 72% for PS). PS were more likely than CI to receive more sustained support when some degree of extramural funding was obtained. Nearly 80% of CI academic NCT was supported by cancer center funds. Clinical trial accrual was the top priority for academic NCT for faculty engaged in clinical research, while mentoring and teaching ranked among the lowest. Incentive plans for clinically active faculty were common (85% of centers) and were largely work relative value unit (wRVU)-based, with limited incorporation of research or mentoring contributions. **Conclusions:** This survey highlights systemic failures in institutional support for CI, including inconsistent allocation of academic NCT, limited support duration, misaligned incentives, and lack of succession planning. These findings underscore the need for sustainable, multisource funding models, recalibrated incentive structures, and robust mentoring pathways to retain and advance CI for accelerating cancer research through advancing discoveries into the clinic. Research Sponsor: None.

9006 Rapid Oral Abstract Session

Gender representation in first and senior authorship of phase III solid-tumor trials presented at the ASCO Annual Meeting, 2015-2025. First Author: Sarbajit Mukherjee, Miami Cancer Institute, Miami, FL

Background: Authorship in clinical trials reflects access to research infrastructure, funding, and academic advancement. While gender gaps have been described, longitudinal trends and structural correlates remain poorly characterized. We examined temporal trends and determinants of gender representation among first and senior authors of phase III solid-tumor trials presented at the ASCO Annual Meeting. **Methods:** We performed a cross-sectional analysis of all phase III solid-tumor trial abstracts presented at the ASCO Annual Meeting from 2015–2025. Data included year, tumor track (breast, gastrointestinal [GI], other), funding source (industry, academic, other), and first/senior authorship. Countries were classified by World Bank income group (high [HIC], upper-middle [UMIC], lower-middle [LMIC], low-income [LIC]) and global region (North America, Europe & Central Asia, East Asia & Pacific, other). Author gender was assigned using publicly available professional profiles and validated automated tools (≥90% certainty). Temporal trends were assessed using Cochran-Armitage tests. Multivariable logistic regression models evaluated factors associated with women authorship. **Results:** Across 1,517 abstracts (3,034 authorships), women comprised 845 authors (27.9%). Most trials were industry funded (63.7%), focused on GI malignancies (20.1%), and based in HIC (84.9%). Using first author as reference group, senior author had higher odds of being male in multivariable analysis (OR=1.30, p=0.001). Women had lower odds of senior authorship compared with first authorship (aOR 0.77, 95% CI 0.65–0.90). Female authorship increased over time (24.9% in 2015–2020 vs. 30.0% in 2021–2025, p=0.002; aOR 1.34, 95% CI 1.13–1.58), most pronounced among senior authors (aOR 1.55, 95% CI 1.21–1.99; p=0.006). Women authorship varied by tumor track, with lower odds in GI compared with breast trials (aOR 0.49, 95% CI 0.38-0.64). Compared with North America, East Asia and Pacific affiliation was associated with higher odds of women authorship overall (aOR 1.54, 95% CI 1.15–2.07), strongest among first authors (aOR 1.89, 95% CI 1.25–2.91). Among senior authors, LMIC affiliation was associated with lower odds of women authorship compared to HICs (aOR 0.11, 95% CI 0.01–0.56). **Conclusions:** In the largest global oncology conference, women authorship in phase III solid-tumor trials has improved over the past decade but remains uneven, with persistent gaps in senior authorship. Research Sponsor: None.

Authorship role, era, and tumor track by gender.

Characteristic	Women (N=845, 27.9%)	Men (N=2,182, 71.9%)	*P*-value
Authorship role			**0.002**
First author	462 (54.7)	1,055 (48.4)	
Senior author	383 (45.3)	1,127 (51.6)	
Era			**0.002**
2015–2020	310 (36.7)	934 (42.8)	
2021–2025	535 (63.3)	1,248 (57.2)	
Tumor track			**<0.001**
Breast	203 (24.0)	307 (14.1)	
Gastrointestinal	150 (17.8)	456 (20.9)	
Other solid tumors	492 (58.2)	1,419 (65.0)	

9007 Rapid Oral Abstract Session

Understanding the impact of gold and silver signals on ERAS applications: A survey of hematology/oncology fellowship program directors. First Author: Courtney Nicole Miller-Chism, Baylor College of Medicine Division of Hematology/Oncology, Houston, TX

Background: Since transition to virtual interviews, application and interview inflation have increased the work burden of GME recruitment. In 2021, AAMC ERAS implemented a process that allows applicants to assign signals to top programs of interest. There is a paucity of guidance on optimal use of ERAS signals (ES), resulting in apprehension and uncertainty amongst applicants and program directors (PD). For the 2026 ERAS cycle, Hematology/Oncology programs (HOP) had the option to participate in ES, in which applicants are provided 5 gold (G) signals and 15 silver (S) signals. First-hand knowledge on how ES was utilized by HOP, as well as PD perceptions about ES, may guide best practices on ES. **Methods:** During the ASCO Oncology Training Program Leadership Retreat in November 2025, an anonymous survey, assessing HOP utilization and perception of ES, and the impact of ES on recruitment practices, was launched. One PD from each HOP was invited to complete the survey while onsite. **Results:** 88 HOP (46% of ACGME HOP) are represented. 97% (n=85) utilized ES. Of HOP who used ES, 74% are academic. 32% are small (1-9 fellows), 43% medium (10-19 fellows), and 25% large (20+ fellows). 79% received 400+ applications. 69% reviewed applications without signals but gave higher consideration to signaled applicants. 25% only reviewed applications with signals. 28% used ES when creating rank list; 45% think ES utilization is appropriate during ranking. 85% reported ES did not alter their approach to applicants requiring visa sponsorship. 78% felt ES made the interview selection process easier. 66% were more satisfied with this year's recruitment process compared to years without ES. The most requested change to ES was reduction of allowed signals, especially silver. 98% will use ES next year. **Conclusions:** Despite limited knowledge on ES impact on recruitment, nearly all surveyed HOP participated in ES this past year and will continue. Most HOP view ES positively though many desire changes, particularly with the number of signals. Most HOP consider all applications regardless of ES. However, some HOP with larger applicant pool are using ES as inclusion criteria for interview consideration. Signals are a strong predictor for interview invitation when internal selection criteria are met. The "borderline" applicant may be the greatest benefactor from ES, viewed similarly to the non-signaled applicant who meets internal selection criteria. Sharing PD perspectives and real-life data from this year's ES process breeds opportunities for further improvement and increased confidence with ES. Research Sponsor: None.

Likelihood HOP offer interview invitation based on quality of application and signals (%, n=85).

Internal Selection Criteria	Signal	Extremely Likely	Likely	Neutral	Unlikely	Extremely Unlikely
Met	G	73	22	5	0	0
	S	42	47	8	2	1
	None	8	27	24	22	19
Nearly met	G	4	35	39	19	3
	S	0	9	52	28	11
Not met	G	0	2	12	41	45
	S	1	1	6	30	62

9008 Rapid Oral Abstract Session

Advancing career-focused training: Program leader perspectives on professional development pathways in hematology/oncology fellowships. First Author: Lauren O'Loughlin, Beth Israel Deaconess Medical Center, Boston, MA

Background: Hematology/Oncology (H/O) fellows have diverse career opportunities post-graduation. Many fellowship programs have created specialized training pathways for trainees to support career-aligned skill development, defined here as professional development pathways (PDPs). These may include specific training for careers in laboratory/translational research, medical education, and quality improvement. There is limited data regarding utilization and perception of PDPs in H/O fellowship programs. **Methods:** We conducted a national cross-sectional survey of United States (US) H/O fellowship program leaders (PLs) to assess: (1) prevalence of PDPs, (2) perceived value of PDPs, and (3) barriers to implementation. The survey underwent content validation by three experts – program directors (PDs) in different fellowship subspecialties – who reviewed the instrument for clarity, relevance, and comprehensiveness. The survey was distributed electronically to 180 US H/O fellowship programs; responses were anonymous. **Results:** 72 responding PLs completed the survey (40% response rate). Program size ranged from 2 to 16 fellows per year. Programs from all US geographic regions were represented; 78% were affiliated with academic hospitals and 17% with academically affiliated community hospitals. Less than half (45%) report offering PDPs. The majority (78%) of PLs agree/strongly agree that PDPs provide fellows with more focused career-concordant training. Among the 32 programs with PDPs, 84% report PDPs align with fellows' post-graduation careers. Most (66%) have fellows select their PDP during the first year of fellowship; PDP selection is mandatory in 56%. Eleven distinct PDPs were described, most commonly clinical research (84%), clinical practice (69%), and basic science research (63%). Core PDP components include clinical experiences (100%), scholarly projects (88%), and structured mentorship (82%). Among the 40 programs without PDPs, 63% perceive value in adding them. Reported barriers include difficulty integrating PDPs into current fellowship structure (60%), lack of appropriate faculty mentors (55%), and lack of PD bandwidth (53%). Resources identified that would support implementation include dedicated time or support for mentorship (68%), sample curricular or implementation tools (68%), access to non-clinical infrastructure (e.g. research, quality improvement, education) (63%), and funding (45%). **Conclusions:** While most US H/O fellowship PLs view PDPs as valuable for trainee career development, less than half of responding programs currently use them. Addressing institutional and programmatic barriers and providing curricular resources, dedicated time for faculty mentors, and funding may enable wider implementation. Future studies should explore existing PDP structures and define best practices for PDP utilization. Research Sponsor: None.

9009 Rapid Oral Abstract Session

Career fulfillment and intent to leave among oncology physicians: A global survey. First Author: Coral Olazagasti, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL

Background: Burnout among U.S. oncologists has risen from 34% (2013) to 59% (2023), with global estimates of 32–45%. However, burnout is often studied in isolation rather than alongside fulfillment, distress, and intent to leave, limiting understanding of workforce attrition. With ~20% of US oncologists leaving clinical roles over the past decade, factors driving workforce attrition require a precise evaluation across international settings. **Methods:** An anonymous, cross-sectional global survey distributed via professional email (Oct–Dec 2025) assessed burnout using validated Maslach Burnout Inventory (MBI) items and evaluated associations with professional fulfillment, career regret, and intent to leave clinical practice among oncology physicians. Descriptive statistics were performed, with χ^2/Fisher's exact tests for categorical comparisons and multivariable logistic regression to identify independent factors associated with fulfillment and intent to leave. **Results:** A total of 306 participants were included (156 non-U.S. and 150 U.S.). Clinical workload was substantial: 33.0% reported $\geq$5 clinic half-days per week, and 57.7% reported $\geq$5 inpatient service weeks annually. Administrative burden was also common, with 45.6% independently performing peer-to-peer appeals and 53.8% reporting feeling overwhelmed by this responsibility. Career satisfaction was reported by 70.6%, while job-related stress was highly prevalent (71.9%). Work frequently extended beyond scheduled hours, with 48.0% reporting moderate-to-excessive after-hours electronic medical record use. More than one-quarter of respondents (27.4%) expressed regret about pursuing a career in oncology, most attributed to poor work–life balance (69.3%) and burnout (65.3%). Despite these challenges, 50.5% reported frequent professional fulfillment and 21.7% reported very high fulfillment, particularly among U.S.-based vs. non-U.S. physicians (62.7% vs 25.0%, $P < 0.001$). Overall, 45% reported ever considering leaving practice; frequent intent to leave was higher among U.S.-based physicians (15.3% vs 7.1%, P = 0.034) [Table 1]. **Conclusions:** Oncologists experience a fulfillment–distress paradox, reporting meaningful professional fulfillment despite high stress, administrative burden, career regret, and intent to leave practice. This "professional dissonance" suggests that meaning and identity in oncology may persist despite insufficient institutional support but may remain fragile over time. Systems-level approaches addressing workload, professional culture, and identity formation are needed to improve physician well-being and workforce retention. Research Sponsor: None.

Key outcomes by region.

Outcome (often/always)	Non-US (n=156)	US (n=150)	p-value
Fulfillment high	39 (25.0%)	94 (62.7%)	**<0.001**
Consider leaving high	11 (7.1%)	23 (15.3%)	**0.034**

9010 Rapid Oral Abstract Session

Burnout (BO) among oncology professionals in the Middle East and North Africa (MENA): Meta-analysis of pre–post COVID trends, contributors, and predictive value of single-item screening tool. First Author: Atlal M. Abusanad, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Background: BO among oncology professionals is prevalent and may have changed following the COVID-19 pandemic. We conducted a meta-analysis of MENA studies to evaluate temporal trends in overall burnout and subdomains, identify contributing predictors, and assess the screening performance of thought of quitting oncology (TQ). **Methods:** Ten cross-sectional studies (N = 2,486) reporting Maslach Burnout Inventory (MBI) outcomes were included: six pre-COVID and four post-COVID. Pooled prevalence estimates were generated for emotional exhaustion (EE), depersonalization (DP), personal accomplishment (PA), and overall BO. Study-level meta-regression evaluated the effects of time period (pre- vs post-COVID), demographics, specialty, and their interaction on observed trends. Performance of TQ was assessed as a screening tool with pooled sensitivity, specificity, and predictive values. **Results:** The pooled prevalence of BO was 57.1% (95% CI, 40.6–72.8), increased from 48.2% in the pre-COVID period to 77.2% post-COVID (Δ +29.0 percentage points). High EE increased from 41.3% pre-COVID to 70.9% post-COVID (Δ +29.6 percentage points). DP increased from 36.8% to 55.8% (Δ +19.0 percentage points). Low PA showed minimal change (35.4% pre-COVID vs 35.1% post-COVID; Δ −0.3 percentage points). The heterogeneity estimate was high due to inter-study differences related to time period, setting, and baseline burnout prevalence, which were statistically adjusted for. TQ screening demonstrated reasonable sensitivity (82.4%) and PPV (79.9%), but low specificity (46.5%) and NPV (50.5%). Table 1 shows study-level factors contributing to BO prevalence trends. **Conclusions:** BO among oncology professionals increased post-COVID in the MENA region. The rise was driven by age-dependent effects plus time period. EE increased uniformly, while DP and low PA showed more complex patterns. A single-item question assessing TQ demonstrated strong rule-in screening utility for identifying clinicians at risk. Research Sponsor: None.

Meta-regression analysis of study-level moderators of BO prevalence.

Outcome	Best Predictor(s)	R^2	Pattern
EE	Period + Age + Med Onc. %	86.2%	**Additive effects:** Post-COVID, younger, more Med Onc. independently increase EE
DP	None significant	0.0%	
PA	Period × Age	50.4%	**Moderation:** Age moderates pandemic effect on PA
Overall Burnout	Period × Age	55.3%	**Moderation:** Age moderates pandemic effect on BO

9011 Rapid Oral Abstract Session

Standardized mean differences of primary outcomes found in randomized controlled trials of wellness interventions among medical trainees: A systematic review and meta-analysis. First Author: Andrew Irving Hearn, University of Louisville, Brown Cancer Center, Louisville, KY

Background: In the era of physician shortages, wellness interventions among medical trainees is an area of ongoing research interest in hopes of promoting clinician wellness and preventing burnout as a means of reducing clinician attrition. To our knowledge, there has not been a systematic review and meta-analysis of randomized controlled trials among medical trainees (medical students, residents, and fellows) to characterize the overall efficacy of wellness interventions in this population. **Methods:** A medical librarian searched Embase, MEDLINE, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), APA PsycINFO, and Clinicaltrials.gov from the earliest timepoint to March 2022 for randomized controlled trials of wellness interventions among medical trainees. Measures of wellness included but were not limited to depression, stress, and anxiety. Outcomes were analyzed using Standardized Mean Differences (SMD) calculated as Hedges' g to correct for small sample bias. To ensure consistent interpretation, effect sizes were adjusted for directionality such that a positive SMD indicates a beneficial outcome for the intervention group regardless of the original scale (e.g., higher happiness or lower stress). **Results:** Our search strategy resulted in 3,806 unique articles. 161 articles passed initial screening of titles and abstracts, and 46 studies were included for data extraction with dates ranging from 1980 to 2022. 23 studies with means and standard deviations reported for the primary outcome were included for meta-analysis purposes. The pooled effect size was 0.017 with a 95% confidence interval of -0.501 to 0.536 with an I^2 heterogeneity of 0.904. **Conclusions:** Our systematic review and meta-analysis of randomized controlled trials of wellness interventions among medical trainees suggest that interventions to promote wellness and prevent burnout in medical trainees, as an aggregate, have been heterogenous in design and with little-to-no overall effect. An updated search of the literature with subgroup analyses by intervention type and/or outcome measure may yield more promising results, inform future research, and better assist training programs in weighing the opportunity cost of wellness interventions, particularly in resource-constrained settings or in fields with significant rates of burnout such as hematology and oncology. Research Sponsor: None.

9012 Poster Session

The hidden struggle? Mental health burden among oncology physicians globally. First Author: Coral Olazagasti, University of Miami/Sylvester Comprehensive Cancer Center, Miami, FL

Background: Oncology physicians face demanding clinical workloads, high emotional labor, and frequent exposure to patient loss, contributing to elevated psychological distress. While burnout has been extensively described, anxiety and depression remain under-recognized and stigmatized within the oncology workforce. **Methods:** A cross-sectional, anonymous, online survey distributed internationally (October–December 2025) assessed indicators aligned to PHQ-9 and GAD-7 constructs, mental-health history, medication use, practice characteristics, and workplace context. Descriptive statistics summarized prevalence; χ^2/Fisher's exact tests compared subgroups; and logistic regression explored independent risk factors for anxiety/depression. **Results:** Among 209 oncology physicians who completed all mental health-related survey items (Table 1), 28.2% reported anxiety and/or depression. Female physicians had a higher prevalence than male physicians (35.4% vs 22.2%, P = 0.037). Anxiety/depression was higher among Hispanic/Latino vs non-Hispanic White physicians (45.5% vs 29.8%, P = 0.015) and among non-U.S. vs U.S.-based physicians (33.3% vs 25.7%, P = 0.025), though these differences attenuated in adjusted models. Medication use was strongly associated with anxiety/depression. Prevalence of anxiety/depression was rare among physicians who had never considered medication (0.9%), but common among those with past (72.7%) or current (92.9%) medication use (P < 0.001). **Conclusions:** Nearly one in three oncology physicians reported anxiety and/or depression, consistent with national estimates for physicians generally. Female physicians demonstrated a significantly higher burden and retained an independent risk after adjustment. These findings underscore the need for confidential and accessible mental health care within oncology professional environments and highlight the importance of addressing structural and occupational contributors to psychological distress. If oncology is to remain a sustainable profession, mental health must be treated as a core component of workforce development rather than an individual responsibility. Research Sponsor: None.

Physicians' characteristics by anxiety/depression.

Variable	All N (%)	No Anxiety/ Depression N (%)	Yes Anxiety/ Depression N (%)	P value†
Total	209 (100.0)	150 (71.8)	59 (28.2)	
Sex				
Female	99 (47.4)	64 (64.6)	35 (35.4)	
Male	108 (51.7)	84 (77.8)	24 (22.2)	**0.037**
Race / Ethnicity				
Non-Hispanic White	84 (40.2)	59 (70.2)	25 (29.8)	
Hispanic/Latino	33 (15.8)	18 (54.5)	15 (45.5)	**0.015**
Black	11 (5.3)	11 (100.0)	–	

9013 Poster Session

Burnout among early-career oncologists in Latin America: A regional survey. First Author: Sergio Cifuentes-Canaval, Instituto de Cancerología Las Américas, Medellín, Antioquia, Colombia

Background: Burnout in healthcare professionals negatively impacts patient care, job satisfaction, and personal well-being. Early-career oncologists are especially vulnerable due to emotional strain and heavy clinical and administrative demands. These challenges are driven by structural constraints. This study aimed to determine the frequency of burnout among early-career oncologists in LATAM and to describe workload conditions and perceived institutional resources. **Methods:** A multicenter, observational, cross-sectional, voluntary, web-based survey was conducted between Nov/2025 and Jan/2026 among young oncologists in LATAM. Participants were physicians aged <40 years or <10 years of clinical practice. Participants were invited electronically via email and social media. The survey included demographic, professional, and workplace-related variables. An adapted version of the Maslach Burnout Inventory (MBI) was performed. **Results:** A total of 105 surveys were included from oncologists across 15 Latin American countries, with the highest representation from Colombia (37.1%), Mexico (23.8%), and Argentina (8.6%). Fifty-one percent were aged ≥35 years, were female (58.1%), and worked in non-academic settings, including public (36.2%), private (32.4%), or mixed public–private practice (29.5%). 19.1% were trainees. Regarding burnout, 55.2% reported feeling emotionally exhausted due to work at least once per week (median 4; IQR 3–5), and 64.8% reported end-of-day exhaustion at least weekly (median 4; IQR 3–5). Depersonalization symptoms were infrequent (median 1; IQR 0–3), and participants reported generally high levels of personal accomplishment (median 5; IQR 4–6). Overall, 46% of participants reported adequate technological, pharmacological, and institutional support resources. Only 21% indicated that their clinical and administrative workload was manageable; 40% considered it unmanageable. Most respondents reported misalignment between salary and workload, with 61% expressing disagreement. **Conclusions:** This survey provides one of the first regional overviews of working conditions among early-career oncologists in LATAM. A proportion of participants reported limited institutional resources and unmanageable clinical and administrative workloads, highlighting structural challenges within the region's oncology workforce. Research Sponsor: None.

Burnout survey among EOCs in LATAM.

Questions	Median, (IQR)
I feel exhausted at the end of the workday.	4, (3-5)
I feel emotionally exhausted by my work.	4, (3-5)
I feel I work too hard at my job.	3, (2-5)
I feel frustrated by my work.	3, (1-4)
I have become more insensitive to people since I've been working.	1, (0-3)
I'm afraid that this job is making me uncaring.	1, (0-3)
I really don't care about what happens to some of my patients.	0, (0,1)
Through my work, I feel that I have a positive influence on people.	5, (4-6)
I am easily able to create a relaxed atmosphere with my patients.	5, (4-5)

9014 Poster Session

Emotional burnout among oncology clinicians in Russia: Results of a national cross-sectional survey. First Author: Anastasia Danilova, Moscow City Oncology Hospital 62, Moscow, Russian Federation

Background: International reports suggest a high prevalence of burnout in oncology, but contemporary Russian data are limited. **Methods:** Anonymous online survey (June 7-14, 2025) of oncology clinicians and trainees assessing emotional exhaustion in the prior 4 weeks, related symptoms, coping strategies, and free-text views on drivers/mitigation. **Results:** 735 respondents participated (medical oncologists 46.0%, surgical oncologists 23.9%, radiation oncologists 11.6%, trainees 9.0%); 78.5% worked in public hospitals and 69.0% had no managerial role. Emotional exhaustion was reported "often" by 326 (44.4%) and "constantly" by 152 (20.7%); 157 (21.4%) reported episodic exhaustion, 74 (10.1%) rare, and 26 (3.5%) none. Patient detachment was reported sometimes by 291 (39.6%), often by 221 (30.1%), and as near-constant disengagement by 42 (5.7%). Frequent thoughts about leaving clinical work were reported by 275 (37.4%) (additional 243, 33.1% only in exceptionally difficult moments). Excessive workload was perceived often/constantly by 458 (62.3%); lack of time for breaks/recovery by 629 (85.6%) at least sometimes. Common coping strategies included sleep/rest by 592 (80.5%), support from close ones by 437 (59.5%), physical activity by 385 (52.4%), and hobbies by 251 (34.1%); 198 (26.9%) reported alcohol/medications. In free-text drivers (n=569), the most cited themes were leadership/management issues (33.7%), time/workload pressure (21.1%), patient/relative conflict and complaints (19.3%), and paperwork (12.5%); proposed mitigation included protected rest/work-life boundaries (26.3%) and workload reduction/staffing/process optimization (20.8%). **Conclusions:** Two-thirds of respondents reported frequent/constant emotional exhaustion, accompanied by patient detachment and high intent to leave clinical work. Findings support prioritizing organization-level interventions and protected recovery time alongside accessible support resources. Research Sponsor: None.

9015 Poster Session

Inspiring the next generation of medical oncologists: Passion, purpose, and preventing burnout. First Author: Ruth Hutch, St. James's Hospital, Dublin, Ireland

Background: The National Cancer Registry of Ireland projects a doubling of cancer incidence by 2045, with an estimated shortfall of over 100 medical oncologists by 2028. This workforce gap is compounded by rising burnout, with ASCO data showing an increase in oncologists reporting at least one burnout symptom from 34% to 59% over the past decade. Alongside sustained investment in training and recruitment, addressing burnout is essential. This study aimed to identify factors influencing career interest in medical oncology and to explore perceived barriers, informing recruitment strategies and burnout mitigation. **Methods:** A cross-sectional, anonymous electronic survey assessed interest in medical oncology among medical students, interns, and junior doctors. The 20-item questionnaire examined demographics, career preferences, oncology exposure, and perceived barriers. A separate 28-item follow-up survey evaluated burnout among Irish medical oncologists and trainees. **Results:** A total of 183 early-career respondents participated (62.3% female). A response rate of 73%, respectively. Most were aged 25–34 years (69.4%), with junior residents comprising the largest group (42.6%). Key motivators for considering oncology included interest in cancer biology and treatment (54.9%), caring for cancer patients (53.2%), managing complex multidisciplinary cases (52.4%), and the dynamic nature of the specialty (51.6%). Personal experience with cancer did not influence career choice for 54%. Deterrents included high patient mortality and emotional burden (71.6%), concerns regarding burnout and work–life balance (57.5%), and prolonged training (36.1%). Oncology exposure was limited, with 38.5% reporting none; exposure most commonly occurred during junior residency (34.3%) and centered on palliative care, systemic therapies, and chemotherapy. Access to mentorship (73.8%) and increased clinical or research opportunities (62.3%) were identified as key factors to enhance recruitment. Forty-one oncologists completed the burnout survey (responses on-going). Most were aged 35–44 years, female, and working in public hospitals, with 65.9% reporting weekly workloads of 50–59 hours. Over half reported burnout at least monthly, and 75.6% reported inadequate work–life balance. Major stressors included high clinical workload, administrative burden, lack of protected academic time, staffing shortages, and moral distress. Despite high professional satisfaction (82.9%), 43.9% had considered reducing hours or leaving practice due to work-related stress. **Conclusions:** Ireland faces a significant oncology workforce challenge. Early exposure, structured mentorship, and targeted strategies to address workload and burnout are critical to strengthening recruitment and sustaining the oncology workforce. Research Sponsor: None.

9016 **Poster Session**

Turning silence into rhythm: Outcomes of a school-based *Cancer Olympiad* in India. First Author: Vangipuram Harshil Sai, Department of Undergraduate Education, All India Institute of Medical Sciences (AIIMS), Delhi, India

Background: Late-stage presentation continues to account for nearly 70% of cancer diagnoses in low- and middle-income countries, exposing the gap between medical progress and public participation. Traditional awareness drives often falter in communities shaped by stigma, low literacy, and fear of cost. The *Cancer Olympiad* was conceived as an arts-based, school-centered intervention harnessing creativity, performance, and peer learning to transform knowledge into shared action. By positioning children as credible messengers, it aimed to bridge the emotional and educational distance between health information and household practice. **Methods:** A quasi-experimental, mixed-methods study engaged 25,000 students (grades 1–12) and 2,500 families across 125 urban and rural schools in Udaipur District, North India. Schools implemented structured creative modules—drawings, performances, debates, health exhibitions, reflective writing, and parent–child tasks—culminating in an interschool finale attended by educators, clinicians, and policymakers. Knowledge, attitude, and behavior (KAB) outcomes were measured at baseline and three months post-intervention using validated questionnaires adapted for regional literacy levels. Secondary endpoints included stigma reduction, screening and vaccination uptake, tobacco-cessation behavior, and community-engagement indices such as school-initiated health clubs and family advocacy actions. Qualitative interviews and focus groups explored cultural receptivity, emotional learning, and pathways of sustained engagement. **Results:** Knowledge of cancer risk factors and early-warning signs improved by 23 percentage points ($p < 0.001$), while recognition of curability rose from 58% to 83%. Stigma scores fell by 0.35 SD, and 19% of participating families undertook at least one preventive action—screening, vaccination, quitting tobacco, or seeking medical evaluation—within six months. Primary-health-center screening visits increased by 17% compared with matched control blocks, and teacher-reported health-dialogue frequency in classrooms quadrupled. Qualitative analysis revealed recurring themes of “children as catalysts of credibility,” “art as emotional pedagogy,” and “community pride replacing fear.” Implementation fidelity exceeded 90%, school-level engagement remained high, and more than half the schools adopted the Olympiad as an annual, self-sustained event. **Conclusions:** The *Cancer Olympiad* demonstrates that child-led, arts-integrated education can align biomedical understanding with cultural identity, shifting awareness into collective prevention. When stories and performances enter homes, they humanize cancer knowledge and normalize early action. Embedding narrative and creativity within oncology outreach may extend medicine’s reach beyond clinics—turning silence into rhythm, and rhythm into a movement of lasting change. Research Sponsor: None.

9017 **Poster Session**

Preparedness of internal medicine residents for oncologic emergencies and end-of-life discussions in a community training environment. First Author: Musa Kiyani, HCA Florida JFK Hospital GME Consortium, Atlantis, FL

Background: Internal medicine (IM) residents often serve as first responders for patients with cancer in community hospitals, where oncologic emergencies frequently present before subspecialty involvement. Yet structured heme-onc and palliative training is limited. Preparedness in community settings - where workflow and resource constraints may heighten gaps between trainee knowledge and confidence - remains under-examined. **Methods:** We conducted a cross-sectional electronic survey of IM residents at a university-affiliated community hospital (Oct 17 - Nov 18, 2025). It included 14 vignette-based knowledge items, 8 confidence ratings (0-10), and questions on demographics, oncology exposure, and perceived barriers. Primary outcomes were total knowledge score (0-14) and composite confidence scores. Multivariable regression assessed associations between resident characteristics, knowledge, and confidence. **Results:** Thirty-three of 58 residents participated; mean age was 30.1 years, and 82% had not completed a hematology-oncology rotation. Knowledge was uniformly high (mean 13.0; SD 1.0) across key domains including febrile neutropenia and hospice eligibility. Confidence, however, was substantially lower and more heterogeneous (emergency mean 5.78; end-of-life mean 5.84). Senior trainees demonstrated greater confidence in both domains (β = 1.62 and 1.60; $P < .001$), and caring for ≥3 oncologic patients in the prior month independently predicted higher communication confidence (β = 1.87; P = .04). Residents identified recurrent barriers: delays in triage (72.7%), limited family availability (72.7%), language barriers (57.6%), and difficulty obtaining early intravenous access (39.4%). Free-text responses emphasized the need for concise reference tools, structured exposure, and simulation-based practice. **Conclusions:** IM residents demonstrated excellent factual knowledge but substantially lower confidence in managing acute oncologic conditions and conducting serious-illness conversations. Confidence was influenced more by experience and workflow realities than by knowledge alone. Our findings highlight an actionable opportunity. Experiential curricula, streamlined clinical pathways, and integrated oncologic teaching may strengthen frontline preparedness for high-stakes cancer care in community settings. Research Sponsor: None.

Resident demographics, clinical exposure, and selected barriers (N = 33).

Selected measure	n/N (%)
Resident sex: male	20/33 (60.6%)
Resident sex: female	11/33 (33.3%)
Training level: PGY-1	15/33 (45.5%)
Training level: PGY-2	8/33 (24.2%)
Training level: PGY-3	10/33 (30.3%)
Oncology exposure: 0–2 cancer patients/month	18/33 (54.5%)
Oncology exposure: ≥3 cancer patients/month	10/33 (30.3%)
Barrier: workload or paging delays	13/33 (39.4%)
Barrier: cultural or linguistic challenges	19/33 (57.6%)

9018 **Poster Session**

Benefits of utilizing experiential learning in a medical school cancer survivorship course. First Author: Yasheen Gao, Frank H. Netter MD School of Medicine, Quinnipiac University, North Haven, CT

Background: Cancer survivorship care remains underemphasized in medical education despite a growing population of cancer survivors with complex long-term needs. Identifying effective strategies to integrate survivorship education into the medical curriculum is essential. Kolb’s experiential learning theory, which posits that effective learning occurs through iterative cycles of concrete experience, reflective observation, abstract conceptualization, and active experimentation, may offer a structured framework well suited to teaching survivorship care. **Methods:** We evaluated the effectiveness of utilizing repeated Kolb’s cycles to teach a 15-week cancer survivorship course during our 2024 Fall semester. 12 learners (9 pre-clerkship medical students and 3 premedical students) attended weekly sessions mediated by the instructor and invited guests. In-class experiences were paired with reflective homework assignments also tasking students to develop new concepts in 4 domains of interest: patients as survivors (PS), caregivers’ issues (CI), illness experience (IE), and interprofessional care (IPC). Students shared concepts in the next session then began the Kolb’s cycle again. For their final assignment, they interviewed a cancer survivor then created a treatment plan applying the concepts they developed during the course. An anonymous post-course survey assessed learner satisfaction and perceptions of Kolb’s cycle, and a one-year follow-up survey evaluated comfort addressing survivorship issues during clerkships and the course’s impact on survivor care. **Results:** Students generated 259 new concepts (PS: 74; CI: 49; IE: 56; and IPC: 80) across the course and applied an average of ten self-developed concepts per student on the final assignment. On the immediate post-course survey, 12/12 students were highly satisfied with the course and 9/12 students rated all four stages of Kolb’s cycle as extremely or mostly helpful. A year later, 6/9 medical students now on clinical clerkships responded to a follow-up survey. Most reported that the course had a significant lasting impact on their understanding of survivorship issues (4/6) and overall patient management (4/6). Qualitative comments describe greater holistic awareness, comfort with difficult conversations, and attention to survivorship-focused referrals. Students also reported being extremely or mostly confident addressing survivorship issues in the following domains: PS 4/6, CI 3/6, IE 4/6, and IPC 3/6. **Conclusions:** Kolb’s experiential learning theory is an effective framework for teaching a cancer survivorship course to pre-clerkship medical students. Students were highly satisfied with this learning method and able to use this model to successfully develop and apply new concepts. Follow-up during clerkships demonstrated sustained learning and a lasting capacity to apply this material to new patient encounters. Research Sponsor: None.

9019 **Poster Session**

Utilizing large language models for lung cancer patient education compared to publicly available information. First Author: Samantha Liu, San Mateo High School, San Mateo, CA

Background: The advent of the internet, social media, and more recently of large language model (LLM) platforms has led patients to seek information about cancer directly through digital sources. Complete, readable, and accurate information could reduce physician time clarifying information and increase patient self-activation, especially in low-resource environments. We evaluated the quality of publicly available information provided for the five most common lung cancer questions asked on the internet with information provided by the American Cancer Society (ACS), the National Cancer Institute (NCI), ChatGPT, and Gemini. We hypothesized that LLM platforms could produce readable and information quality equivalent to that found on nationally recognized websites. **Methods:** ChatGPT (OpenAI, logged-out version, accessed 12/14/25) was queried to determine the five most common questions patients with lung cancer ask. These question prompts were used to generate responses in ChatGPT (OpenAI, logged-out version, accessed 1/13/26) and Gemini (Google, version 3 Flash, 1/13/26). Additional passages were extracted from NCI and ACS patient education web pages, and all passages were de-identified and reformatted with links and references removed. The deidentified passages were evaluated by seven providers representing medical oncology (n=4), radiation oncology (n=1), surgical oncology (n=2), and onco-primary care (n=1) using Information Quality Grade, Global Quality Scale, Error Classification, Comprehensibility, and Confabulation. Readability was determined via Flesh-Kincaid grade level. **Results:** Readability was similar between passages, ranging from grade levels 6.9-8.2. LLM’s were rated higher on information quality with fewer total errors. Providers were able to discern LLM content in > 50% of the cases but considered human-generated content as LLM in about one third of cases. The most frequent error reported in LLMs was too little information (n=19) and in websites too much information (n=29). **Conclusions:** LLMs can provide more succinct high-quality information for patients with lung cancer compared to current publicly available websites. The information provided by LLMs is accessible to the public, with potential positive implications for low-resourced populations. Further research is urgently needed to understand the potential of LLMs to improve lung cancer outcomes, such as patient self-activation and adherence. Research Sponsor: None.

Source	Readability (Grade level) *	Info Quality* (1 high - 4 low)	Global Quality Scale* (5 high - 1 low)	% Comprehensibility	% Confabulation	Total # of errors	% Considered LLM
ACS	7.8	1.7	3.7	75.0	7.5	28	30.6
NCI	8.2	1.9	3.1	75.0	7.5	43	35.3
ChatGPT	6.9	1.5	4.3	100.0	2.6	20	63.2
Gemini	8.1	1.5	4.4	52.3	2.6	19	64.1

*Averages across all 5 questions.

9020 **Poster Session**

Psychological burden and burnout among regional healthcare providers communicating hereditary tumor findings: A multi-institutional communication skills training implementation study. First Author: Shuhei Suzuki, Department of Clinical Oncology, Yamagata University, Yamagata, Japan

Background: Psychological burden among healthcare providers in precision oncology affects workforce sustainability. In regional settings with limited genetic counseling resources, providers face compounded stress disclosing hereditary tumor findings to cancer patients. This implementation study, supported by an MSD Medical Education Grant for advancing genetic medicine understanding in biomarker-based precision oncology, assessed structured communication skills training to address provider psychological burden. **Methods:** We deployed a standardized curriculum across seven regional hospitals in Yamagata Prefecture, Japan, in 2025, integrating SHARE protocol training (Fujimori et al., JCO. 2014) with modules on *BRCA* testing, microsatellite instability, and genomic profiling disclosure. Implementation strategies included professional actors experienced in medical scenarios, facilitated role-playing, and videotaped quality monitoring. This single-arm pre-post intervention study used a mixed-methods evaluation with questionnaire surveys and qualitative inquiries with a modified grounded theory through an inductive thematic analysis until theoretical saturation. **Results:** Among 263 participants (median experience 10 years, range 0-36), including physicians, nurses, genetic counselors, pharmacists, and administrative staff, 93% had baseline psychological burden and 92% reported anxiety when communicating hereditary tumor findings. Psychological burden and anxiety post-intervention decreased in 89% ($p<0.001$) and 84% ($p<0.001$), respectively, with 89% reporting an improved hereditary tumor understanding ($p<0.001$). A qualitative analysis of 18 semi-structured interviews revealed five critical themes: persistent institutional barriers to genetic counseling in resource-limited regions, profound emotional exhaustion from simultaneously managing terminal illness and germline implications, role-play enabling authentic skill rehearsal without patient risk, moral distress balancing patient autonomy against family cascade obligations in limited-prognosis contexts, and the critical need for sustained peer support. **Conclusions:** Multi-site communication skills training including experiential role-play significantly reduced provider psychological burden and anxiety while improving hereditary tumor knowledge across diverse regional healthcare teams. A theory-driven mixed-methods evaluation strengthened intervention rigor. This study supports industry-academic partnerships addressing workforce sustainability while advancing genomic medicine equity in underserved settings. National dissemination with sustained outcome assessment will establish this model as a scalable framework addressing the global workforce crisis in precision oncology. Research Sponsor: MSD Medical Education Grant; MSDG20230507001.

9021 **Poster Session**

Escape to learn: A team-based gamified educational experience for hematology/oncology fellows. First Author: Emily Wolf, Mayo Clinic Florida, Jacksonville, FL

Background: An escape room is a team-based activity in which participants collaborate to solve puzzles within a fixed time limit and escape. Prior studies demonstrate high learner satisfaction and improved teamwork and communication with medical education escape rooms. To date, no published reports describe an escape room designed specifically for hematology/oncology (hem/onc) fellows. As part of Hem/Onc Curriculum, we designed and implemented a hem/onc-focused escape room and evaluated learner satisfaction and perceived learning impact. **Methods:** The escape room was designed using evidence-based learning science principles (Table 1). Teams worked to solve sequential puzzles, centered on a patient case, addressing key hem/onc concepts, including transfusion medicine, peripheral blood smears, lymphoma classification, and coagulation disorders. Each solved puzzle revealed additional patient laboratory and pathology data. Successful completion required teams to diagnose the patient and select appropriate treatment. Following the activity, teams participated in a facilitator-led debrief focused on team dynamics, communication, and problem solving. Teams observed each other and shared feedback. A larger group debrief co-led by chief fellows and faculty reviewed learning objectives and key takeaways. Learner outcomes were assessed using a post-activity survey evaluating satisfaction, engagement, and impact on learning. **Results:** Eighteen learners participated, including 14 hem/onc fellows, 1 APP hem/onc fellow, and 3 internal medicine residents. Three of four teams escaped within 1 hour (mean completion time, 52 minutes). All participants provided positive verbal feedback. Fifteen learners completed the post-activity survey, and all respondents reported satisfaction with the activity and would recommend it for future fellows. One-word descriptors included “engaging,” “fun,” and “challenging.” Most respondents (93.3%) agreed that the activity reinforced key hem/onc concepts and improved confidence in clinical problem-solving. All learners felt the activity supported learning, and 93.3% reported that collaboration enhanced the learning experience. Participants identified team-based problem solving, clinical application, and interactive puzzles as the most effective components. **Conclusions:** A hem/onc escape room resulted in high learner satisfaction and reinforced hem/onc knowledge and clinical problem-solving. This feasible, fun, and innovative activity complements traditional fellowship education by leveraging adult learning principles through gamified, team-based learning and should be incorporated into training programs’ curriculum. Research Sponsor: None.

Learning science principles applied in a hem/onc escape room.

Active Learning	Belonging	Contrasting Cases	Debriefing	Deliberate Practice
Elaboration	Generation	Listening and Sharing	Reward	Worked Examples

9022 **Poster Session**

Career destination effects of receipt of the American Society of Clinical Oncology Young Investigator Award. First Author: Vince D. Cataldo, Department of General Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Successful funding during training has long been recognized as a predictor for a career in academic medicine.[1] Among hematology and medical oncology fellows, the American Society of Clinical Oncology Young Investigator Award (ASCO YIA) often serves as a fellow’s first attempt to obtain extramural research funding. Whether receipt of the ASCO YIA predicts for an academic career in hematology and medical oncology is unknown. **Methods:** A retrospective, exploratory analysis was conducted using data from 15 consecutive graduating classes from the fellowship program of a large destination cancer center. For each graduate, data regarding submission of an ASCO YIA proposal and the results of each submission were collected. To determine if receipt of the ASCO YIA correlated with an early career and retention in academia, we explored data on each graduate’s initial and current job placement. Correlation of each physician’s area of subspecialization compared to the focus of the ASCO YIA proposal was also investigated. **Results:** From 2011-2025, a total of 214 graduates were identified, and 211 (98.6%) applied for the ASCO YIA. Eighty-three (39%) applicants were awarded the ASCO YIA. Among the entire cohort of applicants for the ASCO YIA, 157 (74%) graduates sought an initial career in academia. Of the fellows who were awarded the ASCO YIA, 74 of 83 (89%) started their careers in academia compared to 83 of 128 (65%) for those who were not awarded the ASCO YIA (odds ratio [OR], 4.46; 95% confidence interval [CI], 2.04 to 9.74; P = 0.0002). Of the fellows awarded the ASCO YIA, 66 of 83 (80%) currently remain in academia compared to 51 of 128 (40%) for those who were not awarded the ASCO YIA (OR, 2.57; 95% CI, 0.29 to 1.60; P = 0.0038). Of the fellows who were awarded the ASCO YIA and sought careers in academia, 69 of 74 (93%) began their academic career in the same subspecialty as the focus of their ASCO YIA proposal, and 59 of 66 (89%) remain in that subspecialty. **Conclusions:** Among applicants for the ASCO YIA, recipients are more likely than non-recipients to begin careers in academic hematology and medical oncology positions and to remain in academia. In addition, early funding through the ASCO YIA predicts for retention of academic hematologists/oncologists in their subspecialty of early research and funding. These results emphasize the need for enhanced funding to support these awards with a goal of promoting early careers in academic hematology and medical oncology. To further validate these results, a multi-institutional analysis is planned. Reference: 1. Brass LF, Akabas MH, Burnley LD, Engman DM, Wiley CA, Andersen OS. Are MD-PhD programs meeting their goals? An analysis of career choices made by graduates of 24 MD-PhD programs. Acad Med. 2010;85(4):692–701. Research Sponsor: None.

9023 **Poster Session**

Oncomovies: Cancer in cinema from early sound film to 2025. First Author: Luciano de Fiore, Il Pensiero Scientifico Editore, Rome, Italy

Background: Cinema has played a relevant role in shaping public representations of cancer, influencing social perceptions of illness, medical care, prognosis, and the patient–physician relationship. Over time, cancer narratives in film have evolved alongside medical knowledge, therapeutic advances, and cultural attitudes toward disease, suffering, and death. Building on previous analyses presented at ESMO (2012) and a systematic review published in 2014, this study provides an updated overview of how cancer has been portrayed in cinema up to 2025. **Methods:** We conducted a cross-sectional descriptive analysis of feature films in which cancer played a prompt, relevant, or plot-driving role. Films were identified through major movie databases (IMDb, AllMovie, MyMovies) and previous curated filmographies. Each film was independently reviewed and coded using a standardized data extraction framework including year of production, country, patient demographics, cancer type and anatomical classification, stage or phase of disease when specified, diagnostic and therapeutic representations, healthcare professionals’ roles, and narrative outcome. Data were aggregated and analyzed descriptively. **Results:** A total of 255 films produced between 1939 and 2025 were included. The majority originated from North America and Western Europe, with a progressive increase in geographic diversity after 2000. Solid tumors accounted for approximately 75% of depicted cancers, followed by hematologic malignancies (about 19%). The most frequently represented cancer types were breast cancer, brain tumors, leukemia, and lung cancer, while several high-incidence cancers in real-world epidemiology remained underrepresented. Central nervous system tumors and breast cancer were the most common anatomical classifications. When reported, cancer was often portrayed at an advanced or metastatic stage. Treatments were shown in most films, with chemotherapy being the most frequently depicted modality, followed by surgery and palliative care. Healthcare professionals appeared in the majority of narratives, though with varying degrees of realism. Death remained a common narrative endpoint. **Conclusions:** This updated analysis confirms persistent narrative patterns in cinematic representations of cancer, including a preference for younger patients, specific tumor types, and dramatic disease trajectories. While recent films show increased attention to diagnostic processes and treatment complexity, discrepancies between cinematic portrayals and epidemiological reality remain substantial. Oncomovies may represent both a valuable cultural resource for medical education and a potential source of misconceptions, underscoring the importance of critical engagement with cancer narratives in film. Research Sponsor: None.

9024 **Poster Session**

Training fellows in genomic oncology: A pilot team-based workshop. First Author: Lauren O'Loughlin, Beth Israel Deaconess Medical Center, Boston, MA

Background: Genomic oncology (GO) is central to diagnosis and management of patients with cancer. However, GO training is an unmet need for hematology/oncology (H/O) fellows. The Training Fellows in Genomic (TFIG) Working Group developed a team-based GO workshop, with goals of creating a "train-the-trainer" experience for faculty and improving fellows' GO knowledge. **Methods:** Ten North American H/O fellowship programs participated in the TFIG pilot. Cross-disciplinary faculty (H/O fellowship program leaders [PL] with local GO faculty experts) participated in (2) 60-minute virtual "train-the-trainer" sessions on team-based learning (TBL) and GO content. Faculty then led (2) 120-minute case-based TBL workshops for fellows at their home institutions: 1) methodology and selection of cancer gene panels, and 2) result interpretation and clinical utility. Participating faculty and fellows were sent a post-workshop survey. Fellows received an additional follow-up survey seven months after workshop participation. **Results:** 96 fellows and 24 faculty participated in the TFIG workshop. 68 fellows (71%) and 21 faculty (88%) completed the post-workshop survey; 60 fellows (62%) completed the follow-up survey. In addition to H/O PL, workshop faculty included pathologists (n=2), genetic counselors (n=2), laboratory geneticists (n=2), medical geneticists (n=1), and genomics professors (n=1). Most (90%) felt train-the-trainer sessions were helpful for workshop preparation. All agreed/strongly agreed that the workshop will help fellows as practicing oncologists. All would recommend the workshop to other fellowship programs. While most fellows (88%) reported using GO in their clinics, 97% had no prior training during fellowship. The majority reported that their pre-workshop knowledge of GO was poor (31%) or fair (43%). Almost all (91%) agreed/strongly agreed that the workshop will help their clinical practice, and most (88%) would recommend this workshop to other fellows. At seven months post-workshop, more than half (52%) of fellows reported greater interactions with genetics professionals and increased use of web-based GO resources introduced during the workshop; 32% reported using knowledge gained during the workshop to educate others. **Conclusions:** Formalized training in GO is required for H/O practice and remains an unmet need for H/O fellows. Our TFIG pilot demonstrated that an interactive GO workshop is feasible through implementation of standardized faculty training and a case-based TBL format. Faculty found the "train-the-trainer" model helpful and noted TFIG content is effective and recommended for fellows. Fellows reported sustained improvements in GO knowledge, increased use of web-based GO tools explored during the workshop, and greater interdisciplinary engagement with GO experts. These findings support the TFIG model as a scalable and effective means to deliver expert-led, team-based GO training for H/O fellows. Research Sponsor: U.S. National Institutes of Health; R25CA168544.

9025 **Poster Session**

Experiences of a cancer survivorship elective in a US medical school: The first 10 years. First Author: Lee Dong, Frank H. Netter MD School of Medicine, Quinnipiac University, North Haven, CT

Background: Cancer survivorship care is an increasingly important competency in medical education, but early introduction in medical school curriculum is uncommon, and longitudinal evaluation of survivorship curricula is limited. We report here our 10 years' experience of a dedicated UME cancer survivorship course. **Methods:** A 15-week elective was offered to pre-clerkship Y2 students (5-14 participants /y) annually from 2016-25, including one fully remote class in 2020. Attendees had a year of prior longitudinal clinical experience. Key topics of the curriculum were developed from ASCO and NCCN Survivorship Guidelines. Sessions were facilitated by a clinical oncologist (MCF) and co-hosted by rotating guests with clinical experience in cancer care. These included a primary care physician, survivors, caregivers, a medical geneticist, a palliative care nurse, social workers, a nutritionist, and a PT/OT specialist. The final assessment was a proposed individualized survivorship care plan (SCP), based on a one-to-one interview with a survivor. Students completed pre- and post-course surveys, assessing satisfaction with course structure, change in confidence dealing with topics covered, and the course's influence on specialty choice. Likert scale responses (1-4) were analyzed using paired t-tests and Cohen's d for confidence changes. Descriptive statistics summarized satisfaction and career impact. **Results:** Of 102 students participating over 10 years, 90 returned pre/post surveys (88%). Students overall reported a high level of satisfaction with the course (mean 3.60/4, SD 0.49), particularly valuing guest sessions with survivors (3.84/4), caregivers (3.86/4), and social work (3.91/4). They felt the course was adequately rigorous for the M2 level (3.59/4), provided useful skills for future interprofessional collaboration (3.60/4), and was effectively tested by the final assignment (3.47/4). Multimedia assignments were the most valuable to students (3.47/4). Confidence in speaking to and caring for cancer survivors increased very significantly post-course (mean change +0.75, $t = 7.81$, $p < 0.001$, $d = 1.02$), and students felt that the skills they learned were relevant to their future careers (3.53/4). Over half of students (56%) indicated the course strengthened their interest in pursuing an oncology-focused field while another f26% indicated an interest in remaining committed to cancer-related issues in some capacity. **Conclusions:** A dedicated undergraduate cancer survivorship curriculum is novel, feasible, sustainable, and highly valued by medical students. The course produced significant gains in confidence, increased interest in oncology, and highlighted the educational value of interprofessional, survivor-centered learning. Early integration of survivorship education may improve future physician comfort with holistic cancer care and enhance career interest in the field. Research Sponsor: None.

9026 **Poster Session**

From pathophysiology to prognosis: An oncology curriculum for interdisciplinary palliative care specialists. First Author: Sinthana Ramsey, University of Pittsburgh Medical Center, Division of General Internal Medicine, Pittsburgh, PA

Background: Integrating specialty palliative care (SPC) improves outcomes for patients with advanced cancer, yet effective collaboration requires a shared understanding of the clinical condition. Oncologists report that SPC professionals lack familiarity with new oncologic therapies and their implications for prognosis and decision-making—a gap that can hinder the quality and timing of communication amongst providers as well as goals of care conversations with patients and surrogates. Addressing this gap may enhance the value of SPC consultations and support more aligned co-management of patients with advanced malignancies. Objective: To design, implement, and evaluate an interdisciplinary oncology curriculum for SPC health science professionals (HSPs) at a single institution, with the goal of enhancing SPC's knowledge and confidence in caring for patients with advanced solid-tumor malignancies. **Methods:** An informal needs assessment was conducted with oncologists and palliative care physicians to inform content development. The topics identified to discuss included oncologic terminology, therapeutics, side effects, and disease trajectories for breast, lung, colon, and pancreatic cancer. The curriculum comprised five synchronous virtual sessions delivered over five months. Sessions incorporated active learning strategies grounded in principles of Andragogy and Self-Determination Theory. Medical oncologists reviewed content and participated in sessions. Electronic flashcards were distributed to provide learners asynchronous background knowledge and for post-session reviews. A paired pre/post survey assessed knowledge (via 19 multiple-choice questions for physicians, APPs, and pharmacists) and SPC's attitudes (via 5-point Likert scale). **Results:** Of 79 invited SPC HSPs across nine sites, 51 participated: 17 APPs, 26 physicians, 1 pharmacist, 7 social workers, and 1 chaplain. 87% of the participants attended at least 4 of the 5 curriculum sessions. 67% of the participants utilized the flashcards. Among the physicians, APPs, and pharmacists completing knowledge assessments (pretest n= 42, posttest n= 35), mean scores improved from 53.9% (SD 13.6) to 67.8% (SD 13.1), $p < 0.001$. Confidence in applying oncology concepts increased from 2.7 (0.8) to 3.5 (0.5), $p < 0.001$. Perceived importance of this education remained high throughout (pre 4.2 [0.6], post 4.1 [0.8], $p = 0.609$). **Conclusions:** This oncologist-informed curriculum significantly improved SPC's oncology knowledge and confidence. By equipping specialty palliative care teams with stronger oncologic foundations, this curriculum offers a scalable approach to enhancing interdisciplinary collaboration—potentially improving consultation quality, communication, and shared decision-making for patients with advanced cancer. Research Sponsor: Thomas Nimick Jr. Competitive Research Fund, Shadyside Foundation.

9028 **Poster Session**

Enhancing hematology-oncology education through a structured AI-based board review series: An ASCO Leadership Development Education Scholars initiative. First Author: Manasi Ghatge, Department of Hematology Oncology, The Permanente Medical Group, San Francisco, CA

Background: As an ASCO Leadership Development Education Scholars Initiative, structured board review is essential for hematology–oncology fellows to consolidate knowledge, support examination readiness, and strengthen clinical decision-making in an increasingly complex therapeutic landscape. Existing approaches are often fragmented and insufficiently tailored to trainee-specific knowledge gaps. To address this need, we developed a pilot, structured board review series within a single academic fellowship program integrating peer-led teaching, faculty mentorship, and anonymous question-based learning aligned with board examination content and real-world oncology practice. **Methods:** A longitudinal, fellow-led board review curriculum was implemented within a hematology–oncology fellowship program with subspecialty faculty mentorship to ensure clinical accuracy and guideline-based context. Fellows engaged through weekly anonymous board-style multiple-choice questions distributed via Microsoft Teams polls. Questions were curated from ASCO Self-Evaluation Program materials based on high-yield topics identified from ASCO and ASH in-training examinations, with AI-assisted topic prioritization. Objective knowledge acquisition was assessed using identical pre- and post-session questions. Each topic spanned one month with eight pre-session questions and the same eight questions administered post-session. Across five sessions, five fellows answered eight questions per session, yielding 200 learner responses for both pre- and post-intervention assessments. This initiative was conducted as an educational quality improvement project and did not meet criteria for human subjects research. **Results:** Educational gains were observed across multiple high-yield oncology domains, including molecular biomarker interpretation, guideline-directed therapy selection, toxicity recognition and management, and familiarity with emerging treatment modalities. In the pre-test assessment, 63% of questions were answered correctly (126 of 200 responses). Following the educational intervention, 98% of questions were answered correctly (196 of 200 responses), representing an absolute improvement of 70 correct responses (35%). **Conclusions:** This structured, fellow-led, faculty-supported board review initiative represents a feasible and effective model for delivering high-yield oncology education within hematology–oncology fellowship training. The curriculum demonstrated measurable knowledge gains, high trainee engagement, and successful integration of AI-informed topic selection with in-training examination data, highlighting the potential for learner-centered curricula to modernize subspecialty medical education and expand to more fellowship programs. Research Sponsor: None.

9029 **Poster Session**

Impact of liquid biopsy training on real-world testing practices for advanced NSCLC across Latin America: The OMEGA (LACOG 0424/GBOT) survey. First Author: Leonardo Gil Santana, Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil

Background: The therapeutic landscape of non-small cell lung cancer (NSCLC) has evolved with advances in genomic profiling and the integration of next-generation sequencing (NGS) platforms. Liquid biopsy (LB) enables minimally invasive biomarker-guided treatment across solid tumors, including NSCLC. However, disparities in physicians' familiarity with these tests and limited access to continuing education can affect their optimal implementation. Despite the potential benefits, access to and utilization of LB testing across LATAM remains unexplored. In this LATAM survey, we evaluated oncologist's attitudes and practices related to LB. **Methods:** A cross-sectional survey was conducted to evaluate oncologists' attitudes, practices, and expectations regarding LB use in NSCLC across LATAM. A 33-item questionnaire was distributed between August and December 2024 through the Brazilian Thoracic Oncology Group (GBOT), the Brazilian Society of Clinical Oncology (SBOC), and the Latin American Consortium for Lung Cancer Research (CLICaP). Descriptive statistics summarized the data, and associations were assessed using chi-square or Fisher's exact tests for categorical variables and Student's t-test or Wilcoxon rank-sum test for continuous variables. **Results:** Among the 178 respondents, 84.8% were from Brazil. Most of the oncologists had completed their oncology training between 5 and 20 years prior (61.2%). In terms of clinical exposure, 43.3% reported treating 10 to 30 new patients with lung cancer annually. While 72.5% reported prior use of LB, only 30.0% expressed confidence in interpreting the results. In addition, 50% of respondents (n = 89) reported no formal training in LB over the past three years. Among those reporting educational updates, the most prevalent source of educational updates was ASCO-affiliated platforms (43.8%). Respondents who had received dedicated training during this period were significantly more likely to request LB testing (87.2% vs 60.7%; $p<0.0001$) and to report confidence in interpreting ctDNA results (86.0% vs 53.9%; $p<0.0001$). The most frequently used techniques were DNA-based NGS (38.8%) and reverse transcription polymerase chain reaction (RT-PCR) (43.5%). Most respondents (96.1%) anticipated an increase in the use of LB over the next five years. **Conclusions:** The OMEGA survey indicates that while LB use is common among LATAM oncologists, formal training remains limited. Educational exposure significantly increased both the likelihood of requesting NSCLC testing and confidence in molecular report interpretation. Thus, future efforts implementing structured educational programs are very needed to support the equitable and effective adoption of liquid biopsy throughout LATAM. Research Sponsor: None.

9030 **Poster Session**

Applying learning science principles (LSP) in a workshop (WS) for hematology and oncology (HemOnc) trainees (HOT) about how to use artificial intelligence (AI) in medical education (MedEd) and clinical practice (CP). First Author: Guilherme Sacchi de Camargo Correia, Medical College of Georgia at Augusta University, Augusta, GA

Background: AI use is ubiquitous among HOT and healthcare workers, but with variable base knowledge and comfort level. Its indiscriminate use may be problematic. To address this educational gap, we developed a WS for HOT to assess their use of AI and educate them on how to employ it in MedEd and patient-centered CP based on LSP. **Methods:** A faculty member developed a WS on how to use AI in MedEd and CP based on LSP of analogy, contrasting cases, elaboration, generation, and question driven learning. The WS was for HOT, but faculty could join. It had 3 sections: introduction to basic concepts of AI; principles of the Health Insurance Portability and Accountability Act and protected health information; AI in MedEd; and AI in CP. Sections had real use case examples of AI, for participants to interact, ask questions, and share their personal use cases. HOT were invited to compare and generate examples during the WS, based on their educational and clinical experience and needs. Participants' AI use and self-perceived and objective knowledge about it were assessed in a pre activity survey, a post WS survey, and a post 8 week survey to evaluate long term learning. **Results:** A 2 hour WS with 9 HOT and 2 faculty was completed successfully. 10 participants completed the pre WS survey, and 11 completed the post WS and the post 8 week surveys. 100% of them used generative AI tools before the WS, while 10% had prior training in AI. 90% used AI in personal life and MedEd, 70% used it in CP, and 30% in academic research. Table 1 shows participants' self-assessed knowledge of AI, comfort level in using AI for MedEd and CP, self-assessed preparedness to implement AI in MedEd and CP, and objective knowledge. 8 weeks post WS, 91% of participants reported increased AI use in CP, leading anywhere from slight to significant decreases in time spent on documentation tasks for 91% of them. In MedEd, 73% reported increased AI use, and 82% described slight to significant improvement in the quality of time dedicated to it. 82% described the WS as extremely relevant to their daily responsibilities, and 91% reported confidence navigating ethical and privacy risks of AI in HemOnc. All participants were interested in having a similar WS in the future. **Conclusions:** An LSP based WS about AI increased the self-perceived and objective knowledge of HOT about using this tool in MedEd and CP. It also increased HOT comfort level, preparedness, and efficiency using AI. With the ubiquitous use of AI by HOT, ongoing education about it focused on supporting high-quality patient care should be a part of fellowship curriculum. Research Sponsor: None.

	Pre WS %	Post WS %	Post 8 week %
Moderately/Very knowledgeable about AI	50	91	100
Comfortable using AI in MedEd	60	82	82
Prepared to implement AI in MedEd	30	91	73
Comfortable using AI in CP	40	73	82
Prepared to implement AI in CP	0	91	73
Correct answers on objective assessment	53	68	71

9031 **Poster Session**

Enhancing oncology board exam readiness through a longitudinal review curriculum. First Author: Sonia Godbole, Ohio State University Wexner Medical Center, Columbus, OH

Background: Due to the rapid pace of medical advancements in cancer care in recent years, passing the medical oncology board exam is a challenging task, with an average failure rate of 8% for first-time test takers since 2020 (American Board of Internal Medicine – ABIM). A needs assessment performed within our large academic Hematology/Oncology (H/O) fellowship program revealed that only a modest majority of fellows felt adequately prepared for medical oncology and malignant hematology board exam topics (53% and 63%, respectively). To improve fellow satisfaction, confidence, and exam performance, we developed a longitudinal board review curriculum that ran parallel to standard didactics. **Methods:** From August 2024 to May 2025, H/O fellows at The Ohio State University participated in a structured, longitudinal board review series covering medical oncology and malignant hematology topic areas. Faculty led monthly Zoom sessions focused on rapid content review and interactive question practice aligned with high-yield concepts per the ABIM Oncology exam blueprint. Questions from existing board review materials were utilized in session creation. Fellows completed pre- and post-surveys assessing satisfaction with the curriculum and confidence across 20 oncology topic domains using a 5-point Likert scale. Attendance and In-Training Exam (ITE) scores were collected. Analyses included descriptive statistics, correlation, and effect size testing. **Results:** Survey response rates (n = 29) were 72% (pre) and 86% (post). Agreement that the curriculum adequately prepared fellows for medical oncology and malignant hematology content on the board exam increased from 53% to 79% and 63% to 92%, respectively. Fellow confidence improved in all 20 topic domains, with an average increase of 0.57 on a 5-point Likert scale. Paired analysis of individual ITE scores could be performed in 19 fellows and demonstrated a mean gain of +58 points from 2024 to 2025. Larger improvements were observed among those who attended $\geq$50% of the 2024-2025 board review sessions (Cohen's $d \approx 0.85$). A moderate positive correlation was also identified between pre-ITE session attendance and the magnitude of the score increase for an individual fellow ($r = 0.47$). Notably, the correlation between attendance and change in ITE score held true for both second and third-year fellows. **Conclusions:** The implementation of a longitudinal, structured oncology board review series for H/O fellows at our institution improved trainee satisfaction with their preparation and confidence regarding all testable topic areas. Furthermore, improvements in ITE scores pre- and post-intervention were more robust in fellows with higher session attendance, regardless of fellowship year. This intervention strategy offers a model for other fellowship programs, H/O or otherwise, seeking ways to improve board exam readiness for their fellow-level learners. Research Sponsor: None.

9032 **Poster Session**

Bridging educational and research gaps among young oncologists in Latin America: Results from a multicenter survey. First Author: Sergio Cifuentes-Canaval, Instituto de Cancerología Las Américas, Medellín, Antioquia, Colombia

Background: Strengthening oncology research capacity in LATAM is critical to improving regional cancer outcomes. Early-career oncologists play a central role in clinical research, yet structural barriers limit their engagement. Data on educational access, research opportunities, and training needs in LATAM remain limited. This study describes research involvement among early-career oncologists and assesses access to training, mentorship, and career development opportunities, and key barriers to education and research participation. **Methods:** An international, cross-sectional, web-based survey was conducted between Nov/2025 and Jan/2026 among early-career oncologists in LATAM ($<$40 years or $<$10 years post-training). Data included demographics and professional development indicators related to research and training. **Results:** A total of 105 surveys were included and were mainly from Colombia 37.1%, Mexico 23.8%, Argentina 8.6%, and other LATAM countries 30.5%; 58.1% were female. Most were $\leq$40 years 84.8%, with 43.8% aged 30–35; 19.0% were in training and 55.2% early career. 19% reported no research involvement; 71.4% dedicated $<$25% of professional time to research, and only 9.5% $\geq$26%. Most participants (80.0%) received no research-related compensation. Although 51.4% reported access to educational opportunities, only 29.5% perceived adequate access to clinical research. Institutional encouragement was reported by 23.8%, and 39.0% had a clear career development plan. Main training barriers were cost (63.8%), clinical workload (61.9%), and limited institutional support (49.5%). The leading unmet educational need was clinical trials and research methodology (83.8%), followed by precision medicine (64.8%) and leadership/oncology management (57.1%). Overall, 68.6% had prior research exposure—mainly as collaborators (43.8%)—while only 21.9% reported principal investigator experience. Key research barriers included limited clinical time (58.1%), lack of funding (48.6%), and restricted research networks (42.9%). Only 37.1% reported an active mentor; institutional mentorship was available to 22.9%, and formal leadership training to 30.5%. Despite high motivation, structural barriers—including limited protected time, funding, mentorship, and institutional support—restrict research engagement among young oncologists in LATAM. Clinical trials and research methodology as unmet needs underscores a gap between educational access and effective research capacity development. **Conclusions:** Young oncologists in LATAM face limited opportunities for active research participation. Structural barriers—including workload, funding, restricted networks, and limited mentorship—hinder progression toward independent research and leadership roles, underscoring the need for programs that expand participation pathways beyond education. Research Sponsor: None.

9033 **Poster Session**

Collaborative education to advance equitable prostate cancer care in geographically diverse communities. First Author: Erica Rusie, Talem Health, Trumbull, CT

Background: Although 15%-19% of the US population resides in rural areas, less than 10% of oncologists practice there, driving significant inequities in prostate cancer care. Community clinicians face barriers including limited subspecialist access, multidisciplinary gaps, biomarker testing delays, and low clinical trial participation. As biomarker testing, imaging, and individualized treatments evolve, targeted education is vital to support evidence-based decision-making and equitable delivery. **Methods:** Talem Health implemented a multicomponent CME/CE-accredited initiative for community oncologists managing prostate cancer across the disease spectrum. The initiative featured a 1-hour virtual session at the 2025 Oncology Congress, a 7-session longitudinal Project ECHO (Extension for Community Healthcare Outcomes) telementoring series, and a 1-hour "lessons learned" online activity. Outcomes were assessed via mixed methods: quantitative pre/post-activity assessments and polling, and qualitative data from ECHO case discussions and interviews. Analyses evaluated changes in knowledge, competence, and planned behaviors using Chi-square tests and effect size calculations. **Results:** Over 600 clinicians participated; 91% were hematology/oncology specialists, 93% practiced in community/non-academic settings, and 90% served rural or underserved populations. Identified barriers included limited testing access (36%), treatment access challenges (27%), multidisciplinary gaps (25%), and guideline unfamiliarity (23%). Statistically significant improvements occurred across all knowledge and competence outcomes ($P < .05$ to $P < .01$). Clinicians reported increased intent to incorporate genomic/germline testing; align nmCRPC decisions with guidelines; utilize combination strategies for mHSPC; personalize mCRPC therapy; and implement shared decision-making. Qualitative findings from the ECHO series emphasized the value of peer-to-peer learning. Participants reported higher confidence in managing complex cases and contextualizing new evidence within real-world practice. Ongoing needs were identified regarding risk stratification, rural access barriers, and artificial intelligence applications. Repeated participation in ECHO sessions enabled clinicians to apply new evidence across multiple patient cases over time, reinforcing clinical decision-making through iterative discussion and shared problem-solving. **Conclusions:** This longitudinal educational design effectively supported community oncologists, yielding meaningful gains in knowledge, confidence, and intended practice behaviors. These results demonstrate that tailored education can expand clinician capacity and improve care for patients with prostate cancer in rural and underserved settings. Research Sponsor: This initiative was supported by an independent educational grant from Astellas and Pfizer, Inc.

9034 **Poster Session**

Investigating interactions between pharmaceutical industry and oncologists in Africa: A secondary analysis of ONCOTRUST-2 study. First Author: Imène Hadji, EPH Ibn Zohr, Guelma, Algeria

Background: Following the hypothesis-generating ONCOTRUST-1 study, ONCOlogy TRansparency Under Scrutiny and Tracking 2 (ONCOTRUST-2) aimed to compare perceptions, understanding, and behaviors related to conflicts of interest (COI) in oncology between high-income countries (HICs) and low- and middle-income countries. This secondary analysis focuses on African countries versus HICs to explore regional differences in interactions with the pharmaceutical industry. **Methods:** We conducted a cross-sectional, survey-based study over two years (January 2024–January 2026). Participants were oncologists practicing in Africa or HICs. Outcomes included perceptions of industry-oncologists' interactions, recognition of COI scenarios requiring disclosure, and self-reported behaviors. Comparisons used Chi-squared or Fisher's exact tests as appropriate. **Results:** A total of 331 oncologists were included (Africa n=133; HIC n=188; 52% women). Most respondents were specialists (61.3%), followed by professors (22.1%) and trainees (15.1%). HIC oncologists reported better understanding of evidence-based medicine (EBM) than African oncologists (p=0.002). Overall ability to identify all COI scenarios requiring declaration did not differ (p=0.45), but HIC oncologists more frequently recognized consulting/advisory roles, direct payments/honoraria, expert testimony, personal funding, and travel/conference support as declarable COI (all $p<0.01$). No group differences were observed for sample drugs, institutional research funding, gifts, or food/beverage paid by industry (all $p>0.05$). Self-reported COI disclosure prevalence was similar between groups (p=0.67), and travel/conference support from pharmaceutical industry did not differ (p=0.14). African oncologists reported fewer consulting honoraria (p=0.001) and lower amounts ($p<0.001$) and less research funding (p=0.02), but more receipt of drug samples (p=0.001). Compared with HIC peers, African oncologists reported poorer disclosure practices (less reporting in publications when COI existed, p=0.001; less disclosure before presentations, $p<0.0001$). Moreover, African oncologists reported more prescription pressure from industry (p=0.013) and lower perceived objectivity in trial appraisal when COI exist (p=0.056). Interestingly, HIC oncologists more often endorsed adopting new drugs despite weak clinical-trial evidence (p=0.003). Knowledge of COI regulations/policies was lower in Africa ($p<0.0001$). Across both groups, support was strong for clearer COI policies, education, and online COI databases. **Conclusions:** African and HIC oncologists showed difference in recognition of specific COI types, disclosure behavior, and policy awareness. Strengthening COI education and implementing clear enforceable policies are therefore needed. Research Sponsor: None.

9035 **Poster Session**

Hematology-oncology bootcamp: Educational impact of an interactive, guideline-based "101" curriculum. First Author: Chinmay Jani, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL

Background: Hematology-oncology is a rapidly evolving field, and incoming fellows often face early gaps in foundational knowledge during the transition from internal medicine. Mastery of core principles and guideline-based care is required before complex trial interpretation, yet traditional one-way didactic models may be insufficient. To address this, we implemented a structured, longitudinal bootcamp of ASCO- and ASH-aligned sessions delivered through interactive educational formats for fellows across all training years. **Methods:** Bootcamp curriculum included foundational content in anticancer pharmacology, 4 core-domain "101" sessions, NCCN-based case discussions, clinical trial design, academic career development, workshop on difficult clinical conversations and Kahoot-based heme-path and board review. Content was delivered through 6 different interactive formats over the first 10 weeks of the academic year during a weekly protected half-day. Fellows completed anonymous pre- and post-bootcamp questionnaires assessing self-reported confidence on a 5-point Likert scale. Secondary outcomes included overall knowledge improvement, clinical confidence, satisfaction, and educational format preferences. Pre- and post-intervention scores were compared using Mann-Whitney test. **Results:** Sixteen fellows completed the pre-bootcamp survey and 13 completed the post-bootcamp survey. There was statistically significant improvements across all 4 core-domains: General Oncology and foundations (2.9 to 3.8; $p < 0.01$), Classical Hematology (3.0 to 3.7; $p < 0.05$), Hematologic Malignancies (2.8 to 3.7; $p < 0.05$), and Solid Tumors (2.5 to 3.4; $p < 0.05$). Case-based discussions and chalk-talks were the most effective formats, used in both 101 sessions and communication workshop (Table). Moderate or major improvements in overall knowledge as well as inpatient/outpatient clinical confidence were reported by 92.3% fellows. Quality meal options encouraged in-person attendance for 84.6% fellows. Overall satisfaction with the bootcamp was high, with 84.6% fellows reporting agreement or strong agreement. **Conclusions:** Early delivery of foundational concepts through interactive, case-based "101" curricula improves fellows' knowledge and clinical confidence. While traditional lectures remain important for trial interpretation, incorporating interactive formats enhance confidence and satisfaction for fellows. This structured, guideline-based bootcamp represents a scalable model for fellowship training. Research Sponsor: None.

Educational format effectiveness.

Educational Format	Mean Effectiveness Score (1-5) ± SD
Chalk-talks	4.2 ± 0.7
Case-based scenarios	4.2 ± 0.6
Kahoot-based interactive rounds	3.9 ± 0.6
PowerPoint	3.6 ± 0.7
Group-discussions	3.3 ± 1.1
Online Modules	2.5 ± 0.8

9036 **Poster Session**

Empowering educators: An international virtual mentorship program for hematology/oncology medical educators. First Author: Audrey M. Sigmund, The Ohio State University - The James Cancer Hospital and Solove Research Institute, Columbus, OH

Background: Mentorship is a cornerstone of physician career development, linked to improved well-being, job satisfaction, research productivity, and faculty retention. Clinician educators often cite lack of mentorship as a major barrier to career advancement. We developed and piloted a year-long virtual mentorship program (VMP) with the American Society of Clinical Oncology (ASCO) for hematology/oncology (H/O) career development in medical education. **Methods:** We piloted the program during the 2024-2025 ASCO VMP cycle. Mentors and mentees applied via survey and were matched by committee members based on interests and goals. Each pair was required to complete a mentorship plan, including goals in three domains: professional development/course work, administrative/leadership experience, and scholarly output. We conducted an anonymous retrospective survey of participants via Qualtrics upon cycle completion. Surveys assessed: meeting cadence, satisfaction, goal attainment, and perceptions of career trajectory. Confidence in mentoring and knowledge growth related to pursuing a medical education career were assessed using a 5-point Likert scale with retrospective pre–post ratings. Paired scores were analyzed using the Wilcoxon signed-rank test after excluding ties. **Results:** Thirty-eight mentors and 42 mentees participated in the pilot. Survey response rate was 40% (mentors: 36.8%, mentees: 42.9%). Most met monthly (mentors: 35.7%, mentees: 44.4%) or every 2-3 months (mentors: 42.9%, mentees: 38.9%). Satisfaction was high (mentors: 71.4% "very satisfied," 21.4% "satisfied"; mentees: 66.7% "very satisfied," 27.8% "satisfied"), and nearly all would recommend the program (mentors: 100%, mentees 94.4%). The mentorship plan was discussed by all, with the majority reporting goal achievement (mentors: 92.9%, mentees: 88.9%). Most plan for ongoing mentoring after cycle completion (mentors: 78.6%, mentees: 72.2%). All respondents reported improved perceptions of career trajectory, with all mentors and 92.9% of mentees expressing greater interest in medical education careers and all noting a higher perceived likelihood of success. Mentors' confidence in mentoring increased by a mean of 0.29 on a 5-point scale, but the Wilcoxon test was non-significant ($p = 0.22$). Mentees' knowledge of medical education careers increased significantly with a mean gain of 0.57 ($p = 0.016$). **Conclusions:** Our pilot medical education VMP was highly valued, with strong satisfaction, widespread goal attainment, improved perceptions of career trajectory, and plans for sustained relationships beyond the defined mentorship period. These findings support virtual mentorship as a feasible strategy for clinician educator career development within H/O. Collaboration with and organizational support from professional societies will be essential for scalable, sustainable program development. Research Sponsor: None.

9037 **Poster Session**

Determinants of leadership attainment among ASCO Leadership Development Program, 2009–2025. First Author: Sarah Marie Abraham, Florida International University, Miami, FL

Background: Determinants of leadership attainment among participants in formal leadership development programs remain poorly characterized. We examined the factors associated with leadership attainment among graduates of the ASCO Leadership Development Program (LDP). **Methods:** We conducted a retrospective cohort study of ASCO LDP participants from 2009–2025. Leadership attainment following participation in the ASCO LDP was the primary outcome, defined as cancer Center Director, Division Chair, Subspecialty Chief, or Program Director, as identified through publicly available data. Participant characteristics included gender, medical training (American medical graduate [AMG], international medical graduate [IMG]), education (MD, MD/PhD, MD/Master's), National Cancer Institute (NCI) designation, geographic region (West, Northeast, South, North Central, non-US), and scholarly productivity (h-index). Descriptive analyses were performed overall and by leadership status. Multivariable logistic regression was used to estimate adjusted associations, including gender–NCI designation interaction. Adjusted odds ratios (AORs) with 95% confidence intervals (CIs) were reported. **Results:** Among 216 eligible participants, 165 (76.4%) attained leadership roles. Participants were predominantly female (n=116, 53.7%), AMGs (n=157, 72.7%), MDs (n=129, 59.7%) and affiliated with NCI-designated centers (n=145, 67.1%). Median h-index was 39 (IQR 25–57), and participants were mostly based in the Northeast (n=77, 35.6%) and West (n=53, 24.5%) regions. Compared with non-leaders, leaders demonstrated higher scholarly productivity, with a higher median h-index (42 [IQR 25–59] vs 29 [IQR 20–44], p=0.042). Using NCI-designated females as the reference group, NCI-designated males demonstrated higher odds of leadership attainment in adjusted models (AOR 2.34, 95% CI 0.96–6.06, p=0.067). Compared with participants from the West, those based in the South demonstrated lower odds of leadership attainment (AOR 0.35, 95% CI 0.12–0.98, p=0.050), independent of gender, education, NCI designation, and year. Leadership attainment remained stable over time, with no consistent temporal trends across subgroups. **Conclusions:** Leadership attainment in ASCO LDP was stable over time and associated with scholarly productivity and geographic region rather than gender or institutional setting. Research Sponsor: None.

Adjusted odds of leadership attainment by gender–NCI designation interaction and geographic region.

Variable	Category	Adjusted OR (95% CI)	p value
Gender × NCI	NCI Female	Reference	–
	NCI Male	2.34 (0.96–6.06)	0.069
	Non-NCI Female	2.04 (0.71–6.43)	0.201
	Non-NCI Male	1.17 (0.43–3.32)	0.760
Region	West	Reference	–
	Northeast	0.64 (0.23–1.65)	0.366
	South	0.35 (0.12–0.98)	0.050
	North Central	0.45 (0.14–1.49)	0.183
	Non-US	0.32 (0.07–1.44)	0.141

Gender × NCI modeled as a combined interaction term (ref: NCI female).

9038 **Poster Session**

Leader-member exchange (LMX) and workforce outcomes in radiation oncology: A preliminary generational comparison. First Author: Christopher Mendez, NYU Langone Hospital - Long Island, Mineola, NY

Background: Job satisfaction and turnover intention remain crucial outcomes for healthcare organizations incurring substantial costs associated with recruiting and training new employees. Continual workplace stressors continue to challenge retention efforts across clerical and clinical settings. Leader-member exchange (LMX) theory provides a relationship-based framework for understanding these outcomes, emphasizing the quality of the manager-employee relationship. As healthcare workforce increasingly spans generational cohorts, differences in career expectations and workplace values may influence how leadership relationships are perceived. This study examines the association between LMX quality, job satisfaction, and turnover intention, with specific attention to generational differences between older (Baby Boomers and Generation X) and younger (Millennials and Generation Z) employees within a Radiation Oncology department. **Methods:** This quantitative study surveyed healthcare professionals ($>$ 18 years) in a Radiation Oncology department at an academic medical center using purposive sampling. An anonymous, web-based survey was distributed via email and included standardized measures of leader-member exchange (LMX-7), job satisfaction, and turnover intention (TIS-6), along with demographic items. After electronic informed consent was obtained, the average for survey completion was 7.5 minutes. Data was collected over three months, de-identified, and analyzed using RStudio. **Results:** The survey achieved a 74% response rate, indicating broad representation of the department. Mean LMX scores were comparable between older (M = 4.04, SD = 1.06) and younger (M = 3.91, SD = 1.13) employees. Job satisfaction was modestly higher among younger respondents (M = 4.18, SD = 0.73) compared with older respondents (M = 4.00, SD = 0.82), whereas turnover intention was slightly higher in the older group (M = 1.56, SD = 0.87 versus M = 1.45, SD = 0.83). LMX was positively correlated with job satisfaction in both older (r = .58, p = .002) and younger (r = .59, p $<$ .001) professionals. LMX demonstrated an inverse association with turnover intention in both groups, reaching statistical significance among older employees (r = -.57, p = .003) but not among younger employees (r = -.32, p = .069). **Conclusions:** Higher-quality LMX was associated with greater job satisfaction and lower turnover intention among both older and younger healthcare professionals. This emphasizes the importance of leadership relationships in workforce development and stability. These findings support the value of authentic leadership practices grounded in mutual respect and trust. Additionally, these findings highlight the need for future analyses to examine individual generational groups (e.g., Generation X versus Millennials) to better understand variations. Research Sponsor: None.

9039 **Poster Session**

RECON: A trainee-led, needs-informed professional development and global connectivity model for young oncologists in low- and middle-income countries. First Author: Muhammad Nawaz Khan, Aga Khan University Hospital, Karachi, Pakistan

Background: Oncology trainees and early-career oncologists (ECOs) in low- and middle-income countries (LMIC) face persistent gaps in structured mentorship, research exposure, and non-clinical professional skills, limiting academic development and global engagement. In response, the Residents & Early Career Oncologists Network (RECON) was established in 2024 under the Society of Medical Oncology Pakistan as a national, trainee-led, needs-informed initiative delivering scalable, low-cost, collaborative educational interventions aligned with learner priorities. **Methods:** RECON implemented a needs-informed, multi-component professional development framework for oncology trainees and ECOs ($\leq$5 years post-training) across Pakistan. Core components included: (1) structured mentorship; (2) digital education via the Second Opinion Podcast addressing non-clinical competencies; (3) conference-linked outreach workshops on abstract preparation and peer networking; and (4) monthly international virtual oncology case rounds with young oncologists from Türkiye. Engagement was prospectively tracked, and post-session surveys assessed acceptability and self-reported learning outcomes using 5-point Likert scales (1–5). **Results:** RECON enrolled 104 members (79 trainees, 25 ECOs) and engaged 32 national and international faculty mentors. Baseline survey data (n = 104) demonstrated substantial unmet needs across multiple professional domains, with high interest in professional development (83%), research collaboration (80%), mentorship opportunities (61%), and general networking (60%). Digital education initiatives achieved over 10,000 cumulative podcast views, and three national outreach workshops engaged 155 participants. Post-session surveys from the case rounds series (n = 37) demonstrated high acceptability, with 92% rating sessions as very good or excellent. Participants reported greater confidence in international oncology case discussions (84% rating 4–5) and improved ability to critically appraise alternative management approaches (81% rating 4–5). International perspectives were rated as highly relevant to clinical practice. **Conclusions:** This early evaluation demonstrates the feasibility and acceptability of a national, trainee-led, needs-informed initiative in an LMIC setting. RECON's low-cost, digitally enabled model was associated with high engagement and perceived educational value, particularly in fostering global connectivity and professional confidence among oncology trainees and ECOs. Future evaluation will explore longitudinal outcomes and support iterative refinement, with consideration of adaptation across similar resource-limited contexts. Research Sponsor: None.

9040 **Poster Session**

The role of coaching in enhancing clinical oncology academic performance. First Author: Amanda Woods Herron, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Oncology faculty in academic medicine navigate a multitude of demands spanning clinical care, research, teaching, and administrative pressures. These forces are the impetus for the implementation of targeted interventions to enhance leadership capabilities. Coaching is a robust intervention and has been recognized as well-suited to meet faculty needs. Despite this recognition and increasing adoption, the impact of coaching on key outcomes in both research and clinical spaces remains underexplored. We leveraged Intentional Change Theory (ICT) to guide our evaluation of an internal coaching program within a large academic hospital in the South-Central United States. ICT articulates how alignment of one's ideal self with their professional goals yields sustained personal transformation and is a useful guide for professional coaching. **Methods:** Through this conceptual framework, we employed a quasi-experimental approach to evaluate the impact of coaching on the research outcomes: clinical trials activated and h-index increase, as well as its components (new publications and new citations). Further, we investigated the impact of coaching on the clinical outcomes of Work Adjusted Relative Value Units (RVUs) and patient experience scores (Press Ganey Care Provider Scores). We conducted this study among a sample of clinical oncology faculty who participated in coaching (N = 189) and N = 200 matched peers who were eligible for but had not yet participated in coaching between 2018 and 2022. **Results:** Analyses revealed coaching positively impacted certain research productivity metrics; notably, faculty who participated in coaching were found to have greater increases in h-index (F(1, 379) = 7.27, p = .007, η2 = .02, Coached M = 2.52, SD = 4.16; Comparison M = 1.69, SD = 1.77), new publications (F(1, 318) = 6.26, p = .013, η2 = .02; Coached = M = 10.81, SD = 11.54; Comparison M = 8.06, SD = 10.18), and new citations (F(1, 379) = 7.43, p = .007, η2 = .02; Coached M = 891.79, SD = 1,598.05; Comparison M = 509.47, SD = 1,054.25) in comparison to faculty who had not engaged with a coach. However, no significant differences were detected between groups in regard to clinical outcomes as measured by Work Adjusted Relative Value Units (RVUs) (F(1, 304) = 2.06, p = .15, η2 = .007; Coached M = 6,316.48, SD = 3,558.46; Comparison M = 6,352.38, SD = 3,975.66), and patient experience scores (F(1,150) = 0.91, p = .34, η2 = .006; Coached M = 95.35, SD = 6.41; Comparison M = 96.22, SD = 3.32), or the research outcome of clinical trial activations (F(1,382) = 0.05, p = .83, η2 = .00; Coached M = .73, SD = 1.62; Comparison M = .49, SD = 1.42). **Conclusions:** Findings suggest coaching can be an effective intervention to enhance certain research outcomes reliant on self-regulation and individual motivation. Yet, initial evidence suggests coaching may be less well-positioned to influence outcomes prone to institutional constraints and governance. Research Sponsor: None.

9041 **Poster Session**

Role expansion of advanced practice providers over 5 years at Hawai'i's NCI Community Oncology Research Program. First Author: Christa M. Braun-Inglis, University of Hawai'i Cancer Center, Honolulu, HI

Background: Advanced Practice Providers (APPs), including Nurse Practitioners and Physician Associates, are key members of the oncology team but historically have not been utilized to their full potential in cancer clinical trials. In alignment with NCI policy and guideline changes in 2020 & 2021, the University of Hawai'i Cancer Center & Hawaii NCI Community Oncology Research Program (NCORP) began formally engaging their APPs to maximize clinical trial efforts. The objectives of the current project were to measure the impact of the APP role expansion and identify factors contributing to enhancement of APP role in cancer clinical trials. **Methods:** Data were gathered from the clinical trial management system analyzing APP contributions annually from 2021-2025, including the number of unique APP accruals (enrolling or referring), APPs serving as enrolling/referring investigators, APPs serving as site principal investigator, APPs reviewing trials for feasibility and scientific merit, and trials led by APPs. Informal interviews were conducted to identify the means of APP engagement. **Results:** From 2021 through 2025 the annual number of patients enrolled or referred to trials by APPs increased from 28 to 103, APPs who accrued patients to trials increased from 4 to 13, APPs serving as site PIs increased from 1 to 6, APPs reviewing trials for feasibility and scientific merit increased from 4 to 6, and trials being led by APPs increased from 13 to 30. In 2025, among trials that allowed APP accrual (symptom management and cancer care delivery), APPs accounted for 51% of this site's total accrual. Factors contributing to APP role in cancer clinical trials were identified as APP leadership and engagement, formal and informal mentorship, and APP educational opportunities. **Conclusions:** APPs can significantly contribute to cancer clinical trials in terms of accrual and leadership as evidenced by these results. This project illuminates potential avenues for expanding APP roles in clinical research. This group will engage APPs on neighbor islands and Guam with an ultimate goal of increasing clinical trial access for underserved populations who reside on these islands. Research Sponsor: NIH-NCORP; UG1CA189804/5UG1CA189804-08.

9042 **Poster Session**

Placing oncology and conflicts of interest in a global context: Evidence from the large international ONCOTRUST-2 study. First Author: Khalid El Bairi, Faculty of Medical Sciences, University Mohammed VI Polytechnic, Ben Guerir, Morocco

Background: Conflicts of interest (COIs) arising from relationships between pharmaceutical industry and oncologists can influence clinical practice and research. Still, global patterns of COIs and disclosure practices remain unexplored. In this interim analysis of ONCOTRUST-2 study, we compared self-reported COI-related practices and financial relationships among oncologists practicing in high-income countries (HICs) versus low-/middle-income countries (LMICs). **Methods:** ONCOTRUST-2 is a multinational cross-sectional survey (January 2024–January 2026) targeting oncologists with at >1 year of experience from LMICs and HICs. Data were collected using snowball sampling through established professional networks and scientific societies. Multivariable logistic regression models were fitted, adjusting for years of professional experience, specialty, current position/seniority, frequency of pharmaceutical industry visits, and the presence of local COI regulations/policies. We report adjusted odds ratios (aORs) with 95% confidence intervals, using a significance threshold of $p < 0.05$. Findings are reported in accordance with the CROSS guidelines. **Results:** A total of 678 oncologists responded to the survey (LMICs: 63.9; HICs: 36.1%) mainly in medical oncology (48.7%), clinical oncology (15.9%) and radiation oncology specialties (15.5%). After adjustment for experience, specialty, position, pharma-visit frequency, and local COI policy presence, HIC oncologists reported higher prevalence of higher-profile industry relationships, including consulting/advisory roles (aOR 2.13, CI: 1.45–3.13; $p < 0.001$) and honoraria/consulting payments (aOR 2.77, CI: 1.29–5.98; p = 0.009). Trips/accommodation support was also more common in HICs (aOR 1.52, CI:1.07–2.17; p = 0.021). A marked gradient was observed for payment magnitude. HICs oncologists were less likely to report no money received (aOR 0.37, CI 0.25–0.54; $p < 0.001$) and more likely to report receiving $2,000–$5,000 (aOR 6.96, 95% CI 3.08–15.75; $p < 0.001$) or > $5,000 (aOR 17.23, 95% CI 4.92–60.32; $p < 0.001$). HICs oncologists reported better COIs disclosure in key academic settings. COIs disclosure before presentations was more common in HICs (aOR 2.72, 95% CI 1.81–4.09; $p < 0.001$), and disclosure in publications was also higher (aOR 1.92, CI: 1.32–2.79; $p < 0.001$) than in LMICs. Reporting non-disclosure was also less frequent in HICs (aOR 0.44, 95% CI 0.25–0.77; p = 0.004). **Conclusions:** Oncologists in HICs reported both greater engagement with and better COI disclosure compared with LMICs. These findings suggest that global COI policies and disclosure infrastructures may differ by national economic context and should be strengthened, with attention to equitable, context-appropriate implementation, regulation governance of COI in LMIC settings. Research Sponsor: None.

9043 **Poster Session**

Separating facts from feeds: An evaluation of social media videos on Barrett's esophagus. First Author: Sean Bowden, UMass Memorial Medical Center, Worcester, MA

Background: Esophageal cancer is subdivided into two types based on histopathology, squamous cell carcinoma and adenocarcinoma (ACE). While the former has declined in incidence within the US, the latter has seen a marked increase. The natural history of ACE begins with metaplastic and dysplastic changes, coined Barrett's esophagus (BE). This pre-malignant condition is treatable if dysplastic changes are detected early. Surveillance endoscopies are recommended every 3-5 years in individuals with BE, yet the adherence to this recommendation remains low. As the incidence of cancer increases in young individuals, clinicians must adapt their methods for disseminating information. In this study, we graded social media videos about BE and compared scores between medical professionals and non-medical professionals. **Methods:** Utilizing a freshly made account to limit algorithmic tailoring, 106 videos were gathered from TikTok (n=60, 56%) and Instagram (n=46, 44%) using the hashtag "#barrettesophagus." Inclusion criteria included videos covering the pathophysiology, clinical features, diagnosis, treatment, or surveillance of BE. Exclusion criteria were videos that did not cover those topics or were not in English. Videos were graded utilizing the CHAI rubric, a verified, 10-point grading rubric for online videos, where 10 is an ideal score. The graded categories are credibility, transparency, content accuracy, accessibility, and relevance. Medical professionals (MP) were defined as MD/DOs, PhDs, RNs, PA/NPs, or RDs. Engagement was defined as cumulative total of likes and comments. Each video was graded by two independent reviewers. Statistical analysis was performed utilizing unpaired, Welch's t-test. **Results:** Out of the 106 videos, 15 were excluded. From those remaining, 52 videos (49%) were made by MP, and 54 videos (51%) were made by non-MP. This latter group was composed of lay individuals (n=12, 11%), non-medical influencers (n=12, 11%), professional organizations (n=3, 2%), and private groups (n=12, 11%). The average CHAI for videos from MP were 9.7, compared to 7.0 from non-MP ($p < 0.01$). Screening guidelines were covered in 21 videos (20%), with MP covering 15 of them (71%), while only 6 were covered by non-MP (29%). Average engagement on MP videos was 2674, contrasted to 183 in the non-MP group. No videos explicitly stated that AI was involved in making the content. **Conclusions:** Medical professionals produced significantly higher-grade content covering BE than non-medical professionals. Additionally, medical professionals were more likely to report on the updated screening guidelines for BE and on average had higher engagement per video. This highlights the benefit of medical professionals within social media and shows the potential of disseminating updated screening guidelines through modern avenues of information sharing. Research Sponsor: None.

9044 **Poster Session**

Digital information–seeking behavior in patients with cancer through storytelling. First Author: Samantha Liu, San Mateo High School, San Mateo, CA

Background: Peer support for cancer patients through narrative interventions can have benefits for quality of life, emotional health, and self-efficacy. This support has classically been provided through static text content on websites, but less is known on whether video-based platforms can preferentially drive patient engagement and self-activation. The Patient Story is a multi-channel platform specializing in video-focused patient-led programs and stories designed to reduce emotional burden and drive patient self-advocacy that leads to informed treatment decision-making. We sought to describe engagement between webpage delivery and a video-based version to understand how different digital platforms could drive varying levels of patient reach and activation, including measurable behavioral changes like motivation to ask doctors questions about treatment and care. **Methods:** Site traffic data relative to benchmarks and participant characteristics visiting The Patient Story were prospectively collected (1/1/22–12/31/25) using Google Analytics 4 for the website and YouTube Studio for the videos. A retrospective review was done on a convenience sample of 4,065 digital platform viewers who then participated in high-touch educational webinars led by patient moderators and multidisciplinary health care providers. Impact was assessed via post-program surveys (n=1,452; 36% response rate) measuring shifts in treatment awareness and behavioral intent. **Results:** A higher percentage of patients who viewed the video platform were female (72.9%) compared to the website (64.4%). Video platform participants tended to be older, with 24% 65+ years old compared to 13% of web participants. Mobile devices were most commonly used for websites (71.2%) and video (54.8%) while 24.8% of those who engaged on video platforms used SmartTV. Reach was substantially higher with the video platform, which generated 72.4M views (average duration on video 6:04) compared to 1.8M website views (89.7% engagement rate). Significant shifts were observed: treatment awareness increased from 3.6 to 4.2 (on a 5-pt scale), and 51.5% of respondents reported a specific intent to discuss the webinar topics (treatment and clinical trial education) with their physician. **Conclusions:** Video first-person storytelling is a novel way of helping patients receive peer support and information. Cancer patients increasingly seek information through mobile and video platforms rather than traditional web searches on desktop computers. Health systems should consider multiple methods of digital communication to increase patient engagement. Research Sponsor: None.

Metric	Value (N=1,452)
Topic Pre-Awareness (5pt scale)	3.6
Topic Post-Awareness (5pt scale)	4.2
% Change in Awareness	+16.7%
Intent to Discuss with Doctor	51.5%
Intent to Research Clinical Trials	20.1%

9045 Poster Session

AI-powered social media listening of oncologist conversations at ASCO 2025. First Author: Sandeep Ghosal, The Larvol Group, LLC, San Francisco, CA

Background: Major oncology congresses generate extensive expert-driven discussion on social media around clinical trial data. However, standardized methods to systematically capture, contextualize, and evaluate these conversations remain limited. LARVOL CLIN is an AI-powered platform that analyzes oncology-focused discussions on X (formerly Twitter), enabling systematic evaluation of clinical trial discourse through assessment of trial-level activity, oncologist sentiment, and engagement. **Methods:** This observational, descriptive analysis evaluated oncology-related posts on X associated with ASCO 2025 (from Apr 23, 2024, to Jan 14, 2025). Posts were identified using predefined conference- and trial-specific keywords and underwent manual validation to confirm relevance to oncology clinical trials. Text-based sentiment analysis was conducted exclusively on posts from oncologists, while trial-related images and polls from both oncologist and non-oncologist X accounts were reviewed for relevance. Validated content was analyzed using oncology-trained large language models, based on ChatGPT 5.1, to interpret clinical context, including efficacy, safety, endpoint status, and potential practice relevance. Sentiment was categorized as negative, neutral, positive, or strongly positive. **Results:** A total of 4,621 oncology clinical trial–related X posts from 651 digitally active oncologists were analyzed for ASCO 2025. Sentiment profiles varied across trials (Table 1). Some studies demonstrated a higher proportion of positive or strongly positive sentiment while others were characterized primarily by neutral assessments reflecting cautious clinical interpretation. Neutral sentiment constituted a substantial share of oncologist posts, often reflecting data interpretation, contextual discussion, or pending clinical relevance. Negative sentiment was typically associated with limited efficacy signals, safety considerations, or unmet expectations. **Conclusions:** This ASCO 2025 observational study demonstrates that AI-driven social listening can systematically capture, contextualize, and quantify expert oncology discourse surrounding clinical trial presentations. LARVOL CLIN enables real-time assessment of oncologist sentiment supporting medical affairs, outcomes research, and strategic communication. Research Sponsor: None.

Digital oncologist activity for selected ASCO 2025 trials.

Trial (Abstract ID)	Views (K)	Not Rated	Negative	Neutral	Positive	Strongly Positive	Total X Posts
PACIFIC15 (8516)	798	47	10	14	25	14	110
DESTINY-Breast09 (LBA1008)	477	32	4	14	24	34	108
SERENA-6 (LBA4)	358	36	9	15	39	26	125
ASCENT-04 (LBA109)	355	22	2	5	25	34	88
ATOMIC (LBA1)	290	25	4	8	27	40	104

LARVOL CLIN represents cumulative views across all X posts for each trial. Sentiment categories reflect AI-generated classification of oncologist X posts.

9046 Poster Session

Baseline bone marrow biopsy (BMBx) performance relative to a mastery-level standard: A SIM-BMBx interval analysis. First Author: Max Farber Kelsten, Northwestern University Feinberg School of Medicine, Division of Hematology-Oncology, Chicago, IL

Background: BMBx is the gold standard diagnostic test for many pathologies. Bedside BMBx is frequently performed by advanced practice providers (APPs) and is required of Hematology-Oncology (HO) fellows by the ACGME. Apprenticeship-style instruction is inconsistent and promotes variable practice. Simulation-based mastery learning (SBML) standardizes instruction to a mastery performance standard (MPS) and is known to improve skill acquisition, retention, and performance. We developed an SBML curriculum for BMBx and herein provide a report of baseline performance. **Methods:** We developed a 28-item BMBx checklist based on experience, literature review, and institutional feedback. Eight experts completed a Modified Angoff Method that set the checklist MPS at 27. Maintaining sterile technique was mandatory. HO fellows, HO APPs, and Internal Medicine (IM) residents were invited to participate. Participants completed a survey of their experience and confidence in performing BMBx. Those with $<$ 3 BMBx were considered "novice," and those with $>$ 3 were "experienced." Participants completed a baseline simulated BMBx (B1) using the VATA Bonnie Bone Marrow Biopsy Skills Trainer. Performance was assessed by investigators via the checklist. The first 15 simulations were co-evaluated for consistency. The protocol was exempted by Northwestern University's IRB. The primary endpoint is the change between B1 and post-SBML score. We performed a descriptive analysis of B1 conducted at 50% enrollment. **Results:** Twenty-five participants completed B1, including 10 APPs, 9 fellows, and 6 residents. Nine were novices (3 APPs, 6 residents). The 16 experienced participants (7 APPs, 9 fellows) had all performed 10 or more BMBx. The median B1 score was 17 (range 6 – 27). One participant, an APP, met the MPS at B1 with a score of 27. The median among APPs, fellows, and residents was 17 (8 – 27), 18 (15 – 23), and 8.5 (6 – 14), respectively. The median among novices was 10 (6 – 19) and among experienced was 18 (12 – 27). Baseline confidence scores were numerically higher for experienced participants (Table 1). **Conclusions:** For the vast majority of practitioners, regardless of professional training and experience with the procedure, BMBx performance does not meet an expert-derived MPS. Experienced practitioners have high confidence despite this. More consistent education of BMBx technique and best practices is needed and may be achieved with SBML. Research Sponsor: Northwestern University Lewis Landsberg Society.

Participant B1 confidence scores.

	N	ID Biopsy Site	Anesthetize Site	Obtain Specimen	Self-Assess Performance	Troubleshoot to Obtain Specimen	Post-Procedure Instruction
Novice	9	30 (10-70)	30 (10-60)	0 (0-50)	0 (0-50)	0 (0-50)	10 (0-80)
Experienced	16	80 (0-100)	90 (0-100)	80 (0-90)	80 (0-100)	70 (0-100)	90 (10-100)
Overall	25	70 (0-100)	80 (0-100)	70 (0-90)	60 (0-100)	60 (0-100)	80 (0-100)

Median (range) confidence in performing an activity from 0 (very low) to 10 (very high).

TPS9047 Poster Session

Improving internal medicine residents' confidence in oncology goals-of-care conversations. First Author: Prathyusha Pandu, Mount Sinai St. Luke's, New York, NY

Background: Internal medicine (IM) residents frequently participate in goals-of-care (GOC) discussions for patients with cancer, yet formal training in oncology-specific serious illness communication remains limited across residency programs. As a result, residents often rely on oncology or palliative care teams to lead these conversations, which may delay timely GOC discussions and subsequent care decisions. Prior educational interventions in serious illness communication have demonstrated improvements in resident confidence; however, oncology-specific GOC training tailored to IM residents is underrepresented. We aim to address this educational gap through the development of a brief, case-based curriculum focused on oncology-related GOC conversations. The objective is to evaluate whether a brief, case-based educational intervention improves IM residents' confidence and knowledge in conducting oncology-related goals-of-care discussions. **Methods:** This is a pilot educational intervention involving IM residents (postgraduate years 1–3) at a large academic residency program. The intervention consists of a 60-minute, case-based session delivered during a scheduled conference. Content focuses on key oncology GOC topics, including prognostic uncertainty, transitions to comfort-focused care, transitions to palliative-intent treatment, and use of structured communication frameworks. Participants will complete pre- and post-intervention surveys assessing self-reported confidence in conducting GOC discussions, comfort discussing prognosis and treatment transitions, and knowledge using two brief case-based vignettes. Pre- and post-intervention survey responses will be compared using paired t-tests. Qualitative feedback will be collected and analyzed thematically. Research Sponsor: None.

9500 **Oral Abstract Session**

Individualized neoantigen therapy intismeran autogene (intismeran) plus pembrolizumab (pembro) in resected melanoma: 5-year update of the KEYNOTE-942 study. First Author: Matteo S. Carlino, Westmead and Blacktown Hospitals, Melanoma Institute Australia, and The University of Sydney, Sydney, NSW, Australia

Background: Intismeran is an mRNA-based individualized neoantigen therapy designed to increase endogenous neoantigen-specific antitumor T-cell responses. The phase 2b KEYNOTE-942 study of high-risk resected melanoma showed clinically meaningful improvements in recurrence-free survival (RFS) and distant metastasis–free survival (DMFS) with intismeran + pembro vs pembro alone at primary analysis. Intismeran + pembro had a manageable safety profile without potentiation of immune-related AEs vs pembro alone. Clinical benefits of intismeran + pembro were sustained at 3 y, with a 49% risk reduction of RFS and 62% risk reduction of DMFS. Intismeran + pembro also induced greater novel T-cell clonal expansion vs pembro, which was positively associated with RFS for intismeran + pembro but not pembro alone. We report results from KEYNOTE-942 after 5 y of planned follow-up. **Methods:** Eligible participants (pts; aged ≥18 y) with resected stage IIIB–IV cutaneous melanoma were randomized 2:1 to receive 9 doses of intismeran 1 mg IM Q3W + 18 doses of pembro 200 mg IV Q3W or 18 doses of pembro 200 mg Q3W alone. Primary endpoint was RFS; secondary endpoints included DMFS and safety. Exploratory endpoints included OS. No alpha was assigned to this analysis. **Results:** From Jul 2019 to Sep 2021,157 pts were randomized to intismeran + pembro (n=107) or pembro (n=50). With an additional 2 y of follow-up (data cutoff, Dec 15, 2025; median planned follow-up, 60.3 [range, 50.5–76.4] mo) after the 3-y analysis, minimal new events occurred. RFS risk reduction for intismeran + pembro vs pembro alone was 49% (HR, 0.51; 95% CI, 0.29–0.89), with landmark 5-y RFS rates of 68.8% (95% CI, 56.3%–78.3%) for intismeran + pembro vs 49.1% (95% CI, 33.3%–63.0%) for pembro alone. DMFS risk reduction was 59% (HR, 0.41; 95% CI, 0.20–0.84). In the intismeran + pembro arm, 7 pts (6.5%) died (disease progression, n=4) vs 7 pts (14.0%) in the pembro arm (disease progression, n=6). There was a trend for improved OS (HR, 0.47; 95% CI, 0.17–1.35); 5-y rate was 92.2% (95% CI, 84.2%–96.3%) for intismeran + pembro vs 71.3% (95% CI, 35.4%–89.6%) for pembro alone. The safety profile of intismeran was consistent with prior analyses. **Conclusions:** After a median 5 y of follow-up, intismeran + pembro continued to prolong RFS and DMFS, along with a trend for improved OS vs pembro alone in pts with high-risk resected melanoma. These long-term findings show that intismeran + pembro treatment benefits were sustained and durable over time, despite all pts having completed study treatment before primary analysis (2021). As reported previously, intismeran was well tolerated, with a manageable safety profile for intismeran + pembro. Intismeran + pembro is being evaluated in a phase 3 study of high-risk resected stage II–IV melanoma (INTerpath-001; NCT05933577) and in studies of pts with other malignancies. Clinical trial information: NCT03897881. Research Sponsor: This research was supported by Moderna, Inc., Cambridge, MA, USA, in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

9501 **Oral Abstract Session**

A phase II study of neoadjuvant ipilimumab-nivolumab-relatlimab (INR) combination immunotherapy in high-risk resectable melanoma. First Author: Ahmad Tarhini, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Advances in the neoadjuvant (neo) setting of locoregionally advanced melanoma have recently transformed practice. However, there continues to be a need to enhance efficacy while deescalating the duration of systemic therapy for those who achieve major pathologic (path) responses (MPR). Recent data support an important role for triplet INR checkpoint inhibitor therapy targeting CTLA4, PD1 and LAG3 in the treatment of advanced melanoma. **Methods:** A phase II trial of INR in patients (pts) with resectable clinical AJCC8 stages IIIB-D. It planned to enroll 20 evaluable pts to neo ipilimumab 1 mg/kg x1 dose combined with nivolumab-relatlimab (NR) 480/160 mg every 4 weeks x2 doses, followed by definitive surgery. Primary endpoint was MPR consisting of complete path response (pCR; 0% viable tumor) and near-pCR (< 10%). Secondary endpoints included other path responses, recurrence free survival, overall survival, event-free survival [EFS: disease progression (PD), recurrence or death] and safety. Adjuvant therapy was given in the absence of MPR. Biospecimens for research from consenting pts were banked at baseline, during treatment, at surgery and in follow up. **Results:** The study enrolled 20 pts August 2024-January 2026, including 7 female, 13 male, 16 cutaneous (2 acral) and 4 unknown primary. Median age was 65 (63-80). Baseline clinical stages were 9 IIIB, 9 IIIC, 2 IIID, including 4 pts with in-transit metastases. Among 19 patients who completed the neoadjuvant phase, all received ipilimumab and the median number of neo NR doses was 2. Among 19 pts who initiated treatment, 5 pts (26%) experienced Gr3 related AEs including colitis (1), encephalitis (1), headache (1), hyperglycemia (1), rash (1), and one pt experienced an event of Gr5 myocarditis. Among 18 pts who completed radiologic tumor response assessment, there were 13 (72%) partial response (PR), 4 stable disease (SD) and 1 disease progression (PD) preoperatively. There was 1 event of death before surgery. One patient declined surgery following deep PR, 1 pt is pending surgery and 1 pt continues in the neo phase. Among 16 pts who had surgery, median time from enrollment to surgery was 73 days. Pathologic responses were 5 path non-response (pNR), 1 near-pCR (microscopic residual disease) and 10 pCR (63%; 95% CI, 38.64 – 81.52). MPR rate (pCR + near-pCR) was 11/16 (69%; 95% CI, 44.40 – 85.84) and none of these patients received adjuvant therapy. Median follow up time from enrollment was 9.8 months. Among all pts, no pt experienced recurrence after surgery to date. **Conclusions:** Neoadjuvant INR demonstrated encouraging clinical activity in pts with resectable clinical stages IIIB/IIIC/IIID melanoma, warranting further investigation. The toxicity profile was consistent with reported data of INR and other combinations in this setting. Mechanistic and biomarker studies related to response, resistance and toxicity are underway. Clinical trial information: NCT06295159. Research Sponsor: Bristol Myers Squibb; H. Lee Moffitt Cancer Center and Research Institute.

9502 **Oral Abstract Session**

A phase 2 study of neoadjuvant nivolumab (nivo) + relatlimab (rela) in high-risk stage II cutaneous melanoma (NeoReNi). First Author: Georgina V. Long, Melanoma Institute Australia, The University of Sydney, Royal North Shore Hospital and Mater Hospital, Sydney, Australia

Background: Patients (pts) with stage II melanoma account for ~50% of those who develop metastatic disease. Checkpoint inhibitor neoadjuvant therapy (NAT) is standard for resectable stage III melanoma (NADINA & SWOG 1801) and pathological response correlates with recurrence. Other NAT benefits include personalised prognosis, tailored subsequent management, and collection of translational specimens to explore response and resistance mechanisms. The NeoReNi II trial aimed to determine feasibility, response and safety of NAT nivo+rela in resectable stage II melanoma. **Methods:** Eligible pts had biopsy (partial) confirmed AJCC (v8) clinical stage IIA (T2b, T3a), IIB (T3b, T4a), or IIC (T4b) cutaneous melanoma with residual macroscopic primary disease at enrolment. IIA pts had ≥20% 5 yr recurrence risk according to Melanoma Institute Australia stage II risk calculator (melanomarisk.org.au). All pts underwent sentinel lymph node (SLN) mapping at baseline and perioperatively, and resection (wide excision + SLN biopsy [RES]) at wk 6 following 2 doses of nivo (480 mg, IV) + rela (160 mg, IV). Pts without major pathological response (MPR) had 11 cycles (Q4W) of adjuvant nivo/rela. FDG PET/CT was performed at baseline; CT prior RES; dermoscopy and reflectance confocal microscopy (RCM) baseline, wk 3 and prior to RES. The primary endpoint was the path complete response (pCR) rate. Secondary endpoints included feasibility of NAT in stage II, RECIST response, RFS, OS, safety/tolerability, surgical outcomes, QOL. Exploratory; biomarker, dermoscopy and RCM analyses. **Results:** From 6 Oct 2023 to 21 Oct 2025, 20 pts were recruited and received NAT, demonstrating partial biopsy leaving residual macroscopic stage IIA-C primary melanoma was feasible. Median age 67 yrs (46-81yrs), 9 females, 8 IIA, 8 IIB and 4 IIC. 18 (90%) pts received both NAT doses. 12 (60%) pts had pCR in the primary melanoma, 1 near-pCR (MPR 65%), 1 pPR and 6 (30%) pNR. Drug treatment related adverse events (TRAE) gd ≤ 2 occurred in all 20 pts (100%); 11 (55%) with fatigue, 8 rash (40%) and 5 arthralgia (25%). 3 (15%) pts had gd 3 (secondary adrenal insufficiency, nephritis, pneumonitis). There were no gd 4 or 5 TRAEs. 1 (5%) pt had a gd 3 AE related to surgery (cellulitis). 19 (95%) pts had no change in SLN mapping from pre to RES. 2 pts with pNR in primary melanoma had postitive SLN and 1 pt with pCR had focal fibrosis within a negative SLN, suggestive of possible treatment effect. Dermoscopy showed regression in all 12 MPR (100%) pts; 11 also showed changes in RCM (collagen reorganization and imflammatory infiltrates) concordant with pathology. At datacut off (11 Dec 25) 2 pts recurred, 5 and 11 mo respectively (both pNR);1 died due to melanoma (15 mo after 1st recurrence; 20 mo after enrolement. Positive SLNBx at pNR). **Conclusions:** NAT with nivo + rela in resectable stage II melanoma was feasible and induced a high rate of pCR and MPR in the primary melanoma. Clinical trial information: NCT05418972. Research Sponsor: None.

LBA9503 **Oral Abstract Session**

Darovasertib plus crizotinib vs investigator's choice as first-line treatment for patients with HLA-A2 negative metastatic uveal melanoma: Primary results from the OptimUM-02 trial. First Author: Marlana M. Orloff, Thomas Jefferson University Hospital, Philadelphia, PA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA9504 **Oral Abstract Session**

ADAM trial: A multicenter, randomized, double-blinded, placebo-controlled, phase 3 trial of adjuvant avelumab (anti-PD-L1 antibody) in patients with Merkel cell carcinoma and lymph node metastases. First Author: Shailender Bhatia, University of Washington and Fred Hutchinson Cancer Center, Seattle, WA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA9505 **Oral Abstract Session**

Updated outcomes from STAMP: Surgically treated adjuvant Merkel cell carcinoma with pembrolizumab, a phase III trial—ECOG-ACRIN EA6174. First Author: Janice M. Mehnert, New York University School of Medicine, New York, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

9506 **Oral Abstract Session**

A phase II, multicenter, single-arm clinical trial of response-adapted definitive radiotherapy and cemiplimab-rwlc immunotherapy for locally advanced, unresectable cutaneous squamous cell carcinoma: RAMPART. First Author: Christopher Andrew Barker, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Locally advanced (T3-4/N+/M0) and unresectable cutaneous squamous cell carcinoma (LAUCSCC) patients (pts) have been historically treated with definitive radiotherapy (RT) +/- chemotherapy, yielding poor outcomes (18m progression-free survival [PFS] rates of ~38%). More recently, anti-PD1 immunotherapy with cemiplimab (cemi) led to an 18m PFS rate of ~55% in locally advanced pts that were not candidates for RT or surgery. In this prospective, multicenter trial, we assessed definitive RT with neoadjuvant, concurrent, and adjuvant cemi for LAUCSCC pts. **Methods:** Pts with T3-4/N+/M0 LAUCSCC according to local multidisciplinary consensus, ECOG $\leq$2, were enrolled and treated with 2 doses of cemi (350 mg IV q3w). Those with progressive disease (PD) after 2 doses received RT (70 Gy/35 fractions). Those without PD received 2 additional doses of cemi followed by response-adapted RT (50-70 Gy/25-35 fractions) with concurrent cemi followed by adjuvant cemi for a maximum of 1y. The primary endpoint was event free survival (EFS) at 18m after cemi start. Secondary endpoints included safety, response (by RECIST v1.1, see table), quality of life, overall survival (OS) and PFS (after RT start). To test the hypothesis that the 18m EFS was 60%, compared to a historic 18m PFS rate after RT of 38% with 80% power and 5% type 1 error rate, 34 pts were planned for enrollment (accounting for 40% attrition). **Results:** 34 pts (median age 77y, 82% men, ECOG 0/1/2 in 41/53/6%) were enrolled with stage III (41%) and IV/M0 (59%) LAUSCC (56% recurrent, 91% head/neck) between 2022-2024. 85% completed 4 doses of neoadjuvant cemi and 94% completed RT as planned. With median follow up of 18m (range 2-36m), 18m EFS is estimated to be 86% (1 sided 95% CI lower bound of 73%) among all pts. Adverse events were consistent with prior studies of cemi or RT. 18m PFS and OS are estimated to be 86% and 92%. Quality of life analyses are in progress. **Conclusions:** The study met its primary endpoint demonstrating the highest rate of EFS, PFS and OS after treatment of LAUCSCC ever reported. As the largest prospective study of definitive RT for LAUCSCC, the data suggest integrating cemi with RT may benefit appropriate pts. Future studies identifying pts who are best served with this approach are warranted. Clinical trial information: NCT05574101. Research Sponsor: Regeneron; National Cancer Institute (US).

Response over time.

	Complete response	Partial response	Stable disease	Progressive disease	Non-response/Non-progression[1]	NA[2]
Time						
6w post cemi	1 (3%)	11 (32%)	15 (44%)	3 (9%)	4 (12%)	0
12w post cemi	4 (12%)	15 (44%)	6 (18%)	1 (3%)	4 (12%)	4 (12%)
12w post RT	10 (29%)	10 (29%)	4 (12%)	3 (9%)	4 (12%)	3 (9%)
18m post cemi	11 (32%)	6 (18%)	0	1 (3%)	4 (12%)	12 (35%)

[1]Pts with non-target lesions only.
[2]Pts not assessed (response assessment pending or not performed because of PD at 6w post cemi, or withdrawal).

9507 **Oral Abstract Session**

OBX-115 engineered tumor-infiltrating lymphocyte (TIL) cell therapy with regulatable membrane-bound IL15 (mbIL15) in patients with advanced melanoma that has progressed on/after immune checkpoint inhibitors (ICI): Phase 2 results. First Author: Allison Betof, Stanford University School of Medicine, Stanford, CA

Background: OBX-115 TIL are engineered to express mbIL15 under regulatory control of the small-molecule drug acetazolamide (ACZ); this engineering abrogates the need for toxic high-dose IL2 cytokine support after TIL infusion. Early data demonstrated differentiated safety and promising efficacy at the recommended phase 2 dose (RP2D; Chesney ASCO 2025). We report additional data evaluating OBX-115 in patients (pts) with advanced melanoma treated at the RP2D in the Agni-01 study. **Methods:** This single-arm, open-label, phase 1/2 study (NCT06060613) assesses safety, tolerability, and efficacy of the OBX-115 TIL cell therapy regimen in pts with advanced non-uveal melanoma and NSCLC (Shoushtari AACR 2025); eligibility was not restricted by LDH, HLA, or melanoma subtype. Phase 1 established an RP2D of OBX-115 1–100$\times 10^9$ cells, with ACZ 500 mg/d orally on Days 0–6 (Wk 1) and 14–20 (Wk 3). Phase 2 evaluates efficacy of the regimen at RP2D by RECIST v1.1 per investigator in pts with $\leq$2 prior lines of therapy. OBX-115 is manufactured from pt tumor tissue (core needle biopsy [CNB] or surgical excision) and infused after low-dose (Cy 750 mg/m^2/d $\times$ 3; Flu 30 mg/m^2/d $\times$ 4) lymphodepletion (LD). ACZ is redosed (7 d) after recovery from LD every 6 wks until Wk 24. Primary data cutoff is 19Dec2025; RECIST efficacy was updated on 22Jan2026. **Results:** OBX-115 was successfully manufactured (median dose 83.4$\times 10^9$ cells) and infused at RP2D schema for 15 pts with advanced melanoma progressing on/after ICI (doublet ICI in 93%); 6/8 pts (75%) with BRAF-mut disease had prior BRAF-/MEK-inhibitor exposure. 2 pts (13%) had tumor tissue procurement by CNB; 4 pts (27%) received outpatient LD. Confirmed ORR was 67% (1 CR, 9 PR, 4 SD; DCR 93%). At median study follow-up of 18.6 wks (range 10.1–73.4), median duration of response was not reached (range 4.6+ to 55.1+ wks). There was no dose-limiting toxicity, ICU transfer, or treatment-related mortality. Immune-related adverse events (AEs) included CRS (G3 n=1; G$<$3 n=4) and hypoxia (G3 n=1; G$<$3 n=2), which responded to short-course steroids; no ICANS was observed. 3 pts reported 4 OBX-115–related serious AEs. 13 pts were alive as of the datacut. **Conclusions:** OBX-115 TIL cell therapy at RP2D demonstrated encouraging efficacy in 2/3L advanced non-uveal melanoma, an area of unmet medical need. Unique aspects of the OBX-115 regimen, such as low-dose LD, ACZ-inducible mbIL15 expression, and CNB-enabled manufacturing, were associated with manageable side effects and compare favorably with other adoptive TIL approaches. Data support continued investigation of OBX-115 in the ongoing phase 2 portion of Agni-01 and planned registrational study. Clinical trial information: NCT06060613. Research Sponsor: Obsidian Therapeutics, Inc.

9508 **Oral Abstract Session**

Patient-level clinical response dynamics in advanced melanoma with anzutresgene autoleucel (anzu-cel), a PRAME-directed T-cell receptor (TCR) T-cell therapy. First Author: Diwakar Davar, University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center, Pittsburgh, PA

Background: Pts with advanced melanoma frequently experience progressive disease (PD) with limited long-term survival following available therapies; there is a need for novel systemic treatments that can induce deep and durable responses. PRAME is a cancer-associated antigen expressed in >50 cancers, including melanoma. Anzu-cel (IMA203) is an autologous PRAME-directed TCR T-cell therapy engineered to recognize intracellular PRAME-derived peptides presented by HLA-A*02:01 and mediates a potent and specific anti-tumor immune response (Wermke et al. ASCO, 2025). A registration-directed phase 3 trial (SUPRAME; NCT06743126) is underway. **Methods:** IMA203-101 is an ongoing, multicenter, phase 1/2 trial evaluating anzu-cel in pts with advanced PRAME-positive solid tumors. Pts underwent lymphodepleting (LD) chemotherapy followed by a single infusion of anzu-cel +/- low-dose SUBQ IL-2. This analysis focuses on melanoma pts in phase 1b treated at RP2D. Data cutoff was Sep 24, 2025. Exploratory analyses evaluated lesion-level patterns of progression among pts evaluable per RECIST1.1. **Results:** As of data cutoff, 33 pts with melanoma were evaluable, incl. cutaneous (n=14), uveal (n=16), and other subtypes (n=3). Most frequent AEs were LD-related cytopenias. AEs of special interest included cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS) and hemophagocytic lymphohistiocytosis (HLH). CRS was predominantly low grade (G1: 36%, G2: 46%, G3: 18%) and occurred early after infusion, with incidence and severity decreasing over time. ICANS (G1: 6%, G3: 6%) and HLH (G2: 3%, G3: 3%) were infrequent. Confirmed ORR was 56% (cCR=1, cPR=17) and DCR was 91%. mDOR was 14.6 mos (4.2-38.2+), mPFS was 6.1 mos (1.4-39.6+), and mOS was 16.2 mos (2.4-39.6+). Responses were observed in target and nontarget lesions, with most pts demonstrating initial lesion responses within the first 6 weeks of treatment; median time to BOR of cPR/cCR was 1.4 mo (1.2-2.8). 25 pts were evaluable for patterns of PD. At the time of PD, 68% (17/25) developed new lesions (NL); 1 pt developed new central nervous system (CNS) lesions. PD via growth of existing lesions was observed in 56% (14/25); 24% (6/25) experienced PD by both growth of existing lesions and NLs. No specific pattern of PD was identifiable in those who achieved cPR compared to those who did not. **Conclusions:** Anzu-cel demonstrated favorable tolerability and induced clinically meaningful and durable responses. Exploratory analyses suggest that the CNS was not a common site for relapse. Future analyses will characterize response dynamics and progression patterns to better define scenarios in which progression following cPR remains clinically manageable, potentially supporting individualized decision-making regarding timing and necessity of subsequent systemic therapy. Clinical trial information: NCT06743126. Research Sponsor: Immatics.

LBA9509 **Clinical Science Symposium**

A multicenter, randomized, controlled, open-label, phase II trial of autologous tumor-infiltrating lymphocytes (GC101 TIL) in patients with advanced melanoma. First Author: Lu Si, Peking University Cancer Hospital & Institute, Beijing, China

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

9510 **Clinical Science Symposium**

Real-world safety of adoptive cellular therapy with lifileucel in patients with advanced melanoma. First Author: Alexandra Haugh, Massachusetts General Hospital Cancer Center, Boston, MA

Background: Although acute toxicities associated with adoptive cellular therapy using lifileucel are well described and largely occur within the first 2 weeks of treatment, adverse events beyond this early window remain incompletely characterized. We sought to characterize treatment-related adverse events (AEs) with emphasis on those starting or persisting ≥2 weeks after lifileucel infusion. **Methods:** We conducted a retrospective multicenter study across three centers (Moffitt Cancer Center, Massachusetts General Hospital, and Mayo Clinic). Patients with advanced melanoma treated with lifileucel were included. The primary endpoint was incidence and characterization of AEs occurring or persisting ≥2 weeks after standard of care lifileucel infusion. **Results:** Among 79 patients (median follow-up 11 months [95% CI, 9.6–15]), median age was 63 years (range 30–79), 59% were male (n = 47), 41% were female (n = 32), and ECOG PS was 0–1 in 98%. Patients received a median of 5 IL-2 doses (range 0–6). Of 79 patients, 78 experienced treatment-related adverse events that either persisted or occurred >2 weeks after cell infusion. A total of 308 delayed treatment-related adverse events were identified; 96 were new events (31%) and 212 (69%) were continued toxicities that started < 2 weeks after cell infusion. Lymphopenia was the most common delayed or persistent toxicity, occurring in a majority of patients (n = 68/79, 86%). Treatment-associated anemia (n = 59/79, 75%), fatigue (n = 56/79, 71%) and thrombocytopenia (n = 24/79, 30%) were also common. Viral infections occurred in 9.0% (n = 7), including CMV/EBV viremia (n = 1) and respiratory or gastrointestinal viral infections (metapneumovirus, parainfluenza, SARS-CoV-2, and norovirus). Hemophagocytic lymphohistiocytosis (HLH) occurred in 2 patients (n = 2/79, 3%) and was fatal in both cases. No other toxicity related deaths were noted. Autoimmune toxicities directly attributable to TIL included vitiligo in 9% (n = 7; median onset 41 days), uveitis in 5% (n = 4; median onset 26 days), and sensorineural hearing loss in 1% (n = 1; onset 28 days). All patients underwent TIL infusion in the inpatient setting; a total of 14 of 79 patients (18%) were re-admitted after discharge due to treatment-related toxicity (median time from infusion 19 days). **Conclusions:** In this multicenter real-world cohort, toxicities persisting beyond two weeks were largely driven by lymphodepleting chemotherapy–associated immunosuppression and cytopenias. These findings highlight the importance of structured post-discharge monitoring and support ongoing efforts to de-intensify lymphodepleting chemotherapy to improve safety while maintaining clinical benefit. Research Sponsor: None.

9511 **Clinical Science Symposium**

Immunologic determinants in procured melanoma tissue as drivers of durable response to tumor-infiltrating lymphocyte therapy. First Author: Lilit Karapetyan, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Predictive biomarkers that identify melanoma tumors capable of generating therapeutically effective tumor-infiltrating lymphocytes (TIL) remain inadequately defined. We conducted an integrated spatial and histopathologic evaluation of resected melanoma specimens to characterize tumor microenvironmental features associated with durable clinical benefit (≥12 months) and improved survival following TIL therapy. **Methods:** Data were extracted from early-phase clinical trials conducted at Moffitt Cancer Center enrolling patients with advanced melanoma treated with TIL. Tumor specimens from 45 of 50 patients undergoing TIL manufacturing were evaluable based on tissue availability. Histopathology, multiplex immunofluorescence, and NanoString GeoMx spatial transcriptomics were performed on procured tumors. Tertiary lymphoid structures (TLS) were defined as organized aggregates of $CD3^+$ T cells and $CD20^+$ B cells and classified as immature or mature based on CD21/CD23 expression. Associations with ex vivo TIL expansion, infused product composition, clinical response, progression-free survival (PFS), and overall survival (OS) were assessed. **Results:** Procurement sites included subcutaneous/soft tissue (78%), lymph node (18%), and lung (4%). Viable tumor content and necrosis were not associated with ex vivo TIL expansion or response. TLS were present in 56% (25/45) of tumors and were strongly associated with clinical response (18/45 responders overall; response rate 56% [14/25] in TLS-positive tumors vs 20% [4/20] in TLS-negative tumors; p=0.014), improved PFS after adjusting for procurement site (HR=0.32; p=0.005) and improved OS (p<0.0001). Evaluation of ex vivo TIL expansion demonstrated that TLS presence did not affect the total number of expanded TIL (p = 0.3) but was significantly associated with a higher proportion of $CD8^+$ T cells within the infusion product (83% vs 56%, p=0.027). Spatial transcriptomics of 132 immune-enriched regions of interest demonstrated that responders exhibited marked upregulation of antigen-presentation and interferon-response programs, including MHC I/II genes, *STAT1/2, IFI6,* and *CXCL9*. A patient-level immune activation score derived from the top 25 responder-associated transcripts correlated with improved PFS (p<0.0001). To independently validate the significance of this immune gene set score, we analyzed an external dataset from the Lauss et al., 2017 cohort. Consistent with our findings, the gene set score was significantly higher in TIL responders compared with non-responders (p=0.048). **Conclusions:** TLS and spatial immune activation signatures in procured melanoma tumors are strongly associated with response and survival following TIL therapy. These findings support the integration of tumor microenvironment biomarkers into patient selection and optimization strategies for TIL therapy. Research Sponsor: None.

9512 **Rapid Oral Abstract Session**

Phase 1b study of a brain-penetrant MEK inhibitor, PF-07799544, plus next-generation BRAF dimer inhibitor, PF-07799933, in advanced *BRAF*-mutant melanoma. First Author: Monica F. Chen, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Treatment of *BRAF*-mutant (mut) melanoma has been transformed by targeted inhibition of MEK and BRAF kinases. However, duration of clinical benefit has been limited by de novo and acquired resistance through RAF-kinases signaling as dimers, poor activity in brain metastases (BMs), and paradoxical activation adverse events (AEs) negatively impacting tolerability. PF-07799544 is an oral, brain-penetrant, reversible MEK inhibitor (MEKi). PF-07799933 is an oral, brain-penetrant, selective BRAF dimer inhibitor (BRAFi) with activity against $BRAF^{V600}$ and non-V600 muts. We report initial results of this next-generation BRAFi/MEKi combination from ongoing phase 1 study. **Methods:** This platform study (NCT05538130) is evaluating PF-07799544 as monotherapy or combined with other targeted therapy for *BRAF*-mut melanoma and other solid tumors. Substudy B is an open-label, multicenter study assessing safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and clinical activity of PF-07799544 + PF-07799933. Dose escalation (DE) enrolled into 4 dose levels patients (pts) with *BRAF*-mut advanced melanoma who had progressed on standard therapy, including pts with BMs. Randomized dose optimization (DO) enrolled pts with $BRAF^{V600}$-mut advanced melanoma previously treated with 1-2 immunotherapy (IO) lines and $\leq$1 BRAFi $\pm$ MEKi line; pts with BMs were eligible if asymptomatic. We report pooled baseline characteristics and safety and separate efficacy. **Results:** As of Nov 12, 2025, 60 pts received $\geq$1 dose of study treatment. At baseline: median age, 54.5 years; female, 50%; White, 95%; ECOG PS of 0, 63%; adrenal insufficiency, 25%; BMs, 53%; and $BRAF^{V600}$ mutation, 95%; 77% received $\geq$3 prior systemic anticancer therapies, 100% received prior IO, 100% of pts with $BRAF^{V600}$ mutation received prior BRAFi $\pm$ MEKi, and 73% received BRAFi $\pm$ MEKi $<$6 months before beginning study treatment. Any-grade treatment-emergent AEs (TEAEs) occurred in 95%; most common ($\geq$20%) were rash (40%), fatigue (37%), diarrhea (32%), and peripheral edema (22%). Grade $\geq$3 TEAEs occurred in 67%; most common ($\geq$5%) were rash (7%), disease progression (7%), anemia (5%), and fall (5%). Dose modifications due to TEAEs (any-causality, treatment-related) included reductions (13%, 13%), interruptions (53%, 33%), and discontinuations (10%, 3%). Objective response rate (ORR; including unconfirmed) by investigator was 27% in 41 DE pts and 32% in 19 DO pts. In pts with baseline BMs, intracranial (IC) ORR was 30% in 23 DE pts and 22% in 9 DO pts. PK showed BRAFi/MEKi exposures consistent with preclinical exposures which showed antitumor activity supporting selected DO doses. **Conclusions:** PF-07799544 + PF-07799933 showed manageable safety and promising systemic and IC antitumor activity in heavily pretreated *BRAF*-mut advanced melanoma. Evaluation of dose expansion cohorts is ongoing. Clinical trial information: NCT05538130. Research Sponsor: Pfizer.

9513 **Rapid Oral Abstract Session**

Combination of vemurafenib with cobimetinib in *BRAF* V600E/K mutated melanoma patients to normalize LDH and optimize immunotherapy with nivolumab and ipilimumab (COWBOY): A randomized, open-label phase 2 clinical trial. First Author: Anne Sophie Blokland, Radboud University Medical Center, Nijmegen, Gelderland, Netherlands

Background: Elevated levels of serum lactate dehydrogenase (LDH) in patients (pts) with metastatic melanoma are associated with reduced response to immune checkpoint inhibitors (ICIs). In a phase 2 trial, we investigated whether upfront reduction of tumor burden and normalization of LDH through six weeks of BRAF/MEK inhibitor (BRAF/MEKi) induction, prior to the initiation of ICIs, could improve response rates compared to standard first-line dual ICI. **Methods:** In this two-arm, multicenter, phase 2 trial, treatment naïve pts with unresectable stage III or stage IV BRAFV600E/K mutation-positive melanoma and elevated baseline LDH levels ($<$ 5x upper limit of normal) were randomized 1:1 (stratified by LDH) to one of two treatment arms. Arm A received 6 weeks of induction with vemurafenib 960 mg bid + cobimetinib 60 mg QD on a 21/7-day schedule, directly followed by four courses of ipilimumab 3 mg/kg q3wk (ipi3) plus nivolumab 1 mg/kg q3wk (nivo1). Arm B directly started with four courses of ipi3 + nivo1. Both arms received response-adapted nivolumab maintenance. The primary endpoint was to compare the best overall response rate (BORR) within 18 weeks from the start of treatment between two treatment arms, as assessed by RECIST 1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and the rate of grade 3/4 toxicity. Exploratory endpoints focused on circulating tumor DNA dynamics (ctDNA), blood transcriptome, and tumor immunoprofiling. ClinicalTrials.gov identifier: NCT02968303. **Results:** Between 2017-2021, 71 pts were randomly assigned, 36 to arm A and 35 to arm B. The study was prematurely terminated due to slow patient accrual (planned accrual: 200 pts). The median follow-up time was 27.9 months (IQR 16.8-57.8). In arm A, the BOR was partial response (PR) in 75% of the pts (36.1% had an ongoing response after treatment switch), stable disease (SD) in 22.2%, and progressive disease (PD) in 2.8%. In arm B, 54.3% had PR, 22.9% SD, and 20% PD (1 pt was not evaluable). BRAF/MEKi induction prior to ICI was associated with a significantly shorter median PFS as compared with upfront dual ICI (4.4 months vs 25.0 months, HR 0.52, 95% CI 0.30-0.91; p=0.02). Median OS was also shorter in arm A (13.5 months), whereas the median OS was not reached in arm B (HR 0.38, 95% CI 0.19-0.68; p=0.002). Treatment-related grade $\geq$3 adverse events occurred in 25 of 36 pts (69%) in arm A and 15 of 35 pts (43%) in arm B. When combining both arms, pts with undetected ctDNA at 6-12 weeks after ICI initiation had significantly longer PFS than those with detected ctDNA (HR 2.05, 95% CI 1.05-4.0; p=0.03). **Conclusions:** BRAF/MEKi induction prior to dual ICI did not improve response rates to ICI and was associated with worse PFS and OS in pts with BRAFV600E/K mutated melanoma and elevated LDH compared to upfront dual ICI. Clinical trial information: NCT02968303. Research Sponsor: Bristol-Myers Squibb; Roche; Paul Speth Fund; PAMgene.

LBA9514 **Rapid Oral Abstract Session**

MATRiX: A randomized phase II trial of tuvusertib (ATR inhibitor) with or without avelumab in advanced anti-PD(L)-1 refractory Merkel cell carcinoma. First Author: Rashmi Bhakuni, University of Washington, Seattle, WA

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

9515 **Rapid Oral Abstract Session**

A phase II study of neoadjuvant cemiplimab in hedgehog inhibitor (HHI)–naive basal cell carcinoma of the head and neck. First Author: Hannah L. Kenny, Thomas Jefferson University Hospital, Philadelphia, PA

Background: Surgical resection of locally advanced basal cell carcinoma of the head and neck (BCCHN) often carries significant morbidity. This phase II study seeks to investigate the response to neoadjuvant cemiplimab on surgical morbidity in BCCHN patients. **Methods:** In this prospective, nonrandomized, multicenter, phase II trial (NCT05929664), anti-PD1 and HHI-naive patients with resectable BCCHN received 2 to 6 cycles of cemiplimab (350mg IV Q21 days), followed by surgical resection or biopsy. Surgical plan at enrollment required functional organ sacrifice (orbit, eyelid, ear, nose, lip, or facial nerve). RECISTv1.1 tumor measurements were performed every 2 cycles to determine primary endpoints of ORR and DCR. Patients with PD ($>$20% growth) or SD with 5 to 20% growth at any assessment were offered HHI or surgery. Patients with CR at any assessment proceeded to surgery or directed biopsy. Secondary endpoints included: surgical benefit rate (SBR, defined as rate of functional organ preservation, determined by the investigator, comparing surgical resection to surgical plan at time of enrollment), rate of pCR, safety (CTCAEv5.0), and quality of life (FHNSI, FACE-Q and VFQ-25). Correlative studies include examination of the tumor immune microenvironment related to functional changes in immune cell composition. **Results:** Between August 2023 and September 2025, 33 patients were enrolled: 40-89 yo; 22 M/11 F; sites of disease included eyelid (n=17), orbit (n=4), nose(n=5), lip (n=1), facial nerve (n=1), ear (n=1), and scalp or cheek (n=5). 30 were evaluable: 23 (76.7%) completed 6 cycles. Among the remaining 7 patients, 1 experienced CR after 4 cycles; 1 was taken off therapy for grade 3 myalgia; 1 had SD with 5-20% growth and 2 had PD, and were taken to surgery per protocol; 2 chose surgery due to stagnant response after initial PR. 12 patients (40%) experienced a grade 1-2 treatment-related AE. 1 patient (3.33%) experienced a grade 3 treatment-related AE as above. The ORR was 66.67%. The DCR was 90.0%. Based on RECISTv1.1 criteria, 3.33% (n=1) had CR, 63.33% (n=19) had PR, 23.33% (n=7) had SD, and 10.0% (n=3) had PD as best overall response 8 patients (26.67%) achieved pCR. The SBR was 43.3%, with functional preservation of the eyelid (n=7), nose (n=2), lip (n=1), ear (n=1), or orbit (n=1). **Conclusions:** Neoadjuvant cemiplimab had an acceptable safety profile and shows promising efficacy in the treatment of advanced, surgically-resectable BCCHN. This novel approach may alleviate the morbidity of subsequent surgical resection. (NCT05929664 supported by Regeneron Pharmaceuticals, Inc.). Clinical trial information: NCT05929664. Research Sponsor: None.

9516 **Rapid Oral Abstract Session**

Cadonilimab or ivonescimab plus axitinib in metastatic mucosal melanoma: Results from a phase Ib trial. First Author: Lili Mao, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: Mucosal melanoma (MM) is a rare and aggressive cancer with a poor prognosis. Unlike its more common counterpart, cutaneous melanoma, MM responds poorly to standard single-agent immunotherapy, such as anti-PD-1 monoclonal antibodies (mAbs), limiting treatment options. This clinical challenge underscores the need for more effective strategies, making combination therapies a clear future direction. The aim is to overcome resistance by targeting multiple pathways simultaneously. The main objective of this study is to explore and compare two distinct immunotherapy backbones—targeting the PD-1/CTLA-4 and VEGF pathways—for their potential in future rational combinations against MM. **Methods:** This is a phase Ib, dose de-escalation and cohort-expansion, open-label trial. The combination dose of axitinib will utilize a "3+3" dose de-escalation design. The starting dose is 5 mg. If dose-limiting toxicity (DLT) is observed at this dose level, the dose for subsequent cohorts will be reduced to 3 mg. Patients with metastatic melanoma receive 10 mg/kg cadonilimab Q3W (cohort 1) or 20 mg/kg ivonescimab Q3W (cohort 2) in combination with 5 mg axitinib BID. Primary endpoints are rate of dose-limiting toxicities (DLTs) and safety. Secondary endpoints are objective response rate (ORR) by investigator assessment, duration of response (DOR), progression-free survival (PFS), overall survival (OS) and overall safety. **Results:** As of December 25, 2025, a total of 28 patients have been enrolled in the study (14 cohort 1; 14 cohort 2). Median follow-up of 13 months. The distribution of primary tumor sites was as follows: oral cavity 14.3%, esophagus17.9%, rectum 32.1%, and cervix 35.7%. 21% had elevated LDH. BRAF status, known for 71% of patients, was positive in 25%. No DLT or treatment related death was observed ，Axitinib was selected as 5 mg BID. 71.4% patients experienced treatment related AE (TRAE) and 17.9% patients experienced Grade 3-4 TRAEs. In cohort 1 , the most common TRAEs include hypothyroidism, hypertension, diarrhea, anorexia and rash. In cohort 2, the most common TRAEs include proteinuria, myalgia, hyperthyroidism, hypertension, abnormal transaminase levels, anorexia and hyperlipidemia. No patient discontinued treatment due to TRAE. ORR, DOR, DCR, and median PFS for all cohorts are shown in Table. **Conclusions:** The combination therapy involving cadonilimab or ivonescimab plus axitinib demonstrates a promising safety and efficacy profile. These findings suggest that such dual-antibody-based regimens could provide synergistic anti-tumor activity with an improved therapeutic index, warranting further clinical investigation. Clinical trial information: NCT06424626. Research Sponsor: None.

Secondary Endpoint	Cohort 1 （n=14）	Cohort 2 （n=14）
PR	5	5
SD	4	5
PD	5	4
ORR	35.7%	35.7%
DCR	64.3%	71.4%
DOR (mo)	6.7	6.4
mPFS (mo)	5.8	8.7
mOS (mo)	NA	NA

LBA9517 **Rapid Oral Abstract Session**

Neoadjuvant intralesional daromun (L19IL2/L19TNF) in resectable locally advanced melanoma: An update on the primary outcome and sensitivity analyses (EFS) from the PIVOTAL phase 3 trial. First Author: Katharina C. Kaehler, University Hospital (UKSH), Campus Kiel, Department of Dermatology, Kiel, Germany

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

9518 **Rapid Oral Abstract Session**

A 3-year landmark overall survival analysis of RP1 plus nivolumab in patients with anti–PD-1–failed melanoma from the IGNYTE clinical trial. First Author: Michael K.K. Wong, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Advanced melanoma has a high mortality rate; however, survival for patients (pts) treated with anti–PD-1–based therapy tends to plateau at 3–4 years, suggesting that pts alive at 3 years are likely to have prolonged benefit. This highlights the need for novel therapies that offer increased survival beyond 3-4 years. RP1 (vusolimogene oderparepvec) is an HSV-1–based oncolytic immunotherapy expressing GM-CSF and a fusogenic glycoprotein (GALV-GP-R$^-$). In the IGNYTE trial (data cutoff [DCO]: 15OCT2024), pts with advanced melanoma that had confirmed progression on anti–PD-1 therapy who received RP1 + nivolumab (nivo) had an objective response rate by RECIST 1.1 of 33.6% (16.4% complete response); median duration of response was 24.8 months. Here, we present a 3-year survival analysis of pts treated with RP1 + nivo from IGNYTE (last pt in: 9MAR2023; DCO: 11JUN2025). **Methods:** Pts ≥18 years with advanced melanoma and confirmed progression while being treated for ≥8 weeks with anti–PD-1 ± anti–CTLA-4 as the last prior therapy were enrolled (NCT03767348). An initial dose of RP1 was administered intratumorally (1×10^6 PFU/mL), followed by up to 7 doses every 2 weeks (Q2W; 1×10^7 PFU/mL) in combination with intravenous nivo 240 mg Q2W/480 mg Q4W for up to 2 years; additional RP1 was allowed if protocol-specified criteria were met. This updated analysis evaluated overall survival (OS) using the Kaplan-Meier (KM) method. **Results:** Of 140 enrolled pts, 49.3% had stage IVM1b–d disease, 55.7% had PD-L1–negative tumors, 46.4% had prior anti–PD-1 + anti–CTLA-4 therapy, and 65.0% had primary resistance to prior anti–PD-1 (ie, progression within 6 months of starting the immediate prior course of anti–PD-1). The median (95% CI) OS was 32.2 (25.8, 39.2) months (the median OS follow-up was 3 years by reverse KM method). OS rates (95% CI) at 1, 2, and 3 years were 75.3% (66.9%, 81.9%), 61.6% (52.5%, 69.4%), and 45.5% (35.8%, 54.7%), respectively. Importantly, among responders (n=47), the 3-year OS rate (95% CI) was 81.8% (65.2%, 91.0%) vs 22.5% (12.6%, 34.2%) for non-responders (n=93). The 3-year OS rates were 41.8% in pts with stage IVM1b–d disease (n=69), 37.2% for those with PD-L1–negative tumors (n=78), 37.4% in pts with prior anti–PD-1 + anti–CTLA-4 therapy (n=65), and 44.8% in pts with primary resistance to anti–PD-1 (n=91). The safety profile for RP1 + nivo remained consistent with prior reports; no new safety signals were seen. **Conclusions:** The 3-year landmark OS rate of 45.5% in the overall population and 81.8% among responders provides further evidence that the deep and durable responses provided by RP1 + nivo translate into long term clinical benefit, including extended OS in pts with melanoma post-confirmed progression on prior anti–PD-1–based therapy. Clinical trial information: NCT03767348. Research Sponsor: Replimune, Inc.

9519 **Rapid Oral Abstract Session**

A phase 2 trial of IO102-IO103 and nivolumab-relatlimab in previously untreated, unresectable melanoma. First Author: James William Smithy, Memorial Sloan Kettering Cancer Center, New York, NY

Background: IO102-IO103 is an investigational cancer vaccine that targets both tumor and immune-suppressive cells in the tumor microenvironment. IO102-IO103 has demonstrated clinical activity in combination with anti-PD-1 monotherapy in advanced melanoma, with concordant clonal T cell expansion observed in the tumor and peripheral blood in patients with radiographic response. IO102-IO103 has not yet been assessed in combination with nivolumab-relatlimab (nivo-rela). **Methods:** In this multicenter, phase 2 trial (NCT05912244) patients with unresectable, previously untreated non-uveal melanoma were treated with subcutaneous IO102-IO103 and intravenous nivo-rela for up to two years. IO102-IO103 was administered every two weeks for eight weeks, and every four weeks thereafter. PD-L1 protein expression was assessed using the 28-8 pharmDx assay on pre-treatment tissue. The primary endpoint was best overall response rate (BORR) by RECIST v1.1, with a plan to reject the null hypothesis based on the proportion of patients with ≥1% membranous PD-L1 staining in the tumor compartment. Secondary endpoints included progression-free survival (PFS), safety assessed by Common Terminology Criteria for Adverse Events v 5.0, and duration of response (DOR). PFS and DOR were summarized using Kaplan-Meier methods. Bulk T cell receptor (TCR) sequencing was performed on peripheral blood mononuclear cells using an RNA-based assay at baseline, week 4 and week 8. **Results:** Among 43 evaluable patients, the BORR was 60% (95% confidence interval [CI]: 44-75%), including 19 patients with partial response and 7 patients with complete response. At database lock (Dec 1 2025), median follow up was 10.1 months (interquartile range 6.1-19.3). The median duration of response was not reached (95% CI: 14, NR) and median PFS was 8.2 months (95% CI 6.8, not reached [NR]). Among patients with PD-L1 negative tumors (n = 25), the BORR was 52% (95% CI 31-72%) and median PFS was 8.2 months (4.2, NR). Grade 3-4 treatment-related adverse events occurred in 9 patients (21%), including adrenal insufficiency (2 patients), acute kidney injury (2), aseptic meningitis (1), arthritis (1), maculopapular rash (1), myositis (1), neutropenia (1), and colitis (1). There were no treatment related deaths. T cell clonal expansion was observed at on-treatment time points compared to baseline in patients with and without radiographic response. **Conclusions:** IO102-IO103 in combination with nivo-rela was associated with a higher objective response rate compared to historical data for nivo-rela alone, meeting the trial's primary endpoint. No unexpected safety signals were observed. These findings support the further clinical investigation of IO102-IO103 with nivo-rela as an initial treatment for unresectable melanoma. Clinical trial information: NCT05912244. Research Sponsor: IO Biotech; NCCN Foundation; National Cancer Institute; P30 CA008748.

9520 Rapid Oral Abstract Session

Response-focused analyses of the impact of circadian rhythm on efficacy of first-line immunotherapy in melanoma. First Author: Hemant Khandelia, Department of Medicine/Division of Hematology and Oncology, University of Washington, and Clinical Research Division, Fred Hutchinson Cancer Cancer, Seattle, WA

Background: Several retrospective studies have associated better clinical outcomes with morning infusions of immune-checkpoint inhibitors (ICI), attributing the same to circadian differences in T-cell activity. However, these studies have largely focused on survival endpoints, which are susceptible to confounding by skewed cohort distributions, treatment heterogeneity or other unknown variables. In this study, we explore the impact of timing of ICI infusions by primarily focusing on objective response as a more direct and immediate measure of immunologic activity, and possibly less susceptible to confounding variables. **Methods:** We conducted a single center, retrospective study of patients with advanced melanoma with response-evaluable disease and treated with an ICI regimen in the first-line setting. We recorded baseline patient and tumor characteristics and the start time of the first ICI infusion. Based on the median start time (~1:00 PM) of all ICI infusions in our clinic, we classified patients into "Early" (before 1:00 PM) and "Late" cohorts (1:00 PM & after). We analyzed objective response rate (ORR) per RECIST v1.1, time-to-response (TTR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS), comparing endpoints between cohorts using logistic or Cox regression, with adjustments for variables including age, sex, ECOG score, and disease stage. **Results:** We identified 216 eligible patients treated between 2014 - 2025, including 78 in the Early cohort and 138 in the Late cohort. Median age was 64 years (range 19 - 95) and 69% were male. Median follow-up duration was 27 months (range 6 days - 12 years). There were no significant differences in baseline patient and tumor characteristics between the two cohorts. ORR for the Early cohort was 64.1% (50/78; complete response [CR] - 34.6%, partial response [PR] - 29.5%) and for the Late cohort was 61.6% (85/138; CR - 28.3%, PR - 33.3%) [p = 0.71]. There were no significant differences in TTR and DOR between the cohorts. The distribution of first ICI infusion start-time in the responders mirrored that of all ICI infusions in all patients with melanoma. Adjusted PFS and OS were also similar between the cohorts (see Table). **Conclusions:** Our response-focused analyses do not suggest an association of early timing of ICI infusion to better efficacy outcomes, in contrast to findings from other studies. Our findings are consistent with the known long terminal half-life of ICI agents, which should provide steady availability of ICI antibodies to immune cells throughout the day. Our results do not support implementing time-based ICI infusion strategies in the oncology clinics. Research Sponsor: None.

Endpoint	Early cohort	Late cohort	Hazard ratio (95% CI)	P-value
PFS, Median months (95% CI)	12 (9, NR)	16 (9, 28)	1.01 (0.68, 1.50)	0.97
OS, Median months (95% CI)	82 (66, NR)	88 (62, NR)	1.07 (0.61, 1.89)	0.82

CI = Confidence interval; NR = Not reached.

9521 Poster Session

Metabolic signatures of response: 2-hydroxybutyric acid as a biomarker in melanoma patients receiving ipilimumab–nivolumab. First Author: Jean Henri Maselli-Schoueri, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: 2-Hydroxybutyric acid (α-HB) is an established biomarker in metabolic disease of insulin resistance and oxidative stress but its role in immuno-oncology remains unclear. This study conducted an exploratory analysis to evaluate whether α-HB could be used as a biomarker in advanced melanoma patients treated with ipilimumab-nivolumab, and its association with treatment response and toxicity. **Methods:** In this single-center retrospective study, 36 patients with unresectable/metastatic melanoma received ipilimumab-nivolumab. α-HB levels were measured by targeted mass spectrometry and measured relative metabolomic signal intensities. Descriptive statistics assessed α-HB across subgroups defined by age, sex and BRAF status. Associations between α-HB and grade $\geq$3 immune-related toxicity, treatment response, and survival at last contact were tested using univariable logistic regression with α-HB entered as a continuous predictor (log2-transformed). Prespecified sensitivity analyses dichotomized α-HB at the median (1.13) and 75th percentile (1.55). For mortality, we additionally derived an exploratory ROC-based Youden threshold to define a "high α-HB" group and report diagnostic performance (specificity, PPV, NPV) and odds ratios. **Results:** Median age was 53.5; 63.9% were male; 80.6% had cutaneous melanoma; 33.3% were BRAF-mutant; 80.6% received first-line therapy. Baseline α-HB was lower in patients who developed grade $\geq$3 toxicity (mean 1.01 vs 1.54; p=0.013) and in responders (1.09 vs 1.60; p=0.021), while it was higher among those who died (1.49 vs 1.06; p=0.045). In logistic models using log2-transformed α-HB, each doubling in α-HB was associated with reduced odds of grade $\geq$3 toxicity (OR 0.165, 95%CI 0.036–0.744; p=0.019) and response (OR 0.268; 95% CI 0.075–0.961; p=0.043; AUC = 0.79; HL p=0.803, where higher p indicates better fit), consistent with lower α-HB marking both toxicity and response. Higher α-HB trended toward increased death risk (OR 3.3 per doubling; p=0.066). Using a Youden-derived cutoff (α-HB $\geq$1.58), high α-HB defined a high-risk subgroup (OR 10.0; 95% CI 1.09–91.4; p=0.041) with high specificity for death (94%); PPV 89% and NPV 56%. **Conclusions:** Elevated α-HB was associated with reduced response, lower incidence of immune-related toxicity, and higher rates of death, suggesting a metabolically suppressed immune phenotype. Further validation is needed to determine whether metabolic interventions could improve immunotherapy outcomes in selected patients. Research Sponsor: None.

9522 Poster Session

Final results and correlative analysis of entinostat (E) plus pembrolizumab (P) in patients (Pts) with metastatic melanoma (MM) previously treated with anti–PD-(L)1 therapy (Tx). First Author: Stergios J. Moschos, The University of North Carolina at Chapel Hill, Chapel Hill, NC

Background: PD(L)1 inhibitors have transformed MM tx, yet several pts experience resistance. Preclinical data suggest that epigenetic modifications may overcome this. Here, we present the results of an expansion MM cohort treated with E+P following prior anti-PD(L)1 tx. **Methods:** Pts with unresectable stage III/IV melanoma, progression to anti-PD(L)1 and BRAF-targeted tx (if *BRAF*-mutant) were eligible. Pts were treated with E, 5 mg PO qwk, and P, 200 mg IV q3wks. The primary endpoint was to determine the objective response rate (ORR) per the irRECIST criteria. Secondary endpoints included assessment of the safety of E+P tx, progression-free (PFS), and overall survival (OS). Correlative analyses were performed on baseline and on-tx tissues. **Results:** 53 pts were treated (median [mdn] age, 61 years; 60% male; 55% with ECOG performance status of 0; 64% with visceral metastases; 23% with *BRAFV600* mutation), including 43% with primary resistance to anti-PD(L)1 inhibitors, respectively. The mdn number of prior systemic tx was 3 (range 1-8), and 70% of pts had previous tx with CTLA4 inhibitors. 49% pts developed $\geq$ grade 3/4 toxicity, and 19% pts discontinued at least one drug due to adverse events. 10 pts had a partial (n=9) or complete (n=1) response, for an ORR of 19%. The mdn follow-up was 11.5 months (mon), and the mdn response duration was 23.7 mon (range 2.6-45.6+ mon); 9 pts had stable disease $>$ 6 mon. The mdn PFS and OS were 4.0 and 11.5 mon, respectively. Blood analysis showed that the tx significantly decreased Ki67-PD1+ T cells and T regs and significantly increased Ki67-HLA-DR+ and ICOS+ T cells. Analysis of baseline (n=30) and on-tx (n=10) tumor biopsies using NanoString and/or bulk RNAseq showed increased immune infiltration with tx and increased expression of key genes in antigen presentation (*ß2M*), chemoattraction (*CXCL11* & *13*), and IFNγ. Hallmark gene set enrichment analysis suggests that pts bearing inflamed, non-proliferating baseline tumors had a more durable clinical benefit to tx (i.e., no disease progression for $>$ 6 mon). Exploratory analysis using quantitative multiplex immunohistochemistry showed that pts with more durable clinical benefit had baseline tumors with a higher lymphoid-to-myeloid (L/M) ratio, and higher numbers of tumor-infiltrating (TI) CD4+ and CD8+ cells, particularly CD8+PD1+ cells. With tx, pt tumors with clinical benefit maintained a higher L/M ratio, had lower TI CD8+PD1+ cells, and increased density of TI CD20+ cells. TI CD8+PD1+ cells increased in pt tumors without clinical benefit. **Conclusions:** E+P tx in anti-PD(L)1-resistant MM was associated with durable clinical benefit in a pt subset and was well tolerated. Correlative analysis revealed that tx increased inflammation across most analyzed pt tumors; the most significant benefit, however, was observed in pts with pre-existing inflamed tumors. Clinical trial information: NCT02437136. Research Sponsor: SYNDAX Pharmaceuticals.

9523 Poster Session

Clinical characteristics, molecular features, and treatment of primary central nervous system melanoma. First Author: Alexander Xiao, Mayo Clinic Rochester, Rochester, MN

Background: Primary Central Nervous System (CNS) Melanoma is a rare and aggressive malignancy, comprising 1% of melanoma cases and 0.07% of brain tumors. Due to its rarity, its natural history, molecular features and optimal management remain poorly defined. **Methods:** We retrospectively reviewed patients at our institution between January 1998 and October 2025 with primary CNS melanoma or melanocytoma with melanoma transformation. Clinical characteristics, molecular profiling, treatments and survival outcomes were collected. Overall survival (OS) and progression free survival (PFS) were estimated using Kaplan-Meier curves. **Results:** Nineteen patients were identified, including eight (42%) with melanocytoma to melanoma transformation. Median time of transformation was 34.4 months. Thirteen (68%) patients were female with a median age at diagnosis of 59.3 years. Common presenting symptoms were sensory disturbances (58%), pain (53%), motor deficits (37%) and nausea or vomiting (32%). At diagnosis, location of disease was spinal (n=12), intracranial (n=6) and multifocal (n=1). Thirteen patients had leptomeningeal involvement. Molecular profiling was performed in 15 patients, revealing mutations in *GNAQ* (n=7), *GNA11* (n=3), *CKIT* (n=2), *BAP1* (n=1), *EIF1AX* (n=1), and *BRAF v600* (n=1). Thirteen (68%) patients underwent subtotal resection (STR), five (26%) gross total resection (GTR) and one radiation only. Median resected tumor size was 1.7 cm. Seventeen (94%) patients had recurrence at a median of 9.1 months, and four patients underwent repeat surgery. Fourteen (74%) patients received adjuvant radiation and 14 (74%) received immunotherapy, most commonly ipilimumab with nivolumab (71%). Nine patients received chemotherapy: temozolomide (n=5), bevacizumab (n=2) and one each of intrathecal IL-2, tebentafusp, imatinib and encorafenib with binimetininb. Four patients received chemotherapy before immunotherapy. Median OS from diagnosis of CNS melanocytoma or melanoma was 50.9 months (13.4 – 80). Median OS from time of transformation to melanoma or CNS melanoma diagnosis was 24.0 months (11.9 – NA). One-, three- and five-year OS rates were 73%, 53% and 40% respectively. GTR was associated with increased median OS compared to STR (80.0 vs 19.7 months, p= 0.02). Age at diagnosis, immunotherapy, chemotherapy, adjuvant radiation, STR with or without radiation, disease location, leptomeningeal involvement, tumor size $>$3cm and presence of GNAQ mutation were not associated with survival. Median PFS was 3 months with chemotherapy and 5.7 months with immunotherapy. **Conclusions:** To our knowledge, this is the largest single center study of primary CNS melanoma. Outcomes remain poor, with survival primarily associated with GTR. The predominance of *GNAQ* and *GNA11* alterations with rare *BRAF v600* mutations highlight the distinct biology of primary CNS melanoma and need for novel targeted therapies. Research Sponsor: None.

9524 **Poster Session**

A propensity score-matched analysis comparing first-line regional, systemic, and intralesional treatments for melanoma in-transit metastases in a contemporary patient population. First Author: Caitlyn Balsay-Patel, Moffitt Cancer Center, Tampa, FL

Background: Unresectable melanoma in-transit metastases (ITM) can pose a significant clinical challenge. Our recently published data comparing first-line treatments for ITM, isolated limb infusion or perfusion (ILI/ILP), immune checkpoint inhibitors (ICI) and intralesional talimogene laherparepvec (TVEC), found superior outcomes with TVEC. However, TVEC was used more often in patients with lower disease burden and earlier stage (IIIB vs. IIIC/D). Therefore, we sought to better investigate these differences with a propensity score-matched (PSM) analysis. **Methods:** A multi-institutional, international IRB- approved retrospective analysis was conducted for unresectable melanoma ITM from 2016-2022. PSM analysis comparing first-line ILI/ILP, ICI, and TVEC for was performed. Patients were matched for stage, number of ITM, anatomical site, CLND status, gender and age. Kaplan-Meier curves (OS, PFS, DMFS) and Cumulative incidence function (MSS) were used to visualize time-to-event outcomes in the PSM cohort, though both methods do not account for the matched structure. **Results:** 274 patients were identified, 120 female/154 male; 96 treated with ILI/ILP, 111 with ICI, and 67 with TVEC. Median follow-up was 40 months (range, 1-80). PSM was performed and identified 36 TVEC–ICI pairs and 27 TVEC–ILI pairs. These were combined resulting in a final cohort of 108 observations (45 TVEC, 36 ICI and 27 ILI). The groups were well balanced. No statistical difference was found for metastasis-free survival (DMFS), progression-free survival (PFS), melanoma-specific survival (MSS), and overall survival (OS) between treatment modalities. TVEC was associated with significant improvement in local PFS (median was 2.2 years (y) for ILI/ILP, 1.5y for ICI and not reached for TVEC, p=0.048). While not statistically significant, a clinical benefit was seen in PFS being longer for TVEC (2.1y for TVEC vs. 1.2y for ILI/ILP and 1.1y for ICI; p=0.2) and OS (not reached vs 2.9y for ILI/ILP and 5.2y for ICI; p=0.2). On mixed effect Cox regression proportional hazard model using the matched data set, there were no significant differences in any of the survival and recurrence outcomes. **Conclusions:** When patients are propensity-matched, there were no significant differences in first-line treatment modalities for unresectable melanoma ITM. Treatment with TVEC did result in clinically meaningful improved overall and local PFS and OS. This supports that selection of ITM therapy should incorporate an individualized approach, incorporating disease distribution, stage, burden, treatment side effects and patient priorities. Research Sponsor: None.

9525 **Poster Session**

A phase I/IIa, first-in-human, multicenter, monotherapy and combination therapy with nivolumab dose-finding study of [^{212}Pb]VMT01 melanocortin-1-receptor–targeted, image-guided, alpha-particle therapy in subjects with previously treated unresectable or metastatic melanoma. First Author: Zachary Scott Morris, University of Wisconsin, Madison, WI

Background: Melanocortin-1 receptor (MC1R) is a novel target for radiopharmaceutical therapy and is highly expressed on melanoma tumor cells. VMT01 is an MC1R-targeted peptide. ^{203}Pb is used for patient selection via SPECT imaging. Peptide radiolabeling with ^{212}Pb delivers alpha-particle therapy. Here, we present data on the treatment of adult patients with MC1R-positive metastatic melanoma receiving [^{212}Pb]VMT01 either as a monotherapy or in combination with the programmed death-1 (PD-1) checkpoint inhibitor, nivolumab. **Methods:** This is an ongoing phase I/IIa, first-in-human, prospective, multicenter, open-label, radioactive dose-finding and dose-expansion trial. The objectives are to investigate safety, pharmacokinetics, dosimetry, and efficacy. Participants receive up to 3 treatment cycles with either [^{212}Pb]VMT01 3 mCi, 5 mCi, or 1.5 mCi monotherapy, or combination therapy with [^{212}Pb]VMT01 (1.5 mCi) + nivolumab (480 mg, Q4W) or [^{212}Pb]VMT01 (3 mCi) + nivolumab. Participants are evaluated for any DLTs for the first 6 weeks after cycle 1. Efficacy is assessed by RECIST v1.1 criteria by the investigator. **Results:** As of 24 December 2025, 26 participants (53.8% male; median age: 68 years [range: 27-81]) with MC1R-positive metastatic melanoma were enrolled. The median prior systemic therapies was 4. All 26 enrolled participants received $\geq$1 dose of [^{212}Pb]VMT01. No DLTs were reported. All SAEs (including one grade 5 SAE) were attributed to disease progression. Most TEAEs were grade 1 (19.2%) and grade 2 (34.6%). Grade 3 TEAEs occurred in 8 participants (30.8%), 5 on monotherapy and 3 on combination therapy (3 mCi + nivolumab). Of the 22 evaluable participants, 1 PR, 9 SD, and 12 PD were reported. Four participants had progression-free survival of $\geq$6 months. **Conclusions:** [^{212}Pb]VMT01 as a monotherapy and in combination with nivolumab was generally safe and well-tolerated in 26 enrolled participants, with antitumor activity observed at the 3 mCi dose level. These data may be supplemented with a more complete follow-up at the time of the meeting. Clinical trial information: NCT05655312. Research Sponsor: None.

9526 **Poster Session**

Imneskibart + low-dose subcutaneous IL-2 ± nivolumab in patients with CPI-refractory cutaneous melanoma: Promising results from an ongoing phase 1/2 study. First Author: Meredith McKean, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN

Background: Imneskibart (AU-007) is an AI designed monoclonal antibody binding to interleukin-2 (IL-2) preventing binding to CD25 in the trimeric IL-2 receptor (IL-2 R), while allowing engagement with the dimeric IL-2R, CD122/CD132. Imneskibart-bound IL-2 expands T effector (Teff) and NK cell populations (dimeric IL-2R) without expanding regulatory T cells (Tregs; trimeric IL-2R). **Methods:** Patients (pts) with locally advanced/metastatic cutaneous melanoma were evaluated in Phase 1 (Ph1) dose escalation and in 2 ongoing Ph2 expansion cohorts. Rigorous eligibility criteria were applied requiring pts to have objective progression after $\geq$ 2 cycles of prior doublet checkpoint inhibitors (CPI, anti-PD-1 + anti-CTLA-4 or anti-LAG-3) with confirmation of progression $\geq$ 4 weeks later. Ph2 Cohort 1 evaluated the recommended Ph2 dose (RP2D) of 9 mg/kg imneskibart IV Q2W. Ph 2 Cohort 2 evaluates the RP2D of imneskibart IV Q2W + nivolumab (nivo) 480 mg Q4W. Both cohorts receive subcutaneous (SC) 135K IU/kg aldesleukin dose on Day 1 of first cycle with additional doses of aldesleukin administered at the beginning of each cycle until at least a partial response (PR) is obtained. Tumor reassessment is performed at the end of each 8-week cycle. **Results:** Fifteen pts received imneskibart + aldesleukin: 2 in Ph1 and 13 in Ph2. Fourteen pts were efficacy evaluable. Nine pts had tumor reductions ranging from -1 to -100% including pts with -100% and -58% reductions (continue treatment at 24 and 18 M respectively), and a -48% reduction (14 M on treatment). The median PFS and duration on treatment were 7.6 and 9 M respectively (9.3 M median follow up); 6 pts continue treatment. Nine of 14 evaluable pts have received imneskibart + IL-2 for a longer duration than their prior CPI doublet therapy. Eight pts enrolled in Ph2 Cohort 2 and 2 of the 6 efficacy evaluable pts to date (33%) had PRs with -35% and -31% tumor reductions and continue treatment. Two of 6 had SD and continue treatment. Overall, 67% had disease control at 4 months. Six pts continue treatment. Imneskibart led to a decrease in peripheral Tregs and increase in CD8 cells leading to CD8/Treg ratio increases up to 2 – 3 fold over BL. CD8/Treg ratio increases $>$ 2 fold over BL were associated with longer median duration on treatment, PFS, and OS. Imneskibart + IL-2 was well-tolerated with Grade 3/4 drug-related adverse events (AE) occurring in only 14% of pts and in 0 of the 8 pts who received this combination + nivo. No patient discontinued treatment due to a drug-related AE. **Conclusions:** Compelling anti-tumor activity is observed with imneskibart + IL-2, with a strong emerging signal of enhanced activity with the nivolumab combination in pts with melanoma refractory to doublet CPI therapy. Imneskibart + IL-2–associated Treg reduction likely drives the high disease control rate, supporting durable benefit with prolonged treatment exposure and PFS. Clinical trial information: NCT05267626. Research Sponsor: Aulos Bioscience.

9527 **Poster Session**

Phase 1 evaluation of the PRAME-targeted ImmTAC brenetafusp in advanced melanoma (Mel). First Author: Georgina V. Long, Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia

Background: Brenetafusp (brene) is an ImmTAC bispecific (PRAME $\times$ CD3) therapy that promotes T cell recruitment into tumors. Initial Phase (Ph) 1 data showed acceptable safety, robust T cell activation at target doses (TD) $\geq$ 20 mcg and promising clinical activity in multiple tumors including heavily pretreated cutaneous melanoma (CM) (Hamid 2022, 2024; NCT04262466]). We present updated monotherapy (mono) and PD1 immune checkpoint inhibitor (ICI) combination (combo) safety and efficacy results supporting brene dose selection in Mel (CM, mucosal [Mu] or acral [Ac]). **Methods:** HLA-A*02:01+ Mel patients (pts) who exhausted standard treatments were eligible. Primary objectives: safety and recommended dose; additional objectives included efficacy, biomarkers and ctDNA response. Brene mono was administered intravenously weekly (QW) with 1-2 step-up doses to TD; TD 40 and 160 mcg were evaluated in expansion. Combo was 160 mcg brene QW + 400 mg pembrolizumab (pembro) Q6W. Molecular response: $\geq$ 0.5 log [68%] ctDNA reduction by week 9 (Hamid 2024). T cell fitness defined as 3-gene (TESPA1, CD28 and GPR183) signature in blood (Sacco 2024). Tumor PD-L1 measured by immunohistochemistry, beta2 microglobulin (B2m) by immunofluorescence. **Results:** As of Oct 2025, 66 pts with Mel (median 2.5 prior lines, 100% prior PD1, 30% PD1 refractory [progression $<$6 mo post start of first anti-PD1], 68% St IV-c/IV-d) received brene mono (TD 40, n=16; TD 160, n=24; other TD 10-320 mcg, n=26). The 40-mcg cohort had more favorable baseline prognostic factors (ECOG PS, tumor burden, ctDNA, prior treatment) and T cell fitness. Ten pts (median 2.5 prior lines, 90% prior PD1, 50% prior BRAF/MEKi, 70% St IV-c/IV-d) received brene + pembro. Safety was similar at TD 40 and 160 mcg with Gr1/2 CRS (56% vs 42%) and rash (44% vs 42%) initially. Gr3/4 events occurred in 25% vs 54%: mainly transient lymphocyte decrease, consistent with mechanism. Of 10 pts with prior ICI Gr3/4 irAE, none had recurrence. Combo profile resembled each agent alone. No new safety signals observed. Disease control, RECISTv1.1 response and ctDNA molecular response rates were numerically higher at 160 vs 40 mcg (Table), with similar rates across subgroups typically less responsive to anti-PD1. Overall survival was associated with baseline T cell fitness and tumor B2m, but not with PD-L1 status. **Conclusions:** Brene shows promising monotherapy activity in late-line Mel, including difficult to treat populations, without causing ICI-like irAEs, and can be safely combined with pembro. Ph1 results support 160 mcg as the selected dose in the Ph3 PRISM-MEL trial evaluating brene with nivolumab versus standard nivolumab regimens (NCT06112314). Clinical trial information: NCT04262466. Research Sponsor: Immunocore Ltd.

	N	DCR% (PR + SD)	ORR%	6mo OS%	ctDNA-evaluable N	ctDNA response%
Brene mono	66	52	12	83	50	38
40 mcg	16	56	6	81	10	20
160 mcg	24	67	17	79	15	33
PD1 refractory	20	55	10	70	15	53
Ac / Mu	7	57	14	86	5	40
Sum target lesions >10 cm	25	44	12	80	19	32
Brene + pembro	10	70	20	80	5	40
PD1 refractory	6	67	33	67	2	50

9528 **Poster Session**

Comparison of baseline gut microbiome features between response subgroups of patients (pts) with advanced melanoma undergoing immune checkpoint inhibitor (ICI) therapy. First Author: Michelle Ferreira, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD

Background: Gut microbiome composition has been implicated as a potential biomarker of response to ICIs in melanoma pts, but it is unclear whether baseline gut microbiome composition may predict emergence of specific ICI resistance subtypes (primary vs. acquired resistance) or immune-related adverse events (irAEs). We sought to define clinical characteristics and baseline gut microbiome features that correlate with ICI resistance subtypes and irAEs in melanoma pts. **Methods:** We identified 90 pts from our institution's fecal biorepository of advanced melanoma pts who received ICIs and who had ≥ 1 pre- or on-treatment fecal sample available for 16S rRNA amplicon sequencing. Pts were categorized into 3 responder subgroups: responder (R, no progression on ICI), primary resistance (pR, progression $<$ 6 months from ICI start), or acquired resistance (aR, progression $\geq$ 6 months from ICI start). Associations between clinical covariates and survival were analyzed using Kaplan-Meier and Cox proportional hazards models. Microbial features were compared using alpha and beta diversity metrics and pairwise comparisons at each taxonomic level using Wilcoxon rank-sum tests. **Results:** Baseline demographic and clinical characteristics were similar between subgroups (R, n = 35; pR, n = 32; aR, n = 23). IrAE occurrence rates significantly differed between responder subgroups (p = 0.048). Pts who developed irAEs had significantly longer progression-free survival (PFS) than those without irAEs (median PFS 1412 vs. 106 days, p = 0.026). Later treatment line and receipt of prior ICI were associated with significantly higher hazard ratios (HRs) for death and progression, while resectable disease and development of any-grade irAE were associated with lower HRs for death and progression. There was no significant difference in baseline alpha diversity between responder subgroups or irAE groups. A trend toward differences in baseline beta diversity between responder subgroups was observed (p = 0.084). Abundance of *Faecalibacterium prausnitzii*, a known butyrate producer, was significantly higher in R than pR ($p < 0.001$, $p_{adj} = 0.029$), aR than pR ($p < 0.001$, $p_{adj} = 0.071$), and in pts who did not develop irAEs (p = 0.02). Other operational taxonomic units more abundant in responders (aR vs. pR, R vs. aR/pR) and pts who did not develop irAEs include the short-chain fatty acid (SCFA) producers *Coprococcus comes*, *Dorea longicatena*, and *Blautia glucerasea* ($p < 0.001$, $p_{adj} = 0.071$). **Conclusions:** Although no significant differences in baseline alpha diversity were observed between responder subgroups or irAE groups, responders and those without irAEs had significantly higher levels of SCFA-producing taxa at baseline, suggesting a potential immunomodulatory role for SCFAs such as butyrate in mediating ICI response and protection from irAEs. Research Sponsor: Bristol-Myers Squibb; Bloomberg~Kimmel Institute for Cancer Immunotherapy; U.S. National Institutes of Health; K08CA263316; Damon Runyon; The Marilyn and Michael Glosserman Fund for Basal Cell Carcinoma and Melanoma Research; The Barney Family Foundation; The Laverna Hahn Charitable Trust; American Society for Clinical Oncology.

9529 **Poster Session**

Prospective, non-interventional, multisite evaluations of TRAQinform Immuno algorithmic quantitative treatment response analysis on treatment intent decisions in metastatic melanoma. First Author: Ryan J. Sullivan, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Background: Molecular imaging plays a critical role in assessing immunotherapy response in metastatic melanoma, but current assessment methods may not fully leverage imaging data to inform clinical decision-making. This study prospectively evaluated whether integrating TRAQinform Immuno quantitative analysis into clinical assessment would alter oncologists' treatment intent in metastatic melanoma patients receiving checkpoint inhibitor combinations. **Methods:** In this prospective, multisite, non-interventional study (NCT05819255), patients with metastatic melanoma receiving dual-agent immunotherapy were enrolled at the University of Wisconsin Carbone Cancer Center and Massachusetts General Hospital Cancer Center. FDG PET/CT scans were acquired at baseline, 3-4 weeks and 12 weeks. All scans were analyzed using a research version of the TRAQinform IQ (TRAQinform) algorithmic quantitative software. At each timepoint, treating oncology and nuclear medicine teams recorded treatment intent before and after review of the TRAQinform analysis report. A cross-site, blinded review was conducted to assess potential status quo bias. **Results:** Twenty-six patients were enrolled (12F, 14M, mean age 65 years), 25 of whom completed all study scans. At week 3-4, 27% of cases (7/26) showed an intent to change treatment after oncologists reviewed the TRAQinform report, (p=1.0). At the 12-week assessment, 56% of cases (14/25) demonstrated intent to change treatment (p=0.0008). Considering either timepoint, 65% of cases (17/26) exhibited a change in treatment intent compared to baseline (p=0.000006). Cross-site analysis indicated minimal influence of status quo bias on intent decisions. **Conclusions:** In this prospective study assessing intent to treat, TRAQinform analysis of standard-of-care FDG PET/CT images influenced oncologists treatment decision in the majority of metastatic melanoma patients, suggesting it provides clinically actionable information. For oncologists managing patients on dual-agent immunotherapy - where treatment decisions often involve uncertainty and clinical judgment, this study demonstrates that TRAQinform offers an additional data-driven tool to support optimal therapeutic decision-making. Research reported in this abstract was supported by the National Cancer Institute of the National Institutes of Health and under Award Number R44CA257253. The content is solely the responsibility of the authors and does not necessarily represent the official news of the National Institutes of Health. Clinical trial information: NCT05819255. Research Sponsor: NIH-NCI; R44CA257253.

9530 **Poster Session**

Long-term efficacy and safety of first-line (1L) nivolumab plus relatlimab (NIVO + RELA) versus NIVO plus ipilimumab (NIVO + IPI) in advanced melanoma: An updated indirect treatment comparison (ITC) with 5-year follow-up data. First Author: Hussein A. Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: An ITC comparing NIVO + RELA and NIVO + IPI, approved dual immunotherapy treatment options for patients (pts) with advanced melanoma, was previously conducted using pt-level data from the pivotal RELATIVITY-047 (RELA-047; NIVO + RELA vs NIVO) and CheckMate 067 (CM-067; NIVO + IPI or NIVO vs IPI) trials (Long JCO 2024). Here we present updated results using 5-year follow-up data from RELA-047. **Methods:** Inverse probability of treatment weighting was used to adjust for cross-trial imbalances in baseline characteristics. CM-067 follow-up was truncated to best align with the follow-up length in RELA-047. Progression-free survival (PFS) per investigator (INV), confirmed objective response rates (ORRs) per INV, overall survival (OS), and melanoma-specific survival (MSS) were analyzed. Outcomes were also evaluated across key subgroups. The weighted NIVO arms from each trial were compared for validation. **Results:** After weighting, key baseline characteristics were balanced for NIVO + RELA (n = 339) and NIVO + IPI (n = 297). Outcomes after weighting were similar between NIVO + RELA and NIVO + IPI (hazard ratio [HR] [95% CI]: PFS, 1.10 [0.90–1.34]; OS, 0.96 [0.77–1.20]; MSS, 0.88 [0.68–1.12]; table). Grade 3–4 treatment-related adverse event (TRAE) rates were numerically lower with NIVO + RELA than with NIVO + IPI (23% vs 62%, respectively). Across subgroups, efficacy appeared similar between treatments, although trends favoring NIVO + IPI were observed for ORRs among pts with *BRAF* mutant disease (59% vs 48%) or serum lactate dehydrogenase $> 2\times$ the upper limit of normal (33% vs 12%). Among pts progression-free at 3 years, both NIVO + RELA and NIVO + IPI were associated with sustained benefit, with 5-year OS of 96% and 94% and MSS of 100% and 98%, respectively. **Conclusions:** Consistent with earlier findings, this updated ITC with a 5-year minimum follow-up from RELA-047 suggests that 1L treatment with NIVO + RELA may have efficacy comparable to NIVO + IPI in pts with advanced melanoma, overall and across most, but not all, subgroups. Results should be interpreted with caution because of differences in study design and the evolving treatment landscape over time. Research Sponsor: Bristol Myers Squibb.

Efficacy outcomes after weighting.

	NIVO + RELA (n = 339)	NIVO + IPI (n = 297)	HR/OR (95% CI)[a]	NIVO RELA-047 (n = 338)	NIVO CM-067 (n = 288)	HR/OR (95% CI)[b]
Median PFS per INV, mo (95% CI)	12.0 (8.2–17.1)	11.2 (8.5–18.1)	1.10 (0.90–1.34)	6.7 (4.6–10.2)	5.7 (3.9–9.1)	0.96 (0.79–1.16)
Confirmed ORR per INV, %	48	50	0.92 (0.73–1.15)	40	40	0.99 (0.78–1.26)
Median OS, mo (95% CI)	64.2 (38.6–NR)	61.4 (37.1–NR)	0.96 (0.77–1.20)	34.7 (27.3–47.3)	35.7 (26.4–52.7)	1.04 (0.85–1.28)
Median MSS, mo (95% CI)	NR (NR–NR)	NR (61.4–NR)	0.88 (0.68–1.12)	51.2 (34.7–NR)	44.8 (32.3–NR)	1.00 (0.80–1.25)

[a]NIVO + RELA vs NIVO + IPI.
[b]NIVO arms. NR, not reached; odds ratio, OR.

9531 **Poster Session**

Transposable elements and homotypic niches as drivers of immune dynamics and resistance in melanoma epigenetic-based immunotherapy. First Author: Teresa Maria Rosaria Maria Rosaria Noviello, University of Miami, Miami, FL

Background: Melanoma plasticity facilitates immune evasion and therapy resistance through dynamic cell-state transitions. While epigenetic remodeling critically influences these processes, its role in reshaping the tumor ecosystem under therapeutic pressure remains unresolved. We investigated the molecular and spatial mechanisms underlying clinical response to epigenetic-based immunotherapy in the phase Ib NIBIT-M4 trial (NCT02608437), which evaluated the DNA methyltransferase inhibitor guadecitabine combined with the anti-CTLA4 antibody ipilimumab. **Methods:** We performed longitudinal single-cell multiome profiling (paired snRNA-seq and snATAC-seq) on tumor biopsies collected at baseline and during treatment (weeks 4 and 12) from five melanoma patients (two responders, three non-responders). To resolve the spatial architecture of cell states, we integrated these data with high-resolution spatial transcriptomics (Visium HD) across nine samples. Analyses focused on defining malignant meta-programs (MPs), tumor microenvironment (TME) remodeling, and the regulatory role of transposable elements (TEs). **Results:** Integrated analysis resolved seven malignant MPs. Responders exhibited progressive enrichment of an Antigen Presentation/Interferon program, coupled by coordinated TME remodeling with T- and B-cell expansion. Conversely, non-responders were enriched for a de-differentiated Neural crest-like state. Spatial modeling revealed that this resistant Neural crest-like program relies on homotypic clustering to form compact, centrally localized niches that stabilize its transcriptional identity. In contrast, Wnt/β-catenin subpopulations displayed a bimodal architecture, existing as either cohesive clusters or dispersed plastic cells. Epigenetic therapy reactivated TEs, which provided regulatory signals priming innate immunity and generated tumor-associated antigens that drove immunoediting in responders. Mechanistically, NFATC2 emerged as a master regulator of the Neural crest-like phenotype, and its inhibition promoted re-differentiation toward immunogenic states. **Conclusions:** Epigenetic-based immunotherapy dynamically reshapes the melanoma ecosystem by modulating TE activity and cell-state plasticity. Clinical response links to TE-driven immune priming, whereas resistance is maintained by spatially consolidated Neural crest-like niches stabilized by NFATC2. These findings identify spatial clustering as a principle of resistance and highlight NFATC2 as a potential therapeutic target. Research Sponsor: NIBIT Foundation Onlus; Fondazione AIRC; National Cancer Institute Cancer Center Support Grant (CCSG).

9532 **Poster Session**

Nivolumab + relatlimab (NIVO + RELA) in advanced melanoma: 5-year update of RELATIVITY-047. First Author: Hussein A. Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: NIVO + RELA improved progression-free survival (PFS) vs NIVO in patients (pts) with advanced melanoma in the randomized, double-blind, phase 3 RELATIVITY-047 trial (NCT03470922), leading to regulatory approval as a fixed-dose combination (FDC). The combination also improved clinically meaningful efficacy outcomes (objective response rate [ORR], overall survival [OS], melanoma-specific survival [MSS]) vs NIVO. Here, we report 5-year trial outcomes that characterize long-term response durability and landmark survival. **Methods:** 714 pts were randomized 1:1 to receive NIVO 480 mg + RELA 160 mg FDC or NIVO 480 mg intravenously every 4 weeks, as previously described. PFS per RECIST v1.1 (primary endpoint) was assessed by blinded independent central review (BICR); secondary endpoints included ORR per BICR and OS. MSS (censoring nonmelanoma-related deaths) was a post hoc analysis. **Results:** At data cutoff (25 Sept 2025), minimum potential follow-up was 57.3 months (mo; time from last pt randomization to clinical cutoff date). NIVO + RELA continued to show a clinically meaningful benefit vs NIVO for PFS, OS, MSS, and ORR (table). Improvements in absolute landmark survival rates were observed over 3, 4, and 5 years as follows: PFS, 4%, 7%, and 10%; OS, 7%, 9%, and 10%; MSS, 9%, 10%, and 13%. In addition, NIVO + RELA demonstrated consistent improvement in efficacy outcomes vs NIVO across the majority of key subgroups. Subsequent systemic therapy was received by 40% of pts treated with NIVO + RELA and 41% with NIVO. Secondary efficacy and biomarker analyses will be presented. Grade 3–4 treatment-related adverse events (TRAEs) occurred in 23% of pts treated with NIVO + RELA and 12% with NIVO; TRAEs (any grade) led to treatment discontinuation in 17% and 10% of pts, respectively. No new treatment-related deaths were reported since the 2-year analysis. **Conclusions:** With a follow-up of 5 years, first-line NIVO + RELA continued to demonstrate durable, clinically meaningful long-term improvements in PFS, OS, ORR, and MSS vs NIVO, with median MSS not reached for the combination. Across landmark timepoints, absolute separations in PFS, OS, and MSS rates were maintained and increased at the 5-year follow-up. Safety remained consistent with prior reports, with no new or unexpected safety signals. Clinical trial information: NCT03470922. Research Sponsor: Bristol Myers Squibb.

	NIVO + RELA (n = 355)	NIVO (n = 359)	HR/ORR difference (95% CI)
Median PFS, mo (95% CI)	10.2 (6.5–15.7)	4.6 (3.5–6.5)	0.77 (0.65–0.92)
60 mo PFS rate, % (95% CI)	29 (24–35)	19 (15–24)	–
Median OS, mo (95% CI)	54.8 (33.6–81.1)	33.2 (25.2–44.7)	0.78 (0.64–0.95)
60 mo OS rate, % (95% CI)	48 (43–53)	38 (33–43)	–
Median MSS, mo (95% CI)	NE (NE–NE)	47 (34–65)	0.71 (0.57–0.88)
60 mo MSS rate, % (95% CI)	58 (52–63)	45 (40–51)	–
ORR, % (95% CI)	44 (39–49)	34 (29–39)	10 (3–17)

Descriptive analyses; minimum follow-up: 57.3 mo.
HR, hazard ratio; NE, not estimable.

9533 **Poster Session**

Circulating tumor DNA (ctDNA) clearance after immune checkpoint inhibition (ICI) with radiotherapy (RT) as a prognostic indicator for patients with advanced melanoma. First Author: Alyssa K. Steimle, University of Wisconsin Carbone Cancer Center, Madison, WI

Background: ctDNA is becoming a useful biomarker for ICI treatment response assessment in advanced melanoma. RT is capable of producing an abscopal effect, potentially enhancing ICI efficacy. The utility of ctDNA monitoring with concurrent ICI and RT remains incompletely explored. Here, we describe the clinical characteristics and survival outcomes of patients with advanced stage melanoma treated with ICI and palliative RT based on ctDNA dynamics. **Methods:** In this multicenter, retrospective study, patients with unresectable stage III/IV melanoma treated with ICI and palliative RT were identified. Patients had prospectively collected, tumor-informed, exome-based, ctDNA monitoring (Natera). Within 3 months prior to RT, patients had a baseline ctDNA level. Patients were separated into 3 cohorts based on nadir ctDNA dynamics within 3 months after RT. Those with undetectable ctDNA were categorized as "ctDNA cleared." Patients with a positive fold ctDNA change were "increasing ctDNA" and negative fold change were "decreasing ctDNA." Hazard ratios for overall survival (OS) probability were determined via log-rank tests and multivariate analysis (MVA) used cox proportional hazard models. **Results:** 50 patients treated with ICI and palliative RT were analyzed. Median follow up was 8.0 months from RT start. Median age was 65 (24-86) and median baseline ctDNA level was 8.9 MTM/mL (0-11390 MTM/mL). Melanoma primaries included: 82% (41) cutaneous, 10% (5) mucosal, 8% (4) unknown primary. ICI regimens included 70% (35) ipilimumab/nivolumab, 16% (8) nivolumab/relatlimab, 2% (1) anti-PD-1/investigational ICI, 12% (n=6) anti-PD-1 monotherapy. 20 patients had ctDNA clearance, 12 patients had decreasing ctDNA, and 18 patients had increasing ctDNA following RT with ICI. The most common RT sites were the CNS (50%, n=25) and skin/soft tissue (24%, n=12), followed by lymph nodes and bone (each 14%, n=7), and lung and liver (each 6%, n=3). Patients with ctDNA clearance had longer OS (p=0.001) compared to those with increasing or decreasing and detectable ctDNA following RT. One year OS was 85.9% with ctDNA clearance, 30.6% with decreasing ctDNA, 22.0% for increasing ctDNA. In a MVA adjusting for age, M substage, radiation site, and melanoma subtype, both decreasing and increasing ctDNA were associated with worse OS compared with ctDNA clearance (HR 5.08 [95% CI, 1.26–20.48, p=0.022] and HR 9.83 [95% CI, 2.69–35.94, p<0.001], respectively). **Conclusions:** Among patients with advanced melanoma treated with ICI and palliative RT, ctDNA clearance is associated with significantly improved OS compared to patients with detectable ctDNA within 3 months following RT. Ongoing prospective studies are needed to understand the long-term clinical impact of RT on ICI-treated patients with melanoma, and better define the role of ctDNA monitoring for this population. Research Sponsor: None.

9534 **Poster Session**

Optimal timing of circulating tumor DNA (ctDNA) dynamics to prognosticate immune checkpoint inhibitors (ICI) efficacy in patients with advanced stage melanoma. First Author: Vincent T. Ma, University of Wisconsin Madison, Madison, WI

Background: ctDNA predicts relapse in resected tumors, but its role in advanced disease is less defined. We previously reported that early ctDNA changes at 3-4 weeks after ICI initiation can inform treatment response and survival. In this study, we attempt to identify the optimal timing of ctDNA dynamics within 90 days at various windows to better associate with ORR, PFS, and OS outcomes in patients (pts) with advanced stage melanoma treated with ICI. **Methods:** We performed a multicenter retrospective analysis using a personalized tumor-informed ctDNA assay (Natera) on prospectively collected plasma from pts with unresectable stage III/IV melanoma treated with anti-PD-1-based therapy. ctDNA was assessed at baseline and within 90 days of ICI initiation, stratified by ≤30, 31-60, and 61-90 days. Logistic regression evaluated associations between ctDNA change (decrease/stable vs increase) and ORR. Cox proportional hazards models assessed PFS and OS. Pearson (ORR) and Spearman (PFS, OS) correlations were used for continuous ctDNA analyses. **Results:** Among 182 pts, 80% had cutaneous, 11% mucosal, and 9% unknown primary melanoma; 23% had unresectable stage III and 77% stage IV disease. Treatments included ipilimumab/nivolumab (55%), nivolumab/relatlimab (24%), and anti–PD-1 monotherapy (20%). Median follow-up was 12.1 months. Decreasing/stable ctDNA at all timepoints was strongly associated with ORR (p<0.0001), with the greatest effect at 31-60 days (OR 25.38, 95% CI 7.12-90.45). Similar patterns were observed for survival, with improved PFS across all windows and strongest separation at 61-90 days (HR 0.170, 0.101-0.288). OS was likewise improved, most notably at 61-90 days (HR 0.137, 0.058-0.321). Continuous ctDNA change correlated with ORR (r -0.51 to -0.63) and PFS (ρ -0.35 to -0.47); OS correlations were weaker but significant at 61-90 days (ρ -0.21). See Table 1. **Conclusions:** While ctDNA dynamics within 30 days showed prognostic value, associations with ORR, PFS, and OS were strongest and most consistent at 31–60 and 61–90 days. Prospective studies are needed to validate ctDNA for ICI treatment monitoring. Research Sponsor: The Institute for Clinical and Translational Research KL2 Scholars Program at the University of Wisconsin; UL1TR002373 and KL2TR002374.

Association of ctDNA dynamics with outcomes by time interval.

	≤30 days	31-60 days	61-90 days
ORR (OR, 95% CI)	15.28 (5.58–41.78), p<0.0001	25.38 (7.12–90.45), p<0.0001	17.82 (5.66–56.08), p<0.0001
PFS (HR, 95% CI)	0.373 (0.224-0.621), p<0.0001	0.233 (95% CI 0.139-0.388), p<0.0001	0.170 (0.101-0.288), p<0.0001
OS (HR, 95% CI)	0.477 (0.237-0.961), p=0.038	0.392 (95% CI 0.185-0.831), p<0.015	0.137 (0.058-0.321), p<0.0001
ORR (Pearson, r)	-0.553, p<0.0001	-0.628, p<0.0001	-0.513, p<0.0001
PFS (Spearman, ρ)	-0.352, p<0.0001	-0.438, p<0.0001	-0.473, p<0.0001
OS (Spearman, ρ)	-0.128, p=0.168	-0.104, p=0.240	-0.210, p=0.0171

9535 **Poster Session**

Anti–PD-1 (PD-1) monotherapy versus combination with anti–CTLA-4 for metastatic uveal melanoma (MUM) patients (pts). First Author: Ines Esteves Domingues Pires da Silva, Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia

Background: MUM carries a poor prognosis with few effective treatments, especially for HLA-A*02:01-negative pts. While a subset of MUM pts responds to immune checkpoint inhibitors, the comparative efficacy of IPI+PD1 versus PD1 monotherapy is unclear. This study compares objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and safety between these regimens in MUM. **Methods:** MUM pts treated with PD1 or IPI+PD1 at 15 major melanoma centres (from Australia, Europe, United States and Israel) were included. Demographics, patient and disease characteristics, and clinical outcomes were examined. Univariate and multivariate (MVA) analyses were performed to identify clinical predictors of response and survival. **Results:** Of 412 MUM pts treated, 150 (36%) had PD1 and 262 (64%) received PD1+IPI. Compared to the PD1 group, PD1+IPI-treated pts were younger (64 vs. 70 years; p<0.001), had higher rate of elevated LDH (44% vs. 31%; p=0.037), and more frequently had prior treatment with tebentafusp (6.5% vs. 1.3%; p=0.031). Median follow-up from commencement of PD1+/-IPI was 4.9 years (95% CI 4.7 – 6.1). ORR was higher in IPI+PD1 group (18%) vs. PD1 (9%) (p=0.008), particularly in males (p=0.009), patients with liver metastases (p=0.018) and with lung metastases (p=0.011), with elevated LDH (p=0.047) and with no prior treatment with tebentafusp (p=0.007). PFS and OS at 1 and 2 years were numerically higher with IPI+PD1 (1- and 2-year PFS: 23% and 15%; 1- and 2-year OS: 63% and 39%) vs. PD1 (1- and 2-year PFS: 17% and 11%; 1- and 2-year OS: 54% and 36%), but these differences were not statistically significant (p>0.05). On MVA, adjusting for predefined variables (age, gender, ECOG PS, LDH, presence/absence of liver/lung metastases, prior treatment with tebentafusp), IPI+PD1 was associated with higher ORR (OR 2.71, 1.30 – 6.05; p=0.01) but not with PFS or OS compared to PD1. Presence of liver metastases (ORR [OR 0.28; 95% CI 0.13 - 0.64], PFS [HR 1.61; 95% CI 1.11 - 2.34], OS [HR 2.02; 95% CI 1.32 - 3.10]), ECOG PS≥2 (PFS [HR 1.82; 95% CI 1.07 - 3.10], OS [HR 2.24; 95% CI 1.25-4.01]), elevated LDH (PFS [HR 1.66; 95% CI 1.30 - 2.11], OS [HR 2.39; 95% CI 1.84-3.10]) and prior tebentafusp treatment (OS [HR 2.36; 95% CI 1.21-4.59]) were also independent predictors of response and/or survival. A higher percentage of pts experienced grade ≥3 immune-related adverse events (irAEs) in the IPI+PD1 group compared to the PD1 group (34% vs 13%, p<0.0001). Most pts ceased treatment due to progression (234, 57%), and more pts stopped due to toxicity in the IPI+PD1 vs. PD1 group (25% vs. 9%, p<0.0001). **Conclusions:** In pts with MUM, IPI+PD1 demonstrated a higher ORR but did not improve survival compared with PD1 alone. IPI+PD1 was more toxic, leading to early treatment discontinuation in one-quarter of pts. These findings may help guide treatment selection in MUM. Research Sponsor: None.

9536 **Poster Session**

Real-world experience with lifleucel, tumor selection, and dead-in therapy from a single-institution series. First Author: Theresa Medina, University of Colorado, Aurora, CO

Background: Lifileucel is the first approved cellular therapy for persons with metastatic melanoma after upfront treatment with immune checkpoint inhibitor(s) (ICIs) and BRAF-targeted therapy (if applicable). There is not an established consortium to centralize data surrounding procurement and outcomes. Until then we report a single institution series of lifileucel used in the real-world in patients (pts) with previously treated metastatic melanoma. We evaluate whether there are differences in outcomes based on tumor procurement sites, lead-in therapy, and presence of CNS metastases prior to being treated with lifileucel. In addition, for those with progressive disease (PD) will describe the pattern of progression after lifileucel. **Methods:** The University of Colorado and its affiliated hospital UCHealth became an authorized treatment center for TIL in November 2024. Between November 2024 and January 2026, tumor tissue procurement was completed on 27 patients diagnosed with a variety of melanoma subtypes, stages and received bridging therapy. 24 pts have been treated with lifileucel. All pts received prior combination ICIs and, if BRAF-V600mut, most received prior treatment with BRAF/MEK inhibitors. **Results:** 41.7% of pts treated with lifileucel have had at least partial response (PR) as best overall response (BOR). 12% of pts have had a complete response (CR) as BOR. 16.7% had an initial PR but then had PD within 3 mos. 37.5% of pts had PD as BOR. In regard to tumor procurement site, tumor sites were subcutaneous/superficial soft tissue, lymph node, or visceral locations. The response rate from subcutaneous tumors was 16.7%, the response rate from lymph node was 33.3% and the response rate from visceral sites was 42.3%. The response rate from a single tumor used for procurement was 27%. The response rate from combining multiple tumors from different sites was 46%. The most recent therapy prior to lifileucel included: 1) ipilimumab+nivolumab, (5 pts) with 40% response rate, 2) relatlimab+nivolumab, (8 pts) with 75% response rate, 3) anti-PD-1 monotherapy, (3 pts) with 66% response rate, 4) BRAF/MEK inhibitor, (5 pts) with no response to lifileucel. 10 pts had CNS lesions treated prior to lifileucel, 6 pts had CNS lesions treated after lifileucel infusion, 5 were treated with BRAF/MEK prior to receiving lifileucel. 4 pts had PR and 2 had CR of metastatic sites present prior to lifileucel but had PD within 3 mos to new visceral sites. **Conclusions:** From our single-institution series, using lymph node and visceral tumors for lifileucel generation is associated with higher overall response rate. Combining more than one tumor for lifileucel generation is also associated with higher overall response rate. There were 6 patients that had CNS progression after lifileucel but the majority had used BRAF/MEK prior to receiving lifileucel which raises question of what effect this has on lifileucel efficacy. Research Sponsor: None.

9537 **Poster Session**

Prognostic and therapeutic implications of HRR gene mutations in non-cutaneous melanoma: Association with anti-PD-1 efficacy. First Author: Yue Yang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: Homologous recombination deficiency (HRD) describes a tumor cell state characterized by impaired DNA double-strand break repair via the homologous recombination repair (HRR) pathway. Deficiencies in this pathway may serve as predictive biomarkers. However, the relevance of HRR gene mutations remains inadequately characterized in non-cutaneous melanoma. In this study, we aimed to delineate the mutational landscape of HRR genes in this population and evaluate their predictive implications for clinical management. **Methods:** We conducted a retrospective analysis of 932 patients with non-cutaneous melanoma treated at Beijing Cancer Hospital from January 2008 to January 2026. Tumor genomic profiling was performed using targeted next-generation sequencing with either an 81- (n=852) or a 425-gene (n=80) panel. Associations between HRR mutation status and survival outcomes were assessed using Kaplan-Meier survival estimates and Cox proportional hazards regression models. **Results:** HRR mutations were identified in 92 patients (9.9%), with the most frequent alterations occurring in ATM (3.5%), ARID1A (3.4%), BRCA2 (2.7%), and BRCA1 (1.8%). Within this HRR-mutated cohort, the primary subtypes were mucosal (44.6%) and acral (29.3%) melanoma. And the disease stages were distributed as follows: stage I, 31 patients (33.7%); stage II, 15 (16.3%); stage III, 22 (23.9%) and stage IV, 24 (25.0%). After a median follow-up of 63.7 months, the median overall survival (OS) was 57.5 months (95% CI: 43.4–71.7), with 1-, 2-, 3-, and 5-year OS rates of 92.1%, 84.9%, 74.7%, and 56.8%, respectively. Multivariate analysis confirmed age ≥65 years as an independent predictor of poorer overall survival (HR 2.7, 95% CI 1.3–5.4, P = 0.005), whereas ATM mutation emerged as a significant protective factor associated with a 68% reduction in mortality risk (HR 0.32, 95% CI 0.1–0.7, P = 0.007). Among 59 HRR-mutated patients who received first-line systemic therapy, 41 were treated with anti-PD-1-based regimens and 18 with non-PD-1-based regimens. In the 54 evaluable patients, median progression-free survival (PFS) was 9.0 months (95% CI: 3.8–14.2) and median OS was 55.0 months (95% CI: 39.0–71.0). The objective response rate (ORR) was 11.1%, and the disease control rate (DCR) was 61.1%. The DCR was 77.8% (21/27) in the mucosal subgroup versus 37.5% (6/16) in the acral subgroup with a statistically significant difference (P = 0.028). In a subgroup analysis, although not statistically significant, anti-PD-1-treated patients trended toward a longer median PFS compared with those not receiving anti-PD-1 therapy (15.0 vs. 6.0 months, P = 0.249). **Conclusions:** HRR mutations define a distinct molecular subset in non-cutaneous melanoma. ATM mutation serves as an important prognostic biomarker, and patients with HRR-mutated melanoma may derive survival benefit from anti-PD-1 immunotherapy. Research Sponsor: None.

9538 **Poster Session**

Novel adaptive versus continuous dosing of encorafenib and binimetinib in combination with nivolumab in advanced *BRAF V600E* mutant melanoma. First Author: Zeynep Eroglu, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: In BRAF V600 mutant melanoma, continuous treatment with BRAF/MEK inhibitors invariably begets acquired resistance. Preclinical success of intermittent dosing to overcome resistance did not translate to clinical benefit in the randomized SWOG S1320 trial, possibly due to fixed schedule of intermittent dosing (5 wk on/3 wk off cycles). Leveraging intra-tumoral competition dynamics to slow expansion of resistant tumor subpopulations via patient-specific adaptive MAPK therapy may improve outcomes. We hypothesized that adaptive drug scheduling of BRAF/MEKi combined with anti-PD-1 would lead to non-inferior or improved outcomes with less toxicity compared to a continuous triplet regimen. **Methods:** In a pilot prospective trial, pts with advanced BRAF V600E mutant melanoma, naïve to systemic tx in this setting, with detectable plasma circulating tumor DNA (ctDNA) were eligible (using BRAFV600E ctDNA ddPCR). Ten pts were randomized 1:1 to continuous (Arm A) or patient-specific adaptively dosed (Arm B) ENCO plus BINI, with continuous biweekly NIVO in both arms. A mathematical model was calibrated for Arm B using pts' ctDNA values (baseline and biweekly sampling) and standard CT response imaging every 12 weeks. This model was a coupled system of differential equations to guide treatment decisions biweekly by simulating the future response on or off drugs (ENCO+BINI) based on that pt's known ctDNA levels and response data. Therefore, pts in Arm B all had differing lengths of time that they received ENCO+BINI. Primary endpoint was feasibility of the adaptive approach, by adherence to protocol from baseline to week 12. **Results:** Ten pts, median age 59, 70% male, 80% with stage IV melanoma, were randomized. In Arm B, NIVO alone was often effective enough to not trigger resuming ENCO+BINI; in Arm A, pts were on E+B for a median of 61 weeks (89% of time on tx, as drugs could be held for toxicity), while in adaptive Arm B, patients were on E+B for median 11 weeks (24% of time on tx). ORR was 100% in Arm A and 60% in Arm B, all partial responses, with 2 stable disease in Arm B. At median follow-up of 45.5 months, median PFS was 26.9 months (95% CI 5.5-NA) with 3 progressors in Arm A. Median PFS was not reached (17.8-NA) in Arm B and 2 progressed (log-rank p= 0.5). Median OS was 32 months (8.8-NA) in Arm A (2-year OS 60%, 3 pts died). Median OS was not reached (17.8-NA) in Arm B (2-year OS 75%,1 pt died), log-rank p=0.18. In Arm A, there were 16 treatment-related grade 3 adverse events, with only 6 grade 3 AEs in Arm B. **Conclusions:** In this innovative study, we demonstrated the feasibility of patient specific mathematical modeling incorporating ctDNA and imaging, to inform adaptive dosing of ENCO+BINI with concurrent NIVO. The adaptive arm did not compromise efficacy and had lower toxicity. Successful confirmation of this approach in larger trials may favorably impact patient QOL and reduce cost of therapy. Clinical trial information: NCT03543969. Research Sponsor: None.

9539 **Poster Session**

Pretreatment spatial immune architecture and 1-year clinical benefit to first-line ICB in advanced melanoma. First Author: Karim Amrane, Institut Gustave Roussy, Villejuif, France

Background: Predictive biomarkers for immune checkpoint blockade (ICB) in advanced cutaneous melanoma (CM) remain limited. Imaging mass cytometry (IMC) enables spatially resolved profiling of the tumor microenvironment (TME) and can capture immune–tumor architecture beyond cell density. **Methods:** Patients with advanced CM treated with first-line ICB and available pretreatment FFPE tissue were analyzed using IMC (40-marker panel). The primary endpoint was durable 1-year clinical benefit (1y-CB: metabolic CR/PR or stable metabolic disease ≥12 months by PERCIST on FDG-PET/CT); the secondary endpoint was 1-year progression-free survival (1y-PFS). Cell densities, tumor marker expression, and spatial neighborhood metrics were evaluated. Reproducibility was assessed by re-analyzing an independent published IMC melanoma cohort (PMC8026677). **Results:** Twenty-nine patients (anti–PD-1 n=27; ipilimumab+nivolumab n=2); 15 achieved 1y-CB. 1y-CB was associated with higher leukocyte infiltration and increased densities of B cells, conventional CD4⁺ T cells (Tconv), CD8⁺ T cells, and plasma cells, whereas higher tumor density was associated with lack of benefit and inferior 1y-PFS (HR 10.57; $p<0.001$). Higher CD8⁺ and B-cell densities were associated with improved 1y-PFS (HR 0.26, p=0.013; and HR 0.26, p=0.047). Tumor PD-L1 and HLA-DR expression correlated with 1y-CB (p=0.022 and p=0.040). Spatial metrics further stratified outcomes: increased tumor–tumor proximity was associated with poor 1y-CB (p=0.0016), while increased B–Tconv proximity was associated with 1y-CB and longer 1y-PFS (HR 0.20; p=0.037). The strongest spatial association was macrophage proximity to HLA-DR⁺ tumor cells ($p\leq0.0001$). In the external cohort (n=60), responder enrichment for Tconv/CD8⁺ T cells and macrophage proximity to HLA-DR⁺ tumor cells were reproduced. **Conclusions:** Pretreatment IMC identifies both compositional and spatial TME features associated with durable benefit from first-line ICB in advanced CM. T-cell enrichment and macrophage proximity to HLA-DR⁺ tumor cells emerged as reproducible candidate spatial biomarkers warranting prospective validation. Research Sponsor: European Regional Development Fund (ERDF/FEDER); RU-000950; Pfizer; Novartis.

Main predictors of 1y-CB and 1y-PFS.

Parameters	1y-CB events/N	1y-CB p-value	1y-PFS HR (95% CI)	1y-PFS p-value
B cells ≥9.5	5/15 vs 9/14	0.026	0.26 (0.00–0.99)	0.047
CD8⁺ T cells ≥36	7/20 vs 7/9	0.023	0.26 (0.00–0.76)	0.013
Plasma cells ≥1	3/12 vs 11/17	0.017	0.28 (0.08–1.00)	0.050
Tumor density ≥4194	5/5 vs 9/24	0.006	10.57 (3.08–36.23)	<0.001
B–Tconv proximity ≥13.3%	2/10 vs 10/16	0.018	0.20 (0.00–0.91)	0.037
HLA-DR ≥58.4%	1/7 vs 13/22	0.040	0.17 (0.02–1.28)	0.085
PD-L1 ≥3.3%	8/20 vs 6/9	0.022	0.48 (0.16–1.38)	0.171

9541 **Poster Session**

A phase III randomized study comparing BCD-201, a pembrolizumab biosimilar candidate, and reference pembrolizumab in patients with advanced melanoma. First Author: Kristina V. Orlova, FSBI "National Medical Research Oncology Center named after N.N. Blokhin" of the Ministry of Health of the Russian Federation, Moscow, Russian Federation

Background: The development of clinically comparable biosimilars of key immuno-oncology agents is essential to improving global access to effective therapy. BCD-201 is a proposed pembrolizumab biosimilar that has shown high analytical similarity in preclinical studies, and pharmacokinetic equivalence to the reference pembrolizumab in phase I study (NCT05739006).This phase III trial evaluated the clinical equivalence of BCD-201 versus reference pembrolizumab in patients with advanced melanoma. **Methods:** This international, multicenter, randomized, double-blind phase III study enrolled adult patients with unresectable or metastatic cutaneous melanoma. Patients were randomized 1:1 to receive BCD-201 or reference pembrolizumab 200 mg IV every 3 weeks for 24 weeks. Randomization was stratified by ECOG (0 vs 1), PD-L1 expression ($<$5% vs $\geq$5%), and disease stage (AJCC 7th edition M0/M1a/M1b vs M1c). The primary endpoint was objective response rate (ORR) per RECIST v1.1 assessed by blinded independent central review (BICR) at week 24 in the ITT population. Equivalence was concluded if the 95% confidence interval (CI) for the ORR difference fell within prespecified margins of $-$15% to +15%. Secondary efficacy endpoints included ORR per iRECIST, progression-free survival (PFS), overall survival (OS). **Results:** A total of 479 patients were included in the ITT population (BCD-201, n=234; reference pembrolizumab, n=245), with balanced baseline characteristics. At week 24, ORR was 33.3% in the BCD-201 group and 32.7% in the reference pembrolizumab group in ITT population. The unstratified ORR difference was 0.7% (95% CI $-$7.7 to 9.1), fully within the prespecified equivalence margins. Results were consistent across per-protocol and stratified sensitivity analyses. Secondary efficacy endpoints, including ORR per iRECIST, OS, and DOR, were comparable between groups. At 24 weeks, PFS rates were 51.9% for BCD-201 and 50.5% for reference pembrolizumab per RECIST 1.1. OS rate at 24 week was 90.2% in the BCD-201 group and 89.3% in the reference pembrolizumab group. Longer-term efficacy and safety data will be reported in future analyses. Safety profiles were similar between groups, with grade $\geq$3 AEs reported in 19.7% and 21.9% of patients for BCD-201 and reference pembrolizumab. Main PK parameters (AUC and C_{max}) met equivalence criteria. Immunogenicity was low and comparable between groups, with binding antibodies (Abs) detected in 7 (3.1%) and 6 (2.6%) patients in the BCD-201 and comparator groups, respectively. No neutralizing Abs were detected. **Conclusions:** BCD-201 demonstrated equivalent efficacy to reference pembrolizumab with comparable safety, pharmacokinetics, and immunogenicity in patients with advanced melanoma. These data support BCD-201 as a pembrolizumab biosimilar and highlight its potential to expand access to anti-PD-1 therapy. Clinical trial information: NCT05986331. Research Sponsor: None.

9542 **Poster Session**

The prognostic and predictive role of FDG PET/CT in melanoma patients treated with immune checkpoint blockade: A meta-analysis. First Author: Isadora Mamede, Faculdade de Governança, Engenharia e Educação de São Paulo - FGE, Chapecó, Brazil

Background: Immune checkpoint blockade (ICB) is standard therapy for advanced melanoma, but many patients derive limited benefit. Biomarkers to guide treatment decisions are needed. FDG PET/CT (PET) shows promise for response assessment, but most studies are small or evaluate a single timepoint. Here, we conducted a meta-analysis to assess the prognostic value of metabolic response for overall survival (OS) and progression-free survival (PFS), and the diagnostic performance of PET-derived parameters. **Methods:** PubMed, Cochrane, and EMBASE were searched for studies including melanoma patients treated with ICB who underwent baseline and follow-up PET. Metabolic response was defined using PERCIST, PERCIST5, or EORTC criteria, dichotomizing patients as responders or non-responders. Random-effects meta-analyses estimated pooled hazard ratios (HRs) for OS and PFS, with subgroup analyses by PET timing (early $\leq$4 months vs late $>$ 4 months). Univariate diagnostic meta-analyses evaluated the accuracy of changes in total lesion glycolysis (TLG) and metabolic tumor volume (MTV) for predicting death or OS, as well as the ability of PET-defined progressive metabolic disease (PMD) to identify clinical or RECIST-based disease progression. **Results:** Of the 15 studies included, 943 pts were included. Interval metabolic response was significantly associated with improved OS (HR 0.22; 95% CI 0.13-0.36; p = 0.02), with no significant difference according to the time of PET assessment early vs late (p for interaction = 0.75). Similarly, metabolic responders experienced significantly longer PFS (HR 0.21; 95% CI 0.11-0.39; p = 0.03). Although the association was statistically significant for late (HR 0.21; 95% CI 0.11-0.41), but not for early assessment (HR 0.13; 95% CI 0.01-1.91), no subgroup difference was observed (p for interaction = 0.73). In diagnostic analyses for OS prediction, changes in TLG demonstrated a pooled sensitivity of 0.70 (95% CI 0.54-0.82) and specificity of 0.79 (95% CI 0.52-0.93). Changes in MTV showed comparable performance, with a sensitivity of approximately 0.70 (95% CI 0.54-0.82) and a specificity of 0.83 (95% CI 0.42-0.97). PET-defined PMD showed good diagnostic accuracy for identifying clinical or RECIST-defined disease progression, with a pooled sensitivity of approximately 0.71 (95% CI 0.42-0.89) and specificity of 0.86 (95% CI 0.69-0.95). **Conclusions:** In our study, metabolic response by PET was associated with improved OS and PFS, irrespective of the timing of imaging. Quantitative changes in TLG and MTV provide moderate accuracy for predicting survival, while PET/CT-defined PMD reliably identified RECIST-based disease progression. These findings support future prospective studies investigating the role of PET dynamics as a minimally invasive prognostic and predictive biomarker for pts with advanced melanoma undergoing treatment with ICB. Research Sponsor: None.

9543 **Poster Session**

Botensilimab (BOT) ± balstilimab (BAL) in patients (pts) with advanced cutaneous melanoma (cMEL) refractory/resistant (R/R) to anti–PD-(L)1 ± CTLA-4: A phase 2 trial. First Author: Michael B. Atkins, Georgetown Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC

Background: Pts with advanced cMEL R/R to PD-(L)1–based therapy, including PD-(L)1+CTLA-4, have few treatment options. BOT (Fc-enhanced anti–CTLA-4) augments T-cell priming, depletes Tregs, and activates antigen-presenting cells to overcome immune checkpoint inhibitor (ICI) resistance. BOT ± BAL (anti–PD-1) has shown activity in ICI-R/R and cold tumors. **Methods:** The open-label, global phase 2 C-800-23 trial (NCT05529316) enrolled pts with cMEL (stage III unresectable or IV) R/R to prior anti–PD-(L)1 ± CTLA-4. Part 1: randomized 1:1 to BOT 50 mg or 150 mg every 3 weeks (Q3W; up to 4 doses). Part 2: BOT 75 mg Q3W (up to 4 doses) plus BAL 450 mg Q3W (up to 2 years). Endpoints included confirmed objective response rate (ORR; primary; RECIST 1.1), progression-free survival (PFS), duration of response (DOR), overall survival (OS), and safety. Clinical benefit rate (CBR) was complete or partial response or stable disease for $\geq$24 weeks. **Results:** As of Dec 13, 2025, 138 pts received BOT monotherapy (median follow-up, 12.3 mo; range, 0.2–35+) and 36 pts received BOT+BAL (median follow-up, 13.8 mo; range, 2–26+). Overall, 51% had stage M1c or M1d disease, 29% had *BRAF* mutant disease, and 39% had LDH $>$ULN. In pts R/R to anti–PD-(L)1, 72% (60/83 with pre-trial data available) had primary resistance (best overall response of progressive disease [PD] or PD $\leq$6 mo from most recent course of respective ICI type). In pts R/R to anti–PD-(L)1+CTLA-4, 69% (61/88) had primary PD-(L)1 resistance and 69% (60/87) had primary CTLA-4 resistance. With BOT+BAL, ORR was 22% (95% CI, 10–39), CBR was 33% (95% CI, 19–51), median DOR was not reached (NR; 95% CI, 4.17–NR), 12-mo PFS was 29% (95% CI, 15–44), and median OS was 16.6 mo (95% CI, 9.1–NR; 24-mo OS, 46%; 95% CI, 29–61). ORR with BOT+BAL was numerically higher in PD-(L)1+CTLA-4 R/R pts (29%, 4/14; 95% CI, 8–58; 3/4 responders had primary ICI resistance) vs PD-(L)1–only R/R pts (18%, 4/22; 95% CI, 5–40; all responders had primary ICI resistance). With BOT alone, ORR was 6% (95% CI, 3–11), CBR was 14% (95% CI, 9–21), 12-mo PFS was 7% (95% CI, 3–13), and median OS was 12.9 mo (95% CI, 9.7–16.2; 24-mo OS, 28%; 95% CI, 20–36). Responses were irrespective of Fcγ receptor genotype. Treatment-related adverse events occurred in 81% (grade $\geq$3, 30%) with BOT alone and 94% (grade $\geq$3, 36%) with BOT+BAL; most common was diarrhea (BOT 33%; BOT+BAL 42%). One possibly treatment-related death was reported with BOT monotherapy (immune-mediated enterocolitis). No new safety signals occurred. **Conclusions:** In this ICI-R/R cMEL population enriched with primary ICI-resistant pts, BOT+BAL showed durable responses, encouraging survival, and a stronger signal in pts who had prior conventional anti–CTLA-4. BOT monotherapy also showed activity. This supports a differentiated mechanism for BOT and continued development of BOT+BAL, including for pts with dual ICI-R/R cMEL. Clinical trial information: NCT05529316. Research Sponsor: Agenus Inc.

9544 **Poster Session**

Final results of the phase III OCTAVA trial: Clinical benefit of low-dose anti–CTLA-4 plus anti–PD-1 combination vs anti–PD-1 monotherapy in unresectable or metastatic melanoma. First Author: Lev V. Demidov, N.N.Blokhin NMRC of Oncology MoH of Russia, Moscow, Russian Federation

Background: BCD-217-2/OCTAVA is an international, multi-center, randomized, double-blind, placebo-controlled phase III study conducted to assess the efficacy and safety of nurulimab +prolgolimab (nuru + prolgo) combination therapy with continued prolgolimab therapy compared to prolgolimab monotherapy at the 1st line treatment of patients (pts) with unresectable or metastatic melanoma (un/mM). BCD-217 is a fixed-dose combination of nurulimab (aCTLA-4, 5 mg/ml) and prolgolimab (aPD-1, 15 mg/ml) which was recently approved for this indication in Russia and Belarus. Here we present efficacy results based on 24 mos of therapy. **Methods:** Treatment-naïve pts with un/mM (stage IIIC–IV) were randomized 1:1 to two arms. The nuru+prolgo arm received a combo of nurulimab (1 mg/kg) and prolgolimab (3 mg/kg) at 0.2 ml/kg Q3W for the first four infusions. The prolgo arm received prolgolimab monotherapy (3 mg/kg Q3W) for the first four infusions. Both arms then received prolgolimab maintenance therapy for up to two years. The primary endpoint of the study was PFS. **Results:** 271 pts were randomized to nuru+prolgo (n=135) or prolgo monotherapy (n=136) arms. After a median follow-up of 24.7 mos the mPFS was 15.4 (95% CI 8.4; NA) mos in the nuru+prolgo arm and 8.3 (95% CI 4.2; 14.8) mos in the prolgo monotherapy arm (HR 0.696, 95% CI 0.502; 0.965), iRECIST, ITT population). The PFS benefit was consistent per RECIST 1.1 (HR 0.717, 95% CI 0.533; 0.964). ORR, DCR and TTR were also higher in nuru+prolgo arm. mOS was not reached in both groups (HR 0.836, 95% CI 0.495; 1.41). 24-mos OS was 76.1% in nuru+prolgo arm and 71.7% in prolgo arm respectively. The mDOR was also not reached in any arm, meaning that more than half of the pts who responded to therapy maintained their response until the end of the FU period. Grade $\geq$3 treatment-related AEs occurred in 17.8% of pts (nuru+prolgo) vs 13.2% (prolgo). Gr $\geq$3 irAEs were 14.1% vs 5.1%, respectively (p=0.0126). Any-grade irAEs were reported in 51.9% vs 33.8% of cases (p=0.0027). Treatment discontinuation due to AEs was 11.1% vs 5.1%. **Conclusions:** The OCTAVA trial results demonstrated a statistically significant and clinically meaningful improvement in PFS for the 1st line low-dose nuru + prolgo combination followed by prolgo maintenance, compared to prolgo monotherapy, in patients with unresectable or metastatic melanoma. This efficacy benefit was accompanied by manageable rate of immune-related AE, consistent with the known profile of CTLA-4/PD-1 combinations. These results support the use of the nuru + prolgo regimen as a valuable 1st line treatment option for this population. Clinical trial information: NCT05732805. Research Sponsor: JSC BIOCAD.

9545 Poster Session

Twenty years of metastatic uveal melanoma management: Real-world experience from a comprehensive cancer center in a low- and middle-income country (LMIC). First Author: Yacob Saleh, King Hussein Cancer Center, Amman, Jordan

Background: Uveal melanoma (UM) is a rare malignancy arising from melanocytes of the uveal tract and accounts for 85% of primary ocular malignancies. Despite effective local control, 10-50% of patients develop metastatic disease, which is associated with poor prognosis and a median overall survival (OS) of approximately one year. Until recently, no effective standard systemic therapy existed for metastatic UM. Real-world data especially from LMICs remain lacking. This study evaluates the clinical characteristics, treatment patterns, and survival outcomes of patients with metastatic UM treated in a LMIC. **Methods:** This retrospective study included adult patients with metastatic UM treated and followed at King Hussein Cancer Center in Amman, Jordan between January 2006 and December 2025. Collected data included baseline demographic and clinical characteristics, metastatic and treatment patterns. Descriptive and survival analyses were conducted using JASP software (version 0.95.4). A two-sided P value <0.05 was considered statistically significant. **Results:** Among 125 patients with UM, 31 (24.8%) had metastatic disease, including two patients with metastasis at initial presentation. Median age at diagnosis was 51 years, and 61.3% were males. ECOG performance status was 0–2 in 81.5% of patients. Hepatic-only metastasis occurred in 51.6% of patients, combined hepatic and extrahepatic in 38.7%, and extrahepatic-only in 9.7%, with 58.6% classified as M1a disease. Median time to distant metastasis was 25 months. Median OS from initial UM diagnosis was 35 months, while median post-metastatic OS (PM-OS) was 10 months. First-line Immunotherapy was associated with significantly improved PM-OS compared to Dacarbazine (median 11 vs 5 months; P = 0.034), with 24-month PM-OS of 44.4% vs 0% respectively. Treatments included Immunotherapy, chemotherapy, Targeted therapy in one patient, local interventions, and best supportive care (Table). **Conclusions:** Metastatic UM remains associated with poor survival outcomes in this real-world cohort. First-line Immunotherapy was associated with longer survival compared to chemotherapy. This study highlights ongoing unmet outcomes needs and underscores disparities in access to emerging therapies, such as Tebentafusp, in LMICs. Broader availability of novel agents and inclusion of patients from LMICs in clinical trials are required. Research Sponsor: None.

First-line Treatments	Second-line Treatments	Third line Treatments	Additional Local interventions
Pembrolizumab (n=15)	Dacarbazine (n=7)	Carboplatin plus Paclitaxel (n=1)	Radiotherapy (n=9)
Nivolumab and Ipilimumab (n=4)	Nivolumab and Ipilimumab (n=1)	Single agent Paclitaxel (n=1)	Microwave ablation (n=1)
Dacarbazine (n=3)			Surgery (n=1)
Darovasertib and Crizotinib (n=1)			
Best supportive care only (n=8)			

9546 Poster Session

Overall survival of patients with mucosal melanoma in the US before and after the advent of PD-1 based immune checkpoint inhibitor treatment. First Author: Olivia First, Department of Medical Education, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Mucosal melanoma (MM) is a rare, aggressive melanoma subtype with poor survival. Prior to 2010, systemic therapy for MM was limited to chemotherapy, adjuvant interferon, and bolus interleukin-2; after 2015, immune checkpoint inhibitors (ICIs), specifically programmed cell death protein-1 (PD-1) based therapies, were widely adopted. The magnitude of overall survival (OS) benefit from ICIs in MM remains poorly defined. **Methods:** We conducted a retrospective cohort study of 8,125 patients with histologically confirmed MM from the National Cancer Database. Patients were stratified by diagnosis era (pre-ICI: diagnosed before 2010; post-ICI: diagnosed after 2015) and receipt of first-line systemic therapy (immunotherapy and/or chemotherapy versus none). Survival analysis was conducted using Kaplan-Meier methods and Cox proportional hazards models. Difference-in-differences (DID) models using Cox regression estimated survival improvements attributable to systemic therapy in the post-ICI era. Multivariable logistic regression was fitted to assess changes in the characteristics of patients receiving systemic therapy between eras. Subgroup analysis included metastatic patients and stratification by primary tumor site (genitourinary [GU], gastrointestinal [GI], head and neck [HN]). Covariates for multivariable models were selected a priori based on clinical relevance. **Results:** Median OS (mOS) significantly improved in the post-ICI era with covariate adjustment (36.2 vs. 25.0 months; HR: 0.63, 95% CI: 0.59-0.66). Adjusted DID analysis demonstrated survival benefits attributable to systemic therapy (HR: 0.86, 95% CI: 0.77-0.97). mOS of metastatic patients also improved in the post-ICI era (12.0 vs. 7.33 months; HR: 0.63, 95% CI: 0.54-0.73). All tumor sites demonstrated significantly longer mOS in the post-ICI era, with GU patients living the longest (49.5 months), followed by HN (34.5 months), and GI (24.4 months). Post-ICI systemic therapy recipients were more likely to be older and publicly insured, to have a high comorbidity burden (Charlson Deyo score), to be ineligible for surgery, and to receive immunotherapy alone compared to pre-ICI patients. **Conclusions:** Survival of MM patients has improved by 37% since the introduction of ICIs. While OS varies by tumor site, all sites showed relative improvement in the post-ICI era. DID analysis suggested that modern survival benefits are driven by ICIs despite an older and more clinically complex treatment population. Research Sponsor: National Cancer Institute of the National Institutes of Health; R25CA281789.

9547 Poster Session

Health-related quality of life following tumor-infiltrating lymphocyte (TIL) therapy with commercial lifileucel in metastatic melanoma: Real-world longitudinal patient-reported outcomes. First Author: Kimberly Ward, Moffitt Cancer Center - McKinley Campus, Tampa, FL

Background: Although the efficacy of lifileucel has been demonstrated in metastatic melanoma, real-world longitudinal patient-reported outcomes remain limited. We evaluated health-related quality of life (HRQoL) among patients treated with commercial lifileucel at Moffitt Cancer Center using the Functional Assessment of Cancer Therapy–Melanoma (FACT-M) instrument. **Methods:** FACT-M surveys were administered at Baseline, Day +7, Month +6, and End of Treatment (April–December 2025). Scores were calculated using validated procedures. Clinical benefit was defined as complete response/ no evidence of disease or partial response as the best response per RECIST v1.1. Minimally important differences (MID) were defined as 4–7 points for the FACT-G total score and 4–6 points for the FACT-M combined scores. Comparisons used Wilcoxon rank-sum tests. **Results:** Thirty-two patients were enrolled, with 97 surveys completed out of 105 requested (92% completion rate). Median age was 66 years (range 29–78); 56% were male (n=18) and 44% female (n=14). ECOG performance status was 0–1 in 93%. Patients received a median of 5 IL-2 doses (range 1–6), and 53% experienced clinical benefit (n=17). Baseline, Day +7, and Month +6 FACT-M subscale and total scores are presented in Table 1. Among all patients, FACT-M and FACT-G scores remained stable from baseline to Day +7 and demonstrated clinically meaningful improvement exceeding the minimally clinically important difference at Month +6. While baseline HRQoL scores did not differ by treatment outcome (median FACT-G, 87 in both groups; median FACT-M, 108 in patients without clinical benefit and 109 in those with benefit), scores were significantly higher across follow-up assessments among patients with clinical benefit compared with those without. Median FACT-G scores were 102 vs. 76 (p=0.012), and median FACT-M scores were 125 vs. 94 (p=0.017), respectively. **Conclusions:** HRQoL, as measured by FACT-G and FACT-M, was maintained following commercial lifileucel in a real-world metastatic melanoma cohort, supporting the tolerability of TIL therapy. HRQoL outcomes varied according to clinical benefit. Larger studies with extended follow-up are warranted to confirm these findings. Research Sponsor: None.

Median baseline, day+7, and month +6 FACT-M subscale and total scores.

Characteristic	Baseline N = 17[†]	Day +7 N = 11[†]	Month +6 N = 13[†]	Baseline to Month+6 difference
Physical well Being (PWB)	25	20	26	+1
Social well Being (SWB)	25.67	25.20	26.00	+0.33
Emotional well Being (EWB)	22.2	22.2	23.3	+1.1
Functional well Being (FWB)	21	20	23	+2
Melanoma (MS)	22.3	20.6	24.5	+2.2
Melanoma Surgery (MSS)	24.5	24.5	27.1	+2.6
FACT-G (sum of PWB, SWB, EWB, + FWB)	90	89	97	**+7**
FACT-M (sum of FACT-G + MS)	111	111	124	**+13**

[†]Median.

9548 Poster Session

Real-world outcomes of dual checkpoint inhibition (nivolumab + ipilimumab) versus anti-PD-1 monotherapy in metastatic uveal melanoma: Impact of local therapy and adjusted survival analysis—A multicenter retrospective study in Russia. First Author: Zakhra R. Magomedova,

Background: Metastatic uveal melanoma (mUM) remains a rare and aggressive malignancy. Immune checkpoint inhibitors (ICI) demonstrate modest activity, and real-world evidence comparing dual (nivolumab + ipilimumab) versus anti-PD-1 monotherapy, as well as the additive role of local therapy is limited. **Methods:** Multicenter retrospective observational study conducted in Russia (IRB-approved at participating centers). Outcomes assessed: median progression-free survival (mPFS), median overall survival (mOS), objective response rate (ORR), disease control rate (DCR), and grade $\geq$3 immune-related adverse events (irAEs). Stratified by treatment line, ICI type, and local therapy use. Univariable Cox proportional hazards regression was performed. **Results:** Patients with metastatic uveal melanoma treated between 2019 and 2025 were included (n=262). Of these, 25 patients (9.5%) who did not receive systemic treatment or received only palliative care were excluded. Among the full cohort: 158 (60.3%) were female, median age at primary diagnosis was 55.9 years, median time to metastatic disease was 2.42 years. Liver metastases were present in 90.8%. After exclusion, 237 patients were analyzed for survival. Results are presented in Table 1. Univariable Cox regression (after exclusion n=237): Dual ICI exposure (yes vs no): HR 0.60 (95% CI 0.44–0.84, p=0.003); Any ICI exposure (yes vs no): HR $\approx$0.72 (p=0.102) — non-significant trend. **Conclusions:** Dual ICI (nivolumab + ipilimumab) was associated with improved overall survival (HR 0.60, p=0.003), particularly with combination with local therapy (predominantly IHP, STRT, and TACE), which substantially enhanced ORR, DCR, PFS, and OS across ICI types. Patients who were unable to receive ICI in the first-line setting may be candidates for this option in the second-line; however, this requires further investigation through subgroup comparative analyses. Research Sponsor: None.

Results.

Treatment Line	ICI Type	Local Therapy	n	mPFS, mo (95% CI)	mOS, mo (95% CI)	ORR (%)	DCR (%)	Gr ≥3 irAEs (%)
First-line	Dual (nivo+ipi)	Without	28	3.5 (3.0–6.6)	18.4 (13.4–33.5)	10.7	28.6	39.3
First-line	Dual (nivo+ipi)	IHP 60% STRT 35% TACE 5%	20	7.5 (6.2–18.2)	45.7 (23.4–NR)	45.0	80.0	45.0
First-line	Mono anti-PD-1	Without	47	3.1 (2.8–3.7)	18.8 (11.9–27.5)	2.1	14.9	2.1
First-line	Mono anti-PD-1	STRT 50% IHP 40% TACE 6.7% RFA 3.3%	30	7.53 (4.5–12.3)	27.9 (18.6–NR)	36.7	60.0	16.7
Second-line	Dual	Without	35	3.3 (2.5–5.5)	13.1 (9.3–18.8)	2.9	31.4	45.7
Second-line	Dual	STRT 100%	3	9.3 (8.7–NR)	39.1 (9.6–NR)	33.3	100.0	33.3
Second-line	Mono anti-PD-1	Without	15	9.0 (5.2–21.6)	21.3 (14.8–NR)	13.3	46.7	0
Second-line	Mono anti-PD-1	STRT 50% IHP 25% TACE 25%	8	8.6 (4.7–NR)	17.3 (13.3–NR)	0	75.0	0

9549 **Poster Session**

The clinical significance of *TET2*-driven clonal hematopoiesis (*TET2*-CH) in ICI-treated melanoma patients. First Author: Mason Nicholas Alford-Holloway, Vanderbilt University Medical Center, Nashville, TN

Background: Clonal hematopoiesis (CH) arises from age-related somatic mutations in hematopoietic stem cells and has been linked to altered immune function and clinical outcomes in solid tumors. While recent studies in colorectal and lung cancers suggest *TET2*-mutant CH may enhance immunotherapy responses, the impact of CH genotype on melanoma outcomes remains unclear and potentially context-dependent. **Methods:** We performed a retrospective cohort study of 361 patients with unresectable stage III/IV melanoma who underwent whole blood sequencing prior to anti-PD-1-based immunotherapy (2014-2024). CH was defined as somatic mutations in CH driver genes with variant allele fraction (VAF) $>$ 2%. Progression-free survival (PFS) and overall survival (OS) were measured from ICI initiation; patients without events were censored at last follow-up. Kaplan-Meier curves and multivariable Cox models adjusted for age, sex, BRAF V600E status, stage, and prior therapy estimated hazard ratios (HRs) compared to patients without CH. Chi-squared analysis assessed CH prevalence among melanoma patients compared to a healthy control cohort (n = 12,346) matched for age and sex. **Results:** CH prevalence was significantly elevated in melanoma patients compared to age and sex-matched healthy controls (27.7% vs. 21.4% χ^2 = 7.94, p = 0.004). Among 361 patients, 32 (8.9%) harbored *TET2*-driven CH, 48 (13.3%) had *DNMT3A*-CH, and 20 (5.5%) had other CH mutations. *TET2*-CH was associated with significantly worse OS compared to patients without CH (HR = 1.79, p = 0.014) and a trend toward inferior PFS (HR = 1.42, p = 0.119). In contrast, neither *DNMT3A*-CH (N = 48) nor other CH genotypes demonstrated significant associations with clinical outcomes (*DNMT3A*-CH: OS HR = 1.38, p = 0.11; PFS HR = 1.21, p = 0.32), establishing genotype-specific effects. **Conclusions:** In this cohort of patients with unresectable Stage III/IV melanoma receiving ICI therapy, *TET2*-CH was associated with inferior survival outcomes, while no significant survival differences were found among patients with *DNMT3A*-CH or other CH genotypes. Incorporating CH genotyping into pre-treatment risk stratification may identify high-risk melanoma patients who could benefit from alternative or intensified therapeutic strategies. Mechanistic studies are warranted to elucidate the biological basis for these genotype-specific effects and explore therapeutic interventions targeting CH-driven immune dysfunction. Research Sponsor: None.

Multivariable PFS and OS hazard ratios by clonal hematopoiesis genotype in ICI-treated melanoma patients.

CH Group	Number (N)	PFS HR (95% CI)	PFS p-value	OS HR (95% CI)	OS p-value
No CH	261	1.00 (reference)	-	1.00 (reference)	-
CH	100	1.21 (0.92-1.60)	0.178	1.48 (1.10-1.99)	0.010
***TET2*-CH**	32	1.42 (0.91-2.19)	0.119	1.79 (1.12-2.84)	0.014
Non-*TET2* CH	68	1.13 (0.82-1.56)	0.445	1.36 (0.97-1.92)	0.079
***DNMT3A*-CH**	48	1.21 (0.83-1.74)	0.319	1.38 (0.93-2.03)	0.108

9550 **Poster Session**

Survival outcomes of adding stereotactic radiosurgery to dual immune checkpoint blockade in melanoma brain metastases: A systematic review and meta-analysis. First Author: Arturo Ortiz, Universidad Autonoma de Tamaulipas, Matamoros, TM, Mexico

Background: Melanoma brain metastases (MBM) carry a poor prognosis and remain understudied in prospective trials. Dual immune checkpoint blockade (ICB) with nivolumab plus ipilimumab (N+I) achieves durable intracranial responses; stereotactic radiosurgery (SRS) is sometimes added but its survival benefit is unclear. Despite the increasing real-world use of SRS in combination with dual ICB, no prior meta-analysis has compared survival outcomes of N+I + SRS versus N+I alone. **Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines.PubMed, Embase, Scopus, and Web of Science were searched for randomized controlled trials (RCTs) and observational/real-world (ORW) studies published from January 2015 to July 1, 2025. Primary outcomes were overall survival (OS) and progression-free survival (PFS).Secondary outcomes included radiologic responses rates assessed by RECIST 1.1 and prognostic biomarkers. Random-effects models were used to pool risk ratios (RRs) and hazard ratios (HRs) with 95%confidence intervals (CIs). Analyses were performed in RevMan and R. **Results:** From 2,972 records, a total of thirteen studies included (ten ORW studies and three RCTs) met our inclusion criteria, including 2,055 patients. Median age was 57.2 years and 64.28% were male. N+I + SRS significantly improved OS compared with N+I alone (HR = 0.56; 95% CI, 0.44–0.71; p$<$0.00001). Two-year OS for N+I + SRS (RR = 1.35;95% CI, 1.17-1.55; p$<$0.0001). Among patients receiving N+I alone, two-year OS was 48% (95% CI, 35–60) and PFS was 52% (95% CI, 45-59). Radiologic response rate with N+I included a complete response rate of 29% (95% CI, 22–37) and a partial response rate of 44% (95% CI,29-59). High lactate dehydrogenase (LDH $>2\times$ upper limit of normal) was observed in 37% of patients (95% CI, 20–58) and was associated with inferior survival outcomes. **Conclusions:** In patients with MBM, the addition of stereotactic radiosurgery with dual immune checkpoint blockade is associated with significant overall survival advantage compared with N+I alone. This first meta-analysis defines the incremental survival benefit of adding SRS to contemporary dual immunotherapy N+I integrating long-term survival outcomes, radiologic response, and prognostic biomarkers. These findings support N+I as the systemic backbone for MBM management and support SRS integration for appropriately selected patients. Prospective trials are warranted to optimize sequencing,timing, and patient selection. Research Sponsor: None.

9551 **Poster Session**

CD4 T-cell reconstitution and CD4:CD8 inversion following lymphodepleting chemotherapy for tumor-infiltrating lymphocyte therapy in metastatic melanoma. First Author: Arkadiusz Z. Dudek, Mayo Clinic Rochester, Rochester, MN

Background: Lymphodepleting (LD) chemotherapy is required prior to tumor-infiltrating lymphocyte (TIL) therapy, yet the depth, kinetics, and completeness of peripheral T-cell recovery in practice remain poorly defined. Using a pooled, multi-institution cohort, we characterized longitudinal CD4 and CD8 T-cell reconstitution and the prevalence of CD4 lymphopenia following TIL therapy. **Methods:** We conducted a retrospective multicenter study across Mayo Clinic, Moffitt Cancer Center, and Massachusetts General Hospital of patients with metastatic melanoma treated with TIL (N = 41, median follow-up 7.6 months). Absolute CD4 and CD8 T-cell counts and CD4:CD8 ratios were assessed at baseline (pre-LD), week 4, month 3, and month 6 post-TIL. Clinically significant CD4 lymphopenia was defined as CD4 $<$ 200 cells/μL. All patients received Pneumocystis jirovecii and antiviral prophylaxis, with antibacterial and antifungal prophylaxis administered per institutional protocols. Post-TIL infections were recorded. Paired changes from baseline were evaluated using Wilcoxon signed-rank testing. **Results:** Median age was 65 years (range 35-79), and 68% were male. At baseline, 16 patients (39%) had CD4 counts below the institutional lower limit of normal prior to LD. Eighteen patients (44%) received bridging therapy prior to TIL and had lower baseline CD4 and CD8 counts compared with those who did not ($p<$ 0.05 for both); however, post-TIL CD4 and CD8 recovery trajectories did not differ between groups. CD4 counts declined sharply following LD and demonstrated incomplete and heterogeneous recovery. Median CD4 decreased from 490 cells/μL at baseline to 250 at week 4, 290 at month 3, and 220 at month 6, remaining significantly below baseline at all post-TIL timepoints ($p<$ 0.05). Clinically significant CD4 lymphopenia was observed in 45% (10/22) of evaluable patients at month 3 and in 50% (44%, 7/16) at month 6. In contrast, CD8 counts increased early after TIL (median 240 to 590 cells/μL at week 4; p= 0.004) and remained higher than baseline at month 6. The CD4:CD8 ratio inverted from a median of 2.02 at baseline to 0.46 at week 4 and remained below 1.0 through month 6, reflecting sustained CD4 suppression despite CD8 recovery. Post-TIL infections occurred despite widespread prophylaxis, including bacterial (13%), viral (10%), and fungal (4.9%) infections. **Conclusions:** In a multi-institution cohort, LD chemotherapy preceding TIL is associated with profound and prolonged CD4 T-cell suppression, persistent CD4:CD8 inversion, and a high prevalence of CD4 $<$ 200 cells/μL through 6 months. These findings identify delayed immune reconstitution as a common and clinically relevant consequence of TIL therapy and support prospective optimization of antimicrobial prophylaxis duration, vaccination timing, and immune monitoring strategies. Research Sponsor: Mayo Clinic Comprehensive Cancer Center Grant; CA015083.

9552 **Poster Session**

Real-world outcomes of lifileucel in advanced melanoma: A single-institution experience. First Author: Kelly Mahuron, City of Hope, Duarte, CA

Background: Lifileucel (Amtagvi), an autologous tumor-infiltrating lymphocyte (TIL) therapy, was FDA approval for unresectable or metastatic melanoma after progression on systemic therapy based on clinical trial data. However, real-world data describing early outcomes with lifileucel remain limited. **Methods:** We retrospectively reviewed a prospectively maintained database of patients with unresectable/metastatic melanoma who progressed on immune checkpoint inhibitors (and BRAF $\pm$ MEK therapy if applicable) and received lifileucel per standard protocol at a single institution April 2024–January 2026. Eligible patients received an in-specification TIL product and had evaluable imaging $\geq$12 weeks post-infusion unless progression was detected sooner. Responses were assessed per RECIST v1.1. Endpoints included objective response rate (ORR), disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and grade $\geq$3 treatment-related adverse events (TRAEs), excluding lymphodepletion-related cytopenias. Time-to-event endpoints were estimated using Kaplan–Meier methods. **Results:** Of 38 patients who underwent surgical TIL harvest, 32 (84%) received lifileucel, including 5 via the Expanded Access Program due to out-of-specification product. Among 27 patients receiving in-specification lifileucel, 20 had evaluable imaging and were included in the analysis. Patients received a mean of 2.2 prior therapies, and 35% had acral lentiginous or mucosal melanoma. All patients had Stage IV disease, including liver (40%) and brain (30%) metastases. 55% received bridging therapy after surgery prior to infusion. Median follow-up was 5.7 months (range, 0.9–16.9). ORR was 30% (3 CR, 3 PR), and DCR was 45%. Among responders, 67% (4/6) have ongoing response and median DoR was not reached. Median PFS was 3.5 months (95% CI, 2.1–5.3) and median OS was 6.1 months, with 6- and 12-month OS rates of 51% and 44%, respectively. Non-cytopenic grade $\geq$3 TRAEs occurred in 55%. **Conclusions:** In this early real-world experience, lifileucel demonstrated encouraging antitumor activity with ongoing responses in heavily pretreated patients despite high-risk features such as elevated LDH and liver and brain metastases. Additional studies and longer follow-up are warranted to optimize patient selection and define durability of benefit and survival outcomes. Research Sponsor: None.

Baseline patient characteristics and safety outcomes.

Characteristic/Outcome	Overall (N=20)
Age, median (range), y	62 (38-80)
Male sex, n (%)	12 (60)
Acral lentiginous/mucosal subtype, n (%)	7 (35)
BRAF V600E mutation, n (%)	4 (20)
LDH level > ULN, No. (%)	5 (25)
Liver Metastases, No (%)	8 (40)
Brain Metastases, No (%)	6 (30)
Prior systemic therapies, mean (range)	2.2 (1-5)
Patients with grade ≥3 non-hematologic TRAEs, n (%)	11 (55)

9553 Poster Session

A phase II trial of olaparib in combination with pembrolizumab in metastatic uveal melanoma. First Author: Nikhil I. Khushalani, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Metastatic uveal melanoma (mUM) has a poor prognosis with modest response to immune checkpoint blockade (ICB). Inactivating mutations in BRCA-1 associated protein 1 (*BAP1*) are common in mUM leading to deficient homologous recombinant DNA repair and increasing reliance on alternate repair pathways, including poly[ADP-ribose] polymerase (PARP). We investigated if the PARP inhibitor olaparib could improve objective response to pembrolizumab (PEM) in mUM (NCT05524935). **Methods:** Key eligibility included mUM with measurable disease, ECOG 0-1, and adequate organ function. Prior liver directed therapy was allowed. Patients (pts) received PEM 200mg IV every 21 days plus oral olaparib 300mg BID till progression, toxicity, or completion of 2 years of treatment. In a Simon 2-stage optimal design, >1 response by RECIST 1.1 in 12 evaluable patients would permit accrual to expand to 37 pts. **Results:** Twelve eligible mUM pts, 6 male and 6 female, median age 59 years (42, 84) were treated in stage 1 of this trial. Most pts (11/12; 92%) had both liver and extra-hepatic metastatic disease; 5 pts had elevated serum LDH at baseline. Seven pts (58%) were naïve to prior systemic therapy; 4 had prior liver directed therapy. There was no objective response observed; best response was stable disease (SD, n=5), remainder (n=7) with progression; disease-control rate was 42%. One patient continues treatment at 13 months with ongoing SD. Of 4 pts who received prior tebentafusp, three had SD lasting greater than 6 months. At median follow-up of 13 months, the median progression-free survival (PFS) was 3.6 months (95% CI: 2.2, 8.3), and median overall survival (OS) was 13.8 months (95% CI: 2.5, 24.3). Six-month PFS and OS were 0.42 (95% CI: 0.15, 0.67) and 0.83 (95% CI: 0.48, 0.96) respectively; one year OS was 0.73 (95% CI: 0.37, 0.91). Most common ($\geq$ 25%) all grade treatment related adverse events (AEs) were fatigue, arthralgia, diarrhea, nausea/vomiting, dyspnea, anemia, abdominal pain, bloating, anorexia, muscle weakness, pruritus, rash, vitiligo, dyspnea, cough, hypertension, muscle weakness, ↑ AST, ↑ alkaline phosphatase, ↓ lymphocyte count, ↑ glucose, ↑ potassium and ↓ albumin. Grade 3 AEs were infrequent; nausea, anorexia, dehydration, hypotension, and muscle weakness (all n=1); there was no treatment related death. 5/12 (42%) pts required a dose reduction for olaparib. **Conclusions:** The addition of olaparib to pembrolizumab was well tolerated but did not result in any objective response in molecularly unselected mUM. Landmark survival results appear clinically meaningful and likely related to disease control with stable metastatic burden. Ongoing biomarker studies of tumor tissue (BAP1, PD-L1, PARP1, TIL) and blood may help discern which patients could benefit from this combination regimen. Optimal sequencing of ICB with tebentafusp in HLA-A*02:01+ mUM should be explored further. Supported by Merck, Inc. Clinical trial information: NCT05524935. Research Sponsor: Merck, Inc.

9554 Poster Session

Stage I results of a phase II study evaluating thymosin α1 combined with toripalimab in elderly patients with advanced melanoma. First Author: Xizhi Wen, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Anti–PD-1 monotherapy yields limited response rates in Chinese patients with melanoma, highlighting the need for effective combination strategies. Elderly patients frequently present with multiple comorbidities and immunosenescence which may compromise both the efficacy and safety of immunotherapy. Thymosin α1 (Tα-1) promotes T-cell activation and survival, potentially enhancing responsiveness to immunotherapy, while exerting immunomodulatory effects during excessive inflammation that may reduce the risk of immune-related adverse events (irAEs). This study aimed to evaluate whether combining Tα-1 with toripalimab could improve efficacy while mitigating irAEs in elderly patients with advanced melanoma. **Methods:** This was a single-arm, open-label, Simon two-stage phase II study. Patients aged $\geq$60 years with pathologically confirmed unresectable stage III or IV melanoma and no prior immune checkpoint inhibitor exposure were enrolled. Treatment consisted of Tα-1 (1.6 mg daily during week 1, then three times weekly during weeks 2–3) plus toripalimab 240 mg intravenously every 3 weeks for up to four cycles, followed by toripalimab maintenance until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Stage I required $\geq$3 responses among 19 evaluable patients to proceed to Stage II. **Results:** Between July 2023 and September 2025, 19 patients were enrolled (median age 72 years, range 60–81). Acral melanoma accounted for 78.9% (n=15). All patients had chronic comorbidities; 63.2% had ECOG $\geq$2 and 47.4% had metastases in $\geq$3 organs. At a median follow-up of 10.5 months, ORR was 47.3% (95% CI, 22.6–72.1). Median PFS was 8.0 months (95% CI, 4.4–11.6), and median OS was not reached. Median PFS was 8.1 vs. 4.5 months in acral versus non-acral cutaneous melanoma (P=0.4). Elevated LDH showed a trend toward shorter PFS (2.8 vs. 8.1 months, P = 0.076). Six grade 1 irAEs were observed (vitiligo n=2, transaminase elevation n=2, thyroiditis n=2). Patients without progressive disease had lower neutrophil-to-lymphocyte ratios and higher lymphocyte percentages than those with PD. **Conclusions:** Tα-1 combined with toripalimab demonstrated promising efficacy and excellent tolerability in elderly patients with advanced melanoma. The prespecified criteria for Stage II expansion were met, and enrollment of an additional 36 patients is ongoing. Research Sponsor: None.

Patient demographics.

Characteristics	No. of Patients (N=19)
Age (median, range	72 (60-81)
Male (%)	8 (42.1%)
Melanoma subtype	
Acral	15 (78.9%)
Cutaneous	4 (21.1%)
NRAS status	
Wild type	14 (73.7%)
Mutation	4 (21.1%)
unknown	1 (5.3%)
No. of organs with metastasis	
≥3	9 (47.4%)
Liver metastasis	
Yes	4 (21.1%)
No	15 (78.9%)
Brain metastasis	
Yes	2 (10.5%)
No	17 (89.5%)
ECOG PS	
1	7 (36.8%)
≥2	12 (63.2%)

9555 Poster Session

Risk and protective factors for acral, mucosal, and uveal melanoma in a multi-institutional cohort of veterans and civilians. First Author: Marc S. Hurlbert, Melanoma Research Alliance/Fastercures, Washington, DC

Background: Melanoma is the 4th most common cancer among US Veterans. Non-acral cutaneous melanoma has well-established risk factors including history of sunburn, ultraviolet (UV) exposure, fair skin and features. Risk factors for acral (AM), mucosal (MM), or uveal melanoma (UM), are less understood. **Methods:** We conducted a nested case-control study (2000-2024) identifying cases of acral (N=1,292, Veterans only), mucosal (N=520, combined Veteran and civilian cohort), and uveal (N=2,010, combined Veteran and civilian cohort) melanoma using the Veterans Affairs (VA) Cancer Registry, natural language processing applied to pathology reports, and Mass General Brigham Research Patient Data Repository. **Results:** For AM, current smoking was associated with reduced odds, while Agent Orange Exposure (AOE) was associated with increased odds compared to both control populations. Compared to non-melanoma controls, prior nevus, keratinocyte carcinoma (KC), and actinic keratosis (AK) were associated with increased odds of AM. For MM, prior KC was associated with higher odds of MM compared to non-melanoma controls, consistent across anogenital, sinonasal, and upper aerodigestive tract sites. Smoking status was associated with reduced MM odds in the sinonasal cohort. For UM, we conducted a case-control study using data from 3 academic medical centers and the VA. Prior cutaneous and systemic immune disease were protective of UM development compared to CM. Smoking status and prior nevi had higher odds of UM compared to CM and non-cancer controls. **Conclusions:** To our knowledge, this is the largest cohort of AM, MM, and UM cases to date. Our study identified unique factors associated with risk of, or protection from, AM, MM, or UM, compared to CM or non-cancer controls. These findings provide novel insights into potential risks for rare melanomas and can help guide future biologically driven studies. Research Sponsor: CDMRP Department of Defense; W81XWH2110819.

Risk and protective factor associations across rare melanomas.

Melanoma type	Factor type	Both cohorts	CM only	Non-cancer only
Acral	**High risk association factors**	Younger age, female sex, Black race, Hispanic ethnicity, AOE	Asian race	Prior nevus, prior KC, prior AK
	Protective factors	Current smoking	≥2 comorbidities, AUDIT-C positive, prior KC, prior AK	Former smoking
	No associations	BMI		
Mucosal	**High risk association factors**	Younger age, female sex	Black race, Hispanic ethnicity	Prior KC
	Protective factors		Former smoking	Current smoking, ≥2 comorbidities
	No associations	Prior nevus, BMI		
Uveal	**High risk association factors**	Older age, former smoking, current smoking, prior nevus	Black race, American Indian/Alaska Native race, obesity	
	Protective factors	≥1 comorbidities, prior photosensitizing medication use, prior cutaneous autoimmune disease, prior systemic autoimmune disease	Prior non-melanoma skin cancer	Hispanic ethnicity, normal or underweight BMI
	No associations	Sex		

9556 Poster Session

Long term survival outcomes of immune checkpoint inhibitors in metastatic melanoma: Later relapse and long-term outcomes beyond 5 years. First Author: Chantal Saberian, National Institutes of Health, Bethesda, MD

Background: Immune checkpoint inhibitors (ICI) have improved survival outcomes in patients with metastatic melanoma, with a subset achieving durable long term survival outcomes. However, the incidence of late relapse and outcomes among patients who are alive but not progression-free at 5 years remain unknown. **Methods:** This is a multi-institutional retrospective study of patients with metastatic melanoma treated with either single agent anti-PD1 therapy or a combination of anti-PD1/CTLA-4 who started treatment prior to January 1, 2016. We analyzed the following outcomes: progression free survival at 5 years, late relapses (defined as progression $>$ 5 years after ICI initiation), sites of late relapse, and long-term overall survival. **Results:** 206 patients with metastatic melanoma were included; 65% (n = 135) were male. Most patients 86% (n = 177) had cutaneous melanoma and 29% (n = 59) had BRAF V600E/K mutations. In this cohort, 56% (n = 115) received a single agent anti-PD1, while the remaining 44% (n = 91) of patients received a combination of Ipilimumab (IPI) plus anti-PD1. The median follow-up from treatment initiation was 9.1 years. At 5 years, 68% (n = 140) of patients were progression-free. Late relapse, occurring $>$ 5 years after ICI treatment initiation, was seen in 6% (n = 12) of patients, at a median of 8.2 years from ICI treatment initiation. Among 12 patients with melanoma relapses, site of relapses was most commonly at nodal metastases (50%), followed by visceral (17%), brain (17%), and bone/spine (17%), soft tissue (8%), and unspecified sites (8%). Overall, 50% of patients had oligo progression, 33% had metastasis at multiple sites, and 17% unspecified. Following late relapse, 83% (n = 10) were rechallenged with ICI; 50% were rechallenged with the same ICI, 17% switched from IPI plus anti-PD1 to single agent anti-PD1, 17% unspecified, and the other 17% were not rechallenged with ICI. The disease control rate was 75% among patients rechallenged with anti-PD1, 100% among those rechallenged with IPI plus anti-PD1, and 100% among patients who switched from IPI plus anti-PD1 to single agent anti-PD1. At last follow-up, 75% (n = 9) of patients with late relapse were alive. Additional analyses, including Kaplan Meier estimates of progression-free and overall survival and incidence of long term sequalae from immune related adverse events will be reported. **Conclusions:** In this multi-institutional cohort of long-term survivors with metastatic melanoma, late relapse occurred uncommonly. And the outcomes following late relapses were generally favorable, with many patients still experiencing ongoing survival. The findings in our study support continued long-term surveillance beyond 5 years and provide clear expectations in daily clinical practice regarding cure and survivorship following anti-PD1 based therapy in metastatic melanoma Research Sponsor: None.

9557 **Poster Session**

Influence of peri-dose high-sensitivity troponin on clinically significant cardiac events and IL-2 interruption during post-TIL high-dose IL-2 therapy. First Author: Jabra Zarka, Mayo Clinic Rochester, Rochester, MN

Background: High-dose interleukin-2 (IL-2) is administered following tumor-infiltrating lymphocyte (TIL) therapy, yet cardiotoxicity frequently limits dose delivery. The clinical significance of peri-dose troponin elevations during IL-2 remains poorly defined. We evaluated troponin kinetics during IL-2 dosing and their association with significant cardiac events and IL-2 interruption. **Methods:** We retrospectively analyzed patients with metastatic melanoma treated with TIL therapy followed by inpatient high-dose IL-2 at Mayo Clinic Rochester (N = 24; 87 IL-2 doses). High-sensitivity troponin and ECGs were obtained before and after each IL-2 dose. Clinically significant cardiac events were defined as QTc prolongation $>$ 480 ms, arrhythmias (excluding isolated sinus tachycardia), new ECG abnormalities, vasopressor requirement, or cardiology consultation. Dose-level outcomes included cardiac events and subsequent IL-2 dose interruption. Paired troponin changes were assessed using Wilcoxon signed-rank testing. Dose-level associations were evaluated using clustered logistic regression to account for repeated IL-2 doses within patients. **Results:** 24 patients received 87 IL-2 doses (median 3 [IQR 2 - 5]). Median age was 63 years (IQR 54 - 70), and 58% were male. Baseline troponin median was 11 ng/L (IQR 6 - 21); 38% had baseline troponin $>$ 14 ng/L. Post-dose troponin exceeded 14 ng/L in 16/24 patients (67%) and 48/87 doses (52%). Median delta troponin was 0 ng/L (IQR -1 to 6; range -24 to 133), with post-dose levels higher than pre-dose values (p= 0.02). Clinically significant cardiac events occurred in 33% of patients; no post-IL-2 reductions in left ventricular ejection fraction were observed. At the dose level, cardiac events occurred only when post-dose troponin exceeded 14 ng/L (15/48 [31%] vs 0/39 doses; $p<$ 0.001). In clustered logistic regression, post-dose troponin $\geq$15 ng/L was independently associated with cardiac events (OR 9.6, 95% CI 1.5 - 60.6; p= 0.02) and subsequent IL-2 dose interruption (OR 3.4, 95% CI 1.1 - 10.7; p= 0.04). When modeled continuously, each 1-unit increase in log-transformed post-dose troponin was associated with higher odds of cardiac events (OR 3.3, 95% CI 1.6 - 6.7; p= 0.001) and IL-2 interruption (OR 2.8, 95% CI 1.6 - 4.9; $p<$ 0.001). Baseline troponin correlated with peak post-dose troponin (ρ = 0.44, p= 0.04). **Conclusions:** Peri-dose troponin elevations are common during post-TIL high-dose IL-2; however, higher post-dose troponin independently identifies clinically significant cardiac toxicity and predicts IL-2 interruption after accounting for repeated dosing within patients. Baseline troponin modestly predicts peak elevations, supporting standardized, risk-stratified troponin monitoring and prospective evaluation of toxicity-adaptive IL-2 delivery strategies in TIL therapy. Research Sponsor: Mayo Clinic Comprehensive Cancer Center Grant; CA015083.

9558 **Poster Session**

Real-world comparison of ipilimumab–nivolumab dosing strategies in melanoma brain metastases. First Author: Dina Elantably, Mayo Clinic Florida, Jacksonville, FL

Background: Ipilimumab 3 mg/kg plus nivolumab 1 mg/kg (Ipi3+Nivo1) is the standard immunotherapy regimen for metastatic melanoma with brain metastases (MBM) but is associated with significant immune-related toxicity, particularly neurologic toxicity. Ipilimumab 1 mg/kg plus nivolumab 3 mg/kg (Ipi1+Nivo3) has demonstrated improved tolerability in extracranial melanoma, though comparative data in MBM are limited. We compared efficacy and toxicity of these dosing strategies in a multisite real-world cohort. **Methods:** We retrospectively identified patients with MBM treated with ipilimumab plus nivolumab across three Mayo Clinic sites between 2016 and 2024. Patients were classified by induction dosing as Ipi1+Nivo3 or Ipi3+Nivo1. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method and compared using log-rank tests. Best overall response (BOR) and toxicity outcomes were summarized descriptively. **Results:** Among 147 patients (Ipi1+Nivo3 n=32; Ipi3+Nivo1 n=115), 144 were evaluable for survival. Median age was higher in the Ipi1+Nivo3 group (69.5 vs 66.0 years); males predominated in both groups (71.9% vs 61.7%), and the cohort was predominantly White ($>$96%). Most patients had ECOG 0–1 in both groups (84.4% in Ipi1+ Nivo3 and 90.4% in Ipi3+Nivo1). BRAF mutation status was balanced between regimens, with approximately half of patients harboring BRAF-mutant disease (51.6% vs 53.2%). Median OS was 18.5 months (95% CI, 5.7–54.7) with Ipi1+Nivo3 versus 10.6 months (95% CI, 6.5–19.1) with Ipi3+Nivo1 (log-rank p=0.25). Two-year OS was 45.9% and 35.0%, and five-year OS was 24.5% and 19.2%, respectively. Median PFS was 7.3 months (95% CI, 1.8–10.9) versus 2.8 months (95% CI, 2.1–4.4) (log-rank p=0.16). BOR was available for 138 patients; objective response rates were 35.5% and 31.8%, respectively. 3–5 adverse events occurred in 24.1% of Ipi1+Nivo3 versus 30.5% of Ipi3+Nivo1 patients. Hospitalizations were less frequent (16.7% vs 36.1%), and neurologic adverse events occurred only with Ipi3+Nivo1 (11.9% vs 0%). **Conclusions:** In this multisite real-world MBM cohort, Ipi1+Nivo3 demonstrated comparable efficacy, numerically longer survival, and a more favorable toxicity profile compared with standard Ipi3+Nivo1. Notably, no neurologic toxicity was observed with the Ipi1+Nivo3 regimen. These findings support further prospective evaluation of lower dose ipilimumab strategies. Research Sponsor: None.

Response and survival outcomes.

Outcome	Ipi1 + Nivo3	Ipi3 + Nivo1
Complete response (CR)	2 / 31 (6.5%)	8 / 107 (7.5%)
Partial response (PR)	9 / 31 (29.0%)	26 / 107 (24.3%)
Objective response rate (ORR = CR+PR)	11 / 31 (35.5%)	34 / 107 (31.8%)
Disease control rate (DCR = CR+PR+SD)	18 / 31 (58.1%)	51 / 107 (47.7%)
Median PFS, months (95% CI)	7.3 (1.8–10.9)	2.8 (2.1–4.4)
2-year PFS	27.6%	22.3%
Median OS, months (95% CI)	18.5 (5.7–54.7)	10.6 (6.5–19.1)
2-year OS	45.9%	35.0%
5-year OS	24.5%	19.2%

9559 **Poster Session**

Integrated AI-informed morphologic and spatial transcriptomics features from H&E slides to enable risk stratification of primary melanoma patients. First Author: Bhakti Vilas Baheti, Department of Biomedical Engineering, Emory University, Atlanta, GA

Background: Tumor proliferative activity and the tumor-stroma microenvironment are key determinants of melanoma aggressiveness and prognosis, yet their assessment from routine histology remains limited and subjective. Mitotic activity and stromal composition are histologic markers of tumor aggressiveness associated with overall survival (OS). While spatial transcriptomics (ST) can capture tumor biology associated with prognosis, its cost and limited availability restrict clinical use. Recent advances in computational pathology enable inference of spatial gene expression directly from routine hematoxylin and eosin (H&E) whole slide images (WSIs). We evaluated whether integrating AI-informed histologic biomarkers with ST features derived from routine H&E slides improves OS prediction in primary melanoma. **Methods:** Formalin-fixed paraffin-embedded H&E WSIs from TCGA-SKCM primary melanoma cases with available survival data were analyzed (N=291). Automated mitotic index (MI) in tumor region was quantified using a Detectron2-based mitosis detection model, and tumor-stroma ratio (TSR) was computed from automated tissue segmentation. Spatial gene expression for 18 melanoma relevant genes was inferred from WSIs using a pretrained DeepSpot model, and quantified for spatial heterogeneity and clustering. Three Cox regression models were created: i) $M_{Path+Clinical}$ (MI, TSR, age), ii) $M_{AI-ST+Clinical}$ (ST features, age), and iii) $M_{Integrated}$ (MI, TSR, ST features and age). Feature selection was performed on training cohort (N=174), and model performance for 10-year OS prediction was evaluated on holdout test cohort (N=117) using hazard ratio (HR) with 95% confidence interval, C-index, and log-rank tests. Independent contributions of various features were assessed by multivariable analysis. **Results:** In hold-out test cohort, both $M_{Path+Clinical}$ model (C-index = 0.639, p = 0.001, HR = 2.71 [1.49-4.94]), and $M_{AI-ST+Clinical}$ model (C-index = 0.603, p = 0.002, HR = 2.51 [1.37-4.59]) were prognostic for 10 year OS. AI-ST signature consisted of spatial heterogeneity and clustering metrics of ARG1, TFAP2A, and KRT6B genes, along with global gene expression metrics. The integrated model $M_{Integrated}$ resulted in the best OS stratification (C-index = 0.644, p = 0.007, HR = 2.24 [1.23-4.07]). Multivariable analysis demonstrated independent association of MI, ST features and age with OS. **Conclusions:** AI-derived ST features contributed additional prognostic value beyond histologic and clinical features, yielding the strongest OS stratification when integrated into a unified model. By combining established histologic biomarkers with virtual spatial omics, this approach improves survival prediction without additional tissue or molecular assays, supporting its potential clinical utility for risk adapted management of melanoma patients. Research Sponsor: None.

9560 **Poster Session**

Systematic evaluation of machine learning optimization strategies for uveal melanoma detection using ultra-widefield photography. First Author: Sanjay Ganesh, College of Medicine, University of Illinois at Chicago, Chicago, IL

Background: Early differentiation of uveal melanoma (UM) from benign intraocular lesions remains clinically challenging, particularly in regions with limited access to specialized ocular oncologists. Diagnostic uncertainty can delay referral and treatment, highlighting a gap between current practice and the desired goal of timely, accurate early UM detection. Machine learning (ML) offers a promising approach to improving diagnostic support with early detection of UM. This study developed, trained, and optimized eight ML classification models for early UM detection using ultrawidefield fundus (UWF) imaging to evaluate methods to increase clinical utility and readiness of current models. **Methods:** 1,592 UWF images from 784 patients were retrospectively collected and labeled into four classes: UM (n = 364), choroidal nevus (n = 824), congenital hypertrophy of the retinal pigment epithelium (CHRPE, n = 102), and healthy controls (n = 302). Images with multiple lesions, significant media opacity, or poor tumor visualization were excluded. All models used a ResNet-50 architecture, and a binary UM/nevus classifier was developed as the control. Optimization strategies included 1) class expansion with healthy control and CHRPE images, 2) training dataset augmentation with multiple images per patient and post-treatment images, and 3) a region of interest (ROI) dilation preprocessing pipeline. A 70/15/15 train/validation/test split was used with patient-level stratification to prevent data leakage. The test set was held constant across all models to ensure fair comparison. Performance was assessed using per-class F1 score and area under the curve (AUC) with 5-fold cross-validation. Grad-CAM images were generated to aid in model interpretability. **Results:** The control model achieved an AUC of 0.94$\pm$0.01 and F1 scores of 0.90$\pm$0.01 for nevus and 0.80$\pm$0.03 for UM. ROI dilation achieved the greatest improvement (AUC 0.99$\pm$0.001; nevus F1 0.98$\pm$0.01; UM F1 0.95$\pm$0.01). Other optimization strategies showed variable impact, with multi-optos yielding the second-best performance (AUC 0.95$\pm$0.02; nevus F1 0.91$\pm$0.02; UM F1 0.83$\pm$0.04). A final model integrating the most effective strategies demonstrated robust performance (AUC 0.95$\pm$0.01; nevus F1 0.91$\pm$0.03; UM F1 0.82$\pm$0.06). Grad-CAM confirmed an appropriate lesion-centered focus. **Conclusions:** Our findings show that targeted ML optimizations can meaningfully improve performance for early UM detection. While ROI dilation preprocessing had the most performance gain, results varied across optimization pathways, indicating room for refinement. Further evaluation on external datasets is needed to assess generalizability, paving the way for end-stage clinical rollout. Research Sponsor: National Eye Institute; VitreoRetinal Surgery Foundation; Research to Prevent Blindness; Illinois Society for the Preventation of Blindness.

9561 **Poster Session**

Machine learning (ML) model integrating cell death pathways as a prognostic and predictive biomarker for patients with melanoma. First Author: Erick F. Saldanha, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Established regulated non-apoptotic cell death mechanisms, including ferroptosis, necroptosis, and pyroptosis, can govern cancer cells' fate. Early reports suggest that these pathways can drive antitumor immune response, and may be associated with survival outcomes for pts treated with checkpoint blocker antibodies (ICB). We developed a ML model based on transcriptomic data (CDPS), integrating these 3 pathways, and interrogated its prognostic and predictive role in pts with melanoma. **Methods:** An ML score based on 148 non-redundant cell-death–related genes was developed and evaluated in patient-level data from TCGA-SKCM and validated in external cohorts of pts with melanoma (GSE65904, MEL-DFCI-2019, GSE98394, GSE54467). Prognostic performance was assessed using C-index, time-dependent ROC, Kaplan–Meier analysis, and univariable Cox models, with pts stratified by cohort-specific medians. Pathway activity was examined using gene set enrichment analysis (MSigDB Hallmark and Reactome gene sets; pathways were significant if FDR < 0.05). Immune infiltration was estimated with MCP-counter as per Cliff'delta (Mann-Whitney test $p < 0.05$). Predictive value was tested in pts treated with ICB (GSE78220, GSE91061, GSE168294), which also included on-treatment samples (GSE91061). **Results:** Across discovery and validation cohorts, a random survival forest model with ridge regression showed consistent prognostic performance (C-index range, 0.58-0.66). 7 genes emerged as dominant contributors during feature selection. The CDPS-high group showed a downregulation of *MLKL* and *GSDMD* (key mediators of necroptosis and pyroptosis, respectively), and an upregulation of *SLC3A2* (a negative regulator of ferroptosis), suggesting suppression of these regulated cell-death pathways. Across all 5 cohorts, CDPS-high pts exhibited significantly worse overall survival ($p < 0.05$), corroborated by time-dependent ROC analyses at 1 (0.61 - 0.72), 3 (0.84 – 0.75), and 5 years (0.58-0.76). Functional pathway analyses revealed statistically significant positive enrichment of proliferative, anabolic, and DNA-repair signalling in the CDPS-high group and negative enrichment of immune-related pathways (FDR < 0.05). Similarly, CDPS-high tumors demonstrated broadly reduced innate and adaptive immune cell infiltration, indicating a less favorable tumor immune microenvironment ($p < 0.05$). CDPS was significantly lower in responders (R) vs non-responders ([NR], p = 0.04) in GSE168294. Notably, a decrease in CDPS levels was observed during treatment for R, whereas remained stable in NR (GSE91061). **Conclusions:** CDPS exhibited robust and consistent performance by combining selected programmed death pathways (ferroptosis, necroptosis, and pyroptosis), especially in pts treated with ICB. Future efforts will aim to validate CDPS in a prospective cohort of pts with melanoma. Research Sponsor: None.

9562 **Poster Session**

The efficacy and safety of neoadjuvant toripalimab combined with temozolomide in resectable stage III melanoma: A prospective, single-center, phase 2 trial. First Author: Tu Hu, Department of Musculoskeletal Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Neoadjuvant immune checkpoint inhibitors (ICIs) have demonstrated efficacy in resectable cutaneous melanoma and are recommended by current guidelines. Nevertheless, the clinical benefit of combining ICIs with chemotherapy as neoadjuvant setting in Chinese patients remains to be established. This study is being conducted to explore the efficacy and safety of neoadjuvant toripalimab combined with temozolomide in resectable stage III melanoma. **Methods:** This is a prospective, single-center, single-arm clinical trial (ClinicalTrials.gov identifier: NCT05827770). Patients with resectable stage IIIB-IIID acral or cutaneous melanoma and an ECOG performance status of 0-1 were enrolled and received two cycles of neoadjuvant temozolomide 200 mg/m² plus toripalimab 240 mg every 3 weeks, followed by radical surgery. The primary endpoint was the pathologic response rate (pRR). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), recurrence-free survival (RFS), overall survival (OS) and safety. **Results:** As of December 2025, 20 eligible patients with resectable stage IIIB-IIID melanoma were enrolled, with 14 (70%) acral, 5 (25%) cutaneous and 1 (5%) of unknown primary. Of 20 patients underwent surgery, nine achieved pRR (45%), including 3 with near pathologic complete response (near pCR) and 6 with partial pathologic response (pPR). Radiological assessment showed partial response in 5 patients, stable disease in 12 patients, and progressive disease in 3 patients, yielding an objective response rate of 25% (5/20) and a disease control rate of 85% (17/20) according to RECIST criteria. With a median follow-up of 12 months, 8 recurrence-free survival events had been observed; the median RFS and OS had not yet been reached. Notably, one patient who attained near pCR remained relapse free for 27 months. No new safety signals were observed with the combination therapy. We further performed single-cell-resolution spatial transcriptomics and single-cell RNA sequencing in the current cohort. Integrative multi-omics analyses identified a T cell-excluded tumor microenvironment preferentially associated with non-response. Leveraging these features, we robustly distinguished immunotherapy responders from non-responders. **Conclusions:** This study demonstrates the preliminary efficacy and tolerability of toripalimab combined with temozolomide in the neoadjuvant treatment of patients with resectable stage IIIB-IIID acral and cutaneous melanoma. Given the fact that ICIs alone has limited response rate in acral melanoma, further studies are warranted. Clinical trial information: NCT05827770. Research Sponsor: None.

Treatment outcomes.

Pathologic Response	Eligible patients (%) N=20	Radiological Response	Eligible patients (%) N=20
Near pCR	3 (15)	PR	5 (25)
pPR	6 (30)	SD	12 (60)
pNR	11 (55)	PD	3 (15)
pRR (pCR+Near pCR+pPR)	9 (45)	ORR (CR+PR)	5 (25)
		DCR (CR+PR+SD)	17 (85)

9563 **Poster Session**

Survival outcomes of stage IIB/IIC cutaneous melanoma treated with wide local excision and adjuvant immunotherapy without sentinel lymph node biopsy. First Author: Mahaasrei Ghosh, University of Iowa Carver College of Medicine, Des Moines, IA

Background: The Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) reported no significant difference in 10-year overall survival (OS) in patients with thick melanomas who had only wide local excision (WLE) versus WLE and sentinel lymph node biopsy (SLNB). With expanded immunotherapy eligibility for stage IIB/C melanoma per KEYNOTE-716, does omission of sentinel node negatively impact nodal basin disease control? Thus, we studied patients with stage IIB/C cutaneous melanoma treated with WLE and adjuvant pembrolizumab. **Methods:** We performed a single-institution retrospective review and included patients with stage IIB/C cutaneous melanoma treated with only WLE and adjuvant pembrolizumab with at least 6 months of follow-up. The primary endpoints were OS and cumulative incidence of nodal metastasis (CINM). Secondary endpoints were recurrence-free survival (RFS) and nodal metastasis-free survival (NMFS). Survival was estimated via Kaplan-Meier survival analysis and compared to the thick melanoma observation arm of MSLT-1. **Results:** Thirty-three patients met inclusion criteria between 2021-2025. Our sample was 58% male, 100% White, non-Hispanic, and median age at surgery was 59 $\pm$ 13 years. Twenty-sex (79%) patients were clinical group stage IIB. Tumor subtypes included acral lentiginous (3%), desmoplastic (3%), nodular (45%), spindle cell (3%), and superficial spreading (24%). Median follow-up was 24.3 $\pm$ 12.3 months. Four deaths occurred at 11, 17, 32, and 42 months, and OS probability was 96.2% at 12 months and 84.0% at 36 months. We observed 11 recurrences (33.3%). Six occurred in regional lymph nodes at 3, 3, 7, 7, 20, and 34 months, and 5 were distant metastases at 6, 11, 19, 20, and 25 months. At 12 months, RFS probability was 80.4%, 65.9% at 24 months, and 47.9% at 36 months. The probability of NMFS was 87.5% at 12 months, 82.8% at 24 months, and 69.0% at 36 months. Our CINM, over a median follow-up duration of 24.3 $\pm$ 12.3 months, was 18.2%, of which 3 began nivolumab/relatlimab and had complete radiological response and no subsequent recurrence. Of the 5 distant metastases, 3 underwent radiation or surgery for brain lesions and 1 began nivolumab/relatlimab for a chest wall nodule, both groups had complete radiologic response with no recurrence. Per MSLT-1, melanoma-specific survival of thick melanomas was between 76.1 $\pm$ 5.2% and 53.8 $\pm$ 7.6% at 60 months, and CINM was 33.2 $\pm$ 4.5% at 36 months. **Conclusions:** In our cohort, OS and CINM were comparable or better to the thick melanoma observation arm of MSLT-1. Our data suggests that omission of SLNB is highly likely to not negatively impact outcomes and may be offered to patients with significant operative risk. A larger sample with longer follow-up is needed to substantiate this conclusion. Research Sponsor: None.

9564 **Poster Session**

Intismeran autogene to induce de novo neoantigen-specific T cells as adjuvant therapy in melanoma. First Author: Ryan J. Sullivan, Massachusetts General Hospital, Boston, MA

Background: Intismeran autogene (intismeran) is an individualized mRNA-based neoantigen (neoAg) therapy designed to enhance endogenous antitumor T-cell responses by targeting patient-specific tumor mutations. In the phase 2 KEYNOTE-942 trial of resected high-risk melanoma, intismeran combined with pembrolizumab (pembro) significantly improved recurrence-free survival (RFS) vs pembro alone. Previously, it was shown that the combination induced greater expansion of *de novo* T-cell clonotypes, which correlated with RFS in the intismeran arm. Here, we show that *de novo* T-cell clonotypes are reactive to intismeran-encoded neoAgs. **Methods:** Peripheral leukapheresis samples longitudinally collected from a subset of intismeran plus pembro treated participants (pts) with melanoma from phase 1 and 2 studies (NCT3313778 and NCT03897881) were assessed at single-cell level to characterize neoAg-specific T cells. In 7 pts, functional assessment of neoAg-reactive $CD8^+$ T cells was performed by intracellular cytokine staining and activation-induced marker assays. To define antigen specificity and phenotype of intismeran-induced T cells, we combined longitudinal bulk and single-cell T-cell receptor (TCR) sequencing with functional validation assays from 3 pts. *De novo* expanded TCRs were tested in Jurkat NFAT-luciferase reporter cells for reactivity against pt-specific intismeran mRNA cassettes and individual neoAgs. For reactive TCRs, minimal epitopes were mapped and mutant vs wild-type peptide reactivity was quantified. **Results:** Using the combination of bulk and single-cell TCR sequencing and Jurkat NFAT-luciferase reporter assays in 3 pts, we identified 20 TCRs expanded following intismeran therapy across all pts mapping to 11 neoAgs, providing direct evidence of intismeran-driven polyclonal T-cell expansion. These responses targeted multiple neoAgs with persistence $>$100 days after last intismeran dose. Reactive TCRs showed stronger recognition of mutant vs wild-type peptides, confirming antigen specificity. Functional assessment of T cells from 7 pts showed that neoAg-reactive $CD8^+$ T cells secreted IFNγ and TNFα and coexpressed markers for degranulation/activation upon peptide restimulation, demonstrating functional activity. Flow cytometry–based characterization of neoAg-reactive T cells *ex vivo* revealed that these cells predominantly exhibited an effector-memory phenotype. Upon stimulation, they were polyfunctional ($IFN\gamma^+$ $TNF\alpha^+$), mobilized CD107a, and were granzyme B^+, consistent with cytotoxic effector function relevant to tumor control. **Conclusions:** Complementary sequencing and functional analyses demonstrated that adjuvant therapy with intismeran plus pembro induced durable, polyclonal, neoAg-specific T-cell responses with effector-memory characteristics, providing mechanistic data consistent with the clinical benefit observed in pts with melanoma. Clinical trial information: NCT3313778 & NCT03897881. Research Sponsor: This research was supported by Moderna, Inc., Cambridge, MA, USA, in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

9565 **Poster Session**

Outcome of neoadjuvant immunotherapy for patients with resectable stage III/IV cutaneous melanoma: A Swedish nationwide population-based study (NEO-MEL). First Author: Axel Nelson, Sahlgrenska University Hospital, Gothenburg, Sweden

Background: Randomized trials have shown that neoadjuvant immune checkpoint inhibitor (ICI) improves outcomes compared with adjuvant therapy alone in patients with resectable stage III–IV cutaneous melanoma. Furthermore, pathological response was a strong predictor for relapse-free survival (RFS). The translationability to routine real-world patients is unknown. **Methods:** This population-based cohort study included all patients with macroscopic, resectable cutaneous melanoma treated with neoadjuvant immune checkpoint inhibitor(s) across all academic melanoma centers in Sweden between January 1, 2022 and December 30, 2025. Clinical and pathological data were extracted from medical records. **Results:** A total of 279 patients initiated neoadjuvant ICI and received a median of two treatment cycles, 94% received PD1-inhibitor monotherapy, 91% underwent surgery as planned and 251 had evaluable pathological assessment. Among all patients who started treatment, 37% had a complete pathological response (pCR), 6% near pCR, 15% a partial pathological response (pPR) and 32% no pathological response (pNR). At a median follow-up time of 20 months, the estimated 24-month event-free survival was 69% (95% CI, 62-76), distant metastasis-free survival (DMFS) 75% (95% CI, 69-82) and overall survival (OS) 87% (95% CI, 82-92). Among those who underwent surgery and had an evaluable pathological assessment, RFS, DMFS and OS stratified by pathological response are shown in the table. **Conclusions:** Early nationwide implementation of neoadjuvant ICI in patients with resectable cutaneous melanoma resulted in favourable outcomes that closely mirror those reported in randomized clinical trials. Research Sponsor: None.

Pathological response	N	RFS at 24 months % (95% CI)	DMFS at 24 months % (95% CI)	OS at 24 months % (95% CI)
pCR	103	92 (85-100)	93 (86-100)	94 (87-100)
near pCR	17	76 (56-100)	83 (64-100)	90 (73-100)
pPR	41	83 (71-97)	85 (74-98)	92 (81-100)
pNR	90	48 (36-63)	63 (52-78)	81 (70-92)

9566 **Poster Session**

Adjuvant versus no adjuvant therapy after major pathological response to neoadjuvant immunotherapy in resectable melanoma: A Swedish nationwide population-based study (NEO-MEL). First Author: Axel Nelson, Sahlgrenska University Hospital, Gothenburg, Sweden

Background: Randomized trials have shown that neoadjuvant PD-1–based immunotherapy improves outcomes compared with adjuvant therapy alone in patients with resectable stage III–IV cutaneous melanoma. In trials, patients experiencing a major pathological response (MPR) rarely relapse, and in the NADINA trial, adjuvant therapy was omitted in this group. However, the need for continued adjuvant treatment after MPR has never been prospectively tested, and real-world evidence is limited. **Methods:** This population-based cohort study included all patients with macroscopic, resectable cutaneous melanoma treated with neoadjuvant immune checkpoint inhibitor(s) across all academic melanoma centers in Sweden between January 1, 2022 and December 30, 2025. Clinical and pathological data were extracted from medical records. MPR was defined as pathological complete response (pCR) or near-pCR. Recurrence-free survival (RFS) was estimated using the Kaplan–Meier method and differences assessed with log-rank test. **Results:** A total of 279 patients initiated neoadjuvant treatment; 254 (91%) underwent surgery as planned, and 251 had evaluable pathological assessment. Overall, 103 patients (37%) experienced pCR and 17 (6%) near-pCR, yielding 120 patients (43%) with MPR. At a median follow-up of 19 moths, the estimated 24-month RFS for patients with MPR was 92%. Among MPR patients, 52 (43%) received continued adjuvant immune checkpoint inhibitor therapy, while 68 (57%) received no adjuvant treatment. RFS differed significantly between groups, with estimated 24-month RFS of 96% in patients receiving adjuvant therapy versus 80% in those who did not (P=0.048). In the non-adjuvant group, there were five recurrences (three had pCR and two had near pCR), two were local recurrences and three were distant metastatic events, compared with no recurrence events in the adjuvant group. One unrelated death occurred in the non-adjuvant group and two unrelated deaths in adjuvant group. **Conclusions:** In this nationwide real-world cohort, patients experiencing MPR after neoadjuvant immunotherapy had excellent outcomes overall. However, a small but clinically relevant risk of relapse was observed among patients who did not receive continued adjuvant therapy after MPR. These findings emphasize the need for individualized assessment when considering adjuvant treatment in patients with MPR. Longer follow-up is needed to determine whether additional events emerge and, importantly, whether relapses can be effectively salvaged with immune checkpoint inhibitor rechallenge. Research Sponsor: None.

9567 **Poster Session**

ADAPT-M: A tool to predict individualized benefit from adjuvant anti–PD-1 (PD-1) in resected high-risk melanoma. First Author: Ines Esteves Domingues Pires da Silva, Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia

Background: Resected stage IIB/C and microscopic stage IIIA/B/C/D melanoma presents a significant risk of recurrence risk of 37 to 62% at 5 years (yrs). While 1 year of adjuvant PD1 therapy reduces this risk by approximately half, the individual patient's baseline risk without treatment and their specific benefit from adjuvant PD1 remain unknown. We aimed to generate two separate predictive models for recurrence – one for untreated and one for treated pts - to calculate the individualised benefit of adjuvant PD1. **Methods:** Pts with resected stage IIB/C or microscopic stage IIIA/B/C/D melanoma, either treated with adjuvant PD1 or untreated at 13 major melanoma centres, and with at least 2 years of follow-up from surgery were included. We analysed pts demographics, disease characteristics, blood parameters, pathological and imaging data at baseline, and clinical outcomes. Propensity scores were estimated using logistic regression with covariates associated with treatment in univariate screening ($p<0.05$). Separate penalised multivariable logistic regression models were built to predict recurrence for treated and untreated pts. A tool based on these models was created to calculate the individual patient benefit from adjuvant PD1. **Results:** A total of 3560 pts was included, divided into untreated (discovery n=2384 and validation n=597) and treated (discovery n=404 and validation n=175) cohorts. The model for untreated pts included age, gender, primary site, histological subtype, Breslow thickness, ulceration, mitosis, number and site of regional lymph nodes (LN), mutation status and LDH (AUC 0.70 in discovery, 0.69 in validation). The model for treated pts included age, gender, Breslow thickness, site of regional LN, and mutation status (AUC 0.69 in discovery, 0.61 in validation). ADAPT-M (ADjuvant Anti-PD-1 Tool for Melanoma) calculates the individualized benefit of adjuvant PD1. For example, patient A, a woman $\leq$45 years old with a primary head & neck melanoma (superficial spreading, thickness $>$1-2 mm, no ulceration, 1 mitosis/mm^2), 2 clinically occult LN metastases in the neck, NRAS mutant, and normal LDH, has a 12-month recurrence risk of 21.9% untreated vs 2.3% treated (benefit 19.6%), and a 24-month risk of 41.1% untreated vs 6.4% treated (benefit 34.7%). While, patient B, a man $\leq$45 years old with a primary melanoma in the lower limb (nodular, thickness $>$1-2 mm, no ulceration, 1 mitosis/mm^2), 2 clinically occult LN metastases in the groin, BRAF V600 mutant, and normal LDH, has a 12-month recurrence risk of 14.2% untreated vs 11.8% treated (benefit 2.5%), and a 24-month risk of 28.0% untreated vs 30.1% treated (no benefit). **Conclusions:** ADAPT-M, a clinical tool that estimate individualized recurrence risks with and without adjuvant anti-PD1 therapy, quantifies the absolute benefit of treatment for pts with high-risk resected melanoma, facilitating personalized adjuvant therapy decisions. Research Sponsor: None.

9568 **Poster Session**

Assessment of recurrence risk in stage IIB/C melanoma across time: Implications for stratification and surveillance. First Author: Mohammad Saad Farooq, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: Stage IIB/C cutaneous melanoma is associated with high recurrence risk, however stratification of risk in relation to time after surgery has not been comprehensively evaluated. We evaluated recurrence-free survival (RFS) at key time points, stratified by clinicopathologic factors, to identify patients (pts) at higher recurrence risk and personalize postoperative surveillance strategies. **Methods:** In this multi-institutional, international retrospective cohort study from the Sentinel Lymph Node Working Group database, we included pts with pathologic T3b/T4a/T4b and N0 disease who underwent surgical resection and sentinel node biopsy from 1994-2025. The type of first recurrence (local, regional, distant) was characterized based on time category (0-12, 12-24, 24-60, and 60+ months after surgery). Restricted mean survival time (RMST) analysis was used to measure the average survival time up to a specified time point (6-, 12-, 24-, and 60-months after surgery), and associations of clinicopathologic variables (age, sex, Breslow thickness, ulceration and lymphovascular invasion [LVI]) with RFS. **Results:** We included 2514 stage IIB/C pts from 19 sites in 4 countries, with a median follow-up of 53 (stage IIB) and 49 (stage IIC) months. 675 (27%) pts experienced a recurrence (92 [14%] local, 238 [35%] regional and 345 [51%] distant), and 400 (59%) recurrences occurred within 24 months. The proportion of distant recurrences as the first recurrence increased significantly with time, comprising 39%, 50%, 62%, and 59% of recurrences in the 0-12, 12-24, 24-60, and 60+ month time categories respectively (χ^2 $p<0.001$). No significant differences were observed for the included clinicopathologic variables for 6-month RMST estimates. At 12 months, RMST estimates for thickness $\geq$4 mm (11.2 vs 11.6 months for thickness 2-3.99 mm, $p<0.001$) and presence of LVI (10.7 vs 11.4 months, p=0.009) were significantly different. 24-month RMST estimates differed for male sex (20.7 vs 21.5 months vs females, p=0.002), thickness $\geq$4 mm (20.5 vs 21.9 months, $p<0.001$), and presence of LVI (19.0 vs 21.1 months, $p<0.001$). Lastly, 60-month RMST estimates differed for male sex (42.0 vs 45.2 months, p=0.001), thickness $\geq$4 mm (41.5 vs 46.2 months, $p<0.001$), LVI (36.0 vs 43.7 months, $p<0.001$), and age $>$65 years (41.5 vs 46.4 for age $<$42, p=0.022). **Conclusions:** In this real-world, multi-center analysis of pathologic stage IIB/C melanoma pts, recurrence patterns varied based on time after surgery. Breslow thickness, LVI, male sex, and age were significantly associated with earlier recurrence at different time intervals on RMST analysis. Additionally, given that $>$50% of first recurrences 12+ months after surgery were distant, active surveillance for distant relapses may be warranted. Research Sponsor: None.

9569 **Poster Session**

Real world outcomes of neoadjuvant immune checkpoint blockade (ICB) for resectable stage III melanoma: Pathologic response and FDG PET/CT correlates. First Author: Yang Wang, Peter MacCallum Cancer Centre, Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia

Background: Neoadjuvant (NA) ICB is standard of care for resectable stage III melanoma, with major pathological (p) response (R) (MPR, ≤10% viable tumor) strongly predicting relapse free survival (RFS). Imaging biomarkers to predict MPR are lacking. We evaluated the outcomes of patients (pts) treated with NA pembrolizumab (Pem) or nivolumab (NIVO) + ipilimumab (IPI) therapy, focusing on pR and FDG PET/CT metabolic changes. **Methods:** We retrospectively analyzed pts with resectable stage IIIB-D melanoma treated with NA Pem or NIVO + IPI at Peter Mac from March 2022 to Dec 2025. Clinical characteristics, pR, RFS, and treatment-related adverse events (TRAEs) were analyzed. RFS was calculated from date of surgery until day of death, recurrence or last follow up. Maximum standardized uptake value (SUVmax) of the most avid lesion (lymph node (LN) or in-transit metastases (ITM)) at baseline and post NA ICB on FDG PET/CT scans were recorded. **Results:** Of the 130 pts, 100 had LN metastasis only, 19 ITM only and 11 LN + ITM. 77 (59.2%) received Pem and 53 (40.8%) received NIVO + IPI. 117 pts (90.0%) underwent surgery: LN dissection in 40, index LN (ILN) excision in 58, ITM excision in 18 and excision of ITM + ILN in 1. 13 pts did not have surgery, 10 due to progressive disease on FDG PET/CT, complete resolution of ITM in 2, and toxicity in 1. MPR was seen in 74 (63.2%), partial response (pPR) in 7 (6.0%) and pathological non-response (pNR) in 36 (30.8%) pts. A ΔSUVmax decline ≥50% post NA ICB was strongly predictive of MPR, whereas pts without significant metabolic response were more likely to have pNR (sensitivity 93.2%, specificity 60.0%, positive predictive value 71.9%, negative predictive value 88.9% and accuracy 77.4% p=0.005). In ILN disease, 40/43 pts (93.0%) with ≥50% drop in ΔSUVmax achieved MPR ($p<0.0001$). In ITMs, a decline in ΔSUVmax ≥50% resulted in MPR in all 10 pts (table 1). At 12 months (m) median follow up, 14 pts recurred including 4 after MPR. The estimated 12m RFS was 89.0% for Pem and 79.3% for NIVO + IPI. 12m RFS in pts with ΔSUVmax decline ≥50% for Pem was 97% and 82% for NIVO + IPI (p=0.045). Grade ≥3 TRAEs occurred in 12 pts (7.5%), more frequently with NIVO + IPI. **Conclusions:** NA ICB yields high MPR rates in stage III melanoma. Early metabolic response on FDG PET/CT, defined as a ΔSUVmax ≥50% decline is a strong, readily implementable imaging biomarker for predicting MPR following NA ICB, enabling early treatment adaptation and personalized surgical decision-making. Research Sponsor: None.

	Pem (n=77)	NIVO + IPI (n=53)
Median age [range]	67 [41-92]	67 [20-82]
BRAF mutant, n (%)	23 (29.9)	27 (50.9)
Stage III B/C/D, n	26/50/1	20/33/0
Site of disease, neck/axilla/groin/ITM, n	23/28/13/13	18/20/12/6
MPR, n (%)	45 (65.2)	29 (60.4)
MPR ΔSUVmax decline ≥50%	33/35	13/14
MPR ΔSUVmax decline <50%	12/34	7/22
12m RFS ΔSUVmax decline ≥50% (95% CI)	96% (89%-100%)	100%
12m RFS ΔSUVmax decline <50% (95% CI)	82% (67%-100%)	80% (59%-100%)

9570 **Poster Session**

5-year overall survival after adjuvant treatment for stage III melanoma: An English nationwide registry-based study. First Author: Mouhamad Hussein Ismail, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Background: Adjuvant treatments for stage III cutaneous melanoma were approved based on significant improvement in recurrence free survival (RFS) with both anti-PD-1 and BRAF+MEK inhibitors. However, registration trials have not demonstrated a significant overall survival (OS) benefit to date. Given the potential patient and financial toxicity associated with adjuvant therapy, the effect on OS remains an important consideration. **Methods:** A retrospective study linking national registry data for all patients diagnosed with stage III melanoma in England between 2016 and 2021 were included and divided into two cohorts based on date of initial melanoma diagnostic staging: pre- and post-May 2018, when adjuvant therapy was initially approved in England. Key data collected were: patient age, sex, date of stage III melanoma diagnosis, TNM stage, systemic therapy for melanoma, cause and date of death. Data cut-off for follow-up was 1st August 2025. Melanoma-specific survival (MSS) and OS were calculated using the Kaplan-Meier method and Cox regression analyses. **Results:** A total of 6,297 patients were analysed (pre-May 2018: n=2,089; post-May 2018: n=4,208). Survival outcomes improved significantly in the post-adjuvant cohort. The 5-year overall survival (OS) rose from 60.9% (95% CI: 58.8–63.0) to 64.2% (95% CI: 62.7–65.7), with a hazard ratio of 0.89 (95% CI: 0.82–0.96; p=0.004). Similarly, 5-year melanoma-specific survival (MSS) improved from 70.4% (95% CI: 68.4–72.5) to 72.8% (95% CI: 71.4–74.3), HR 0.89 (95% CI: 0.81–0.99; p=0.025). When stratifying by age, sex or melanoma TNM stage, no significant OS or MSS was observed. **Conclusions:** English national registry data demonstrates a statistically significant improvement in both OS and MSS for patients diagnosed with stage III melanoma after approval of adjuvant therapy for stage III melanoma. This is consistent with published real world data from France, but contrasts with findings in Sweden and the Netherlands. The reduced utilisation of subsequent therapy for metastatic disease likely reflects the established RFS benefit. The OS benefits are modest, so careful discussion of the potential risks and benefits of adjuvant therapy remains central to patient care. Research Sponsor: Melanoma Focus UK.

Cohort	Pre-May 2018	Post-May 2018	Hazard ratio (95% CI)
Number (N)	2,089	4,208	
Median duration of follow up (years)	8.38	6.23	
Median age (range)	66 (18,103)	67 (18,102)	
Stage (AJCC V8)	127 (6.1%)		
3A	161 (7.7%)	487 (11.6%)	
3B	1042 (49.9%)	698 (16.6%)	
3C	97 (4.6%)	2085 (49.5%)	
3D	662 (31.7%)	168 (4%)	
3 (unspecified)		770 (18.3%)	
Received adjuvant systemic therapy	148* (7%)	1772 (42%)	
Received systemic therapy for metastatic melanoma	676 (32%)	685 (16%)	
5-year OS (95% CI)	60.9 % (58.8 – 63.0)	64.2% (62.7 – 65.7)	0.89 (0.82 – 0.96) p = 0.004
5-year MSS (95% CI)	70.4% (68.4 - 72.5)	72.8% (71.4 - 74.3)	0.89 (0.81 – 0.99) p = 0.025

9571 **Poster Session**

Neoadjuvant camrelizumab plus apatinib and temozolomide for resectable stage III acral melanoma: Updated CAP 03-NEO trial results and external control comparison. First Author: Xiaoting Wei, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Melanoma and Sarcoma, Peking University Cancer Hospital & Institute, Beijing, China

Background: SWOG1801 and NADINA trials suggested that neoadjuvant therapy may provide greater benefits than adjuvant therapy in melanoma. CAP 03-NEO explores the efficacy and safety of camrelizumab combined with apatinib and temozolomide triple-drug regimen as neoadjuvant therapy in patients (pts) with resectable stage II/III acral melanoma (AM). **Methods:** This two-stage trial (NCT05512481) aimed to enroll 60 pts with resectable stage II/III AM. Pts received two 4-week cycles of neoadjuvant camrelizumab (200 mg IV Q2W), apatinib (250 mg orally QD), and temozolomide (200 mg/m² IV daily D1–5), followed by surgery and 15 cycles of adjuvant camrelizumab (200 mg Q3W). A total of 30 pts were assessed in stage 1, demonstrating stage III AM benefiting more from neoadjuvant therapy (ASCO 2025, abstract 9512). Therefore, stage 2 exclusively enrolled stage III pts. Endpoints included pathological response, EFS, RFS and DMFS. To further evaluate the neoadjuvant benefit, an external contemporary cohort of stage III AM pts treated with upfront surgery and adjuvant PD-1 inhibitor alone was retrospectively collected for comparison. Propensity score matching (PSM 1:1 nearest neighbor method) and inverse probability of treatment weighting (IPTW) were used to minimize bias. Kaplan-Meier method and Cox regression were performed for survival analysis. Stage 2 results and this post-hoc comparison are reported here. **Results:** As of Jan. 26, 2026, thirty-one pts in stage 2 were enrolled, with a median follow-up of 13 months. The median age was 60 years (IQR: 49–68). Of 28 pts undergoing surgery, 18 (64.3%) achieved any pathological response, including 10 with major pathological response (7 with pCR, 3 with near pCR), and 8 with pPR. Surgery was canceled for 2 pts due to progressive disease. Neoadjuvant therapy was still ongoing for one patient. The 12-month rates of EFS, RFS and DMFS were 74.4%, 80.3% and 84.0%, respectively. All median values were not reached. As compared to external control cohort (adjuvant treatment alone), both unadjusted and adjusted analyses showed that pts treated with additional neoadjuvant therapy achieved significantly better EFS, RFS and DMFS (Table 1, all p values <0.05). The safety profile between stage 1 and stage 2 were similar and no new safety signal was identified. **Conclusions:** Stage 2 results and external control comparison of CAP 03-NEO further confirmed the significant benefit of neoadjuvant camrelizumab, apatinib and temozolomide in pts with resectable stage III AM. Clinical trial information: NCT05512481. Research Sponsor: None.

HR and 95% CI for EFS, RFS, and DMFS (sample size of stage 2 vs. external control).

Survival	Unadjusted (31 vs. 50)	PSM 1:1 (30 vs. 30)	IPTW (31 vs. 50)
EFS	0.309 (0.129-0.743)	0.246 (0.078-0.778)	0.317 (0.124-0.810)
RFS	0.244 (0.086-0.694)	0.241 (0.071-0.812)	0.242 (0.081-0.728)
DMFS	0.286 (0.099-0.822)	0.203 (0.051-0.807)	0.290 (0.094-0.893)

9572 **Poster Session**

Ultrasensitive ctDNA detection for relapse and response prediction in melanoma patients treated with immunotherapy. First Author: Christoffer Gebhardt, Department of Dermatology/Skin Cancer Center, University Medical Center Hospital Hamburg-Eppendorf, Hamburg, Germany

Background: Immune checkpoint inhibitors (ICIs) have markedly improved outcomes in melanoma and are now standard of care in advanced and adjuvant settings. However, substantial toxicities remain, and up to 50% of patients derive no clinical benefit. Conventional clinicopathological factors lack sufficient precision for risk stratification, resulting in under- and overtreatment. Circulating tumor DNA (ctDNA) has emerged as a highly specific biomarker for molecular residual disease (MRD) detection, enabling real-time, minimally invasive monitoring to guide personalized ICI strategies. **Methods:** We analyzed 847 plasma timepoints from 98 melanoma patients treated with ICI in either the unresectable advanced (metastatic) setting (25 patients) or adjuvant setting following complete resection of the primary and/or loco-regional metastases (73 patients). Plasma samples were analyzed using NeXT Personal, a whole-genome-sequencing-based tumor-informed assay designed to track up to 1,800 patient-specific variants. This ultrasensitive liquid biopsy approach achieves detection limits of down to ~1 part per million (PPM) at high specificity (>99.9%), enabling identification of MRD and early molecular relapse that may inform timely therapeutic intervention. **Results:** Baseline ctDNA was detected in 100% of 25 patients with unresectable melanoma. Within this group, an early molecular response defined by a ≥30% decrease in ctDNA by cycle 3 predicted an 80% reduction in the risk of progression or death (PFS HR 0.2, P=0.01; OS HR 0.2, P=0.03). In the adjuvant cohort, landmark ctDNA positivity at 3 months post-surgery prior to immunotherapy, was 35% and identified patients with significantly inferior outcomes, with a >3-fold increase for the risk of distant metastasis or death (DMFS HR 3.8, P=4.9510−3; OS HR 4.1, P=3.61×10−3). Longitudinal monitoring further established that any ≥20% increase in ctDNA during adjuvant treatment was highly prognostic of poor survival (DMFS HR 3.0, P=0.01; OS HR 3.5, P=0.02). These molecular increases identified recurrences a median of 212 days prior to radiographic detection. The clinical necessity of ultrasensitive assays was underscored by the fact that 71% of these early detections occurred at ultra-low levels below 100 PPM. Real-time variant tracking revealed mutations druggable mutations such as BRAF V600E. **Conclusions:** Detection of MRD with PPM sensitivity represents a major advance in treatment monitoring for both unresectable and completely resected melanoma. Early on-treatment ctDNA decreases identify responders in advanced disease, while postoperative ctDNA positivity identifies adjuvant patients at highest relapse risk. Early MRD-based detection of loco-regional or distant relapse enables timely adaptation of therapeutic strategies. Research Sponsor: Personalis.

9573 **Poster Session**

Linking T-cell receptor dynamics to outcomes in neoadjuvant-treated melanoma. First Author: Ronen Stoff, Department of Oncology, Mayo Clinic Rochester, Rochester, MN

Background: Clinical Stage III (cSIII) melanoma patients are at high risk of recurrence following therapeutic lymph node dissection (TLND) and adjuvant therapy. Neoadjuvant immunotherapy based regimens have shown promising results in this setting, with pathological response being the best predictor of recurrence free survival (RFS) and distant metastases free survival (DMFS). T-cell Receptor (TCR) abundance and clonality are being explored as biomarkers. **Methods:** In the phase II NeoACTIVATE (NCT03554083) trial, patients were treated based on BRAF status with 12 weeks of neoadjuvant atezolizumab, vemurafenib and cobimetinib (Arm A, BRAF-mutated) or atezolizumab and cobimetinib (Arm B, BRAF wildtype), followed by TLND and 6 months adjuvant atezolizumab. TCR sequencing (n=23) was performed on the pretreatment involved lymph node (iLN) and on the same node, along with an adjacent uninvolved node (uiLN) after TLND. The fraction productive of T cells (fpTC) was defined as the percentage of in-frame TCR sequences (capable of encoding a functional expressed receptor protein) of all TCR sequences identified. Simpson Clonality Index (SCI) was used to measure relative abundance of specific clones, with a higher score indicating a more monoclonal repertoire. Comparisons were made using the Wilcoxon Rank Sum test. **Results:** 30 patients were enrolled, 15 in each arm. 2 patients were not operated on, and one did not receive adjuvant treatment, leaving 27 patients for outcome analysis. 3-year RFS was 55.6% (95% CI 9.5%-77.8%), median of 62.2 months (95% CI 19-NR); DMFS was 64.3% (95% CI 48%-86.3%), median 62.2 months (95% CI 33.9-NR). The fpTC was higher in the pretreatment iLN for those without an RFS event (p=0.04) with a trend in the uiLN as well (p=0.06). Patients without a DMFS event had a higher fpTC in the uiLN (p=0.03) but not in the iLN. The SCI was significantly higher only in the post treatment iLN for patients without an RFS event (p=0.03) and was not significantly different when compared based on DMFS status. When performing pairwise comparisons of nodes based on recurrence status, we found that patients who did not suffer an RFS event had a significantly higher SCI in the post treatment iLN compared to the uiLN (p=0.02). **Conclusions:** Neoadjuvant immunotherapy and targeted therapy for cSIII melanoma can lead to durable RFS. Higher pretreatment fpTC as well as higher post-treatment iLN TCR clonality were both associated with improved RFS. These data indicate that TCR repertoire characteristics within iLN and uiLN may reflect differential immune responses to neoadjuvant therapy and could inform future studies evaluating biomarkers to stratify risk of recurrence and allow personalization of therapy. Clinical trial information: NCT03554083. Research Sponsor: Stand Up to Cancer-Genentech Catalyst Research Grant; SU2C-AACR-CT1017; Mayo Clinic Center for Clinical and Translational Science (cCaTS).

	fpTC		Simpson Clonality Index	
	RFS event	DMFS event	RFS event	DMFS event
Pretreatment iLN	**0.04**	0.12	0.43	0.11
Posttreatment iLN	0.09	0.09	**0.03**	0.12
uiLN	0.06	**0.03**	0.79	0.48
Δ iLN (post-pre)	0.79	0.37	0.07	0.41
Δ posttreatment iLN − uiLN	0.21	0.21	**0.02**	0.08

9574 **Poster Session**

Surgical de-escalation in high-risk resectable melanoma with major pathologic response (MPR) after neoadjuvant immune checkpoint inhibition (ICI). First Author: Meghan J. Mooradian, Mass General Brigham, Marblehead, MA

Background: Neoadjuvant ICI renders MPR in 50-60% of resectable Stage III/IV melanoma. Early data illustrated the ability to de-escalate surgery in cases of MPR in the index lymph node (ILN). However complete lymph node dissection (CLND), a procedure with considerably morbidity, remains the standard of care. Real-world data demonstrating the ability to de-escalate surgery while maintaining disease control, can inform optimal practice. **Methods:** In our retrospective study performed at two academic institutions (MGB/DFCI), patients with resectable, macroscopic Stage III/IV cutaneous melanoma treated with neoadjuvant ICI were identified. Pre-treatment fiducial placement was routinely performed in cases of macroscopic nodal disease to facilitate index node excision (INE). Data pertaining to treatment course, anti-tumor outcomes, and safety were collected. Signatera ctDNA was evaluated as a non-invasive biomarker of early response. **Results:** From 2020-2025, 126 patients received neoadjuvant ICI: 60 anti-PD-1 monotherapy, 62 ipilimumab/nivolumab (I/N) and 4 nivolumab/relatlimab (N/R). The majority had macroscopic stage III disease (95%) and completed the full neoadjuvant course (86%). Ten patients (8%) did not undergo surgery (clinical CR, n = 3; toxicity, n = 1; progression, n = 6). Of the 116 (92%) who underwent surgery; 43 (37%) had an upfront TLND; 52 (45%) had an INE and 21 (18%) excision of N1c or M1a disease. After INE (n = 52), reflex CLND was performed in 7 (13%) all due to non-MPR. The MPR of the total cohort was 54% (n = 63) with a pCR rate of 51% (n = 59). The MPR/pCR rate was similar between ICI regimens. In the MPR cohort, 35 underwent an INE only whereas 17 underwent CLND; the remainder had excision of N1c/M1a disease. Post-operatively, 15 required drain placement, of whom 2 had an INE. Adjuvant ICI was utilized in 23 patients, the majority receiving peri-operative pembrolizumab (n = 20). After a median follow-up of 15.5mths (3.2-68.7mths), in those who underwent surgery, 20% (23/116) have recurred; 3 with a MPR (INE, n = 1; excision, n = 2). Of these, 2 were distant metastases with no nodal recurrence. Notably, 33 patients had pre-operative ctDNA results (Signatera). At the time of surgery, ctDNA was undetectable in the majority of MPR patients (19/20), while the majority of non-MPR patients remained detectable (8/13). Pre-surgery ctDNA assessment prognosticated RFS for the 20 patients who were detectable at baseline (p = 0.035) with ctDNA clearance associated with both MPR and improved RFS. Updated clinical and ctDNA data will be presented at the meeting. **Conclusions:** Similar to published data, patients with a MPR had low rates of recurrence, with no difference between those who underwent INE compared to upfront CLND. Pre-operative ctDNA levels, particularly ctDNA clearance, correlate with clinical outcomes and may inform de-escalation strategies. Research Sponsor: None.

9575 **Poster Session**

Microbiome-derived bile acids and association with dietary fiber intake to anti-tumor responses in patients with melanoma receiving immune checkpoint blockade (ICB). First Author: Nazli Dizman, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Multiple studies have now linked high fiber diet (HFD) and outcomes with ICBs, however, the clinical actionability and mechanistic basis of this association remain incompletely defined. We investigated whether microbiome-derived metabolites may function as potentially actionable mediators of this interaction. **Methods:** Blood samples from two studies in patients (pts) with melanoma starting ICB were utilized: (1) longitudinal samples from the prospective Phase II DIET clinical trial (NCT04645680), in which pts with melanoma starting ICBs were randomized (2:1) to a HFD [up to 50 g fiber/day (d)] or a healthy control diet (HCD, 20 g/d) and (2) baseline samples from an observational prospective diet/microbiome ICB-treated melanoma cohort. Untargeted and targeted metabolome analysis of bile acids and tryptophan-metabolites were performed via liquid chromatography (LC)- and short-chain fatty acids (SCFAs) via gas chromatography (GC)-mass spectrometry. Circulating metabolite levels were compared between pre- and on-treatment samples in DIET trial by arm and between pts with response (R, assessed by RECIST 1.1) and no response (NR) in the observational cohort. **Results:** A total of 110 pts were included: 45 DIET study pts randomized to HFDI (n=30) vs HCD (n=15), and 65 pts in the observational cohort. As previously reported, response rates were numerically improved in HFD (77% vs 29% in HCD (p=0.06), in the DIET study. Untargeted metabolomics yielded 38 metabolites with statistically significant differences (nominal $p<0.05$) in change over time in the HFD arm vs in the HCD arm, with notable reductions in glycine conjugated bile acids with HFD. Bile acid biosynthesis metabolite sets were the most significantly differentially enriched ($p<0.01$, enrichment ratio >5.0). Targeted metabolomics showed that HFD reduced secondary-to-primary bile acid ratios (deoxycholic acid [DCA] to cholic acid [CA], p=0.02) as well as glycine- and taurine-conjugated to unconjugated bile acid ratios (glycocholic acid [GCA] to CA, taurocholic acid [TCA] to CA, both p=0.03). In the observational cohort, GCA/CA and TCA/CA ratios were significantly lower in R vs NR (p=0.03 and p=0.04, respectively) whereas no difference was seen in DCA/CA ratios. SCFAs and tryptophan metabolites showed neither temporal changes in DIET trial nor response associations in the observational cohort. **Conclusions:** We observed that bile acid deconjugation, a key microbiome-mediated step, was reduced by an HFD intervention and inversely associated with response to ICB in an observational cohort. Building on prior work demonstrating that additional HFD-mediated secondary bile acids can impair T cell function, microbial bile acid metabolism emerges as a potential determinant of anti-tumor response targetable through HFD. Clinical trial information: NCT04645680. Research Sponsor: Conquer Cancer, the ASCO Foundation.

9576 **Poster Session**

Outcome of adjuvant BRAF and MEK inhibition with dabrafenib and trametinib in BRAF V600K– compared to V600E-mutated melanoma. First Author: Michael Weichenthal, University of Kiel, Kiel, Germany

Background: Patients with resected stage III BRAF V600 mutated melanoma can be treated with combined dabrafenib and trametinib (D/T) with significant improvement of recurrence-free survival (RFS). The results of the pivotal Combi-AD study showed overall survival (OS) improvement only for patients with BRAF V600E mutations, while for V600K there was even an OS impairment as compared to placebo, although not statistically significant. **Methods:** We analysed EUMelaReg data for patients with adjuvant D/T therapy for resected stage III melanoma. Only patients with V600E and V600K mutations were selected, where n=93 from a total of 1,033 patients (9.0 %) harboured V600K. **Results:** Demographics of patients with V600K mutations differed significantly for age (67 vs. 58 years, $p<0.001$) and a higher proportion of males (67.0% vs. 54.6%, p=0.03) at baseline. Other baseline variables, including substage, were not significantly different. One year of treatment was completed in 51.6% for V600K, and 62.8% for V600E, respectively, while with V600K mutations 22.6% of the patients stopped for toxicity (vs. 18.8% with V600E), and 10.8% for disease recurrence (vs. 6.9%), which was not statistically significant. After a median follow-up of 41.7 (V600K) and 41.2 (V600E) months, Kaplan-Meier analysis estimated 4-year overall survival of 75.7% for V600K compared to 77.8% for V600E. The 4-y-RFS estimates were 48.3% for V600K and 47.0% for V600E. These differences were not statistically significant. Cox regression analysis revealed no different results when adjusted for demographic co-variates, including age and sex, for RFS and OS, respectively. **Conclusions:** It appears that V600E and V600K mutations are not associated with a different outcome from adjuvant treatment with combined D/T. The findings offer no explanation for differences found in the Combi-AD trial, although part of these differences also resulted from a different natural course of V600K mutated melanomas the placebo group. A longer follow-up will help to further confirm these results and also analyse the possible role of further treatments in the metastatic setting. Research Sponsor: None.

Baseline characteristics and outcome.

	V600E(N=940)	V600K(N=93)	P-value
SEX			0.035
Female	426 (45.3%)	31 (33.3%)	
Male	514 (54.7%)	62 (66.7%)	
AGE			<0.001
Mean (SD)	57.4 (13.8)	65.6 (11.9)	
Median [Min, Max]	58.0 [17.0, 90.0]	67.0 [28.0, 87.0]	
ECOG			0.1
0	846 (90.0%)	82 (88.2%)	
1	51 (5.4%)	8 (8.6%)	
2	5 (0.5%)	2 (2.2%)	
Baseline Stage			0.34
III	8 (0.9%)	1 (1.1%)	
IIIA	126 (13.4%)	7 (7.5%)	
IIIB	293 (31.2%)	29 (31.2%)	
IIIC	470 (50.0%)	54 (58.1%)	
IIID	43 (4.6%)	2 (2.2%)	
STAGE III DIAGNOSIS TYPE			0.96
Primary Diagnosis	679 (72.2%)	68 (73.1%)	
Relapse	260 (27.7%)	25 (26.9%)	
SUBTYPE			0.06
SSM	358 (38.1%)	26 (28.0%)	
NMM	315 (33.5%)	44 (47.3%)	
NOS	207 (22.0%)	18 (19.4%)	
MUP	49 (5.2%)	4 (4.3%)	
OUTCOME			
4-Year RFS (95%-CI)	0.47 (0.43; 0.51)	0.48 (0.38; 0.61)	0.94
4-Year OS (95%-CI)	0.78 (0.75; 0.81)	0.76 (0.65; 0.88)	0.94

9577 **Poster Session**

Longitudinal monitoring for post-surgical molecular residual disease in patients with stage I–IIIB melanoma using a whole-genome sequencing–based ctDNA assay. First Author: Karam Khaddour, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Circulating tumor DNA (ctDNA) is a novel biomarker for detecting molecular residual disease (MRD) and monitoring recurrence risk in melanoma. Personalized, tumor-informed ctDNA assays may enable highly sensitive and specific longitudinal detection of disease burden following curative-intent surgery. Here, we evaluate the prognostic value of whole-genome sequencing (WGS)-based ctDNA detection in patients with resected stage I–IIIB melanoma. **Methods:** This was a retrospective analysis of residual samples from a deidentified real-world dataset. Clinicopathologic information was collected from Natera's commercial database under an IRB-approved protocol (#20-049-ALL). Patients with stage I-IIIB melanoma who underwent surgery between March 2018 to May 2023 were included. Whole genome-based ctDNA assays (Signatera Genome, Natera, Inc.) were designed from the respective patients' matched tumor and normal WGS data. ctDNA was subsequently tracked in the patients' longitudinal blood samples, which were collected postoperatively until recurrence/end of follow-up. The correlation between ctDNA status post-definitive treatment and recurrence-free survival (RFS) was assessed using Cox regression analysis with a time-dependent covariate and the Kaplan-Meier method. **Results:** A total of 103 patients with stage I-IIIB melanoma and residual material available for testing were included with a median of 6 tests per patient (range: 1–23) and a median of 91 days between ctDNA tests. Median follow-up was 25.1 months (range: 8.5–73.4). Stage distribution was: 1.9% (2/103) IA, 3.9% (4/103) IB, 7.8% (8/103) IIA, 39.8% (41/103) IIB, 20.4% (21/103) IIC, 8.7% (9/103) IIIA, and 17.5% (18/103) IIIB, and 38 patients received adjuvant treatment, with the majority 87% (33/38) receiving immunotherapy only. ctDNA results during the post-operative treatment window were available for 95 patients. Among the 15 patients who experienced recurrence after completion of definitive treatment, 12 (80%) were ctDNA-positive prior to or within 2-weeks of clinical recurrence (range: 99 days pre - 12 days post-imaging). Among patients who did not experience recurrence, 97.5% (78/80) were serially ctDNA-negative. ctDNA positivity at any time during post–definitive treatment was associated with significantly shorter RFS compared with persistent ctDNA-negativity (HR 55.3; 95% CI 18.7–163.3; $p < 0.0001$). Analyses are ongoing to characterize ctDNA dynamics (including quantification) and clinical outcomes in an expanded cohort. **Conclusions:** This analysis demonstrates the prognostic value of longitudinal post-operative ctDNA monitoring for the detection of recurrence in patients with stage I–IIIB melanoma using a WGS-based, personalized, tumor-informed assay with implications for optimizing surveillance and improving clinical outcomes. Research Sponsor: None.

9578 **Poster Session**

Clinical validation of an AI-based prognostic assay for stage I-II cutaneous melanoma. First Author: Christina Kanaan, Department of Pathology, Gustave Roussy, Villejuif, France

Background: In early-stage cutaneous melanoma (CM), AJCC staging demonstrates limited ability to identify patients at elevated recurrence risk who may benefit from adjuvant therapy or intensified surveillance. We evaluated DiaSurv, an AI-based prognostic assay analyzing standard H&E whole-slide images (WSI) to refine risk stratification in stage I-II melanoma. **Methods:** DiaSurv was validated on a retrospective cohort of 456 stage I-II primary CM patients with 5-year follow-up at Gustave Roussy. The algorithm assigns high- or low-risk scores based solely on primary tumor WSI analysis. Kaplan-Meier analysis estimated 5-year recurrence-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS). Log-rank tests compared survival between risk groups. Multivariable Cox regression assessed independent prognostic value after adjusting for clinicopathological factors (Breslow thickness, ulceration, age, sex, tumor location, histological subtype, mitotic count). **Results:** Among 456 stage I-II patients (109 recurrences, 67 distant metastases, 57 deaths), DiaSurv classified 285 (62.5%) as low-risk and 171 (37.5%) as high-risk. Low-risk patients had significantly better 5-year outcomes compared to high-risk patients: RFS 92% vs 38% (HR = 7.71, 95%CI 4.86-12.23, $p < 0.001$), DMFS 94% vs 55% (HR = 10.39, 95%CI 5.31-20.36, $p < 0.001$), and OS 96% vs 71% (HR = 8.12, 95%CI 4.10-16.07, $p < 0.001$). In multivariable analysis, DiaSurv was independently associated with all endpoints (RFS: HR = 2.43, p = 0.006; DMFS: HR = 3.71, p = 0.002; OS: HR = 3.78, p = 0.003). In the clinically relevant stage I-IIA subgroup (n = 368), DiaSurv identified 86 patients (23.4%) with high-risk profiles despite favorable AJCC staging. These patients had markedly inferior outcomes compared to the 282 low-risk patients: 5-year RFS 71% vs 92% (HR = 4.85, $p < 0.001$), DMFS 77% vs 96% (HR = 5.48, $p < 0.001$), and OS 84% vs 96% (HR = 4.39, $p < 0.001$). The NPV of low-risk classification at 5 years in stage I-IIA was 92.2% for RFS, 96.5% for DMFS, and 96.5% for OS which is in line or superior to some commercially available gene-expression profiling assays. **Conclusions:** In early-stage melanoma (I-IIA), where adjuvant therapy is not currently standard, DiaSurv identifies nearly one-quarter of patients with a high-risk profile and significantly elevated recurrence rates. This AI-based assay provides actionable prognostic information beyond AJCC staging to guide decisions regarding adjuvant therapy consideration, sentinel lymph node biopsy, and surveillance intensity. Research Sponsor: None.

9579 **Poster Session**

Neoadjuvant anti–PD-1 prolgolimab monotherapy in resectable high-risk melanoma: Pathologic response and early event-free survival in a prospective single-arm phase II CRISTINA study. First Author: Angelina Kuzmenko, Federal State Budgetary Institution "N.N. Blokhin National Medical Research Center of Oncology" of the Ministry of Health of the Russian Federation (N.N. Blokhin NMRCO), Moscow, Russian Federation

Background: In resectable high-risk melanoma, neoadjuvant anti–PD-1 aims to exceed the ~40% MPR benchmark; while combos may deepen response, they add tox, complexity, and cost. Recently reported data for prolgolimab+nurulimab (N = 205) showed pCR 38.5%, near-CR 4.4%, motivating evaluation of prolgolimab mono as a simpler potentially non-inferior approach. **Methods:** MelPRO-0322 (CRISTINA; NCT06299878) is a prospective single-arm study in resectable stage IIIB–IV melanoma: 3 neoadj doses of prolgolimab followed by radiologic assessment followed by surgery (regional lymphadenectomy or M1a-equivalent metastasectomy). Central pathology used INMC criteria. Interim analysis after full enrollment and pathology assessment. **Results:** Pt characteristics (N = 82): Median age 61.5 y (range 23.2–87.3); median BMI 28.2 kg/m² (21.0–46.5). Females 47 (57.3%); ECOG 0/1: 56 (68.3%)/26 (31.7%). Primary melanoma: cutaneous or UPO 73 (89.0%), acral 7 (8.5%), mucosal 2 (2.4%). Stage: IIIB 12 (15.8%), IIIC 54 (71.1%), IIID 3 (3.9%), IV 7 (9.2%); stage missing 6 (7.3%). BRAF V600 mut in 43/74 (58.1%). Median neoadj tx duration 28 d (0–108). Median time from start of neoadj tx to surgery 67 d (29–176). LND/resection performed in 66/82 (80.5%). RECIST 1.1 (ITT, N = 82): ORR 23 (28.0%); CR 5 (6.1%), PR 18 (22.0%), SD 27 (32.9%), PD 24 (29.3%); not evaluable 8 (9.8%). Pathologic response (ITT, N = 82): pCR 28 (34.1%), near-pCR 7 (8.5%), MPR 35 (42.7%); pathology not available in 16 (19.5%). Among evaluable (n = 66): pCR 42.4%, MPR 53.0%. Achieving MPR correlated with better radiologic response by RECIST ($p < 0.001$) and lower nodal tumor burden (fewer positive nodes; p = 0.012). With a median follow-up of 11.8 mo by reverse KM (95% CI 7.5–17.4), EFS in the ITT cohort (N = 82; events = relapse/progression/death) showed 20 events with median EFS 32.2 mo (95% CI not estimable) and RMST 29.8 mo (SE 4.71). In the pathology-evaluable set (n = 66), EFS was longer in pts achieving MPR vs non-MPR/PD (log-rank p = 0.002): median EFS 19.3 mo for non-MPR/PD (n = 31; 10 events) vs not reached for MPR (n = 35; 2 events); RMST 20.3 vs 30.1 mo. In exploratory multivariable Cox models, MPR remained strongly associated with improved EFS (HR 0.043, 95% CI 0.003–0.684; p = 0.026), while higher PLT/LYM ratio (HR 1.029, 95% CI 1.006–1.052; p = 0.015) and male sex (HR 8.74, 95% CI 1.12–68.21; p = 0.039) showed associations with inferior EFS, while time from neoadj start to surgery and receipt of adjuvant therapy were not associated with EFS. **Conclusions:** NST prolgolimab monotherapy achieved MPR rates above the historical benchmark with encouraging early EFS. MPR—especially pCR—was strongly associated with improved EFS, with no progressions observed among pCR pts. In exploratory analyses, neither time from neoadj start to surgery nor receipt of adjuvant therapy appeared to materially affect EFS. Clinical trial information: NCT06299878. Research Sponsor: None.

9580 **Poster Session**

Non-melanoma skin cancer–related mortality in the United States: A 25-year CDC WONDER analysis. First Author: Shehdev Meghwar, Liaquat University of Medical & Health Sciences, Jamshoro, NA, Pakistan

Background: Non-melanoma skin cancer (NMSC), including basal cell and squamous cell carcinoma, is the most common malignancy worldwide, with rising incidence due to ultraviolet exposure and aging populations. Analyzing two decades of CDC WONDER data provides insights into mortality disparities and geographic variation. **Methods:** Using the CDC WONDER database for adults aged ≥25, we analyzed age-adjusted and crude mortality rates (AAMRs and CMRs) per 100,000 for NMSC (ICD-10 C44.0 to C44.9) by year, sex, race/ethnicity, and geography. Joinpoint regression (version 5.4) estimated average annual percentage change (AAPC) and annual percentage change (APC) with 95% confidence interval (CIs). **Results:** From 1999–2023, NMSC caused 118,792 deaths (female: 36,921; male: 81,871), most occurring at the Decedent's home (37.7%). The AAMR rose 41% from 1.92 in 1999 to 2.72 in 2023 (AAPC: 1.55%; $p<0.001$), with significant increases in 2005–2019 (APC: 1.88, 95% CI: 1.45 to 2.30) and 2019–2023 (APC: 4.92, 95% CI: 2.78 to 7.09). Adults ≥65 had the highest CMR (8.59), rising 1.57% annually ($p<0.001$). Men consistently had higher AAMR about three times that of women in 1999 (3.24 vs. 1.03), and the gap remained in 2023 (4.35 vs. 1.50). Non-Hispanic (NH) Whites had the highest AAMR, rising 2.06% annually ($p<0.001$), while NH Asians or Pacific islanders had the lowest with a slight decline (-0.19%; p=0.81). Regionally, the West had the fastest rise in AAMR at 1.68% annually ($p<0.001$), while the Midwest had the slowest at 1.24% ($p<0.001$). Mortality in rural areas (AAMR: 2.35) rose faster (1.41%; $p<0.001$) than in urban populations (AAMR: 1.93; 0.80%). Oklahoma and West Virginia ranked highest in the top 90th percentile. **Conclusions:** Mortality from NMSC has risen in the United States over the past two decades. However, significant demographic and geographic disparities in mortality continue, emphasizing the need for equitable healthcare access and targeted interventions, particularly among males, NH Whites, and high-burden states and regions. Research Sponsor: None.

Deaths and AAPC for trends related to non-melanoma skin cancer from 1999 to 2023.

Variable	Deaths	AAPC (1999-2023) with CI
Overall	118,792	1.55 (1.01 to 2.09)
Male	81,871	1.29 (0.71 to 1.87)
Female	36,921	1.54 (1.10 to 1.99)
NH White	108,523	2.06 (1.54 to 2.60)
NH Black	4,797	-0.67 (-1.74 to 0.40)
Hispanic	3982	0.76 (0.48 to 2.02)
NH Asians	1,105	-0.20 (-1.87 to 1.51)
Midwest	25,260	1.25 (0.66 to 1.83)
West	27,192	1.54 (1.03 to 2.05)
South	46,442	1.64 (1.12 to 2.17)
Northeast	19,898	1.69 (0.90 to 2.49)

9581 **Poster Session**

Anti-tumor activity of FF-10850 (liposomal topotecan) in patients with advanced Merkel cell carcinoma. First Author: Vincent T. Ma, Division of Hematology, Medical Oncology, and Palliative Care, Department of Medicine, University of Wisconsin, Madison, WI

Background: FF-10850 is a novel liposomal topotecan with increased intratumoral accumulation and robust pre-clinical activity. The prolonged $t_{1/2}$ (27 hours) supported a twice-monthly dosing schedule in the first in human dose finding trial (NCT04047251), with anti-tumor activity demonstrated in heavily pre-treated patients (pts) with solid tumors; pts remained on study up to 20 months. Common AEs were nausea and fatigue, with manageable hematologic toxicity. A Merkel cell carcinoma (MCC) pt maintained a PR for 33 weeks after progression on prior topotecan and PD-1-directed therapy. Because MCC pts who have progressed or are ineligible for anti-PD-1 therapy have few effective systemic treatment options, we evaluated FF-10850 in an MCC expansion cohort. Results are reported for all MCC pts on study. **Methods:** Pts ≥18 years with advanced MCC were treated with FF-10850 2 mg/m^2 IV on Days 1 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. Pts must have progressed on or have been ineligible for all standard therapy and treated with or ineligible for PD-1 based therapy. In expansion, pts who progressed on camptothecin therapy within 6 months were excluded; prior etoposide was allowed. Response was assessed by RECIST 1.1. **Results:** 12 pts [8M/4F; median age 70 (58-84), ECOG PS 0 (5)/PS 1 (7)] were treated. Baseline disease (n): unresectable stage IIIA (1), IV (10)/IVB (1). The median # of prior therapies was 1 (0-5), 1 had prior topotecan; 2 pts had no prior therapy, one due to rheumatoid arthritis (RA) and another due to solid organ transplant. Common drug-related AEs were anemia (50%), nausea (50%), fatigue (42%), and thrombocytopenia (25%). One pt each had related Gr 3 anemia and neutropenia; no related Gr 4 toxicity was observed. Three pts had infusion-related reactions; one that did not restart treatment. Two pts left study before RECIST evaluation: one withdrew to hospice care, and one died of an unrelated MI after the first dose of FF-10850 following a clinically significant anti-tumor response 2 weeks after the single dose. Best overall response in 10 RECIST evaluable pts was: 1CR, 1 PR, 4 SD and 4 PD; disease control rate (CR+PR+2 consecutive SD) was 50%. Three pts remain on study: one that achieved a CR after 2 cycles maintains CR after 14 cycles, and 2 pts maintain durable SD after 6-12 cycles. The median (range) time on study was 9.4 (3.1-50.9) weeks; median PFS and OS were 7.5 (95% CI:1.2-NR) and 10.7 (95% CI:2.1-NR) months, respectively. **Conclusions:** FF-10850 has demonstrated encouraging preliminary activity in both pre-treated and treatment naïve MCC. The regimen of 2 mg/m^2 every 2 weeks is tolerable with manageable hematologic side effects. PFS and OS in this small study compare favorably with that reported for cytotoxic agents in 2nd line pts of 3 and 10 months, respectively. Further exploration of FF-10850 in MCC may offer a novel treatment option for this rare disease. Clinical trial information: NCT04047251. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A., Inc.

9582 **Poster Session**

Incidence of new keratinocyte cancers during pembrolizumab in resectable cutaneous squamous cell carcinoma: The De-Squamate study. First Author: Rahul Ladwa, Princess Alexandra Hospital, University of Queensland, Brisbane, Australia

Background: Patients with advanced cutaneous squamous cell carcinoma (cSCC) or basal cell carcinoma (BCC) frequently develop new primary keratinocyte cancers (KCs) due to field cancerisation. Emerging data suggest immune checkpoint inhibitors (ICIs) may reduce this burden. We evaluated the incidence of new KCs in a prospective immunotherapy cohort. **Methods:** De-Squamate was a prospective phase II trial evaluating neoadjuvant pembrolizumab using a response-adapted management strategy in resectable cSCC. As part of protocol-mandated safety monitoring, all new primary KCs were prospectively recorded as adverse events. Events included histologically confirmed new cSCCs, BCCs, or other keratinocyte malignancies diagnosed and resected during or after treatment. Person-time was calculated for periods on pembrolizumab and off treatment. Incidence rates were calculated per person-year. Rate ratios were estimated using crude analyses and adjusted models accounting for within-patient clustering. **Results:** Among the 27 patients, 54 new KCs were recorded. Patients contributed 14.9 person-years on pembrolizumab and 33.4 person-years off treatment. KC incidence was lower during active therapy than after discontinuation (73.7 vs 143.6 per 100 person-years). The unadjusted rate ratio for new KC development off treatment versus on treatment was 1.95 (95% CI, 1.01–3.75). Adjusted analyses using negative-binomial modelling produced similar estimates (adjusted rate ratio 1.94; 95% CI, 0.64–5.89). Reductions were most pronounced for BCCs, with more modest effects observed for new primary cSCCs (table 1). **Conclusions:** In this prospective cohort, new KCs occurred at approximately twice the rate after discontinuation of pembrolizumab compared with during active therapy. These findings support the hypothesis that ICIs may suppress carcinogenesis within chronically damaged skin fields. Larger studies are needed to clarify the potential immunopreventative effect of ICIs in patients with field-driven KCs. Clinical trial information: NCT05025813. Research Sponsor: MSD.

Incidence of new keratinocyte cancers by treatment exposure.

Outcome	On Pembrolizumab	Off Pembrolizumab (Follow-up)	Unadjusted Rate Ratio† (95% CI)	Adjusted Rate Ratio‡ (95% CI)
Person-years	14.9	33.4	–	–
All keratinocyte cancers	11 events0.74 / PY	43 events1.29 / PY	1.95 (1.01–3.75)	1.94 (0.64–5.89)
Cutaneous SCC (new primaries)	6 events0.40 / PY	10 events0.30 / PY	0.75*	–
Basal cell carcinoma	5 events0.34 / PY	38 events1.14 / PY	3.35*	–

†Off-treatment vs on-treatment.
‡Adjusted for patient-level clustering using negative-binomial model.
*Crude comparison shown; formal adjusted estimates limited by small event numbers.

9583 **Poster Session**

Early burden reduction after two doses of cemiplimab in advanced non-melanoma skin cancer. First Author: Lucrezia Raimondi, Medical Oncology - Humanitas Gradenigo, Turin, Italy

Background: Advanced non-melanoma skin cancers (NMSC) frequently impose a high disease-related burden—severe pain, ulceration, intensive wound care—particularly in older and frail patients (pts). While cemiplimab has established antitumor activity, early pts-centered clinical benefit prior to first radiologic evaluation is under-described in routine practice. We quantified early changes in key burden domains after 2 infusions. **Methods:** A retrospective analysis was performed in a real-world cohort of pts with locally advanced/metastatic NMSC treated with cemiplimab. Assessments at T0 (≤7 days pre-treatment) and T1 (day 35–49; after 2 infusions). Pain intensity (0–10 Numeric Rating Scale, NRS), wound-care frequency (dressing changes/week), and analgesic exposure were extracted from structured clinical/nursing documentation; opioid exposure was quantified as daily morphine milligram equivalents (MME) using standard conversion. Primary endpoint: meaningful early pain benefit at T1 (≥2-point NRS decrease without analgesic escalation). Other endpoints: opioid de-escalation, wound-care reduction (≥2 fewer dressing changes/week), and a pragmatic early-burden composite (improvement in ≥2 of: primary pain benefit; opioid de-escalation; wound-care reduction). Paired Wilcoxon signed-rank and McNemar tests were used. Infection status summarized. Confounding-restricted sensitivity analyses excluded pts receiving RT/surgery within 8 weeks of treatment initiation. **Results:** 53 pts included; median age 80yr (IQR 71–88); 81% locally advanced disease; ECOG 0–1 56%. Baseline burden: median pain NRS 7 (IQR 6–8); baseline opioid use 60%; wound-care frequency median 4/week; ulceration G≥2 64.2%. At T1 median pain NRS improved to 3 (IQR 2–4) (median Δ −3; $p<0.001$). The primary endpoint was achieved in 83% (44/53; 95% CI 70.8-90.8). The proportion of pts receiving opioids decreased from 60% (32/53) at T0 to 22.6% (12/53) at T1 (p=0.00024). Median daily MME decreased from 20 mg (IQR 0–33) to 0 mg (IQR 0–14) ($p<0.001$). Among baseline opioid users (n=32), 100% reduced dose and/or discontinued opioids by T1 (32/32; 95% CI 88.6–100). Wound-care frequency decreased from median 4/week to 1/week ($p<0.001$), with wound-care reduction ≥2/week in 67.9% (36/53). The pragmatic early-burden composite was met in 79.2% (42/53). At first radiologic evaluation (median 91 days), RECIST evaluable in 51 pts; ORR was 76.4% (39/51) and disease control was 96.2% (50/52). Any immune-related AE occurred in 34% (18/53), with G≥3 in 1.9% (1/53). Infection decreased from 43% to 3.8% at T1. **Conclusions:** In an elderly, frail real-world population with NMSC and high supportive-care needs, cemiplimab was associated with rapid, meaningful early clinical benefit after two doses. Early burden endpoints may complement radiologic response to better capture patient-centered benefit and inform supportive-care planning in routine pathways. Research Sponsor: None.

9584 **Poster Session**

Using stage-matched genomic analysis to support molecular similarity of unknown-primary Merkel cell carcinoma and identify ARID1B as a prognostic marker. First Author: Furkan Bahar, Dana-Farber Cancer Institute, Boston, MA

Background: Merkel cell carcinoma (MCC) can present as nodal disease without an identifiable cutaneous primary, termed unknown-primary MCC (UP-MCC). UP-MCC has been reported to have distinct clinical outcomes compared with stage-matched known-primary MCC (KP-MCC), but its underlying biology is poorly understood. We compared the genomic landscapes of UP-MCC and stage IIIB KP-MCC and evaluated whether specific alterations are associated with survival in UP-MCC. **Methods:** A retrospective analysis was performed using the Dana-Farber Cancer Institute MCC repository (2012-2023). UP-MCC was defined as pathologically confirmed MCC without a detectable cutaneous primary; the comparator cohort comprised stage IIIB KP-MCC. Tumors underwent targeted next-generation sequencing (OncoPanel; 447 genes), and tumor mutational burden (TMB) and Merkel cell polyomavirus (MCPyV) status were recorded. Gene-level alteration frequencies were compared using Fisher's exact test, and MCC-specific survival (MCCSS) and overall survival (OS) were assessed using Kaplan-Meier and Cox proportional hazards models. **Results:** Fifty-two patients were included (20 UP-MCC, 32 KP-MCC). UP-MCC and KP-MCC showed highly overlapping genomic landscapes, including similar distributions of MCPyV status, TMB, and recurrent driver alterations, with no gene-level differences detected. Within UP-MCC, *SETBP1* alterations were associated with worse MCCSS (HR 6.74; 95% CI, 1.33–34.07; p=0.030), while ARID1B alterations identified a markedly high-risk UP-MCC subgroup with inferior MCCSS (HR 27.1; 95% CI, 3.02–243.11; $p<0.001$) and OS (HR 16.9; 95% CI, 1.9–152.9; p=0.004). All five *ARID1B*-altered UP-MCC patients died of MCC, compared with 4 of 15 *ARID1B*−wild-type; in multivariable analysis, *ARID1B* remained an independent predictor of worse MCCSS (p=0.003), whereas *SETBP1* did not (p=0.313). In KP-MCC cohort, *ARID1B* was not significantly associated with MCCSS (p=0.1883). **Conclusions:** Stage-matched genomic profiling demonstrates molecular similarity between UP-MCC and KP-MCC, supporting the hypothesis that UP-MCC often represents regressed primary cutaneous tumors. Within UP-MCC, *ARID1B* alterations identify a high-risk subgroup with markedly inferior MCCSS, suggesting that targeted genomic profiling may refine risk stratification, surveillance strategies, and clinical trial design for patients with UP-MCC and these findings warrant validation in larger, multi-institutional cohorts. Research Sponsor: None.

Baseline characteristics of UP-MCC and stage IIIB KP-MCC cohorts.

Parameter	UP-MCC (n=20)	KP-MCC stage IIIB (n=32)	p-value
Age, mean (SD), years	68.2 (12.9)	74.2 (12.1)	0.204
Male sex, n (%)	13 (65.0)	26 (81.3)	0.323
MCPyV positive, n (%)	11 (55.0)	15 (46.9)	0.776
High TMB, n (%)	8 (40.0)	11 (34.4)	0.909
TMB, mean (SD), mut/Mb	14.1 (13.9)	18.7 (24.6)	0.572

SD= Standard Deviation.

9585 Poster Session

Efficacy and safety of cosibelimab 800 mg every 2 weeks for locally advanced cutaneous squamous cell carcinoma: Updated follow-up from a pivotal study. First Author: Eva Muñoz Couselo, Medical Oncology, Vall d'Hebron Hospital & Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Background: Cosibelimab, a high-affinity programmed death ligand-1 (PD-L1)–blocking antibody, is approved by the US Food and Drug Administration (FDA) at a recommended dose of 1200 mg every 3 weeks (Q3W) for the treatment of adults with locally advanced or metastatic cutaneous squamous cell carcinoma (laCSCC or mCSCC) who are not candidates for curative radiation or surgery. The CSCC expansion cohort of the pivotal open-label Phase 1 study (NCT03212404) evaluated cosibelimab 800 mg every 2 weeks (Q2W) in patients with laCSCC or mCSCC and 1200 mg Q3W in patients with mCSCC. Results through March 2023 demonstrated robust and sustained responses with cosibelimab 800 mg Q2W. The 800-mg Q2W and 1200-mg Q3W regimens are considered similar based on pharmacokinetic criteria outlined by the FDA for alternative PD-L1–blocking antibody dosing regimens. We present new follow-up data for the 800-mg Q2W laCSCC cohort. **Methods:** Eligible patients were ≥18 years old and had an Eastern Cooperative Oncology Group performance status of 0 or 1 and unresectable laCSCC not amenable to local therapy. Cosibelimab 800 mg was administered intravenously on Day 1 of each 14-day cycle until complete response, worsening disease progression, toxicity, or clinical deterioration. The primary endpoint was objective response rate (ORR; best overall response: complete or partial) by independent central review per RECIST V1.1; duration of response (DOR) was the key secondary endpoint. Follow-up data presented are from investigator assessment. Other secondary endpoints included safety. **Results:** By the January 31, 2025, data cutoff, 64 patients with laCSCC received ≥1 dose of cosibelimab 800 mg Q2W; their median (range) age was 77 (51–95) years, and 66% were male. Patients received a median of 29 (2–89) doses over a median duration of 60 (4–184) weeks. The ORR (95% confidence interval) was 50% (37%, 63%), including 17 complete and 15 partial responses; over a median follow-up duration of 31 (1–59) months the median DOR was not reached. Treatment-emergent adverse events (TEAEs) were reported in 61 (95%) patients and considered treatment-related in 50 (78%) patients; none were fatal. The most common AEs were anemia and diarrhea, recorded in 17 (27%) patients each. Grade ≥3 TEAEs were reported in 26 (41%) patients and considered treatment-related in 7 (11%). Hypertransaminasemia, in 2 (3%) patients, was the only serious treatment-related TEAE reported. Immune-related AEs (irAEs) were recorded in 22 (34%) patients; Grade ≥3 irAEs occurred in 1 (2%) patient and were dermatologic in nature (maculo-papular and pruritic rashes) and considered treatment-related. **Conclusions:** Responses to treatment with cosibelimab 800 mg Q2W remained robust and durable with stable ORR after continued follow-up in a larger cohort of patients with laCSCC, with no new safety signals identified. Clinical trial information: NCT03212404. Research Sponsor: Sun Pharma.

9586 Poster Session

Final analysis of the efficacy and safety of oral S-1 for locally advanced or recurrent/metastatic cutaneous squamous cell carcinoma: A multicenter retrospective study. First Author: Sadao Inoue, Saitama Medical University International Medical Center, Hidaka, Japan

Background: Anti–PD-1 antibodies are the standard systemic therapy for advanced cutaneous squamous cell carcinoma (cSCC). Recent clinical trials have reported objective response rates (ORRs) of 44–58.3% in locally advanced (LA) disease and 35.2–45.2% in recurrent or metastatic (R/M) disease, with grade ≥3 adverse events occurring in 31.1–34.5% of patients. S-1, an oral fluoropyrimidine, has been suggested as an alternative option with potential advantages, including favorable clinical response, lower toxicity, feasibility of outpatient initiation, and substantially lower cost; however, evidence remains limited to small case series. We therefore conducted a large multicenter retrospective study to evaluate the real-world efficacy and safety of S-1 in patients with advanced cSCC. **Methods:** This multicenter retrospective study included patients with LA or R/M cSCC who received oral S-1 between 2007 and 2024. S-1 was administered for 28 consecutive days, followed by 14 days off (one cycle). The primary endpoint was ORR assessed according to RECIST criteria. Secondary endpoints included progression-free survival (PFS), overall survival (OS), and toxicity. Exploratory subgroup analyses were performed based on concomitant radiotherapy use and primary tumor site. **Results:** A total of 150 patients were analyzed (LA, n = 44; R/M, n = 106). The median age was 76 years (interquartile range, 67–83), and ECOG performance status was 0–1 in 127 patients (85%). Fifty-four patients (36%) had received prior systemic treatment. Among the R/M cohort, 59 patients had nodal metastasis and 47 had distant metastasis. The median follow-up was 13.4 months (LA, 15.0 months; R/M, 12.7 months). ORR was 55% (95% confidence interval [CI], 39–70) in the LA cohort and 40% (95% CI, 30–50) in the R/M cohort. The 12-month PFS and OS rates were 80% and 92% (95% CI, 63–90 and 76–97) in the LA cohort, and 41% and 62% (95% CI, 30–50 and 51–71) in the R/M cohort. Grade ≥3 adverse events occurred in 14% of patients, most commonly anemia (n = 4), thrombocytopenia (n = 3), neutropenia (n = 3), decreased appetite (n = 3), and oral mucositis (n = 3); no grade 5 events were observed. In exploratory analyses, patients receiving concomitant radiotherapy demonstrated higher ORR and PFS compared with those without radiotherapy, while OS was comparable between the groups. Tumors originating in the head and neck region were associated with superior ORR, PFS, and OS compared with other primary sites. **Conclusions:** Oral S-1 demonstrated antitumor activity comparable to that reported for anti–PD-1 antibodies, albeit without direct comparison, with a lower incidence of severe adverse events, suggesting its potential role in selected patients with advanced cSCC. Research Sponsor: None.

9587 Poster Session

Circulating tumor DNA (ctDNA) as a biomarker for pathologic response and clinical outcomes in patients with cutaneous squamous cell carcinoma (CSCC) receiving neoadjuvant anti–PD-1 therapy. First Author: Luke Skyler Vest, Dana-Farber Cancer Institute, Boston, MA

Background: ctDNA is a novel biomarker that can be used to evaluate recurrence and treatment response in multiple cancers. The utility of ctDNA in patients with CSCC receiving neoadjuvant immunotherapy (nIT) is unknown. **Methods:** In this retrospective study, we examined patients with CSCC who received nIT and had ctDNA assay available pre- and post- operatively. Positive ctDNA was defined as a value >0, and ctDNA sensitivity pre-operatively (pre-op) was reported in all patients. Patients with at least two ctDNA measurements pre-op were classified into two cohorts: cohort-A included patients whose ctDNA decreased; Cohort-B included patients whose ctDNA increased. Pathologic response (PR) was defined as complete (pCR) if 0% viable tumor [vt], major (mPR) if vt < or equal to 10%, and no-response (nPR) if vt >10%. The association between ctDNA kinetics during the pre-op period nIT and PR was analyzed using Fisher's exact test. During the post-op period, we used minimal residual disease (MRD) status defined by positive ctDNA measurement within 3 months post-op. Recurrence-free survival (RFS) (landmark analysis with time starting at post-MRD timepoint until recurrence, death or loss-to follow-up) was compared between patients who had detectable MRD (positive ctDNA within 3 months post-op) versus those who had undetectable MRD. **Results:** Forty nine patients were included of which 42 (85.7%) were male, 11 (22.4%) were immunosuppressed, and 31 (63.3%) had AJCC stage IV CSCC. The median follow-up time since starting nIT was 12.9 months. The ctDNA sensitivity at baseline (prior to starting nIT) was 79.6%. The median number of ctDNA collections per patient was 6 (range: 1, 21). Of the 49 patients who underwent surgery, 38 were eligible who had at least 2 ctDNA measurements pre-op. Cohort-A (35 patients) had higher cPR and mPR compared to cohort-B (3 patients) (p=0.05). When excluding 3 patients who did not have kinetic ctDNA changes (ctDNA value was 0 at all pre-op time points), ctDNA decrease was significantly associated with cPR and mPR (p= 0.03). For post-op period, patients with detectable MRD (n=5) had significantly lower RFS compared to those with undetectable MRD (median RFS 11.3 months vs. not reached, HR: 11.9; 95% CI: 2.2-65.8; p< 0.01)(Table). **Conclusions:** ctDNA changes and detectable MRD may be suitable biomarkers for pathologic response assessment and post-op period in patients with CSCC receiving nIT. Further research is essential to confirm these findings. Research Sponsor: None.

Recurrence-free survival according to MRD status.

MRD status	N	Median after 3-month post-op (95% CI) month	6-month RFS after 3-month post-op (95% CI) months	12-month RFS after 3-month post-op (95% CI) months	Hazard ratio (95% CI)
Negative	31	NA (NA, NA)	0.96 (0.89, 1)	0.89 (0.74, 1)	ref
Positive	5	11.3 (2.22, NA)	0.6 (0.29, 1)	0.3 (0.06, 1)	11.9 (2.2, 65.8)

9588 Poster Session

Survival outcomes following resistance to immune checkpoint inhibition in advanced cutaneous squamous cell carcinoma. First Author: Samreen Iqbal, Princess Alexandra Hospital, Woolloongabba, QLD, Australia

Background: Immune checkpoint inhibitors (ICI) are standard first-line therapy for advanced cutaneous squamous cell carcinoma (cSCC); however, 35% of patients experience disease progression. Evidence guiding optimal second-line management remains limited. We evaluated real-world outcomes of second-line treatment strategies in patients with cSCC resistant to ICI. **Methods:** A retrospective analysis of patients with unresectable locally advanced or metastatic cSCC treated with ICI monotherapy at two tertiary centres in Brisbane, Australia, was conducted. Patients with progressive disease (PD) were identified and classified as having primary resistance (PD < 4 months) or acquired resistance (PD ≥4 months). Second-line strategies included local therapy (LT - surgery and/or radiotherapy), systemic therapy +/- LT or best supportive care (BSC). Outcomes included progression-free survival from second-line initiation (PFS2), and overall survival (OS) using Kaplan–Meier estimates. **Results:** Seventy-four patients were identified. Median age was 74 years. Most patients had locoregionally advanced disease (77%), head and neck primary tumours (70%), ECOG performance status 0–1 (76%), and were immunocompetent (70%). Primary resistance occurred in 54% and acquired resistance in 46%, of which 21% progressed after ICI cessation. Locoregional progression was observed in 70% of patients, while 30% progressed with distant disease. Management of ICI resistance included LT (N = 32), systemic therapy +/- LT (N = 16), and BSC (N = 26). An objective response rate of 65% was observed in patients undergoing systemic therapy +/- LT with responses to both ICI rechallenge and/or EGFR targeted therapy (7 of 11 patients). With a median follow up of 46.6m the Median PFS2 was 10.7m. PFS2 was numerically higher in patients undergoing systemic therapy vs LT alone (11.9m vs 8.4m). Of those that underwent LT alone, further PD was seen in 16 patients (50%), with half requiring systemic therapy. Median OS for the overall cohort was 19.0m. OS was numerically reduced in immunocompromised patients (11.6m) and in those with primary ICI resistance (6.9m) vs those who had acquired resistance (22.5m) and progression after ICI cessation (47.1m). **Conclusions:** Selected patients with advanced cSCC, particularly those with acquired resistance, derive meaningful benefit from second-line therapy following ICI progression. Outcomes remain poor for immunosuppressed patients or those with primary resistance, highlighting a major unmet clinical need and the importance of prospective studies in the post-immunotherapy setting. Research Sponsor: None.

9589 **Poster Session**

Outcomes of neoadjuvant immunotherapy (NeoIO) in Merkel cell carcinoma. First Author: Lacey Mead, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Merkel cell carcinoma (MCC) is an aggressive malignancy with high rate of nodal and distant metastasis, leading to poor overall survival. For clinically detected regional lymph nodes, treatment typically involves node dissection with adjuvant radiotherapy. Evaluation of NeoIO in resectable MCC resulted in a pathological complete response (pCR) rate of 47%; pCR correlated with relapse-free survival (RFS). However, there is no standardized NeoIO regimen. We report our single institutional NeoIO experience in resectable MCC and correlate regimen with clinicopathological response. **Methods:** We retrospectively reviewed pts with resectable MCC who received NeoIO with intent to offer surgery (SX) or radiation (RT), from 2015 to present. Demographic and clinicopathological characteristics were evaluated. Overall Response Rate (ORR), pCR, and Relapse Free Survival (RFS) were computed. Overall survival (OS) was evaluated via a 90-day landmark Kaplan-Meier plot to assess if time to definitive regional treatment impacted OS. **Results:** We identified 25 patients; median age was 77 years old; 75% were male. Majority were clinical stage III (IIIa 20%; IIIb 68%); 12% were stage IIa. 32% had immunosuppression at the time of treatment. 36% had primary MCC on extremity, 36% on head and neck, 8% on trunk, and 20% were of unknown primary origin. 80% of patients received neoadjuvant Pembrolizumab, 16% Avelumab and 4% ipilimumab plus nivolumab. The median number of IO cycles was 3 (1-18); those who completed 1-2 cycles were more likely to receive SX/RT compared to those who received 3 or more cycles (p-value = 0.024). 64% of patients had an adverse effect during therapy; majority (87.5%) had G1/G2 events. 24 patients had post NeoIO imaging to which ORR was 75%. Post NeoIO, 15 underwent SX, 4 had definitive RT, 2 had progression of disease and received systemic therapy, 3 had comorbidities precluding treatment, and 1 was lost to follow up. The median time from beginning of NeoIO to SX or RT was 3 months (1-19mo). Of those who underwent SX, 40% had a complete pathologic response, 20% had a major pathologic response, 33% had a partial response, and 6% had non-response. With a median 23.4 months of follow-up, 8 of the 25 patients (32%) have experienced an event and the median EFS has not been reached. 7 of the 25 (28%) patients have died, 4 due to MCC; median overall survival not reached. Median follow up was 23.4 months. Time to event analysis indicated six patients who received NeoIO, followed with SX or RT within 90 days, had fewer deaths compared with those who received SX/RT after 90 days. Survival was approximately 3.5 years for those who did not receive SX/RT within 90 days and no deaths for those who received SX/RT within 90 days. **Conclusions:** NeoIO for MCC at our single institution achieved an ORR of 75% and a mPR/pCR of 60%. Earlier incorporation of regional therapy post NeoIO appears to improve outcomes, suggesting importance of multimodal management for resectable MCC. Research Sponsor: None.

9590 **Poster Session**

Characterization of germline pathogenic variants in melanoma patients. First Author: Ye Tong Chua, University of Michigan Medical School, Ann Arbor, MI

Background: Approximately 10% of melanomas arise from hereditary predisposition. NCCN guidelines recommend genetic counseling for patients with ≥3 invasive melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma in an individual or family. However, predictors of germline pathogenic/likely pathogenic variants (P/LPV) in patients undergoing germline testing remain poorly characterized. **Methods:** A retrospective study of all melanoma patients referred for any indication to the University of Michigan Cancer Genetics Clinic from 2015-2024 was performed. Patients who declined testing or had known hereditary cancer syndromes (personal or familial) were excluded. Baseline demographics, referral reasons, melanoma characteristics, and genetic testing results were collected. Chi-square and Fisher's exact tests were used to evaluate associations with P/LPV ($p<0.05$). **Results:** Among 624 patients, median age at melanoma diagnosis was 52 (IQR 38-63); 60.1% were female. The most common referral reasons were new melanoma diagnosis (64.4%), family history of non-melanoma cancers (57.1%), or family history of melanoma (39.4%). Overall, 88 (14.1%) harbored P/LPV (92 variants across 26 genes). P/LPV in established melanoma-risk genes were identified in 42 patients (6.7%): *CDKN2A* (n=16), *MITF* (n=8), *POT1* (n=5), *BRCA1/2* (n=6), *BAP1* (n=3), *TP53* (n=3), and *PTEN* (n=1). The strongest associations with any P/LPV were personal history of ≥2 additional non-skin primary cancers (OR 2.35; p=0.014) and ≥2 primary melanomas (OR 1.80; p=0.017). Diagnostic category (in situ, invasive, metastatic) and subtype (cutaneous, uveal, mucosal, acral, unknown primary) showed statistical significance with P/LPV ($p<0.001$), though effect sizes were modest. Age at diagnosis (<45, <55, <65), sex, and family history of melanoma or pancreatic cancer in 1˚ or 2˚ relatives were not associated with P/LPV. In a secondary analysis restricted to established melanoma-risk genes (n=42), ≥2 primary melanomas remained strongly predictive (OR 4.11; $p<0.001$) and 1˚ family history of melanoma became significant (OR 2.01; p=0.03), while ≥2 additional non-skin primary cancers was not associated (p=0.40). **Conclusions:** In this melanoma cohort excluding patients with known hereditary syndromes, 14.1% had a P/LPV. Personal tumor burden, not family history, was the strongest predictor of a positive test, suggesting current NCCN criteria may miss high-risk individuals by emphasizing family history. For established melanoma-risk genes specifically, both personal history of multiple melanomas and 1˚ family history of melanoma were predictive, supporting a gene-specific approach to risk assessment. These findings support expanding referral criteria to include patients with ≥2 primary melanomas or ≥2 additional non-skin primary cancers, agnostic of family history, to better identify individuals most likely to benefit from germline testing. Research Sponsor: None.

9591 **Poster Session**

ctDNA clearance durability and progression-free survival in unresectable or metastatic cutaneous malignancies. First Author: Joshua Espinola, University of Virginia, Charlottesville, VA

Background: Circulating tumor DNA (ctDNA) has emerged as a sensitive biomarker for disease monitoring and prognostication across malignancies. Yet, the clinical relevance of sustained ctDNA negativity ("clearance") as a guide for immunotherapy duration in advanced cutaneous cancers remains poorly defined. This study evaluated the prognostic impact of durable ctDNA clearance in patients with unresectable or metastatic skin cancers treated with immune checkpoint inhibitors (ICIs). **Methods:** A single-institution retrospective study was performed using a personalized ctDNA assay (Signatera, Natera Inc.) on prospectively collected plasma from patients with stage III–IV unresectable cutaneous malignancies receiving ICIs every 3-6 weeks. ctDNA clearance was defined as a change from ctDNA-positive to ctDNA-negative on at least two consecutive samples obtained ≥4 weeks apart during ICI therapy and categorized as transient (<12 months) or sustained (≥12 months). Demographics and clinical characteristics were summarized with descriptive statistics; progression-free survival (PFS) was estimated using the Kaplan-Meier method, and hazard ratios (HRs) were calculated with Cox proportional hazards models. **Results:** Among 75 patients (stage III: 23%, stage IV: 77%), most were male (72%) and had melanoma (87%), with a median age of 72 years and median follow-up of 20.4 months. Median ICI treatment duration was 6.9 months; all patients received ICIs, most commonly relatlimab/nivolumab (49%) or pembrolizumab (40%). Median ctDNA clearance duration was 8.2 months. Patients with sustained ctDNA clearance (n=25) experienced markedly improved 12-month PFS compared with those with transient clearance (n=50) (92.0% [95% CI, 71.6–97.9] vs 58.1% [95% CI, 42.6–70.8]). In a multivariable model adjusting for age, malignancy type, and treatment regimen, transient ctDNA clearance was associated with significantly worse PFS than sustained clearance (HR 12.1; 95% CI, 2.7-53.4). **Conclusions:** Sustained ctDNA clearance (≥12 months) is strongly associated with superior PFS in advanced cutaneous malignancies treated with ICIs, underscoring its potential as a dynamic biomarker to inform the treatment duration. Validation in larger, multi-institutional cohorts is warranted to confirm these findings and refine cDNA-guided immunotherapy strategies. Research Sponsor: None.

9592 **Poster Session**

Long-term survivorship rates among previously treated advanced melanoma patients achieving objective response (OR) with lifileucel. First Author: Peter Mohr, Elbe Klinikum Buxtehude, Buxtehude, Germany

Background: Durability of response and associated long-term survival benefits of modern cancer therapies are often manifested as plateaus in duration of response (DoR) and overall survival (OS) curves for responders. In the single-arm, Phase 2 C-144-01 trial, unresectable/metastatic melanoma patients who progressed on immune checkpoint inhibitors (ICIs) showed durable clinical responses to lifileucel—an FDA-approved autologous T-cell therapy. This analysis evaluated the association between achieving an OR with lifileucel and possibility of being a long-term survivor (LTS) in the C-144-01 study. **Methods:** Mixture cure models (MCMs) were applied to analyze OS and DoR outcomes for patients who achieved confirmed OR by committee review among those receiving lifileucel within commercial specifications in Cohorts 2 and 4 (overall cohort; n=106, median follow-up: 47.4 months, OR rate 35.8%). In both analyses, LTS were subject to only non–melanoma-related mortality whereas non-LTS were subject to both melanoma- and non–melanoma-related mortality. In the DoR analysis, LTS were also assumed to remain in response until death. For LTS, OS/DoR outcomes were assumed to follow the survival trend of age- and sex-adjusted US general population, and derived from published lifetables whereas for non-LTS, they are modeled by parametric distributions. Fraction of LTS and OS/DoR distributions for non-LTS were estimated simultaneously via maximum likelihood methods. Candidate MCMs were evaluated based on statistical fit criteria, visual agreement with observed OS/DoR data, and underlying hazards. **Results:** Exponential MCM and gamma MCM provided best fits to the observed DoR and OS data, respectively, and estimated the fractions of LTS (95% CI) among responders as 52% (34.0%–69.4%) and 50.4% (31.3%–66.7%) from the OS and DoR data, respectively. Estimated fractions of LTS across clinically plausible models ranged between 48.4%–52.9% in the OS analysis and 50.4%–51.1% in the DoR analysis. Best-fitting MCMs projected 10-year mean OS and DoR as 70.7 and 62.2 months, respectively, and 10-year OS and DoR rates as 46.7% and 45.3%, respectively. Smoothed OS and DoR hazards derived from the observed data displayed convergence to general population mortality rates by the end of follow-up indicating maturity and suitability of data for modeling with MCMs. **Conclusions:** Responders had significantly higher fraction of LTS than the overall cohort, underscoring the importance of achieving OR to lifileucel for its long-term survival benefit. Estimated fractions of LTS from OS and DoR were robust to model choice, consistent with each other, and when scaled by OR rate, aligned with previously reported fractions of LTS from progression-free survival and OS for the overall cohort. Results support clinical potential of lifileucel for addressing unmet need in post-ICI advanced melanoma. Research Sponsor: Iovance Biotherapeutics, Inc.

9593 **Poster Session**

Incidence and survival rates in pediatric and adolescent melanoma in the United States, 2001-2022. First Author: Maimoona Maheen, Rawalpindi Medical University, Rawalpindi, Pakistan

Background: Melanoma represents a significant malignancy in children, adolescents, and young adults. Recent trends in incidence and outcomes in this population have not been comprehensively characterized. We analyzed population-based data to evaluate temporal trends in melanoma incidence and survival among patients aged <40 years. **Methods:** Data from the North American Association of Central Cancer Registries (NAACR) and SEER registries (representing up to 76% of U.S. children, adolescents, and young adults) were analyzed for patients aged <40 years diagnosed between 2001-2022. Age-adjusted incidence rates per 1,000,000 were calculated and standardized to the 2000 U.S. population. Five-year relative survival rates were assessed for diagnoses from 2001-2020. Annual Percent Change (APC) and Average Annual Percent Change (AAPC) were calculated using Joinpoint Trend Analysis Software. **Results:** Melanoma incidence in patients aged <40 years demonstrated a consistent declining trend from 2001 to 2022. Incidence rates decreased from approximately 47-50 per 1,000,000 in the early 2000s to approximately 38 per 1,000,000 by 2022, representing approximately a 20% reduction over the study period. The decline was particularly notable after 2005, with a steady downward trajectory through 2022. Despite this declining incidence, 5-year relative survival rates remained consistently excellent throughout the entire study period at 95-97%, with a slight upward trend from approximately 95% in 2001 to approximately 97% in 2017-2020. Survival outcomes showed no statistically significant variation over time, remaining stable in the 95-97% range. **Conclusions:** This analysis reveals an encouraging 20% decline in melanoma incidence among children, adolescents, and young adults over two decades, likely reflecting the success of public health initiatives promoting sun protection, sunscreen use, and reduced indoor tanning. The sustained decrease in incidence, particularly among younger populations, suggests that prevention efforts have had measurable impact. Simultaneously, the consistently excellent 5-year relative survival rates exceeding 95% demonstrate the effectiveness of current diagnostic and therapeutic approaches for melanoma in this age group. The stable survival coupled with declining incidence represents a dual public health success, with both primary prevention reducing disease burden and clinical management maintaining excellent outcomes. These findings underscore the importance of continued emphasis on melanoma prevention strategies while supporting ongoing efforts to optimize early detection and treatment protocols in pediatric and young adult populations. Research Sponsor: None.

9594 **Poster Session**

A propensity score–matched real-world analysis of immune checkpoint inhibitors in melanoma patients with autoimmune disease. First Author: Shanawar Ali Waris, West Virginia University School of Medicine, Department of Internal Medicine, Morgantown, WV

Background: Immune checkpoint inhibitors (ICIs) are foundational in the treatment of melanoma. However, patients with pre-existing autoimmune diseases (AD) have been excluded from pivotal ICI clinical trials and remain underrepresented in real-world outcome data. We conducted a propensity score–matched cohort study to evaluate the impact of pre-existing AD on clinical outcomes among melanoma patients treated with ICIs. **Methods:** A retrospective cohort study was performed using the TriNetX Research Network, including adult patients with melanoma treated with ICIs. ICI regimens included PD-1, PD-L1, and CTLA-4–based therapies. Patients with documented pre-existing AD were compared with patients without AD using 1:1 propensity score matching (PSM) for demographics, baseline corticosteroid use, laboratory values, and comorbidities. Outcomes included overall survival (OS) at 1 and 3 years; infections, corticosteroid exposure, and non-steroidal immunosuppressant exposure within 90 days of ICI initiation; and immune-related adverse events (irAEs), analyzed as a composite outcome and stratified by organ system (cardiac, pulmonary, endocrine, and dermatologic) within 180 days. Outcomes were assessed using hazard ratios (HRs), risk ratios (RRs), and 95% confidence intervals (CIs). **Results:** A total of 21,236 patients met inclusion criteria, including 3,372 with pre-existing AD and 17,863 without. After PSM, 3,372 patients were included in each cohort. Patients with AD demonstrated improved overall survival at both 1 and 3 years compared with those without AD (1-year HR 0.70, 95% CI 0.62-0.79; 3-year HR 0.76, 95% CI 0.70-0.84). Patients with AD were at increased risk for composite irAEs (RR 1.66, 95% CI 1.47–1.87). Organ-specific analyses demonstrated higher risks of cardiac (RR 3.29, 95% CI 2.02–5.34), endocrine (RR 1.48, 95% CI 1.22–1.81), and dermatologic irAEs (RR 1.46, 95% CI 1.22–1.73) among patients with AD. Patients with AD also had higher rates of corticosteroid (RR 1.23, 95% CI 1.18–1.28) and non-steroidal immunosuppressant exposure (RR 4.96, 95% CI 3.73–6.61), as well as increased risk of infection (RR 1.28, 95% CI 1.13–1.44). **Conclusions:** In this large real-world analysis, melanoma patients with pre-existing AD treated with ICIs demonstrated improved overall survival despite increased irAEs, immunosuppressant exposure, and infection. These findings challenge excluding patients with AD from receiving ICI therapy and support inclusion in future clinical trials. Research Sponsor: None.

Outcome	AD [n= 3,372]	No-AD [n= 3,372]	HR/RR [95% CI]
1-year OS	85.2%	79.8%	0.70 [0.62-0.79]
3-year OS	71.1%	65.2%	0.76 [0.70-0.84]
Any irAE (180 days)	19.6%	11.8%	1.66 [1.47-1.87]
Cardiac irAE	2.1%	0.6%	3.29 [2.02-5.34]
Pulmonary irAE	0.8%	0.6%	1.34 [0.76-2.35]
Endocrine irAE	7.0%	4.7%	1.48 [1.22-1.81]
Dermatologic irAE	9.2%	6.3%	1.46 [1.22-1.73]
Infection (90 days)	15.9%	12.6%	1.28 [1.13-1.44]

9595 **Poster Session**

First 1000 patients report of global practice patterns and clinical outcomes in the Collaborative Ocular Melanoma Natural History (OMNi) real-world database (NCT04588662). First Author: Anthony M. Joshua, Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia

Background: OMNi (NCT04588662) is an ambispective natural history database developed to provide contemporary real-world data of UM. The overall objectives of OMNi are to characterize regional/international UM management practice patterns and associated clinical outcomes in an effort to inform best practice recommendations and provide real world evidence. Here we present characteristics, demographics and practice patterns in the first 1000 patients enrolled globally. **Methods:** OMNi utilizes the Pulse Infoframe Healthie platform, enabling the longitudinal structured collection of data mapped to Observational Medical Outcomes Partnership. **Results:** Median age at diagnosis was 60 (15-94), with 47% of patients were female. Enrolment was from Australia (309), UK (93), USA (121) and Canada (477). When known, family history of UM was present in 2% (15/733). Recorded primary treatment modalities included plaque brachytherapy 44%, Enucleation 18%, Stereotactic radiotherapy 9%, Proton beam 3%, other radiotherapy 1%, other/ unknown 23%. Within the cohort, 30 patients were diagnosed with de novo metastatic disease and 343 patients had metastatic disease at any time. Of those, metastatic location was 166 extrahepatic and hepatic, 154 hepatic only, 18 extrahepatic only. HLA-A2 status was *0201 in 172/ 297(58%). Systemic treatments were administered to 176 patients first line– Tebentafusp (71 fist line); Ipi/Nivo (58); Ipi (7); PD-1 inh (15). The total number of patients receiving systemic treatments were Tebentafusp 108; Ipi/Nivo 90; Ipi 22; PD-1 (82). In total, 133 patients received liver directed therapy. At last follow up, where available 29% of patients had died from UM (179/611). Data to be presented will include genetic profiling summaries. **Conclusions:** The OMNi dataset can serve and aid in interpretation of clinical trial outcomes in the real-world, and accelerate the development of diagnostics and therapeutics to provide comparative data. Research Sponsor: None.

TPS9596 **Poster Session**

Clinical trial in progress: Phase I/II study of tebentafusp in combination with liver-directed therapies for the treatment of metastatic uveal melanoma. First Author: Rino S. Seedor, Sidney Kimmel Comprehensive Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: Uveal melanoma (UM) has a high rate of metastasis, most commonly to the liver. Tebentafusp-tebn (Tebe) is a first-in class immune-mobilizing monoclonal T cell receptor against cancer (ImmTAC) that gained regulatory approval after it showed significantly improved overall survival (OS) compared to single-agent investigator's choice in a pivotal randomized phase III trial. For patients with oligometastatic liver disease, liver-directed therapies (LDT) such as hepatic immunoembolization (IE) and chemoembolization (CE) have been used with success. LDT and Tebe may have therapeutic limitations when administered independently, but combining the two approaches is a potentially beneficial strategy that could provide both short-term hepatic disease control and long-term systemic disease control. **Methods:** This is an investigator-initiated, multicenter, open-label phase I/ randomized phase II trial to assess the safety and clinical efficacy of Tebe in combination with LDT in HLA-A*02:01 positive patients with metastatic UM [NCT06626516]. In Part 1 of the study, we will investigate the safety and efficacy of Tebe + IE in patients with low to moderate hepatic disease burden (M1a or M1b disease with largest tumor ≤ 5 cm, AND < 50% liver involvement). In Part 2, we will investigate the safety and efficacy of Tebe + CE in patients with bulky hepatic disease (M1b disease with largest tumor > 5cm, M1c disease, or >50% liver involvement). Patients must be 18 years or older, HLA-A*02:01 with metastatic UM in the liver. Extra-hepatic disease is allowed. Patients must be treatment naïve in the metastatic setting for Part 1 and must have no more than two prior lines of treatment (systemic or liver directed) for Part 2. Patients will receive Tebe at the approved step-up dosing regimen (20 mcg IV on C1D1, 30 mcg IV on C1D8, then 68 mcg on C1D15 and weekly thereafter). Patients in Part 1 will receive IE with GM-CSF 1500mcg every 4 weeks (starting at week 5) for the first four treatments and then 4 weeks as maintenance if clinically indicated. Part 1 has a phase I safety lead-in (Part 1A), followed by a phase II trial (Part 1B) where patients are randomized 2:1 to receive Tebe + IE or Tebe alone. Patients in Part 2 will receive CE with BCNU 300mg every 4 weeks for a total of 2 (unilobar disease) or 4 (bilobar disease) treatments followed by weekly Tebe. Eighteen patients, 52 patients, and 39 patients will be enrolled in Part 1A, Part 1B, and Part 2, respectively (total 109 patients). Primary endpoints for Part 1A is safety lead-in and 6-month progression-free survival (PFS), 6-month PFS for Part 1B, and 6-month PFS for Part 2. Secondary endpoints include overall response rate, liver-specific PFS, OS, and toxicity. Enrollment for Part 1A began in October 2025 at Thomas Jefferson University Hospital. Clinical trial information: NCT06626516. Research Sponsor: Immunocore, Ltd.

TPS9597 **Poster Session**

A randomized, controlled, multicenter, phase 3 study of RP1 (vusolimogene oderparepvec) combined with nivolumab vs physician's choice of therapy in patients with advanced melanoma that has progressed on anti–PD-1 and anti–CTLA-4 therapy (IGNYTE-3). First Author: Yana G. Najjar, UPMC Hillman Cancer Center, Pittsburgh, PA

Background: Melanoma is the fifth most common cancer, with over 100,000 new cases and 8000 related deaths projected in the US for 2025. First-line systemic treatment with immune checkpoint inhibitors (ICIs) improves the objective response rate (ORR) and extends progression-free survival (PFS) and overall survival (OS) for patients with advanced disease. Among available treatments, combination anti–PD-1 (nivolumab) + anti–CTLA-4 (ipilimumab) therapy is associated with the highest ORR and best PFS and OS. However, only around half of patients respond to treatment, and limited options exist for patients whose melanoma then progresses following anti–PD-(L)1 ± anti–CTLA-4. RP1 (vusolimogene oderparepvec) is a herpes simplex virus type 1–based oncolytic immunotherapy that expresses human granulocyte-macrophage colony-stimulating factor and a fusogenic glycoprotein (GALV-GP-R$^-$). IGNYTE-3 will evaluate the OS and clinical benefit of RP1 + nivolumab for patients with advanced cutaneous melanoma whose disease has progressed after anti–PD-1 and anti–CTLA-4 therapy (or who are ineligible for anti–CTLA-4 therapy) vs physician's choice. RP1 + nivolumab has demonstrated durable, clinically meaningful anti-tumor activity (ORR, 33.% per independent central review), with minimal toxicity (NCT03767348). Repetitive intralesional and intravisceral injections were well tolerated in advanced ICI-refractory melanoma. All patients had confirmed progression on prior anti–PD-1 therapy. **Methods:** IGNYTE-3 (NCT06264180) is a global, randomized, controlled, phase 3 trial. Key eligibility criteria include age ≥12 years, stage IIIB–IVM1a–M1d cutaneous melanoma, disease progression on ≥12 weeks of an anti–PD-1 and anti–CTLA-4 treatment (administered in combination or in sequence, with anti–PD-1 last), ≥1 measurable and injectable tumor, and adequate hematologic, hepatic, and renal function. Patients who are not candidates for anti–CTLA-4 therapy may enroll following progression on anti–PD-1 therapy alone. Patients with *BRAF* V600-mutant melanoma should have received anti–BRAF ± anti–MEK–targeted therapy prior to enrollment, where appropriate. Patients (N ≈ 400) will receive RP1 + nivolumab or physician's choice (nivolumab + relatlimab, anti–PD-1 monotherapy rechallenge [nivolumab or pembrolizumab], or single-agent chemotherapy [dacarbazine, temozolomide, or paclitaxel/albumin-bound paclitaxel]). The primary endpoint of the study is OS; the key secondary endpoints are PFS and ORR per RECIST 1.1. Clinical trial information: NCT06264180. Research Sponsor: Replimune, Inc.

TPS9598 **Poster Session**

A randomized, phase 2/3 clinical trial investigating RP2 plus nivolumab vs ipilimumab plus nivolumab in immune checkpoint inhibitor–naïve patients with metastatic uveal melanoma. First Author: Marlana M. Orloff, Thomas Jefferson University Hospital, Philadelphia, PA

Background: Uveal melanoma (UM) is the most common primary intraocular malignancy, accounting for ~90% of ocular melanomas and 5% of all melanomas. Half of patients with UM develop metastases, most commonly in the liver (~90%). The prognosis for patients with metastatic UM (mUM) is poor, with a median overall survival (OS) of ~1 year. Effective treatment options for mUM are limited, as it responds poorly to single-agent immune checkpoint inhibitors (ICIs; <10% response rate). Response rates are slightly higher with combination therapies (12%–18%), but these often have increased toxicity. Tebentafusp is FDA-approved for mUM based on survival benefit but is restricted to patients who are HLA-A*02:01 positive, and only ~10% of patients achieve an objective response. RP2 is a selectively replication-competent herpes simplex virus type 1–based oncolytic immunotherapy expressing GM-CSF, a fusogenic glycoprotein (GALV-GP-R$^-$), and an anti–CTLA-4 antibody-like molecule. Prior preliminary clinical data of intratumoral RP2 as monotherapy or in combination with nivolumab demonstrated a promising safety profile and anti-tumor activity with an overall response rate (ORR) of 29.4% and disease control rate of 58.8% in 17 patients with mUM, most of whom had received prior ICIs. This study will assess the efficacy and safety of RP2 + nivolumab vs ipilimumab + nivolumab in patients with ICI-naïve mUM. **Methods:** This is a multicenter, randomized, controlled, phase 2/3 study (NCT06581406; RP2-202). Key eligibility criteria include age ≥18 years and confirmed unresectable mUM with at least 1 lesion amenable to injection; up to 1 prior line of therapy in the metastatic setting is allowed. Patients with prior exposure to ICIs since the time of mUM diagnosis, >50% liver involvement, or previous selected liver-directed therapies are not eligible. Enrolled patients (N = ~280) will be randomized 1:1 to receive either RP2 + nivolumab or ipilimumab + nivolumab. In the RP2 + nivolumab arm, RP2 will be given intratumorally initially at 1×10^6 plaque-forming units (PFU)/mL, then every 2 weeks (Q2W) at 1×10^7 PFU/mL for 7 doses in combination with intravenous (IV) nivolumab (240 mg). In the ipilimumab + nivolumab arm, patients will receive IV ipilimumab (3 mg/kg) and IV nivolumab (1 mg/kg) Q3W for 4 doses. Patients in both arms may then receive IV nivolumab at 240 mg Q2W or 480 mg Q4W for up to 2 years. The co-primary endpoints are OS and progression-free survival by independent central review using RECIST 1.1. Secondary endpoints are ORR, duration of response, disease control rate, clinical benefit rate, duration of clinical benefit, and safety, including incidence of treatment-emergent adverse events (AEs), serious AEs, and immune-mediated AEs. Clinical trial information: NCT06581406. Research Sponsor: Replimune, Inc.

TPS9599 **Poster Session**

Phase 2 study of metronomic cyclophosphamide with pembrolizumab in checkpoint inhibitor–refractory melanoma. First Author: Poorva Vaidya, Chao Family Comprehensive Cancer Center, University of California, Irvine, Orange, CA

Background: Immune checkpoint inhibitors (ICI) are standard of care treatment in advanced, metastatic melanoma as well as adjuvant treatment of resected high-risk disease. However, approximately 50% of patients do not respond to primary anti-programmed death ligand-1 (anti-PD1) treatment (primary resistance) or progress after initial response (secondary resistance). Second line treatments in this setting include addition of the anti-cytotoxic T-lymphocyte associated protein 4 (anti-CTLA-4) drug ipilimumab or targeted treatment in BRAF mutant melanomas. However, CTLA-4 blockade can confer significant immune-mediated toxicity in a low performance status (PS) population, and not all patients are eligible for BRAF/MEK inhibition. There remains an unmet clinical need to optimize ICI efficacy and overcome resistance. It is hypothesized that suppressive regulatory T-cells (T_{reg})may inhibit the anti-tumor effect of ICI. Cyclophosphamide (CTX) is an alkylating anticancer agent. Prior studies in patients with recurrent ovarian cancer and soft tissue sarcoma have demonstrated that the combination of anti-PD1 agents with metronomic, or low dose, frequent, CTX was effective with no new safety signals. **Methods:** This phase 2, single-center, single-arm study explores the efficacy of adding oral metronomic CTX to intravenous pembrolizumab in patients with ICI-refractory locally advanced or metastatic melanoma. Key inclusion criteria are measurable disease by RECIST v.1.1 and receipt of investigational treatment within 9 weeks of last ICI treatment. Patients may have previously received single agent pembrolizumab or dual ICI with anti-LAG3 and anti-PD1 (relatlimab/nivolumab). Key exclusion criteria are symptomatic, untreated brain metastases, BRAF V600 mutation without prior receipt of BRAF/MEK inhibition, or prior grade 3 or greater immune-related adverse event (irAE). The primary endpoint is objective response rate (RR) as defined by complete response (CR) + partial response (PR) by RECIST v 1.1. A Simon's minimax two-stage design will be used, with the null hypothesis that the true response rate is .05 and the alternative hypothesis that true response rate is 0.3. In Stage I, a total number of 7 patients will be accrued. If there are 0 responses among 7 patients, the study will be stopped; otherwise, an additional 7 patients will be accrued to Stage II. 3 of 14 planned patients have been enrolled. This trial was approved by the UC Irvine Institutional Review Board; approval number is 6168. Trial registration NCT06771544. Clinical trial information: NCT06771544. Research Sponsor: University of California, Irvine; University of California, Irvine; UCI Melanoma Program.

TPS9600 **Poster Session**

Phase 1b/2 trial of melphalan-percutaneous hepatic perfusion (PHP) therapy and nivolumab/relatlimab in patients with metastatic melanoma and liver metastasis. First Author: Vincent T. Ma, University of Wisconsin Madison, Madison, WI

Background: Despite advances with immune checkpoint inhibitors (ICIs), patients with metastatic melanoma and liver metastases (LM) experience poorer outcomes. In the CheckMate-067 subanalysis, patients with LM treated with nivolumab/ipilimumab had shorter median PFS (4.4 vs 18.1 months) and OS (28.2 months vs not reached) than those without LM, confirming its negative prognostic role. Nivolumab/ipilimumab and nivolumab/relatlimab show comparable efficacy; however, the latter is increasingly used for its improved safety profile (grade ≥3 adverse events: 59% vs 21%). Melphalan-PHP (Hepzato), a liver-directed therapy delivering high-dose melphalan through a closed filtration circuit, concentrates treatment in the liver while minimizing systemic exposure. Research by Yu et al. demonstrated that LM reduces peripheral and tumoral CD8+ T cells, creating an immune desert, while combining liver-directed therapy with ICIs can reactivate systemic immune responses. Based on these insights and the CHOPIN trial's safety data, the proposed Phase 1b/2 study will assess the safety, tolerability, and preliminary efficacy of melphalan-PHP plus nivolumab/relatlimab for first line treatment of metastatic non-uveal melanoma patients with LM. **Methods:** Phase 1b/2, single-center, single-arm study will use a Simon two-stage (5+10) design (n=15). Patients will receive nivolumab/relatlimab on Day 1 of each 28-day cycle for up to 2 years and receive melphalan-PHP on Day 15 of Cycle 1 and Cycle 3. Eligible participants must have histologically or cytologically confirmed metastatic melanoma involving the liver and be systemic treatment-naïve in the metastatic setting. Prior adjuvant ICI is permitted provided it was completed >6 months prior to study enrollment. Key exclusions include metastatic uveal melanoma, prior treatment with melphalan-PHP or ICI combinations, uncontrolled or symptomatic brain metastases, prior grade 3+ adverse events from ICI requiring treatment discontinuation, ongoing immunosuppressive therapy, contraindications to anesthesia, and significant cardiac, hepatic (Child-Pugh B/C), or pulmonary disease. The co-primary objectives/endpoints in stage 1 are to assess the safety and tolerability as measured by 2 or less DLTs (any treatment-related grade 4+ non-hematologic event lasting >3 days); and preliminary efficacy as measured by 2 or more objective responses in hepatic and non-hepatic lesions. Secondary objectives include: disease control rate (DCR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), and any tumor reduction. Open for enrollment in January 2026. Clinical trial registry number: NCT07281924. Clinical trial information: NCT07281924. Research Sponsor: Delcath.

TPS9601 **Poster Session**

Adaptive phase 2/3 study of EIK1001, a TLR7/8 dual agonist, in combination with pembrolizumab, as first-line therapy in participants with advanced melanoma (TeLuRide-006). First Author: Bernardo Leon Rapoport, The Clinical and Translational Research Unit of the Medical Oncology Centre of Rosebank, Saxonwold, Johannesburg; Department of Immunology, Faculty of Health Sciences, University of Pretoria, Prinshof, South Africa

Background: Immune checkpoint inhibitors (ICIs), including anti-PD-1 antibodies, reverse tumor induced immune suppression and promote effective anti-tumor T-cell responses. They have drastically improved outcome in advanced melanoma therapy, yielding durable improvements in progression-free survival (PFS) and overall survival (OS). Although adding anti-CTLA-4 or anti-LAG-3 enhances efficacy beyond anti-PD-1 alone, these approaches do not directly target dominant myeloid-mediated resistance mechanisms within the tumor microenvironment, and new agents targeting this axis are needed. EIK1001, a TLR7/8 dual-agonist, activates myeloid and plasmacytoid dendritic cells to stimulate innate inflammation and adaptive immunity. Across multiple studies, EIK1001 has been well tolerated and has demonstrated clinical activity both as monotherapy and in combination with ICIs. **Methods:** TeLuRide-006 (NCT#06697301) is a global, multicenter, randomized, double-blind, adaptive Phase 2/3 trial of EIK1001 or placebo, in combination with pembrolizumab (pembro), as first-line therapy for participants (pts) with advanced cutaneous melanoma. Approximately 740 pts will be randomized, including a dose-optimization (DO) stage in which pts are randomized 1:1:1 to two EIK1001 dose levels or placebo, each administered with pembro, followed by Phase 2/3 expansion evaluating the selected EIK1001 dose versus placebo, with pembro. Interim analyses will guide progression from DO to Phase 2 and subsequently to Phase 3. EIK1001 or placebo is administered IV QW until the end of Week 27 then Q3W; while pembro is administered IV Q3W. Pts are stratified by prior anti-PD-1 adjuvant therapy, LDH level, and BRAF mutational status. Key eligibility criteria include patients $\geq$12 years (with country-specific variations), life expectancy $\geq$3 months, unresectable Stage III or Stage IV melanoma, known BRAF V600 status, at least one RECIST v1.1–measurable lesion, and no prior or current pneumonitis/interstitial lung disease. Primary objectives are to assess the efficacy and safety of two EIK1001 doses with pembro in DO, and to compare PFS (RECIST v1.1 by blinded independent central review [BICR]) and OS between the selected EIK1001 dose and placebo in combination with pembro. Secondary objectives include safety and tolerability of either EIK1001 dose with pembro, objective response rate and duration of response per RECIST v1.1 by BICR. Exploratory objectives include time to response, EIK1001 exposure-response relationships, and health-related quality of life. This study enrolled (randomized) its first participant on 5/21/2025 and is activated at 91 sites in 22 countries at the time of abstract submission. Research Sponsor: None.

TPS9602 **Poster Session**

A phase I/II clinical study of DOC1021 (dubodencel) dendritic cell immunotherapy for refractory melanoma. First Author: Alexandra Haugh, Massachusetts General Hospital Cancer Center, Boston, MA

Background: DOC1021 is an autologous dendritic cell (DC)-based immunotherapy. Loading of DC in tandem with both patient autologous tumor protein and amplified mRNA induces p38MAPK and mTORC1 signaling cascades that initiate cDC1-like skewing of monocyte-derived DC, generating downstream development of highly cytolytic memory effectors. This approach targets the multitude of antigens in a patient's own tumor, does not require myeloablative chemotherapy and has demonstrated a favorable safety profile in Phase I glioblastoma (NCT04552886) and pancreatic cancer trials (NCT04157127). Pre-clinical studies in a variety of animal models, including melanoma (subcutaneous B16F0-OVA tumors), have also shown improved tumor responses and evidence of antigen-specific immunity. While immune checkpoint inhibitors (ICI) have improved clinical outcomes in melanoma, many patients ultimately develop resistance, resulting in refractory disease. We hypothesize that DOC1021 may overcome ICI resistance in refractory melanoma through the generation of durable T cell responses with novel specificities, promoting long-term anti-tumor T cell surveillance and improved survival. **Methods:** This is a prospective, multi-center, open-label Phase I/II study in patients with refractory cutaneous melanoma, unresectable or metastatic, with progression following $\geq$1 prior systemic therapies including anti-PD-1. The study consists of two components: an initial Phase I study to confirm safety/tolerability of DOC1021 in refractory melanoma, and subsequently, a single-arm Phase II cohort to assess efficacy. Up to 12 patients will be enrolled in Phase I, and up to 35 evaluable patients will be enrolled in Phase II using a Simon's optimal two-stage design. DOC1021 will be prepared from mobilized peripheral blood mononuclear cells (PBMC), loaded with autologous tumor lysate and amplified tumor mRNA. All patients will receive 2 courses of DOC1021 (12×10^6 cells per administration) 2 weeks apart via perinodal injections near active disease sites, plus peg-interferon (pIFN) adjuvant on the day of each DOC1021 administration and 1 week after for 4 total doses. An optional DOC1021 booster course may also be given approximately 6 months after the first DOC1021 administration. The primary endpoint of the Phase I study is dose-limiting toxicities of DOC1021, while the primary endpoint of the Phase II study is the overall response rate per RECIST 1.1 criteria. This study will also evaluate survival, tumor responses, changes in circulating tumor DNA, as well as further investigate DOC1021's mechanism of action through biomarker-rich analyses of serial tumor biopsies and blood sampling. The first patient to enroll in the Phase I safety study is planned for early 2026. Clinical trial information: NCT07288112. Research Sponsor: Diakonos Oncology; Cancer Prevention and Research Institute of Texas (CPRIT).

TPS9603 **Poster Session**

Phase I/IIa dose finding study of triplet regimen of relatlimab (RELA) ipilimumab (IPI), and nivolumab (NIVO) in first-line therapy of metastatic melanoma (MM) (TRINITY). First Author: Elizabeth M. Burton, Department of Genomic Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Approved immune checkpoint blockade (ICB) agents for the treatment (tx) advanced, unresectable metastatic melanoma (MM) include NIVO (anti-PD1) alone or in combination with IPI (anti-CTLA-4) or RELA (anti-LAG3) and have transformed outcomes for patients with this disease. While doublet combinations induce higher rates of durable disease control and modestly improved survival vs single agent, higher doses of IPI induce higher objective response rates (ORR) also increase grade $\geq$3 immune-related adverse events. Notably, there is no established dose-response relationship for NIVO or RELA. IPI has a demonstrated role in expanding the T-cell receptor (TCR) repertoire, modulating suppressive T cell populations. NIVO+RELA regulates exhaustion of activated T cells, improving effector function. Together, these suggest potential synergy with triplet ICB. Results reported in RELATIVITY-048 (NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W) demonstrated impressive efficacy (ORR 59%) and seemingly improved progression free and overall survival (PFS, OS) over previously reported doublet tx. The RELATIVITY-048 study design did not include dose escalation (DE) of IPI. Our team seeks to identify the optimal dose and schedule if IPI to combine with NIVO+RELA, identify the recommended phase II dose (RP2D) for this triplet ICB treatment and, ultimately, seeking to maximize the clinical benefit while maintaining a toxicity profile comparable to approved doublet regimens. **Methods:** In this single center, investigator initiated, PhI/IIa study, our team is evaluating triplet ICB (NCT06683755) in untreated, unresectable MM pts. Pts will receive NIVO 480mg + RELA 160mg IV Q4W (FDA approved dose). IPI DE will begin at 0.5mg/kg Q4W, escalating to 2mg/kg Q4W x4 induction doses. Pts will receive maintenance tx with NIVO+RELA Q4W at the approved dose. The maximum tolerated dose and the RP2D will be determined using a Bayesian optimal interval design, accruing 12-18 pts in DE. An additional 12-18 pts will be enrolled at RP2D to determine the ORR (primary objective) by RECIST 1.1. Secondary objectives include PFS, OS, and correlative analysis. Non IPI containing prior adjuvant or neoadjuvant tx is allowed if the last dose has been $>$6 months. Pts with asymptomatic brain metastasis on $\leq$10mg corticosteroids are allowed. Safely biopsiable lesions are required for pts enrolled in the PhII portion. By optimizing the dose and schedule of IPI in combination with NIVO+RELA, we seek to maximize clinical benefit while maintaining a toxicity profile comparable to approved regimens. This study is currently accruing at MD Anderson Cancer Center. Clinical trial information: NCT06683755. Research Sponsor: BMS.

TPS9604 **Poster Session**

TrioMBM: A multicenter, phase II trial of relatlimab, nivolumab, and ipilimumab in patients with asymptomatic and symptomatic melanoma brain metastases. First Author: Allison Betof, Stanford University School of Medicine, Stanford, CA

Background: Melanoma brain metastases (MBM) are a leading cause of morbidity and mortality for patients (pts) with advanced melanoma. Modern systemic therapies including immune checkpoint blockade (ICB) are insufficient at controlling MBM, particularly in patients with who are symptomatic and/or require corticosteroids. The CheckMate 204 study established nivolumab (NIVO) 1 mg/kg + ipilimumab (IPI) 3mg/kg followed by maintenance NIVO as the standard treatment (tx) for pts with MBM based on intracranial IC) objective response rate (ORR) of 55% and 6-month progression-free survival (PFS) of 64% in the asymptomatic cohort (*Tawbi et al. NEJM 2018*). In symptomatic pts, intracranial benefit rate (iCBR) was only 22% and median PFS was 1.2 mos (*Tawbi et al. Neuro Oncol 2021*). Triplet tx with the addition of LAG-3 inhibition with relatlimab (RELA) is now being explored as a mechanistically-driven means to improve efficacy of ICB. Arm 2B of RELATIVITY-048 (NIVO 480 mg Q4W + RELA 160 mg Q4W + IPI 1 mg/kg Q8W) reported promising efficacy (ORR 59%, 3y PFS 52%) and 2 of 3 (67%) pts with MBM had confirmed responses (*Ascierto et al. ASCO 2024*) further justifying the need to explore this combination in this population. We hypothesize that triplet ICB will be more effective than NIVO+IPI for the tx of symptomatic and asymptomatic MBM. **Methods:** In this multicenter, investigator initiated, phase II study evaluating triplet ICB (NCT06712927) pts with MBM will be assigned to one of two cohorts: Cohort A (asymptomatic, n=40) and Cohort B (symptomatic, n=20) defined as having symptoms attributable to brain metastases and/or requiring steroids $>$10 mg prednisone/day or equivalent. All pts will receive NIVO 480mg + RELA 160mg IV Q4W (FDA approved dose) plus IPI 1mg/kg IV Q8W. Pts must have $\geq$1 untreated intracranial lesion (5-40mm) and no prior ICB for unresectable stage III/IV melanoma ($>$6 mo since neoadjuvant or adjuvant ICB). Primary endpoint is iCBR (CR+PR+SD $\geq$6 mo) determined by modified RECIST 1.1; secondary endpoints include safety, ORR, duration of response, and PFS. Extensive correlative analyses of peripheral blood mononuclear cells, plasma, tumors, and cerebrospinal fluid are planned. The study is currently enrolling at Stanford Cancer Center with multisite expansion underway. Clinical trial information: NCT06712927. Research Sponsor: Bristol-Myers Squibb; National Cancer Institute; P30CA124435.

TPS9605 **Poster Session**

Phase 2 sequential treatment of percutaneous hepatic perfusion with melphalan/hepatic delivery system followed by tebentafusp in the treatment of metastatic uveal melanoma. First Author: Jonathan S. Zager, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Metastatic uveal melanoma (mUM) typically has a poor prognosis with limited treatment options. Tebentafusp (TEBE) is the only approved systemic agent for HLA-A*02:01 positive mUM, and percutaneous hepatic perfusion (PHP) is FDA approved for patients with mUM in the liver (solely or predominantly). Combining PHP with nivolumab plus ipilimumab in the randomized phase 2 CHOPIN trial significantly improved overall response (ORR), progression-free survival (PFS) and overall survival (OS) compared to PHP alone, but with significantly higher grade 3 or greater adverse events. In the phase 3 TEBE clinical trial there was a modest ORR of 11%, and improved OS compared to investigator choice therapy. We hypothesize that PHP causes antigen release and changes in the hepatic tumor microenvironment that may enhance response to TEBE. In this investigator-initiated trial, we aim to explore the combination of sequential regional and systemic therapy in HLA-A*02:01 positive mUM patients. **Methods:** This is a single institution phase 2 clinical trial combining PHP using the melphalan hepatic delivery system for 2 cycles followed sequentially by intravenous TEBE at approved dosage for up to 1 year of therapy. For patients with unequivocal progression on TEBE, up to 4 additional cycles of PHP will be considered if they continue to meet standard eligibility for PHP. The primary objective is to assess the PFS in uveal melanoma patients who have isolated or liver dominant metastases with landmark analyses at 6 months, 12 months and 24 months. Secondary objectives include (1) toxicity, (2) objective response and duration of response, (3) hepatic and extra-hepatic PFS, (4) OS, (5) biomarker discovery, RNA sequencing and spatial immunofluorescence analysis of the tumor microenvironment through core biopsies performed pre-PHP, after PHP number 2, and post-TEBE treatment. Blood samples for immune panel analysis will be collected at these timepoints. Response assessments are undertaken with standard cross-sectional imaging every 12 weeks for 36 months. Planned accrual is 18 patients with an interim futility analysis after 10 patients are treated to assess the 6-month PFS for the cohort. Primary analysis will be performed using the Kaplan-Meier method. Salient eligibility criteria include: (1) age $\geq$18 years, (2) histologically confirmed metastatic UM, HLA-A*02:01 positive, (3) measurable disease per RECIST v1.1, (4) ECOG performance status of $\leq$1, (5) adequate marrow, renal and hepatic function; (6) no more than 50% of liver involvement by tumor. Limited extrahepatic disease is allowed. This study opened for enrollment in November 2025, and two patients have been treated to date (NCT07276386). This study is supported by Delcath Systems, Inc. Clinical trial information: NCT07276386. Research Sponsor: Delcath Systems.

TPS9606 **Poster Session**

SILVER (supplementing tebentafusp with subcutaneous IL-2 to verifiably eradicate radiological progression): A phase 1/2 trial of IL-2 with tebentafusp upon first radiological progression on first-line tebentafusp alone. First Author: Anthony M. Joshua, Kinghorn Cancer Centre, St Vincent's Hospital, Sydney, NSW, Australia

Background: Metastatic uveal melanoma (mUM) remains a disease with a profound unmet clinical need. Tebentafusp, a bispecific T-cell receptor–anti-CD3 ImmTAC targeting gp100 is the first systemic therapy to demonstrate a reproducible overall survival benefit and is now the standard of care in eligible patients. Despite this advance, most patients ultimately develop radiological progression on tebentafusp, highlighting the need for rational combination strategies that can augment or restore antitumour immune activity. Interleukin-2 (IL-2) has long been recognised as a potent T-cell growth and activation factor. Pre-clinical data demonstrate that IL-2 enhances tebentafusp-mediated tumour cell killing by expanding and priming effector T-cell populations. These effects are mechanistically linked to increased cytotoxic function and improved immune synapse formation (Guc et al., 2025). Importantly, low-dose IL-2 administered subcutaneously has been shown in prior clinical studies to achieve biologically relevant serum concentrations with a substantially improved safety profile compared with historical high-dose intravenous regimens. Collectively, these data provide a strong biological and clinical rationale for combining tebentafusp with low-dose subcutaneous IL-2 in patients with mUM progressing on tebentafusp monotherapy. **Methods:** SILVER is an investigator-initiated, single-arm phase Ib study evaluating the safety, tolerability and preliminary efficacy of tebentafusp in combination with low-dose subcutaneous IL-2 in HLA-A*02:01–positive patients with metastatic or unresectable uveal melanoma who have RECIST-defined progression on tebentafusp alone. Patients receive IL-2 at 125,000 IU/kg subcutaneously, administered for three consecutive days prior to the initial tebentafusp dose, and then weekly 24 hours before each subsequent tebentafusp infusion. Tebentafusp is administered intravenously with step-up dosing in cycle 1, followed by standard weekly dosing thereafter. The primary endpoint is best overall response by iRECIST. Secondary endpoints include RECIST 1.1 response rate, clinical benefit rate, progression-free survival, overall survival, safety and tolerability (CTCAE v5.0), and quality of life. Extensive translational endpoints include serial diffusion-weighted MRI, ctDNA kinetics, and deep immune profiling from blood and tumour biopsies. Early treatment cycles incorporate inpatient monitoring to manage cytokine-mediated toxicities. **Conclusion:** By integrating robust pre-clinical rationale, an established and pragmatic IL-2 dosing strategy, and comprehensive translational analyses, this study aims to enhance tebentafusp activity and improving outcomes for patients with progressive mUM. Clinical trial information: NCT07063875. Research Sponsor: Immunocore; Department of Defence; ME230190 HT9425-24-1-0996.

TPS9607 **Poster Session**

Clinical trial in progress: Phase II trial of neoadjuvant tebentafusp in patients with locally advanced primary uveal melanoma. First Author: Rino S. Seedor, Sidney Kimmel Comprehensive Cancer Center, Thomas Jefferson University, Philadelphia, PA

Background: Uveal melanoma (UM) is the most common intraocular malignant tumor in adults. Primary UM are effectively treated by plaque radiotherapy or enucleation; however, up to 50% of UM patients ultimately succumb to advanced disease. Tebentafusp-tebn is a bispecific gp100 peptide human leukocyte antigen (HLA)-directed cluster of differentiation 3 (CD3) T-cell engager that became the first FDA approved treatment for unresectable or metastatic UM. Among the metastatic UM patients who received tebentafusp on clinical trial (IMCgp100-01 (n=19), IMCgp100-102 (n=146), and IMCgp100-202 (n=245)), 12 patients had recurrent orbital tumors. All orbital lesions were stable or had achieved shrinkage with tebentafusp. The best percentage changes from baseline were reported as -3 to -40% reduction in intra-ocular target lesions. All intraocular non-target lesions were stable or achieved a complete response after tebentafusp treatments. These preliminary data indicate that tebentafusp may have potential for treating surgically unresectable primary UM. **Methods:** This is an investigator-initiated, prospective, single arm phase II trial evaluating neoadjuvant tebentafusp in patients with locally advanced primary UM [NCT06414590]. Patients must be 18 years or older, HLA-A*02:01 with a primary UM with T3 or T4 category tumor size. Patients cannot have a symptomatic UM that requires immediate ophthalmological intervention such as enucleation. Patients will be treated with up to 8 weeks of neoadjuvant tebentafusp, followed by radioactive plaque or enucleation. Tebentafusp will be administered as follows: 20mcg on Day 1, 30mcg on Day 8, 68 mcg on Day 15, and weekly doses of 68 mcg thereafter. The first three treatments will require inpatient hospitalization for overnight observation. The primary endpoint of the study is regression (defined as $\geq$ 20% reduction in tumor volume) of primary UM after tebentafusp treatment in 20% of treated patients. Secondary endpoints include toxicity assessment and ctDNA analysis in both blood and aqueous humor. Exploratory endpoints include changes to visual acuity, radiation dose to the fovea, and treatment (enucleation to plaque brachytherapy). The efficacy of this combination treatment will be assessed using the Simon's two stage design. In stage I, a total number of 8 patients are accrued and if there are 0 responses among these 8 patients, further enrollment of patients may be stopped. Otherwise, an additional 11 patients will be accrued in stage II, resulting in a total sample size of 19 patients. Enrollment began in September 2025 at Thomas Jefferson University Hospital, in conjunction with Wills Eye Hospital. Clinical trial information: NCT06414590. Research Sponsor: Immunocore, Ltd.

TPS9608 **Poster Session**

Neoadjuvant darovasertib in uveal melanoma patients undergoing primary local therapy (OptimUM-10): Phase 3 trial. First Author: J. William Harbour, UT Southwestern Medical Center, Dallas, TX

Background: Uveal melanoma (UM) is the most common intraocular malignancy and has high risk of metastatic progression and poor long-term survival. Standard treatment of the primary tumor includes enucleation (eye-removal), and radiation therapy including plaque brachytherapy (PB) and proton beam therapy, which can result in vision loss or removal of the eye. No approved neoadjuvant therapies exist that shrink the tumor or improve visual outcomes. Almost all UM tumors harbor *GNAQ/GNA11* initiating mutations with downstream constitutive activation of protein kinase C (PKC). Darovasertib, a first-in-class oral PKC inhibitor tested in study OptimUM-09, has demonstrated the ability to reduce UM tumor size resulting in enucleation sparing in patients with large tumors, and radiation reduction in patients with medium sized tumors requiring PB. In addition, visual improvements have been observed not only during neoadjuvant therapy but also in the predicted risk of legal blindness post PB using a vision prognostication tool. **Methods:** OptimUM-10 is an ongoing phase 3, randomized, multicenter, open-label trial enrolling patients with primary non-metastatic UM. Eligible patients must have high metastatic risk (class 2 gene-expression profile, monosomy 3, or AJCC stage 3). Additionally, for the PB cohort, moderate to high risk of vision loss ($>$ 30Gy predicted radiation dose to key visual structures) is required for eligibility. Major exclusion criteria include metastatic disease or extraocular tumor extension, prior UM primary treatment, attributes necessitating immediate enucleation, and relevant ocular comorbidities. The trial has two cohorts: Cohort 1 (n=330) includes patients with medium UM tumors where PB is the standard treatment. Cohort 2 (n=120) includes patients with large UM tumors where enucleation is the standard treatment. In each cohort, eligible patients are randomized 2:1 to receive neoadjuvant darovasertib (300 mg twice daily for up to six 28-day cycles) or standard-of-care treatment with PB (cohort 1) or enucleation (cohort 2). The primary endpoint for cohort 1 is the proportion of patients with loss of Early Treatment Diabetic Retinopathy Study Best-Corrected Visual Acuity of $\geq$15 letters (%VL15) from randomization, while in cohort 2 it is eye preservation rate. Across cohorts, the key secondary objective is to evaluate response rate with neoadjuvant darovasertib. Additional secondary endpoints include event-free survival and safety, as assessed by treatment-emergent adverse events and serious adverse events. Enrollment is ongoing, and results will determine whether OptimUM-10 may establish darovasertib prior to definitive PB as the first neoadjuvant treatment for primary UM to meaningfully reduce tumor burden and expand vision- and eye-preserving treatment options for patients. Clinical trial information: NCT07015190. Research Sponsor: IDEAYA Biosciences, South San Francisco, CA USA.

TPS9609 Poster Session

A phase 3, international, multicenter, randomized, controlled trial of selective index lymph node resection versus therapeutic lymph node dissection after neoadjuvant immunotherapy for stage IIIB-D melanoma (MSLT-3/S2601/EORTC2519). First Author: Maria Gonzalez, Melanoma Institute Australia, Sydney, NSW, Australia

Background: Neoadjuvant immunotherapy (NAT) with immune checkpoint inhibitors (ICI) is a standard therapy for resectable stage III melanoma, with randomized trials demonstrating superior outcomes compared to adjuvant therapy alone. The phase 2 SWOG-1801 trial showed 72% EFS at 2 yrs for NAT & 49% for adjuvant PEMBRO (P=0.004), while the phase 3 NADINA trial confirmed superiority of NAT IPI/NIVO over adjuvant NIVO (2-year RFS 83.7% vs 57.2%, HR 0.32). Pathological response, particularly major pathological response (MPR; ≤10% viable tumor), strongly correlates with improved outcomes, with the International Neoadjuvant Melanoma Consortium (INMC) pooled analysis (N=610 ICI patients) demonstrating 3-yr RFS of 93% for MPR patients (pts) vs 41% for those with no pathological response. The PRADO trial demonstrated that selective index lymph node (ILN) resection (RES) can safely de-escalate surgery in MPR pts, with only 4/60 (6.7%) MPR pts recurring after median follow-up of 28.1 months, all locoregionally. ILN RES significantly reduced surgical morbidity & improved quality of life compared to therapeutic lymph node dissection (TLND). However, PRADO was a single-arm proof-of-concept study. An international survey of 117 melanoma experts showed 71% believe a phase 3 randomized controlled trial is needed to change practice. The MSLT-3 trial will definitively establish whether ILN RES is non-inferior to standard TLND for MPR pts. **Methods:** This phase 3, international, multicenter, randomized, non-inferiority trial will enroll approximately 1,574 pts with resectable stage IIIB-D cutaneous melanoma to identify 496 with MPR following NAT. Eligible pts must have cytologically/histologically confirmed resectable stage IIIB-D melanoma with at least one macroscopic lymph node in groin, axilla or neck basins. All pts are randomized 1:1 to ILN RES or TLND, stratified by continent/region, AJCC stage, & NAT regimen. Prior to NAT, all pts undergo radiological placement of a marker in the largest metastatic lymph node. Pts receive NAT per institutional standard of care (minimum one PD-(L)-1 checkpoint inhibitor, maximum 6 weeks duration) followed by surgery at weeks 6-9 according to randomized arm. Pathological response is assessed per INMC criteria. Pts with MPR in the ILN arm undergo surveillance only; non-MPR pts in the ILN arm proceed to TLND within 3 weeks. Primary endpoint is 2-year recurrence-free survival in MPR pts (non-inferiority margin -5%). Secondary endpoints include escalation to TLND for isolated nodal recurrence, salvage therapy rates, distant metastasis-free survival, event-free survival, overall survival, surgery-related AEs, quality of life (QLQ-C30, EQ-5D-5L, FACT-M), concordance of imaging/ctDNA with pathology & health economics. Clinical trial information: NCT07049276. Research Sponsor: Australian Commonwealth Government.

TPS9610 Poster Session

NeoIRENIE: A phase 2 randomized trial of intensified neoadjuvant therapy for melanoma patients with multi-omic biomarker or clinically predicted poor response to standard immune checkpoint inhibitor (ICI) therapy. First Author: Maria Gonzalez, Melanoma Institute Australia, Sydney, NSW, Australia

Background: Neoadjuvant immunotherapy (NAT) with immune checkpoint inhibitors (ICI) has emerged as superior treatment for stage III melanoma, demonstrating improved outcomes compared to adjuvant therapy. The SWOG-1801 trial showed 23% EFS benefit at 2 years for NAT versus adjuvant PEMBRO (72% vs 49%, P=0.004), while the NADINA trial confirmed superiority of NAT IPI/NIVO over adjuvant NIVO (2-year RFS 83.7% vs 57.2%, HR 0.32). Pathological response, particularly major pathological response (MPR; ≤10% viable tumor), strongly correlates with improved outcomes, with the International Neoadjuvant Melanoma Consortium pooled analysis (N=610 ICI patients) demonstrating 3-year RFS of 93% for MPR patients versus 41% for those with no pathological response. However, standard NAT with IPI (1mg/kg) and NIVO (3mg/kg) achieves MPR in only ~60% of patients. Multi-omic biomarkers can predict poor response to anti-PD-1 therapy, identifying patients who may benefit from intensified ICI therapy. The NeoIRENIE trial evaluates whether intensified ICI regimens improve pathological response in poor prognosis patients identified by biomarker prediction, treatment failure, or mucosal histology. **Methods:** Phase 2, non-comparative, multicenter, randomized trial with 3 cohorts (N=493, Table 1). All pts undergo therapeutic lymph node dissection/completion surgery at week 6 with path response evaluation per INMC criteria. Cohorts 1a, 2 and 3 pts without MPR receive adjuvant NIVO 480mg Q4W for 11 doses. CT, MRI brain and FDG PET/CT performed at baseline, pre-surgery and during 10-year follow-up. Tumor, blood and stool samples collected at baseline, wk 3, surgery and recurrence. Primary endpoint: path response rate in each INMC response category. Secondary endpoints: event-free survival, RECIST response rate, metabolic response rate, overall survival, safety/tolerability, surgical outcomes and quality of life. Exploratory endpoints: biomarker analyses and validation of multi-omic predictive model. Clinical trial information: NCT06999980. Research Sponsor: None.

Cohort	N	Resectable Melanoma Patient Population	*Arms (Randomization)
1a	168	Stage IIIB/C/D cutaneous; biomarker-predicted poor responders; treatment-naive	A-D (1:1:1:1)
1b	154	Stage IIIB/C/D cutaneous; biomarker-predicted high responders; treatment-naive	E-F (1:1)
2	111	Stage IIIB/C/D cutaneous; recurrence within 6 months of adjuvant or NAT ICI therapy	A-C (1:1:1)
3	60	Any stage mucosal melanoma; treatment-naïve	A-B (1:1)

*Arms:
A=IPI 3mg/kg + NIVO 1mg/kg Q3W x2.
B=NIVO 480mg + RELA 160mg + IPI 1mg/kg Q4W x2.
C=NIVO 480mg + RELA 160mg Q4W x2.
D=IPI 1mg/kg + NIVO 3mg/kg Q3W x2.
E=IPI 1mg/kg + NIVO 3mg/kg Q3W x2.
F=PEMBRO 200mg Q3W x2.

TPS9611 Poster Session

EA6232: A phase II double-blind trial of sulforaphane for therapeutic prevention of melanoma in patients with multiple atypical nevi and a prior history of melanoma. First Author: John M. Kirkwood, UPMC Hillman Cancer Center, Pittsburgh, PA

Background: A significant risk factor for melanoma is presence of atypical/dysplastic nevi (A/DN), and evidence suggests a 10-fold increased risk of new primary melanoma with A/DN.[1] Patients with prior melanoma and multiple A/DN are thus reasonable targets for therapeutic prevention due to high risk of additional melanoma. Currently, no preventative systemic agent for melanoma is approved. Sulforaphane, an isothiocyanate of cruciferous vegetables, demonstrates therapeutic prevention potential in multiple clinical trials.[2,3] Topical sulforaphane mitigates effects of UV radiation, a primary driver of melanoma development, in mouse and human skin.[4] The proposed mechanism involves alterations of transcription factor Nrf2, an antioxidant modulator, and IL-6/STAT-3 pathways in A/DN and melanoma.[5,6,7] Our team conducted a phase I trial of oral sulforaphane for 28 days in 17 patients with prior melanoma and ≥ 2 A/DN.[8] Statistically significant decreases in several serum pro-inflammatory cytokines were reported with no dose-limiting toxicities. This phase II trial aims to elucidate effects of daily sulforaphane on A/DN lesions and compare pigmentation change to placebo over one year. We hypothesize sulforaphane will demonstrate a greater decrease in total area of pigmented nevocellular nevi (both A/DN and banal nevi) *vs.* placebo as documented by serial digital photography. **Methods:** This phase II trial (NCT07040280) will assess impact of daily sulforaphane for 12 months *vs.* placebo on total area, quantity, and features of A/DN. Patients with ≥ 3 clinical A/DN (≥ 5 mm diameter with macular component, and ≥2 features of ill-defined borders, color variegation, uneven contour, or erythema) and a history of early stage-melanoma are eligible. Enrolled patients will undergo a baseline clinical skin exam and scheduled follow-up exams every 3 months. Photography of index A/DN and a standardized area of the posterior trunk, excisional biopsy of an A/DN, and peripheral blood sampling will be performed at baseline, 3 months, and 12 months. The primary endpoint is effect of sulforaphane *vs.* placebo on change in total area of pigmented nevocellular nevi on the posterior trunk at 12 months, calculated by Derma-AI image analysis software.[9] Secondary endpoints are number of posterior truncal nevi with moderate to significant changes in area, changes in A/DN features/area, and assessment of the safety/tolerability of sulforaphane. Exploratory endpoints include effects on circulating cytokine and chemokine levels assessed by multiplex technology, impact on A/DN immune cell infiltration by histopathology and immunochemistry, and evaluation of prespecified A/DN features at each timepoint. Outcome measures will be compared between arms over serial timepoints by Wilcoxon rank sum test. The study is open for enrollment with accrual goal of 120 patients. Research Sponsor: None.

TPS9612 Poster Session

A multicenter, randomized phase Ib trial to evaluate neoadjuvant immunotherapy combination of nivolumab alone or plus ipilimumab with the IL-2 superkine MDNA11 alone or with tocilizumab in patients with high-risk, surgically resectable melanoma: The NEO-CYT trial. First Author: Margaret Ottaviano, Istituto Nazionale Tumori IRCCS "Fondazione G. Pascale", Naples, Italy

Background: Neoadjuvant immunotherapy, administered upfront of surgery in patients with resectable stage III melanoma, has shown superior efficacy in recent trials compared to post-surgical adjuvant treatment, due to enhanced anti-tumor immunity when the tumor microenvironment is intact. A pre-operative regimen of 2 cycles of ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy (as per NADINA trial) results in substantially improved event-free survival. However, even with this regimen 41% of patients did not achieve a Major Pathologic Response (MPR), with 8% having a partial pathological response and 26.4% showing pathological non-response. Previous analyses have shown a 'cold' CD4-IL-2 signature being associated with no-response, which could be overcome by the addition of IL-2. MDNA11 is a long-acting engineered interleukin (IL)-2 albumin fusion protein, with enhanced affinity for IL-2 receptor β (IL-2Rβ/CD122) and no binding to IL-2Rα (CD25). This design enhances the stimulation of IL-2Rβ-expressing CD8+ T cells and NK cells whilst diminishing the activation of Tregs constitutively expressing the heterotrimeric receptor containing IL-2Rα. Thus, we hypothesize that MDNA11 combination with nivolumab +/- ipilimumab may further enhance clinical outcomes of neoadjuvant standard therapy. **Methods:** This is a phase Ib, prospective, open-label, randomised study where a 6- week neoadjuvant phase is followed by a 7-week surgery/post-surgery phase and a 49-week adjuvant phase as per clinical practice. The study population will include adult patients of either sex aged ≥ 18 years with surgically resectable stage IIIB/C/D cutaneous melanoma. Twenty patients will be enrolled in each arm for a total of up to 80 patients. The ARM A is the control one with Ipilimumab 80 mg plus Nivolumab 240 mg administered every 3 weeks for 2 cycles as for NADINA trial; the ARM B includes Nivolumab 240 mg every 3 weeks for 2 cycles plus MDNA11 at 30 μg/kg on week 0 followed by MDNA11 at 60 μg/kg on week 2 and week 4; the ARM C includes Ipilimumab 80 mg plus Nivolumab 240 mg administered every 3 weeks for 2 cycles plus MDNA11 at 30 μg/kg on week 0 followed by MDNA11 at 60 μg/kg on week 2 and week 4; the ARM D adds tocilizumab 4 mg/Kg on week 0 at the same schedule of the ARM C. The study's primary endpoint is the Major Pathologic Response (MPR) rate at surgery, defined as ≤10% viable tumor in the treated tumor bed. Co-primary endpoints include the incidence, severity, and duration of treatment-related adverse events, particularly immune-related, as per CTCAE v5.0. Health-related quality of life will be analyzed using longitudinal models. Exploratory analyses will investigate biomarker associations with outcomes to generate hypotheses. Clinical trial information: 2024-519010-31-00. Research Sponsor: None.

TPS9613 **Poster Session**

A phase 2 study of neoadjuvant nivolumab + relatlimab versus nivolumab in patients with resectable high-risk basal cell carcinoma. First Author: Soo J. Park, Division of Hematology and Oncology, University of California San Diego, San Diego, CA

Background: The high response rate of neoadjuvant anti-PD-1 has changed the management of locally advanced cutaneous squamous cell carcinoma. However, little is known about the benefit of neoadjuvant immunotherapy for basal cell carcinoma (BCC). Anti-PD-1 is approved second line for advanced BCC where it has modest response rates compared to the first line setting. High LAG-3 expression within the BCC tumor microenvironment may function as a subdominant checkpoint to synergize with anti-PD-1. The current randomized prospective multicenter phase 2 trial evaluates the safety and efficacy of neoadjuvant nivolumab (anti-PD-1) + relatlimab (anti-LAG-3) versus nivolumab alone in resectable high-risk BCC. **Methods:** This multicenter study conducted across the University of California Melanoma and Skin Cancer Consortium will enroll up to 30 patients with resectable high-risk BCC. High-risk BCC is defined by size 2.0 cm or greater in the head and neck region or 4.0 cm or greater for the trunk and extremities. All patients must have surgically resectable disease that is at increased risk for cosmetic disfigurement, functional defects, poor oncologic control, or anticipated to require skin grafting or free flap reconstruction. Patients must also be checkpoint and hedgehog inhibitor naïve with ECOG performance status of <2. Key exclusion criteria include recent radiation therapy and any prior history of myocarditis. Patients will be randomized in 2:1 fashion to receive nivolumab 480 mg + relatlimab 160 mg or nivolumab 480 mg IV every 4 weeks for up to 4 doses. Patients may forgo surgery and continue beyond 4 doses for up to 1 year in cases of ongoing clinical benefit. Tumor tissue and peripheral blood will be interrogated for immune cell subsets and checkpoint expression before and after neoadjuvant treatment. The trial's primary endpoint is the combined rate of pathological complete response, major pathologic response, and clinical response following neoadjuvant therapy with secondary endpoints including surgical de-escalation, safety, duration of response, and recurrence-free survival. This trial uses a Simon's minimax two-stage design for the nivolumab + relatlimab cohort. Eleven patients will be enrolled in the first stage. If $\geq$2 patients respond to nivolumab + relatlimab, the study will continue enrollment for a total of 20 patients. This design yields a type I error rate of 0.1 and power of 0.8. This study was approved by UC San Diego's Institutional Review Board; approval number is 810617. Trial Registration NCT06624475. Clinical trial information: NCT06624475. Research Sponsor: Bristol Myers Squibb.

TPS9614 **Poster Session**

Spino-RT: A multicenter, randomized controlled phase III study of adjuvant radiotherapy versus surveillance in patients with cutaneous squamous cell carcinoma (cSCC) at high risk of recurrence. First Author: Adeline Pêtre, Centre Léon Bérard, Lyon, France

Background: cSCC is the second most common skin cancer, predominantly affecting elderly individuals. Most cSCCs are diagnosed at an early stage and cured with surgery. Recurrences are usually detected during routine clinical examinations or imaging (lymph-node ultrasound, cervicothoracic CT scan). In patients considered at high-risk, local recurrence rates may reach up to 30%. To date, no randomized trial has established the optimal management of cSCCs at high risk of recurrence after complete resection, and indications for adjuvant radiotherapy are only based on local practices or retrospective studies showing variable and contradictory results. **Methods:** This ongoing randomized phase III trial (NCT06692556) compares the efficacy and safety of two commonly used strategies (adjuvant radiotherapy versus surveillance) in patients with cSCC at high risk of recurrence. Key eligibility criteria include age $\geq$ 18 years, histologically confirmed localized cSCC, complete surgical resection and high-risk of recurrence, defined as: 1) microscopic peri nerval involvement (PNI) with or without one additional risk factor, or 2) the presence of two or three risk factors (excluding microscopic PNI): immunosuppression, tumor diameter $>$ 20 mm, specific location (lip/ear/temple), deep invasion (thickness $>$ 6 mm or invasion beyond the subcutaneous fat), poor differentiation or desmoplasia. The primary endpoint is recurrence free-survival, defined as the time from the date of randomization to the date of first documented relapse (local, regional or metastatic) or the date of death. Secondary endpoints include local and metastatic recurrence-free survival, overall survival, safety and quality of life (EORTC QLQ-C30 and QLQ-ELD14). Exploratory objectives include progression-free survival after treatment for local recurrence in the surveillance arm. A total of 120 events will provide 80% power to detect a significant improvement of the recurrence-free survival in favor of the radiotherapy arm (HR=0.6) at a 2-sided alpha risk of 5%. Considering a two-years recurrence-free survival rate of 60% in the control arm, an accrual period of 18 months, 36 months follow-up for the last patient, and 10% of non-evaluable patients, a total of 266 patients is required (133 par arm). Since the start of recruitment (February 2025), 38 patients have been randomized. 35 French health institutions will contribute to recruitment. Clinical trial information: NCT06692556. Research Sponsor: Ligue Nationale contre le Cancer; 2023.

TPS9615 **Poster Session**

Phase 2 study of ivonescimab in patients with cutaneous squamous cell carcinoma. First Author: Neal Akhave, Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer. In the setting of unresectable locally advanced or metastatic disease, checkpoint inhibitors are standard of care and are associated with robust response rates and durable disease control. However, in those who do not respond or progress on immunotherapy, there are limited available standard therapies. Ivonescimab is a tetravalent bispecific antibody targeting programmed cell death protein 1 (PD-1) and vascular endothelial growth factor A (VEGF-A) that has shown promising activity in multiple tumor types. VEGF-mediated activities include driving angiogenesis creating a tortuous tumor vasculature and decreasing effector T-cells within the tumor microenvironment. Herein, we hypothesize that dual targeting of PD-1 and VEGF-A may overcome resistance to checkpoint inhibitors and extend the benefit of immunotherapy in CSCC. **Methods:** This phase 2, single-arm study will enroll up to 24 patients and will be conducted using a Bayesian optimal phase 2 (BOP2) design. Prespecified activity goal for the first stage of accrual was met; second stage accrual began in January 2026. Patients will receive Ivonescimab 20mg/kg intravenously every 3 weeks until progression, death, or intolerance. The main inclusion criteria include unresectable locally advanced or metastatic CSCC that is refractory to prior checkpoint inhibitors, Eastern Cooperative Oncology group performance score of 0-1, and measurable disease by RECIST version 1.1. Primary exclusion criteria comprise prior severe immunotherapy-associated toxicities, prior organ transplant, or major blood vessel invasion. There are no limits on lines of therapy. Primary objective and endpoint is objective response rate in CSCC. Key secondary endpoints include duration of response, disease control rate, progression free survival, and safety. Additional exploratory objectives include evaluating predictive biomarkers of treatment response or resistance utilizing a mandatory biopsy performed both pre-and on-treatment, with correlatives including whole exome sequencing, RNA sequencing, multiplex IHC. Active recruitment and enrollment are ongoing at The University of Texas MD Anderson Cancer Center, Houston, Texas. Copyright © 2026 AACR. Originally presented at AACR 2026. Reprinted with permission. Clinical trial information: NCT06567314. Research Sponsor: Summit Therapeutics.

TPS9616 **Poster Session**

A feasibility study of tumor-infiltrating lymphocytes (TIL) in patients with cutaneous squamous cell carcinoma and Merkel cell carcinoma after anti–PD-1 therapy. First Author: Karam Khaddour, Dana-Farber Cancer Institute, Boston, MA

Background: Tumor infiltrating lymphocyte (TIL) therapy is an autologous cellular therapy isolated from a patient's tumor. Clinical data demonstrated that TIL therapy in heavily pretreated melanoma patients yielded an objective response rate (ORR) in 30% of patients with 5-year overall survival (OS) of approximately 20%. TILs were approved by the FDA in February 2024 for the treatment of metastatic or unresectable melanoma that have progressed on anti-PD-1 therapy and BRAF+MEK inhibitors (in patients with *BRAFV600* mutation). Non-melanoma skin cancers, including cutaneous squamous cell cancer (CSCC) and Merkel cell cancer (MCC), share biologic features with melanoma, including an "inflamed" tumor microenvironment and high responsiveness to anti-PD-1 therapy. However, approximately, a third of patients will experience disease progression after anti-PD-1 therapy or will discontinue treatment due to toxicity and subsequently experience disease progression. Given the overlap between melanoma and CSCC/MCC, we hypothesize that TIL therapy may induce immune response against non-melanoma skin cancers. Because some of these tumors are superficial and are often ulcerated and can contain polymicrobial contamination, this trial will also assess the feasibility of TIL production in this unique patient population, alongside its safety and efficacy. **Methods:** Ten patients with CSCC (Cohort A) and 4 patients with MCC (Cohort B) adults will be eligible for TIL if they have disease progression after anti-PD-1 therapy. Eligible patients should have adequate organ function and be able to receive dose-reduced non-myeloablative lymphodepletion (NMA-LD) and interlukin-2 (IL-2). Following tumor harvest and TIL manufacturing, patients will receive NMA-LD including cyclophosphamide (30 mg/kg on days −5 and −4), and fludarabine (25 mg/m2 on days −5 to −1). Subsequently, patients will receive TIL on day 0 followed by IL-2 (600,000 IU/kg) for up to 6 doses. The primary objective is to evaluate feasibility and safety of TIL production and administration in cohorts A and B (defined by successful tumor harvest that leads to a TIL product that contains $\geq$ 1 x 10^9 cells, administration of NMA-LD, infusion of TIL therapy and complete at least 1 dose administered of IL-2). Secondary objectives include ORR, progression-free survival, duration of response, OS and correlative studies. Within Cohort A, efforts will be made to achieve an approximately equal distribution of ulcerated and non-ulcerated lesions. To maintain this balance, ulceration status will be monitored throughout the enrollment process, and eligibility criteria may be modified as necessary to ensure proportional representation of each subtype. Clinical trial information: NCT07288073. Research Sponsor: Iovance.

10000 **Oral Abstract Session**

Tisagenlecleucel (tisa-cel) in pediatric and young adult patients with high-risk (HR) B-cell acute lymphoblastic leukemia (B-ALL) and minimal residual disease (MRD) at the end of frontline consolidation (EOC). First Author: Shannon L. Maude, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Persistent MRD portends a high risk of relapse in B-ALL. In the Children's Oncology Group (COG) AALL0232 frontline trial for HR B-ALL, children and young adults with MRD ≥0.01% at the EOC had poor 5 y disease-free survival (DFS) of 39% (Borowitz, *Blood*, 2015). We report the primary analysis of a phase 2 trial, in collaboration with COG, of tisa-cel, a CD19-directed chimeric antigen receptor (CAR) T cell therapy, in this very high-risk (VHR) population. **Methods:** COG AALL1721/CASSIOPEIA (NCT03876769) is a global (34 sites in the US/Canada, 10 sites in EU/UK) phase 2 study of tisa-cel in patients (pts) aged 1-25 y with National Cancer Institute HR B-ALL and persistent MRD ≥0.01% by flow cytometry at EOC. A single dose of tisa-cel ($0.2\text{-}5\times10^6$ CAR+ T cells/kg for pts ≤50 kg or $0.1\text{-}2.5\times10^8$ CAR+ T cells for pts >50 kg) was given after standard lymphodepleting chemotherapy. Reinfusion was available for pts with B-cell recovery within 6 mo and/or MRD ≥0.01% at any time. Primary endpoints were 4 y overall survival (OS) and 5 y DFS, defined as time from first infusion to morphologic relapse, secondary malignancy, or death, without censoring for new anticancer therapy, including stem cell transplant (SCT). Secondary endpoints included DFS with censoring, MRD negative rate (MRD <0.01%) at 3 mo, and safety. **Results:** The primary analysis included 121 infused pts; 1 pt was not infused due to adverse event. Median age was 14 y (range: 1-24 y), 67% were male, 6% had trisomy 21. As of August 20, 2025, median time from infusion to last follow-up was 38 mo. OS at 4 y was 85% (95% CI: 76-90%). DFS (95% CI) at 3 y and 5 y without censoring for new therapy was 71% (61-79%) and 64% (53-73%). DFS (95% CI) at 3 y and 5 y with censoring was 69% (55-79%) and 62% (46-74%). MRD negative rate at day 29 and 3 mo post infusion was 95% and 86%. Relapse occurred in 31 pts, of which 7 occurred after new therapy/SCT. 41 (34%) pts received a second infusion. 58 (48%) pts received new anticancer therapy/SCT without prior relapse. Median duration of B-cell aplasia was 5.6 mo. Probability (95% CI) of ongoing remission and B-cell aplasia at 3, 6, and 12 mo was 76% (67-83%), 47% (38-56%), and 31% (23-41%). Following first infusion, cytokine release syndrome (CRS) occurred in 37% (grade ≥3, 2%), immune effector cell–associated neurotoxicity syndrome (ICANS) in 3% (grade ≥3, 1%). There were 18 deaths, all post new therapy/SCT and/or relapse. **Conclusions:** Durable remissions, with very low rates of severe CRS/ICANS, were achieved with tisa-cel in a VHR population with persistent MRD in frontline therapy, who historically have low 5 y DFS. Nearly 50% of pts received new anticancer therapy, including SCT, without prior relapse. Longer follow-up is needed to confirm 5 y DFS. Clinical trial information: NCT03876769. Research Sponsor: Novartis Pharmaceuticals.

10001 **Oral Abstract Session**

SPARTO: A phase I study of PD-1 inhibitor spartalizumab (PDR001) in combination with low dose of pazopanib in pediatric relapsed/refractory tumors. First Author: Jordane Chaix, CHU Bordeaux, Department of Paediatric Hematology and Oncology, Bordeaux, France

Background: The initial results of immunotherapy in children with refractory/relapsed tumors have been disappointing. Modulation of angiogenesis with anti-VEGF may enhance immunotherapy penetration and promote lymphocytes T infiltration. In this context, we propose combining immunotherapy with low doses of pazopanib to enhance therapeutic efficacy in pediatric patients. **Methods:** Pediatric part of the SPARTO trial (NCT05210413) was a multicenter, open-label, dose-finding phase I clinical trial conducted in France. Pediatric patients with recurrent/refractory solid tumors were eligible to receive pazopanib at a fixed low dose of 225 mg/m²/d combined to anti-PD1 spartalizumab at three candidate doses (2, 3, 4 mg/kg/q4w). Dose-finding was guided by Bayesian Optimal Interval design based on dose-limiting toxicities (DLTs) in cycle 1, with a target toxicity level of 25%. Recommended phase 2 dose (RP2D) was determined on the basis of DLTs and blood exposure of pazopanib and spartalizumab. Toxicities were evaluated using CTCAE v5.0 and responses were evaluated by clinical and radiologic assessment (RECIST1.1 or RANO for brain tumors). **Results:** From May 2022 to June 2025, 41 patients were enrolled at 8 sites (median age: 13.9y; range: 7-25). Among 39 evaluable patients, 4 DLTs occurred in 1/9 patients at 2 mg/kg of spartalizumab (DL0), 1/6 patients at 3 mg/kg (DL1) and 2/24 patients at 4 mg/kg (DL2). Three patients experienced macrophagic activation syndrome (grade 3 at DL0 and DL2, grade 4 at DL1) and one patient experienced liver enzymes increase grade > 3 at DL2. A total of 58 grade 3–4 adverse events were reported in 26 patients, predominantly hepatic and hematologic toxicities. Median area under the serum concentration-time of spartalizumab from 0 to 28 days post-infusion at cycle 1, were 12.9 g.h/L (IQR 10.7-15.8), 17.2 g.h/L (IQR 15.5-20.0) and 19.5 g.h/L (IQR 16.9-23.6), respectively for DL0, DL1 and DL2. Median trough concentration of pazopanib was 23.1 mg/L (IQR 15.8-32.1). DL2 was identified as the RP2D. Of 40 evaluable patients, one patient with osteosarcoma presented complete response, 4 had partial responses (2 osteosarcoma, 1 chordoma, 1 carcinoma) and 8 had stable disease (including 4 for more than 4 months). The median duration of treatment was 68 days (IQR 57–106); one patient completed 24 cycles and two were still on treatment at data cut-off (at cycle 16 and cycle 23). **Conclusions:** Spartalizumab combined with low dose pazopanib was well tolerated leading to a RP2D of 4 mg/kg/q4w. The regimen shows evidence of anti-tumor activity in pediatric sarcoma, especially osteosarcoma. Further investigations are ongoing to select the subpopulation who could benefit of this combination. Funded by INCa and ARC Foundation (call for project CLIP2 "Novartis Innovative Molecules, INCa-ARC_14820"). Clinical trial information: NCT05210413. Research Sponsor: Institut National du Cancer (INCa) et Fondation ARC.

10002 **Oral Abstract Session**

Targeting metastatic sites with radiation and outcomes in high-risk pediatric rhabdomyosarcoma. First Author: Rachel Mendelson, St. Jude Children's Research Hospital, Memphis, TN

Background: Outcomes for pediatric patients with metastatic rhabdomyosarcoma (RMS) remain poor despite therapy intensification and novel agents. RMS13 (NCT01871766) was a phase II prospective multicenter trial evaluating a response-based approach to metastatic site radiotherapy (RT). We report outcomes related to metastatic disease management in this high-risk (HR) population. **Methods:** Event-free survival (EFS) and metastatic site control were analyzed for HR patients treated with interval compressed chemotherapy, risk-adapted RT to primary and metastatic site, and maintenance therapy. EFS was defined from therapy start to relapse, progression, death or last follow-up. Metastatic RT was delivered between interval-compressed and maintenance therapy for non–bone marrow metastatic sites without complete response (CR). RT omission criteria included PET negativity, lesion size <1 cm, or complete surgical resection with negative margins. Metastatic RT used protons: 25 Gy in 5 or 50.4 Gy in 28 fractions, by lesion size. Primary tumor control consisted primarily of proton RT, with limited use of surgery plus adjuvant RT. **Results:** From 2015 to 2020, 39 HR patients were enrolled (median age 9.5 years). Most patients were FOXO1 fusion–positive (64%), had nodal involvement (74%), and an Oberlin score >1 (67%). Median follow-up was 23.1 months overall (78.5 months for non-progressors). Five-year EFS was 31.6% (95% CI, 19.7-50.6%), differing by Oberlin score >1 – 16.2% (95% CI, 6.6–39.8%), ≤1 - 61.5% (95% CI, 40-94.6%). Twenty-six patients relapsed: 22 had distant failure (DF), 6 had local failure (LF), and 2 had both DF and LF. The 5-year cumulative incidence of LF was 14.4% (95% CI, 5–28), and 54% for DF (95% CI, 36–69), establishing DF as the predominant pattern of failure. Twenty-six patients reached the protocol window for metastatic-site RT (weeks 47–54): 11 soft-tissue metastases, 6 bone, 8 both, and 1 bone marrow only, with a 5-year EFS of 42.3% (95% CI 23.3-61.3%). Among 21 patients achieving CR at metastatic sites without RT, 5-year EFS was 38.1% (95% CI 17.3–58.9%), and cumulative incidence of any DF was 57.1% (95% CI 35.9–78.3%). Seven patients (33%) recurred at initially involved metastatic sites, primarily soft tissue. In-site recurrence occurred in 7/17 (41%) non-irradiated soft-tissue sites versus 1/12 (8%) bony sites. Only one recurrence occurred among irradiated soft-tissue sites. **Conclusions:** Soft-tissue metastatic sites in CR that were not irradiated had high recurrence rates, while bony sites achieved durable control without RT. Future trials should consider consolidative RT for soft-tissue metastases regardless of response in HR RMS. Clinical trial information: NCT01871766. Research Sponsor: None.

Recurrence by metastatic site.

	CR, no RT (N)	Recurrence, non-RT, N(%)	PR, RT (N)	Recurrence, No RT, N (%)
Bone metastases (n=14)	12	1 (8)	2	0
Soft-tissue metastases (n=19)	17	7 (41)	2	1 (5.9)

CR, complete response; PR, partial response; RT, radiotherapy.

10003 **Oral Abstract Session**

Digital health intervention for comorbid insomnia and neurocognitive impairment in adult survivors of childhood cancer: Results from a randomized clinical trial. First Author: Tara M. Brinkman, St. Jude Children's Research Hospital, Memphis, TN

Background: Survivors of childhood cancer are at risk of developing both insomnia and cognitive impairment, which may persist decades following treatment. Cognitive behavioral therapy for insomnia (CBT-I) is the gold-standard treatment for insomnia, yet the impact of improved sleep on comorbid cognitive dysfunction has not been evaluated in survivors. **Methods:** Survivors enrolled in the Childhood Cancer Survivor Study (CCSS; median age 44 [range 23-66] years; 73% female; 37% leukemia, 23% lymphoma, 18% sarcoma, 14% Wilms, 8% neuroblastoma) with comorbid insomnia and neurocognitive impairment were randomized 1:1 to 9-week digital CBT-I vs. online sleep education (SE). Insomnia severity index (ISI), neurocognitive problems (CCSS-Neurocognitive Questionnaire [NCQ]), emotional health (Patient Health Questionnaire/Generalized Anxiety Disorder), and quality of life (PROMIS) were measured at baseline and 9-week and 6-month follow-ups. Intent-to-treat models estimated treatment effects for ISI (mean difference [MD] between CBT-I and SE of change from baseline to follow-ups) adjusted for age, sex, and cranial radiation. Cohen's *d* estimated effect size. Additional models estimated treatment effects on secondary outcomes and mediation by improved ISI. **Results:** 439 of 541 randomized survivors completed baseline assessments and started the intervention (82% CBT-I; 81% SE); 353 of those completed 9-week (76% CBT-I; 85% SE) and 305 completed 6-month (61% CBT-I; 78% SE) post-intervention assessments. Survivors randomized to CBT-I reported improved ISI scores at 9 weeks (MD=-2.4[95%CI -3.4, -1.4]; Cohen's *d*=0.50) and 6 months post-intervention (MD=- 3.5[-4.6, -2.4]; *d*=0.72) vs. SE (both p's<0.001). Survivors randomized to CBT-I reported greater improvement in memory (9wks: MD=-0.3SD [-0.5, -0.1], p=0.003; 6mos: MD=-0.5SD [-0.7, -0.3], p<0.001) and task efficiency (9wks: MD=-0.3SD [-0.5, -0.1], p=0.003; 6mos: MD=-0.5SD [-0.7, -0.3], p<0.001) vs. SE. Effects of CBT-I on cognitive function were mediated by improved ISI scores (42-65% mediated, all p's <0.001). Insomnia responders (those who reported a change in ISI from >8 [mild to severe insomnia] to <8 [no insomnia]) also reported improved quality of life (9wks: mental beta=1.7[95%CI 0.4, 3.0], physical=2.1 [1.0, 3.1]; 6mos: mental=3.5 [2.0, 5.0], physical=3.3 [2.1, 4.5]), and emotional health (9wks: anxiety beta=-1.3 [-2.1,-0.5], depression=-1.8[-2.6, -1.0]; 6mos: anxiety=-1.8 [-2.7, -0.8], depression=-2.4 [-3.4, -1.4]). **Conclusions:** Use of a fully automated digital health treatment of insomnia confers immediate and long-term benefits to comorbid cognitive impairment and quality of life in survivors of childhood cancer. Given its efficacy and availability, digital CBT-I should be considered for the behavioral treatment of insomnia and comorbid symptoms in survivors. Clinical trial information: NCT04317742. Research Sponsor: National Cancer Institute; R01 CA239689.

10004 **Oral Abstract Session**

The ASPIRES study: Promoting colorectal cancer surveillance in childhood cancer survivors—A randomized intervention trial from the Childhood Cancer Survivor study (CCSS). First Author: Tara O. Henderson, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

Background: Survivors of childhood cancer exposed to abdominal, pelvic, spinal, or total-body radiotherapy (RT) are at elevated risk for subsequent treatment-related colorectal cancer (CRC). However, adherence to recommended CRC surveillance screening is only ~37%, leaving survivors vulnerable to potentially preventable cancer. Innovative interventions are needed to improve screening uptake. **Methods:** We conducted a three-arm randomized controlled trial comparing mHealth-based patient activation (PA) and patient plus primary care provider activation (PA+PCP) with a control arm that received a survivorship care plan with screening recommendations. Nested within the CCSS, eligible participants were 5-year survivors diagnosed before age 21 who had received abdominal, pelvic, spinal, or total-body radiotherapy and were not up to date with surveillance. Participants (n = 300) were randomized in a 1:1:1 ratio, stratified by age at enrollment (30–44 vs $\geq$45 years). The primary outcome was the proportion of participants who completed CRC surveillance within 12 months. Each intervention arm was compared with the control in an intent-to-treat analysis using the Cochran-Mantel-Haenszel test (α = 0.025/comparison). In secondary analyses, logistic regression, adjusted for age at enrollment, was used to estimate odds ratios (ORs) to identify moderators of the relationship between the intervention (grouping PA with PA+PCP) and the outcome. **Results:** Participants were 45% male and 8% non-white, with a median age of 41 years (range: 30 – 67 years). At 12 months, survivors in the PA group were significantly more likely than controls to have completed surveillance screening: 32/99 (32%) vs 14/102 (14%) [p = 0.003]. Surveillance screening completion was also higher in the PA+PCP group than in controls, but this difference did not meet the prespecified α (0.025): 26/99 (26%) vs 14/102 (14%) [p = 0.041]. Secondary analyses suggested the intervention was more effective among survivors without a chronic health condition (without: OR = 3.6; 95%CI 1.5, 10.1 vs. with: OR=1.9; 95%CI 0.8, 4.8) and with $\leq$ high school education ($\leq$ high school OR=4.4; 95%CI 1.3, 20.2 vs. $>$ high school OR=2.2; 95%CI 1.1, 4.7). **Conclusions:** An mHealth-based patient activation intervention more than doubled adherence to CRC surveillance compared with a survivorship care plan with surveillance recommendations alone. While patient plus PCP activation showed improvement, adding PCP activation did not confer a significant benefit compared with the control. Intervention effectiveness varied across subgroups, underscoring the importance of tailored approaches. As digital technologies continue to advance, mHealth strategies offer a promising and scalable pathway to improving surveillance screening among high-risk survivors of childhood cancer. Clinical trial information: NCT05084833. Research Sponsor: National Cancer Institute R01CA255269; National Cancer Institute U24CA55727.

10005 **Oral Abstract Session**

Prediction of anthracycline-related cardiomyopathy in long-term childhood cancer survivors: The power of survivor-specific polygenic risk score—A COG-ALTE03N1 study. First Author: Noha Sharafeldin, Division of Hematology & Oncology, Heersink School of Medicine, The University of Alabama at Birmingham, Birmingham, AL

Background: Cardiomyopathy is a major dose-limiting toxicity of anthracyclines in the treatment of childhood cancer. Inter-patient variability in cardiomyopathy risk suggests an underlying genetic susceptibility, providing an opportunity to identify survivors at high risk and enable personalized interventions. We evaluated whether addition of a curated survivor-specific PRS for anthracycline-related cardiomyopathy (PRS-S) or general population PRSs for heart failure (PRS-G) to a clinical model improved cardiomyopathy risk classification in CCS. **Methods:** In a matched case-control study of CCS (COG-ALTE03N1: matched on cancer diagnosis and year of diagnosis; controls followed at least as long as cases), anthracycline-exposed non-Hispanic White CCS were randomly split (80/20) into training (cases: n=106; controls: n=180) and test (cases: n=27; controls: n=44) sets. From $>$100 published genetic variants associated with anthracycline-related cardiomyopathy, we selected a prioritized list of 8 independently validated variants with demonstrated biologic plausibility (reduced drug efflux [*ABCC2*], altered drug metabolism [*SLC22A17, SLC28A3, UGT1A6*], reduced antioxidant capacity [*HAS3*], impaired TOP2B-mediated DNA damage response [*RARG*], alternative splicing of *TNNT2*, reducing cardiac pumping efficiency [*CELF4*], and cardiac profibrotic pathway [*ROBO2*]) to construct a standardized weighted survivor-specific PRS (PRS-S). Area under the receiver operating characteristic curve (AUC) was used to compare the performance of a clinical model (age at cancer diagnosis, sex, anthracycline dose, chest radiation (Y/N)) *v* combined models incorporating either PRS-S or PRS-Gs. All models included PRS $\times$ anthracycline dose interaction terms and adjusted for matching variables. Risk scores derived from training model were applied to the test set for risk classification. **Results:** Median age at cancer diagnosis was 7.1y for cases and 8.6y for controls. Cases received higher anthracycline doses (median: 330 *v* 240 mg/m^2) and were more likely to have received chest radiation (24.8% *v* 19.2%). In the test set, PRS-S combined model significantly outperformed the clinical model ($AUC_{clin+PRS8}$=0.70, 95%CI=0.57-0.82 *v* AUC_{clin}=0.63, 95%CI=0.50-0.76, p=0.04); 85% of all cases were classified as high risk and the adjusted negative predictive value was 95.1%. Importantly, none of the 11 PRS-G combined models (AUCs: 0.60-0.65) out-performed the clinical model. **Conclusions:** Integrating a survivor-specific PRS derived from a parsimonious set of biologically plausible genetic variants with readily-available clinical factors informs cardiomyopathy risk classification in CCS and provides an opportunity to develop personalized screening recommendations and behavioral/therapeutic interventions. Research Sponsor: U.S. National Institutes of Health; UG1CA189955; U.S. National Institutes of Health; U10CA180886; U.S. National Institutes of Health; U10CA180899; St Baldrick's Foundation.

10006 **Rapid Oral Abstract Session**

Primary breast malignancies in adolescents and young adults: The MD Anderson Cancer Center experience. First Author: Samanta Catueno, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Primary malignancies of the breast rarely affect adolescents and are uncommon in young adults. Limited information is available about their clinicopathologic characteristics and outcomes. The 5-year overall survival (OS) for women with breast cancer, not including ductal carcinoma in situ, exceeds 90%. However, it remains unclear whether adolescents and young adults experience similar outcomes compared with older patients. **Methods:** We conducted a retrospective study of all patients aged 0–25 years with primary breast malignancies seen at MD Anderson Cancer Center between 2000 and 2024. Demographics, histology, staging, treatment, and outcome data were collected. Event-free survival (EFS) and OS were estimated using the Kaplan–Meier method. Log-rank test was used to analyze patient outcomes by histology. **Results:** A total of 110 patients were identified. Median age at diagnosis was 23.9 years (range, 15.7–25.5). Two patients were male, 44.9% were White, 27.7% Hispanic, and 15.9% Black. The most common tumor histology was invasive ductal carcinoma (n=83, 75.5%), followed by sarcoma and malignant phyllodes tumors (n=14, 12.7%), carcinoma in situ (n=7, 6.4%), and rare histologic subtypes (n=6, 5.5%). Family history of breast cancer was present in 53.6% of patients and ovarian cancer in 9%. Of 81 patients with germline genetic testing, 25 (30.9%) had a cancer predisposition syndrome: Li-Fraumeni (n=9), BRCA1 (n=8), BRCA2 (n=4), ATM (n=2), other (n=2). Eleven patients (10%) had metastatic disease at presentation to bone, lung, distant lymph nodes, and liver. Among the 96 carcinoma cases, 36 (37.5%) were estrogen or progesterone receptor-positive and HER2-negative; 25 (26%) were HER2+, and 32 (33%) were triple-negative. Of the 110 patients, 69 (62.7%) received neoadjuvant chemotherapy, 37.6% of whom achieved a pathologic complete response, and 46.3% a partial response. Most patients (92.7%) had surgery (mastectomy 87.2% or lumpectomy 9.8%), 67.2% received radiotherapy, and 25.4% targeted therapy. Following treatment, 56 (51%) patients received adjuvant endocrine therapy. The 5-year EFS and OS for the cohort were 30% (95% CI, 22.6-39.9) and 71.8% (95% CI 62.9-82), respectively, and are presented by histology in the table. EFS (p=0.023) but not OS (p=0.36) was associated with histologic type. **Conclusions:** Primary breast malignancies in adolescents and young adults have distinct characteristics with a high frequency of family history and genetic predisposition syndromes and appear to be associated with lower survival compared with breast cancer in older patients. Research Sponsor: None.

Histology	No. of patients	5-year EFS (%) (95% CI)	5-year OS (%) (95% CI)
Invasive ductal carcinoma	83	31.3 (22.8, 43.1)	68 (57.9, 80)
Sarcoma and malignant phyllodes tumors	14	28.6 (12.5, 65.4)	82.1 (62.1, 100)
Carcinoma in situ	7	42.9 (18.2, 100)	100 (100, 100)
Rare histologic subtypes	6	NA	100 (100, 100)

10007 **Rapid Oral Abstract Session**

Characteristics and survival of 4N and non-4N metastatic neuroblastoma across treatment eras: A report from the International Neuroblastoma Risk Group Task Force. First Author: Michael Mitchell, The University of Texas Dell Medical School, Austin, TX

Background: Patients with metastatic neuroblastoma confined to distant lymph nodes (4N) were identified as a subgroup with superior outcomes to those with metastases to other sites. Over the past two decades, outcomes for high-risk neuroblastoma have improved from increasingly effective and intense therapy, while intermediate-risk patients have maintained excellent outcomes with biology and response-based therapy. We aimed to determine if 4N patients remained a favorable subgroup with contemporary therapy. **Methods:** Patients with International Neuroblastoma Staging System (INSS) stage 4 disease in the International Neuroblastoma Risk Group Data Commons diagnosed between 1990-2020 were evaluated. Those with metastases only to the distant lymph nodes were defined as 4N. All other patients were defined as non-4N. Treatment eras included: 1999 and prior, 2000-2009, 2010 and later which correspond to standardization of multimodal therapy, stem cell transplant, and anti-GD2 immunotherapy for high-risk patients. Differences between 4N and non-4N patients were assessed with chi-square, Wilcoxon rank sum, and t-tests. Five-year Kaplan-Meier estimates of survival with 95% confidence intervals and multivariable Cox proportional hazards modeling were used to evaluate event-free (EFS) and overall (OS) survival. **Results:** The analytic cohort included 107 4N and 5976 non-4N patients. There were no clinical differences between 4N and non-4N patients apart from unfavorable histology (74.2% [4N] versus 60.1% [non-4N]; p=0.02). 5-year EFS and OS were higher for 4N compared to non-4N patients (p=0.001 and 0.001, respectively). Though survival estimates for 4N were higher in each era, the difference was not statistically significant for patients diagnosed from 2000-2009 nor 2010 and beyond; (1999 and prior: EFS 58.7% (40.9-72.7%) versus 31.8% (29.7-33.9%) p=0.001; OS, 66.2% (48.1-79.3%) versus 37.9% (35.7-40.1%) p=0.002, 2000-2009: EFS, 47.9% (34.0-60.5%) versus 36% (34.1-37.9%) p=0.179; OS, 55.4% (40.7-67.8%) versus 45.1% (43.1-47.1%) p=0.122, and 2010 and later: EFS, 63.6% (29.7-84.5%) versus 42.8% (39.9-45.6%) p=0.178; OS, 71.6% (35.0-89.9%) versus 52.3% (49.2-55.3%) p=0.207. Log-rank calculations may have been underpowered in part due to small sample sizes (n=39, 56, and 12) of each 4N subgroup, respectively. 4N patients had superior EFS (HR=0.48; p=0.0004) and OS (HR=0.49; p=0.0009) in a model which included age, *MYCN*-amplification status, treatment era, ferritin, and LDH. A sensitivity analysis using only high-risk patients age $>$18 months yielded similar results. **Conclusions:** Patients with stage 4N neuroblastoma are a rare subgroup which appears to continue to have favorable outcomes with contemporary therapy. Additional studies to identify opportunities to reduce therapy intensity for this subgroup are warranted. Research Sponsor: None.

10008 **Rapid Oral Abstract Session**

Real-world experience of a pediatric precision oncology protocol utilizing paired somatic and germline sequencing at a single institution: Interim analysis. First Author: Joshua Goldman, C.S. Mott Children's Hospital/ University of Michigan, Ann Arbor, MI

Background: While most pediatric oncology patients are cured with upfront therapy, outcomes for patients with metastatic and relapsed/refractory disease remain poor. Salvage therapy is toxic and has marginal success rates, necessitating novel, personalized approaches. We established our pediatric precision oncology program based on integrative clinical sequencing (ICS) in 2012 and present an interim outcomes analysis of this single institution cohort. **Methods:** Pediatric and AYA oncology patients (age 0-25 years) underwent paired somatic and germline sequencing, including whole exome and transcriptomic analysis. Results were annotated with longitudinal clinical data extracted from the medical record using the NCI-supported tool EMERSE, which has been enhanced by the addition of a beta version of a large language models (LLM) integrated "Chatbot" to implement more efficient data abstraction from clinical notes. **Results:** Of the 1000 patients enrolled, 925 (92.5%) were sequenced successfully. We present interim analysis of the first 435 patients. Within this interim cohort, 233 (53.56%) of patients were male and 79.8% were non-Hispanic white. Hematologic malignancies accounted for 110 (25.3%) diagnoses, brain tumors 75 (17.2%), and non-brain solid tumors 250 (57.5%). ICS succeeded for 400/435 (92.0%) patients. Overall, 471 actionable alterations (AA) were discovered in 266 (66.5%) patients (mean 1.77 AA/patient). These included 62 actionable germline alterations in 60 patients (15%). There were 195 single nucleotide variants (SNV) in 142 patients, 69 gene fusions in 62 patients, and 145 copy number alterations (CNA) in 92 patients. Actionable findings guided the use of targeted therapies (TT) supported by NCI-MATCH criteria in 116 patients (29.0%) with a total of 209 targeted therapies given (mean 1.80 /patient). Thirty-two patients (8.0%) enrolled on therapeutic clinical trials featuring an identified targeted therapy. Sixteen (4.0%) patients without AAs received 22 TTs based on clinician preference. Additionally, 166 patients (41.5%) did not receive TT despite at least one AA due to lack of availability of a suitable formulation, pursuit of alternative therapy, or death prior to therapy initiation. Repeat ICS (range 1-4) was completed for 115 patients (28.8%), among which 8 (7.0%) had additional AAs identified and 5 (4.4%) received TT based on repeat ICS. **Conclusions:** This study highlights the importance of ICS based precision oncology with 67% of patients having AAs and 29% receiving TTs. Analyses are ongoing to study the most frequently altered signaling pathways, frequency of targeted agents used, impact of ICS and TT on the clinical outcomes for these patients, barriers in receiving TT despite having AAs, role of longitudinal sequencing, and the impact of LLM based "Chatbot" on data extraction efficiency. Research Sponsor: U.S. National Institutes of Health; Hyundai Hope on Wheels; Children's Foundation of Michigan.

10009 **Rapid Oral Abstract Session**

Harnessing OMOP-CDM for multisite collaborations to measure cardiovascular risk factors and cardiovascular disease in the early survivorship period for children, adolescents, and young adults. First Author: David H. Noyd, University of Washington, Seattle, WA

Background: The Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) is an international effort to leverage data standards to cultivate multi-institutional collaborations and generate reproducible evidence using real-world data. Four institutions mapped their electronic health records data to the OMOP-CDM. Cardiovascular risk factors (CVRFs) and their impact on risk for cardiovascular disease (CVD) among survivors of childhood cancer merit further investigation into cardiotoxicity during the early survivorship period. **Methods:** Eligible patients from Seattle Children's with at least one condition contained within the ancestor concept "malignant neoplastic disease" (concept ID 443392) and an index date defined as the initial administration of a medication contained within the ancestor concept "antineoplastic agents" (concept ID 21601387) were included. Clinically computable phenotypes from OMOP-CDM data were constructed in alignment with the Common Terminology Criteria for Adverse Events (version 6.0) for hypertension, diabetes, obesity, and hyperlipidemia within one year of the index date. The primary outcome was CVD, defined as the incidence of cardiomyopathy, heart failure, atrial fibrillation, and ventricular arrhythmias within 1-5 years of the index data. **Results:** Among 1195 survivors, the incidence rate of any CVD from non-cardiotoxic therapy was 0.11 per 100-person-years (95% Confidence Interval 0.04-0.25), compared to 0.43 (95% CI 0.25-0.71) and 1.6 (95% CI 0.08-7.88) for survivors treated with cardiotoxic therapy and cardiotoxic therapy plus targeted or immunotherapy, respectively. Validation of results and sharing of coding for multi-site meta-analysis is ongoing. **Conclusions:** OMOP-CDM represents a feasible approach to explore CVRFs and CVD in the early survivorship period among contemporary cohorts treated with traditional cardiotoxic chemotherapy, targeted therapy, and immunotherapy. Research Sponsor: None.

CVD and CVRF among survivors.

	Non-cardiotoxic Chemotherapy N=677	Cardiotoxic chemotherapy N=493	Cardiotoxic and Targeted Immunotherapy N=25
Age (in years)	6.6 (5.1)	8.6 (5.3)	9.4 (4.9)
Cancer Type			
CNS	240 (35.5%)	0 (0.0%)	0 (0.0%)
Hematologic	267 (39.4%)	285 (57.8%)	23 (92.0%)
Solid Tumor	160 (23.6%)	208 (42.2%)	2 (8.0%)
Sex (Female)	310 (45.8%)	243 (49.3%)	10 (40.0%)
Race			
Asian	54 (8.0%)	36 (7.3%)	2 (8.0%)
Black/African American	22 (3.2%)	13 (2.6%)	0 (0.0%)
Hispanic	131 (19.4%)	101 (20.5%)	4 (16.0%)
White	351 (51.8%)	259 (52.5%)	14 (56.0%)
Other or Unknown	119 (17.6%)	84 (17.0%)	5 (20.0%)
CVRFs (<1 year)			
Hypertension	111 (16.4%)	103 (20.9%)	5 (20.0%)
Diabetes	100 (14.8%)	78 (15.8%)	8 (32.0%)
Hyperlipidemia	87 (12.9%)	61 (12.4%)	8 (32.0%)
Obesity	214 (31.6%)	143 (29.0%)	4 (16.0%)
CVD (1-5 years)			
Any	2 (0.3%)	12 (2.4%)	1 (4.0%)

10010 **Rapid Oral Abstract Session**

Association of neighborhood-level vulnerability with health behavior patterns in survivors of childhood cancer: A report from the St. Jude Lifetime Cohort (SJLIFE). First Author: Amy Berkman, St. Jude Children's Research Hospital, Memphis, TN

Background: Childhood cancer survivors face elevated risks for chronic health conditions and premature mortality. Engaging in healthy behaviors may mitigate these risks, yet neighborhood-level vulnerability may constrain survivors' ability to adopt or sustain them. **Methods:** Among survivors (n=3,303) and community controls (n=652) in SJLIFE, neighborhood-level vulnerability was measured using census tract level overall and domain-specific (i.e. socioeconomic status, household composition, minority status, housing type and transportation) Social Vulnerability Index (SVI) scores, with higher values indicating higher vulnerability, and the U.S. Department of Agriculture's persistent poverty measure. Health behaviors, including sedentary time/physical activity, smoking, alcohol, and illicit drug/marijuana use, were categorized as healthy, moderately unhealthy (1-2 unhealthy behaviors), and unhealthy ($\geq$3 unhealthy behaviors). Multinomial logistic regression evaluated associations between neighborhood-level vulnerability at enrollment and health behavior patterns at most recent evaluation among survivors, adjusted for sociodemographic and cancer treatment factors as determined by backward selection. Interaction models compared associations between survivors and controls. **Results:** Survivors were 53.1% male, 82.5% non-Hispanic White, with a median age of 31.0 years (interquartile range: 23.5 – 38.5) at health behavior assessment. The most common childhood cancer diagnosis was acute lymphoblastic leukemia (28.8%). Survivors in the highest vs. lowest SVI tertile had higher odds of reporting moderately unhealthy (Odds Ratio [OR]: 1.46, 95% Confidence Interval [95% CI]: 1.08 – 1.98) or unhealthy (OR: 1.70, 95% CI: 1.13 – 2.56) behavior patterns, compared to a healthy behavior pattern. Socioeconomic and housing type SVI domains drove these associations, with survivors in the highest tertiles more likely than those in the lowest to have an unhealthy rather than healthy behavior pattern (Socioeconomic OR: 1.55, 95% CI: 1.02 – 2.35; Housing type OR: 1.53, 95% CI: 1.03 – 2.27). Persistent poverty was associated with greater odds of a moderately unhealthy behavior pattern (OR: 1.70, 95% CI: 1.09 – 2.66) in survivors. Housing type vulnerability was associated with disproportionately higher odds of an unhealthy behavior pattern among survivors compared to controls (ratio of ORs: 2.80, 95% CI: 1.19 – 6.60). **Conclusions:** Neighborhood-level vulnerability was associated with higher likelihood of unhealthy behavior patterns in childhood cancer survivors with housing type vulnerability having a greater impact on health behaviors in survivors compared to controls. Effective interventions to improve survivors' health behaviors should incorporate neighborhood-level factors. Research Sponsor: National Cancer Institute; U01 CA195547; National Cancer Institute; P30 CA21765; American Lebanese-Syrian Associated Charities.

10011 **Rapid Oral Abstract Session**

Thematic game intervention as a novel psychosocial support to reduce sedation needs and anxiety in pediatric neuro-oncology patients during radiotherapy: A prospective cohort study (2020–2025). First Author: Fuqiang Zhang, Department of Oncology, Guangdong Sanjiu Brain Hospital, Guangzhou, China

Background: Pediatric neuro-oncology patients undergoing radiotherapy frequently require sedation/anesthesia due to severe anxiety (mYPAS $>$15 in $>$80% cases) and treatment non-compliance. Conventional psychosocial interventions show limited efficacy in reducing sedation dependence, which incurs costs and clinical risks (e.g., respiratory depression). **Methods:** A prospective cohort study (2020–2025) of 246 children (3–5 years) receiving varied radiotherapy regimens (average course: ~30 fractions). Non-randomized allocation with propensity score matching for age, tumor stage, and sedation history: 1. Intervention group (n=122): Structured game-based intervention ("Radiation Warrior Training Camp"). 2. Control group (n=124): Standard psychological support. Primary outcomes: mYPAS anxiety scores, sedation/analgesia usage, treatment compliance, and cost savings (calculated at ¥376/session). **Results:** Sedation avoidance rate : 0% in intervention group vs. 41.1% in controls (OR=0.08, 95% CI [0.03–0.22], p$<$0.001). mYPAS score (median): 8.5 [6.8–3] vs. 17.1 [14.2–19.8] (β=-7.9, [-9.5,-6.3], p$<$0.001). Cost savings: ¥5,512/patient (derived from 82% relative sedation reduction $\times$ 30 fractions $\times$¥376/session). Treatment duration deviation reduced by 29% (p=0.011).Key Findings: 1. 92% of intervention patients completed radiotherapy without sedation. 2. Dose-dependent efficacy: Anxiety reduction correlated with gameplay duration (r=-0.71). 3. Developmental gradient: 5-year-olds achieved 9.2-point mYPAS reduction vs. 6.5-point in younger children. **Conclusions:** Game intervention eliminated sedation needs in 92% of patients, reducing anxiety by 7.9 mYPAS points and yielding ¥5,512/patient cost savings. This model demonstrates high clinical utility and economic efficiency for pediatric radiotherapy support. Research Sponsor: None.

10012 Rapid Oral Abstract Session

Alrizomadlin (APG-115) alone or in combination with lisaftoclax (APG-2575) for the treatment of pediatric patients with relapsed/metastatic rhabdomyosarcoma (RMS) or other soft-tissue sarcomas (STSs). First Author: Yizhuo Zhang, Department of Pediatric Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

Background: Pediatric tumors rarely harbor *TP53* mutations but often overexpress anti-apoptotic BCL-2 family proteins (BCL-2, BCL-XL, MCL-1), making MDM2 and BCL-2 inhibitors attractive therapeutic approaches. Preclinical data have shown that dual targeting these proteins results in synthetic lethality, which may overcome chemoresistance in pediatric patients with STSs. The study evaluated the safety and preliminary efficacy of alrizomadlin alone or combined with lisaftoclax in heavily pretreated relapsed/metastatic pediatric RMS, neuroblastoma (NB) and other STSs. **Methods:** This Chinese multicenter trial (NCT05701306; APG115XC103) assessed alrizomadlin (± lisaftoclax) in children with heavily pretreated relapsed/metastatic RMS, Ewing sarcoma (EWS), NB, or other STSs; Lansky or Karnofsky PS ≥ 50; and no CNS metastases. Alrizomadlin alone was administered orally at 30, 60, or 90 mg/m^2 QOD (2 weeks on, 1 week off). When combined with lisaftoclax (250, 375, or 500 mg/m^2 oral QD), alrizomadlin dose was 90 mg/m^2 QOD in 21-day cycles until progression or toxicity. The primary endpoints were safety and RP2D for the combination. ORR was assessed per INRC for NB or RECIST v1.1 for other solid tumors. **Results:** As of January 16, 2025, 16 pediatric patients received alrizomadlin monotherapy at 30 (n = 5), 60 (n = 4), or 90 mg/m^2 (n = 7). No DLT was observed; the recommended dose was 90 mg/m^2 when combined with lisaftoclax. Most common TRAEs were gastrointestinal and hematologic. Grade ≥ 3 TRAEs included thrombocytopenia (42.9%) and neutropenia (28.6%). One patient (14.3%) experienced treatment-related SAEs (thrombocytopenia, febrile neutropenia, and leukopenia). No treatment-related discontinuation or death occurred. In the combination arm, 18 patients were treated with alrizomadlin (90 mg/m^2) combined with lisaftoclax at 250 (n = 13) or 375 mg/m^2 (n = 5). No DLT was observed. Most common TRAEs were gastrointestinal and hematologic. Grade ≥ 3 TRAEs included thrombocytopenia (38.9%), neutropenia (33.3%), leukopenia (27.8%), and anemia (27.8%). One (5.6%) treatment-related SAE of thrombocytopenia was reported. No treatment-related discontinuation or death occurred. In monotherapy, 1 patient with refractory RMS achieved CR; 2 patients with STSs maintained stable disease. In the combination arm, 10 patients were evaluable for response, showing 1 CR (EWS), 1 PR among 4 patients with RMS, and 1 PR among 3 patients with NB. ORR (CR + PR) was 30% and DCR 80%. **Conclusions:** Alrizomadlin alone or in combination with lisaftoclax showed a manageable safety profile, with preliminary antitumor activity in heavily pretreated R/R RMS, EWS, and NB. The potential mechanisms, safety, and efficacy of alrizomadlin combined with lisaftoclax for pediatric RMS and other STSs warrant further investigation. Clinical trial information: NCT05701306. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

10013 Rapid Oral Abstract Session

RAPID: A pilot feasibility study of rapid dinutuximab infusion in patients with relapsed/refractory (RR) high-risk neuroblastoma (HRNBL). First Author: Sara-Jane N. Onyeama, Cancer and Blood Disease Institute, Children's Hospital Los Angeles; Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: Dinutuximab is a key component of therapy for HRNBL and is widely used in the RR setting. Standard administration requires inpatient infusions of ~10 hours daily. Emerging pediatric and adult data support shorter infusion durations. Evaluating rapid infusion of dinutuximab (RID) with chemotherapy may reduce pain, facilitate outpatient delivery, and decrease healthcare burden. **Methods:** This prospective, single-institution pilot study enrolled patients from 11/2022-12/2025 following IRB approval. Eligible patients included those ≥1 year old with RR-NBL, adequate organ function, and prior dinutuximab exposure. Patients received chemoimmunotherapy consisting of dinutuximab 17.5 mg/m²/day for 4 days (over 2-4 hours) combined with irinotecan/temozolomide (ITD) or cyclophosphamide/topotecan (CTD) for up to 6 cycles. Outpatient administration was permitted after cycle 1 if tolerated. The primary feasibility endpoint was successful dinutuximab administration over ≤5 hours with ≤1 patient experiencing unacceptable toxicity (UT) during cycle 1 in a 10-patient cohort. Secondary and exploratory endpoints included infusion duration, serial pain scores assessed during and post-infusion, opioid use in morphine milligram equivalents (MME), toxicity, feasibility of outpatient administration, pharmacokinetics (PK) and human anti-chimeric antibody (HACA). Changes in MME were compared using a one-sample t-test. **Results:** Eleven patients (median age 14 years, range: 3-24) received ITD (n=6) or CTD (n=5). All patients met the primary feasibility endpoint. Median infusion time was 2 hours (range 2-4) across all cycles. One patient (3 years old), enrolled in the early post-transplant period developed UT (grade 3 ventricular dysfunction). The protocol was amended to exclude patients within 6 months of transplant, require dinutuximab tolerance within 2 months, and extend cycle 1 infusion to 4 hours for patients <12 years of age; this patient was replaced per protocol. Across cycles 1-6, mean pain score was 0.4 (SD 0.46), and mean opioid usage was 0.04mg/kg MME (SD 0.07), reflecting a 78% reduction of opioid use in cycle 1 RID compared to the pre-enrollment standard-infusion cycle ($p<0.001$). Outpatient RID was administered in seven patients without hospital admission; 1 patient was admitted for chemotherapy-related toxicity, 3 patients remained inpatient (social reasons). RID showed expected PK levels; HACA was noted in 1 patient. Most common grade 3 toxicities (27%): increased ALT and hypokalemia; 1 patient (with UT) had grade 4 toxicity (dyspnea, hypocalcemia). **Conclusions:** RID was feasible and well tolerated, including in the outpatient setting. Pain control was achieved with standard premedication and significantly reduced opioid requirements compared with standard infusion. These data support planned multi-institutional evaluation of RID. Clinical trial information: NCT05421897. Research Sponsor: United Therapeutics.

10014 Rapid Oral Abstract Session

Interim analysis of CaboMain: A prospective, single-arm phase 2 clinical trial of cabozantinib as maintenance therapy for patients with "ultra-high-risk" pediatric solid tumors. First Author: Nilay Shah, Nationwide Children's Hospital, Columbus, OH

Background: There are patients with pediatric solid tumors, including those with relapsed/refractory disease, with "ultra-high" risk (UHR) disease (1-year progression free survival (1-yr PFS) <25%) even when achieving disease control. Most pediatric solid tumors do not have a therapeutically-targetable oncogenic driver, limiting treatment options for maintenance therapy. Cabozantinib is a multitargeted tyrosine kinase inhibitor with demonstrated activity against many solid tumors, with a defined safety profile and dosing in pediatric and young adult patients. We hypothesize that use of cabozantinib for 1 year, after achieving disease control, can improve 1-yr PFS to ≥ 45%. **Methods:** We are performing a multisite, open-label, single-arm Phase 2 clinical trial for patients with pediatric solid tumors with 4 strata; Stratum A, primary stratum for analysis, enrolls patients with UHR disease. Patients must have completed prior therapy at least 4 weeks and no longer than 12 weeks before enrollment with stable disease or better at time of enrollment. Enrolled patients receive cabozantinib as per dosing nomogram at 40 mg/m^2/day, taken for up to 365 days from start of therapy. Primary outcome is 1-yr PFS, with Bayesian time-to-event optimal phase 2 design for analysis. Interim analysis follows the rules: assuming a Beta (0.25,0.75) prior distribution for efficacy and 88% statistical power, at interim at least 5/18 evaluable patients must have achieved 1-yr PFS to justify ongoing enrollment. Interim analysis reporting has been recommended by the Data Safety and Monitoring Committee. **Results:** We report the interim results as of 11/1/2025, which includes all enrolled patients on Stratum A who have reached 1 year after start of therapy (n=13). Eight of thirteen patients reached 1-yr PFS; by diagnosis, neuroblastoma (NBL) = 2, Ewing sarcoma (EWS)= 3, osteosarcoma (OST)= 3. Of those not reaching the one-year time point, 2 patients progressed after voluntarily discontinuing cabozantinib (1 NBL, 1 month after discontinuation; 1 OST, 5 months after discontinuation), 1 NBL elected radiation therapy and was removed from study, and 2 OST progressed on study treatment. Having reached the interim analysis benchmark, enrollment continues. Three additional strata (metastatic EWS, metastatic OST, and fusion-positive metastatic rhabdomyosarcoma, each at end of 1st line therapy) also continue to enroll, as secondary endpoints. Longer-term PFS and overall survival, patient reported outcomes, and exploratory biological measures continue to be tabulated for later analysis. **Conclusions:** Use of cabozantinib as maintenance therapy, after prior treatment and achievement of stable disease or better response, has been determined to be feasible to demonstrate improvement of 1-yr PFS by at least 20%, and ongoing enrollment is justified. Clinical trial information: NCT05135975. Research Sponsor: Exelixis, Inc.

10015 Rapid Oral Abstract Session

Phase II trial of olaparib and ceralasertib in patients with recurrent osteosarcoma: Lung-only resectable cohort efficacy and correlative biomarker results. First Author: Suzanne J. Forrest, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Patients with osteosarcoma recurrence have limited treatment options and poor outcomes. The observed response to cisplatin in osteosarcoma, in vitro susceptibility of osteosarcoma cell lines to ATR and PARP inhibitors, and the presence of mutations in genes involved in DDR served as the basis for the development of this trial. **Methods:** We conducted a phase II trial of olaparib and ceralasertib in patients aged 12-40 with recurrent osteosarcoma. The primary endpoint for patients with resectable disease limited to the lung (Cohort 2) was submission of paired pre- and post-treatment tumor samples. Secondary endpoints for Cohort 2 included event-free status at 12-months, event-free survival (EFS) and overall survival (OS). Patients received Olaparib 150mg twice a day on days 1-28 and ceralasertib 80mg twice a day on days 1-14 of a 28-day cycle. Patients with unilateral disease received 2 cycles of treatment prior to surgery. Patients with bilateral disease had one side resected, then received 2 cycles of treatment followed by surgery of the contralateral side. Tumor, blood and plasma samples were obtained from Cohort 1 (measurable unresectable disease, efficacy results previously reported) and Cohort 2 patients for correlative studies. **Results:** Between 3/2021-9/2024, 10 patients from 4 centers were enrolled in Cohort 2. Four patients had bilateral and six had unilateral lung metastases. Median age was 19.3 (range 15.7-24.6). Patients had received a median of three prior therapy regimens. Seven patients (70%, 95%CI: 35%-93%) underwent planned thoracic surgery and had paired pre- and post-treatment tumor samples submitted for correlative studies. Four patients (40%, 95%CI: 12%-74%) were event-free at 12 months and received >12 cycles of olaparib and ceralasertib. The 12-month EFS±SE and OS±SE were 40±15.5% and 90±9.5%, respectively. Initial review of clinical sequencing on a subset of Cohort 1 and 2 patients suggests therapy resistance may be associated with high-risk genomic features, like MYC amplification. **Conclusions:** Patients with recurrent resectable osteosarcoma limited to the lung parenchyma can be included as a separate cohort in phase II trials of novel agents. In this cohort, it is feasible to incorporate pre-surgical treatment with experimental agents followed by surgical resection of pulmonary nodules and collection of pre- and post-treatment tumor samples, enabling correlative biology. 12-month EFS was 40% but with a wide confidence interval crossing the confidence interval of historical 12-month EFS of 20% from prior COG studies. Sequencing and ctDNA analyses for all enrolled patients (both cohorts) with available samples (N=40 patients with tumor samples and N=48 patients with ctNDA samples) are underway to further assess potential biomarkers of treatment response. Clinical trial information: NCT04417062. Research Sponsor: St. Baldrick's Foundation; Osteosarcoma Institute; Alex's Lemonade Stand.

10016 Rapid Oral Abstract Session

Characterization and validation of a methylation signature as a prognostic marker in osteosarcoma. First Author: Rachel M. Hurley, Children's Hospital of Philadelphia, Philadelphia, PA

Background: Despite extensive research efforts, outcomes for patients with osteosarcoma have not substantially improved since the 1980s. Moreover, no prognostic features are used clinically to risk adapt therapy. Here, we performed methylation and RNA sequencing of pre-treatment osteosarcoma tumor samples to identify distinct features of tumor biology and to generate and validate a prognostic signature. **Methods:** All patients diagnosed with osteosarcoma at the Children's Hospital of Philadelphia (CHOP) before March 15, 2024 with tissue available for analysis were eligible. Of the 100 eligible patients, three were excluded for lack of clinical data and one for initial diagnostic uncertainty. Methylation and RNA sequencing were performed on DNA and RNA extracted from FFPE or frozen tumor. Unsupervised analyses characterized global methylation structure and differential methylation analyses compared differences between progression groups. Tumor and immune cell fractions were estimated using a reference-based deconvolution algorithm. CpGs were filtered using an unsupervised variability criterion (top 20% MAD) and a ridge-penalized Cox model was used to derive a methylation risk score as a linear predictor. The publicly available TARGET-OS cohort was used for validation with median-based risk stratification defined in the CHOP cohort. **Results:** Of 96 patients, 44 patients had pre-treatment samples that passed methylation QC and 13 passed RNA sequencing QC. Within the CHOP cohort, 34/44 (77%) had localized disease with a median age of 13 years. Variability in methylation profiles was driven by leukocyte infiltration, supported by strong correlations between global methylation levels and mitotic index estimates. Tumors from patients with progressive disease displayed 12,338 significantly different CpGs (FDR < 0.01) and enriched for hypomethylated CpGs. A methylation-derived risk score was established for overall survival (OS) in the CHOP cohort. In multivariable Cox models, the methylation risk score remained significantly associated with OS (HR 1.54 [1.05–2.26]; p = 0.026) together with metastatic status (HR 5.13 [2.49–10.59]; $p < 0.001$), yielding improved model discrimination (C-index 0.77 [0.70–0.83]). This was replicated in event-free survival (EFS, HR 2.49 [1.49,4.19], $p<0.01$). In the TARGET-OS cohort, after adjustment for metastatic status, methylation risk score remained independently associated with EFS (HR 1.6 [1.15, 2.23], p = 0.005). and OS (HR 1.54 [1.05, 2.26], p = 0.003). **Conclusions:** In this single-institution cohort analysis, a methylation-based risk score predicts survival and adds prognostic value when combined with metastasis status. Integration of CpG methylation with downstream pathway activation via RNA sequencing is ongoing and will be reported. Further validation of this prognostic signature should be considered in future osteosarcoma trials. Research Sponsor: Connor Initiative (Philanthropy); National Cancer Institute; 1R50CA305079; National Human Genome Research Institute; 5T32HG009495; Conquer Cancer, the ASCO Foundation; Abramson Cancer Center, University of Pennsylvania; Rally Foundation for Childhood Cancer Research,.

10017 Rapid Oral Abstract Session

Dexamethasone-free antiemetic prophylaxis with olanzapine in children and adolescents receiving highly emetogenic chemotherapy: A multicenter, phase III non-inferiority randomized trial. First Author: Venkatraman Radhakrishnan, Cancer Institute (WIA), Chennai, India

Background: Dexamethasone, with a 5-HT3 receptor antagonist and a neurokinin-1 antagonist, is the guideline-recommended prophylaxis for chemotherapy-induced nausea and vomiting (CINV) in children and adolescents receiving highly emetogenic chemotherapy (HEC), but is associated with clinically relevant toxicities. The role of olanzapine as a dexamethasone-sparing agent for pediatric CINV prophylaxis remains uncertain. **Methods:** This investigator-initiated, multicenter, open label, phase III randomized non-inferiority (NI) trial (INPHOG-SUPP-22-03) enrolled patients aged 4–18 years receiving single or multi-day HEC. Patients were randomized 1:1 (single chemotherapy cycle) to receive dexamethasone, palonosetron, and fosaprepitant (DEX; standard-of-care) or olanzapine, palonosetron, and fosaprepitant (OLANZ; dexamethasone-free). The primary endpoint was complete response (CR) to vomiting (no vomiting and no rescue anti-emetics) during the overall period (0–120 h after the last chemotherapy dose). A NI margin of -15% was prespecified based on adult dexamethasone-sparing trials. Assuming a control CR rate of 70% from prior pediatric studies, 310 patients provided 80% power at a one-sided α of 0.025, allowing for 5% dropout. Absolute differences in CR rates were analyzed using the Miettinen–Nurminen method; NI was concluded if the lower bound of the 95% confidence interval (CI) was above -15%. **Results:** Between December 2022 and January 2026, 310 patients were randomized (DEX, n=156; OLANZ, n=154). The per-protocol (PP) population included 299 patients (DEX, n=151; OLANZ, n=148). Median age was 13 years; 62.2% were male, and 56.8% received multi-day HEC. In the PP population, the CR rate for vomiting during the overall period was 56.9% in the DEX arm and 63.5% in the OLANZ arm (absolute difference, 6.6%; 95% CI, -4.5% to 17.7%). Non-inferiority was demonstrated, as the lower 95% CI (-4.5%) was above -15%. Results were consistent in the intention-to-treat population. For secondary endpoints, CR to vomiting during the acute period (0-24 h) was 64.2% vs 68.9%, and during the delayed period (24-120 h) 78.8% vs 79.1%, in the DEX and OLANZ arms, respectively. CR to nausea during the overall period was 54.3% vs 53.4%, during the acute period 59.6% vs 59.5%, and during the delayed period 69.5% vs 68.9%, respectively. Grade $\geq$2 non-hematologic and hematologic laboratory toxicities were uncommon and similar between arms. Any-grade somnolence was significantly higher with OLANZ than DEX (52.0% vs 25.8%), with all events being $\leq$ grade 2. **Conclusions:** A dexamethasone-free antiemetic regimen was non-inferior to standard dexamethasone-based prophylaxis for prevention of vomiting in children and adolescents receiving HEC. These findings support the use of olanzapine as an effective steroid-sparing alternative. Clinical trial information: CTRI/2022/08/045009. Research Sponsor: CanKids KidsCan, the National Society for Change For Childhood Cancer In India.

10018 Poster Session

Integrating genomics, imaging, and clinical data for late-onset cardiomyopathy prediction in pediatric cancer survivors: A multi-modal machine-learning comparison using St. Jude Cloud. First Author: Masab Mansoor, Edward Via College of Osteopathic Medicine, Monroe, LA

Background: Pediatric cancer survivors face substantial risk of anthracycline- and radiation therapy (RT)-related cardiomyopathy (CM). Current risk stratification using clinical factors alone demonstrates suboptimal discriminative capacity. We hypothesized that integrating multi-modal data (clinical, genomic, and cardiac imaging/electrocardiography) would enhance predictive accuracy for late-onset CM beyond single-modality models. **Methods:** We analyzed data from 1,217 adult survivors of childhood cancer enrolled in the St. Jude Lifetime Cohort (SJLIFE), accessed via St. Jude Cloud. The primary endpoint was CM, defined as left ventricular ejection fraction (LVEF) $<$50% or $\geq$10% absolute decline from baseline. Four progressively complex feature sets were evaluated: (1) Clinical-Only (anthracycline/RT dose, age at diagnosis, sex); (2) Clinical+Genomic (adding 31 protective variants from PeCan); (3) Clinical+ECG/Imaging (adding 86 signal-processed ECG features and global longitudinal strain [GLS]); and (4) Multi-Modal (comprehensive integration). Logistic regression, random forest (RF), and extreme gradient boosting (XGBoost) algorithms were compared using 5-fold stratified cross-validation. Model interpretability was assessed via SHapley Additive exPlanations (SHAP) analysis. **Results:** Clinical-Only models demonstrated limited discrimination (AUC 0.70; 95% CI, 0.65-0.75). Incremental addition of genomic data (AUC 0.85) or ECG/GLS parameters (AUC 0.89) substantially improved performance. The Multi-Modal XGBoost model achieved superior predictive accuracy (AUC 0.93; 95% CI, 0.90-0.95; sensitivity 0.88; specificity 0.89), marginally outperforming RF (AUC 0.91). SHAP analysis identified GLS as the dominant predictor, followed by cumulative anthracycline dose and protective genomic variants, demonstrating synergistic contribution of multi-modal features. **Conclusions:** Multi-modal machine learning integration using open-source St. Jude Cloud data enables highly accurate prediction of late-onset CM in pediatric cancer survivors (AUC 0.93). The demonstrated superiority over single-modality approaches supports a paradigm shift toward comprehensive risk stratification. This XGBoost-based model could facilitate precision survivorship care, enabling risk-adapted surveillance intensification and early cardioprotective intervention for high-risk patients. Research Sponsor: None.

Comparative performance of machine learning models for 10-year cardiomyopathy risk prediction.

Model Type	Algorithm	AUC (95% CI)	Sensitivity	Specificity
Clinical-Only	Log. Reg.	0.70 (0.65-0.75)	0.62	0.66
Clinical + Genomic	Random Forest	0.85 (0.81-0.89)	0.79	0.82
Clinical + ECG/GLS	XGBoost	0.89 (0.86-0.91)	0.78	0.81
Multi-Modal (Full)	XGBoost	0.93 (0.90-0.95)	0.88	0.89

10020 Poster Session

Longitudinal genomic characterization of pediatric acute myeloid leukemia at diagnosis and relapse. First Author: Jagdish Prasad Meena, All India Institute of Medical Sciences, New Delhi, India

Background: Relapse remains the leading cause of treatment failure and mortality in pediatric acute myeloid leukemia (pAML). In AML, relapse is common and is increasingly recognized as a consequence of therapy-driven clonal evolution rather than mere persistence of the diagnostic clone. This study aimed to delineate mutational trajectories from diagnosis to relapse and identify relapse-associated genomic alterations of potential clinical relevance. **Methods:** This prospective study was conducted from July 2021 to December 2025. Bone marrow or peripheral blood samples were collected from children $\leq$18 years at diagnosis and relapse. Genomic DNA from paired samples was sequenced exomically to identify somatic mutations. Longitudinal comparative analyses assessed clonal persistence, emergence of relapse-specific mutations, and pathway-level enrichment. **Results:** A total of 100 children with AML were enrolled. Paired longitudinal analysis (n=18) identified 133 mutated genes. Seventy-nine (59.4%) were shared between diagnosis and relapse, forming a conserved truncal genomic backbone. Fifty genes (37.6%) were exclusive to diagnosis, while only four (3.0%) were exclusive to relapse, suggesting strong therapeutic selection pressure rather than widespread genomic diversification. At diagnosis, missense variants predominated (88.4%), followed by in-frame insertions/deletions (6.5%), nonsense (2.4%), and frameshift alterations (2.5%). Relapse samples showed further enrichment of missense variants (90.5%) and a relative depletion of truncating events, consistent with selection for functionally adaptive mutations. Truncal alterations were consistently observed in epigenetic regulators TET2 and KMT2C, supporting their role as early leukemogenic events. In contrast, relapse samples showed enrichment of signaling and transcriptional regulators, including FLT3 and PTPN11, along with relapse-exclusive emergence of WNT pathway components (FZD7, LEF1) and the PI3K regulator PIK3R1. Functional enrichment analysis revealed that diagnostic samples were primarily enriched for DNA damage response, p53 signaling, apoptosis, and cell-cycle checkpoint pathways ($p<0.05$). At relapse, these core programs persisted alongside marked enrichment of oncogenic signaling pathways (WNT, PI3K–AKT, FLT3) and metabolic processes, including glycolysis and ATP generation. Reactome analysis highlighted convergence on FLT3- and AKT-driven signaling, TP53-mediated DNA repair, and escape from apoptosis. **Conclusions:** Longitudinal genomic profiling demonstrates that pAML relapse is driven by the persistence of early truncal mutations, coupled with the selective expansion of signaling- and metabolism-adapted subclones. Enrichment of WNT, PI3K–AKT, and FLT3-associated pathways at relapse reveals potential targets for relapse-directed precision strategies. Research Sponsor: Indian Council of Medical Research.

10021 Poster Session

Distinct immunologic vs progenitor landscapes in myeloid leukemia recurrence: Adaptive immune persistence in pediatrics vs niche exhaustion in adults. First Author: Karen Dong-Tran, UNR School of Medicine, Reno, NV

Background: Recurrent myeloid leukemia remains a therapeutic challenge with distinct clinical trajectories across age groups. While our parallel study identified a "universal adipogenic shift" in the marrow stroma common to all ages, the specific cellular drivers distinguishing pediatric from adult relapse remain undefined. We hypothesized that against this shared stromal background, the mechanism of recurrence diverges: the pediatric marrow mounts an adaptive immune response, whereas the aging adult marrow suffers from hematopoietic reservoir depletion. **Methods:** We analyzed the tumor microenvironment (TME) of 2,378 myeloid leukemia samples (2,007 primary, 371 recurrent) using xCell transcriptomic deconvolution. The cohort was stratified into Pediatric ($<$ 18y, n = 2,071) and Adult ($\geq$ 18y, n = 307) subgroups to control for ontogenic baselines. We compared differential expression rankings between primary and recurrent states using Mann-Whitney U tests with Bonferroni correction (Padj) to identify age-specific dominance in TME remodeling. **Results:** Comparative analysis revealed divergent TME landscapes between age groups. In pediatrics, recurrence was characterized by an "Immune-Adaptive" program; CD4+ Memory T-cells were the dominant signature (rank 4, $p < 10^{-27}$), alongside significant increases in Preadipocytes ($p < 10^{-49}$) and pro-B cells. Conversely, adult recurrence exhibited "Niche Exhaustion," primarily losing hematopoietic progenitors (CMP/GMP, $p < 10^{-7}$) and mesenchymal stem cells (MSC, $p < 10^{-9}$). While CD4+ Memory T-cells increased in adults, the signal was less prominent (rank 18, $p < 10^{-5}$). Both groups shared significant vascular collapse (Pericyte loss, $p < 10^{-7}$), identifying it as a universal hallmark of relapse. **Conclusions:** Myeloid leukemia recurrence is driven by age-distinct microenvironmental remodeling. Pediatric relapse is defined by immune adaptation and adipogenesis, while adult relapse is characterized by progenitor and niche exhaustion. Vascular collapse represents a universal therapeutic target. These findings suggest that immunotherapy and niche-directed treatments must be tailored to the patient's age-specific TME landscape to improve outcomes. Research Sponsor: None.

Top age-specific trends in recurrent vs. primary myeloid leukemias.

Cohort	Cell Type	Direction	Mean Diff (Rec - Pri)	Padj
Pediatric (<18y)	Pericytes	Primary- High	-0.085	$P < 0.05$
	Preadipocytes	Recurrence- High	+0.064	$P < 0.05$
	MSC	Primary- High	-0.099	$P < 0.05$
	CD4+ Memory T-cells	Recurrence- High	+0.849	$P < 0.05$
	pro-B cells	Recurrence- High	+0.301	$P < 0.05$
Adult (≥18y)	MSC	Primary- High	-0.165	$P < 0.05$
	Pericytes	Primary- High	-0.078	$P < 0.05$
	CMP	Primary- High	-0.526	$P < 0.05$
	Smooth muscle	Primary- High	-0.094	$P < 0.05$
	GMP	Primary- High	-0.765	$P < 0.05$
	CD4+ Memory T-cells*	Recurrence- High	+1.184	$P < 0.05$

*Manually added row for comparison purposes.

10022 Poster Session

The burden of childhood cancers in the South Asian Association for Regional Cooperation (SAARC) region: A GLOBOCAN 2022 analysis. First Author: Tara Pattilachan Menon, Virginia Tech Carilion School of Medicine, Roanoke, VA

Background: Countries of the South Asian Association for Regional Cooperation (SAARC) are home to approximately 600 million children aged 0–14 years, representing a quarter of the global child population. We report incidence and mortality for childhood cancers among South Asia's eight nations to inform priority setting for research, programming for health services, and policy for childhood cancers. **Methods:** Incidence and mortality of new childhood cancer diagnoses for all cancers combined and for selected leading diagnostic groups were retrieved from the GLOBOCAN 2022 database of Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka. Age-standardized incidence rates (ASR) and mortality-to-incidence ratios (MIR) were calculated, together with statistical examination of cross-country variation in diagnostic structure and survival trends. **Results:** In SAARC nations, 37,716 new childhood cancer diagnoses and 17,700 deaths were estimated in 2022. India contributed 68.7% of subregional cases (25,939), and Pakistan contributed 20.8% (7,841). Age-standardized rates differed and were greatest in Sri Lanka (10.4/100,000) and Pakistan (10.1) and lowest in Bhutan (2.3) and Bangladesh (3.7). Boys represented 60% of cases overall, with significant cross-country variation in sex distribution (χ^2=18.0, p=0.012). Leukemia was the most common cancer in all countries (35–50%), followed by central nervous system (CNS) tumors. MIR ranged from 0.30 (Sri Lanka) to 0.57 (Afghanistan), reflecting extreme survival differences, with CNS tumors demonstrating disproportionately high mortality relative to incidence. **Conclusions:** SAARC childhood cancer trends reflect both population size influences and health system capacity, with a preponderance of leukemia but alarming survival gaps, particularly for CNS cancers. These findings highlight actionable priorities, including strengthening population-based childhood cancer registries, centralizing care pathways for CNS tumors, expanding standardized leukemia treatment protocols with abandonment-prevention strategies, and improving equitable access to specialty care through subregional collaboration. Research Sponsor: None.

10023 Poster Session

A capacity assessment of pediatric oncology research biorepositories across a regional collaborative group in the Middle East, North Africa, and Asia. First Author: Sushmitha Grama Srinivasan, Stanford University School of Medicine, Palo Alto, CA

Background: Biobanks advance translational research in pediatric oncology. Understanding the existing biobanking infrastructure is critical for fostering collaboration and improving research capacity in low- and middle-income countries (LMICs). **Methods:** A previous research capacity survey within institutions of the Pediatric Oncology East and Mediterranean (POEM) Group collaborative network identified 26 out of 69 institutions across 23 countries, with access to clinical tissue specimens for research use. We surveyed these centers regarding sample/data management, patient population, governance, standard operating procedures (SOPs), quality systems, and funding. This study was determined non-human subjects research by the Stanford IRB. Biobanking capacity and participation were evaluated using descriptive statistics (medians, ranges, and frequencies). **Results:** Fifteen of the 26 (58%) institutions confirmed that they have a research-specific biobank; 10 of 15 (67%) participated. All surveyed biobanks collect cancer samples using broad consent, and have ongoing funding through institutional support, external collaborations or both. Principal investigators lead 20% of the biobanks, the others are institution-based and led. A median of 7 staff are involved in biobanking activities per institution (range, 3–28). Most institutions (80%) rely on Microsoft Excel for sample tracking. A quality management system is implemented in 7 of 10 (70%) of institutions, with most adhering to ISBER best practices. Five of 10 (50%) of the biobanks lack disaster management SOPs. Eight of 10 (80%) biobanks are capable of sharing samples and associated clinical data with other institutions through material/data sharing agreements. A median of 3500 samples (range, 368–6000) are stored yearly with a median of 300 samples (range, 100–1000) released for authorized research. While most biobanks viewed their national legal frameworks as supportive, 2 biobanks (20%) indicated that national regulations constrain biobanking activities. All the respondents indicated a need to improve their national regulation to support ethical biobanking practices – specifically need for improved regulation for cross-border collaborations, data privacy, and intellectual property (60%, 40% and 30%, respectively). **Conclusions:** Biobanks exist in 21.7% (15 of 69) centers within the POEM group. Biobanks in the region have robust consenting and sample collection procedures. Significant opportunities exist to enhance capacity through implementation of international quality standards, and improved disaster preparedness. Further understanding of the determinants of successful initiation and maintenance of these biobanking efforts in LMICs will guide targeted initiatives to further expand regional biobanking infrastructure and augment research collaborations. Research Sponsor: None.

10024 Poster Session

Cancer outcome among adolescents in Canada. First Author: Samuel Sassine, Division of Pediatric Hematology-Oncology, Department of Pediatrics, Charles-Bruneau Cancer Center, CHU Sainte-Justine, Montreal, QC, Canada

Background: Adolescents and young adults (AYA) with cancer, commonly defined as patients aged 15–39 years at diagnosis, experience higher morbidity and mortality compared with other age groups. In this study, we compared outcomes of adolescents with newly diagnosed cancer treated at Canadian pediatric oncology centers with those of younger children. **Methods:** We conducted a retrospective cohort study using the population-based CYP-C database, including children aged 1–18 years with newly diagnosed cancer across Canada (2015–2020). Event-free survival (EFS) and overall survival (OS) were compared between adolescents (15–18 years) and younger children (1 to $<$15 years) across cancer subtypes using Kaplan–Meier analyses and univariable and multivariable Cox proportional hazards models. **Results:** Of the 6,794 patients, adolescents aged 15–18 years comprised 16% (n=1,075) of the cohort. Median age at diagnosis was 16 years (IQR: 15.7–17.2), and among those with solid tumors, 26% (n=150) had metastatic disease at diagnosis. The most frequent adolescent cancers were Hodgkin lymphoma (20%), gliomas and other glioneuronal tumors (12%), acute lymphoblastic leukemia (11%), osteosarcoma (6%), thyroid carcinoma (6%), malignant extracranial germ cell tumors (5%), and Ewing sarcoma (4%). Adolescents with leukemia had comparable 5-year EFS (71% vs. 79%; p=0.06) and OS (83% vs. 89%; p=0.07) to younger children, as did those with non-central nervous system (CNS) solid tumors for EFS (65% vs. 65%; p=0.55) and OS (74% vs. 75%; p=0.23). Among patients with sarcomas, adolescents had similar 5-year EFS (50.7% vs. 52.0%, p=0.55) and OS (55.6 vs. 59.7%, p=0.14) to younger children. Adolescents with CNS tumors had superior EFS (83% vs. 66%; p=0.005) and OS (89% vs. 73%; p=0.006), primarily driven by ependymoma and choroid plexus tumors, and other gliomas/glioneuronal tumors excluding pilocytic astrocytoma. **Conclusions:** Although AYA with cancer are often reported to have poorer outcomes, adolescents aged 15–18 years treated exclusively in Canadian pediatric oncology centers did not have inferior outcomes to younger children, underscoring the effectiveness of pediatric treatment approaches. Research Sponsor: None.

5-year EFS and 5-year OS of adolescents (≥15 years-old) vs. younger children (1 to < 15 years old) across major cancer categories.

-	Adolescents 5-year EFS (%) [95% CI]	Younger children 5-year EFS (%) [95% CI]	p-value	Adolescents 5-year OS (%) [95% CI]	Younger children 5-year OS (%) [95% CI]	p-value
All cancers	76.4 [72.8-79.9]	72.6 [70.8-74.3]	0.12	84.7 [81.4-87.4]	81.1 [79.6-82.7]	0.13
Leukemias	71.2 [58.7-80.5]	79.0 [75.8-81.9]	0.06	83.2 [73.3-89.7]	88.6 [86.2-90.6]	0.07
Lymphomas	88.5 [82.6-92.5]	87.3 [82.6-90.7]	0.63	96.2 [91.9-98.3]	95.5 [92.7-97.3]	0.50
Non-CNS solid tumors	65.4 [58.6-71.3]	65.2 [61.8-68.3]	0.55	73.5 [66.7-79.0]	74.8 [71.5-77.9]	0.23
CNS tumors	83.1 [74.2-89.1]	66.3 [62.5-69.8]	0.005	89.1 [82.0-93.5]	72.5 [68.8-75.9]	0.006

10025 **Poster Session**

Beyond translation: Leveraging interpreter expertise to enhance clinician training and language equity in pediatric oncology. First Author: Joseph S. Kang, Stanford University School of Medicine, Palo Alto, CA

Background: Medical interpreters play a critical role in pediatric oncology beyond translation by guiding conversations, interpreting cultural and emotional cues, and ensuring families with limited English proficiency (LEP) can access medical information. Yet few clinician training resources focus on interpreter-mediated communication. This study aimed to (1) identify communication best practices and challenges from the perspective of professional medical interpreters and (2) develop an educational toolkit for clinicians to promote equitable, patient-centered communication for families with LEP. **Methods:** We conducted semi-structured individual interviews and a focus group with Spanish medical interpreters from six freestanding children's hospitals across the United States between 12/2024-10/2025. Verbatim transcripts were thematically analyzed in Dedoose, and resulting themes directly informed creation of an educational toolkit. **Results:** Sixteen interpreters (15 female, 1 male) who provide in-person interpretation participated. Benefits of in-person professional interpretation included perceiving non-verbal communication cues, serving as patient/family advocates, providing cultural and linguistic tailoring, explaining idiomatic or metaphorical clinical language, and continuity of interpreters across visits. Challenges included fragmented communication across medical teams, limited clinician understanding of cultural nuance, exclusion of parents from conversations, and remote interpreting. Based on these themes, we developed recommendations for clinicians focused on building collaborative relationships with interpreters, allowing time for interpretation, and actively checking patient and family understanding. We then designed a toolkit comprising three resources for clinicians working with interpreters: a badge reference card with a pre-, during-, and post-visit checklist; a decision-making learning module with case-based, first-person scenarios navigating interpreter-mediated encounters; and a self-paced modular course with structured lessons for in-depth learning. **Conclusions:** Interpreters identified concrete practices that enhance patient-centered care, with particular strengths evident during in-person interpretation, and challenges that undermine equitable communication. These insights informed a clinician-facing educational toolkit to improve interpreter-clinician encounters. Future studies will pilot the toolkit with ongoing, iterative refinement guided by interpreter input. Research Sponsor: Conquer Cancer, the ASCO Foundation; 2023CDA-5176592918.

10026 **Poster Session**

Immunogenicity profiles in pediatric extra-cranial rhabdoid tumors: A framework for future risk stratification. First Author: Omnia Al Qadi, Department of Pediatric Oncology, Children Cancer Hospital Egypt, Cairo, Egypt

Background: Malignant rhabdoid tumors (MRTs) are highly aggressive pediatric cancers driven by SMARCB1 loss. Emerging evidence suggests that the tumor immune microenvironment may influence the biological behavior of tumors. However, data on immune patterns in extra-cranial MRTs remain extremely limited, particularly in low- and middle-income settings. This study characterizes immune marker expression and immune phenotypes in a large single-center cohort to explore their potential relevance for future risk stratification. **Methods:** Formalin-fixed paraffin-embedded specimens from pediatric extra-cranial MRTs were evaluated for $CD4^+$, $CD8^+$, and $CD68^+$ immune infiltrates using immunohistochemistry. Marker expression was categorized as high or low. Tumor immune phenotypes were subsequently classified based on the balance of infiltrating populations into: (immune-cold (uniformly low), mixed (variable across markers), and inflamed (uniformly high). Associations between immune phenotypes, clinicopathologic features, and survival trends were explored to determine whether immune architecture could serve as a biologically meaningful correlate of clinical behavior. **Results:** Individually, none of the immune markers (CD4, CD8, CD68) showed statistically significant correlation with overall survival. However, higher $CD4^+$ and $CD8^+$ T-cell infiltration demonstrated a consistent trend toward improved clinical outcomes. The most informative observation emerged at the phenotype level: tumors with a mixed immune profile exhibited more favorable survival trends and delayed progression compared with immune-cold tumors, whereas fully inflamed tumors were rare. These findings suggest that the equilibrium and interaction of immune infiltrates—rather than absolute immune cell density—may shape clinical behavior. **Conclusions:** Pediatric extra-cranial MRTs demonstrate distinct immune microenvironment patterns that are readily identifiable using routine immunohistochemistry. Although individual immune markers did not independently predict survival, immune-cold versus mixed phenotypes reflected meaningful biological divergence and aligned with clinical outcomes. Integrating immune phenotyping into diagnostic workflows may provide a pragmatic foundation for future risk stratification and help identify patients most likely to benefit from emerging immuno-epigenetic treatment strategies. Statement of Clinical Significance: Immune profiling using routine immunohistochemistry can classify pediatric extra-cranial rhabdoid tumors into clinically relevant immune phenotypes. Identifying immune-cold versus mixed tumors may support future risk stratification and guide biologically informed treatment selection. Research Sponsor: None.

10027 **Poster Session**

Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE in pediatric, adolescent, and young adult neuroendocrine tumors: A single-center experience from Bambino Gesù Children's Hospital. First Author: Maria Debora De Pasquale, Bambino Gesù Children's Hospital (IRCCS), Rome, Italy

Background: Neuroendocrine tumors (NETs) in pediatric, adolescent, and young adult (AYA) patients are rare and often associated with hereditary syndromes such as Von Hippel Lindau (VHL) and type 1 neurofibromatosis (NF1). Peptide receptor radionuclide therapy (PRRT) with ^177Lu-DOTATATE is well established in adults with somatostatin receptor–positive NETs, but data in younger populations remain limited. We report our single-center experience evaluating feasibility, safety, and efficacy of PRRT in this age group. **Methods:** We retrospectively analyzed patients $<$20 years treated with ^177Lu-DOTATATE at Bambino Gesù Children's Hospital between 2019 and 2025. Eligibility required somatostatin receptor expression confirmed by PET-DOTA imaging (Krenning score $\geq$2). Data included demographics, age at diagnosis and PRRT, tumor characteristics, prior therapies, PRRT cycles, cumulative dose, toxicity, and best response per RECIST. Follow-up status was assessed at last visit. **Results:** Six patients (median age at diagnosis 11 years, range 7–16; median age at PRRT 15 years, range 10–19) received PRRT for metastatic or unresectable NETs (pheochromocytoma/paraganglioma, n=5; bronchial carcinoid, n=1). All completed 4 cycles of ^177Lu-DOTATATE (median cumulative dose ~30 GBq). Prior treatments included surgery, chemotherapy (temozolomide), and MIBG therapy. No grade $\geq$3 hematologic or renal toxicity occurred; treatment was well tolerated. Best responses: 4 partial responses (PR), and 2 stable disease (SD). At a median follow-up of 18 months, all patients were alive: one in complete remission after surgery, others with stable disease or ongoing therapy. Genetic predisposition was present in 3 patients (VHL, NF1). SUVmax on baseline PET ranged from 1.2 to 43.8, correlating with Krenning score $\geq$2 in all cases. **Conclusions:** PRRT with ^177Lu-DOTATATE is feasible and well tolerated in pediatric, adolescent, and young adult patients with somatostatin receptor–positive NETs, achieving meaningful disease control with minimal toxicity. This single-center experience supports PRRT as a valuable option in selected cases and highlights the need for prospective studies and age-specific guidelines. Research Sponsor: None.

10028 **Poster Session**

Clinical impact of panel-based next-generation sequencing in a real-world cohort of neuroblastoma patients. First Author: Samantha Martin, Dana-Farber/Boston Children's Cancer and Blood Disorders Center; Harvard Medical School, Boston, MA

Background: Neuroblastoma is a malignant childhood tumor with a low somatic mutation rate, making targeted therapy challenging. Using a targeted NGS panel in a large real-world cohort, we identified recurrent variants and assessed the clinical impact of NGS for this disease. **Methods:** A real-world cohort of 185 peripheral neuroblastic tumor samples from 181 patients were sequenced with a targeted NGS assay (OncoPanel). Samples were either obtained at baseline ("diagnostic") or at relapse/progression ("relapse"). Variants include SNVs, CNAs, and SVs and were manually curated for pathogenicity. Recurrently altered genes were those curated as Pathogenic/Likely Pathogenic and occurring in more than 4% of samples. Clinically impactful findings were those with therapeutic implications (e.g., targetable *ALK* aberration) and those with prognostic implications at diagnosis (e.g. *MYCN* amplifications or segmental chromosomal aberrations (SCAs) included in the Children's Oncology Group (COG) risk stratification system). SCAs were defined as regions of loss or gain of at least 3Mb. Mutual exclusivity analyses utilized false-discovery rate corrected Fisher exact tests. **Results:** All COG risk groups were represented. At time of last follow-up (median 65.9 months), 103 (59%) were alive with no disease, 31 (18%) were alive with disease or unknown disease status, and 41 (23%) were deceased. Of the diagnostic cohort (n=144), 78 (54%) had at least one clinically impactful alteration (n=42 prognostic only, n=13 therapeutic only, n=23 both). Of the relapse cohort (n=41), 14 (34%) had a therapeutically impactful variant. Recurrently altered genes in the diagnostic samples included *MYCN*, *ALK*, *ATRX* and *MYCN*, *ALK*, *ATRX*, *BRAF*, *CREBBP*, *MLH3*, *PHOX2B* and *TERT* in the relapse samples. The most commonly observed SCA was 17q gain. Among the 144 diagnostic samples, no patients were observed to have both *MYCN* amplification and an ATRX variant nor *MYCN* amplification and 11q loss; this mutual exclusivity was statistically significant for *MYCN* amplification and 11q loss (adjusted p $<$0.001). **Conclusions:** Targeted NGS panels provided clinically impactful results in a majority of cases in a real-world cohort of children with neuroblastoma. Future analyses will include survival analysis by genomic features and comparison of NGS to standard clinical testing. Research Sponsor: None.

Key genomic findings across clinical cohorts.

	Diagnosis (n=144)	Relapse (n=41)	High-risk (HR)(n=53)	Non-HR(n=62)
***ALK* variant**	29 (20.1%)	8 (19.5%)	14 (26.4%)	9 (14.5%)
***ATRX* variant**	7 (4.9%)	3 (7.3%)	5 (9.4%)	1 (1.6%)
***BRAF* variant**	1 (0.7%)	3 (7.3%)	0 (0%)	1 (1.6%)
***PHOX2B* variant**	5 (3.5%)	2 (4.9%)	4 (7.5%)	1 (1.6%)
***MYCN* amplification**	27 (18.8%)	10 (24.4%)	16 (30.2%)	3 (4.8%)
17q gain	87 (60.4%)	27 (65.9%)	33 (62.3%)	39 (62.9%)
1p loss	17 (11.8%)	11 (26.8%)	12 (22.6%)	3 (4.8%)
11q loss	35 (24.3%)	12 (29.3%)	14 (26.4%)	17 (27.4%)

10029 Poster Session

Results of a phase II trial of nivolumab and ipilimumab in children and young adults with relapsed or refractory INI1-deficient cancers. First Author: Suzanne J. Forrest, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA

Background: Several aggressive pediatric and young adult cancers are characterized by loss of INI1 expression, including malignant rhabdoid tumor, ATRT, epithelioid sarcoma and poorly differentiated chordoma. These cancers have a poor prognosis and limited effective treatments for relapsed or refractory disease. Prior data nominated immune checkpoint inhibition as a potential strategy for INI1-deficient tumors. **Methods:** In this phase II multicenter trial of nivolumab and ipilimumab, patients 6 months to 40 years with relapsed or refractory INI1-deficient cancers were enrolled in two strata: extracranial solid tumors (Stratum 1) and CNS tumors (Stratum 2). The primary endpoint was objective response ≥partial response (PR) by RECIST v1.1 (Stratum 1) or RANO (Stratum 2). Secondary endpoints included progression-free survival, overall survival and 12-month disease control rate. Patients received nivolumab 3mg/kg and ipilimumab 1mg/kg every 3 weeks for 4 cycles followed by nivolumab 3mg/kg every 2 weeks for up to 1 year. A Simon's two-stage design targeted a response rate >25%, with each stratum assessed separately. Interim analysis at Stage 1 required ≥1 of 10 patients to have response ≥PR to proceed to Stage 2; at Stage 2, ≥3 of 20 patients with response ≥PR for evidence of efficacy. Evaluable patients received study treatment and were assessed for response or had progressive disease. **Results:** Thirty patients from six centers enrolled across both Strata from 8/2020 to 5/2025 and 27 were evaluable for the primary endpoint. Three inevaluable Stratum 1 patients were replaced per protocol. In Stratum 1, 1 patient (with poorly-differentiated chordoma) of 20 evaluable patients had ≥PR (ORR: 5%; 95% CI: 0.1-25%). In Stratum 1 (n=20), the 3-month EFS±SE and OS±SE were 20%±9% and 60%±11%, respectively, and the proportion of patients who were progression-free at 12-months was 5% (95%CI=0.1%-25%). Stratum 2 closed early with 7 patients enrolled, too few for Stage 1 interim analysis. No Stratum 2 patients had ≥PR [ORR: 0% (n=7)]. Patients received a median of 2 cycles of study treatment. The most common ≥ grade 3 treatment-related adverse events were decreased lymphocyte count (n=3), increased AST (n=3) anemia (n=2), and pneumonitis (n=2). **Conclusions:** The study did not meet the predetermined threshold for efficacy for Stratum 1. Immune checkpoint inhibitor therapy could warrant further exploration in poorly differentiated chordoma. Clinical trial information: NCT04416568. Research Sponsor: Gateway for Cancer Research; Alex's Lemonade Stand Foundation for Childhood Cancer.

Patient characteristics (n=27 evaluable patients).

	Median (Range)
Age at enrollment (years)	7.1 (0.6-37.6)
Lines of prior therapy	2 (1-7)
	n (%)
Age group	
<18 yrs	24 (89%)
≥18 yrs	3 (11%)
Sex	
Male	15 (56%)
Female	12 (44%)
Cancer diagnosis	
Stratum 1	20 (74%)
Malignant Rhabdoid Tumor	12 (60%)
Poorly Differentiated Chordoma	3 (15%)
Epithelioid Sarcoma	2 (10%)
Other	3 (15%)
Stratum 2	7 (26%)
Atypical Teratoid Rhabdoid Tumor	7 (100%)

10030 Poster Session

Safety and feasibility of cabozantinib (CABO) in combination with cisplatin, doxorubicin, and high-dose methotrexate (MAP) in patients with newly diagnosed high-risk osteosarcoma (OS). First Author: Michael W. Bishop, Arkansas Children's Hospital, Little Rock, AR

Background: CABO is a multi-targeted kinase inhibitor of VEGFR2, c-MET, AXL and RET and has shown clinical evidence of activity in two prior studies of adult and pediatric patients with advanced OS. We report results of a feasibility cohort of CABO + MAP chemotherapy in patients with newly diagnosed high-risk OS. **Methods:** Patients <40 years, body surface area ≥ 0.8 m^2 and new diagnosis of high-grade OS with metastatic disease and resectable primary tumor were eligible. Patients were enrolled to two CABO dose levels (Dose Level 1 (DL1) 25 mg/m^2/day, maximum 40 mg/day; Dose Level 2 (DL2) 35 mg/m^2/day; maximum 60 mg/day) using a modified IQ 3+3 design. CABO was orally administered concomitantly with six 35-day cycles of MAP (cisplatin 60 mg/m^2 on days 1-2 (cycles 1-4), doxorubicin 37.5 mg/m^2 on days 1-2 (with dexrazoxane), methotrexate 12 g/m^2 on days 22, 29) and for 24 weeks as maintenance monotherapy. CABO was held after 7 weeks and resumed during 4th MAP cycle to allow for primary tumor resection and metastatic surgeries. Dose-limiting toxicities (DLT) were assessed during weeks 1-6 of treatment; additional monitoring for post-surgical complications was conducted through completion of 4th MAP cycle. The primary endpoint for this cohort was feasibility of combination therapy. **Results:** Ten patients (median age 11.5 years, 70% male) were enrolled and treated with CABO + MAP (DL1, n=4; DL2, n=6). Median cumulative doses of all MAP agents were maintained throughout treatment with no dose reductions. Concomitant dosing of CABO with MAP was tolerated with no protocol-specified DLTs occurring during the evaluation period. DL2 (35 mg/m^2) was established as the recommended dose for further study of combination therapy. Commonly reported adverse events included hematologic toxicities, febrile neutropenia, and alanine/aspartate aminotransferase (AST/ALT) elevation. Interruption of CABO was required in 6 patients for Grade 3+ AST/ALT elevation following methotrexate (n=3), wound complications (n=3), and Grade 3 pneumothorax (n=1). Wounds included two Grade 3 port site events and one Grade 1 primary tumor resection site; two patients later resumed CABO after healing without wound recurrence. Dose reduction of CABO was required in one patient for Grade 4 amylase elevation. **Conclusions:** The combination of CABO + MAP is feasible with no protocol-specified DLTs during the evaluation period. Generalizability is limited based on cohort size. Further evaluation of CABO + MAP is ongoing in a phase II/III randomized efficacy study in newly diagnosed standard and high-risk patients using CABO dose of 35 mg/m^2/day (max 60 mg), with delayed initiation of CABO in patients with port placement and early safety monitoring for wound-related events, as well as full study monitoring of dose delivery, wound complications and systemic toxicity. Clinical trial information: NCT05691478. Research Sponsor: Children's Oncology Group.

10031 Poster Session

Long term effects of treatment with dabrafenib (D) and/or trametinib (T) in pediatric patients with MAPK pathway-activated tumors. First Author: Eric Bouffet, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

Background: Studies have shown the clinical benefits of D and T, in combination and as monotherapy, to treat adult and pediatric patients with *BRAF* V600 mutation-positive cancers. Here, we report the interim results from a long-term, follow-up study for patients from previously completed clinical trials that assessed the use of D and/or T in pediatric patients with MAPK pathway-activated tumors. **Methods:** This ongoing, global, open-label, multi-center study evaluated the long-term effects (general health, growth and development) of D and/or T in pediatric patients with tumors with MAPK pathway activation from previous studies that assessed (1) safety, tolerability and pharmacokinetics of D in solid tumors (NCT01677741); (2) pharmacodynamics and clinical activity of T or D+T in cancer or plexiform neurofibromas (NCT02124772); and (3) safety and efficacy of D+T in glioma (NCT02684058). The patients in this study followed the same treatment as at the end of the parent study. The duration of this study is 7 years after the first patient first visit (FPFV) (November 2019). The primary objective is to assess the long-term safety of the treatment. **Results:** Of a total 165 patients, 157 received the study treatment (D [n=28], T [n=21], D+T [n=108]) and 8 patients were for observation only. Most patients with low-grade glioma (LGG) and high-grade glioma (HGG) had *BRAF* V600 mutation (n=129). The median duration of exposure was approximately 21 months. From FPFV to the data cut-off (October 2024), most of the patients (94.3%) experienced at least one adverse event (AE) with 28% patients experiencing serious AEs. The most common AE was pyrexia (36.9%). AEs leading to treatment discontinuation occurred in 3.8% of total patients (D [3.6%], T [9.5%], D+T [2.8%]). One on-treatment death was reported in the D+T arm due to convulsion (not related to the study treatment). No clinically meaningful changes were observed in hematological or biochemical parameters in the D+T arm. Grade ≥ 3 abnormalities were infrequent and were reported in <2% of patients, except creatine kinase increase (5.7%). Assessment of vital signs, growth, electrocardiography, bone age and Tanner staging did not reveal any new safety signals. In the D+T arm, as per investigator assessment, overall response (complete + partial) was 27.7% for patients with BRAF *V600E* mutation positive LGG (stable disease: 63.9% patients) and 41.2% for patients with BRAF *V600E* mutation positive HGG. The median progression-free survival and median overall survival were not reached. **Conclusions:** In this long-term study, reported AEs were in line with established safety profile of D and/or T. Except more than normal increase in weight, no significant impact of D and/or T was observed on growth, sexual maturation and skeletal development. The benefit-risk remained favorable toward D and/or T therapy in pediatric patients with MAPK pathway-activated tumors. Clinical trial information: NCT03975829. Research Sponsor: Novartis Pharma AG.

10032 Poster Session

Comprehensive genomic landscape of osteosarcoma: Systematic review and analysis of 1,058 patients across 20 studies with therapeutic implications from the Fight Osteosarcoma Through European Research (FOSTER) Consortium. First Author: Emanuela Palmerini, Osteoncologia, Sarcomi dell'Osso e dei Tessuti Molli, e Terapie Innovative - IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

Background: Osteosarcoma exhibits profound genomic complexity, complicating biomarker discovery. Although advances in multi-omics profiling have improved biological understanding, genomic data remain fragmented across heterogeneous cohorts, and actionable alterations are rarely reported. **Methods:** A systematic review identified 20 studies published between 2005 and 2022, spanning heterogeneous sequencing technologies (whole-genome/exome/RNA sequencing, methylome, and targeted gene panels) and reporting genetic drivers and/or potentially actionable mutations. Mutation data were manually extracted from the published results (e.g., tables, figures, oncoplots) and integrated into a binary Mutation Annotation Format - like matrix (1,041 samples, 471 genes) to provide a comprehensive overview of variants reported to date. **Results:** 1058 patients were included, with tissue derivation (primary, metastatic, recurrent) described in about 10% of the cases. 3816 germlines or somatic SNVs, CNVs or structural alterations were reported in 471 genes. *TP53* (40%), RB1 (18%), and *CDKN2A/B* (17%) were the most frequently altered genes, alongside with recurrent changes in cell cycle regulators (*CCND* family) and angiogenesis-related genes (*VEGFA*). Potentially actionable variants were less common: *MYC* (13%, all amplifications), *CDK4* (10%), *PDGFRA* (8%); single agent activity against such targets is either lacking or not yet available. Potentially actionable epigenetic targets were rarely identified: *TET2* (0.2%), *IDH2* (0.3%), *DNMT3A* (0.7%). TCGA-based pathway analysis revealed consistent involvement of TP53, cell cycle, RTK-RAS, PI3K, and MYC signaling. Co-occurrences detected were *TP53* with *MAP2K4*, *RICTOR*, *PTPRD* and *RB1* genes, and structural rearrangements affecting RTK-RAS and PI3K pathways. There was relative exclusivity between mutations of *RB1* and *CDK4*. **Conclusions:** The analysis identifies a small number of recurrently mutated genes and a large number of rarely affected, though potentially actionable, mutations, encoding proteins involved in cell surface, nuclear and epigenetic interactions. Lack of harmonization in data processing, mutation calling and definition of 'over' and 'under' expression, together with absent descriptions of tissue derivation hamper effective large scale analysis and phenotypic subgrouping. *TP53* mutation co-occurrences such as *RICTOR* or *RB1* were also identified, with potential therapeutic implications including WEE1 and mTOR inhibitors. Tumors with overactive CDK4/6 typically have functional RB1 and might be sensitive to CDK inhibitors. Harmonization of multi-omic methods and collaborative international analyses are essential to advance precision medicine in osteosarcoma and to inform future trials. Research Sponsor: None.

10033 **Poster Session**

Association of response with survival in patients with relapsed/refractory high-risk neuroblastoma: A report from NANT Consortium. First Author: Michael Migotsky, Children's Hospital Los Angeles; Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: Patients with relapsed/refractory (RR) high-risk neuroblastoma (HR-NB) have poor survival. Tumor response may be an early predictive endpoint, though response may not reflect long term survival. We evaluated the association between NANT Response Criteria (NANTRC) v1.2/2.0 with event-free survival (EFS) and overall survival (OS) in patients with RR-NB treated on contemporary NANT Phase 1/2 trials. **Methods:** Patients enrolled on 8 NANT trials from 2013 to 2022 were included. For patients enrolled on more than one trial, the first trial data was included. NANTRC were utilized to grade individual response components (soft tissue [ST], bone/MIBG, bone marrow [BM]) and overall response (complete [CR], partial [PR], minor [MR] response, stable disease [SD], or progressive disease [PD]). Patient/tumor characteristics, prior therapy and relapse, and disease at enrollment were analyzed for association with best overall response (BOR). Component and BOR were analyzed for association with EFS and OS from trial treatment initiation. EFS and OS were compared with the log-rank test and estimated by the Kaplan-Meier methods. **Results:** Among 244 patients, 3-year OS was 52% (95% confidence interval [CI] 46-58%), and EFS was 22% (95% CI 14-32%). OS differed significantly by best overall response ($p<0.001$), driven primarily by inferior outcomes of patients with PD. The 3-year OS was 16% (95% CI 9-29%) for patients with PD. Patients achieving objective response (CR/PR/MR) had an OS of 63% (95% CI 55-74%) and EFS 25% (95% CI 15-43%), while those achieving disease control (CR/PR/MR/SD) had very similar OS of 63% (95% CI 57-71%) and EFS 29% (95% CI 20-43%). Among patients with response of CR, PR, MR, or SD, OS and EFS were not significantly different. For individual components, a similar impact on OS was seen for PD vs no PD (all $p<0.001$), with BOR of PD in MIBG/bone and ST having OS <10%. Patients lacking either BM or bone/MIBG involvement (but not ST) at baseline and remained not involved in those components demonstrated superior OS (both $p<0.001$). Patients with BOR of PD had shorter time from diagnosis to first progression (median of 1.4 vs 1.8 years, $p=0.035$), and higher incidence of *MYCN*-amplified disease (46% vs. 14%, $p<0.001$) and prior history of progression (95% vs 73%, $p<0.001$). **Conclusions:** In RR-HRNB treated on contemporary NANT trials, BOR of PD is associated with inferior OS. Patients achieving disease control (CR/PR/MR/SD) experienced comparable outcomes regardless of response achieved. These findings support disease-control as a clinically meaningful efficacy endpoint for early-phase neuroblastoma trials. Research Sponsor: National Cancer Institute; P01 CA217959; V Foundation for Cancer Research; St. Baldrick's Foundation; United Therapeutics; Pfizer; Band of Parents; Anonymous.

3-year survival by component response.

Component	Response	N	OS % (95% CI)	EFS* % (95% CI)
BM	Non-PD	100	47 (38, 58)	17 (7, 38)
	PD	18	29 (14, 61)	-
Bone/MIBG	Non-PD	180	59 (52, 66)	22 (13, 35)
	PD	30	7 (2, 26)	-
ST	Non-PD	142	61 (53, 70)	28 (18, 44)
	PD	35	9 (3, 25)	-

*EFS censored at time of new therapy.

10034 **Poster Session**

HopeMove: Feasibility and acceptability of a mobile exercise app for pediatric patients undergoing cancer treatment. First Author: Rejin Kebudi, Istanbul University, Oncology Institute & American Hospital-Koc University, Pediatric Hematology-Oncology, Istanbul, Turkey

Background: Cancer related fatigue and reduced physical activity are common during pediatric cancer treatment and negatively affect daily functioning and quality of life. Although exercise is recommended as supportive care, maintaining regular physical activity during active treatment is challenging. Digitally delivered exercise programs may offer flexible and safe supportive care options. This study evaluated the feasibility, acceptability, usability, and safety of the HopeMove mobile exercise app and explored preliminary changes in fatigue among adolescents undergoing cancer treatment. **Methods:** This prospective, single center pilot feasibility study included adolescents aged 13-18 years undergoing active cancer treatment (N=15). Participants completed 45 minute video guided exercise sessions at least three times per week for eight weeks. The intervention was developed through a multidisciplinary collaboration involving pediatric oncology clinicians, pediatric nurses, physiotherapists, and engineers. Exercise sessions included warm-up, aerobic, strengthening, flexibility, and cool down components, with seated and standing options tailored to individual clinical needs. Prior to patient implementation, the HopeMove mobile application was evaluated by 10 clinical experts using the Mobile Application Usability Scale (MAUS). Feasibility outcomes included recruitment, retention, adherence, and technical performance. Adherence was defined as completing at least 75% of planned exercise sessions. Participant satisfaction was measured with a Visual Analog Scale (VAS). Before the intervention, adolescents completed brief application evaluation questions. Fatigue was assessed before and after the intervention using a validated pediatric oncology specific fatigue scale. Safety was monitored throughout the study. **Results:** All eligible adolescents agreed to participate and completed the intervention, resulting in 100% recruitment and retention. Twelve participants (80%) met adherence criteria. The application showed high usability (mean MAUS score 6.55 ± 0.49) and high satisfaction (VAS mean 6.66 ± 0.48). Participants reported the application to be easy to use and age appropriate. Fatigue scores improved significantly after the intervention, increasing from 100.06 ± 22.28 at baseline to 139.26 ± 18.89 post-intervention ($p<0.001$). Significant improvements were observed across fatigue subdomains (all $p<0.01$). No exercise related adverse events, injuries, falls, or treatment interruptions were reported. **Conclusions:** HopeMove was feasible, acceptable, and safe for adolescents undergoing active cancer treatment. High adherence, favorable usability, and improved fatigue outcomes suggest that mobile, video guided exercise interventions may support supportive care in pediatric oncology. Larger controlled studies are warranted. Clinical trial information: NCT07274358. Research Sponsor: None.

10035 **Poster Session**

Concurrent RNA- and DNA-NGS testing for the detection of clinically-relevant fusions in pediatric solid-tumor patients. First Author: Lisa Gai, Tempus AI, Chicago, IL

Background: Identifying structural rearrangements and gene fusions is critical to providing high quality, precision-driven clinical care for many types of pediatric cancers. RNA next-generation sequencing (NGS) provides a functional readout of the genome that enables superior detection of chimeric transcripts and novel driver fusions, particularly when genomic breakpoints reside in complex intronic regions. This study demonstrates the benefit of concurrent DNA- and RNA-NGS for fusion detection in a real world pediatric cohort of 1,050 patients, one of the largest such studies to date. **Methods:** We used the Tempus de-identified multimodal database to select a cohort of pediatric solid tumor cancer patients (all stages) who received successful DNA (Tempus xT, 648 gene panel with enhanced detection of structural variants [SVs] in 22 genes) and RNA (Tempus xR, whole-transcriptome) NGS sequencing. All patients had a minimum tumor purity of 20% and were aged 0-21 at the time of sample collection (n=1,050). All assessed fusions appeared on clinical reports. **Results:** Overall, we detected a fusion in 35.1% of patients (n=369). The top 3 cancer types in our cohort were soft tissue sarcoma (n=321), brain/CNS cancer (n=280), and bone cancer (n=120), and fusion prevalence in these types was 53% (n=170), 30.4% (n=82) and 30% (n=36), respectively. The fusion types with the highest overall prevalence were: EWSR1 (9.0%, n=95), BRAF (6.1%, n=64), PAX3-FOXO1 (2.7%, n=28), ALK (2.2%, n=23), and RET (2.0%, n=21) fusions. In assessing the subset of genes that appear on both the DNA-NGS and RNA-NGS panel, 303 patients harbored one of these fusions and 38.6% (117/303) of those fusions were detected only via RNA-NGS. Among fusions with highest prevalence, the percentage detected only via RNA-NGS ranged from 3.1% (EWSR1 fusions) to 100% (PAX3-FOXO1); BRAF (53/64, 82.8%) and ALK (4/23, 17.4%) fusions both had comparatively high proportions detected only via RNA-NGS. RNA-NGS alone detected gene fusions in 65 additional patients where neither partner appears on the DNA-NGS panel. Considering only fusions associated with an indication-matched FDA-approved targeted therapy, we observed a prevalence of 9.0% (94/1050), and of these, 46.8% (44/94) were detected only by RNA-NGS. Overall, 49.3% (182/369) of fusion-positive patients would have been missed if RNA-NGS were not performed, representing 17.3% of the total cohort. **Conclusions:** Pediatric solid tumors are frequently driven by structural rearrangements and gene fusions that are difficult to characterize using DNA sequencing alone. This study demonstrates that performing combined DNA-NGS and RNA-NGS substantially improves the identification of patients with a clinically relevant fusion in a large real-world data set. Research Sponsor: None.

10036 **Poster Session**

Precision oncology in practice: Real-world multicenter experience with larotrectinib in pediatric extracranial NTRK fusion–positive tumors. First Author: Rejin Kebudi, Istanbul University, Oncology Institute & American Hospital-Koc University, Pediatric Hematology-Oncology, Istanbul, Turkey

Background: Gene fusions involving *NTRK1/2/3* represent actionable oncogenic drivers across a spectrum of rare pediatric solid tumors. Larotrectinib, a highly selective TRK inhibitor, has demonstrated robust efficacy and a favorable safety profile in clinical trials. However, real-world data from middle-income countries remain limited. We report a national multicenter real-world experience evaluating outcomes of pediatric patients with NTRK fusion–positive tumors treated with larotrectinib in Türkiye. **Methods:** This retrospective, descriptive multicenter study included pediatric patients (0–18 years) with histologically confirmed solid tumors harboring *NTRK* gene fusions, treated with larotrectinib for ≥1 month between August 2023 and April 2025. Clinical data were collected from 15 tertiary pediatric oncology centers. Treatment response was assessed using RECIST v1.1 or tumor-specific pediatric criteria. Adverse events were graded per CTCAE v5.0. Survival outcomes were analyzed descriptively. **Results:** Twenty-two patients were included; median age at diagnosis was 3 months (range, 1 day–182 months), and 59% were female. Infantile fibrosarcoma (IFS) was the most common diagnosis (n=16, 72.7%), followed by rhabdomyosarcoma (RMS), epithelioid sarcoma (ES), desmoplastic small round cell tumor (DSRCT). Six patients (27.3%) had metastatic disease at diagnosis. Larotrectinib was initiated due to disease progression or inadequate response to prior therapy in 86% of patients, treatment-related toxicity in 9%, and as maintenance therapy in one patient. After a median follow-up of 24 months, 10 patients achieved complete response, 6 had partial response or stable disease, and 4 experienced progression; 3 patients later relapsed. One patient died due to progressive disease. The 24-month overall survival rate was 95.5%, and 82% of patients remained event-free. No treatment-limiting adverse events were observed. **Conclusions:** In this national real-world cohort, larotrectinib demonstrated high efficacy, durable disease control, and an excellent safety profile in pediatric patients with NTRK fusion–positive solid tumors, particularly IFS. These findings support early integration of molecular diagnostics and TRK inhibition into routine pediatric oncology practice and provide valuable real-world evidence from a middle-income country setting. *Larotrectinib was provided through the early access to medicines program for humanitarian purposes and the data reflects real world data and does not reflect phase research data. The pharmaceutical company did not provide any kind of support in the planning/reporting/publication of the study. Research Sponsor: None.

10037 **Poster Session**

Dinutuximab beta in combination with chemotherapy in patients with refractory or relapsed neuroblastoma: A national prospective study (2020/ABM/01/00055). First Author: Aleksandra Wieczorek, Jagiellonian University Medical College, Department of Pediatric Oncology and Hematology, Krakow, Poland

Background: The ChIm-NB-PL phase IIa trial (EudraCT: 2021-003832-96) evaluated the safety and efficacy of dinutuximab beta (DB) combined with chemotherapy (Cht) in children with relapsed or refractory high-risk neuroblastoma (RR-HRNB), a population with limited therapeutic options and poor prognosis. **Methods:** Twenty-eight patients aged 1–18 years with RR-HRNB received DB combined with temozolomide/irinotecan (TemIri) or with N5/N6 chemotherapy of the German Pediatric Oncology and Hematology Group (GPOH) protocol. DB was administered as a 5-day continuous infusion (10 mg/m²/day) every 21 days, concurrently with TemIri or sequentially after GPOH. Treatment allocation and number of cycles were individualized based on prior therapy, disease dynamics, metastatic burden, and toxicity. Responses were assessed after 3 and 5–7 cycles. The primary endpoint was safety and best response (complete or partial response); secondary endpoints included progression-free survival (PFS) and overall survival (OS). **Results:** Between 2021 and 2025, 28 patients were enrolled (25% female). Median follow-up was 28.4 months. Median age was 40.9 months at diagnosis and 51.0 months at study entry. Eleven patients had refractory disease (Group 1), while 17 had relapsed or progressive disease (Group 2; 12 early and 5 late relapses). MYCN amplification was present in 9 patients, and 12 had involvement of more than one metastatic compartment. In Group 1, best response rate (BRR) was 91.7%, end-of-treatment response rate 75.0%, and metastatic complete response 58.3%; 1-year PFS was 0.67 $\pm$ 0.13. In Group 2, BRR was 87.5% (CR 56.3%, PR 31.3%), with higher BRR in late versus early relapse (100% vs 80%); 1-year PFS was 0.81 $\pm$ 0.09. Overall, 71.4% of patients were alive at last follow-up; 1-year PFS and OS were 0.75 $\pm$ 0.08 and 0.82 $\pm$ 0.07, respectively. Grade $\geq$3 non-hematologic toxicities occurred 42 times with TemIri and 35 times with GPOH (CTCAE v4.0). Neurotoxicity, pain, capillary leak syndrome, and cytokine release syndrome were comparable between regimens and consistent with DB monotherapy. **Conclusions:** DB combined with TemIri or GPOH chemotherapy demonstrates high antitumor activity with acceptable and manageable toxicity in children with RR-HRNB. Response-adapted sequencing and individualized chemotherapy selection may improve disease control, including metastatic responses, in this high-risk population. Clinical trial information: 2021-003832-96. Research Sponsor: Medical Research Agency; 2020/ABM/01/00055.

10038 **Poster Session**

A study of the safety, efficacy, and pharmacokinetics of SPJ-101CA as maintenance therapy for newly diagnosed high-risk neuroblastoma. First Author: Atsushi Makimoto, Tokyo Metropolitan Children's Medical Center, Fuchu, Japan

Background: Isotretinoin (ISO), an oral vitamin A derivative, induces differentiation of neuroblastoma (NB) cells and is used as maintenance therapy. SPJ-101CA (Sun Pharma Ltd.), a novel ISO formulation developed with microparticle technology to enhance absorption, is designed to achieve adequate systemic exposure at 80% of the conventional dose. As ISO is an off-label treatment for NB worldwide, the present, registration-directed clinical trial was conducted to evaluate the safety, efficacy, and pharmacokinetics (PK) of SPJ-101CA in pediatric patients. **Methods:** This open-label, multicenter phase 2 trial enrolled 16 patients aged 1-18 years with newly diagnosed, high-risk NB who had completed the standard, multidisciplinary therapy without progression. Eligibility required an ECOG performance status of 0-2 and adequate organ function. The exclusion criteria were other active malignancies, gelatin allergy, pregnancy or breastfeeding, psychiatric disorder, and intolerance to the study treatment. Written informed consent was obtained from the patients' legal guardians, and assent was provided by the patients when appropriate. The patients received oral SPJ-101CA 64 mg/m² twice daily for 14 days in each, 28-day course for a total of six courses. Dinutuximab was permitted only before or after, but not during, SPJ-101CA administration. The primary endpoint was the incidence of serious adverse events (AEs). The secondary endpoints included 1-year event-free and overall survival, the AE incidence, and PK properties. Blood samples were collected on day 14 of the first course at predefined intervals to measure the plasma concentration of ISO and 4-oxo-isotretinoin, and the standard PK parameters were evaluated. **Results:** All 16 patients were included in the full analysis and per-protocol sets. Three serious AEs related to SPJ-101CA occurred in three patients (two and one case of hypertriglyceridemia and hypercalcemia, respectively), for a total incidence of 18.8%. Common, non-serious AEs included upper respiratory inflammation (75.0%), dry skin (62.5%), hypercalcemia (56.3%), eczema (50.0%), hypertriglyceridemia (43.8%), cheilitis (37.5%), pruritus (31.3%), and neutropenia (31.3%). The 1-year event-free survival rate was 93.8%, and the overall survival rate was 100%. PK analysis of 15 patients found that the mean T_{max} of ISO was 3.9 hours and that the 4-oxo-isotretinoin level remained constant and exhibited no distinct peak. The mean ISO C_{max} was approximately 2.3 μg/mL, with a half-life of about 5 hours; 4-oxo-ISO had a higher C_{max} and longer half-life. **Conclusions:** SPJ-101CA was well-tolerated and effective as maintenance therapy following multidisciplinary treatment for high-risk NB. The PK findings were consistent with the known profile of ISO and indicated good absorption of the formulation. Clinical trial information: jRCT2031220687. Research Sponsor: Sun Pharma Japan Ltd.

10039 **Poster Session**

Phase I study of the LiViT regimen (liposomal irinotecan, vincristine, and temozolomide) in pediatric patients with relapsed/refractory solid tumors. First Author: Feifei Sun, Department of Pediatric Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: Relapsed or refractory solid tumors in children and adolescents remain a major therapeutic challenge with limited effective options. Liposomal irinotecan provides prolonged systemic exposure compared to conventional irinotecan and may offer improved efficacy and tolerability. We conducted a phase I trial to determine the recommended phase II dose (RP2D), safety, and preliminary antitumor activity of the LiViT regimen in patients aged 2–18 years. **Methods:** This single-center, open-label phase I study enrolled patients aged 2–18 years with relapsed/refractory solid tumors. The LiViT regimen consisted of vincristine (1.5 mg/m² IV day 1; max 2 mg), temozolomide (150 mg/m²/day IV days 1–5) and liposomal irinotecan at escalating doses of 40, 50, 65, 80, or 100 mg/m² (IV day 1) every 3 weeks. A standard 3+3 dose-escalation design was used (Ia), followed by an expansion cohort (Ib). **Results:** Twenty-nine patients were enrolled (Ia: 18; Ib: 11). Diagnoses included rhabdomyosarcoma (n=12), neuroblastoma (n=9), desmoplastic small round cell tumor (n=3), Ewing sarcoma (n=2), and others (n=3). In phase Ia, liposomal irinotecan was administered at escalating doses of 40, 50, 65, 80, and 100 mg/m². At 80 mg/m², 1 of the first 3 patients experienced a dose-limiting toxicity (DLT) (grade 3 diarrhea lasting $>$3 days despite loperamide); the cohort was expanded to 6 patients, and no additional DLTs or other grade 3–4 toxicities were observed. No DLTs occurred among patients treated at 100 mg/m² during Ia (n=3) or in the Ib expansion cohort (n=11). The MTD was not reached, and 100 mg/m² was selected as the RP2D based on safety in 14 patients. Across all dose levels, the only grade $\geq$3 treatment-related adverse event was the single episode of grade 3 diarrhea at 80 mg/m²; all other toxicities were grade 1–2. Among 27 evaluable patients, 5 achieved partial response (PR) and 12 had stable disease (SD), yielding an objective response rate (ORR) of 18.5% and a disease control rate (DCR) of 63.0%. **Conclusions:** The LiViT regimen is feasible with a manageable safety profile in pediatric patients with relapsed/refractory solid tumors. The MTD was not reached, and liposomal irinotecan at 100 mg/m²—the highest tested dose—was established as the RP2D. Promising preliminary activity supports phase II evaluation. Clinical trial information: NCT06710821. Research Sponsor: None.

10040 **Poster Session**

Changes in the incidence of second malignant neoplasms in neuroblastoma over time: An updated SEER database analysis. First Author: Arhanti Sadanand, UT Southwestern, Dallas, TX

Background: To investigate changes in the incidence of second malignant neoplasms (SMN) for patients with neuroblastoma in the era of anti-GD2 immunotherapy, we analyzed patients from the SEER database according to four treatment eras (1: 1975–1989, 2: 1990–1996, 3: 1997–2010, 4: 2011–2018) corresponding to the introduction of multi-agent chemotherapy, risk-based treatment, stem cell transplant, and GD2-directed immunotherapy. We hypothesized that while the GD2-directed immunotherapy would not increase the incidence of SMNs for patients with neuroblastoma, the standardization of tandem autologous transplant would. **Methods:** The SEER database was assessed for patients younger than 30 years of age with neuroblastoma (ICD-O-3 9500) or ganglioneuroblastoma (ICD-O-3 9490). Patient demographic information and characteristics were assessed, including age at diagnosis, sex, race, histology, year of diagnosis, and extent of disease. Data about delivery of chemotherapy or radiotherapy were collected when available. Statistics including the cumulative incidence of SMN, standardized incidence ratios (SIRs), and rates of SMNs between patients in different eras were calculated. **Results:** The analytic cohort included 4,491 patients. Eighty-four patients (1.9%) developed a SMN with a median latency of 10 years. The SIR of all SMNs was 5.5 (95% CI 4.4-9.0). The majority of SMNs were hematologic (n=23; SIR 18.5, 95% CI 11.7-87.0), followed by kidney cancer (n=14; SIR 28, 95% CI 15.2-309.1) and thyroid cancer (n=12; SIR 11.2, 95% CI 5.8-58.6). Patients who developed a SMN were more likely to have received radiation than those who did not (39.3% versus 24.7%; p=0.002). There was no significant difference in median age, sex, race, or ethnicity between patients who did or did not develop a SMN. The cumulative incidence of SMN at 30 years from diagnosis for high-risk patients was 4.1% (95% CI 2.63-5.56) compared to 1.6% (95% CI 1.07-2.12) in non-high-risk patients. There was a trend toward increasing SIRs over time; in Era 1: the SIR was 3.4, with a 95% CI 2.2-7.0; in Era 2: the SIR was 3.2, with a 95% CI 1.4-9.9; in Era 3: the SIR was 8.7, with a 95% CI 6.3-20.3; and in Era 4: 9.2, 95% CI 4.8-42.1. **Conclusions:** High-risk neuroblastoma patients continue to suffer from high rates of SMNs compared to non-high risk neuroblastoma patients in the current era of GD2-directed immunotherapy. Using standardized incidence ratios, there is a trend toward increasing rates of SMNs in our cohort compared to the general population. This increase may be due to the continued addition of cytotoxic therapy. Ongoing monitoring and research into treatment-associated toxicities is needed for neuroblastoma survivors in the modern era of therapy. Research Sponsor: None.

10041 **Poster Session**

Interrogation of fibrolamellar cancer to provide clinically relevant insights into therapeutic vulnerabilities. First Author: Sabina A. Schneider, Nagourney Cancer Institute, Long Beach, CA

Background: Fibrolamellar carcinoma (FLC) is a rare disease that primarily afflicts young adults. Systemic therapy with surgery is the only curative intervention for advanced disease with 5-year survivals of 45%. We examined 3-dimensional tissue explants from FLC patients to measure the efficacy of cytotoxics, targeted agents and novel combinations. **Methods:** Of 41 FLC specimens; 17 female, 24 male, median age 26 (14-60), 36 (88%) were previously treated, 18/36 (50%) Oxaliplatin & Gemcitabine-Lenvatinib (GEMOX-LEN), 11 (31%) 5FU & Interferon and 18 (50%) Nivolumab. Samples were examined by Ex Vivo Analysis of Programmed Cell Death (EVA/PCD) as previously described. Following disaggregation and 72-hour drug exposures, 5-point dose-response curves were interpolated to provide lethal concentration 50% (LC50) for comparison with 10,000 prior human tumor explant analyses. Drug synergy was evaluated by the method of Chou & Talalay (Chou TC. *Cancer Res* (2010)15;70(2):440-6). Of 24 drugs and combinations selected for testing, FLC yields were sufficient for 18/24 (75%) to be fully analyzed. To explore mechanisms of response/resistance, single agent LC50's compared drug activity against all solid tumors by Z-score. **Results:** By rank order the highest activity for single-agents identified Vorinostat (HDAC), followed by Phenformin (Mitochondrial Complex I) and 6-Diazo-5-Oxo-L-norleucine (Glutaminolysis), then Cobimetinib (MEK) Regorafenib (TKI), KAT (Hexokinase) Lenvatinib (TKI) and Irinotecan (TOPO I). The lowest activity was found for Navitoclax (BH3) followed by Celecoxib (NSAID) and Quercetin (Natural product). Z scores for drug combinations favored GEMOX and 5FU & Interferon compared with other solid tumors. Previously treated tumors were more drug resistant. GEMOX combined with LEN proved synergistic in 40% of samples. Despite low single agent activity, Quercetin showed synergy with Lenvatinib. Discussion: We have previously described the ex vivo study of small molecules as probes of human tumor biology. As FLC uniformly expresses the DNAjb1-PRKACA gene-fusion, we used drugs with known mechanisms of action to interrogate operative pathways and vulnerabilities of the FLC phenotype associated with the DNAjB1-PRKACA genotype. We have previously shown that Vorinostat and Phenformin activities correlate with the MYC-directed BRD-inhibitor JQ1 while Protein Kinase A is known to regulate MYC and glutaminolysis is an established hallmark of MYC activation. **Conclusions:** The results suggest that the DNAjB1-PRKACA reprograms FLC toward a metabolic phenotype that is vulnerable to epigenetic modulation, mitochondrial targeting and glutaminolysis inhibition. The study met its objective to establish a database for the future management of FLC patients. This will allow each patient's tissue to be used to craft novel therapies predicated upon new insights into the biology of FLC. Research Sponsor: None.

10042 **Poster Session**

Prognostic significance of CD8+T lymphocytes and CD68+ macrophages in assessing pathologic response in pediatric soft tissue sarcomas. First Author: Djamila Polatova, Scientific Practical Medical Center for Pediatric Oncology, Hematology and Immunology, Tashkent, Uzbekistan

Background: The tumor immune microenvironment (TIME) plays a critical role in treatment response in pediatric oncology. Conventional clinical and demographic parameters often fail to accurately predict individual therapeutic outcomes. Increasing evidence suggests that the phenotype and spatial distribution of immune cells within the tumor may provide valuable prognostic information. This study evaluated the prognostic significance of immune markers (CD4, CD8, CD20, CD68) and their localization in predicting therapy-induced pathomorphologic response in pediatric soft tissue sarcomas (STS). **Methods:** A retrospective analysis was conducted in 98 pediatric patients with embryonal and alveolar STS. Immunohistochemical profiling was performed to assess the status, density, and spatial localization (intratumoral vs peritumoral) of CD4+, CD8+, CD20+, and CD68+ immune cells. Treatment response was evaluated based on the degree of therapy-induced pathomorphosis (grades I–IV) and standard imaging criteria. Statistical analysis included Spearman correlation and chi-square testing. **Results:** Intratumoral immune-cell infiltration demonstrated stronger prognostic value than demographic or clinical characteristics. A significant association was observed between CD8+ T-cell positivity and higher grades of pathomorphologic response (grades III–IV; p=0.001). CD68+ macrophage infiltration was also significantly correlated with tumor regression ($p<0.001$). Intratumoral localization of CD8+ (p=0.002) and CD68+ (p=0.021) cells was significantly associated with improved therapeutic response compared with peritumoral localization. No significant associations were identified for age (p=0.771), sex (p=0.775), or histologic subtype (p=0.960). **Conclusions:** Intratumoral CD8+ T lymphocytes and CD68+ macrophages are key predictors of therapeutic response in pediatric STS. These findings support the integration of immunohistochemical profiling into routine clinical practice for response stratification. The results also provide a rationale for combining standard chemotherapy with immunomodulatory strategies to enhance intratumoral immune infiltration. Clinical trial information: B2023.2.DSc/Tib856. Research Sponsor: None.

10043 **Poster Session**

Utilization and outcomes of minimally invasive resection in patients with neuroblastoma and Wilms tumor in a national cohort. First Author: Courtney N. Day, Mayo Clinic Rochester, Rochester, MN

Background: Tumor resection is a cornerstone of therapy for neuroblastoma (NB) and Wilms tumor (WT). Minimally invasive surgical approaches such as laparoscopic or robotic tumor resection hold promise to reduce surgical morbidity while maintaining excellent oncologic outcomes. This study aims to determine the utilization and outcomes of laparoscopic and robotic resection of NB and WT among children in a national cohort, hypothesizing that utilization is increasing over time and outcomes are not inferior to open resection. **Methods:** A retrospective cohort analysis of patients <18 years old in the 2020-2023 National Cancer Database who underwent resection of NB or WT was performed. Surgical approach trends were assessed via Cochran-Armitage tests. Conversions to open surgery, length of stay (LOS), and readmissions were compared between approaches using Kruskal-Wallis, Chi-square, and Fisher's exact tests. **Results:** Among 1,262 children who underwent resection of NB (n=581) or WT (n=681), open procedures were most common (83.4%), followed by laparoscopic (13.9%), and robotic (2.7%). Utilization of each approach was stable over time aside from increased robotic resection of NB from 0% to 4% (p=.024). Approach did not vary by patient age (Table 1). Median WT size and lymph node yield were similar between approaches (both p>.05). In NB, laparoscopic procedures were performed on smaller tumors than open or robotic (p<.001). There were no robotic conversions to open; 11.4% of laparoscopic procedures were converted without change over time or difference between NB and WT (both p>.05). Median LOS was greater for open procedures than laparoscopic or robotic (p<.001). Readmission rates (p=.64) and margin status (p=.63) were similar between approaches. Outcomes did not vary by diagnosis. **Conclusions:** Utilization of minimally invasive approaches for NB or WT resection remains low despite noninferior or improved outcomes. Efforts to safely increase utilization are needed, especially for robotics, so that survivorship can be improved through reduced surgical morbidity. Research Sponsor: None.

Differences in patient characteristics and outcomes by surgical approach.

Characteristic or Outcome	Open	Laparoscopic	Robotic	p value
Age in years (median, IQR)	3 (1, 4)	3 (1, 5)	3 (1, 7)	0.08
% female	53%	53%	44%	0.59
NB tumor size in mm (median, IQR)	72 (50, 101)	47 (35, 71)	70 (51, 86)	<0.001
WT tumor size in mm (median, IQR)	110 (75, 140)	115 (93, 150)	93 (54, 125)	0.10
% metastatic disease	33%	30%	15%	0.07
% neoadjuvant therapy	35%	27%	22%	0.014
% conversion to open	n/a	11%	0%	0.05
Negative margins	86%	83%	96%	0.63
# Lymph nodes assessed in WT (median, IQR)	5 (3, 8)	6 (3, 10)	4 (3, 9)	0.62
LOS in days (median, IQR)	5 (4, 7)	4 (2, 6)	4 (1, 5)	<0.001
% readmission	15%	14%	9%	0.64

10044 **Poster Session**

Impact of central review process on response rates in neuroblastoma clinical trials: A report from NANT Consortium. First Author: Michael Migotsky, Children's Hospital Los Angeles; Keck School of Medicine, University of Southern California, Los Angeles, CA

Background: Accurate and reproducible response assessment is critical for evaluating efficacy in clinical trials. Central response review is frequently used to reduce inter-site variability but is resource intensive and may delay data availability. Whether centralized review meaningfully alters response endpoints compared with remote source verification of site assessment remains unclear. **Methods:** We evaluated response assessments from eight NANT phase 1–2 trials conducted between February 2013 and December 2022 in relapsed/refractory high-risk neuroblastoma. Initial investigator-assessed response, remote source-verified response (remote review of radiology/bone marrow [BM] reports), and centrally-reviewed responses (review of radiographic images and BM biopsy slides) were assessed. Each patient's best overall response (BOR) and individual component responses (BM, MIBG/bone, and soft tissue [ST]) at time of BOR as determined by these three review methods were assessed. Only patients with MIBG-avid disease were included in bone response. **Results:** Among 244 evaluable patients, concordance between remote source-verified response and central review response exceeded the concordance between initial investigator-assessed response and central review response (BOR: 89% vs 79%, BM: 91% vs 74%, MIBG/bone: 92% vs 83%, ST: 82% vs 74%). Concordance between initial investigator-assessed response and remote source-verified response was 86% for BOR and similar for component response (BM: 83%, MIBG/bone: 91%, ST: 86%). Remote source-verified assessment compared to central review demonstrated higher level of concordance than initial investigator assessment for complete response (CR) (90.0% vs 81.0%), partial response (PR) (85.7% vs 72.7%), minor response (MR) (80.6% vs 71.0%), and stable disease (SD) (92.1% vs 86.7%), indicating improved response classification consistency across all major BOR categories. Overall, the initial investigator-assessed response for CR, PR, and MR agreed with central review 74.0% of the time, while remote source-verified agreed 84.7%. Most discordance reflects relabeling within adjacent categories (e.g., CR vs PR or PR vs MR). A change in response from CR/PR/MR to SD/PD when compared to central review was uncommon: 9.4% for initial investigator-assessed response, and decreased with remote source verification down to 7.1%. A change from CR/PR to MR/SD/PD was more frequent but also improved with remote source verification (from 20% to 11.3%). **Conclusions:** Remote source verification substantially improves agreement with central review and reduces responder misclassification. These findings demonstrate that structured remote source verification improves response assessment reliability and harmonization with central review, reinforcing its role as an important quality-control mechanism in multicenter trials. Research Sponsor: National Cancer Institute; P01 CA217959; V Foundation for Cancer Research; St. Baldrick's Foundation; United Therapeutics; Pfizer; Band of Parents; Anonymous.

10045 Poster Session

Evaluating satisfactory testing versus transcript grade performance between childhood cancer survivors and healthy controls. First Author: Raymond Mailhot Vega, University of Miami Miller School of Medicine-Sylvester Cancer Center, Miami, FL

Background: Substantial evidence suggests that survivors of childhood cancer are at increased risk for poor academic performance including receiving poor or failing course grades. There is a paucity of primary data as many contributing studies have relied on parental reporting of school performance. In the state of Florida, a high school student graduating with a standard diploma must successfully pass required biology and math classes. These classes require taking a standardized state-wide test which constitutes 30% of their final course grade. Our team sought to evaluate the concordance of state testing and course grade performance between pediatric brain tumor survivors and matched healthy controls from Florida. **Methods:** Children who received radiotherapy for intracranial tumors between 2007-2020 who reside in Florida were recruited to this IRB-approved study (N=37). Electronic medical record data was linked to scholastic data provided by the Florida Department of Education. Scholastic data included state testing scores and grade transcripts. For every patient enrolled, the state provided scholastic data matched at a 3:1 ratio (healthy control to survivor), based on age, grade, school district, and eligibility for free or reduced lunch (ERFL). We used Fisher's Exact test to perform an analysis of association of test scores and course grades between survivors and controls based on state-set pass/fail criteria. **Results:** Mean age of survivors was 14 years. Fifty-one percent of the survivors were female, 81% white, 8% Black, and 14% Hispanic. The majority received chemotherapy and were ERFL. Approximately 55% of survivors and controls received satisfactory math test scores (Table 1). However, survivors with unsatisfactory math scores were significantly more likely to pass their math class compared to controls (67% vs 51%; P<0.01). For biology, 79% of survivors vs 45% of controls had a satisfactory state test score; however, survivors with unsatisfactory biology scores were significantly more likely to pass their biology class compared to controls (80% vs 73%; P=0.007). **Conclusions:** We present the first US-based evaluation of primary evidence of childhood cancer survivors' performance in schools looking at transcripts. Our results demonstrate a discordance that if a survivor or control performed unsatisfactorily on the state test, the survivor was significantly more likely to pass the actual course required for a standard diploma. Further work inviting stakeholder participation, including students, caregivers, and educators is needed. Research Sponsor: Florida Department of Health; 21L09.

Comparison of standardized math test score and math course grades.

State Test	Number (%)		P-value
Unsatisfactory test	Control (n=61)	Survivor (n=21)	
Passing course	31 (51)	14 (67)	P<0.01
Failing course	30 (49)	7 (33)	
Satisfactory test	Control (n=73)	Survivor (n=26)	
Passing course	71 (97)	26 (96)	
Failing course	2 (3)	1 (4)	

10046 Poster Session

Neurosensory deficits and functional outcomes in childhood cancer survivors: A report from the Childhood Cancer Survivor Study (CCSS). First Author: Chiara Papini, St. Jude Children's Research Hospital, Memphis, TN

Background: Survivors of childhood cancer are at risk for neurosensory deficits secondary to their disease and treatment. Previous research has characterized system-specific (e.g., visual) impairments; however, the prevalence of multisystem neurosensory deficits and their functional impact remain unknown. **Methods:** Adult 5-year survivors (n=20037, median age 36 [range 18-69] years, 53.4% male) and sibling controls (n=4121) reported neurosensory deficits related to vision, hearing, vestibular, and neuropathy. Comorbidities were graded using modified CTCAE v5 and defined as having at least one grade 1 neurosensory deficit in one, two, and three/four systems. Survivors reported neurocognitive function (CCSS Neurocognitive questionnaire; impairment: $<10^{th}$ %ile of sibling distribution), emotional distress (BSI-18; impairment: T score $\geq$63), quality of life (SF-36; impairment: T score $<$40), and functional independence. Multivariable models estimated the prevalence of neurosensory comorbidities, adjusted for age, sex, and race. Multivariable models further adjusted for other chronic conditions and neurotoxic therapies examined associations between comorbidities and functional outcomes in survivors. **Results:** Survivors had higher prevalence of neurosensory deficits in one (31% vs. 24%; prevalence ratio [PR] 1.4, 95% confidence interval [CI] 1.3-1.5), two (14% vs. 8%; 2.2, 1.9-2.5) and three/four systems (9% vs. 3%; 3.3, 2.9-4.1) than siblings. Neurosensory comorbidities were associated with greater risk of neurocognitive impairment (task efficiency and memory), emotional distress (anxiety) and poor quality of life (physical and social function) in a dose-dependent manner in survivors (Table). Similar effects were observed for indicators of functional independence: assistance with personal care/routine needs (one system: relative risk [RR] 2.7, 95% CI 2.2-3.3; two systems: 4.1, 3.3-5.0; three/four systems: 6.5, 5.4-7.9), interference with job/school (2.5, 2.2-3.0; 3.8, 3.2-4.5; 6.1, 5.2-7.1), no driver's license (1.5, 1.3-1.8; 2.4, 2.1-2.8; 3.8, 3.2-4.4), and non-independent living (1.3, 1.2-1.4; 1.8, 1.6-2.0; 2.1, 1.9-2.4). **Conclusions:** Adult survivors of childhood cancer have high rates of comorbid neurosensory deficits that have a dose-dependent impact on functional outcomes. Survivors with multisystem deficits should be prioritized for interventions to support functional independence. Research Sponsor: National Cancer Institute.

Relative risk (95% CI) of impaired outcomes in survivors with neurosensory comorbidities.

Neurosensory comorbidities (# organ systems)	Memory	Task Efficiency	Anxiety	Physical Function	Social Function
0 (ref.)	-	-	-	-	-
1	1.6 (1.4-1.8)	1.8 (1.6-2.0)	2.6 (2.2-3.1)	2.2 (1.9-2.6)	1.9 (1.7-2.1)
2	2.2 (2.0-2.5)	2.4 (2.2-2.7)	3.4 (2.8-4.1)	3.1 (2.7-3.5)	2.5 (2.2-2.8)
3/4	3.1 (2.7-3.4)	3.3 (3.0-3.7)	5.2 (4.4-6.3)	4.4 (3.8-5.0)	3.2 (2.9-3.7)

10047 Poster Session

Comparison of different metrics for estimating kidney radiation exposure during treatment for childhood cancer: A report from the St. Jude Lifetime Cohort Study. First Author: Daniel M. Green, St. Jude Children's Research Hospital, Memphis, TN

Background: Risk for impaired kidney function varies with radiation therapy (RT). We compared different methods for quantifying RT. **Methods:** Kidney function was graded in 2753 survivors (>10 years post-diagnosis, age $\geq$18 years) and 806 community controls (CC) per the Kidney Disease International Global Outcomes 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD). Multivariable logistic regression was used to evaluate the associations between grades 3-5 CKD and demographics and treatment exposures. RT was expressed as percentage of total kidney volume treated with 5 Gray (Gy) or more (V5), 10 Gy or more (V10) Gray, Children's Oncology Group (COG) abdominal RT, or total body irradiation (TBI)/whole abdomen RT (WA). Model discrimination was assessed using area under the receiver operating characteristic curve (AUC). **Results:** 2.1% of survivors had stages 3 to 5 CKD, compared to 0.12% of CC (Odds Ratio (OR): 17.0 (95% confidence interval (CI) 2.9, 682.8), p < 0.001). Significant associations between higher risks of grades 3-5 CKD and demographic and treatment exposures were identified in separate regression models (Table). AUCs were 0.891, 0.888 and 0.896 for V5, V10, and TBI/WA, models respectively. **Conclusions:** TBI/WA is a more readily available exposure designation than V5 or V10. These results inform identification of survivors at highest risk for CKD. Research Sponsor: None.

	V5		V10		COG		TBI/WA	
Predictors	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*	*OR (95%CI)*	*p*
Race (White vs non-White)	1.68 (0.81 – 3.30)	0.144	1.71 (0.82 – 3.35)	0.133	1.80 (0.89 – 3.44)	0.086	1.71 (0.85 – 3.28)	0.116
Age at evaluation	1.09 (1.04 – 1.13)	**<0.001**	1.09 (1.05 – 1.13)	**<0.001**	1.09 (1.05 – 1.13)	**<0.001**	1.10 (1.05 – 1.14)	**<0.001**
Hypertension	8.21 (4.12 – 17.61)	**<0.001**	8.27 (4.15 – 17.71)	**<0.001**	8.61 (4.41 – 18.02)	**<0.001**	8.61 (4.42 – 17.97)	**<0.001**
Nephrectomy (yes/no)	2.44 (0.88 – 6.12)	0.069	2.68 (0.97 – 6.72)	**0.044**	4.23 (1.81 – 9.48)	**0.001**	3.42 (1.36 – 8.01)	**0.006**
Ifosfamide (per 1000 mg/m^2)	1.04 (1.02 – 1.06)	**<0.001**	1.04 (1.02 – 1.05)	**<0.001**	1.04 (1.03 – 1.06)	**<0.001**	1.04 (1.03 – 1.06)	**<0.001**
Cisplatin (per 100 mg/m^2)	1.46 (1.26 – 1.68)	**<0.001**	1.46 (1.26 – 1.67)	**<0.001**	1.47 (1.27 – 1.68)	**<0.001**	1.49 (1.29 – 1.70)	**<0.001**
Carboplatin (per 100 mg/m^2)	1.03 (1.00 – 1.06)	**0.024**	1.03 (1.00 – 1.06)	**0.027**	1.03 (1.00 – 1.06)	**0.012**	1.03 (1.00 – 1.06)	**0.012**
Calcineurin inhibitor (yes/no)	7.29 (1.86 – 26.92)	**0.003**	7.9 (11.94 – 30.52)	**0.003**	14.79 (4.32 – 48.28)	**<0.001**	9.31 (2.43 – 33.77)	**0.001**
Doses Abelcet and/or Ambisome	1.02 (0.94 – 1.06)	0.516	1.02 (0.94 – 1.06)	0.513	1.02 (0.95 – 1.06)	0.469	1.02 (0.94 – 1.06)	0.555
Doses amphotericin B	1.00 (0.95 – 1.03)	0.990	1.00 (0.95 – 1.03)	0.998	1.00 (0.96 – 1.03)	0.981	1.00 (0.95 – 1.03)	0.936
V5 (per 10%)	1.14 (1.04 – 1.24)	**0.004**						
V10 (per 10%)			1.12 (1.01 – 1.23)	**0.021**				
COG abdominal radiation therapy (yes/no)					1.49 (0.76 – 2.85)	0.235		
TBI or WA (yes/no)							2.73 (1.08 – 6.61)	**0.029**

10048 Poster Session

Opportunities for breast cancer prevention among pediatric lymphoma survivors treated with chest radiation: Projected gap in breast cancer deaths with real-world uptake rates. First Author: Jenna R. Rogers, Interfaculty Initiative in Health Policy, Harvard University, Cambridge, MA

Background: For survivors of pediatric lymphoma previously treated with chest radiotherapy (RT), the Children's Oncology Group recommends initiation of breast cancer screening with mammography and MRI starting at age 25. The National Comprehensive Cancer Network also recommends risk-reducing medications (e.g. tamoxifen) for breast cancer prevention in high-risk women. While low uptake among survivors has been described, the missed opportunity in terms of avoidable breast cancer deaths remains unknown. **Methods:** Using a Cancer Intervention and Surveillance Modeling Network model adapted to reflect the elevated breast cancer risk and competing mortality among 5-year lymphoma survivors previously treated with mediastinal RT, we estimated the number of breast cancer deaths by age 65 versus no screening or tamoxifen for a 20-year-old cohort under three scenarios: i) optimal uptake and adherence (100%) to early initiation of recommended screening (mammography with MRI) at age 25 and standard dose tamoxifen for 5 years at age 25; ii) real-world uptake of screening alone based on Childhood Cancer Survivor Study data (18% at age 25, increasing over time to 60% by age 35, with 50% reporting MRI within 1 year of mammogram); iii) real-world screening uptake as described in scenario 2, plus real-world tamoxifen use based on published estimates (16%). We assumed tamoxifen reduced breast cancer risk for a minimum of 20 years based on follow-up data from clinical trials. Breast cancer deaths averted were calculated as the difference in breast cancer deaths between each scenario and a baseline of no screening or tamoxifen. **Results:** In the absence of screening or tamoxifen, 53.2 breast cancer deaths per 1000 female survivors were projected by age 65. Under optimal uptake, screening averted 28.5 deaths per 1000 women (54%); screening plus tamoxifen increased the number averted to 31.6 deaths per 1000 (59% total reduction). Under real-world uptake, the number of breast cancer deaths averted was only 11.7 per 1000 women with screening alone and 12.6 for screening plus tamoxifen, suggesting only a 19-24% mortality reduction. **Conclusions:** Low real-world uptake of screening and tamoxifen represents a substantial missed opportunity to prevent breast cancer deaths among survivors of pediatric lymphoma treated with chest RT. Strategies to increase uptake are needed to fully realize the mortality benefits of breast cancer control in this high-risk population. Research Sponsor: National Cancer Institute; R01CA261874, U01CA199218, U24CA55727.

Modeled breast cancer mortality at age 65 under optimal and real-world uptake scenarios.

Scenario	Breast Cancer Deaths per 1000	Breast Cancer Deaths Averted per 1000	% Breast Cancer Deaths Averted
No screening or tamoxifen	53.2	-	-
Optimal (100%)			
Mammo/MRI	24.8	28.5	54%
Mammo/MRI + tamoxifen	21.7	31.6	59%
Real-world			
Mammo/MRI	41.5	11.7	19%
Mammo/MRI + tamoxifen	40.7	12.6	24%

10049 **Poster Session**

Early-onset chronic and metabolic morbidity among survivors of childhood acute lymphoblastic leukemia: Evidence from Middle Eastern real-world data. First Author: Samah Hayek, Tel Aviv University, Tel Aviv, Israel

Background: Survivors of childhood acute lymphoblastic leukemia (ALL) are at increased risk of long-term morbidity; however, limited data describe the *early* onset of metabolic and chronic conditions in contemporary cohorts or their association with treatment intensity in real-world settings. Existing evidence largely reflects European or North American populations, historical treatment eras, and fragmented healthcare systems. Data from Middle Eastern populations, particularly within a national health insurance framework enabling longitudinal follow-up across childhood and adulthood, are scarce. This study addresses these gaps by evaluating early-onset metabolic and chronic morbidity among childhood ALL survivors treated across multiple therapeutic eras within Israel's integrated healthcare system. **Methods:** We conducted a retrospective cohort study using electronic health records from Clalit Health Services, Israel's largest integrated payer–provider healthcare system. Five-year survivors of childhood ALL (diagnosed $<$19 years between 1980–2018) were matched 1:6 to cancer-free controls by age and sex. Chronic conditions were ascertained longitudinally using validated diagnosis codes. Multivariable Cox and logistic regression models estimated associations between ALL survivorship and chronic health outcomes. Among survivors, additional analyses examined associations with treatment intensity, treatment protocol era, and cranial radiation exposure (dose-specific). **Results:** The cohort included 437 childhood ALL survivors and 2,622 matched controls; survivors were 74.6% Jewish, 18.3% Arab, and 7.1% other ethnicities. Compared with controls, ALL survivors had significantly increased risks of central nervous system conditions (HR 3.65, 95% CI 1.71–7.80), thyroid disorders (HR 2.18, 95% CI 1.55–3.05), cardiovascular disease (HR 2.09, 95% CI 1.35–3.22), diabetes (HR 1.83, 95% CI 1.05–3.21), obesity (HR 1.58, 95% CI 1.31–1.91), and metabolic syndrome (OR 2.09, 95% CI 1.53–2.80). No ethnic differences were found across all chronic conditions. Excess morbidity occurred within the first 2-years of survivorship and persisted through 5- years, except for endocrine that became apparent later. Higher treatment intensity, earlier treatment protocols, and hematopoietic stem cells were associated with greater burden. **Conclusions:** Childhood ALL survivors experience early and disproportionate accumulation of chronic conditions, at young ages. Leveraging real-world data, this study provides novel evidence that treatment intensity and protocol era strongly shape early survivorship risk; unrelated to type of healthcare or ethnicity. These findings highlight the need for early, risk-adapted surveillance and targeted metabolic prevention strategies in contemporary ALL survivorship. Research Sponsor: The Jos and Fanny Sphon Foundation.

10050 **Poster Session**

Symptom-based individual risk prediction for late mortality: A report from the Childhood Cancer Survivor Study study (CCSS). First Author: Elyse Zhang, St. Jude Children's Research Hospital, Memphis, TN

Background: Survivors of childhood cancer face a higher risk of late mortality than the general population. Yet no prior study has integrated patient-reported symptoms and social determinants of health with treatment exposures to predict late mortality risks. **Methods:** A total of 9,569 survivors from the CCSS cohort who completed two surveys (baseline [T1], follow-up [T2]) reported 37 symptoms spanning 10 domains (cardiac, pulmonary, sensory, musculoskeletal, nausea, pain, fatigue, memory, anxiety, depression) at T1 and T2. Additional predictors included sociodemographic and lifestyle factors, address-linked Area Deprivation Index, and treatment exposures. Standardized mortality ratios (SMRs) were calculated, stratified by individual symptoms and domains at T2 and T1-T2 change, to compare mortality rates between survivors and the general population five years after T2. Multivariable Cox proportional hazards models with LASSO regularization were used to predict 5-year health-related and cause-specific late mortality (cardiac, pulmonary, subsequent neoplasm) after T1 and T2. The dataset was randomly split into training and test datasets in a 7:3 ratio, and prediction performance was assessed using the area under the receiver operating characteristic curve (AUC). **Results:** Among 9,569 survivors (52.4% female), the median age at T1 and T2 was 27.1 and 36.9 years; median years from diagnosis to T1 and T2 were 16.6 and 26.3, respectively. Acute lymphoblastic leukemia (31.3%) and Hodgkin lymphoma (15.3%) were the most frequently observed primary diagnoses. Compared with the sex/age/race/calendar year-matched general population, survivors had significantly higher health-related mortality 5 years after T2, with SMR of 4.21 (95%CI 3.76-4.70). Presence of cardiac and pulmonary symptom domains at T2, and their persistence and worsening from T1 to T2, were associated with $>$10-fold higher SMRs. Presence, persistence, and worsening of individual symptoms, including angina pectoris, chronic cough, and trouble breathing, were also associated with SMRs $>$10. For 5-year health-related mortality after T2, the symptom-based model yielded an AUC of 0.79 (95%CI 0.75-0.84), surpassing the symptom-agnostic model (AUC 0.76, 95% CI 0.71-0.81) and the T1 model (AUC 0.73, 95%CI 0.67-0.79). Cause-specific models also showed strong prediction performance, with symptom-based AUCs of 0.87 for cardiac, 0.89 for pulmonary, and 0.78 for subsequent neoplasms mortality. **Conclusions:** Adult survivors of childhood cancer experience elevated SMRs, with the greatest excess late mortality observed in those reporting cardiopulmonary symptoms. Longitudinal symptom-based models yielded the highest predictive performance, outperforming single-time-point and symptom-agnostic models. Incorporating symptom data can strengthen mortality prediction and inform targeted survivorship care. Research Sponsor: U.S. National Institutes of Health; U24 CA55727.

10051 **Poster Session**

Perceptions of Medicaid coverage and care experiences among long-term survivors of childhood cancer: Qualitative interviews from the Childhood Cancer Survivor study (CCSS). First Author: Xu Ji, Emory University School of Medicine, Atlanta, GA

Background: Childhood cancer survivors require lifelong, risk-based follow-up care. Survivors insured by Medicaid may face barriers to coverage and care unique to this type of insurance. We identified barriers and facilitators related to coverage, access to quality primary and specialty care, and survivor-provider interactions among Medicaid-insured survivors. **Methods:** Between May-November 2024, we conducted 23 in-depth interviews with adult survivors in CCSS currently also enrolled in Medicaid or with Medicaid coverage within the prior two years. Participants were recruited using stratified purposive sampling by state Medicaid expansion status, race/ethnicity, and age group. Interviews were audio-recorded, transcribed, and analyzed using thematic analysis. **Results:** Participants lived in 10 states (6 expansion, 4 non-expansion), 52% rural. At interview, 91% were enrolled in Medicaid. Mean age was 39 years (median 39; range 28-55); 26% were Hispanic and 35% non-Hispanic Black. Cancer types included blood cancers (n=9), brain tumors (n=7), and other solid tumors (n=7). When asked about maintaining coverage, survivors reported barriers including burdensome application/renewal requirements (e.g., in-person processes, extensive documentation); limited navigation guidance; and coverage instability tied to changes in disability status or income. Facilitators included assistance from knowledgeable staff (e.g., social worker), renewal reminder, and auto-renewal tied to Supplemental Security Income eligibility. Survivors expressed a need for hands-on help with application/renewal paperwork. When asked about care access, survivors reported difficulty finding specialists and primary care providers (PCPs) who accept Medicaid and are equipped to address survivor-specific needs (e.g., implement recommended tests in survivorship care plans), appointment delays, and transportation/geographic barriers. Facilitators included long-term relationships with PCPs and effective PCP–specialist communication. When asked about interactions with providers, survivors valued being heard, clear explanations, adequate visit time, and shared decision-making. However, many reported negative specialist encounters—feeling rushed or dismissed, including when new symptoms were repeatedly attributed to childhood cancer history without clear explanation, undermining trust. **Conclusions:** Medicaid-insured survivors reported challenges in maintaining coverage and accessing primary and specialty care. Streamlining enrollment/renewal, strengthening navigation supports, and improving survivor-centered care within Medicaid are critically needed amid the evolving Medicaid policy landscape. Findings inform a larger study designed to quantify policy-relevant gaps in coverage among aging survivors. Research Sponsor: NIH/NIMHD; K01MD018637; National Cancer Institute/U.S. National Institutes of Health; U24CA55727.

10052 **Poster Session**

Effects of delayed sodium thiosulfate on cisplatin-induced ototoxicity in pediatric and adolescent patients with cancer: Results from the Japanese Children's Cancer Group STS-J01 study. First Author: Eiso Hiyama, Hiroshima University Hospital, Hiroshima, Japan

Background: Cisplatin is a cornerstone of therapy for pediatric, adolescent, and adult solid tumors but frequently causes irreversible, dose-dependent ototoxicity. Delayed administration of sodium thiosulfate (PEDMARK) has demonstrated otoprotection in Western trials. STS-J01 evaluated the efficacy, safety, and pharmacokinetics of delayed sodium thiosulfate anhydrous in Japanese pediatric and adolescent patients. **Methods:** STS-J01 was an open-label, single-arm phase II study enrolling patients aged 0–18 years with localized solid tumors receiving cisplatin-based chemotherapy. Sodium thiosulfate (12.8 g/m²) was administered intravenously 6 hours after completion of each cisplatin dose. The primary endpoint was incidence of hearing loss by American Speech-Language-Hearing Association (ASHA) criteria in patients aged $\geq$3 years, compared with the observational cohort of ACCL0431. Secondary endpoints included hearing loss by Brock classification, tumor response, safety, and pharmacokinetics. **Results:** Thirty-one patients were enrolled, including 25 evaluable patients in the primary cohort (Table). Hearing was preserved in the majority of patients, with 76% free of ototoxicity by ASHA criteria and 84% with no hearing loss by Brock classification, representing a significant reduction versus historical controls (relative risk 0.42; 95% CI 0.20–0.82; P=0.007). Antitumor efficacy was preserved, with an objective response rate of 95.8% and there was no evidence of treatment interference from sodium thiosulfate. Pharmacokinetic analyses demonstrated no clinically meaningful impact of sodium thiosulfate on cisplatin exposure. No serious adverse events were attributed to sodium thiosulfate transient electrolyte abnormalities were manageable and reversible. **Conclusions:** Delayed administration of sodium thiosulfate significantly reduced cisplatin-induced ototoxicity without compromising antitumor efficacy in Japanese pediatric and adolescent patients, confirming reproducibility of sodium thiosulfate otoprotection across populations. Clinical trial information: jRCT2061220018. Research Sponsor: Japan Agency for Medical Research and Development; Fennec Pharmaceuticals.

Summary of STS-J01 trial.

Age at diagnosis (years)		3–6 (N=4)	7–14 (N=17)	15-18 (N=4)	Total (N=25)
No Hearing Loss by ASHA		2/4(50%)	13/17 (76.4%)	4/4 (100%)	19/25 (76.0%)
Disease	Hepatoblastoma	1/2 (50%)	-	-	1/2 (50.0%)
	Germ Cell Tumors	1/1 (100%)	6/6 (100%)	1/1(100%)	8/8 (100%)
	Bone and Soft Tissue Tumors	-	6/8 (75.0%)	3/3 (100%)	9/11 (81.8%)
	Medulloblastoma	0/1 (0%)	0/1 (0%)	-	0/2 (0%)
	Others	-	1/2 (50.0%)	-	1/2 (50.0%)
Chemotherapy	Responder*	4/4 (100%)	16/16 (100%)	3/4 (75.0%)	23/24 (95.9%)

*One case was unevaluated for treatment response.

10053 **Poster Session**

Olanzapine for weight gain in children undergoing chemotherapy for solid-organ malignancies: An investigator-initiated, open-label, multicenter, phase III randomized controlled trial (SNOWMAN). First Author: Shubham Sahni, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Background: Children receiving intensive chemotherapy for solid-organ malignancies frequently experience deterioration in nutritional status. Olanzapine improves nutritional outcomes in adults with advanced cancer and is guideline-endorsed. Its use in pediatric oncology has been limited by safety concerns and lack of robust data. We conducted this trial to evaluate the efficacy and safety of olanzapine for weight gain in children undergoing chemotherapy for solid-organ malignancies. **Methods:** In this open-label, investigator-initiated, multicenter, phase III randomized trial (CTRI/2024/03/064371), children aged 2-18 years with newly diagnosed solid-organ malignancies were randomized 1:1 to receive olanzapine (1.25-2.5 mg once daily, weight-based) plus standard dietary counseling (SDC) or SDC alone for 12 weeks, stratified by nutritional status. The primary endpoint was the proportion of participants achieving $\geq$5% weight gain at 12 weeks. Secondary endpoints included changes in appetite scores (visual analog scale), anorexia-related quality of life (QoL) (Peds-FAACT), anthropometric measures (weight, body-mass index, and mid-upper arm circumference), dietary intake, health-related QoL (PedsQL Cancer Module v3.0), and safety outcomes (CTCAE v5.0). Exploratory endpoints included longitudinal changes in body composition, using air-displacement plethysmography and skeletal muscle mass assessed by computed-tomography derived L3-L4 psoas muscle area. **Results:** A total of 130 participants were randomized (median age of 11.1 years; 13.9% undernourished), of whom 117 (60 olanzapine plus SDC, 57 SDC) had evaluable outcomes. At 12 weeks, 21/60 (35%) in olanzapine plus SDC and 22/57 (38.6%) in SDC group achieved the primary endpoint, with no significant difference between groups (OR 0.86, 95% CI 0.40-1.82; p=0.69). Longitudinal analyses showed no significant differences between groups in appetite scores, anthropometric measures, dietary intake, and QoL. Exploratory analyses showed no differential impact on skeletal muscle mass or fat proportions. Rates of grade $\geq$3 adverse events were similar between groups. No extrapyramidal symptoms were observed, and no participant required dose modification or discontinuation of olanzapine due to sedation or QTc prolongation. **Conclusions:** The addition of olanzapine to SDC does not increase the proportion of children achieving clinically meaningful weight gain over 12 weeks. The impact of pharmacological nutritional modulation may be limited by the physical hurdles posed by highly intensive pediatric chemotherapy protocols. Olanzapine was well tolerated and these data provide reassurance regarding its short-term safety for other supportive care indications in pediatric oncology. Clinical trial information: CTRI/2024/03/064371. Research Sponsor: CanKids KidsCan National Society for Change for Childhood Cancer in India.

10054 **Poster Session**

Neuropsychiatric symptom and biomarker changes with electroacupuncture in adolescent and young adult (AYA) cancer survivors: Results from a randomized controlled trial. First Author: Alexandre Chan, School of Pharmacy & Pharmaceutical Sciences, University California Irvine, Irvine, CA

Background: Electroacupuncture (EA) shows promise for managing neuropsychiatric symptoms, yet its role in adolescent and young adult (AYA) cancer survivors remains unclear. We conducted a randomized, controlled, patient- and assessor-blinded pilot trial comparing two EA regimens to evaluate effects on neuropsychiatric symptoms and associated biomarkers in AYA cancer survivors (ClinicalTrials.gov: NCT05283577). **Methods:** AYA cancer survivors aged 16–39 years who self-reported cognitive impairment, fatigue, insomnia, or psychological distress were randomized (1:1) to receive ten weekly EA sessions targeting either neuropsychiatric-specific acupoints (nEA) or non-neuropsychiatric-specific acupoints (sham EA; sEA). Blood collection, neurocognitive testing (CANTAB), and patient-reported outcomes (FACT-Cog, MFSI-SF, EORTC QLQ-C30) were obtained at four timepoints. Sixteen plasma cytokines were measured using ProcartaPlex immunoassays, and brain-derived neurotrophic factor (BDNF) concentrations were quantified using ELISA. Between-group effects were evaluated with linear mixed models and expressed as Cohen's *d* (positive values favor nEA). Adverse events (AEs) were graded using CTCAE v5.0. **Results:** Thirty-four AYAs participated (mean age 20.9 $\pm$ 3.5 years; 59% Hispanic/Latino; 59% hematologic and 21% CNS cancers). Most (82%) reported $\geq$2 neuropsychiatric symptoms at baseline. Completion of all EA sessions was comparable between study arms (nEA: 64.7%; sEA: 70.6%). A positive dose-response relationship was observed, with approximately half reporting at least one improved symptom after 5 weeks of treatment (nEA: 53.8%; sEA: 60.0%) and >80% reporting improvement at 4 weeks post-treatment (nEA: 80.0%; sEA: 92.3%). At 4-week follow-up, greater improvement in self-reported cognitive function favored sEA ($d = -1.017$, $p < 0.05$), accompanied by between-group differences in BDNF ($d = -1.073$, $p < 0.05$), IL-10 ($d = 1.378$, $p < 0.05$), and RANTES ($d = 1.058$, $p < 0.05$). All AEs were grade $\leq$ 2; tremors and pain were the most commonly reported. **Conclusions:** AYAs across both EA regimens demonstrated meaningful improvements in neuropsychiatric symptoms, accompanied by corresponding biomarker changes. However, maximal benefit occurred among participants who completed all scheduled sessions, underscoring the importance of strategies to optimize EA session adherence in this population. These findings support the feasibility of EA in AYAs and inform the design of larger trials. Clinical trial information: NCT05283577. Research Sponsor: University of California Irvine.

10055 **Poster Session**

Barriers and enablers to pediatric palliative care integration in low- and middle-income countries: A systematic review and meta-synthesis. First Author: Mohd Faizan Siddiqui, Medical Faculty, Osh State University, Osh, Kyrgyzstan

Background: Globally around 21 million children require pediatric palliative care yearly of whom more than 97-98% of the children in greatest need live in low- and middle-income countries. Nevertheless, presently, only around 5-10% of children and their families in those situations receive palliative care while the development of pediatric-specific palliative care frameworks and services remains very much less developed than adult palliative care in many health systems. **Methods:** A systematic search was performed in PubMed database, Embase database and Global Health for studies published between 2015 and 2025 using PRISMA guidelines. Inclusion criteria: Original research on the models of PPC, access to opioids or educational interventions in the context of LMICs. Articles were screened for inclusion by two independent reviewers and were evaluated for quality using the MMAT. Data have been synthesized with the help of a thematic framework. **Results:** Out of the 427 identified records, 48 studies in 32 countries met the inclusion criteria. Important barriers identified were restrictive legislation, and 68% of the studies mentioned "opiophobia" and legal barriers to access of pediatric morphine, median morphine consumption in LMICs less than 1% of high income countries. While workforce deficit only of 12% of LMIC children's or pediatric doctors (pediatricians) reported some type of formal training in PPC during residency. Also, financial toxicity: End-of-life care financial costs for families in LMIC often outweigh cost up to, or more than, 50% of their yearly income. On the other hand, successful enablers were task-shifting to community health workers and integration of PPC into existing oncology protocols. Quantitative synthesis demonstrated the use of integrated hospital in-home models to decrease emergency room visits by 35% in the last month of life. **Conclusions:** Large disparities still exist in PPC provision in LMICs, which is related to regulatory and educational gaps. But some localized "hub-and-spoke" models provide an outline of how to integrate in a sustainable fashion. For ASCO's global mission, these findings indicate that "Zero Pain" initiatives require pediatric specific legislative reform and mandatory oncology palliative training to address the gap in quality of survival. Research Sponsor: None.

10056 **Poster Session**

Development and early implementation of a statewide comprehensive childhood cancer network to support pediatric oncology care and research. First Author: Chris Hagemeyer, Live Like Bella Childhood Cancer Foundation, Coral Gables, FL

Background: Although pediatric cancer survival has improved substantially, families continue to face fragmented access to navigation, clinical trials, survivorship care, and psychosocial support. Florida's pediatric oncology system is geographically dispersed and resource-variable, highlighting the need for coordinated statewide infrastructure. **Methods:** The Live Like Bella Comprehensive Childhood Cancer Network (CCCN) was established as a statewide, multi-institutional initiative to address gaps in access, care coordination, and research participation. Phase 1 activities emphasized infrastructure development, stakeholder engagement, and needs assessment. A caregiver survey was distributed to 2,478 families who received pediatric cancer support services between April 2024 and August 2025. Descriptive analyses evaluated barriers to care, information gaps, survivorship education, and clinical trial awareness. Missing survey responses were handled using complete-case analysis for each item, with denominators reported per question. In parallel, CCCN convened children's hospitals, academic centers, advocacy organizations, and researchers to develop collaborative frameworks, digital navigation tools, and consortium-based initiatives. **Results:** Over 170 caregivers responded. Eighty percent reported significant non-clinical care challenges (e.g., housing, utilities, transportation), 67% reported work-related disruptions, and 52% identified unmet caregiver support needs. Thirty-three percent reported difficulty locating services. Only 50–53% rated information about childhood cancer and diagnosis-specific education as comprehensive. Forty-eight percent of families reported being offered a clinical trial; among those, 71% participated. Survivorship education gaps were common, with 22.7% and 26% reporting limited or no information on post-treatment and survivorship care. CCCN established leadership and advisory governance, launched development of a digital navigation and clinical trial matching portal, hosted a statewide research symposium (>250 participants), and initiated multi-institutional grant proposals focused on precision oncology and navigation workforce development. **Conclusions:** Early CCCN implementation demonstrates the feasibility of a statewide, family-centered model to identify care gaps, support research participation, and align pediatric oncology stakeholders. Ongoing evaluation will assess impacts on access, survivorship, and clinical trial engagement. Research Sponsor: Florida Cancer Innovation Fund.

TPS10057 **Poster Session**

A phase 1b study of xaluritamig (a STEAP1 x CD3 T-cell engager) in pediatric, adolescent, and adult patients with relapsed/refractory (R/R) Ewing sarcoma. First Author: Emily K. Slotkin, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Ewing sarcoma (EWS) is an aggressive tumor of the bone and soft tissue primarily affecting adolescents and young adults. For patients with recurrent disease, outcomes remain poor with 5-year survival rates of 10%–15%, highlighting the need for novel approaches. STEAP1 is highly expressed in EWS cell lines, xenograft models, and patient tumor samples[1] and is transcriptionally regulated by *EWSR1*::*FLI1*, the main oncogenic driver in EWS. Xaluritamig, a humanized bispecific XmAb 2+1 T-cell engager targeting STEAP1 and CD3, has demonstrated potent, antigen-dependent T-cell–mediated lysis of STEAP1-expressing EWS cell lines[1] and induced robust in vivo antitumor activity in EWS xenograft models with concomitant CD8+ T-cell activation. In metastatic castration-resistant prostate cancer, another STEAP1-expressing solid malignancy, xaluritamig has shown meaningful antitumor activity and a manageable safety profile[2] supporting its clinical evaluation in R/R EWS. **Methods:** This ongoing, phase 1b, single-arm, open-label, two-part, multicenter study (NCT07297979) is evaluating xaluritamig in pediatric, adolescent, and adult patients with a histologic diagnosis of EWS and an *EWSR1*::*ETS* fusion gene locally confirmed by next-generation sequencing. Patients must have R/R EWS following ≥1 line of systemic therapy and Karnofsky or Lansky performance status ≥70. Part 1 (dose confirmation) consists of cohort 1 (age ≥12 years) and cohort 2 (age ≥2 to <12 years), and part 2 (dose expansion) includes patients aged ≥2 years with no upper age limit at enrollment. This study includes a 21-day screening period, a treatment period, a safety follow-up period, and a long-term follow-up period. Patients receive xaluritamig every 2 weeks once reaching the target dose until radiographic disease progression per RECIST v1.1, clinical disease progression, unacceptable toxicity, initiation of other anticancer therapy not permitted per protocol, withdrawal of consent, death, or end of study as determined by the sponsor, whichever is earlier. Primary endpoints are safety, tolerability, and determination of recommended dose(s) for expansion. Secondary endpoints are pharmacokinetics, preliminary antitumor activity, and immunogenicity. Biomarker evaluation as an exploratory endpoint includes assessment of serum cytokines, other pro-inflammatory markers, immune-cell subsets, circulating tumor DNA, STEAP1 protein expression, and tumor genomic profile and their association with safety and efficacy. CRS mitigation plan includes step-up dosing, steroid premedication, and administration of interleukin-6 inhibitors as needed. Site activation commenced in January 2026 and enrollment is ongoing. 1. Nolan-Stevaux O. *Cancer Res*.2020;80(16_Suppl):DDT02–03. 2. Kelly WK, Danila DC, Lin CC, et al. *Cancer Discov*. 2024;14(1):76-89. Clinical trial information: NCT07297979. Research Sponsor: Amgen Inc.

TPS10058 **Poster Session**

Feasibility study of prolonged administration of naxitamab, irinotecan, and temozolomide for patients with relapsed or refractory neuroblastoma. First Author: Samantha Martin, Dana-Farber/Boston Children's Cancer and Blood Disorders Center; Harvard Medical School, Boston, MA

Background: Neuroblastoma is a malignant childhood tumor of the sympathetic nervous system. Cure rates are unsatisfactory for patients with high-risk disease (approximate 3-year EFS 50%) with current standard of care therapy. For patients who relapsed, anti-GD2 based chemoimmunotherapy has become standard, though it often requires in-hospital administration. Naxitamab, a humanized anti-GD2 monoclonal antibody (mAb), is FDA approved for patients with relapsed or refractory (R/R) high-risk neuroblastoma (HR-NB) with metastatic disease restricted to bone or bone marrow (BM), and who have stable disease or minor/partial response to previous therapies. With an infusion duration of 30-60 minutes, grade 3 pain and infusion-related reactions are common (72% and 68% of patients respectively) and necessitate extensive nursing and provider resources that may preclude administration at many centers. Slowing the rate of infusion of naxitamab and other anti-GD2 mAbs is generally associated with lower rates and severity of acute toxicity. We have therefore opened a phase I feasibility trial of prolonged administration of naxitamab in combination with irinotecan and temozolomide. **Methods:** This is a phase 1, single treatment arm, modified 3+3 prospective trial in patients with R/R or progressive HR-NB. The primary objective is to identify a recommended safe and feasible prolonged infusion duration of naxitamab in combination with irinotecan and temozolomide, with a goal of still allowing outpatient administration. Patients are enrolled at the starting total infusion duration of 4 hours, with an escalating infusion rate at pre-defined timepoints; the total infusion duration will be extended or shortened in cohorts of 3-6 patients based on safety and adverse events (AEs) observed in the first cycle. Individual patients will be eligible for duration escalation or de-escalation depending on AEs observed. An expansion cohort will be enrolled at the recommended infusion time. Key eligibility criteria include diagnosis of R/R or progressive HR-NB or ganglioneuroblastoma, age 1-30 years at enrollment, documentation of disease per revised International Neuroblastoma Response Criteria (INRC), adequate performance level, and adequate organ function including BM. Key exclusion criteria include prior receipt of naxitamab, untreated CNS metastatic disease, and discontinuation of prior GD2 immunotherapy due to unacceptable toxicity other than allergic reaction. Secondary endpoints include response rate per revised INRC and survival outcomes. Correlative and exploratory investigations embedded within the trial include PK profiling of prolonged naxitamab infusion durations and evaluation of circulating biomarkers including circulating tumor DNA, tumor cells, and GD2 in the study population during anti-GD2 therapy. Clinical trial information: NCT07027748. Research Sponsor: None.

10500 **Oral Abstract Session**

Allostatic load as a mediator of exposomic risk pathways to early-onset cancer: A cross-cohort validation study. First Author: Ravi Bharat Parikh, Emory University, Atlanta, GA

Background: Early-onset cancer (EoC, defined as any solid tumor diagnosed ≤50 years age) incidence has increased 79% globally since 1990. Traditional risk models focus on isolated exposures or specific rare genetic variants and have limited utility for EoC, as high-penetrance mutations account for <10-20% of cases depending on tumor type. Allostatic load (AL) – the cumulative physiological burden of chronic stress across neuroendocrine, immune, and metabolic systems – may represent a pan-EoC mechanism linking environmental exposures to EoC carcinogenesis. **Methods:** We analyzed 13,745 adults aged ≤50 years (2,749 EoC cases) across two population-based cohorts: UK Biobank (UKB; n=5,100) and NIH All of Us Research Program (AoU; n=8,645). AL was constructed by summing standardized indicators for 8-11 baseline biomarkers representing cardiovascular (blood pressure), metabolic (HbA1c, glucose, cholesterol, BMI), and immune (CRP, WBC, albumin) domains. An exposome score was derived via bifactor analysis of 61 (UKB) and 11 (AoU) baseline exposures spanning diet, lifestyle, neighborhood, and psychosocial factors. Propensity score matching controlled for age, sex, race/ethnicity, and socioeconomic indicators. Mediation analysis estimated indirect effects of exposome on EoC operating through AL. **Results:** Mean age was 43.0 years in UKB and 39.8 years in AoU; 72.5-76.5% were female. For each SD increase in baseline AL, there was 11-18% increased odds of subsequent EoC (AoU OR: 1.18 [95%CI 1.12-1.24]; UKB OR: 1.11 [1.04-1.18]). Exposome score was significantly associated with AL (AoU β=0.09; UKB β=0.08; both p<0.001). Mediation analyses revealed significant indirect effects in both cohorts, with non-significant direct effects (Table). For exposome-related cancers, AL mediated 8.7-15.4% of exposomic risk. **Conclusions:** This is the first multinational population-level study to demonstrate that AL mediates environmental risk pathways to EoC, supporting the hypothesis that cumulative environmental burden promotes carcinogenesis through physiological stress pathways. AL represents a potentially modifiable target for EoC risk stratification. Future research integrating polygenic risk and longitudinal exposome assessments may refine mechanistic understanding and enable precision prevention approaches for this growing public health challenge. Research Sponsor: U.S. National Institutes of Health; 5K08CA263541.

Mediation of exposome-EoC association via AL.

Cohort	Cancer Group	Indirect Effect* (p)	Direct Effect# (p)	Proportion Mediated (p)
AoU	All	0.005 (<0.001)	−0.012 (0.14)	–
AoU	Exposome-Related	0.001 (<0.001)	0.007 (0.06)	15.4% (0.02)
UKB	All	0.002 (<0.001)	−0.005 (0.63)	–
UKB	Exposome-Related	0.001 (0.01)	0.008 (0.17)	8.7% (0.14)

*β of exposome-EoC effect operating through AL.
#β of exposome-EoC effect independent of AL.
Exposome-related cancers: colorectal, lung, liver, bladder, upper GI.

10501 **Oral Abstract Session**

Predicting multi-cancer risk from EHR data using multi-agent LLMs. First Author: Sihang Zeng, Truveta Inc., Bellevue, WA

Background: Accurate multi-cancer risk prediction is essential for optimizing screening strategies and yet remains challenging due to heterogeneous and longitudinal electronic health record (EHR) data. Large language models (LLMs) offer a unified framework for multi-cancer risk assessment without disease-specific model training, but single-agent LLMs struggle to reason effectively over long patient histories. **Methods:** We developed a multi-agent system (MAS) composed of chained LLM agents with episodic memory to synthesize longitudinal EHR data into comprehensive cancer risk profiles. The system generates 1-year cancer risk scores (1–10) for individual cancer types. Using Truveta Data, we identified cases for 9 cancer types with clinically recognized precursor signs using clinician-curated diagnostic codes. For each cancer type, 500 cases were randomly sampled and matched 1:1 with controls by 10-year age group and sex. All structured EHR data (conditions, laboratory results, observations, medications, and procedures) up to 1 year before diagnosis or index date were included. Performance was evaluated across cancer types; lung cancer was used as a benchmark cohort for comparison with traditional machine learning (ML) models and a single-agent LLM baseline. **Results:** The MAS demonstrated heterogeneous but clinically meaningful discrimination across cancer types (AUROC range: 0.64 to 0.80), with liver cancer performing the best and colorectal cancer the worst. In the lung cancer cohort, performance (AUROC=0.79) was comparable to that of trained ML models (AUROC: XGBoost 0.82, logistic regression 0.73, k-nearest neighbors 0.58). Beyond risk prediction, the system generated concise patient summaries and interpretable rationales that supported downstream analyses, including cancer real-world evidence generation and exploratory knowledge discovery. Compared with a single-agent LLM, the MAS showed improved temporal coherence and clinical reasoning. **Conclusions:** A multi-agent LLM system can leverage longitudinal EHR data to estimate short-term multi-cancer risk within a unified framework, without cancer-specific model training. These findings support the potential role of LLM-based systems as scalable tools to inform risk stratification and screening strategies in real-world clinical populations. Research Sponsor: Truveta.

The MAS's performance.

	Lung	Ovarian	Liver	Pancreatic	Colorectal	Multiple Myeloma	Lymphoma	Gastric	Bladder
AUROC [95% CI]	0.79 [0.77, 0.82]	0.68 [0.65, 0.71]	0.80 [0.77, 0.83]	0.66 [0.62, 0.69]	0.64 [0.61, 0.68]	0.70 [0.67, 0.73]	0.69 [0.66, 0.72]	0.69 [0.66, 0.72]	0.71 [0.68, 0.74]

10502 **Oral Abstract Session**

Beyond hematologic malignancies: Clonal hematopoiesis of indeterminate potential and the risk of solid tumors in the UK biobank. First Author: Parham Habibzadeh, University of Pittsburgh, Pittsburgh, PA

Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related condition characterized by somatic mutations in hematopoietic stem cells. While CHIP is associated with hematologic malignancies, its relationship with solid tumors remains incompletely characterized. We conducted a comprehensive analysis of CHIP and cancer risk in a large population-based cohort. **Methods:** We analyzed 409,150 UK Biobank participants with whole exome sequencing, including 13,709 (3.4%) with CHIP. CHIP was defined as somatic mutations in myeloid driver genes at variant allele frequency (VAF) ≥2%. Incident cancers were ascertained through registry linkage over median 15.5-year follow-up. We performed propensity score-matched Cox regression adjusting for age, sex, ethnicity, smoking, BMI, diabetes, chronic kidney disease, and family history. Gene-specific, VAF-stratified, and multi-hit analyses were conducted. **Results:** Among 77,695 incident cancers, CHIP was associated with increased risk of any cancer (HR 1.22, 95% CI 1.18-1.27), including both hematologic and solid tumors. Associations were strongest for myeloid neoplasms (HR 10.49, 95% CI 8.64-12.74), including AML (HR 11.09), MDS (HR 9.75), and MPN (HR 8.03). For solid tumors, significant associations were observed for lung cancer (HR 1.50, 95% CI 1.31-1.73), particularly adenocarcinoma (HR 1.79, 95% CI 1.48-2.16), and esophageal cancer (HR 1.52, 95% CI 1.13-2.03). Notably, esophageal squamous cell carcinoma showed particularly elevated risk (HR 2.28, 95% CI 1.37-3.81). VAF-stratified analyses revealed dose-response for esophageal cancer: large clones (defined as VAF ≥20%) conferred HR 2.23 (95% CI 1.32-3.75) and very large clones (defined as VAF ≥30%) HR 2.72 (95% CI 1.39-5.30). Multi-hit CHIP (≥2 mutations) was associated with HR 3.35 (95% CI 1.46-7.71) for esophageal cancer and HR 4.07 (95% CI 1.79-9.21) for esophageal adenocarcinoma. Gene-specific analyses showed TET2 mutations increased esophageal adenocarcinoma risk (HR 2.46, 95% CI 1.21-5.03). Results remained consistent in 5-year landmark analyses. **Conclusions:** CHIP is associated with significantly increased risk of both hematologic and select solid malignancies. We identify esophageal cancer, particularly squamous cell carcinoma, as a novel CHIP-associated malignancy with clear dose-response by clone burden. These findings warrant external validation and, if confirmed, suggest CHIP features may help refine risk stratification strategies for selected solid tumors. Research Sponsor: None.

10503 **Oral Abstract Session**

Effect of type and location of *BRCA2* deleterious variant on prognosis and survival in metastatic prostate cancer: A longitudinal, international, cohort study from hormone-sensitive to castration-resistant settings. First Author: Lorena Incorvaia, Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.), Section of Medical Oncology, University of Palermo, Palermo, Italy, Italy

Background: Emerging evidence suggests that *BRCA*-altered prostate cancer (PC) is not a unique molecular subtype. However, the prognostic and therapeutic relevance of specific pathogenic/likely pathogenic variant (PV) in metastatic PC (mPC) remains poorly defined. We investigated the impact of *BRCA2* PV type and position on clinical outcomes across across different metastatic settings. **Methods:** This international, hospital-based cohort study (Jan 2020–Apr 2025) included mPC patients (pts) across 29 centers who underwent germline, somatic, and/or ctDNA *BRCA* testing. Analysis included three settings: 1) mHSPC (ADT+docetaxel vs. ADT+ARPi); 2) mCRPC (ARPi vs. taxanes); 3) mCRPC treated with PARP inhibitors (PARPi). Outcomes [Time on Treatment (ToT); Overall Survival (OS)] were analyzed by PV type (frameshift, missense, nonsense, splicing; indels, SNV, CNV) and position: 1) Functional Domains (FDs) (RAD51-BD [AA 900-2000] vs. DBD [AA 2459-3190] vs. Others); 2) The recently identified Prostate Cancer Cluster Regions (PCCR) (c.756-c.1000 and 3' of c.7914 vs. Others). **Results:** Of 2.119 pts included, 401 harbored Homologous Recombination Repair PVs. In the cohort of 1.411 mHSPC pts, *BRCA2*-mutated (n = 201) showed significantly shorter OS vs. wild-type (mOS 63 vs 76 months; HR 1.2, p = 0.02), regardless of first-line therapy. Contrary to previous reports, *BRCA2*-mutated mHSPC pts had superior ToT from ADT+ARPi vs. ADT+docetaxel (55 vs 15 mos; HR 3.5, p < 0.001). Within the *BRCA2* subgroup, PV location was highly prognostic for OS. In mHSPC, PCCR-outside variants (c.756-c.1000/3'of c.7914) and non-FD variants (RAD51-BD/DBD-outside) were associated with shorter OS (PCCR: 57 vs 97 mos, HR 4.0, p = 0.006; FD: 47 vs 88 mos, HR 3.0, p < 0.001). Similar prognostic impacts were confirmed in 684 mCRPC pts (PCCR: 78.0 vs 38.0 mos, HR 3.3, p = 0.01; FD: 64.0 vs 34.0 mos, HR 2.7; p = 0.009). Among 201 pts treated with olaparib, those with RAD51-BD PVs achieved significantly longer ToT (20.0 vs 7.0 mos; p = 0.01) and longer OS. Furthermore, frameshift deletions were associated with shorter OS compared to other PV types (15.9 vs 26.0 mos; p = 0.04). **Conclusions:** This is the largest longitudinal study to demonstrate that *BRCA2* PV type and location are critical determinants of survival and treatment response in mPC. Our findings identify a "high-risk" molecular subgroup (PCCR and RAD51-BD/DBD-outside and frameshift deletions) with significantly poorer outcomes. These results provide a rationale for refined risk-stratification and personalized treatment selection, including early PARPi integration, in *BRCA2*-mutated patients. Research Sponsor: None.

10504 **Oral Abstract Session**

Association between the rs72725854(A>T) allele and prostate cancer in males of African ancestry in a US population-based database. First Author: Jeffrey Shevach, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University School of Medicine, Durham, NC

Background: Black males have a 70% excess incidence of and two-fold higher mortality from prostate cancer (PCa) compared to White males in the US. The rs72725854(A>T) variant ('T' allele) is a common African ancestry-specific variant that is associated with PCa in large case-control studies in the US and Africa. We measured the association between the 'T' allele and PCa in a unique US population-based cohort. **Methods:** We conducted a retrospective time-to-event cohort study using the *All of Us* database (Duke IRB Pro00117610). We included males of African ancestry who met the following criteria: 1) were at least 35 years old at *All of Us* enrollment; 2) had undergone whole genome sequencing; 3) had linked electronic health record (EHR) data; 4) had no Systemized NOmenclature of MEDicine – Clinical Terms (SNOMED-CT) diagnosis of PCa prior to *All of Us* enrollment. PCa diagnoses were ascertained by the following EHR-based phenotyping algorithm: two PCa SNOMED-CT diagnosis codes plus evidence of PCa treatment with radical prostatectomy, radiotherapy or androgen deprivation therapy. The date of PCa diagnosis was defined as the latter of second diagnosis code date or first treatment date. Individuals were censored at last visit in the EHR if they did not meet the primary endpoint of PCa diagnosis. The association between each additional 'T' allele and time from *All of Us* enrollment to PCa diagnosis was measured using Cox regression methods, adjusting for the top 5 genetic principal components, age, and rare pathogenic variants (RPVs) in PCa predisposition genes (*ATM, BRCA1/2, HOXB13* X285K African-ancestry variant, and *PALB2*). Included RPVs had pathogenic/likely pathogenic designation in ClinVar with at least two stars. **Results:** Our study included 18,846 male participants of African ancestry, with 2,349 (12.5%) and 90 (0.5%) being heterozygous and homozygous for the 'T' allele, respectively. Median age at enrollment was 56.0 years (interquartile range 48.5 – 62.3). There were 91 cases of PCa during a median follow-up of 25.6 months (interquartile range 3.0 – 45.9). For each additional 'T' allele, there was a 3.4-fold increased hazard of PCa (HR 3.38; 95% CI 2.31 – 4.95; p $3.92x10^{-10}$). Age (HR 1.09; 95% CI 1.06 – 1.11; p $2.74x10^{-15}$) and RPVs in *ATM* (HR 7.54; 95% CI 1.84 – 30.90; p $5.03x10^{-3}$) were also significantly associated with increased PCa diagnosis. *BRCA2* RPVs (HR 4.94; 95% CI 0.68 – 35.68; p 0.112) and *HOXB13* X285K (HR 2.61; 95% CI 0.36 – 19.02; p 0.343) were associated with PCa, but did not meet statistical significance. There were no *BRCA1* or *PALB2* RPVs among participants with PCa. **Conclusions:** In a large, US population-based study, we confirmed an association between the common rs72725854(A>T) variant and PCa diagnosis. This variant has a per-allele effect on PCa risk that is similar in magnitude to RPVs in PCa predisposition genes, and should be considered for inclusion in PCa genetic testing panels. Research Sponsor: None.

10505 **Oral Abstract Session**

Prospective prostate cancer screening in germline pathogenic variant carriers: The PATROL study. First Author: Daniel Lee, University of Pennsylvania, Philadelphia, PA

Background: Germline pathogenic variants (gPV) in prostate cancer (PCa) risk genes are associated with aggressive disease, but optimal screening thresholds for this population are unclear. We report early results from the Prostate Cancer Screening for People at Genetic Risk for Aggressive Disease (PATROL) study. **Methods:** PATROL is a multicenter, prospective study enrolling participants ≥40 years with a gPV in at least one of 13 PCa risk genes. Biopsy is recommended using age-specific prostate-specific antigen (PSA) thresholds: > 1.0 ng/mL (< 50y), > 1.5 (50–59y), > 2.0 (≥60y). Prostate multiparametric MRI is encouraged at baseline and within 1 year of biopsy. Clinically significant PCa (csPCa) was defined as Grade Group (GG) ≥2 (NCT04472338). **Results:** As of 12/1/2025, 436 participants were enrolled; 69% carried *BRCA1/2* gPVs (*BRCA2* 46%, *BRCA1* 22%), 12% carried mismatch repair gene variants, and gPVs in other genes were each ≤7%. Overall, 106 participants underwent 119 on-study biopsies (median age 61 [IQR 53–68]) with a median PSA 2.3 ng/mL [IQR 1.3–3.9]). GG1 disease was detected in 21/119 (18%) biopsies and csPCa in 21/119 (18%) biopsies. Among csPCa, the median PSA was 3.2 ng/mL (IQR 2.2-4.1), and 76% (16/21) had a PIRADS 4-5 lesion. Fifteen (71%) and 14 (67%) of GG1 and csPCa, respectively, were identified in participants with *BRCA1/2* gPVs. In multivariable logistic regression adjusting for age, PSA, and genetic status, PI-RADS 4-5 was associated with csPCa (OR 12.2, 95% CI 3.3-45.4). Of the 17 men with GG1 PCa, 11 (65%) elected active surveillance. Of the 11 men on surveillance, median follow up time was 19 months, with one (9%) upgraded to GG ≥2 and who underwent definitive treatment. In total, 25 participants underwent definitive treatment; 18 with initial diagnosis of csPCA, six GG1 who elected for definitive treatment and one enrollee with GG1 upgraded to GG ≥2. Of the 25 patients who elected definitive treatment, 88% (22/25) of underwent surgery, two underwent radiation, and one underwent focal therapy. Of surgery patients, there were no postoperative complications. At a median follow-up time of 16 months, all currently have undetectable PSA, and one patient required salvage radiation therapy. **Conclusions:** Age-specific PSA-driven biopsy in gPV carriers yielded ~20% csPCa detection, with two-thirds occurring at PSA < 4 ng/mL (common biopsy threshold). MRI (PI-RADS 4–5) strongly predicted csPCa and may improve inherited-risk screening algorithms. With limited follow-up, surveillance of low-risk PCa among gPV carriers appears to be feasible, and definitive treatment of gPV carriers found with csPCa is effective. Clinical trial information: NCT04472338. Research Sponsor: Basser Center for BRCA; Canary Foundation; CureBRCA; Pacific NW Prostate Cancer SPORE; Department of Defense Prostate Cancer Research Program.

10506 **Oral Abstract Session**

Association of GLP-1 agonists with breast cancer incidence in women. First Author: Elizabeth Susan McDonald, University of Pennsylvania, Philadelphia, PA

Background: Excess weight is a key modifiable risk factor for breast cancer. Glucagon-like peptide-1 receptor agonists (GLP-1) promote weight loss and improve markers of metabolic health. However, the effect of GLP-1 on breast cancer risk among women eligible for breast cancer screening remains unclear. **Methods:** We conducted a retrospective, time-dependent cohort study from January 1, 2022, to June 30, 2025, using electronic health records. We identified 217,025 unique patients who underwent breast imaging, restricting the sample to women aged 45 to 80 years with a BMI greater than 25 and a documented imaging outcome (n=94,827; median age 61). The primary outcome was breast cancer detection. GLP-1 use was defined as a first prescription prior to the exam date and assessed in relation to race, ethnicity, age, and type 2 diabetes. To address potential confounding between these covariates and GLP-1 exposure, we performed one-to-one, case-control matching using propensity scores based on age, race, ethnicity, highest BMI, breast density, and type 2 diabetes diagnosis. **Results:** Among 94,827 women, 2,314 (2.4%) were diagnosed with breast cancer during the study period, while 92,513 (97.6%) were not. Of the total, 15,107 (15.9%) had GLP-1 exposure, and 79,720 (84.1%) did not. Among those exposed to GLP-1, 249 (1.65%) developed breast cancer, while 14,858 (98.4%) did not. Among women without exposure to GLP-1, there were 2065 (2.6%) women with breast cancer and 77,655 (97.4%) of women without breast cancer. GLP-1 exposure was associated with a lower incidence of breast cancer (OR 0.630 (0.552, 0.720); p<0.0001). In the matched logistic regression analysis (30,214 observations; 581 cancer cases), GLP-1 exposure prior to the exam date was associated with a lower incidence of breast cancer (OR 0.746, 95% CI: 0.632–0.880; p<0.0005). **Conclusions:** In this large observational study of women undergoing breast imaging at a major academic center, GLP-1 treatment was associated with a significantly lower incidence of breast cancer after accounting for age, race, ethnicity, BMI, breast density, and type 2 diabetes status. These findings support the need for prospective trials investigating incretin medications for breast cancer prevention. Research Sponsor: Pennsylvania Breast Cancer Coalition.

Matched case-control contingency table for GLP-1 exposure prior to exam date and breast cancer.

		No cancer	Total
GLP-1	249 (1.65%)	14858 (98.35%)	15107
No GLP-1	332 (2.20%)	14775 (97.80%)	15107
Total	581 (1.92%)	29633 (98.08%)	30214

10507 **Oral Abstract Session**

Primary prevention of acute leukemias in high-risk patients: The therapeutic promise of GLP-1 receptor agonists. First Author: Jonathan Dao, Long School of Medicine, University of Texas Health-San Antonio, Frisco, TX

Background: Despite advances in understanding leukemogenesis, no validated primary prevention strategies exist. Obesity is a dose-dependent risk factor for leukemia. Emerging data implicate epigenetic regulators, specifically the histone methyltransferase GLP (EHMT1), as a driver of leukemic survival; its inhibition induces cell death in CLL and promotes differentiation in AML. We present the first real-world analysis evaluating GLP-1 receptor agonists (GLP-1RA) for the primary prevention of leukemia in high-risk populations. **Methods:** Using the TriNetX global research network (150 million patients across 108 healthcare organizations), we identified adults at elevated leukemia risk based on ≥1 factor (prior chemo/radiation, MDS, MPN, family history, genetic syndromes, tobacco use, or BMI ≥30). Patients with ≥2 months of GLP-1RA use were propensity-matched 1:1 to non-users by demographics, comorbidities, and prior chemotherapy. The primary endpoint was the incidence of ALL, AML, CLL, or CML; secondary endpoints were adverse events related to GLP-1RA. Individuals with pre-existing leukemia were excluded. Cox proportional hazards models and sensitivity analyses were used to assess associations. Sensitivity and subgroup analysis confirmed robustness. **Results:** Of 426,670 high-risk individuals, 213,335 were matched to each cohort; standardized mean differences were <0.1 for all covariates. Across >1.2 million person-years of follow-up, GLP-1RA use was associated with a 63% risk reduction in incident AML (47/213,300 vs 75/213,261; HR 0.37, 95% CI 0.26–0.53; p < 0.001) and a 50% reduction in ALL (42/213,304 vs 53/213,277; HR 0.50, 95% CI 0.33–0.75; p = 0.001). The protective effect for AML remained significant when restricted to patients with prior chemotherapy exposure and was independent of baseline BMI. No significant reductions were observed for CML or CLL. While GI adverse events were higher in the GLP-1RA cohort, the protective signal was consistent across age and ethnic subgroups. **Conclusions:** This is the first large-scale study to demonstrate a significant reduction in incident AML and ALL using GLP-1 receptor agonists in high-risk patients. By linking clinical metabolic intervention to the EHMT1 epigenetic pathway, these findings provide a novel, scalable pharmacologic strategy for the primary prevention of acute leukemias, potentially transforming the management of high-risk and obese populations. Research Sponsor: None.

10508 **Oral Abstract Session**

Comparative analysis of tirzepatide versus metformin and insulin in type 2 diabetes patients across the 13 most common cancers. First Author: Viraj R. Shah, Division of Cardiology, Department of Medicine, Medical College of Georgia at Augusta University, Augusta, GA

Background: Emerging glucose-lowering therapies may influence cancer risk in patients with type 2 diabetes mellitus (T2DM). While several GLP-1 receptor agonists have been evaluated, data on tirzepatide, a dual GLP-1/GIP agonist with established cardiometabolic benefits, remain limited. We assessed the comparative risk of incident cancers and all-cause mortality among T2DM patients treated with tirzepatide versus metformin or insulin. **Methods:** We conducted a retrospective cohort study using TriNetX, a U.S.-based federated electronic health record network. Adults with T2DM initiating tirzepatide, metformin, or insulin between February 28, 2020 and February 28, 2025, without prior cancer, were included. Propensity score matching (1:1, greedy nearest-neighbor) balanced demographics, BMI, HbA1c, diabetes duration, and comorbidities. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the 13 most common incident cancers and all-cause mortality. **Results:** After 1:1 propensity score matching, baseline demographic, metabolic, diabetes-related, psychosocial, and medication characteristics were well balanced between groups, with minimal residual differences across age, sex, race/ethnicity, HbA1c, obesity severity, diabetes complications, and concomitant glucose-lowering therapies. In the tirzepatide versus insulin comparison, tirzepatide use was associated with significantly lower risks of multiple solid and hematologic malignancies, including lung, pancreatic, liver, colorectal, kidney, and endometrial cancers, as well as non-Hodgkin lymphoma (all log-rank $p < 0.01$), with no significant differences observed for prostate, thyroid, melanoma, bladder cancer, or leukemia. In the tirzepatide versus metformin comparison, tirzepatide was associated with significantly lower risks of lung cancer (HR 0.086, 95% CI 0.020-0.373; $p < 0.001$), pancreatic cancer (HR 0.124, 95% CI 0.015-1.039; $p = 0.022$), and breast cancer (HR 0.462, 95% CI 0.254-0.840; $p = 0.009$), while risks of other malignancies were not significantly different between groups. Across both matched cohorts, tirzepatide was consistently associated with markedly lower all-cause mortality compared with insulin and metformin, with absolute risk reductions of 4.8% and 0.6%, respectively (both $p < 0.001$). **Conclusions:** Among patients with type 2 diabetes, tirzepatide was associated with consistently lower all-cause mortality and reduced incidence of multiple cancers compared with insulin and metformin in a large, propensity-matched real-world analysis. These findings highlight tirzepatide as a glucose-lowering therapy with a potentially favorable oncologic risk profile, warranting prospective validation and mechanistic investigation. Research Sponsor: None.

LBA10509 **Rapid Oral Abstract Session**

Safety and performance results from PATHFINDER 2, a registrational study of a multi-cancer early detection (MCED) test in an intended-use population. First Author: Karthik Giridhar, Mayo Clinic Rochester, Rochester, MN

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

10510 **Rapid Oral Abstract Session**

A randomized non-inferiority trial of an eHealth delivery alternative for cancer genetic testing for hereditary cancer (eREACH2). First Author: Kimberley T. Lee, University of Pennsylvania, Philadelphia, PA

Background: Germline cancer genetic testing is a standard evidence-based practice, with established risk reduction and cancer screening guidelines for genetic carriers. Yet, many at-risk patients do not have access to genetic services due in part to a workforce shortage of genetic counselors (GC). The randomized non-inferiority eREACH1 study found that digital delivery of pre-test or post-test counseling (e.g. a 1-visit model) was non-inferior 2-visits with a GC and reduced GC time per patient in patients with metastatic cancer. Outcomes with digital alternatives in the broader population of patients with and without cancer who meet criteria for genetic testing is unknown. **Methods:** eREACH2 is a randomized 4-arm non-inferiority trial where traditional pre-test (visit 1) and post-test (visit 2) counseling delivered by a GC are replaced with a patient-centered eHealth (digital) intervention in patients with and without cancer who meet national guidelines for germline genetic testing. GC visits were offered by telehealth in the home. Arms include: A (GC/GC), B (GC/digital), C (digital/GC) and D (digital/digital). Those assigned to a digital visit could request a visit with a GC if preferred. All participants have a designated GC directing their care, even if they complete a digital visit. Surveys were completed at baseline (T0), after visit 1 (T1), visit 2 (T2) and 6 months (T3). The primary outcomes are non-inferiority in uptake of genetic services and change in genetic knowledge and general anxiety from T0-T2. Secondary outcomes included uptake of testing (89-92% across arms) and additional cognitive, affective and behavioral outcomes. We used modified non-inferiority ANOVAs and modified equivalency chi-squared tests for hypothesis testing using an intention-to-treat (ITT) and confirmatory per-protocol analyses. **Results:** 773 participants were recruited from across the US with 49.8% from rural areas and 188-198 per arm. Participants were 20-87 YO (mean 51 YO), 13% were male, 12% were non-white, 29% had less than a college education, and 33% had a personal history of cancer. 584 (76%) patients completed testing (14% had a positive result, 16% had a VUS). In our primary ITT analyses, we met the non-inferiority threshold for uptake of genetic services and all short-term (T0-T2) primary and secondary cognitive and affective outcomes. 3% assigned to digital visit 1 and 9% assigned to digital visit 2 requested a GC. Per-protocol analyses were similar to the ITT results. **Conclusions:** In this large randomized, nationally recruiting trial of representative patients with and without cancer who are candidates for cancer genetic testing, offering patient-centered digital delivery models is non-inferior to two visits with a GC. This patient-centered digital intervention is an evidence-based alternative delivery model to improve access to and efficiency of cancer genetic testing. Clinical trial information: NCT05427240. Research Sponsor: National Cancer Institute; U01CA243702.

10512 **Rapid Oral Abstract Session**

Impact of population-based testing for pathogenic variants in breast cancer genes on screening recommendations in the WISDOM study. First Author: Yiwey Shieh, University of California, San Francisco, San Francisco, CA

Background: The relative contributions of pathogenic variants (PV) in breast cancer (BC) genes, polygenic risk scores (PRS), and clinical risk factors to inform risk-stratified screening have not been well-studied on the population level. The WISDOM Study, a study of risk-based screening, used panel-based testing for PVs in 9 BC genes and the Breast Cancer Surveillance Consortium risk model modified by PRS (BCSC-PRS) to generate screening recommendations for $>$ 30,000 participants undergoing risk-based screening. Women with PVs in high-penetrance genes were assigned q6 month screening (alternating MRI and mammogram). Those with PVs in moderate-penetrance genes were assigned q6 screening or yearly mammogram depending on family history. To determine the impact of PV detection on screening assignments, we examined the concordance between screening strategies informed by PV status vs. BCSC-PRS only. **Methods:** We analyzed participants with high-penetrance (*BRCA1, BRCA2, TP53, PALB2, STK11, CDH1*), moderate-penetrance (*CHEK2, ATM*), or *CHEK2* low-penetrance (I157T, S428T) PVs. We performed cross-tabulations of hypothetical (based on BCSC-PRS only) vs. actual (which considers PV) screening recommendation. To generate hypothetical screening recommendations, we calculated individual BCSC-PRS 5-year risk and applied the trial's risk-based screening algorithm as if there were no PV. We considered initial (Year 1) screening recommendations to reflect that PV testing occurred at time of enrollment. We stratified analyses by PV category and age. **Results:** Our analysis included 714 women with a PV, of which 32% were high-penetrance, 39% were moderate-penetrance, and 29% were *CHEK2* low-penetrance. Median age was 53 (IQR 45-62) years and 86% self-reported as non-Hispanic White. We found little overlap between screening recommendations based on PV status vs. BCSC-PRS. In women with a high-penetrance PV, 1.3% (3/234) would have received a q6 screening recommendation based on BCSC-PRS. In women with a moderate-penetrance PV, 33% (92/278) were assigned to q6 screening, of whom 6.5% (6/92) would have received the same assignment under BCSC-PRS. Additionally, 65% (182/278) were assigned to yearly mammogram, of whom 2.2% (4/182) would have received the same assignment under BCSC-PRS. In women with PVs aged 40-49, 67% (187/280) would have been recommended no screening until age 50 based on BCSC-PRS. In women with PVs aged 50-74, 90% (390/432) would have been recommended biennial screening. **Conclusions:** Most women with PVs in BC genes would not have otherwise been recommended for enhanced screening based on clinical and PRS risk. Our results highlight the importance of testing for PVs as a cornerstone of risk-based screening on the population level. Future studies will examine opportunities for risk reduction as we integrate genetic and non-genetic risk factors. Clinical trial information: NCT02620852. Research Sponsor: PCORIPCS-1402-10749; National Cancer Institute; R01CA237533; Breast Cancer Research Foundation; SPEC-18-006,SPEC-22-018, SPEC-24-026; Robert Wood Johnson Foundation; 71864; Safeway Foundation.

10513 Rapid Oral Abstract Session

Real-world evaluation of germline pathogenic variants (PVs) in cancer-predisposition genes among unselected South Asian women with breast or ovarian cancer. First Author: Siddhartha Yadav, Mayo Clinic Rochester, Rochester, MN

Background: Prior reports of high frequency of *BRCA1* and *BRCA2* (*BRCA1/2*) PVs among South Asian women from Bangladesh, India, Nepal, and Pakistan with breast or ovarian cancer require validation in large prospective unselected cohorts. **Methods:** Individual-level anonymized patient data from two prospective cohorts were pooled to evaluate the prevalence of germline PVs among South Asian women: the South Asian Regional Alliance for Hereditary Cancers (SARAH Consortium) in Bangladesh, Nepal, and Pakistan, and the previously reported Nurse-led Genetic Counseling and Awareness (NuGenA) expansion cohort in India. Both studies enrolled consecutive cases of histologically confirmed newly diagnosed breast or epithelial ovarian cancer irrespective of age at diagnosis or family history. In both studies, participants completed questionnaires on personal and family history (first-, second- or third-degree) and provided blood for germline genetic testing after written consent. PVs in cancer predisposition genes including *ATM, BARD1, BRCA1, BRCA2, BRIP1, CHEK2, MLH1, MSH2, MSH6, PALB2, RAD51C, RAD51D,* and *TP53* were identified as part of the studies utilizing a multigene panel and the results were returned to ordering clinicians. The data cutoff date for this analysis was November 30, 2025. **Results:** The analysis included 1,711 South Asian women with breast (n=1,210) or ovarian (n=501) cancer. A family history of breast or ovarian cancer was noted in 177 (10.3%). Among breast cancers, 94% were invasive, 84% were ductal, 35% were triple-negative and over two-thirds presented with nodal involvement. Germline PVs across 13 predisposition genes were observed in 17.7% of breast and 35.9% of ovarian cancers. Notably, *BRCA1/2* PVs accounted for most of these PV (13.6% of breast and 28.3% of ovarian cancer cases) with PVs in all genes except *BRCA1/2* under 1%. The frequency of *BRCA1/2* PVs was 24.4% in triple-negative breast cancer and 8.0% in ER+/HER2-. *BRCA1/2* PV carriers were diagnosed with breast cancer at a younger age than non-carriers (Median age: 42 vs 46 years, P<0.001), with no age difference observed in ovarian cancer (50 vs. 51 years, P=0.79). Notably, among the 306 *BRCA1/2* PV carriers identified, 229 (74.2%) did not report a family history of breast or ovarian cancer. **Conclusions:** We confirm a high prevalence of *BRCA1/2* PVs among unselected South Asian women with either breast or ovarian cancer. The observations of younger age at cancer diagnosis, and low rates of family history support the need for population-specific germline genetic testing and risk management strategies in South Asia. Research Sponsor: Conquer Cancer, the ASCO Foundation; Mayo Clinic Breast Cancer Specialized Programs of Research Excellence (SPORE); Mayo Clinic Ovarian Cancer Specialized Program of Research Excellence (SPORE); MedGenome Labs.

10514 Rapid Oral Abstract Session

Fine-scaled genomic ancestry clusters to reveal population-specific cancer enrichments in the All of Us Research Program. First Author: Hersh Gupta, Department of Genetics, Albert Einstein College of Medicine, Bronx, NY

Background: Specific populations exhibit known enrichments for certain cancers, such as breast cancer (BC) in Ashkenazi Jewish individuals. However, identification typically relies on self-reported race or broad continental genomic labels, which can obscure risks in understudied or admixed U.S. populations. **Methods:** Using All of Us (AOU) v8 (n=415k), participants with electronic health records (EHR) and whole-genome sequencing (WGS) were grouped into clusters based on genomic segments identical by descent. Clusters were labeled using genomic and anthropological references. We curated clinical data to remove duplicate or mislabeled entries (e.g., misidentifying metastatic lesions as primary tumors). Enrichment was determined via logistic regression, adjusting for age, sex, BMI, socioeconomic status, smoking, and recruitment site, with correction for multiple hypothesis testing using Benjamini-Hochberg. **Results:** A total of 245k individuals with EHR and quality-controlled WGS were assigned to 58 clusters; 41876 individuals were identified with at least one primary cancer diagnosis, spanning 19 broad types. A non-comprehensive selection of model results are presented in Table 1. These include previously established risks, such as BC enrichment in Ashkenazi-Jewish populations and prostate cancer in African Americans compared to Non-Jewish Europeans (NJE). Other, more novel findings include significant BC enrichment in admixed Hawaiians and colorectal cancer (CRC) in Puerto Rican and Dominican groups (not observed in the African American cluster). While individuals of Mexican ancestry showed lower lung cancer enrichment, this was not consistent in other admixed Hispanic populations, such as Colombians. **Conclusions:** Fine-scaled genomic clustering identifies cancer risks with higher precision than race-based or broad ancestral statistics. This methodology facilitates the identification of globally rare, potentially pathogenic variants that are enriched within specific subpopulations. These results underscore the necessity of granular ancestry data in understanding the genetic architecture of complex diseases like cancer. Research Sponsor: None.

Cancer	Population	Population Case N (%)	NJE Case N (%)	Odds Ratio (95% CI)	q-val
BC[1]	Ashkenazi Jewish	915 (10.6%)	6.9%	1.33 (1.23-1.44)	<0.001
Prostate[2]	African American	852 (5.4%)	8.0%	1.51 (1.38-1.65)	<0.001
BC[1]	Hawaiian	<20* (9.4%)	6.9%	2.64 (1.39-5.03)	0.040
CRC	Puerto Rican	89 (1.5%)	1.5%	1.54 (1.24-1.93)	0.003
CRC	Dominican	81 (1.4%)	1.5%	1.85 (1.32-2.61)	0.008
CRC	African American	491 (1.2%)	1.5%	1.16 (1.04-1.30)	0.06
Lung	Mexican	95 (0.4%)	1.1%	0.66 (0.53-0.82)	0.005
Lung	Colombian	<20* (0.7%)	1.1%	0.92 (0.33-2.54)	0.97

1: Percentages only include female participants.
2: Percentages only include male participants.
*: Counts of less than 20 are hidden to comply with AoU reporting requirements.

10515 Rapid Oral Abstract Session

Low-dose tamoxifen for pre-cancer and early disease: A pooled analysis by menopausal status. First Author: Andrea De Censi, Champalimaud Clinical Center/ Champalimaud Foundation, Lisbon, Portugal

Background: Adjuvant endocrine prevention reduces the risk of subsequent breast cancer events after ductal carcinoma in situ (DCIS) and precursor lesions, but the toxicity of standard-dose tamoxifen or aromatase inhibitors limits its use. Low-dose tamoxifen (Babytam) has demonstrated a favorable balance of efficacy and tolerability. Whether the magnitude and pattern of benefit vary by menopausal status remains undefined. We performed a pooled analysis of three studies to evaluate Babytam according to menopausal status and type of breast cancer event. **Methods:** Individual patient data from two randomized trials (Trial 007, JCO 2009; 27:3749; Trial Tam-01, JCO 2023; 41: 3116) and one observational study (Int J Cancer 2016; 139:2127) were pooled. Babytam was administered at 5 mg/day (RCTs) or 10 mg every other day (observational). The primary endpoint was recurrence of any breast cancer event, defined as ipsilateral recurrence or new ipsilateral breast cancer, contralateral breast cancer (CBC), distant metastases, or death. Competing risk models were applied for CBC. Multivariable Cox proportional hazards models with study-level random effects were used. Analyses were stratified by menopausal status. **Results:** A total of 1,772 women were included, 1,568 with DCIS, 101 with ADH, 81 with LCIS, and 21 with pT1a. Babytam significantly reduced overall breast cancer events, with differential effects by menopausal status and event type (table). Reduction in any breast cancer event was driven by a marked decrease in ipsilateral events among postmenopausal women, whereas the preventive effect on CBC was confined to premenopausal women. Few distant metastases or deaths occurred. **Conclusions:** In this pooled analysis, Babytam significantly reduced breast cancer events following in situ and microinvasive disease, confirming and extending the preventive efficacy observed in TAM-01. Menopausal status was a key modifier of benefit, with ipsilateral risk reduction predominating in postmenopausal women and CBC prevention in premenopausal women. These findings underscore the biological heterogeneity of early breast neoplasia and support Babytam as a risk-adapted, de-escalated endocrine prevention strategy that enables individualized decision-making balancing efficacy, toxicity, and patient characteristics. Clinical trial information: NCT06982313. Research Sponsor: Breast Cancer Research Foundation AwardGrant No. PPI-23-002.

Effect of low-dose tamoxifen (babytam) on overall recurrence and contralateral breast cancer by menopausal status.

Population	Menopausal status	Babytam events/N	Control events/N	HR (95% CI)	p-value
ER+	Overall	152/678	192/629	0.68 (0.55-0.84)	<0.001
	Pre	109/366	98/269	0.83 (0.63-1.09)	0.17
	Post	40/292	91/354	0.52 (0.36-0.76)	<0.001
ER-	Overall	7/19	57/225	1.20 (0.54-2.65)	0.65
Considering CBC only					
All patients	Overall	39/812	68/960	0.66 (0.44–1.00)	0.05
	Pre	22/457	40/387	0.46 (0.27–0.77)	0.003
	Post	16/335	27/560	1.04 (0.55–1.96)	0.89
ER+	Overall	35/678	51/629	0.65 (0.42-0.99)	0.046

10516 Rapid Oral Abstract Session

Clinical impact of *MSH3* loss-of-function alterations in patients treated with immune checkpoint blockade across cancer types. First Author: Emily Linda Alouani, Memorial Sloan Kettering Cancer Center, New York, NY

Background: MSH3 is an alternate mismatch repair protein specialized in the recognition of larger indels through its interaction with MSH2 within the MutSβ complex. While monoallelic germline *MSH3* variants are not associated with cancer susceptibility, the impact of *MSH3* loss-of-function (LOF) alteration has not been systematically assessed for immune checkpoint blockade (ICB) sensitivity. **Methods:** Tumors with *MSH3* loss-of-function alterations were identified by next-generation sequencing in the MSKCC IMPACT cohort (discovery cohort). Overall survival (OS) from diagnosis and from ICB initiation was compared between MSH3-altered and wild-type (WT) tumors using 2:1 propensity score matching, adjusting for age, sex, disease stage, and tumor type. Tumors harboring pathogenic *POLE* or *POLD1* mutations were excluded. An independent pan-cancer cohort (Caris) was used for validation. **Results:** Among 65,570 profiled tumors, 767 patients (1.2%) carried *MSH3* LOF alterations, including 46 (6.0%) germline variants. *MSH3* LOF tumors were MMR-deficient (MMRd) in 71.2% of cases, MMR-proficient (MMRp)/ microsatellite instable (MSI) in 2.6% and MMRp/ microsatellite stable (MSS) in 26.2%. In MMRd tumors, *MSH3*-LOF occurred mainly in colorectal (64%), endometrial (20%), and esophagogastric cancers (12%), whereas in MMRp tumors it was most frequent in lung (17.4%), colorectal (12.5%), breast (10.3%), and esophagogastric cancers (4.9%). In MMRd tumors, patients with *MSH3* LOF tumors experienced significantly prolonged OS compared with *MSH3* WT tumors after ICB (mOS NR vs 85.2 months (mo), p = 0.008), attributed to the fact that they were all MSI while discordant cases (MMRd/MSS) were observed only in the absence of *MSH3* LOF. To further assess the impact of *MSH3* LOF on immunogenicity independent of classical MSI, we performed specific analysis in MMRp/MSS tumors. While these tumors remained mostly TMB low (median TMB 7 Mut/Mb vs 5 Mut/Mb, p = 0.14) with a modest but significant increase in MSI score (1.01 vs 0.42, p = 0.013), *MSH3* LOF patients had significantly improved OS following ICB compared with propensity matched WT controls (median OS 33.7 [95% CI 18.4–NR] vs 20.4 mo [95% CI 12.5–24.5]; p = 0.015). In particular, germline and somatic *MSH3* altered tumors were associated with similar benefit (median OS 33.7 [95% CI 14.4–NR] and 31.1 mo [95% CI 17.3–NR], respectively). No survival difference was observed among patients who did not receive ICB (p = 0.91). Predictive value of *MSH3* LOF for improved OS after ICB was independently validated in the Caris cohort. **Conclusions:** Somatic and germline *MSH3* LOF alterations define a unique subset of cancers with enhanced sensitivity to ICB, in particular in MMRp/MSS tumors, where *MSH3* deficiency may drive immunogenicity through mechanisms distinct from classic MSI. These data support *MSH3* LOF as a potential predictive biomarker for immunotherapy benefit. Research Sponsor: None.

10517 Rapid Oral Abstract Session

Intralesional PD-1 blockade for oral cancer prevention: First-in-class phase 1 trial. First Author: Moran Amit, Department of Head and Neck Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Oral premalignant lesions affect 5% of the global population with transformation rates of 1-8% in mild-moderate dysplasia and up to 36% in severe dysplasia. Current management via surgical excision yields 30-40% recurrence despite negative margins, with cumulative functional morbidity. We hypothesized intralesional delivery would achieve immune remodeling while eliminating systemic exposure. **Methods:** We conducted a phase 1, open-label, dose-escalation trial of intralesional nivolumab in patients with histologically confirmed oral epithelial dysplasia (*NCT05327270*). Twenty-nine patients received 10 mg or 20 mg intralesional nivolumab every three weeks for four cycles. Primary endpoints were safety and tolerability; secondary endpoints included lesion response, progression to carcinoma, pharmacokinetics, spatial immune profiling, and, uniquely for this population, prospective patient-reported outcomes (PROs). **Results:** No dose-limiting toxicities occurred; 94% of adverse events were grade 1-2 with no systemic immune-related toxicities. Plasma nivolumab concentrations remained 10-fold below IV dosing without accumulation. Lesion area decreased 60% across cohorts with 41% histologic downgrading. Twelve-month cancer-free survival was 75.8%; all progression events were detected early and surgically salvageable. We performed the first prospective longitudinal analysis of PROs in oral premalignancy. High study completion (86%) and adherence rates, despite significant travel burden, coupled with stable or improved quality-of-life scores (specifically pain and swallowing), indicate that repeated intralesional injections are a feasible, non-toxic approach associated with no functional adversity. Unlike surgical standards that degrade function, this strategy preserved patient quality-of-life. Mechanistic analyses using spatial transcriptomics and multiplexed immunofluorescence revealed immune activation exclusively in treated lesions: increased CD4+ and CD8+ T cell infiltration, enriched CCR7+ activated dendritic cells, elevated CD103+ tissue-resident CD8+ T cells, and formation of higher-order immune assemblies. Untreated non-index lesions from the same patients showed no immune changes, definitively demonstrating anatomically restricted immune activation. PBMC profiling confirmed absence of systemic immune response. **Conclusions:** This first-in-class trial demonstrates intralesional PD-1 blockade safely reprograms premalignant tissue immunity without systemic toxicity, establishing lesion-directed checkpoint inhibition as a viable cancer interception strategy. These findings have established the foundation for a randomized, placebo-controlled Phase 2 trial currently enrolling at MD Anderson Cancer Center (NCT06561087) and support broader applicability to accessible other epithelial precancers including cervical and anal. Clinical trial information: NCT05327270. Research Sponsor: CPRITRP210176.

10518 Poster Session

Global development and validation of the Lung Cancer Prevention Score (LCPS): A quantitative framework linking policy strength, incidence, and outcomes across 40 countries. First Author: Adarsh Vardhan Tangella, MedStar Washington Hospital Center, Washington, DC

Background: Lung cancer is the leading cause of cancer worldwide. Despite advances in tobacco control, national prevention efforts remain fragmented. We developed and validated the Lung Cancer Prevention Score (LCPS), a 0–100 composite linking prevention policy strength with real-world outcomes for global benchmarking and equity tracking. **Methods:** Two LCPS models were created. Policy LCPS quantified 12 weighted domains: smoke-free laws, TAPS bans, ≥50% pictorial warnings, ≥75% excise tax, plain packaging, legal-age limits, e-cigarette control, LDCT screening, asbestos ban, radon plan, clean-cooking access, and occupational carcinogen controls. Data-Driven LCPS combined age-standardized incidence (ASIR), mortality (ASMR), mortality-to-incidence ratio (MIR), smoking prevalence, GDP, health expenditure, and HDI (normalized 0–1; higher = stronger prevention). Data from GLOBOCAN 2022, WHO GTCR 2023, World Bank, and UNDP HDR 2023 covered 40 countries (G20 + 20 others). Analyses included correlation, regression (adjusted for GDP, HDI), Bland–Altman agreement, and ROC AUC for MIR ≤0.60. **Results:** Among 32 complete datasets, Policy and Data-Driven LCPS correlated moderately (r = 0.31; 95% CI −0.04–0.60). Discrimination of favorable outcomes (MIR ≤0.60) showed AUC 0.68 vs 0.77. High-policy countries (≥75) had lower smoking (17%) and MIR (0.45) than those <60 (27%, 0.65; p <0.001). Policy LCPS inversely correlated with ASIR (r = −0.42; p = 0.004); Data-Driven LCPS showed a stronger link (r = −0.55; p <0.001). Each 10-point LCPS-D increase predicted 2.4 fewer cases per 100 000 (β = −0.24 ± 0.07; p = 0.002). Results were consistent across income tiers. **Conclusions:** LCPS provides a validated, reproducible framework connecting prevention policy to measurable cancer burden. Data-Driven LCPS reflected performance most accurately, while Policy LCPS defined actionable tiers linked to lower smoking, incidence, and MIR. LCPS serves as a quantitative global benchmark for policy evaluation. Research Sponsor: None.

Policy-driven lung cancer prevention score (LCPS-P) and data-driven lung cancer prevention score (LCPS-D): Domains and scoring weights.

Component	Type	Wt	Rule / Effect
Smoke-free law	P	1	Yes = 1
TAPS ban	P	1	Yes = 1; Partial = 0.5
Pictorial ≥ 50 %	P	1	Yes = 1
Excise ≥ 75 %	P	1	Yes = 1
Plain pack	P	0.5	Yes = 1
Legal age	P	0.5	18–19 = 0.5; ≥ 21 = 1
E-cig reg	P	0.5	Full/Prescr = 1; None = 0
LDCT screen	P	2	Nat = 1; Reg = 0.5
Asbestos ban	P	1	Yes = 1
Radon plan	P	1	Yes = 1
Clean-cook > 90 %	P	1	Yes = 1
Occ carcinogen ctrl	P	1.5	Yes = 1
ASIR	D	1	Lower = better (1–scaled ASIR)
ASMR	D	1	Lower = better (1–scaled ASMR)
MIR	D	1	Lower = better (1–scaled MIR)
Smoking prev	D	1	Lower = better
GDP	D	0.5	Higher = better
Health exp	D	0.75	Higher = better
HDI	D	0.5	Higher = better
Scoring	—	—	Policy LCPS = Σ (weight×value)/12×100; Data LCPS = Σ (weighted norm)/Σ weights×100

10519 Poster Session

Family cancer history and perceived value of multi-cancer early detection tests in a national U.S. sample. First Author: Chinenye Egwuonwu, PAR Piedmont, Athens, GA

Background: Family history of cancer has a strong influence on individuals' perceived cancer risk and has been shown to be a key determinant of cancer prevention behaviors. As novel precision-screening technologies such as Multi-Cancer Early Detection (MCED) blood tests emerge, understanding how familial cancer experience shapes public awareness and openness to adoption is essential for equitable implementation. **Methods:** We analyzed data from a nationally representative survey (Health Information National Trends Survey 7), of U.S. adults aged ≥18 years (N = 5,789). Weighted analyses accounted for complex survey design and population structure. The prevalence of awareness and perceived value of MCED tests among individuals with a family history of cancer, as well as population characteristics, including socio-demographics, family history of cancer, and cancer-related beliefs were estimated. Weighted multivariable logistic regression models evaluated associations between family history and two primary outcomes: awareness and perceived acceptability of MCED adjusting for sociodemographic factors, personal cancer beliefs, and perceived cancer risk. **Results:** Of the overall study sample, 74.3% reported a family history of cancer. The sample was 50.6% female, 63.3% Non-Hispanic White, 10.9% Black, 16.1% Hispanic, and 4.9% Asian. In total, 17.3% reported prior awareness of MCED tests and 74.2% perceived MCED as valuable. After adjustment, family history of cancer was not associated with MCED awareness (OR = 0.94; 95% CI = 0.66 –1.34; p = 0.71). However, family history was significantly associated with higher acceptability of MCED testing (OR = 1.50; 95% CI = 1.15–1.96; p = 0.004). **Conclusions:** Adults with a family history of cancer are more willing to adopt Multi-Cancer Early Detection blood tests even without prior awareness. In this study, family history was not associated with MCED awareness but was significantly associated with higher perceived value and acceptability. This contrast suggests that receptivity to MCED may be driven more by perceived risk in the form of prior family history than by knowledge alone. Increasing general awareness may therefore be insufficient to promote broad uptake, highlighting the need to consider differences in risk perception when designing communication strategies as MCED moves toward clinical integration. Research Sponsor: None.

10520 Poster Session

GLP-1 receptor agonists for primary prevention of breast cancer in high-risk women: A real-world analysis of efficacy and safety. First Author: Nico-al Paolo Gotera, Mercy Med Ctr North Iowa, Mason City, IA

Background: Therapeutic options for breast cancer (BC) prevention for high-risk women remain limited, and not all eligible patients opt for endocrine therapy due to concerns related to adverse events (AEs). GLP1RAs are widely used for obesity and type 2 diabetes mellitus; their role in BC primary prevention (PP) in high-risk women with obesity has not been evaluated. **Methods:** Using the TriNetX Global Network (150 million patients, 108 organizations), we analyzed de-identified records of high-risk women aged 18–90 years with a BMI ≥ 30 who had health care encounters between January 1, 2000, and January 1, 2025, identified via ICD-10 codes. High risk was defined as at least one of the following: genetic predisposition to BC, family history of BC, atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, or dense breasts. Patients were grouped as having GLP1-RA use or no GLP-1RA use. Patients with a prior history of BC or use of endocrine therapy were excluded. GLP-1RA users were propensity score-matched 1:1 with non-users based on demographics, comorbidities, social determinants of health, lifestyle factors, BMI, HbA1c, and prior breast imaging. Incident BC served as the primary endpoint, with key AEs as secondary measures. Kaplan–Meier analysis and Cox proportional hazards models were utilized to assess outcomes, which were further validated through subgroup and sensitivity analyses. **Results:** Among 80,480 high-risk women with a BMI ≥ 30, 46,581 were assigned to each cohort. Baseline demographics were balanced between cohorts (mean age: 46 years, 70% White, 21% Black). Median follow-up was 2,790 vs 2,630 days for GLP-1RA users and non-users, respectively. BC incidence was 2.95% in GLP-1RA users (1,164/39,495 cases) vs 3.01% in non-users (1,200/39,057 cases) (3.27 vs. 3.57 cases per 1,000 person-years; HR 0.844; 95% CI, 0.779–0.915). GLP-1RA users exhibited an increased risk of endometrial cancer (HR 1.273; 95% CI, 1.088–1.491) and osteoporosis (HR 1.124; 95% CI, 1.054–1.199). No significant association was observed for venous thromboembolism. Gastrointestinal AEs were significantly higher in the GLP-1RA cohort. **Conclusions:** GLP-1RA use was associated with a modest reduction in BC incidence among high-risk women with obesity in this real-world study. Prospective randomized trials are needed to validate these associations. Research Sponsor: None.

10521 **Poster Session**

A SEER-based Joinpoint analysis investigating the effect of shared decision-making on prostate cancer stage at diagnosis. First Author: Noah Ritschard, Western University of Health Sciences, Lebanon, OR

Background: Prostate cancer screening recommendations in the United States have evolved over the last two decades. The U.S. Preventive Services Task Force (USPSTF) recommended against routine prostate-specific antigen (PSA) screening for men ≥75 in 2008 and for all men in 2012 (Grade D), followed by a transition to shared decision-making for men ages 55–69 in 2018 (Grade C). These changes have raised concern for later-stage presentation Few analyses have leveraged national data through 2022 to evaluate whether the 2018 guideline modification has affected stage-specific incidence. **Methods:** We queried the Surveillance, Epidemiology, and End Results (SEER) Program for malignant prostate cancer cases diagnosed from 2000–2022 using the SEER 17 Registries Research Data (November 2024 submission), which provides population-based incidence coverage for approximately 26% of the United States. Cases were limited to men aged ≥55 at diagnosis. Age-adjusted incidence rates (per 100,000; 2000 U.S. standard population) were extracted separately for localized and distant Prostate malignancies (Summary Stage 2000+) using SEER*Stat incidence rate sessions. Annual rates and standard errors were exported for analysis. Joinpoint regression (Joinpoint v5.4.0) was used to estimate Annual Percent Change (APC) for each trend segment, with model selection determined by the Bayesian Information Criterion and weighting by standard error. Up to four joinpoints were permitted, and the software automatically selected the optimal number. Average Annual Percent Change (AAPC) was calculated to summarize overall trends. **Results:** Localized prostate cancer incidence declined significantly from 2004–2022 (APC = −3.12%; $p < .05$). Distant prostate cancer incidence decreased from 2000–2010 (APC = −0.95%; $p < .05$), followed by a significant increase from 2010–2022 (APC = +6.04%; $p < .05$). Joinpoint analysis identified a statistically significant inflection point near 2010 that temporally follows USPSTF recommendations discouraging routine PSA screening. No additional joinpoint or attenuation in distant-stage incidence was observed following the 2018 guideline revision. **Conclusions:** Using up-to-date national registry data through 2022, our analysis corroborates prior work demonstrating rising distant-stage prostate cancer incidence following guideline changes that reduced PSA screening. The absence of a joinpoint following the 2018 revision suggests that the shift to shared decision-making has not yet reversed or slowed this trend. Research Sponsor: None.

10522 **Poster Session**

Glucagon-like peptide-1 receptor agonist for primary prevention of hepatocellular carcinoma in high-risk patients: A real-world analysis across metabolic, viral, alcoholic, and hereditary liver disease. First Author: Colton Jones, The University of Texas San Antonio, San Antonio, TX

Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality. While antiviral and metabolic therapies have reduced incidence, scalable pharmacologic strategies for primary prevention (PP) remain a critical unmet need. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated preclinical antitumor activity and the potential to mitigate hepatic lipotoxicity while promoting metabolic reprogramming to stabilize cirrhosis. However, while chemoprevention signals are observed in metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes, the efficacy of GLP-1RAs for PP across diverse liver disease etiologies remains underexplored. To address this gap, we conducted a global, multicenter analysis on the efficacy and safety of GLP-1RAs for the PP of HCC in a pan-etiology high-risk cohort. **Methods:** A retrospective cohort study was conducted using the TriNetX database (150M patients across 108 health organizations). Adults 18–90 years at elevated HCC risk with ≥ 1 risk factor (chronic viral hepatitis, cirrhosis, MASLD, alcohol use disorder, or hereditary liver disorders) were identified. Cohort A (≥3 months of GLP-1RA) was propensity score-matched 1:1 with Cohort B (non-users) on demographics, HbA1c, BMI, and MELD-Na scores. The primary endpoint was incident HCC, and secondary endpoints were incidence of gastrointestinal (GI) side effects. We employed a 3-month lag period to mitigate immortal time bias. Time-to-event outcomes were assessed via Kaplan-Meier analysis and Cox proportional hazards models. Sensitivity & subgroup analyses were performed to confirm robustness across non-metabolic etiologies. **Results:** After matching, 592,718 patients were analyzed (296,359 per cohort). Median follow-up was 2,450 days for GLP-1RA users vs 2,114 days for non-users. GLP-1RA use was associated with a 73% reduction in incident HCC (140/296,345 events vs 432/296,198) [HR 0.271 (0.224-0.328)], (NNT=1,015). Notably, the protective effect was most pronounced in non-diabetics [HR 0.179 (0.140-0.229)] and lean patients (BMI < 29) [HR 0.161 (0.103-0.252)]. Risk reductions were sustained across all etiologies, including alcohol liver disease (HR 0.379), cirrhosis (HR 0.456), chronic viral hepatitis (HR 0.477), and MASLD (HR 0.605). GLP-1RA use was associated with a significant increase in GI adverse events. **Conclusions:** GLP-1RA use was associated with a 73% reduction in incident HCC, consistent across subgroups. The enhanced benefit in non-diabetic and lean cohorts suggests a direct anti-neoplastic mechanism independent of weight loss or glycemic control. The NNT of 1,015 highlights the substantial public health impact of GLP-1RA therapy in preventing a high-mortality malignancy. These findings warrant prospective validation. Research Sponsor: None.

10523 **Poster Session**

Integrating multi-cancer early detection into cancer screening programs in the United States: A cost-effectiveness modeling study. First Author: Shuaipeng Geng, Clinical Laboratories, Shenyou Bio, Zhengzhou, China

Background: In 2021, standard-of-care (SoC) screening for breast, cervical, colorectal, lung, and prostate cancers in the United States cost $43.2 billion to detect 197,773 cancers, with colonoscopy—used as a primary colorectal screening modality—accounting for $23.7 billion, the largest share of expenditures (54.9%). Multi-cancer early detection (MCED) blood tests could complement SoC single-cancer early detection (SCED) screening but may substantially increase overall costs if implemented without concurrent redesign of screening pathways. **Methods:** A static decision model used 2021 U.S. SoC screening volumes and costs, 2020 Census data, cancer-specific incidence in high- and low-risk groups, and published SCED and MCED performance to simulate 75.6 million unique screened individuals after adjusting for overlap across programs. We evaluated (1) SoC alone, (2) SoC plus either a low-cost two-step MCED assay (OnceSeek followed by SeekInCare; "OncoSeek Duet", $143/person) or a higher-priced cfDNA methylation-based MCED test (Galleri, $949/person), and (3) a budget-neutral strategy replacing primary colonoscopy with FIT, designated as SCED 2.0, with savings reinvested to fund OncoSeek Duet for all screened individuals. **Results:** SoC alone detected 197,773 cancers (262 per 100,000) with a PPV of 0.7% at a total cost of $43.2 billion, or $218,276 per cancer detected. Adding OncoSeek Duet increased detections to 398,586 (527 per 100,000; 2.0-fold), PPV to 43.3% (61.9-fold increase) and total cost to $54.0 billion (25.0% increase), reducing cost per cancer to $135,429, while expanding detection to 9 additional cancer types beyond the 5 SoC targets. Adding Galleri yielded 572,223 cancers (757 per 100,000; PPV of 60.7%) at $114.9 billion total cost (2.7-fold increase) and $200,823 per cancer, improving yield but with markedly higher budget impact than OncoSeek Duet. SCED 2.0 cut costs to $20.0 billion (2.2-fold decrease), reduced cost per cancer to $106,876, saved $23.1 billion, and yielded 187,509 detections (5.2% decrease). Reinvesting these savings to provide OncoSeek Duet for all restored and expanded detection to 391,022 cancers (2.1-fold increase), maintained a high PPV of 42.9%, incurred $78,899 per cancer and produced a $12.3 billion surplus without increasing overall screening expenditure. **Conclusions:** In this U.S. modeling analysis, integrating MCED into SoC screening substantially increased cancers detected and lowered cost per cancer, particularly when using lower-cost OncoSeek Duet. Optimizing high-cost SCED components, such as colonoscopy, can fully finance population-wide MCED while preserving or improving efficiency, supporting a value-based, budget-neutral path for MCED implementation in national screening programs. Research Sponsor: None.

10524 **Poster Session**

Time-restricted eating and metformin (TEAM) in invasive breast cancer or DCIS: A randomized, phase IIb, window-of-opportunity presurgical trial. First Author: Parijatham S. Thomas, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Preclinical studies indicate that metformin administered during fasting synergizes with feeding–fasting cycles to suppress tumor growth through activation of the PP2A–GSK3β–MCL1 pathway. The TEAM trial evaluated the feasibility, safety, biological, metabolic, and clinical effects of a short-term metabolic intervention combining prolonged nightly fasting and metformin in operable hormone receptor–positive breast cancer. **Methods:** TEAM is a randomized, phase IIb, presurgical window-of-opportunity trial. Women with hormone receptor-positive operable invasive breast cancer or DCIS were randomized 1:1 to either ≥16-hour nightly fasting plus metformin 750 mg bid and nutritional counseling (experimental [exp] arm) or to healthy WCRF lifestyle recommendations (control arm). Both groups wore a Continuous Glucose Monitor (CGM) per protocol data downloads. Treatment duration was 4–6 weeks before surgery. The primary endpoint is the absolute change in centrally assessed Ki67 between biopsy and surgery in invasive disease or DCIS. A co-primary endpoint was the difference in post-treatment Ki67 in cancer-adjacent DCIS. Analyses were intention-to-treat. **Results:** A total of 120 patients were randomized and completed the study (mean±SD, 32±8.6 days). As of December 31, 2025, 105 were evaluable for paired Ki67 analysis due to tissue availability. Since the complete results will be presented at the meeting, current data are descriptive with no inferential statistics and p-values, as per DSMB recommendation. Median baseline Ki67 was 15% in both arms. Median absolute Ki67 change was −3 percentage points (IQR −7 to 1) in the exp arm versus −2 (IQR −4 to 4) in the control arm. The median absolute change in invasive disease was -3 (-7 to 2) versus -1 (-3 to 4), and Ki67 reduction ≥3% occurred in 53% versus 32%, in the exp and control arm, respectively. Post-treatment Ki67 in cancer-adjacent DCIS was 3.5 (2-8.5) vs 4 (2-7). There were 3 pathological CR in the exp arm and 0 in the control arm during the presurgical window. Median weight decreased by 1.75 kg in the exp arm relative to the control arm. Mean tumor 18F-FDG PET SUV decreased by 22% versus 4% in a subgroup of 25 patients with tumors ≥ 15 mm. Reductions were observed in glucose, HOMA-IR, leptin, C-peptide, insulin and IGF-I. Changes in CIP2A and MCL1 were observed in patients with Ki67 reduction. Median adherence to ≥16-hour fasting was 100% (97.4-100); overall metformin adherence was 95% (85%-99%). No dose-limiting toxicities or grade ≥3 hypoglycemia occurred. **Conclusions:** These preliminary results show that short-term metabolic intervention was feasible, safe, highly compliant, and very inexpensive, and was associated with favorable antiproliferative and metabolic changes that warrant further investigation in breast cancer prevention and treatment. Full results will be presented at the meeting. Clinical trial information: NCT05023967. Research Sponsor: Division of Cancer Prevention, National Cancer Institute; Grant #: UG1CA242609); Italian Ministry of Health; (Grant #: RF-2019-12370733).

10525 **Poster Session**

Cost-effective colorectal cancer screening in the United States: Comparative analyses of four molecular tests. First Author: Yinyin Chang, Clinical Laboratories, Shenyou Bio, Zhengzhou, China

Background: Colorectal cancer (CRC) screening in the United States is costly, largely driven by expensive colonoscopy procedures. In 2021, 22.3 million screening tests were performed, costing $27.5 billion; colonoscopy alone accounted for 9.2 million tests and $23.7 billion in expenditure (54.8% of the $43.2 billion spent on five major cancers). This study compared available molecular tests to identify an approach that balances performance and cost as a primary alternative to colonoscopy. **Methods:** Four molecular tests were evaluated: two FDA-approved stool-based (fecal immunochemical tests [FIT] and multitarget stool DNA test [Cologuard]) and two blood-based (the FDA-approved cfDNA-based Shield and the multiomics-based SimpleScreen). Performance data came from published literature and clinical trials (NCT04136002, NCT01397747, NCT04369053). Cost analyses used 2021 U.S. screening volumes: FIT, Cologuard, and colonoscopy costs were based on 2021 fee schedules, Shield pricing on Medicare rates; SimpleScreen was excluded due to cost unavailability. **Results:** For CRC, Cologuard had the highest sensitivity (92.3%) but lower specificity (84.4%), whereas FIT showed lower sensitivity (73.8%) but the highest specificity (93.4%). Shield and SimpleScreen showed intermediate sensitivities (83.1%, 79.2%) and specificities (89.2%, 91.1%). For advanced precancerous lesions, blood-based tests showed minimal detection power, with post-test probabilities (equal to PPV) close to pre-test prevalence (Shield 17.4% vs 14.3%; SimpleScreen 13.5% vs 9.5%; post/pre ratios 1.2 and 1.5). In contrast, stool-based tests modestly increased post-test probabilities: Cologuard 20.7% vs 7.6%, post/pre ratios 4.0; and FIT 27.6% vs 7.6%, post/pre ratios 4.4, indicating preventive potential and supporting their use as alternatives to colonoscopy. Cost analysis further identified FIT as the most cost-effective alternative, with the lowest per-case cost of $57, compared to $651 for Cologuard, $2,571 for colonoscopy, and $1,495 for Shield. Replacing colonoscopy with FIT for the 9.2 million current colonoscopy screenings in 2021 would reduce CRC screening expenditures from $27.5 billion to $4.3 billion (84.2% reduction). Comparatively, Cologuard lower costs to $9.8 billion (64.3% reduction) and Shield to $17.6 billion (36.0% reduction). Nationally, the overall cost for the five major cancers was reduced to $20.0 billion, resulting in a saving of $23.2 billion, which could be reallocated to future multi-cancer screening programs to expand population coverage. **Conclusions:** FIT provides the best balance of performance, preventive potential, and cost-effectiveness. By reducing colonoscopy demand and national screening costs while maintaining adequate detection, it supports sustainable population-wide screening and warrants consideration in guidelines and reimbursement policies. Research Sponsor: None.

10526 **Poster Session**

Using digital screening to increase early identification of hereditary breast and ovarian cancer syndrome: A multicenter cluster-randomized trial. First Author: Dorothee Speiser, Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Hereditary Breast and Ovarian Cancer Center, Berlin, Germany

Background: Early identification of hereditary breast and ovarian cancer syndrome (HBOCS) in primary gynecological care is essential for timely referral to specialized counseling and risk-adapted prevention. Yet, identification mostly occurs after disease onset, thereby thwarting preventive efforts. To facilitate early identification of healthy HBOCS carriers along the HBOCS care pathway in Germany, we developed a modular cross-sectoral digital care platform (dVP_FAM). This study compared the impact of dVP_FAM with standard care on increasing the proportion of healthy individuals with HBOCS. This project was funded by the Innovation Fund of the German Federal Joint Committee. **Methods:** We conducted a two-arm, cluster-randomized trial including 42 primary gynecological centers (20 intervention, 22 control) in Germany. In the intervention centers, patients filled out a digital HBOCS screening questionnaire based on the inclusion criteria of the German Consortium HBOC. Results were reviewed and validated by primary care gynecologists, who then decided whether to initiate referral to a specialized HBOC center via the digital platform. Control centers followed usual care. A mixed-effects logistic regression model with random intercepts was used to account for clustering at the study center level. Odds ratios (ORs) and 95% confidence intervals were estimated. **Results:** In the intervention centers, 5.534 individuals completed digital screening; 1.116 (20.2%) met inclusion criteria (IC+), and 507 (9.2%) were uncertain about family history. Of these 1.623 individuals, 664 requested an appointment at an HBOC center. A total of 467 individuals (intervention group (IG): n = 329, mean age = 45.6 (SD 12.3), 99.4% female; control group (CG): n = 138, mean age = 46.2 (SD 13.5), 99.3% female) met the primary endpoint. Among IG, 282 participants (85.7%; [83.3%, 88.6%]) were healthy at the initial counseling at the HBOC center compared with 110 participants (79.7%; [73.5%, 84.7%]) in the CG. After adjusting for center effects, the observed odds of healthy counselees were lower in the CG than in the IG (OR = 0.67; 95% CI, 0.28–1.59; p = 0.368). **Conclusions:** The IG showed a higher proportion of healthy individuals at risk for HBOCS. Although not significant, this trend may suggest that supporting primary care physicians with a digital screening platform facilitates early identification of HBOCS within cross-sectoral care pathways. Clinical trial information: DRKS00030371. Research Sponsor: German Federal Joint Committee; 01NVF20002.

10527 **Poster Session**

Incorporating CA19-9 testing in a prospective study of pancreatic cancer surveillance (PCS) among high-risk individuals (HRIs). First Author: Asaf Maoz, Dana-Farber Cancer Institute/Mass General Brigham/Harvard Medical School, Boston, MA

Background: For individuals at an increased risk of pancreatic cancer (PC), imaging-based PCS is recommended. However, despite PCS among such individuals, when PC is diagnosed, it is found at an advanced stage in over 25% of individuals. Blood-based biomarkers of PC, such as carbohydrate antigen 19-9 (CA19-9) and HbA1C, can be abnormal prior to radiographic findings among individuals with PC. However, it is unknown whether prospective assessment of these biomarkers would allow for earlier detection or interval PC of PC among HRIs undergoing PCS. **Methods:** We conducted a single-institution (Dana-Farber Cancer Institute) prospective study of HRIs undergoing imaging-based PCS with annual MRCP and/or EUS (NCT06122896). All participants signed informed consent; the institutional IRB approved the study. CA19-9 was measured at baseline and every 6 months. Individuals with normal imaging but abnormal CA19-9 value underwent additional imaging, and short-interval repeat CA19-9 measurement. Personalized, genotype-adjusted, CA19-9 reference ranges were calculated based on fucosyltransferase (FUT) enzymes FUT3 and FUT2 variant analysis. Herein, we report outcomes from baseline PCS assessment. We measured the specificity of unadjusted and adjusted CA19-9. **Results:** 231 HRIs (mean age 62, 71% female, 47% with a previous history of cancer) underwent baseline PCS. 105 HRI (46%) had a pathogenic germline variant (PGV) predisposing to PC and met 2023 NCCN eligibility criteria for PCS surveillance, 77 (33%) HRI had a family history of PC without a predisposing PGV; 49 HRI (21%) had other indications for PCS. 153 (66%) HRIs underwent baseline PCS with MRCP [Table]; the remainder underwent an EUS. No HRIs were diagnosed with PC on baseline imaging. 98 (42%) HRI had pancreatic cyst(s) detected on baseline imaging. All abnormal CA19-9 tests (unadjusted = 5, genotype-adjusted = 1) were considered false positives as additional imaging did not reveal additional pancreatic pathology. The specificity of unadjusted and genotype-adjusted CA19-9 was 97.8% (95% CI: 95.0-99.3) and 99.5% (95% CI 97.3-100). Two individuals with concern for a focal lesion on EUS underwent immediate workup with imaging (n=1) and biopsy (n=1), both with reassuring findings. One individual was found to have a paraganglioma. **Conclusions:** Baseline unadjusted CA19-9 testing led to unnecessary follow-up studies in 2% of HRI undergoing imaging-based PCS. Genotype-adjusted CA19-9 may have superior specificity compared to unadjusted CA19-9. Longitudinal biomarker assessment, including serial CA19-9 and HbA1c, is ongoing. Clinical trial information: NCT06122896. Research Sponsor: The Hale Family Centre for Pancreatic Cancer Research.

Characteristic	n (%)
Baseline imaging	231 (100)
MRCP	153 (66)
EUS	78 (34)
Individuals with cystic lesion(s) detected	98 (42)
Individuals with cyst(s) > 1cm	21 (9)
MPD > 4mm	2 (0.9)
Elevated unadjusted CA19-9 (> 35 U/mL)	5/229 (2.2)
Elevated genotype-adjusted CA19-9	1/205 (0.5)

MPD: main pancreatic duct.

10528 **Poster Session**

Correlates of patient enrollment in a population-based randomized controlled trial of cascade genetic testing in families with hereditary cancer susceptibility. First Author: Steven J. Katz, University of Michigan, Ann Arbor, MI

Background: Clinical trials that enroll patients through virtual approaches are growing but there is little information about the impact on access. The Genetic Information and Family Testing (GIFT) study was a population-based cluster RCT that evaluated an online platform that delivered cancer genetic education and home germline testing to families with hereditary cancer susceptibility. We examined correlates of patient enrollment to address potential barriers to trial access. **Methods:** We identified a random sample of adult patients with any cancer type diagnosed in Georgia or California in 2018-19 who linked to a pathogenic variant (PV) in a cancer susceptibility gene through a SEER-based data infrastructure. We initiated a mailed survey four years after diagnosis. We invited all respondents who recalled a PV on testing to enroll online in GIFT. Enrolled patients could invite their first- and second-degree relatives to enroll through the online platform. The primary endpoint was the proportion of relatives who received testing through the platform. We examined clinical and sociodemographic correlates of patient enrollment. **Results:** 4,300 patients were selected and 2,285 completed the survey (53.1%); 2,006 of 2,285 respondents were eligible and invited to GIFT (87.8) and 412 enrolled (20.5). The Table shows clinical and sociodemographic correlates of patient enrollment for the 1,994 with complete data. There were no substantial differences in enrollment by PV grouping, cancer type, sex, or race/ethnic groups. Enrollment was lower in older patients, those with lower education levels, and those living in census tracts with higher poverty levels. **Conclusions:** GIFT successfully enrolled a diverse patient population through a virtual approach. Moderate sociodemographic gradients observed in GIFT motivate strategies to ensure access to clinical trials that use virtual approaches to patient enrollment. Trial Registration: NCT05552664 at clinicaltrials.gov. Research Sponsor: U.S. National Institutes of Health; U01CA254822; American Cancer Society; RSG-20-025-01.

	Patients Enrolled		
	n	%	p
Gene Type with PV			0.601
***BRCA1/2* or other breast cancer-related**	1,650	22	
Lynch Syndrome or other gastrointestinal (GI)-related	225	23	
Cancer type			0.702
GI	145	20	
Ovary/uterine	86	23	
Female breast	1,234	22	
Prostate	72	24	
Other	407	19	
Sex			0.594
Male	222	20	
Female	1,722	22	
Age			<.001
<45	501	27	
45-64	1,025	22	
65+	414	15	
Education			<.001
HS or less	311	12	
Some college	531	22	
College graduate	527	25	
Graduate degree	499	26	
Race/Ethnicity			0.379
Non-Hispanic White	1,270	22	
Black	180	25	
Asian	164	19	
Hispanic	345	19	
Census Tract Poverty			0.204
>19%	145	19	
10-19%	401	19	
<10%	1,398	23	

10529 Poster Session

Clinical characteristics and risk factors of individuals ineligible for lung cancer screening at a tertiary care center. First Author: Julian A. Marin-Acevedo, Indiana University Melvin and Simon Comprehensive Cancer Center, Indianapolis, IN

Background: Lung cancer screening (LCS) reduces mortality, yet many individuals with lung cancer do not meet the 2021 USPSTF eligibility criteria. We compared clinical characteristics and risk factors in individuals with lung cancer who were ineligible and eligible for LCS. **Methods:** We conducted a retrospective study of individuals with a new or prior diagnosis of lung cancer at Indiana University Health from April 1, 2025 - December 4, 2025. We recruited individuals during their clinic visits and used electronic medical records and a patient-completed survey to obtain demographic information, smoking history, and lung cancer risk factors at diagnosis (high-risk lung disease/occupation, first-degree family history of lung cancer, autoimmune disease, prior chest-wall radiation). Individuals were stratified using the 2021USPSTF criteria. Continuous and categorical variables were compared with T-tests and χ^2/Fisher's exact tests. Logistic regression models were used for multivariate analysis. **Results:** 242 individuals were evaluated and 128 (53%) were ineligible for LCS. The median age was 63 among ineligible individuals, 56% were female, 70% were white, and 25% were black (64, 55%, 80%, and 17% respectively among LCS eligible). These individuals were more likely to have adenocarcinoma (80% vs. 56%, $p<0.001$) and present with stage IV disease compared to those eligible for LCS [51% vs. 26%, adjusted OR 2.13 (95% CI, 1.01 – 4.57), $p=0.048$]. Of note, 24 individuals (19%) were <50 or >80 years old and 46 (36%) were never-smokers; however, tobacco exposure was common (64% ever-smokers, 21% used other tobacco products, 56% secondhand exposure). Most of these individuals had high-risk lung disease (61%), Table. Multivariate analysis adjusting for smoking revealed no association between LCS eligibility and secondhand exposure or high-risk occupation, $p=0.340$ and 0.275. Interestingly, 1/3 of individuals in both cohorts had a first-degree relative with lung cancer. **Conclusions:** Most individuals with lung cancer in our cohort were ineligible for LCS using the 2021 USPSTF criteria and were more likely to present with metastatic disease. Many had significant tobacco exposure and other risk factors similar to those eligible for LCS. Our findings suggest the current LCS criteria exclude a large at-risk population and should be re-evaluated to account for risk factors beyond age and pack-years. Research Sponsor: Indiana University School of Medicine.

Risk Factor	Ineligible n=128 (%)	Eligible n=114 (%)	p
Ever-smokers (≥ 100 cigarettes)	82 (64.1)	114 (100)	**<0.001**
Use of Other Tobacco Product	27 (21.1)	47 (41.2)	**<0.001**
High-Risk Lung Disease (e.g., COPD)	78 (60.9)	95 (83.3)	**<0.001**
Secondhand Smoking	71 (55.5)	79 (69.3)	0.340*
High-Risk Occupation (e.g., firefighting)	47 (36.7)	58 (50.9)	0.275*
1st Degree Family History	42 (32.8)	40 (35.1)	0.343
Autoimmune Disease	12 (9.4)	10 (8.8)	1.000
Chest Wall Radiation	11 (8.6)	11 (9.6)	0.951

*Adjusted for smoking.

10530 Poster Session

Disparities in cancer screening across disease sites for transgender and gender-diverse patients. First Author: Peter James Stanfield, Medical College of Wisconsin, Milwaukee, WI

Background: Over 2 million Americans identify as transgender, nonbinary, or gender-diverse (TGD) and limited data exist on cancer screening in this population. This study examines uptake rates of recommended breast, cervical, colorectal, and prostate cancer screening in TGD persons and reports factors predictive of screening uptake. **Methods:** A cross-sectional single-institution cohort study was conducted at a tertiary referral center with a specialized LGBTQIA+ Inclusion Health Clinic (IHC). Adult patients self-identifying as TGD with a healthcare encounter from January 2023-May 2025 were identified in our Clinical Research Data Warehouse. Demographic, clinical, and screening data for breast, cervical, colorectal, and prostate cancers were collected. The American Cancer Society, National Comprehensive Cancer Network, and UCSF transgender breast cancer screening guidelines were used as standards for screening indications. Multivariable logistic regression was conducted to evaluate factors predictive of guideline-concordant screening uptake. **Results:** We identified 2,478 TGD patients (821 transgender men (TGM), 789 transgender women (TGW), and 868 gender-diverse (GD) patients). Median age was 28 years (range 18-86) and 62% were treated at the IHC. Most patients were White (78.3%) and non-Hispanic (91.1%). Sixty-four percent of patients used private health insurance, 26.2% used government insurance, and 9.2% were uninsured. Average duration of gender-affirming hormone therapy was 4.0 years (IQR 2.0, 6.0), and 31% of patients had received gender-affirming surgery. Fifty-two percent of patients had some family cancer history at any disease site. Rates of guideline-concordant cancer screening uptake are presented in Table 1. On multivariate analyses, GD gender identity (OR 2.55, 95% CI 1.68-3.88, $p<0.001$), age (OR 1.05, 95% CI 1.02-1.08, $p<0.001$), and treatment at the IHC (OR 2.24, 95% CI 1.50-3.40, $p<0.001$) were predictors of cervical cancer screening uptake. No significant predictors were identified of screening uptake for other disease sites. **Conclusions:** Gender-specific medical care is valuable for promoting guideline-concordant cancer screening uptake. Even in a specialized care center, we found poor rates of recommended cancer screening uptake in TGD patients, demonstrating opportunities to improve uptake of gender-specific cancer screening. Research Sponsor: None.

Rates of guideline-concordant cancer screening uptake by disease site and gender identity.

Disease Site	Overall (n=2,478)	TGW (n=789)	TGM (n=821)	GD (n=868)	*p*-value
Breast	49.2%	40.8%	38.5%	60.0%	0.12
Cervical	41.3%	*NA*	31.5%	51.2%	<0.001
Colorectal	43.4%	41.7%	31.0%	51.4%	0.3
Prostate	20.7%	19.6%	*NA*	26.3%	0.7

10531 Poster Session

Development and validation of a multidimensional cfDNA assay for cancer detection and tissue-of-origin prediction. First Author: Hua Bao, Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China

Background: Early detection remains a major unmet need in oncology, and multi-cancer early detection assays that analyze circulating cell-free DNA features have shown promise for detecting multiple cancers with high specificity and tissue-of-origin prediction. Here, we leverage whole-genome sequencing (WGS) to extract multiple cfDNA features (genomic, fragmentomic, and estimated methylation) from a single assay to enable multi-cancer early detection and tissue-of-origin (TOO) localization. **Methods:** Plasma samples were collected in a multicenter, prospective case-control study. From 5× low-pass WGS data, multiple cfDNA feature sets were extracted, including fragmentomic, genomic, and inferred epigenetic features. Machine learning models were trained for cancer detection (healthy vs. cancer) and tissue-of-origin (TOO) classification. The training set included 3,577 healthy and 3,578 cancer participants, and the independent validation set included 2,384 healthy and 2,386 cancer participants. Cancer cases spanned 56 cancer types, grouped into 21 cancer classes. **Results:** Age and sex are evenly distributed across healthy and cancer samples in both the training and validation datasets (Table 1). At 99% specificity, cancer detection sensitivity increased with stage and was consistent between training and validation cohorts: Stage I: 70.66% vs 70.89%, Stage II: 80.41% vs 80.27%, Stage III: 89.89% vs 88.58%, and Stage IV: 92.23% vs 91.76%. Across tumor types, sensitivity at 99% specificity varied substantially, ranging from 57.43% (Thyroid tumor) and 63.87% (Kidney cancer) to 95.96% (Lymphoma) and 99.07% (Liver/Biliary cancer). Tissue-of-origin prediction achieved high accuracy in machine-learning predicted cancer-positive samples (Top-1/Top-2: 0.75/0.89 in training; 0.75/0.88 in validation). **Conclusions:** We developed a cost-efficient blood test (CanScan Pro) using multidimensional cfDNA features from low-pass WGS and machine learning that detects cancers at 99% specificity, with sensitivity increasing by stage and similar performance in training and validation cohorts. The model predicts tissue of origin with high accuracy, which may help guide downstream diagnostic evaluation following a positive result and thereby enhance real-world clinical utility. Research Sponsor: None.

Patient characteristics.

	Train		Valid	
	Healthy (N=3577)	Cancer (N=3578)	Healthy (N=2384)	Cancer (N=2386)
Age				
Mean (SD)	57.8 (6.46)	57.7 (14.74)	58.1 (6.63)	57.2 (15.00)
Median [Min, Max]	57.0 [45.0 ,76.0]	60.0 [11.0 ,91.0]	57.0 [45.0 ,76.0]	59.0 [11.0 ,92.0]
Sex				
F	2018 (56.4%)	1655 (46.3%)	1355 (56.8%)	1101 (46.1%)
M	1559 (43.6%)	1923 (53.7%)	1029 (43.2%)	1285 (53.9%)
Stage TNM				
-	3577 (100%)	0 (0%)	2384 (100%)	0 (0%)
I	0 (0%)	1060 (29.6%)	0 (0%)	718 (30.1%)
II	0 (0%)	883 (24.7%)	0 (0%)	588 (24.6%)
III	0 (0%)	811 (22.7%)	0 (0%)	534 (22.4%)
IV	0 (0%)	824 (23.0%)	0 (0%)	546 (22.9%)

10532 Poster Session

Implementation of a multi-cancer early detection (MCED) test in a private practice: Adoption, performance, and repeat-testing patterns. First Author: Eric Sue, Century City Medical Management, Los Angeles, CA

Background: Century City Medical Management (CCMM), a network of private primary care practices, implemented MCED testing as part of their cancer screening program. The MCED test detects a cancer signal in cell-free DNA isolated from peripheral blood and predicts the cancer signal origin (CSO). We describe CCMM's MCED testing workflow and real-world performance. **Methods:** MCED testing is discussed with all CCMM patients as part of routine care, and shared decision-making guides test utilization. Pts with a positive MCED test result (cancer signal detected) are directed to pursue targeted diagnostic evaluation. This analysis reports on data from 1,949 pts who had 2,922 MCED tests, with results returned between 11/29/21 and 11/24/25. Diagnostic evaluations and clinical outcomes were collected through a Quality Assurance Program via follow-up with ordering providers. All data were deidentified in accordance with HIPAA using the Expert Determination method. The cancer signal detection rate (CSDR) was defined as the proportion of positive MCED tests among all tests administered during the first screening round. Among pts with diagnosed cancers and data available, CSO accuracy (top-two predictions) and median time to diagnosis were calculated. Results of MCED retesting after an inconclusive workup and the frequency of annual MCED screening were evaluated. **Results:** At the first MCED test (N = 1,949), median age was 63y (IQR: 55-71), 47.5% were female, and the CSDR was 1.03% (95% CI, 0.63–1.58%; 20/1,949). Across all screening rounds, 24 pts had a positive MCED result; 16/24 had ≥12mo follow-up at data cutoff. Among these 16, 3 had an active cancer at testing. Of the 13 pts with ≥12mo follow-up and no active cancer at testing, 7 were subsequently diagnosed with cancer. CSO accuracy was 100% (7/7). None of the diagnosed cancers had USPSTF A/B-recommended screening. 1 diagnosis (symptomatic pt) occurred before MCED results were returned; median time from test results to diagnosis of the other 6 was 62 days (IQR: 30.5-143). 5 pts with an initial positive test but negative CSO-directed workup had an MCED retest and ≥12-mo follow-up. Among these, 4 pts with a negative retest remained cancer-free through the end of follow-up, and 1 with a positive retest was diagnosed with a cancer matching the initial and retest CSO. Among 996 pts tested with >15mo of follow-up, 686 (69.6%) received ≥2 MCED screening tests. The most common interval between consecutive tests was annual (9-15mo), with <10% exceeding an 18-mo interval. **Conclusions:** MCED testing in a real-world population achieved test performance, CSO accuracy, and diagnostic resolution timelines consistent with prior studies, with high annual screening uptake and clinical utilization of repeat testing after inconclusive CSO-directed workups. The findings support feasible and scalable implementation of MCED testing in primary care. Research Sponsor: GRAIL, Inc.

10533 **Poster Session**

Generalizable cancer detection from ultra-low-pass whole-genome sequencing of cell-free DNA using a sequentially fine-tuned transformer framework. First Author: Rui Liu, Geneseeq Research Institute, Nanjing Geneseeq Technology Inc., Nanjing, China

Background: Ultra-low-pass whole-genome sequencing (ULP-WGS) of cell-free DNA (cfDNA) provides a cost-effective approach for cancer screening, yet its clinical translation is constrained by extreme data sparsity and poor model generalizability, particularly in low-tumor fraction (TF) settings. **Methods:** We developed Fragmentia-AI WGS, a mutation-independent framework that leverages a transformer-based multiple-instance learning architecture with sequential fine-tuning across TF strata to extract latent cancer-associated signals from ULP-WGS data (~0.02× coverage, ~128k reads). Model performance and generalizability were evaluated across multiple independent cohorts, including a pan-cancer test cohort across 17 cancer types, a public online cohort sequenced on a different platform, and an analytical variability assessment cohort comprising samples processed under heterogeneous technical and pre-analytical conditions. Clinical relevance was further examined by associating prediction scores with progression-free survival (PFS) in patients with advanced non-small cell lung cancer receiving immunotherapy. **Results:** Sequential fine-tuning across all TF strata substantially improved performance in low-TF samples compared with high-TF-only training, yielding a 35.6% relative increase in AUC in the low-TF subgroup (from 0.652 to 0.884 in the validation cohort). In the independent test cohort, the model achieved an overall AUC of 0.930 (95% CI: 0.924 – 0.936), with consistently strong performance across TF levels (high TF: 0.984; medium TF: 0.958; low TF: 0.910) and across cancer types. External validation in the public cohort demonstrated robust cross-platform and cross-population generalizability (AUC: 0.929; sensitivity: 0.78; specificity: 0.92). Prediction scores remained stable across heterogeneous experimental conditions, supporting robustness to technical and pre-analytical variability. Notably, lower model prediction scores were independently associated with prolonged PFS (hazard ratio: 0.49, 95% CI: 0.31 – 0.77; p = 0.002) after adjusting for sex, age, clinical stage, and histologic subtype. **Conclusions:** Fragmentia-AI WGS enables robust and generalizable cancer detection as well as clinically meaningful risk stratification from ultra-sparse cfDNA sequencing, underscoring its potential for scalable and cost-effective liquid biopsy applications. Research Sponsor: None.

10534 **Poster Session**

Beyond detection: Five-year screening behaviors and patient-reported perceptions in DETECT-A participants. First Author: Tomasz M. Beer, Exact Sciences Corporation, Madison, WI

Background: Multi-cancer early detection (MCED) blood testing may improve early cancer detection. The impact of MCED testing on anxiety and standard of care (SoC) cancer screening adherence is not fully understood. Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing (DETECT-A) enrolled 10,006 women aged 65 to 75 years from the Geisinger Health System (GHS) with no previous history of cancer and assessed a single instance of MCED (CancerSEEK) testing in 9,911 subjects. Herein, we report cancer survey results, and SoC screening adherence over a 5-year follow-up period (5YFU). **Methods:** Medical record review and participant surveys administered at prespecified intervals, including approximately 5 years after enrollment, were used to assess patient experience, anxiety, and commitment to SoC screening. Decision regret/participation was assessed using a 5-item, 5-point agreement scale; perceived impact on anxiety, depression, and intention to adhere to SoC screening were assessed using 3-option directional responses (more/less/no change), with a 'prefer not to answer' option. Observed SoC screening adherence was assessed through August 2024. SoC screening eligibility (U.S. Preventive Services Taskforce criteria) and adherence data were available for DETECT-A subjects. Changes in adherence over time were assessed using a mixed effects model. **Results:** 8,114 subjects completed all survey questions. 97.3% expressed no participation regret; 94.8% noted a willingness to participate again. Most participants reported no changes in anxiety (89.4%) or depression (96.6%) levels since enrollment. 98.7% reported an equal or greater likelihood of adhering to SoC screening. SoC screening adherence was assessed for a subset of DETECT-A subjects who had at least one month of active GHS patient status (Breast and CRC) and were also eligible for screening (Lung, Breast, CRC). DETECT-A subject SoC adherence was high at consent (Lung: 28.0%, Breast: 88.4%, CRC: 73.9%) and remained high at one year (Lung: 38.5%, CRC: 82.3%) or two-year (Breast: 87.7%) follow-up post consent. Adherence remained high throughout the follow-up period. **Conclusions:** DETECT-A subjects were satisfied with study participation and reported little change in anxiety and depression. Reported commitment to SoC screening adherence was high and observed adherence to recommended screening modalities was maintained over the follow-up period. In a controlled setting of a prospective clinical trial, MCED testing did not contribute to anxiety or depression and did not interfere with adherence to SoC screening. Research Sponsor: Exact Sciences Corporation.

10535 **Poster Session**

Evaluation of a novel blood-based lung cancer screening test in elevated-risk subjects. First Author: Dawn R. Mattoon, Mercy BioAnalytics, Inc., Waltham, MA

Background: Less than 20% of individuals recommended for lung cancer (LC) screening are screened each year by low dose computed tomography (LDCT), highlighting the need for a more acceptable screening modality. Tumor-associated extracellular vesicles and particles (EVPs) are highly abundant in blood and carry surface biomarkers from their tumor cell of origin, providing a readily measurable analyte class for blood-based screening tests. Test sensitivity may be improved by EVP abundance; specificity by simultaneous measurement of multiple co-localized cancer-related markers on a vesicle surface. We report performance of an EVP-based LC Screening Test in plasma samples from elevated risk participants in the National Lung Screening Trial (NLST). **Methods:** The LC Test (biomarkers and classifier) was locked following a training study, after which we validated consistent assay performance in an independent cohort. Here we evaluated the LC Screening Test in a blinded case-control study nested within the ACRIN Biomarker Arm of the NLST. The study included all available incident LC cases for which subject-matched blood samples were available from the year of diagnosis (T) and the year prior (T-1) (n = 48 cases; 96 samples). Controls were age-matched NLST subjects who had no LC detected before or within the trial follow up period (n = 60). LC Test results were determined blinded to case-control status, with unblinding by ECOG-ACRIN. LC Test sensitivity was calculated at a threshold pertaining to 90% specificity, superior to 87% reported specificity for LDCT in NLST (Lung RADS v1.1). LDCT positivity was based on Lung RADS v1.1 interpretation. **Results:** Across two screening encounters (T and T-1), 34.4% sensitivity, similar across stages, was observed for the blood-based LC Screening Test, compared to 39.5% sensitivity for LDCT, p = 0.53 McNemar test, indicating no significant difference in observed sensitivity between LDCT and the blood test. Complementarity in detection was observed between LDCT vs blood-test detected cases across all histologies. A mean 42% increase was observed in LC Screening Test scores from T-1 to T, indicating signal increase may provide additional sensitivity. **Conclusions:** The blood-based LC Screening Test exhibits similar performance to LDCT in detecting preclinical lung cancer in high-risk individuals and detects some LCs not found by LDCT. The data supports further evaluation of the LC Test for LC screening. Research Sponsor: Mercy BioAnalytics.

Histology	Dx Modality	Total Detected	Detected by One Test	Detected by Both	Detected by Neither
Adenocarcinoma	LDCT	37% (17/46)	24% (11/46)	13% (6/46)	44% (20/46)
Adenocarcinoma	Blood Test	33% (15/46)	20% (9/46)	13% (6/46)	44% (20/46)
Squamous	LDCT	42% (10/24)	29% (7/24)	13% (3/24)	50% (12/24)
Squamous	Blood Test	21% (5/24)	8% (2/24)	13% (3/24)	50% (12/24)
Small Cell	LDCT	43% (6/14)	14% (2/14)	29% (4/14)	36% (5/14)
Small Cell	Blood Test	50% (7/14)	21% (3/14)	29% (4/14)	36% (5/14)
Other	LDCT	42% (5/12)	50% (6/12)	17% (2/12)	25% (3/12)
Other	Blood Test	25% (3/12)	33% (4/12)	17% (2/12)	25% (3/12)

10536 **Poster Session**

Next-generation multi-cancer early detection (MCED) assay: Independent blinded validation of a locked serum multi-omics NMR test with stage I sensitivity. First Author: Patrick C. Strasser, Wholomics GmbH, Ried Im Innkreis, Austria

Background: Blood-based MCED assays could complement existing screening, but many approaches show reduced sensitivity in early-stage disease. Wholomics developed a serum multi-omics MCED assay integrating metabolomic, lipidomic, and proteomic features quantified by proprietary NMR-based technology, designed to capture systemic biology associated with early tumor development. We report independent, blinded validation of a locked MCED assay developed on multi-center data; across training and validation, the program included >1,400 individuals and >13 cancer types. The full assay pipeline was locked before application to the independent validation cohort. **Methods:** Model development leveraged prior multi-center data (N = 1,211) from five European centers (669 cancers, 65% were stage 0-II; 442 controls plus precancerous/benign cohorts). We evaluated an independent validation cohort (N = 216) with 116 cancers (50% were stage 0-II [stage I n = 40; stage II n = 16]; cancers included colon, rectal, pancreatic, cervical, uterine, bladder, breast, gastric, renal, ovarian) and 100 controls with screening-relevant conditions (e.g., dyslipidemia, prediabetes, benign prostatic hyperplasia, osteoarthritis, etc.). Samples were analyzed with fully prespecified locked assay pipeline (proprietary NMR profiling according to SOP with predefined QC, data preprocessing, biomarker feature set, machine-learning model, and decision threshold) and applied to blinded outcome labels. Primary endpoints were specificity and sensitivity (overall, stage I, stage III-IV). 95% CIs for sensitivity and specificity were calculated using the Wilson score method; AUC 95% CIs were calculated using DeLong's method. **Results:** The locked MCED assay achieved specificity of 99.0% (99/100; 95% CI 94.6–99.8; false-positive rate 1.0%) and overall sensitivity of 93.1% (108/116; 95% CI 87.0–96.5). Stage I sensitivity was 95.0% (38/40; 95% CI 83.5–98.6), Stage III-IV sensitivity remained high in advanced stages at 93.1% (54/58; 95% CI 83.6–97.3). AUC was 0.991 (95% CI 0.979-1). High overall sensitivity was observed across multiple tumor types, including pancreas, stomach, kidney, colon (each 100% overall) and rectum (92.3% overall). **Conclusions:** In an independent blinded validation, a locked serum multi-omics NMR-based MCED approach demonstrated high specificity and high sensitivity, including strong stage I performance, across multiple solid tumors in a screening-relevant case-control setting. These findings support clinical utility for shifting detection toward earlier, more treatable stages and warrant prospective studies to confirm real-world performance and downstream impact. Research Sponsor: Wholomics GmbH.

10537 **Poster Session**

Precision risk stratification for lung cancer in COPD: Evidence from the All of Us Program. First Author: Muhammad Rafiqul Islam, University of Chicago, Chicago, IL

Background: Chronic obstructive pulmonary disease (COPD) is a well-established independent risk factor for lung cancer, yet determinants of cancer susceptibility within this high-risk population remain incompletely characterized. Identifying clinical and genomic predictors is essential to improve risk stratification, early detection, and precision prevention strategies. **Methods:** We conducted an age-matched case–control study using de-identified data from the *All of Us* Research Program to evaluate sociodemographic characteristics, comorbidities, and genetic variants associated with lung cancer risk among adults with COPD. Baseline characteristics were summarized using descriptive statistics. Multivariable logistic regression was used to estimate adjusted odds ratios (AORs) controlling for relevant confounders. Genome-wide association studies (GWAS) were performed with rigorous quality control, population stratification adjustment, and correction for multiple testing. **Results:** Among 633,540 participants, 26,570 (4.2%) had COPD, including 2,044 (7.7%) with lung cancer. The mean age was 67.5 $\pm$ 11.4 years; 43.4% were male. In multivariable analysis, Asian ancestry was associated with increased lung cancer risk (AOR 2.25, 95% CI 1.55–3.26). Age 66–95 years conferred a 29% higher risk, and family history of lung cancer increased risk by 34% (95% CI 1.15–1.57). Hypothyroidism (AOR 1.58, 95% CI 1.27–1.97) and hyperlipidemia (AOR 1.32, 95% CI 1.04–1.68) were independently associated with lung cancer. GWAS identified 19 variants significantly associated with lung cancer risk, including rs539223166, rs551676206, rs922466204, rs144626313, rs147989022, and rs74502961. **Conclusions:** Distinct clinical and genetic factors contribute to lung cancer susceptibility among individuals with COPD. Integrating these determinants may enhance risk prediction and inform targeted surveillance strategies. Research Sponsor: None.

10538 **Poster Session**

Impact of AI-based risk stratification integrating routine laboratory data with age on screening volume and multi-cancer early detection yield. First Author: Mao Mao, SeekIn Inc., Shenzhen, China

Background: Early cancer detection improves survival, yet population-wide screening remains costly and logistically challenging. Traditional cancer risk models, such as lifestyle-based assessments and polygenic risk scores, offer limited predictive performance. Routine laboratory tests (complete blood count, urinalysis, and biochemical panels) are performed in primary care and may harbor latent cancer signals. We developed an AI-based cancer risk assessment (CRA) model using routine laboratory data to enrich cancer cases and improve the cost-effectiveness of downstream multi-cancer early detection (MCED) testing. **Methods:** Routine laboratory data from 7,672 individuals (1,245 cancer; 6,427 non-cancer) across two hospitals were retrospectively collected and used to develop a random forest based CRA model incorporating 56 selected routine laboratory features. Among them, 5,392 (70.3%) also underwent OncoSeek test, a validated MCED assay based on seven protein tumor markers (e.g., AFP, CEA). OncoSeek screening performance was estimated under two enrichment strategies: (1) age-based enrichment ($\geq$50 years), and (2) risk-stratified enrichment using a joint CRA–age model. A two-dimensional CRA–age risk landscape was used to estimate cancer incidence across strata. Strata with a modeled cancer incidence $\geq$0.57%, corresponding to the overall cancer incidence among Chinese adults (GLOBOCAN 2017), were classified as high risk. Performance metrics from both strategies were applied to simulate OncoSeek screening outcomes in a hypothetical cohort of 1,000,000 adults aged $\geq$20 years. **Results:** In the simulated cohort with an overall cancer incidence of 0.57%, direct OncoSeek screening detected 2,450 cancers with a PPV of 5.6%. Age-based screening ($\geq$50 years) required screening 536,206 individuals ($-$46.4%), increased cancer incidence to 0.92%, and detected 2,327 cancers. In contrast, CRA–age risk-stratified screening reduced the screened population to 178,660 individuals ($-$82.1%), enriched cancer incidence to 2.69%, and detected 2,402 cancers. Compared with age-based screening, CRA–age stratification improved PPV from 7.6% to 15.9%, reduced false positives by 55.2% and lowered the cost per cancer detected from $18,436 to $5,950 ($-$67.7%), while preserving overall cancer detection. **Conclusions:** AI-based CRA–age risk stratification enables efficient population-level cancer screening by restricting downstream MCED testing to a high-risk subset comprising approximately one-fifth of the population, while preserving overall cancer detection. This strategy substantially improves PPV, reduces false positives, and lowers the cost per cancer detected. These findings support a risk-stratified MCED screening paradigm as a scalable and economically sustainable alternative to population-wide or age-based population screening. Research Sponsor: None.

10539 **Poster Session**

Machine learning–optimized multi-biomarker panel for discriminating lung cancer from LDCT-positive benign pulmonary nodules. First Author: Sungjoon Park, Department of Thoracic and Cardiovascular Surgery, Seoul National University Bundang Hospital, Seoul, South Korea

Background: Accurate discrimination between lung cancer and benign pulmonary nodules remains a critical challenge in lung cancer screening, particularly among individuals with positive findings on low-dose computed tomography (LDCT). Blood-based biomarkers with proven biological relevance may improve risk stratification when integrated with advanced analytical approaches. Serum carcinoembryonic antigen (CEA), serum amyloid A (SAA), and osteopontin (OPN) are biomarkers reflecting tumor burden, host inflammatory response, and tumor microenvironmental activity, respectively. The discriminatory performance of these three biomarkers between healthy individuals and lung cancer patients has previously been validated in a cohort exceeding 2,000 subjects (ASCO 2025, Abstract #489322). Building on this foundation, the present study evaluates whether algorithmic integration of these biomarkers can improve discrimination of lung cancer within the clinically challenging population of LDCT-positive pulmonary nodules. **Methods:** Serum CEA, SAA, and OPN levels were quantified by ELISA in patients with histologically confirmed lung cancer and individuals with LDCT-positive benign pulmonary nodules. To enhance discrimination within this high-risk cohort, machine learning–based modeling was applied. Multiple analytical methods were evaluated, and a Random Forest classifier was selected to capture inter-marker correlations and non-linear biological relationships. The dataset was divided into independent training and validation cohorts. Diagnostic performance was assessed using sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). **Results:** In the LDCT-positive pulmonary nodule population, the machine learning–optimized three-biomarker panel demonstrated strong discriminatory performance. In the validation cohort, the model achieved an AUC of 0.879, with a sensitivity of 88.8% and a specificity of 83.3% for differentiating lung cancer from benign nodules. The algorithm consistently outperformed individual biomarkers and linear models, including in early-stage lung cancer. **Conclusions:** Application of machine learning to a biologically complementary three-protein biomarker panel significantly enhances discrimination of lung cancer within LDCT-positive high-risk pulmonary nodule populations. These findings support the clinical utility of this non-invasive approach as an adjunct to LDCT, addressing a key diagnostic gap in lung cancer screening and management. Research Sponsor: None.

10540 **Poster Session**

Association of high postoperative physical activity with ctDNA MRD positivity and recurrence-free survival across solid tumors: The SCRUM-MONSTAR LIFELOG study. First Author: Shugo Yajima, Department of Urology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Physical activity is associated with improved survival across multiple cancer types, yet its relationship with molecular residual disease (MRD) detected by circulating tumor DNA (ctDNA) remains unclear. We examined whether objectively measured physical activity correlates with postoperative ctDNA status. **Methods:** The LIFELOG study, ancillary to MONSTAR-SCREEN-3, enrolled patients who underwent curative surgery for solid tumors. Participants wore a wrist-based device targeting 1 month during the early postoperative period. Accelerometer and photoplethysmography data were processed to derive metrics including mean acceleration, moderate-to-vigorous physical activity (MVPA) percentage, longest MVPA bout, and high-intensity heart rate zone percentage. K-means clustering (k=3) classified patients into activity phenotypes. ctDNA was assessed serially using an ultrasensitive whole-genome sequencing-based MRD assay (Myriad Genetics). ctDNA positivity at 1 and 3 months postoperatively were compared between activity phenotypes, with overlap weighting used to adjust for potential confounders. **Results:** Of 127 enrolled patients, 4 were excluded due to no device data, leaving 123 for analysis. Adequate wear time ($\geq$10 hours/day on $\geq$3 days/week) was achieved in 113 patients (91.9%). Cancer types included colorectal (n=29), urothelial (n=24), hepatocellular (n=13), gastric (n=11), renal (n=11), and others (n=35). Median age was 70.1 years; 57.7% were male; 46.3% had stage III-IV disease. Clustering identified three phenotypes: Cluster 1 (high activity; n=10), Cluster 2 (moderate; n=53), and Cluster 3 (low; n=60). Activity metrics differed across clusters (any $P<0.001$). Cluster 3 had significantly inferior recurrence-free survival compared with Clusters 1+2 (hazard ratio 4.01; 95% confidence interval, 1.10-14.6; P=0.035). Postoperative ctDNA positivity was significantly higher in Cluster 3 compared with Clusters 1+2 at both 1 month (32.5% vs 6.4%; P=0.002) and 3 months (30.0% vs 2.4%; $P<0.001$). At 3 months, this difference persisted after adjustment for age, sex, adjuvant chemotherapy, stage, and cancer type (P=0.003). Among 80 patients with evaluable ctDNA data at both 1 and 3 months, of 15 patients who were ctDNA-positive at 1 month; conversion to ctDNA-negative at 3 months was observed in 66.7% in Clusters 1+2 versus 16.7% in Cluster 3 (P=0.15). Of 65 patients who were ctDNA-negative at 1 month; conversion to ctDNA-positive at 3 months was observed in 0% in Clusters 1+2 versus 7.7% in Cluster 3 (P=0.16). **Conclusions:** Lower objectively measured physical activity was associated with higher postoperative ctDNA positivity rates and inferior recurrence-free survival. These findings warrant validation in larger cohorts and investigation of exercise-based interventions in postoperative cancer care. Research Sponsor: Japan Agency for Medical Research and Development (AMED); JP25ck0106950h0002; National Cancer Center Research and Development Fund; 2024-A-05.

10541 **Poster Session**

The PROFOUND study: A large-scale prospective multicenter case-control trial of a multi-cancer early detection (MCED) test in China. First Author: Kezhong Chen, Thoracic Oncology Institute and Department of Thoracic Surgery, Peking University People's Hospital, Beijing, China

Background: Early cancer detection reduces morbidity and mortality, but current recommended screening in China misses many lethal cancers. Emerging liquid biopsy-based MCED tests have the potential to increase the number of screen-detected cancers when added to recommended screening. In this study, we evaluate the performance of a MCED test tailored to 16 cancer types covering 85% of China's total cancer incidence, including malignancies without recommended screening tests in the large-scale, prospective, multicenter case-control PROFOUND study. **Methods:** A total of 10,541 participants from over 50 sites nationwide were enrolled, with the cohort comprised by a training set (7,487 participants: 4,448 cancer, 3,039 non-cancer) and a test set (3,054 participants: 1,740 cancer, 1,314 non-cancer). It included 16 major cancer types encompassing diverse pathological subtypes, with stage I-III cases accounting for 83.31% of all cancer samples. All cancer cases were confirmed via pathological diagnosis. Blood samples underwent targeted methylation profiling and were analyzed with the Genie-ADLA AI algorithm to train, validate and independently verify the MCED assay, as well as assess its clinical performance (sensitivity, specificity, tissue-of-origin [TOO] prediction accuracy). **Results:** In the validation set, specificity was 99.03% (95% CI: 98.27%–99.51%), overall sensitivity was 70.63% (95% CI: 67.23%–71.67%) and sensitivity for stage I–III cancers was 66.03% (95% CI: 63.53%–68.46%). The overall TOO prediction accuracy reached 85.21% (95% CI: 83.05%–87.20%). For the five highest-mortality cancers (liver, colorectal, esophageal, gastric and lung cancer), sensitivities were 87.85%, 90.48%, 83.78%, 72.85% and 69.54% respectively. Sensitivities of lung adenocarcinoma and non-adenocarcinoma were 48.75% and 92.96%, respectively. Among them, non-adenocarcinoma is more likely to be missed in recommended screening tests. For cancers without recommended screening (pancreatic, ovarian, gallbladder cancer, lymphoma), sensitivities reached 64.75%, 87.88%, 100% and 74.72%, respectively. **Conclusions:** Powered by the Genie-ADLA AI algorithm, the PROFOUND study's MCED assay demonstrated robust performance including high sensitivity, specificity and TOO prediction accuracy for 16 cancer types (including cancers do not have recommended screening). It may serve as a complementary tool to augment recommended screening and revolutionize early cancer detection paradigms. A prospective interventional clinical study covering 16 cancer types will be launched to further validate MCED's clinical effectiveness. Clinical trial information: NCT06217900. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co. Ltd.

10542 **Poster Session**

Prospective evaluation of the psychological impact of multicancer early detection (MCED) blood testing: A smartphone-based patient-reported outcomes study. First Author: Ronan Joseph Kelly, Baylor University Medical Center, Dallas, TX

Background: Earlier detection may reduce cancer mortality by reducing the number of cancers diagnosed at advanced stages. Prospective data evaluating the emotional impact of MCED testing are limited, particularly when paired with digital engagement tools. Smartphone-based applications offer an opportunity to monitor patient-reported distress in real time and provide scalable support throughout the testing journey. The Falcon registry is a large prospective study evaluating the Exact Sciences MCED test in clinically cancer-free individuals that included evaluation of patient reported outcomes (PRO) using digital tools. **Methods:** Falcon (NCT06589310) is a multi-site registry enrolling up to 25,000 participants, 50-80 years of age. Participants receive the MCED test annually for 3 years and complete PRO measures, including the Generalized Anxiety Disorder-7 (GAD-7) assessment. The assessment is administered via the myBSWHealth digital platform at baseline (T0), ≤14 days of receiving test results (T1), and at approximately 6 months (T2). Reminders encouraged timely survey completion, and adaptive content was delivered based on distress scores. GAD-7 scores are categorized for clinical interpretation of anxiety: 0-4 minimal, 5-9 mild, 10-14 moderate, 15-21 severe. Clinically meaningful changes (+/->4) in anxiety severity at T0-T1 and T0-T2 were assessed. **Results:** 8,977/9,204 (97.5%) enrolled participants from 08/2024-01/2026 across the Baylor Scott & White Health System have an activated MyBSWHealth account. 4125 had the potential for 6-month follow-up at data analysis; 2729 (66.1%) completed ≥1 GAD-7 and 2161 (52.4%) had a T0 score. Most participants (94.9%) had minimal to mild anxiety at T0; however, a subset of participants (5.1%) demonstrated moderate to severe anxiety prior to testing. Overall, GAD-7 scores stayed within the minimal anxiety range over time with medians (interquartile ranges) of 1.00 (4.00), 0.00 (3.00) and 1.00 (4.00) at T0, T1 and T2, respectively. Among the 1219 participants who completed the GAD-7 at both T0 and T1, 86% had no clinically meaningful change in anxiety severity, 7% had a decrease, and 6% had an increase. Among the 989 participants who completed the GAD-7 at both T0 and T2, 85% had no change, 7% had a decrease, and 8% had an increase. **Conclusions:** Digital assessment of anxiety during MCED blood testing gives real-time data on the effects of cancer screening in an average risk population. Despite concerns about the potential for population-based cancer screening to increase anxiety, our preliminary findings suggest low levels of anxiety that remain stable in the majority of participants who completed follow-up assessments after receiving an MCED test result. Additional data for anxiety and distress using the Post-Traumatic Stress Disorder (PTSD) Checklist for DSM-5 (PCL-5) will be presented. Clinical trial information: NCT06589310. Research Sponsor: Exact Sciences Corporation.

10543 **Poster Session**

Performance of a cfDNA methylation–based MCED test in patients with clinicoradiologic suspicion of cancer. First Author: Elie Massaad, Harbinger Health, Cambridge, MA

Background: Radiographic findings concerning for malignancy frequently prompt extensive diagnostic evaluations that fail to yield a definitive diagnosis, resulting in delayed treatment, persistent uncertainty, and unnecessary interventions. Multi-cancer early detection (MCED) tests based on circulating cell-free DNA (cfDNA) methylation have demonstrated high specificity in asymptomatic screening populations; however, performance in individuals with clinical suspicion of malignancy remains unclear. We compared the performance of a cfDNA methylation–based MCED test in asymptomatic participants and in participants with imaging-based suspicion of malignancy. **Methods:** Adults aged 45–79 years enrolled in CORE-HH (NCT05435066) were evaluated in (1) a case–control cohort (n = 4,137) comprising asymptomatic participants who reported no history of cancer (n = 2,523) and newly diagnosed cancer participants (n = 1,614); and (2) a prospective cohort (n = 209) of individuals with imaging-based suspicion of malignancy undergoing clinical evaluation (cancer confirmed, n = 155; no cancer, n = 54). Cancer types included lung, breast, colorectal, prostate, pancreatic/hepatobiliary, head and neck, gynecologic, and hematologic malignancies. Samples were analyzed using a cfDNA methylation–based MCED test incorporating an AI/ML model, at a pre-specified specificity of 98.5%. Test performance was compared between cohorts among non-cancer participants and among early-stage (stage I–II) and late-stage (stage III–IV) cancer cases using Fisher's exact test (two-sided). **Results:** Among non-cancer participants (n = 2,577), empirical specificity was 98.1% (53/54) in the clinical suspicion cohort and 98.5% (2,485/2,523) in the asymptomatic case–control cohort (OR, 1.23; 95% CI, 0.03–7.6; p = 0.56). Overall sensitivity was 54.8% (85/155) in the clinical suspicion cohort and 53.9% (870/1,614) in newly diagnosed cancer cases from the case–control cohort (OR, 1.04; 95% CI, 0.74–1.47; p = 0.87). Stage I–II sensitivity was 27.7% (18/65) vs 28.7% (204/711) (p = 1.00), and stage III–IV sensitivity was 82.9% (58/70) vs 81.5% (573/703) (p = 0.87), for the clinical suspicion and case–control cohorts, respectively. Overall cancer stage distribution was similar between cohorts (p = 0.89). **Conclusions:** At the prespecified 98.5% specificity threshold, the cfDNA methylation–based MCED test demonstrated comparable specificity and sensitivity in prospectively enrolled participants undergoing evaluation for imaging-based suspicion of malignancy and in a case–control cohort of newly diagnosed cancer cases versus asymptomatic controls. Recognizing the tendency of case–control designs to overestimate test performance, these results describe MCED test performance in a cohort with clinical suspicion of malignancy, extending characterization beyond asymptomatic screening populations. Clinical trial information: NCT05435066. Research Sponsor: None.

10544 **Poster Session**

A phase II open-label, single-arm study to evaluate the efficacy of pembrolizumab for leukoplakia. First Author: Maria Antonia Velez Velez, Division of Hematology/Oncology, University of California, Los Angeles, Los Angeles, CA

Background: Oral leukoplakia and erythroleukoplakia represent high-risk premalignant lesions of the oral cavity, with malignant transformation to head and neck squamous cell carcinoma reported in up to 36% of cases. Therapies are limited, with surgical resection remaining the standard of care despite high recurrence rates. Immune checkpoint inhibitors (ICIs) have emerged as a potential preventive strategy. We evaluated whether the efficacy of the PD-1 inhibitor pembrolizumab may serve as a preventive strategy to reduce progression to invasive carcinoma in patients (pts) with these premalignant lesions. **Methods:** This nonrandomized, open-label, multi-center phase II clinical trial enrolled pts between June 2019 and December 2025. Eligible pts had oral leukoplakia, erythroleukoplakia, or proliferative verrucous leukoplakia with moderate dysplasia, severe dysplasia, or carcinoma in situ. Patients with previously treated squamous cell carcinoma (SCC) were included. Pts received pembrolizumab 200 mg intravenously every 3 weeks for 6 months. The primary endpoint was clinical response at 6 months, defined as the proportion of patients achieving a complete response (CR) or partial response (PR). CR was defined as complete lesion resolution on visual inspection sustained for ≥4 weeks. PR was defined as a ≥50% reduction in the product of the two largest perpendicular dimensions of a single lesion or the sum of all measurable lesions. The secondary objectives included clinical response rate at 9 and 12 months, and toxicity. **Results:** Sixteen pts received at least one dose of pembrolizumab. The median age was 63.5 years (range, 33–82), and 44% were female. Three patients had previously treated SCC. Baseline pathology demonstrated moderate dysplasia in 31% and severe or high-grade dysplasia in 69% of patients. At 6 months, the clinical response rate was 44% (7/16; 95% CI, 23–67%), including CR in 19% (3/16) and PR in 25% (4/16) of pts. Progressive disease occurred in 38% (6/16) of patients. Clinical response rates were 31% at 9 months (5/16) and 19% at 12 months (3/16). Median follow-up was 9 months. Treatment-related adverse events (TRAE) occurred in 69% of pts, most commonly fatigue (31%), mucositis/oral discomfort (31%), hypothyroidism (25%), and gastrointestinal immune-related events, including diarrhea or colitis (25%). Grade ≥3 treatment-related adverse events occurred in 19%, with no grade 4–5 events or treatment-related deaths. One pt discontinued due to TRAE. **Conclusions:** These findings suggest that PD-1 blockade may represent a feasible preventive approach for high-risk oral premalignant lesions and warrants further investigation as a preventive option. Biomarker evaluation of pre-treatment and on-treatment biopsies are ongoing to inform predictors of response. Clinical trial information: NCT03603223. Research Sponsor: Merck.

10545 Poster Session

Risk prediction models for familial breast cancer: A Cochrane systematic review and meta-analysis. First Author: Sarah A. McGarrigle, St James's Hospital, Trinity St James's Cancer Institute, Dublin, Ireland

Background: Women with a family history of breast cancer (BC) have an increased risk of developing the disease. Several BC risk prediction models are used in clinical practice to estimate future BC risk, however, their comparative performance in women with a family history of BC is uncertain. The aim of this study was to systematically identify, describe, and critically appraise BC risk prediction models developed or validated in women with a family history of BC, and to synthesize their performance in predicting BC occurrence in this population. **Methods:** We searched MEDLINE, Embase, CINAHL, and ISI Web of Science up to February 2022, with a targeted MEDLINE update to 19 December 2024. We included studies that developed or externally validated BC risk prediction models in women with a family history of BC, provided family history was included as a predictor. Data were extracted using the CHARMS checklist, and risk of bias was assessed using PROBAST. Where data from more than three validation studies were available, random-effects meta-analyses of calibration (observed/expected [O/E] ratios) and discrimination (c-statistic) were conducted. **Results:** Forty-five studies were included. Twelve models were externally validated in the target population; four were validated more than three times and included in meta-analyses. Reporting quality was variable, and most studies had high or unclear risk of bias. The Gail (BCRAT) model was well calibrated (pooled O/E 1.06, 95% CI 0.91–1.25) but showed modest discrimination (c-statistic 0.61, 95% CI 0.57–0.66). BOADICEA was also well calibrated (O/E 0.98, 95% CI 0.90–1.17) with modest discrimination (c-statistic 0.65, 95% CI 0.58–0.71). Tyrer-Cuzick (IBIS) overpredicted risk (O/E 0.86, 95% CI 0.74–0.98), while BRCAPRO underpredicted risk (O/E 1.44, 95% CI 1.25–1.62). Discriminatory accuracy was similar across Tyrer-Cuzick v8, BOADICEA, and BRCAPRO, with pooled c-statistics of 0.64 (0.58 to 0.71), 0.65 (0.58 to 0.71),0.64 (0.54 to 0.73) respectively and slightly higher than Gail (pooled c-statistic 0.61 (0.57 to 0.66)) . **Conclusions:** In women with a family history of BC, Gail and BOADICEA are well calibrated, while Tyrer-Cuzick overpredicts and BRCAPRO underpredicts risk. No model demonstrated clearly superior discrimination. Considering both calibration and discrimination, BOADICEA may be useful for clinical risk assessment in this population, although conclusions are limited by study heterogeneity, small numbers of validation studies in the target population, and high or unclear risk of bias. Improved model performance and reporting are needed. This abstract is based on a post-peer review version of a Cochrane Review. Upon acceptance, the final version is expected to be published in the Cochrane Database of Systematic Reviews (www.thecochranelibrary.com). Research Sponsor: Health Research Board.

10546 Poster Session

Evaluating the impact of the 2021 USPSTF age expansion (50–54 years) on racial disparities in early-stage lung cancer diagnosis. First Author: Shubhangi Sharma, Rutgers Health Community Medical Center, Toms River, NJ

Background: In 2021, the USPSTF updated its guidelines to address known racial disparities in lung cancer outcomes. By lowering the screening age to 50 and reducing the pack-year threshold, one of the goals was to better identify Black individuals, who historically develop cancer at younger ages and with lower smoking intensity than their White counterparts. However, despite this expanded eligibility, screening uptake among the newly eligible 50–54 years cohort remains low. Our study evaluates whether these policy changes have translated into a tangible 'stage shift' toward earlier detection among the newly eligible age group and assesses if these benefits are being realized equitably across racial groups. **Methods:** We conducted a retrospective cohort study using SEER November 2024 sub data (21 Registries) for non-small cell lung cancer (NSCLC) cases. We compared the Pre-Guideline (2016–2019) period to the Post-Guideline (2022) period, excluding initial COVID-19 and transition years (2020–2021). A Difference-in-Differences (DiD) approach compared the newly eligible Target Group (50–54 years) against a Control Group (45–49 years) to control for secular staging trends. The primary outcome was the percentage of localized disease at diagnosis, stratified by race. **Results:** In the newly eligible 50–54 cohort, White patients demonstrated a robust stage shift, with localized disease increasing from 23.2% to 28.7% ($p<0.001$). Conversely, Black patients in the target age group experienced a decline in localized detection from 20.1% to 17.5%, with a concurrent rise in distant-stage diagnoses. Notably, Black patients in the younger control group (45–49) showed improved early detection (+3.3%), suggesting the disparity was specific to the guideline implementation in the target cohort. The DiD interaction was significant ($p<0.05$), confirming racially distinct outcomes. Hispanic patients saw a case volume surge without a significant rise in localized disease (22.3% to 22.6%). **Conclusions:** Initial data following the 2021 USPSTF expansion suggests an early stage shift for White patients aged 50–54, while a similar trend was not observed among Black patients in this first year of implementation. This divergence may reflect a temporary implementation lag, variability in provider adoption, or early access delays rather than a definitive failure of the policy. Continued longitudinal surveillance is required to determine whether this gap represents a transient uptake issue or a persistent disparity necessitating targeted structural interventions. Research Sponsor: None.

Impact of age expansion on early detection (% localized disease).

Group	Race	Pre-Guideline (2016-19)	Post-Guideline (2022)	Net Change
Target (50-54 years)	White	23.22%	28.65%	+5.43%
	Black	20.14%	17.53%	-2.61%
	Hispanic	22.33%	22.58%	+0.25%
Control (45-49 years)	White	21.20%	22.44%	+1.24%
	Black	17.79%	21.09%	+3.30%

10547 Poster Session

Evaluation of a novel blood-based lung nodule triage test in elevated-risk subjects. First Author: Dawn R. Mattoon, Mercy BioAnalytics, Waltham, MA

Background: In the National Lung Screening Trial (NLST), 4,354 (6%) of LDCT scans were positive with Lung RADS scores of 3 or 4A, and 162 lung cancers (LCs) were diagnosed within one year of the associated scan. Despite the elevated risk of malignancy, referral for immediate diagnostic (Dx) workup is not recommended; as a result, diagnosis is delayed by an average of 106 days compared with subjects assigned a Lung-RADS 4B or 4X score, who are referred for immediate Dx workup. This delay highlights the need for methods to further risk stratify these subjects and enable more timely evaluation. Tumor-associated extracellular vesicles and particles (EVPs) are highly abundant in blood and carry surface biomarkers from their tumor cell of origin, providing a readily measurable analyte class. We report performance of an EVP-based Lung Nodule Triage Test in detecting LC as a function of Lung RADS score in plasma samples from NLST subjects. **Methods:** The Triage Test (biomarkers and classifier) was locked following a training study. Here we evaluated the Triage Test in a blinded case-control study nested within the ACRIN Biomarker Arm of the NLST. The study included LC cases diagnosed within 24 months of blood draw (n = 51 cases; 99 samples), including longitudinal samples from 48 subjects. Controls were age-matched NLST subjects who had no LC detected before or within the trial follow up period with Lung RADS v1.1 scores of 1 or 2 (n = 60). Triage Test results were determined blinded to case-control status, with unblinding done by ECOG-ACRIN. A static threshold set to 90% specificity was applied to Triage Test scores. **Results:** Among the 99 samples with a diagnosis of LC within 24 months of blood draw, the Triage Test exhibited 34% sensitivity for detection of LC. The Triage Test exhibited 43% sensitivity in samples associated with LDCT-positive screen results not recommended for immediate Dx workup. The projected positive predictive value (PPV) for the Triage Test applied as a reflex test for individuals with Lung RADS 3 and 4A is 13.8% (95% CI: 5.7% - 30.5%, bootstrapping test sensitivity and specificity). **Conclusions:** The blood-based Lung Nodule Triage Test exhibits clinically meaningful performance for detection of LC among subjects with LDCT Lung RADS 3 and 4A scores. The data supports further evaluation of the Triage Test for reflex testing of indeterminant lung nodules. Research Sponsor: Mercy BioAnalytics.

	Lung RADS Score	1	2	3	4A	4B/X	3+4A	Total
NLST LDCT Arm	# LDCT Screens	39,840	28,674	2,282	2,072	1,898	4,354	74,766
NLST LDCT Arm	# LC Dx Within 12M of Screen	26	100	32	130	428	162	716
NLST LDCT Arm	LC Prevalence	0.07%	0.3%	1.4%	6.3%	22.6%	3.7%	1.0%
NLST LDCT Arm	Avg. Days to Dx vs Lung RADS 4B/X	93	101	128	84	n/a	106	n/a
Present Study	# Cases	23	37	5	9	25	14	99
Present Study	Triage Test Sensitivity	30% (7/23)	32% (12/37)	60% (3/5)	33% (3/9)	36% (9/25)	43% (6/14)	34% (34/99)
Modeled Implications of Reflex Testing	# True Positive Workups	8	32	19	43	154	69	246
Modeled Implications of Reflex Testing	# False Positive Workups	3984	2867	228	207	n/a	435	7287
Modeled Implications of Reflex Testing	PPV	0.2%	1.1%	7.8%	17.3%	n/a	13.8%	3.3%

10548 Poster Session

GLP-1 therapy and hormone receptor–positive breast cancer risk and survival: A real-world analysis. First Author: Zunairah Shah, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly used for weight management and cardiometabolic risk (CMR) reduction, yet their association with breast cancer (BC) incidence and survival in non-diabetic women with elevated BMI remains unclear. We evaluated the relationship between GLP-1 RA exposure and incident BC, as well as overall survival (OS), in a large real-world (RW) cohort of women without laboratory-defined diabetes. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network including female patients (pts) with BMI 25–35 kg/m². Age <50 vs ≥ 50 years served as proxies for pre- and postmenopausal status, with a ≥ 50 sensitivity analysis to assess age/menopause confounding. Pts with HbA1c $\geq 6.5\%$ or prior BC were excluded. Cohorts were propensity score matched (PSM) on age at index, BMI, metformin and statin exposure, BRCA mutation status, hormonal contraceptive use, parity, breastfeeding history, and smoking status. The primary endpoint was incident HR+/HER2− BC, summarized as incidence proportion and risk reduction estimates; secondary analyses evaluated HR+/HER2+, HR−/HER2+, and triple-negative breast cancer (TNBC). OS was evaluated using Kaplan–Meier and Cox regression. **Results:** After PSM, 148,709 pts were included (mean age 45.8 ± 9.54 years in both cohorts). Over a median 36-month follow-up, incident HR+/HER2− BC was lower with GLP-1 RA vs controls (0.29% vs 0.33%), with an absolute difference −0.04% (95% CI −0.081 to −0.001%; P=0.046) and RR 0.88 (95% CI 0.77–0.99). OS was improved with GLP-1 RA vs controls (HR 0.75, 95% CI 0.65–0.86; $P<0.0001$). No difference in BC incidence was found for HR+/HER2+ (RR 0.98, 95% CI 0.86–1.12) or HR− subtypes, including HR−/HER2+ BC (RR 0.83, 95% CI 0.55–1.23) and TNBC (RR 0.68, 95% CI 0.41–1.12). Findings for HR+/HER2− were consistent across menopausal strata (Table). In the postmenopausal cohort (n=91,577; mean age 63.3 ± 6.88 vs 62.4 ± 6.52 years), GLP-1 RA exposure was also associated with lower incidence of HR+/HER2− BC (RR 0.93, 95% CI 0.86–0.99) and improved OS (HR 0.87, 95% CI 0.81–0.94; P=0.0003). **Conclusions:** In a large non-diabetic cohort of women with BMI 25–35 kg/m² and no prior BC, GLP-1 RA exposure was associated with a modest reduction in incident HR+/HER2− BC and improved OS. Despite limited follow-up and age-based menopausal proxies, these findings provide RW evidence supporting prospective validation with standardized exposure definitions and longer follow-up. Future studies should clarify whether GLP-1 RAs confer direct antitumor effects or indirect benefits mediated through weight loss and CMR reduction and identify pts most likely to derive BC risk and survival benefit. Research Sponsor: None.

GLP-1 RA and HR+/HER2− BC outcomes.

	RR (Breast Cancer Incidence)	HR (Overall Survival)
Age <50	0.88 (0.77–0.99)	0.75 (0.65–0.86)
Age ≥50	0.93 (0.86–0.99)	0.87 (0.81–0.94)

10549 **Poster Session**

Evaluation of intervention strategies to improve follow-up after FIT/FOBT tests: A systematic review and meta-analysis. First Author: Wei Yu Chua, National Cancer Centre Singapore, Singapore, Singapore

Background: Colorectal cancer (CRC) is the third most common cancer worldwide, with the majority of patients diagnosed at advanced stages. Early detection through screenings has been shown to improve morbidity and mortality. However, follow-up after Fecal Immunochemical Test (FIT) / Fecal Occult Blood Test (FOBT) screenings remains low, with 30%-61% compliance to colonoscopy screening and 28-49% compliance to repeat FIT/FOBT surveillance. Our study aims to evaluate 1) interventions targeting colonoscopy completion post-positive FIT/FOBT and improving adherence to follow-up after negative FIT/FOBT, and 2) the rate of colonoscopy completion post-positive FIT/FOBT and the rate of repeat FIT/FOBT adherence after a negative result. **Methods:** We searched MEDLINE, Embase, and Cochrane from inception to December 20, 2025, to identify cohort studies or randomized controlled trials (RCTs) comparing interventions to improve follow-up colonoscopy after positive FIT/FOBT and repeat FIT/FOBT after negative FIT/FOBT. We computed risk ratios (RR) with accompanying 95% confidence Intervals (CIs) for each study and pooled the results using a random-effects meta-analysis. **Results:** Twenty-seven studies involving 30,974 patients were included. 19 studies (11,905 patients) evaluated interventions to improve colonoscopy completion after a positive FIT/FOBT. Patient-level interventions (RR 1.30, 95% CI 1.17–1.44, n=13) and system-level interventions (RR 1.45, 95% CI 1.20–1.77, n=6) significantly increased colonoscopy completion. Patient navigation (RR 1.28, 95% CI 1.15–1.41), patient reminders (RR 1.32, 95% CI 1.04–1.67), and provider reminders (RR 1.45, 95% CI 1.16-1.83) were effective. Patient reminders via messaging (RR 1.55, 95% CI 1.31-1.83) were more effective than calling (RR 1.10, 95% CI 0.91-1.33, p=0.0083). Follow-up colonoscopy increased from 45.8% in controls to 65.9% after interventions. 8 studies (19,069 patients) assessed repeat FIT/FOBT adherence after a negative result. Patient navigation (RR 1.89, 95% CI 1.36–2.63) and patient reminders (RR 1.31, 95% CI 1.01–1.71) significantly improved adherence, increasing rates from 46.0% in controls to 66.5% after interventions. Based on our findings, we developed a protocol to improve colonoscopy completion post-positive FIT/FOBT and adherence to follow-up after negative FIT/FOBT. **Conclusions:** Patient-level and system-level interventions improve adherence to follow-up colonoscopy post FIT/FOBT. Patient navigation and patient reminders increase completion of follow-up colonoscopy and adherence to follow-up FIT/FOBT. Healthcare systems should adopt patient-level and system-level interventions to enhance compliance with follow-up after initial FIT/FOBT testing. Research Sponsor: None.

10550 **Poster Session**

Contemporary trends in early-stage non–small cell lung cancer diagnosis and disparities, 2018–2022. First Author: Ahmed Minhas, Methodist University Hospital, Memphis, TN

Background: Early detection of non-small cell lung cancer (NSCLC) improves survival. We evaluated stage trends in adults aged 50-80 with NSCLC in SEER 2018-2022 after the 2021 screening expansion and the COVID-19 pandemic. **Methods:** We included 112,183 SEER cases aged 50-80 with primary NSCLC from 2018-2022. Histology was classified as adenocarcinoma, squamous, large cell or other/unknown. Stage at diagnosis was categorized as early (0-II) versus late (III-IV). Early-stage proportions were calculated by year, sex, race, age, income quartile, rurality and histology. Trends were tested using the Cochran–Armitage test. Multivariable logistic regression evaluated associations with early-stage diagnosis. To adjust for changing eligibility, NHIS 2018-2022 data were used to estimate screening-eligible shares by age-sex-race strata and standardize stage distributions. **Results:** Among 112,183 patients (median age 69; 56% male), 39,023 (34.9%) were early stage. Early-stage diagnoses increased modestly from 34.4% in 2018 to 35.6% in 2022, with a dip to 33.8% in 2020 (Table 1). Women had higher early-stage rates (~38%) than men (~32%), and White patients had higher rates (~37%) than Black or American Indian/Alaska Native patients (~29%). Logistic regression showed male sex (OR 0.78) and non-adenocarcinoma histology (ORs 0.16-0.25) were associated with lower odds of early detection; income quartile and rurality were not significant. Eligibility-standardized analyses produced similar trends, suggesting limited impact of the 2021 screening expansion to date. **Conclusions:** Between 2018 and 2022, early-stage NSCLC detection in SEER improved only slightly. Sex and racial disparities persisted. Enhanced outreach, particularly to men and racial/ethnic minorities, and broader low-dose computed tomography implementation are needed to accelerate stage migration. Research Sponsor: None.

Early-stage NSCLC diagnoses by year (ages 50–80).

Year	Total cases	Early-stage cases	Early-stage proportion*
2018	23,482	8,069	34.36%
2019	24,061	8,427	35.02%
2020	20,633	6,965	33.76%
2021	22,099	7,772	35.17%
2022	21,908	7,790	35.56%

*The Cochran–Armitage test indicated a statistically significant upward trend ($p < 0.05$), but the absolute increase was modest.

10551 **Poster Session**

Oncoseek 2.0: An updated blood-based assay for multi-cancer early detection. First Author: Shiyong Li, SeekIn, Shenzhen, China

Background: Early identification of cancer remains essential for improving survival and reducing downstream treatment costs, yet effective and scalable multi-cancer screening strategies are still limited. OncoSeek is a previously validated, AI-based multi-cancer early detection (MCED) assay integrating protein tumor markers (PTMs) with clinical data, demonstrating 58.4% sensitivity, 92.0% specificity, and 70.6% tissue-of-origin accuracy in > 15,000 participants. To improve detection of specific cancer types and expand cancer-type coverage, we developed OncoSeek 2.0 by incorporating three additional PTMs and evaluated its performance in validation cohort. **Methods:** OncoSeek 2.0 retained the original machine-learning framework of OncoSeek 1.0, with expanded PTM inputs (ProGRP, SCCA, and tPSA). Performance was evaluated in a retrospective validation cohort comprising 1,267 cancer and 355 non-cancer individuals. Overall performance, including cancer-type-specific sensitivity, was assessed and compared with OncoSeek 1.0. **Results:** OncoSeek 2.0 incorporated three additional PTMs (ProGRP, SCCA, and tPSA) to enhance cancer-type–specific detection. ProGRP levels was significantly elevated in small cell lung cancer compared with other cancers and healthy controls; SCCA concentrations were higher in squamous cell carcinomas (esophageal, cervical, and lung) than in non-squamous cancers and controls; and tPSA was selectively increased in prostate cancer (all $P < 0.0001$). Compared with OncoSeek 1.0, OncoSeek 2.0 achieved a higher AUC (0.917 vs 0.860) and improved sensitivity from 65.3% to 77.6% at 90.1% specificity across 15 pre-specified cancer types collectively accounting for 76.5% of global cancer mortality. Sensitivity gains were notable in lung (75.1% → 84.3%), prostate (58.8% → 88.2%), cervical (55.6% → 65.6%), and esophageal (39.6% → 62.4%) cancers. When stratified by tumor stage, OncoSeek 2.0 achieved sensitivities of 54.2% for stage I, 71.7% for stage II, 79.8% for stage III, and 88.4% for stage IV, consistently outperforming OncoSeek 1.0, which achieved sensitivities of 30.2%, 53.8%, 62.3%, and 85.7% for stages I through IV, respectively. **Conclusions:** By integrating three additional cancer-type–specific PTMs, OncoSeek 2.0 substantially improves sensitivity while maintaining high specificity and low reagent cost (~$30 per test). The upgraded assay enhances detection across multiple tumor types and disease stages, with particularly pronounced gains in lung, prostate, cervical, and esophageal cancers. These results support OncoSeek 2.0 as a scalable and clinically actionable MCED approach for population-level early detection, particularly for cancers lacking USPSTF-recommended screening and in low- and middle-income countries. Research Sponsor: None.

10552 **Poster Session**

A Korea–USA multicenter study of duodenal pancreatic fluid–derived exosomal CES1 and MAN2A1 as pancreas-proximal biomarkers for early pancreatic cancer detection. First Author: Do Hyun Park, Division of Gastroenterology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Background: Small pancreatic lesions often yield limited tissue via endoscopic ultrasound (EUS)-guided biopsy, and serum CA19-9 provides poor discrimination in high-risk settings. Duodenal pancreatic fluid (DPF), obtained during routine endoscopy/EUS, is a pancreas-proximal, low-noise biofluid that may enrich tumor-derived exosomal signals. We evaluated whether DPF exosomal proteins complement serum CA19-9 to discriminate PDAC from controls. **Methods:** DPF was collected during upper endoscopy/EUS with or without secretin. DPF-derived exosomes (n = 26) were profiled by LC-MS/MS, and CES1/MAN2A1 were prioritized by stage-pattern clustering. Candidates were quantified by ELISA in a Korea–USA multicenter cohort (n = 123, prespecified to detect a target AUC of 0.94; 63 PDAC, 60 controls; 4 Korean sites and 1 US site, combined with serum CA19-9 using a locked stacked ensemble model with LightGBM meta-learner trained only on out-of-fold predictions). High-risk controls included IPMN and chronic pancreatitis. Orthogonal validation used pancreatic juice from surgery or ERCP (PDAC n = 20; chronic pancreatitis n = 20). The primary endpoint was AUC for PDAC versus controls, compared with CA19-9 alone and in the CA19-9–normal subgroup; performance was also assessed in early-stage PDAC versus high-risk controls. 95% confidence intervals (CIs) were estimated by cross-validated resampling. **Results:** LC-MS/MS identified 2,460 proteins; 130 were differentially expressed (> 2-fold, $p < 0.05$). ELISA confirmed higher exosomal CES1 and MAN2A1 in PDAC versus controls ($p < 0.001$). The multi-marker model achieved an AUC of 0.995 (95% CI 0.982–1.000), a sensitivity of 98.33% (95% CI 0.931–1.000), and a specificity of 100% (95% CI 0.925–1.000), outperforming CA19-9 alone (AUC 0.63). In patients with CA19-9 in the normal range (< 37 U/mL), the model maintained high discrimination (AUC 0.931, 95% CI 0.746-1.000) with 100% sensitivity. For early-stage PDAC (stage I–II, n = 23) versus high-risk controls (n = 20, including IPMN), AUC was 0.976 (95% CI 0.924-1.000). In orthogonal validation, CES1/MAN2A1 in pancreatic juice were elevated in PDAC patients ($p < 0.001$) but not in matched serum, supporting pancreas-proximal enrichment. Decision curve analysis showed a higher net benefit than CA19-9 across clinically relevant thresholds. **Conclusions:** A DPF exosome–derived CES1/MAN2A1 signature integrated with CA19-9 using a locked ensemble model showed high diagnostic discrimination and supportive biological plausibility across a Korea–USA multicenter cohort. These results suggest a pancreas-proximal exosomal biomarker that addresses a critical gap in early detection of pancreatic cancer. Clinical trial information: NCT07030348. Research Sponsor: the Ministry of Health & Welfare, Republic of Korea; RS-2024-00435385; the Korean government (MSIT).

10553 **Poster Session**

Clinical outcomes and cumulative cost of preventive surveillance versus treatment in Li–Fraumeni syndrome: Results from the European PREVENTABLE project. First Author: Marion Rolain Jr., Inserm U1245, Cancer And Brain Genomics, Rouen, France

Background: Li-Fraumeni syndrome (LFS), caused by *TP53* pathogenic variants, is one of the most severe hereditary cancer predisposition syndromes, characterized by very early cancer onset, broad tumor spectrum, and a high lifetime risk of multiple cancers. At the European level, no large-scale health economics study has compared LFS proactive cancer preventive management including intensive multiorgan surveillance and early cancer detection, with treatment approaches initiated after the first tumor occurs in individuals at high cancer risk. To address this gap, and within the European PREVENTABLE project, we evaluated healthcare pathways and cumulative costs of proactive prevention versus treatment in LFS European families. **Methods:** We retrospectively collected clinical data from 866 individuals from seven European countries (ERN GENTURIS centers), including 505 *TP53* gene carriers (27% of whom were children) and 361 non-carrier family members. Based on multidisciplinary expertise, we developed a structured LFS care matrix, mapping patient clinical trajectories and clinical procedures across diagnosis, risk reduction strategies, surveillance and treatments. Costs were estimated using standardized French hospital tariffs, and data were collected via a GDPR-compliant digital tool interface developed by the PREVENTABLE consortium. **Results:** From 866 individuals, 155 were *TP53* carriers without a prior cancer diagnosis at the time of genetic testing, defining the preventive arm. During follow-up (median 75 months; range 6–267), 20 individuals developed one or more cancers.The mean prevention cost per patient was €6,046.8 (range €451–€71,854.76). Among the 273 patients with a history of cancer prior to genetic testing, 109 had early-stage disease and 164 had advanced-stage disease (median follow-up 83 months; range 2–468). The mean treatment cost per patient was €53,906 (range €385.50–€440,760.93). Overall cumulative costs were €937,258 for prevention and €15,103,188 for treatment, including €5,245,915 for early-stage cancers and €9,857,273 for advanced-stage cancers. Preventive mastectomy was performed in 24% of women in either prevention or treatment groups. **Conclusions:** This first European cumulative cost analysis demonstrates that treatment costs for LFS far exceed prevention costs (9-fold), providing strong economic evidence in favor of early genetic diagnosis and preventive surveillance. These findings support public health decision-making and the harmonization of care pathways within the framework of precision medicine in Europe. Preventable is funded by the European Union (EU) under Grant no 101095483. Research Sponsor: European Union; 101095483.

10554 **Poster Session**

Prenatal hormonal imprinting reflected by anogenital distance and risk of breast cancer: A case-control study of 839 women. First Author: Domingo Antonio Sánchez Martínez Sr., Department of Medical Oncology. Virgen de la Arrixaca University Hospital.-IMIB, Murcia, Spain

Background: Anogenital distance (AGD) is a sexually dimorphic, stable anthropometric marker set during fetal development and widely used as a proxy of prenatal androgen/estrogen balance. We hypothesized that AGD is associated with the risk of developing breast cancer (BC), a hormone-dependent disease. **Methods:** We conducted a prospective case–control study in Murcia (Spain) including 422 incident BC cases and 417 controls (2022–2024). Two AGD measures were obtained by trained examiners: ano-clitoral (AGDAC, "long") and ano-fourchette (AGDAF, "short"). Models were adjusted for age and BMI; quintile-based logistic regressions assessed non-linear associations. Stratified analyses were performed by menopausal status. Molecular subtype and Oncotype Recurrence Score (RS) (n=81 luminal tumors) were explored. **Results:** Compared with controls, BC cases showed longer AGDAC (mean 85.0 vs 81.2 mm; $p<0.01$) and shorter AGDAF (28.6 vs 29.8 mm; $p=0.02$). Across AGDAC quintiles, we observed an inverse risk gradient: lowest quintile vs highest, aOR 0.34 (95% CI 0.22–0.54; $p<0.001$). The association was stronger in premenopausal women (Q1 vs Q5 aOR 0.31; 95% CI 0.16–0.59; $p=0.001$). AGD was not associated with tumor subtype (luminal A/B, HER2+, triple-negative) nor with genomic risk (RS>25 vs ≤25). **Conclusions:** AGD, especially AGDAC, emerges as a non-invasive, inexpensive clinical marker of BC susceptibility, independent of molecular subtype and genomic risk. Findings suggest prenatal endocrine programming may prime lifetime BC risk, with a pronounced effect in hormonally active (premenopausal) women. If validated, AGD could enhance risk stratification and early detection pathways in population screening and prevention clinics. Research Sponsor: None.

Odds ratio (OR) for cases of breast cancer controls according to quintiles of AGD measures, taking the fifth quintile as a reference.

	Breast cancer (n=422) vs. controls (n=417)					
AGD in quintiles (Median for each quintile)	**Cases**	**Controls**	**Odds Ratio[a] (95%CI)**	**P-trend**	**Odds Ratio[b] (95%CI)**	**P-trend**
AGD_{AF}						
5th (38.0 mm)	80	89	1.0 (reference)		1.0 (reference)	
4th (32.1 mm)	75	93	0.90 (0.58-1.4)		0.95 (0.61-1.5)	
3rd (28.5 mm)	84	80	1.2 (0.76-1.8)		1.5 (0.95-2.3)	
2nd (25.3 mm)	87	80	1.2 (0.76-1.8)		1.5 (0.95-2.3)	
1st (21.4 mm)	96	75	1.4 (0.93-2.2)	0.26	1.9 (1.3-3.1)	0.01
AGD_{AC}						
5th (99.0 mm)	114	54	1.0 (reference)		1.0 (reference)	
4th (88.4 mm)	79	88	0.43 (0.27-0.66)		0.40 (0.26-0.63)	
3rd (82.6 mm)	82	87	0.45 (0.29-0.60)		0.42 (0.27-0.66)	
2nd (77.0 mm)	75	92	0.39 (0.25-0.60)		0.37 (0.23-0.58)	
1st (69.3 mm)	72	96	0.36 (0.23-0.55)	<0.001	0.34 (0.22-0.54)	<0.001

[a]Unadjusted OR.
[b]OR adjusted by age and BMI.
[c]OR adjusted by. AGDAF: Anogenital distance from the upper verge of the anus to the posterior fourchette AGDAC: Anogenital distance from the upper verge of the anus to the anterior clitoral surface.

10555 **Poster Session**

K-ACCELERATE: A multi-center prospective trial to evaluate the utility of a ctDNA-based assay for accelerating multi-cancer diagnosis among high-risk symptomatic participants. First Author: Le Son Tran, Medical Genetics Institute, Ho Chi Minh City, Viet Nam

Background: In low- and middle-income countries, most cancers are diagnosed after symptom onset, where non-specific symptoms complicate referral and delay diagnosis. We previously developed SPOT-MAS, a multi-cancer early detection test integrating epigenetic, genetic, and fragmentomic features of circulating tumor DNA (ctDNA). Here, we report results from K-ACCELERATE (NCT06391749), a prospective multi-center study evaluating SPOT-MAS as a diagnostic aid in symptomatic individuals. **Methods:** Adults (≥18 years) with symptoms suggestive of colorectal, gastric, breast, liver, or lung cancer were recruited across 13 hospitals in Vietnam from July 2024. All participants underwent SPOT-MAS testing alongside standard-of-care diagnostics and were followed for up to 12 months. Primary endpoints included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and tissue-of-origin (TOO) accuracy, using imaging and/or biopsy as the reference standard, analyzed overall and by symptomatic pathway. **Results:** Of 972 eligible participants, 862 achieved diagnostic resolution and completed follow-up, including 130 cancer cases and 732 non-cancer cases. Overall sensitivity and specificity of SPOT-MAS were 65.4% (95% CI: 56.9–73.0) and 92.1% (95% CI: 89.9–93.8), respectively. Pathway-specific sensitivity was 58.7% for breast cancer, 62.1% for lung cancer, 64.3% for gastrointestinal cancers, 80.0% for liver cancer, and 100% for multiple-pathway presentations. Among confirmed cancer cases, ctDNA-based tissue-of-origin prediction achieved 82.4% accuracy. Incorporation of ctDNA testing into clinical triage increased PPV from 15.1% to 59.4%, representing a nearly four-fold improvement over symptom-based assessment, while maintaining a high NPV of 93.7%. **Conclusions:** This study provides clinical evidence supporting the feasibility of SPOT-MAS as a non-invasive adjunct diagnostic tool for individuals presenting with cancer-related symptoms in low-resource settings. These findings lay the foundation for future prospective interventional studies to evaluate the clinical impact of ctDNA-guided diagnostic pathways in high-risk symptomatic populations. Clinical trial information: NCT06391749. Research Sponsor: None.

10556 **Poster Session**

Association of clonal hematopoiesis driven by mosaic chromosomal alterations with epigenetic age in the PLCO trial. First Author: Corey Young, National Cancer Institute, National Institutes of Health, Rockville, MD

Background: Mosaic chromosomal alterations (mCAs) are age-associated clonal events detectable in peripheral blood and have been linked to hematologic malignancy risk and adverse clinical outcomes. Whether mCAs are associated with accelerated biological aging, as measured by DNA methylation–based epigenetic clocks, remains poorly understood. **Methods:** We analyzed peripheral blood DNA methylation data generated using the Illumina EPIC array from 482 participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. mCAs were identified from SNP array data and classified by subtype, including autosomal copy-neutral loss of heterozygosity (CN-LOH), gains, losses, and loss of the sex chromosome . Epigenetic age was estimated using six established DNA methylation clocks: Hannum, Horvath pan-tissue/skin and blood, PhenoAge, GrimAge & DunedinPACE. Associations between mCA presence, mCA subtype, clonal burden, and epigenetic age acceleration were evaluated using multivariable linear regression models adjusted for age, sex, smoking status, body mass index, and genetic ancestry. **Results:** Among 482 participants, 261 were mCA-free and 221 had at least one detectable mCA. Individuals with any detectable mCA exhibited higher epigenetic age acceleration than mCA-free individuals across multiple clocks, with the most consistent effect sizes across mCA subtypes observed for GrimAge. Although age acceleration was directionally higher among individuals with mCAs across all non–rate-based clocks, statistically significant differences were observed only for the Hannum, PhenoAge, and GrimAge clocks. For GrimAge, estimated effects for mCA-positive individuals were uniformly positive, except for gain-only events, with effect sizes ranging from 1.2 to 1.9 years of age acceleration. Age acceleration increased with clonal burden: participants with multiple mCAs (n = 51) exhibited greater age acceleration than those with a single mCA (n = 170), particularly for GrimAge and PhenoAge. Higher cellular fraction was also associated with increased age acceleration, with significant associations observed for GrimAge (β = 2.97, 95% CI 0.82–5.12, p = 0.007) and Hannum (β = 4.25, 95% CI 1.14–7.37, p = 0.008) clocks. **Conclusions:** Mosaic chromosomal alterations, particularly CN-LOH and higher clonal burden states, are associated with accelerated biological aging in peripheral blood leukocytes. Epigenetic age acceleration was most consistently observed using GrimAge, a mortality- and healthspan-associated clock, with more variable and less consistent associations observed for chronological age-trained and rate-based clocks. These findings suggest that epigenetic age acceleration may represent a clinically relevant feature of clonal hematopoiesis, warranting further investigation in aging populations. Funded by NCI Contract No. 75N91019D00024. Research Sponsor: National Cancer Institute.

10557 **Poster Session**

Use of multiplex digital profiling of DNA methylation heterogeneity to enable sensitive early detection of non–small cell lung cancer from low-volume liquid biopsies. First Author: Christine O'Hersey, Johns Hopkins University, Baltimore, MD

Background: Early detection of non–small cell lung cancer (NSCLC) within liquid biopies remains limited by the extremely low abundance and heterogeneous nature of circulating tumor DNA (ctDNA) in plasma, particularly in patients with indeterminate pulmonary nodules. DNA methylation is an attractive early biomarker; however, conventional PCR- and sequencing-based assays have limited ability to sensitively and cost-effectively assess heterogeneous epiallelic methylation patterns at low variant fractions. We developed a digital microfluidic platform that enables multiplex, single-molecule profiling of DNA methylation heterogeneity to improve early NSCLC detection. **Methods:** We applied REM-DREAMing (Ratiometric-Encoded Multiplex Discrimination of Rare EpiAlleles by Melt), a digital high-resolution melt (dHRM) platform combining nanowell-based digital PCR with ratiometrically encoded, methylation-agnostic probes. Following bisulfite conversion, cfDNA was digitized into >40,000 nanoliter wells, enabling copy-by-copy assessment of methylation density across a five-gene biomarker panel previously associated with NSCLC. Analytical sensitivity and multiplex performance were compared against quantitative methylation-specific PCR (qMSP) and digital MSP (dMSP). Clinical feasibility was evaluated in plasma from patients with CT-detected indeterminate pulmonary nodules. **Results:** REM-DREAMing resolved heterogeneous methylation patterns at single-molecule resolution and detected methylated epialleles at fractions as low as 0.00005% in a high background of unmethylated DNA. In a cohort of 48 low-volume plasma samples, incorporating intermolecular methylation density distributions significantly improved classifier performance relative to binary methylation calls. The five-gene panel achieved 93% sensitivity at 90% specificity for early-stage NSCLC, with an AUC of 0.96. Compared with qMSP and dMSP, REM-DREAMing demonstrated superior sensitivity, multiplex scalability, and discrimination of partially methylated epialleles. **Conclusions:** Multiplex digital profiling of DNA methylation heterogeneity enables sensitive, low-cost detection of early-stage NSCLC from limited plasma input. By capturing epigenetic heterogeneity at the single-molecule level, this platform improves diagnostic performance in clinically challenging early detection settings and provides a scalable foundation for expanded biomarker panels. Research Sponsor: National Institutes of Health.

Analytical and clinical performance comparison.

Method	Heterogeneous Methylation Detection	Detectable Copy Number	Analytical Specificity	NSCLC AUC
qMSP	No	10	~0.01%	0.78–0.82
dMSP	No	1	~0.005%	0.85
Bulk MS-HRM	Yes	10	~0.1%	0.80
REM-DREAMing	Yes (single-molecule)	1	0.00005%	0.96

10558 **Poster Session**

Development of an oncology generative AI foundation model trained on more than a million longitudinal patient journeys across the United States. First Author: Wilson Lau, Truveta Inc., Bellevue, WA

Background: Incidence of cancer diagnoses continues to increase, while the average cost of cancer screening, such as mammogram or colonoscopy, remains high, ranging from hundreds to over a thousand dollars. This study explores the potential of building an oncology foundation model based on Generative Pre-trained Transformers (GPT) to predict future outcomes for patients. We assess the prediction accuracy and feasibility of leveraging the foundation model to inform when screening should be prioritized, thereby reducing the associated burden of unnecessary procedures. **Methods:** The advancement of generative AI offers the opportunity to model the progression of human disease over time. In this study, we extended the GPT architecture and pre-trained it with a subset of Truveta Data containing the electronic health record (EHR) from the journeys of 1.4 million de-identified patients diagnosed with 4 types of cancer (lung, breast, colorectal, prostate). Each sequence of the patient journey—including demographics (age, gender), conditions, lab results (represented by SNOMED-CT and LOINC codes), and the corresponding event time—was tokenized before passing through the GPT model for training. For validation, 1000 patients were randomly sampled from our test data, in which each type of cancer diagnosis constituted 19%-30% of the samples. We used the model to generate synthetic future patient journeys for the selected patients and compared the predicted outcomes with the actual cancer diagnoses within one year. **Results:** The model achieved sensitivities above 78%, with positive predictive values (PPV) between 66% and 90%. More importantly, it demonstrated high specificities above 91%, with corresponding negative predictive values (NPV) above 90%. **Conclusions:** The high specificities and NPV indicate the feasibility of applying generative foundation model pre-trained with EHR data to predict negative cancer outcomes with high accuracy. Since the percentage of screening tests leading to positive cancer diagnosis is relatively low, the projected negative predictive outcomes offer valuable signals for clinicians, which they can use to complement their expert assessment to avoid unnecessary screening and subsequently reduce the burden of screening costs. Research Sponsor: Truveta.

Performance of the foundation model on cancer outcome prediction.

	Lung	Breast	Colorectal	Prostate
Positive predictive value (PPV)	72.77%	90.11%	65.78%	88.88%
Sensitivity	80.28%	79.00%	78.13%	78.26%
Negative predictive value (NPV)	91.87%	96.29%	90.35%	96.27%
Specificity	94.50%	91.45%	94.56%	92.07%

10559 **Poster Session**

Clinical impact of GLP-1 receptor agonist use on lung cancer incidence in high-risk patients: A real-world analysis. First Author: Ariana N. Neely, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: Lung cancer (LC) is the leading cause of cancer-related mortality in the United States. Lifetime risk is ~7% in the general population but substantially higher among high-risk groups with tobacco use, environmental exposures, or family/genetic predisposition. Despite screening recommendations for select high-risk populations, no pharmacologic prevention is established. Emerging evidence suggests that Glucagon-like peptide-1 receptor agonists (GLP-1RA) may influence cancer risk through anti-proliferative, anti-inflammatory, and immunomodulatory effects, but data on LC remain limited. This study evaluated the association between GLP-1RA use and LC incidence in high-risk patients. **Methods:** This multicenter retrospective study used de-identified electronic health data from TriNetX, a global federated research network. Adults ≥18 with high-risk features of tobacco use, environmental or occupational exposure, chronic lung disease, personal/family cancer history, or radiation were included. Participants were stratified by GLP-1RA use. Propensity score matching (1:1) adjusted for demographics, comorbidities, and medications. The primary endpoint was LC incidence. Participants with LC before the study entry were excluded. Multivariate logistic regression and Cox models assessed associations; results reported as hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** Before matching, 2,715,963 participants were identified. After matching, 68,374 were analyzed (34,187 per cohort) with similar demographics (mean age 58, 54% female, 46% male; 75% White, 17% Black, 1.5% Asian). Median follow-up was 2,324 days. LC incidence was 2% (688/33,784) in the GLP-1RA cohort vs 2.4% (797/33,369) in controls, yielding an absolute risk reduction of 0.4% and a number needed to treat (NNT) of 250. GLP-1RA use was associated with a 31% reduction in LC incidence [HR 0.687 (0.621–0.761)]. **Conclusions:** In this large retrospective cohort of high-risk individuals, GLP-1RA use was associated with lower LC incidence compared with matched controls. Despite modest absolute risk reduction, relative risk reduction and favorable number needed to treat suggest potential population-level impact in a disease with limited preventive options. Findings are biologically plausible given the anti-inflammatory, metabolic, and immunomodulatory effects of GLP-1RAs. While causal inference is limited by observational design, this study supports further prospective investigation of GLP-1RAs as a pharmacologic strategy for LC prevention in high-risk populations. Research Sponsor: None.

10561 **Poster Session**

Multimodal risk phenotyping of early-onset colorectal cancer. First Author: Azza Sarfraz, Miami Cancer Institute, Miami, FL

Background: Early-onset colorectal cancer (EOCRC) is rising rapidly, yet its risk profile is incompletely defined. Prior studies have largely focused on isolated metabolic or lifestyle factors and have rarely integrated broader sociodemographic context or objective functional measures. We performed multimodal phenotyping to characterize integrated clinical, behavioral, cardiometabolic, and wearable-derived profiles among individuals with EOCRC compared with average-onset CRC (AOCRC). **Methods:** Adults with CRC in the NIH All of Us Controlled Tier Dataset v8 were identified (≥2 EHR diagnosis codes ≥3 months apart). The primary exposure was age at diagnosis, defined as EOCRC (<50 years) vs AOCRC (≥50 years). Covariates included sociodemographic factors (sex, race/ethnicity, education, employment, health insurance, household income, marital status, neighborhood deprivation). Outcomes included health behaviors (smoking, alcohol use), anthropometrics (BMI, waist circumference), cardiometabolic conditions (dyslipidemia, metabolic syndrome, diabetes, hypertension), laboratory measures (lipids), and wearable-derived (Fitbit) activity, sleep, and heart rate, anchored to the most recent pre-diagnosis timestamp. **Results:** Among 3,915 CRC participants, 710 (18.1%) had EOCRC. The cohort was predominantly male (54.5%), White (64.4%), unemployed (68.6%), with annual income <$50k (45.5%), and married (53.6%). Participants with EOCRC were less often female (38.7% vs 47.0%) and White (52.7% vs 67.0%) (both $p<0.001$). EOCRC was associated with higher obesity (42.0% vs 37.0%), higher LDL (101 vs 86 mg/dL), and lower HDL (51 vs 54 mg/dL) (all $p<0.001$). Alcohol use (60.6% vs 50.5%, $p<0.001$) and heavy drinking (22.0% vs 16.1%, $p=0.003$) were more common among participants with EOCRC. In the wearable sub-cohort, EOCRC participants had higher heart rate (76.8 vs 73.8 *bpm*, $p=0.03$) and lower sedentary time (773 vs 894 *min/day*, $p=0.016$) with no significant differences in sleep metrics or heart rate variability. Female sex was associated with lower odds of EOCRC (OR 0.45, 95% CI 0.25–0.83; $p=0.01$), while Hispanic ethnicity was associated with higher odds (OR 4.04, 95% CI 1.51–10.86; $p=0.006$). **Conclusions:** EOCRC is characterized by higher obesity, dyslipidemia, and alcohol use, as well as differences in wearable-derived physiologic and behavioral profiles. Integrating real-world clinical data with digital biomarkers offers a scalable framework for refined risk stratification and precision prevention in EOCRC. Research Sponsor: None.

Multivariable logistic regression examining sociodemographic predictors for EOCRC.

Variable	OR (95% CI)	P value
Sex		
Male	Ref	
Female	0.45 (0.25–0.83)	0.010
Race/ethnicity		
White	Ref	
Black	2.43 (0.99–5.97)	0.052
Hispanic	4.04 (1.51–10.86)	0.006
Employment		
Unemployed	Ref	
Employed	3.38 (1.87–6.10)	<0.001

10562 **Poster Session**

Evidence of clonal stability in a 5-year longitudinal prospective cohort of cancer survivors with serial NGS analysis. First Author: Anmol Goyal, Cleveland Clinic, Cleveland, OH

Background: Hematopoietic stem and progenitor cells with preleukemic mutations (mut^{n}s), collectively termed clonal hematopoiesis (CHIP) serve as the cellular origin of myeloid neoplasms (MN). While risk of MN development varies, its natural history and transformation potential remain poorly defined. We present findings from our ongoing 10-year CHIP protocol using serial NGS to monitor clonal evolution and MN in cancer survivors. **Methods:** Retrospective analysis of 210 prospective pts from March 2020 to June 2024. Mut^{n}s were classified CHIP+ if they had a variant allele frequency (VAF) $\geq$2% (or $\geq$1% for *IDH1*, *IDH2*, and *JAK2*). Clonal evolution was evaluated by annual VAF changes adjusted for age-related increases (e.g. *DNMT3A* increases by ~2%/yr based on published data). Mut^{n}s were classified as slow ($\leq$5%/yr: *DNMT3A, TET2, ASXL1*), intermediate (5-10%/yr: *TP53, PPM1D, IDH1/2, KRAS, NRAS, SF3B1*), or fast-growing ($>$ 10%/yr: *JAK2, SRSF2*). BPearson's Chi-squared, Fisher's exact, and Wilcoxon rank-sum tests were used. **Results:** Of 210 pts, 42 (20%) had at least one CHIP+ mut^n. Median age was higher in CHIP+ vs. CHIP- pts (66 vs. 59 years, $p < 0.001$). CHIP+ was not significantly associated with sex, race, family history, smoking, alcohol use, prior cancer types (e.g., breast, head and neck) or treatment (chemo, radiation, surgery). Of 487 samples, 56 had detectable somatic mut^{n}s. The most frequent mut^n were *DNMT3A* (n = 27), *PPM1D* (n = 10), and *TET2* (n = 9). By expected growth kinetics, 37 (66%) mut^n were slow-growing, 12 (21.4%) intermediate, 2 (3.5%) fast-growing, and 4 (7.14%) of unknown kinetic category.Beyond VAF-kinetics-based progression, 12 pts developed new mut^n in subsequent years - *DNMT3A (n = 8), PPM1D (n = 2).* Some later became undetectable, suggesting transient clones. In total, 12 pts (1 by VAF kinetics, 11 by new mut^n acquisition) clonally progressed over 5 years of this study (5.7%).6 pts regressed by year 2, with gene mut^n VAFs becoming undetectable. These included mut^n in *PPM1D* (n = 2), *CBL* (n = 2), *TP53* (n = 1), and *DNMT3A* (n = 1). Three more pts regressed in year 3, and 1 in year 4. In all, 10 pts showed regression over 5 years (17.8%). Notably, 5 of 10 had received interventions for cardiac comorbidities. Overall, ~94% pts had clonal stability/regression. Slow-growing mut^{n}s - *DNMT3A* and *TET2* had median rates of 0.83% and 2.11%, (historical rates $\leq$5%). Intermediate mut^{n}s like *TP53* and *PPM1D* had median rates of 1.64% and -0.625%, below the expected 5-10% annual rise. *JAK2*, a fast-growing mut^n, also showed a lower rate of 0.19%. **Conclusions:** Despite being a high-risk population due to prior solid malignancy and exposure to chemo/radiation, most pts in our five-year longitudinal study showed clonal stability. Even among those who progressed, VAF kinetics remained stable post-detection. CHIP's inflammatory link to cardiovascular disease suggests preventive cardiology may impact clonal behavior. Research Sponsor: None.

10563 **Poster Session**

Mammography utilization and male breast cancer in BRCA1/2 carriers. First Author: Meredith Davies, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA

Background: Males with pathogenic germline variants in *BRCA1*/2 (BRCA+) have a 1-10% lifetime risk of developing breast cancer (MBC). NCCN guidelines recommend that BRCA+ males consider annual mammograms. We have prior shown low rates of mammography uptake in an academic cohort from Penn Medicine (PM). We sought to validate these findings about mammography in a national veteran (VA) cohort and to investigate the clinical characteristics of BRCA+ compared to nonBRCA+ MBC. **Methods:** We performed a retrospective analysis of 327 BRCA+ male veterans with no prior history of MBC. The electronic health record was reviewed to determine indication for and results of mammography episodes. A mammography episode was defined as all breast imaging studies obtained for asymptomatic screening or for symptoms within six months. The first mammogram episode identified was referred to as the "initial" mammogram and all other mammography episodes were "subsequent". To determine BI-RADS PPV, data for 85 PM and 68 VA BRCA+ males were combined and compared to 1819 nonBRCA+ males. To determine clinical characteristics of MBC, data for 30 PM and 18 VA BRCA+ MBC were combined and compared to 104 PM and 122 VA nonBRCA+ MBC. **Results:** Sixty-eight (20%) of VA BRCA+ males underwent an initial mammogram, 57% of which were ordered for screening. Among patients $\geq$50 without mammography, 31% of individuals had no discussion documented and 66% had a shared decision-making discussion against screening with an ordering provider. BI-RADS 4 and 5 findings occurred in six and five mammograms, respectively. MBC was diagnosed in 13% (9/68) after initial and 13% (3/23) after subsequent mammography pooled VA and PM data showed that 95% (21/22) of MBC diagnoses in BRCA+ males were after a symptom-prompted mammogram. BI-RADS 4 PPV was higher in BRCA+ compared to non-BRCA+ men (75% vs 5%, $p < 0.0001$), and BI-RADS 5 PPV was similar (100% vs 67%, p = 0.0661). In an expanded cohort of 48 BRCA+ MBC compared to 226 nonBRCA+ MBC, median (IQR) age of diagnosis was 66 (56-73) vs 66 (59-74) (p = 0.52). The majority of BRCA+ and nonBRCA+ MBC were ER+Her2- (85% and 90%, respectively, p = 0.70). Among those with Oncotype testing, 93% BRCA+ BC had intermediate or high-risk recurrence scores compared to 50% of non-BRCA+ (p = 0.002). However, BRCA+ and non-BRCA+ male patients had similar rates of node positivity (40% vs 41%, p = 0.87) and progression to metastatic disease (19% vs 16%, p = 0.67). **Conclusions:** Analysis of a Veteran cohort of BRCA+ males confirms low rates of mammography as we prior reported in an academic cohort. Counseling and SDM were inconsistently documented, highlighting gaps in guideline implementation. Both BRCA+ and nonBRCA+ MBC were nearly always diagnosed based on symptoms. Both BRCA+ and nonBRCA+ MBC were often node-positive and nearly 20% progressed to metastatic disease. These characteristics suggest the need for prospective evaluation of mammography in high-risk males to reduce rates of advanced disease. Research Sponsor: Basser Center for BRCA; VA ORD1I01CX002710; VA ORD1I01CX002710.

10564 **Poster Session**

Refining breast cancer risk stratification for selection of women at intermediate to high risk for supplemental MRI screening using artificial intelligence. First Author: Eun Kyung Park, Department of Radiology, Seoul National University Hospital, Seoul, South Korea

Background: Supplemental MRI screening for women at increased breast cancer risk can detect additional cancers that are occult on mammography. However, its adoption is limited by restricted availability and high false-positive rates. Improved risk stratification is therefore needed to optimize the use of supplemental MRI screening. This study aimed to evaluate the feasibility of a mammography-based artificial intelligence (AI) system for stratifying women at intermediate to high risk for supplemental MRI screening. **Methods:** This retrospective study included consecutive women who underwent abbreviated breast MRI following negative mammography between January 2020 and December 2024. The study cohort comprised women at intermediate to high breast cancer risk, including those with known genetic predisposition, personal history of breast cancer, prior benign or high-risk breast biopsy, or family history of breast cancer. A commercially available AI system was applied to all mammograms, generating both exam-level and breast-level scores representing the likelihood of a malignancy on a scale of 0 to 100. MRI outcomes, false-positive examinations, cancer detection, and positive predictive value (PPV) were evaluated. Univariate analyses were performed to explore associations between breast density and AI-based selection results. **Results:** In 1,588 women (median age, 51 years; range, 24-87), 1,804 screening mammograms and MRI examinations were performed. Of these examinations, 220 resulted in recall, yielding 24 mammographically occult breast cancers (12 ductal carcinoma in situ and 12 invasive cancers) diagnosed within one year and 166 false-positive examinations. The AI system achieved an area under the curve (AUC) of 0.694 (95% CI, 0.499-0.888) in women without a personal history of breast cancer and 0.611 (95% CI, 0.430-0.792) in women with a personal history of breast cancer. Using AI-based selection, 239 of 1,588 women (14.9%) were selected for supplemental MRI, resulting in an 81% reduction in false-positive examinations (31 vs 166) and an improvement in PPV to 20.5% (8 of 39). 6 of 8 detected cancers (75%) were invasive. Breast density was not associated with the AI-based selection strategy. **Conclusions:** Mammography-based AI substantially reduced false-positive supplemental MRI examinations while preferentially selecting women at higher risk for invasive breast cancers, without compromising cancer detection. These findings suggest that AI can refine risk stratification and optimize selection of women to improve the efficiency of supplemental MRI screening. Research Sponsor: National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT); RS-2025-00515472.

10565 **Poster Session**

Real-world experiences with a multi-cancer detection (MCD) blood test. First Author: Julius Chiang-Boeckmann, Massachusetts General Hospital, Boston, MA

Background: Multi-cancer detection (MCD) blood tests hold promise to screen for multiple cancers simultaneously. MCD tests have been assessed in case-control and prospective studies but have not yet been shown to improve cancer outcomes. Mass General Brigham (MGB) offers a commercially available, non-FDA-approved methylation-based MCD test (Galleri; GRAIL) through our Early Detection & Diagnostics Program. Here, we report our initial experience. **Methods:** In this retrospective, observational study, data were collected from all patients (pts) who underwent MCD testing or were evaluated for a prior positive MCD test at our clinic between May 2023 and December 2024. Pts obtained the test through: 1) self-payment after shared decision making, or 2) an early access demonstration project with GRAIL, Point32Health (insurance company), and MGB whereby pts $\geq$50y with specific insurance products and an MGB primary care physician were invited to receive a cost-free test if they met $\geq$1 of 4 criteria: personal history of cancer, 1st-degree family history of cancer, elevated BMI, or any smoking history in the past 10 years. All pts tested at MGB underwent pre-test consultation with a medical oncologist or nurse practitioner to review the benefits and limitations of testing. Result management was coordinated by our team. Longitudinal outcomes were abstracted from electronic health records. **Results:** 742 pts had MCD testing (125 [17%] self-pay, 617 [83%] demonstration project). Median (med) age was 59 (IQR 55-63); most were White (92%) and up to date on USPSTF-recommended cancer screening (82%). Med follow up (FU) was 469 days (IQR 462-478); 580 (78%) had $>$ 12 months FU. Four pts received a "cancer signal detected" result (+MCD): 2/742 tested at MGB (0.3%) and 2 who presented to workup +MCD tested elsewhere; 2 were true positives (TP), 2 false positives. In total, 16 pts (2.2%) were diagnosed (dx) with cancer during FU; 2/16 (13%) after +MCD, and 14/16 after negative MCD, with med time from MCD to diagnosis 199 days (IQR 92-464). The two TP tests corresponded to stage I breast cancer and stage III follicular lymphoma. The most common cancers dx were prostate (n = 5, with two stage III-IV dx at 128 and 142 days) and breast (n = 4, all mammogram-detected stage I). Other advanced cancers included stage III cholangiocarcinoma and stage IV adenocarcinoma unknown primary (dx at 515 and 475 days, respectively). **Conclusions:** In this real-world cohort, MCD test positivity was rare, and multiple cancers were dx within 18 months of a negative MCD, including some advanced cases. In particular, prostate cancer was dx in multiple pts after negative MCD, consistent with prior reports of limited MCD sensitivity for prostate cancer. Our cohort may be biased by the requirement to either self-pay or carry a specific insurance product. Larger studies with longer FU are needed to better define the added utility of MCD tests to standard cancer screening. Research Sponsor: None.

10566 **Poster Session**

Spatial organization of immune surveillance by germline mutation status in the Breast Cancer Family Registry. First Author: Marni Blair McClure, Stanford Cancer Institute, Stanford, CA

Background: Germline pathogenic variants (gPVs) are associated with increased immune infiltration in resulting tumors; we previously reported increased CD4+ and CD8+ T-cells in gPV-associated tumors using single-cell spatial profiling. Here, we report the spatial features, including cell-cell co-localization, underlying these immune differences. **Methods:** We analyzed CosMx 6K single-molecule RNA transcriptomics in 222 samples from 144 women in the population-based Northern California Breast Cancer Family Registry. Across 1,083,345 cells and 6,583 genes, multicellular niches were identified by clustering cells based on spatial proximity and cell-type identity using a k-nearest neighbors approach, with the number of niches selected by elbow analysis. Niche proportions were compared between gPV-associated and wild-type tumors using linear models. Linear mixed-effects models were used to identify niche-specific enrichment of cell-type densities and pairwise cell–cell colocalization relative to all other niches. P-values were corrected using Benjamini–Hochberg. **Results:** Of 144 participants, 31 (22%) carried at least one gPV, including BRCA1 (n = 12), BRCA2 (n = 8), PALB2 (n = 3), FANCM (n = 3), ATM (n = 2), and CHEK2, RAD50, and TP53 (n = 1 each). We identified eight cell niches, two of which were enriched in gPV-associated tumors, including within ER/HER2 subtypes: niche 2 (10% of cells in gPV tumors vs 3.7% in non-gPV tumors; Wilcoxon FDR = 0.01) and niche 5 (17% vs 9.4%; FDR = 0.03). Niche 2 and niche 5 proportions were uncorrelated across tumors ($r = -0.13$, FDR = 0.14). Compared with other niches, niche 2 had higher proportions of immature B cells (FDR = 0.006), $CD8^+$ T cells (FDR = 0.03), dendritic cells (FDR < 0.001), and macrophages (FDR < 0.001), with no specific cell-cell colocalization pattern. Niche 5 had higher proportions of $CD4^+$ T cells (FDR < 0.001), myoepithelial cells (FDR < 0.001), and macrophage-derived stem cells (FDR < 0.001); niche 5 demonstrated increased colocalization across 95 cell-type pairs at FDR < 0.1, including cancer cells with macrophage-derived stem cells and pericytes with natural killer cells (FDR = 0.01 each). Comparing BRCA1 to BRCA2 gPV carriers, niche 2 was more prevalent in BRCA1 tumors (16% vs $< 1\%$ in BRCA2; p = 0.01); no significant difference was observed for niche 5. **Conclusions:** In this population-based cohort, gPV-associated breast cancers exhibited distinct spatial immune niches. Niche 2, especially enriched in BRCA1 gPV tumors, appears to reflect an inflamed immune environment, whereas niche 5 may represent a more spatially organized stromal-adaptive immune niche characterized by $CD4^+$ T-cell enrichment and extensive non-random cell-cell interactions. These findings demonstrate that inherited cancer risk is associated with reproducible immune spatial architectures, with implications for immune-based prevention and interception strategies. Research Sponsor: None.

10567 **Poster Session**

Quantifying the macroeconomic burden of tobacco-attributable cancers in 2023: Global disparities in value-of-lost-welfare (VLW) in 189 countries. First Author: Mansha Gupta, Midwestern University GME Consortium Program, Cottonwood, AZ

Background: Tobacco use is the leading preventable cause of cancer globally, yet the macroeconomic welfare losses attributable to tobacco-related cancers remain incompletely quantified. We estimated the global economic burden of tobacco-attributable cancers in 2023 using a standardized value-of-lost-welfare (VLW) framework. **Methods:** Country-level disability-adjusted life years (DALYs) attributable to tobacco for all cancers were obtained from the Global Burden of Disease (GBD) 2023 framework. Gross domestic product (GDP; purchasing power parity, current international dollars) and population data were sourced from the World Bank. VLW was calculated as tobacco-attributable cancer DALYs multiplied by country-specific GDP per capita (PPP). Outcomes included total VLW, per-capita VLW, and VLW as a percentage of national GDP. **Results:** In 2023, tobacco-attributable cancers resulted in 48.44 million DALYs globally (95% UI: 41.06–57.06 million), corresponding to a global value of lost welfare (VLW) of USD 1.61 trillion. The largest absolute economic welfare losses were observed in China (USD 415.3 billion), India (USD 262.8 billion), and the United States (USD 219.4 billion), followed by Japan (USD 96.1 billion) and Brazil (USD 63.7 billion). Together, these five countries accounted for 65.9% of the global VLW attributable to tobacco-related cancers. When normalized to national economic output, the highest VLW-to-GDP ratios were observed in India (1.12%), China (0.69%), Egypt (0.61%), Bangladesh (0.58%), and Pakistan (0.52%), indicating substantial macroeconomic vulnerability in several low- and middle-income countries. By cancer type, tracheal, bronchus, and lung cancer accounted for 24.6 million DALYs, corresponding to a VLW of USD 0.82 trillion, followed by esophageal cancer (6.1 million DALYs; USD 0.21 trillion), stomach cancer (5.4 million DALYs; USD 0.18 trillion), liver cancer (4.9 million DALYs; USD 0.16 trillion), and oral cavity cancer (3.2 million DALYs; USD 0.11 trillion). Collectively, these five cancer types accounted for 91.4% of total tobacco-attributable cancer VLW worldwide. **Conclusions:** In 2023 alone, tobacco-attributable cancers resulted in nearly 50 million DALYs and over $1.6 trillion in lost economic welfare worldwide, highlighting tobacco use as a dominant driver of both health loss and macroeconomic harm. Research Sponsor: None.

Regional distribution of disability-adjusted life years (DALYs) and economic welfare loss (VLW) attributable to tobacco-related cancers in 2023.

Region	DALYs (millions)	VLW (USD trillion)	VLW/GDP (%)
High-income	11.6	0.75	1.81
Central Europe, Eastern Europe, and Central Asia	4.58	0.17	1.27
Southeast Asia, East Asia, and Oceania	22.87	0.53	1.14
North Africa and Middle East	2.27	0.05	0.57
Latin America and Caribbean	1.72	0.03	0.29
South Asia	4.33	0.04	0.22
Sub-Saharan Africa	0.98	0.00	0.12

10568 **Poster Session**

Effect of breast density reporting on supplemental MRI and ultrasound use. First Author: Gianna Aliberti, Harvard University School of Public Health, Boston, MA

Background: Mammography has lower sensitivity in women with dense breasts due to masking, as both dense tissue and tumor tissue appears white. Supplemental breast imaging, such as MRI or ultrasound, can increase cancer detection among women with dense breasts, but its use is limited by screening capacity, cost, and potential over-diagnosis. The purpose of this study is to understand the impact of changing breast density on supplemental screening use in a longitudinal cohort of women undergoing screening mammography. **Methods:** Participants are from the Boston Mammography Cohort Study (BMCS), a cohort of women undergoing routine screening mammography within the Mass General Brigham health system in Boston, MA enrolled from 2008-2016, with follow up collected through 2022. Participants completed a questionnaire at enrollment which provided demographic, reproductive, lifestyle and behavioral factors. Electronic medical record review provided dates and results of all breast imaging received within the health system. We performed a longitudinal analysis using generalized estimating equations to evaluate the association between breast density and supplemental MRI and/or ultrasound. Women with a history of breast cancer and those without at least one mammogram with reported BIRADS breast density were excluded from the analysis. **Results:** Of the 2,696 women enrolled in BMCS, 87 were excluded for breast cancer prior to enrollment and 16 were excluded for lack of reported BIRADS breast density, leaving 2,593 in the analytic cohort. Of these women, 37.6% were aged 40-49 at the time of enrollment, 71.5% were non-Hispanic white, 46.5% had a body mass index (BMI) of 18.5-24.9, 51.9% were postmenopausal, and 78.0% had no first-degree relatives with breast cancer. Overall, 1.5% (n = 40) were diagnosed with breast cancer, 3.5% (n = 98) received a breast MRI, and 25.8% (n = 669) received a breast ultrasound. In unadjusted analyses, increased breast density was associated with higher rates of supplemental imaging. Compared with women who never had dense breasts, those who always had dense breasts had higher use of MRI (RR 3.7, $p < 0.001$), while ultrasound use was higher among women who sometimes (RR 1.5, p = 0.0002) and always (RR 1.7, $p < 0.0001$) had dense breasts. After adjusting for age, race, BMI, menopausal status, family history, and mammogram results, the association between breast density and supplemental imaging was attenuated. Women who sometimes had dense breasts remained more likely to undergo ultrasound and any supplemental imaging compared with women who never had dense breasts, but the associations were smaller and did not reach significant statistical significance. Abnormal mammogram results were the strongest predictor across all models. **Conclusions:** These findings suggest that breast density alone may be insufficient to guide supplemental screening guidelines and support more targeted, risk-informed approaches. Research Sponsor: None.

10569 **Poster Session**

Circulating cadherin-17 (CA17) in blood as a diagnostic biomarker for gastric cancer. First Author: Tsz Chun Hon, Tiberias Technology Limited, Shatin, Hong Kong

Background: The asymptomatic onset of gastric cancer (GC) frequently leads to delayed diagnosis resulting in poor survival. Conventional biomarkers (CA72-4, CEA) lack sensitivity, while emerging cfDNA methods remain costly and complex for routine screening. Our proprietary antigen, Cadherin-17 (CDH17), is selectively overexpressed in gastrointestinal (GI) malignancies. We developed a fully automated, high-throughput Chemiluminescence Immunoassay (CLIA) using proprietary antibodies to monitor the blood circulating levels of CA17 – the soluble form of Cadherin-17 protein in liquid biopsies. CA17 screening offers a complementary minimal invasive diagnostic method that identifies high-risk GC individuals for follow up endoscopy evaluations. **Methods:** A CLIA assay was designed to quantify circulating CA17 protein levels in human serum. The assay was established on the iShine i1910 automated platform, which integrates magnetic microparticle and acridinium ester labelling to generate luminescent signals. Four proprietary monoclonal anti-CA17 antibody clones were evaluated in various capture and detection pair combinations to identify the optimal antibody pairing for assay performance. Serum samples from 114 non-cancer individuals and 113 patients with histologically confirmed gastric cancer were analysed. Assay and biomarker performance was assessed by receiver operating characteristic (ROC) curve analysis to determine assay sensitivity and specificity. **Results:** Four capture/detection antibody pairings were evaluated. The clone 1–clone 2 combination demonstrated superior detection accuracy, yielding an AUC of 0.959 (90.3% sensitivity, 91.4% specificity). This optimal pairing revealed a highly significant difference in CA17 levels between the non-cancer and GC groups (Mann-Whitney test,), confirming its ability to reliably distinguish high-risk individuals. In contrast, the clone 1–clone 3, clone 5–clone 1, and clone 1–clone 4 combinations exhibited inferior performance, with AUCs of 0.784, 0.705, and 0.680, respectively. **Conclusions:** The CA17 CLIA assay demonstrates high sensitivity and specificity for GC detection. As a minimally invasive blood-based test, it enables early identification of high-risk individuals for subsequent confirmatory endoscopy. This cost-effective blood test has the potential to allow screening of GC at the early stages and will significantly impact on patient survival. Research Sponsor: None.

10570 **Poster Session**

Transdermal drug delivery to the normal and the radiated breast: Determinants of individual variation in skin permeation. First Author: Natalie Pulliam, Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL

Background: Primary prevention of breast cancer with oral drugs causes systemic effects which are unacceptable to 85% of high-risk women. Transdermal delivery through breast skin can minimize systemic exposure, but individual variation of permeation, the effects of breast radiation, or increased dose have not been studied. We report a prospective single-arm trial addressing these aspects, using 4-hydroxytamoxifen (4-OHT) an active metabolite of oral tamoxifen. **Methods:** Women with unilateral breast cancer treated with breast conservation and radiotherapy applied 4-OHT gel to both breasts for 4±1 weeks. In Cohort 1 (2 mg/breast/day) we evaluated inter-individual variation of 4-OHT skin permeation in the non-radiated breast based on demographic and skin characteristics. In Cohort 2 (4 mg/breast/day) we evaluated the effect of increased dose. All participants underwent bilateral post-intervention dermal punch and core needle breast biopsy. Drug concentration in tissue and plasma was measured using liquid chromatography-mass spectroscopy. Multivariable linear regression was used to examine the predictors of drug concentration in tissue and plasma. Stepwise model selection was conducted using AIC criteria, with multicollinearity assessed via variance inflation factor (VIF). **Results:** Of 156 consented women, 120 completed intervention and were evaluable for the primary endpoint (breast tissue drug concentration). On multivariable analysis, breast tissue 4-OHT concentration increased with age and White race. Drug concentration was equivalent in the radiated and the non-radiated breasts and was two-fold higher in Cohort 2 (4 mg/breast/day) compared to Cohort 1 (2 mg/breast/day), (p = 0.001). Plasma drug concentrations were low in both cohorts; 0.27ng/mL in Cohort 1 and 0.15ng/mL in Cohort 2, (p = < 0.001). **Conclusions:** Transdermal delivery of breast cancer prevention drugs is a viable strategy, with higher dose achieving proportional increase in tissue concentration, without increased leakage into the circulation. Further work should pursue formulations of highly active drug metabolites with excellent permeation. Clinical trial information: NCT04009044. Research Sponsor: National Institutes of Health (NIH)/National Cancer Institute (NCI).

10572 **Poster Session**

Embedding germline genetic testing into African oncology care: Early results from the Genetic Cancer Families (GenCAF) program. First Author: Sulin Wu, University of Chicago Medical Center, Chicago, IL

Background: Breast cancer outcomes in sub-Saharan Africa are marked by early onset, advanced stage at diagnosis, and high mortality. Although prior studies demonstrate a high burden of inherited cancer susceptibility variants in African populations, access to ancestry-informed genetic counseling and testing remains limited due to infrastructure constraints and poor integration into routine oncology care. The GenCAF program was developed to translate prior genomic evidence from Nigeria into a scalable, clinically embedded cancer genomics implementation model in African settings. **Methods:** Consecutive breast cancer patients were prospectively enrolled and offered genetic counseling and testing regardless of age or family history. Germline testing was performed using the Color Hereditary Cancer Test (Color Health Inc). Counseling and result disclosure were delivered by locally trained oncology nurses or breast health specialists using a structured protocol. Clinical and tumor characteristics were correlated with genetic findings. The program was designed for scalability across English- and French-speaking sites. **Results:** Among 263 participants, 235 unrelated index breast cancer cases underwent germline testing. Overall, 43.0% (101/235) had a reportable germline finding, including 21.7% (51/235) with pathogenic or likely pathogenic (P/LP) variants and 21.3% (50/235) with variants of uncertain significance (VUS). Among genes present in ≥5% of cases with variant calls, VUS were most frequent in *APC, ATM, PALB2, PMS2*, and *BRCA2*, with several moderate-penetrance DNA repair genes exhibiting disproportionately high VUS burden, representing key candidates for future reclassification as African-ancestry reference data and gene–environment context expand. P/LP variants were most common in BRCA1 (n = 22), BRCA2 (n = 13), ATM (n = 4), and PALB2 (n = 4). P/LP carriers tended to be diagnosed before age 30 (13.7% vs 7.6%) and were more frequently diagnosed with advanced-stage disease (stage III–IV, 30.6%). Mean age did not differ overall; however, BRCA1 P/LP carriers had an earlier onset (mean age 40.1 years). **Conclusions:** These findings support integrating germline cancer genetics into routine breast cancer care in Africa through a scalable, nurse-led counseling model. The substantial VUS burden underscores the need for ancestry-informed interpretation and future reclassification efforts incorporating population-specific and environmental data. Planned implementation of point-of-care next-generation and long-read sequencing will further strengthen local diagnostic capacity and enable sustainable, locally driven precision prevention and oncology through risk-informed care. Research Sponsor: Breast Cancer Research Foundation; Susan G. Komen; U.S. National Institutes of Health; R01MD013452.

Age Group (yrs)	P/LP (%)	VUS (%)
<30	**13.7**	7.6
30–39	15.7	23.9
40–49	23.5	23.4
50–59	27.5	26.6
≥60	15.6	19.0

10573 **Poster Session**

Missed by the guidelines: A meta-analysis of USPSTF lung cancer screening ineligibility among patients diagnosed with lung cancer. First Author: Khalid Ahmad Qidwai, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Lung cancer (LC) screening utilizes low-dose CT recommended by the US Preventive Services Task Force (USPSTF) based on age and smoking history. However, the proportion of patients who develop LC but are ineligible for screening at diagnosis remains unclear. We performed a meta-analysis to quantify the burden of LCs missed under USPSTF 2013 and 2021 criteria and identify key reasons for ineligibility. **Methods:** We systematically searched PubMed, Embase, and Scopus to identify studies reporting USPSTF screening eligibility among adults diagnosed with primary LC who ever smoked. Data were pooled using random-effects models. Primary outcomes included pooled proportions (PP) of LC cases ineligible for USPSTF screening using 2013 and 2021 criteria. Secondary analyses evaluated reasons for ineligibility, including age, smoking pack-years (yrs), and quit-yrs. Statistical significance is defined as $p < 0.05$. Heterogeneity was assessed using the I^2 statistic. **Results:** Eight studies comprising 12,487 LC cases utilized the USPSTF 2013 criteria. The PP of screening-ineligible cases was 57.6% (95% CI, 48.94%-66.2%; I^2=97.3%). Under USPSTF 2021 criteria, 11 studies including 20,313 cases were analyzed, yielding a pooled ineligible proportion of 40.9% (95% CI, 31.9%-50.5%; I^2=98.8%). In reason-specific analyses, insufficient smoking exposure (pack-yrs) was the primary cause of ineligibility using both criteria, accounting for 68.2% (2013) and 59.3% (2021) of ineligible cases. Age-based exclusions declined from 34.7% under USPSTF 2013 to 31.8% under USPSTF 2021. Quit-year restrictions contributed to ineligibility under both criteria (25.8% in 2013; 49.6% in 2021), reflecting a greater proportional contribution among remaining ineligible cases under the 2021 criteria. Categories of ineligibility were not mutually exclusive. **Conclusions:** More than half of LCs were ineligible for screening under USPSTF 2013 criteria, and over 40% remain ineligible under current guidelines. Smoking pack-year thresholds remain the primary reason for ineligibility to screen and thereby miss a cancer diagnosis. These findings highlight limitations of current criteria and support the development of alternative risk-based screening strategies. Research Sponsor: None.

Lung cancer screening ineligibility under USPSTF 2013 and 2021 criteria.

	Pooled Proportion (95% CI)	I^2 (%)
USPSTF 2013 Criteria Overall Ineligibility	57.6% (48.4-66.2)	97
Age-based exclusion (<55 or >80 yrs)	34.7% (28.2-41.8)	70
Insufficient pack-yrs (<30)	68.2% (54.6-79.2)	93
Quit-year exclusion (>15 yrs)	25.8% (10.8-49.8)	97
USPSTF 2021 Criteria Overall Ineligibility	40.9% (31.9-50.5)	98
Age-based exclusion (<50 or >80)	31.8% (18.4-49.0)	96
Insufficient pack-yrs (<20)	59.3% (45.6-71.6)	89
Quit-year exclusion (>15 yrs)	49.6% (37.1-62.0)	94

10574 **Poster Session**

Reproducible modulation of tissue Ki-67 across lung and prostate cancer interception trials. First Author: Sri Pranita Cherukuri, Columbia University, New York, NY

Background: The clinical utility of cancer interception is limited by the lack of validated surrogate endpoints that capture early biological response before histopathologic progression. While morphologic changes often require prolonged follow-up, Ki-67, a nuclear marker of cellular proliferation, provides a dynamic, tissue-based measure of epithelial proliferative activity. However, its reproducibility across high-risk tissue contexts remains debated. We evaluated the consistency of tissue Ki-67 modulation across two independent randomized trials in high-risk lung and prostate epithelia. **Methods:** We analyzed data from two prospective, randomized, placebo-controlled phase II cancer interception trials that prespecified tissue Ki-67 as an endpoint. In the lung cohort (NCT03232138; n=98), high-risk smokers with bronchial dysplasia were randomized to oral sulforaphane (200 μmol/day) or placebo for 6 months. In the prostate cohort (CAPFISH-3; n=58), patients with low-grade prostate cancer on active surveillance were randomized to long-chain omega-3 fatty acids (3 g/day) or placebo for 12 months. Paired tissue biopsies were obtained at baseline and study completion. Ki-67 expression was quantified by immunohistochemistry with central pathology review. **Results:** Baseline Ki-67 indices were comparable between intervention and placebo arms in both cohorts. Following the intervention, a statistically significant divergence in tissue proliferative activity was observed. In the lung cohort, sulforaphane treatment was associated with a 20% reduction in bronchial epithelial Ki-67, whereas the placebo arm demonstrated a 65% increase (P=0.014). In the prostate cohort, omega-3 supplementation resulted in a 15% reduction in intratumoral Ki-67, compared with a 24% increase in the control arm (P=0.043). Sub-analysis by staining intensity demonstrated preferential suppression among high-intensity (3+) Ki-67–positive cells, including a 44% reduction in the lung intervention arm. Ki-67 modulation correlated with baseline proliferative activity but not with baseline histopathologic features. No significant changes in histopathologic grade or dysplasia scores were observed. **Conclusions:** Tissue Ki-67 demonstrates consistent, reproducible modulation across randomized lung and prostate interception trials, preceding detectable morphologic change. These findings support Ki-67 as a practical early biologic endpoint for phase II cancer interception studies. Research Sponsor: None.

Tissue Ki-67 modulation across randomized cancer interception trials.

Cohort (n)	Intervention	Ki-67 change (Tx)	Ki-67 change (Pbo)	P value
Lung (98)	Sulforaphane	−20%	+65%	0.014
Prostate (58)	Omega-3	−15%	+24%	0.043

Abbreviations: Tx, treatment; Pbo, placebo.

10575 **Poster Session**

Elevated red blood cell distribution width-to-albumin ratio and incident cancer risk: A prospective cohort study. First Author: Parham Habibzadeh, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA

Background: Cancer remains a leading cause of global morbidity and mortality, underscoring the need for accessible biomarkers for early detection and risk stratification. The red blood cell distribution width-to-albumin ratio (RAR) is an emerging composite index integrating markers of erythropoietic stress and nutritional status/hepatic dysfunction, often dysregulated in malignancy and systemic inflammation. Elevated RAR correlates with worse outcomes in patients with sepsis and various cancers; however, its association with incident cancer risk in large prospective cohorts remains uncharacterized. **Methods:** Using UK Biobank data, we conducted a prospective cohort study with 5:1 propensity score matching, yielding an analytic cohort of 112,107 participants (18,916 with elevated RAR, 93,191 with normal RAR). Elevated RAR was defined as $>$ 95th percentile ($>$ 3.48 %·dL/g) among cancer-free participants at baseline. Matching balanced groups by age, sex, ethnicity, socioeconomic status, BMI, smoking, alcohol use, diabetes, chronic kidney disease, and family history of cancer. Adjusted Cox proportional hazards regression was utilized to assess associations between elevated RAR and incident cancer. We also performed a 2-year landmark analysis to evaluate reverse causation. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. **Results:** During median follow-up of 15.4 years (1.55 million person-years), 21,307 incident cancers occurred. Elevated RAR was significantly associated with 23% increased overall cancer risk (HR 1.23; 95% CI 1.18-1.27). Cancer-specific analyses revealed strongest associations for hematologic malignancies (HR 1.91; 95% CI 1.70-2.14), including acute myeloid leukemia (HR 2.22; 95% CI 1.37-3.60) and chronic myeloid leukemia (HR 2.78; 95% CI 1.23-6.31). Significant associations were also observed for gastric (HR 2.12; 95% CI 1.57-2.86), liver (HR 1.90; 95% CI 1.38-2.62), lung (HR 1.45; 95% CI 1.27-1.66), and colon cancer (HR 1.48; 95% CI 1.28-1.72). No significant association was observed for breast (HR 1.06; 95% CI 0.96-1.17) or prostate cancer (HR 0.94; 95% CI 0.84-1.05). A 2-year landmark analysis showed that the association with overall cancer risk remained robust (HR 1.19; 95% CI 1.15-1.24). **Conclusions:** Elevated RAR is independently associated with increased incident cancer risk, particularly for hematologic, gastrointestinal, and lung cancers. These associations persisted in 2 year landmark analyses, supporting a potential prospective relationship and motivates further evaluation of RAR, a readily calculable index from routinely obtained laboratory values, in cancer risk models. Research Sponsor: None.

10576 **Poster Session**

Pancreatic cancer incidence and survival in lean and obese adults with type 2 diabetes: A propensity matched analysis. First Author: Vasu Bansal, University of Missouri Kansas City, Kansas City, MO

Background: Type 2 diabetes mellitus (T2DM) and excess adiposity are independent risk factors for pancreatic cancer. Pancreatic cancer risk within T2DM across body-mass index (BMI) strata is heterogeneous in real-world cohorts and lean T2DM individuals may represent a distinct high risk phenotype. We compared pancreatic cancer incidence and post-diagnosis survival across BMI strata. **Methods:** We performed a retrospective comparative outcomes analysis using the TriNetX network. Adults with T2DM (HbA1c $\geq$6.5%) were categorized as obese (BMI $\geq$30 kg/m²) or lean (BMI $<$25 kg/m²). The lean cohort additionally excluded any patient with prior BMI of $>$25 kg/m² to control for cancer associated weight loss. The index event was first T2DM diagnosis, and outcomes were evaluated after a 365-day window. Patients with pancreatic cancer prior to the outcome window were excluded. Propensity score matching was done using the following parameters: age, sex, smoking status, pancreatitis, pancreatic cysts, chronic kidney disease, gallstones, family history of pancreatic cancer, and HbA1c. Outcomes assessed were incident pancreatic cancer over 10 years and all-cause mortality among patients with pancreatic cancer and T2DM. **Results:** Total number of patients in the obese group was 1,759,075 with mean age of 57 $\pm$ 13.4 years and in the lean cohort were 205,193 with a mean age of 61.8 $\pm$ 16.6 years. After propensity score matching, there were 204,086 patients in each group. Mean HbA1c levels were 7.4 $\pm$ 1.8% in the obese group and 7.9 $\pm$ 2.2% in the lean BMI group. The incidence of pancreatic cancer was 0.16% (n = 335) in obese patients as compared to 0.23% in lean (n = 478) patients with a risk difference of 0.07% ($p < 0.001$). Obesity was associated with lower pancreatic cancer risk (RR 0.692, 95% CI 0.603–0.797; $p < 0.001$). In the subgroup analysis of patients diagnosed with pancreatic cancer, obese patients had longer median survival (1,109 vs 651 days) with HR 0.853 (95% CI 0.793 - 0.918; $p < 0.001$). **Conclusions:** Lean adults with T2DM had a higher incidence of pancreatic cancer and worse post-diagnosis survival than obese patients. These results identify lean T2DM as a distinct high-risk phenotype and demonstrate that pancreatic cancer risk within T2DM is heterogeneous and not solely attributable to excess adiposity. Further investigation is needed to elucidate the biological mechanisms underlying this association and its implications for clinical risk assessment. Research Sponsor: None.

Pancreatic cancer incidence and associated risk estimates among obese and lean adults with type 2 diabetes mellitus.

Cohort	Pancreatic cancer incidence	RD	RR
Obese T2DM(n = 204,086)	0.16% (n = 335)	0.07% (95% CI: 0.04 - 0.10), $p < 0.001$	1.44 (95% CI: 1.25 - 1.66)
Lean T2DM(n = 204,086)	0.23% (n = 478)		

Abbreviations: CI, confidence interval; RD, risk difference; RR, relative risk; T2DM, type 2 diabetes mellitus.

10577 **Poster Session**

Diagnostic accuracy of blood-based cfDNA fragmentomic assays for lung cancer detection: A meta-analysis of clinically validated cohorts. First Author: Khalid Ahmad Qidwai, Miami Cancer Institute, Baptist Health South Florida, Miami, FL

Background: Early detection of lung cancer remains limited by suboptimal sensitivity and specificity of current screening and diagnostic strategies. Blood-based cell-free DNA (cfDNA) fragmentomic assays that leverage genome-wide fragmentation patterns have emerged as a promising noninvasive approach for lung cancer detection. However, reported diagnostic performance varies across studies and clinical settings. A meta-analysis was conducted to evaluate the pooled diagnostic accuracy of cfDNA fragmentomic assays in clinically validated cohorts. **Methods:** We systematically searched PubMed, Cochrane Library, and Scopus for studies evaluating blood-based cfDNA fragmentomic assays for lung cancer detection. Eligible studies were required to be lung cancer-specific, use fragmentomics-based features derived from plasma cfDNA, include an independent validation or test cohort, and report extractable binary diagnostic accuracy data. Training-only studies, multi-omic assays, and studies lacking sensitivity and specificity at a prespecified threshold were excluded. Sensitivity and specificity were jointly pooled using a bivariate random-effects model based on 2$\times$2 contingency tables, accounting for threshold effects and between-study heterogeneity. **Results:** Five studies with independent validation cohorts comprising 725 lung cancer cases and 435 non-cancer controls were included, spanning screening-eligible populations, LDCT-positive pulmonary nodules, early-stage disease, and mixed-risk cohorts. Using a bivariate random-effects model, pooled sensitivity was 87.5% (95% CI, 77.4%–93.4%) and pooled specificity was 85.7% (95% CI, 63.6%–95.4%), corresponding to a pooled positive likelihood ratio of 6.14 (95% CI, 2.34–19.26) and negative likelihood ratio of 0.146 (95% CI, 0.074–0.295), and diagnostic odds ratio of approximately 42. Moderate inter-study heterogeneity was observed (I^2=62%), largely attributable to differences in clinical setting, disease spectrum, and control composition; however, diagnostic performance remained directionally consistent across cohorts. The summary receiver operating characteristic curve demonstrated excellent overall discrimination (AUC 0.92). **Conclusions:** Across clinically validated cohorts, blood-based cfDNA fragmentomic assays demonstrated strong discriminative performance for lung cancer detection. Despite heterogeneity across study populations and clinical use cases, pooled sensitivity and specificity were robust, supporting the potential role of cfDNA fragmentomics as a noninvasive adjunct to existing screening and diagnostic strategies. Research Sponsor: None.

Diagnostic performance of cfDNA fragmentomic assays for lung cancer detection.

Measure	Estimate	95% CI
Sensitivity	87.5%	77.4–93.4
Specificity	85.7%	63.6–95.4
LR+	6.14	2.34–19.26
LR–	0.15	0.07–0.30
AUC	0.92	–

10578 **Poster Session**

Enterprise-wide implementation of multicancer detection testing across a large academic health system. First Author: Aditya Kumar Ghosh, Mayo Clinic Rochester, Rochester, MN

Background: Multicancer detection (MCD) testing using cell-free DNA methylation patterns is a novel blood-based approach to cancer screening. In 2022, Mayo Clinic implemented offering MCD testing into routine clinical practice. Prior real-world reports have been limited to single-site experiences. We evaluated enterprise-wide implementation of MCD testing across all three Mayo Clinic sites using the Mayo Clinic Platform. **Methods:** We performed a retrospective analysis of de-identified clinical data from Mayo Clinic Platform Discover, including GRAIL Galleri tests performed at Mayo Clinic sites in Rochester, MN; Scottsdale, AZ; and Jacksonville, FL. This activity did not require IRB review per 45 CFR 46.102. Demographics, test results, cancer diagnoses, and prior cancer history were extracted using a privacy-preserving protocol, with data de-identified by expert determination. ICD-10 diagnostic codes were used to identify subsequent cancer diagnoses. **Results:** A total of 8,201 Galleri tests were performed in 7,300 patients; some patients underwent repeat testing. Fifty-seven tests (0.7%) were positive. Among MCD-positive patients, cancer diagnostic codes were identified in 32 patients, yielding a positive predictive value (PPV) of 58.7%. The most common cancers identified were oropharyngeal (34.4%), lymphoid and hematopoietic (34.4%), and gastrointestinal malignancies (18.8%).Among 8,144 MCD-negative tests (99.3% of all testing performed), 423 patients (5.2%) subsequently received a cancer diagnostic code, yielding a negative predictive value of 92.5%. The most commonly identified cancers in this group were male genital organs (36.6%), urinary tract (10.6%), and thyroid or other endocrine glands (7.3%). Overall, 10.1% of patients had a prior cancer history, which was more common in MCD-positive than MCD-negative patients (22.6% vs 10.0%). Patients with positive tests were older (mean age 68.4 vs 61.5 years) and more often male (67% vs 62%). Race distribution was similar. **Conclusions:** Enterprise-wide implementation of MCD testing across diverse clinical settings is feasible within routine workflows. Over half of positive tests were associated with cancer diagnostic codes, supporting the clinical promise of MCD testing. Limitations include incomplete capture of externally diagnosed cancers and lack of cancer signal-of-origin data. The Mayo Clinic Platform enables scalable, secure analytics to support future cancer interception strategies. Research Sponsor: None.

10579 **Poster Session**

Structural disparities in early-onset colorectal cancer mortality: A national county-level analysis. First Author: Varshini Odayar, University of Michigan Medical School, Ann Arbor, MI

Background: Early-onset colorectal cancer (CRC) incidence and mortality are rising, with significant disparities by geography and socioeconomic status. We examined county-level disparities in early-onset CRC mortality (ages $<$ 55) across the United States to identify modifiable factors associated with mortality rates. **Methods:** We analyzed age-adjusted CRC mortality rates from CDC WONDER. Predictors included rurality (Rural–Urban Continuum Codes 2023: non-metro vs metro), socioeconomic factors (median income, % uninsured, % poverty from County Health Rankings 2025), demographic composition (% non-Hispanic Black, % Hispanic), health behaviors (current smoking, obesity, routine checkup from PLACES 2025), and healthcare access (gastroenterologist, primary care physician, and hospital counts from AHRF 2024–2025). Multivariable linear regression assessed associations between predictors and mortality, with continuous variables standardized to z-scores. Counties with missing or unreliable mortality data were excluded ($p < 0.05$ for significance). **Results:** The final sample included 672 counties. Mean mortality was 4.26 per 100,000 (range 1.7–11.9). Non-metro counties comprised 12.2% (n = 82). The model explained 54.8% of variance in mortality ($F = 66.5$, $p < 0.001$). Current smoking was the strongest predictor ($\beta = 0.54$ per SD, 95% CI: 0.38–0.70, $p < 0.001$), indicating a one-SD increase in smoking prevalence corresponded to a 0.54 per 100,000 higher mortality rate. Non-metro counties had 0.80 more deaths per 100,000 than metro counties (95% CI: 0.56–1.05), a 19% increase relative to the mean. Poverty ($\beta = 0.21$ per SD, $p = 0.011$), uninsured rates ($\beta = 0.20$ per SD, $p < 0.001$), and % Black ($\beta = 0.21$ per SD, $p < 0.001$) were also significant. Higher Hispanic population was associated with lower mortality ($\beta = -0.20$ per SD, $p = 0.001$). Healthcare provider variables (gastroenterologist count, primary care count, hospital count) were not significantly associated ($p \geq 0.051$). **Conclusions:** Geographic, socioeconomic, and health behavior factors accounted for 54.8% of variation in early-onset CRC mortality, with smoking showing the strongest association. Non-metro counties and areas with higher poverty, uninsured rates, and smoking prevalence had higher mortality, though these relationships are not causal. Remaining unexplained variance suggests roles for screening uptake, stage at diagnosis, treatment quality, and genetic susceptibility. Findings identify high-risk counties and highlight the need for future causal analyses to clarify pathways underlying disparities and support targeted interventions. Research Sponsor: None.

10580 **Poster Session**

Quantifying the macroeconomic burden of cancer: Global disparities in value-of-lost-welfare (VLW). First Author: Sai Varun Gadde, UCF HCA GME Consortium, Orlando, FL

Background: Cancer (CA) remains a leading global driver of disability and premature death, yet its full macroeconomic toll is rarely quantified. In this study, we estimated the global economic welfare loss attributable to all cancers in 2023 across 183 countries using a standardized Value of Lost Welfare (VLW) framework. **Methods:** We obtained country-level disability-adjusted life years (DALYs) for CA from the Global Burden of Disease Study 2023. Corresponding GDP (PPP, current international dollars) and population data were sourced from the World Bank. We calculated VLW by multiplying DALYs by a fixed monetary value of USD 14,403.29 per DALY, yielding estimates of total VLW, per-capita VLW, and VLW/GDP (%). CA-specific estimates were derived using cause-wise DALY distributions across global and regional levels. **Results:** In 2023, CA caused 268.9 million DALYs globally, resulting in a global VLW of USD 3.87 trillion—equivalent to 2.12% of global GDP, with an average per-capita economic loss of 522 billion. The largest absolute economic losses were reported in China (915.5 billion), India (458.7 billion), and the United States, followed by Japan (126.7 billion) and Brazil (108.6 billion). When adjusted for national GDP, the highest VLW-to-GDP ratios were observed in Zimbabwe (4.24%), Cambodia (4.00%), Mongolia (3.45%), India (3.09%), and Egypt (1.63%), reflecting intense economic vulnerability. Across SDI strata, high-SDI countries bore the greatest economic burden, incurring a VLW of 1.80 trillion, followed by high-middle SDI (808.7 billion), low SDI (568.0 billion), low-middle SDI (406.5 billion), and middle SDI (384.9 billion). While absolute losses were highest in high-SDI settings, VLW/GDP ratios were notably elevated in low- and low-middle SDI regions, signaling disproportionate economic strain in resource-limited contexts. By CA type, lung CA led the global burden with 672 billion in welfare losses, followed by colorectal CA (377 billion), breast CA (355 billion), stomach CA (324 billion), and esophageal CA (202 billion). **Conclusions:** The global macroeconomic cost of CA surpassed USD 3.6 trillion in 2023, with marked disparities across countries and regions. High-burden nations such as China, India, and the U.S. faced the steepest absolute losses, while several low-income countries suffered disproportionately high economic strain relative to GDP. The concentration of losses in five major CA types signals an urgent need for enhanced global investments in CA prevention, early detection, and control. Research Sponsor: None.

Regional cancer burden and economic losses in 2023.

Region	DALYs (Millions)	VLW ($ Billion)	VLW/GDP (%)
Sub-Saharan Africa	28.82	415.14	6.64
South Asia	43.72	629.68	3.48
Southeast Asia, East Asia & Oceania	89.19	1284.6	2.76
North Africa & Middle East	14.34	206.6	2.50
Latin America & Caribbean	18.39	264.91	2.36
Central/Eastern Europe & Central Asia	20.89	300.85	2.20
High Income	60.37	869.53	1.25

10581 **Poster Session**

Multimodal profiling of STIC lesions to identify precursor states with genomic features of high grade serous ovarian cancer. First Author: Duaa Al-Rawi, Memorial Sloan-Sloan Kettering Cancer Center, New York, NY

Background: High-grade serous ovarian cancer (HGSC) is a lethal gynecologic malignancy characterized by near-universal *TP53* inactivation, chromosomal instability (CIN), and frequent whole-genome doubling. Because population screening is ineffective, risk-reducing salpingo-oophorectomy (RRSO) remains the only proven risk-reduction strategy. Nonetheless, some individuals develop primary peritoneal carcinoma (PPC), and identification of serous tubal intraepithelial carcinoma (STIC) at RRSO is associated with $>$ 30-fold higher PPC risk. We sought to define the molecular steps required for HGSC initiation and identify features of high-risk STIC. **Methods:** We assembled a 201-patient cohort spanning stages of HGSC development, including normal fallopian tube epithelium, p53 signatures, STIC, and early- and advanced-stage HGSC. All specimens underwent multiplex immunofluorescence (mpIF). Forty-five samples from 36 patients were profiled using Visium HD spatial transcriptomics ($>$ 20 million 8-μm bins). We analyzed epithelial state transitions using unsupervised clustering and trajectory inference. Copy-number variation (CNV) was inferred using spatial inferCNV; CNV calls were validated with matched formalin-fixed paraffin-embedded (FFPE) single-cell whole-genome sequencing. **Results:** mpIF demonstrated lesion-to-lesion variability in cyclic GMP–AMP synthase (cGAS) staining within STIC, consistent with evolving tolerance to CIN before invasion. Spatial transcriptomic clustering identified distinct, reproducible STIC epithelial programs that mapped to histologic features. STIC programs were enriched for NFκB and TGF-β signaling and lacked evidence of the JAK/STAT activation observed in advanced HGSC. CNV inference showed that normal fallopian tube and p53 signature lesions were chromosomally stable, whereas STIC displayed broad, genome-wide alterations resembling advanced HGSC, including losses encompassing *TP53*, *BRCA1*, and *BRCA2* and amplifications of *MYC* and *CCNE1*. In a germline *BRCA2* carrier, we identified polyclonal STIC with distinct CNV profiles; trajectory analysis suggested early CNV changes within an expanded secretory population, followed by loss of chromosome 17 (*TP53*), loss of chromosome 13 (*BRCA2*), and subsequent oncogene amplifications (e.g., *MYC*). As lesions became invasive, spatial CNV profiling revealed neighborhoods of clonally related invasive cells with distinct microenvironments, including differences in fibroblast states and vascularization. **Conclusions:** A multimodal atlas of fallopian tube transformation supports a model in which *TP53* loss precedes *BRCA1/2* inactivation and indicates that STIC is genomically similar to advanced HGSC. These findings provide a framework to study early HGSC evolution, stratify STIC risk after RRSO, and inform early-interception strategies. Research Sponsor: Ovarian Cancer Research Alliance; MIG-2023-1-1012; Conquer Cancer Research; U.S. National Institutes of Health; CA281928-01.

10582 **Poster Session**

Texture and color enhancement imaging (TXI) for polyp detection in colorectal neoplasia screening: A meta-analysis of randomized controlled trials. First Author: Haroon Alamy, Desert Regional Medical Center, Inc., Palm Springs, CA

Background: Colonoscopy remains the gold standard for preventing colorectal cancer; however, variable adenoma detection rates (ADR) among endoscopists highlight the need for improved visualization technologies. Texture and Color Enhancement Imaging (TXI) is a novel image-enhanced endoscopy modality designed to optimize the visibility of mucosal lesions by enhancing surface texture and brightness. This meta-analysis evaluates the efficacy of TXI compared to standard high-definition white-light imaging (HD-WLI) in the detection of colorectal neoplasia, specifically assessing whether enhanced visualization translates to higher detection rates of adenomas and polyps in a randomized controlled setting. **Methods:** We conducted a systematic review and meta-analysis of prospective randomized controlled trials (RCTs) published between 2023 and 2025. The analysis included adult patients undergoing colonoscopy for screening, surveillance, or diagnostic indications where TXI was compared to HD-WLI during the withdrawal phase. Primary outcomes included ADR, polyp detection rate (PDR), and adenomas per colonoscopy (APC). Secondary outcomes included polyps per colonoscopy (PPC) and flat lesion detection. Statistical analysis was performed using a random-effects model (DerSimonian-Laird method). Risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI) were calculated, with heterogeneity assessed via I^2 statistics. **Results:** The analysis pooled data from four RCTs comprising 2,308 patients. The chief finding was a statistically significant 25.5% increase in the Polyp Detection Rate (PDR) with TXI compared to WLI (pooled RR = 1.255; 95% CI: 1.050–1.498; $p < 0.05$). Regarding the Adenoma Detection Rate (ADR), TXI showed a positive trend with a 22% relative increase (pooled RR = 1.220; 95% CI: 0.981–1.519); however, this did not reach statistical significance ($p > 0.05$). Analysis of Adenomas per Colonoscopy (APC) showed no significant difference (MD = 0.153; $p > 0.05$). Substantial heterogeneity was observed across outcomes ($I^2 > 60\%$), suggesting variability in endoscopist experience or study populations. **Conclusions:** Texture and Color Enhancement Imaging demonstrates clear superiority over white-light imaging for overall polyp detection, establishing it as a promising tool for identifying colorectal neoplasia. While TXI significantly improved PDR, the improvement in ADR showed a strong positive trend that did not reach statistical significance, likely due to high between-study heterogeneity. These findings suggest that TXI enhances lesion visibility, particularly for general polyps, but further large-scale RCTs are necessary to definitively establish its impact on adenoma detection and long-term interval cancer prevention. Research Sponsor: None.

10583 **Poster Session**

GLP-1 receptor agonist therapy and cancer risk and mortality in patients with moderate CKD: A national matched cohort study of 58,000 patients. First Author: Muneeb Asad, Texas Tech University Health Sciences Center Paul L. Foster School of Medicine, EL Paso, TX

Background: Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been associated with reduced mortality in patients with Type 2 Diabetes Mellitus (T2DM) and may lower cancer risk. However, the impact of GLP-1 RAs on cancer incidence and mortality in patients with chronic kidney disease (CKD) remains understudied. Thus, in this study we evaluated whether GLP-1 RA use modifies cancer risk and mortality in a contemporary national cohort of patients with moderate CKD. **Methods:** We performed a retrospective cohort study using the TriNetX Research Network, identifying adults aged 18–90 years with T2DM and newly diagnosed stage-3 CKD between January 2015 and February 2025. Patients with prior malignant neoplasms or end-stage renal disease were excluded. Exposure was defined as a prescription for a GLP-1 RA within 90 days before CKD diagnosis; controls had no documented GLP-1 RA use. Outcomes were evaluated beginning 90 days after the index CKD diagnosis to reduce reverse-causation and immortal-time bias. Our primary outcome was any malignant neoplasm. Our secondary outcomes were site-specific malignant neoplasms (colorectal, lung, liver, kidney, pancreatic, breast, and prostate) as well as all-cause mortality. We performed 1:1 propensity score matching balancing demographics, comorbidities, laboratory values (hemoglobin A1c and estimated glomerular filtration rate), and cardiometabolic medications. After matching, we calculated absolute risks, risk differences, hazard ratios, risk ratios, and 95% confidence intervals. Statistical significance was defined as $p < 0.05$. **Results:** After matching, 28,948 patients remained in each group. GLP-1 RA use was associated with significantly lower all-cause mortality (8.6% vs 15.0%; HR 0.57; 95% CI, 0.546-0.599; $p < 0.001$). Overall malignant neoplasm incidence was significantly lower with GLP-1 RA use (7.0% vs 7.7%; RR 0.90; $p < 0.001$). Among site-specific malignancies, the GLP-1 RA group demonstrated lower incidence of lung cancer (0.5% vs 0.8%; RR 0.56; $p < 0.001$), colorectal cancer (0.5% vs 0.7%; RR 0.74; p = 0.006), and liver cancer (0.3% vs 0.4%; RR 0.63; p = 0.001). Pancreatic cancer (0.2% vs 0.3%; RR 0.89; p = 0.46), kidney cancer (0.5% vs 0.6%; RR 0.98; p = 0.87), prostate cancer (1.1% vs 1.0%; RR 1.08; p = 0.32), and breast cancer (0.7% vs 0.7%; RR 1.11; p = 0.30) did not differ significantly based on GLP-1 RA receipt. **Conclusions:** In patients with T2DM and stage-3 CKD, GLP-1 RA therapy was associated with substantially lower mortality and reduced incidence of several major malignancies, particularly lung, colorectal, and hepatocellular cancers. These findings highlight a potential role for GLP-1–mediated metabolic modulation in cancer prevention among high-risk populations. Prospective studies are warranted to clarify mechanisms and confirm these observations. Research Sponsor: None.

10584 **Poster Session**

Non-random patterns of multiple primary malignancies in the era of cancer survival. First Author: Thomas George, Boston University Chobanian & Avedisian School of Medicine and Boston Medical Center, Boston, MA

Background: Improved cancer therapies have increased survival, placing survivors at risk for subsequent primary cancers, yet the epidemiology of multiple primary cancers (MPC) is poorly defined. **Methods:** Using the VA Cancer Registry (2003–2023), we quantified MPC frequency, classified cancers by SEER ICD-O-3 codes and histology, and analyzed incidence and expected versus observed occurrence. **Results:** Among 822,564 veterans with cancer, 11.1% (n=91,279) developed ≥2 primary cancers. The frequencies of patients with 2, 3, 4, or ≥5 MPC were 81715 (9.9%), 8655 (1.1%), 800 (0.1%), and 109 (0.01%), with similar relative risks across successive cancers. Interestingly, the median age at first cancer was similar across groups (67.3 years for 1 cancer; 66.6, 65.8, and 65 years for 2, 3 and 4 cancers). In contrast, intervals between successive cancers progressively shortened (2.7 years – 2 cancers; 2.5 and 1.8 years – 3 cancers; 2.2, 1.9, and 1.4 years – 4 cancers), suggesting prior cancer influences the risk of subsequent cancer. The 7 most common first and subsequent cancers were prostate, bladder, lung, colon, melanoma, kidney, and oral cavity cancers. We identified three etiologic patterns underlying MPC. First, exposure-related cancers, clustered as expected, lung cancer was the most common 2nd and 3rd cancer after bladder (n=1850 and 231) and oral cavity (n=1581 and 148) cancers, suggesting a relationship to smoking. Second, genetically predisposed cancers did not cluster, likely reflecting the older population. Third, therapy-related cancers increased, with acute myeloid leukemia (AML)/acute lymphoblastic leukemia (ALL) standard rates rising from 0.02/0.003 (1st) to 39.01/3.19 (AML) and 5.04/0.03 (ALL) as 2nd and 3rd primary cancers. Interestingly, the frequency of prostate cancer and chronic lymphocytic leukemia (CLL) declined with increasing cancer order, consistent with earlier detection through established screening practices, and in contrast, lung cancer and multiple myeloma (MM) frequency increased as subsequent cancers, suggesting more complex etiologies, including aging-related risk. **Conclusions:** In this large VA registry analysis, over 11% of cancer survivors developed MPC with consistent patterns of occurrence, shortening intercancer intervals, and non-random clustering by exposure-, therapy-, and disease-specific factors. These findings underscore the need for risk-adapted surveillance and long-term survivorship strategies that account for shared etiologies and treatment-related risks rather than assuming stochastic occurrence. Research Sponsor: None.

Frequency of a cancer as MPC.

		1st primary	2nd primary	3rd primary	4th primary
Pts with 2 cancers	Prostate	29.4%	14.1%		
	CLL	2.3%	1.1%		
	Lung	7.8%	20%		
	MM	1.1%	1.7%		
Pts with 3 cancers	Prostate	28.1%	15.6%	9.3%	
	CLL	2.8%	2.2%	1%	
	Lung	5.4%	11.7%	20.6%	
	MM	0.8%	1.5%	2%	
Pts with 4 cancers	Prostate	26%	14.8%	12.1%	7.3%
	CLL	2.4%	1.8%	1.9%	1.4%
	Lung	5.4%	8.4%	13.9%	22.9%
	MM	1%	1.1%	1.8%	2.1%

10585 **Poster Session**

Differential risk patterns of secondary breast cancer in medullary versus papillary thyroid carcinoma survivors: A SEER-based analysis. First Author: Li Liu, The Second People's Hospital of Hefei, Hefei, China

Background: Prior studies suggest that thyroid cancer (TC) survivors may have an elevated risk of secondary malignancies. However, whether this risk differs by TC histology, specifically with breast cancer (BC), remains unclear. We aimed to investigate the association between TC subtype—papillary thyroid carcinoma (PTC) versus medullary thyroid carcinoma (MTC)—and subsequent BC risk, adjusting for demographic factors. **Methods:** We conducted a retrospective cohort study using the SEER (2000–2022), including adults with a primary, microscopically confirmed PTC or MTC. Subsequent BC occurrence was defined as a binary outcome (yes/no). Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) for MTC versus PTC, controlling for age (<50 vs ≥50 years), sex, and race. Stratified analyses by age and race were also performed. Stata 15 was used for statistical analyses. **Results:** 14,840 patients (14,563 PTC, 277 MTC) were included. MTC patients were older (mean 59.08±12.66 vs 56.16±12.98 years, p<0.001) and had a higher proportion of males (44.4% vs 29.4%, p<0.001). The overall incidence of secondary BC was lower in MTC patients (7.6% vs 22.5%, p<0.001). In unadjusted logistic regression, MTC was associated with significantly lower BC risk (OR=0.28, 95% CI: 0.18–0.44, p<0.001). After adjustment, MTC remained significantly protective (aOR=0.34, 95% CI: 0.22–0.55, p<0.001). Stratified analyses demonstrated consistent findings across age groups (<50: aOR=0.10, 95% CI: 0.03–0.42; ≥50: aOR=0.34, 95% CI: 0.21–0.54), , as well as white and Hispanic patients. **Conclusions:** Survivors of MTC have a substantially lower risk of developing secondary BC compared to PTC survivors. This association persists after adjustment for age, sex, and race, and is consistent across age and most racial subgroups. However, different BC types were not assessed due to limited number of BC patients among MTC survivors, and the small MTC sample size and potential survival differences between groups may affect the results. These findings highlight a possible effect of TC subtype on BC risk, suggesting the potential influence of underlying biological or genetic mechanisms. Research Sponsor: None.

Baseline demographic characteristics of patients with papillary and medullary thyroid carcinoma.

Characteristic	Papillary Thyroid Carcinoma (PTC) (N=14,563)	Medullary Thyroid Carcinoma (MTC) (N=277)	P-value
Age at Diagnosis			0.0002*
Mean ± SD, years	56.16 ± 12.98	59.08 ± 12.66	
Median, years	57	61	
Sex, n (%)			<0.001†
Female	10,288 (70.6)	154 (55.6)	
Male	4,275 (29.4)	123 (44.4)	
Race, n (%)			0.015†
White	10,263 (70.5)	197 (71.1)	
Black	921 (6.3)	15 (5.4)	
American Indian	77 (0.5)	1 (0.4)	
Asian	1,379 (9.5)	13 (4.7)	
Hispanic	1,903 (13.1)	50 (18.1)	

SD: Standard Deviation.
*P-value from two-sample t-test (equal variances assumed).
†P-value from chi-square test for the overall distribution across categories.

10586 **Poster Session**

Association of prior SARS-CoV-2 infection with advanced cancer presentation in newly diagnosed solid tumors: A real-world data analysis. First Author: Anushareddy Muddasani, University of Arkansas for Medical Sciences, Little Rock, AR

Background: Emerging evidence suggests that the impact of SARS-CoV-2 infection may extend beyond acute respiratory illness, with potential implications for cancer biology. Recent proteomic analyses and reviews have highlighted several ways in which SARS-CoV-2 might interact with host pathways relevant to oncogenesis, tumor progression, and cellular plasticity. Taken together, these findings support a plausible biological rationale that COVID-19 infection may influence the clinical behavior or progression of solid tumors, potentially leading to diagnosis at later stages or the emergence of more aggressive phenotypes. In this study, we use real-world data from the TriNetX US Collaborative network to test the hypothesis that patients with solid tumors who have had COVID-19 are more likely to present with advanced-stage disease compared to those without a history of SARS-CoV-2 infection. **Methods:** We conducted a retrospective cohort study of adults (≥18 years) with newly diagnosed solid tumors, including breast, lung, colorectal, and prostate cancers, between January 1, 2021, and December 1, 2025. Patients were categorized based on documented SARS-CoV-2 infection prior to cancer diagnosis (COVID-positive vs COVID-negative), defined using ICD-10 codes and laboratory-confirmed PCR or antigen testing. Patients with any prior cancer diagnosis were excluded. The primary outcome was aggressive presentation, defined as AJCC Stage IV, M1 classification, or ICD-10 codes C77–C79 within 90 days of diagnosis. To reduce confounding, 1:1 propensity score matching was performed based on age, sex, race, ethnicity, cancer type, and comorbidities, including obesity, chronic lung disease, chronic kidney disease, diabetes, and hypertension. **Results:** After 1:1 propensity score matching, 201,131 patients were included in each cohort. Aggressive cancer presentation occurred in 16.8% of COVID-positive patients compared with 15.1% of COVID-negative patients. COVID-positive patients had a higher risk of aggressive disease presentation, corresponding to an absolute risk increase of 1.73% (95% CI, 1.50–1.96) and a relative risk of 1.11 (95% CI, 1.10–1.13). The odds of aggressive presentation were also higher among COVID-positive patients (OR, 1.14; 95% CI, 1.12–1.16; $p < 0.0001$). **Conclusions:** Prior COVID-19 infection was associated with a higher likelihood of advanced and metastatic cancer presentation at diagnosis, even after adjustment for demographic factors and comorbidities. These findings highlight the potential long-term oncologic impact of the COVID-19 pandemic and warrant further investigation. Research Sponsor: None.

10587 **Poster Session**

Distinct immunogenomic features of cancers arising in solid organ transplant recipients. First Author: Shyfuddin Ahmed, National Cancer Institute, National Institutes of Health, Rockville, MD

Background: Solid organ transplantation recipients (SOTRs) are at increased risk of cancer due to long-term immunosuppressive therapy to prevent organ rejection. However, the immunogenomic characteristics of cancers arising in SOTRs remain poorly defined, limiting evidence-based treatment decisions, particularly regarding immunotherapy. **Methods:** Next-generation sequencing (NGS) of tumor tissue for DNA (592-gene panel/whole exome) and RNA (whole transcriptome) was carried out at Caris Life Sciences for SOTRs (n=1,024) and individuals without a transplant matched by age, sex, and cancer type (10:1 ratio, n=10,240). Immune cell infiltration in the tumor microenvironment (TME) was estimated by quanTIseq. Interferon-gamma (IFN-γ) signaling was assessed by a 10-gene transcriptomic signature. Tumor mutational burden (TMB) was assessed by NGS. Microsatellite instability (MSI) was assessed by immunohistochemistry (IHC) and NGS, and PD-L1 expression by IHC. Among SOTRs treated with immunotherapy, overall survival was assessed from insurance claims and calculated from treatment initiation to last contact. **Results:** The median age at sample collection was 65 years, with kidney recipients comprising the majority of SOTR cases (59.6%). Non-small cell lung cancer (NSCLC) was the most common malignancy (18.5%), followed by colorectal cancer (CRC, 10.5%). For all tumors combined, SOTRs exhibited significantly reduced adaptive immune cell infiltration in the TME, including $CD8^+$ T-cells (SOTR vs non-SOTR median: 0.11% vs 0.23%), regulatory T-cells (1.60% vs 2.10%) and B-cells (3.69% vs 3.91%); no significant differences were observed in innate immune cell fractions except for myeloid dendritic cells (0.64% vs 0.79%). While IFN-γ signatures were similar among all SOTRs and non-SOTRs, SOTRs had significantly lower IFN-γ for NSCLC and cutaneous squamous cell carcinoma (cSCC). Median TMB was significantly higher in SOTRs than non-SOTRs for NSCLC, colorectal cancer (CRC), pancreatic cancer, cSCC, melanoma, and esophageal cancer. MSI was more common in SOTRs overall (4.9% vs 1.9%; $p<0.0001$) and for CRC (15.8% vs. 6.8%; $p<0.0001$). PD-L1 positivity was less common in SOTRs than non-SOTRs (12.4% vs 18.6%; p=0.021). Finally, among SOTRs treated with immunotherapy, those with high TMB ($\geq$10 mutations/Mb) tended to have better survival than those with low TMB (hazard ratio 0.79, 95%CI 0.47-1.34, p=0.374). **Conclusions:** Despite higher prevalence of tumors with high TMB and MSI for select cancer types, SOTRs had lower adaptive immune infiltration and IFN-γ signaling within the TME, likely reflecting the immunosuppressive anti-rejection treatment. Our findings highlight distinct immunogenomic features of transplant-associated cancers and provide biologic rationale for further study of immunotherapy strategies in carefully selected SOTRs. Research Sponsor: None.

10588 **Poster Session**

PCSK9 inhibitors and association with lower risk of metastasis. First Author: Gin Yi Lee, Brigham and Women's Hospital, Boston, MA

Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that regulates degradation of membrane proteins including the low-density lipoprotein (LDL) receptor and major histocompatibility complex class I (MHC-I) independently. Beyond lipid metabolism, preclinical studies have shown that PCSK9 inhibition reduces metastasis in animal models, suggesting potential to suppress tumor cell proliferation, migration, and immune evasion. However, population-level evidence across malignancies is limited. We evaluated whether PCSK9 inhibitor (PCSK9i) use is associated with risk of cancer metastasis in a large real-world cohort. **Methods:** In this new-user, active-comparator cohort study using the TriNetX U.S. Collaborative Network ($\approx$134 million patients), eligible patients were adults who initiated PCSK9i or statins alone for hyperlipidemia between 01/01/2015 and 01/01/2025 and subsequently received a cancer diagnosis. Index date was first prescription of PCSK9i or statin, with follow-up period continued until occurrence of study outcomes. To reduce reverse causation and early detection bias from intensified workup around drug initiation, patients with any cancer diagnosis within 6 months after index were excluded. 1:1 propensity score matching (PSM) balanced pre-index demographics, ASCVD and liver comorbidities, cancer screening procedures (low-dose chest CT, Pap smear, colonoscopy), BMI, and LDL. Primary outcome was time to any metastatic cancer (ICD-10 C77–C79); secondary outcomes were site-specific metastases (liver, lung, bone, brain, lymph node, adrenal gland). Cox proportional hazards models estimated hazard ratios (HRs) with 95% CIs. **Results:** Among 1,149,843 adults newly prescribed PCSK9i or statin (mean age 61.7 years, SD 10.6), median follow-up was 2,926 days. After 1:1 PSM, 8,674 patients remained in each cohort with balanced baseline characteristics (all standardized mean differences <0.1). Metastatic cancer was diagnosed in 435 PCSK9i patients versus 741 statin patients. The overall hazard of metastasis did not differ significantly (HR 0.96, 95% CI 0.85–1.08). In site-specific analyses, PCSK9i use was associated with lower hazards of liver metastasis (HR 0.64, 95% CI 0.50–0.85) and lung metastasis (HR 0.78, 95% CI 0.65–0.94); hazards for lymph node, brain, adrenal, and bone metastases were similar between groups. Sensitivity analyses accounting for competing risk of death showed consistent directionality. **Conclusions:** In this nationwide cohort study, overall metastatic risk was similar between PCSK9i and statin-only users, but PCSK9i use was associated with lower hazards of liver and lung metastases. Further mechanistic and prospective investigation are warranted to elucidate the role of PCSK9 inhibition in tumor progression and metastasis. Research Sponsor: None.

10589 **Poster Session**

The effects of the COVID-19 pandemic on cancer incidence and cancer-specific mortality. First Author: Reba Dhillon, Trinity Health Ann Arbor, Ypsilanti, MI

Background: The 2020 COVID-19 pandemic had a significant impact on cancer screening rates and cancer-related outcomes. The purpose of our study was to determine how the pandemic has affected cancer incidence, incidence by Surveillance, Epidemiology and End Results (SEER) stage, and cancer-specific mortality for the most common cancers in incidence and cancer-specific mortality. **Methods:** The data for our population-based cohort study was accessed by permission from the SEER dataset. We aggregated data for incidence and cancer-specific mortality regarding the leading ten cancers in incidence and cancer-specific mortality, plus cervical cancer, between January 1, 2017 and December 31, 2022 and further divided this time period into two 36-month pre-pandemic and post-pandemic groups. Demographic variables were collected for stratified analyses. Poisson regression models were used to estimate incidence and mortality rates for each cancer type, incorporating the natural logarithm of the total population as an offset term to account for differences in population size. **Results:** Nine of eleven cancers showed significantly higher IRRs (incidence rate ratios) for distant SEER stages during the 36-month post-pandemic period. Most importantly, several cancers with established screening modalities had significantly increased IRRs for distant SEER stage of disease including prostate cancer (IRR 1.175, 95% CI: 1.155-1.195, $p<0.001$), breast cancer (IRR 1.060, 95% CI: 1.040-1.080, $p<0.001$), and colorectal cancer (IRR 1.034, 95% CI: 1.020-1.048, $p<0.001$). Cancer-specific mortality showed significantly increased post-pandemic mortality rate ratios (MRRs) for pancreatic cancer (MRR 1.049, 95% CI: 1.041-1.056, $p<0.001$), prostate cancer (MRR 1.042, 95% CI: 1.032-1.051, $p<0.001$), and liver cancer (MRR 1.026, 95% CI: 1.016-1.036, $p<0.001$). Lung cancer (MRR 0.931, 95% CI: 0.927-0.935, $p<0.001$), Non-Hodgkin's Lymphoma (MRR 0.972, 95% CI: 0.961-0.983, $p<0.001$) and breast cancer (MRR 0.989, 95% CI: 0.981-0.996, p=0.004) all had significantly lower cancer-specific mortality in our post-pandemic period. **Conclusions:** In this large population-based cohort, we observed a shift towards more distant SEER stage cancer diagnoses in the post–pandemic period. The increase in advanced-stage diseases reflects a higher burden of disease and is particularly concerning for cancers with proven screening benefit. These findings suggest persistent downstream effects of disruptions in routine healthcare and cancer screening which have added to the public health crisis of the COVID-19 pandemic. Research Sponsor: None.

10590 **Poster Session**

Association of SGLT2 inhibitors and GLP-1 receptor agonists or DPP-4 inhibitors with incident cancer in patients with type 2 diabetes. First Author: Nikitha Vobugari, University of Minnesota, Minneapolis, MN

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) exert potential anti-tumor effects. Emerging data suggest SGLT2i are associated with reduced cancer incidence in type 2 diabetes (T2D), while incretin-based therapies show mixed results varying by cancer type. Among patients with T2D, we tested that hypothesis that use of SGLT2i, as compared to GLP-1 receptor agonists (GLP-1RA), and dipeptidyl peptidase-4 inhibitors (DPP-4i), would be associated with lower risk of overall and individual cancer types. **Methods:** Matched cohort study using MarketScan US claims database (2016–2022). T2D patients with $\geq$1 metformin prescription and $>$90 days enrollment before 2nd line therapy initiation were included. SGLT2i users were matched with up to 5 users of other therapies by age, sex, enrollment, and 2nd line therapy initiation dates. ICD codes were used to identify cancer. Cox models adjusted for demographics, comorbidities, and medications. **Results:** Among 365,494 matched patients (mean$\pm$SD age 54.2$\pm$10.0 years, 48.5% female), 5,422 incident cancers occurred over median 1.43 (maximum 6.75) years follow-up. Cohort included 133,210 SGLT2i users (empagliflozin 55%, dapagliflozin 32%, canagliflozin 12%) and 232,284 comparators (GLP-1RA 60.4%, DPP-4i 39.6%). SGLT2i users showed modestly lower composite cancer risk versus other therapy users [Hazard ratio (HR) 0.94, 95% CI 0.89-0.99]. Compared with DPP-4i use, SGLT2i use demonstrated 10% lower cancer risk (HR 0.90, 95% CI 0.85-0.97), but showed no significant difference versus GLP-1RA use (HR 0.97, 95% CI 0.91-1.04). Analyses by cancer type revealed no significant differences in HR for breast (0.92, 0.84-1.04), prostate (0.96, 0.84-1.08), colorectal (0.96, 0.82-1.12), lung (0.95, 0.78-1.16), pancreatic (1.04, 0.84-1.28), hepatocellular (1.01, 0.76-1.33), renal cell (0.92, 0.76-1.11), endometrial (1.01, 0.79-1.29), or thyroid cancers (0.84, 0.66-1.06). Cancer risk was comparable across individual SGLT2i($p>0.05$). **Conclusions:** SGLT2i demonstrated a 10% reduction in overall cancer risk versus DPP-4i and comparable efficacy to GLP-1RA, reinforcing SGLT2i's potential oncologic benefits. No associations were observed with individual cancer types, though interpretation is nuanced due to poor precision and short follow-up. Comparable risk among individual SGLT2i suggest a class-wide effect. Future prospective studies with extended follow up are needed to validate these associations and clarify whether SGLT2i offer meaningful cancer risk reduction beyond their established cardiometabolic benefits. Research Sponsor: None.

Hazard ratios (95% CI) for incident cancer, Marketscan databases, 2016-2022.

	N (events / total)	HR (95% CI)
SGLT2i vs. DPP-4i		
SGLT2i	1,559 / 93,494	0.90 (0.85 - 0.97)
DPP-4i	1,749 / 93,494	Ref
SGLT2i vs. GLP-1RA		
SGLT2i	1,699 / 123,955	0.97 (0.91 - 1.04)
GLP-1RA	1,757 / 123,955	Ref

10591 **Poster Session**

Predictors of EGFR-mutant primary lung adenocarcinoma. First Author: Lauren Kriger Groner, University of Miami, Miami, FL

Background: The proportion of lung cancer cases in individuals who have never smoked (INS) is increasing. Most of these cases are adenocarcinoma (AC) harboring Epidermal Growth Factor Receptor (EGFR) mutations. As predictors of AC and mutational status (EGFR positive [EGFRp] vs EGFR negative [EGFRn]) are incompletely elucidated, we sought to identify demographic, clinical, and imaging predictors of EGFRp AC. **Methods:** Data were obtained from Weill Cornell's Lung Cancer Database, integrating EGFR mutation status derived from genomic testing, validated natural language processing of unstructured clinical data, and individual and area-level predictors from a large New York City health system. We included patients with early stage, surgically resected primary lung AC, allowing for uniform, robust pathologic and genomic characterization. Lesions were identified on computed tomography (CT) prior to diagnosis The primary outcome was EGFR positivity. LASSO-penalized logistic regression with 10-fold cross-validation was used to identify key predictors in high-dimensional, correlated data. Model performance was evaluated using cross-validated AUC and classification accuracy. **Results:** Among 1145 adults with primary lung AC (312 subsolid nodules [SSNs] and 833 solid nodules; mean age 69.9 [SD, 9.6]), 58.1% were female and 75.4% had a history of smoking. EGFRp ACs (vs EGFRn) were more likely to present as SSNs (39.3% vs 21.7%, $p<0.001$) and occur in women (63.6% vs 55.7%, p=0.013), Asian patients (32.7% vs 8.4%, $p<0.001$), and INS (44.9% vs 15.3%, $p<0.001$). Those with EGFRp AC were less likely to meet USPSTF lung cancer screening (LCS) criteria (12.5% vs 36.0%, $p<0.001$) and had lower prevalence of chronic obstructive pulmonary disease, other pulmonary disease, and weight loss at presentation; $p<0.05$. LASSO-selected predictors of EGFR positivity included SSN density and >1 SSN on CT, former smoking status, family history of LC, and higher exposure to ambient air pollutants (PM2.5, NO2, O3). The model demonstrated good discrimination (AUC 0.77, 0.77-0.78). In the SSN subgroup, new LASSO-selected features positively associated with EGFR positivity included right middle lobe location and lobulated margins on CT and SO2 exposure. Cystic morphology, reticulation, and a new or growing solid component on CT were inversely associated with EGFR positivity. **Conclusions:** In a robust genomically linked and clinically, radiologically, and environmentally enriched dataset, we identified distinct demographic characteristics (female sex, Asian race, family history of LC), CT features (SSN density, multiplicity, lobulated margins), and environmental exposures (PM2.5, NO2, O3, SO2) that may predict EGFR positivity. Moreover, three-fold fewer adults with EGFRp AC met USPSTF LCS criteria. These findings support integrating imaging and non-tobacco risk factors to inform lung AC risk stratification, genomic testing, and more inclusive screening strategies. Research Sponsor: Weill Cornell Medicine Meyer Cancer Center.

10592 **Poster Session**

Association of sociodemographic, environmental, and health factors with early-onset cancer in a diverse urban cohort. First Author: Devon Kathleen Dietrich, The University of Chicago Pritzker School of Medicine, Chicago, IL

Background: Early onset cancer (EOC; diagnosed before age 50) is rising globally, yet its drivers are incompletely understood, especially in diverse community-based populations. We examined sociodemographic, environmental, and health factors associated with EOC in the community-based Chicago Multiethnic Prevention And Surveillance Study (COMPASS) cohort spanning 72 Chicago neighborhoods. **Methods:** This nested case-control study within COMPASS matched EOC cases to controls without cancer 1:2 by age and sex. Standardized mean differences (SMD) compared sample characteristics. Conditional logistic regressions evaluated EOC associations with odds ratios (OR) and 95% confidence intervals (CI), adjusted for race/ethnicity. Meaningful imbalance was defined as $SMD>0.2$ and statistical significance as $p<0.05$. **Results:** Among 13,309 COMPASS participants, 265 EOC cases were matched to 530 controls. While the full sample was well balanced by sex (51.4% male), cases were predominantly female (72.8%) and non-Hispanic Black (72.3%). Breast (28.3%) and cervical (16.2%) cancers were most reported. A greater proportion of cases identified as unemployed/disabled but were also college educated and with incomes ≥$35,000 (SMD=0.382, 0.326, 0.267). Parental cancer history was more common in cases (SMD=0.504). No imbalances were observed in neighborhood-level characteristics, including area deprivation index, particulate matter concentration, and healthcare access strain. Cases reported more recent mammography and prostate-specific antigen screening (SMD 0.385, 0.407) but not pap smears (SMD=0.195). Cigarette use did not differ (SMD=0.141). Cases had higher prevalence of type 2 diabetes (T2D), anxiety, and depression (SMD=0.216, 0.302, 0.242), and lower prevalence of allergies (SMD=0.229). EOC was associated with parental cancer history (OR=3.62, CI 2.31-5.67, $p<0.001$), T2D (OR=1.65, CI 1.02-2.69, p=0.043), and anxiety (OR=2, CI 1.24-3.23, p=0.005), but not sociodemographic or neighborhood factors. **Conclusions:** In this diverse cohort, EOC was associated with multiple factors, including family cancer history, breast/prostate screening, and select health comorbidities. No associations were observed with reported neighborhood-level environmental metrics, current tobacco use, or cervical cancer screening. Our results highlight challenges in measuring sociodemographic and environmental contributors to EOC. Our results align with existing hypotheses on cancer development: familial risk, the potentially protective role of allergies, and T2D-related cancer risk. While causality cannot be inferred, the observed EOC-screening and EOC-anxiety associations warrant further investigation with longitudinal, multilevel research to better define EOC drivers and inform EOC prevention and detection strategies. Research Sponsor: None.

10593 **Poster Session**

Racial differences in clinical, genomic, and survival outcomes in colorectal cancer. First Author: Nour Maher Mustafa, University of Jordan, Amman, Jordan

Background: Racial differences influence colorectal cancer incidence, biology, and survival, but the clinical and genomic drivers remain unclear. This study evaluates race-based variation in clinical features, metastatic patterns, and key mutations in a large real-world cohort to improve risk stratification and promote equitable treatment. **Methods:** Clinical and genomic data were obtained from MSK-CHORD via cBioPortal, including patients identified as Asian, White, or Black. Variables were analysed in RStudio. Group differences were assessed using chi-square, Fisher's exact tests, or Kruskal–Wallis. Survival was analysed with Kaplan–Meier and Cox models. Significance was set at $p < 0.05$. **Results:** Among 5,168 colorectal cancer patients (White 83.9%, Asian 8.8%, Black 7.4%), several clinical and genomic features varied. Age differed significantly ($p < 0.001$), with Asians and Blacks diagnosed younger (median 58 y vs. 61 y) than Whites. Gender distribution was similar (p = 0.303). MSI-instability varied (p = 0.0321), lowest in Asians (7.7%) and Blacks (8.3%), and highest in Whites (11.9%). Right-sided tumours differed ($p < 0.001$), being least common in Asians (23.7%) and most common in Blacks (40.8%). Stage at diagnosis was similar (p = 0.0961). TMB differed modestly (p = 0.042): 5.87 in Asians vs. 6.05 in Black and White patients. FGA showed similarly small variation (p = 0.046): 0.17 in Asians, 0.16 in Blacks, and 0.15 in Whites. Liver metastases varied by race ($p < 0.001$): Asians 52%, Blacks 66%, Whites 56%. Reproductive organ involvement differed (p = 0.012): Asians 25%, Blacks 27%, Whites 20%; all other metastatic sites showed no differences ($p > 0.05$). Overall survival varied significantly ($p < 0.001$), highest in Asians (71.6 months) and Whites (54.3 months) and lowest in Blacks (32.3 months); Asians had similar mortality risk to Whites (HR 0.94), whereas Blacks had higher risk (HR 1.44). Genomic variation was notable: KRAS ($p = 1.6\times10^{-7}$) was highest in Blacks (56.8%), TP53 ($p < 0.001$) was highest in Asians (81.5%), and BRAF (p = 0.0046) was lowest in Blacks (7.1%), with no other genes differing. **Conclusions:** Racial differences were evident across outcomes. Black patients had the highest KRAS mutations and worst survival; Asians had the highest TP53 rates and best survival; Whites had the most MSI-H tumours. Other clinical features were similar. These patterns suggest biologic differences relevant to risk and treatment. Research Sponsor: None.

10594 **Poster Session**

Progestin-only implant and breast cancer risk in adolescents and premenopausal women: A systematic review and meta-analysis. First Author: Angela Theresa Zuffo Yabrude, Universidade Regional de Blumenau, Blumenau, Santa Catarina, Brazil

Background: Progestin-only long-acting reversible contraception via subdermal etonogestrel implants (Implanon/Nexplanon) is widely used. However, the breast cancer (BC) risk signal potentially attributable to implant exposure remains under-characterized, limiting evidence-based, shared contraceptive counseling. **Methods:** We systematically searched PubMed/MEDLINE, Embase, and the Cochrane Library and screened reference lists for observational cohort and case-control studies comparing etonogestrel/progestin-only implant exposure versus non-use in adolescents and reproductive-aged/premenopausal women (as defined by each study) without prior BC. Studies restricted to hereditary breast cancer predisposition cohorts (BRCA1/2 pathogenic variant carriers) were excluded. The primary endpoint was incident BC (invasive with/without in situ). Maximally adjusted estimates were extracted and harmonized to odds ratios (ORs). Risk of bias was assessed using ROBINS-E. Pooled estimates were generated using inverse-variance random-effects meta-analysis. Heterogeneity was quantified with I2 and Tau2. **Results:** Five studies met inclusion criteria, including three nationwide cohort studies from Denmark/Sweden and two nested case–control studies from the UK and Australia. Across cohort studies, implant exposure contributed 1,659,309 person-years of follow-up with 510 incident BC events. The largest case-control dataset included 67,470 BC cases. Study-specific adjusted ORs ranged from 0.93 to 1.24. In pooled analysis, implant exposure was associated with an increased risk of incident BC (OR 1.23. 95% CI 1.19–1.27, $P < 0.0001$), with no between-study heterogeneity (I2 = 0%, Tau2 = 0). **Conclusions:** In large, contemporary population-based observational studies excluding hereditary breast cancer predisposition cohorts, use of etonogestrel/progestin-only subdermal implants is consistently associated with a modestly increased risk of incident breast cancer (~23%) compared with non-use. While the absolute risk increase is likely small in younger women, the consistent signal across study designs supports its relevance for individualized risk–benefit discussions and shared contraceptive counseling in routine clinical practice. Research Sponsor: None.

Study (Year)	Design / Country	Population	Implant Type	Odds Ratio (95% CI)
Mørch et al. (2017)	Nationwide cohort, Denmark	Women 15-49 y	Progestin-only	0.93 (0.48-1.80)
Fitzpatrick et al. (2023)	Case-control, UK	Women 16-39 y	Progestin-only	1.22 (0.93-1.60)
Hadizadeh et al. (2025)	Register-based cohort, Sweden	Women 13-49 y	Etonogestrel	1.22 (1.11-1.35)
Hultstrand et al. (2022)	Nationwide cohort, Sweden	Women 15-34 y	Etonogestrel	1.22 (0.98-1.52)
Tuesley et al. (2025)	Case-control, Australia	Women 20-55 y	Etonogestrel	1.24 (1.17-1.32)

10595 **Poster Session**

Endocrine therapy non-adherence and recurrence risk in patients with breast cancer and major depressive disorder. First Author: Maya Aboumrad, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Background: We evaluated whether non-adherence to oral endocrine therapy explains the increased hazard of recurrence among women with major depressive disorder (MDD) and estrogen receptor-positive breast cancer. **Methods:** We established a retrospective cohort of veteran women (age ≥18 years), with and without MDD, diagnosed with early-stage invasive estrogen receptor-positive breast cancer between 2010-2019 within the United States Veterans Affairs Healthcare System with follow-up through 2022. We assessed adherence to oral endocrine therapy among continuous users (no treatment gaps ≥ 6 months) over two-years (N = 2,722) and five-years (N = 1,666). Adherence was measured using the proportion of medication days covered and evaluated across thresholds from ≥20%-100%. We used multivariable competing-risks regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the statistical interaction between MDD and endocrine therapy adherence on breast cancer recurrence, adjusting for sociodemographic, clinical, and prognostic factors. **Results:** The hazard of breast cancer recurrence significantly differed between adherent and non-adherent women with MDD beginning at adherence thresholds of ≥60% over two-years and ≥40% over five-years. At these minimal adherence thresholds, breast cancer recurrence was higher for women with MDD who were non-adherent to endocrine therapy over two-years (HR = 1.65; 95% CI = 1.02-2.62) and five-years (HR = 2.10; 95% CI = 1.16-3.79) compared with adherent women without MDD. In contrast, women with MDD who remained adherent over two-years (HR = 1.21; 95% CI = 0.91-1.64) and five-years (HR = 1.38; 95% CI = 0.85-2.22) had hazards of breast cancer recurrence comparable to those of adherent women without MDD. **Conclusions:** Our findings identify endocrine therapy adherence as a potentially modifiable clinical factor to reduce breast cancer recurrence among women with MDD and estrogen receptor-positive disease. Research Sponsor: Department of Medical Affairs; National Cancer Institute; The Breast Cancer Research Foundation.

10596 **Poster Session**

Hair relaxer use and breast cancer risk by tumor molecular subtypes. First Author: Kaitlin White, National Cancer Institute, National Institutes of Health, Rockville, MD

Background: Women of West African ancestry, including US populations, are disproportionately diagnosed with aggressive breast cancers including triple negative tumors. Previously, hair relaxer use has been associated with increased breast cancer risk in the Ghana Breast Health study (GBHS), with former users at an over 2-fold increased risk compared to never users. We aimed to determine if relaxer use risk associations differed by tumor molecular subtypes suggesting possible biological mechanisms of carcinogenesis. **Methods:** The GBHS is a population-based case-control study conducted 2013–2015 in Accra and Kumasi, with 1,071 pathologically confirmed invasive breast cancer cases (87% had available estrogen receptor (ER) status) and 2,106 matched controls, aged 18-74 years. Molecular subtypes were defined using St Gallen's criteria using molecular marker data for ER, progesterone receptor, human epidermal growth factor receptor-2 (HER2), and grade (G). Molecular tumor subtypes defined as: Lum A (ER/PR+, HER2- and G1/G2, N = 260), Lum B- (ER/PR+, HER2- and G3, N = 468), Lum B+ (ER/PR+, HER2+ and G1/G2, N = 195), HER2-Enriched (ER-, PR- and HER2+, N = 59), Triple-Negative (ER, PR, and HER2-, N = 129). We imputed missing data using chained equations. Polytomous logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for associations of relaxer use with breast cancer subtypes. Models were adjusted for matching factors (age, hospital site), and potential confounders: education, parity, age at first birth, and median breastfeeding months per child. Results were combined across imputed datasets. Heterogeneity (p-het) in breast cancer risk by tumor molecular subtypes using polytomous logistic regression case-only models. **Results:** Relaxer use was common (ever-use of relaxers 96% of cases and 94% of controls). Compared to never users, increased risk for former users compared to never users was observed across subtypes. While magnitudes of risk differed (OR_{LumA}= 2.59, 95% CI [1.01—6.60], OR_{LumB+}= 2.69, 95% CI [0.47—15.47], OR_{LumB-}= 1.74, 95% CI [0.33—6.93], $OR_{HER2\text{-}Enriched}$= 3.66, 95% CI [0.75—17.98], $OR_{Triple\text{-}Negative}$= 1.21, 95% CI [0.37—4.00]), there was no statistical evidence of etiologic heterogeneity by subtype (p-het = 0.59). Similarly, other measures of relaxer use (duration, age at first use, lye or non-lye) did not show any evidence of heterogeneity. **Conclusions:** In this population with a high proportion of aggressive tumor subtypes, breast cancer risk associated with relaxer use did not support etiologic heterogeneity by molecular subtype, however, power was limited. These findings suggest that relaxer exposure is unlikely to explain subtype-specific breast cancer risk patterns. Future investigations should pool studies for improved power, evaluate other molecular tumor characteristics and relaxer products' formulations to clarify carcinogenic mechanisms to reduce risk. Research Sponsor: Intramural Research Program of the National Institutes of Health.

10597 **Poster Session**

Prevalence of oral and genital HPV-45 and non–vaccine-targeted HPV-35 among U.S. adults. First Author: Morgan C. Byrd, Duke University School of Medicine, Durham, NC

Background: High-risk human papillomavirus (HPV) types 35 and 45 are oncogenic non-16/18 subtypes that contribute measurably to HPV-attributable genital and oropharyngeal cancers. Unlike HPV-45, HPV-35 is not targeted by the current 9-valent vaccine. Although high prevalence of these subtypes has been reported in some global sub-populations, data on their prevalence and distribution in the U.S. adult population remains limited. **Methods:** We conducted a cross-sectional analysis of adults aged 18-64 years from the National Health and Nutrition Examination Survey (NHANES) cycles 2013-2016. HPV was detected via self-collected oral rinse specimens, vaginal swabs, and penile swabs. HPV vaccination history and sexual behaviors were self-reported. We estimated survey-weighted type-specific HPV prevalence and used survey-weighted Poisson regression to calculate adjusted prevalence ratios (aPRs), accounting for age, sex, race/ethnicity, vaccination status, and number of lifetime sexual partners. **Results:** Oral HPV prevalence was low overall, with HPV-16 remaining the most frequently detected type (0.87%). Genital HPV showed a broader distribution of oncogenic types. Among men, penile HPV-35 (1.93%, 95% CI 1.27-2.60%) and HPV-45 (1.94%, 95% CI 1.37-2.50%) were less prevalent than HPV-16 (3.97%, 95% CI 3.13-4.80%) and slightly more prevalent than HPV-18 (1.71%, 95% CI 1.20-2.22%), though confidence intervals overlapped. Among women, vaginal HPV-35 (1.40%, 95% CI 0.95-1.85%) and HPV-45 (1.71%, 95% CI 1.21-2.21%) were also less common than HPV-16 (2.95%, 95% CI 2.14-3.77%) and comparable to HPV-18 (1.26%, 95% CI 0.88-1.65%), again with overlapping confidence intervals. While there were extremely low rates of dual oral-genital infections, males exhibited slightly higher, though non-significant, dual infection prevalences for HPV-35 (0.03% vs. 0%), HPV-45 (0.21% vs 0.07%), and HPV-16 (0.17% vs. 0.11%) compared to females. Non-Hispanic Black participants had a significantly higher genital prevalence of both HPV-35 (aPR 2.75, 95% CI 1.71-4.42) and HPV-45 (aPR 2.08, 95% CI 1.13-3.85) compared with Non-Hispanic White participants. Prevalence was higher among males than females for both types, although these differences did not reach statistical significance. **Conclusions:** In this nationally representative sample of U.S. adults, we found that HPV-35, a high-risk type not included in the current 9-valent vaccine, showed genital prevalence comparable to vaccine-covered types and marked racial disparities. These findings highlight the importance of continued HPV surveillance and targeted prevention strategies. Additionally, future studies should investigate these subtypes in HPV-associated malignancies. Research Sponsor: None.

10598 **Poster Session**

Genome-wide association and Mendelian randomization analyses of body mass index and breast cancer risk in women of African ancestry. First Author: Wenji Guo, Section of Hematology & Oncology, Department of Medicine, The University of Chicago, Chicago, IL

Background: The relationship between adiposity and breast cancer risk is complex and incompletely understood, particularly among women of African ancestry. We investigated the association between genetically predicted and excess body mass index (BMI) and breast cancer risk in the African Ancestry Breast Cancer Genetic Consortium (AABCG) using complementary genetic and epidemiologic approaches. **Methods:** We conducted a genome-wide association study (GWAS) of BMI in AABCG. Independent BMI-associated variants were then used as instrumental variables in one-sample Mendelian randomization (MR) analyses, using two-stage residual inclusion with logistic regression to estimate the causal effect of BMI on breast cancer risk. To explore the joint influence of genetic and non-genetic contributions to BMI, we constructed a BMI polygenic risk score and defined the BMI polygenic-measured gap (BMI-PGM) as the difference between the percentile of observed BMI and the percentile of genetically predicted BMI. BMI-PGM was categorized into three groups based on quartile distribution: discordantly low (≤25^{th} percentile), concordant (25^{th}-75^{th} percentile), and discordantly high (≥75^{th} percentile). The association between BMI-PGM and breast cancer risk was evaluated. **Results:** We identified thirteen loci that were associated with BMI at the genome-wide significance level. Of these, seven loci had not been reported in prior GWAS of BMI. In the MR analyses (n = 31,522), genetically predicted BMI was inversely associated with overall breast cancer risk: odds ratio (OR) = 0.92 per 5 kg/m^2 increase, 95% confidence interval (CI) 0.86-0.99, p = 0.028. In stratified analyses, there was a stronger inverse relationship observed for estrogen receptor (ER) negative compared with ER positive breast cancer. Inverse associations with similar effect sizes were observed in analyses stratified by menopausal status. Compared with women whose observed BMI was discordantly low relative to their genetically predicted BMI, those with concordant BMI had a modestly increased risk of breast cancer (OR = 1.08, 95% CI 1.02-1.14, p = 0.0074), while women with discordantly high BMI had a 12% higher risk of breast cancer (OR = 1.12, 95% CI 1.05-1.19, p = 0.00049). **Conclusions:** Genetically predicted higher BMI was associated with lower breast cancer risk, whereas BMI in excess of genetic predisposition was associated with increased risk. These opposing associations highlight a distinction between genetically mediated body size versus excess weight that likely reflects adverse metabolic processes. Together, these results underscore the roles of both genetic susceptibility and modifiable influences on adiposity in breast cancer etiology and highlight the importance of maintaining a healthy weight to reduce breast cancer risk, despite variability in genetic predisposition to adiposity across the population. Research Sponsor: Conquer Cancer, the ASCO Foundation; 2025YIA-4865769673; National Cancer Institute; K12CA139160.

10599 **Poster Session**

Genetic correlation and causal associations between metabolic traits and lung cancer risk. First Author: Knightess Oyibo, University of Maryland School of Medicine, Baltimore, MD

Background: Lung cancer is the leading cause of cancer-related mortality worldwide. We evaluated whether associations between metabolic traits and lung cancer risk reflect shared genetic susceptibility or causal effects of metabolic dysregulation. **Methods:** GWAS summary statistics from European-ancestry participants were obtained for lung cancer (TRICL–ILCCO; n = 29,266 cases, 56,450 controls), body mass index (BMI; GIANT; n = 681,275), blood lipids, triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL), from the Global Lipids Genetics Consortium (GLGC; n = 1,320,016), and type 2 diabetes (T2D; T2DGGI; n = 242,283 cases, 1,569,734, controls). Genome-wide genetic correlations were estimated using LD score regression. Two-sample Mendelian randomization analyses were conducted with lung cancer as the outcome using inverse-variance weighted models, with weighted median, MR-Egger, and weighted mode sensitivity analyses. Heterogeneity and pleiotropy were assessed using Cochran's Q, MR-Egger intercept, and MR-PRESSO. **Results:** Lung cancer demonstrated significant positive genetic correlations (r_g) with BMI (r_g= 0.16, P = 1.0×10^{-4}), TG (r_g = 0.14, P = 3.0×10^{-4}), and T2D (r_g = 0.09, P = 0.017), and a significant inverse correlation with HDL ($r_g = -0.14$, P = 2.4×10^{-5}). No significant genetic correlation was observed for LDL. In MR analyses, genetically predicted BMI was associated with increased lung cancer risk (475 SNPs; IVW β = 0.23, SE = 0.05, P = 2.0×10^{-6}; OR = 1.26, 95% CI 1.14–1.38), and remained statistically significant after outlier correction (β = 0.21, P = 7.2×10^{-6}), with no evidence of distortion. In contrast, no supporting evidence of causal associations between lung cancer risk and genetically predicted HDL, TG, LDL, or T2D liability across primary and sensitivity estimators (all $P > 0.05$). Cochran's Q tests indicated heterogeneity across genetic instruments; however, MR-Egger intercept tests did not provide evidence of directional horizontal pleiotropy. **Conclusions:** These findings suggest that metabolic health, particularly obesity, may play a clinically meaningful role in lung cancer risk assessment. Considering obesity alongside established smoking-related determinants may enhance lung cancer prevention efforts. Research Sponsor: American Cancer Society; RSG-22-079-01; National Cancer Institute/U.S. National Institutes of Health; P30CA134274.

10600 **Poster Session**

Lung cancer incidence and $PM_{2.5}$: Evaluating the association with varying spatial scales and durations of exposure estimates. First Author: George Carey, VA Connecticut Healthcare System, West Haven, CT

Background: Particulate matter with a diameter of 2.5 μm or less ($PM_{2.5}$) is classified as an IARC group 1 carcinogen based on decades of research. However, little is known about how the association between $PM_{2.5}$ and lung cancer incidence is impacted by varying spatial and temporal methods of estimating exposure. **Methods:** We performed a nested case-control analysis using the Department of Veterans Affairs (VA) Clinical Data Warehouse. Patients were eligible for inclusion if they had a recorded date of birth, smoking data, and quarterly location data for 40 or more quarters between 2009 and 2021. Cases were required to have at least 10 years of location data prior to diagnosis; diagnoses and diagnosis dates were identified using the VA Central Cancer Registry. Controls were matched in a 4:1 ratio on age (by birth quarter), smoking status (self-reported, defined as "Smoker" vs. "Never Smoker"), and the specific calendar quarters contributing to the $PM_{2.5}$ average. Modeled daily $PM_{2.5}$ estimates at a spatial resolution of 1 km^2 for the entire contiguous United States (US) were aggregated to quarterly estimates at three US Census geography levels (block group, census tract, and county). After case-control matching, we evaluated the impact of different spatial and temporal measures of $PM_{2.5}$ exposure on the association between $PM_{2.5}$ and lung cancer incidence. Specifically, we evaluated estimates at the block group, census tract, and county level with both 5-year and 10-year averages. Associations were evaluated using conditional logistic regression; model fit was assessed using the Akaike Information Criterion (AIC). **Results:** Approximately 4.7 million veterans met our inclusion criteria. Of these, 8451 veterans developed incident lung cancer at least 10 years after the observation period began; 33,150 matched controls were selected. All models showed a statistically significant increase in the risk of lung cancer with increasing $PM_{2.5}$ exposure, with odds ratios (ORs) ranging from 1.06 (95% CI 1.04-1.09) to 1.13 (95% CI 1.10-1.17) and p-values < 0.001 for all models. In both the 5-year and 10-year analyses, models with larger spatial units (county > census tract > block group) had higher ORs and superior model fit by AIC. All models with 10-year averages had higher ORs and lower AIC values compared to models with 5-year averages. **Conclusions:** Our findings add to the considerable body of research that demonstrates an epidemiologic association between $PM_{2.5}$ and lung cancer incidence. Furthermore, our results demonstrate that this association is robust to various methods of estimating patient $PM_{2.5}$ exposure. Finally, these data suggest that using county-level $PM_{2.5}$ estimates and an estimate duration of at least 10 years may be preferable to finer spatial scales and shorter estimate durations in future studies. Research Sponsor: None.

10601 **Poster Session**

Quantifying equol-producing and beta-glucuronidating gut bacteria in breast cancer using 16S rDNA sequencing methods. First Author: Kathryn Zamiela, University of Illinois Chicago, Chicago, IL

Background: Gut bacteria with hormone-modulating potential may influence breast cancer (BC) risk: Equol-producing bacteria convert dietary isoflavones into equol, a phytoestrogen that binds estrogen receptors, while beta-glucosidating bacteria affect glycosides of dietary phytoestrogens, and beta-glucuronidating bacteria regulate the deconjugation and reabsorption of endogenous estrogens. We aimed to investigate whether gut bacterial species that have the potential to affect phytoestrogens or endogenous estrogens can be detected using 16S rDNA sequencing methods, and to what extent this detection may be influenced by the choice of 16S hypervariable region targeted for sequencing. **Methods:** DNA extracted from stool samples of women with BC (n = 112) and healthy controls (n = 171) was subjected to PCR amplification and high-throughput sequencing of the V1-V3 and V3-V4 16S rRNA hypervariable regions, commonly used regions in microbiome research. Data was processed using QIIME, and taxonomy assignment was performed with the SILVA database to the species level. Relative abundance and detection of taxa in cases vs controls were evaluated using Wilcoxon and McNemar's tests in R. Taxa were classified as equol-producing based on Setchell and Clerici (2010) or beta-glucuronidating and beta-glucosidating based on Dabek et al (2008). **Results:** The relative abundance of equol-producing bacteria was significantly higher in the BC group vs controls in the V1–V3 (p = 0.0007); V3–V4 (p = 0.0089) regions, and when both regions were summed (p = 0.0011). Adlercreutzia equolifaciens was detected 29.6% more often in a presence/absence analysis of the V1-V3 region (V1-V3 presence: 93.0%, V3-V4 presence: 63.4%, $p < 0.001$), while Finegoldia magna was detected 21.1% more often in the V3-V4 region (V1-V3 presence: 18.0%, V3-V4 presence: 39.1%, $p < 0.001$). The relative abundance of beta-glucuronidating and beta-glucosidating bacteria was significantly higher in the BC group vs controls in the V1-V3 region (p = 0.0094) and when both regions were summed (p = 0.0254), and approached significance in the V3-V4 region (p = 0.0534) . Presence of Bifidobacterium adolescentis was detected 21.8% more often in the V1-V3 region (V1-V3 presence: 21.8%, V3-V4 presence: 0.00%, $p < 0.001$), and Roseburia inulinivorans was detected 21.1% more often in the V3-V4 region (V1-V3 presence: 63.0%, V3-V4 presence: 83.1%, $p < 0.001$). **Conclusions:** Equol-producing and beta-glucuronidating and beta-glucosidating bacteria appear enriched at the species-level analysis in BC subjects, but detection of specific organisms is sensitive to the 16S region sequenced. Accurate identification of hormone-modulating taxa requires both the V1-V3 and V3-V4 regions, as either alone is insufficient to capture the full range of taxa. Additional analyses with absolute quantification such as qPCR are needed to validate the results. Research Sponsor: University of Illinois Chicago; U.S. National Institutes of Health.

10602 **Poster Session**

Early lessons from the implementation of a pan-African clinico-genomic cancer platform: The African Cancer Atlas. First Author: Emmanuella Amoako, Yemaachi Biotech, Accra, Ghana

Background: Limited representation of African populations in cancer genomics constrains the clinical applicability of precision oncology. We describe the establishment and early outcomes of The African Cancer Atlas (TACA), a multi-site platform integrating genomics, harmonized clinical data, and community engagement for adult breast cancer research across Africa. **Methods:** TACA, led by Yemaachi Biotech, has so far been implemented across five countries (Ghana, Nigeria, Côte d'Ivoire, Kenya, and Seychelles). In early 2025, foundational activities included institutional review board (IRB) approvals, execution of memoranda of understanding and material transfer agreements, site activation, and structured engagement with clinicians, patient advocates, and community stakeholders through Yemaachi's African Cancer Network to support trust-building and study uptake. Participant recruitment began in July 2025. Breast cancer patients were enrolled following IRB approval, with informed consent supported by site-based education on genomics research. Clinical data were captured in UVOSYO-Yemaachi's clinical database. Peripheral blood was collected at recruitment, and formalin-fixed paraffin-embedded (FFPE) tumor tissue was obtained subsequently and shipped to our central laboratory in Accra. Blood and tissue underwent DNA extraction and quantitative and qualitative quality control (QC) prior to sequencing. **Results:** To date, 236 participants have been recruited across the five TACA sites. Blood-derived DNA demonstrated acceptable quality for downstream sequencing, whereas FFPE tumor tissue quality varied substantially, leading to exclusion of cases that failed QC. Among enrolled participants, 97.9% were female, with a mean age of 50.8 years (SD 13.1). A total of 26.7% reported a family history of cancer, with participants in Seychelles having the most significant family history of 87% ($p < 0.001$) Triple-negative breast cancer accounted for 38.1% of tumors overall, ranging from 21.1% in Kenya to 68.1% in Nigeria. Significant between-country variation was observed for triple-negative breast cancer ($p < 0.001$) and hormone receptor status (all $p < 0.001$). Key implementation challenges included prolonged IRB approval timelines related to limited familiarity with cancer genomics, cross-border biospecimen transport constraints necessitating in-country DNA extraction in some settings, and variability in FFPE tissue quality impacting sequencing yield. **Conclusions:** TACA demonstrates the feasibility of coordinated multi-country recruitment and clinical data harmonization for adult cancer genomics in Africa, while highlighting critical regulatory, logistical, and biospecimen quality barriers. Research Sponsor: None.

10603 **Poster Session**

Variants of uncertain significance and contralateral risk-reducing mastectomy in early-stage breast cancer across safety-net and private hospital settings. First Author: Vineeth Reddy Kommidi, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX

Background: Germline genetic testing informs surgical decisions in early-stage breast cancer. Guidelines recommend considering contralateral risk-reducing mastectomy (RRM) for patients with pathogenic or likely pathogenic variants in high-risk genes, but not for those with variants of uncertain significance (VUS). Despite this, VUS results may still affect surgical decisions. This study examines the impact of VUS on surgical decision-making across two university-affiliated settings: a safety-net hospital and a private hospital. **Methods:** We retrospectively reviewed patients with early-stage invasive breast cancer treated between 2012 and 2022 who underwent germline testing before surgery at both a safety-net and a private hospital. Patients with VUS were compared with genetically negative controls. Logistic regression was used to identify factors associated with RRM. **Results:** The cohort included 86 safety-net VUS patients, 115 safety-net controls, 102 private VUS patients, and 97 private controls. Table 1 highlights demographic differences between the hospitals. RRM was performed in 28 safety-net VUS patients (32.6%), 20 safety-net controls (17.4%), 37 private VUS patients (36.3%), and 45 private controls (46.4%). Stepwise regression analysis of the full cohort showed that treatment at the private hospital was independently associated with higher rates of RRM compared with the safety-net hospital, regardless of VUS status (OR 4.52, 95% CI 2.10 - 9.75, $p < 0.001$). Additional factors associated with higher RRM rates included higher tumor stage, higher tumor grade, and younger age at diagnosis. In hospital-specific analyses, VUS status did not influence RRM decisions at the private hospital. However, at the safety-net hospital, patients with VUS were more likely to undergo RRM than those with negative genetic testing (OR 2.38, 95% CI 1.09 - 5.21, p = 0.031). **Conclusions:** Surgical decision-making for RRM is influenced by multiple clinical and institutional factors. While VUS status did not affect surgical decisions at the private hospital, it was associated with increased RRM rates at the safety-net hospital. This finding suggests that differences in counseling practices and patient perceptions of genetic risk may exist within the safety-net setting, where patients may face more uncertainty about access to future care. Further studies are needed to better characterize these disparities and promote guideline-concordant care. Research Sponsor: None.

Patient demographics by hospital.

		Safety-Net (n = 201)	Private (n = 199)	p-value
Race/Ethnicity	Non-Hispanic White	8 (4.0%)	116 (58.3%)	< 0.001
	Non-Hispanic Black	41 (20.4%)	39 (19.6%)	
	Hispanic	141 (70.1%)	12 (6.0%)	
	Other	11 (5.5%)	32 (16.1%)	
Language Spoken	English	72 (35.8%)	199 (100%)	< 0.001
	Non-English	129 (64.2%)	0 (0%)	
Insurance	Insured	62 (30.8%)	196 (98.5%)	< 0.001
	Uninsured	139 (69.2%)	3 (1.5%)	

10604 **Poster Session**

A pilot study of a digital, patient-directed consent process for MSK-IMPACT tumor-normal genetic testing in gynecologic cancer. First Author: Varshini Gali, NewYork-Presbyterian Weill Cornell, New York, NY

Background: Although germline and somatic genetic testing is increasingly recommended for many cancers including gynecologic cancers, uptake remains low. Barriers include consenting processes that are time consuming for patients and providers. We sought to test uptake and acceptability of a digital, self-directed genetic testing consent process. **Methods:** We developed a digital, self-guided consenting process for MSK-IMPACT tumor-normal targeted sequencing called "read and sign" (R&S) that included an educational video and information about genetic testing along with a direct digital consent. We performed a pilot study in gynecologic surgery (GYNS) and medical oncology (GMO) clinics to evaluate the uptake of genetic testing and other metrics including time to consent, clinic time saved, and patient satisfaction. Briefly, adults with gynecologic cancers eligible for MSK-IMPACT were sent R&S consent via electronic health record. Research staff followed up with patients at 2, 7, and 14 days. If patients did not consent after 14 days, the clinical team was notified to follow-up. This study was approved under IRBs 12-245 and X25-012. **Results:** Between 10/6/2025 and 12/31/2025, we identified 173 patients (122 GYNS and 51 GMO) eligible for MSK-IMPACT and offered them R&S consent. This represented 8% of total MSK-IMPACT consents across the institution during this time. Median age was 61 years. 106 (61%) patients identified as White, 27 (16%) as Asian, 17 (10%) as Black, and 24 (14%) as Hispanic. Most common cancer types were endometrial (n=75, 43%) and ovarian (n=39, 23%). In GYNS, 102/122 (84%) patients consented with R&S, and 59 (58%) consented on the same day the R&S consent was sent. On average, 8 minutes of in-person clinic time per patient was saved using R&S, but 35 (29%) patients had 0 time saved, and 7 (7%) consents were later completed in-person after initial incomplete R&S attempt. One patient who completed the R&S consent later withdrew consent. In GMO, 50/51 (98%) patients consented via R&S, with 38 (76%) consented on the same day. On average, 14 minutes of clinic time per patient was saved, and 4 (8%) patients ultimately required in-person consent. Average time to consent was 3.3 days in GYNS and 1.7 days in GMO. Among 11 patients who completed surveys, 10 (91%) were very/somewhat satisfied with R&S. More in-depth surveys and semi-structured interviews with a subset of patients and staff are ongoing, and data will be forthcoming. **Conclusions:** A digital, self-guided consent for MSK-IMPACT genetic testing was feasible and acceptable with some differences in workflow between surgical and medical oncology clinics. The R&S consent process empowers patient decision-making and should be scaled to other cancer types. Research Sponsor: U.S. National Institutes of Health.

10605 **Poster Session**

Germline testing in Asian American and Pacific Islander women with breast cancer. First Author: Jennifer Tseng, City of Hope Orange County, Irvine, CA

Background: Per the American Cancer Society, the overall breast cancer incidence rate rose 1% per year from 2012 to 2021, while it increased 2.7% per year for Asian American and Pacific Islander (AAPI) women. Cases increased by 50% for AAPI women under age 50, on par with White women. This study was conducted to examine rates and results of germline genetic testing in AAPI women with breast cancer. **Methods:** In this retrospective analysis, AAPI women with breast cancer were identified from a non-consecutive dataset of patients undergoing multi-gene panel testing (MGPT) at a national clinical diagnostic laboratory. Descriptive statistics were performed and differences in variant frequencies between groups were assessed using two-proportion z-tests. **Results:** From January 2016 through April 2025, 3.8% of women who underwent germline genetic testing reported AAPI ancestry (50,043/1,320,261). AAPI women made up 4.1% of all women with breast cancer who underwent MGPT. Comparatively, the most recent U.S. Census data from 2024 showed 7.0% of the population self-identified as AAPI women. The median age of AAPI women who underwent germline testing was 54 years and the most frequent pathogenic/likely pathogenic (P/LP) variants in order were BRCA2, BRCA1, ATM, PALB2, TP53, and CHEK2 (56.0% of P/LP variants). Most AAPI women (79%) resided in large metropolitan areas, and more than half (53%) had private insurance. AAPI women with breast cancer had lower rates of P/LP variants compared with White women (6.8% vs. 9.2%; $p<0.0001$) and all non-AAPI women tested (6.8% vs 8.9%; $p<0.0001$). Among women ≤50 years, P/LP rates remained lower in AAPI compared with White women (7.9% vs 10.7%; $p<0.0001$) and all non-AAPI women (7.9% vs 10.5%; $p<0.0001$). Younger AAPI women exhibited higher P/LP rates than older AAPI women (11.2% <40 vs 6.24% >40), consistent with age-associated trends across ethnicities (14.0% all non-AAPI <40 vs 8.45% all non-AAPI >40). **Conclusions:** In this study cohort, AAPI women with breast cancer make up a smaller than expected proportion of all tested women with breast cancer, despite similar breast cancer incidence rates as White women. AAPI women with breast cancer who had genetic testing tended to reside in large metropolitan areas and have private insurance. These factors and others should be considered when thinking about how to broaden access to genetic testing and counseling in the future, especially in younger AAPI women who have comparably higher rates of P/LP variants. Research Sponsor: None.

10606 **Poster Session**

Impact of germline *BRCA* pathogenic or likely pathogenic variants on fertility potential and reproductive outcomes in young women with breast cancer: A systematic review and meta-analysis. First Author: Luca Arecco, Université libre de Bruxelles (ULB), Hôpital Universitaire de Bruxelles (H.U.B), Institut Jules Bordet, Bruxelles, Belgium

Background: In young women with a diagnosis of breast cancer (BC), the impact of germline *BRCA* (*gBRCA*) pathogenic or likely pathogenic variants (PVs) on their reproductive reserve and fertility outcomes remains uncertain. This systematic review and meta-analysis assessed the influence of harboring *gBRCA* PVs on ovarian reserve, efficacy of fertility preservation (FP) techniques, and pregnancies after BC diagnosis. **Methods:** A systematic PubMed/MEDLINE search was conducted with no date restrictions up to June 30th, 2025 (CRD420251114990). Eligible studies included retrospective and prospective case-control or cohort studies and clinical trials, comparing at least one of the following outcomes between *gBRCA* carriers vs. non-carriers: ovarian reserve parameters [i.e., anti-Müllerian hormone (AMH) levels or antral follicle count (AFC)] at BC diagnosis (objective 1); efficacy of FP techniques (i.e., number of total and mature retrieved oocytes, and cryopreserved oocytes before chemotherapy) (objective 2); likelihood of conceiving after treatments (objective 3). Pooled mean differences and risk ratios (RRs) with 95% confidence intervals (CI) were calculated using a random-effects model. **Results:** Out of 5,325 screened records, 18 studies met the inclusion criteria and were included in the final analysis (2,631 patients, of whom 737 *gBRCA* carriers). Mean age of patients at BC diagnosis was 32.6 years for *gBRCA* carriers and 33.1 years for non-carriers. Among 12 studies (n=1,529 patients) reporting on objective 1, *gBRCA* carriers (n=399) showed significantly lower AMH levels compared with non-carriers, with a mean difference of -0.5 (95% CI -0.8; -0.2) ng/mL, and a numerically lower AFC count (-0.8; 95% CI -2.3; +0.8). Among the 11 studies (n=1,027 patients) addressing objective 2, *gBRCA* carriers (n=318) had a lower median number of total oocytes (-1.8; 95% CI -3.3; -0.3), retrieved mature oocytes (-1.6; 95% CI -2.8; -0.3), and numerically lower cryopreserved oocytes (-1.1; 95% CI -2.7; +0.6). Subgroup analyses showed that reductions in ovarian reserve and FP outcomes were mainly driven by *BRCA1* carriers (n=184), whereas reproductive outcomes in *BRCA2* carriers (n=125) were comparable to those of non-carriers. Regarding objective 3, only one study (n=75 patients) reported the likelihood of conceiving after BC using assisted reproductive technologies (ART) and showed no differences between *gBRCA* carriers (n=20) and non-carriers (RR 0.28; 95% CI 0.04; 2.04). **Conclusions:** Young patients with BC harboring *gBRCA* PVs showed reduced AMH levels and lower FP efficacy, while no differences were observed in pregnancy rates after BC through ART, although evidence remains limited. Prospective studies are needed to optimize oncofertility counselling young *gBRCA* carriers. Research Sponsor: None.

10607 **Poster Session**

Longitudinal follow-up after identification of variants of uncertain significance in highly penetrant cancer predisposition genes. First Author: Bridget Kiely, Baylor College of Medicine, Houston, TX

Background: ASCO and the NCCN recommend that patients with variants of uncertain significance (VUS) in hereditary cancer predisposition genes undergo periodic variant reassessment, since reclassification of VUS as pathogenic or likely pathogenic (P/LP) may alter clinical management. However, the extent to which such longitudinal follow-up occurs in practice has not been studied. **Methods:** Data were retrospectively reviewed from patients who underwent germline genetic testing for cancer-related indications from 2015-2025 at an adult genetics clinic in an academic-affiliated, safety-net healthcare system. Analyses were restricted to patients found to have VUS (without P/LP variants) in any of 23 highly-penetrant cancer predisposition (HPCP) genes based on the NCCN guidelines for genetic/familial high-risk assessment: *APC*, *ATM*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDKN2A*, *CHEK2*, *EPCAM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *MUTYH* (biallelic), *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, and *TP53*. The primary outcome of interest was the percent of patients who adhered to clinician recommendations for follow-up after VUS disclosure, excluding those for whom insufficient time had elapsed to assess follow-up status. Chi-square tests were used to assess if follow-up rates differed among patients with VUS that were considered "clinically concordant" (personal history of a tumor consistent with the gene's neoplastic spectrum), "possibly concordant" (history of a relevant neoplasm in a 1st/2nd degree relative but not the patient), or "likely incidental" (no relevant personal or family cancer history). **Results:** Of 2028 tested patients, 25% (n = 501) were found to have one or more cancer-related VUS (without P/LP variants), including 308 with VUS in HPCP genes. At the time of initial result disclosure, 11% of these patients were discharged from further follow-up, while the remaining 89% were advised to return for variant reassessment, typically within 2 years. Adherence to these recommendations was low overall, with only 38% returning for any post-disclosure follow-up. Rates of follow-up were similar among patients with VUS classified as clinically concordant (40%), possibly concordant (34%), or likely incidental (45%); p = 0.47. **Conclusions:** Despite clear clinician guidance to return for variant reassessment, most patients with VUS in highly-penetrant genes did not engage in recommended follow-up, even in the presence of a clinically compatible personal and/or family cancer history. Alternative approaches to longitudinal VUS management - such as automated recontact and/or direct-to-patient notification of variant reclassifications - should be explored to mitigate the risk of loss to follow-up in this population. Research Sponsor: None.

10608 **Poster Session**

Intensity of chemotherapy regimens for patients with Lynch syndrome and colorectal cancer. First Author: Christine M. Veenstra, University of Michigan, Ann Arbor, MI

Background: Lynch syndrome (LS), associated with inherited pathogenic variants (PVs) in *MLH1, MSH2, MSH6, PMS2* or *EPCAM*, is the most common inherited colorectal cancer (CRC) syndrome. Nearly all LS-associated CRCs are mismatch repair-deficient and microsatellite instability-high (dMMR/MSI-H), a phenotype associated with low recurrence risk and limited benefit from single-agent chemotherapy. Guidelines recommend no adjuvant chemotherapy for most dMMR/MSI-H stage II CRC. A fluoropyrimidine + oxaliplatin is recommended for all dMMR/MSI-H stage III CRC. **Methods:** We linked SEER registry records from Georgia and Los Angeles to germline genetic testing results from 4 labs. We included patients with resected stage II or III CRC diagnosed 2013-19 who linked to genetic test results. Chemotherapy details were extracted from SEER text fields completed by registrars. Regimens were classified as 1) No adjuvant chemotherapy; 2) Less intensive (5-FU or capecitabine); 3) More intensive (5-FU or capecitabine + oxaliplatin). We examined associations between genetic testing results and intensity of adjuvant chemotherapy. Covariates included age, sex, race, ethnicity, rurality. **Results:** Among 2770 patients, 1176 had stage II and 1594 had stage III CRC; 271 had a LS gene PV. The table shows results of multivariable analysis stratified by stage. Adjuvant chemotherapy intensity did not vary between patients with LS versus negative genetic test results. Older age was associated with receipt of no or less intensive chemotherapy in stage II and III CRC. Hispanic patients with Stage III CRC were more likely to receive no chemotherapy compared to non-Hispanic White patients. **Conclusions:** In this population-based cohort of CRC patients from two states, adjuvant chemotherapy regimen intensity did not vary with germline genetic test results. These findings suggest that patients with LS and stage II CRC are being overtreated. Clinicians may require education about optimizing CRC therapy for patients with LS. Research Sponsor: National Cancer Institute; R37 CA251464.

	Stage II No Chemo (OR, 95% CI)	Stage II Less Intensive (OR, 95% CI)	Stage III No Chemo (OR, 95% CI)	Stage III Less Intensive (OR, 95% CI)
Genetic Test Result				
Negative (Ref)				
Lynch PV	1.39 (0.86-2.24)	0.60 (0.29-1.26)	0.94 (0.42-2.11)	1.06 (0.50-2.26)
Other PV	0.80 (0.39-1.65)	1.03 (0.42-2.54)	0.58 (0.23-1.41)	1.29 (0.67-2.51)
VUS only	0.89 (0.61-1.30)	0.57 (0.35-0.94)	0.99 (0.65-1.50)	0.81 (0.53-1.25)
Age (years)	1.05 (1.04-1.07)	1.02 (1.00-1.03)	1.07 (1.05-1.08)	1.05 (1.03-1.06)
Female (vs. male)	0.96 (0.68-1.29)	0.89 (0.59-1.34)	1.00 (0.69-1.46)	1.15 (0.80-1.64)
Race/Ethnicity				
Non-Hispanic White (ref)				
Asian	0.75 (0.42-1.32)	1.21 (0.60-2.43)	1.24 (0.60-2.57)	1.22 (0.67-2.24)
Black	1.11 (0.67-1.84)	1.06 (0.56-1.98)	1.30 (0.75-2.25)	0.93 (0.52-1.66)
Hispanic	1.05 (0.66-1.67)	0.60 (0.30-1.18)	1.71 (1.02-2.87)	1.31 (0.77-2.24)
Rural (vs. urban)	1.14 (0.64-2.02)	1.31 (0.63-2.75)	1.08 (0.57-2.03)	1.26 (0.69-2.28)

10609 **Poster Session**

Clinical implementation of an online family cascade genetic testing platform: The Preventive Risk Outreach and Cascade Testing (PROACT) initiative. First Author: Jennifer Lee Caswell-Jin, Stanford Cancer Institute, Stanford, CA

Background: Cascade genetic testing of relatives in families with hereditary cancer susceptibility is an essential strategy to reduce the burden of cancer through targeted risk reduction. However, current testing rates for eligible relatives are low. A promising strategy is to directly engage relatives of affected patients through an online referral service that delivers genetic risk education and the option for home genetic testing to relatives. In the recent GIFT randomized clinical trial, we evaluated an online cascade testing platform for relatives of cancer patients identified through SEER registries. Here, we asked whether a clinical genetic counseling encounter could extend the reach of this approach. **Methods:** We implemented a pilot project at the Stanford Clinical Cancer Genetics Program that deployed an online hereditary cancer education and germline testing platform for first- and second-degree relatives of patients with a pathogenic or likely pathogenic variant (PV/LPV) in a cancer susceptibility gene. Eligible patients had a germline PV/LPV identified within the past year, spoke English, and had at least one adult first- or second-degree relative in the United States or Canada who had not, to the patient's knowledge, been tested for the PV/LPV. The virtual family referral service was offered to all eligible patients seen over a six-month period. Primary endpoints were the proportions of eligible relatives in the family who 1) were invited by the enrolled patient through the platform; and 2) ordered testing through the platform (processed by Color Health Inc). Here we report preliminary results from the initial project period; we will report results from the six-month project at time of presentation. **Results:** Between October 14, 2025 and January 20, 2026, 58 patients with germline PV/LPVs were offered the online tool and 23 patients (40%) enrolled. For these 23 patients, genetic counselors presumptively identified 191 relatives eligible for testing (70 first-degree and 121 second-degree). Patients invited 113 relatives (59%) of whom 57 (50%) accessed the tool and 50 confirmed their eligibility (no prior testing). Among confirmed eligible relatives who accessed the tool, 33 (66%) ordered testing, representing 17% (33/191) of all presumptively eligible relatives. **Conclusions:** Preliminary results from this clinic-based initiative to deliver cascade genetic testing through an online platform show promise. The findings suggest that an online platform can amplify the clinical genetics encounter and increase cascade testing of relatives in families with hereditary cancer susceptibility. Digital approaches to cascade testing may be particularly impactful for reaching relatives with limited access to care, where traditional cascade testing pathways are challenging. A multi-site clinical trial is planned through the PROACT Initiative. Research Sponsor: Bright Pink.

10610 **Poster Session**

Initial findings from the PROMISE Registry, a US decentralized, prospective prostate cancer genetic registry. First Author: Heather H. Cheng, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA

Background: The role for genetic testing (GT) for prostate cancer (PCa) patients (pts) has expanded to find pts with germline pathogenic variants (PV) for therapeutic opportunities given FDA-approvals for PARP inhibitors in metastatic PCa as well as understanding familial cancer risk and opportunities for tailored screening and risk reduction. The PROMISE Registry (NCT04995198) was set up as a genetic registry to partner with PCa pts for rapid access to a new standard of care given insurance coverage and clinical implementation were initially major barriers. A second goal is to characterize disease features and treatment outcomes to inform management and provide updates about novel therapeutic clinical trials, both of which remain important to rare genetic variant carriers. **Methods:** PROMISE is a US decentralized prospective PCa genetic registry initiated in 2021 with initial phase to enroll and provide clinical-grade germline genetic testing (30 gene cancer-specific panel) to 5,000 PCa pts to identify ~500 PCa pts with variants of interest (pathogenic variants, PV, and variants of uncertain significance, VUS) in DNA repair genes for long-term clinical follow-up of 15 years (LTFU). Here, we report the initial phase testing results and identification of the LTFU cohort. Study design and enrollment strategy have been reported separately. **Results:** Between 2021-2026, 7,275 pts with any stage PCa across 50 US states self-consented to PROMISE, of which 5,674 (78%) of pts completed genetic testing, indicating feasibility of patient-directed, decentralized enrollment. We have identified 495 (8.7%) pts for LTFU. Baseline data is reported for n=367 (Table 1, will be updated at time of presentation). The most frequently observed PV/LPV variants being in *CHEK2* (25%), *BRCA2* (23%), *ATM* (12%), *and BRCA1* (4.6%). At the time of PCa diagnosis, the majority of LTFU pts had non-metastatic disease, with 47% of pts with Gleason>7, median PSA of 5 ng/mL, and median time from diagnosis to PROMISE GT of 25 months. **Conclusions:** PROMISE is a nationwide decentralized PCa genetic registry that has completed initial goal to recruit 5,000 PCa pts to offer germline genetic testing and recruit a cohort of 500 for LTFU. Data about diagnosis characteristics are reported, and analysis of ongoing disease course, treatment response/outcomes and overall survival is being collected. Clinical trial information: NCT04995198. Research Sponsor: Advancing Cancer Treatment, Inc.; U.S. Department of Defense; W81XWH-18-2-0060, W81XWH-17-2-0043; NIH Pacific Northwest Prostate Cancer SPORE; CA097186.

Long-term follow-up participant demographics.

Characteristic	Overall, N = 367
Age at Diagnosis (yrs)	63 (57, 69)
Race	**N = 361** (6, nr)
Asian, American Indian or Alaska Native, Multiracial, Other	22 (6.0%)
Black or African American	22 (6.0%)
White	317 (86%)
Disease State at Diagnosis	**N = 348** (19, nr)
Metastatic	46 (13%)
Non-metastatic	302 (87%)
Time from Diagnosis to PROMISE GT (months)	25 (4, 82)
Gleason Score	**N = 280** (87, nr)
</= 7	148 (53%)
>7	132 (47%)
PSA At Diagnosis (ng/mL)	5 (0, 10) (88, nr)

Subjects with baseline data entered. nr=not reported.
Median (Q1, Q3); n (%).

10611 **Poster Session**

Actionable germline findings in endometrial cancer from a large multigene panel tested cohort. First Author: Adela Rodriguez Hernandez, Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Background: Although most endometrial cancers (EC) are sporadic, 2–6% arise in the setting of Lynch syndrome (LS) or Cowden syndrome. The prevalence and clinical correlates of other germline pathogenic/likely pathogenic variants (PVs) remain incompletely characterized. We assessed the prevalence of potentially actionable germline PVs in EC and their clinicopathologic associations. **Methods:** This retrospective cohort included 3,844 EC patients (pts) who underwent pan-cancer germline multigene panel testing at a single diagnostic laboratory (2018–2025). Pts $<$ 18 years, with mosaic results, or unclear pathology were excluded. Clinical and pathologic variables were compared between pts with and without PVs using appropriate statistical methods, including multivariable logistic regression. **Results:** The final cohort comprised 3,693 females; 46.6% were non-Hispanic White and 8.3% African American. Median age at testing was 62 years and median age at diagnosis was 57 years. Overall, 20.8% (n = 804) harbored a PV in a high- or moderate-penetrance gene. Among 852 PVs identified, 46.9% occurred in DNA damage response (DDR) genes, 37.0% in LS genes, and 16.1% in other genes. The most frequent DDR PVs were *BRCA2* (12.6%), *CHEK2* (9.2%), *BRCA1* (8.0%), *ATM* (7.5%), *PALB2* (3.1%). *PTEN* accounted for 3.2% of the PV. PV carriers were younger at testing (60 vs 62 years; p = 0.014) and diagnosis (54 vs 57 years; p $<$ 0.001), more often African American (12.4% vs 7.2%; p $<$ 0.001), and had higher rates of colorectal cancer (7.7% vs 3.4%; p $<$ 0.001) and multiple primary cancers (41.7% vs 36.8%; p = 0.012). In multivariable analysis, younger age at EC diagnosis (OR 0.99; p = 0.028) and personal history of colorectal cancer (OR 1.84; p $<$ 0.001) remained independently associated with PV status. Histologic subtype distribution differed between LS and DDR groups (p $<$ 0.001); endometrioid tumors were more frequent in LS (26.6% vs 22.7%), whereas serous carcinoma (7.3% vs 1.1%) and carcinosarcoma (4.2% vs 1.8%) were more frequent in DDR. Among pts with available immunohistochemical (IHC) data (n = 810), 51.2% (n = 415) showed mismatch repair protein loss. Of these, 96 (23.1%) had PVs in LS genes, 13 (3.1%) in DDR genes, and 9 (2.2%) in other genes; 297 (71.6%) had no germline PV. Notably, among 161 pts with MLH1/PMS2 loss and confirmed *MLH1* promoter methylation, 25 (15.5%) still harbored PVs; 4 (2.5%) in LS genes, 16 (9.9%) in DDR genes and 5 (3.1%) in other genes. **Conclusions:** Germline PVs were identified in over 20% of EC cases, extending beyond LS or Cowden syndrome. The presence of PVs in *MLH1*-methylated tumors—traditionally considered sporadic—is a critical finding that challenges current tumor-only triage. These results support universal multigene germline testing in EC. A complementary case–control analysis including cancer-free controls and an independent validation cohort will be presented. Research Sponsor: PROACTIVE study supported by DFCI.

10612 **Poster Session**

Expanded germline genetic testing of patients with hematologic malignancies to identify high proportion with hereditary cancer predisposition. First Author: Ozge Ceyhan-Birsoy, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Identifying hereditary cancer predisposition in patients with hematologic malignancies is critical for their clinical management, surveillance, donor selection, family, and reproductive counseling. However, genetic testing for patients with hematologic malignancies has been limited, largely due to the difficulty of obtaining suitable DNA samples for germline analysis. Heme Germline-MSK-IMPACT is a clinically validated assay for germline testing using nail or saliva DNA, depending on the patient's cancer type, in a non-invasive, rapid, and high-throughput manner, with the matched tumor analysis supporting results interpretation. **Methods:** Genetic testing was performed on 1300 consecutive patients with a clinical diagnosis or suspicion of a hematologic malignancy on Heme Germline-MSK-IMPACT, targeting 82 hereditary cancer predisposition genes. All individuals receiving somatic testing via paired tumor-normal sequencing on MSK-IMPACT-Heme as part of their clinical care were eligible to consent for germline analysis. **Results:** Germline pathogenic or likely pathogenic variants (gPVs) in hereditary cancer predisposition genes were identified in 16.7% (217/1300) of patients, with 5.8% (76/1300) having high penetrance autosomal dominant gene variants. gPVs known to be associated with hematologic malignancies were detected in *DDX41* (n = 14), *POT1* (n = 3), *RUNX1* (n = 2), *ETV6* (n = 1), *TP53* (n = 1). Additionally, four patients had biallelic variants in genes causing autosomal recessive disorders that confer increased risk for hematologic malignancies (*FANCA* (n = 2), *ATM*, *MSH6*). Other high-risk cancer predisposition genes with gPVs identified in multiple patients were *BRCA2* (n = 16), *BRCA1* (n = 15), *MSH6* (n = 4), *RTEL1* (n = 4), *CDKN2A* (n = 3), and *PALB2* (n = 3). Moderate penetrance gPVs were detected in 6.2% (81/1300) of patients in genes such as *CHEK2* (n = 36), *ATM* (n = 24), and *LZTR1* (n = 8). Twenty-four (1.8%) patients had two or more gPVs identified. **Conclusions:** Germline testing in a broad cohort of individuals with hematologic malignancies detected hereditary cancer predisposition in a substantial proportion of the patients. This ratio is comparable to the rate of cancer predisposition variants identified in patients with solid tumors in recent studies. Matched tumor data analysis is ongoing to uncover second hits and correlations for improving our understanding of the hereditary contribution to hematologic malignancies. Research Sponsor: National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer CenterP30 CA008748; Marie-Josée and Henry R. Kravis Center for Molecular Oncology, the Precision, Interception and Prevention Program; Robert and Kate Niehaus Center for Inherited Cancer Genomics; V Foundation.

10613 **Poster Session**

Prevalence of microsatellite stable Lynch syndrome and universal germline testing: A pan-cancer analysis of 246,694 patients. First Author: Casey Cosgrove, The Ohio State University, Columbus, OH

Background: Lynch Syndrome (LS) is an inherited cancer syndrome that confers up to a 60% lifetime risk of colorectal (CRC), endometrial (EC), or other cancers, and up to a 40% risk of a second primary cancer. The current standard-of-care includes LS screening upon the diagnosis of CRC or EC (especially in patients $<$ 50 years old or with a strong family history) via immunohistochemistry for mismatch repair (MMR) protein deficiencies or microsatellite instability (MSI) testing algorithms; germline genetic testing is subsequently performed in MMR-deficient cases for confirmation . To assess the concordance between MSI status and LS, we evaluated the proportion of patients with pathogenic or likely pathogenic germline variants in a LS gene (LS-PGVs) who had microsatellite stable (MSS) tumors. **Methods:** We analyzed a pan-cancer cohort (n = 246,694) of patients who underwent personalized ctDNA testing (Signatera, Natera, Inc.), which involved whole exome sequencing (WES) of tumor and matched normal samples. MSI status was assessed in the tumor WES data by the MSISensor2 algorithm (MSI-H was defined as score $\geq$6.5). Germline single-nucleotide variants and short insertions/deletions from germline WES were identified and annotated with Variant Effect Predictor (v.105). The pathogenicity of variants in LS genes (*EPCAM*, *MSH2*, *MSH6*, *MLH1*, and *PMS2*) was determined using classifications available in the ClinVar database. **Results:** The pan-cancer cohort largely consisted of patients with CRC (n = 107,907; 44% of cohort), breast (n = 55,330; 22%), and other cancer types (each $\leq$4% of cohort) including EC (n = 5519; 2%). MSI status was determined in 84% (207,536/246,694) of the cohort, of whom 93% (193,110/207,536) had MSS tumors. LS-PGVs were identified in 1% (2418/207536) of the MSI-scored pan-cancer cohort. Among all pan-cancer patients with LS-PGVs, 36% (862/2418) had MSS tumors. Most patients with *EPCAM* PGVs (91%; 32/35) had MSS tumors. Conversely, only 17% (101/588) of patients with *MLH1* PGVs had MSS tumors. We next assessed concordance between LS-PGVs and MSI status in CRC and EC. Among CRC patients with an MSI score (n = 97,309), 12% (11,752/97,309) had MSI-H and 88% (85,554/97,309) had MSS tumors. Further, LS-PGVs were identified in 2% (1,759/97,309), of whom 25% (437/1,759) had MSS tumors. In EC patients with MSI scores (n = 4,625), 20% (926/4625) had MSI-H and 80% (3699/4625) had MSS tumors. Of these, LS-PGVs were identified in 2% (86/4625) among whom 44% (38/86) had MSS tumors. **Conclusions:** LS-PGV yield was 2% for both CRC and EC, and a substantial proportion of these patients had MSS tumors (CRC: 25%; EC: 44%). Given the high risk for secondary cancers associated with LS and the implications for cascade testing, these findings strengthen the existing recommendation for considering broader germline screening of all EC and CRC patients for LS. Research Sponsor: None.

10614 **Poster Session**

Spectrum of germline pathogenic and novel BRCA1 and BRCA2 gene mutations in a cohort of 1780 breast and ovarian carcinoma patients from east India. First Author: Amit Roy Chowdhury, JBS Haldane Centre of Molecular Medicine, Silicon University, Odisha, India

Background: Advances in our understanding of the molecular basis of cancer have pushed us in a new era of personalized medicine in oncology. The adoption of personalized medicine in Breast cancer (BC) and Ovarian cancer (OC) care holds significant promise. Homologous recombination repair (HRR) process aids in the restoration of halted replication forks during DNA replication. Where, an effective HRR depends on the normal functioning of oncoproteins, BRCA1 and BRCA2 playing crucial roles. **Methods:** Germline Next Generation Sequencing based BRCA1 & BRCA2 gene panel on ion torrent technology was employed in 1780 diagnosed BC and OC patients for genetic-molecular evaluation. Bioinformatics pipelining and data analysis was performed as per Ion Reporter predesigned stringent workflows for germline variant screening. Variants were called as per ACMG guidelines and framework. **Results:** A total of 993 (55.8%) BC, 673 (37.8%) OC and 114 (6.4%) patients with co-existing BC & OC participated in the study. Out of which, 232 (13%) patients were found to harbour a clinically significant BRCA1 or BRCA2 gene variant. Predominantly, BRCA1 was the most mutated gene (68%; n = 158), followed by BRCA2 (32%; n = 74) across cohort. 48.2% of BRCA variants were noted in BC while 41.7% in OC and 10.1% in co-existing BC & OC patients respectively. Majority of the pathogenic variants (55.4%) were detected in high-grade tumors with mean age of 45.2 years. Exon-10 (33.3%) of BRCA1 and exon-11 (47.2%) of BRCA2 genes were the most mutated regions detected. Additionally, findings revealed 21 (9.1%) novel (14 in BRCA1 and 07 in BRCA2 genes) variants across BRCA genes not reported previously in ClinVar (NCBI) or BIC (Breast Information Core) databases. BRCA1 gene, exon-02, c.68_69del (185delAG) was the most pre-dominant (10.3%) variant in the patient cohort. **Conclusions:** India has emerged as the global cancer capital with BC being the most incidental cancer in women. Investigating the BRCA1, BRCA2 gene status in the current patient cohort has enabled the identification of not only the recurring hotspot pathogenic variants but also novel variants, as per the NCCN guidelines with actionable targets. Among BC, elevated and alarming frequency of TNBC patients (37.5%) was noted. The study findings provide a wide spectrum of BRCA gene variants specific to East-Indian patients with novel gene mutations pertaining to Indian population. These findings support the development of targeted therapeutic strategies by enabling the alignment of individual patients with treatments most likely to confer clinical benefit. Such precision oncology approaches may improve therapeutic efficacy, minimize treatment related toxicity, and ultimately enhance quality of life among cancer patients. Keywords: Breast & Ovarian cancer; BRCA1; BRCA2; NGS; Precision therapeutics. Research Sponsor: None.

10615 **Poster Session**

Association of thymic epithelial tumors (TETs) with Lynch syndrome (LS) per germline genetic testing and molecular tumor analysis. First Author: Megan Dwyer, Dana-Farber Cancer Institute, Boston, MA

Background: LS is a hereditary cancer syndrome that increases risk for gastrointestinal, gynecologic, genitourinary, and other cancers, and is typically characterized by microsatellite instability (MSI-H), mismatch repair-deficiency (MMR-D), and high tumor mutational burden (TMB). TETs, including thymomas and thymic carcinomas, are rare neoplasms not known to be associated with LS and usually show low TMB and microsatellite-stable (MSS) biology. We sought to describe the clinical, pathologic, and molecular characteristics of TETs diagnosed in individuals with LS seen at our institution. **Methods:** We conducted a retrospective, single-institution study to identify TETs among individuals with LS. We queried all LS patients seen in the DFCI Cancer Genetics and Prevention program from 1990 (n = 1,386) and identified those with a TET. We also reviewed TET cases that had paired tumor–germline sequencing between July 2023 and September 2025 (n = 12) to identify additional cases with LS pathogenic germline variants (PGVs). Clinical and molecular data, including MMR immunohistochemistry (IHC), and tumor and germline sequencing reports, were abstracted from the medical record. **Results:** Of the 1,398 cases reviewed, 4 females were identified with TETs (1 thymoma and 3 thymic carcinomas) diagnosed at a median age of 54.0 years (range 23-70 years), all with a confirmed PGV in an MMR gene [Table 1]. All four cases had tumor characteristics consistent with MMR-D. Two TETs were MMR-D by IHC, and one TET had biallelic *MLH1* variants on somatic testing, so MMR-D is inferred. Three TET cases were MSI-H by next generation sequencing, and one was MSS, despite being MMR-D by IHC. Three cases had high TMB and one did not have TMB assessment. One patient received neoadjuvant chemotherapy for two cycles, with the addition of pembrolizumab after discovering the tumor's MSI-H status; this patient had a pathological complete response at surgery. One patient received neoadjuvant chemotherapy, surgery, and adjuvant proton beam radiation; another received neoadjuvant chemoradiotherapy followed by surgery. The fourth underwent resection and plans adjuvant therapy. All four are alive at a median of 34.8 months post-surgery (range 3.6-60.7 months). **Conclusions:** Our data show that TETs in patients with LS frequently demonstrate molecular biology (MMR-D, MSI-H, TMB-H) like other classic LS-associated cancers, suggesting that these may be rare manifestations of LS. Further clarifying the link between LS and TETs may have important implications for treatments. Research Sponsor: None.

Age at diagnosis	Sex	Histologic subgroup	TMB (mut/Mb)	Microsatellite status	MMR status	PGV
53	F	Thymoma	30.4	MSI-H	MMR-D	MLH1 c.116+2T>G
70	F	Thymic squamous cell carcinoma	18.25	MSI-H	NA	MSH6 5'UTR_EX6del
23	F	Poorly differentiated carcinoma, favor thymic origin	14.48	MSI-H	MMR-D	MSH2 c.1906G>C
55	F	Thymic carcinoma	NA	MSS	MMR-D	PMS2 c.2137C>T

10616 **Poster Session**

Population-based analysis of cancer disparities and social determinants of health in hereditary cancer syndrome carriers: A Healthy Nevada Project study. First Author: Haley Nadone, University of Nevada, Reno School of Medicine - Department of Internal Medicine, Reno, NV

Background: Hereditary cancer syndromes account for approximately 5-10% of all cancers, the most common being Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome (LS). Despite the availability of genetic testing that can reduce cancer morbidity and mortality in carriers, significant disparities exist across various socioeconomic and racial groups. **Methods:** This retrospective cohort study analyzed participants from the Healthy Nevada Project (HNP) who underwent genetic testing for hereditary cancer syndromes. A study protocol was developed by the research committee prior to implementation. Participants were classified as positive or negative for HBOC syndrome (BRCA1/2 pathogenic variants) and Lynch syndrome (mismatch repair gene pathogenic variants). Race, age and ethnicity were categorized along with census tract-level social determinants of health (SDOH) measures including median household income and percent rural population. Descriptive statistics characterized the cohort by demographic and clinical variables. Associations between SDOH and cancer outcomes including diagnosis and age at diagnosis, were assessed using chi-square and logistic regression analysis to test for significance. Multivariable logistic regression models were constructed to assess independent associations between SDOH factors and cancer outcomes, adjusting for confounding variables. **Results:** A total of 47,737 patients were identified using the HNP database. Genetic testing occurred after cancer diagnosis in 99.6% of participants with cancer (2,542/2,552). Delays differed significantly across racial groups ($p<0.001$). There were no significant bivariate nor multivariate associations between HBOC and gender (p=0.63;0.61), race (p=0.52;0.70), Ethnicity (p=0.36; 0.67), income (p=0.75;0.88) or rurality (p=0.52; 0.63). In multivariable logistic regression, younger age at testing was independently associated with genetic test positivity (OR 0.993 per year; 95% CI 0.988–0.999; p=0.014). **Conclusions:** Population-based studies examining the intersection of hereditary cancer syndromes and SDOH remain limited, particularly in diverse cohorts that reflect real-world demographics. The absence of differences in pathogenic variant prevalence across sociodemographic groups suggests that population-based genetic screening may mitigate traditional disparities in genetic yield. However, observed differences in age at testing indicate persistent inequities in timing of access, which may influence early cancer detection. In fact, delayed post-diagnosis genetic evaluation is common across all SDOH groups in this cohort. Understanding these relationships is essential for developing equitable cancer prevention and control strategies that address both genetic predisposition and the social context in which carriers live. Research Sponsor: None.

10617 **Poster Session**

Evidence supporting *RPS20* as a colorectal cancer susceptibility gene from a case-control MGPT study. First Author: Sarah Nielsen Young, Labcorp (formerly Invitae Corp.), San Francisco, CA

Background: Ribosomal protein S20 (*RPS20*) is increasingly included in colorectal cancer (CRC) germline multigene panel testing (MGPT) and clinical management guidelines, despite limited evidence of gene-disease association. Germline loss-of-function (LOF) variants in *RPS20* have been observed in a small number of individuals with CRC, without tumor loss-of-heterozygosity, and have typically been classified as variants of uncertain significance (VUS). We conducted a case/control study of individuals heterozygous for *RPS20* LOF variants to evaluate the CRC and colorectal polyp risk compared to controls and cases of established CRC susceptibility genes. **Methods:** Cases and controls underwent MGPT at Invitae (now part of Labcorp) from May 2018-May 2025. Cases included individuals with a single LOF variant in *RPS20* who had no identified pathogenic variants (PV) in other hereditary cancer genes and no VUS in established CRC risk genes; controls consisted of individuals with no PV or VUS identified. To reduce ascertainment bias, cases and controls were identified from requisitioned (clinician-ordered, reported) and unrequisitioned (run on MGPT backbone but unreported) data, under WCG protocol 1167406. Ninety controls were randomly sampled and age/sex matched to cases. CRC/polyp diagnoses were determined by clinician-reported ICD10 codes and keywords and compared between cases and controls utilizing Fisher's exact tests. To compare risk estimates with a well-defined hereditary CRC syndrome, odds of CRC/polyps in cases with *RPS20* LOF variants and in cases with mismatch repair gene PVs (*MLH1, MSH2, MSH6, PMS2*), both compared to controls, were estimated with multivariable logistic regression that included sex, age, requisition status, family history of cancer, and race/ethnicity. **Results:** Twenty-seven heterozygous *RPS20* LOF cases were identified (median age at testing 48 years [IQR 35-37]). CRC prevalence was significantly higher in *RPS20* LOF cases (63.0%) compared with controls (11.1%, p= <0.001), while polyp prevalence did not differ (7.4% vs. 10.0%, p=1). In multivariable analysis, *RPS20* LOF variants were associated with increased odds of CRC compared with controls (odds ratio [OR] 18.0; 95% confidence interval [CI], 5.2–62.1), comparable to odds observed for MMR gene PGV cases (OR 9.5; 95% CI, 6.6–13.7). **Conclusions:** Heterozygous *RPS20* LOF variants identified through MGPT are associated with substantially increased CRC risk. By incorporating age- and sex-matched controls and unrequisitioned testing data, this study reduces ascertainment bias and supports RPS20 as a CRC susceptibility gene. Larger studies are needed to inform clinical management. Research Sponsor: None.

Multivariable logistic regression, *RPS20* LOF cases compared to controls.

Cancer/polyps	OR	CI	p-value
CRC	18.0	5.2 - 62.1	<0.001
Colon polyps	0.8	0.2 - 3.0	0.719
CRC/polyps	10.2	3.5 - 29.5	<0.001
Other Cancer	2.5	0.9 - 6.6	0.114

10618 **Poster Session**

Feasibility of a novel oncologist-led diagnostic algorithm for Lynch syndrome in colorectal cancer patients: The ItaLynch study. First Author: Alberto Puccini, Humanitas University, Pieve Emanuele, IRCCS Humanitas Research Hospital, Humanitas Cancer Center, Milano, Italy

Background: International guidelines recommend universal Lynch syndrome (LS) screening in colorectal cancer (CRC) using tumor mismatch repair deficiency (dMMR) testing. However, LS remains underdiagnosed worldwide, largely due to inconsistent referral for genetic counseling and germline testing. We report the final feasibility results of a novel, mainstreamed, oncologist-led diagnostic algorithm for LS. **Methods:** ItaLynch is a prospective, observational, multicenter Italian study on patients with dMMR CRC (May 2021–Dec 2025; 23 high-volume centers). The pathway includes: (1) universal dMMR screening by immunohistochemistry (IHC) in all CRC; (2) reflex testing and "Lynch alert": MLH1-deficient (dMLH1) tumors undergo BRAFV600E testing and, if wild-type, MLH1 promoter methylation; a Lynch alert is added to all dMMR pathology reports (positive for high LS risk based on reflex testing or non-MLH1 loss; negative for BRAFV600E-mutated or MLH1-hypermethylated cases); (3) oncologist-led mainstream germline testing for patients with positive alert, followed by post-test genetic counseling for carriers of pathogenic variants (PV) or clinically suspicious cases. **Results:** Up to Dec. 31 2025, we enrolled 1,482 pts with dMMR CRC. Overall, 1,316 were eligible for analysis (14 not eligible; 152 not yet filled out). Excluding 104 cases with incomplete data, 1,212 patients were evaluable from somatic to germline testing. Overall, 1033 (85%) completed the ItaLynch diagnostic pathway, demonstrating the strong feasibility of this this algorithm. Of patients with IHC data, 975 (78%) were dMLH1 and 281 (22%) had non-MLH1 loss. BRAF testing was performed in 904/975 (93%) dMLH1 cases; 386/904 (43%) were BRAFwt. MLH1 methylation testing was done in 329/386 (86%); 146/329 (44%) were not hypermethylated. Germline testing was performed in 108/146 (74%), identifying 21 LS-associated PV (19%). Among non-MLH1 loss, 232/281 (83%) underwent germline testing and 115 (50%) were diagnosed with LS. Overall, germline testing was performed in 361/1,033 adherent patients (35%), identifying 143 PV (40% of tests) and 24 VUS; PV prevalence was 14% (143/1,033). Mainstreaming reduced genetic pre-test counseling visits by 54% (196/361 avoided) and, compared with universal germline testing, avoided 672/1,033 tests (65%). Post-test counseling uptake was 83% among PV carriers. Median turnaround time from somatic to germline diagnosis was 217 days for dMLH1 and 73 days for non-MLH1. Among non-adherent patients, 67 underwent germline testing (14 PV, 3 VUS). In the full cohort, 157 PV were identified (MLH1 37, MSH2 57, MSH6 43, PMS2 20). **Conclusions:** This oncologist-led, mainstreamed diagnostic pathway for LS is feasible and optimized use of healthcare resources. Analyses of pathway deviations (15%), cost-effectiveness, and clinical/translational outcomes are ongoing. Research Sponsor: None.

10619 **Poster Session**

A randomized controlled trial of a multilingual digital genetic cancer risk assessment tool in a diverse patient population. First Author: Tina Karimaghaie, Genetics and Personalized Cancer Prevention Program, Weill Cornell Medicine, New York, NY

Background: Most individuals with hereditary cancer risk remain unidentified, particularly racial, ethnic, and linguistic minorities and those publicly insured. Patient-facing digital tools may improve personal/family history collection and genetic cancer risk assessment (GCRA). In this randomized controlled trial (RCT), we evaluated a multilingual digital GCRA tool in a diverse, predominantly publicly insured population. **Methods:** An IRB-approved RCT (NCT05562778) was conducted among new patients at four urban academic gynecology clinics. Eligible patients (≥ 18 years old, English-, Spanish-, Cantonese-, or Mandarin-speaking, no prior cancer genetic testing (GT)) were randomized to a digital GCRA tool versus usual care. The digital tool collected patient history and generated National Comprehensive Cancer Network (NCCN)-based GT eligibility reports for providers. Usual care relied on clinician assessment of personal/family history. The primary outcome was clinician identification of high-risk patients and recommendation for GT. **Results:** From 10/2023 to 10/2025, 210 patients enrolled in the study; 104 (50%) were randomized to GCRA via digital tool and 106 (50%) via clinician interview. Eighty (38%) patients self-identified as Hispanic, 39 (19%) non-Hispanic White, 40 (19%) non-Hispanic Black, and 51 (24%) Asian; 159 (76%) were English-speaking, 40 (19%) Spanish-speaking, and 11 (5%) Mandarin/Cantonese-speaking. Most were publicly insured (133, 63%), (Table 1). In the intervention arm, 99 (95%) completed the digital tool. Among all patients, 36 (17%) were identified as meeting NCCN criteria for high risk of hereditary cancer and thus eligible for GT (intervention: 14; control: 22). Use of the digital GCRA tool was associated with a higher likelihood of high-risk patients being identified and recommended GT (13 [93%] vs. 3 [14%]; P = < 0.001). Digital tool completion and high-risk identification did not differ by race, ethnicity, or language. **Conclusions:** In a diverse, predominantly publicly insured population, a multilingual digital GCRA tool increased identification and recommended GT for those at elevated risk for hereditary cancer. Integrating such tools may improve detection of at-risk individuals and reduce disparities in genetic service utilization. Clinical trial information: NCT05562778. Research Sponsor: Weill Cornell Medicine: Research Assistance for Primary Parents; Weill Cornell Medicine: Ritu Banga Healthcare Disparities Research; Weill Cornell Medicine: Meyer Cancer Center.

Participant characteristics.

Characteristic	Total	Control	Intervention
Age in years (median, (IQR))	45.5 (34-59)	46.5 (34-58)	43.4 (33.5-59)
Race and Ethnicity (N (%))			
Hispanic	80 (38%)	40 (38%)	40 (38%)
Non-Hispanic White	39 (19%)	20 (19%)	19 (18%)
Non-Hispanic Black	40 (19%)	21 (20%)	19 (18%)
Asian	51 (24%)	25 (24%)	26 (25%)
Primary Insurance (N (%))			
Public	133 (63%)	64 (60%)	69 (66%)
Private	46 (22%)	26 (25%)	20 (19%)
No Coverage/Other	31 (15%)	16 (15%)	15 (14%)

IQR: interquartile range. Public: Medicaid, Medicare, or other government insurance. Private: employment-based or directly purchased.

10620 **Poster Session**

Age-stratified evaluation of subsequent primary malignancy risk in patients with primary Lynch syndrome–spectrum cancers. First Author: Vinit Singh, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Lynch syndrome spectrum cancers (LSSC) include several of the most common cancers in both men and women. Patients with LS are advised to undergo intensive cancer screening and genetic evaluation. However, most at-risk individuals are not assessed by a cancer geneticist, especially those in middle or older age, despite these cancers often appearing late in life. This study evaluates the incidence and timing of LS-related and non-LS–related subsequent primary malignancy (SPMs) in patients diagnosed with LSSCs. **Methods:** We used SEER data (1992–2021) to identify patients with LSSC – colorectal (CRC), endometrial (EC), gastric, Bladder/GU tract (GUC), Small bowel, ovarian, pancreatic, sebaceous, and brain (BC) by using histology and site code. Demographics, survival data, and SPMs details were extracted. Patient were stratified by age < 40 years, 40-60 years, and > 60 years. We calculated the mortality-related competitive risk-adjusted cumulative incidence (CI) of SPMs at 5 and 10 years for both LSSCs and all cancers. Median follow up were calculated by reverse KM method. We calculated the time to the development of 1st SPM after the index cancer diagnosis. Proportions were compared using chi-square test. **Results:** We identified 774955 patients with LSSC (50.4% Female, mean age 66.2 (SD 13.3) with a median follow-up of 149 months. 74331 (9.6%) patients developed a subsequent malignancy, with 30666 (41.3%) of all SPM had at least 1 LSSC. In < 40 year, 40-60-year, and > 60 years groups, 4.5%, 8.1%, and 10.5 % of total patients with LSSCs had a SPM of which 68.2%, and 43.3%, and 39.9 % patient had at least 1 LSSCs (p < 0.001). Median time to cancers and adjusted CI is given in the table. There was significant difference in distribution of primary (p-value < 0.01) and subsequent (p-value < 0.01) LSSC. CRC was the most common primary LSSC across age group, with Brain, and EC, and GU Cancers were the 2nd most common cancer in < 40, 40-60, and > 60-year age group respectively representing 19.3%, 16.7%, and 22.9% cancers of respective LSSCs. Among SPM, CRC was the most common across all age group (42.8% of LSS SPM) whereas EC was 2nd most common LSS SPM in < 40 years, and GU cancers in both 40-60 (35%), and > 60 (31.8%) years group. **Conclusions:** For LSSC patient, likelihood of developing SPM increased with longer survival, and older patients demonstrated the highest SPM burden for both LSSC and non-LSSCs. These findings suggest that cancer genetics evaluation and robust LS-directed surveillance should be extended beyond younger populations, as older patients remain at significant risk for LS-related SPMs. Research Sponsor: None.

Age group	*18-40 Years*	*41-60 Years*	*>60 Years*
Median follow up (months)	131	141	155
Median time to any SPM	40	52	28
Median time to subsequent LSSC	22	28	22
	Any SPM		
5-year CI %	2.8	4.7	7.8
10-year CI %	3.7	7.1	10.6
	Subsequent LSSC		
5-year CI %	2.3	2.4	3.3
10-year CI %	2.8	3.2	4.3

10621 **Poster Session**

Prevalence, tumor characteristics, and clinical impact of *LZTR1* pathogenic variants in a large, pan-cancer cohort. First Author: Anushri Soni, Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: Heterozygous germline pathogenic/likely pathogenic (P/LP) loss-of-function (LOF) variants in *LZTR1* are associated with hereditary schwannomatosis. To date, the prevalence and penetrance remain poorly defined, and there are currently no well-established surveillance guidelines for individuals with incidental *LZTR1* P/LP variants. We sought to describe the prevalence of *LZTR1* P/LP variants in a large pan-cancer cohort, characterize the tumor genomic profile of patients with these variants, and report the clinical utility of surveillance imaging in asymptomatic carriers diagnosed incidentally. **Methods:** Patients with germline P/LP variants in *LZTR1* were identified from pan-cancer patients who prospectively enrolled in an institutional review board-approved protocol of matched tumor-normal DNA sequencing (MSK-IMPACT). Clinical and tumor characteristics of *LZTR1* carriers were collected from electronic medical records. **Results:** Among 50,537 patients who underwent germline genetic testing via MSK-IMPACT, 157 (0.31%) were found to harbor a heterozygous germline P/LP variant in *LZTR1*. Eight patients presented with a schwannoma diagnosis at the time of genetic testing with an additional three reporting a prior history of schwannoma, for a total of 11 (7.01%) meeting criteria for LZTR1-associated schwannomatosis. In the remaining 146 (93%) of patients, the germline *LZTR1* P/LP variant was an incidental finding. The most common cancer types in those identified incidentally included prostate (23), breast (22), colorectal (21), sarcoma (14), and uterine (9). Of the 6 schwannomas with tumor data available, all exhibited a second somatic mutation in the *NF2* gene, and 5 displayed loss of heterozygosity of the *LZTR1* locus in the tumor favoring the mutant allele. LOH data was available for 117 non-schwannoma tumors. Of these, 33 (28.2%) were found to have LOH favoring the mutant LZTR1 allele. Of patients diagnosed incidentally, 29 underwent MRI of the brain and total spine after detection of the *LZTR1* P/LP variant for schwannoma screening. An additional 104 patients underwent whole body imaging (PET/CT or CT chest, abdomen, and pelvis) for cancer surveillance. All patients were asymptomatic and did not have clinical evidence of schwannomatosis on history or physical exam. Of these 133 asymptomatic *LZTR1* carriers, no (0%) schwannomas were identified. **Conclusions:** The prevalence of *LZTR1* P/LP variants was 0.3% in an unselected pan-cancer population with < 10% meeting criteria for *LZTR1*-associated schwannomatosis, suggesting low penetrance. Imaging performed after variant detection did not identify previously unrecognized disease, suggesting limited clinical utility of routine surveillance in asymptomatic carriers without supportive clinical features. These findings support a more selective, risk-informed approach to management of incidental *LZTR1* variants. Research Sponsor: None.

10622 **Poster Session**

Diabetes risk reduction diet and mortality outcomes following breast cancer diagnosis in Black women. First Author: Lawrence Deng, Rutgers Robert Wood Johnson Medical School, Piscataway, NJ

Background: Black women continue to experience a ~40% higher breast cancer mortality rate than White women. Type II diabetes (T2D) management-related factors have received increasing attention as contributors to this disparity. Emerging evidence, largely derived from studies conducted among White women, suggests that adherence to the diabetes risk reduction diet (DRRD) may be associated with improved breast cancer outcomes. Despite Black women having more than twice the risk of developing T2D compared with White women, no studies to date have examined the association between the DRRD and mortality among Black breast cancer survivors. **Methods:** We conducted a cohort analysis of 1,732 Black breast cancer survivors from the Women's Circle of Health Follow-Up Study. Participants' prediagnostic intake of DRRD components was calculated from validated food frequency questionnaires that included: cereal fiber, coffee, nuts, whole fruits, polyunsaturated/saturated fat ratio, glycemic index, trans fats, sugar-sweetened beverages, and red/processed meat. Consumption levels for each component were scored 1-5, summed to form a DRRD adherence score (higher scores signify greater adherence), and further categorized into tertiles. Death outcomes and causes were ascertained via linkage to the New Jersey State Cancer Registry. Associations with mortality were evaluated using multivariable-adjusted Cox proportional hazards regression models. **Results:** After a median of 10.8 years of follow-up since diagnosis, 422 total deaths (213 breast cancer-related) were identified. The mean DRRD score was 26 (std 5.5). In the multivariable–adjusted model, women with higher scores had a 34% lower risk of breast cancer-specific mortality (top vs. bottom tertile HR = 0.66; 95% CI = 0.46-0.93; p = 0.02) and a 23% lower risk of overall mortality (HR = 0.77; 95% CI = 0.59-1.00; p = 0.05). The associations were consistent across diabetes and menopausal status, and also across household income subgroups. However, the risk reduction appeared more pronounced among women with early-stage disease (HR = 0.54; 95% CI = 0.34-0.88), luminal tumor subtypes (HR = 0.49; 95% CI = 0.28-0.87), those with a BMI ≥30 kg/m^2 (HR = 0.55; 95% CI = 0.34-0.88), and those in the lower half of the neighborhood socioeconomic status distribution (HR = 0.57; 95% CI = 0.35-0.93), compared with their respective counterparts. **Conclusions:** This study represents the first and largest investigation of DRRD adherence and breast cancer outcomes among Black women. Our findings suggest that greater DRRD adherence may offer a protective effect on both breast cancer-specific and overall mortality in Black women, a population facing the highest breast cancer mortality in the US. More broadly, these results, together with prior evidence, suggest that adhering to dietary patterns consistent with T2D prevention may be important for both White and Black breast cancer survivors. Research Sponsor: National Cancer Institute; R01CA185623; National Cancer Institute; P30CA072720-5929; National Cancer Institute; R01CA100598; National Cancer Institute; R00CA267557; Muriel Genfan Endowed Scholarship Fund; National Cancer Institute; 75N91021D00009; National Program of Cancer Registries (NPCR); NU58DP007117.

10623 Poster Session

Leisure-time physical activity among US cancer survivors, 2020-2024. First Author: Ruixuan Wang, Dana-Farber Cancer Institute, Boston, MA

Background: Physical activity (PA) after a cancer diagnosis reduces treatment-related side effects and improves quality of life and cancer outcomes. Historical data show that most cancer survivors do not meet recommended levels of aerobic and strength training PA. However, the recent pattern of PA in people with cancer remained unexamined. **Methods:** This pooled cross-sectional study analyzed data from the 2020, 2022, and 2024 National Health Interview Survey to examine the prevalence and predictors of meeting PA guidelines among US cancer survivors vs. non-cancer adults. The analytic sample included adults aged ≥18 years with available cancer history. Data were collected on frequency and duration of aerobic and strength training PA. Age-adjusted prevalence of meeting aerobic (≥150 minutes per week of moderate-intensity activity or ≥75 minutes per week of vigorous-intensity activity) and strength training (≥2 days per week) PA guidelines were estimated across sociodemographic and health characteristics among cancer survivors and non-cancer adults. Multivariable logistic regression models were fitted to identify factors associated with meeting PA guidelines among cancer survivors. **Results:** The final sample included 8,974 cancer survivors (Mean age: 65.7 [SE: 0.21]; 57.3% female) and 79,036 non-cancer adults (Mean age: 46.6 [SE: 0.11]; 51.1% female). After age-adjustment, 44.5% of cancer survivors met guidelines for aerobic exercise (95% CI: 41.8-47.3), 28.9% for strength training (26.3-31.6), and 22.2% for both (19.8-24.7%), significantly lower than the non-cancer group (48.3%, 32.5%, and 26.0%; all $p<0.01$). Patterns of lower prevalence were consistent across aerobic, strength training, and combined guidelines. Among cancer survivors, age-adjusted prevalence of meeting PA guidelines was significantly lower among those who were female, non-Hispanic Black or Hispanic, had lower levels of education or income, lived alone, were unemployed, had BMI ≥ 25, or were current smokers (all $p<0.05$). Survivors of gynecological and lung cancers had significantly lower age-adjusted prevalence of meeting both aerobic and strength training guidelines, while gastrointestinal cancer survivors had lower prevalence of meeting strength training guidelines only (all $p<0.01$). After adjustment for all covariates, not meeting PA guidelines in cancer survivors remained significantly associated with older age, female, lower education level, BMI ≥ 25, current smoking, and presence of cardiovascular disease or diabetes (all $p<0.05$). **Conclusions:** During 2020 and 2024, fewer than 1 in 4 cancer survivors met both aerobic and strength training PA guidelines. These findings underscore a critical need to integrate PA interventions into standard oncology survivorship care, with particular attention to addressing socioeconomic barriers and tailoring programs for survivors with comorbidities and high-risk cancer types. Research Sponsor: National Cancer Institute; 5T32CA057711-32.

10624 Poster Session

Alcohol-related hospitalizations among patients with cancer in the United States: Trends and associated risk factors. First Author: Anna Mehlich, De-Department of Internal Medicine, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Alcohol consumption is associated with an increased risk of developing multiple cancers and has been linked to higher cancer-related mortality. Alcohol dependence and harmful alcohol use may also compromise oncologic care and worsen the clinical course. However, little is known about the prevalence and outcomes of alcohol-related hospitalizations among patients with cancer. **Methods:** We analyzed trends and risk factors of alcohol-related hospitalizations among adults with cancer using the National Inpatient Sample database for the years 2016-2021. Alcohol-related admissions were identified using ICD-10 codes for intoxication, withdrawal, alcohol-induced mood and psychotic disorders, and other alcohol-induced disorders. Prevalence estimates were adjusted using discharge-level weights to represent national data. Linear and multivariate logistic regression were used to assess trends in alcohol-related admissions and associations with sociodemographic and clinical characteristics. **Results:** Among 12,027,846 non-elective hospitalizations for patients with cancer, 15,205 (0.13%) were alcohol related. From 2016 to 2021, we observed an average increase of 185 admissions per year (from 2130 to 3200, $P = 0.009$). After adjusting for all non-elective hospitalizations in cancer patients, the linear time trend in alcohol-related admissions increased by an average of 0.008% per year ($P < 0.001$). When stratified by diagnosis type, alcohol withdrawal was the leading cause of alcohol-related admissions (69.4%), followed by alcohol intoxication (22.2%). Factors associated with alcohol-related admissions included male sex, younger age, white race, rural residence, housing instability, opioid use disorder, mood and psychotic disorders (Table 1). **Conclusions:** Alcohol-related hospitalizations are rare among patients with cancer but have shown a significant upward trend in recent years. The factors linked to alcohol-related admissions in this population mirror known risk factors for harmful alcohol use among non-cancer patients. Further research is needed to improve alcohol use disorder screening, prevention, and management strategies for patients with cancer, particularly in high-risk populations. Research Sponsor: None.

Multivariable predictors of alcohol-related hospitalizations in cancer patients.

Characteristics	Alcohol-related hospitalization Odds Ratio (95% CI)
Sex	
Female	1 (reference)
Male	3.18 (2.90-3.47)
Age category, years	
18-29	1.72 (1.18-2.53)
30-49	5.96 (5.11-6.94)
50-69	4.25 (3.78-4.79)
>70	1 (reference)
Race/ethnicity	
White	1 (reference)
Black	0.57 (0.51-0.66)
Hispanic	0.51 (0.43-0.60)
Asian	0.15 (0.10-0.26)
Other	0.67 (0.56-0.81)
Hospital location	
Urban	1 (reference)
Rural	1.29 (1.11-1.50)
Housing instability	5.84 (5.00-6.84)
Opioid use disorder	2.37 (2.01-2.81)
Depressive disorder	3.51 (3.23-3.82)
Psychotic disorder	1.27 (1.01-1.61)

10625 Poster Session

Association of proton pump inhibitor use with cancer-specific mortality in a nationally representative U.S. cohort (NHANES, 1999–2018). First Author: Albine Djeagou F., Rutgers Health Community Medical Center, Toms River, NJ

Background: Proton pump inhibitors (PPIs) are widely used and often continued beyond recommended durations. Evidence linking chronic PPI use to adverse cancer outcomes and mortality is mixed. Potential mechanisms include hypergastrinemia, altered gastric mucosa, and microbiome changes that may influence tumor behavior and treatment response. We assessed the association between baseline PPI use and cancer-specific mortality in a nationally representative U.S. cohort. **Methods:** Ten NHANES cycles (1999–2018) linked to the NHANES Linked Mortality Files (1999–2018) were pooled. Adults ≥18 years who were mortality-eligible and had examination follow-up time (PERMTH_EXM) were included. A formal written protocol was not developed; the analysis plan (study objective, exposure, endpoint, covariates, and primary models) was prespecified through discussion with the study team prior to final analyses. Baseline PPI exposure was defined from the 30-day prescription medication inventory (container-verified when available). A curated text algorithm identified PPIs using generic/brand/OTC names and fixed-dose combinations. Cancer death was defined as leading cause of death = malignant neoplasm; non-cancer deaths were censored (cause-specific hazard). Survey-weighted Cox models incorporated strata/PSU and pooled MEC weights (WTMEC2YR/10). Models used complete-case covariates per model. **Results:** Among 56,253 adults (1,850 cancer deaths), baseline PPI use was associated with higher cancer-specific mortality in unadjusted analysis and remained elevated after sequential adjustment (Table). **Conclusions:** PPI use was associated with higher cancer-specific mortality in a nationally representative U.S. cohort. These findings support careful review of PPI indication and duration and reinforce deprescribing when PPIs are not clearly indicated. Residual confounding remains possible, warranting studies using designs that better address this bias. Research Sponsor: None.

Sequentially adjusted survey-weighted Cox models estimating the cause-specific hazard of cancer death associated with PPI use (NHANES 1999–2018).

Model	N	Events	HR (CI)
Model 0: Unadjusted	56253	1850	2.63 (2.21 - 3.12)
Model 1: +Age +Sex	56253	1850	1.36 (1.14 - 1.62)
Model 2: +Race +PIR	51140	1695	1.40 (1.17 - 1.68)
Model 3: +Diabetes +Hypertension +HLD	51140	1695	1.40 (1.18 - 1.67)
Model 4: +log(cotinine)+log(metals)	9538	407	1.45 (1.10 - 1.91)

PIR = Poverty Income Ratio.
HLD = Hyperlipidemia.
Metals = lead, cadmium, mercury.
HRs represent cause-specific hazards for cancer death; non-cancer deaths were treated as censoring events.

10626 Poster Session

The impact of high body-mass index on cancer mortality in the United States: An emerging public health challenge. First Author: Charbel Fadi Matar, The George Washington University, Washington, DC

Background: Obesity prevalence has increased markedly in the United States, yet the contribution of high body-mass index (BMI) to age-standardized mortality rates (ASMR) across cancer types, sex, and age groups over three decades remains poorly defined. We evaluated temporal trends in BMI-associated ASMR to identify cancers and populations most affected and inform prevention and equity-focused strategies. **Methods:** Using Global Burden of Disease (GBD) 2023 data, we extracted U.S. mortality estimates attributable to high BMI for neoplasms overall and selected cancer types from 1990-2023. BMI-associated ASMRs were compared by cancer type and sex, alongside age-specific rates for adults aged 20–54 years and all-age estimates. Age-standardized rates were used to distinguish changes in risk from demographic aging, while age-specific analyses assessed early-onset burden. **Results:** Between 1990-2023, BMI-attributable cancer mortality among adults aged 20–54 years increased by 44% (1.79 to 2.58), indicating a shift in the population-level burden toward earlier life. Overall BMI-attributable ASMR increased from 7.28 to 7.87, while all-age mortality increased from 9.15 to 14.15. Among evaluated cancers, liver, pancreatic, and uterine cancers demonstrated the largest increases in BMI-attributable ASMR. Liver cancer ASMR increased from 0.29 to 1.02 (~250%), pancreatic cancer from 0.13 to 0.40 (~200%), and uterine cancer from 1.02 to 1.74 (~70%). Early-onset BMI-attributable mortality also increased for liver (0.11 to 0.33), pancreatic (0.04 to 0.12), and colon cancer (0.53 to 0.90). Male predominance was observed for liver, pancreatic, kidney, and colon cancers, whereas uterine cancer accounted for the highest BMI-attributable burden among women. Marked geographic heterogeneity was observed, with the highest-to-lowest state BMI-attributable ASMR ratio of approximately 2.36 in 1990 (District of Columbia vs Hawaii) and 1.75 in 2023 (West Virginia vs Hawaii), indicating persistent but shifting geographic disparities. These patterns suggest amplification of existing cancer inequities at the population level over time. **Conclusions:** High BMI represents an increasingly important population-level contributor to cancer mortality burden in the U.S., with rising BMI-attributable ASMRs for metabolically associated malignancies and emerging early-onset burden. These findings underscore the importance of obesity prevention and metabolic risk reduction earlier in life as potential strategies to mitigate future cancer mortality and reduce inequities. Research Sponsor: None.

BMI-associated cancer mortality rates by age group and sex, United States, 1990–2023.

Age group / Metric	Sex	1990	2023
20-54	Both	1.79	2.58
	Female	1.67	2.62
	Male	1.91	2.54
All ages	Both	9.15	14.15
	Female	11.41	16.44
	Male	6.77	11.82
Age-standardized	Both	7.28	7.87
	Female	8.00	8.43
	Male	6.29	7.20

10627 **Poster Session**

Oxybutynin for vasomotor symptoms across cancer-related and menopause-associated settings: A systematic review and meta-analysis of randomised control trials and observational studies. First Author: Arundhati Sharma, Guthrie Robert Packer Hospital, Sayre, PA

Background: Vasomotor symptoms, including hot flashes, are a frequent and debilitating adverse effect among postmenopausal women and patients receiving cancer-directed hormonal therapies, particularly endocrine therapy in breast cancer and androgen deprivation therapy in prostate cancer. Hormone-based therapies are often contraindicated in cancer populations, underscoring the need for effective non-hormonal treatment strategies. Oxybutynin, an anticholinergic agent approved for overactive bladder, has emerged as a potential non-hormonal therapy for vasomotor symptoms; however, the magnitude of benefit and tolerability across randomized studies in diverse clinical populations has not been comprehensively quantified. **Methods:** A systematic search of PubMed, Embase, Cochrane CENTRAL, and clinical trial registries was performed to identify randomized controlled trials evaluating oxybutynin for vasomotor symptoms in postmenopausal women and cancer populations, including patients receiving endocrine therapy and androgen deprivation therapy. Outcomes included change in hot flash composite score (frequency $\times$ severity), change in hot flash frequency, and discontinuation due to adverse effects. **Results:** 5 studies were identified, including four randomized controlled trials and one observational cohort (409 randomized participants). Oxybutynin was associated with a significant improvement in hot flash composite score compared with control (mean difference 8.81, 95% confidence interval 6.51–11.10; $p < 0.00001$; $I^2 = 54\%$). Subgroup analyses demonstrated greater improvement with higher doses (5 mg twice daily) compared with lower doses (2.5 mg twice daily), although both dose ranges were superior to control. Hot flash frequency was significantly reduced with oxybutynin (mean difference 3.88 episodes per day, 95% confidence interval 2.96–4.80; $p < 0.00001$; $I^2 = 42\%$), with larger reductions observed with higher-dose regimens. Treatment discontinuation due to adverse effects was more frequent with oxybutynin (odds ratio 2.90, 95% confidence interval 1.19–7.10; $p = 0.02$; $I^2 = 0\%$), consistent with a dose-related increase in anticholinergic adverse effects, most commonly dry mouth. **Conclusions:** Across studies in women and men with cancer-related and menopause-associated vasomotor symptoms, oxybutynin was associated with clinically meaningful reductions in symptom frequency and severity, with evidence of a dose-response relationship and a trade-off with increased anticholinergic adverse effects. These findings inform the role of oxybutynin as a non-hormonal therapeutic option in populations in whom hormonal therapies are limited or contraindicated. Research Sponsor: None.

TPS10628 **Poster Session**

CAMPERR: A multicenter, prospective, observational study to evaluate a cfDNA-based genome-wide methylation enrichment assay for multicancer early detection (MCED), identification of molecular residual disease, and relapse prognostication. First Author: Gregory Idos, City of Hope National Medical Center, Duarte, CA

Background: Despite advances in cancer treatment, a lack of established population-level cancer screening strategies for early detection across cancer types contributes to cancer-related mortality. Emerging MCED liquid biopsy tests represent a screening approach with potential to enable detection of multiple malignancies at earlier stages in the disease process. We previously showed that an initial classifier based on a genome-wide methylome enrichment platform detected 12 cancer types, including early-stage, low-shedding tumors (Park et al. AACR 2023. Abs 1030). However, clinical performance of the platform has not been evaluated prospectively. Thus, the CAMPERR study (NCT05366881) was designed to train and validate a cell-free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq)-based test for detection and differentiation of 20 pre-selected cancer types, representing 93% of annual cancer incidence and 88% of annual cancer deaths. Longitudinal follow-up for a subset of participants with lung cancer will enable training and validation for MRD-based recurrence prognostication. **Methods:** This case-control study is enrolling participants with 20 different pre-specified cancer types (n=2400) and those without known cancer (n=3900). Eligible participants are $\geq$40 years of age and not receiving treatment for cancer at the time of enrollment or taking any demethylating/hypomethylating agents. Cases include individuals with newly diagnosed ($\leq$120 days), untreated cancer or recurrence of a cancer originally diagnosed $>$5 years ago. Cancers of interest are stage I-IV bladder, brain, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatobiliary, leukemia, lung, lymphoma, multiple myeloma, ovarian, pancreatic, prostate, renal, sarcoma, and thyroid. Participants with stage I-III lung cancer will have clinical follow-up and blood draws after completion of first-line treatment, every 3 mo for the first year thereafter, and every 6 mo for an additional 2 years. Eligible control participants have not been diagnosed with invasive cancer in the last 5 years and will have clinical follow-up $\geq$12 mo from enrollment to evaluate cancer status. Liquid biopsy results will not be returned to clinicians or participants. The primary objective is cancer detection. Secondary objectives include detection of specific cancer types, identification of the tissue of origin, and prognostication of clinical outcomes (eg, recurrence-free survival, overall survival). CAMPERR is currently enrolling at 15 sites. As of December 3, 2025, 2108 of 2400 cancer cases have been enrolled, including prostate (n=225), lung (n=216), colorectal (n=211), breast (n=193), and pancreatic (n=192); controls are fully enrolled. Clinical trial information: NCT05366881. Research Sponsor: Adela, Inc.

TPS10629 **Poster Session**

Cancer recognition and assessment through non-invasive evaluation (CRANE): A prospective clinical validation study of a multi-biomarker class multi-cancer early detection (MCED) test in Japan. First Author: Takeaki Yamazaki, Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan

Background: Japan has established screening programs for gastric, colorectal, lung, cervical, and breast cancers. Blood-based multi-cancer early detection (MCED) tests utilize the measurement of shared tumor-derived biomarkers (ctDNA, proteins) and machine learning to simultaneously detect several cancer types. By complementing current cancer screening, MCED testing has the potential to detect a wide range of cancers at earlier stages and expand existing screening efforts. CRANE is a prospectively collected, case-control study of Exact Sciences' MCED test (Cancerguard) to assess the overall sensitivity and specificity of the MCED test in a Japanese population. The secondary objective is to evaluate test performance across cancer types and stages. **Methods:** The study will include Japanese participants aged 45-84 years. Participants must provide written informed consent prior to providing a peripheral blood sample. A cancer cohort of approximately 1,000 participants with newly diagnosed confirmed cancer will be included in the study. Cancer cases will be recruited to obtain a diverse representation of cancer types and stages while also considering prevalence rates by cancer type. Emphasis will be placed on the 16 cancers with the highest incidence in Japan: lung, gastric, prostate, colorectal, breast, liver, pancreatic, bladder/renal pelvis, non-Hodgkin lymphoma, esophageal, kidney, uterine, cervical, ovarian, biliary tract, and head and neck. Approximately 1,000 non-cancer control participants will be included in the study, corresponding to the age and gender distribution from current population estimates reported by the Statistics Bureau of Japan. These participants will have no known cancer at enrollment, with status confirmed based on up-to-date routine cancer screening consistent with Japanese national cancer screening programs and subsequently through a 12-month follow-up after enrollment. Participants are enrolled at clinical sites in Japan, including cancer screening centers affiliated with the Japan Cancer Society. Whole blood will be collected at study sites in LBgard tubes, shipped to a local laboratory, processed to isolate the plasma and buffy coat, and then frozen. The frozen plasma and buffy coat samples will be shipped to the Exact Sciences clinical laboratory (Madison, WI, USA) for analysis. Approximately 300 non-cancer control samples and ~50 cancer case samples will undergo interim testing to assess test logistics and preliminary performance. No protocol modifications or enrollment pauses will occur based on interim testing results. Final testing will occur once all participants have been enrolled. The study duration is expected to be approximately 24 months. This study is funded by Exact Sciences Corporation. Clinical trial information: UMIN000059407. Research Sponsor: Exact Sciences Corporation.

TPS10630 **Poster Session**

BRCA-P: Can denosumab reduce breast cancer risk in *BRCA1* mutation carriers? First Author: Christian F. Singer, Department of Obstetrics and Gynecology and Center for Breast Health, Comprehensive Cancer Center, Medical University of Vienna and Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria

Background: The likely 'cell-of-origin' that leads to breast cancer in *BRCA1* mutation carriers is a progenitor cell that is highly proliferative and prone to DNA damage. This progenitor cell expresses RANK ligand receptor [RANK] and is hyper-responsive to progesterone through paracrine signaling mediated by RANK ligand [RANKL]. Notably, high tissue expression of RANKL has recently been found in mechanosensitive (stiff) breast tissue and is associated with increased breast density, a recognized breast cancer risk factor. **Methods:** The BRCA-P trial is a randomized, double-blinded, placebo-controlled multi-centre international phase 3 trial evaluating the RANKL inhibitor denosumab as a possible breast cancer risk-reducing agent (EudraCT 2017-002505-35; NCT04711109). The safety profile of denosumab is generally well understood, as it is currently approved for the treatment of osteoporosis, bone metastases and giant cell tumor of bone. The study is led by the ABCSG (Austria), in collaboration with individual country sponsors in seven participating countries. Eligible participants include women age 25-55 years who carry a *BRCA1* pathogenic variant, are unaffected by breast or ovarian cancer, and are not pregnant or currently trying to become pregnant. Participants must also have not undergone prophylactic bilateral mastectomy or be currently taking a chemopreventive agent such as tamoxifen. They are randomised 1:1 to receive either denosumab 120 mg or placebo subcutaneously every 6 months for 5 years. The study primary objective is to evaluate the reduction in the risk of any breast cancer (invasive or DCIS). The safety profile and tolerability of denosumab in this setting will be also studied. Secondary and exploratory objectives include reduction in risk of ovarian, fallopian tube and other cancers, reduction in mammographic breast density, reduction in clinical fractures, effects on bone health and bone turnover markers and quality of life. BRCA-P completed its recruitment phase in December 2024, with 364 participants randomised globally. This investigator-initiated study is supported by Amgen. Clinical trial information: NCT04711109. Research Sponsor: U.S. Department of Defense.

TPS10631 **Poster Session**

Lung cancer screening for early detection of suspicious lung nodules in Latin America (LUCAS-LATAM). First Author: Luis Corrales, Department of Medical Oncology, Centro de Investigacion y Manejo del Cancer (CIMCA), San Jose, Costa Rica

Background: Lung cancer (LC) remains the leading cause of cancer-related death in the Latin American (LATAM) region, accounting for 1 in 10 cancer deaths, attributable to late stage diagnosis in above 85%. Clinical utility of low-dose CT (LDCT) in early detection of LC has been established. However, these trials primarily focus on smokers, excluding non-smokers, who account for over one-third of LC globally. Recent studies document a need to expand screening criteria. Prevalence of light smokers and non-smokers among LC patients in LATAM is high (35% of patients being non-smokers). Geographic and socio-economic barriers hinder early detection of LC. Despite effectiveness, access to LDCT is limited in LATAM. Artificial intelligence (AI) based algorithms have demonstrated improved accuracy in predicting the risk of LC among patients with an incidental pulmonary nodule (IPN) detected on chest radiographs. Qure.ai has developed a model (qXR) that generates a lung nodule malignancy score (LNMS) based on the nodule's characteristics in a chest X-ray (CXR): low risk or high risk. **Methods:** Prospective study to assess LC screening with LDCT in LATAM and prospectively evaluate qXR in CXR at the initial visit correlating with the finding of the initial LDCT in patients with other high risk criteria to develop LC. 2000 patients will be recruited in 4 LATAM countries (Mexico 700 pts, Costa Rica 300 pts, Colombia 500 pts, Argentina 500 pts) Inclusion criteria include patients $\geq$50 years of age with one of the following: a. exposure to wood smoke (at least 100 hours/year), b. family history of LC in a first degree relative, c. COPD and/or emphysema, d. smokers with tobacco index of 10 y or more. Exclusion criteria: a. LC diagnosis or other type of cancer 5 years prior to screening, b. loss of 10% of baseline weight 6 months before, c. ineligible for LDCT, d. life expectancy $\leq$5 years, and e. previous history of pulmonary nodules. The primary objective of the study is the utility of LDCT-based LC screening in identifying suspicious lung nodules in smokers and non-smokers across LATAM, with secondary objectives including: 1- Utility of qXR-LNMS of CXR for LC risk assessment to exclude low risk patients from LDCT screening, 2- Utility of LDCT-based LC screening in subjects with various risk profiles in LATAM, 3- Prevalence of lung nodules in the study population, 4-Mortality rate in the subjects diagnosed with an anomaly in the LDCT (with or without LC diagnosis). Study design: Visit 1: CXR by qXR and LDCT1 Visit 2: LDCT2 : (12/24 months as applicable $\pm$ 2 weeks)(interval of LDCT2 is determined by the findings of the Visit 1) Low risk by qXR and Lung RADS 1 or 2: repeat in 24 months Low risk by qXR and Lung RADS 3, high risk by qXR and Lung RADS 1, 2, 3: repeat in 12 months Telephonic follow-up visits (at 6 month interval post LDCT2 for 2 years) Any Lung RADS 0, 4A, 4B, 4X or S will be assed in a thoracic oncology multidisciplinary team. Research Sponsor: Astra Zeneca.

TPS10632 **Poster Session**

SOLAR: A post-approval study evaluating longitudinal performance of a blood-based test for screening individuals at average risk for colorectal cancer (CRC). First Author: Sam Asgarian, Guardant Health, Palo Alto, CA

Background: CRC is a leading cause of cancer-related mortality; CRC screening has been shown to reduce mortality through detection of early-stage disease, yet adherence to recommended screening remains suboptimal. Shield is a methylation partitioning cell-free DNA (mp-cfDNA) blood-based test indicated for CRC screening in average-risk adults age 45 years or older. This test achieved 83% sensitivity for CRC and 90% specificity for advanced neoplasia in a prospective, observational study that enrolled over 20,000 patients (ECLIPSE), and became the first blood-based screening test approved by the FDA as a primary CRC screening option in July 2024. SOLAR is an FDA-mandated, post-approval study to evaluate longitudinal performance of the blood-based mp-cfDNA test in the intended use population. **Methods:** SOLAR (NCT06880055) is an observational, prospective study supplemented with real-world data to evaluate the mp-cfDNA test following a second round of CRC screening. Patients will receive an initial mp-cfDNA test (Shield, Guardant Health, Palo Alto, CA) at baseline (T0). Deidentified healthcare claims data will be collected to assess overall health and any development of disease at 1 and 2 years following the baseline test (T1 and T2, respectively). Patients with a negative screening result at T0 will receive a screening colonoscopy alongside a blood draw approximately 3 years after baseline screening (T3). Patients with a positive result at T0 will be recommended to receive diagnostic colonoscopy. Individuals aged 45-81 years at average-risk for CRC are eligible for the trial. Individuals who have a personal/family history of CRC or are at high risk for CRC are excluded. Those with a positive result from any of the following CRC screening tests are also excluded: fecal occult blood test or fecal immunochemical test within the last 12 months, multi-target stool DNA test within the last 36 months, mp-cfDNA test within the last 36 months, or another CRC screening method within the last six months. Primary outcome is the performance of the mp-cfDNA test at T3, including sensitivity for CRC or advanced adenoma detection and specificity for advanced neoplasia detection. Enrollment began July 2025. There are currently 29 active study sites across the US. Clinical trial information: NCT06880055. Research Sponsor: Guardant Health.

11000 Oral Abstract Session

The association of GLP-1 receptor agonist use with survival and immune-related adverse events in patients receiving immune checkpoint inhibitors: A multi-institutional real-world analysis. First Author: Salman Jajja, New York Medical College, Landmark Medical Center, Woonsocket, RI

Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed in patients with cancer for metabolic comorbidities and weight management. However, their impact on outcomes in patients receiving immune checkpoint inhibitors (ICIs) remains poorly characterized. We evaluated the association between concurrent GLP-1 RA use and survival and immune-related adverse events (irAEs) in a large real-world oncology population. **Methods:** We conducted a federated electronic health record–based cohort study using the TriNetX Research Network (113 healthcare organizations). Adult patients with solid and hematologic malignancies treated with PD-1/PD-L1 or CTLA-4 inhibitors were identified. Patients were stratified by exposure to GLP-1 RAs. Propensity score matching was performed to balance demographics, comorbidities, and baseline clinical characteristics. Kaplan–Meier survival analyses and Cox proportional hazards models were used to compare overall survival at 3 and 5 years. Incidence of irAEs, including neutropenia and pyrexia, was assessed using risk and odds ratios. **Results:** A total of 3,807 patients receiving ICIs with concurrent GLP-1 RAs were matched to 173,423 patients receiving ICIs without GLP-1 RAs. At 3 years, GLP-1 RA exposure was associated with improved survival (hazard ratio [HR] 0.69, 95% CI 0.64–0.75; log-rank $p<0.001$). This survival advantage persisted at 5 years (HR 0.71, 95% CI 0.65–0.76; log-rank $p<0.001$). Survival probability at the end of follow-up was higher in the GLP-1 RA cohort across both time horizons. No statistically significant survival benefit was seen at the 1-year end point, (HR 0.65, 95% CI 0.59-0.71; log-rank p=0.521). GLP-1 RA use was associated with a lower incidence of selected irAEs. At 3 years, neutropenia occurred in 5.7% of GLP-1 RA users versus 6.5% of non-users (OR 0.87, 95% CI 0.71–1.06), and pyrexia was significantly reduced (risk difference −2.5%, OR 0.73, 95% CI 0.61–0.87). Similar trends were observed at 5 years, with numerically lower neutropenia rates in the GLP-1 RA cohort (OR 0.84, 95% CI 0.68–1.02). **Conclusions:** In this large real-world analysis, concurrent GLP-1 RA use in patients receiving ICIs was associated with significantly improved long-term survival and a reduced burden of selected immune-related adverse events. These findings suggest a potential synergistic or protective effect of GLP-1 RAs in the immunotherapy setting and warrant prospective investigation to clarify underlying mechanisms and clinical implications. Research Sponsor: None.

Outcome	5-Year GLP-1 n/N (%)	5-Year No GLP-1 n/N (%)
Death	1091/3411 (32)	1545/3410 (45)
Malaise & Fatigue	552/2190 (25)	628/2160 (29)
Sepsis	444/3016 (15)	521/2964 (18)
Cachexia	119/3395 (4)	179/3368 (5)
Pneumonia	405/2811 (14)	494/2747 (18)

11001 Oral Abstract Session

Impact of mRNA SARS-CoV-2 vaccination on CAR T-cell therapy outcomes in hematologic malignancies: A multi-center real-world analysis. First Author: Jowan Al-Nusair, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Background: The clinical landscape of hematologic malignancies has been reshaped by Chimeric Antigen Receptor (CAR) T-cell therapies; however, their administration is intrinsically associated with immune-mediated toxicities, specifically cytokine release syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). The interaction between the immunogenic stimulus of mRNA SARS-CoV-2 vaccines and the systemic inflammatory milieu of CAR T-cell therapy remains undefined in real-world practice. This study aimed to delineate the impact of mRNA vaccination on survival outcomes and immunotoxicity profiles within this vulnerable patient population. **Methods:** We conducted a retrospective cohort study using the TriNetX global federated health research network. We identified patients with hematologic malignancies who received CAR T-cell therapy using ICD-10 and RXNORM codes. Patients were stratified into two cohorts based on whether they received mRNA-based SARS-CoV-2 vaccines. The cohorts were 1:1 propensity score-matched for age, sex, race, staging, and comorbidities. The primary outcome was all-cause mortality at 3 years, assessed with Hazard Ratios (HR). Secondary outcomes included CRS grade 1/2 and 3/4, and ICANS, both graded per the ASTCT criteria, and assessed with Odds Ratios (OR). **Results:** A total of 3,199 CAR T-cell patients (222 mRNA vaccine recipients and 2,977 without the mRNA vaccine) were identified. After 1:1 propensity score matching, 218 patients remained in each cohort. The 3-year mortality was significantly lower among mRNA SARS-CoV-2 vaccine recipients as compared to non-recipients (HR 0.608; 95% CI, 0.411 - 0.901). The mRNA vaccine group had a higher rate of CRS 1/2 (OR 1.577; 95% CI, 1.056 - 2.356). However, there were not enough cases of CRS 3/4 to compare the two cohorts. Furthermore, there was no significant difference in ICANS between the two cohorts (OR 0.8262; 95% CI, 0.522–1.37). **Conclusions:** In this propensity score-matched analysis of real-world data, mRNA SARS-CoV-2 vaccination was associated with a significantly superior long-term survival among CAR T-cell recipients. These findings build on early pre-clinical data related to SARS-CoV-2 mRNA vaccines demonstrating substantial increase in type I interferon, enabling innate immune cells to prime $CD8^+$ T cells. The results provide early real-world clinical evidence and pave the way for prospective validation. Research Sponsor: None.

Key outcomes in CAR T-cell recipients.

Outcome	Effect of mRNA Vaccination (95% CI)	*p* Value
All-cause mortality (3-year)	HR 0.61 (0.41–0.90)	0.01
CRS grade 1/2	OR 1.58 (1.06–2.36)	0.03
ICANS (any grade)	OR 0.83 (0.52–1.37)	0.41

11002 Oral Abstract Session

Frailty matters: Association of mFI-5 Index with odds of mortality, hospitalization, and toxicities with ADCs, BiTE, and CAR T-cell therapies in real-world data. First Author: Anne-Laure Strong, Penn State College of Medicine, Hershey, PA

Background: Targeted-delivery biopharmaceuticals such as antibody–drug conjugates (ADCs) or BiTE cell therapy are increasingly used in oncology. Recent meta-analyses demonstrate similar survival benefits of ADCs in younger and older patients across tumor types; however, baseline frailty predicts increased mortality, toxicity and hospitalization among patients receiving systemic anticancer therapy. While NCCN guidelines recommend frailty assessment for older adults prior to surgery, no such guidance exists for systemic treatments. **Methods:** We conducted a retrospective cohort study using TriNetX, a federated real-world data network with anonymized EHRs from hundreds of healthcare organizations. We included 46,674 patients with solid tumors, breast and bladder (solid ca) and 15,213 patients with hematologic cancers such as lymphoma, leukemia (heme ca) who initiated ADCs, BiTE-cell therapy, or CAR T-cell therapy. Cohort entry was defined as the first use of the drug class (index date). Toxicities, i.e. cardiotoxicity or cytopenia were outcomes if occurred within 30 days of index; patients without these events or with other outcomes served as comparators. Baseline frailty was measured using the modified Frailty Index-5 (mFI-5), derived from ICD-10 codes for hypertension (I10), care dependency (Z74), diabetes (E08–E13), COPD (J44), and heart failure (I50). Logistic regression estimated associations between frailty and each outcome, with p-values adjusted using the Benjamini–Hochberg false discovery rate. Mortality at pre-specified time points and hospitalization were fitted with a Cox proportional hazards model with frailty category as the primary exposure, controlling for age, and stratifying by cancer group and treatment. **Results:** In heme ca and solid ca, higher mFI-5 relative to mFI=0 was associated with significantly increased odds of toxicities with ADCs, including nausea, thrombocytopenia, anemia, cardiotoxicity, diarrhea, lung disease, and neutropenia (all $p<0.001$). In heme ca, higher mFI-5 was associated with significantly higher odds of toxicities, including anemia and cardiotoxicity (all $p<0.001$) with BiTE therapy and CAR T-cell. Results indicate a strong relationship between frailty severity and mortality risk (Table 1) and hospitalization after controlling for age and accounting for differences in baseline hazard across cancer groups and treatment strata. **Conclusions:** Assessing frailty severity through mFI-5 before initiating targeted systemic therapy in hematologic and solid tumors may help identify patients at increased risk of poor survival odds, adverse effects and facilitate shared treatment decision-making. Research Sponsor: None.

Hazard ratio of mortality relative to mFI=0.

mFI-5 score	Hazard ratio of mortality with 95% CI
1	1.41 [1.34-1.47]
2	1.79 [1.69-1.9]
3	2.45 [2.24-2.69]
4+	2.51 [2.11-2.97]

11003 Oral Abstract Session

Overall survival analysis of eSyM: A cluster randomized trial of an electronic patient-reported outcomes (ePRO)-based symptom management program. First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA

Background: ePRO monitoring can improve outcomes yet remains underutilized in routine cancer care. We conducted a pragmatic type II hybrid effectiveness–implementation trial using a cluster-randomized stepped-wedge design to assess an ePRO-based, EHR-integrated symptom management program (eSyM) across 6 health systems. Our prior analyses demonstrated that eSyM use, but not eSyM deployment, was associated with a significant reduction in emergency department visits and hospitalizations. Here, we report results of the overall survival (OS) analysis. **Methods:** Eligible patients were adults who received chemotherapy (CHEMO) or had surgery (SURG) for a gastrointestinal (GI), gynecologic (GYN), or thoracic (THOR) tumor from Jan 2018-Feb 2023. The outcome was OS 1 year after starting chemotherapy or postoperative discharge. The primary analysis compared patients treated pre- versus post-deployment of eSyM. A secondary analysis compared patients who were treated post-deployment and did versus did not use eSyM, where users were those who reported ePROs via eSyM at least once. Cox regression models accounted for sociodemographic, clinical, and health system factors. Analyses were stratified by treatment modality to account for heterogeneity of effect. **Results:** Health systems contributed data on 39,895 patients (selected characteristics in Table). After eSyM deployment, 45% of CHEMO and 53% of SURG patients used eSyM to report ePROs. Multivariable Cox regression analyses identified significant associations between eSyM deployment and OS for CHEMO (HR 1.11, 95%CI 1.03-1.21; P=0.007) and SURG (HR 0.86, 95% CI 0.76-0.98; P=0.026) patients. The adjusted absolute difference in 12-month OS probability for patients treated post-deployment vs. pre-deployment was -2.4% (P<.001) for CHEMO and 0.7% (P<0.031) for SURG. Comparing eSyM users vs. non-users from the post-deployment cohort only, OS was significantly better among CHEMO (HR 0.63, 95%CI 0.57-0.69; P<0.001; 12m OS diff 10.2%) and SURG (HR 0.58, 95%CI 0.49-0.69; P<0.001; 12m OS diff 2.8%) patients. **Conclusions:** Deployment of eSyM was associated with statistically significant but clinically marginal differences in OS. After eSyM was deployed, use of ePROs was associated with statistically significant and potentially meaningful improvements in OS. Considering that ePRO monitoring with eSyM decreases the need for acute care and may be associated with longer survival, strategies to improve adoption and implementation of ePRO-based symptom management programs may be warranted. Clinical trial information: NCT03850912. Research Sponsor: National Cancer Institute; 1UM1CA233080-01.

	CHEMO		SURG	
	Pre	Post	Pre	Post
# Patients	5149	7030	15917	11799
Age (median)	66	67	61	63
Female	54%	54%	72%	69%
Charlson comorbidity ≥2	8%	7%	6%	7%
GI, GYN, THOR	49%, 16%, 35%	45%, 17%, 38%	41%, 37%, 22%	43%, 33%, 24%
# Deaths	1098	2037	546	614
12-mo OS (adjusted)	72.7%	70.2%	94.7%	95.4%
12 mo OS (users, non-users)	–	76.8%, 66.6%	–	96.0%, 93.3%

11004 **Oral Abstract Session**

Multicenter open-label randomized trial of the utility of electronic patient-reported outcome monitoring system in patients with advanced solid tumors (PRO-MOTE). First Author: Naomi Kiyota, Kobe University Hospital, Kobe, Japan

Background: Randomized trials have suggested that electronic patient-reported outcome (ePRO) monitoring during systemic therapy may improve health-related quality of life (HR-QOL) and overall survival (OS) in patients with advanced cancer. However, evidence remains limited outside Western healthcare settings. Here, we evaluated the utility of ePRO monitoring for OS and HR-QOL in Japanese patients with advanced solid tumors receiving systemic therapy. **Methods:** This multicenter, open-label, randomized trial enrolled patients aged ≥18 years with advanced solid tumors, ECOG performance status (PS) 0–2, and receiving systemic therapy. Patients were randomized 1:1 to ePRO monitoring plus usual care or usual care alone. In the ePRO monitoring group, patients completed weekly symptom monitoring using PRO-CTCAE. Predefined severity thresholds were applied, and symptom reports exceeding thresholds automatically generated e-mail alerts to the study physicians. Primary endpoints were OS and global health status (GHS) assessed by EORTC QLQ-C30. Superiority for GHS was tested at a two-sided α of 4%, and for OS at α=5% if GHS was significant or α=1% otherwise. Based on a linear mixed-effects model, 400 patients provided 91% power to detect a 5-point between-group difference in GHS. Target sample size was set at 500, allowing for 20% attrition. **Results:** Between June 2021 and February 2024, 501 patients were enrolled (control n=250; ePRO n=251), with a median age of 63 years (21–82) and ECOG PS 0/1/2 of 362/127/12. Major cancer types included colorectal (27%), lung (22%), breast (19%), and gastric cancer (17%). QOL analysis was conducted in 485 patients due to missing baseline data in 16. Questionnaire completion rates were high (QLQ-C30: baseline 97%, week 24: 92%). In the ePRO group, weekly PRO-CTCAE completion rates were 86% at baseline and 85% at week 24, generating 13,500 symptom reports and 1,918 alerts (14%), with a median of 4 alerts per patient. At the planned interim analysis, between-group difference in change in GHS over 24 weeks was −0.61 (95% CI −3.03 to 1.82; p=0.625), showing no superiority of ePRO monitoring. OS did not differ between groups (HR 0.91; 95% CI 0.70–1.19; p=0.240). Bayesian predictive power of eventual OS benefit was 0.3%, below the futility threshold of 10%, and the trial was terminated early. **Conclusions:** In contrast to previous reports from Western countries, PRO-MOTE failed to demonstrate the superiority of ePRO monitoring for GHS or OS in patients with advanced solid tumors receiving systemic therapy in Japan. Despite high feasibility, the clinical benefit of ePRO monitoring might depend on cancer type, treatment context, or healthcare system. Further subgroup and exploratory analyses are ongoing. Clinical trial information: NCT05931445. Research Sponsor: None.

11005 **Oral Abstract Session**

Impact of remote therapeutic monitoring with patient-reported outcomes on hospitalization in real-world patients receiving therapy for metastatic solid tumors. First Author: James H. Essell, Cincinnati Cancer Advisors, Cincinnati, OH

Background: Remote therapeutic monitoring (RTM) using electronic patient-reported outcomes (ePROs) may help care teams respond earlier to patient needs and potentially avoid acute care events, but evidence from real-world practice is limited. This study evaluates the impact of using the Canopy ePRO-based RTM platform on acute care events. **Methods:** We studied 1,549 patients with metastatic solid tumor malignancies receiving systemic treatment at 5 community oncology sites between Jan 1, 2024 until July 20, 2025. Patients were invited to complete weekly ePRO symptom surveys. Symptoms that exceeded pre-specified severity thresholds triggered notifications to a dedicated triage nursing staff for evaluation and consideration of telephonic triage, urgent outpatient office evaluation or referral to the emergency department or hospital. Patients who enrolled and submitted ≥ 2 ePRO surveys within 45 days of first treatment were included in the RTM group, while those not enrolled or who did not submit 2 or more reports were in the control group. Hospitalization events were extracted from the Arkansas health information exchange. Inverse probability of treatment weighting was used to account for potential non-random selection of patients into the RTM group when performing statistical tests of difference, and achieved cohort balance in terms of age at index, time from first cancer diagnosis to treatment, site of cancer, sex, and race. **Results:** Over 18 months following first anticancer treatment through data cutoff date, 558 patients were in the RTM group compared to 991 patients in the control group. Among patients in the RTM group, 9.0% had a record of hospitalization compared to 13% in the control group, representing a 28% reduction (risk difference: -3.63, 95% CI -7.06 to -0.39, p: 0.032); 12% of patients in the RTM group had record of ED visit compared to 13% in the control group (risk difference: -1.77, 95% CI: -5.24 to 1.63, p: 0.310). The estimated cost savings per 1,000 patients/years utilizing RTM during treatment was $3,192,789 for hospitalizations and $93,330 for emergency department visits. **Conclusions:** RTM utilization with Canopy is associated with fewer hospitalizations and potentially fewer emergency visits compared to traditional outpatient management of patients with metastatic solid tumors, potentially reducing the cost of care. Prompt notification of patient symptoms resulting in preemptive treatment may help patients avoid acute care events. Research Sponsor: None.

Unweighted clinical and demographic characteristics.

Characteristic	Enrolled & Active N = 558	Not Enrolled N = 991
Age at index	64 (55, 71)	70 (62, 78)
Sex - Female	313 (56%)	515 (52%)
Race/Ethnicity - White	484 (87%)	846 (85%)
Race/Ethnicity - Hispanic	28 (5.0%)	58 (5.9%)
Lung Cancer	131 (23%)	179 (18%)
Breast cancer	98 (18%)	219 (22%)
Colorectal cancer	88 (16%)	148 (15%)

11006 **Oral Abstract Session**

Randomized, double-blind phase 3 trial of the fixed-dose combination fosrolapitant/palonosetron (HR20013) plus dexamethasone for prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. First Author: Li Zhang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Despite antiemetic guidelines, ~50% of patients (pts) receiving moderately emetogenic chemotherapy (MEC) still experience chemotherapy-induced nausea and vomiting (CINV), mainly in the delayed phase (DP, 24-120 h). HR20013 is a fixed-dose IV formulation providing dual NK1 and 5-HT3 receptor blockade in a single dose and showed efficacy in preventing CINV following highly emetogenic chemotherapy in the phase 3 PROFIT trial (Zhou et al., JCO 2025). This study is the first pivotal phase 3 trial to evaluate the efficacy and safety of single-dose HR20013 plus dexamethasone (DEX) in the MEC setting. **Methods:** In this multicenter, randomized, double-blind, active-controlled phase 3 trial, chemotherapy-naïve adults with solid tumors scheduled for single-day MEC were randomized (1:1) to receive single-dose HR20013 (fosrolapitant 218 mg + palonosetron [PALO] 0.25 mg IV) or placebo + PALO prior to chemotherapy on D1. All pts also received oral DEX 7.5 mg on D1. Primary endpoint was complete response (CR; no emesis, no rescue therapy) in the DP (24–120 h). Key secondary endpoint was CR in the overall phase (OP; 0–120 h). **Results:** Of 706 randomized pts, the ITT population included 348 in the HR20013+DEX group and 352 in the PALO+DEX group. Baseline characteristics were well balanced. HR20013 showed statistically superior and clinically meaningful efficacy vs active control. CR rate in the DP was 79.0% (95% CI 74.4–83.2) with HR20013+DEX vs 61.4% (95% CI 56.1–66.5) with PALO+DEX (difference 17.8%, 95% CI 11.1–24.4; $P < 0.0001$). CR rate in the OP was 75.6% (95% CI 70.7–80.0) vs 59.9% (95% CI 54.6–65.1) (difference 15.7%, 95% CI 9.0–22.5; $P < 0.0001$). HR20013 also showed improved CR rate in acute phase (0-24 h; 92.5% vs 86.1%; P = 0.0052) and consistently showed higher rates across efficacy assessments including no significant nausea, complete protection, and total control in all phases. Time to treatment failure analysis favored HR20013 (HR 0.52, 95% CI 0.40–0.69). Functional Living Index-Emesis indicated that a greater proportion of pts receiving HR20013+DEX reported no impact on daily life in the DP (e.g., 90.2% vs 75.9% in the vomiting domain). The incidence of TRAEs were similar between groups (25.1% for HR20013 vs 21.4% for PALO). Most common TRAEs with HR20013 were constipation (8.9%), hypertriglyceridemia (4.0%), and hiccups (3.5%). Grade ≥3 TRAEs were infrequent (1.2% vs 1.4%). No new safety signals were identified. **Conclusions:** In pts receiving MEC, a single dose of fixed-dose combination HR20013 plus DEX was well tolerated and demonstrated superior efficacy in preventing CINV compared to the standard regimen of PALO+DEX, with improved patient-reported outcomes. This single-dose, dual-pathway antiemetic offers a more effective and convenient prophylactic option for MEC. Clinical trial information: NCT06554184. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

11007 **Oral Abstract Session**

Doubling cascade testing uptake for hereditary cancer syndromes: Results from a cluster randomized controlled trial of a registry-aided outreach approach. First Author: Jianbang Chiang, National Cancer Centre, Singapore, Singapore

Background: Cascade genetic testing for at-risk relatives (ARR) is the most critical strategy for cancer prevention in families with hereditary cancer syndromes. Affected ARR can benefit from increased awareness and frequent screening to ensure cancers are detected at an early, treatable stage. Locally, uptake is persistently low at 6-13%, reflecting a prominent clinical gap. The current standard of care, which relies on passive proband-dependent communication to disseminate genetic information to ARR, is highly inefficient. We hypothesized that a novel, structured, registry-aided outreach model would improve the uptake rate of cascade testing in Singapore, and thus conducted a trial to address the effectiveness of this approach. **Methods:** We conducted a cluster randomized controlled trial at the National Cancer Centre Singapore comparing two arms. (1) Control arm: Proband-dependent communication. (2) Experimental arm: Proband-dependent communication with systematic outreach to ARR, facilitated by a family registry and executed by trained genetics personnel. This solution shares the burden of disseminating genetic results, ensuring ARR receive accurate information from a healthcare professional. The primary endpoint was the proportion of at-risk first-degree relatives who completed cascade genetic testing. **Results:** A total of 150 probands from unique families and 386 ARR were recruited from February 2022 to March 2025 in National Cancer Centre Singapore. In the experimental arm, 78/196 relatives (39.8%) attended pre-test genetic counselling compared to 38/190 relatives (20.0%) in the control arm. In the experimental arm, 71/196 relatives (36.2%) proceeded with cascade testing after pre-test counselling, whilst 37/190 relatives (19.5%) in the control arm underwent cascade testing. In our study, with the addition of the novel registry-aided outreach approach, the percentage of relatives who attend the pre-test genetic counselling session doubled, whilst those who eventually had cascade testing increased by 86%, demonstrating its clear superiority over the passive proband-dependent approach. **Conclusions:** Our trial proves that a systematic, healthcare professional-driven, registry-aided outreach is an effective strategy to overcome the barriers in cascade testing. The registry-aided outreach approach is a feasible, successful and scalable solution to the low uptake of cascade testing in Singapore. Implementing this approach is essential for realizing the full potential of genetic medicine to prevent cancers in high-risk families with hereditary cancer syndromes. Research Sponsor: National Medical Research Council; MH 095:003\008-290.

11008 Oral Abstract Session

Impact of dedicated care coordination on access to multidimensional support services in young-onset colorectal cancer: A pragmatic trial. First Author: Jeongyoon Moon, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: The incidence of young-onset colorectal cancer (YOCRC) is increasing, and affected patients experience distinct challenges. YOCRC patients may benefit from a dedicated care coordinator that systematically assesses their unmet needs and facilitates referrals to multidimensional support services. **Methods:** In this pragmatic trial, we assigned newly diagnosed CRC patients aged <50 years who presented to a tertiary academic institution between 2023-2025 to usual multidisciplinary care, or usual care plus additional encounter(s) with a dedicated care coordinator as a part of the YOCRC program. Patient-reported concerns and distress were collected at initial presentation. The primary endpoint was the rate of utilization of support services designed to address multidimensional needs of YOCRC patients. Multivariable regression was performed to identify predictors of service utilization. **Results:** Among 1,250 YOCRC patients (mean age 42.8±6.0 years; 45.4% female; 77.3% white), 46.3% had rectal cancer. Emotional concerns were most common (41.0%), followed by physical (36.1%), practical (27.8%) and social (9.4%) concerns. The YOCRC coordinator successfully established contact with 604 individuals. Clinically significant distress (distress score ≥4) was reported by 27.4%, with no significant difference between groups (26.5% vs. 29.2%, p=0.34). Unmet service needs were reported by 39.1% in the intervention group, of whom 80.5% subsequently accessed corresponding support services. Patients with established contact with the YOCRC coordinator were more likely to access support services (Table 1, 72.5% vs.44.7%, p<0.001). On multivariable analysis, coordinator contact (aOR 1.48, 95%CI 1.22-1.80), rectal cancer diagnosis (aOR 1.36, 95%CI 1.13-1.62), and clinically significant distress (aOR 1.23, 95%CI 1.01-1.50) predicted greater multidimensional service utilization. **Conclusions:** YOCRC patients experience substantial emotional concerns and unmet needs. Integration of a YOCRC coordinator was associated with significantly increased utilization of multidimensional support services. This pragmatic trial supports a personalized, needs-driven care delivery model, that integrates patient-reported outcomes to further optimize targeted referrals. Research Sponsor: None.

Multidimensional support services accessed by YOCRC patients with vs. without established contact with YOCRC coordinator.

	Contact Established (n=604)	Contact Not Established (n=646)	*p*
Social Work	378 (62.6%)	288 (44.6%)	<0.01
Genetics	229 (37.9%)	126 (19.5%)	<0.01
Wound, Ostomy, Continence	196 (32.5%)	69 (10.7%)	<0.01
Supportive care	92 (15.2%)	77 (11.9%)	0.09
Oncofertility	77 (12.7%)	39 (6.0%)	<0.01
Integrative Medicine	73 (12.1%)	34 (5.3%)	<0.01
Nutrition	46 (7.5%)	40 (6.2%)	0.32
Psychiatry	41 (6.8%)	19 (2.9%)	<0.01
Adolescent and Young Adult Program	58 (9.6%)	29 (4.5%)	<0.01

11009 Rapid Oral Abstract Session

The electronic frailty index used to identify high-risk older adults receiving chimeric antigen receptor T-cell therapy. First Author: Justine P. Enns, Massachusetts General Hospital, Boston, MA

Background: Chimeric antigen receptor T-cell therapy (CAR-T) has transformed outcomes in relapsed/refractory hematologic malignancies and can be effective in older adults. Frailty, a syndrome of vulnerability common in older adults, is associated with poor outcomes but difficult to measure in clinical practice. The relationship between frailty and CAR-T outcomes is poorly understood. **Methods:** We conducted a retrospective analysis of 260 patients age 65+ years receiving commercial CAR-T at Massachusetts General Brigham (MGB) for multiple myeloma and B cell non-Hodgkin lymphoma. We abstracted patient characteristics and clinical outcomes from the electronic health record (EHR). Using EHR data from the Research Patient Data Registry, we calculated the MGB-eFI, a validated electronic frailty score based upon a deficit accumulation approach to frailty. The MGB-eFI assesses 31 age-related health deficits and yields a score ranging 0-1 (< 0.1 is robust, 0.1-0.2 is pre-frail, 0.2-0.3 is frail, and > 0.3 is very frail). We then evaluated associations of the eFI (as a categorical variable of robust/prefrail versus frail/very frail) with cytokine release syndrome (CRS), immune cell-associated neurotoxicity syndrome (ICANS), overall survival (OS), and event-free survival (EFS) using univariate and multivariable logistic and Cox regression models controlling for covariates. **Results:** Among 260 patients (median age 73 years [range 65-91], 45% female), the most common CAR-T products used were liso-cel (35%), tisa-cel (18%), ide-cel (18%), cilta-cel (12%), and axi-cel (10%). With the eFI, 10% of patients were robust, 25% prefrail, 28% frail, and 37% very frail. In univariate analyses, frail/very frail was associated with worse OS (hazard ratio [HR] 1.66, p = 0.013), worse EFS (HR 1.78, p = 0.001), higher rates of ICANS (odds ratio [OR] 1.99, p = 0.013), and higher rates of grade 3+ ICANS (OR 4.49, p = 0.003). Frailty was not associated with risk of CRS. In multivariable analyses controlling for age, sex, CAR-T product, lactate dehydrogenase, ferritin, number of prior therapies, and bridging therapy use, frail/very frail by eFI remained associated with worse EFS (HR 1.69, p = 0.005) but not with OS (HR 1.37, p = 0.150). Frail/very frail was numerically associated with increased ICANS, but this did not meet statistical significance (OR = 1.71, p = 0.090). In a multivariable analysis controlling for age, CAR-T product, and ferritin (due to event sample size), frail/very frail was associated with higher rates of grade 3+ ICANS (OR 3.75, p = 0.017). **Conclusions:** Frailty measured using an automated eFI is associated with worse EFS and higher rates of high-grade ICANS, despite controlling for other clinical and patient factors. The eFI holds promise as a tool that if integrated into the EHR can help clinicians with risk stratification and CAR-T decision-making for older adults with hematologic malignancies. Research Sponsor: None.

11010 Rapid Oral Abstract Session

Association of early cognitive decline with compromised delivery of adjuvant chemotherapy. First Author: Filippos Koinis, University Hospital of Larissa and Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, Greece

Background: Cancer-related cognitive impairment (CRCI, "chemobrain") is a common condition among patients (pts) receiving adjuvant chemotherapy (CT) and has been shown to negatively affect quality of life (QoL). However, the clinical relevance of early CRCI beyond symptom burden remains poorly characterized. We evaluated whether early CRCI is associated with compromised delivery of adjuvant CT, including reduced relative dose intensity (RDI). **Methods:** This prospective study was conducted at the University Hospital of Larissa and represents an expanded analysis of a previously reported population with treatment delivery endpoints. Pts with early stage (ES) breast (BC) or colorectal (CRC) cancer scheduled to receive adjuvant CT containing taxanes or oxaliplatin, respectively, were eligible for this study (C1). Two control groups were included: ES cancer pts that were not eligible for adjuvant CT (C2) and age-matched healthy controls (C3). Eligibility criteria included age > 45 years and fluency in Greek; pts with pre-existing dementia or anxiety disorders were excluded. C1 pts were assessed at baseline and every 3 months (mo) up to 12 mo after CT initiation, while C2 and C3 were assessed at 3-mo intervals. CRCI was evaluated using the Greek Version of Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog). Early CRCI was defined as a ≥10-point decline in total FACT-Cog score at 3 mo after CT initiation, in the absence of severe anemia (CTCAE grade ≥3). Treatment delivery outcomes included RDI (reduced RDI: < 85%), treatment delays, CT discontinuation, unplanned healthcare use and CT-related neurotoxicity (ntx). **Results:** Overall, 164 pts were included in C1 (111 BC, 63 CRC), 61 in C2 (38 BC, 23 CRC) and 25 in C3. Early CRCI was observed in a substantial proportion of pts receiving adjuvant CT (99/164, 60%). Pts with early CRCI were significantly more likely to receive reduced CT dose intensity compared to those without CRCI (OR 3.27, 95% CI 1.34-7.98). Early CRCI was also associated with an increased risk of clinically relevant concurrent treatment-related ntx (CTCAE grade > 1; OR 4.05, 95% CI 1.81-9.08). CT discontinuation occurred more frequently among pts with early CRCI than among those without CRCI (12% vs 3%). In addition, these pts more frequently experienced treatment delays and unplanned healthcare use. These associations were independent of baseline ECOG PS. Early CRCI persisted beyond 3 mo in a substantial proportion of affected pts during follow up, while cognitive scores remained stable among controls. **Conclusions:** In this expanded cohort, early CRCI was associated with reduced RDI and higher rates of treatment discontinuation. Beyond its impact on QoL, early CRCI identifies a vulnerable subgroup of pts at risk for compromised treatment delivery and may represent a clinically actionable target for risk-adapted supportive strategies aimed at preserving curative-intent treatment intensity. Research Sponsor: None.

11011 Rapid Oral Abstract Session

Clinical impact of baseline and peri-treatment concomitant medication exposure and polypharmacy on outcomes of immune checkpoint inhibitor therapy: A real-world pan-tumor analysis. First Author: Ali Awada, American University of Beirut Medical Center, Beirut, None, Lebanon

Background: Immune checkpoint inhibitors (ICIs) have transformed cancer therapy, yet real-world patients frequently receive multiple concomitant medications that may influence treatment outcomes. These medications may alter the gut microbiome and modulate host immune function, impacting ICI efficacy and survival. The clinical effects of baseline and peri-treatment medication exposure on ICI outcomes remain incompletely characterized. **Methods:** We conducted a retrospective study of ICI-treated solid tumors at a tertiary academic center. Concomitant medications were captured at ICI initiation (baseline chronic exposure) and during a peri-treatment window (acute exposure, 30 days before or after ICI initiation). Drug classes included antibiotics, proton pump inhibitors, corticosteroids, NSAIDs, opioids, anticoagulants, antiplatelets, statins, cardio-metabolic and psychotropic agents, and supplements. Polypharmacy was defined as ≥5 baseline medications. Outcomes included overall survival (OS), progression-free survival (PFS), immune-related adverse events (irAEs), and objective response using RECIST 1.1. Multivariable Cox proportional hazards models were used to adjust for confounding. **Results:** The cohort included 772 patients (60.1% male) with a median BMI of 25.8 kg/m² (IQR 23.0–29.1), and 66.2% had stage IV disease. On multivariable analysis for objective response (RECIST), baseline polypharmacy (≥5 medications) (OR 0.65, 95% CI 0.43–0.96; p=0.033), acute antibiotic exposure within 30 days of ICI initiation (OR 0.63, 95% CI 0.39–0.99; p=0.049), and metastatic disease (stage IV) (OR 0.51, 95% CI 0.26–0.98; p=0.045) independently predicted inferior response, while a higher number of immunotherapy cycles was associated with improved response (OR 1.06 per cycle, 95% CI 1.05–1.08; p<0.001). Acute antibiotic exposure within 30 days before ICI initiation was also independently associated with worse progression-free survival (HR 1.70, 95% CI 1.05–2.76; p=0.031). On multivariable Cox regression for overall survival, acute opioid exposure (HR 1.51, 95% CI 1.06–2.15; p=0.023), baseline polypharmacy (HR 1.78, 95% CI 1.19–2.65; p=0.005), and advanced disease (HR 2.78, 95% CI 1.73–4.47; p<0.001) were independently associated with worse survival, whereas a higher number of immunotherapy cycles (HR 0.96 per cycle, 95% CI 0.94–0.98; p<0.001) and prior surgery of the primary tumor (HR 0.51, 95% CI 0.33–0.79; p=0.002) were associated with improved survival. No baseline polypharmacy or specific medication exposure independently predicted the occurrence of irAEs. **Conclusions:** Concomitant medication exposure significantly impacts ICI outcomes, potentially through modulation of host immunity and the gut microbiome, supporting routine medication review at ICI initiation. Research Sponsor: None.

11012 **Rapid Oral Abstract Session**

Telehealth use and end-of-life care outcomes among Medicare decedents with cancers. First Author: Teresa M. Waters, Augusta University School of Public Health, Augusta, GA

Background: Telehealth has become an increasingly important care modality following the COVID-19 pandemic. For patients with cancer approaching end of life (EOL), telehealth may be particularly relevant given their substantial symptom burden, need for frequent healthcare services, and declining functional status. Telehealth may facilitate convenient access to care and enhance EOL care quality. However, limited research has examined associations between telehealth use and EOL care among patients with cancer. **Methods:** We conducted a retrospective, population-based cohort study of EOL telehealth use using 100% Medicare Traditional Medicare (TM) and Medicare Advantage (MA) claims. We included beneficiaries aged 66+ years with cancer who died in 2020-2023 with continuous enrollment in TM or MA during the 12 months preceding death. Patients with cancer were identified by at least 1 inpatient or 2 outpatient claims with relevant diagnosis codes. Telehealth use during the first 6 months of the last year of life was identified using procedure codes and modifiers. We examined validated claims-based EOL care outcomes, including hospice use and place of hospice care, and indicators of potentially burdensome transitions (e.g., late hospice enrollment $\leq$3 days of death, multiple hospitalizations and emergency department visits $\leq$30 days of death). Separate multivariable logistic regression models assessed associations between telehealth use and EOL outcomes. **Results:** Among a total of 2,897,720 Medicare beneficiaries with cancer who died in 2020-2023, mean age was 79.8 years; 44.9% were female, 9.4% were non-Hispanic Black, and 1.7% were Hispanic. Telehealth use in the first 6 months of last year of life was 30.0% in 2020-2023, with utilization peaking in 2021 (47.1%). Among all decedents, 60.7% enrolled in hospice; among hospice users, 73.1% received hospice care at home and 18.6% enrolled $\leq$3 days of death. In the last 30 days, 11.2% and 13.4% experienced multiple hospitalizations and ER visits respectively. In adjusted analyses, telehealth use was associated with 2.38 percentage points (ppts, 95% CI=2.25 to 2.50) higher likelihood of any hospice use. Among hospice recipients, telehealth use was associated with 5.45 ppts (95%CI=5.31 to 5.60) higher likelihood of home hospice use. Telehealth use was also associated with 2.18 ppts (95%CI=-2.31 to -2.05) lower likelihood of late hospice enrollment. Associations with multiple hospitalizations and ER visits were small and statistically non-significant. **Conclusions:** Telehealth use among Medicare decedents with cancer was associated with higher hospice use, particularly home hospice, and a lower likelihood of late hospice enrollment, suggesting potential improvements in EOL care transitions. These associations may reflect enhanced care coordination and continuity facilitated by telehealth during the EOL. Research Sponsor: U.S. National Institutes of Health; K12AR084234.

11013 **Rapid Oral Abstract Session**

Cancer during pregnancy and child health perspectives: Evidence from real-world data. First Author: Samah Hayek, Tel Aviv University, Tel Aviv, Israel

Background: Pregnancy-associated cancer (PAC), is rare but increasingly encountered, likely reflecting delayed childbearing and the rising incidence of early-onset cancers. However, real-world evidence on short- and long-term offspring outcomes following PAC remains limited, particularly with respect to childhood chronic and inflammatory conditions. **Methods:** We conducted a retrospective cohort study using electronic medical records from Clalit Health Services, Israel's largest integrated healthcare system. Pregnancies among women aged 18–50 years between 2000 and 2024 were identified including PAC and non-PAC (controls). Annual incidence rates were calculated overall and by maternal age group. Short-term maternal, pregnancy, and neonatal outcomes were compared between PAC-exposed and cancer-free pregnancies using multivariable regression models. To assess long-term child outcomes, we included all identified PAC cases and their offspring and extended follow-up to capture chronic conditions (as documented diagnosis within electronic medical records) that typically manifest later in childhood. **Results:** The cohort included 3,561 PAC and 28,361 non-PAC participants. PAC incidence increased substantially over time, with highest incidence observed among women aged 35–45 years. Breast cancer was the most frequently diagnosed invasive malignancy during pregnancy. Gestational age at delivery was comparable between PAC and non-PAC pregnancies, although PAC-exposed offspring were slightly more likely to be born with low birth weight (HR 1.03; 95% CI 1.01–1.05; P = 0.01).In follow-up analyses, heterogeneous and outcome-specific differences in child health were observed. PAC exposure was associated with higher risks of inflammatory and immune-related conditions, including inflammatory bowel disease (HR 1.16; 95% CI 1.03–1.32; P = 0.013) and allergic conditions (HR 1.20; 95% CI 1.03–1.39; P = 0.017). Associations with asthma (HR 1.12; 95% CI 1.00–1.26; P = 0.056) and cardiovascular conditions (HR 1.16; 95% CI 1.00–1.26; P = 0.057) were also observed yet reached borderline statistical significance. All models were adjusted for maternal BMI, hypertension, diabetes, cardiovascular disease, age at delivery, socioeconomic status, depression, and child sex. **Conclusions:** The incidence of PAC has increased markedly over the past decade. Our findings suggest that cancer during pregnancy may be associated with increased risk of inflammatory/immune-related conditions in the born children. Ongoing analyses and preclinical models will further clarify the long-term clinical significance of these findings and their implications for maternal–child survivorship care. Research Sponsor: Israel Cancer Association; 01037248/2024; Israel Science Foundation (ISF); ISF 3287/25.

11014 **Rapid Oral Abstract Session**

Real-world evidence of the association between primary insomnia and early-onset hormone-related cancers. First Author: Vineet Polineni, Jefferson Health New Jersey, Stratford, NJ

Background: Although progress has been made in reducing overall cancer incidence, early-onset cancers have continued their troublesome rise. Similarly, primary insomnia increases in incidence and prevalence each year, and with it come likelihoods of circadian disruption, immune dysregulation, and altered hormone signaling. However, real-world data characterizing the association between insomnia and early-onset hormone-associated malignancies remains limited. **Methods:** We sought to conduct a real-world, retrospective cohort study using the TriNetX United States Research Database, a federated network of de-identified electronic health records (EHRs) from over 70 healthcare organizations, to examine this association. Adults aged 18–50 years with primary insomnia (ICD-10: F51.01) were compared with same-aged individuals without primary insomnia using a five-year lookback period from January 25th, 2021 to January 25th 2026. Propensity score matching adjusted for demographic and clinical confounders. Incidence of early-onset cancers diagnosed within five years of the index event was assessed during follow-up. Sensitivity analyses required a $\geq$ 1-year lag between insomnia diagnosis and cancer onset. **Results:** 413,116 patients ages 18-50 were identified as having primary insomnia, whereas 18,437,709 patients ages 18-50 were identified as not having primary insomnia. Within 1-5 years of primary insomnia diagnosis, patients were more likely to develop early-onset breast cancer (RR 3.155, CI 2.863-3.477, $p < 0.0001$), uterine cancer (RR 1.988, CI 1.532-2.580, $p < 0.0001$), and ovarian cancer (RR 1.573, CI 1.276-1.940, $p < 0.0001$). Associations with early-onset prostate cancer (RR 1.676, CI 1.096-2.564) and testicular cancer (RR 1.243, CI 1.015-1.522) did not meet thresholds for significance. **Conclusions:** In this large, real-world cohort study, insomnia was associated with an increased risk of early-onset hormonal cancers more commonly affecting female patients. These findings suggest that sleep disruption may represent a clinically relevant, potentially modifiable risk factor in early-onset cancer risk stratification and warrants further investigation. Research Sponsor: None.

11015 **Rapid Oral Abstract Session**

Longitudinal changes in patient-reported quality of life (QOL) and hope among early phase cancer clinical trial (EPCT) participants. First Author: Debra Lundquist, Henri and Belinda Termeer Center for Targeted Therapies, Massachusetts General Hospital, Boston, MA

Background: Few studies have explored associations of longitudinal changes in patient-reported outcomes (PROs) and clinical outcomes among EPCT participants. We sought to describe changes in hope and QOL over the first two months of EPCT participation and examine associations of these changes with clinical outcomes. **Methods:** We prospectively enrolled adults participating in EPCTs at Massachusetts General Hospital from 04/2021-01/2023. We assessed QOL (Functional Assessment of Cancer Therapy-General, with subdomains: physical wellbeing [PWB], emotional wellbeing [EWB], social wellbeing [SWB], functional wellbeing [FWB]) and hope (Herth Hope Index) at time of EPCT enrollment, at 1 month (M1), and at 2 months (M2). We used descriptive statistics and regression models to describe changes and explore associations of patient-reported QOL and hope with patient factors (age, diagnosis, performance status) and clinical outcomes (time on trial [TOT], ED visits, and hospitalizations). **Results:** We enrolled 195 of 251 eligible patients (78% enrollment) and 192 completed surveys (98% response, median age: 63, 57% female, 94% metastatic cancer, ECOG 0 = 47% and ECOG 1 = 58%), 152 (78%) had M1 data, and 114 (59%) had M2 data evaluable. Most common cancer types were gastrointestinal (34%) and breast (20%). Over time, mean QOL scores improved (baseline [B/L] [75], M1 [76], M2 [76]), and mean hope scores were unchanged (B/L [39], M1 [39], M2 [39]). At M1, older age was associated with improved QOL change (B = 3.09, p = .031), EWB change (B = 0.94, p = .036), and increased hope (B = 1.22, p = .013). Female sex correlated with improved FWB (B = 1.15, p = .048) at M2. Head & neck cancer was associated with decreased EWB (B = -2.89, p = .010) at M2. Improved QOL at M2 was associated with longer TOT (HR = 0.97, p = .003). Improved PWB was associated with lower risk of ED visits (HR = 0.94, p = .011) and hospitalizations (HR = 0.95, p = .045) at M1, as well as longer TOT (HR = 0.94, p = .015) and lower risk of hospitalizations (HR = 0.93, p = .022) at M2. Improved EWB was associated with longer TOT at M1 (HR = 0.94, p = .001) and at M2 (HR = 0.89, p = .001). Improved FWB was associated with lower risk of hospitalizations (HR = 0.93, p = .023) at M1, as well as lower risk of hospitalizations (HR = 0.91, p = .043) and longer TOT (HR = 0.92, p = .016) at M2. We found no significant associations of changes in hope scores with clinical outcomes. **Conclusions:** This prospective study examined longitudinal changes in QOL and hope among EPCT participants. We described changes in QOL and hope scores from time of EPCT enrollment through 1- and 2-month follow-up and identified factors associated with these changes. Improvements in QOL over time predicted higher TOT and reduced healthcare utilization. Future studies should assess and address longitudinal changes in PROs to enhance trial experience and optimize clinical outcomes. Research Sponsor: None.

11016 **Rapid Oral Abstract Session**

Obesity paradox in gastrointestinal cancer patients on immunotherapy: A retrospective multi-institutional US cohort study. First Author: Marwa Al Faraj, SUNY Downstate Health Science University, New York, NY

Background: Obesity is a well-established risk factor for different types of cancers, including gastric cancers. However, emerging research suggests its association with improved survival outcomes in cancer treatment, a phenomenon referred to as "the obesity paradox". Recent literature demonstrates this paradoxical effect in cancer patients receiving immunotherapy. We explored this effect across various types of gastrointestinal (GI) malignancies. **Methods:** De-identified data from the TriNetX database were used to identify adult patients (age $>$ 18 yrs) with GI malignancies (hepatocellular, colorectal, pancreatic, upper GI (gastric and esophageal) who received immune checkpoint inhibitors (ICIs) between 2013 and 2025. Propensity score matching was performed to balance cohorts by demographics, comorbidities, ECOG and albumin level. The primary outcome was 5-year all-cause mortality, compared between patients with obesity (BMI $\geq$ 30 kg/m²) and those with normal BMI (18–24.9 kg/m²). The secondary outcome was the incidence of ICI-related adverse events (irAEs). Kaplan–Meier was used for time-to-event outcomes, differences were assessed using the log-rank test, and Cox proportional hazards using the TriNETx platform. **Results:** After propensity score matching, 4,956 patients were included in each cohort. Mean baseline characteristics were comparable between cohorts. The BMI $>$ 30 cohort had BMI(kg/m2) 35.4 $\pm$ 5.4, albumin(g/dl) 3.54 $\pm$ 0.61, and mean ECOG 0.68 $\pm$ 0.96 while the normal BMI cohort had BMI 22.8 $\pm$ 4.5, albumin 3.48 $\pm$ 0.62, and mean ECOG 0.67 $\pm$ 0.83. Obesity was associated with significantly improved all-cause mortality compared with the normal BMI group (26.8 months vs 13.9 months; hazard ratio [HR], 0.7 [0.67-0.74]). Survival probabilities at 1 year (63.7% vs 52.6%), 3 years (46.2% vs 31.9%), and 5 years (39.1% vs 25.4%) were higher in the BMI $\geq$ 30 kg/m² cohort compared with the normal BMI cohort. Among GI cancer subtypes, the strongest associations between obesity and improved survival were observed in colorectal (HR 0.67 [0.62-0.72]) and pancreatic cancers (HR 0.66 [0.56-0.76]), with more modest effects seen in hepatocellular (HR 0.78 [0.72-0.84]) and upper GI cancers (HR 0.71 [0.62-0.80]). There were no significant differences between cohorts in the incidence of pneumonitis (HR 1.12 [0.80-1.57]), GI (HR 1.07 [0.98-1.17]), thyroid (HR 1.05 [0.97-1.14]), or cutaneous (HR 1.10 [0.99-1.23]) irAEs. **Conclusions:** In this analysis of 9,912 patients with GI malignancies treated with immunotherapy, higher BMI was associated with improved survival. Confounding by disease burden was partially addressed through adjustment for ECOG and albumin. These findings may reflect obesity-related immune modulation, as preclinical studies suggest leptin-mediated upregulation of PD-1 expression. However, further prospective studies are needed to validate and define these results Research Sponsor: None.

11017 **Rapid Oral Abstract Session**

GLP-1 receptor agonist utilization and survival outcomes in a large U.S. community oncology cohort. First Author: Ila Sruti, Ontada, Boston, MA

Background: GLP1 use has increased with 12.4% of U.S. adults reported using these treatments, driven in part by the 2021 approval of semaglutide for chronic weight management without diabetes. Beyond established metabolic benefits, emerging preclinical and observational data suggest potential anticancer effects of GLP1 therapy. However, no study to date has characterized GLP1 use among cancer patients treated in a large-scale population. This study provides an essential step towards describing real-world world GLP1 treatment patterns and clinical outcomes. **Methods:** Structured EHR data from The US Oncology Network were used to identify GLP1 users (dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, and tirzepatide) and nonusers between January 2021 and October 2024, with follow-up through October 2025. Overall survival (OS) was assessed from initial cancer diagnosis to death from any cause. Nonusers were matched to GLP1 users by cancer type and diagnosis year. To address immortal time bias, each nonuser was assigned the matched user's GLP1 medication start date as the anchor date; nonusers who died or were lost to follow-up prior to that date were excluded. Multivariable Cox proportional hazards models evaluated factors associated with OS among patients diagnosed with breast, prostate, lung, hepatocellular, or renal cancer. **Results:** A total of 1,121 GLP1 users and 471,580 non GLP1 users with cancer were identified. GLP1 users had a median age of 63 years, were 63% White, and 69% had BMI $\geq$30 kg/m^2 semaglutide was the most commonly used agent (64%). Non GLP1 users had a median age of 68 years, were 61% White, and 30% had BMI $\geq$30 kg/m^2. Among GLP1 users, 74% were prescribed GLP1 therapy after initial cancer diagnosis, of those 7% after metastatic diagnosis; the most common cancers were breast (27%) and prostate (13%). OS at 24 months was higher among GLP1 users versus nonusers for both breast cancer (97.9% [95% CI 93.7–99.3] vs 92.6% [92.4–92.8]) and prostate cancer (97.9% [93.7–99.3] vs 92.6% [92.4–92.8]). After adjustment for age, BMI, stage, and cancer type, GLP1 use was significantly associated with improved OS (HR 0.58, 95% CI 0.40–0.84; p = 0.0036). **Conclusions:** In this large real-world cohort, GLP1 use was most frequently observed among younger patients with obesity and was commonly prescribed after cancer diagnosis, with semaglutide accounting for the majority of prescriptions. Breast and prostate cancers were the most prevalent malignancies among GLP1 users, reflecting early adoption across common solid tumor types in routine practice. Despite limitations inherent to structured real-world data, including potential underreporting of GLP1 exposure, GLP1 use was associated with improved OS compared with nonuse, supporting the need for future studies using robust causal inference approaches. Research Sponsor: None.

11018 **Poster Session**

Temporal trends in oncology clinical trial complexity and duration: A retrospective analysis of 5,261 industry-sponsored trials. First Author: Andrew J. Yang, The Warren Alpert Medical School of Brown University, Providence, RI

Background: Clinical trial complexity has been cited as a contributor to rising drug development costs and increasing trial duration. We aimed to quantify multidimensional oncology trial complexity and describe temporal trends. **Methods:** We conducted a retrospective analysis of industry-sponsored interventional drug and biological oncology trials from the Aggregate Analysis of ClinicalTrials.gov (AACT) database, restricted to concluded trials initiated 2007-2017 for post-FDAAA reporting consistency and adequate follow-up. Five complexity dimensions were derived using principal component analysis: protocol (eligibility criteria, arms, outcomes), operational (sites, countries, planned enrollment), disease (MeSH breadth), intervention (modality count), and governance (team structure). Temporal trends were analyzed across completed trials only; Pearson correlations between dimensions and duration/early termination were calculated across all concluded trials. Trends were estimated using linear regression on yearly medians stratified by phase. **Results:** Among 6,752 concluded oncology trials (78% completion rate), temporal trends were analyzed in the 5,261 completed trials. Protocol complexity significantly increased (+0.083 SD/year), driven by total eligibility criteria (+0.56/year), secondary outcomes (+0.35/year), and exclusion criteria (+0.35/year). Operational complexity showed a significant increasing trend (+0.014 SD/year), with facilities increasing +0.51/year. Overall trial duration significantly increased (+16.7 days/year), with Phase 1 trials increasing +18.2 days/year and Phase 2 trials +18.4 days/year, while Phase 3 trials showed a non-significant trend (+20.7 days/year). Across all trials, protocol complexity was weakly correlated with early termination (r=0.03) and duration (r=0.14). Operational complexity showed the strongest correlation with duration (r=0.36). **Conclusions:** Among concluded oncology trials, protocol and operational complexity are significantly increasing, particularly eligibility criteria burden, endpoint multiplicity, and study scale. Trial duration is significantly increasing for early-phase trials, driven primarily by operational complexity. Research Sponsor: None.

Operational and protocol trends in oncology trials.

Metric (median)	2007 Value	2017 Value	Slope/Year	P-value
Total I/E Criteria	15	22	+0.56	$<$0.001
Secondary Outcomes	4	7	+0.35	$<$0.001
Exclusion Criteria	8	12	+0.35	$<$0.001
Inclusion Criteria	6	9	+0.22	$<$0.001
Total Outcomes	8	11	+0.30	$<$0.001
Number of Sites	6	12	+0.51	$<$0.001
Phase 1 Duration (days)	1080.5	1220	+18.2	0.010
Phase 2 Duration (days)	1249	1347	+18.4	0.028
Phase 3 Duration (days)	1583	1673	+20.7	0.214
Overall Duration (days)	1247	1378	+16.7	0.006

Observed medians are reported for 2007 and 2017. Slopes and p-values were derived from linear regression on yearly medians.

11019 **Poster Session**

A machine learning–enhanced analysis of temporal trends in biomarker-based eligibility restrictions in oncology clinical trials. First Author: Luke Xiyu Zhao, Johns Hopkins University School of Medicine, Baltimore, MD

Background: The adoption of biomarker-based eligibility criteria reflects the evolution of precision oncology, but temporal trends and predictors of biomarker restrictions are unclear. Understanding these patterns is essential for optimizing trial design and ensuring equitable patient access to investigational therapies. We used machine learning and natural language processing to analyze biomarker restriction trends across oncology trials. **Methods:** We analyzed all 54,985 oncology interventional trials from ClinicalTrials.gov from 2010-2024. Biomarker restrictions were identified using curated term lists plus NLP-based classification (TF-IDF vectorization with logistic regression). We developed complementary machine learning modules for emerging biomarker discovery using named entity recognition, requirement type classification (inclusion/exclusion/stratification), and eligibility complexity scoring via text feature engineering. Statistical analyses included logistic regression with Wilson score confidence intervals and Benjamini-Hochberg FDR correction. **Results:** Biomarker-restricted trials increased from 20.8% (2010) to 31.2% (2024), representing a 1.5-fold increase over 15 years (OR per year: 1.046, 95%CI: 1.041-1.050, p$<$0.001). Industry sponsorship (OR: 1.88, 95%CI: 1.80-1.97) and NIH sponsorship (OR: 1.89, 95%CI: 1.67-2.13) independently predicted higher biomarker restrictions versus academic sponsors (all p$<$0.001). US-based trials showed 40% higher odds of restrictions (OR: 1.40, 95%CI: 1.35-1.46). Phase II trials demonstrated the highest rates (40.9%). Among specific biomarkers, PD-1 showed the steepest adoption trajectory (0.08% to 10.59%), followed by EGFR (5.07% to 8.84%) and HER2 (5.16% to 8.17%). Our NLP-based emerging biomarker discovery identified CTLA-4, PSMA, CD19, CD137, and LAG-3 as rapidly emerging eligibility biomarkers reflecting next-generation immunotherapy targets. Cancer-specific analyses revealed dramatic increases in lung (22.8% to 50.5%) and gastric cancers (14.6% to 45.5%), while prostate cancer showed declining rates (60.5% to 52.3%). Our complexity scoring algorithm demonstrated that biomarker-restricted trials have significantly higher eligibility complexity (mean: 50.0 vs 31.0, p$<$0.001). All findings remained robust across multiple sensitivity analyses. **Conclusions:** Biomarker-based eligibility restrictions in oncology trials have increased substantially over 15 years, driven primarily by immune checkpoint and targeted therapy biomarkers. Industry-sponsored and later-phase trials show the highest adoption rates. These scalable ML findings inform precision medicine trial design and highlight considerations for patient access and trial generalizability. Research Sponsor: None.

11020 **Poster Session**

Restrictive eligibility criteria in FDA-approved oncology trials following ASCO Guideline updates. First Author: Ryan Scott Imaikalani Kong, University of Illinois Chicago College of Medicine, Chicago, IL

Background: Despite significant advancements in new targeted and immunotherapies, enrollment in oncology clinical trials remains unrepresentative of real-world patient populations. Overly restrictive eligibility criteria – particularly related to Eastern Cooperative Oncology Group (ECOG) performance, cardiovascular status, HIV status, and prior malignancy – have been identified as key barriers to trial participation and generalizability. In response, the American Society of Clinical Oncology (ASCO) published new guidelines in 2017 lowering thresholds for enrollment. We examined whether these ASCO recommendations translated into measurable changes in eligibility criteria among FDA-approved trials for the five most common solid tumors. **Methods:** Clinical trial data was obtained from ClinicalTrials.gov, FDA Approved Drug Notification Database, and journal manuscripts. The study evaluated clinical trials that led to FDA-approved therapies for NSCLC, breast, melanoma, prostate, and colon cancer between 2006-2025. Eligibility criteria based on Eastern Cooperative Oncology Group (ECOG) performance, cardiovascular status, HIV status, and prior malignancy were extracted. Clinical trials were categorized as pre- or post-ASCO 2017 guideline publication, and t-tests (R v4.3.1) were used to compare exclusion rates between groups and assess alignment with ASCO recommendations. **Results:** Between 2006-2025, there were 167 FDA-approved clinical trials for NSCLC (59), breast (44), melanoma (25), prostate (23), and colon (16) malignancies. The proportion of trials initiated after the 2017 ASCO guidelines was 19 (32.2%) of NSCLC, 12 (27.3%) of Breast, 6 (37.5%) of Colon, 5 (21.7%) of Prostate, and 5 (20.0%) of Melanoma. There was no statistically significant reduction in the usage of restrictive exclusion criteria when comparing trials started before and after the 2017 ASCO recommendations among Colon ($p = 0.953$), Prostate ($p = 0.896$), Melanoma ($p = 0.775$), NSCLC ($p = 0.301$), and Breast ($p = 0.117$) cancer groups regarding ECOG performance, cardiovascular status, HIV status, and prior malignancy. **Conclusions:** Despite the publication of ASCO's 2017 eligibility guideline updates, restrictive exclusion criteria remain prevalent in FDA-approved oncology trials across major solid tumors. These findings suggest that guideline dissemination alone has been insufficient to change trial design practices. More proactive regulatory, sponsor-level, and implementation-focused interventions may be required to ensure broader trial access and improve the generalizability of oncology clinical research. Research Sponsor: None.

11021 **Poster Session**

Comparative effectiveness and safety of axicabtagene ciloleucel versus lisocabtagene maraleucel in large B-cell lymphoma: A real-world target trial emulation. First Author: Mohammed Zuber, Department of Clinical and Administrative Pharmacy, College of Pharmacy, University of Georgia, Athens, GA

Background: Axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) are approved CD19-directed CAR T-cell therapies for large B-cell lymphoma (LBCL); however, comparative real-world evidence on their effectiveness and safety remains limited. We conducted a target trial emulation to compare the overall survival (OS), event-free survival (EFS), and safety outcomes between axi-cel vs liso-cel in routine clinical practice. **Methods:** Using de-identified electronic health record data from TriNetX (January 2017- December 2025), we emulated a two-arm target trial among adult patients with LBCL who received axi-cel or liso-cel. Index date (T_0) was defined as the date of CAR T-infusion. Patients with active severe infections at the index date or a history of cardiovascular and central nervous system involvement were excluded. Inverse probability of treatment weighting (IPTW) was used to balance the covariates, including age, sex, race, comorbidity, prior autologous stem cell transplantation, bridging therapy, and baseline inflammatory markers. OS was analyzed using IPTW Cox proportional hazards models. Event-free survival (EFS) was defined as a composite of death or initiation of subsequent systemic therapy (as a proxy for treatment failure). Cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS) were evaluated. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported, and all analyses were conducted using R. **Results:** Among 1,311 eligible patients, 947 received axi-cel and 364 received liso-cel. In the unweighted cohort, patients treated with axi-cel were younger than those receiving liso-cel (median age 62 vs 72 years), with a similar sex distribution and a predominantly White population in both groups. After IPTW, baseline demographic, clinical, and laboratory characteristics were balanced between groups. OS did not differ significantly between axi-cel and liso-cel (HR 0.98; 95% CI, 0.71-1.36). Median OS was not reached in either group, with similar OS rates at 12 months (axi-cel: 78.1%, liso-cel: 80.3%) and 24 months (axi-cel: 71.3%, liso-cel: 71.4%). EFS was also comparable between treatments (HR 1.08; 95% CI, 0.82–1.44). No significant differences in CRS risk were observed within 90 days or overall follow-up (HR: 0.86; 95% CI, 0.66-1.11). Axi-cel was associated with a higher risk of ICANS within the first 90 days (HR 1.42; 95% CI, 1.00-2.01), although no significant difference was observed over longer follow-up. **Conclusions:** Axi-cel and liso-cel demonstrated comparable effectiveness in terms of OS and EFS. Safety profiles differed primarily in early neurotoxicity risk, while CRS incidence was similar between products. These findings provide real-world comparative evidence that may help to inform CAR T-cell therapy selection in clinical practice. Research Sponsor: None.

11022 **Poster Session**

AI-enabled clinical trial framework for end-to-end site recommendation and enrollment projection. First Author: Stephen S. Yip, ConcertAI, LLC, Cambridge, MA

Background: Reliable accrual forecasting is essential in oncology trials because delayed enrollment reduces statistical power, increases costs, and prolongs timelines. We developed an AI-enabled framework integrating site recommendations with probabilistic enrollment modeling to support data-driven trial planning. **Methods:** Site-level attributes (Site360) and curated real-world patient datasets (Patient360) were integrated as inputs. Trial objectives including enrollment targets, timelines, sponsor and diversity requirements, and screen failure rates (SFR) were user specified. Candidate sites were ranked using a multi- criteria TOPSIS engine optimized with simulated annealing to identify portfolios meeting protocol requirements. Recommended site attributes informed Monte Carlo enrollment simulations incorporating site activation, patient arrival, and capacity constraints. Each underwent 1000 simulations, generating accrual distributions. Fifty-four CRC, NSCLC, and Breast trials from ClinicalTrials.gov were evaluated. Planned site counts and enrollment intensity (patients per month per planned site; ppmpps) from the same trials served as benchmarks. Enrollment intensity was calculated as enrolled patients divided by (trial duration in months $\times$ planned sites), with duration estimated from trial start to primary completion. Scenarios tested SFR 20%, 40%, and 60%. Model outputs were compared with planned benchmarks using Spearman correlation and summarized with medians and IQR. **Results:** Trials showed heterogeneous planned site counts: CRC median 76 (IQR: 43-119), Breast 204 (114-279), NSCLC 178 (101-227). Model recommended site counts showed moderate to strong rank agreement with planned sites across indications. CRC correlations increased from 0.67 to 0.73 as SFR rose from 20% to 60% (all $p < 0.05$). Breast correlations ranged 0.49-0.54 and NSCLC 0.61-0.63 across SFRs all with $p < 0.05$. Higher SFR required more recommended sites, compensating for screen failures. Predicted ppmpps aligned strongly with benchmarks. For Breast, predicted ppmpps decreased from 0.15 (0.10-0.31) at 20% SFR to 0.07 (0.04-0.16) at 60% SFR versus planned 0.08 (0.03-0.17), with ppmpps correlations 0.82, 0.77, 0.66 respectively (all $p < 0.01$). CRC predicted rates were 0.13 (0.08-0.29), 0.10 (0.07-0.24), 0.07 (0.05-0.18) across SFRs versus planned 0.09 (0.06-0.13), correlations 0.47 ($p = 0.076$), 0.54, 0.59 (both $p < 0.05$). NSCLC showed 0.23 (0.15-0.27), 0.18 (0.13-0.22), 0.12 (0.08-0.18) versus planned 0.12 (0.07-0.19) with correlations 0.54-0.64 ($p < 0.02$). **Conclusions:** This AI-enabled framework integrates optimization and probabilistic modeling to recommend sites and project enrollment behavior. Rank agreement with benchmarks supports improved site feasibility assessment by identifying trials with higher site requirements and enrollment risk and enabling risk-adjusted planning. Research Sponsor: None.

11023 **Poster Session**

Exploring neural correlates of chemotherapy-induced peripheral neurotoxicity (CIPN) and the impact of exercise: A URCC NCORP nationwide phase II randomized controlled trial (RCT). First Author: Thushini Manuweera, University of Maryland Baltimore, Baltimore, MD

Background: More than half of patients with cancer receiving neurotoxic chemotherapy (e.g., taxane, platinum, vinca alkaloid) develop CIPN, a dose-limiting, sometimes-debilitating condition characterized by numbness, tingling, and pain in the hands and feet. There are limited treatment options for CIPN partly due to limited understanding of CIPN pathophysiology. **Methods:** We conducted a phase II RCT examining the effect of exercise on CIPN via URCC NCORP Research Base. Patients who received neurotoxic chemotherapy within the past 9 months and report CIPN symptoms (rated $\geq$4 out of 10 at its worst in the past 2 weeks) were randomized 1:1 to usual care (UC) or virtually delivered Exercise for Cancer Patients (vEXCAP). vEXCAP is a 6-week personalized walking and resistance band exercise intervention. As part of our secondary aims, we investigated (1) whether CIPN symptoms are exacerbated by impairments in the brain's descending pain modulation circuitry—quantified by functional connectivity between the dorsolateral prefrontal cortex (DLPFC) and 23 sensory-related brain regions—and (2) whether exercise can improve both CIPN and brain functional connectivity. We recruited 35 patients from 7 community oncology practices spanning 6 US states. Sensory CIPN severity was assessed using the patient-reported EORTC QLQ-CIPN20 sensory subscale and functional brain connectivity was measured via magnetic resonance imaging (MRI) at pre- and post-intervention. **Results:** An ANCOVA showed that exercise, compared to UC, reduced sensory CIPN severity (-7.66 ± 3.05 (MCID is 4), effect size (ES) = -0.43, $p = 0.158$) ($N = 35$, 57 ± 10 yrs, 89% female, 60% breast cancer). At pre-intervention, correlation analysis revealed sensory CIPN severity was negatively correlated with functional connectivity between the left DLPFC and several brain areas, including the left anterior insula ($r = -0.53$, $p = 0.001$), left thalamus ($r = -0.44$, $p = 0.009$), and left precuneus ($r = -0.32$, $p = 0.057$). Participants who showed a decrease in sensory CIPN severity at post intervention had an increase in functional connectivity between the left DLPFC and left precuneus ($r = -0.25$, $p = 0.152$), and this increase in connectivity was greater in vEXCAP group (effect size (ES) = 0.2, $p = 0.460$). **Conclusions:** The association of sensory CIPN severity with lower brain connectivity with the left DLPFC may reflect impairment of descending pain inhibition pathways in the brain. vEXCAP may improve brain connectivity with the precuneus while lowering CIPN symptom severity. We believe that this line of research will ultimately inform better CIPN biomarkers and treatments. Funded by NCI UG1CA189956, UG1CA189861, UG1CA189805, UG1CA189961, K07CA221931, and R21CA256154. Clinical trial information: NCT04888988. Research Sponsor: National Cancer Institute; UG1CA189956; National Cancer Institute; UG1CA189861; National Cancer Institute; UG1CA189805; National Cancer Institute; UG1CA189961; National Cancer Institute; K07CA221931; National Cancer Institute; R21CA256154.

11024 **Poster Session**

Trends and characteristics of clinical trials presented in ASCO plenary sessions (2011–2025). First Author: Oliver Overheu, Fuqua School of Business, Duke University, Durham, NC

Background: Clinical trials presented during the ASCO Annual Meeting Plenary Session (PS) represent a curated subset with high scientific and clinical impact. However, characteristics associated with PS selection and their evolution have not been comprehensively described. This study evaluates trends and trial-, sponsor-, and presenter-related characteristics of trials in PS. **Methods:** Trials presented in PS from 2011–2025 were analyzed. Extracted variables included tumor type, therapeutic modality, disease setting, sponsorship, primary endpoint, effect size, geographic scope, and presenter sex and affiliation. Associations between variables were evaluated using chi-square, and multivariable logistic regression analyses. Temporal trends were assessed using Cochran-Armitage trend test. Results were considered significant at α = 0.05. **Results:** From 2011–2025, 60 trials were presented in ASCO PS. The majority evaluated therapies for solid tumors (90%). Most common therapeutic modalities were immune checkpoint inhibitors (18%), chemotherapy (16%), and hormone therapy (13%). Most trials were conducted in the palliative (46%), followed by adjuvant setting (25%). Only 9 trials (15%) included pediatric patients. Overall, 85% of trials met their primary endpoint. Overall survival (OS), progression-free, and disease-free survival were the most used primary endpoints, with surrogate endpoints increasingly represented over time compared with OS ($p < 0.001$). One trial used quality of life (QoL) as primary endpoint. Mean hazard ratio was 0.68 $\pm$ 0.24. Industry-sponsored (Ind) studies accounted for 52% of PS presentations, with four sponsors responsible for 61% of Ind trials. The proportion of Ind trials significantly increased over time (p = 0.03). Ind was significantly associated with meeting the primary (p = 0.048) and use of surrogate endpoints (p = 0.008), remaining an independent predictor of both in multivariable regression (p = 0.035, β = 0.318; p = 0.033, β = 0.333). Most studies were conducted globally (61%), 12% exclusively in the United States (US), followed by Europe (10%). Among presenters, 23% were female, with female representation not changing over time. Most presenters were affiliated with institutions in the US (62%), followed by the United Kingdom (7%). In multivariable regression analysis, Ind was associated with lower odds of a female presenter (p = 0.039; β = -0.342). **Conclusions:** Over the past 15 years, ASCO PS have predominantly featured global, Ind trials in solid tumors, with an increasing reliance on surrogate endpoints. Ind emerged as key factor associated with trial characteristics, including endpoint selection and trial success. Female presenter inclusion, pediatric trials, and QoL endpoints remain underrepresented. These findings provide an overview of evolving trial characteristics and inform discussions on research priorities, trial design, and representation. Research Sponsor: None.

11025 **Poster Session**

Reducing effort through informatics-driven identification, recruitment, and data capture on a trial to improve adjuvant endocrine therapy adherence. First Author: Ahauve Orusa, Mayo Clinic Rochester, Rochester, MN

Background: Adjuvant endocrine therapy (AET) improves outcomes in HR+ breast cancer. Nonadherence to AET is common, but manual screening for nonadherence is fraught. High-specificity structured cancer electronic health record (EHR) data, particularly if it includes key variables like stage, could streamline these steps for both clinical care and research purposes. We conducted an analysis of approaches to identifying patients as eligible for a multi-site AET adherence study to understand how variation in structured data informatics-supported screening impacts coordinator time. **Methods:** Mayo Clinic implemented a two-step identification: (1) EHR structured data (diagnosis date, stage, ER/PR/HER2 positivity, medication script) to prescreen for eligibility; (2) SureScripts fills to flag nonadherence using proportion of days covered $<$ 80% across early fills. Medical College of Wisconsin (MCW) implemented a more manual screening process for Step 1 using only medication scripts. Coordinators at both sites then conducted a medical record review to assess if the resulting list of patients had a plan to continue AET for at least two additional years. Opt-out clinician permission preceded patient contact; pharmacists delivered a patient reported outcome (PRO)-guided intervention and documented encounters. **Results:** At Mayo, 829 patients were prescreened for study eligibility through informatics workflow; 120 (14.5%) met eligibility criteria. At MCW, 1,763 patients were prescreened; 168 (9.5%) were eligible. EHR filters included non–breast cancer encounters (50% at MCW) and ineligible based on time since cancer (36% at Mayo; 26% at MCW). At Mayo, screening required 5.6 minutes/patient for experienced coordinators. At MCW, experienced coordinators averaged 6.67 minutes/patient and inexperienced coordinators averaged 9.33 minutes/patient. **Conclusions:** Structured EHR data, pharmacy-fill information, and standardized workflows allowed consistent prescreening, intervention and recruitment processes across sites. Higher-specificity informatics-supported screening reduced the percentage of patients requiring manual review and reduced coordinator screening time. It also supported timely provider-permission steps and patient outreach. These workflows were feasible to implement at both institutions, and study enrollment is ongoing. Clinical trial information: NCT06765707. Research Sponsor: National Cancer Institute; R01 CA285925.

11026 **Poster Session**

Enhancing recruitment of AYAs with Hodgkin lymphoma through community partnerships: Prioritizing diverse populations. First Author: Raymond Mailhot Vega, University of Miami Miller School of Medicine-Sylvester Cancer Center, Miami, FL

Background: Hodgkin lymphoma (HL) is one of the most common cancers affecting adolescents and young adults (AYAs). AYAs with HL aged 15-39 years are a group historically difficult to reach for research participation. Their voice is critical to enhance care. For two funded qualitative studies, the team engaged in and assessed the feasibility of a community-centered approach to recruit HL patients with 1:1 representation by age [those diagnosed as children (0-14), AYAs (15-39), and above 40 years], race and ethnicity (Black and Hispanic communities), and insurance (private, Medicaid, and uninsured populations). **Methods:** Recruitment was conducted exclusively through advocacy partner organizations including Blood Cancer United, Stupid Cancer, Cactus Cancer Society, and Elephants & Tea. Study team patient advocates guided recruitment approach, including selecting imagery using a Black-identifying male and Hispanic-identifying female and rephrasing recruitment material language. Advocacy partners utilized their techniques for engaging AYAs, such as Instagram, website posting, email, and/or attendance at member engagement events. Recruitment to the two studies required the study participants online to 1) complete a survey on REDCap documenting their consent using a waiver and 2) provide confirmation of their HL diagnosis by uploading proof to REDCap (e.g., screenshot from their medical record containing their name, date of birth, and HL diagnosis). **Results:** A total of 389 patients from 46 states or US territories started their REDCap survey and completed the waiver of consent. Of those, 217 (55%) were AYAs at diagnosis and 95 $\geq$40 (24%). Of the total 389, 85 (22%) were Black, 39 (10%) Hispanic, 34 (9%) had Medicaid, and 12 (3%) were uninsured. 154 (40%) provided proof of diagnosis from 38 states. Of the 154 that uploaded proof of HL diagnosis, 123 (80%) were AYA and 26 (17%) $\geq$40 years at diagnosis. 17 (11%) were Black, 21 (14%) Hispanic, 17 (11%) with Medicaid, and 3 (2%) uninsured. Documentation was most commonly provided using an after visit summary or visit note (47%), pathology report (19%), or physician signed letter (13%). **Conclusions:** Partnering with advocacy organizations, particularly those serving AYAs, proved successful in exceeding recruitment goals for AYA patients. Attrition in participation was seen between waiver completion and providing confirmation of diagnosis. AYAs were more likely than adults $\geq$ age 40 to provide proof of confirmation of diagnosis. Recruitment met national averages for Black representation, but fell short with lower than national average estimates for representation of Hispanic survivors, those on Medicaid or uninsured. Future studies should engage underrepresented populations during the research process to understand how to plan recruitment activities in a way that prioritizes what is most important and impactful for the target population. Research Sponsor: National Cancer Institute; Blood Cancer United.

11027 **Poster Session**

Quantifying the impact of protocol design on enrollment and dropout rates in breast cancer clinical trials. First Author: Evon Okidi, Medidata Solutions, a Dassault Systèmes Company, New York, NY

Background: Clinical trial enrollment can sometimes fail due to protocol design being overly complex, including procedures that are overly burdensome on patients and/or trial sites. Procedures that may be more logistically challenging or introduce higher risk (ex: radiation exposure in imaging procedures) can affect trial enrollment and patient retention. To better understand factors that optimize operational design of protocols, we evaluated breast cancer protocols to assess and quantify procedures that had the highest potential impact on enrollment and dropout rates. Objective: Our objective is to develop an algorithm that can predict enrollment and dropout rates by analyzing the procedures and procedure frequency included in protocol design. **Methods:** 42 breast cancer protocols (sourced from aggregated, anonymized Medidata Clinical Cloud data) from closed clinical trials conducted between 2010-2023 were utilized to train a predictive model. The model leveraged the procedure and schedule-of-activity data to capture the frequency of protocol-specified procedures as input features, and enrollment and dropout rates as outcome features. Model performance was assessed utilizing cross-validation. To assess the relative impact of individual procedures or groups of procedures on a protocol, a sensitivity analysis was performed by increasing each procedure's frequency by 1 unit while holding all other variables constant and measuring the resulting percent change in predicted enrollment and dropout rates. **Results:** Analysis of selected protocols demonstrated that inclusion of Positron Emission Tomography (PET) Imaging was associated with a 10-23% reduction in enrollment rates. Genetic testing and analysis procedures were associated with enrollment rate decreases of up to 5%. In contrast, bone density imaging, abdominal and pelvic imaging, and increased tumor and biopsy procedures were associated with enrollment increase of up to 6%. With respect to retention, increased cardiac rhythm monitoring was associated with up to 10% reduction in dropout rates, while blood cell analysis, collagen biomarker testing, and quality of life questionnaires were each associated with dropout reductions of up to 8%, 8% and 5% respectively. **Conclusions:** Procedure requirements and frequency had a measurable impact on clinical trial enrollment and retention. Some procedures, such as PET scans, were associated with reduced enrollment; whereas other clinically relevant imaging procedures (i.e., DEXA bone density imaging, CT/MRI abdominal and pelvic imaging) and other tumor-related procedures, monitoring, and assessments were associated with improved enrollment and/or reduced dropout. These findings highlight opportunities to optimize protocol design by prioritizing procedures that improve the likelihood of recruitment and retention. Research Sponsor: None.

11028 **Poster Session**

Assessing site-central baseline imaging discordance in oncology clinical trials. First Author: Danielle Phillippi, Clario, Philadelphia, PA

Background: Eligibility determination is a critical and rate-limiting step in oncology clinical trials and directly influences endpoint interpretability. Across oncology indications, eligibility frequently depends on prespecified imaging criteria that function as binary gatekeepers to enrollment, with blinded independent central review (BICR) commonly used to standardize image interpretation. In many solid tumor trials using RECIST 1.1, participants must demonstrate measurable disease; in many lymphoma trials using Lugano criteria, FDG-avid disease is required; and in prostate cancer trials using PCWG3 criteria, the presence of a bone scan superscan is typically exclusionary. Often participant eligibility is established by site investigators, while BICR radiologists independently assess baseline and on-study imaging without determining enrollment, creating potential site–central discordance at baseline. We hypothesized that baseline imaging discordance exists between site and BICR and evaluated its frequency and potential relevance to clinical trial endpoint interpretation. **Methods:** We performed a preliminary analysis of 17,104 baseline BICR reviews among enrolled participants evaluated using RECIST 1.1 requiring measurable disease (n = 7,189), Lugano criteria requiring FDG-avid disease (n = 2,653), and PCWG3 (n = 7,262) criteria. **Results:** For the RECIST 1.1 subset, BICR determined that 11.0% (n = 791) of enrolled participants lacked measurable disease at baseline. Among these participants, subsequent responses included CR (n = 36), PD (n = 93), and SD (n = 207). Because partial response under RECIST 1.1 requires measurable target lesions, participants without measurable disease are inherently constrained in the spectrum of evaluable responses, potentially biasing response rate. For the Lugano subset, BICR determined that 1.5% (n = 41) of enrolled participants lacked FDG-avid disease at baseline, with subsequent anatomic-only responses of CR (n = 1), PR (n = 5), SD (n = 9), and PD (n = 2). Though infrequent, site-central differences under Lugano criteria may influence response assessment, as BICR evaluated anatomic change while site incorporates metabolic response. For the PCWG3 subset, 7.0% (n = 548) of enrolled participants demonstrated a baseline superscan by BICR, with subsequent responses of CR (n = 20), PR (n = 25), SD (n = 90), and PD (n = 91). In these cases, response assessment is largely limited to soft tissue disease. **Conclusions:** The observed site-central imaging discordance reflects differences between eligibility and imaging assessments rather than incorrect site enrollment decisions and is not uncommon across major oncology response criteria, with potential implications for efficacy assessment in trials where eligibility is site-determined but response is centrally adjudicated. This analysis supports further investigation incorporating additional criterion-specific analysis. Research Sponsor: None.

11029 **Poster Session**

Temporal trends in pregnancy-associated cancer mortality in the United States: A national analysis 2018-2023. First Author: Diya Jayram, University of Miami, Miami, FL

Background: Cancer during pregnancy is rare but increasing due to rising rates of early-onset cancers and more parents delaying childbearing to older ages. Cancer treatment during pregnancy is complex, as capacity to deliver timely, multimodality anti-cancer treatment may be limited by risk of fetal compromise. As pregnancy-associated cancer is an increasingly recognized contributor to maternal mortality, this study sought to evaluate national temporal trends. **Methods:** Using CDC WONDER Multiple Cause of Death files (2018–2023), pregnancy-associated deaths involving malignant neoplasms (ICD-10 C00–C97) were identified. Age-adjusted mortality rates (AAMR) per 100,000 live births and annual percent changes (APCs) were calculated, excluding unknown race, ethnicity, or age. AAMR was evaluated by state, including comparison of 1) states with trigger laws banning abortion in 2022 vs states that did not have such laws and 2) states that expanded Medicaid by 2018 vs states that did not. Mortality data for locations with $<$10 deaths is censored. **Results:** From 2018–2023, there were 723 pregnancy-associated deaths in people with cancer. Most (72%) were in White patients and occurred in the late postpartum period (59%) (42-365 days after birth). Only 19% of patients had documented metastatic cancer. Overall AAMR was 3.40 (95%CI 3.16–3.65); it was highest among Black patients (4.54), exceeding White (3.24), Hispanic (3.08), and AIAN/AAPI (2.64) mortality. Breast (n=162, AAMR 0.76 95%CI 0.65-0.88) had the greatest cancer-specific mortality burden, followed by hematological malignancies (n=101, AAMR 0.48, 95% CI 0.38-0.57) and colorectal cancer (n=71, AAMR 0.12, 95%CI 0.088-0.15). AAMR for those with metastatic disease was 0.64 and increased over time (APC +7.54%; 95%CI 1.52–14.55; p=0.009). Late maternal deaths also rose (APC +4.75%; 95% CI 0.99–8.87; p=0.006). Otherwise, overall (APC $-$0.37%, 95%CI -0.37-4.30, p=0.83) and race/ethnicity specific pregnancy-associated cancer mortality have not significantly changed over time. Among 25 states with $\geq$10 deaths, state-level mortality ranged from 1.37 in California to 6.95 in Virginia. Limited state comparative analysis found that AAMR for pregnancy-associated cancer was higher in states with trigger laws (4.43) compared to non-trigger states (3.22); it was also higher in non-Expansion states (4.00) compared to states that expanded Medicaid (3.31). **Conclusions:** Despite known improvements in cancer mortality, pregnancy-associated cancer mortality remains stagnant, with notable mortality rises in pregnant patients with metastatic disease and late postpartum deaths. The large variability in state-level mortality may reflect state policies that affect access to prenatal or oncological care. More research and advocacy work to optimize care for pregnancy patients with cancer is essential to improve outcomes for this vulnerable population. Research Sponsor: None.

11030 **Poster Session**

Fair inclusion in clinical trials: Updated Good Pharma Scorecard evaluations of FDA oncology drugs approved by the FDA, 2018-2023. First Author: Tanvee Varma, Brigham and Women's Hospital, Boston, MA

Background: Adequate representation of demographic subgroups in clinical trials is essential for understanding the safety and efficacy of novel therapies. We previously developed and piloted the "fair inclusion" measure, which assesses (1) transparency in participant demographics and (2) demographic representation. These metrics were incorporated into the Good Pharma Scorecard, a system evaluating pharmaceutical company performance in bioethics and social responsibility, with sponsors ranked by fair inclusion scores. However, it remains unclear whether sponsors have improved fair inclusion of women, older adults, and racial and ethnic minorities in pivotal trials since the most recent Scorecard. **Methods:** For transparency, we assessed 6 measures [whether the number of (1) women, (2) older adults, (4) Black, (5) Asian, and (6) Latinx participants were publicly reported], and for representation, 5 measures [whether the proportion of enrolled (1) women, (2) older adults, (3) Black, (4) Asian, and (5) Latinx represents $>$80% of the US population with the studied condition]. Fair inclusion scores averaged transparency and representation, overall and by subgroup. Results were reported at the trial, product, and sponsor levels and compared across 2012–2017 vs 2018–2023 approvals. Data sources included Drugs@FDA, ClinicalTrials.gov, publications, US Cancer Statistics, and the American Cancer Society. **Results:** Between January 1, 2018 and December 31, 2023, the FDA approved 75 oncology therapeutics based on 80 pivotal trials from 52 sponsors. At the sponsor level, transparency improved for older adults (2012–2017: 78%, 2018–2023: 95%, p = 0.002) and racial and ethnic minorities (67% vs 91%, p = 0.003). Representation did not improve for women (94% vs 94%, p = 0.99), older adults (85% vs 81%, p = 0.29), or racial and ethnic minorities (75% vs 67%, p = 0.13). Fair inclusion scores improved modestly (81% vs 86%; p = 0.04). **Conclusions:** Sponsors have improved demographic reporting, particularly for older adults and racial and ethnic minorities. However, representation has not improved for any subgroup. Overall gains in fair inclusion were driven by transparency. Research Sponsor: None.

Comparison of mean sponsor scores on transparency, representation, and fair inclusion for 2012-2017 vs 2018-2023 oncology FDA approvals, by sex, age, race and ethnicity.

	2012-2017 Scores (n = 25)	2018-2023 Scores (n = 52)	p-value
Women			
Transparency	96%	99%	0.32
Representation	94%	94%	0.99
Fair Inclusion	97%	95%	0.28
Older Adults			
Transparency	78%	95%	$<$ 0.01
Representation	85%	81%	0.29
Fair Inclusion	79%	86%	0.07
Race and Ethnicity			
Transparency	67%	91%	$<$ 0.01
Representation	75%	67%	0.13
Fair Inclusion	66%	78%	0.06
Overall			
Transparency	82%	95%	$<$ 0.001
Representation	85%	80%	0.06
Fair Inclusion	81%	86%	0.04

11031 **Poster Session**

Insurance and cost-related access barriers to specialty oral anticancer medications for blood cancers in a nationwide sample of Medicare and commercially insured patients. First Author: Jalpa A. Doshi, University of Pennsylvania, Philadelphia, PA

Background: Specialty oral anticancer medications improve survival across blood cancers but may have access challenges. This study examined approval and fill rates of specialty oral anticancer medication prescriptions indicated for blood cancers in a nationwide sample of Medicare and commercially insured patients. **Methods:** Using nationwide claims (Symphony Health Solutions Integrated Dataverse), we identified patients with $\geq$1 new specialty oral anticancer medication prescription during 2022. Outcomes were measured for the initial prescription as well as any prescription for the same drug within 90 days and were classified as: (i) rejected by insurer, (ii) approved by insurer but not filled by patient, or (iii) approved by insurer and filled by patient. Among rejected prescriptions, we examined rejection reasons, eventual approval rates, and time to approval. Among approved prescriptions, we compared fill rates across out-of-pocket cost levels. Adjusted outcomes were estimated using multivariable logistic regressions. **Results:** The study included 12,134 patients (61.0% Medicare, 39.0% commercial) with a specialty oral anticancer medication prescription. Initially, very few prescriptions were both approved and filled (9.6%, Medicare; 4.0%, commercial). Insurers initially rejected most prescriptions (64.9% for Medicare; 84.0% for commercial), frequently due to prior authorization or formulary restrictions. By 90 days, approval rates rose to 85.0% (Medicare) and 62.9% (commercial), but many approved prescriptions were never filled; ultimately, only 54.5% of Medicare patients and 45.5% of commercial patients both received insurer approval and filled their prescription. Fill rates dropped sharply when out-of-pocket costs exceeded $175 per SOAM prescription. When out-of-pocket costs exceeded $2,000 per prescription, only 31.9% of Medicare patients and 26.9% of commercial patients filled their prescriptions. Adjusted rates were similar to unadjusted rates. **Conclusions:** This study found substantial access barriers to specialty oral anticancer medications for blood cancer, particularly among commercially insured patients. Even after insurer approval, many patients never filled their prescription. This highlights the importance of addressing both payer-level restrictions and patient-level affordability challenges to ensure treatment access. Research Sponsor: Leukemia & Lymphoma Society (LLS).

11032 **Poster Session**

Trends in cancer drug revenue retained by providers under buy-and-bill reimbursement, 2010-2024. First Author: Aaron Philip Mitchell, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Cancer care providers, including physician offices and hospitals, retain "markup" fees on clinician-administered drugs (such as chemotherapies and immunotherapies) which are proportional to drug price. Under this system, commonly known as "buy and bill," multiple external factors may impact provider revenue: increasing cancer drug prices, increasing care delivery in hospitals (where markups are higher) rather than offices, the 340B Drug Pricing Program, and payer "bagging" strategies to avoid paying markups to providers. Study goals were to estimate changes in provider revenue retained on clinician-administered cancer drugs from 2010-2024 and to quantify the contribution of four factors: 1) cancer drug sales, 2) site of care (office vs. hospital), 3) 340B participation, and 4) payer "bagging" strategies. **Methods:** We included all clinician-administered cancer drugs with available US sales data, including biosimilars and cancer-specific supportive care drugs (e.g., growth factors). We obtained cancer drug sales from manufacturer SEC filings (aggregated in SSR Health data), inflated to 2024 USD. We estimated the proportion of cancer drug sales administered within each of nine payer-care settings (three major payers: Medicare, Medicaid, commercial, and three major sites of care: physician office, 340B-participating hospital outpatient, and non-340B hospital outpatient), using Surveillance, Epidemiology, and End Results (SEER), the National Health Interview Survey (NHIS), and CMS and commercial claims. To estimate markup revenue, we applied setting-specific markup rates (from statute for Medicare/Medicaid, from peer-reviewed literature for commercial) to the drug sales in each setting. Plausible estimates of "bagging" prevalence were obtained from the literature. **Results:** Cancer drug sales increased from $27.3 billion (B) in 2010 to $64.9B in 2024, a 138% increase. Provider markup revenue on cancer drugs increased from $8.7B in 2010 to $35.7B in 2024, a 309% increase. Of the 2010-2024 increase, increasing drug sales accounted for 73.3%, shifting site-of-care to hospitals for 24.2%, and 340B participation growth for 2.5%. During this period, drug revenue retained by physician offices increased by 30%, non-340B hospitals by 49%, and 340B-participating hospitals by 739%. Accounting for bagging reduced 2024 markup revenue from $35.7B to $28.4B. **Conclusions:** Provider revenue from cancer drug markups grew substantially during 2010-2024. The largest single factor was growing cancer drug sales, although shifts in site of care also contributed. Revenue retained by 340B-participating hospitals increased much more than offices or other hospitals. Growth in provider markups was reduced modestly by growth in payer bagging strategies. Policymakers should consider whether growing markups on clinician-administered drugs reflects an efficient use of healthcare spending. Research Sponsor: National Institute of Health Care Management.

11033 **Poster Session**

Association of Medicaid expansion with pre-diagnosis coverage continuity and 2-year overall survival in pediatric patients with blood cancer. First Author: Rebecca Williamson Lewis, Aflac Cancer & Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA

Background: Continuous insurance coverage is critical for timely cancer diagnosis and treatment, yet many patients gain Medicaid only around the time of diagnosis. Although the Affordable Care Act Medicaid expansion targeted adults, it may indirectly influence children via a "welcome mat" effect by increasing outreach and boosting uptake among families with eligible children. The extent to which state expansion status influences Medicaid coverage continuity and survival among Medicaid-insured children with blood cancers—conditions lacking routine screening and often with acute presentation—remains unclear. **Methods:** Using linked SEER-Medicaid data, we identified 7,536 patients age ≤21 newly diagnosed with leukemia or lymphoma between 2009-2019 who had ≥1 month of Medicaid enrollment from 12 months pre-diagnosis through two months post-diagnosis. Coverage patterns were categorized as: 1) continuous Medicaid (12-13 months enrolled pre-/peri-diagnosis), 2) newly gained Medicaid (enrollment starting at diagnosis or within two months post-diagnosis), and 3) other coverage patterns. Difference-in-differences (DD) models compared post- vs. pre-expansion changes in coverage patterns and 2-year overall survival in 11 SEER expansion states vs. four non-expansion states, adjusting for sociodemographic factors. Survival models additionally adjusted for coverage patterns to assess the extent to which the patterns accounted for expansion-associated survival changes. **Results:** The percentage with continuous Medicaid increased more in expansion states (52.9% to 67.5%) than non-expansion states (41.5% to 50.8%), leading to a net increase of 8.2 percentage points (ppts; 95% CI = 2.3 to 14.2; p= 0.007) in adjusted DD model. The percentage with newly gained Medicaid decreased more in expansion states (24.6% to 14.2%) than non-expansion states (31.8% to 24.5%), resulting in a net reduction of 7.9 ppts (95% CI = -13.9 to -1.9; p= 0.010). No significant changes were observed post-expansion for other coverage patterns. Two-year overall survival increased in expansion states (85.7% to 86.9%) but declined in non-expansion states (87.7% to 82.9%), yielding a net increase of 6.2 ppt (95% CI = 2.8 to 9.6; $p<$ 0.001) in adjusted DD model. This association was slightly attenuated after further adjusting for coverage patterns (DD = 5.9 ppts; 95% CI = 2.5 to 9.3; $p<$ 0.001), suggesting coverage continuity accounted for approximately 4.9% of the expansion-associated gain in 2-year survival. **Conclusions:** Medicaid expansion was associated with improved coverage continuity pre-/peri-diagnosis and better early survival among Medicaid-insured children with leukemia or lymphoma. Amid ongoing Medicaid policy changes, these findings add evidence that stable coverage matters for vulnerable children. Future work will evaluate longer-term outcomes (e.g., 5-year survival). Research Sponsor: Blood Cancer United, Equity-in-Access Program; HSRP9015-23.

11034 **Poster Session**

Association between low muscle mass assessed by bioelectrical impedance analysis and clinical outcomes in hospitalized cancer patients. First Author: Diogo Toledo, Albert Einstein Israeli Hospital, São Paulo, SP, Brazil

Background: Low muscle mass is an independent prognostic marker associated with increased clinical risk, functional impairment, and mortality in patients with cancer. Conventional indicators such as body mass index (BMI) may fail to identify individuals at nutritional and functional risk. Bioelectrical impedance analysis (BIA) offers a feasible bedside method for body composition assessment, particularly in resource-constrained hospital settings. This study aimed to evaluate body composition using BIA, determine the prevalence of low muscle mass, and examine its association with clinical, laboratory, and functional parameters in hospitalized oncology patients. **Methods:** This observational study included 104 adult cancer patients admitted to a tertiary public hospital between January and October 2025. Baseline assessments at hospital admission included BMI, skeletal muscle mass index (SMI), appendicular muscle index, phase angle, fat mass percentage, handgrip strength (HGS), calf circumference (CC), urea-to-creatinine ratio, length of hospital stay, and in-hospital outcome (discharge or death). Low muscle mass was defined according to established cutoffs for SMI and appendicular muscle index. Comparisons were performed between patients with and without low muscle mass, and correlations between appendicular muscle index and functional and nutritional parameters were analyzed. **Results:** Low muscle mass was identified in 29.8% of patients at admission. Compared with patients without low muscle mass, those affected had significantly lower BMI (23.3 vs 27.6 kg/m², p=0.001), appendicular muscle index (6.20 vs 7.61, p<0.001), phase angle (3.6° vs 5.1°, p<0.001), total muscle mass (25.1 vs 29.4 kg, p<0.001), HGS (30.0 vs 37.0 kgf, p=0.041), and CC (32.5 vs 37.0 cm, p<0.001). Length of hospital stay did not differ significantly between groups. In-hospital mortality was higher among patients with low muscle mass (18.5% vs 7.0%), although this difference did not reach statistical significance (p=0.133). Appendicular muscle index showed moderate to strong positive correlations with BMI, phase angle, HGS, CC, and SMI. **Conclusions:** BIA proved to be a feasible and informative tool for identifying low muscle mass and functional impairment in hospitalized cancer patients. Appendicular muscle index and SMI were superior to BMI in detecting patients at increased nutritional and functional risk. Given its low cost and bedside applicability, BIA represents a valuable strategy for early risk stratification and supportive care planning in resource-limited oncology settings. Research Sponsor: None.

11035 **Poster Session**

Longitudinal changes in coping among early phase cancer clinical trial (EPCT) participants. First Author: Anh B. Lam, The University of Oklahoma Health Sciences Center, Oklahoma City, OK

Background: EPCT participants use varying strategies to cope with uncertainty related to their cancer, treatment, and prognosis. However, little is known about how coping strategies change over time among EPCT participants and how longitudinal changes correlate with patient-reported outcomes (PROs) and clinical outcomes. **Methods:** We prospectively enrolled adults with cancer participating in EPCTs at Massachusetts General Hospital from 4/2021-1/2023. Participants completed monthly PROs assessing coping strategies (Brief COPE), symptoms (Edmonton Symptom Assessment System [ESAS]), quality of life (QOL; Functional Assessment of Cancer Therapy General), hope (Herth Hope Index), and financial wellbeing (COST tool). We used regression models to assess associations of baseline (B/L) PROs with changes in coping scores over time (B/L to month 1 [M1] and B/L to month 2 [M2]). We also explored how changes in coping predicted clinical outcomes (time on trial [ToT], overall survival [OS]). **Results:** We enrolled 195 of 251 eligible patients (78% enrollment), and 188 completed the B/L surveys (96% response, median age=63 [range: 32-89], 56% female, most common cancer types: gastrointestinal [34%] and breast [21%]). Higher B/L QOL predicted decreased behavioral disengagement coping at M1 (B=-0.01, p=.037) & M2 (B=-0.02, p=.001) and self-blame at M2 (B=-0.02, p=.038), as well as increased emotional support (B=0.22, p=.001) and religion (B=0.02, p=.024) coping at M1. Higher B/L ESAS symptoms predicted decreased use of emotional support coping at M1 (B=-0.01, p=.048). Higher B/L ESAS physical symptoms predicted decreased use of emotional support at M1 (B=-0.02, p=.046) & M2 (B=-0.03, p=.016). Higher B/L psychological symptoms predicted increased use of self-blame at M2 (B=0.08, p=.007). Higher B/L financial wellbeing predicted increased emotional support at M1 (B=0.02, p=.025). Higher B/L hope predicted increased positive reframing at M1 (B=0.07, p=.010) and religion coping at M2 (B=0.05, p=.038) as well as decreased behavioral disengagement at M1 (B=-0.04, p=.001) & M2 (B=-0.06, p=.001). For clinical outcomes, increased acceptance (HR=0.85, p=.028) and religion (HR=0.85, p=.016) coping at M1 and increased positive reframing (HR=0.84, p=.010) at M2 predicted longer ToT. Increased use of behavioral disengagement at M1 predicted shorter ToT (HR=1.42, p=.002). Increased use of positive reframing (HR=0.83, p=.009) and self-blame (HR=0.78, p=.012) coping at M1 predicted better OS; increased use of behavioral disengagement (HR=1.41, p=.007) predicted worse OS. **Conclusions:** In this longitudinal cohort study, EPCT participants' B/L PROs correlated with changes in their coping over time. We also found longitudinal changes in coping predicted ToT and OS. These findings highlight opportunities to enhance care delivery and outcomes for EPCT participants by addressing their PROs and coping behavior over time. Research Sponsor: None.

11036 Poster Session

The association of baseline fatigue and severe cancer treatment toxicity by comorbid conditions: A pooled analysis. First Author: Michael M. Caplan, Herbert Irving Comprehensive Cancer Center, Columbia University Irving Medical Center, New York, NY

Background: Fatigue is commonly reported by patients with cancer. Patients who report fatigue are at greater risk of severe adverse events during treatment. However, it is unknown whether the relationship between baseline fatigue and toxicity risk persists after accounting for comorbid conditions. **Methods:** Data from 6 SWOG phase 2/3 clinical trials in advanced cancer (1999 to 2018) were pooled. Baseline fatigue (classified by 5-point Likert scale) was analyzed as any vs none. Patients were linked to Medicare claims by SSN, date of birth, and sex to identify comorbidities at study registration. Adverse events (AEs) were classified using the Common Terminology Criteria for Adverse Events. The primary outcome was severe (≥ grade 3) events. Odds ratios (ORs) were calculated using generalized estimating equations, clustered by study, and adjusted for age, sex, race, and obesity. Interaction tests between fatigue and each comorbidity were examined. **Results:** Among 1195 patients (median age, 73; 13.1% female; 11.8% Black; 74% prostate cancer), 629 (52.6%) had ≥1 severe AE. Among patients with ≥1 comorbid condition, those with any fatigue had a 132% (OR=2.32, 95% CI, 1.26-4.27, p=.007) increased risk of having severe AEs; among patients with no comorbidities, the association was nearly identical (OR=2.33, 95% CI, 1.51-3.60, p<.001; p-interaction=.97). Those with any fatigue had a twofold or greater risk of severe AEs across all comorbidities (Table). The association between fatigue and severe toxicity was greater for those with anemia (interaction p=.03) and those with depression (interaction p=.02). **Conclusions:** The association between baseline fatigue and severe treatment toxicity persisted after accounting for comorbid conditions, indicating baseline fatigue is an independent risk factor. The association was stronger among patients with anemia and those with depression, suggesting these conditions may amplify the risk of baseline fatigue. These findings support early identification of baseline fatigue and targeted supportive interventions for these high-risk populations. Research Sponsor: None.

Association of baseline fatigue and severe toxicity by comorbid conditions.

	No comorbidity		Comorbidity		
Comorbidity	OR (95% CI)	p-value	OR (95% CI)	p-value	p-interaction
Depression	2.24 (1.28-3.92)	0.005	4.32 (2.58-7.23)	<0.0001	0.02
Anemia	2.15 (1.30-3.57)	0.003	3.05 (1.35-6.87)	0.007	0.03
Respiratory disorders (COPD, sleep apnea)	2.30 (1.35-3.94)	0.002	2.73 (0.99-7.55)	0.05	0.58
Hypothyroid	2.30 (1.34-3.95)	0.003	2.64 (1.33-5.23)	0.005	0.57
Diabetes	2.29 (1.35-3.89)	0.002	2.41 (1.24-4.71)	0.01	0.73
Hypertension	2.26 (1.36-3.78)	0.002	2.37 (1.25-4.50)	0.008	0.73
Cardiovascular disease	2.42 (1.39-4.22)	0.002	2.04 (1.15-3.63)	0.02	0.25
Autoimmune diseases	2.33 (1.34-4.04)	0.003	1.99 (1.15-3.43)	0.01	0.7
Any comorbidity (all comorbidities)	2.33 (1.51-3.60)	<0.001	2.32 (1.26-4.27)	0.007	0.97

11037 Poster Session

Decline in credit score and excess mortality risk among cancer patients: Evidence from Washington State. First Author: Scott David Ramsey, Fred Hutch Cancer Center, Seattle, WA

Background: Patients experiencing bankruptcy following a cancer diagnosis have been shown to have increased mortality, but few studies have evaluated the impact of other types of financial hardships on mortality risk. We conducted an analysis to understand the relationship between a drop in credit score, a marker of less severe types of financial strain, and mortality among cancer patients in Washington State. **Methods:** We linked records from cancer patients (age 18+) diagnosed with any cancer (except in situ) between 2010 - 2023 from the Western Washington SEER cancer registry to credit report data from a national credit reporting agency. We excluded patients without a valid credit score near diagnosis (±100 days). In a Cox proportional hazards model using a landmark approach, we examined the relationship between a drop in credit score (25-49, 50-99, or 100+ points) in the first year of diagnosis and subsequent mortality after year 1, using no- or low-drop (<25 points) as the reference. Hazard ratios (HRs) and 95% confidence intervals were derived. Model covariates included age, gender, race/ethnicity, marital status, Area Deprivation Index, urban/rural residence, diagnosis year, cancer type, stage, and credit score at diagnosis. **Results:** Among 212,898 evaluable patients [49% male, 84% white, median age 65 (IQR 56 - 73)], credit scores at diagnosis were: 42% excellent (800-850), 25% very good (740-799), 15% good (670-739), 12% fair (580-669), and 6% poor (300-579). In the year following diagnosis, 40,078 patients' credit scores fell ≥25 points (18.8%), including 21,716 falling 25-49 points (10.2%), 12,954 falling 50-99 points (6.1%), and 5,408 falling ≥100 points (2.5%). Among all cancers combined, patients experiencing 50-99 point and ≥100 point reductions (but not 25-49 point reductions) in credit scores had excess mortality (Table). Excess risk of death was observed for nearly all individual cancer types at the ≥100-point reduction level except kidney. **Conclusions:** In this retrospective study, a substantial reduction in credit scores, typically reflecting the experience of adverse financial events, was associated excess mortality compared to those with stable credit scores. Future studies are needed to understand the mechanisms of the relationship. Research Sponsor: National Cancer Institute; R01CA274541; IRONMAN Foundation.

Excess risk of death following a post-diagnosis fall in credit score (vs no/low reduction).

	25-49 points		50-99 points		≥100 points	
Cancer Type	HR	CI	HR	CI	HR	CI
All	0.96	0.94 - 0.99	1.06	1.02 - 1.10	1.33	1.27 - 1.39
Breast	1.00	0.92 - 1.08	1.07	0.97 - 1.18	1.39	1.23 - 1.59
Colorectal	1.02	0.93 - 1.11	1.11	0.99 - 1.23	1.31	1.14 - 1.51
Kidney	0.85	0.73 - 1.00	0.86	0.70 - 1.05	1.23	0.95 - 1.59
Leukemia/lymphoma	0.87	0.79 - 0.96	0.94	0.82 - 1.07	1.29	1.09 - 1.54
Lung	1.00	0.93 - 1.08	1.13	1.04 - 1.24	1.15	1.02 - 1.30
Melanoma	0.90	0.78 - 1.04	1.01	0.85 - 1.20	1.60	1.23 - 2.09
Prostate	0.95	0.87 - 1.03	1.06	0.96 - 1.17	1.39	1.20 - 1.61
Other	0.97	0.92 - 1.01	1.05	1.00 - 1.11	1.31	1.22 - 1.42

11038 Poster Session

Cost-effectiveness analysis of teclistamab plus daratumumab in relapsed or refractory multiple myeloma. First Author: Wing Fai Li, Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY

Background: Relapsed or refractory multiple myeloma (RRMM) remains a significant therapeutic and economic challenge as patients progress through successive lines of therapy. Teclistamab, a CD3×B-cell maturation antigen (BCMA) bispecific antibody, has demonstrated deep and durable responses in heavily pretreated patients in the phase 1–2 MajesTEC-1 trial. Daratumumab, an anti-CD38 monoclonal antibody, is a cornerstone of modern myeloma treatment. The phase 3 MajesTEC-3 trial evaluated teclistamab plus daratumumab versus daratumumab-based regimens, including daratumumab with pomalidomide and dexamethasone (DPd) or with bortezomib and dexamethasone (DVd) in patients with RRMM. While teclistamab-based combinations have demonstrated strong clinical efficacy, their economic value relative to standard daratumumab-based regimens remains uncertain. **Methods:** We extracted event-free survival (EFS) and overall survival (OS) data from published Kaplan–Meier curves and reconstructed individual patient data using a validated algorithm (IPDfromKM). A Markov model was developed to compare lifetime costs and health outcomes between treatment strategies. Model inputs were obtained from the Centers for Medicare & Medicaid Services, the Medicare Physician Fee Schedule, and published literature. Health state utilities, adverse event rates, treatment discontinuation probabilities, and toxicity costs were derived from the MajesTEC-3 trial and peer-reviewed sources. Analyses were conducted from a U.S. third-party payer perspective, with costs reported in 2025 U.S. dollars. Cost-effectiveness was assessed using incremental cost-effectiveness ratios (ICERs) with a $150,000/QALY willingness-to-pay (WTP) threshold, and robustness was examined through one-way and probabilistic sensitivity analyses. **Results:** Gompertz and lognormal distributions were selected based on Akaike Information Criterion to extrapolate EFS and OS for the teclistamab–daratumumab and DPd/DVd arms, respectively. Using a Markov model, teclistamab plus daratumumab yielded an incremental gain of 1.16 QALYs compared with DPd/DVd, at an additional cost of $95,376, resulting in an ICER of $82,074 per QALY, well below the WTP threshold. Probabilistic sensitivity analysis showed that 88.9% of simulations favored teclistamab plus daratumumab at the $150,000/QALY threshold. Treatment discontinuation rates and the cost of daratumumab in the DVd regimen were the primary drivers of ICER estimates. **Conclusions:** From a U.S. payer perspective, teclistamab plus daratumumab is cost-effective compared with DPd or DVd in patients with RRMM, supporting its broader adoption in clinical settings. Research Sponsor: None.

Base-case model.

Strategy	Cost, USD	Incremental cost, USD	Effectiveness, QALY	Incremental effectiveness, QALY	ICER, USD/QALY
Teclistamab-Daratumumab	445,405	95,376	16.72	1.16	82,074
DPd or DVd	350,029		15.55		

11039 Poster Session

Association of baseline clinical factors and treatment-related variables with survival in phase I solid tumor trials. First Author: Jonathan Boiarsky, UCLA Division of Hematology-Oncology, Santa Monica, CA

Background: Phase I trials in solid oncology increasingly use biomarker-based enrollment and evaluate diverse therapeutic mechanisms. However, outcomes among patients with advanced solid tumors remain heterogeneous, and the relative contribution of baseline patient factors versus treatment-related variables to survival is incompletely defined. **Methods:** We conducted a retrospective analysis of patients with advanced solid tumors treated on Phase I clinical trials in UCLA's Drug Development Program between Jan 2013 and Sept 2025. Outcomes included objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Survival was estimated using the Kaplan–Meier method. Multivariable Cox proportional hazards models identified factors independently associated with OS, adjusting for clinical variables, treatment characteristics (including combination vs monotherapy, mechanism of action [MOA] of study therapy, and participation in biomarker-selected trials vs unselected patients), and baseline laboratory values. **Results:** 726 patients were included across 106 trials. ORR was 13.3%, and DCR was 61.7%. Median PFS was 2.9 months (95% CI 2.66–3.39), and median OS was 10.4 months (95% CI 9.15–12.34). In univariable analysis, treatment-related characteristics, including combination therapy, were associated with OS, whereas participation in biomarker-selected trials and specific MOA was not consistently associated with survival. In multivariable analysis, OS was independently associated with baseline performance status (ECOG 1 vs 0: HR 1.35, 95% CI 1.12-1.63, p = 0.0015), combination therapy (HR 0.81, 95% CI 0.68-0.98, p = 0.0283) and female sex (HR 0.79, 95% CI 0.65-0.96, p = 0.0164). Baseline physiological parameters were strong predictors of OS, including higher hemoglobin (HR 0.90 per 1g/dL increase, 95% CI 0.85-0.96, p = 0.0018), higher albumin (HR 0.48 per 1g/dL increase, 95% CI 0.38-0.61, p < 0.0001), and higher lymphocyte count (HR 0.75 per 1.0K/μL increase, p = 0.0005). **Conclusions:** In this large retrospective cohort of patients treated on Phase I solid oncology trials, survival outcomes were primarily dictated by baseline physiological reserve and functional status rather than trial design features. While combination-based regimens were independently associated with OS, participation in biomarker-selected trials and MOA of study therapy did not retain prognostic significance after adjustment for clinical and laboratory factors. These findings suggest that baseline function and nutritional status remain the primary determinants of survival in early phase trials, highlighting the importance of rigorous clinical selection even in the era of increasingly diverse and novel therapeutic mechanisms. Ongoing analyses will further delineate prognostic factors associated with survival in this cohort. Research Sponsor: None.

11040 **Poster Session**

Reduced treatment adherence and cancer mortality in patients with depression. First Author: Edmund Men Qiao, Department of Radiation Medicine and Applied Sciences, University of California, San Diego, La Jolla, CA

Background: Depression affects up to 20% of cancer patients and is associated with poorer cancer outcomes. The lack of mechanistic explanations for this interaction greatly limits clinical interventions. We hypothesize that patients with late-stage malignancies have lower treatment adherence that may increase risk of cancer-specific mortality (CSM). **Methods:** We selected patients age 66+ years diagnosed with breast, colon, rectal, prostate, or non-small cell lung cancer (NSCLC) from 2010-2017 using Surveillance, Epidemiology, and End Results (SEER)-Medicare. International Classification of Diseases (ICD)-9 or ICD-10 codes identified depression. Late-stage included locally advanced (Stage III+ or high-risk prostate) or metastatic. Locally advanced treatment adherence was defined as receiving curative therapy <1 year from diagnosis. In metastatic patients, this was defined as receiving systemic therapy along with number of cycles/months, <6 months from diagnosis. Multivariate Fine Gray regression with non-cancer death as a competing event evaluated CSM. Multivariate logistic regressions modeled the impact of depression on receiving therapy, and multivariate linear regression modeled its role on cycles/months of systemics received. **Results:** The cohort included 93,384 patients, with median age of 74 years and follow-up of 4.2 years. In total, 21,690 patients (23.2%) had depression, highest in NSCLC (27.1%) and lowest in prostate (13.4%). Depression was associated with 6-36% increased risk ($p<0.01$) of CSM (Table 1). Locally advanced patients with depression had 15-32% lower odds ($p<0.01$) of receiving curative treatment. Patients with metastatic disease and depression had significantly lower odds of receiving systemic therapy, reduced cycles/months of systemics, or both (Table 1). **Conclusions:** Depression was associated with increased risk of CSM across five tumor histologies. Patients with depression exhibited decreased treatment adherence for all subtypes, underscoring a possible mechanistic explanation for increased CSM in this population. Research Sponsor: None.

Multivariate regressions for depression effect.

Endpoint	CSM: SHR 95% CI, p	Received treatment: Locally advanced OR 95% CI, p	Received treatment: Metastatic OR 95% CI, p	Therapy cycles/ months: Metastatic, B Coefficient, p
Histology				
Breast	1.11 [1.02-1.24], <0.01	0.78 [0.65-0.92], <0.01	0.85 [0.71-1.03], 0.10	-0.52, <0.01
Colon	1.15 [1.10-1.20], <0.01	0.71 [0.63-0.79], <0.01	0.67 [0.59-0.75], <0.01	-0.63, <0.01
Rectal	1.13 [1.02-1.25], <0.01	0.68 [0.53-0.87], <0.01	0.67 [0.52-0.88], <0.01	-0.24, 0.33
Prostate	1.36 [1.25-1.48], <0.01	0.85 [0.78-0.93], <0.01	0.94 [0.69-1.31], 0.71	-0.22, 0.02
NSCLC	1.06 [1.04-1.09], <0.01	0.75 [0.67-0.84], <0.01	0.94 [0.88-0.999], 0.045	-0.21, <0.01

SHR: Subdistribution hazard radio; OR: odds ratio; CI: confidence interval.

11041 **Poster Session**

APS-TMA phenotypes as a failure-to-rescue signal during U.S. cancer hospitalizations: National Inpatient Sample, 2018–2022. First Author: Tarek Tabbah, Sunrise Health GME Consortium, Las Vegas, NV

Background: Failure-to-rescue (FTR), defined as mortality following major inpatient complications, reflects both patient disease pathology and hospital rescue capacity. Antiphospholipid syndrome (APS) and thrombotic microangiopathy (TMA) phenotypes are rare, high-acuity thrombotic syndromes observed during cancer hospitalizations, but whether excess mortality reflects independent risk factor versus complication-mediated risk is unclear. **Methods:** A serial cross-sectional, hospitalization-level analysis was performed using the 2018–2022 Healthcare Cost and Utilization Project National Inpatient Sample (NIS). Adult hospitalizations with a principal diagnosis of malignancy were identified using ICD-10-CM codes (C00–C97; D45–D47). APS and TMA phenotypes were defined using any-diagnosis ICD-10-CM proxies for APS and TMA, including TTP/HUS, and combined as an APS/TMA phenotype. Because laboratory and medication data are unavailable in the NIS, exposures were analyzed as inpatient phenotypes rather than presumed diagnoses. Major complications included mechanical ventilation and acute kidney injury requiring dialysis. Failure-to-rescue was defined as in-hospital mortality among admissions with ≥1 major complication. National estimates incorporated discharge weights, hospital clustering, and stratification; multivariable models adjusted for All Patient Refined Diagnosis Related Group (APR-DRG) severity. **Results:** Among an estimated 4.81 million principal malignancy hospitalizations nationally, APS/TMA phenotypes occurred in 0.48% of admissions. Compared with non-phenotype admissions, APS/TMA phenotype hospitalizations had higher mortality (9.43% vs 4.35%) and higher rates of major complications, including mechanical ventilation (5.85% vs 2.57%) and dialysis-requiring acute kidney injury (2.11% vs 0.61%). In severity-adjusted modeling incorporating APR-DRG severity, APS/TMA phenotype was not independently associated with mortality (adjusted OR 0.99, 95% CI 0.70–1.40), indicating that excess mortality was largely mediated by complications and underlying illness severity. **Conclusions:** APS/TMA phenotypes identify a rare but high-acuity subgroup of cancer hospitalizations characterized by disproportionate ICU-level support and dialysis utilization, functioning as a national failure-to-rescue signal rather than an independent driver of mortality after severity adjustment. These findings highlight the importance of early recognition and severity-directed rescue strategies for high-risk thrombotic phenotypes during cancer admissions. Research Sponsor: None.

11042 **Poster Session**

Premature cancer mortality in the United States, 1999–2023: Analysis of CDC WONDER data. First Author: Kwame Adjei Sefah, Bridgeport Hospital/Yale New Haven Health System, Bridgeport, CT

Background: Premature cancer deaths (defined as mortality in adults aged 20-69 years) represent significant years of potential life lost (YPLL) and substantial disease burden, yet comprehensive national trends remain insufficiently characterized. **Methods:** CDC WONDER cancer mortality database (1999-2023) was queried for cancer-related deaths among individuals aged 20-69 years across USA. Age-standardized mortality rates (ASMR) per 100,000 person-years were calculated using 2000 U.S. Census standard population. Join point regression analysis identified temporal trend inflection points with annual percentage change (APC) and 95% confidence intervals (CI). Stratification included sex, race/ethnicity, geographic region, and 15 major cancer types. **Results:** From 1999–2023, 3,847,200 premature cancer deaths occurred in the U.S. (mean 153,888/year). Annual deaths increased 12.4% (152,100 in 1999 to 171,000 in 2023), while age-standardized mortality declined 18.6% (ASMR 87.3 to 71.1 per 100,000). Joinpoint analysis identified three phases: stability in 1999–2005 (APC −0.42%), accelerated decline in 2005–2015 (APC −2.18%), and slower improvement in 2015–2023 (APC −0.73%). Males had higher mortality than females in 1999 (ASMR 105.4 vs 69.2), with declines in both sexes (APC −1.89% males; −2.34% females), narrowing the male–female gap from 52.2% to 37.8% by 2023. Racial/ethnic disparities persisted: Black Americans had the highest ASMR in 2023 (84.3), 18.6% higher than Whites (71.1), with slower declines (APC −1.23% vs −2.07%); Hispanics/Latinos had the lowest ASMR (52.8) and fastest declines (APC −3.12%); American Indian/Alaska Native populations showed persistently high rates (89.2) with minimal change (APC −0.18%). In 2023, leading contributors were lung (38,200 deaths; ASMR 17.5; APC −3.78%), breast (23,100; 10.5; −2.45%), colorectal (11,800; 5.3; −3.12%), pancreatic (8,400; 3.8; −0.28%), and ovarian cancer (6,200; 2.8; −1.86%), together accounting for 58.2% of premature deaths. Cervical cancer declined sharply (APC −4.23%), while melanoma increased (APC +2.15%). **Conclusions:** Premature cancer mortality in the United States declined 18.6% from 1999-2023, yet significant and widening disparities persist by race/ethnicity, geography, and socioeconomic status. Alarming stagnation in declining rates post-2015, coupled with increasing absolute deaths among aging cohorts, signals necessity for intensified prevention efforts targeting modifiable risk factors. Research Sponsor: None.

11043 **Poster Session**

Dose-response relationship of serum iron, ferritin, and transferrin saturation with cancer-related mortality: An analysis of population-based data. First Author: Saima Gill, Department of Medicine, King Edward Medical University, Lahore, Pakistan

Background: Altered iron homeostasis has been linked to cancer outcomes, with epidemiologic evidence suggesting that both reduced iron availability (low transferrin saturation or anemia) and elevated iron markers, particularly ferritin, may correspond to higher cancer mortality. However, population-level data quantifying dose–response relationships between continuous iron indices and cancer-related mortality remain limited. This study evaluates the dose–response association of serum iron, transferrin saturation (TSAT), and ferritin with cancer mortality using nationally representative NHANES data. **Methods:** NHANES laboratory data were linked to National Death Index mortality files (1999–2019). Survey-weighted Cox proportional hazards models and Fine–Gray competing-risk models were used to assess linear, quintile-based, and restricted cubic spline–modeled non-linear relationships between iron biomarkers and cancer mortality. Models were further adjusted to evaluate independent effects of each biomarker. **Results:** A total of 52,593 participants were included, with 6,875 recorded deaths. In survey-weighted $\log_2$ Cox models, serum iron (HR 1.41; 95% CI 0.17–11.68) and ferritin (HR 1.14; 95% CI 0.84–1.55) showed no significant linear association with cancer mortality, while TSAT suggested a nonsignificant inverse trend (HR 0.30; 95% CI 0.02–5.43). Quintile analyses revealed no consistent dose–response pattern for serum iron or TSAT; ferritin showed lower mortality in the second quintile (HR 0.33; 95% CI 0.12–0.92) without a graded pattern across higher quintiles. In mutually adjusted models including all three biomarkers, none demonstrated independent linear associations. Fine–Gray analyses identified a statistically significant but clinically small association for ferritin, whereas serum iron and TSAT remained nonsignificant. Restricted cubic spline models showed no clear non-linear dose–response for any biomarker. **Conclusions:** Among the iron indices evaluated, ferritin demonstrated the strongest and most consistent association with cancer-related mortality, although no clear linear or non-linear dose–response pattern emerged. Ferritin may serve as a more informative marker for risk stratification, but further mechanistic and longitudinal studies are warranted. Research Sponsor: None.

11044 **Poster Session**

Predictors of mechanical ventilation in metastatic cancer hospitalizations: A National Inpatient Sample study. First Author: Davin Turku, The Brooklyn Hospital Center, Brooklyn, NY

Background: Invasive mechanical ventilation (MV) represents a major escalation of supportive care in metastatic cancer and is consistently associated with high short-term mortality in prior observational cohorts. We sought to identify patient and hospital factors associated with MV utilization in metastatic cancer hospitalizations using national inpatient data. **Methods:** We analyzed the National Inpatient Sample (2016–2020), including adult hospitalizations with metastatic cancer (ICD-10-CM C77–C79). MV was identified using ICD procedure codes. Survey-weighted multivariable logistic regression estimated adjusted odds ratios (aOR) for MV utilization, adjusting for age group, sex, race/ethnicity, payer, hospital bed size, hospital region, and comorbidity burden using vwcheck (van Walraven score derived from Elixhauser comorbidities). **Results:** In the complete-case regression cohort (weighted N=6,859,238), MV utilization varied across demographic and health-system factors. MV was less likely with older age (≥65 vs 18–44: aOR 0.80, 95% CI 0.75–0.87) and in females (aOR 0.96, 95% CI 0.93–0.99). Black race was associated with higher MV odds compared with White race (aOR 1.18, 95% CI 1.13–1.23). Compared with Medicare, Medicaid (aOR 1.08, 95% CI 1.01–1.14) and self-pay (aOR 1.17, 95% CI 1.05–1.30) had higher MV odds. MV was more likely in medium vs small hospitals (aOR 1.08, 95% CI 1.03–1.14) and large vs small hospitals (aOR 1.08, 95% CI 1.03–1.13). Regional variation persisted (South vs Northeast: aOR 1.11, 95% CI 1.06–1.17; West vs Northeast: aOR 1.07, 95% CI 1.01–1.13). Higher vwcheck was strongly associated with MV (aOR 1.07 per unit). **Conclusions:** Among hospitalized patients with metastatic cancer, the use of mechanical ventilation varied by patient demographics, payer status, hospital size, and region, even after adjustment for comorbidity burden. These differences suggest heterogeneity in illness severity and/or thresholds for escalation of care across health systems. Mechanical ventilation remains a marker of high-risk hospitalization in advanced cancer, and understanding the factors associated with its use may help inform inpatient supportive-care planning and quality improvement efforts. Research Sponsor: None.

Predictors of mechanical ventilation in metastatic cancer hospitalizations (NIS 2016–2020).

Predictor	Adjusted OR (95% CI)	p-value
Age ≥65 vs 18–44	0.80 (0.75–0.87)	<0.001
Female vs male	0.96 (0.93–0.99)	0.01
Black vs White	1.18 (1.13–1.23)	<0.001
Medicaid vs Medicare	1.08 (1.01–1.14)	0.02
Self-pay vs Medicare	1.17 (1.05–1.30)	0.004
Medium vs small hospital	1.08 (1.03–1.14)	0.002
Large vs small hospital	1.08 (1.03–1.13)	0.001
South vs Northeast	1.11 (1.06–1.17)	<0.001
West vs Northeast	1.07 (1.01–1.13)	0.01
van Walraven score (per unit)	1.07 (1.06–1.08)	<0.001

11045 **Poster Session**

Addressing housing instability as a quality-of-care determinant in cancer: A meta-analysis across national and Veterans Affairs cohorts. First Author: Adarsh Vardhan Tangella, MedStar Washington Hospital Center, Washington, DC

Background: Housing instability is an under-recognized determinant of cancer outcomes that directly affects screening adherence, treatment delivery, and survival. Over 650,000 Americans experience homelessness nightly, yet its impact on oncologic quality-of-care metrics remains poorly quantified. We conducted a meta-analysis to evaluate disparities in cancer screening, treatment, and survival among persons experiencing homelessness (PEH) versus housed individuals, and to assess whether housing status functions as a system-level quality indicator. **Methods:** Real-world evidence from the Veterans Health Administration (VHA), National Inpatient Sample (NIS), and community cohorts (2011–2024) was pooled using random-effects DerSimonian–Laird models. Eligible studies reported odds ratios (ORs) or hazard ratios (HRs) comparing PEH with housed counterparts. Heterogeneity was summarized using I^2 statistics, and all analyses were performed in Stata. **Results:** Six cohorts contributed sixteen effect estimates encompassing >200,000 cancer cases. PEH were less likely to be up to date for colorectal cancer screening (pooled OR 0.56, 95% CI 0.23–1.31; I^2 = 93.9%). Homelessness was associated with markedly lower odds of surgery or other invasive procedures (pooled OR 0.42, 95% CI 0.26–0.66; I^2 = 98.4%) and substantially higher odds of discharge against medical advice (pooled OR 5.37, 95% CI 3.39–8.50; I^2 = 92.9%). In gastrointestinal cancer admissions, PEH also had longer hospital stays and higher costs. Within VHA datasets, homelessness independently predicted higher all-cause mortality after lung (HR 1.09–1.29) and colorectal cancer (HR 1.18–1.22). Veterans who gained housing after diagnosis achieved survival comparable to continuously housed peers (HR ≈ 1.0). **Conclusions:** Across diverse U.S. datasets, homelessness is consistently associated with lower screening uptake, reduced treatment receipt, and higher mortality—outcomes that represent measurable quality-of-care failures. Stable housing acts as a protective, modifiable factor influencing survival independent of access or insurance. Incorporating housing status screening into oncology intake workflows can close equity gaps, improve safety, and advance value-based cancer care. Housing stability should be recognized as a core quality metric in oncology. Research Sponsor: None.

Cohorts included in the meta-analysis of homelessness and cancer outcomes.

Study	Cancer Type(s)	Main Outcomes	Effect (95% CI)
Asgary 2014	Colorectal	Screening	OR 0.35 (0.23–0.53)
VA Cohort 2011–21	CRC, Breast	Screening / Colonoscopy	aIRR 0.84 (0.83–0.84); 0.88 (0.84–0.92)
Shah 2024	All cancers	Procedure / Therapy / AMA	AOR 0.53; 0.73; 4.29
Mevawalla 2019	GI	Surgery / AMA	OR 0.33; AOR 6.86
VA Mortality 2011–20	Lung	Mortality	HR 1.21 (0.93–1.57)
Health Affairs 2024	Lung, CRC, Breast	Mortality by housing	HR 1.09–1.29 (lung); 1.22 (CRC)

11046 **Poster Session**

Impact of symptom burden, psychological distress, and treatment accessibility on quality of life in people with cancer in Syria. First Author: Mohamad Yousef Almawaz, Damascus University- Faculty of Medicine, Damascus, Syrian Arab Republic

Background: In low-resource and conflict-affected settings, barriers to cancer care may amplify symptom burden and psychological distress, leading to poor quality of life (QoL). This study aimed to evaluate the impact of symptom burden (fatigue), psychological distress (depression), sources of psychological support, and treatment accessibility on the quality of life (QoL) of people with cancer in Syria. **Methods:** A cross-sectional study was conducted between April and May 2025 at Albairwni Hospital, Syria'national cancer center. Adult outpatient oncology patients completed validated Arabic versions of the Patient Health Questionnaire-9 (PHQ-9), Brief Fatigue Inventory (BFI), and Functional Assessment of Cancer Therapy–General 7 (FACT-G7). Socio-demographic and clinical data included cancer type, stage, metastasis, relapse, complications, treatment accessibility, and sources of psychological support. Statistical analyses included group comparisons and Spearman correlation. **Results:** Among 225 participants (median age 53; 71.6% female; 65.8% rural). 41.8% reported difficult access to treatment, while only 18.7% reported easy access. Psychosocial support was primarily provided by family (87.1%), followed by religious sources (37.3%) and healthcare providers (18.2%). Breast cancer comprised 49.3% of cases. By PHQ-9, 77.3% had depressive symptoms (mild 26.7%, moderate 25.8%, moderately severe 17.8%, severe 7.1%). Mean BFI total score was 32.5 ± 23.6. Worse depression, greater fatigue and poorer QoL were associated with difficult treatment access (PHQ-9 P = 0.01; BFI P = 0.01; FACT-G7 P = 0.005), advanced stage (PHQ-9 & FACT-G7 P<0.001; BFI P=0.001), presence of metastases (PHQ-9 P = 0.001; BFI P = 0.01; FACT-G7 P < 0.001). Relapse was associated with higher depression and greater fatigue (PHQ-9 P = 0.04; BFI P = 0.03), while cancer-related complications were associated with worse scores across all scales (PHQ-9 P < 0.001; BFI P = 0.001; FACT-G7 P < 0.001). Health-provider support was associated with lower symptom severity and better QoL (BFI P = 0.01; FACT-G7 P = 0.003). Spearman correlations showed strong inverse relationships between fatigue measures and QoL (BFI total vs. FACT-G7 $\rho = -0.71$, P < 0.001), while QoL scores showed a graded decline as depression severity increased (P < 0.001). **Conclusions:** Depressive symptoms and fatigue are strongly associated with poorer QoL in cancer patients. Modifiable factors-notably treatment accessibility and health provider support- correlate with better outcomes and may be targets for interventions to improve patient wellbeing in low-resource oncology settings. Research Sponsor: None.

11047 **Poster Session**

The AI paradox in precision oncology: Prospective blinded validation of large language models against molecular tumor board. First Author: Arun Seshachalam, Dr. GVN Cancer Institute, Tiruchirappalli, India

Background: Molecular tumor boards (MTBs) are central to precision oncology but remain limited in accessibility. Large language models (LLMs) are increasingly proposed as scalable clinical decision-support tools, yet prospective validation is sparse. We evaluated multiple LLMs against MTB consensus, focusing on molecular pathway interpretation, actionability, and evidence strength. **Methods:** This prospective, blinded, cross-sectional validation study included consecutive cases discussed at a Tamil Nadu Medical and Pediatric Oncologist Society–initiated national MTB (July 2025–January 2026). Anonymized clinical and genomic data were analyzed using a standardized prompt across 4 latest LLM versions [ChatGPT (5, 5.1, 5.2), Perplexity, Gemini (2.5 Flash, 3 Pro), and DeepSeek], each queried in 2 independent runs to assess reproducibility; AI systems were blinded to MTB decisions, and reviewers to AI identity. Concordance was classified as concordant, discordant, AI non-evaluable (extraction failure or non-reproducible), or MTB non-evaluable (no predominant molecular pathway). The primary endpoint was end-to-end concordance; conditional concordance excluding non-evaluable outputs was secondary. Predictors of concordance were evaluated using univariate and multivariate logistic regression. **Results:** Of 108 cases, 80 were evaluable for AI comparison. Mean age was 56 years; 65% were male; 90% had ECOG 0–2; 73% had metastatic disease; and 82% were treated with palliative intent. The cohort was heavily pretreated, with 48% receiving ≥3 prior lines. Common pathways included EGFR/RAS/RAF/MAPK (34%), PI3K/AKT/mTOR (23%), and HRD/DDR (18%). End-to-end concordance was 88%, 74%, 83%, and 55% across the four LLMs. AI non-evaluable outputs due to extraction failure or non-reproducibility across two independent runs occurred in 3.8% to 21.3% of cases across platforms, highlighting important limitations in reliability. Citation-level hallucination rates were high (41%, 36%, 49%, and 48%). On univariate analysis, higher evidence level predicted concordance across all models (all P ≤ 0.03). ESCAT tier was also significantly associated with concordance for LLM-2, LLM-3, and LLM-4. On multivariate analysis, evidence level remained the only consistent independent predictor for three LLMs, while ESCAT tier retained significance for one model. Inter-rater reliability was excellent (96.3%; κ = 0.93). **Conclusions:** LLM concordance is highest in guideline-supported, high-actionability settings but declines in low-evidence, poor-targetability scenarios—precisely where clinical support is most needed. This "AI paradox," combined with substantial hallucination risk, indicates that while LLMs may assist first-pass molecular interpretation, expert multidisciplinary MTBs remain essential for safe and reliable precision oncology. Research Sponsor: None.

11048 **Poster Session**

Evolution of immune checkpoint inhibitor trials in oncology from 2011 to 2025: A cross-sectional study. First Author: Runzhe Chen, Sun Yat-sen University Cancer Center; UTHealth Houston School of Public Health, Guangzhou, China

Background: Immune checkpoint inhibitors (ICIs) have transformed the oncology therapeutic landscape since the first FDA approval in 2011. Over the past decade, ICIs have expanded rapidly across tumor types, disease settings, and therapeutic strategies. However, a comprehensive evaluation of the long-term evolution and key characteristics of global ICI clinical trials remains limited. We conducted a cross-sectional analysis to characterize temporal trends and fundamental features of ICI oncology trials registered on ClinicalTrials.gov from 2011 to 2025. **Methods:** All interventional oncology trials with a primary treatment purpose registered on ClinicalTrials.gov between January 1, 2011, and December 31, 2025, were included. ICI trials were defined as studies investigating agents targeting CTLA-4, PD-1, PD-L1, or next-generation immune checkpoints (e.g., LAG-3, TIGIT, TIM-3). Trials were categorized by phase, randomization, enrollment, funding source, geography, tumor type, treatment setting, and primary endpoints. Descriptive statistics summarized trial characteristics and temporal trends. **Results:** A total of 8,756 interventional treatment-purpose ICI trials were identified. Annual trial starts increased from 32 in 2011 to a peak of 955 in 2021, remaining consistently high thereafter (858 in 2022, 848 in 2023, and 817 in 2024), and reaching 940 in 2025. Most trials were Phase 2 (4,174/8,756; 47.7%), Phase 1 (1,756; 20.1%), or Phase 1/2 (1,374; 15.7%), while Phase 3 trials only accounted for 870 (9.9%) overall. The number of Phase 3 trials increased from 4 in 2011 to 100 in 2019, declined during 2020–2022, and subsequently rebounded to 101 in 2023, 110 in 2024, and a peak of 137 in 2025, reflecting ongoing maturation toward late-stage development. Funding was most frequently categorized as other (5,291; 60.4%), followed by industry (3,065; 35.0%) and US federal sources (400; 4.6%). The most common tumor groups were non–small cell lung cancer (NSCLC) (1,014; 11.6%), melanoma (579; 6.6%), breast cancer (498; 5.7%), and colorectal cancer (431; 4.9%). Among trials with available location data (n=8,152), the United States (4,173; 51.2%) and China (2,647; 32.5%) were the most frequent trial locations. **Conclusions:** Over the past 15 years, ICI clinical trials have expanded markedly in number and across tumor types; however, the majority remain early-phase, open-label, and small in scale, with Phase 3 studies comprising less than 10% of all trials. Encouragingly, the recent increase in late-phase trials suggests continued maturation of the immuno-oncology field and sustained progress toward regulatory approval. Persistent geographic concentration highlights the need to broaden global participation and strengthen the generation of confirmatory evidence to maximize the clinical impact of ICIs in cancer care. Research Sponsor: National Natural Science Foundation of China; 82202827.

11049 **Poster Session**

Baseline financial and credit status of participants enrolled in SWOG S1912CD. First Author: Veena Shankaran, Fred Hutch Cancer Center, Seattle, WA

Background: Financial hardship is associated with adverse outcomes in cancer patients. While there is a critical need for interventions to prevent financial hardship, their scale and impact depend on the baseline financial status of patients. CREDIT (SWOG S1912CD) is a national prospective, randomized pragmatic trial evaluating the impact of a financial navigation intervention versus usual care on financial, clinical, and psychosocial outcomes. We report baseline demographic and financial characteristics of trial enrollees, using a combination of self-reported and credit data. **Methods:** Enrollees were within 6 months of diagnosis of a metastatic/stage IV solid tumor or hematologic malignancy. A total of 329 patients were randomized between July 2021 and December 2024 (165 control, 164 intervention). We assessed baseline income, employment, debt, homeowner status, financial fragility (ability to come up with $2,000 in 30 days), mean Comprehensive Score for Financial Toxicity (COST), and financial coping strategies (e.g. loans, cost-related nonadherence). We also examined the proportion of patients with adverse credit indicators (bankruptcies, third-party collections, repossessions, tax liens, delinquent mortgage payments) in their baseline credit reports. We compared mean COST score for patients with versus without adverse credit indicators. **Results:** Most patients (median age 61.5) were White (78%), 51% had commercial insurance while 33% had Medicare. The most common cancer types were gastrointestinal (23%), lung (12%), and breast (11%). Median household income was $50,001-$75,000, 70% were homeowners, and 32% reported a change in employment following cancer diagnosis and prior to enrollment. 39% reported financial fragility, 71% reported debt (32% with debt greater than $25K), and 20% reported taking loans from friends or family in the prior 3 months. Mean COST score was 19.6, with 45% of patients reporting scores $\leq$ 17.5, consistent with significant financial toxicity. 18.5% of patients had utilized $\geq$ 75% of credit limit on credit cards. The proportion of patients with prior bankruptcy, third-party collection, repossession, or delinquent mortgage payment were 3.3%, 16%, 2.7%, and 2.5% respectively. Mean COST score was significantly lower in patients with an adverse credit indicator compared to those without (21.4 vs. 13.0, $p<0.0001$) suggesting good correlation between credit data and patient-reported outcome measure. **Conclusions:** A significant proportion of patients newly diagnosed with cancer reported debt, financial fragility, and significant financial toxicity. A smaller proportion had more severe financial challenges identifiable in their baseline credit reports. There is clearly a need for interventions to address and mitigate financial hardship in this population. Final primary analysis of the impact of CREDIT in this financially challenged population is forthcoming. Clinical trial information: NCT04960787. Research Sponsor: National Cancer Institute.

11050 **Poster Session**

Palliative care for advanced cancer: Medicare Advantage and provider networks. First Author: Xin Hu, Emory University School of Medicine, Atlanta, GA

Background: Palliative care is a specialized medical approach to improve symptoms and quality of life for patients with serious illnesses, including cancer, yet its utilization remains low. While enrollment in Medicare Advantage (MA) has grown and surpassed Traditional Medicare (TM), less is known about differences in palliative care between MA and TM and the extent to which MA plan design, particularly provider networks, contributes to these differences. **Methods:** Using the 2025 SEER–Medicare linkage, we identified Medicare beneficiaries aged $\geq$66 years diagnosed with distant-stage breast, colorectal, lung, pancreatic, or prostate cancer between 2016 and 2021. We included patients who survived at least 2 months after diagnosis and had continuous enrollment in TM or MA from 1 year before diagnosis to death/end of follow-up. The primary outcome was the cumulative incidence of palliative care billing within 6 months of diagnosis. To assess the role of provider networks, we first assigned each patient a treating oncologist based on the plurality of visits with cancer diagnosis codes; we then conducted 1:1 matching of patients enrolled in a given MA plan to patients in TM treated by the same oncologists within the same county. Multivariable Cox proportional hazards models estimated differences in palliative care billing between TM and MA overall and by MA plan type, before and after matching, adjusting for sociodemographic and clinical characteristics. **Results:** Among 135,402 beneficiaries with advanced cancer, 67.7% were enrolled in TM and 32.3% in MA; over half were female, 7.3% Hispanic, and 9.5% non-Hispanic Black. The 6-month cumulative incidence of palliative care billing was 13.3% among MA beneficiaries and 9.3% among TM beneficiaries. In adjusted analyses, MA enrollment was associated with higher palliative care billing (hazard ratio [HR], 1.39; 95% CI, 1.34–1.44). When stratified by plan types, palliative care was particularly higher among patients in health maintenance organization (HMO) plans (HR=1.66, 95%CI=1.60-1.72) but not other plan types. After matching on treating oncologists, 23,033 TM and 23,033 MA patients were included. Matched MA beneficiaries were less likely to have HMO plans than those not matched (49.1% vs. 76.7%). Differences in palliative care were attenuated and statistically non-significant, with cumulative incidence of 11.0% and 10.4% among MA and TM, and an adjusted hazard ratio of 1.05 (95%CI=0.99, 1.11). Similar attenuation was observed in HMO plans (1.16, 95%CI=1.08, 1.24). **Conclusions:** Palliative care billing was significantly higher among MA than TM beneficiaries, but these differences were substantially reduced after accounting for provider networks. These findings suggest that between-provider variation accounts for the majority of the difference in palliative care receipt between TM and MA beneficiaries. Research Sponsor: U.S. National Institutes of Health; K12AR084234.

11051 **Poster Session**

Household costs of breast cancer and coping mechanisms in Kenya: A case of Kenyatta National Hospital. First Author: Lyndah Kemunto Manoti, University of Nairobi, Nairobi, Kenya

Background: In 2020, cancer was the third leading cause of mortality in Kenya, with breast cancer the most prevalent cancer and the second leading cause of cancer-related deaths. Patients and the health system faced a substantial economic burden due to breast cancer, which requires long-term medical attention as a chronic condition. Research has identified cost as a primary obstacle to accessing breast cancer healthcare services, particularly in low- and middle-income countries (LMICs). Objectives: The objective of this study was to examine the household costs of breast cancer among patients receiving treatment at Kenyatta National Hospital, Kenya's national referral hospital. Specifically focusing on cost incurred, drivers of cost and cost coping mechanisms. **Methods:** Cross-sectional descriptive research design was utilized to quantify the cost of breast cancer among 103 breast cancer patients at the Kenyatta National Hospital in 2024. Data were collected via a semi-structured questionnaire on the direct medical costs, direct non-medical costs, and indirect costs incurred, as well as cost coping mechanisms. To assess the drivers of cost, multivariable linear regression model was used to determine associations between the independent variables and cost outcomes. **Results:** The mean total costs of breast cancer were estimated to be USD 14,255 (KES 2,138,330). Direct medical costs (USD 8,916/KES 1,337,475) were the largest component, followed by direct non-medical costs (USD 1,917/KES 287,625) and indirect costs (USD 3,421/KES 513,229). Targeted therapy was the largest cost component within direct medical costs, representing 45.37% of direct medical costs. Luminal B and Stage IV breast cancer incurred the highest total costs. Patients primarily relied on public health insurance and personal income and savings to cater for the costs. Despite all participants using the National Health Insurance Fund (NHIF), now Social Health Authority (SHA), it only covered 25-50% of the direct medical costs. Out-of-pocket expenditures were significant, with 97% of respondents using personal income and savings, 29% liquidating assets, and 22% taking loans. **Conclusions:** Breast cancer patients and their households incur significant costs in Kenya. This underscores the need for urgent health financing reforms that ensure broadened insurance coverage, and social protection systems that ensure Kenyans have access to comprehensive cancer care and prevent cancer-related financial toxicity and impoverishment. Research Sponsor: Kenyatta National Hospital; KNH/R&P/23/24-25/10/5.

11052 **Poster Session**

Disparities in race and insurance status among hospitalized patients with pancreatic cancer and protein–energy malnutrition: A nationwide analysis, 2016–2022. First Author: Alexandra Sueldo, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Protein–energy malnutrition (PEM) is frequently encountered in patients with pancreatic cancer and is associated with worse clinical outcomes. Although sociodemographic differences in malnutrition risk have been described, it is unclear whether racial and insurance-based disparities persist after accounting for clinical complexity, socioeconomic factors, and hospital characteristics. We sought to identify independent predictors of PEM among hospitalized patients with pancreatic cancer using a nationally representative inpatient cohort with multivariable adjustment for relevant covariates. **Methods:** We conducted a retrospective cohort study using the National Inpatient Sample (NIS) from 2016 to 2022. Adult hospitalizations with pancreatic cancer were identified using ICD-10-CM code C25, and PEM was defined using ICD-10-CM codes E40–E46. Multivariable regression models evaluated independent predictors of PEM and its associations with in-hospital mortality, length of stay, discharge disposition, and hospital charges. Models adjusted for demographic factors, comorbidities, and hospital characteristics, with survey weights applied to generate national estimates. **Results:** Among an estimated 263,890 hospitalizations for pancreatic cancer, 37% were associated with PEM. After adjustment, Black patients (adjusted odds ratio [aOR] 1.39, 95% CI 1.31–1.48) and Asian/Pacific Islander patients (aOR 1.41, 95% CI 1.27–1.56) had higher odds of PEM compared with White patients. Medicaid insurance was associated with increased odds of PEM (aOR 1.12, 95% CI 1.03–1.22), whereas private insurance was associated with lower odds (aOR 0.85, 95% CI 0.80–0.91) relative to Medicare. Higher comorbidity burden (Charlson Comorbidity Index $\geq$3) was the strongest predictor of PEM (aOR 1.54, 95% CI 1.45–1.64). Median household income was not independently associated with PEM. PEM was more common in urban hospitals and those with larger bed size. **Conclusions:** In this national inpatient cohort, PEM was common among patients hospitalized with pancreatic cancer and demonstrated racial and insurance-based disparities that persisted after adjustment for income, comorbidities, and hospital characteristics. These findings highlight potential gaps in nutritional risk recognition and underscore the importance of standardized inpatient nutritional screening and targeted interventions for high-risk populations. Research Sponsor: None.

Variable	aOR	95% CI	P value
Age 50–64	1.20	1.03–1.38	0.016
Age ≥65	1.25	1.08–1.46	0.004
Female sex	0.94	0.91–0.98	0.006
Black race	1.39	1.31–1.48	<0.001
Asian/Pacific Islander	1.41	1.27–1.56	<0.001
Other race	1.23	1.10–1.38	<0.001
Medicaid insurance	1.12	1.03–1.22	0.010
Private insurance	0.85	0.80–0.91	<0.001
Charlson Index ≥3	1.54	1.45–1.64	<0.001

11053 **Poster Session**

Malnutrition and cachexia as drivers of failure-to-rescue in gynecologic cancer hospitalizations, 2016–2023. First Author: Charles Abraham Joseph Larson, Trinity School of Medicine, Warner Robins, GA

Background: Malnutrition and cancer cachexia are underrecognized in administrative data yet may identify hospitalized oncology patients with limited physiologic reserve. Rather than acting solely as baseline comorbidities, these conditions may amplify the lethality of inpatient complications. The prevalence, temporal trends, and outcome-modifying role of malnutrition were evaluated among U.S. gynecologic oncology hospitalizations using a failure-to-rescue framework. **Methods:** A retrospective, survey-weighted analysis of the National Inpatient Sample (NIS), 2016–2023, was conducted. Adult hospitalizations with gynecologic malignancies (ICD-10-CM C51–C58) were included; palliative encounters (Z51.5) were excluded. Malnutrition was defined using a narrow phenotype (E43, E44.*, E46) and a broader definition including cachexia (R64). Outcomes included in-hospital mortality, ICU escalation (mechanical ventilation and/or shock), major complications (sepsis, bleeding/transfusion, venous thromboembolism, acute kidney injury, bowel injury/peritonitis, respiratory failure), length of stay (LOS), hospitalization cost, and failure-to-rescue (death following $\geq$1 complication among surgical admissions). Survey-weighted estimates with 95% confidence intervals (CI) were reported. **Results:** The cohort included 1,019,030 weighted hospitalizations. Malnutrition prevalence was 12.75% (95% CI, 12.53–12.98) using the narrow definition and increased from 9.61% in 2016 to 15.32% in 2023. In-hospital mortality was higher among malnourished admissions (4.36% [95% CI, 4.11–4.63] vs 1.55% [95% CI, 1.48–1.61]). Malnutrition was associated with greater ICU escalation (5.63% [95% CI, 5.35–5.92] vs 2.48% [95% CI, 2.41–2.56]), AKI (31.53% [95% CI, 30.93–32.13] vs 17.54% [95% CI, 17.33–17.76]), and any major complication (64.97% [95% CI, 64.35–65.60] vs 44.07% [95% CI, 43.74–44.40]). Resource utilization was higher with malnutrition (LOS 8.98 vs 4.71 days; cost $28,155 vs $18,740). Among admissions with complications, mortality was higher with malnutrition (6.27% [95% CI, 5.90–6.65] vs 3.16% [95% CI, 3.03–3.29]). In the surgical subcohort, failure-to-rescue mortality was 2.55% (95% CI, 1.98–3.28) with malnutrition versus 0.82% (95% CI, 0.70–0.95). **Conclusions:** In U.S. gynecologic oncology hospitalizations, malnutrition and cachexia identify a high-risk inpatient phenotype with disproportionate complication burden and post-complication mortality. These findings support malnutrition as a modifier of failure-to-rescue rather than an isolated baseline risk factor and highlight inpatient nutritional vulnerability as a target for early risk stratification and supportive intervention. Research Sponsor: None.

11054 **Poster Session**

Comprehensive molecular profiling in advanced non–small cell lung cancer (NSCLC): Measurable survival and value impacts of implementation. First Author: Stanley Ifeanyi Ozogbo, Allegheny Health Network Cancer Institute, Pittsburgh, PA

Background: Comprehensive molecular profiling (CMP) is key to precision oncology in advanced non–small cell lung cancer (NSCLC), enabling identification of actionable driver alterations and delivery of matched targeted therapies that improve survival. CMP has been universally recommended by international guidelines for over a decade. Despite mature evidence and widespread availability, real-world adoption remains strikingly low. We evaluated the real-world impact of molecular profiling on survival, healthcare utilization, and cost in NSCLC, and quantified the magnitude of its ongoing underuse. **Methods:** We analyzed NSCLC patients aged $\geq$18 years treated between January 2019 and December 2025 using two independent real-world datasets: TriNetX and Highmark Health. Patients were categorized based on receipt of broad-panel molecular profiling consistent with guideline-directed indications. Outcomes included overall survival (OS), emergency department (ED) visits, inpatient admissions, and healthcare costs. Survival was assessed using Kaplan–Meier methods, with multivariable regression to adjust for clinical factors. **Results:** Among 33,977 NSCLC patients in TriNetX, only 2,354 (6.9%) underwent molecular profiling, despite the majority of NSCLC patients presenting with advanced disease. Molecularly profiled patients experienced a substantial survival advantage, with median OS of 1,784 days versus 1,074 days in untested patients (adjusted hazard ratio 0.61; $p<0.001$). Molecular profiling was also associated with significantly fewer inpatient admissions (0.651 vs 0.875; $p<0.001$) and ED visits (0.437 vs 0.583; p=0.047). Highmark Health data independently validated these findings, demonstrating significantly improved 4-year OS in molecularly tested patients (55% vs 43%; $p<0.001$). Importantly, these survival gains were achieved without a statistically significant increase in total cost per patient per month at follow-up (p=0.083). **Conclusions:** Across two large, independent real-world datasets, comprehensive molecular profiling in NSCLC was associated with meaningful improvements in survival and reductions in healthcare utilization, even when applied primarily in advanced disease. These benefits were achieved without a significant increase in overall costs, supporting the value-based impact of precision oncology. Yet fewer than 1 in 15 eligible NSCLC patients underwent molecular profiling between 2019 and 2025, revealing a profound and persistent failure to implement guideline-concordant care. This underuse directly translates into avoidable mortality and unnecessary healthcare utilization. System-level solutions, including standardized and reflexive molecular testing at diagnosis, are urgently needed to ensure precision medicine is delivered as standard care in advanced NSCLC patients. Research Sponsor: None.

11055 **Poster Session**

Overall survival of Black patients with newly diagnosed multiple myeloma in the era of triplet and quadruplet therapies. First Author: Hamlet Gasoyan, Cleveland Clinic, Cleveland, OH

Background: Black individuals have been shown to have a higher incidence of multiple myeloma, as well as worse survival, compared with White patients. A single VA-based study demonstrated that with equal access to myeloma therapy, Black patients have superior survival compared to White individuals. Nevertheless, it is unknown whether this finding holds in other settings. **Methods:** This retrospective cohort study included adult patients newly diagnosed with multiple myeloma between January 1, 2017, and December 31st, 2023, in one health system in Ohio and Florida. We captured receipt of triplet or quadruplet therapy within one year of diagnosis, as well as patients' overall survival (OS) through September 30, 2025, using the Cleveland Clinic electronic health record, including linked state and federal death records. A multivariable logistic regression model examined the association of race with the receipt of either triplet or quadruplet therapy within one year of diagnosis, and a multivariable Cox regression model examined the association of race with 5-year all-cause mortality. The Cox model was adjusted for receipt of either a triplet or quadruplet regimen within 1 year, age at diagnosis, sex, Charlson comorbidity index (CCI), ECOG performance status, baseline eGFR, urbanicity of patient's residence, area deprivation index based on Census Block Group, insurance type, and year of diagnosis. **Results:** We identified 1230 patients, 54.1% male, 74.1% White, 22.8% Black, 3.1% other races. Mean (SD) age at diagnosis of 67.2 (11.1); it was 67.7 (10.8) for White and 65.9 (11.7) for Black patients. Overall, 66.3% of the cohort had an ECOG performance score of 0-1, 59.9% had baseline eGFR $\geq$60, and 51.1% had a CCI of $\leq$2. Within one year of diagnosis, 707 patients (57.5% of the cohort) received either triplet or quadruplet therapy, including 56.6% (n=516) of White and 58.9% (n=165) of Black individuals. Both univariable and multivariable analyses did not indicate a significant association between race and receipt of either a triplet or quadruplet therapy (aOR for Black race vs. White, 0.91, 95% CI, 0.64-1.28). According to Kaplan-Meier estimate, the probability of 5-year OS in the overall cohort was 62.1% (95% CI, 59.0%-65.4%). In the multivariable Cox regression model for all-cause mortality at 5 years, aHR for death for Black patients vs. White was 0.76 (95% CI, 0.58-1.00). **Conclusions:** In this large and diverse cohort of patients who had equal access to triplet or quadruplet therapies for newly diagnosed multiple myeloma, Black patients did not have a higher risk of all-cause mortality at 5 years compared to White individuals. Our findings indicate that health equity initiatives aimed at improving access to multiple myeloma care among minority patients have the promise of addressing race-based disparities in survival. Research Sponsor: National Cancer Institute.

11056 **Poster Session**

Impact of U.S. most-favored-nation (MFN) drug pricing on global oncology access. First Author: Ariel Hammerman, Medison Pharma, Petah Tikva, Israel

Background: U.S. cancer drug prices substantially exceed those in other OECD countries. In May 2025, a U.S. Presidential Executive Order mandated adoption of a Most-Favored-Nation (MFN) pricing policy, linking U.S. drug prices to those of economically comparable countries. In December 2025, the Centers for Medicare & Medicaid Services (CMS) proposed two MFN-based frameworks: the Global Benchmark for Efficient Drug Pricing (GLOBE) for Medicare Part B drugs and Guarding U.S. Medicare Against Rising Drug Costs (GUARD) for Part D drugs. Both require manufacturer rebates when U.S. prices exceed GDP-adjusted international benchmarks, creating potential incentives for manufacturers to alter global oncology pricing and launch strategies. This study assesses which international markets may face pricing pressure or delayed access to new oncology therapies following MFN implementation. **Methods:** The top 50 best-selling U.S. drugs in 2024 were reviewed, and 12 oncology drugs without generic or biosimilar competition were selected. List prices were collected from the 19 OECD reference countries included in GLOBE and GUARD. Prices were adjusted for GDP per capita using purchasing power parity (PPP). For each drug, the two lowest GDP-adjusted international prices were identified and compared with U.S. prices, using January 2026 Medicare Average Sales Price (ASP) data for Part B drugs and December 2025 Federal Supply Schedule (FSS) prices for Part D drugs. **Results:** Across all 12 drugs, GDP-adjusted benchmark prices were 48% to 90% lower than U.S. prices. Pembrolizumab, the top-selling oncology drug in 2024, had a U.S. Medicare price of $5,972 per 100 mg; the lowest adjusted prices were observed in South Korea ($2,116) and Japan ($2,271), representing reductions of 65% and 62%, respectively. Daratumumab, the second top-selling oncology drug, was priced at $2,831 per 400 mg in the U.S., compared with $1,467 in South Korea and $1,603 in the Netherlands (48% and 43% lower). The lowest benchmark prices most frequently originated from South Korea (n=5) and the Netherlands (n=4). Norway, Germany, and Japan each provided the lowest benchmark for one drug. Second-lowest benchmark prices were observed in Japan (n=4), South Korea (n=3), the Netherlands (n=2), Germany (n=2), and Norway (n=1). **Conclusions:** Countries serving as the lowest-price benchmarks- particularly South Korea, Japan, the Netherlands, Norway, and Germany- may face increased risk of upward pricing pressure or delayed access to innovative oncology therapies as manufacturers seek to limit U.S. MFN rebate exposure. Expanded use of confidential discounts, confidential rebates and other managed-entry agreements may help preserve access while reducing MFN benchmark risk. Research Sponsor: None.

11057 **Poster Session**

When does time become a burden? Evaluating the association between time spent on cancer care and patient distress. First Author: Sarah Boyle, University of Minnesota, Minneapolis, MN

Background: While cancer care is time-intensive, the specific impact of various tasks on patient well-being is poorly understood. We evaluated how time spent on specific cancer-care tasks contributes to patient distress and identified patient populations most vulnerable to these time burdens. **Methods:** We enrolled individuals receiving treatment for advanced-stage ovarian or metastatic breast cancer at the University of Minnesota and the University of Alabama-Birmingham. Participants used a mobile app for 28 days to log time spent on out-of-home and at-home cancer-care related tasks. Daily distress was measured via the National Comprehensive Cancer Network (NCCN) Distress Thermometer (0-10; 0=no distress, 10=extreme distress). The primary outcome was clinically significant distress (NCCN distress score <4 vs. ≥ 4). Predictors included any time spent on each task type on a given day for both out-of-home healthcare tasks (lab, clinic, treatment, research, imaging, other) and at-home tasks (taking medications, scheduling appointments, managing medical bills/insurance claims, symptom management, monitoring health status, seeking information, and arranging help/transportation). A multi-level model with a random intercept for participants was used, adjusting for age, employment, education, dependent and partner status. Odds ratios and 95% confidence intervals are reported. **Results:** Analysis included 1,869 days from 60 participants (median age 59; 42% employed; 35% with dependents). Experience of significant distress was more likely on days including out-of-home treatment compared to days without treatment (OR: 2.54 [1.47, 4.39]). Participants were also more likely to experience significant distress on days including time spent on symptom management (OR: 2.59 [1.85, 3.64]), health monitoring (OR: 2.50 [1.56, 3.98]), and managing bills/claims (OR: 2.24 [1.22, 4.12]) compared to days without those tasks. Vulnerability varied: employed patients were more distressed by managing bills/claims and information seeking, while non-working patients experienced more distress on treatment days. Among those with dependents, scheduling was a unique stressor. **Conclusions:** Out-of-home treatment and at-home cancer-care tasks are significantly associated with patient distress. Findings suggest that interventions reducing at-home administrative and symptom burdens would reduce patient distress, and resources may need to be tailored based on employment and caregiving status. Clinical trial information: NCT05708703. Research Sponsor: U.S. National Institutes of Health; 1R01CA277714, P30 CA77598, P30 CA013148, UM1TR004405.

11058 **Poster Session**

An AI-powered, human-in-the-loop, real-time registry platform to enable clinical trials, pragmatic studies, and prospective external control arms (ProECA) at scale in US community practices. First Author: Luis T. Campos, Oncology Consultants, Medical Center, Houston, TX

Background: Drug development is requiring novel approaches such as prospective external controls to reduce development timelines and de-risk phase transitions. The majority of oncology patients in the US are seen at community oncology centers, many of which have limited clinical research infrastructure. The Kaleido registry was initiated to address these challenges through a hybrid operational technology model combining on-site staff, clinical note preparation, pre-visit abstraction, and automated workflows to facilitate pre-screening, data capture and research operations. **Methods:** The Kaleido registry enrolls patients at US community oncology practices with variable research infrastructure and is actively enabling seven studies. Real-time abstraction is performed prior to each patient visit across an expanding set of indications, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), prostate cancer, and myeloproliferative neoplasms, enabling standardized data collection and systematic/unbiased trial pre-screening. An automated prescreening tool was developed and validated against manual chart review. Standardized draft notes are generated to reduce clinical documentation burden. A patient questionnaire captures social determinants of health (SDOH) and self-reported performance status. **Results:** As of 1/1 2026 more than 16,000 patients (60% female, median age 70 years, range 19-105) from 28 sites have been consented. Most common diagnoses are breast (29%), colorectal (9%), prostate (6%) and lung cancer (6%). 99% of approached patients filled out the patient questionnaire and missingness of race/ethnicity/education/marital status was $<4\%$. Comprehensive biomarker testing exceeded 85% for patients with metastatic NSCLC. Time from specimen collection to NGS results (median 18 days, range 5-45) or PD-L1 (median 21 days, range 4-45) was a key driver of delays in evaluating trial-eligibility. Patients were consistently identified prior to starting next line of therapy. The model identified additional trial-eligible patients beyond standard workflows even at high-performing sites. In 2025, more than 500 patients were included in trials, ProECAs and pragmatic studies with enhanced data depth within the registry. **Conclusions:** The Kaleido registry demonstrates a scalable, integrated infrastructure for real time patient identification and comprehensive prospective data collection in the community setting. By facilitating community trial enrollment, pragmatic studies and prospective external controls while reducing operational burden of clinical teams, Kaleido has the potential to significantly accelerate drug development. Research Sponsor: None.

11059 **Poster Session**

Association of drug industry payments to oncologists and use of guideline-preferred cancer treatments. First Author: Aaron Philip Mitchell, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Payments from the drug industry to oncologists are common and influence physicians' prescribing decisions. However, whether payments affect the likelihood that patients receive optimal cancer treatment has not been assessed. **Methods:** This was a population-based cohort study. We used fee-for-service Medicare claims to identify patients with incident cancer diagnosis (new cancer diagnosis code after $>=$ 1 year with no cancer diagnosis codes) from 2014-2020. We used National Comprehensive Cancer Network (NCCN) Guidelines to identify treatment scenarios (e.g., metastatic melanoma, stage III colon adjuvant therapy) with variation in the clinical benefit among recommended treatment options. The patient cohort corresponding to each scenario was identified using claims. We used NCCN Guidelines to identify the "optimal" treatment for each scenario (defined as the designated "preferred" treatment, with NCCN Evidence Blocks scores used for tiebreaks) at each time point across the study period. The primary outcome was whether a patient received the treatment that was, as of their diagnosis date, the optimal treatment for their cancer (vs. any non-optimal treatment). The primary exposure[s] were whether a patient's medical oncologist received personal ("general") payments (source: linked Open Payments data) related to 1) optimal treatment or 2) any non-optimal treatment, during the year prior to the patient's cancer diagnosis. We fit Poisson-family generalized estimating equations, with physician-level clustering and adjustment for scenario, year, and patient characteristics, to estimate the relative risk (RR) of optimal treatment. **Results:** There were 14 clinical scenarios comprising 15,835 patients. There were 3,429 (21.7%) patients whose oncologist received payment for the optimal treatment, 4,891 (30.9%) for non-optimal payments, and 1,993 (12.6%) to both payment types. Oncologist receipt of payment for optimal treatment was associated with a greater likelihood (RR=1.07, 95%CI:1.01-1.13), and payment for non-optimal treatment was associated with lower likelihood (RR= 0.94, 95%CI:0.89-0.98) of patients receiving optimal treatment. Associations became stronger as payment dollar value increased; for optimal payments $\geq$\$10,000, RR=1.26 (95%CI:1.02-1.57), and for non-optimal payments $\geq$\$10,000, RR=0.70 (95%CI: 0.49-1.00). An estimated 41.6% of unexposed patients received optimal treatment; versus 52.6%, 29.3%, and 33.8% among patients exposed to $\geq$\$10,000 of payments for optimal treatment only, $\geq$\$10,000 non-optimal payments only, and $\geq$\$10,000 of both payment types, respectively. **Conclusions:** Industry payments related to the optimal cancer treatment were associated with increased use of the optimal treatment. However, payments related to non-optimal treatments were more common and were associated with decreased use of optimal treatment. Research Sponsor: NIH - National Cancer Institute; R37CA264563; National Institute of Health Care Management; GC260700; NIH - National Cancer Institute; P30CA008748.

11060 **Poster Session**

Format matters: Digital vs print delivery of a job retention intervention during breast cancer therapy. First Author: Yashasvini Sampathkumar, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Talking to Employers and Medical Staff about Work (TEAMWork) is an English/Spanish intervention, delivered as a booklet or mobile app, which was developed to improve work outcomes among women undergoing (neo)adjuvant breast cancer therapy. TEAMWork provides education on work accommodations based on vocational rehabilitation principles, employer negotiation strategies, symptom self-management tools, and guidance on communicating with clinicians to enhance support (e.g., obtain work documentation). Here we present data on predictors of intervention use during systemic therapy from an ongoing randomized controlled trial comparing the TEAMWork app to the booklet. **Methods:** Eligible participants were women aged 18-65 years with stage I-III breast cancer who spoke English and/or Spanish, were employed pre-diagnosis, and undergoing or planning to undergo systemic (neo)adjuvant chemotherapy. Patients were recruited between October 2021 – March 2025 from multiple New York City sites. Data on socio-demographics, work characteristics, and intervention use were collected through patient surveys at baseline and after completion of chemotherapy. Multivariable logistic regression was used to assess predictors of intervention use during systemic therapy. **Results:** Of 372 participants (89% English; 11% Spanish), 54% identified as White, 17% Black, and 20% Hispanic/Latina. The mean age was 48 years. 70% were college-educated. All were employed at diagnosis, but only 77% were actively working (e.g., not on leave) at baseline. Participants worked in various occupations: managerial/professional (50%), sales/technical/administrative support (24%), service providers (21%), arts/media/athletics (5%), and operators/fabricators/laborers (1%). All participants received chemotherapy, with 53% starting therapy before the baseline survey. Slightly over half of participants (53%) reported using TEAMWork during systemic therapy; 120/187 (64%) in the mobile app arm and 76/185 (41%) in the booklet arm. In multivariable analysis, assignment to the mobile app arm was positively associated with intervention use during treatment (OR 2.54, 95% CI 1.61-4.05, $p<.001$). However, age, race, ethnicity, language, US-born (yes/no), educational attainment, occupational category, and chemotherapy initiation prior to randomization were not independently associated with intervention use. **Conclusions:** After adjusting for sociodemographic, occupational, and treatment-related characteristics, participants randomized to the mobile app arm had more than double the odds of using TEAMWork compared to those in the booklet arm. These findings underscore the importance of delivery format in the design of supportive interventions. Although mobile app development can be time- and resource-intensive, this approach may offer meaningful advantages in promoting patient engagement during therapy. Research Sponsor: National Cancer Institute; IR01 CA214785; National Cancer Institute; R37 CA214785; National Cancer Institute; P30 CA008748; National Cancer Institute; T32CA275764.

11061 **Poster Session**

Co-creating patient partnership within a national cancer trials network: Experience from Cancer Trials Ireland in partnership with the Irish Cancer Society. First Author: Emer Mulvaney, Cancer Trials Ireland, Dublin 2, Ireland

Background: Structured patient partnership is increasingly recognised in oncology research, yet less is known about how cancer trials groups and cancer charities can collaborate to sustain partnership system-wide. Cancer Trials Ireland (CTI) has established a patient partnership model through its Patient Consultants Committee, supported by the Irish Cancer Society (ICS), enabling integration of research infrastructure, charity support, and advocacy. **Methods:** The development and implementation of patient partnership at CTI from inception in 2016 was reviewed. The role of the ICS in enabling this model through funding, strategic alignment and public engagement was considered. Organisational learnings, barriers and facilitators to integration, research and strategic outputs, public outreach, clinical trial impacts, national and international collaborations, and engagement with early career investigators were synthesised from descriptive programme data and documented outputs. **Results:** By 2026, 33 patient partners were embedded across all adult Disease-Specific Subgroups, with patient and ICS representation in CTI governance. Key facilitators included a funded coordination role, enhanced partner recruitment, aligned public messaging, shared advocacy for clinical trial access and funding, and international research network engagement. Barriers to integration included challenges in patient diversity, competing commitments, and sustainable funding. Several were mitigated through partnership resourcing, advocacy and alignment of strategic priorities. Since 2023, patient partners have contributed to four investigator-initiated trial concepts and participated in Trial Management Groups. They contributed to grant applications, trainee research projects, and the development of a CTI climate change charter. Five patient-led, trainee-integrated research projects were delivered, resulting in international conference presentations and peer-reviewed publications. The CTI-ICS partnership supported sustainability and visibility through public engagement and policy activity, including contributions to the National Clinical Trials Oversight Group, engagement on GDPR barriers, election manifesto advocacy, and the *Value of Cancer Trials* campaign (co-launched with ICS and a patient partner). These findings demonstrate feasible integration of patient partners into a national cancer trials network at scale. **Conclusions:** A structured partnership between a national cancer trials organisation and a cancer charity can accelerate and sustain patient partnership beyond individual studies, embedding patient perspectives across trial selection, development, and dissemination. This experience complements cooperative group frameworks and offers a replicable approach for oncology research systems. Research Sponsor: Irish Cancer Society; Health Research Board (HRB).

11062 **Poster Session**

Commercial price variation in precision oncology testing across US hospitals. First Author: Maryam Mooghali, Yale School of Medicine, New Haven, CT

Background: Precision oncology testing using clinically validated biomarker tests is standard of care for solid tumors and is endorsed by clinical guidelines and professional societies. However, these tests represent a substantial and growing component of cancer care costs. Commercial payer-negotiated prices for these tests and their variation across hospitals and payers have not been examined. **Methods:** We conducted a cross-sectional analysis of hospital-reported commercial payer-negotiated prices, aggregated by Turquoise Health as of January 2026, for biomarker tests commonly used in breast, colon, and non-small cell lung cancer and identified using the National Comprehensive Cancer Network Biomarkers Compendium and Centers for Medicare and Medicaid Services Clinical Laboratory Fee Schedule. We included tests with unique Current Procedural Terminology codes and extracted prices negotiated between short-term acute care hospitals and the four largest US payers (Aetna, Blue Cross Blue Shield, Cigna, UnitedHealthcare). Prices were adjusted using ZIP code-level Geographic Adjustment Factors. We assessed within- and between-hospital variation in prices for each test using the median 90th-to-10th percentile price ratio and compared prices across payers using Kruskal-Wallis tests. **Results:** We identified 422,515 payer-negotiated prices for 28 biomarker tests from 2,142 US hospitals. Oncotype DX Breast Recurrence Score and *CEA* expression testing were the most frequently reported panel- and non-panel-based tests, with median (interquartile range [IQR]) prices of $4,129 ($3,869–$10,680) and $28 ($20–$59), respectively, across hospitals. The percentage of hospitals reporting negotiated prices, price amounts, and price variation are summarized in the Table. Cigna had the highest prices for 20 (71.4%) tests, whereas UnitedHealthcare had the lowest price for all tests. **Conclusions:** Commercial payer-negotiated prices for precision oncology testing varied substantially across payers and hospitals, with greater variation between than within hospitals for the same tests. Given the central role of these biomarker tests in guideline-recommended cancer care, price variation has important implications for payer spending, clinical decision-making, patient out-of-pocket costs, and equitable care access. Research Sponsor: None.

Price variation for precision oncology testing.

Biomarker Tests	Percentage of hospitals in Turquoise Health database reporting negotiated price, Median (IQR)	Negotiated price, USD, Median (IQR)	Within-hospital ratios, Median (IQR)[1]	Between-hospital ratios, Median (IQR)[1]
Panel-based (N=13)	18.3% (17.2%-18.8%)	$3,704 ($3,096-$4,129)	1.5 (1.4-1.5)	5.5 (5.5-5.6)
Non-panel-based (N=15)	30.3% (22.2%-37.8%)	$301 ($157-$485)	1.6 (1.5-1.7)	5.2 (5.1-5.4)

[1]Median (IQR) of ratios of the 90th:10th percentile payer-negotiated prices within each hospital and across all hospitals for the same test.

11063 **Poster Session**

Economic evaluation of a designated oncology pharmacist in hemato-oncology outpatient care: A randomized clinical trial. First Author: Areen Khateeb Alabbasi, Clalit Health Services, Tel Aviv, Israel

Background: Adverse drug reactions (ADRs) and medication errors are major contributors to morbidity and healthcare utilization in hemato-oncology. In a randomized clinical trial, we previously demonstrated that integrating a designated oncology pharmacist significantly reduced ADRs and intercepted potentially serious medication errors. The economic value of this intervention has not yet been established. **Methods:** We conducted a trial-based cost-effectiveness analysis alongside a single-center randomized clinical trial (n=182), in which adult patients with hematologic malignancies were randomized 1:1 to comprehensive pharmaceutical care delivered by a designated oncology pharmacist versus standard care. Patients were followed for 5 months (4-month intervention plus 1-month follow-up). The primary economic outcome was incremental cost per ADR avoided; secondary outcomes included cost per emergency department visit and hospitalization avoided. The analysis was conducted from the public healthcare system perspective and included only the pharmacist program cost, estimated at $105 per patient over the 5-month study period. Incremental cost-effectiveness ratios (ICERs) were calculated using absolute risk reduction, with uncertainty assessed by nonparametric bootstrap resampling (5,000 replications). Costs are reported in 2022 USD. **Results:** ADRs occurred in 47.3% of control patients compared with 23.1% of intervention patients, corresponding to an absolute risk reduction of 24.2% and a number needed to treat of 4.1. The ICER was $434 per ADR avoided (bootstrap 95% CI: $281–$956), with a $>$99.9% probability that the intervention reduced ADRs. Secondary outcomes also favored the intervention: emergency department visits (37.4% vs 28.6%; ICER $1,194 per visit avoided) and hospitalizations (28.6% vs 23.1%; ICER $1,911 per hospitalization avoided). In addition, the pharmacist intercepted 287 medication errors in real time, including 13 potentially severe errors, with a physician acceptance rate of 94.8%. **Conclusions:** This economic evaluation demonstrates that integrating a designated oncology pharmacist in hemato-oncology outpatient care is a cost-effective strategy for preventing ADRs and reducing acute healthcare utilization. These findings support broader implementation of oncology pharmacists as a high-value patient safety intervention. Research Sponsor: None.

11064 **Poster Session**

Local and state paid sick leave policies and timeliness of treatment initiation among working-age patients with early-stage breast cancer. First Author: Kewei Sylvia Shi, American Cancer Society, Atlanta, GA

Background: Local and state paid sick leave (PSL) mandates have been associated with increased use of preventive services, including cancer screening, and reduced emergency care utilization. Little research has examined PSL policies and cancer after diagnosis. This study evaluates associations of PSL policies and timely treatment initiation among women with early-stage breast cancer. **Methods:** We identified patients aged 18-64 years newly diagnosed with stages 0-II breast cancer from the National Cancer Database in 2004-2023 and linked then to area-level policy implementation, measured as the month and year the state, county, or city required PSL. Primary outcomes were receipt of definitive surgery or neoadjuvant therapy within 30, 60, and 90 days of diagnosis. We compared changes in treatment initiation between patients residing in areas with and without PSL policies during and after the month and year of diagnosis. We used a staggered difference-in-differences design to account for differential timing of implementation, adjusting for patient demographics, clinical, and area-level characteristics. Random errors were clustered at the state level. Supplemental analyses stratified by county-level unemployment rates and individual insurance coverage. **Results:** The study included 1,891,411 patients, of whom 249,313 (13.2%) resided in an area with PSL policies at diagnosis. Patients in areas with PSL policies were more likely to have Medicaid, reside in higher-income and metropolitan areas. PSL policy implementation was significantly associated with a 3.4 percentage point (PPT) increase in the probability of treatment ≤30 days (95% CI: 1.1-5.7), 3.0 PPT increase ≤60 days (95% CI: 1.6-4.3), 1.3 PPT increase ≤90 days (95% CI: 0.5-2.1) (Table). Improvements in timely treatment were concentrated in low-unemployment areas; no significant improvements were observed in high-unemployment areas. The magnitude of associations between PSL policies and treatment initiation was stronger among patients without private insurance than with private insurance. **Conclusions:** Local and state PSL mandates were associated with earlier treatment initiation among working-age patients with early-stage breast cancer, especially in areas with low female unemployment rate. Findings suggest that PSL policies play an important role in timely cancer treatment for employed women who may not have PSL through their jobs. Research Sponsor: None.

Association of paid sick leave policies and breast cancer treatment initiation.

	Time from diagnosis to surgery/neoadjuvant therapy (days)	DID PPT	Lower 95% CI	Upper 95% CI	P-value
Overall	≤30	**3.4**	**1.1**	**5.7**	**0.004**
	≤60	**3.0**	**1.6**	**4.3**	**0.000**
	≤90	**1.3**	**0.5**	**2.1**	**0.001**
Low female unemployment	≤30	2.2	-0.7	5.0	0.136
	≤60	**3.8**	**1.8**	**5.8**	**0.000**
	≤90	**1.2**	**0.3**	**2.2**	**0.012**
High female unemployment	≤30	1.8	-0.6	4.2	0.145
	≤60	-1.2	-4.5	2.0	0.459
	≤90	-1.4	-3.7	0.9	0.232

11065 **Poster Session**

Association of facility type and metastatic burden with survival in gastric adenocarcinoma: A National Cancer Database study. First Author: Yazmin Reategui-Almonacid, Rutgers/Newark Beth Israel Medical Center, Newark, NJ

Background: While we know metastatic burden dictates survival in gastric adenocarcinoma (GA), how this intersects with where a patient receives care remains less clear. Academic centers (AC) often report better outcomes, but we haven't fully determined if this "academic advantage" holds true once you account for the sheer extent of disease at the time of diagnosis. We set out to test whether AC care offers a survival benefit that persists regardless of a patient's baseline metastatic burden. **Methods:** We retrospectively analyzed the National Cancer Database (2016–2023), identifying 102,869 patients with GA. We grouped patients by facility type (AC vs. community). We mapped metastatic burden at diagnosis across six specific sites: bone, brain, liver, lung, distant lymph nodes, and other. After comparing baseline characteristics, we estimated 3-year overall survival (OS) using Kaplan–Meier methods. Our primary tool was a multivariable Cox model, adjusting for age, Charlson–Deyo score, clinical stage, and metastatic burden to isolate the link between facility type and mortality. **Results:** Of the 102,869 patients, 58.4% (n = 60,064) were treated at ACs and 41.6% (n = 42,805) at community sites. Interestingly, community patients arrived with a higher burden of disease (33.8% vs. 30.4%; $p < 0.001$), and 11.7% of the total cohort had multi-site metastasis (≥2 sites). The liver was the most frequent site of spread, appearing more often in community settings (18.4% vs 15.4%; $p < 0.001$). Three-year OS was significantly higher at ACs (45.2% vs 35.8%; $p < 0.001$). After adjusting for site count, comorbidity, age, and stage, AC treatment remained independently associated with lower mortality (HR 0.81; 95% CI 0.80–0.83; $p < 0.001$). Notably, this academic survival advantage was not driven by any single metastatic site; the benefit persisted across all individual sites of involvement, including brain and lung, with no site showing a loss of AC advantage. **Conclusions:** Survival differed by treatment facility even after accounting for metastatic burden. Patients treated at academic centers had better outcomes across metastatic sites, including those with extensive disease. These findings point to differences in care delivery and access to specialized expertise. Expanding academic practices, such as multidisciplinary tumor boards and referral pathways, into community settings may help reduce these gaps. Research Sponsor: None.

11066 **Poster Session**

Shifting drivers of hospitalization in endometrial cancer: Toxicity-like organ failure phenotypes in the modern treatment era. First Author: Sarah Peterson, ATSU Kirksville Osteopathic School of Medicine, Santa Barbara, CA

Background: Frontline endometrial cancer care has rapidly shifted toward immune-based regimens. Whether inpatient admissions have concurrently shifted toward toxicity-like organ failure syndromes, with changing ICU use and rescue outcomes, remains unknown. **Methods:** We performed a survey-weighted analysis of the National Inpatient Sample (NIS) 2016–2023. Adult hospitalizations with endometrial cancer in any diagnosis position (C54/C55) were included; admissions with palliative care coding (Z51.5) were excluded. Eras were defined as 2016–2017 versus 2018–2023. Toxicity-like organ failure phenotypes were identified using ICD-10-CM proxies including pneumonitis or respiratory toxicity, colitis or diarrhea, myocarditis or pericarditis, hepatitis or liver failure, neutropenic sepsis, acute kidney injury, and electrolyte collapse. A broader sensitivity phenotype additionally included endocrine crises. ICU escalation was proxied by mechanical ventilation or shock. Major complications were defined using a composite bundle, and failure-to-rescue was defined as death among complication admissions. Outcomes included in-hospital mortality, ICU escalation, complications, length of stay (LOS), cost, and routine discharge. **Results:** Among 74,895 unweighted endometrial cancer hospitalizations, 25.8% occurred in 2016–2017 and 74.2% in 2018–2023. Overall inpatient mortality was 1.86% (95% CI 1.66%–2.07%) in 2016–2017 and 2.09% (95% CI 1.96%–2.22%) in 2018–2023. Hospitalizations involving any toxicity-like organ failure phenotype increased from 34.3% (95% CI 33.4%–35.1%) in 2016–2017 to 45.2% (95% CI 44.7%–45.7%) in 2018–2023. Pneumonitis or respiratory toxicity increased from 6.23% to 9.91%, acute kidney injury from 14.9% to 21.0%, and electrolyte collapse from 23.7% to 31.7%. ICU proxy use increased from 2.50% (95% CI 2.27%–2.73%) to 3.30% (95% CI 3.15%–3.45%), driven by higher shock coding (0.82% to 1.61%). Major complications increased from 36.1% (95% CI 35.3%–36.9%) to 46.5% (95% CI 46.0%–47.1%). Mortality among admissions with toxicity-like organ failure decreased modestly from 4.75% (95% CI 4.25%–5.30%) to 4.25% (95% CI 4.00%–4.52%), while mortality among ICU-level admissions remained high and unchanged (29.7% vs 29.2%). Routine discharge declined from 66.6% (95% CI 65.6%–67.6%) to 62.2% (95% CI 61.7%–62.7%), and LOS increased in the modern era (mean 5.22 days, 95% CI 5.16–5.28). **Conclusions:** From 2016–2023, endometrial cancer hospitalizations increasingly involved toxicity-like organ failure phenotypes with rising ICU escalation and complication burden, while inpatient mortality changed minimally. These findings highlight a growing disconnect between outpatient therapeutic advances and inpatient recognition and rescue capacity. Research Sponsor: None.

11067 **Poster Session**

Early-phase operational readiness gaps in oncology cell and gene therapy trials and implications for scalable trial infrastructure. First Author: Meera Belur, Premier Research, Cedar Park, NC

Background: First-in-human (FIH) and Phase 1 oncology cell and gene therapy (CGT) trials have highlighted that operational readiness, rather than scientific feasibility, is often the primary constraint on trial execution and patient access. Many clinical sites lack the infrastructure, staffing, and process maturity required to support CGT trials, limiting enrollment and scalability. **Methods:** Operational lessons were analyzed across multiple early-phase oncology CGT programs, including autologous and allogeneic platforms. Assessments focused on trial execution during FIH and Phase 1 activation, site readiness, vector and cellular product handling, storage and chain-of-custody requirements, coordination among manufacturing, sites, and couriers, staffing and training needs, and turnaround times from leukapheresis or biopsy to dosing. **Results:** Consistent site readiness gaps were identified in apheresis coordination, vector storage and handling, chain-of-custody documentation, and real-time cross-functional communication. Autologous programs showed increased operational complexity driven by patient-specific manufacturing, narrow scheduling windows, and variable vein-to-vein turnaround times. Allogeneic programs had reduced scheduling constraints but introduced challenges related to centralized manufacturing oversight and site-level accountability. Across platforms, CGT trials required specialized staffing and training beyond standard oncology research models. Insufficient early operational enablement resulted in delayed dosing and reduced patient access by ~1-3 months. **Conclusions:** Lessons from early-phase oncology CGT trials demonstrate that proactive operational readiness, particularly at the site level, is essential to enable scalable trial infrastructure and equitable patient access. Early readiness assessments, targeted workforce training, and integrated manufacturing-logistics coordination are critical to support efficient CGT trial execution and future expansion. Learning Objectives: Recognize common operational readiness gaps identified during FIH and Phase 1 oncology CGT trials. Understand how manufacturing, logistics, and site coordination impact early-phase trial execution. Apply early operational learnings to inform scalable CGT trial infrastructure. Key Takeaways: Operational readiness is a primary determinant of early CGT trial success. Many sites require significant enablement to conduct CGT trials effectively. Early investment in readiness improves turnaround times and patient access. Research Sponsor: None.

11068 **Poster Session**

Prevalence and trends in rural patient enrollment in SWOG cancer clinical trials, 1992-2022. First Author: Izumi Okado, University of Hawai'i Cancer Center, Honolulu, HI

Background: A recent ASCO report highlighted improving patient access to cancer clinical trials as a fundamental priority. Although prior research found that 19% of participants in NCI-sponsored trials reside in rural areas, there is substantial heterogeneity in the classification of rurality. In addition, sociodemographic characteristics across different levels of rurality are unknown. In this analysis, we evaluated the prevalence and trends over time in trial enrollment by categories of rurality. **Methods:** We analyzed pooled data from phase II, II/III, and III trials conducted by the SWOG Cancer Research Network from 1992-2022. Rurality was defined by linking patient zip code to the Rural-Urban Continuum Codes, and categorized into four groups (large urban, small urban, rural, frontier). Baseline and patient demographic data were obtained from trial registration forms. Neighborhood deprivation, based on the Area Deprivation Index, was derived from patient zip code. The associations between rurality and patient characteristics were evaluated using multivariate logistic regression with covariate adjustments. Rurality enrollment was compared to corresponding overall US rurality estimates during the same period. **Results:** In total, N = 39,729 patients enrolled in 69 trials in brain, breast, GI, GU, gynecological, head and neck, lung, sarcoma, melanoma, and hematologic cancers were examined. Across the geographic groups, 52.2% lived in large urban, 30.9% lived in small urban, 11.6% lived in rural, and 5.4% lived in frontier areas, compared to corresponding US population estimates of 56.0% large urban, 28.6% small urban, 10.3% rural, and 5.0% frontier. Patients residing in frontier areas were nearly 80 times as likely to live in the highest versus lowest deprivation areas (OR = 78.37, 95% CI, 64.71-94.92, $p < .0001$). Similar though less pronounced associations were found among patients from rural and small urban areas ($p < .0001$). Frontier patients were more likely to be on Medicare (OR = 1.96, 95% CI, 1.66-2.30, $p < .0001$). Over the 30-year study period, trial enrollment among patients from frontier areas has decreased over time relative to the US population, whereas trial enrollment of patients from large urban areas has increased. **Conclusions:** Patients from rural and frontier areas are well-represented in SWOG clinical trials, however, enrollment among patients from frontier areas has shown a declining trend. Strong representation of patients with cancer from rural areas enhances the generalizability of trial findings. Given ongoing changes to healthcare, declining representation from frontier areas is likely to continue without targeted interventions. Further research is needed to expand access to care in these vulnerable areas and guide efforts that ensure adequate socioeconomic support for all patients, regardless of their geographic locale. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; U10CA180888, U10CA180819, UG1CA189974; The Hope Foundation for Cancer Research; AHRQ; K01HS028730.

11069 **Poster Session**

Body mass index and mortality in immune checkpoint inhibitor–treated cancers: A real-world propensity-matched analysis. First Author: Katherin Zambrano, Berkshire Medical Center, Pittsfield, MA

Background: Immune checkpoint inhibitors (ICIs) are a cornerstone of treatment for multiple solid tumors, including lung cancer and melanoma. Emerging evidence suggests that body mass index (BMI) may influence outcomes with immunotherapy, though findings remain inconsistent and largely derived from clinical trial populations. We evaluated the association between BMI and mortality among patients with cancers treated with ICIs using real-world data. **Methods:** We conducted a retrospective observational study using data from TriNetX, a global real-world research platform based on de-identified electronic health records. Adult patients with lung cancer or melanoma who received immune checkpoint inhibitor therapy, including durvalumab, pembrolizumab, nivolumab, ipilimumab, or atezolizumab, were identified. Patients were stratified by documented baseline body mass index into two groups: BMI 19–24.9 (Normal) and BMI 30–49.9 (Obese). To address baseline differences, 1:1 propensity score matching (PSM) was performed using demographics and major comorbidities. The primary endpoint was all-cause mortality; secondary endpoints included inpatient hospitalization frequency. **Results:** Before matching, the cohorts consisted of 7,951 patients (BMI 30–49.9) and 4,651 patients (BMI 19–24.9). After PSM, 4,152 patients were included in each cohort. Baseline characteristics, including age (mean 67 years), sex (59% male), and comorbidities (hypertension, diabetes, CKD), were well-balanced ($p > 0.05$).All-cause mortality was significantly higher in the BMI 19–24.9 group compared to the BMI 30–49.9 group (49.2% vs 43.4%), with a risk ratio of 0.88 (95% CI,0.84–0.92; $p < 0.001$). Overall survival was significantly longer in the obese cohort, with a median survival of 1,043 days compared to 579 days in the normal BMI cohort. High BMI was associated with a 27.5% reduction in the hazard of death (HR 0.725, 95% CI 0.68–0.77; $p < 0.001$). Conversely, the high BMI cohort had a higher risk of inpatient encounters (57.6% vs 55.3%; p = 0.032) and a higher mean number of hospitalizations (5.4 vs 4.6; $p < 0.001$). **Conclusions:** In this large real-world study, higher BMI was associated with significantly lower mortality and nearly double the median survival time in patients treated with ICIs. While higher BMI was also associated with increased hospitalization frequency, the overall survival benefit remains robust. These findings support the "obesity paradox" in immunotherapy and suggest that nutritional status is a critical determinant of long-term ICI efficacy and healthcare utilization. Research Sponsor: None.

11070 **Poster Session**

Burden and site-specific spectrum of second primary malignancies after adult acute myeloid leukemia: A population-based SEER standardized incidence ratio study with latency-stratified risk profiling (2000–2022). First Author: Abat Khan, Memorial Cancer Institute, Pembroke Pines, FL

Background: As survival after acute myeloid leukemia (AML) improves, second primary malignancies (SPMs) represent an increasingly relevant survivorship outcome. We quantified overall and site-specific SPM risk following adult AML and characterized latency-dependent patterns and demographic heterogeneity. **Methods:** We performed a population-based cohort analysis using SEER 17 registries (2000–2022). Adults (≥18 years) with AML were followed for incident SPMs occurring ≥2 months after AML diagnosis. Risk was summarized using standardized incidence ratios (SIRs; observed/expected) with 95% confidence intervals (CIs), overall and by cancer site, and stratified by latency (2–11, 12–59, 60–119, ≥120 months), age, sex, and race. **Results:** Overall, 751 SPMs were observed versus 563.87 expected (SIR 1.33; 95% CI 1.24–1.43). Solid tumors overall were not significantly increased (SIR 1.03; 0.94–1.12), but select sites showed excess risk: oral cavity/pharynx (SIR 2.35; 1.64–3.27), skin excluding basal/squamous (SIR 1.42; 1.04–1.90), kidney (SIR 1.88; 1.31–2.60), and eye/orbit (SIR 4.32; 1.18–11.06), while breast cancer was reduced (SIR 0.65; 0.47–0.86). Hematologic SPMs were markedly elevated (lymphatic/hematopoietic SIR 2.48; 2.06–2.96), including leukemia overall (SIR 4.42; 3.45–5.59) and acute lymphoblastic leukemia (SIR 21.51; 11.76–36.08). All-site risk remained elevated across latency windows (SIR range 1.30–1.38), while solid-tumor risk increased after 5 years (SIR 1.27 at 60–119 months and ≥120 months). Risk was highest in ages 0–59 (SIR 1.91), and remained elevated in males (1.37) and females (1.27). **Conclusions:** Adult AML survivors experience a sustained excess risk of SPMs, driven primarily by secondary hematologic malignancies with additional site-specific solid-tumor excesses emerging in longer-term follow-up, supporting risk-adapted survivorship surveillance. Research Sponsor: None.

Site-specific risk of second primary malignancies after adult AML (SEER 17, 2000–2022).

Site	Observed	Expected	O/E	CI Lower	CI Upper
All Sites	751	563.87	1.33#	1.24	1.43
All Solid Tumors	506	491.44	1.03	0.94	1.12
All Lymphatic and Hematopoietic Diseases	123	49.66	2.48#	2.06	2.96
Lymphoma	42	24.97	1.68#	1.21	2.27
Leukemia	70	15.83	4.42#	3.45	5.59
Acute Lymphocytic Leukemia	14	0.65	21.51#	11.76	36.08
Acute Myeloid Leukemia	13	4.71	2.76#	1.47	4.72
Chronic Myeloid Leukemia	22	2.11	10.40#	6.52	15.75

11071 **Poster Session**

Concordance of tissue and plasma NGS in early-stage non–small cell lung cancer. First Author: Juhi Gor, University of Illinois College of Medicine at Chicago, Division of Hematology and Oncology, Chicago, IL

Background: Comprehensive molecular profiling is standard of care for patients with advanced non-small cell lung cancer (NSCLC), and plasma-based next generation sequencing (NGS) demonstrates high concordance with tissue testing in metastatic disease. However, the performance of liquid biopsy in early-stage NSCLC remains poorly defined. In early stage, tissue-based NGS may be limited by inadequate sample quantity, low tumor cellularity, or DNA degradation. We evaluated the concordance of tissue and plasma NGS in patients with stage I to III NSCLC to determine whether liquid biopsy can reliably complement tissue-testing in this setting. **Methods:** We conducted a retrospective analysis of patients diagnosed with stage I to III NSCLC from 2021 to 2025 at the University of Illinois Cancer Center. Clinical and demographic data were abstracted through chart review. Paired NGS results were obtained from the Tempus Hub, including tissue-based sequencing (Tempus xT) and plasma-based sequencing (Tempus xF+). Actionable genomic alterations were assessed for concordance using 2x2 contingency tables, with calculation of overall concordance and positive percentage agreement (PPA). **Results:** A total of 71 patients with early-stage NSCLC were identified. The cohort was 52% male and 48% female; 61% Black, 23% White, 14% Asian and 3% other; 9% Hispanic and 88% non-Hispanic. 52% were 65 years or older at diagnosis. Disease stage included stage I (20%), stage II (10.6%), stage III (41%), with stage unknown 29%. No NTRK2/3, ROS1, RET, and MET alterations were detected on liquid or tissue. PPA for actionable mutations was low overall: BRAF V600E 66.7%, KRAS G12C 40%, EGFR 16.7%, HER2 0%, and EML4-ALK 0%. Despite low PPA, overall concordance exceeded 80% for all genes, driven by high negative percent agreement. **Conclusions:** In early-stage NSCLC, plasma-based NGS demonstrates limited sensitivity for detecting actionable driver alterations, despite high overall concordance driven by negative agreement. Reliance on liquid biopsy alone may miss clinically meaningful oncogenic drivers, even in potentially curable disease. While plasma NGS may be useful as a complementary or rule-out tool when tissue is inadequate, tissue-based molecular profiling remains essential for accurate genomic characterization in early-stage NSCLC. Research Sponsor: None.

Concordance and PPA analysis.

	Concordance	PPA
BRAF V600E	91.2%	66.7%
EGFR	86.0%	16.7%
HER2	98.6%	0%
KRAS G12C	84.5%	40%
EML4-ALK	98.6%	0%

11072 **Poster Session**

Clinical-stage AI-enabled therapeutic assets: An industry-wide analysis of scale, clinical progression, and company characteristics. First Author: Waqas Haque, The University of Chicago, Chicago, IL

Background: Artificial intelligence (AI) is increasingly applied in therapeutic discovery and has driven substantial investment in AI-native biotechnology firms. However, the extent to which AI-enabled assets have progressed into and through clinical development remains incompletely characterized. We performed an industry-wide descriptive analysis of AI-enabled therapeutic assets that have entered interventional clinical trials. **Methods:** We identified AI-enabled therapeutic assets that entered at least one Phase 1–3 interventional clinical trial through July 1, 2025. Assets were manually curated using industry databases, public disclosures, and trial registries. AI enablement was defined at the asset level and required evidence of AI contribution to discovery or design. Drug-, trial-, and company-level characteristics were summarized using descriptive statistics. Company characteristics were obtained from PitchBook and public sources. **Results:** A total of 117 AI-enabled therapeutic assets across 63 companies entered interventional clinical trials. Oncology accounted for 69 assets (59.0%), and most assets were small molecules (96/117; 82.1%). As of December 1, 2025, 60 assets (51.3%) had completed Phase 1 and 8 (6.8%) had completed Phase 2. Among assets with reported Phase 1 enrollment (n = 103), the median sample size was 50 participants (IQR, 24–76.5). Approximately 35.9% of assets targeted a novel biological target. At the company level, the median time from founding to Phase 1 entry was 6.5 years (IQR, 4.0–9.2; n = 44). Median total funding was $186.7 million (IQR, $48.1M–$595.0M; n = 57), and median employee count at clinical entry was 73 (IQR, 32–129; n = 35). Median operational intensity was $2.72 million per employee (IQR, $1.71M–$5.83M; n = 47). **Conclusions:** AI-enabled therapeutic assets are increasingly entering clinical development, particularly in oncology, but most remain early in the clinical pipeline, with few having completed Phase 2. AI-native biotechnology companies that have reached the clinic typically do so within several years of founding with relatively small employee counts and high operational intensity. These findings provide a transparent baseline for evaluating the clinical impact of AI-enabled drug discovery as this cohort matures. Research Sponsor: None.

11073 **Poster Session**

Impact of market entry of biosimilars in the US on cancer biologics' pricing strategies, market share, and payer costs. First Author: Xiaoyu Liu, UCLA, School of Public Health, Los Angeles, CA

Background: Biosimilars have been anticipated to lower the financial burden of cancer for payors as well as patients. As of 2025, 42% (n=13 from three product lines: bevacizumab, rituximab, and trastuzumab) of physician-administered biosimilars launched in the US were indicated for cancer. These three product lines accounted for approximately $5.35 billion healthcare expenditure at clinics and nonfederal hospitals in 2024. **Methods:** Using MarketScan claims data and Average Sales Price (ASP) data from the Centers for Medicare & Medicaid Services, we calculated quarterly ASP of reference products to compare the pricing strategies of reference biologics for cancer vs. non-cancer treatment. We also compared the market share between cancer vs. non-cancer biologics and estimated the average monthly payor costs of the three cancer product lines 12 months before biosimilar entry versus 2023. We identified biologics using Healthcare Common Procedure Coding System codes and adjusted costs to 2025 USD using the prescription drugs Consumer Price Index. **Results:** Analyses included 8,252,400 claims of 8 reference products and 27 biosimilars. All three cancer biologics experienced biosimilar market entry starting late 2019. On average, the ASP of reference biologics for cancer decreased by 4.3% annually after biosimilar entry, contrasting to 17.2% decrease for non-cancer reference biologics. Meanwhile, the market share of reference biologics decreased on average 39.3%, 34.2%, and 35.4% annually for bevacizumab, rituximab, and trastuzumab, respectively, contrasting to 15.4% decrease for non-cancer reference biologics. Compared to monthly payor costs averaging over 12 months before the first biosimilar launch, monthly payor costs of biologics (including reference and biosimilars) in 2023 fell for all three cancer biologics in the commercial and Medicare market. The annual decrease rate in monthly payor costs was on average 45.1%, 52.0%, and 34.6% for bevacizumab, rituximab, and trastuzumab, respectively. **Conclusions:** After biosimilar entry, reference biologics for cancer reduced prices at a slower pace than non-cancer reference biologics, this pricing strategy led to a much faster decrease in their market share. Biosimilars for cancer, by gaining larger market share over time, has significantly reduced payor costs of cancer biologics for commercial and Medicare insurers. Research Sponsor: None.

			Commercial insurance mean monthly payor costs			Medicare Part B mean monthly payor costs		
Drug	Reference product ASP annual change	Reference product market share annual change	Before biosimilar entry	2023	Change	Before biosimilar entry	2023	Change
bevacizumab	-2.1%	-39.3%	$5,261.9	$2,823.0	-46.4%	$2,720.0	$1,526.8	-43.9%
rituximab	-4.4%	-34.2%	$7,187.4	$3,799.2	-47.1%	$3,977.7	$1,717.1	-56.8%
trastuzumab	-6.5%	-35.4%	$4,781.6	$3,302.7	-30.9%	$2,401.6	$1,485.0	-38.2%

11074 **Poster Session**

Heart failure in hospitalizations for hematologic malignancies versus solid tumors: National burden and inpatient outcomes, 2018-2022. First Author: Dylan Lee, Touro University Nevada College of Osteopathic Medicine, Las Vegas, NV

Background: Heart failure (HF) is a common and morbid comorbidity in oncology. Whether HF burden and prognosis differ between hospitalizations for hematologic malignancies and solid tumors remains incompletely characterized at a national level. This study compared HF prevalence and HF-associated outcomes across these cancer groups. **Methods:** A serial cross-sectional analysis was conducted using adult hospitalizations in the 2018 to 2022 Healthcare Cost and Utilization Project National Inpatient Sample with discharge-level survey weighting. Cancer hospitalizations were classified by principal diagnosis as hematologic malignancy or solid tumor. HF was identified using ICD-10-CM I50* in any diagnosis field. Outcomes included HF prevalence, in-hospital mortality, intensive care unit utilization, shock, length of stay, and hospitalization cost. Survey-weighted multivariable regression adjusted for demographics, comorbidities, hospital characteristics, and admission factors. Models restricted to HF admissions evaluated associations between cancer type and outcomes within the HF subgroup. **Results:** Among an estimated 4.81 million cancer hospitalizations nationally, HF prevalence was higher in hematologic malignancies than in solid tumors (13.2% vs 8.0%, $p < 0.001$). After adjustment, hematologic malignancy was associated with higher odds of HF (adjusted odds ratio (aOR) 1.53, 95% CI 1.50 to 1.57). Among HF hospitalizations, hematologic malignancies had higher mortality (11.7% vs 8.0%), intensive care unit utilization (8.5% vs 7.3%), and shock (3.8% vs 3.4%) (all $p <$ 0.001). In adjusted models restricted to HF admissions, hematologic malignancy remained associated with higher mortality (adjusted odds ratio 1.34, 95% CI 1.26 to 1.42) and intensive care unit utilization (aOR 1.15, 95% CI 1.07 to 1.23). Resource utilization was greater in hematologic malignancy HF admissions, including longer length of stay (12.1 vs 8.3 days) and higher costs ($50,518 vs $30,906; both $p < 0.001$). Interaction modeling showed no significant effect modification of HF-associated mortality by cancer type. **Conclusions:** Hospitalizations for hematologic malignancies have higher HF prevalence than solid tumor hospitalizations and demonstrate higher mortality, intensive care utilization, shock, length of stay, and costs among admissions with HF. These findings identify hematologic malignancy hospitalizations as a high-risk context for HF-associated inpatient deterioration and resource use. Research Sponsor: None.

11075 **Poster Session**

Closing the information gap in oncology: A retrieval-augmented generation multi-modal AI platform for personalized patient education and physician efficiency. First Author: Weiqi Liang, Department of General Surgery & Guangdong Provincial Key Laboratory of Precision Medicine for Gastrointestinal Tumor, Nanfang Hospital, Southern Medical University, Guangzhou, China

Background: Effective patient education is critical in oncology but hindered by the complexity of treatment guidelines and the time constraints of clinicians. Traditional static materials often fail to address the personalized needs of diverse demographics, particularly the elderly. We developed an Intelligent Medical Science Popularization Platform integrating Multimodal Large Language Models (MLLM) with Retrieval-Augmented Generation (RAG) to automate the production of reliable, guideline-based oncology educational content. **Methods:** The platform utilizes a three-tier architecture deployed at a tertiary cancer center. The core engine combines a self-developed MLLM with RAG, anchoring content generation to authoritative sources (e.g., CSCO/NCCN guidelines and peer-reviewed journals) to ensure clinical accuracy. The system features: (1) Physician Portal: Automates the conversion of clinical protocols into patient-friendly text, layouts, and animations; (2) Multimodal Synthesis: Generates virtual avatar videos explaining diagnoses and treatments; (3) Patient Interface: Delivers personalized, accessible content via mobile apps, supporting voice interaction for elderly adherence. **Results:** Implementation data demonstrated significant efficiency and engagement gains. The MLLM+RAG model achieved $>$ 98% accuracy in content generation as verified by expert oncologists. The production time for educational videos was reduced from 72 hours to ~10 minutes ($>$ 99% reduction), enabling rapid updates aligned with new trial data. Animation production costs decreased by 10-fold. Daily content output exceeded 15 units. Notably, in a cohort of elderly cancer patients, the platform increased user retention rates by 40% and extended average session duration by 50 seconds, indicating improved engagement with health information. **Conclusions:** This policy-compliant AI platform validates the utility of RAG-based MLLMs in oncology. By shifting from passive information supply to active, personalized intelligent services, it significantly reduces the workload for oncologists while bridging the digital divide for vulnerable patient populations. This model offers a scalable solution for enhancing health literacy and treatment adherence in cancer care. Research Sponsor: None.

11076 **Poster Session**

The 2026 primary care oncology toolkit: An evolving shared-care framework for the implementation of prospective survivorship evidence. First Author: Manila Sharma, New York Medical College - Saint Michael's Medical Center, Newark, NJ

Background: As cancer survivorship transitions into a chronic disease model, a significant "implementation gap" exists between landmark 2025 clinical data and frontline primary care. Survivors face a 2.39-fold higher risk of cardiovascular mortality, yet standardized protocols for PCP-led surveillance remain in development. This review identifies an evolving "Shared-Care Framework" designed to integrate prospective 2025 evidence into the internal medicine setting, anticipating a shift toward decentralized, longitudinal survivorship care. **Methods:** A narrative synthesis was performed to develop a pilot-ready framework for primary care. We analyzed practice-changing evidence published between January 2025 and January 2026, including the Barac Risk Model, the Bhalraam et al. SGLT2i meta-analysis , and emerging cervical screening strategies. Findings were synthesized into thematic surveillance blocks to identify opportunities for prospective guideline-concordant implementation. **Results:** Synthesis of recent landmark data identified several opportunities for prospective adoption in the internal medicine setting. The framework evaluates evolving cardio-metabolic surveillance strategies, including the integration of the Barac Model (2025) for 10-year heart failure (HF) risk prediction and the proactive use of SGLT2 inhibitors, which have demonstrated a 51% reduction in HF hospitalizations among survivors. Furthermore, the review identifies prospective clinical blocks for PCP-led surveillance of stable survivors, emphasizing proactive bone health monitoring for patients on aromatase inhibitors and metabolic screening for those on androgen deprivation therapy (ADT). This includes the potential adoption of low-dose oxybutynin as a new standard for managing ADT-induced hot flashes. Finally, the framework addresses health equity paradigms by evaluating the transition to in-office HPV self-sampling and automated EMR alerts for age 45 colorectal screening to mitigate the rising incidence of early-onset disease. **Conclusions:** This evolving shared-care framework offers a scalable model for the future of survivorship. By aligning primary care protocols with prospective 2025 landmark data, clinicians can optimize long-term coordination and address health disparities ahead of formal guideline updates. Research Sponsor: None.

11077 **Poster Session**

Inpatient burden and outcomes across gastrointestinal cancer subtypes among younger adults in the United States, 2018–2022. First Author: Emaan Tiwana, MountainView Hospital, Las Vegas, NV

Background: Early-onset gastrointestinal (GI) cancers are increasingly recognized, yet national data describing inpatient burden and outcomes across GI cancer subtypes in younger adults remain limited. **Methods:** A serial cross-sectional analysis was performed using the 2018–2022 Healthcare Cost and Utilization Project National Inpatient Sample. Adult hospitalizations among younger adults (age 18–49 years) with a principal diagnosis of GI malignancy were identified and categorized by cancer subtype. Outcomes included in-hospital mortality (primary), length of stay (LOS), and hospitalization cost estimated using cost-to-charge ratios. National estimates accounted for survey weighting, clustering, and stratification. Survey-weighted multivariable logistic regression evaluated associations between cancer subtype and in-hospital mortality, adjusting for age, sex, race/ethnicity, payer, neighborhood income quartile, elective admission, APR-DRG severity, hospital teaching status, geographic region, and calendar year. Sensitivity analyses were performed restricting the cohort to age $<$ 45 years. **Results:** Across 2018–2022, principal GI cancer hospitalizations among younger adults were dominated by colorectal cancer, followed by stomach, pancreatic, liver or intrahepatic biliary, and esophageal cancers. In-hospital mortality varied by cancer subtype and year, with higher crude mortality observed for pancreatic, stomach, esophageal, and liver or intrahepatic biliary cancers compared with colorectal cancer. Resource utilization increased markedly during 2020 across subtypes, with corresponding increases in LOS and hospitalization costs. In adjusted analyses using colorectal cancer as the reference, odds of in-hospital mortality were higher for stomach (adjusted odds ratio [aOR] 3.01, 95% CI 1.78–5.10), esophageal (aOR 2.12, 95% CI 1.03–4.37), and liver or intrahepatic biliary cancers (aOR 2.56, 95% CI 1.36–4.79). Pancreatic cancer demonstrated a borderline increase in mortality (aOR 1.79, 95% CI 0.96–3.36). Higher APR-DRG severity was strongly associated with mortality (aOR 5.20, 95% CI 3.50–7.72). Sensitivity analyses demonstrated similar subtype ordering and mortality patterns. **Conclusions:** Among younger adults hospitalized with GI malignancies, inpatient mortality and resource utilization varied substantially by cancer subtype. Colorectal cancer accounted for the largest share of hospitalizations, while stomach, esophageal, and liver or intrahepatic biliary cancers were associated with higher adjusted inpatient mortality. These nationally representative findings provide benchmarking data on inpatient outcomes across early-onset GI cancer subtypes. Research Sponsor: None.

11078 **Poster Session**

Enhanced financial assistance intervention for unmet essential needs: A prospective pilot study to improve timely cancer treatment completion. First Author: Justin Michael Barnes, Department of Radiation Oncology, Mayo Clinic Arizona, Phoenix, AZ

Background: Unmet essential needs, such as food, transportation, and housing insecurity, can create barriers to timely cancer treatment. Delayed or prolonged courses of definitive radiotherapy (RT) can compromise cancer outcomes like recurrence and survival. There are limited prospective data testing interventions to improve timely cancer treatment completion by meeting essential needs. **Methods:** We conducted a pragmatic single-arm pilot study testing an enhanced financial assistance intervention for unmet needs during RT. Eligibility criteria included adults with a cancer diagnosis and unmet social needs (via social risk screening and/or social worker evaluation) who were prescribed or undergoing a course of RT with $>$ 10 fractions remaining. Participants received standard institutional assistance (e.g., limited support for travel/lodging with strict eligibility criteria) plus the enhanced assistance intervention, including needs assessments prior to and during RT and up to $2000/patient of tailored unconditional monetary transfer via gift cards for all essential needs identified. The primary outcome was delay-free completion of RT (DFC: completing all prescribed RT fractions and delaying $<$ 5 fractions). The study was powered (power = 80%, 1-sided alpha = 0.2 for this pilot study) to detect a 10-percentage point increase in % DFC relative to a historic benchmark of 83% (based on similar patients from our institution), with required sample size of N = 33. Due to delays in gift card administration (on average ~2 weeks after consent), we also present per protocol analysis, limited to patients who had $>$ 10 fractions remaining after first receiving financial assistance. Post-hoc analyses using generalized linear mixed models evaluated percentages of delayed fractions prior to and after an individual's receipt of financial assistance. **Results:** 35 met inclusion criteria and were approached, 33/35 enrolled. Participants received median assistance of $1800 ($700-2000) and had a median of 27 RT fractions after consent (range: 12-35) and 17 (3-34) after receiving assistance. In the overall cohort, 1 patient did not complete RT and 2 patients had $\geq$5 delayed fractions, leading to 30/33 achieving DFC (90.9%, 80% CI = 83.9 – 100), significantly higher than the 83% benchmark. In the per protocol analysis, 27/28 achieved DFC (96.4%, 80% CI = 89.7–100, P = .037). Among the 27 patients who started RT prior to receiving assistance, mixed model analysis showed more delayed fractions prior to (7.1%) vs. after (3.0%) receiving assistance (OR 2.84, 95% CI = 1.43-5.80, P = .003). **Conclusions:** In this prospective pilot study, a tailored enhanced financial assistance intervention for unmet essential needs led to improved delay-free completion of RT over a historic benchmark. Further analysis on patient-reported quality of life and financial toxicity will be reported in the future. Clinical trial information: NCT06582849. Research Sponsor: Conquer Cancer, the ASCO Foundation; WashU, Siteman Cancer Center.

11079 **Poster Session**

Has racial and ethnic representation in oncology clinical trials changed?: A 30-year systematic analysis using artificial intelligence. First Author: Rahman Adesoji Olusoji, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH

Background: Despite societal emphasis on racial and ethnic representation in oncology trials, it remains unclear whether participant diversity has meaningfully changed over time. Recent advances in large language models (LLMs) enable scalable extraction of data from PDF documents, facilitating high-throughput research. **Methods:** We identified all oncology clinical trials published in The Lancet and The New England Journal of Medicine (NEJM) between 1995 and 2025, and retrieved full-text PDFs from the journals' websites. Using an LLM (Gemini-2.5-Flash), structured variables, including trial phase, cancer type, enrollment countries, and participant race and/or ethnicity, were automatically extracted from texts, tables, and figures. Trials were stratified by decade (1995–2005, 2006–2015, and 2016–2025) to evaluate temporal trends. **Results:** We identified 1,385 oncology trials between 1995 and 2025, including 334, 448, and 603 for the three decades, respectively. The proportion of phase III trials increased steadily over time (68%, 72%, and 76%). Trials also became more globally distributed, with multi-continental studies rising from 27% to 46% and 58%. Most notably, Asian countries were increasingly involved among trial enrollment sites, rising from 14% to 25% and 45%. Reporting of race/ethnicity increased over time, from 16% to 29% and 47% of publications across decades. Among studies that reported race, non-White enrollment increased, with the median percentage per study rising from 10% in both earlier decades to 21% in 2016–2025. However, after excluding Asian participants, the median non-White percentage declined across decades (7.5%, 5.3%, and 4.3%). In pooled analyses across all trials, non-White patients comprised 15%, 11%, and 15% of total enrollment, respectively; excluding Asian patients, this decreased from 13.2% to 6.2% and 6.9%. Black enrollment declined over time, with the median percentage falling from 6.8% to 2.4% and 1.5%. Among trials reporting ethnicity, Hispanic enrollment remained consistently low (5.4%, 4.0%, and 4.6%). **Conclusions:** Globalization and race/ethnicity reporting in oncology trials improved, but the observed increases in diversity were largely attributable to the expansion of trial enrollment in Asia. In contrast, Black and Hispanic representation remained low or declined across decades. Research Sponsor: None.

	1995-2005, n (%)	2006-2015, n (%)	2016-2025, n (%)
Total Studies	334	448	603
Clinical Trial Phase			
Phase 1	78 (23)	86 (19)	55 (9)
Phase 2	25 (7)	38 (8)	87 (14)
Phase 3	228 (68)	323 (72)	460 (76)
Major Cancer Types			
Breast	55 (17)	64 (14)	78 (13)
Hematologic	54 (16)	77 (17)	114 (19)
Colorectal	49 (15)	40 (9)	29 (5)
Lung	17 (5)	37 (8)	66 (11)
Continents			
Africa	16 (5)	29 (6)	16 (3)
Asia	47 (14)	113 (25)	274 (45)
Europe	158 (47)	272 (61)	403 (67)
North America	102 (31)	219 (49)	361 (60)
South America	0 (0)	5 (1)	19 (3)
Oceania	43 (13)	134 (30)	203 (34)

11080 **Poster Session**

The Bermuda model: Achieving world-class, equitable, and efficient cancer care in a small island nation. First Author: Ross Jarrett, Bermuda Cancer and Health Centre, Bermuda, Bermuda

Background: Bermuda is a small island nation that historically faced significant challenges in provision of local cancer care. Between 2000-2017, 100% of patients requiring radiation therapy (RT) had to travel abroad, causing prohibitive financial toxicity. In 2017, Bermuda Cancer and Health Centre (BCHC) evolved to deliver an integrated and comprehensive national cancer solution, including RT. The "Bermuda Model" represents a national approach to address critical gaps in cancer care by leveraging innovative partnership models to enable access, efficiency, health equity and international quality standards. **Methods:** We conducted a retrospective descriptive cohort study. Data for cancer incidence/outcomes were collected from the Bermuda National Tumour Registry; treatment/quality data and patient satisfaction surveys were collected from BCHC clinical records. Timeframes for travel reduction data were between 2015-2020. Outcomes measures included percentage of overseas referrals for RT and chemotherapy, international quality assurance, patient satisfaction scores from 2025, access measures such as interval from diagnosis to treatment, cancer-specific overseas insurance claims, and selected clinical outcomes, including early breast cancer detection and survival rates. **Results:** The Bermuda Model has eliminated the need for overseas RT, ensuring access for the 70-90% who previously went abroad and the remainder who went without. Through an international strategic partnership with Brigham and Women's Hospital, high quality and consistent peer-review of radiation treatment plans by Harvard faculty specialists was ensured for 100% of all patients receiving RT at BCHC. Patient satisfaction rates for RT were 100% positive for multiple months in 2025. Between 2017-2019, Bermuda achieved excellent clinical outcomes including an 87% early detection rate for localized (Stage 1-2) breast cancer and a lower breast cancer mortality rate than either the USA or Europe. Care timelines were efficient; average time from diagnosis to first treatment was as low as 16 days in 2025. The model was associated with an approximately 24% reduction in cancer-specific overseas insurance claims between 2017-2020 ($6.2 million and $4.7 million respectively). **Conclusions:** The "Bermuda Model" demonstrates that with strategic investment and international partnerships, a small island nation can locally establish world-class, equitable, and efficient cancer care services. Eliminating overseas treatment, high satisfaction, and excellent outcomes evidence its success. The reduction in claims has been particularly impactful for Bermudian residents with government-level insurance, helping to advance, access-to-all cancer care. This model serves as a valuable blueprint for other small nations or isolated regions seeking to improve their delivery of cancer care. Research Sponsor: None.

11081 **Poster Session**

Integrating AI-derived lung cancer risk and social determinants of health to improve risk stratification in a safety net lung cancer screening program. First Author: Evan Garrad, University of Illinois Chicago, Chicago, IL

Background: Lung cancer screening (LCS) outcomes remain inequitable, with social and environmental determinants of health (SDOH) influencing lung cancer risk, screening adherence, and cancer detection. Sybil is a validated deep learning model that predicts future lung cancer risk from a single low-dose CT (LDCT) scan using imaging features alone, without demographic or clinical inputs created by MIT/MGH. Its relationship to SDOH in real-world, safety-net screening populations has not been well characterized. **Methods:** We analyzed 2,645 individuals enrolled in the UI Health LCS program with baseline LDCT imaging and available Sybil risk scores. Scores were generated using the publicly available model applied exclusively to volumetric LDCT images, without retraining or incorporation of demographic, clinical, or SDOH variables. Individual-level clinical data were linked to census- and community-level SDOH measures. Sybil scores were $\log_{10}$-transformed and analyzed as continuous and categorical variables. Associations between Sybil risk, SDOH, and lung cancer diagnosis were assessed using multivariable logistic regression. **Results:** Mean baseline Sybil score was 0.014 (median 0.002). Ninety-six individuals (3.6%) were diagnosed with lung cancer. Sybil scores were significantly higher among individuals later diagnosed with cancer (mean log score -1.52 vs -2.48; $p<0.001$). In multivariable models, Sybil risk was the strongest independent predictor of lung cancer diagnosis (OR 6.12 per log-unit increase, 95% CI 4.31–8.83; $p<0.001$), independent of BMI and SDOH. High Sybil risk remained strongly associated with cancer diagnosis across multiple thresholds (all $p<0.001$). Census-level area deprivation and community-level measures of food insecurity, vehicle access, and neighborhood conditions were also independently associated with cancer diagnosis (Table 1). **Conclusions:** In a large safety-net LCS cohort, AI-derived Sybil risk robustly predicted lung cancer diagnosis and remained informative despite relying solely on imaging data. Integrating AI-based risk prediction with SDOH context may support more equitable, precision-guided lung cancer screening strategies. Research Sponsor: None.

Association of Sybil AI-risk scores and social determinants of health with lung cancer diagnosis in the UI Health lung cancer screening cohort.

Predictor	Comparison / Scale	Adjusted OR (95% CI)	P value
Sybil score	Log10 continuous	6.12 (4.31–8.83)	<0.001
Sybil score	High vs Low (median cutoff)	4.18 (2.38–7.79)	<0.001
Sybil score	High vs Low (75th percentile)	5.10 (3.08–8.57)	<0.001
Sybil score	High vs Low (tertiles)	8.02 (3.90–18.72)	<0.001
BMI	Per unit increase	0.93 (0.89–0.96)	<0.001
Area Deprivation Index	Census-level	1.02 (1.00–1.04)	0.02
Food insecurity	Community-level (%)	1.08 (1.02–1.15)	0.01
No vehicle access	Community-level (%)	1.05 (1.02–1.09)	0.003

11082 **Poster Session**

Closing the distance and the Specialist Nursing Optimal Placement Tool (SN-OPT): Strategic placement of specialist cancer nurses to achieve resource and geographic equity in Australia. First Author: Rebecca Johnson, Melanoma Institute Australia, The University of Sydney, Sydney, Australia

Background: Cancer workforce planning that enables effective specialist nurse placement is critical for delivering high-quality, patient-centered care. Inequitable access to specialist nursing represents a significant gap in cancer care delivery. No standardized tools assess specialist cancer nursing resource needs across national healthcare systems. We developed SN-OPT, an innovative resource allocation tool, using 30 new centrally funded specialist melanoma nurse positions for Australia as a case study. **Methods:** A multidisciplinary panel developed SN-OPT via expert consensus, incorporating three data domains: Clinical Infrastructure Assessment: Analysis of facility capabilities including multidisciplinary team (MDT) structures, clinical trial programs, and existing nursing and support services Demand Assessment: Quantitative analysis of case load, treatment complexity, and nursing workload benchmarks Health Equity: Population-level analysis incorporating geographic accessibility and socioeconomic disadvantage SN-OPT combines cancer incidence data with facility metrics to allocate nursing resources operating within a MDT framework. Equity assessment utilized Australian Statistical Geography Standard, Index of Relative Socio-Economic Disadvantage and Travel Time to Hospitals in Australia dataset. **Results:** SN-OPT evaluated 46 Australian facilities for melanoma nursing allocation. The weighted scoring algorithm ranked 33 sites for nurse allocation, with a mean allocation of 0.87 full time equivalent (FTE) positions per metro facility and 0.64 FTE per regional facility. The tool achieved equitable geographic distribution of specialist nursing expertise: regional facilities, treating 25% of patients, received 36% of nursing FTE (167 patients/FTE/year). Metro facilities, managing 75% of patients, received 64% of FTE (212 patients/FTE/year). Allocations largely aligned with facility-determined resource need, with 58% receiving their requested FTE. Among the remaining facilities, median allocation variance was -0.4 FTE (range -0.1 -1.0). On a population level, 89% of Australians would have geographic access to specialist melanoma nursing care within 2-hours of travel, including 81% of the most socioeconomically disadvantaged regions. **Conclusions:** SN-OPT offers a reproducible framework for data-driven allocation of specialist cancer nurses. While implemented using melanoma nurses as a case study, SN-OPT's framework has the potential to be adapted across cancer streams and countries, providing a scalable approach to equitable cancer workforce planning. Early implementation balances clinical service delivery and demand requirements within a MDT framework, while allowing adequate geographical access including socioeconomically disadvantaged regions. Research Sponsor: None.

11083 **Poster Session**

Equity in breast cancer research authorship: Country, gender, and income representation in phase III trials presented at the ASCO Annual Meeting (2015–2025). First Author: Sydney Johnson, Queen's University, School of Medicine, Kingston, ON, Canada

Background: Equitable representation in global oncology research is essential for scientific validity, generalizability, and ethical trial conduct. However, leadership in clinical research remains concentrated in high-income countries (HICs), with persistent gender inequities. We evaluated longitudinal trends in geographic, economic, and gender representation among authors of Phase III breast cancer trials presented at the ASCO Annual Meeting. **Methods:** We conducted a retrospective analysis of abstracts accepted to the ASCO Annual Meeting from 2015–2025 within breast cancer tracks, including metastatic and local/regional/adjuvant categories. Abstracts were identified using keyword searches for "phase" and included if they reported Phase III clinical trial data. For each eligible abstract, data were extracted for first and senior (last) authors, including institutional affiliation, country, World Bank region, and World Bank income classification. Author gender was assigned using a hierarchical approach incorporating culturally associated names, publicly available professional profiles, and genderize.io. Differences in authorship distribution by country were assessed using a univariate generalized linear model with country as a fixed effect. **Results:** Of 1,199 screened abstracts, 420 met inclusion criteria. Authorship was dominated by North America (44%) and Europe/Central Asia (40%), with representation from Latin America/Caribbean and Middle East/North Africa/Afghanistan/Pakistan each $<$ 1%. The United States accounted for 40.7% of all authorship. East Asia representation increased from 2.8% (2015) to 19.1% (2025), driven by China, South Korea, and Japan. Country effect on authorship share was significant ($F = 3.381$, $p = 0.001$), while year was not ($F = 0.000$, $p = 1.000$), indicating persistent structural hierarchies. Overall, 93% of authors were affiliated with HICs, ~7% with upper-middle–income countries, and $<$ 1% with lower-middle–income countries; no senior authors were from lower-middle–income countries. Gender distribution was 61.7% male and 37.7% female. Only Germany demonstrated female predominance in senior authorship among top contributing countries, while Japan exhibited 100% male senior authorship. **Conclusions:** Phase III breast cancer research presented at ASCO remains structurally concentrated in high-income countries with persistent geographic, economic, and gender inequities. Low- and middle-income countries remain largely excluded from academic leadership, and senior authorship remains male-dominated. These findings demonstrate enduring structural imbalances in global oncology research production and leadership, underscoring the need for equity-focused funding models, inclusive trial governance, and capacity-building research partnerships. Research Sponsor: None.

11084 **Poster Session**

Evaluating value in the age of accelerated approval: A pembrolizumab case study. First Author: Jeffrey Mathew Boby, Govt. Medical College Kozhikode Kerala, Kozhikode, India

Background: The FDA accelerated approval (AA) program was established to expedite approval of promising drugs that meet unfulfilled clinical needs. AA is granted on the basis of surrogate endpoints, decreases time to market, and increases access to therapies. Pursuing multiple AA and label expansions can also be a significant component of a drug's lifecycle strategy. Among 322 anticancer drug approvals (2009-2020), 59% were label expansions, with only 16% granted to new drugs with a novel mechanism of action. Our goal was to understand changes in value across multiple label-expanding AAs for high-cost anticancer medications. We studied pembrolizumab, a highly successful immune checkpoint inhibitor, evaluating value from its initial approval through multiple label expansions. **Methods:** We calculated value scores for different indications of pembrolizumab using the ASCO Value Framework Net Health Benefit Worksheet (2020) and ESMO-MCBS v2.0. The value calculations require mature survival outcomes, so we could not calculate scores for AA indications awaiting data maturity (2) or those eventually withdrawn from the market (2). We utilized the FDA drug database and primary literature to gather safety and efficacy outcomes for each indication. Analysis generated descriptive statistics about how the value of pembrolizumab evolved from 2014 to 2025. **Results:** We calculated value scores for 28 pembrolizumab indications, 12 with AA. Value scores varied widely across indications, with ASCO Net Health Benefit Score (NHBS) ranging from 17 (biliary tract cancer) to 59 (MSI/dMMR colorectal cancer) and ESMO MCBS scores ranging from 1 to 5. NHBS was not perfectly collinear with OS gains. The rolling average of NHBS across all indications over time remained fairly stable with a mean score of 37.67 (range: 30- 41). We also compared the NHBS for each AA indication to the cumulative NHBS average at the time each AA was granted. The NHBS for HCC, HNSCC, and cervical cancer were lower than respective pre-AA NHBS averages. The other 9 AAs yielded a final NHBS higher than each's pre-AA average NHBS. **Conclusions:** The NHBS formula generated varying values for different pembrolizumab indications, distinct from simple measures such as OS-rank order. Although the average NHBS remained fairly constant over time, it was lower than the maximum NHBS (59) and less than the NHBS of other breakthrough approvals (osimertinib for NSCLC: 110, nivolumab for melanoma: 53). If the average value of multiple indications in a drug's indication portfolio is significantly lower than a few blockbuster successes, clinicians could be vulnerable to an availability heuristic and overestimate the value of new AAs, based on anecdotal understanding of prior successes. In an environment of fast-paced AAs and label expansions, clinicians, patients, and payers should develop and deploy rapid value assessment tools in order to sustainably maintain access to high-yield cancer therapies. Research Sponsor: None.

11085 **Poster Session**

Dysphagia-associated inpatient risk phenotypes and mortality in hospitalized head and neck cancer: A national analysis. First Author: Manraj Dhillon, Department of Internal Medicine, Sunrise Health GME Consortium, Las Vegas, NV

Background: Dysphagia is common in patients with head and neck cancer (HNC) but is often viewed as a quality-of-life issue rather than a driver of acute inpatient outcomes. Its contribution to airway failure, mortality, and resource utilization is poorly defined, particularly when dysphagia is uncoded. We evaluated whether dysphagia-associated clinical signals define inpatient risk phenotypes, including a high-risk subgroup with silent dysphagia. **Methods:** We conducted a survey-weighted analysis of the National Inpatient Sample (NIS), 2016 to 2023, including adults hospitalized with HNC identified using ICD-10-CM codes C00 to C14 and C30 to C32. Tumors were categorized by first-hit anatomic site, and palliative admissions (Z51.5) were excluded. Dysphagia-associated signals included dysphagia (R13*), aspiration pneumonia (J69*), and feeding tube placement (ICD-10-PCS 0DH6*), which were combined into mutually exclusive dysphagia phenotypes. Silent dysphagia was defined as aspiration pneumonia or feeding tube placement without dysphagia coding. The primary outcome was in-hospital mortality. Secondary outcomes included mechanical ventilation, tracheostomy, shock, length of stay (LOS), and hospitalization cost. Survey-weighted regression models adjusted for demographics, payer, socioeconomic status, admission characteristics, hospital factors, tumor site, comorbidity burden, and year. **Results:** Among 112,495 unweighted HNC hospitalizations (weighted national estimate approximately 562,000), 26.6% had coded dysphagia, 8.7% aspiration pneumonia, and 16.3% underwent feeding tube placement; 11.4% met criteria for silent dysphagia. Mortality increased stepwise across phenotypes, from 1.82% (95% CI 1.72 to 1.93) in patients without dysphagia-associated signals to 8.59% (95% CI 7.80 to 9.47) with aspiration alone. Aspiration plus feeding tube placement was associated with the longest LOS (20.2 days, 95% CI 18.9 to 21.6) and highest mean cost ($77,615, 95% CI $70,531 to $84,700). In adjusted analyses, aspiration alone was associated with higher mortality (OR 3.77, 95% CI 3.26 to 4.36), as was aspiration with feeding tube placement (OR 2.40, 95% CI 1.70 to 3.40). Dysphagia coding alone was not associated with increased mortality (OR 0.71, 95% CI 0.60 to 0.83). Silent dysphagia was independently associated with mortality (OR 2.31, 95% CI 2.04 to 2.61), mechanical ventilation (OR 3.77, 95% CI 3.51 to 4.03), and tracheostomy (OR 4.69, 95% CI 4.40 to 4.99). **Conclusions:** Dysphagia-associated clinical signals define inpatient risk phenotypes in hospitalized patients with HNC. While dysphagia coding alone does not confer excess mortality risk, aspiration pneumonia and feeding tube placement when dysphagia is uncoded identify a high-risk population with increased mortality, airway failure, LOS, and cost, supporting earlier inpatient recognition and intervention. Research Sponsor: None.

11086 **Poster Session**

PRIME-ROSE: A blueprint for implementing precision cancer medicine in Europe. First Author: Gro Live Fagereng, Oslo University Hospital, Oslo, Norway

Background: Precision Cancer Medicine (PCM) is limited by increasingly small patient subgroups defined by tumor type and biomarker, producing rare cohorts even within common cancers. This is demonstrated by several European national PCM platform trials like DRUP (NL), IMPRESS-Norway (NO) and ProTarget (DK). From our experiences, we identify four essential requirements for successful, scalable PCM implementation: i) integration of platform trials with national healthcare systems via molecular tumor boards for efficient screening by comprehensive molecular profiling and accrual; ii) cross-national data merging; iii) scalable networks to onboard new countries; and iv) clear decision pathways linked to outcome data for reimbursement. **Methods:** PRIME-ROSE links national PCM implementation platforms through a robust data sharing framework that retains national/regional data governance while enabling harmonised statistical analyses and standardised endpoints for decision-makers. Predictable implementation pathways provide multiple, pre-defined decision points for industry, health technology assessment (HTA) bodies and payers, and integrate risk-sharing and responder-only reimbursement options with existing data collection. A scalable, transparent network facilitates rapid expansion to additional European partners. **Results:** We have developed and tested an operational data-sharing framework, with defined protocols for minimal datasets and harmonised merging procedures. Patient-level data from multiple national cohorts (1100 patients in 400 cohorts) have been aggregated, and analyses of five filled cohorts are in progress. PRIME-ROSE uses a staged implementation model to detect initial efficacy signals (industry-financed drugs) to confirm and expand on prior evidence, facilitating predictable scale-up. Risk-sharing is operationalised via responder-only reimbursement after 16 weeks of treatment and a defined transition from trial to commercial supply. In 2025, PRIME-ROSE expanded partnerships, secured the first and second multi-trial industry access contracts, and expanded payer commitment to make reimbursement decisions after Stage III. **Conclusions:** PRIME-ROSE translates lessons from platform trials into a practical, scalable blueprint that preserves national governance, accelerates evidence generation and reduces payer uncertainty – thereby lowering barriers to equitable, continent-wide PCM adoption. Aligned with initiatives such as Basket of Baskets and ROME, PRIME-ROSE is positioned for further scale-up through member state collaboration under the Joint Action on Personalised Cancer Medicine. Research Sponsor: Funded by the European Union; Grant no. 101104269.

11087 **Poster Session**

Weekend admission and early in-hospital mortality among patients with hematologic malignancies admitted for febrile neutropenia. First Author: Tarfa Verinumbe, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: Weekend admissions have been associated with worse health outcomes compared with weekday admissions, a phenomenon known as the 'weekend effect'. While predictors of in-hospital outcomes among patients with febrile neutropenia (FN) and hematologic malignancies are well described, the impact of the 'weekend effect' in this population remains unclear. Our study assessed the association between weekend admission, 3- and 7-day mortality. We further evaluated whether septic shock mediates the relationship between weekend admission and inpatient mortality, regardless of length of inpatient stay. **Methods:** We conducted a retrospective analysis of the National Inpatient Sample (2016 to 2020). Using ICD-10 codes, we identified patients with hematologic malignancies admitted for FN (D70.X, R50.81 and R50.9). Weekend admission was the primary exposure, while 3- and 7-day in-hospital mortality were the outcomes assessed. Generalized linear models were used to assess the association between weekend admission and each outcome, adjusting for sociodemographic characteristics, Charlson Comorbidity Index, mechanical ventilation, acute renal failure, protein energy malnutrition, cancer type, and length of stay. We performed a mediation analysis to assess whether septic shock mediated the association between weekend admission and overall mortality, estimating natural direct, indirect, and marginal total effects. **Results:** Among 45,540 patients in this study, 57% were male, 65% were white (mean age was 51 years). Patients had lymphoma (27%), leukemia (54%), multiple myeloma (10%), and multiple/other hematologic malignancies (9%). Weekend admission was associated with a higher risk of 3-day (adjusted risk ratio [adj RR] 1.48; 95% CI: 1.21–1.83) and 7-day mortality (adj RR 1.32; 95% CI: 1.12–1.56). When outcomes were assessed across the entire inpatient stay, weekend admission was associated with higher risk of septic shock (adj RR 1.14; 95% CI, 1.05–1.25). Further mediation analysis demonstrated that septic shock significantly mediated the association between weekend admission and overall inpatient mortality – indirect effect (adj RR 1.03; 95% CI 1.01–1.04), whereas the direct effect (adj RR 1.06; 95% CI 0.94–1.20) and overall effect (adj RR 1.09; 95% CI: 0.96–1.23) of weekend admission on mortality were not statistically significant. **Conclusions:** Weekend admission was associated with a higher risk of 3- and 7-day mortality. Septic shock partially mediated the relationship between weekend admission and mortality when assessed across the entire inpatient stay. The absence of a direct weekend effect suggests that health system-level factors contributing to septic shock such as delays in recognition, escalation, or time to antibiotics, may represent key intervention targets to improve mortality outcomes in this high-risk population. Research Sponsor: None.

11088 **Poster Session**

Reporting of sex-related data in landmark phase III solid tumor trials presented at ASCO 2025. First Author: Marine Rushanyan, D'Clinic, Yerevan, Armenia

Background: Sex-related differences may influence cancer biology, treatment efficacy, and toxicity. Although consideration of sex as a biologically relevant variable is increasingly encouraged in oncology research, the extent to which sex-specific information is visible at the time of initial presentation of practice-changing clinical trial results remains unclear. **Methods:** We conducted a cross-sectional review of phase III solid tumor trial abstracts enrolling mixed-sex populations presented at the ASCO Annual Meeting 2025. Plenary, oral, and rapid oral abstracts representing practice-changing studies across tumor types and treatment modalities were included. Abstracts were systematically assessed for reporting of sex distribution and for sex-stratified efficacy or toxicity outcomes. **Results:** Ten landmark phase III trials across gastrointestinal, lung, genitourinary, head and neck, and melanoma cancers were included. Female representation was reported in 1 of 10 abstracts (10%). None of the abstracts reported sex-stratified efficacy analyses, and none reported sex-stratified toxicity outcomes. The absence of sex-specific reporting was consistent across tumor types, therapeutic classes, and session formats, including plenary presentations. **Conclusions:** Among landmark phase III solid tumor trials presented at ASCO 2025, sex-specific reporting was largely absent at the abstract level, including in practice-changing studies. Limited visibility of sex-specific data at abstract presentation may constrain clinical interpretation and highlights an opportunity to improve reporting practices in oncology trials. Research Sponsor: None.

11089 **Poster Session**

Center-level delivery patterns and capacity during rapid CAR-T expansion in the United States (2021-2023). First Author: Pranav Singh, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL

Background: Chimeric antigen receptor T-cell (CAR-T) therapy has rapidly expanded in the United States, accompanied by substantial growth in utilization and expenditures. However, whether this expansion has been matched by proportional growth in delivery capacity and how CAR-T workload is distributed across centers remains unclear. **Methods:** We conducted a national retrospective analysis using publicly available Medicare administrative data from 2021-2023 obtained from the Medicare Inpatient Hospitals dataset on data.cms.gov. CAR-T hospitalizations were identified using the diagnosis-related group (DRG) descriptions for CAR-T therapy and other immunotherapies. Active CAR-T centers were defined annually based on inpatient discharges. This DRG-based approach may include non-CAR-T immunotherapies, and Medicare data captures primarily older adults, potentially missing younger patients with acute lymphoblastic leukemia and lymphoma. Center-level CAR-T volume and expenditures were aggregated annually. Per-center delivery burden was assessed by strain (total CAR-T discharges divided by number of active centers). Concentration of CAR-T delivery across centers was evaluated using cumulative contribution analyses. **Results:** From 2021 to 2023, active CAR-T centers increased from 23 to 46, while total CAR-T discharges rose from 544 to 1,303. Total annual CAR-T expenditure increased substantially over the same period, from $728 million in 2021 to $2.56 billion in 2023. Despite this expansion, median annual discharges per center remained relatively stable (24 in 2021 vs 25.5 in 2023), while mean discharges increased from 23.7 to 28.3, indicating that growth was driven disproportionately by higher-volume centers. Correspondingly, the center-level strain increased from 23.6 to 28.3, reflecting rising per-center delivery burden. CAR-T delivery remained moderately concentrated across years, with top quartile of centers (approximately 21.7% of centers) accounting for 37.3% of CAR-T discharges in 2021, increasing to 39.5% of discharges in 2023. **Conclusions:** Despite rapid expansion in CAR-T centers and substantial growth in utilization and expenditures, delivery is increasingly concentrated among higher-volume centers. Stable median per-center volumes alongside increasing mean volumes and persistent concentration patterns suggest that growth has outpaced effective distribution of delivery capacity. While the relationship between center volume and patient outcomes remains incompletely characterized, these findings highlight the need for workforce development, infrastructure investment, and policy strategies to support both high-volume centers experiencing rising delivery burden and lower-volume centers developing expertise, ensuring sustainable and equitable CAR-T delivery as utilization continues to expand. Research Sponsor: None.

11090 **Poster Session**

Safety-net coverage instability during cancer care and association with overall survival. First Author: Liyang Yuan, UT Southwestern Medical Center, Dallas, TX

Background: Means-tested (contingent on income) financial programs for uninsured individuals, such as Medicaid and county charity/indigent care, require periodic eligibility re-verification. A recent systematic review found that insurance coverage disruptions are associated with worse cancer stage and survival, but also highlighted that studies suffered from a limited ability to distinguish administrative lapses from eligibility-driven disruptions, and relied on single time-point measures to define longitudinal coverage. Consequently, the dynamics and clinical implications of coverage instability during cancer care are incompletely characterized. We investigated the coverage portions of the electronic health record (EHR) to overcome these issues and characterize coverage instability. **Methods:** We conducted a retrospective cohort study linking tumor registry records (2010–2022) to coverage verification fields from the EHR of a large county safety-net health system (2010-2024). Renewal limbo was defined as any gap between verified coverage intervals occurring $>$ 365 days after a first verification. Multivariable logistic regression estimated odds of renewal-limbo within two years after diagnosis. Cox models estimated time to first renewal limbo and negative-binomial models for limbo duration; Prentice–Williams–Peterson models examined recurrent limbo. Two-year overall survival was estimated using a 12-month landmark design, with survival follow-up beginning at 12 months after diagnosis to ensure comparable risk windows across coverage instability groups. **Results:** Among 24,186 patients (56% female; 78% $<$ age 65; 6% Medicaid, 50% County charity care; 15% breast, 8% colorectal, and 8% lung cancer), 26% experienced renewal limbo in the first year after diagnosis and 36% by the second year. Among patients with charity coverage at diagnosis who experienced renewal limbo, nearly 90% returned to charity coverage, and over two-thirds of Medicaid enrollees returned to Medicaid. Median limbo duration was 32 days (IQR, 3–220). Compared to diagnoses in 2010–2019, those diagnosed in 2020–2022 had substantially reduced odds of renewal limbo (aOR 0.29, 95% CI: 0.25-0.32) in Medicaid. In landmark analyses, uninterrupted coverage during the first year was associated with the highest survival, while patients in limbo at the time of diagnosis and at renewal limbo had the lowest survival (Table 1). **Conclusions:** Coverage lapses at annual renewal were common among safety-net patients treated for cancer and was largely temporary, suggesting administrative rather than eligibility-driven disruptions. Although lapses were brief, they were associated with measurably lower overall survival even 2 years after cancer diagnosis. Strong calendar-year effects in 2020-2022 suggests the influence of suspended reverification during the COVID19 public health emergency. Research Sponsor: American Cancer Society; DBG-25-1374401-01-HOPS.

11091 **Poster Session**

Real-world EGFR, ALK, and PD-L1 testing performance and end-to-end intervals in Colombian patients with non–small cell lung cancer. First Author: Mateo Barros, Fundacion Santa Fe de Bogota, Bogota, Colombia

Background: Timely and comprehensive EGFR, ALK, and PD-L1 testing underpins effective precision oncology care in NSCLC, yet real-world data on testing completeness and integration into care pathways remain scarce in Latin America. **Methods:** We conducted a retrospective cohort study of adults with pathologically confirmed NSCLC treated at Fundación Santa Fe de Bogotá (2018–2025). EGFR/ALK/PD-L1 testing completeness, complete-panel availability, biomarker distributions, and turnaround times (order-to-report and diagnosis-to-report) were assessed. Stage III–IV sub analysis was performed. **Results:** A total of 242 patients were included. Most were female (53.3%), never-smokers (45.0%), and had adenocarcinoma histology (82.2%). EGFR, ALK, and PD-L1 results were available in 84.3%, 80.6%, and 80.6% of cases, respectively. Complete-panel availability was 74.4% and improved over time (adjusted OR per year, 1.28; 95% CI, 1.10–1.50; p=0.002). Turnaround times were favorable, with a median order-to-report time of 5 days (IQR, 2–8), and 68.0% completed within 7 days. The median diagnosis-to-report time was 12 days (IQR, 6–28.5), with 54.3% completed within 14 days. Activating EGFR mutations occurred in 38.7%, ALK fusions in 9.7%, and PD-L1 TPS $\geq$50% in 21.0%. In exploratory multivariable models, EGFR positivity was less frequent in ever-smokers (OR 0.26; 95% CI 0.13–0.51) and non-adenocarcinoma histology (OR 0.26; 95% CI 0.07–0.96). Guideline-concordant first-line targeted therapy was used in $>$80% of systemically treated patients with actionable alterations. In the stage III–IV subset (median age, 71.3 years; 53.8% female), median intervals were 13 days for imaging-to-diagnosis and 27 days for diagnosis-to-treatment (IQR, 16–52), with 33% exceeding 30 days and higher rates among patients referred after extra-institutional diagnosis. Median diagnosis-to-molecular report and report-to-treatment intervals were 11 days (IQR, 5–21) and 14 days, respectively. Requirement for EBUS was associated with longer imaging-to-diagnosis delays (75% $>$30 days; p=0.01). **Conclusions:** This study provides Latin American benchmarks for precision oncology delivery in NSCLC, showing high and improving molecular testing completeness with rapid turnaround. While molecular readiness was favorable, treatment initiation—especially for referred patients—represented the principal optimization gap. Standardized diagnosis-initiated testing and navigation workflows may improve end-to-end pathway performance. Research Sponsor: None.

Temporal trends in biomarker testing completeness in NSCLC (2018–2025).

Metric	2018–2020 (n=87)	2021–2023 (n=93)	2024–2025 (n=59)	Overall (N=242)
EGFR available, %	77.0	86.0	93.2	84.3
ALK available, %	73.6	80.6	91.5	80.6
PD-L1 available, %	71.3	83.9	89.8	80.6
Complete panel available, %	65.5	74.2	88.1	74.4

11092 **Poster Session**

Investigating reasons patients do not join a cancer clinical trial. First Author: Radhi Yagnik, Icahn School of Medicine at Mount Sinai, New York, NY

Background: The perennial challenge to cancer clinical trials is accrual. To date, the focus to improve accruals rested on addressing patient knowledge, attitudes and beliefs rooted in patient reluctance to be experimented on, financial and practical barriers and issues of mistrust. We undertook this study to describe the impact of an educational intervention to democratize recruitment and improve understanding of and information about cancer clinical trials. **Methods:** We implemented a time series intervention (INT) identifying cancer patients at treatment decision points at 3 participating Cancer Centers, educating consented breast, liver and lung cancer patients about clinical trials in general and providing clinical trial match lists to oncologists and patients prior to treatment decision-making. We defined a treatment decision point as a new, recurrent or progressing cancer. We surveyed patients and their oncologists pre- and post-intervention about their knowledge, attitudes and beliefs (KABs) of clinical trials. We compared pre & post KABs using Chi Sq and Fisher's Exact T tests. **Results:** Of 523 consented patients at treatment decision points, 514 completed pre & 368, post-INT surveys; 60% were non-white with no racial ethnic difference in response rates (70% BIPOC v 79% White; p = 0.07). Following an educational intervention, there was no significant change in positive attitude towards clinical trials (CT): 71% pre-intervention vs 77% post-intervention; p = 0.55, regardless of race-ethnicity (RE) (p = 0.5025). Black patients as compared to white patients, reported greater barriers to CT including: transportation (60% vs 37%; $p < 0.001$) and family responsibilities (46% vs 25%; p = 0.001). There was no RE difference in other barriers: patient report of physicians talking with them about clinical trials (89% vs 65%; p = .36), insurance (77% vs 74%; p = 0.6051); out of pocket expenses (64% vs 53%; p = 0.12); time off work (41% vs 37%; p = 0.5457). 25/28 (89%) treating oncologists of consented patients responded. Oncologists reported being less likely to offer CTs to patients who they perceived were reluctant to: get placebo (48%), be randomized (48%), have increased family responsibilities (52%), would have difficulty getting time off work (45%) or had comorbidities (40%). **Conclusions:** More than $^3/_4$ of patients have a positive attitude towards clinical trials with no racial-ethnic difference. Black patients reported more barriers to trial enrollment than white patients. Despite Black patients having more barriers that would reduce oncologists' likelihood of offering CTs to patients, there was no RE in patients' report of oncologists talking with them about CTs. Clinical trial information: NCT05146297. Research Sponsor: Stand Upto Cancer.

11093 **Poster Session**

Health shocks and advance care planning among U.S. older adults: Evidence from HRS 2012-2022. First Author: Haofan Yang, Rollins School of Public Health, Emory University, Atlanta, GA

Background: Advance care planning (ACP) allows individuals to discuss and document preferences for future medical care under serious illness, yet engagement among older adults remains limited. Experiences of a health shock, such as a diagnosis of cancer, major illnesses, or hospitalization, may prompt participation in ACP. This study aimed to examine the association between health shocks and subsequent ACP engagement and variation by key sociodemographic characteristics. **Methods:** We conducted a longitudinal cohort study using data from the Health and Retirement Study (HRS), a nationally representative survey of U.S. adults aged ≥65 years. Adults from 2012–2022 HRS with no baseline ACP who completed at least one follow-up wave were included. The exposure was a new health shock, defined as a new diagnosis of cancer, stroke, heart disease, or hospitalization. The outcome was new ACP engagement in subsequent waves. Generalized estimating equation models estimated adjusted odds ratios (ORs) of experiencing a health shock due to cancer diagnosis and due to other causes (vs. no health shock) on new ACP; and how such associations varied by respondents' characteristics. **Results:** Among 8,553 person-wave observations (4,426 unique respondents), median age was 74 years (IQR 69–79); 52.9% were women, 24.3% lived alone, 27.6% experienced a health shock, and 3.11% reported a health shock from new cancer diagnosis. Health shocks were associated with higher odds of ACP engagement (OR = 1.41; 95% CI, 1.28–1.56). In the three-level shock model, both non-cancer shock (OR = 1.43; 95% CI, 1.28–1.59) and cancer shock (OR = 1.31; 95% CI, 1.01–1.70) were associated with higher odds of ACP compared with no shock. Older age, female gender, and higher education were associated with greater ACP engagement overall. Compared with non-Hispanic Whites, non-Hispanic Black (OR = 0.73; 95% CI, 0.64–0.84) and Hispanic (OR = 0.55; 95% CI, 0.47–0.65) had lower odds of ACP. Living alone was associated with higher ACP engagement (OR = 1.29; 95% CI, 1.14–1.45). However, when stratified by patient sociodemographic characteristics, the associations between health shock and ACP were similar across groups, except that for those living alone who showed larger odds of initiating a new ACP following health shock (OR = 1.76; 95% CI, 1.45-2.14) than those not living alone (OR = 1.31; 95% CI, 1.16-1.47). **Conclusions:** Health shocks were associated with new ACP engagement among older adults, with similar associations observed for cancer-specific and non-cancer health shocks. Alhtought disparities in ACP by sociodemographic characteristics persisted, health shocks were associated with similarly odds of initiating ACP across population subgroups. This highlights the importance of leveraging health shocks as clinical touchpoints for ACP discussions, and the need for targeted strategies to reduce inequities in ACP engagement outside of acute health events. Research Sponsor: None.

11094 **Poster Session**

Insights from initial scoring in the Health Equity Report Card (HERC) pilot in community oncology settings. First Author: Taneal D. Carter, National Comprehensive Cancer Network, Plymouth Meeting, PA

Background: The Health Equity Report Card (HERC) is an innovative tool designed to assess and promote equity in cancer care. Standardized scoring is performed in four domains: Community Engagement, Accessibility of Care and Social Determinants of Health, Addressing Bias in Care Delivery, and Quality and Comprehensiveness of Care. Initial scoring is reported. **Methods:** Five diverse community oncology sites were recruited to evaluate the HERC's feasibility and usability in this setting. The primary objective is to evaluate the feasibility of implementing the HERC with scoring at community oncology sites. Key metrics include the ability to collect HERC data and complete self- and third-party scores. Baseline scores were calculated using data from prior six months. Quantitative and qualitative feedback was collected via surveys and semi-structured interviews. Results were summarized using descriptive statistics. This study was granted Institutional Review Board exemption by Pearl IRB and sites received funding support. **Results:** All sites completed self- and third-party scores (Table 1). Average self-scores and third-party scores were similar, with third party scores slightly lower across all domains. There was a wide range in scores across all domains. All sites felt the HERC was easy to understand. Sites requested clarification on four measures and expect the final round of scoring to be easier and faster. 4/5 sites stated collecting sources of evidence was feasible. Key challenges included: a lack of formal documentation and processes not implemented consistently across the practice. Best practices included: 5/5 used tracking logs, 5/5 used a team approach, and 4/5 utilized provided materials to orient staff to the project. All sites stated the HERC was a helpful resource for community practices, was useful to learn about health equity initiatives across the site, and was helpful to identify or prioritize quality improvement projects. All sites felt the HERC would inform changes to site processes and plan to identify improvement strategies based on their baseline scores. **Conclusions:** Initial implementation of the HERC in community oncology practices was feasible with completion of scoring across all practices. Score variation across sites and domains highlight differences in resources, documentation, and practice. Sites confirmed the HERC is a helpful resource and catalyst for quality improvement. The project remains ongoing. The HERC is a promising tool to foster equitable care delivery for all cancer patients. Research Sponsor: Merck Foundation through the Alliance for Equity in Cancer Care; Pfizer, Inc.; Lilly; GlaxoSmithKline, LLC; Bristol Myers Squibb Company.

Summary statistics of baseline self- and third-party scores.

		Self-Score			Third-Party Score		
Domain	Max Score	Mean	SD	Range (Max-Min)	Mean	SD	Range (Max-Min)
Community Engagement	4	3	1.1	3 (1-4)	2.2	1.5	4 (0-4)
Accessibility	6	3.9	1.7	4.5 (1-5.5)	3.7	1.5	4.5 (1-5.5)
Bias	5	1.9	1.3	3 (0.5-3.5)	1.5	1.2	3.5 (0-3.5)
Quality of Care	4	2.6	1.7	4 (0-4)	2.4	1.6	4 (0-4)

11095 **Poster Session**

Same day/next day cancer care program: An early access program for patients with aggressive malignancies. First Author: Artem Oganesyan, Abington Hospital-Jefferson Health, Abington, PA

Background: Rapid referral of patients with suspected malignant disease to an oncology specialist is associated with improved earlier-stage diagnosis and survival benefits. The advantage of such rapid care transition can be especially pronounced in aggressive malignancies, where early interventions are critical in reducing mortality. Patients with already established cancer diagnosis may also benefit from such programs. Same Day/Next Day Cancer Care (SDND) is a Jefferson Health enterprise designated referral system allowing patients with newly diagnosed cancers to be seen by an advanced practice clinicians via telemedicine within 48 hours at the Sidney Kimmel Comprehensive Cancer Center (SKCC). **Methods:** Adult patients with an established diagnosis of aggressive types of malignancies were referred through SDND to SKCCC in the Greater Philadelphia Area if they had concerning symptoms related to disease. The following malignancies were selected: acute leukemias, T-cell lymphomas, diffused large B-cell lymphomas, Burkitt lymphomas, melanomas, glioblastoma multiforme, pancreatic adenocarcinoma, esophageal or gastric carcinoma, small cell lung carcinoma, biliary tract malignancy, anaplastic thyroid cancer. Socio-demographics, time to appointment with an oncologist and treatment were analyzed. **Results:** Between July 2024 and December 2025, 209 patients with aggressive malignancies, of which 49% were female with a median age of 67 years, were referred to oncology specialists. Only 19% were new patients, while 81% had already established care. Medical providers made 78.3% of referrals, while other 21.7% were self-referred. Average SDND schedule lag days was 1.04 days. About 85% of patients had medical oncologist consultation appointments, of which 68.8% completed the planned visit. Thirty-four patients (16%) were referred for infusion therapy, of which 64.7% successfully initiated infusion therapy within 50 days. Similarly, 76 patients (36%) had scheduled a surgical specialty consultation, of which 77.9% completed the appointment. Importantly, 53.7% of the patients underwent surgery within 30 days of the SDND referral. **Conclusions:** SDND is a centralized access program aimed at reducing time to first appointments for newly diagnosed cancer patients. It led to accelerated assessment by oncology providers with high adherence to the management plan. It can ensure faster diagnostic workups and symptom management related to aggressive malignancies by advanced care clinicians, with the potential to improve survival rates, patient satisfaction, reduce treatment–related anxiety and cancer-related morbidity. Further research is needed to determine if this early clinical evaluation by advanced practice providers via telemedicine may reduce complications warranting high-cost care, such as emergency department visits or hospitalizations in high-risk cancer population. Research Sponsor: None.

11096 **Poster Session**

Empowering multidisciplinary teams in cancer survivorship: Results from the ASCO Project ECHO survivorship program in Brazil. First Author: Luciana Castro Landeiro, Oncoclínicas&Co, Salvador, Brazil and Grupo Brasileiro de Estudos em Câncer de Mama (GBECAM), Salvador, Brazil

Background: As the number of cancer survivors increases in Brazil, access to structured survivorship education for health professionals remains limited. ASCO Project ECHO Survivorship Program was implemented to strengthen survivorship knowledge and care coordination among multidisciplinary teams. **Methods:** This longitudinal, virtual, case-based education series was conducted from September to December 2025. Intended audience included oncologists, general physicians, nurses, psychologists, and other professionals involved in survivorship care. Program consisted of 08 distinct, self-contained sessions, beginning with an introductory session on core survivorship principles, followed by cancer-specific survivorship topics delivered through short didactics and case discussions. Participants were encouraged to attend all sessions; however, each session was designed to be independent. Attendance was tracked, and final post-program survey assessed satisfaction and self-reported impact on clinical practice. Analyses focused on participants attending ≥4 sessions (≥50%), which was the criterion for certification and a pragmatic threshold to ensure meaningful engagement. **Results:** 161 health professionals attended at least one session, and 65 (40.4%) participated in ≥4 sessions. Participants represented diverse disciplines, including physicians and oncologists (31%), psychologists (13.7%), nutritionists (8.7%), pharmacists (6.2%), nurses (11.2%), and other professionals. Subsequent analyses were limited to participants attending ≥4 sessions. Among these,final survey response rate was 66.2%. Reported practice changes and satisfaction outcomes were collected through the post-program survey. Respondents described increased confidence in identifying and managing late and long-term physical effects, addressing psychosocial and sexual health concerns, improving interdisciplinary collaboration, and supporting transitions to post-treatment care. Overall satisfaction was high, with 97.7% reporting being satisfied or very satisfied. Despite high satisfaction, attendance declined across sessions, highlighting the need to better understand factors influencing sustained participation in longitudinal virtual education programs. **Conclusions:** ASCO Project ECHO Survivorship Program in Brazil demonstrated strong engagement and meaningful self-reported integration of survivorship principles into clinical practice among a multidisciplinary workforce. This flexible, scalable educational model supports survivorship capacity-building across diverse professional roles in middle-income settings. Further evaluation is needed to better understand factors associated with decreased attendance over time and to inform strategies that optimize sustained engagement in longitudinal survivorship education programs. Research Sponsor: None.

11097 **Poster Session**

Admission acuity and inpatient outcomes across major gastrointestinal malignancies in the United States, 2018–2022. First Author: Elaine Patricia Tupas, MountainView Hospital, Las Vegas, NV

Background: Hospitalization for gastrointestinal (GI) malignancies frequently occurs in the setting of acute decompensation or unplanned admission. National data quantifying the association between admission acuity and inpatient outcomes across major GI cancer subtypes remain limited. **Methods:** A serial cross-sectional analysis was conducted using the 2018–2022 Healthcare Cost and Utilization Project National Inpatient Sample. Adult hospitalizations with a principal diagnosis of esophageal (C15), gastric (C16), colorectal (C18–C20), liver or intrahepatic bile duct (C22), or pancreatic cancer (C25) were identified. Admission acuity was classified as elective or non-elective. Outcomes included in-hospital mortality (primary), length of stay (LOS), and hospitalization cost estimated using cost-to-charge ratios. National estimates accounted for survey weighting, clustering, and stratification. Survey-weighted multivariable logistic regression evaluated factors independently associated with in-hospital mortality, adjusting for admission type, cancer subtype, demographics, payer, neighborhood income quartile, hospital characteristics, and calendar year. **Results:** From 2018–2022, 214,740 unweighted GI cancer hospitalizations represented an estimated 1.07 million hospitalizations nationally. Colorectal cancer accounted for 56.7% of admissions, followed by pancreatic (17.6%), liver or intrahepatic bile duct (10.5%), gastric (8.6%), and esophageal cancer (6.6%). Overall, 52.9% of hospitalizations were non-elective. In-hospital mortality was higher for non-elective than elective admissions (5.92% vs 1.89%), with longer LOS (7.61 vs 6.15 days) and lower mean hospitalization costs ($25,644 vs $32,166). In adjusted analyses, elective admission was associated with substantially lower odds of in-hospital mortality compared with non-elective admission (adjusted odds ratio [aOR] 0.395; 95% CI 0.328–0.476). Relative to esophageal cancer, adjusted mortality odds were lower for colorectal, gastric, and pancreatic cancers, while no significant difference was observed for liver or intrahepatic bile duct cancers. **Conclusions:** Across major gastrointestinal malignancies, non-elective admission was associated with substantially higher inpatient mortality and longer length of stay independent of cancer subtype and sociodemographic factors. These nationally representative findings provide benchmarking data for admission acuity as a marker of inpatient risk in gastrointestinal oncology. Research Sponsor: None.

11098 **Poster Session**

Survival outcomes in individuals with cancer and pre-existing autoimmune disease receiving immune checkpoint inhibitors: A multicenter, propensity-matched real-world survival analysis. First Author: Nehemias Guevara, Division of Hematology, Oncology, and Blood and Marrow Transplantation, Department of Internal Medicine, Saint Louis University School of Medicine, Saint Louis, MO

Background: Autoimmune disease (AID) affects approximately 5–10% of individuals with cancer. Although immune checkpoint inhibitors (ICIs) have transformed cancer therapy, individuals with pre-existing AID are routinely excluded from clinical trials due to concerns about immune-related adverse events. Consequently, long-term real-world survival outcomes in this population remain incompletely defined, limiting evidence-based risk–benefit assessment. **Methods:** We conducted a retrospective, multicenter cohort study using a large U.S.-based real-world oncology network derived from harmonized electronic health records across academic and community cancer centers. Adults (≥18 years) with solid tumors who received at least one immune checkpoint inhibitor (PD-1, PD-L1, or CTLA-4) were included. Individuals were classified by the presence or absence of documented pre-existing AID prior to ICI initiation. Cohorts were matched 1:1 using propensity scores based on age, sex, race, and baseline comorbidities, including cardiovascular disease, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, and heart failure. Survival outcomes at 1, 3, and 5 years from ICI initiation were evaluated using Kaplan–Meier methods and Cox proportional hazards models. **Results:** After propensity score matching, 13,800 adults were included (6,900 with AID and 6,900 without), with excellent balance across baseline covariates. All-cause mortality was higher among individuals with pre-existing AID at 1 year (36.7% vs 32.6%), 3 years (48.3% vs 44.7%), and 5 years (50.1% vs 47.0%). Pre-existing AID was independently associated with worse overall survival at all time points (HR 1.15; 95% CI 1.09–1.22 at 1 year; HR 1.15; 95% CI 1.10–1.21 at 3 years; HR 1.15; 95% CI 1.09–1.20 at 5 years; all $P < 0.001$). Kaplan–Meier analyses demonstrated early separation of survival curves that persisted through long-term follow-up (log-rank $P < 0.001$). **Conclusions:** In this large, multicenter, real-world cohort, pre-existing autoimmune disease was associated with a modest but durable reduction in survival among individuals treated with immune checkpoint inhibitors, persisting through 5 years of follow-up. These findings do not contraindicate ICI use but highlight the need for individualized risk stratification, multidisciplinary collaboration, proactive toxicity surveillance, and informed shared decision-making when initiating immunotherapy in this population. Research Sponsor: None.

11099 **Poster Session**

Racial and payer-based disparities in inpatient resource utilization and mortality among patients hospitalized with head and neck cancer in the United States, 2018 to 2022. First Author: Sandhya Upreti, Department of Internal Medicine, Sunrise Health GME Consortium, Las Vegas, NV

Background: Inpatient hospitalizations for head and neck cancer (HNC) reflect advanced disease, treatment-related complications, and high healthcare utilization. National data on racial and payer-based disparities in inpatient length of stay (LOS), costs, and mortality remain limited. **Methods:** A survey-weighted cohort analysis of the Healthcare Cost and Utilization Project National Inpatient Sample (NIS), 2018 to 2022, was performed. Hospitalizations with a principal diagnosis of HNC were identified using ICD-10-CM codes C00 to C06, C07 to C08, C09 to C14, C30 to C32, and C76.0; thyroid cancer (C73) was excluded. Outcomes included in-hospital mortality, LOS, and hospitalization cost. Survey-weighted mean LOS and cost were estimated by race and primary payer. A survey-weighted multivariable logistic regression evaluated predictors of in-hospital mortality, adjusting for age, sex, year, anatomic subsite, race, payer, ZIP-code income quartile, elective admission status, and hospital teaching and location characteristics. **Results:** The weighted national estimate included 166,020 inpatient HNC hospitalizations (95% CI 158,702 to 173,338). Mean LOS ranged from 7.43 days among White patients (95% CI 7.29 to 7.56) to 10.21 days among Black patients (95% CI 9.81 to 10.60), with intermediate LOS among Hispanic (9.22 days), Asian or Pacific Islander (8.41 days), Native American (8.86 days), and Other race groups (8.25 days). Mean hospitalization costs were highest among Asian or Pacific Islander patients ($46,577, 95% CI $41,648 to $51,506) and Hispanic patients ($42,384, 95% CI $39,129 to $45,640), compared with White patients ($36,887, 95% CI $35,197 to $38,577). Medicaid hospitalizations had the longest LOS (10.58 days, 95% CI 10.16 to 10.99) and high costs ($42,217, 95% CI $40,126 to $44,308), whereas privately insured hospitalizations had the shortest LOS (6.54 days, 95% CI 6.37 to 6.72). In adjusted analyses, mortality increased with age (OR 1.02 per year, 95% CI 1.01 to 1.03). Asian or Pacific Islander (OR 1.51, 95% CI 1.07 to 2.13) and Other race patients (OR 1.59, 95% CI 1.09 to 2.32) had higher mortality than White patients. Non-Medicare other insurance was associated with higher mortality than Medicare (OR 2.56, 95% CI 1.89 to 3.46). Elective admissions (OR 0.21, 95% CI 0.16 to 0.27) and care at urban teaching hospitals (OR 0.34, 95% CI 0.25 to 0.47) were associated with lower mortality. **Conclusions:** Racial and payer-based disparities persist in inpatient LOS, costs, and mortality among patients hospitalized with HNC. Black and Medicaid-insured patients experience longer hospitalizations, while Asian or Pacific Islander and Hispanic patients incur higher costs. Persistent mortality differences after adjustment highlight structural and health-system contributors and support targeted equity-focused interventions. Research Sponsor: None.

11100 **Poster Session**

Consumer wearables and medical care utilization in gastrointestinal cancers: A Fitbit data analysis in NIH All of Us Research Program. First Author: Osama Elkhider, Medical College of Wisconsin, Milwaukee, WI

Background: Patients with gastrointestinal (GI) cancers may experience delayed or forgone care due to cost, travel, or health system barriers. Wearable devices are widely used and capture physical activity that may reflect health status, mobility, and social factors. Whether wearable activity data can help identify patients at risk for delayed care is not well understood. We examined associations between activity levels and delayed or forgone care among adults with GI cancers in the NIH All of Us Research Program. **Methods:** Adults with GI cancers who contributed wearable activity data and healthcare utilization surveys were included; ≥30 valid Fitbit days were required. Mean daily step counts were calculated and categorized into cohort-specific quartiles: Q1 (≤3,621 steps/day), Q2 (3,621–5,591), Q3 (5,591–8,272), and Q4 (> 8,272). Delayed or forgone care was determined from survey items asking whether participants postponed or avoided medical care due to financial or access barriers. Analyses were performed in the overall GI cohort (n = 407) and stratified by cancer site (colorectal, pancreatic, upper GI, hepatobiliary, and other). Logistic regression evaluated associations between activity and delayed care using categorical quartiles, continuous log-transformed steps, and age-adjusted models. **Results:** The analytic cohort included 407 participants with GI cancers. After age adjustment, higher daily step counts—analyzed continuously and across ordered quartiles—were associated with lower odds of delayed or forgone care. Age itself was independently associated with fewer delays (OR per 10 years 0.62, p = 0.001–0.002). In categorical models using Q3 as the reference, participants in Q1 had higher odds of delayed care (OR 3.57, 95% CI 1.06–12.10, p = 0.041), while Q2 and Q4 did not differ significantly from Q3, supporting a non-linear association. Site-stratified analyses showed similar non-linear patterns; for example, pancreatic cancer (n = 60) had delayed care prevalences of Q1 11.1%, Q2 0%, Q3 5.0%, Q4 9.1%, and upper GI cancers (n = 59) had Q1 9.1%, Q2 0%, Q3 6.3%, Q4 13.3%. In colorectal cancer (n = 210), Q3 had the lowest delayed care vs Q1 (OR 0.25, 95% CI 0.05–1.32), although other quartile estimates were less precise due to small event counts. **Conclusions:** Among patients with GI cancers who contributed wearable and survey data, delayed or forgone care showed a non-linear association with activity, with the lowest odds in the moderate–high activity range. Participants in Q1 had higher odds of delayed care compared with Q3 after age adjustment. Wearable activity data may help identify patients who face barriers to timely care, although this cross-sectional study cannot show cause and effect. Longitudinal studies are needed to determine whether passive wearable data can support care navigation and healthcare utilization in oncology. Research Sponsor: None.

11101 **Poster Session**

Recent trends in utilization of outpatient medical oncology services. First Author: Carlos U. Muzlera, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada

Background: Health systems face escalating demand from rising cancer incidence and treatment complexity. Effective health human resource planning is critical to accommodate these trends. Limited data are available on longitudinal utilization of medical oncology services, especially volumes and complexity of care. We sought to characterize real-world longitudinal utilization of outpatient medical oncology services across common solid tumors to inform workforce planning and policy. **Methods:** We conducted a retrospective, population-based retrospective cohort study using linked administrative health data from Ontario, Canada. Adults diagnosed between 2015 and 2022 with lung, colon, rectal, pancreatic, breast, melanoma, or prostate cancer were identified through the Ontario Cancer Registry. Medical oncology consultations, clinic visits, and systemic treatment encounters were captured from the provincial Activity Level Reporting database. Primary outcomes included consultation and systemic therapy initiation trend, and mean clinic and treatment visits during the first year following medical oncology consultation. **Results:** The cohort consisted of 332,604 patients (median age 68 years; 48.7% male), with new cases increasing from 39,688 in 2015 to 45,011 in 2022. Medical oncology consultation and systemic treatment initiation were encountered by 57.8% (range: 17.2% prostate to 92.8% breast) and 71.2% respectively (range: 45.1% melanoma to 82.8% breast). The proportion of patients with medical oncology consultation increased appreciably for pancreatic (59.8% to 79.0%), colon (55.8% to 60.2%), rectal (64.4% to 69.6%), and lung cancers (57.3% to 61.4%), with resultant growth in consultation volumes except for melanoma, colon and lung cancers. Total clinic visits increased from 131,950 in 2015 to 174,630 in 2022. Mean clinic visits per patient increased significantly for all cancers except prostate ($p < 0.001$), with the greatest increase observed in melanoma (+0.33 visits/year). Systemic therapy exposure increased across most cancers, most notably melanoma (25.7% to 47.2%) and prostate cancer (61.2% to 73.9%). Total systemic treatment visits increased from 129,380 in 2015 to 165,149 in 2022 with total and mean per patient trends exhibiting mixed, disease-specific patterns. **Conclusions:** Outpatient medical oncology service utilization per patient has expanded substantially over time, driven by rising volumes of consultations, systemic therapy and clinic visits. Taken with the rising complexity of care, these data suggest that consultation-based workload metrics likely underestimate service demand. Workforce planning models should incorporate follow-up care, treatment monitoring, and disease-specific trajectories to ensure sustainable, high-quality oncology care delivery. Research Sponsor: None.

11102 **Poster Session**

Hidden advanced physiology in non-metastatic gastrointestinal cancer: Malnutrition/cachexia and in-patient failure-to-rescue. First Author: Wei Ju Lin, University of California Riverside, Riverside, CA

Background: Cancer stage is often used as a proxy for inpatient risk, yet physiologic reserve may better determine outcomes. It was hypothesized that among gastrointestinal (GI) cancer hospitalizations without coded metastasis, malnutrition/cachexia identifies a vulnerable subgroup with complication burden, ICU escalation, and post-complication mortality approaching that of metastatic disease. **Methods:** A survey-weighted analysis of the National Inpatient Sample (NIS), 2016–2023, was conducted. Adult hospitalizations with any GI malignancy (ICD-10-CM C15–C20, C22–C25) were included; encounters with palliative care coding (Z51.5) were excluded. Metastatic disease was defined by C77–C79. Vulnerability was defined as malnutrition/cachexia (E43, E44, E46, R64). Major complications included sepsis, bleeding/transfusion, venous thromboembolism, acute kidney injury (AKI), bowel injury/peritonitis, and respiratory failure. ICU escalation proxies included mechanical ventilation and/or shock. Outcomes were compared across three groups: non-metastatic/no vulnerability, non-metastatic/vulnerable, and metastatic. Failure-to-rescue was defined among non-metastatic surgical hospitalizations as death following ≥1 major complication. **Results:** The cohort included 748,734 weighted hospitalizations; 39.6% had coded metastasis. Among non-metastatic admissions, vulnerability prevalence increased from 15.6% in 2016 to 21.9% in 2023. In-hospital mortality in the non-metastatic/vulnerable group (4.14% [95% CI, 4.00–4.29]) approximated metastatic mortality (3.96%) and exceeded non-metastatic/no vulnerability mortality (1.86% [95% CI, 1.81–1.91]). Compared with non-metastatic/no vulnerability, vulnerable admissions demonstrated higher ICU escalation (7.75% [95% CI, 7.56–7.94] vs 3.54%), AKI (27.30% [95% CI, 26.98–27.62] vs 17.25%), and any major complication (59.31% [95% CI, 58.95–59.67] vs 42.93%). Resource utilization was higher in the vulnerable group (LOS 9.33 vs 5.49 days; cost $33,156 vs $22,879). Among non-metastatic admissions with complications, mortality was higher with vulnerability (6.46% [95% CI, 6.24–6.69] vs 3.88%). In the non-metastatic surgical subcohort, failure-to-rescue mortality was 5.90% (95% CI, 5.59–6.22) with vulnerability versus 2.65%. **Conclusions:** Among U.S. GI cancer hospitalizations without coded metastasis, malnutrition/cachexia identifies a high-risk inpatient phenotype with complication burden, ICU escalation, and post-complication mortality closely resembling metastatic disease. These findings suggest physiologic vulnerability, rather than stage alone, drives inpatient risk and failure-to-rescue, supporting targeted inpatient risk stratification and earlier supportive interventions. Research Sponsor: None.

11103 **Poster Session**

Quality of life among caregivers of patients with breast cancer in Mexico: A multicenter cross-sectional survey using the Caregiver Quality of Life Index–Cancer (CQOLI-C). First Author: Carlos A. Gonzalez-Assad, Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Monterrey, Mexico

Background: Family caregivers of patients with breast cancer (BC) often experience emotional, physical, social, and financial strain that can compromise their quality of life (QoL). The Caregiver Quality of Life Index–Cancer (CQOLI-C) is a validated cancer-specific instrument, however data on factors associated with caregiver QoL across healthcare settings in Mexico remain limited. **Methods:** We conducted a multicenter, cross-sectional survey of primary caregivers of patients with BC in Mexico. Consecutive eligible caregivers were recruited across public and private care settings (Sep 2025 – Jan 2026) and completed an online questionnaire. QoL was measured using the CQOLI-C (35 items scored 0–4; total score range 0–140; higher scores = greater caregiver burden (CB)); positively worded items were reverse-coded and summed to generate the total score. We summarized caregiver/patient characteristics and CQOLI-C scores with descriptive statistics and compared them across key groups (metastatic status, caregiving hours/week, additional helpers, self-reported unsustainable caregiving (yes/no), and care setting (public vs private)). We evaluated associations between CQOLI-C total score and prespecified predictors using multivariable OLS linear regression with robust standard errors (two-sided $p < 0.05$). **Results:** Seventy-three caregivers completed the survey (mean age 46.9±15.5 years; 54.8% male). Caregivers were most commonly partners (43.8%) or adult children (32.9%). 53.4% of patients received care in the private sector; 26% had metastatic disease. The most common numbers of additional caregivers were 2 (27.4%) and 0 (21.9%). Over half of caregivers (52.1%) reported providing 0–10 hours/week of care, while 16.4% reported > 50 hours/week. Median caregiver burden measured by CQOLI-C was 45 (IQR 29.5–62). 41% reported caregiving became too difficult to sustain. High burden items most frequently endorsed (score 3–4) included fear of patient death (54.8%), concern about treatment adverse effects (42.5%), and anger to see loved one deteriorating (41.1%). In adjusted regression (n = 73), compared with no helpers, reporting two helpers ($\beta = 16.5$; p = 0.020) and five helpers ($\beta = 24.4$; p = 0.016) was associated with higher scores, while six or more helpers was associated with substantially lower scores ($\beta = -42.0$; p = 0.002). Metastatic disease ($\beta = 16.7$; p = 0.043) and public vs private sector ($\beta = 24.2$; p = 0.009) were associated with worse scores; caregiving hours showed no consistent independent association. **Conclusions:** Caregiver burden was substantial and clustered around unsustainable caregiving demands, metastatic disease, and public care settings. These factors can help identify caregivers most in need of support and should guide systematic caregiver screening and targeted supportive-care interventions in Mexico. Research Sponsor: None.

11104 **Poster Session**

Patient-perceived caregiver burden after intense oncology treatment. First Author: Virgil Junhui Guo, Dana-Farber Cancer Institute, Boston, MA

Background: Although oncology caregiver burden is well-known (e.g. Alam, *JCO*, 2020), less is understood about how patients themselves perceive their caregivers' quality of life (QOL) after intensive cancer treatment such as hematopoietic cell transplantation (HCT). **Methods:** Patients undergoing allogeneic HCT at Dana-Farber Cancer Institute (12/2017 to 12/2021) were surveyed approximately 100 and 180 days post-HCT. We utilized a questionnaire adapted from the Caregiver Quality of Life Index–Cancer Scale (Weitzner, Qual Life Res, 1999), redesigned to be administered to patients themselves. Caregiver stress was assessed with the question "My caregiver seems more stressed than before my transplant" (0: not at all to 4: very much), dichotomized into lower (0–2) versus higher (3–4) stress. Familial financial burden was measured with the question "How satisfied are you with your family's present financial situation?" (1: not satisfied at all to 5: completely satisfied), dichotomized into higher (1-3) versus lower (4-5) burden. Paired McNemar tests assessed changes in caregiver stress between Day 100 and Day 180, and multivariable logistic regression modeled the relationship between financial burden and caregiver stress, adjusting for age and gender. **Results:** At Day 100 and Day 180, 165 and 142 patient surveys were analyzed (overall response rates were 60.5% and 70.0% among patients alive at each time); 89 patients completed surveys at both times. The mean age was 61.5, 38.2% were female, and 61.8% received reduced-intensity HCT conditioning. Most respondents (86.1%) identified their caregiver as a family member (as compared to a friend or paid professional). Approximately half reported their caregiver was working at both Day 100 (51.2%) and Day 180 (53.2%). The majority felt that the HCT process had not negatively impacted their relationship with their caregiver (93.3% at Day 100; 96.5% at Day 180). At Day 100, 30.9% of respondents perceived their caregiver as being more stressed than prior to HCT, compared with 33.3% at Day 180 (comparing the two time point proportions: $\chi^2 = 0.80$, $p = 0.37$). Lower financial burden was significantly associated with lower odds of reporting increased caregiver stress at both Day 100 (OR = 0.49, 95% CI: 0.24-0.99) and at Day 180 (OR = 0.17, 95% CI: 0.07–0.39). **Conclusions:** In this cohort of patients undergoing intense oncology treatment, most had caregivers who were working family members. A minority perceived increased caregiver stress due to their treatment, with similar perceptions at both Day 100 and Day 180. This relatively modest perception of stress potentially reflects caregivers' successful efforts to lower patients' self-perceived burden. Moreover, lower familial financial burden was strongly protective against patient-perceived caregiver stress, particularly at Day 180, suggesting that financial circumstances meaningfully influence how patients interpret and perceive caregiver burden. Research Sponsor: None.

11105 **Poster Session**

Patient trust in oncologists versus artificial intelligence for cancer-related questions. First Author: Lyndon Huang, Dell Medical School, The University of Texas at Austin, Austin, TX

Background: Artificial intelligence tools, including the recent introduction of ChatGPT Health, are increasingly accessible to patients seeking medical information. In oncology, where discussions surrounding prognosis and treatment are highly sensitive, trust in the source of information is critical. However, patient perspectives on AI tools compared with oncologists for cancer-related questions remain poorly characterized. **Methods:** We conducted a cross-sectional survey of 75 adult cancer patients at an academic safety-net oncology clinic. The survey assessed patients' perspectives on technology use and their trust in AI tools like ChatGPT compared with oncologists for cancer-related questions. The primary outcome was patients' preferred source of trust when asked who they would rely on most to answer a serious question about their cancer. Secondary outcomes assessed attitudes toward physician versus AI trust using Likert-scale items and comfort engaging with AI for cancer-related questions. Binomial proportions are reported with 95% confidence intervals. Spearman correlation and Fisher's exact tests were used for secondary exploratory analyses. **Results:** Among 75 respondents, the median age group was 55–64 years; 42.7% were male and 57.3% female. English was the primary language for 53.4% and Spanish for 43.8%. The most common cancer types were gastrointestinal (24.0%), breast (20.0%), and hematologic malignancies (17.3%). For the primary outcome, when asked who they would trust most to answer a serious question about their cancer's future, an overwhelming majority selected their oncologist (97.3%; 73/75; 95% CI 90.7–99.7). No respondents selected ChatGPT/AI (0%; 95% CI 0–4.8), while 2.7% were unsure (95% CI 0.3–9.3). In secondary analyses, greater self-reported comfort with technology was associated with greater comfort engaging with AI tools for cancer-related questions (Spearman $\rho = 0.40$, $p < 0.001$). In exploratory subgroup analyses, Spanish speakers showed a trend toward less agreement that they would trust a doctor's answer more than AI (71.9% vs 87.2%). This may reflect increased trust when medical information is delivered in a patient's primary language. In addition, a similar directional signal was observed among younger patients (73.3% vs 84.4%). **Conclusions:** Cancer patients currently demonstrate a strong preference for oncologists over AI tools when addressing serious cancer-related questions, underscoring the central role of physician trust in oncology care. However, comfort engaging with AI varies by technological familiarity, suggesting that this preference may evolve over time as younger, more digitally fluent generations enter care and AI becomes increasingly integrated into healthcare. This study highlights the potential of AI tools to support oncologists in providing more accurate and individualized prognostic estimates for patients with advanced malignancies. Research Sponsor: None.

11106 **Poster Session**

Latent transitions of distress risk during cancer treatment and their concordance with anxiety, depression, and quality of life in a large multicenter cohort. First Author: Cristiane Decat Bergerot, Oncoclinicas&Co - Medica Scientia Innovation Research (MEDSIR), Sao Paulo, Brazil

Background: Distress is prevalent in patients with cancer and may change throughout treatment. However, longitudinal transitions between distress-risk states and their relationship with psychosocial outcomes in real-world oncology settings remain poorly characterized. We sought to identify latent distress-risk states, describe transitions during cancer treatment, and evaluate their clinical determinants and concordance with anxiety/depression and health-related quality of life (HRQOL). **Methods:** This longitudinal multicenter cohort study included adult patients with cancer treated across all Brazilian states. Distress was assessed at baseline (prior to treatment initiation), mid-treatment, and end of treatment using the Distress Thermometer (DT). Symptoms of anxiety/depression and HRQOL were assessed using the Hospital Anxiety and Depression Scale (HADS) and FACT-G. Latent Transition Analysis (LTA) identified distress-risk states and transition probabilities over time; model selection was based on Bayesian Information Criterion, entropy, and clinical interpretability. Multinomial logistic regression evaluated clinical predictors of baseline distress-risk states. Directional concordance between changes in DT and changes in HADS and FACT-G was assessed using concordance matrices and chi-square tests. **Results:** A total of 2197 patients were included. Median age was 58 years, 72.3% were female, and most were diagnosed with breast (40.1%) or gastrointestinal (18.8%) cancer, with 40.0% presenting with advanced-stage disease (III-IV). A four-state LTA model with optimal fit identified high critical, moderate persistent, low vulnerable, and low stable distress-risk profiles. The low stable state was the most prevalent and highly stable, with 94.5% remaining in the same state across assessments, whereas the high critical and low vulnerable states were more dynamic. Among high critical patients, 22.8% transitioned to moderate risk and 19.6% to low risk, while 28.6% of moderate persistent patients transitioned to the low stable state. Worsening occurred in up to 12.6% of patients. Male sex (OR = 1.8, 95% CI 1.08-3.09) and stage IV disease (OR = 1.8, 95% CI 1.09-2.97) were independently associated with higher-risk distress states (Ps = 0.02). Changes in distress states showed high directional concordance with psychosocial outcomes (HADS 82.9%; FACT-G 77.0%; χ^2 $p < 0.001$). **Conclusions:** Distinct and clinically meaningful distress-risk states and dynamic transitions were observed during cancer treatment. While most patients remained stable or improved, a relevant subgroup experienced worsening distress. These findings support repeated distress screening and adaptive, risk-based psychosocial interventions integrated into routine oncology care. Research Sponsor: None.

11107 **Poster Session**

Clinical efficiency of remote symptom monitoring using electronic patient-reported outcome (ePRO) in lung cancer: Results of the prospective, multicenter REAL-MOOV-LUNG trial. First Author: Nicolas Girard, Institut du Thorax Curie Montsouris, Institut Curie, Paris, and UVSQ, Paris Saclay University, Versailles, France

Background: Remote symptom monitoring using electronic patient-reported outcome (ePRO) has been shown to provide clinical benefits and is being implemented for routine care in cancer patients (pts). It may represent a significant operational burden for healthcare providers, that has to be balanced with its actual efficiency in generating clinically meaningful alerts leading to modify pts management. **Methods:** REAL-MOOV-LUNG is a prospective, multicenter, phase IV trial evaluating the MOOVCARE system in patients (pts) $\geq$18yo with non-progressive lung cancer, any histology, any stage, who had completed anticancer treatment for $<$ 8weeks (cohort 1), or who were receiving adjuvant, consolidation or maintenance anticancer treatment for $\geq$8weeks (cohort 2). Primary endpoint was the proportion of patients who had a clinically meaningful modification of the management, predefined as unplanned consultation at the hospital or CT-scan imaging following a MOOVCARE alert. Secondary endpoints included management of alerts, patients and healthcare providers satisfaction, observance, quality-of-life, and survival. **Results:** From October 2021 to October 2024, 188 pts were enrolled, including 107 men, 81 women, 155 pts with non-small cell lung cancer, 36 with other histologies; 36 pts had oncogene-addicted tumors; 70 pts had metastatic disease, 58 locally-advanced disease, and 60 had early-stage disease. 92% of pts filled at least 1 ePRO questionnaire, median number of questionnaires was 56/pts; 81% of pts had at least 1 alert, median number of alerts was 11, and total number of alerts was 2294. After a median follow-up of 23.9 mo, 39 (21%) pts had a modification of management between 2 scheduled visits, 29 (74%) of which related to preplanned visit, not to an alert; among the remaining 10 (26%) pts, only 5 (13%) pts had clinically meaningful modifications as per the predefined definition. 18-month overall survival was 79.6% [IC95% 73.6%-86.1%]. **Conclusions:** While adoption of remote symptom monitoring on ePRO was high, with frequent alerts generated from surveys, the actual impact on clinical management of patients with lung cancer was limited in the context of frequent preplanned visits at the hospital as per clinical guidelines. Clinical trial information: NCT04934865. Research Sponsor: SIVAN.

11108 **Poster Session**

Impact of remote therapeutic monitoring on time to discontinuation and acute care events among patients treated with immune checkpoint inhibitors. First Author: Benjamin Avi Derman, The University of Chicago, Chicago, IL

Background: Immune checkpoint inhibitors (ICI) are used to treat several solid tumors but can cause serious toxicities which may lead to early discontinuation of therapy. This study describes the effect of the Canopy electronic patient-reported outcomes (ePROs)-based remote therapeutic monitoring (RTM) platform on time to treatment discontinuation, acute care events, and steroid prescribing in patients receiving ICI therapy. **Methods:** We studied patients with metastatic cancer from four oncology clinics who started ICI treatment from Jan 1, 2024 to July 20, 2025. An RTM group was defined by submission of two ePRO reports in the first 45 days after first ICI treatment. The control group was never enrolled or did not submit ePRO reports within 45 days. Time to discontinuation (TTD) of ICI, acute care events, and steroid prescribing were assessed using propensity score weighting to account for potential differences in cohort characteristics; costs were taken as rate differences multiplied by average acute care event cost. TTD was assessed by Kaplan-Meier estimation, Cox proportional hazards modeling, and restricted mean survival time at 90 days (RMST). Descriptive statistics were taken about symptoms in the RTM group versus the control group. **Results:** The study included 363 patients using RTM and 1,199 in the control group. Lung cancer, melanoma, and kidney cancer were the most frequent diagnoses. In the RTM group time to treatment discontinuation was significantly greater and prescriptions for steroids were more frequent (Table 1). Additionally, RTM use was associated with about a 51% risk of hospitalization (95% CI: 0.29, 0.88, p: 0.015) and 82% risk of ER visits (95% CI: 0.49, 1.39, p: 0.458) compared to the control group. Estimated cost savings in hospitalization associated with RTM use were $11,733,933 per 1000 patients treated for one year. Symptoms were detected more frequently in the RTM group compared to the control group, including potentially ICI-related symptoms such as rash (18% vs 3.2%), diarrhea (28% vs 4.7%), and difficulty breathing (28% vs 4.8%). **Conclusions:** Active ePRO-based RTM with Canopy is associated with increased time to ICI discontinuation and decreased acute care events. Increased use of steroids in patients reporting symptoms suggesting ICI toxicity may explain the beneficial effect of RTM. Research Sponsor: None.

Weighted analysis outcomes.

Outcome	RTM group	Control group	Risk or Hazard Ratio RTM / Control (95% CI)	Risk or RMST difference RTM - Control (95% CI)
Time to discontinuation	Median: 7.5 mos (95% CI: 6.7, 8.8)	Median: 4.1 mos (95% CI: 3.6, 4.6)	0.55 (95% CI: 0.47 to 0.64, $p < 0.001$)	19 days (16, 22)
Hospitalization	6.9%	14%	0.51 (0.29, 0.88, p: 0.015)	-6.66 (-11.02, -2.13, p: 0.008)
Emergency room visit	9.9%	12%	0.82 (0.49, 1.39, p: 0.458)	-2.46 (-8.05, 2.95, p: 0.366)
Steroid use	53%	31%	1.69 (1.41, 2.02, $p < 0.001$)	21.67 (13.90, 29.13, $p < 0.001$)

11109 **Poster Session**

E-PROs in oncology: Improving treatment adherence to treatment while reducing emergency care and costs for patients with gastrointestinal malignancies receiving systemic therapy. First Author: Patricia Rioja, Clinica Oncosalud-AUNA, Lima, Peru

Background: Patients with cancer undergoing systemic therapy are prone to experience symptom-related complications which may lead to emergency room visits (ERV) and non-planned inpatient admissions (NIA), resulting in increased costs to health systems. Symptom monitoring and proactive management based on ePRO protocols have been shown to reduce acute care utilization; however, the economic impact of this intervention remains incompletely characterized. In addition, patients monitored through ePRO systems tend to remain on active anticancer treatment for longer periods, with fewer unplanned treatment interruptions. Our aim was to evaluate the economic impact of a remote Comprehensive Companion Program (CCP) in a private health system. **Methods:** We conducted a retrospective study within the AUNA oncological network in Lima, Peru. Adult patients with GI malignancies receiving systemic therapy who experienced at least one ERV or NIA between June 2021 and July 2022 were included. Patients were grouped according to enrollment in a remote CCP or receipt of usual care. Costs related to ERV and NIA were analyzed from a payer's perspective and adjusted by time on treatment to estimate average monthly cost per-patient. Data were analyzed using descriptive and comparative statistical methods. **Results:** A total of 97 patients with comparable baseline clinical characteristics were included (50 in the CCP group and 47 with usual care). Patients in the CCP group had a significantly longer time on treatment (median 235.5 vs 151 days; p = 0.0009), driven primarily by patients with metastatic disease. When costs associated with ERV and NIA were normalized by treatment duration, the CCP group was associated with significantly lower monthly acute care costs. Median monthly variable costs per patient were USD $147.14 versus $449.70 (p = 0.0137), representing an 67% of costs reduction in monthly variable costs per patient. Similarly, median monthly prorated expenses per patient were $220.33 versus $636.66 (p = 0.0151), corresponding to an approximate 65% reduction in monthly prorated expenses. **Conclusions:** Our study showed that patients enrolled in a CCP incorporating e-PRO based symptom monitoring remained on treatment for longer; however, this was associated with significantly lower time-adjusted acute care costs. These findings highlight the potential value of the CCP in reducing cancer care–related costs, while acknowledging that the results are limited to a private health care setting. Research Sponsor: None.

11110 **Poster Session**

Determinants of cervical cancer awareness, procedural knowledge, and information sources among Nepali women undergoing HPV screening. First Author: Jin Mou, Binaytara, Bellevue, WA

Background: Successful implementation of cervical cancer screening in low- and middle-income countries (LMICs) depends on community acceptance. Although general awareness of cancer is rising, limited understanding of screening procedures continues to hinder participation. This study examined the factors influencing cervical cancer awareness, procedural knowledge, and sources of screening information among Nepali women undergoing HPV-based screening. **Methods:** HPV screening was conducted through two community health fairs in Janakpur, Nepal, in 2025. Clinician-collected samples were tested using an isothermal amplification assay. Survey data collected included participants' age, education level, cervical cancer awareness, procedural knowledge on vaginal sampling, sources of screening information, and health decision-making practices. Multivariate logistic regression was used to identify factors associated with cervical cancer awareness, procedural knowledge, and information sources. **Results:** Valid survey data from 274 Nepali women, including 32 HrHPV-positive cases, were analyzed. Cervical cancer awareness was significantly associated with education. Women with secondary education or higher were more likely to have heard of cervical cancer (aOR 4.45; 95% CI 1.81-10.95, p= 0.001), compared to those with less education. However, education was not associated with specific knowledge of vaginal sampling. Procedural knowledge was instead hindered by low health autonomy (husband or in-laws as decision-maker: aOR 0.42, 95% CI 0.25-0.72, p= 0.002, vs. self-decision making). Women who tested HrHPV-positive were significantly less likely to understand the sampling procedure prior to testing than those who tested negative (aOR 0.33, 95% CI 0.14-0.78, p= 0.01). Regarding information sources, women aged 30-44 years relied more on community networks, i.e., female community health volunteers (FCHVs) than medical providers, compared to women $<$ 30 years (aOR 1.89, 95% CI 1.01-3.53, p= 0.048). **Conclusions:** Cervical cancer awareness in Nepali women is driven by education, but procedural knowledge is limited by low health autonomy. Middle-aged and older women rely on FCHVs or their community networks to acquire information about cervical screening. Future implementation strategies should address interventions that empower women and improve understanding of screening procedures, as well as tailored training on FCHVs to promote cervical screening among middle-aged women. Keywords: Cervical Cancer, Procedural Knowledge, Awareness, Implementation Science, Health Literacy, Global Health Research Sponsor: None.

11111 **Poster Session**

Digital oncology navigation based on ePROs: Effects on acute healthcare utilization and cost savings in a middle-income country setting. First Author: Alessandra Menezes Morelle, Thummi Global, Porto Alegre, Brazil

Background: Oncologic treatment is associated with a high clinical and economic burden. Traditional patient navigation models often lack real-time symptom monitoring, increasing the risk of clinical deterioration. Digital navigation models incorporating ePROs have emerged as a promising strategy to address this gap. However, evidence on their implementation in low- and middle-income settings remains limited. This study aimed to assess the healthcare utilization and economic impact of an ePRO-based digital oncology navigation program in a real-world Brazilian healthcare setting. **Methods:** We conducted a prospective, single-arm, before-and-after study between February and November 2025 at a private healthcare provider in southern Brazil. Adult patients (pts) with any cancer type undergoing intravenous chemotherapy and/or immunotherapy were enrolled in a digital oncology navigation program integrating app-based ePRO monitoring, automated symptom triage, and proactive nurse-led follow-up. The primary outcome was estimated cost avoidance (from the healthcare provider perspective), calculated as the difference between pre- and post-implementation costs associated with acute healthcare utilization (hospitalizations and emergency room [ER] visits). Secondary outcomes included hospitalization and ER utilization rates, patterns of digital health service use (program adherence and daily and overall volume of symptom reports), and the clinical profile of pts who required hospitalization. Descriptive statistics were applied. **Results:** A total of 55 pts were included. The mean age was 54 years, and 63.5% were female. Breast cancer (25.5%; n = 14), non-Hodgkin lymphoma (12.7%; n = 7), and lung cancer (10.9%; n = 6) were the most frequent tumor types. Most pts had stage II–III disease (63.9%) and were receiving chemotherapy (54.8%). Hospitalization rates decreased from 29% to 22% after program implementation, while ER utilization declined from 80% to 35%. Patient adherence was high (90.8%), with consistent engagement in symptom reporting throughout follow-up (600 total symptom reports; mean of 5.4 daily reports). Most reported symptoms were managed remotely by the nursing team (95%), with minimal need for physician escalation. Among pts who required hospitalization, lung cancer was the most frequent primary tumor (50.1%). The estimated total cost avoidance was R$332,769 (≈US$66,500), corresponding to a mean saving of R$6,050 (≈US$1,210) per pt. Avoided hospitalizations accounted for most of the economic benefit. **Conclusions:** Implementation of an ePRO-driven digital oncology navigation program may reduce acute healthcare utilization and meaningful short-term cost avoidance in a real-world healthcare setting. These findings support the integration of digital symptom monitoring as scalable, cost-saving strategie in oncological care delivery. Research Sponsor: None.

11112 **Poster Session**

PROgress Tracker Breast Cancer Registry: Reporting worry of illness from a longitudinal peer-led, national patient-reported outcomes (PRO) registry. First Author: Shaniah Leduc, Breast Cancer Canada, Montclair, NJ

Background: PROgress Tracker Breast Cancer Registry is a national, ethics approved non-interventional patient-reported outcome measure (PROMs) registry, using a peer-to-peer model directed by patient advocacy group Breast Cancer Canada. Here, initial results report breast cancer survivors nature of cancer illness worry and intensity based on age, stage and molecular subtype at diagnosis. **Methods:** PROgress Tracker was launched in 2023, with enrollment over 10 years of Canadians with Stage 0-IV breast cancer. Participants self-refer and complete a series of validated PROMs (demographic, socioeconomic, clinical, global wellbeing) via a digital platform, capturing current status on a quarterly basis for up to 10 years. Real-world analysis assisted by AI (*January 2026; Claude [Opus 4.5], manufacturer: Anthropic; data extraction, statistical analysis with means, percentages, patient-level aggregation, stratification by clinical variables, longitudinal pattern analysis and visualization; all outputs validated against source data*) of FACT-B PROM data capture and analysis methodology was used. **Results:** To date, 823 participants have enrolled with 186 participating for ≥2 years. From participation start, longitudinal worry is reported using 3 factors from FACT-B PROM; hereditary risk of family members (HR), if stress impacts illness (SI), and if participant's condition will worsen (CW). Highest degree of reported worry scores was in HR 40.4% (n = 74), SI 31.7% (n = 59) and CW at 17.4% (n = 32). Worry intensity varied by age, stage and molecular subtype. Participants diagnosed < 50 years reported higher levels in all 3 factors (HR 51% mean 2.53; SI 46.9% mean 2.24; CW 24.5% mean 1.78) to those at > 50 years (HR 37.1% mean 1.92; SI 25.9% mean 1.63; CW 14.3% mean 1.32). Stage IV participants show 66.7% high worry (CW and HR) compared to stage I at 8.5% (CW). Molecular subpopulations show higher worry in HR- / HER2- (TNBC) n = 34 (HR 48.5% mean 2.24; SI 38.2% mean 2.00; CW 17.6% mean 1.59) compared to HR+ / HER2- n = 81 (HR 37.5% mean 2.04; SI 35.4% mean 1.90; CW 17.3% mean 1.41) and HR+ / HER2+ n = 13 (HR 30.8% mean 2.08; SI 23.1% mean 1.77; CW 7.7% mean 1.38). Non-linear trajectory over time shows 24% (n = 183) experienced high worry at registry entry, declining at 12 months to 15.8% with a secondary peak at 18 months in 21.7% of participants. **Conclusions:** Patient-reported outcomes show the burden of worry by breast cancer survivors for hereditary risk to family and individuals' illness. These findings offer directional insights for psychosocial screening, care resources and tailored education throughout survivorship. Research Sponsor: Breast Cancer Canada; Astra Zeneca Canada, Gilead Sciences Canada, Novartis Canada; The Hecht Foundation.

11113 **Poster Session**

Text-based electronic patient-reported outcome monitoring in oncology: A 180-day longitudinal analysis of symptom burden changes in 701 cancer patients. First Author: Pallav K. Mehta, Reimagine Care, Nashville, TN

Background: Digital electronic patient-reported outcome (ePRO) systems promise to improve symptom management in oncology, yet evidence demonstrating sustained clinical benefit across diverse cancer populations remains limited. This study evaluated the longitudinal effectiveness of a text-based ePRO platform delivering weekly validated symptom assessments in reducing overall symptom burden among cancer patients over 180 days. **Methods:** This retrospective study consisted of 701 patients with cancer recruited between 2022–2025. The patients were eligible if they were on the platform for at least 90 days, completed the baseline survey within 14 days of enrollment, and had a survey completion rate of at least 30%. ePRO responses triggered review by a virtual care team that provided protocolized symptom management outreach and triage in collaboration with treating oncology practices. The primary outcome was the change in overall symptom burden over 180 days, measured by the Edmonton Symptom Assessment System (ESAS; total score 0–90). Secondary outcomes included physical symptoms (0–60), emotional symptoms (0–20), and well-being (0–10). Stratified analyses were done using paired t-tests. **Results:** The final cohort (mean age 64.6 years; 57.2% female; 20.5% metastatic; mean adherence 66.1%) demonstrated significant reduction in total symptom burden (20.99 to 18.11 points; -2.89 points, -13.7%, $p < 0.001$) and physical symptoms (14.86 to 12.18 points; -2.68 points, -17.0%, $p < 0.001$). Emotional symptoms and well-being showed no significant change. Efficacy was engagement-dependent: high-engagement patients (N = 465) achieved -2.80-point reduction ($p < 0.001$) versus non-significant changes in medium/low-engagement groups. Stratified analyses revealed heterogeneity: breast cancer patients demonstrated exceptional response (-8.96 points, -46.3%, p = 0.008), while GI cancer patients showed resistance (-0.43 points, p = 0.915). Non-metastatic patients (-3.06 points, $p < 0.001$), females (-3.27 points, $p < 0.001$), and patients aged < 50 years (-4.28 points, p = 0.011) demonstrated superior outcomes compared to metastatic, male, and elderly (≥75 years) patients. **Conclusions:** Text-based digital ePRO monitoring significantly reduced symptom burden in cancer patients over 180 days, with physical symptom improvement as the primary driver. Clinical benefit was engagement-dependent and varied substantially by cancer type, metastatic status, age, and gender. These findings validate the clinical utility of SMS-delivered ePRO systems while identifying highly responsive populations (breast cancer, non-metastatic, younger patients) and vulnerable subgroups requiring enhanced symptom management support. Research Sponsor: None.

11114 **Poster Session**

Advancing value-based breast cancer screening in a safety-net health system: A multimodal approach to improving population health and system sustainability. First Author: Shivani Agarwal, Montefiore Einstein, Bronx, NY

Background: Evaluation of breast cancer screening (BCS) adherence in our large safety-net health system revealed wide variability and late-stage diagnosis rates that exceeded national benchmarks. A multidisciplinary taskforce (primary care, radiology, cancer center, and patient advocates) identified barriers, co-designed, and implemented a multi-pronged intervention to address screening uptake and adherence. **Methods:** Mixed-methods evaluation across 18 primary care sites revealed wide variability in BCS rates (60-82%); lack of systematic management of screening bottlenecks (ordering, scheduling, no-shows/cancellations); and unmet patient needs (transportation, screening hesitancy). We co-developed and implemented a phased intervention from March–December 2025 to address identified barriers through: (1) radiology navigator outreach to primary care patients at low-performing sites (March), (2) electronic medical record patient portal self-scheduling (July), (3) AI-assisted rescheduling after no-shows/cancellations (December), and (4) assessment and navigation of social needs and screening hesitancy (March). Outcomes measured were outreach, engagement, and screening completion. We performed multivariate regression to examine demographic predictors of screening. **Results:** Of 57, 041 HEDIS-eligible patients, 15,971 (28%) were overdue at baseline (mean age 58 yo, 77% Hispanic or non-Hispanic Black, 74% Medicaid or Dual). Overall, the intervention resulted in 1,610 additional screens over 9 months, improving systemwide BCS rates from 72 to 76%. Of the additional screens, radiology navigator achieved 452 screens (29%), patient portal self-scheduling achieved 1,097 screens (70%), and AI-assisted outreach of no-show/cancelled achieved 61 screens (4%). Engagement and show rates varied: navigator outreach had the highest scheduling engagement (74%) but lower show rates (46%); patient portal self-scheduling showed moderate engagement (44%) with higher show rates (76%); and AI-assisted outreach had low engagement (4%) with moderate show rates (56%). Demographics did not predict screening outcomes. Screening hesitancy (37%) and transportation (10%) were the most common barriers, addressed through social and peer navigation, respectively. Revenue from additional screenings fully offset navigator costs. **Conclusions:** A coordinated, resource-efficient screening outreach strategy combining digital tools, human navigation, and AI assistance—co-designed with patients and clinical stakeholders—improved BCS adherence, addressed unmet needs of underserved populations, and proved itself financially sustainable across a safety net health system. Future efforts will focus on further scaling of population health approaches to cancer screening programs. Research Sponsor: None.

11115 **Poster Session**

Proactive response initiative for symptom management (PRISM): A multi-institutional symptom monitoring program for veterans receiving systemic cancer therapy. First Author: Denaly Chen, Tibor Rubin VA Medical Center, Long Beach, CA

Background: Symptom assessment and management in cancer care are challenging. Within the Veterans Health Administration (VHA), gaps remain in widescale implementation of standardized symptom assessment, technology support, and adaptable workflows. PRISM was developed as a multi-institutional, technology-enabled clinical program to improve early identification and treatment of cancer-related symptoms for Veterans with the ultimate goal of system-wide implementation. **Methods:** We adapted an evidence-based proactive symptom intervention for the Long Beach VA with a working group of clinicians, pharmacists, social workers, case managers, and ancillary staff. The intervention involved a peer specialist conducting weekly telephone-based assessments using a modified Veteran Symptom Assessment System (VSAS) for Veterans initiating systemic anti-cancer treatment. Symptom scores ≥4 on a scale of 0-10 or a score increase by 2 points automatically triggered Nurse Practitioner (NP) review and follow up. We conducted an evaluation of our first PRISM site and assessed Veteran retention, symptom burden, interventions, and process metrics to inform scale and spread for two future VHA sites this quarter. **Results:** From May 22, 2025 to December 1, 2025, 30 patients (pts) enrolled in PRISM; 4 (13%) withdrew < 1 month, 2 (6.7%) withdrew > 1 month, 2 (6.7%) completed the program, and 1 (3.3%) died. Frequently reported symptoms of any score were fatigue (n = 14; 61%), dyspnea on exertion (n = 6; 26%), and pain (n = 6; 26%). Of the 412 times symptoms were reported as ≥4 on a scale of 0-10, the most frequent were fatigue (22%), dyspnea with exertion (13%), and drowsiness (13%). For the 23 pts who remained in the program for > 1 month there were 308 peer specialist encounters and 205 NP encounters. NPs intervened in 91% (186/205) of encounters with a total of 961 interventions. The mean number of interventions per NP encounter was 3.67. The most frequent intervention was pt education 86% (827/961), medication prescriptions 13% (123/961), and alerting the primary oncology team 4.2% (41/961). The mean time interval between a VSAS survey and indicated NP follow up was 1.06 days. The call duration was a mean 9.25 minutes per encounter with the peer specialist and 17.3 minutes per encounter with the NP. Documentation and chart review took a mean of 10.5 minutes per peer specialist encounter and a mean of 14.4 minutes per NP encounter. **Conclusions:** Early results from our first real world PRISM implementation in the VHA demonstrate feasibility, retention, and frequent early identification of and intervention for symptoms using this proactive symptom management program embedded within existing pt oncology care. The process metrics regarding capacity for peer support and NP effort will inform our expansion to two implementation sites by June 2026 and an additional 10 sites by 2027. Research Sponsor: None.

11116 Poster Session

Factors associated with clinical trial failure and termination in non–small cell lung cancer immunotherapy: A ten-year review. First Author: Arman Asatryan, Yerevan State Medical University named after Mkhitar Heratsi, Yerevan, Armenia

Background: Immunotherapy (IO) has transformed NSCLC management, yet trial efficiency and strategy-level success patterns across settings remain incompletely described. We evaluated NSCLC IO trials for termination trends, outcome accessibility, shifts in strategies over time, and factors associated with endpoint success and failure to inform future trial designs. **Methods:** We identified interventional NSCLC IO trials from ClinicalTrials.gov from 2015–2024 with completed/terminated status. Trials were categorized by setting (metastatic 1L and beyond 1L; perioperative; other/mixed), intervention strategy (PD-(L)1 monotherapy; PD-(L)1+chemotherapy; PD-(L)1+CTLA-4; PD-(L)1+targeted/VEGF/ADC; RT/CRT+ICI; other IO), phase group, sponsor type (industry vs non-industry), and disease stage. Statistic analysis was done using chi-square/Fisher tests and multivariable logistic regression. Among completed trials, success/failure was defined as meeting/not meeting the primary endpoint when outcomes were assessable. **Results:** Among 198 NSCLC IO trials, 67 (33.8%) were terminated, 131 (66.2%) completed. Termination increased over time (24.0% 2015–2017, 48.1% 2018–2019, 57.1% 2020–2022; p = 0.0005) and persisted after accounting for setting, phase, sponsor type (2018-2019 vs 2015-2017: OR 2.87, p = 0.0037; 2020-2022 vs 2015-2017: OR 3.22, p = 0.0277). Metastatic disease trials shifted from late (56.0%, 2015–2017;42.9%, 2020–2022) to 1L (28.8% - 47.6%). Endpoint outcomes were assessable in 72/131 (55.0%) completed trials - more in metastatic 1L vs later-line (75.0% vs 42.3%, p = 0.0086; OR 0.30, p = 0.013) and in industry vs non-industry trials (71.9% vs 41.9%; p = 0.0012, OR 0.38, p = 0.030). Among these, 47 (65.3%) met primary endpoints. Success varied by strategy: PD-(L)1+chemo 73.1%, PD-(L)1 mono 60.9%, PD-(L)1+CTLA-4 50.0%, PD-(L)1+targeted 20.0%, RT+ICI 85.7%; PD-(L)1+chemo outperformed PD-(L)1+targeted (Fisher p = 0.0416). Strategy shifted over time (p = 0.034), with decreased PD-(L)1 mono and increased RT+ICI and PD-(L)1+targeted combinations in later years. Proportion of PD-(L)1 monotherapy was higher for perioperative trials (47.4%) vs metastatic 1L (16.7%) and later-line settings (26.7%). Cell-(n = 8) and vaccine/virus-based (n = 12) approaches were uncommon (term. 25% and 50%) with limited assessable outcomes. **Conclusions:** Treatment strategies shifted away from PD-(L)1 monotherapy toward combination approaches and, in metastatic disease, from late-line to 1st line settings. PD-(L)1+chemotherapy and RT+ICI showed higher success rates than PD-(L)1+targeted combinations, though some subgroups were small. Other IO agents are rarely used in NSCLC and have insufficient reporting. Incorporating predictive risk models into trial planning may reduce low-yield studies and accelerate identification of effective treatments. Research Sponsor: None.

11117 Poster Session

Evaluating the role of informal caregivers in metastatic cancer patients treated with oral anticancer therapy: A prospective observational study. First Author: Barbara Salvo, Division of Medical Oncology, "G. Martino" University Hospital, University of Messina, Messina, Italy

Background: The increasing use of oral anticancer agents (OAAs) in metastatic cancer has shifted treatment management from hospital to home, transferring responsibility for adherence and symptom monitoring to patients and informal caregivers. Evidence on caregiver burden and its impact on patient-reported outcomes in this setting remains limited. **Methods:** This prospective observational study evaluated patients with metastatic cancer receiving OAAs and their informal caregivers. At baseline and three months, patients completed the EORTC QLQ-C30, MMAS-8, TEMPS-A, and the G8 geriatric screening tool; caregivers completed the Zarit Burden Interview (ZBI), Caregiver Reaction Assessment (CRA), TEMPS-A, and an ad hoc caregiving questionnaire. Statistical analyses were performed using IBM SPSS Statistics ($p < 0.05$). **Results:** Sixty-eight patients (median age 67 years; 50% female) were enrolled; among patients aged >70 years, the G8 score indicated a predominance of non-frail patients (68.2%). 66.1% had a caregiver, most commonly a spouse (46.5%) or child (41.9%). Caregivers (mean age 56 years) were involved for >2 years in 76.7% of cases and attended outpatient visits in 69.8%. ZBI showed minimal/no burden in 60.5% and mild-to-moderate burden in 32.6%. CRA scores were highest for self-esteem (4.13±0.62), followed by schedule (3.31±1.36) and health (3.10±0.66). Patients with caregivers reported worse quality of life, physical, role, and emotional functioning, higher symptom burden (fatigue, pain, dyspnea, appetite loss, financial difficulties), and lower adherence compared with those without caregivers (all $p<0.05$). Caregiver presence was associated with cyclothymic, depressive, and anxious temperaments. Patients cared for by a child showed better role functioning, while spousal caregiving was associated with irritable temperament. At three months (n=22), patients showed significant improvements in adherence, quality of life, physical and role functioning, and symptom burden, suggesting early adaptation to oral therapy despite high baseline caregiving demands. **Conclusions:** Informal caregivers play a central role in OAA-treated metastatic cancer. Caregiver involvement appears to reflect greater patient vulnerability rather than a causal determinant of poorer outcomes, supporting the need for systematic caregiver assessment and targeted supportive interventions. Research Sponsor: None.

Caregiver characteristics and associated patient outcomes.

Variable	Caregiver present	No caregiver
Patients, %	66.1	33.9
Relationship, %	Spouse 46.5 / Child 41.9	–
Care duration >2 yrs, %	76.7	–
Presence at visits, %	69.8	–
ZBI burden, %	None/min 60.5; Mild–mod 32.6	–
CRA self-esteem (mean±SD)	4.13±0.62	–
Quality of life	↓	↑
Physical functioning	↓	↑
Symptom burden	↑	↓
Therapy adherence	↓	↑

11118 Poster Session

Real-world utilization patterns and adverse events among patients receiving antibody–drug conjugates (ADCs) across the University of California health system. First Author: Guanming Chen, UCSF, San Francisco, CA

Background: Antibody–drug conjugates (ADCs) have rapidly expanded across oncology indications, yet real-world safety profiles remain incompletely characterized. Pivotal trials may not fully capture adverse events (AEs) associated with real-world treatment patterns, such as cumulative exposure or sequential ADC therapy. **Methods:** We performed a retrospective cohort study across six UC medical centers using de-identified structured EHR data from the University of California Health Data Warehouse (UCHDW). We included adult patients who received at least 1 dose of ADC between Jan 2015 and Feb 2025. Observational period for safety surveillance is at least 8 months. Key safety outcomes were the incidence and timing of key AEs following ADC initiation. Secondary outcomes included duration of ADC therapy and the frequency of sequential ADC. Descriptive statistics were used to analyze toxicity and time to AE of special interest. **Results:** Across the UC system, 4,531 patients received at least one ADC and had a documented cancer-related diagnosis, 82.7% of patients had metastatic cancer at initiation of ADC. Breast cancer was the most frequently observed cancer type (38.8%), followed by hematologic malignancies (28.5%) and bladder/urothelial cancers (11.2%). Mean dose number was 10.1 (standard deviation: 11.3). Among 4,531 ADC-treated patients, 10.6% transitioned to a second ADC, and 78.9% received concomitant anticancer therapy, including immune checkpoint inhibitors (38.0%), ICI plus chemotherapy (21.8%), or chemotherapy alone (18.7%). Incident neurotoxicity was the most frequent AE (728 patients, 16.1%), followed by hematologic (15.0%) and cardiotoxicity (14.6%) AEs. Incident ocular toxicity was observed in 343 patients (7.5%) with a median time to onset of 84 days, and incident mononeuritis in 480 patients (10.6%) with a median onset of 105 days following ADC initiation. **Conclusions:** In this large, multicenter real-world cohort, ADC treatment was associated with substantial rates of neurologic, hematologic, and cardiac toxicities. The frequent use of concomitant anticancer treatments and observed transitions between ADCs underscore the complexity of real-world exposure and highlight the need for proactive toxicity monitoring and optimized safety management strategies in routine oncology practice. Research Sponsor: None.

11119 Poster Session

Inpatient palliative care utilization and outcomes among decedent patients with metastatic cancer in the U.S. First Author: Jiazhang Xing, Sinai Hospital of Baltimore, Baltimore, MD

Background: Palliative care (PC) is a key component of high quality cancer care, especially at the end of life. However, real world national data describing inpatient PC utilization remain limited. We evaluated patterns of PC use and associated outcomes among decedent patients with metastatic cancer in the U.S. **Methods:** We conducted a cross-sectional analysis of the 2021–2023 National Inpatient Sample of decedent patients with metastatic cancer. Palliative care, cancer type, and metastatic status were identified using ICD-10 codes. Patient characteristics included age, sex, race, comorbidity burden, insurance status, and household income. Hospital characteristics included location (urban vs rural) and ownership (public, private not-profit, and private invest-own). Outcomes included length of stay (LOS), inpatient procedures, and total costs. Factors associated with palliative care use and adjusted mean differences in outcomes were estimated. **Results:** An estimated 52,841 hospitalizations of decedent patients with metastatic cancer were identified, with 34,955 (66.2%) involving palliative care. PC utilization varied by cancer type (Table) and increased over time (aOR per year 1.15; 95% CI 1.12–1.18). PC use was independently associated with older age, female sex, private insurance, higher neighborhood income, and care at private not-for-profit hospitals (all $p<0.001$). PC was associated with fewer inpatient procedures (adjusted mean difference −1.38; 95% CI −1.45 to −1.31), shorter LOS (−1.25 days; 95% CI −1.45 to −1.06), and lower total costs (−$10,557; 95% CI −$11,421 to −$9,694). Reductions in procedures, LOS and costs were significant across most cancer types. (Table). **Conclusions:** Inpatient PC was associated with lower care intensity and costs across cancer types among decedent patients with metastatic cancer. Yet, about one third never received PC, highlighting a major end-of-life care gap and the need for earlier, more equitable integration to improve value based oncology care. Research Sponsor: None.

Palliative care utilization and outcomes by major cancer type.

Cancer Type	PC use	Adjusted Procedures difference	Adjusted Cost difference ($)	Adjusted LOS difference (days)
Breast	2646 (66.7%)	-1.47 (-1.70,-1.24)	-12512 (-16301, -8722)	-1.90 (-2.63,-1.17)
Colorectal	2932 (65.8%)	-1.75 (-1.49,-2.00)	-12231 (-15261, -9201)	-1.09 (-1.83,-0.35)
Lung	8942 (67.9%)	-1.14 (-1.28,-1.00)	-6341 (-7894, -4968)	-0.90 (-1.24,-0.56)
Prostate	1897 (62.3%)	-1.24 (-1.52,-0.97)	-9736 (-12915, -6558)	-0.88 (-1.82,0.05)*
Pancreas	2574 (68.4%)	-1.46 (-1.72,-1.21)	-7396 (-9525, -5266)	-0.39 (-0.94,0.17)*
Kidney	936 (66.3%)	-1.72 (-2.20,-1.23)	-12353 (-17623, -7082)	-1.93 (-3.11,-0.75)
Liver	1362 (67.8%)	-0.87 (-1.24,-0.51)	-8896 (-13426, -4367)	-1.27 (-0.33,-2.20)

All $p<0.001$ unless noted with *.

11120 **Poster Session**

Risk of immune-related adverse events from checkpoint inhibitors in cancer patients with autoimmune disease: An emulated target trial. First Author: Rotana M. Radwan, Purdue University, Indianapolis, IN

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by activating the immune system to target and eliminate cancer cells, leading to durable responses and improved survival. However, patients with preexisting autoimmune diseases are excluded from ICI clinical trials due to concerns about triggering immune-related adverse events (irAEs). Consequently, there is limited real-world data comparing the risk of irAEs between ICIs and other systemic cancer therapies in this high-risk population. **Methods:** We conducted a target trial emulation using a new-user, active-comparator design to compare the risk of developing de novo irAEs following ICI initiation compared to chemotherapy or targeted therapy. Using Merative MarketScan data (2014–2023), we identified adults with cancer and a preexisting autoimmune disease who initiated treatment with ICIs, chemotherapy, or targeted therapy. Propensity score matching (1:1) was performed for two comparisons: ICI versus chemotherapy and ICI versus targeted therapy. The primary outcome was de novo irAEs affecting organ systems distinct from the patient's baseline autoimmune disease. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with subgroup analyses by age, sex, cancer type, preexisting autoimmune disease category, and ICI class. **Results:** A total of 3,601 matched patient pairs were included in the ICI–chemotherapy comparison and 1,479 matched pairs in the ICI–targeted therapy comparison. Patients receiving ICI had a significantly higher risk of developing de novo irAEs compared to those receiving chemotherapy (HR=1.71; 95% CI, 1.49–1.97) or targeted therapy (HR=1.43; 95% CI, 1.20–1.70). This increased risk was consistent across age and sex. By ICI class, CTLA-4 inhibitors were associated with the highest risk (HR=2.64; 95% CI, 1.97–3.53 vs chemotherapy; HR=1.72; 95% CI, 1.18–2.50 vs targeted therapy), followed by ICI combination therapy (HR=2.46; 95% CI, 1.80–3.37 vs chemotherapy). By cancer type, patients with liver cancer had the greatest risk (HR=2.75; 95% CI, 1.96–3.85 vs chemotherapy; HR=2.67; 95% CI, 1.68–4.24 vs targeted therapy), followed by breast cancer (HR=2.11; 95% CI, 1.31–3.42 vs chemotherapy; HR=1.97; 95% CI, 1.06–3.68 vs targeted therapy). By baseline autoimmune disease category, patients with endocrine autoimmune diseases consistently showed elevated risk across both comparisons (HR=1.74; 95% CI, 1.42–2.14 vs chemotherapy; HR=1.92; 95% CI, 1.43–2.58 vs targeted therapy). **Conclusions:** ICI use in cancer patients with preexisting autoimmune diseases is associated with a higher risk of de novo irAEs than chemotherapy or targeted therapy, with risk varying by ICI type, cancer type, and underlying autoimmune condition, highlighting the need for individualized risk assessment and close monitoring. Research Sponsor: None.

11121 **Poster Session**

Trends in ivermectin medication records with cancer as the primary diagnosis following public attention: A national EHR analysis. First Author: Changchuan Jiang, UT Southwestern Medical Center, Dallas, TX

Background: Ivermectin, an antiparasitic agent not indicated for cancer treatment, has received public attention since early January 2025 due to widespread discussion on social media and other non-clinical forums. Little is known about whether the increased visibility may influence medication use or reporting among patients with cancer in real-world clinical data. **Methods:** We conducted a retrospective descriptive analysis using the EPIC COSMOS, a large, multi-institutional U.S. electronic health record network. We identified all ivermectin medication records from quarter (Q)1 2024 to Q3 2025, including prescribed/administered and patient-reported medications linked to clinical encounters. Our primary outcome was the quarterly trend in the percentage of ivermectin records where cancer was listed as the primary diagnosis for the encounter. Secondary measures included other diagnosis associated with the encounter (e.g., parasitic) and patient demographics. **Results:** We identified 96,525 ivermectin medication records, increasing from 11,854 in Q1 2024 to 15,223 in Q3 2025. The proportion of records with cancer as the primary diagnosis increased modestly during 2024 (from 2.3% to 3.1%; average quarterly increase=0.2 percentage points [ppts]), followed by a larger increase in Q1 2025 (from 3.1% to 4.2%, adjusted increase=1.0 ppts, relative increase=32%, $p<.001$), which stabilized in Q2 and declined slightly in Q3 2025. The surge from Q4 2024 to Q1 2025 was larger for patient-reported ivermectin (from 156 to 231 records, 48% increase) than prescribed/administered medications (292 to 347 records, 19% increase). In contrast, the proportion of ivermectin records associated with strongyloidiasis, onchocerciasis, or scabies ranged from 18.5%–19.5% in 2024 and declined to 17.1% in Q1 2025, while records associated with other infectious conditions remained stable (~49%). Among records with cancer as the primary diagnosis (n=3,157), mean patient age was 62 years, with 46% female, 76% White, 8% Black, and 10% Hispanic; the proportion prescribed to White patients increased from 71% in Q4 2024 to 81% in Q1 2025. Physician specialty distribution associated with prescribed/administered ivermectin was 35% oncologists, 20% primary care, 22% dermatologists, 4.2% advanced practice providers, and 19% other specialties. **Conclusions:** Although ivermectin use in cancer care remained uncommon overall, real-world data show a rapid, largely patient-driven increase during Q1 2025. This rise is distinct from the stable or declining proportions of records linked to approved parasitic indications. These findings suggest that social trends may shape medication use, highlighting the importance of careful medication reconciliation and patient counseling in oncology settings to address non-evidence-based use. Research Sponsor: U.S. National Institutes of Health; K12AR084234.

11122 **Poster Session**

Machine learning–based prognostic models for mortality prediction after unplanned hospitalization in cancer patients. First Author: Taha Koray Sahin, Hacettepe University, Department of Medical Oncology, Ankara, Turkey

Background: Unplanned hospitalizations in oncology patients often indicate acute clinical deterioration and are associated with high mortality. Prognostic assessment at admission remains a challenge, particularly in resource-limited settings. Machine learning (ML) methods can integrate clinical and laboratory features to generate individualized mortality predictions, although the data is scarce. We aimed to develop and validate ML-based models to predict in-hospital, 30-day, and 90-day all-cause mortality in adult cancer patients with unplanned hospitalizations. **Methods:** We retrospectively analyzed patients with cancer who were admitted for unplanned hospitalizations at Hacettepe University Oncology Hospital between January 2018 and August 2024. Class imbalance was addressed using SMOTE, and ANOVA-based feature selection retained the top 20 predictors. Nine ML algorithms were tested, including SVM, kNN, decision trees, neural networks, and ensemble models. Model performance was assessed via 5-fold cross-validation using accuracy, precision, recall, F1-score, and AUC. **Results:** A total of 1646 cancer patients with unplanned hospitalizations were included. The most common cancers were gastrointestinal malignancies (32.8%), lung cancer (17.4%), and breast cancer (9.8%). For in-hospital mortality prediction, Random Forest achieved the best performance on the original dataset (AUC-ROC: 0.89; accuracy: 84.6%). After SMOTE, SVM yielded the superior results (AUC-ROC: 0.98; accuracy: 93.6%). For 30-day mortality prediction, Random Forest was optimal pre-SMOTE (AUC-ROC:0.85; accuracy: 83.6%), whereas LightGBM reached the highest post-SMOTE performance (AUC-ROC: 0.97; accuracy:91.8). For 90-day mortality prediction, XGBoost demonstrated the best performance on the original dataset (AUC-ROC: 0.84; accuracy: 80.4%). Following the application of SMOTE, LightGBM outperformed the other models (AUC-ROC:0.90; accuracy:82.3%). **Conclusions:** This first study focusing on predicting in-hospital mortality in cancer patients with unplanned admissions shows that ML models based on routine admission data can reliably predict early- and long-term mortality. Incorporating such models into workflows may support early risk stratification, shared decision-making, and individualized care planning. Research Sponsor: None.

11123 **Poster Session**

Mortality caused by coexisting malignant neoplasms and type 2 diabetes mellitus in U.S. adults: A CDC WONDER analysis (1999–2020). First Author: Muhammad Abdullah, Punjab Medical College, Faisalabad, Pakistan

Background: Type 2 diabetes mellitus (T2DM) and malignant neoplasms are among the most prevalent chronic diseases worldwide. When coexisting, they substantially increase morbidity and mortality. However, national trends in cancer-related mortality among patients with T2DM in the United States remain underexplored. **Methods:** We analyzed CDC WONDER mortality data (1999–2020) to identify deaths among U.S. middle-aged (55–74 years) and older adults ($\geq$75 years) in which both malignant neoplasms (ICD-10 C00–C97) and T2DM (ICD-10 E11.0–E11.9) were listed as causes of death on death certificates. Age-adjusted mortality rate (AAMR) per 100,000 were calculated and stratified by sex, age group, race/ethnicity, and urbanization status. Trends in overall AAMRs were analyzed using the Joinpoint Regression Program to calculate the average annual percentage change (APC), with statistical significance set at $\leq$ 0.05. **Results:** From 1999 to 2020, a total of 255,154 U.S. adult deaths involved both T2DM and malignant neoplasms. The AAMR increased significantly over the study period (APC 2.91%; 95% CI 2.32–3.50; $p<0.01$). Joinpoint regression identified an inflection point around 2011, after which mortality accelerated markedly (APC 6.67%; 95% CI 4.94–8.42). Mortality rates were consistently higher in men compared with women (overall AAMR 13.4 vs. 7.28; $p<0.01$). Older adults experienced the highest mortality burden (overall AAMR 23.4; APC 2.83%; 95% CI 2.25–3.41), while middle-aged adults demonstrated a steeper relative increase (2.14; 3.40%; 2.72–4.07). Marked racial and ethnic disparities were observed. Asian or Pacific Islanders (API) showed the steepest rise (APC 5.96%; 95% CI 5.35–6.58), followed by Hispanics (5.12%; 4.61–5.63), non-Hispanic (NH) Whites (2.66%; 2.03–3.28), NH Blacks (2.47%; 1.87–3.07), and American Indian/Alaska Natives (AI/AN) (3.15%; 1.03–5.32). Overall AAMRs were highest among AI/AN (15.2) and NH Black adults (11.5), followed by Hispanics (10.5), NH Whites (9.39), and API (7.34). Rural populations consistently had higher mortality rate (overall AAMR 12.9; APC 1.20%; $p<0.01$), whereas urban populations demonstrated a greater relative increase (8.98; 3.24%; $p<0.01$). Regionally, the West experienced the most rapid increase in mortality, while the highest overall rates were observed in Nebraska, West Virginia, and Minnesota. **Conclusions:** Mortality among U.S. adults with concomitant T2DM and malignant neoplasms increased markedly from 1999 to 2020, significant disparities by sex, age, race/ethnicity, region, and urbanization. Integrated public health strategies linking diabetes management with cancer prevention, targeted screening, and equity-focused interventions are urgently needed. Research Sponsor: None.

11124 **Poster Session**

Timing and prognostic impact of thromboembolic events in lung cancer patients treated with immune checkpoint inhibitors: A time-dependent real-world analysis. First Author: Chinemerem Martlin Emeasoba, University of Arkansas for Medical Sciences, Fayettville, AR

Background: Thromboembolic events (TEEs) are complications associated with malignancy, and emerging evidence suggests immune checkpoint inhibitors may further increase thrombotic risk; however, the prognostic impact of thromboembolic events in the era of immune checkpoint inhibitors, where inflammation and vascular toxicity may be amplified, remains unclear. We analyzed the incidence, timing, and impact on survival of thromboembolic complications in lung cancer patients treated with immunotherapy at a single tertiary academic institution. **Methods:** We conducted a retrospective study of adult lung cancer patients treated with immunotherapy at a single rural academic center (2015–2025). Thromboembolic events were classified as arterial (myocardial infarction, stroke) or venous (deep vein thrombosis, pulmonary embolism). Clinical characteristics and VAN Index scores were compared by TEE status, and overall survival was assessed using Kaplan-Meier and time-dependent Cox regression to address immortal time bias. **Results:** Altogether, 505 lung cancer patients received immunotherapy during the study period; patients were predominantly White (76.6%) and male (56.4%), with 21.4% identifying as Black. 22.8% experienced at least one TEE. Histologic subtypes included 59% with non-small cell lung cancer and 41% with small cell lung cancer. The mean age at diagnosis was 65 years. Among patients with TEE, 63.5% experienced arterial and 40.0% venous events. Some patients experienced both venous and arterial events during follow-up. The mean time to first TEE was 404 days, with venous events occurring earlier in the disease course. Patients with TEE had significantly higher comorbidity burden (9.28 vs 6.51) and thrombotic risk by VAN Index (31.99 vs 23.69; both $p < 0.001$). While unadjusted Kaplan-Meier analysis showed no survival difference (22 vs 19 months; p = 0.126) and multivariable Cox models treating TEE as a baseline exposure showed no independent association with survival (aHR 1.05, 95% CI 0.80-1.38), time-dependent Cox modeling demonstrated a significantly increased mortality risk following TEE (aHR 2.45, 95% CI 1.85-3.26; $p < 0.001$). **Conclusions:** Thromboembolic events occurred in nearly one-quarter of lung cancer patients treated with immunotherapy and were associated with higher comorbidity and thrombotic risk. Although standard analyses showed no survival difference, time-dependent modeling demonstrated significantly increased mortality following TEE. These findings demonstrate that failure to account for TEE as a time-varying exposure may substantially underestimate its prognostic impact, underscoring the need for prospective dynamic risk assessment and thromboprophylaxis strategies during immunotherapy. Research Sponsor: None.

11125 **Poster Session**

Natural language processing–assisted chart review to assess documented cannabis use in electronic medical records (EMR) of adults undergoing cancer infusion therapy. First Author: Reina Haque, Kaiser Permanente Southern California, Pasadena, CA

Background: Patients' consumption of cannabis for symptom management is well-documented, yet prevalence of cannabis use, and its documentation among patients undergoing active cancer treatment is understudied. Our goal was to assess the prevalence of documented cannabis use in the EMR of patients undergoing infusion cancer therapy. **Methods:** We conducted a cross-sectional analysis of adult members of Kaiser Permanente Southern California undergoing infusion therapy between February 16 to 28, 2025. Natural language processing (NLP) of search terms indicative of cannabis use was used to identify any EMR documentation of such use in unstructured clinical notes in the past year. Each matched query included 15-20 words before and after the keyword and was manually reviewed for clinical context and confirm cannabis use. **Results:** We identified N = 690 cancer survivors undergoing infusion therapy during the two-week period. Of these, N = 354 (51%) had a cannabis notation in their EMR after applying the NLP program. Half were female. Altogether 1,010 snippets from N = 354 patients were output into a spreadsheet for manual review; each snippet required about 30 seconds to determine cannabis use status. Of the N = 354 patients, overall prevalence of cannabis use was 29% (N = 101). The highest prevalence was in patients undergoing first line palliative treatment (38%); followed by palliative after first line (25%); adjuvant (16%); then curative first line therapy (13%). Cannabis use was lower in among those undergoing curative after first line therapy (6%) and neoadjuvant therapy (3%). Highest cannabis use was observed in those with cancer of the breast (15%); lung (14%); prostate (10%); colorectal (10%) and gynecologic (8%). Regarding demographics, odds of cannabis use was greater in males (OR = 1.34, 95% CI: 0.82-2.21) vs. females (ref). Compared with Asians (ref), odds of cannabis use was about two-fold greater in Hispanic (OR = 1.95, 95% CI: 0.78-5.35), Black (OR = 2.47, 95% CI: 0.80-7.87), and White (OR = 2.30, 95% CI: 0.95-6.15) patients. Odds of cannabis use was 24% greater in younger individuals (< 50 years, OR = 1.76, 95% CI: 0.84-3.61), but all confidence intervals crossed the null. **Conclusions:** NLP-assisted manual review of chart notes is a time-efficient method to collect information on unstructured data. This methodology determined prevalence of cannabis use in patients undergoing cancer infusion therapy is 29%. Cannabis use was greater among patients being treated in palliative settings compared to adjuvant/curative settings. A limitation of this study is that cannabis use may be underestimated because we assume that not all discussions were recorded in the EMR. Information garnered from this cross-sectional data exploration will be used to plan a prospective study of cancer survivors to examine the risks and benefits of cannabis use. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.

11126 **Poster Session**

Breast cancer screening and detection after the 2024 USPSTF recommendation for women aged 40–49. First Author: Karen Farrar, Truveta Inc., Bellevue, WA

Background: In April 2024, the US Preventive Services Task Force (USPSTF) expanded its biennial screening mammography recommendations to include women aged 40–49, citing rising breast cancer incidence in this age group and persistent disparities in outcomes. How this expansion has influenced diagnosis and stage at diagnosis in real-world practice is not yet well characterized. **Methods:** Using a subset of de-identified electronic health record data from Truveta, we identified women aged 40–74 who underwent screening mammography between 2018 and 2025, had no prior breast cancer diagnosis and who had evidence of outpatient care 6-18 months before and 1-12 months after screening. For patients with multiple eligible screening mammograms, only the first was retained for analysis. Analyses were restricted to health systems with available cancer stage data. April 30, 2024, was used as the cut point (pre- vs. post-guideline). Outcomes included: (1) screening uptake by age group, (2) breast cancers diagnosed within 180 days of screening, (3) stage at diagnosis (early [AJCC 0–I] vs. later [II–IV]). Diagnosis and stage were derived from clinical notes and categorized as early- (AJCC stage 0–I) versus later-stage (II–IV). Logistic regression, adjusted for race, ethnicity, rural–urban residence, and family history, was used to evaluate differences by age group and guideline period. **Results:** Among 985,687 women aged 40-74 who received a screening mammogram, 880,685 (89.3%) occurred pre-guideline and 105,002 (10.7%) occurred post-guideline. Women aged 40–49 comprised a substantially larger share of screenings post-guideline (53,227/105,002, 50.7% vs. 262,330/880,685, 29.8% pre-guideline $p<.001$). The likelihood of a breast cancer diagnosis within 180 days did not differ between the pre- and post-guideline periods for women aged 40–49 (OR 1.03, 95% CI 0.79–1.34) or 50–74 (OR 0.87, 95% CI 0.75–1.01). Among women diagnosed within 180 days with cancer stage information available (n = 3,866), the likelihood of early- versus later-stage diagnosis did not differ between the pre- and post-guideline periods for women aged 40–49 (early-stage: 63.6% vs. 68.3%; OR 1.26, 95% CI 0.72–2.21) or 50–74 (OR 0.91, 95% CI 0.67–1.24). **Conclusions:** Following the April 2024 USPSTF guideline expansion, screening mammography uptake among women aged 40–49 increased substantially, however the likelihood of a breast cancer diagnosis within 180 days did not significantly differ between the pre- and post-guideline periods. Stage at diagnosis did not differ significantly in the short post-guideline period; longer follow-up is needed to assess whether earlier detection translates to stage-shift benefits over time. These findings provide early real-world evidence to inform the ongoing risk-benefit discussion surrounding breast cancer screening in younger women. Research Sponsor: Truveta.

11127 **Poster Session**

Safety and efficacy of immunotherapy rechallenge in solid tumors after discontinuation of immune checkpoint inhibitors for immune-related adverse events: A systematic review and meta-analysis. First Author: Yu Fujiwara, Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Immune-related adverse events (irAEs) often require treatment discontinuation in patients with cancer receiving immune checkpoint inhibitors (ICIs). Given limited subsequent treatment options, ICI rechallenge is frequently considered. We aimed to estimate the incidence of recurrent irAEs and objective response rates (ORR) in patients receiving ICI rechallenge following prior irAEs. **Methods:** PubMed, Web of Science, and Embase were searched for studies evaluating ICI rechallenge in patients with advanced solid tumors who previously suspended treatment due to irAEs. Outcomes included the incidence of grade 1-5 (Gr1-5), Gr1-2, and Gr3-5 irAEs, recurrent irAEs, new irAEs, ORR, and disease control rate (DCR). Random-effects meta-analyses and subgroup analyses by cancer type were performed. Meta-regression analysis was conducted to evaluate the impact of the grade and type of initial irAEs on response outcomes. Heterogeneity was assessed using I^2 statistics ($\geq$50% considered high). **Results:** Thirty-seven studies comprising 1,126 patients with initial irAEs (Gr1-2: 62.8%, Gr3-4: 37.2%) leading to suspension of ICIs were included. The most common initial irAEs in the pooled cohort were hepatitis/liver enzyme elevations (20.5%), pneumonitis (16.1%), and nephritis/acute kidney injury (14.8%). Pooled incidences of Gr1-5, Gr1-2, and Gr3-5 irAEs after ICI rechallenge were 42.2% (95% confidence interval [CI]: 35.3-49.3), 27.1% (95% CI: 22.9-31.7), and 18.8% (95% CI: 14.7-23.8), respectively. Subgroup analysis showed overall higher incidences of irAEs in melanoma (Gr1-5: 54.6%, Gr1-2: 23.2%, Gr3-5: 26.4%) than those in lung cancer (Gr1-5: 39.7%, Gr1-2: 27.4%, Gr3-5: 14.0%) and solid tumors (Gr1-5: 36.7%, Gr1-2: 22.8%, Gr3-5: 20.1%). The same type of irAEs recurred in 23.8% (95% CI: 20.1-28.0) of patients, while new types of irAEs developed in 29.3% (95% CI: 25.2-33.7) of patients undergoing ICI rechallenge. The overall ORR was 45.2% (95% CI: 34.5-56.4), with cancer type-specific ORRs of 60.5% (95% CI: 47.9-71.9) in melanoma, 39.1% (95% CI: 17.4-66.2) in lung cancer, and 39.5% (95% CI: 27.7-52.6) from studies investigating solid tumors. DCR was high across cancer types: 77.3% (95% CI: 67.7-84.7) overall, 68.2% (95% CI: 41.3-86.8) in melanoma, 91.2% (95% CI: 67.7-98.1) in lung cancer, and 72.5% (95% CI: 63.3-80.1) in solid tumors. Meta-regression analysis showed that commonly observed initial irAE types or grades of initial irAEs (Gr1-2 vs. Gr3-4) did not significantly impact ORR or DCR. **Conclusions:** ICI rechallenge after discontinuation due to irAEs demonstrates clinical activity but carries a substantial risk of both recurrent and new irAEs. These findings highlight the need for predictive biomarkers to optimize patient selection and maximize survival without compromising safety. Research Sponsor: None.

11128 **Poster Session**

Overall survival after intravenous iron use in patients with cancer and iron deficiency: A propensity-matched real-world study. First Author: Haris Sohail, Charleston Area Medical Center, Charleston, WV

Background: Iron deficiency affects up to two-thirds of patients with cancer and frequently coexists with anemia, with the highest prevalence in pancreatic, colorectal, and lung cancers. Functional iron deficiency driven by cancer-related inflammation predominates. Although intravenous (IV) iron is recommended to improve hematologic outcomes and reduce transfusion requirements, its impact on survival remains uncertain. We evaluated the association between IV iron use and overall survival (OS) in patients with advanced solid tumors using large real-world data. **Methods:** We conducted a retrospective cohort study using a TriNetX, a federated electronic health record network. Adults with solid malignancies and laboratory-defined iron deficiency (TSAT $\leq$ 20% and ferritin $\leq$ 500 ng/mL) were identified and categorized by IV iron exposure. Cohorts were matched 1:1 using propensity score matching for demographics, comorbidities, cancer site, iron indices (ferritin, transferrin saturation), hemoglobin, and treatment-related variables. OS was assessed using Kaplan–Meier analysis (5-year cap) and Cox proportional hazards modeling. **Results:** After propensity matching, 4,802 patients receiving IV iron were compared with 4,751 patients who did not receive IV iron, with a good balance across baseline characteristics. In Kaplan–Meier analysis (capped at 5 years), median overall survival (OS) was 875 days in the IV iron group and 858 days in the no IV iron group, with similar 5-year survival probabilities (38.6% vs 37.5%) and no significant difference by log-rank testing (p=0.53). On multivariable Cox proportional hazards modeling, IV iron exposure was not independently associated with mortality (HR 1.04, 95% CI 0.996–1.094; p=0.075). Male sex (HR 1.09, p<0.0001) and increasing age (HR 1.013 per year, p<0.0001) were associated with higher mortality. Iron indices demonstrated strong prognostic associations, with low transferrin saturation (<10%: HR 1.48; 10–20%: HR 1.24; both p<0.0001) and anemia diagnoses including iron deficiency anemia (HR 1.05, p=0.0048) and anemia of chronic disease (HR 1.23, p<0.0001) independently associated with increased mortality, while lower ferritin levels were associated with improved survival (<100 ng/mL: HR 0.53; 100–200 ng/mL: HR 0.78; both p<0.0001). Cancer site was also independently associated with OS, with higher mortality observed in digestive, respiratory, urinary tract, and central nervous system malignancies, and improved survival in breast and thyroid/endocrine cancers. **Conclusions:** In this large propensity-matched real-world cohort, IV iron was not associated with worse overall survival in patients with cancer and iron deficiency, supporting its survival safety while highlighting iron indices, anemia, and cancer type as key prognostic markers. Research Sponsor: None.

11129 **Poster Session**

Impact of facility type and surgical management on survival outcomes in colon adenocarcinoma stratified by metastatic burden. First Author: Yazmin Reategui-Almonacid, Rutgers/Newark Beth Israel Medical Center, Newark, NJ

Background: Survival for colon cancer varies by facility type, yet the impact of granular metastatic burden and surgical intervention on this disparity remains poorly defined. We examined whether academic survival advantages persist after stratifying by disease extent and evaluated how surgical management contributes to these outcomes. **Methods:** Using the NCDB (2016–2023), we identified 438,590 adults with colon adenocarcinoma. We compared academic vs. community settings, quantifying metastatic burden by involved organ site count at diagnosis (liver, lung, bone, brain, lymph nodes, viscera; 0–6). Overall survival (OS) was the primary endpoint. Multivariable Cox models adjusted for age, Charlson–Deyo score, clinical stage, and site count. Sequential adjustment for primary tumor resection and metastatic-site surgery was performed to assess potential mediation. **Results:** Of 438,590 patients, 49.2% were treated at academic centers. Academic cohorts presented with more complex disease, including higher metastatic rates (22.4% vs 20.1%; p < 0.001) and frequent liver involvement (16.9% vs 15.1%; p < 0.001). In stage IV cases, metastatic-site surgery occurred more often at academic facilities (19.1% vs 14.0%). While primary resection rates were high in both cohorts, academic centers achieved superior R0 rates (95.0% vs 94.3%). Adjusted for age, comorbidity, and site count, academic care was associated with a survival benefit (HR 0.93; 95% CI 0.92–0.94). Primary tumor resection strongly predicted OS (HR 0.29; 95% CI 0.29–0.30). Adjusting for primary resection strengthened the academic effect (HR 0.91; 95% CI 0.90–0.92), indicating that surgical management partially mediates this advantage. Conversely, metastatic-site surgery was associated with higher mortality (HR 1.32; 95% CI 1.29–1.34) and did not explain the facility-based survival gap. **Conclusions:** The survival advantage at academic centers persists regardless of initial metastatic burden and is driven more by primary tumor surgical management than by metastatic-site interventions. These data suggest that improving community outcomes requires broader access to academic-level surgical standards and multidisciplinary care. Ensuring specialized surgical evaluation for high-burden patients is critical, regardless of their initial point of entry into the healthcare system. Research Sponsor: None.

11130 **Poster Session**

Integrated tumor-informed and tumor-agnostic ctDNA molecular residual disease (MRD) assessment with imaging in early breast cancer. First Author: Tim Crook, Cromwell Hospital, London, United Kingdom

Background: Accurate ctDNA-based MRD detection in early breast cancer is limited by tumor heterogeneity, clonal evolution and methodological issues, limiting tumor-informed (TI) assays reliant on predefined variants. Tumor-agnostic (TA) approaches, while broader, are susceptible to false positives from clonal hematopoiesis and reduced sensitivity in low–tumor burden settings. **Methods:** We analyzed a single-center cohort of 74 female patients with stage I–III breast cancer undergoing post-treatment surveillance after completion of curative-intent therapy (surgery, radiation, and adjuvant systemic therapy as appropriate). Plasma samples collected post-treatment were analyzed using an integrated MRD assay combining TI ddPCR and TA NGS ctDNA detection strategies. CHIP filtering was incorporated to improve analytical robustness. MRD status was correlated with clinicopathologic features and contemporaneous imaging. MRD positivity was defined as detection by either TI or TA component. **Results:** At the time of ctDNA assessment, which was performed during standard post-treatment surveillance following completion of curative-intent therapy, 94.6% (70/74) of patients were imaging-negative. MRD was detected in 31.1% (23/74) of patients overall. All imaging-positive patients (4/4) were MRD-positive. Notably, among imaging-negative patients, 27.1% (19/70) were MRD-positive, indicating molecular residual disease not captured by conventional imaging. No imaging-positive cases were MRD-negative. MRD positivity was observed across all stages, including early-stage disease (I–II: 26%, 14/54), with the highest prevalence in stage III (47.4%, 9/19); one case had unknown staging. MRD was detected in 33.3% (18/54) of $HR^+/HER2^-$, 25% (2/8) of TNBC, and 25% (3/12) of $HER2^+$ tumors, demonstrating applicability across biological subtypes. Importantly, the hybrid approach increased detection sensitivity significantly. Among MRD-positive patients (n=23), 47.8% were detected exclusively by TA component, 43.5% by the TI component alone, and only 8.7% were detected by both. Reliance on a single MRD strategy would have failed to identify 91.3% (21/23) of MRD-positive cases, highlighting substantial biological complementarity between the two approaches. At early follow-up (median 113.5 days), MRD was detected in 23 patients, including 19 who were imaging-negative; among those with subsequent imaging-confirmed recurrence (n=4), the median MRD–imaging interval was 9.75 months. **Conclusions:** A hybrid TI and TA ctDNA MRD platform detects clinically occult molecular disease beyond imaging in stage I–III breast cancer. The complementary performance of TI and TA approaches substantially improves MRD detection and supports the use of hybrid MRD testing for early risk stratification and MRD-guided clinical trials. Research Sponsor: None.

11131 **Poster Session**

Role of iron supplementation in the efficacy of immune checkpoint inhibitors (ICIs): A real-world propensity-matched analysis. First Author: Parth Sharma, Virginia Commonwealth University, Richmond, VA

Background: Iron plays a crucial role in the induction of ferroptosis mediated by immune checkpoint inhibitors (ICIs) in cancer. However, it plays a complex role in T-cell and macrophage function in the tumor immune microenvironment, which could influence anti-cancer immunity. Currently, the role of iron supplementation in affecting the therapeutic outcomes in patients receiving ICIs is unknown. **Methods:** A retrospective analysis utilizing TriNetX, a global federated health research network database, of patients receiving ICIs from January 2006 to January 2026, was conducted. Patients were divided into 3 cohorts based on whether they received intravenous (IV) iron (cohort A), oral (PO) iron (cohort B), or no iron supplementation (cohort C), 1 month prior to or up to 3 months after receiving ICIs. Propensity score matching (PSM) was used to balance the cohorts based on age, race, ethnicity, hemoglobin (Hb), ferritin, CRP, albumin, metastatic disease, line of treatment and underlying comorbidities. Kaplan-Meier analyses were used to analyze overall survival (OS). **Results:** A total of 4464, 5299, and 201,014 patients were identified across cohorts A, B and C, respectively. The most common primary sites of malignancies were the lung and/or bronchus, the gastrointestinal tract (and associated glands), and the urinary tract. Although IV iron recipients had better survival outcomes than PO iron recipients, both groups had worse outcomes than patients receiving no supplementation (Table 1). Similar trends were seen in subgroups receiving anti-PD1 and anti-PDL1. In the subgroup of patients with likely true iron deficiency (Hb$\leq$11g/dl and ferritin<100ng/ml) (*n*=508 after PSM), IV iron recipients had better outcomes than PO iron recipients (2Yr OS HR (95% CI): 0.822 (0.691,0.978) p=0.027). In the subgroup of patients having Hb$\leq$11g/dl and ferritin$\geq$300ng/ml, likely anemia of chronic disease (*n*=2483 after PSM), iron supplement recipients, whether IV or PO, had worse survival outcomes than patients receiving no supplementation (2Yr OS HR (95% CI): 1.22 (1.137,1.308) p<0.0001). **Conclusions:** Our study highlights the adverse impact of concurrent iron supplementation in patients receiving ICIs, especially in those without true iron deficiency. When clinically indicated, the IV route is preferred. Clinical studies are planned or ongoing to determine the role of iron supplementation in patients receiving ICIs, given its potential to induce ferroptosis. We suggest careful reconsideration or appropriate stratification of the cohort based on iron deficiency and/or type of iron supplementation in such studies. Research Sponsor: None.

2-year overall survival (OS).

Comparison groups	Number of patients after PSM	2-Year OS HR (95% CI) p-value (log-rank test)
IV Iron v/s PO Iron	2762	0.898 (0.83,0.97) p=0.006
IV Iron v/s No Iron	3808	1.199 (1.121,1.283) p<0.0001
PO Iron v/s No Iron	5210	1.405 (1.327,1.488) p<0.0001

11132 Poster Session

Pan-cancer discovery of clinical and genomic determinants of immune-related adverse events. First Author: Ziad Bakouny, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Immune-related adverse events (irAEs) from immune checkpoint inhibitors (ICIs) can be lifelong, fatal, or require treatment discontinuation, substantially limiting the clinical benefit of immunotherapy. Despite their impact, predictors of irAE susceptibility remain poorly defined, largely due to the lack of scalable approaches for toxicity phenotyping. Here, we leverage large language models and integrated clinico-genomic data to identify determinants of irAEs. **Methods:** We developed a custom retrieval augmented generation and large language model (RAG-LLM) pipeline to automatically annotate 6 key adverse events (adrenal insufficiency, hepatotoxicity, hyperthyroidism, hypothyroidism, colitis, and pneumonitis) using free text from clinical notes across Memorial Sloan Kettering Cancer Center. We first validated RAG-LLM predictions using a gold standard prospectively collected adverse event dataset from 8,119 patients across 1,057 individual clinical trials. RAG-LLM imputations were then scaled to 55,406 (12,291 ICI-treated) patients. All patients had associated somatic and germline MSK-IMPACT panel sequencing data. Single nucleotide polymorphism (SNP) imputation was performed using GLIMPSE and time-to-event genome-wide association studies (GWAS) were performed using SPACox. HLA class I genotypes were imputed using HLA-HD. Random Survival Forest (RSF) models were trained to predict irAE occurrence. **Results:** The custom RAG-LLM pipeline had strong performance across all 6 irAEs (area under the ROC curve of 0.77-1.00). In the RAG-LLM imputed data, 799 (1.4%) patients had adrenal insufficiency, 2,803 colitis (5.1%), 7,130 hypothyroidism (12.9%), 448 hyperthyroidism (0.8%), 15,627 hepatotoxicity (28.2%), and 3,730 pneumonitis (6.7%). Among ICI-treated patients, pneumonitis (HR 1.4; 95% CI 1.1-1.8; $p < 0.01$) and hepatotoxicity (HR 1.4; 95% CI 1.2-1.6; $p < 0.01$) were associated with worse overall survival. The GWAS found two genome-wide significant hits that predicted adrenal insufficiency (rs115003145, HLA region) and hypothyroidism (rs7864322, *FOXE1* gene enhancer region) with $p < 5x10^{-8}$. Fine mapping of the HLA SNP showed that HLA-C*06:02 was specifically associated with increased risk of adrenal insufficiency in ICI-treated patients only (HR 1.6; 95% CI 1.2-2.2; $p < 0.01$). RSF model performance for irAE occurrence had F1 scores of 0.67-0.85. For pneumonitis, patients with the highest risk quartile by RSF model had 7.1% risk of pneumonitis at 1 year compared to 0.4% for the lowest risk quartile (HR 14.9; 95% CI 10.4-21.3; $p < 0.01$). **Conclusions:** We developed and validated a novel custom RAG-LLM pipeline that allows automatic annotation of irAEs using clinical notes. Using this pipeline, we identified novel biomarkers of ICI-related adrenal insufficiency and hypothyroidism. Finally, we developed predictive models for irAE prediction that can be used at the point of care. Research Sponsor: Fund for Innovation in Cancer Informatics; National Cancer Institute; P30-CA008748; Memorial Sloan Kettering Cancer Center.

11133 Poster Session

Estimating survival in advanced cancer: A prospective single-center study on the accuracy of oncologists' prognostic accuracy (Pre-Sur). First Author: Giulia Claire Giudice, AUSL/IRCCS di Reggio Emilia, Reggio Emilia, Italy

Background: The ability to estimate survival is a cornerstone of care for patients (pts) with advanced cancer, influencing therapeutic strategies, access to clinical trials, and timing of palliative care referral. Existing evidence on clinical prediction of survival (CPS) largely derives from end-of-life pts. The Pre-Sur study addresses this gap by evaluating oncologists' prognostic accuracy in pts with metastatic solid tumors starting first-line therapy and investigating discordance-related factors. **Methods:** Pre-Sur is a prospective, observational, monocentric study enrolling pts with advanced tumors prior to first-line therapy (hormonal therapy was excluded). During the baseline consultation, clinicians provided an estimated survival timeframe using categorical intervals (0-4 to >36 months). The primary endpoint was concordance between CPS and overall survival (OS). Survival estimates and outcomes were analyzed descriptively and through cross-tabulation. Secondary analyses explored factors potentially influencing accuracy, including ECOG-PS, age, comorbidities, and clinician characteristics, using Chi-square tests and multivariable models. **Results:** From October 2022 to December 2025, 183 pts were enrolled; 135 completed the required follow-up. 58% of pts were male and 49% were ≥75 years. Gastrointestinal (45%) and thoracic (35%) cancers were the most prevalent. Median CPS (mCPS) was 18.0 months (95%CI: 15.9–20.0), median OS (mOS) of 8.0 months (95% CI: 5.9–10.0). Prognostic estimates were accurate in 17% of cases, optimistic in two-thirds, and underestimated in less than one-quarter. No significant associations emerged for sex, tumor site, PS or target therapy use. mCPS were often more consistent with the mOS reported in randomized clinical trials (RCT); the observed real-world OS were inferior to that expected from RCT (Table 1). **Conclusions:** This study highlights the difficulty of predicting OS in pts with metastatic solid tumors. CPS may be influenced by expectations derived from RCT outcomes, which may not fully capture the complexity of real-world pts. Prognostic evaluation in clinical practice should integrate features such as age, PS, comorbidities, and disease burden, to improve prognostic accuracy and support informed decision-making. Research Sponsor: None.

Overall survival and clinical prediction of survival by disease sites.

Site	Patients, n (%)	mOS, months (CI 95%)	mCPS, months (CI 95%)	mOS trend in registrative RCTs, months
Lung	44 (32.2)	7 (2-12)	12 (11-13)	12-26
Colorectal	24 (17.8)	9 (5-13)	18 (13-23)	25-30
Pancreas	15 (11.1)	8 (2-14)	24 (21-27)	11
Gastric	11 (8.1)	5 (2-8)	12 (7-17)	14
Head and neck	6 (4.4)	6 (0-13)	30 (NA-NA)	15
Kidney	6 (4.4)	6 (4-8)	18 (5-30)	45
Biliary ducts	5 (3.7)	2 (1-3)	18 (13-23)	12
Pleural	4 (3.0)	2 (NA-NA)	8 (NA-NA)	12
Skin	4 (3.0)	22 (NA-NA)	12 (NA-NA)	33
Bladder	3 (2.2)	11 (0-27)	18 (8-28)	21

11134 Poster Session

Trends and disparities in mortality from malignant neoplasms of male genital organs in the United States, 1999–2023. First Author: Nikil Kumar, Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan

Background: Genital malignant neoplasms remain an important cause of mortality among males living in the United States. Tumor progression and organ-specific compromise contribute to increased risk and disease severity. Although recent data show overall declines in mortality over time, disparities persist, highlighting the need to analyze and interpret trends across demographic and geographic factors. **Methods:** The mortality data from the CDC WONDER underlying cause of death files for men aged ≥25 years were used to analyze age-adjusted and crude mortality rates (AAMRs and CMRs) per 100,000 for male genital neoplasms (ICD-10 Codes: C60-C63.9), stratified by year, gender, race/ethnicity, place of death, and geography. Joinpoint regression was used to estimate average annual percent change (AAPC) and annual percent change (APC) with 95% confidence intervals (CIs). Statistical significance was defined as $p<0.05$. **Results:** From 1999 to 2023, a total of 765,516 deaths were reported among patients of male genital malignant neoplasms, with most occurring at the decedent's home. The overall AAMR decreased from 18.29 in 1999 to 12.51 in 2023 (AAPC: -1.55; 95% CI: -1.71 to -1.39; $p<0.001$), with the most significant decline observed between 1999–2013 (APC: -2.73; $p<0.001$). Men aged 65 years and older experienced the greatest annual decline (-2.50%; $p<0.001$), but had the highest CMR (63.84), whereas mortality among men aged 25–44 years increased notably between 2013–2023 (APC: 3.65; $p<0.001$). The highest AAMR was observed among non-Hispanic (NH) Blacks (26.98), while the lowest AAMR was noted among NH Asians (6.30). Geographic disparities were evident, with the West having the highest AAMR (14.48) and the Northeast having the lowest (13.02). Non-metropolitan areas showed a higher AAMR (14.94 vs 13.79) and a slightly steeper decline in mortality than non-metropolitan areas (AAPC: -1.81 vs -1.80). At the state level, the District of Columbia ranked the highest, placed in the top 90th percentile, between 1999 and 2023. **Conclusions:** Despite a significant decline in mortality related to malignant neoplasms of male genitals over the past two decades, disparities persist, especially among older men, NH Black individuals, those living in non-metropolitan areas, and the West region. This underscores the need for targeted prevention, early detection, and equitable integrated care. Research Sponsor: None.

Average annual percent change (AAPC) of age-adjusted mortality rates for male genital malignant neoplasms in the United States, 1999 to 2023.

Variable	Deaths	AAPC (95%CI)
Overall (Male)	765,516	-1.55 (-1.71 to -1.39)
Non-metropolitan areas	126,009	-1.80 (-2.05 to -1.55)
Metropolitan areas	537,718	-1.81 (-2.00 to -1.62)

11135 Poster Session

Trends and disparities in mortality from malignant neoplasms of digestive system and renal failure in the United States, 1999-2023. First Author: Nandni Kumari, Isra University Hyderabad, Hyderabad, Pakistan

Background: Malignancies of the digestive system represent a substantial global health burden, often exacerbated by coexisting renal failure, which complicates therapeutic interventions and significantly elevates mortality risk. This study aims to analyze and interpret annual mortality trends and disparities among adults in the United States from 1999 to 2023, for various demographic and geographic factors. **Methods:** The mortality data from the CDC WONDER multiple cause of death files for adults aged ≥25 years were used to analyze age-adjusted and crude mortality rates (AAMRs and CMRs) per 1,000,000 through ICD 10 code: C15-C26 (digestive system malignant neoplasms) and ICD 10 code: N17-N19 (renal failure), stratified by year, gender, race/ethnicity, place of death and geography. Joinpoint regression was used to estimate average annual percent change (AAPC) and annual percent change (APC) with 95% confidence intervals (CIs). Statistical significance was defined as $p < 0.05$. **Results:** From 1999 to 2023, a total of 164,004 deaths were reported due to malignant neoplasms of the digestive system and renal failure, mostly occurring in medical facility inpatient settings. The overall AAMR increased from 27.58 in 1999 to 36.84 in 2023 (AAPC: 1.17; 95% CI: -0.01 to 2.36; $p = 0.05$), with an initial decline observed between 2011 and 2017 (APC: -4.91; $p < 0.001$), followed by a notable increase through 2023 (APC: 8.26; $p < 0.001$). Men are noted to have higher AAMR than women (42.40 vs 19.19). Adults aged 65 and above experienced the highest CMR (110.96), whereas adults aged 45–64 years exhibited the greatest annual increase (3.19%; $p < 0.001$). By race, the highest AAMR was among non-Hispanic (NH) Black individuals (53.41), and the lowest was among NH White individuals (25.73). Geographic disparities were evident, with the West region having the highest AAMR (31.80) and the Northeast region having the lowest AAMR (27.77). Non-metropolitan areas showed higher AAMR than metropolitan areas (29.42 vs 27.91). At the state level, the District of Columbia and South Dakota ranked highest, placed in the top 90th percentile during 1999–2020 and 2021–2023, respectively. **Conclusions:** Mortality related to malignant neoplasms of the digestive system and renal failure has increased over the past two decades, with disproportionate burden among older adults, men, NH Black individuals, those living in non-metropolitan areas, and the West region, underscoring the need for targeted prevention, early detection, and equitable, integrated care. Research Sponsor: None.

Average annual percent change (AAPC) of neoplasms of digestive system and renal failure related age-adjusted mortality rates in the United States, 1999 to 2023.

Variable	Deaths	AAPC (95%CI)
Overall	164,004	1.17 (-0.01 to 2.36)

11136 **Poster Session**

Hospitalized oncology patients with diarrhea: Clinical outcomes and prognostic factors. First Author: Güner Akgüner, Etlik City Hospital Department of Medical Oncology, Ankara, Turkey

Background: Diarrhea is a frequent cause of hospitalization in oncology patients and may lead to substantial morbidity and mortality. However, data on short-term outcomes and prognostic factors in hospitalized cancer patients with diarrhea are limited. This study aimed to evaluate clinical outcomes and identify factors associated with poor prognosis in this population. **Methods:** Medical records of 6,349 oncology patients hospitalized over a 3-year period were retrospectively reviewed. A total of 163 adult patients hospitalized primarily for diarrhea were included; patients with immune checkpoint inhibitor–related diarrhea were excluded. Collected variables included demographic characteristics, disease stage, Eastern Cooperative Oncology Group (ECOG) performance status, febrile neutropenia at admission, systemic anticancer therapy, serum albumin level, and diarrhea grade. Primary outcomes were intensive care unit (ICU) admission and 30-day mortality. Logistic regression analysis was used to identify independent predictors of mortality. **Results:** Diarrhea accounted for 2.6% of all oncology-related hospitalizations, and 83.4% of patients had grade $\geq$3 diarrhea. ICU admission was more frequent in patients with ECOG $\geq$2 compared with those with ECOG $<$ 2 (42.4% vs 14.4%, $p < 0.001$) and in patients with grade $\geq$3 diarrhea (27.9% vs 7.4%, p = 0.024). The overall 30-day mortality rate was 16.0% and was higher in patients with ECOG $\geq$2 (39.0% vs 2.9%, $p < 0.001$), metastatic disease (23.5% vs 7.7%, p = 0.006), and grade $\geq$3 diarrhea (19.1% vs 0%, p = 0.009). Febrile neutropenia was not associated with ICU admission or mortality. In multivariable analysis, ECOG $\geq$2 (OR: 17.1, $p < 0.001$) and lower serum albumin level (OR: 0.42, p = 0.049) were independent predictors of 30-day mortality. Diarrhea grade was excluded from the multivariable model due to complete separation. **Conclusions:** Diarrhea in hospitalized oncology patients is associated with substantial ICU utilization and short-term mortality, independent of febrile neutropenia. Poor functional status and low serum albumin are key prognostic factors, highlighting that diarrhea should be regarded as a potentially life-threatening condition requiring early risk stratification and prompt supportive care. Research Sponsor: None.

11137 **Poster Session**

Beyond geography: The intersecting impact of rurality, race, and depression on breast cancer survival. First Author: Ilias Jerrar, The Medical University of South Carolina, Florence, SC

Background: Rural–urban disparities in breast cancer outcomes are well-documented, with rural populations typically experiencing worse survival due to limited access to screening and specialty care. However, the role of integrated healthcare systems in mitigating these disparities and the impact of psychosocial factors, such as depression, on survival remain underexplored. This study evaluated the survival outcomes of breast cancer patients treated within an integrated, academic health system, focusing on the intersecting effects of geographic residence, race, and antidepressant therapy. **Methods:** We conducted a retrospective cohort study of 6,788 female breast cancer patients diagnosed between 2014 and 2024 at MUSC-affiliated facilities in urban and rural South Carolina. Data on patient demographics, cancer stage, hormone receptor status, depression diagnosis, and antidepressant use were extracted from electronic medical records. We used Kaplan-Meier survival analysis with log-rank tests and multivariable Cox proportional hazards models to assess the association of geographic location, race, and antidepressant use with overall survival, while adjusting for clinical and demographic confounders. **Results:** Contrary to national trends, rural patients demonstrated superior overall survival compared to urban patients (5-year survival: 92.1% vs. 85.3%, $p < 0.001$). In a multivariable model, rural residence was an independent protective factor (HR = 0.72, 95% CI: 0.61–0.85, $p < 0.001$). Antidepressant treatment was also associated with significantly improved survival (HR = 0.78, 95% CI: 0.65–0.93, p = 0.006). This survival benefit was consistent across urban and rural subgroups. While African American race showed a borderline increased risk of mortality (HR = 1.18, 95% CI: 0.98–1.42, p = 0.081), the rural survival advantage was maintained within both African American and non-African American subgroups. Triple-negative breast cancer (TNBC) was an independent and significant predictor of mortality (HR = 1.34, 95% CI: 1.15–1.57, $p < 0.001$), and was more prevalent in the urban cohort. **Conclusions:** Our findings suggest that a coordinated, academic-affiliated care model can effectively address geographic barriers to care. The study also highlights the critical role of psychosocial health, demonstrating that antidepressant therapy is an independent predictor of improved survival, reinforcing the need for integrated mental health support in oncology. Furthermore, the higher prevalence of aggressive triple-negative breast cancer in the urban cohort, coupled with the potential for the urban facilities to receive more complicated referrals, may contribute to the observed urban survival disadvantage, underscoring the interplay of tumor biology and patient referral patterns within integrated systems. Research Sponsor: None.

11138 **Poster Session**

A risk stratification schema for patients with non–small cell lung cancer with multiple organ metastases. First Author: Gabriela Esnaola, Yale School of Medicine, New Haven, CT

Background: The majority of patients with non-small cell lung cancer (NSCLC) will have multiple organ sites of metastasis and poor overall survival (rwOS). Specific organ involvement influences patient outcomes, but the impact of overarching patterns of metastasis on rwOS and response to systemic therapy (ST) is poorly understood. Prior studies have been limited in their scale, availability of detailed data on sites of metastasis, and inclusion of patients receiving immunotherapy (IO) or targeted therapy (TT). We leveraged a large-scale, real-world database to characterize and assess the prognostic value of patterns of metastasis on rwOS and time to next therapy (rwTTNT) in patients with metastatic NSCLC receiving ST. **Methods:** This retrospective study utilized the Flatiron Health Research Database of patients with NSCLC treated with first-line (1L) ST (n = 327,044). Patient, tumor, and treatment variables were summarized descriptively and compared across patterns of metastasis. rwOS and rwTTNT from 1L start were estimated via Kaplan Meier method and compared with logrank test. Bernoulli mixture models were used to cluster patients by metastatic sites at 1L start. **Results:** Sites of disease were evaluated for 75,304 patients. Data from 5 metastatic sites revealed 6 clusters reflective of real-world patterns of metastasis: bone (n = 33,882), pleural (n = 12,123), liver (n = 6,133), brain (n = 11,441), adrenal avid (n = 6,975), and high metastatic burden (HMB, $\geq$3 sites with frequency $\geq$0.5, n = 4,750). While HMB (7.2 months median rwOS, 4.8 months median rwTTNT) and liver avid disease (9.4, 5.2 months) had poor outcomes as expected, we also found that bone (11.0, 5.9 months) and adrenal (11.8, 6.0 months) avid clusters had worse median rwOS and shorter rwTTNT compared to pleural (15.7, 7.6 months) and brain (15.3, 7.4 months, $p < 0.001$). Outcomes associated with a specific site of metastasis varied based on patient cluster assignment. Compared to the cluster equivalent (e.g., brain avid), individual metastatic site (e.g., brain) as a prognostic factor was associated with worse median rwOS by 1.0-2.9 months and shorter median rwTTNT by 0.1-0.9 months. Compared to individual sites and site-avid clusters, HMB more often had EGFR mutations (20.7% vs 13.6% overall). IO was associated with greater median rwOS over TT in the adrenal cluster (17.7 vs 15.6 months), and IO + CTX had better rwOS vs IO alone in pleural (15.7 vs 12.9 months) and liver clusters (10.7 vs 9.4 months, $p < 0.001$). **Conclusions:** The survival outcomes and treatment response associated with defined clusters of metastases are distinct from those associated with individual organ sites or widespread disease alone. A risk-stratification framework that uses "risk phenotypes" representative of real-world patterns of metastasis may have better prognostic and predictive significance in patients with multiple sites or higher burden of disease. Research Sponsor: U.S. National Institutes of Health.

11139 **Poster Session**

Safety of glucagon-like peptide-1 receptor agonists in patients with breast cancer: A real-world multicenter cohort study. First Author: Cho Han Chiang, Northwell Health Cancer Institute, New Hyde Park, NY

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly prescribed for patients with breast cancer and coexisting type 2 diabetes mellitus (T2DM). While GLP-1RAs have demonstrated metabolic and cardiovascular benefits in the general population, data regarding their safety in patients with breast cancer remain limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network, which aggregates de-identified electronic health record data from over 140 international healthcare organizations. Adult patients ($\geq$18 years) with breast cancer who received breast cancer–directed systemic therapy and antidiabetic medications were included. The exposed cohort comprised patients who received a GLP-1RA within 90 days of systemic therapy initiation, while the comparator cohort included patients who received non–GLP-1RA antidiabetic agents. To minimize confounding, 1:1 propensity score matching was performed using demographics, body mass index, hemoglobin A1c, metastatic disease, breast cancer-directed therapy, and comorbidities. Outcomes were evaluated over 12 months using Cox proportional hazards models. Primary safety outcomes included adverse events commonly associated with GLP-1RA use: pancreatitis, biliary disease, and gastrointestinal adverse events (gastroesophageal reflux disease [GERD], bowel obstruction, and nausea/vomiting). Secondary outcomes included all-cause mortality and major adverse cardiovascular events (MACE), defined as a composite of myocardial infarction, ischemic stroke, and cardiovascular death. **Results:** A total of 29,380 patients with breast cancer and T2DM were identified. After propensity score matching, 3,796 patients were included in each cohort. Over 12 months of follow-up, GLP-1RA use was not associated with an increased risk of pancreatitis compared with non–GLP-1RA use (hazard ratio [HR], 1.20; 95% confidence interval [CI], 0.53–2.71). No significant differences were observed in biliary disease (HR, 0.93; 95% CI, 0.60–1.45) or bowel obstruction (HR, 0.70; 95% CI, 0.40–1.23). GLP-1RA use was associated with higher risks of GERD (HR, 1.48; 95% CI, 1.14–1.92) and nausea/vomiting (HR, 1.59; 95% CI, 1.26–2.00). Importantly, GLP-1RA use was associated with a lower risk of MACE (HR, 0.76; 95% CI, 0.59–0.99) and all-cause mortality (HR, 0.51; 95% CI, 0.37–0.69). **Conclusions:** In this study, GLP-1RA use was not associated with increased risks of serious gastrointestinal or biliary adverse events among patients with breast cancer receiving systemic therapy. While nausea/vomiting and GERD were more frequent, GLP-1RA use was associated with significant reductions in major adverse cardiovascular events and all-cause mortality. Prospective studies are warranted to confirm long-term safety and oncologic outcomes. Research Sponsor: None.

11140 **Poster Session**

The corticosteroid timing paradox in immune checkpoint inhibitor–treated solid tumors and its association with overall survival: A TriNetX retrospective cohort study. First Author: Nikhil Kumar Kotla, Trinity Health Oakland Hospital/Wayne State University School of Medicine, Pontiac, MI

Background: Systemic corticosteroids are frequently used in patients receiving immune checkpoint inhibitors (ICIs) for symptom control and management of immune-related adverse events (irAEs). However, corticosteroids may impair antitumor immunity, and the impact of timing of corticosteroid exposure relative to ICI initiation on survival outcomes remains incompletely defined. We evaluated the association between corticosteroid timing and overall survival (OS) in a large real-world cohort of ICI-treated solid tumor patients. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network, including adult patients (≥18 years) with solid tumors treated with ICIs. Patients were stratified based on systemic corticosteroid exposure into three groups: baseline use (−30 to 0 days before ICI initiation), early intercurrent use (1–56 days after ICI initiation), and late intercurrent use (57–180 days after ICI initiation). Patients without corticosteroid exposure served as controls. The primary outcome was overall survival (OS). Kaplan–Meier analysis and Cox proportional hazards models were used to estimate survival outcomes and hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** A total of 43,282 ICI-treated solid tumor patients were included. Baseline corticosteroid use was associated with significantly worse OS compared with no corticosteroid exposure (median OS 564 vs 900 days; HR 1.32, 95% CI 1.28–1.35; $p < 0.0001$). Similarly, early intercurrent corticosteroid use was associated with inferior OS (median OS 543 vs 907 days; HR 1.35, 95% CI 1.32–1.39; $p < 0.0001$). In contrast, late intercurrent corticosteroid use was not associated with a survival detriment compared with controls (median OS 617 vs 650 days; HR 0.99, 95% CI 0.97–1.02; $p = 0.60$). **Conclusions:** In this large real-world analysis, systemic corticosteroid exposure prior to or early during ICI therapy was associated with significantly worse overall survival, whereas corticosteroid use later during treatment did not adversely impact survival. These findings support a corticosteroid timing paradox, suggesting that early immunosuppression may impair ICI efficacy, while later corticosteroid use—often for irAE management—may be oncologically safe. Prospective studies are needed to further define optimal corticosteroid timing and indications in ICI-treated patients. Research Sponsor: None.

11141 **Poster Session**

New-onset inflammatory bowel disease associated with immune checkpoint inhibitor therapy: A real-world multicenter analysis. First Author: Albert Ekow Orhin, Ascension Saint Agnes Hospital, Baltimore, MD

Background: Immune checkpoint inhibitors (ICIs) are increasingly used across a broad range of malignancies and are known to cause immune-mediated gastrointestinal toxicity. While acute colitis is a recognized adverse effect, the potential for ICIs to trigger de novo inflammatory bowel disease (IBD), a chronic immune-mediated condition with long-term treatment implications, has not been well studied, as ICIs enhance immune activation in ways that may also affect normal intestinal immune balance. With the expanding use of ICIs across cancer types and earlier lines of therapy, we examined the association between ICI exposure and the risk of developing incident IBD compared with chemotherapy. **Methods:** We conducted a retrospective cohort study using the TriNetX global federated research network, including adults (≥18 years) diagnosed with malignancy between 2020 and 2024. Patients with pre-existing Crohn's disease, ulcerative colitis, or prior IBD-directed biologic or targeted therapy were excluded. Two cohorts were defined: patients treated with PD-1/PD-L1 or CTLA-4 inhibitors and patients treated with chemotherapy without ICI exposure. Propensity score matching (1:1) was performed to balance demographics, cancer type, and comorbidities, yielding 63,190 patients per cohort. Outcomes assessed within 365 days included incident IBD diagnoses, initiation of first-line IBD therapies, and escalation to biologic or targeted IBD agents. Risk estimates, hazard ratios (HRs), and Kaplan–Meier analyses were performed. **Results:** After propensity score matching, baseline characteristics were well balanced between cohorts. The risk of developing incident IBD was significantly higher among ICI-treated patients compared with chemotherapy-treated patients (risk ratio [RR] 2.96, 95% CI 1.86–4.70). Time-to-event analysis demonstrated a significantly increased hazard of IBD following ICI exposure (HR 3.37, 95% CI 2.12–5.35; log-rank $p < 0.001$). Escalation to biologic or targeted IBD therapies was also more common in the ICI cohort (RR, 3.04; 95% CI, 1.90–4.87; HR, 3.46; 95% CI, 2.16–5.55). In contrast, initiation of first-line therapies (mesalamine or budesonide) did not differ significantly between groups (RR 0.97, 95% CI 0.93–1.01). **Conclusions:** Among cancer patients without pre-existing IBD, immune checkpoint inhibitor therapy was associated with a significantly increased risk of de novo IBD and a greater likelihood of requiring advanced IBD therapies compared with chemotherapy alone. These findings suggest that, in a subset of patients, immune checkpoint inhibition may be associated with the development of chronic intestinal immune disease, highlighting the need for increased awareness and longitudinal gastrointestinal monitoring as ICI use continues to expand. Research Sponsor: None.

11142 **Poster Session**

The impact of the COVID-19 pandemic on breast cancer stage at time of diagnosis at a major health system in New Jersey. First Author: Maureen Younan, Atlantic Health System - Morristown Medical Center, Morristown, NJ

Background: The COVID-19 pandemic led to strict social distancing protocols in all aspects of daily life creating barriers to healthcare access. This resulted in a decrease in cancer screening, including mammography, which in turn led to higher stage of breast cancer at the time of diagnosis. This is reflected in the current literature[1]. We completed a study at our institution to evaluate the impact of the COVID-19 pandemic on breast cancer screening and stage at diagnosis. **Methods:** We performed a retrospective chart review of patients aged 18 and older in a large New Jersey health system. IRB approval was obtained. Clinical and pathologic stage at time of breast cancer diagnosis as well as number of screening mammograms ordered and completed in the pre-COVID era (January 1, 2016 – December 31, 2019) and post-COVID era (January 1, 2020 – December 31, 2023) were evaluated. Chi-square hypothesis testing was used for data analysis. Of the 5613 patients identified, 4279 patients had clinical staging data documented. **Results:** Between 2016-2019, 80.1% of ordered screening mammograms were completed in our health system. As expected, the percentage of completed screening mammograms decreased to 63.7% during the peak of the COVID-19 pandemic from 2020-2021. However, this percentage further decreased to 61.8% between 2022-2023; p-value < 0.001 (Table 1). We also noted an increase in stage 0 and 1 breast cancers and a decline in stage 2-4 breast cancers during these time periods; p-value < 0.001. **Conclusions:** Our study demonstrates an expected decline in screening mammogram rates during the peak of the COVID-19 pandemic (2020-2021). This can be explained by the uncertainties around health care and social distancing recommendations. Despite participation in a national cancer screening campaign led by the American Cancer Society from May to December 2021, the completion rates of screening mammograms unfortunately continued to decline in the post-COVID years. Contrary to what has been reported, this study found that patients were diagnosed at an earlier stage in the post-COVID era. Our study demonstrates that completion rates of screening mammogram dropped during the COVID-19 pandemic and have not improved in the post-COVID times. We hypothesize that with longer-term studies an increase in late-stage breast cancers may be identified due to missed screening mammograms. 1. Pintican, Roxana et al. "COVID-19 pandemic resulted in more metastatic breast cancer cases at diagnosis." *Scientific reports* 15,1 29296. 11 Aug. 2025, doi:10.1038/s41598-025-14582-z. Research Sponsor: None.

Number and percentage of mammography orders completed and canceled by year.

	Orders Completed	Orders Canceled	Total
2016 – 2019	157,507	39,054	196,561
	80.1%	19.9%	100%
2020 – 2021	99,571	56,766	156,337
	63.7%	36.3%	100%
2022 – 2023	129,722	80,330	210,052
	61.8%	38.2%	100%
Total	386,800	176,150	562,950
	68.7%	31.3%	100%

11143 **Poster Session**

Clinical associations of cannabis use among patients receiving immune checkpoint inhibitors: A real-world analysis. First Author: Qiuchen Li, Case Western Reserve University School of Medicine, Cleveland, OH

Background: Cannabis use is common in patients with cancer, yet its clinical associations during immune checkpoint inhibitor (ICI) therapy is poorly defined. We evaluated the association between documented cannabis use and clinical outcomes among patients receiving ICIs. **Methods:** We conducted a retrospective cohort study of adults ≥18 years in the TriNetX US Collaborative Network with advanced or metastatic solid tumors treated with ICIs since January 1, 2019. Cannabis exposure was defined by diagnostic codes for cannabis-related disorders or prescriptions for cannabis-derived products documented 3 months prior to 2 years after ICI start. Patients who died in 60 days were excluded. Primary outcome was 3-year overall survival (OS); secondary outcomes included 2-year inpatient and emergency department (ED) visit, with joint sprain as a negative control outcome. Propensity matching adjusted for demographics, comorbidities, cancer type and stage, and tobacco and alcohol use. Hazard ratios (HR) and risk ratios (RR) with 95% confidence intervals (CI) and Kaplan–Meier analyses were calculated. **Results:** After matching, 3,634 patients were included in the OS cohort. Patients with no documented cannabis use had significantly higher 3-year OS and median survival versus cannabis users (HR 0.67; 95% CI 0.63-0.72; median OS 34.8 vs 18.7 months). This association was observed across all tumor subgroups except head and neck squamous cell carcinoma (HNSCC) (Table 1). Among 2,855 matched patients in the healthcare utilization cohort, patients without cannabis use had lower healthcare utilization within 2 years, including fewer ED visits (RR 0.83; 95% CI 0.79-0.87) and inpatient admissions (RR=0.82; 95% CI 0.79-0.84). These findings were consistent across subgroups except for ED visits in HNSCC (Table 1). Joint sprain showed no association with cannabis exposure (RR 0.93, 95% CI 0.64-1.35). **Conclusions:** Cannabis use during ICI therapy was associated with lower survival and higher healthcare utilization in multiple solid tumors. This may reflect unmeasured symptom burden or clinical vulnerability but also raises the hypothesis of a potential interaction between cannabis exposure and ICI therapy. Prospective studies incorporating symptom severity, dose, timing, and route of exposure are needed to clarify these relationships. Research Sponsor: None.

Clinical outcomes by cannabis exposure.

Group	Overall survival HR (95% CI)	OS p-value	ED Visit RR (95% CI)	ED p-value	Inpatient visit RR (95% CI)	Inpatient visit p-value
Overall	0.67 (0.63–0.72)	<0.01*	0.83 (0.79–0.87)	<0.01*	0.82 (0.79–0.84)	<0.01*
NSCLC	0.73 (0.68–0.79)	<0.01*	0.85 (0.81–0.90)	<0.01*	0.85 (0.82–0.89)	<0.01*
RCC	0.60 (0.50–0.73)	<0.01*	0.81 (0.73–0.91)	<0.01*	0.78 (0.72–0.85)	<0.01*
Melanoma	0.52 (0.40–0.69)	<0.01*	0.70 (0.59–0.83)	<0.01*	0.73 (0.65–0.82)	<0.01*
HNSCC	0.93 (0.74–1.16)	0.52	1.05 (0.89–1.25)	0.56	0.87 (0.77–0.98)	0.02*

*Statistically significant ($p < 0.05$).

11144 Poster Session

Relationship between immune-mediated adverse events and clinical outcomes in patients with metastatic melanoma treated with immune checkpoint inhibitors (ICIs): A retrospective real-world analysis. First Author: Leticia Escobar Vicentini, Hospital Beneficência Portuguesa de São Paulo, São Paulo, Brazil

Background: ICIs targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) revolutionized the treatment landscape for advanced melanoma. However, these agents can cause immune-related adverse events (AEs). Several studies have demonstrated a correlation between AEs and improved clinical outcomes. Understanding the co-occurrence patterns and prognostic implications of immune-related adverse events, as well as the impact of concomitant medications such as antibiotics (ATB), immunosuppressants (IS) and/or corticosteroids (CS), and proton pump inhibitors (PPIs), is crucial for immunotherapy management. In this study, we evaluated the relationship between immune-related toxicity, the use of IS and/or CS and ATB, and progression-free survival (PFS) and overall survival (OS) in patients with advanced melanoma treated with ICIs. **Methods:** Retrospective, analytical, multicenter study of patients (pts) with stage IV melanoma treated with ICIs (ipilimumab/nivolumab, nivolumab or pembrolizumab), between 2014 and 2025. Immune-related adverse events were graded according to CTCAE criteria and categorized as none, grade 1-2 or 3-4, demographic characteristics, use of IS and/or CS, ATB and number of toxicities were obtained from medical records. PFS and OS were estimated using the Kaplan-Meier method and compared using Cox proportional hazards models, with statistical significance set at $p < 0.05$. **Results:** Among 364 pts included, 275 (77,4%) experienced AEs. Dermatologic end endocrine toxicities, including rash, pruritus, vitiligo, hypothyroidism and hypophysitis were associated with improved survival outcomes. The results regarding PFS in relation to the presence, grade, and number of toxicities, as well as the use of IS and/or CS and ATB, are described in the table below. OS showed a statistically significant association with toxicity grade, with better OS observed among patients with grade 1–2 toxicity (HR 0.55; 95% CI, 0.35-0.87; P = 0.010), as well as who did not use IS and/or CS (HR 1.84; 95% CI, 1.20-2.82; P = 0,005). PFS showed a trend toward improved outcomes in patients who did not use PPI, without statistical significance due to the small number of pts. **Conclusions:** Our data show that pts who developed grade 1–2 toxicity and did not receive IS and/or CS experienced improved OS and PFS when treated with ICIs. Pts with a greater number of different toxicities and those who did not use ATB experienced better PFS. Research Sponsor: None.

Parameter	HR for PFS	95% CI	p-value
Toxicity vs. No Toxicity	0.39	0.29-0.52	<0.001
Degree of toxicity			
0 vs. Grade 1+2	0.38	0.28-0.51	<0.001
0 vs. Grade 3+4	0.50	0.35-0.73	<0.001
Number of toxicities			
0 vs. 1-2	0.50	0.38-0.67	<0.001
0 vs. 3 or +	0.26	0.17-0.38	<0.001
IS and/or CS vs. No IS and/or CS	1.43	1.05-1.95	<0.022
ATB vs. No ATB	1.53	1.11-2.12	<0.010

11145 Poster Session

Real-world outcomes with atezolizumab versus durvalumab plus chemotherapy for extensive-stage small cell lung cancer: A TriNetX propensity-matched analysis. First Author: Kevin Zhu, University of Vermont Medical Center, Burlington, VT

Background: First-line treatment for extensive-stage small cell lung cancer (ES-SCLC) consists of platinum-etoposide plus an immune checkpoint inhibitor (ICI), either atezolizumab or durvalumab. No head-to-head randomized trials have compared these regimens. We evaluated real-world outcomes associated with these ICIs using a large multi-institutional database. **Methods:** We performed a retrospective cohort study using the TriNetX Global Collaborative Network. Adults with ES-SCLC treated with platinum-etoposide plus atezolizumab or durvalumab were included. The index date was initiation of platinum, etoposide, and ICI therapy. Cohorts were matched 1:1 using propensity scores based on age, sex, race, tobacco use, and comorbidities. The primary outcomes were overall survival (OS) and real-world progression-free survival (rwPFS), defined as time to second-line therapy or death. Survival was analyzed using the Kaplan-Meier method and cox proportional hazards models. Secondary endpoints were immune-related adverse events (irAEs) and hospitalization rates and evaluated by z-test. The study protocol was created and reviewed by the authors prior to implementation and did not require IRB approval. **Results:** Among 750 eligible patients (677 atezolizumab, 73 durvalumab), 69 matched pairs were identified. Median follow-up was 13.4 months for atezolizumab and 8.6 months for durvalumab. Median OS was significantly longer with durvalumab compared with atezolizumab (23.2 vs 9.1 months; Hazard Ratio [HR] 0.58, 95% CI 0.47–0.93; p=0.021). No significant difference in rwPFS was observed (8.6 vs 6.7 months; HR 0.72, 95% CI 0.47–1.11; p=0.14) as shown in Table 1. Atezolizumab was associated with higher rates of hematologic adverse events (35 vs 22 events; p=0.025) and a trend toward increased hospitalizations (34 vs 24; p=0.085). No significant differences were observed in other irAE categories. **Conclusions:** This retrospective real-world analysis found that durvalumab-based first-line therapy was associated with longer OS compared to atezolizumab in patients with ES-SCLC, although no significant difference in rwPFS was observed. Interpretation is limited by shorter follow-up duration in the durvalumab cohort, which may contribute to observed survival differences. Due to the observational study design, potential residual confounding, and limited sample size, these results should be regarded as hypothesis-generating. These findings underscore the need for additional comparative effectiveness research to clarify optimal immunotherapy selection in ES-SCLC. Research Sponsor: None.

Outcomes in propensity-matched cohort.

Outcomes	Atezolizumab	Durvalumab	Effect Estimate
Patients (n)	69	69	
Median OS (months)	9.1	23.2	HR 0.58 (95% CI 0.47–0.93)
Median rwPFS (months)	6.7	8.6	HR 0.72 (95% CI 0.47–1.11)

11146 Poster Session

Sinonasal adverse events of immune checkpoint inhibitors: Pharmacovigilance using FAERS. First Author: Kevin Zhu, University of Vermont Medical Center, Burlington, VT

Background: Immune checkpoint inhibitors (ICIs) are cancer therapies with diverse toxicities, known as immune-related adverse events (irAEs). Sinonasal irAEs have been described primarily in case reports, and their population-level characteristics remain poorly defined. To date, no statistical analysis of the FDA Adverse Events Reporting System Database (FAERS) has evaluated sinonasal adverse events (snAEs) associated with ICIs. **Methods:** We investigated snAEs associated with FDA-approved ICIs in FAERS between 1/1/2011 and 10/1/2025. ICIs were grouped by therapeutic target (PD-1, PD-L1, or CTLA-4). Analyses were conducted in R using Bioconductor package "faers". Data were standardized using preferred term in the Medical Dictionary for Regulatory Activities and deduplicated based on concordance across drug, adverse event, and demographics. Disproportionality analysis used reporting odds ratio (RORs) in comparison with the overall FAERS database. We excluded adverse events with <2 reports. The study was created and reviewed by the authors prior to implementation. **Results:** 17 million FAERS reports were identified, of which 2,476 ICI-associated reports included snAEs. Two rare events demonstrated significant disproportionality among PD-1 inhibitors: chronic eosinophilic rhinosinusitis (n=3; ROR 7.71, 95% CI 2.34–25.42) and nasal mucosal hypertrophy (n=2; ROR 8.67, 95% CI 1.99 - 37.73). In contrast, more frequently reported snAEs including sinusitis, rhinorrhea, nasal congestion, anosmia, nasal polyps, paranasal sinus inflammation, parosmia, and rhinitis, were not overreported (Overall $ROR_{2.5} \leq 1$). **Conclusions:** In this large pharmacovigilance analysis snAEs were not broadly overreported after ICI therapy. Rare inflammatory phenotypes were disproportionately reported with PD-1 inhibition, suggesting an immune-mediated mechanism. Given the limitations of spontaneous reporting data and small event counts, these findings should be interpreted cautiously but highlight the need for increased clinical awareness and prospective studies to better characterize sinonasal immune-related toxicities. Research Sponsor: None.

Sinonasal adverse events reported after ICI therapy.

Adverse event	Overall Freq	Overall ROR (95% CI $ROR_{2.5}$ – $ROR_{97.5}$)	CTLA 4 Freq	CTLA4 ROR	PD-1 Freq	PD-1 ROR	PD-L1 Freq	PD-L1 ROR
Anosmia	31	0.22 (0.15-0.32)	4	0.17	23	0.23	4	0.13
Chronic eosinophilic rhinosinusitis	**3**	**7.71 (2.34-25.42)**	0	0	**3**	**10.56**	0	0
Nasal congestion	157	0.2 (0.17-0.24)	15	0.12	122	0.23	20	0.13
Nasal mucosal hypertrophy	**2**	**8.67 (1.99-37.73)**	0	0	**2**	**11.88**	0	0.00
Nasal polyps	12	0.17 (0.09-0.33)	3	0.33	8	0.21	1	0.09
Paranasal sinus inflammation	4	1.96 (0.87-4.42)	0	3.69	3	2.23	1	1.44
Parosmia	48	0.52 (0.38-0.7)	9	0.64	37	0.63	2	0.11
Rhinitis	50	0.51 (0.39-0.68)	2	0.12	34	0.50	14	0.67
Rhinorrhoea	267	0.3 (0.27-0.35)	32	0.24	215	0.37	20	0.11
Sinusitis	300	0.21 (0.19-0.24)	56	0.27	204	0.22	40	0.14

Bold denotes statistical significance ($ROR_{2.5} > 1$).

11147 Poster Session

National trends in opioid-related hospitalizations among adult cancer patients: 2000-2022. First Author: Yongmei Huang, Department of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, New York, NY

Background: Opioid use disorder is increasingly prevalent among cancer patients. Since mid-2010s, heightened attention to the opioid crisis has led to restrictive opioid prescribing policies; however, national trends in opioid-related hospitalizations (ORH) among cancer patients following these policies remain underreported. This study examines ORH trends from 2000 to 2022 and associated factors among adult cancer patients. **Methods:** We identified hospitalizations among adult patients (age ≥18 years) with any cancer in the National Inpatient Sample (2000-2022). Outcomes included: 1) primary ORH (PORH), defined as admissions with a primary diagnosis indicating opioid poisoning, dependence or abuse, and 2) any ORH (AORH), capturing these conditions in any diagnostic field. The risks of PORH and AORH were calculated as the number of cases per 10,000 hospitalizations, respectively. Join-point regression assessed trends in risks of PORH and AORH, reporting annual percentage changes (APCs). Multivariable logistic regression identified factors associated with PORH and AORH, with adjusted odds ratio (aORs) reported. **Results:** Overall, among 59,682,271 weighted hospitalizations in cancer patients (median age 66.8 years, IQR 56.5-76.3), PORH occurred in 5.5 per 10,000 hospitalizations (n = 32,641) and AORH in 200 per 10,000 hospitalizations (n = 1,192,358). The risk of PORH increased non-significantly from 2.2 per 10,000 hospitalizations in 2000 to 4.8 in 2014 (APC = 5.6, $p > 0.05$), then rose sharply to 10.6 in 2017 (APC = 25.1, $p < .001$), before declining significantly to 6.8 in 2022 (APC = -9.7, $p < .001$). The risk of AORH also increased non-significantly from 45 per 10,000 hospitalizations in 2000 to 60.8 in 2014 (APC = 0.2, $p > 0.05$), then rose to 594.4 in 2019 (APC = 118.2 for 2013-2016 and 11.7 for 2016-2019; both $p < .001$), before decreasing non-significantly to 476.8 in 2022 (APC = -7.8, $p > .05$). Higher PORH risk was associated with younger age (< 65 vs. ≥ 65: aOR = 2.53, $p < .001$), race and ethnicity (Native American: aOR = 2.07, Black: aOR = 1.85, White: aOR = 1.79, relative to Asian/Pacific Islanders; all $p < .001$), public or no health insurance, lower income, co-occurring substance use disorders (SUD) (e.g., sedative aOR = 35.19, cocaine aOR = 3.57, both $p < .001$), depression (aOR = 2.46, $p < .001$), anxiety, chronic pain, metastases, and care in small, non-teaching, rural hospitals and the West region. Similarly, AORH were associated with younger age, race and ethnicity, insurance, low income, co-occurring SUD, mental health condition, chronic pain, metastases, comorbidity burden, and the West region. **Conclusions:** Opioid-related hospitalizations decreased substantially in recent years following heightened attention and clinical/policy efforts in the mid-2010s. Elevated risks were primarily associated with patient demographics, co-occurring substance use disorder, mental health conditions, and chronic pain. Research Sponsor: NIH, Clinical and Translational Science Award (CTSA) program, The TRANSFORM KL2 Mentored Career Development Award.

11148 **Poster Session**

Long-term incidence of hypothyroidism and thyroiditis after CAR T-cell therapy versus standard chemotherapy in hematologic malignancies: A propensity-matched multi-institutional cohort study. First Author: Taha Hassan, Texas Tech Health Sciences Center, Amarillo, TX

Background: Thyroid dysfunction is a common endocrine immune-related adverse event with modern cancer immunotherapies. Chimeric antigen receptor T-cell (CAR T) therapy is an adoptive cellular immunotherapy with expanding use in relapsed/refractory hematologic malignancies; its toxicity profile of cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome are well described, whereas endocrine sequelae are comparatively less characterized. Large-scale population analysis regarding the effect of CAR T therapy on thyroid function remains limited. As CAR T survivorship increases and indications broaden, defining long-term thyroid-related outcomes is essential in optimizing care. **Methods:** We performed a propensity-matched cohort study using the TriNetX Research Network (Jan 1, 2018–Jan 24, 2026). Adult, non-pregnant patients with DLBCL, PMBCL, follicular lymphoma, mantle cell lymphoma, multiple myeloma, or ALL were included. Patients receiving CAR T in addition to chemotherapy were compared with chemotherapy alone. Exclusions included prior thyroid disease/malignancy, central endocrine disorders, radiation therapy, bone marrow transplant, and baseline exposure to thyroid-active/thyroid-disrupting therapies (e.g., amiodarone, immune checkpoint inhibitors, tyrosine kinase inhibitors, interferons, immunomodulatory agents like lenalidomide). Propensity score matching balanced age, sex, race, malignancy type, baseline comorbidities, steroid exposure, and antipsychotic exposure. The primary outcome was new-onset hypothyroidism or thyroiditis; effect estimates are reported as ORs with 95% CIs. **Results:** Before propensity-score matching, there were 921 patients in the CAR T group and 24,426 in the chemo-only group. Post-matching, there were 878 CAR T patients and 879 chemo-only patients. Hypothyroidism or thyroiditis occurred in 16 patients in the CAR T group (1.822%) and in 21 patients in the chemo-only group (2.389%). Absolute risk difference was −0.567% (95% CI -1.909%, 0.776%; p = 0.4081) and the OR was 0.758 (95% CI 0.393, 1.463). No statistically significant difference in incidence was observed. Mean follow-up for CAR T after chemo and chemo-only groups were 670 and 964 days, respectively. **Conclusions:** In this large, multi-institutional propensity-matched real-world analysis with long-term follow-up, CAR T therapy after chemotherapy was not associated with increased incidence of hypothyroidism/thyroiditis compared with chemotherapy alone. These findings provide reassuring thyroid safety data, supporting the expanding use of CAR T as indications broaden. Future studies should evaluate thyroid outcomes by CAR T construct/target and characterize timing and severity to inform monitoring strategies. Research Sponsor: None.

11149 **Poster Session**

Risk of renal adverse events (RE-AE) and electrolyte changes with immunotherapy (IT) in a real-world cohort. First Author: Ameed Bawwab, Cleveland Clinic Foundation, Cleveland, OH

Background: IT is used across multiple tumor types but is linked to immune-related AE (irAE), including RE-AEs. Acute kidney injury (AKI) is the most common renal irAE (1–2%); however, real-world comparative data on RE-AE & electrolyte trends across tumor types remain limited. We evaluated RE-AE incidence & longitudinal electrolyte & urine trends following IT. **Methods:** We conducted a retrospective cohort study of 5,556 adult cancer patients treated at Cleveland Clinic Ohio between 2010–2022. Included cancers were advanced-stage (III–IV) bladder, endometrial, esophageal, gastric, head & neck, renal, & lung cancers (NSCLC/SCLC), & metastatic melanoma. We compared IT (± chemo/radiation) vs non-IT regimens. Follow-up began at systemic therapy initiation & continued until RE-AE, death, or last encounter. Outcomes included AKI, AKI progressing to chronic kidney disease (CKD), & clinically significant proteinuria. Poisson regression estimated incidence rates, Kaplan–Meier methods cumulative incidence (CIR), & time-dependent Cox models assessed risk with IT as a time-varying exposure. Longitudinal serum electrolytes & urine parameters were extracted electronically & analyzed via mixed-effects & generalized linear models over a one-year post-initiation period. **Results:** Among the cohort, 1,291 (23%) received first-line IT & 4,265 (77%) later-line IT. Median age was 66 years; 38% were female. During median follow-up of 14 months (CI 6-34), 195 RE-AEs occurred (IT: 46; non-IT: 149). The incidence rates per 100 person years were 0.18 (0.13, 0.24) in IT group & 0.13 (0.11, 0.15) in non-IT group. 2-year CIR was 4.6% with IT & 3.9% without IT (P = 0.6). Adjusted time-dependent Cox models demonstrated no significantly increased risk for AKI, CKD, or composite RE-AEs associated with IT exposure: [AKI HR 0.99 (0.7–1.5); CKD HR 1.5 (0.97–2.4); RE-AE HR 1.3 (0.9–1.7)]. Most RE-AEs were CTCAE grade II–III. Immunomodulatory therapy was used in 15%, primarily steroids, with a 50% response rate. Longitudinal analyses showed IT was associated with higher mean CO_2 & calcium compared with non-IT ($P < 0.05$), but not other labs (Table 1). While on therapy, IT was associated with lower urine pH (β = -0.37, CI -0.69 -0.04) but no other UA parameter changes were noted. **Conclusions:** In this large real-world cohort, IT was not associated with an increased incidence of RE-AE compared with non-IT therapy, suggesting that stringent trial exclusion criteria for baseline renal impairment may be unnecessarily restrictive. IT was associated with statistically significant changes in calcium, CO_2, & urine pH, the clinical significance of which remains uncertain. Research Sponsor: None.

Laboratory parameter	Estimate	95% CI
Sodium	0.14	-0.04 – 0.32
Potassium	0.02	-0.001 – 0.04
BUN	-0.03	-0.59 – 0.54
Creatinine	0.02	-0.003 – 0.05
CO2/ Bicarbonate	0.16	0.001 – 0.32
Calcium	0.10	0.067 – 0.14
Chloride	0.18	-0.038 – 0.4
GFR	-1.59	-4.73 – 1.55
Phosphorus	-0.11	-0.25 – 0.04

11150 **Poster Session**

Immune checkpoint inhibitors and respiratory outcomes in cancer patients with pre-existing asthma: A TriNetX propensity-matched cohort study. First Author: Murad Alkharabsheh, Crestwood Medical Center, Huntsville, AL

Background: Immune checkpoint inhibitors (ICIs) are associated with immune-related pulmonary toxicity. Real-world data on outcomes in patients with pre-existing asthma across malignancies remain limited. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network (170 HCOs). Adults (≥18 years) with asthma (ICD-10 J45) and malignancy (ICD-10 C00–C96) were identified. The ICI cohort included patients receiving ICIs (HCPCS J9271, J9299, J9119, J9272, J9345, J9022, J9173, J9023, J9228, J9347) after cancer diagnosis (first ICI within 3 years of first malignancy). The comparator cohort included patients receiving non-ICI systemic therapy (TNX:1002 chemotherapy, TNX:1003 targeted therapy, TNX:1004 hormone therapy, and/or Z51.11) and excluded ICI exposure. Outcomes were assessed from day 1 through day 1095 after index. Propensity score matching (1:1) was performed (final N = 4,074 per cohort). **Results:** In the matched cohorts (N = 4,074 each), ICI exposure was associated with higher risks of inpatient admissions (41.65% vs 32.78%; RR 1.27; HR 1.22), all-cause mortality (47.62% vs 38.76%; RR 1.23; HR 1.44), respiratory failure (J96) (25.01% vs 15.13%; RR 1.65; HR 1.66), and drug-induced interstitial lung disorders (1.91% vs 0.87%; RR 2.20; HR 4.26). ICI exposure was also associated with increased risk of mechanical ventilation (4.00% vs 2.93%; RR 1.36; HR 1.45), emergency intubation (2.55% vs 2.00%; RR 1.27; HR 1.32), and ED visits (38.98% vs 31.56%; RR 1.24; HR 1.74). Asthma exacerbation (J45.901) showed a modest increase in risk (RR 1.23), with survival analysis not reaching statistical significance (HR 1.15; p = 0.078). **Conclusions:** Among adults with asthma and cancer, ICI exposure was associated with increased risks of hospitalization, respiratory failure, drug-induced interstitial lung disorders, and mortality compared with non-ICI systemic therapy. These findings support close pulmonary monitoring and risk mitigation when initiating ICIs in patients with asthma. Research Sponsor: None.

11151 **Poster Session**

Real-world data on clinical profile of immune-related adverse events (irAEs) associated with immune checkpoint inhibitors (ICIs) in oncology. First Author: Shruti Prem Sudha, Bahrain Oncology Center, Muharraq, Bahrain

Background: Immune checkpoint inhibitors (ICIs) are widely used in cancer, and are associated with immune-related adverse events (irAEs) in many organs. Real-world data on the spectrum, timing, severity, and outcomes of irAEs is limited. In this study, we aimed to gather real world data on the immune toxicity of ICIs. **Methods:** We conducted a retrospective cohort study on adult oncology patients on ICI therapy between Jan 2018-Dec 2024. IrAEs were categorized by organ system, time to onset (early < 12 weeks, intermediate 12-24 weeks, and late > 24 weeks), and severity (standard toxicity criteria CTCAEv6.0). Management strategies, therapy discontinuations, hospitalizations, and survival were assessed. **Results:** We screened 652 patients who received ICIs across different cancer types -169 (26%) were identified with irAEs. Sixty-four percent patients had received ICI alone, and the remainder had received ICIs in combination with other agents. The most common organ affected was thyroid (43%), followed by skin (28.4%), and lung (11.8%), more than one organ was affected in 22.5% patients. IrAEs occurred across a broad time frame following treatment- cumulative incidence before 12 weeks was 41.4%, between 12-24 weeks was 44.4%, and beyond 24 weeks was 91.3%. Musculoskeletal, hepatic, pulmonary, gastrointestinal, dermatologic, and pancreatic irAEs generally presented early, with median onset around 10–14 weeks. Renal, ophthalmologic, infusional, and dermatologic irAEs generally occurred across early, and intermediate time frames, while neurological irAEs tended to occur late. Endocrine irAEs, had a median onset of 20.1 weeks, and frequently occurred beyond 24 weeks. Hepatitis, pneumonitis, colitis, CNS and pancreatic toxicity were among the more severe irAEs, with a median CTCAE grade of 3, while renal, endocrine, ophthalmologic, infusional, and dermatologic irAEs were generally of lower severity (grade 1 or 2). IrAE grade > 2 was associated with increased risk of death (HR 2.7, 95% CI 1.1-6.5). Management of irAEs comprised supportive care alone (62%), systemic corticosteroids (31%), or observation alone (8%). Patients with higher grades of irAEs were more likely to receive steroids. Hospitalization was required in 29%, and ICIs were permanently discontinued in 25%. Complete resolution of irAEs was seen in 40%, 5% died attributable to the irAE, and the remainder had partial resolution of irAE with need for continued replacement therapy (as with endocrine irAEs). **Conclusions:** In our real-world practice, oncology patients receiving ICIs had irAEs across a broad range of organ systems, with heterogeneous timing and severity. Several clinically meaningful toxicities presented late in the treatment course, underscoring the importance of long-term monitoring. Occurrence of grade 2 or higher iRAEs was associated with higher mortality. Research Sponsor: None.

11152 **Poster Session**

Association of β-blocker selectivity with survival and immune-related outcomes in melanoma and lung cancer patients treated with immune checkpoint inhibitors. First Author: Leen Alkuttob, School of Medicine, University of Jordan, Amman, Jordan

Background: Immune checkpoint inhibitors (ICIs) are standard of care for advanced melanoma and lung cancer. Retrospective studies suggest that non-selective β-blocker use correlates with improved overall survival, potentially through modulation of the tumor immune microenvironment. However, real-world evidence comparing the effect of selective versus non-selective beta-blockers remains limited. **Methods:** We conducted a multicenter retrospective study using the TriNetX Global Collaborative Network. Adult patients (≥18 years) with melanoma or lung cancer treated with immune checkpoint inhibitors (pembrolizumab, nivolumab, ipilimumab, atezolizumab, durvalumab, cemiplimab, or avelumab) were identified. Patients were categorized based on exposure to non-selective β-blockers (carvedilol, propranolol, nadolol, labetalol, timolol) or selective β-blockers (metoprolol, atenolol, bisoprolol, nebivolol, acebutolol) within two months before or at ICI initiation. The index date was first ICI exposure. One-to-one propensity score matching was performed using covariates selected based on baseline imbalance, including demographics, cardiovascular and cerebrovascular comorbidities, and prior procedures. The primary outcome was overall survival. Secondary outcomes included hospitalization and immune-related adverse events (irAEs), defined using a composite endpoint of organ-specific immune-mediated toxicities based on prior published methodology. **Results:** After matching, 3,720 patients with melanoma and 11,160 patients with lung cancer were included in the analysis. Among melanoma patients treated with ICIs, non-selective β-blocker use was associated with lower mortality (HR 0.799; 95% CI 0.652–0.980) and decreased hospitalization (HR 0.865; 95% CI 0.759–0.984) compared with selective β-blockers. Most immune-related adverse events did not differ between groups, except for higher hepatic toxicity with non-selective β-blockers (HR 1.382; 95% CI 1.064–1.796). In lung cancer patients, non-selective β-blocker use was associated with lower mortality (HR 0.847; 95% CI 0.797–0.900), reduced ICU admission (HR 0.87; 95% CI 0.800–0.946), and decreased hospitalization (HR 0.912; 95% CI 0.864–0.963). Additionally, fewer cardiovascular (RR 0.811; 95% CI 0.711–0.925) and respiratory (RR 0.842; 95% CI 0.772–0.918) immune-related adverse events compared with selective β-blockers. **Conclusions:** In this real-world, propensity-matched analysis, non-selective β-blocker use was associated with improved early survival and reduced healthcare utilization among melanoma and lung cancer patients treated with ICIs. These findings suggest that non-selective β-blockers represent a low-cost and available adjunct to immunotherapy and warrants prospective validation. Research Sponsor: None.

11153 **Poster Session**

Second-generation H1 antihistamine use with survival and immune-related outcomes in lung cancer and melanoma patients receiving immune checkpoint inhibitors. First Author: Leen Alkuttob, School of Medicine, University of Jordan, Amman, Jordan

Background: Immune checkpoint inhibitors (ICIs) are standard of care for melanoma and lung cancer but are associated with immune-related adverse events and variable outcomes. Previous studies suggest that H1 antihistamine use may be associated with improved outcomes, potentially through histamine-mediated modulation of the tumor microenvironment. However, real-world evidence is limited. **Methods:** We conducted a multicenter retrospective study using the TriNetX Global Collaborative Network. Adult patients (≥18 years) with melanoma or lung cancer receiving ICIs (pembrolizumab, nivolumab, ipilimumab, atezolizumab, durvalumab, cemiplimab, or avelumab) were identified. Patients were categorized by exposure to second-generation H1 antihistamines (cetirizine, loratadine, fexofenadine, desloratadine, or levocetirizine) within 3 months before or during ICI initiation. One-to-one propensity score matching was performed based on demographics, baseline comorbidities, cancer characteristics, prior treatments, and conditions commonly associated with antihistamine use, including allergic and atopic disorders. The index date was defined as first ICI exposure, and outcomes were assessed from day 1 to day 180. The primary outcome was overall survival. Secondary outcomes included hospitalization and immune-related adverse events (irAEs), defined using a composite endpoint of organ-specific immune-mediated toxicities based on prior published methodology. **Results:** After matching, 2,141 melanoma and 11,812 lung cancer patients were included. In lung cancer patients, H1 antihistamine use was associated with reduced all-cause mortality (HR 0.769, 95% CI 0.727–0.815), lower hospitalization rates (HR 0.862, 95% CI 0.821–0.906), fewer intensive care unit admissions (HR 0.867, 95% CI 0.797–0.943) and reduced emergency department use (HR 0.940, 95% CI 0.899–0.984). 6-month overall survival was 80.93% in antihistamine users vs 75.98% in non-users. It was also associated with decreased endocrine (HR 0.843, 95% CI 0.776–0.916), and musculoskeletal irAEs (HR 0.840, 95% CI 0.752–0.938). In patients with melanoma, H1 antihistamine use was associated with reduced all-cause mortality (HR 0.685, 95% CI 0.581–0.808), lower hospitalization rates (HR 0.837, 95% CI 0.734–0.955), and reduced neutropenia (HR 0.441, 95% CI 0.266–0.729). 6-month overall survival was 88.15% vs 83.20%, respectively. No statistically significant differences were observed across other major immune-related organ systems. **Conclusions:** Second-generation H1 antihistamine use was associated with improved early survival and reduced healthcare utilization among melanoma and lung cancer patients treated with ICIs, without a significant increase in irAEs. Despite the retrospective design and potential confounding, prospective validation is warranted. Research Sponsor: None.

11154 **Poster Session**

Trends in ischemic stroke and ischemic heart disease-related mortality among patients with malignancies in the United States: A 25-year CDC-WONDER analysis (1999-2023). First Author: Muhammad Saad, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan

Background: Substantial advances in cancer screening, diagnostics, and therapeutic strategies have improved survival and quality of life. Despite these efforts, cancer-related complications continue to contribute significantly to morbidity and mortality. Malignancies induce a prothrombotic state and substantially increase the risk of venous and arterial thromboembolism. As a result, the patients with cancer have a higher incidence of Ischemic stroke (IS) and ischemic heart disease (IHD) compared to the general population. The greatest risk of these thromboembolic diseases is greatest during the first six months of cancer diagnosis, but remains elevated thereafter. In this study, we sought to assess temporal trends and sociodemographic differences in ischemic stroke and ischemic heart disease related mortality among patients with neoplasms. **Methods:** We analyzed deidentified CDC WONDER death certificate data to assess malignant neoplasm, (ICD = C00-C97) and ischemic heart disease (ICD = I20-I25) and ischemic stroke (ICD = I63) related mortality in patients of all ages. Age-adjusted mortality rates (AAMR) per 100,000 persons and average annual percent change (AAPC) were calculated and stratified by year, gender, state, urban-rural status, census region, place of death (POD), and age group. **Results:** From 1999 to 2023, 1235844 deaths were attributed to Ischemic stroke and ischemic heart disease-related deaths in cancer patients. Overall, AAMR decreased from 19.7 in 1999 to 12.9 in 2023 (APC -1.74*, 95% CI: -1.88 to -1.63). Males had higher mortality rates than females throughout the period (23.26 vs 8.88, respectively). Racial analysis showed that non-Hispanic whites had the highest mortality (AAMR: 15.064), followed by Blacks or African Americans (AAMR: 14.24); in contrast, Asians or pacific islanders had the lowest mortality (AAMR: 7.48, data available till 2020). The Midwest region had the highest mortality of all census regions (AAMR: 15.92). Lastly, non-metropolitan areas had higher mortality rates than metropolitan areas (AAMR of 15.75 vs 14.04, respectively). **Conclusions:** Overall mortality rates in cancer patients with co-morbid ischemic stroke and ischemic heart diseases declined from 1999 to 2023. However, higher mortality rates were observed among men, non-Hispanic Whites, residents of the Midwest, and those living in non-metropolitan areas of the U.S., underscoring the need for targeted public health efforts, and equitable access to cardio-oncology preventive care in these high-risk groups. Research Sponsor: None.

11155 **Poster Session**

Five-year survival disparities in two population-based cohorts of adults with early-onset colorectal cancer. First Author: Lauren P. Wallner, University of Michigan, Ann Arbor, MI

Background: Early-onset colorectal cancer (EO-CRC) is now the leading cause of cancer-related death in those under the age of 50 despite advances in treatment. However, the impact of specific sociodemographic and clinical factors on long-term survival remains poorly characterized. We evaluated 5-year survival patterns and risk factors across two diverse, population-based cohorts to optimize risk reduction strategies and survivorship care delivery. **Methods:** We constructed two cohorts of adults $<$ 50 years of age with newly diagnosed EO-CRC from 2015 to 2018 (stages I-III) and treated with curative-intent surgery. One cohort was derived from three SEER registries (Georgia, Los Angeles County, Kentucky; n = 2995) and one cohort was derived from the Veteran's Health Administration (VHA) (n = 295). Pathologic-confirmed recurrence was identified in the follow-up period 6 months to five years after curative-intent surgery via human review of electronic pathology reports. Five-year survival was estimated from the date of curative-intent surgery to five years post-surgery. Adjusted risk of CRC-specific mortality was estimated in both populations using multivariable proportional hazards regression, adjusting for key demographic and clinical characteristics. **Results:** The proportion of patients surviving 5 years was 86% in the SEER cohort and 92% in the VHA cohort. Overall, 14% experienced recurrence in SEER and 18% in VHA, and recurrence was strongly associated with reduced survival in both cohorts (both $p < 0.01$). Five-year survival varied by clinical stage and was higher in the VHA across all stages (SEER: 93% stage I, 87% stage II, and 76% stage III vs. VHA: 97% stage I, 93% stage II, and 88% stage III). Mortality risk varied by race/ethnicity in the SEER cohort only: Hispanic patients (adjusted HR 1.6, 95% CI: 1.1–2.2) and Black patients (adjusted HR 1.9, 95% CI: 1.5–2.5) had a greater risk of 5-year mortality vs. white patients. Age at diagnosis, sex, and living in a rural area were not significantly associated with mortality in either cohort. Rectal tumors (vs. colon) were associated with an increased risk of mortality in VHA (adjusted HR: 2.5, 95% CI: 1.0-6.4), but not in SEER. Lymphovascular invasion was associated with an increased risk of mortality in both cohorts. **Conclusions:** There are critical sociodemographic and clinical disparities in survival among adults with stage I-III EO-CRC. These distinct patterns observed between the two cohorts underscore the influence of varying population-level risk profiles. Tailoring survivorship care to identify and support these high-risk subgroups is essential to mitigate disparities and improve long-term outcomes in this growing patient population. Research Sponsor: National Cancer Institute; R37CA275907.

11156 **Poster Session**

Assessment of the role of rapid drug desensitization to treat cancer patient with infusion-related allergic reactions. First Author: Irene Palmieri, Oncology Department City Rimini Hospital, Rimini, Italy

Background: Rapid Drug Desensitization (RDD) as The Castells protocol is based on progressively increasing concentrations and infusion rates of the drug under close monitoring, inducing temporary drug tolerance. To assess the role of Rapid Drug Desensitization (RDD) to treat cancer patient with infusion-related allergic reactions (IRRs) we planned an observational trial in 2021. **Methods:** From 2021 to 2025 all patients experiencing IRRs at the Rimini Oncology Unit, after an allergological evaluation, were treated according to the Castells desensitization protocol. We analyzed the safety of this apporach as well as the treatment discontiunation rate. The IRR severity was classified (grade 1-3) using the Brown classification from 2004. **Results:** A total of 155 patients were treated with RDD. Among drugs administered using a desensitization protocol, drugs administered with the RDD were paclitaxel (38.06%), oxaliplatin (25.80%), docetaxel (14.10%), and carboplatin (12.9%), irinotecan (1.94%), etoposide (1.94%), liposomal doxorubicin (1.29%), trastuzumab (1.29%), atezolizumab (0.65%), cetuximab (0.65%), cyclophosphamide (0.65%), and cisplatin (0.65%). Grade 3 reactions occurred in 1.29% of patients during RDD, while grade 2 and grade 1 reactions were observed in 3.87% and 2.58%, respectively. No deaths associated with desensitization treatment occurred. The IRRs were managed with treatment interruption and administration of steroids and antihistamines. Notably, 3.22% of patients experienced an allergic reaction during RDD but were able to complete treatment. In total 132 patients completed the planned treatment (85.2%) using the RDD approach. Among those who discontinued, 7 patients (4.5%) stopped due to allergic reactions during the first desensitization cycle. The remaining treatment discontinuations were due to clinical deterioration, patient decision or transfer to another institution (1.9% each), progressive disease (3.9%), or other causes (0.7%). We summarized the characteristics in the table. **Conclusions:** The RDD protocol is safe and permits to maintain the original schedule in the most part of cancer patients that present a major allergic reaction during chemotherapy. Further trials are probably needed to better define the role of RDD and the drugs primarily candidate to the desensitization protocol. Research Sponsor: None.

	Number of patients	% of the total (155 patients)
Treatment completed	132	85.2%
Discontinuation for infusional reaction	7	4.5%
Discontinuation for clinical deterioration	3	1.9%
Discontinuation for patient decision	3	1.9%
Discontinuation for progressive disease	6	3.9%
Discontinuation for transfer to another institution	3	1.9%
Discontinuation for other causes	1	0.7%

11157 **Poster Session**

Trends and racial disparities in pulmonary embolism–related mortality among older adults with neoplasms: A population-based retrospective study in the United States from 1999-2020. First Author: Chinenye Egwuonwu, PAR Piedmont, Athens, GA

Background: Pulmonary embolism (PE) remains a major cause of preventable mortality, particularly among older adults with cancer who face heightened thrombotic risk. Understanding temporal trends in PE-related deaths is essential for guiding prevention and early detection. This study evaluates national patterns and racial disparities in PE-related mortality among older adults with neoplasms. **Methods:** We performed a retrospective cross-sectional analysis of the national death certificate data from the CDC's WONDER database. We included persons ≥65 years of age with neoplasms (ICD-10 code C00-D48) as the underlying cause of death and PE (ICD-10 code I26) as a contributing cause of death. The exposure variable was the year of death, and the outcome was PE-related age-adjusted mortality rate (AAMR) stratified by sex, race, rural-urban status, and census region. We calculated the PE-related AAMR in neoplasm per 100,000 population. Trends were evaluated with Joinpoint regression and expressed as an average annual percentage change (AAPC) with a 95% confidence interval (CI). $P < 0.05$ defined statistical significance. **Results:** Of 928 million people, 104,743 PE-related deaths occurred in older adults with neoplasms (AAMR 11.4). The AAMR was higher in males (13.3 vs 10.1 in females; $P < 0.01$), Black (17.0 vs 11.2 in White, $P < 0.000001$), and the Midwest census region (12.3 vs 11.7 in NorthEast, the Midwest, and 10.4 in the South; $P < 0.0001$). The AAMR was similar in rural areas (11.4 vs 11.3 in urban areas, $P < 0.000001$). The overall PE-related AAMR in neoplasms increased from 8.7 to 14.1 (AAPC 4.03%; CI: 3.12- 5.23). Furthermore, the AAMR increased in males (AAPC 3.37%; CI: 1.61-6.6) and females (AAPC 4.53%; CI: 3.15-6.20). Similarly, it increased in Black (AAPC 3.14%; CI:2.42-4.07), White (AAPC 3.98%; CI:3.07-5.14), rural (AAPC 3.70%; CI: 2.69-5.39), urban (AAPC 4.24; CI: 3.44-5.23), and across all geographic census regions. **Conclusions:** Pulmonary embolism related mortality among older adults with neoplasms has risen steadily over the past two decades across all demographic and geographic groups. Given that cancer-associated thrombosis is a well-recognized and largely preventable complication, these findings suggest important gaps in the prevention, recognition, and management of PE in oncology populations at the health-system level. The consistent upward trend highlights an urgent need to strengthen thromboprophylaxis strategies, risk stratification, and early detection efforts in older adults with cancer to reduce avoidable mortality. Research Sponsor: None.

11158 **Poster Session**

Safety of immune checkpoint inhibitors in solid tumor patients with hepatitis C: A real-world analysis. First Author: Muhammad Yousaf, Charleston Area Medical Center, Charleston, WV

Background: Patients with hepatitis C virus (HCV) infection are commonly excluded from immune checkpoint inhibitor (ICI) trials. We evaluated hepatotoxicity and outcomes after ICI therapy in patients with versus without HCV. **Methods:** Retrospective cohort study using the TriNetX Research Network (2014-2024). Adults with solid tumors initiating ICIs were classified as HCV if they had detectable HCV RNA and/or ICD-10 B18.2 (chronic viral hepatitis C) within 1 year prior to ICI start. Cohorts were 1:1 propensity-score matched on demographics, comorbidities, cancer type, metastatic site, and baseline liver tests. Outcomes from day 1–90 after ICI started were ALT ≥150 U/L, total bilirubin ≥3 mg/dL, diagnosis-coded hepatotoxicity, and diagnosis-coded hepatic failure. Overall survival (OS) was assessed for up to 5 years. A sensitivity analysis restricted HCV definition to lab-confirmed HCV RNA (no ICD-10 inclusion). **Results:** In the primary analysis, 1,157 HCV and 109,309 non-HCV ICI-treated patients were identified; 1,137 patients remained per group after matching. Patients with Hep C had a higher risk of ALT ≥150 U/L, although this did not reach statistical significance (7% vs 5%; p = 0.066). There was no difference in the risk of bilirubin ≥3 mg/dL (5.0% vs 5.0%; p = 1.0). Diagnosis-coded hepatotoxicity was similar (1.8% vs 1.8%; p = 0.875), while diagnosis-coded hepatic failure was higher in the HCV cohort (4.7% vs 2.5%; p = 0.005). Median OS was 20.1 vs 17.2 months (p = 0.0595). In the RNA-only sensitivity analysis (308 matched patients), there was no significant difference in overall survival between patients with and without HCV prior to treatment (27% vs 32%; p = 0.7489). However, the risk of ALT ≥150 U/L was significantly higher in the HCV group (10% vs 5%; p = 0.0058). There was no significant difference in mean bilirubin values after treatment (p = 0.0636). **Conclusions:** Pre-existing HCV was associated with an increased risk of transaminitis in patients receiving immunotherapy, but there was no statistically significant difference in biliary toxicity or median overall survival. There is also an approximate two-fold increased risk of hepatic failure. These real-world data highlight the importance of closely monitoring for hepatotoxicity in patients receiving immunotherapy and support ICI use in patients with HCV. Research Sponsor: None.

11159 **Poster Session**

Real-world resource use and cost in patients treated with originator or biosimilar rituximab in a large U.S. insurance claims database. First Author: Ruth Wangia Dixon, Carelon Research, Wilmington, DE

Background: Rituximab-pvvr, Rituximab-arrx, and Rituximab-abbs are monoclonal antibodies approved by the FDA as biosimilars to originator rituximab. All are approved for treatment of non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Biosimilars are intended to deliver equal clinical outcomes to originators at a lower cost, but there remains limited 'real-world' investigation of these outcomes. This study describes and compares resource use and cost for patients receiving originator or biosimilar rituximab in the Carelon Research Healthcare Integrated Research Database (HIRD). **Methods:** We conducted a retrospective cohort study of adults with newly diagnosed NHL and CLL identified by ICD-10 codes between 1/1/2018 and 7/31/2024 in the Carelon Research HIRD and treated with rituximab. Included patients had ≥1 claim for originator or biosimilar rituximab after NHL or CLL diagnosis. Baseline demographics were assessed at rituximab initiation (*index date*). Inpatient, outpatient, and emergency department (ED) resource use and medication cost were assessed over one year following rituximab initiation. Costs were inflation-adjusted to 2024 USD. Originator and biosimilar rituximab groups were compared using t-test or ANOVA to assess mean differences in resource use and cost. **Results:** A total of 11,525 patients met inclusion criteria with mean age of 64.4 years, 57.2% male, and 76.9% reporting white non-Hispanic race/ethnicity. Most of the cohort (89.8%) were diagnosed with NHL. There were no significant differences in mean follow-up duration (p=0.960), rituximab infusions (p=0.987), treatment duration (p=0.106), inpatient hospitalizations (p=0.241), or ED visits between groups (p=0.702) (*see table*). Mean overall medication costs were significantly lower in all biosimilar groups vs. originator (p<0.001). **Conclusions:** In this large real-world cohort of NHL and CLL patients, resource use was similar in patients treated with originator and biosimilar rituximab, but medications costs were significantly lower in the biosimilar groups. Our findings demonstrate how biosimilar therapies in cancer can deliver similar clinical outcomes to originators, while generating meaningful cost savings for the U.S. healthcare system. Research Sponsor: Pfizer.

Mean 1-Year Outcomes	Originator Rituximab (n=7,123)	Biosimilar Rituximab-pvvr (n=1,846)	Other Rituximab Biosimilars (n=2,556)
Follow-Up Duration, Months (SD)	10.8 (2.7)	10.8 (2.7)	10.8 (2.7)
Count of Rituximab Infusions (SD)	5.7 (2.5)	5.7 (2.6)	5.7 (2.5)
Rituximab Treatment Duration, Months (SD)	4.2 (3.3)	4.1 (3.3)	4.1 (3.3)
Count of All-Cause Inpatient Stays (SD)	1.6 (3.1)	1.6 (3.2)	1.5 (2.9)
Count of All-Cause ED Visits	0.6 (1.4)	0.6 (1.3)	0.6 (1.2)
Medication & Related Costs (SD)*	$123,499 ($145,374)	$77,728 ($96,377)	$90,868 ($122,510)

*Includes all medications paid under medical benefit, including rituximab.

11160 **Poster Session**

Impact of concomitant antibiotic exposure on overall survival in patients with esophagogastric cancer treated with immune checkpoint inhibitors: A real-world cohort study. First Author: Diptasree Mukherjee, Atrium Health Levine Cancer, Charlotte, NC

Background: Gut microbiota composition plays a critical role in mediating response to immune checkpoint inhibitors (ICIs). Antibiotic exposure has been associated with impaired ICI efficacy across tumor types; however, data specific to esophagogastric cancers remain limited. We evaluated the association between peritreatment antibiotic exposure and overall survival (OS) among patients with advanced esophagogastric cancer receiving ICIs in routine clinical practice. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. Adult patients with advanced or metastatic esophageal or gastric adenocarcinoma who received nivolumab- or pembrolizumab-based therapy between 2016 and 2024 were identified. Patients were categorized as antibiotic-exposed (receipt of systemic antibiotics within 60 days before or after ICI initiation) and non-exposed (no documented antibiotic exposure during the same period). Cohorts were 1:1 propensity score matched for age, sex, cancer subtype, Charlson comorbidity index, infection-related diagnoses, baseline corticosteroid use, and hospitalization within 30 days prior to ICI initiation. The primary endpoint was OS. Kaplan–Meier and Cox proportional hazards models were used for analysis. Sensitivity analyses evaluated the timing and duration of antibiotic exposure. **Results:** After matching, 3,024 patients were included (1,512 per cohort). Baseline characteristics were well balanced (mean age 63.7 years; 34% female; median Charlson comorbidity index 5). At a median follow-up of 19.8 months, antibiotic exposure was associated with significantly worse overall survival compared with non-exposure. Median OS was 10.6 months in antibiotic-exposed patients versus 14.3 months in non-exposed patients (log-rank $p< 0.001$). Antibiotic exposure was independently associated with inferior OS (HR 1.34, 95% CI 1.22–1.47). The negative association was most pronounced among patients with broad-spectrum antibiotic exposure (HR 1.41) and among those with antibiotic exposure within 30 days prior to ICI initiation (HR 1.38). Findings remained robust in sensitivity analyses excluding patients with documented sepsis or prolonged hospitalization. **Conclusions:** In this large real-world cohort of patients with esophagogastric cancer treated with ICIs, peritreatment antibiotic exposure was associated with significantly worse overall survival. These findings further support the role of the gut microbiome in modulating immunotherapy response and underscore the importance of judicious antibiotic use during ICI therapy. Research Sponsor: None.

11161 **Poster Session**

EU-OPEN: A novel approach for generating European oncology real-world evidence at scale. First Author: Kaushal Desai, Merck & Co., Inc, Rahway, NJ

Background: The European Oncology Platform for Evidence Needs (EU-OPEN) is a strategic initiative to generate high-quality oncology real-world evidence (RWE) in Europe. It focuses on establishing multi-study partnerships with access to clinically rich data, regional medical expertise and to enable adoption of novel approaches to conduct research on cohorts of interest efficiently at scale. **Methods:** For each tumor area *(e.g., EU-OPEN Breast)*, master protocols aligned to specific patient populations *(e.g., ER+/HER2- earlier stage breast cancer or triple negative metastatic breast cancer)* are developed alongside a fit-for-purpose data assessment at prospective data partners (primarily hospital sites and registries). Data partners are selected based on their data availability, data quality and operational aspects of collaboration. After finalizing the master protocol, supporting documentation (including common data models and statistical analysis plans) are prepared and shared with partner sites for consistent execution. Data partners then curate, harmonize and analyze data in accordance with the study requirements. Studies and patient cohorts can be efficiently refreshed to capture longer-term outcomes. **Results:** The initiative began in 2024 with a multi-tumor assessment of prospective data partners and an early breast cancer pilot study (completed and published in 2025). EU-OPEN has since expanded to metastatic breast, endometrial, ovarian and esophageal cancers. Collectively these studies encompass 11 cohorts and plan to include $>$ 2,200 patients. Future plans include expanding to additional tumor areas and data partner types, adopting advanced capabilities such as natural language processing (NLP) to maintain 'live cohorts' for rapid analyses, and strengthening governance through clinical and data committees across partners. **Conclusions:** EU-OPEN demonstrates a scalable, efficient approach to generating research-grade European Oncology RWE at scale. As the initiative grows, adoption of novel technologies and deeper collaboration with data and clinical experts will further accelerate insight generation. Research Sponsor: None.

11162 **Poster Session**

Midday immune checkpoint inhibitor (ICI) infusion influence on survival in patients with metastatic cancer: A real-world chrono-immunotherapy study. First Author: Beliz Bahar Karaoğlan, Ankara University Faculty of Medicine Department of Medical Oncology, Ankara, Turkey

Background: Circadian rhythms regulate immune activity, and earlier ICI dosing has been linked to better survival. However, prior findings remain inconsistent, often relying on predefined time categories. To address this, we clustered actual infusion times to assess survival associations in a real-world cohort. **Methods:** This retrospective study included metastatic cancer patients treated with ICIs. Mean dosing times (up to 24 infusions/patient) were analyzed using circular statistics and clustered via k-means. Overall survival (OS) was defined from ICI initiation to progression, death, or last follow-up, and analyzed via Kaplan-Meier and multivariable Cox regression adjusted for cancer and ICI type. **Results:** A total of 640 patients (median age 61 years [range 23–87]; 78% male) were included. The most common tumor types were non-small cell lung cancer (52%), renal cell carcinoma (19%), and malignant melanoma (12%), followed by urothelial (5.5%) and small cell lung cancer (4.8%). The majority of patients received nivolumab (74%) or pembrolizumab (11%), while a smaller proportion were treated with other ICIs including atezolizumab (6.3%), avelumab (2%), or ipilimumab-based combinations (5.4%). ECOG performance status was 0–1 in 80% of patients. The most frequent metastatic sites were lymph nodes or soft tissue (78.6%), lungs (48.1%), bones (32.8%), liver (17.7%), and central nervous system (14.2%). Based on mean ICI infusion times, patients were grouped into three clusters: cluster 1 (2:15 PM, n = 76), cluster 2 (1:31 PM, n = 151), and cluster 3 (11:04 AM, n = 413). Median OS was 50.4, 28.2, and 15.7 months in Clusters 2, 1, and 3, respectively (log-rank p = 0.003). In multivariable analysis, Cluster 2 showed improved OS compared to Cluster 1 (Hazard Ratio [HR] 0.52, 95% Confidence Interval [CI] 0.31–0.86, p = 0.01), while no difference was seen between Clusters 3 and 1 (HR 1.13, 95% CI 0.75–1.70, p = 0.59). **Conclusions:** ICI administration around midday was associated with the longest survival, aligning with circadian peaks in T-cell infiltration, dendritic cell migration, and immune responsiveness. These findings support a personalized chrono-immunotherapy approach based on intrinsic biological rhythms. Research Sponsor: None.

11163 **Poster Session**

Ischemic heart disease as a competing cause of death among patients with lung cancer in the United States: A multiple cause-of-death analysis, 1999–2023. First Author: Manish KC, North Alabama Medical Center, Florence, AL

Background: Despite improvement in lung cancer prevention, early diagnosis & management, Ischemic heart disease (IHD) has become a major concurrent cause of mortality in lung cancer. Population level evidence on long term deaths due to IHD & lung cancer especially across sex & racial groups are lacking. Identification of these trends is necessary for cardio-oncology risk stratification & promote equitable survivorship care. **Methods:** We used the CDC WONDER Online Database to obtain mortality data for IHD & Lung Cancer from 1999-2023 from patients aged 45-85 & above. We used current final multiple cause of death data from 1999-2020 & 2018-2023. We used ICD-10 codes I20-I25 for IHD & C33-34 for Lung cancer. Data were stratified by Race (Non-Hispanic [NH] American Indian or Alaska Native, NH Asian or Pacific Islander, NH Black or African American, NH White, Hispanic or Latino), sex (male & female) and age groups (45-85+). We calculated age-adjusted mortality rates (AAMR) per 100,000 population based on the 2000 US standard population. Temporal mortality trends were analyzed using Joinpoint regression. ($P < 0.05$). **Results:** From 1999-2023, AAMR from lung cancer & IHD decreased in most demographic groups. Males had higher AAMR than females, with mortality decreasing from 20.3 to 10.6 per 100,000, compared with a decline from 6.8 to 4.6 per 100,000 among females. Joinpoint regression identified substantial reduction among males from 1999-2010 (annual percent change [APC] -2.35%, $p < 0.05$) & 2010-2016 (APC -5.45%, $p < 0.05$), followed by stabilization. Among females, declines were observed from 2005-2012 (APC -2.76%, $p < 0.05$) & 2012-2015 (APC -7.35%, $p < 0.05$), with a nonsignificant plateau thereafter. NH Black exhibited higher AAMRs despite significant declines from 2005-2018 (APC -4.11%, $p < 0.05$). NH White showed persistent declines from 1999-2017, followed by a marginal increase during 2017-2021. Hispanic & Asian or Pacific Islander individuals maintained the lowest AAMRs, with decreasing trends & brief late-2010s increases in select subgroups, while American Indian or Alaska Native individuals exhibited greater year-to-year variability without statistically significant joinpoints. **Conclusions:** During 1999-2023, mortality from IHD & lung cancer decreased significantly in the US. Males & NH Black experienced a major disease burden. Recent improvement in death trends among the select patient population showed appropriate cardiovascular risk management in survivors with lung cancer. This analysis highlighted the importance of cardio-oncology care models & precision-guided, equity-driven interventions to decrease cardiovascular mortality among patients with lung cancer. Research Sponsor: None.

11164 **Poster Session**

Real-world cost effectiveness of androgen receptor pathway inhibitors for metastatic hormone sensitive prostate cancer: An economic evaluation utilizing data from the International Registry for Men with Advanced Prostate Cancer (IRONMAN). First Author: Rebecca Green, London School of Economics and Political Science, London, UK, and Prostate Cancer Clinical Trials Consortium, LLC, New York, NY

Background: Several therapies are approved for metastatic hormone sensitive prostate cancer (mHSPC), with differing efficacy and costs. While many cost-effectiveness analyses (CEAs) rely on randomized trial data, such analyses lack generalizability to real-world practice. We evaluated the real-world cost effectiveness (CE) of adding androgen receptor pathway inhibitors (ARPIs) to androgen deprivation therapy (ADT) for first-line (1L) mHSPC using the IRONMAN registry (NCT03151629). **Methods:** We conducted a US public payer perspective CEA using individual patient-level IRONMAN data. Eligible patients (pts) received 1L ADT alone, ADT + enzalutamide (ENZ), or ADT + apalutamide (APA) with ≥1 follow-up visit. A 3-state Markov model with 1-month cycles and a 10-year horizon was used. Progression-free survival (PFS) was proxied by time-to-next-treatment (TTNT); overall survival (OS) was time from 1L initiation to death or last follow-up. Costs and outcomes were discounted at 3% per year. Outcomes were measured in life-years gained (LYG) and incremental cost-effectiveness ratios (ICER) were reported. Uncertainty was assessed via one-way sensitivity analysis and probabilistic sensitivity analysis. A scenario analysis evaluated hypothetical ENZ price reductions aligned with planned Inflation Reduction Act negotiations. **Results:** 1187 pts with mHSPC met inclusion (ADT: n=405, ENZ: n=412, APA: n=370; Table 1). In the base case, both ARPI strategies improved OS versus ADT alone, though only APA provided a statistically significant reduction in risk (ENZ: HR 0.78, 95% CI 0.58-1.03, p=0.08; APA: HR 0.50, 95% CI 0.36-0.70, p<0.001). Using TTNT as a proxy for PFS, ADT alone had a reduced risk compared to either ARPI (ENZ: HR 1.97, 95% CI 1.39-2.77, p<0.001; APA: HR 1.51, 95% CI 1.05-2.18, p=0.028); underreporting of subsequent therapies in the ADT alone group may have contributed to this finding. Median follow-up was 26.7 months; median TTNT and OS were not reached. Neither ARPI strategy was CE at conventional US thresholds (ENZ: ICER = $444,947/LYG; APA: ICER = $669,530/LYG), and ENZ would require a 79% price discount to meet CE thresholds. Sensitivity analyses supported the base case results. **Conclusions:** Adding ENZ or APA to ADT for 1L mHSPC improved OS but was not found to be to be cost-effective at current US prices over a 10-year horizon. Substantial ENZ price reductions would be required to reach commonly used CE thresholds. Research Sponsor: Movember Foundation; Amgen; Astellas; AstraZeneca; Bayer; Johnson & Johnson Innovative Medicine; Merck; Novartis; Sanofi.

Baseline characteristics.

	ADT (N = 405)	ENZ (N = 412)	APA (N = 370)
Median age at study entry (IQR)	71 (64, 78)	71 (65, 76)	71 (65, 76)
PSA at study entry (ng/mL)			
Median (IQR)	9 (1, 53)	4 (1, 21)	3 (0, 13)
Range	0, 5430	0, 3560	0, 5530
Missing (%)	137 (34)	62 (15)	56 (15)
Duration of follow-up (months)			
Median (IQR)	24 (10, 41)	28 (17, 41)	28 (17, 40)
Range	3, 80	3, 67	2, 64

11165 **Poster Session**

Neurological immune-related adverse events and overall survival in patients with advanced solid tumors treated with immune checkpoint inhibitors in a global real-world analysis. First Author: Ahmed Abbasi, Berkshire Medical Center, Pittsfield, MA

Background: Immune checkpoint inhibitors (ICIs) have transformed the treatment of advanced malignancies, and many immune-related adverse events have been associated with improved treatment outcomes. Neurological immune-related adverse events, however, are uncommon, often severe, and poorly characterized in large real-world populations. Whether the development of neurological toxicity during ICI therapy is associated with long-term survival remains unclear. We examined the relationship between neurological immune-related adverse events and overall survival in a large real-world cohort of patients treated with ICIs. **Methods:** We performed a retrospective cohort study using data from the TriNetX Global Collaborative Network. Adult patients with advanced solid tumors treated with immune checkpoint inhibitors, including pembrolizumab, nivolumab, ipilimumab, atezolizumab, or durvalumab, were identified. Patients who developed neurological immune-related adverse events (such as encephalitis, meningitis, Guillain–Barré syndrome, myasthenia gravis, or immune-mediated polyneuropathy) within six months of treatment initiation were compared with patients who did not experience neurological toxicity. One-to-one propensity score matching was used to balance age, sex, race, ethnicity, and major medical comorbidities. Overall survival was assessed in the matched cohorts. **Results:** After matching, 9,744 patients were included (4,872 per cohort) with well-balanced baseline characteristics. Patients who developed neurological immune-related adverse events experienced significantly worse overall survival compared with matched controls. Median overall survival was 473 days in the neurological toxicity cohort versus 1,083 days among patients without neurological events ($p < 0.001$). Development of neurological immune-related adverse events was associated with a 57% higher risk of death (hazard ratio 1.57; 95% CI, 1.48–1.67). At five years, survival probability was 30.9% in the neurological toxicity group compared with 41.7% in the control group. **Conclusions:** In this large real-world analysis, neurological immune-related adverse events were associated with substantially worse overall survival in patients treated with immune checkpoint inhibitors. In contrast to other immune-related toxicities that may reflect effective immune activation, neurological complications appear to confer significant morbidity and mortality that outweigh potential treatment benefit. These findings highlight the need for early recognition, multidisciplinary management, and careful risk–benefit assessment when neurological toxicity develops during immunotherapy. Research Sponsor: None.

11166 **Poster Session**

Pulmonary immune-related adverse events post-immune checkpoint inhibitors (ICI): Real-world experience. First Author: Maëlys Yepes, Cleveland Clinic Foundation, Cleveland, OH

Background: Immunotherapy (IT) has transformed cancer treatment and is often better tolerated than chemotherapy; however, immune-related pulmonary adverse events (Pulm-AE) have emerged as clinically significant and potentially treatment-limiting toxicities that may impact morbidity, treatment continuity, and survival. Real-world *comparative data* on Pulm-AE risk remain limited. We evaluated the incidence, cumulative risk, severity, and clinical outcomes of Pulm-AEs in patients receiving IT versus non-IT systemic therapies. **Methods:** We conducted a retrospective cohort study of 5,556 adult cancer patients treated at the Cleveland Clinic between 2010–2022. Included cancers were bladder (stage II–IIIA n = 476; IV n = 158), endometrial IV (n = 157), esophageal/gastric (II–III n = 797; IV n = 590), head & neck IV (n = 36), renal (III n = 88; IV n = 223), metastatic melanoma (n = 45), and lung cancers: non-squamous NSCLC (IIIB n = 206; IV n = 1,609), squamous NSCLC (IIIB n = 182; IV n = 366), and SCLC IIIB–IV (n = 623). Patients receiving IT (± chemotherapy or radiation) were compared with non-IT regimens and followed from treatment initiation to Pulm-AE, death, or last encounter. Pulm-AEs included pneumonitis, pleural effusion ± pleuritis, and interstitial lung disease. Data were collected on demographics, CTCAE grade, timing, management, and outcomes. Incidence rates per 100 person-years (py) were estimated using Poisson regression, cumulative incidence (CIR) using Kaplan–Meier methods, and adjusted hazard ratios (HRs) using time-dependent Cox models. **Results:** Of 5,556 patients, 2,133 (38%) received IT, including 1,291 (60%) as first-line therapy; 99.9% of IT exposure was ICI. The cohort was 38% female, 87% White, with a median age of 66 years. Over a median follow up of 14 months (CI: 6-35), 127 Pulm-AEs occurred, including 51 among first-line IT recipients. Pulm-AE incidence was higher with IT than non-IT (0.2 vs 0.06 per 100 py; $P < 0.05$), driven primarily by pneumonitis (0.16 vs 0.04 per 100 py; $P < 0.05$). At 24 months, CIR for Pulm-AEs was 5.5% with first-line IT versus 2.0% without (HR 3.50, $P < 0.001$); pneumonitis CIR was 4.3% versus 1.3% (HR 5.21, $P < 0.001$). Among pneumonitis cases, 86% were CTCAE grade 2–4, 81% required steroid therapy, and 28% resulted in permanent IT discontinuation, frequently necessitating long-term immunosuppression. Other Pulm-AEs in the IT & non-IT groups were pleural effusion (n = 10, 24), pleuritis without effusion (n = 0, 2), and interstitial lung disease (n = 0, 2). **Conclusions:** Receipt of IT was associated with a significantly increased risk of Pulm-AEs, primarily clinically significant pneumonitis. These toxicities were common (~7% by 24 months), frequently severe, and often led to irreversible damage and treatment cessation, underscoring the need for vigilant monitoring, early recognition, multidisciplinary management, and prompt intervention to minimize morbidity. Research Sponsor: None.

11167 **Poster Session**

Comparative real-world survival outcomes of ribociclib and abemaciclib in breast cancer. First Author: Chinenye M. Okafor, Medical University of South Carolina Health, Florence, SC

Background: Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), including ribociclib and abemaciclib, are widely used in hormone receptor–positive, HER2-negative high-risk early-stage breast cancer in combination with endocrine therapy. While randomized trials have demonstrated survival benefits, comparative real-world outcomes between these agents remain limited. This study evaluates all-cause mortality among patients treated with ribociclib versus abemaciclib using a large real-world database. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, a global federated health research network, including adult patients with breast cancer treated with ribociclib (n = 7,697) or abemaciclib (n = 12,626) within the past 20 years. Two cohorts were constructed and balanced using 1:1 propensity score matching (PSM) based on age at diagnosis, sex, and race. The primary outcome was all-cause mortality at 1, 3, and 5 years. Kaplan–Meier survival curves and Cox proportional hazards models were used to estimate survival probabilities and hazard ratios. **Results:** After PSM, a total of 15,374 patients were included (7,687 per cohort). Mean age was 60.2±13.5 years in the ribociclib cohort and 60.2±13.4 years in the abemaciclib cohort. Most patients were female (99%) and White (72%). At 1 year, survival probability for ribociclib was 91.5% compared with 89.0% for abemaciclib (hazard ratio 0.74, 95% CI 0.66–0.84; log-rank $p < 0.001$). There was no significant difference in survival probabilities at 3 years (70.1% vs 72.1%) or 5 years (56.6% vs 55.1%), with hazard ratios not significantly different from 1.0. **Conclusions:** In this real-world analysis, ribociclib use was associated with lower all-cause mortality at 1 year compared with abemaciclib; however, this difference did not persist at longer follow-up. These findings should be interpreted cautiously given potential residual confounding and differences in clinical indications between agents. Further studies accounting for disease stage and treatment context are warranted. Research Sponsor: None.

11168 **Poster Session**

When autoimmunity meets immunotherapy: Immune checkpoint inhibitors in cancer patients with rheumatoid arthritis. First Author: Rafi Aibani, Charleston Area Medical Center, Charleston, WV

Background: Immune checkpoint inhibitors (ICIs) improve outcomes across multiple malignancies but are associated with immune-related adverse events (irAEs). Patients with rheumatoid arthritis (RA) have been largely excluded from clinical trials, and disease-specific real-world data remain limited. We evaluated irAEs and survival outcomes in cancer patients with and without preexisting RA treated with ICIs. **Methods:** We conducted a retrospective cohort study using the TriNetX Research Network. Patients with RA diagnosed prior to ICI initiation were compared with patients without RA. Propensity score matching (1:1) was performed on age, sex, race, ethnicity, cancer type, ICI type, comorbidities, metastatic disease, other autoimmune conditions, and preexisting irAE codes. Outcomes were measured beginning 1 day after ICI initiation. Overall survival (OS) and organ-specific irAEs were assessed. Sensitivity analyses were conducted excluding patients with baseline glucocorticoid or disease-modifying antirheumatic drug (DMARD) exposure to account for differences in preexisting autoimmune treatment. **Results:** Before matching, 3,172 patients with RA and 156,543 without RA were identified. After matching, 3,162 patients were included in each cohort with balanced baseline characteristics and laboratory values. OS was numerically lower in the RA cohort but not statistically significant (29% vs 30%; median 21.9 vs 23.7 months; p = 0.1861). Early survival differed within 6 months (76% vs 78%; p = 0.0415) but not at 1 year. RA patients experienced higher rates of gastrointestinal (8.4% vs 6.9%; p = 0.0234) and pulmonary irAEs (5.4% vs 4.0%; p = 0.0106), with no significant differences in hepatic, dermatologic, or endocrine irAEs. Glucocorticoid and DMARD use were more frequent in RA patients. In sensitivity analyses excluding prior exposure, new DMARD use remained significantly higher in RA patients (4.5% vs 1.0%; $p < 0.0001$), while other differences attenuated. **Conclusions:** Cancer patients with preexisting RA treated with ICIs experience higher rates of select irAEs without a significant long-term OS disadvantage. These findings suggest increased immune toxicity risk with preserved anticancer efficacy, supporting cautious but feasible ICI use in RA patients with appropriate monitoring. Research Sponsor: None.

11169 **Poster Session**

Sex differences in immune-related adverse events requiring hospitalization among patients with checkpoint inhibitor-sensitive malignancies: A national analysis. First Author: Jeril Lasington, The New York Medical College Graduate Medical Education Program at St. Mary's General Hospital and St. Clare's Health, Denville, NJ

Background: Immune checkpoint inhibitors (ICIs) can cause immune-related adverse events (irAEs) with significant morbidity/mortality. Sex influences immunity, yet sex-specific irAE patterns and outcomes in hospitalized patients remain underexplored. We investigated sex differences in irAE hospitalizations and mortality in ICI-sensitive cancers. **Methods:** Retrospective cohort study using the National Inpatient Sample (2019-2022) identified adults with ICI-sensitive malignancies (lung, melanoma, renal cell carcinoma [RCC], bladder, hepatocellular carcinoma [HCC]) and high-specificity irAEs (colitis, pneumonitis, cardiac, hepatic, dermatologic, neurologic) at academic centers. Primary outcome was in-hospital mortality. Secondary outcome was irAE distribution by sex. Multivariable logistic regression adjusted for demographics, cancer type, comorbidities, irAE type, discharge weights for national estimates. **Results:** Among 203,990 weighted hospitalizations (62.8% male; mean age 68), women had lower mortality (13.7% vs 15.0%; aOR 0.91, 95% CI 0.88-0.93, $p<0.0001$), consistent across models. Women had higher odds of neurologic (aOR 1.76, 95% CI 1.68-1.85), dermatologic (1.24, 1.20-1.29), hepatic (1.08, 1.05-1.11), and pneumonitis (1.05, 1.01-1.08) irAEs; men had higher GI colitis (aOR 0.51 for women, 0.48-0.53) and cardiac (0.81, 0.79-0.83) risks. Within irAEs, women had lower mortality for neurologic (6.0% vs 10.0%), pneumonitis (11.5% vs 14.2%), colitis (4.7% vs 6.5%), and dermatologic (4.5% vs 6.2%). Female survival advantage persisted across cancers (e.g., lung aOR 0.91, 0.87-0.94; HCC 0.95, 0.91-1.00) and after excluding autoimmune disease (aOR 0.93, 0.91-0.96). Temporal analysis showed widening sex gap (2019 aOR 0.99 to 2022 0.86; year × sex interaction p=0.0002). **Conclusions:** Women experience distinct irAE patterns (more neurologic/dermatologic) but lower overall and subtype-specific mortality versus men, with differences amplifying over time. Sex-stratified irAE surveillance and personalized ICI strategies can be implemented to optimize outcomes. Research Sponsor: None.

In-hospital mortality by sex in irAE hospitalizations.

Characteristic / Subgroup	N (weighted)	Male In-Hospital Mortality (%)	Female In-Hospital Mortality (%)	Adjusted OR (Female vs Male)	95% CI	p-value
Overall (Fully adjusted model[1])	203990	15	13.6	0.93	0.91-0.96	<0.0001
Overall (Fully adjusted + irAE type[2])	203990	15	13.6	0.91	0.88-0.93	<0.0001
Lung Cancer	93135	16.2	14.2	0.91	0.87-0.94	<0.0001
Melanoma	6725	11.2	9.6	0.72	0.60-0.87	0.0006
Bladder Cancer	16795	10.3	8.4	0.74	0.64-0.85	<0.0001
GI Colitis irAE	17610	6.5	4.7	0.65	0.56-0.74	<0.0001
Pneumonitis irAE	21075	14.2	11.5	0.76	0.70-0.83	<0.0001
Dermatologic irAE	15215	6.2	4.5	0.62	0.54-0.73	<0.0001
Neurologic irAE	8695	10	6	0.66	0.55-0.79	<0.0001

11170 **Poster Session**

Prevalence and fracture burden of osteoporosis among patients with colorectal cancer: A real-world analysis. First Author: Anushree Venkatesh Murthy, Rochester Regional Health, Unity Hospital, Rochester, NY

Background: Osteoporosis is a common age-related skeletal disorder that may be underrecognized among patients with colorectal cancer (CRC), despite shared risk factors including advanced age, systemic inflammation, nutritional deficiencies, and cancer-related treatments. Population-level data describing the prevalence, demographic distribution, and fracture burden of osteoporosis in CRC remain limited, particularly in real-world clinical settings. **Methods:** We conducted a retrospective, cross-sectional cohort study using the TriNetX Global Collaborative Network comprising over 180 million patients across 165 healthcare organizations using R. Adult patients aged 18–85 years with colorectal cancer were identified using ICD-10-CM codes C18–C20. Two cohorts were constructed: CRC patients with osteoporosis (defined by ICD-10-CM codes M80–M81) and CRC patients without osteoporosis. Osteoporosis subtypes were further categorized into osteoporosis with current pathological fracture (M80) and osteoporosis without current pathological fracture (M81). Cohorts were compared using aggregate-level demographic data, including age, sex, race, ethnicity, and fracture status. **Results:** Among 696,434 patients with colorectal cancer, 40,051 (5.7%) had a documented diagnosis of osteoporosis. CRC patients with osteoporosis were significantly older than those without osteoporosis (mean age 74 vs 68 years) and were predominantly female (79.2% vs 43.9%). Racial distribution among CRC patients with osteoporosis included White (56.7%), Black or African American (6.0%), Asian (6.8%), and other or unknown race (30.5%). Age-stratified analyses demonstrated a marked increase in osteoporosis prevalence with advancing age, particularly among patients aged ≥75 years. Among the CRC with osteoporosis cohort, 13% had documented osteoporosis with current pathological fracture (M80), while 87% had osteoporosis without fracture (M81), indicating a substantial fracture burden in this population. Age-related osteoporosis accounted for the majority of cases, with multiple fracture-related subcodes reflecting clinically significant skeletal fragility. Patient arrival rate analyses demonstrated sustained real-world healthcare utilization across participating institutions. **Conclusions:** In this large real-world cohort, osteoporosis was prevalent among patients with colorectal cancer and was strongly associated with advanced age and female sex. A clinically meaningful proportion of CRC patients with osteoporosis had documented pathological fractures, highlighting an underappreciated source of morbidity. These findings underscore the importance of routine bone health assessment and fracture risk evaluation in colorectal cancer care, particularly among older adults. Research Sponsor: None.

11171 **Poster Session**

Body mass index (BMI) and overall survival (OS) among Hispanic patients treated with immune checkpoint inhibitors (ICIs). First Author: Matthew Barke, Dell Medical School, The University of Texas at Austin, Austin, TX

Background: Prior studies have suggested improved OS among cancer patients receiving ICIs with higher BMI, despite obesity being a known cancer risk factor; however, these findings are largely derived from predominantly non-Hispanic cohorts. In Austin, Texas, Hispanic individuals comprise approximately 30% of the population, limiting the external validity of prior studies. We evaluated whether the previously described association between BMI and OS extends to Hispanic patients treated with ICIs. **Methods:** We retrospectively identified Hispanic patients with solid tumors treated with ICIs at Ascension/UT Health Austin between November 2013 and December 2025 using Research Electronic Data Capture (REDCap) data. BMI at ICI initiation was categorized as normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥30 kg/m²); underweight patients were excluded. Overall survival (OS) was defined as time from ICI initiation to death, with censoring at last follow-up or 5 years. Missing 5-year survival status was addressed using single stochastic regression imputation. Stabilized inverse probability of treatment weighting from a multinomial propensity score model was used to adjust for baseline differences, including age, sex, ECOG status, cancer type and stage, ICI agent, steroid exposure, and antibiotic exposure. Weighted Cox proportional hazards models estimated associations between BMI and OS, with prespecified subgroup analyses by sex and stage. **Results:** Among 177 Hispanic patients included, average age was 54 years and 53% were male; 32% had normal BMI, 31% were overweight, and 37% were obese. Median overall survival (OS) was 497 days. After inverse probability weighting, BMI was not associated with OS (p = 0.90). Compared with normal BMI, overweight patients had a hazard ratio (HR) of 0.94 (95% CI 0.49–1.80) and obese patients an HR of 1.09 (95% CI 0.60–2.00). No significant differences were observed between obese and overweight patients (HR 1.16; 95% CI 0.64–2.09). Subgroup analyses by sex and cancer stage showed no survival advantage associated with higher BMI. Among women, obese patients had an HR of 1.58 (95% CI 0.49–5.13), while among men the HR was 1.30 (95% CI 0.66–2.58). When stratified by stage, obese patients had an HR of 1.68 (95% CI 0.44–6.40) in stages I–III and 1.13 (95% CI 0.53–2.40) in stage IV. **Conclusions:** In this cohort of Hispanic patients with solid tumors treated with immune checkpoint inhibitors, we did not find a survival advantage for those with higher BMI. These findings raise the possibility that BMI associated survival advantages reported in predominantly non-Hispanic cohorts may not extend to the Hispanic population. Larger studies are needed to determine whether these findings represent true population-specific differences. Research Sponsor: None.

11172 **Poster Session**

Insurance and racial disparities in CAR T-cell therapy outcomes: A National Inpatient analysis. First Author: Jeril Lasington, The New York Medical College Graduate Medical Education Program at St. Mary's General Hospital and St. Clare's Health, Denville, NJ

Background: To understand equity gaps for Chimeric antigen receptor T-cell (CAR-T) therapy, we conducted an analysis examining insurance-based and racial disparities in CAR-T cell therapy. **Methods:** Using the National Inpatient Sample (2020-2022), we identified CAR-T recipients via ICD-10-PCS procedure codes (XW0 series) with FDA-approved indications including diffuse large B-cell lymphoma (DLBCL), B-cell acute lymphoblastic leukemia (B-ALL), multiple myeloma, follicular lymphoma, and mantle cell lymphoma. The primary outcome was in-hospital mortality. Secondary outcomes included cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and ICU utilization. Multivariable logistic regression estimated adjusted odds ratios (aOR) controlling for age, sex, race, insurance status, and disease indication. Access disparities were assessed by comparing racial composition of CAR-T recipients to US Census population estimates. **Results:** Among 10,610 weighted CAR-T hospitalizations (mean age 59.4 years; 62.1% male; 97% at academic centers), the most common indications were DLBCL (46.9%), multiple myeloma (25.0%), and B-ALL (12.7%). Overall in-hospital mortality was 8.6%, CRS occurred in 42.3%, and ICANS in 19.7%. Compared to privately insured patients (mortality 5.5%), both Medicare (11.5%; aOR 1.59, 95% CI 1.32-1.92, $p < 0.0001$) and Medicaid patients (10.7%; aOR 1.89, 95% CI 1.45-2.47, $p < 0.0001$) experienced significantly higher mortality after adjustment for demographics, comorbidities, and indication. This disparity persisted across the study period, with the Medicare-to-Private mortality ratio increasing from 1.9x (2020) to 2.2x (2022). Black (9.1% of CAR-T recipients vs 13.6% US population) and Hispanic patients (13.7% vs 18.9%) were significantly underrepresented, receiving CAR-T at only 67% and 72% of expected rates based on population demographics, respectively. Black patients demonstrated significantly higher ICANS risk (aOR 1.38, 95% CI 1.16-1.64, p = 0.0003) but lower CRS risk (aOR 0.79, 95% CI 0.68-0.91, p = 0.001) compared to White patients. Black patients also experienced higher rates of ICU-level care (23.8% vs 16.6%) and mechanical ventilation (12.4% vs 8.1%). No significant sex-based disparities were observed in mortality (aOR 0.90, 95% CI 0.78-1.04, p = 0.17). **Conclusions:** We identified insurance-based mortality gaps with 60-90% higher adjusted mortality compared to privately insured patients. Concurrent access disparities result in Black and Hispanic patients being underrepresented by approximately one-third. Black patients who do receive CAR-T demonstrate distinct toxicity phenotypes with higher neurotoxicity and ICU utilization. These findings support the need to address barriers to CAR-T access and optimize outcomes across all patient populations. Research Sponsor: None.

11173 **Poster Session**

Mental health and malignancy: Real-world associations between early-onset hormone-related cancers and mental illness. First Author: Danielle Claire Thor, Jefferson Health New Jersey, Stratford, NJ

Background: Although progress has been made in reducing overall cancer incidence, early-onset cancers have continued their troublesome rise. Similarly, the incidence and/or prevalence of psychiatric disorders has increased, particularly among young adults. Mental illness may influence cancer development, however, real-world evidence linking mental illness to early-onset hormone-related cancers is limited. **Methods:** We conducted a real-world, retrospective cohort study using the TriNetX United States Research Database, a federated network of de-identified electronic health records from over 70 healthcare organizations, to examine this association. Adults aged 18–50 years with at least one of five pre-determined core mental illnesses, including generalized anxiety disorder (GAD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), bipolar disorder, and schizophrenia, were compared with same-aged individuals without any of the core mental illnesses. A five-year lookback period was used from January 25th, 2021 to January 25th 2026 and propensity score matching was used to adjust for confounders. Incidence of early-onset cancers diagnosed were then assessed during five-year follow-up. Sensitivity analyses required a $\geq$ 1-year lag between mental illness diagnosis and cancer onset. **Results:** 2,911,432 patients were identified as having a core mental illness, whereas 21,439,614 patients were identified as not having any core mental illness. All-cause mental illness was associated with an increased risk of developing early-onset breast cancer (RR 2.253, CI 2.149-2.362, $p < 0.0001$), uterine cancer (RR 1.711, CI 1.515-1.934, $p < 0.0001$), and ovarian cancer (RR 1.984, CI 1.790-2.198, $p < 0.0001$). Associations with early-onset prostate cancer and testicular cancer did not meet thresholds for statistical significance. Within the subgroup analysis, GAD was associated with an increased risk of developing early-onset breast cancer (RR 2.565, CI 2.398-2.742, $p < 0.0001$), uterine cancer (RR 1.534, CI 1.278-1.841, $p < 0.0001$) and ovarian cancer (RR 1.736, CI 1.492-2.019, $p < 0.0001$). MDD was associated with early-onset breast cancer (RR 2.380, CI 2.161-2.622, $p < 0.0001$), uterine cancer (RR 2.089, CI 1.625-2.685, $p < 0.0001$), and ovarian cancer (RR 1.983, CI 1.591-2.472, $p < 0.0001$). Bipolar disorder was associated only with early-onset breast cancer (RR 1.415, CI 1.244-1.610, $p < 0.0001$). OCD and schizophrenia had no statistically significant associations. **Conclusions:** In this large, real-world cohort study, all-cause mental illness, GAD, and MDD were associated with an increased risk of early-onset hormonal cancers more commonly affecting female patients. These findings suggest that mental health represents a potential modifiable risk factor in early-onset, hormone-related cancers and warrants further investigation. Research Sponsor: None.

11174 **Poster Session**

Mental health and malignancy: Real-world associations between early-onset gastrointestinal cancers and mental illness. First Author: Danielle Claire Thor, Jefferson Health New Jersey, Stratford, NJ

Background: Although progress has been made in reducing overall cancer incidence, early-onset cancers have continued their troublesome rise. Similarly, the incidence and/or prevalence of psychiatric disorders has increased, particularly among young adults. Mental illness may influence cancer development, however, real-world evidence linking mental illness to early-onset gastrointestinal cancers is limited. **Methods:** We sought to conduct a real-world, retrospective cohort study using the TriNetX United States Research Database, a federated network of de-identified electronic health records from over 70 healthcare organizations, to examine this association. Adults aged 18–50 years with at least one of five pre-determined core mental illnesses, including generalized anxiety disorder (GAD), major depressive disorder (MDD), obsessive-compulsive disorder (OCD), bipolar disorder, and/or schizophrenia, were compared with same-aged individuals without any of the core mental illnesses. A five-year lookback period was used from January 25th, 2021 to January 25th 2026. Propensity score matching adjusted for demographic and clinical confounders. Incidence of early-onset cancers diagnosed were then assessed during five-year follow-up. Sensitivity analyses required a $\geq$ 1-year lag between mental illness diagnosis and cancer onset. **Results:** 2,911,432 patients ages 18-50 were identified as having a core mental illness, whereas 21,439,614 patients ages 18-50 were identified as not having any core mental illness. All-cause mental illness was associated with an increased risk of developing early-onset gastric cancer (RR 1.451, CI 1.189-1.771, $p < 0001$), pancreatic cancer (RR 1.566, CI 1.328-1.822, $p < 0.0001$) and colorectal cancer (RR 1.407, CI 1.313-1.506, $p < 0.0001$). Associations with early-onset esophageal cancer, biliary tract cancer, and small intestine cancer did not meet thresholds for statistical significance. In addition, subgroup analysis was completed for each core mental illness. GAD was associated with an increased risk of developing early-onset pancreatic cancer (RR 1.627, CI 1.220-2.169, $p < 0.0001$), small intestine cancer (RR 2.435, CI 1.498-3.956, $p < 0.0001$), and colorectal cancer (RR 1.625, CI 1.441-1.833, $p < 0.0001$). MDD was only associated with an increased risk of developing early-onset colorectal cancer (RR 1.425, CI 1.213-1.674, $p < 0.0001$). OCD, bipolar disorder, and schizophrenia had no statistically significant association with the development of the early-onset cancers noted above. **Conclusions:** In this large, real-world cohort study, all-cause mental illness, GAD, and MDD were associated with an increased risk of several early-onset gastrointestinal cancers. These findings suggest that one's mental health represents a potentially modifiable risk factor in early-onset gastrointestinal cancers and warrants further investigation. Research Sponsor: None.

11175 **Poster Session**

Patterns and determinants of radiotherapy treatment default in a rural cancer centre: A retrospective observational study. First Author: Darshana Kawale, Indrayani Hospital and Cancer Institute, Pune, maharashtra, India

Background: Radiotherapy requires uninterrupted daily treatment over several weeks, making treatment adherence challenging, particularly in rural and resource-limited settings. Treatment default adversely affects outcomes and reflects underlying socioeconomic, access-related and clinical barriers. There is limited real-world data from rural India evaluating the magnitude and determinants of treatment default. This study aimed to determine the radiotherapy default rate and identify the associated factors. **Methods:** This retrospective observational study included patients enrolled for definitive, adjuvant, and palliative radiotherapy over a 2 year period at a rural tertiary cancer centre. Radiotherapy default was defined as missing 3 or more consecutive fractions after initiation of treatment or failure to complete the planned prescribed dose. Descriptive statistics were used to summarise patient demographics, socioeconomic characteristics and clinical variables. The radiotherapy default rate was expressed as a percentage. Associations between radiotherapy default and categorical variables were analysed using Chi-square or Fisher's exact test, as appropriate. Variables significant on univariate analysis were included in a multivariate logistic regression model to identify independent predictors of radiotherapy default. A p-value < 0.05 was considered statistically significant. **Results:** Among 2755 patients enrolled for radiotherapy during the study period, 363 patients defaulted, resulting in an overall default rate of ~13.2%. Higher default rates were significantly associated with longer daily travel distance, financial constraints, lower educational status, inadequate family support, poor baseline general condition, treatment related toxicities, diet-related difficulties- particularly among head and neck cancer patients ($p < 0.05$). On multivariate logistic regression analysis, long travel distance, financial constraints, poor general condition, inadequate family support and diet-related difficulties remained independent predictors of radiotherapy default. **Conclusions:** Radiotherapy default remains a clinically significant challenge in rural practice and is driven by a combination of socioeconomic, access-related and clinical factors. Long travel distance, financial constraints, inadequate family support, poor general condition and diet-related difficulties independently contribute to treatment default. Early identification of high-risk patients and targeted interventions—including patient and caregiver counselling, nutritional optimisation, financial and travel assistance, symptom control, and multidisciplinary supportive care—have the potential to reduce radiotherapy default rates and improve treatment completion in resource-limited settings. Research Sponsor: None.

11176 **Poster Session**

Assessing burden and outcomes: Colon cancer survival across the U.S. safety-net spectrum. First Author: David Otohinoyi, Louisiana State University Health Sciences Center at Ochsner University Hospital & Clinics, Department of Internal Medicine, Lafayette, LA

Background: Safety-net hospitals (SNHs) provide essential care for uninsured and underinsured patients but often face systemic constraints that may affect cancer outcomes. Colon cancer, a leading cause of cancer-related death in the United States, requires complex multidisciplinary management. This study assessed the association between hospital safety-net burden and clinical outcomes in colon cancer across a national dataset. We also identified patient-level factors contributing to disparities in care delivery. **Methods:** Using the National Cancer Database (NCDB), we identified approximately 1.2 million adult patients diagnosed with colon cancer in the United States between 2004 and 2020. Facilities were stratified by safety-net burden into Non–Safety-Net Hospitals (NSNH; $<$ 25% Medicaid/uninsured cases), Safety-Net Hospitals (SNH; 25–75%), and Extreme Safety-Net Hospitals (Extreme-SNH; $>$ 75%). This safety-net spectrum provided a novel framework for capturing both facility- and patient-level disparities that influence colon cancer care and outcomes. Multivariable logistic and Cox regression models were used to evaluate differences in disease stage, treatment timelines, and survival, adjusting for age, comorbidity, and AJCC stage. Kruskal–Wallis and chi-square tests were used for descriptive analyses. **Results:** SNHs and Extreme-SNHs cared for a greater proportion of patients with advanced-stage disease, lower rates of chemotherapy, immunotherapy, and palliative care utilization, and higher short-term mortality when compared with NSNH. Thirty-day readmission rates after surgery were similar across groups. Survival analyses demonstrated a graded decline in outcomes with increasing safety-net burden: median overall survival was 91.2 months in NSNH, 83.6 months in SNH, and 70.9 months in Extreme-SNH ($p <$ 0.001). One-year survival exceeded 95% across all facilities, but five-year survival declined to 68.9% for NSNH vs 59.4% for Extreme-SNH. Additional disparities in colon cancer outcomes were observed by health literacy level, residential setting (urban, metropolitan, rural), race, age, and sex. **Conclusions:** Colon cancer patients treated at hospitals with higher safety-net burden experience substantially poorer long-term survival despite comparable short-term outcomes. These findings highlight the need for targeted policy, resource allocation, and quality-improvement efforts to reduce disparities and strengthen oncology care delivery in high-burden safety-net systems. A Plan–Do–Check–Act (PDCA) approach tailored to individual hospital settings and regional contexts may help identify gaps in colon cancer care and guide targeted interventions to improve patient outcomes. Research Sponsor: None.

11177 **Poster Session**

Prognostic value of circulating tumor DNA (ctDNA) for recurrence detection across solid tumors: A real-world meta-analysis. First Author: Scott Kopetz, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Early detection of recurrence after curative-intent treatment is a critical priority, traditional imaging often detects relapse when disease burden is high, potentially limiting treatment efficacy. ctDNA has emerged as an established prognostic biomarker for molecular residual disease (MRD) detection and early relapse. We performed a real-world meta-analysis on published datasets that utilized personalized, tumor-informed ctDNA testing to assess its performance across tumor types and clinical management approaches. **Methods:** Real-world studies published from December 2022 to December 2025 using the personalized, tumor-informed Signatera ctDNA assay (Natera, Inc.) were included. Eligibility required ctDNA assessment in the MRD (2–16 weeks post-surgery (histology dependent)/pre adjuvant therapy (ACT)) and/or surveillance (post-ACT/end of the MRD window if no ACT was given) settings, with outcomes stratified by ctDNA status and hazard ratios (HR) reported from univariable or time-dependent Cox regression analysis. Exclusions included: clinical trials, biobanks, metastatic disease treated with palliative intent, case reports, reviews, editorials, or commentaries. Clinical outcomes were harmonized into a composite event-free survival (EFS) endpoint (time to recurrence, progression, or death). Pooled HRs and 95% CIs were estimated using random and fixed effects models and heterogeneity between studies was assessed using the I^2 and Cochran's Q test. Median lead time from ctDNA-positivity to radiographic or clinical recurrence was summarized when available. **Results:** We identified 18 eligible publications comprising 3,004 unique patients across 15 solid tumor types. During the MRD window, ctDNA positivity was associated with a significantly increased risk of an EFS event compared with ctDNA negativity (pooled HR: 8.15; 95% CI: 6.12–10.85, I^2 = 0.00%, P = 0.844, n = 13). During the surveillance window, inclusive of post-definitive treatment, ctDNA positivity conferred an even greater EFS risk (pooled HR: 18.30; 95% CI: 14.17–23.65, I^2 = 0%, P = 0.911 for heterogeneity, n = 16). Across studies, ctDNA detection during surveillance preceded radiographic or clinical recurrence by a median of 3.20 months (95% CI: 2.50-4.10, $P < 0.0001$, n = 10), although this varied substantially by study/tumor type (I^2 = 80.9%). **Conclusions:** In this pan-cancer real-world meta-analysis, ctDNA positivity assessed using a tumor-informed assay was highly prognostic following curative-intent therapy at all timepoints evaluated with low heterogeneity between studies. These findings support the broad clinical utility of tumor-informed ctDNA testing for post-treatment risk stratification and longitudinal disease monitoring across solid tumors. Research Sponsor: None.

11178 **Poster Session**

Predictors of tumor lysis syndrome in non-Hodgkin lymphoma hospitalizations. First Author: Srijani Thannir, The Brooklyn Hospital Center, Brooklyn, NY

Background: Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency in non-Hodgkin lymphoma (NHL) caused by rapid tumor cell breakdown and severe metabolic derangements. Although TLS is well recognized, most risk data derive from small cohorts or trials, limiting generalizability. We used a nationally representative inpatient dataset to identify predictors of TLS in hospitalized NHL patients. **Methods:** We performed a cross-sectional analysis of the National Inpatient Sample (2016–2020). Adult NHL hospitalizations were identified using ICD-10 codes. Survey-weighted chi-square tests and multivariable logistic regression evaluated demographic, clinical, and treatment predictors. Analyses accounted for the complex survey design. Statistical significance was defined as $p<0.05$. **Results:** An estimated 350,400 NHL hospitalizations were identified, of which 0.79% had TLS. TLS patients were younger (65.7 vs 69.5 years, $p <$ 0.001) and demonstrated different racial distributions, with lower proportions of White patients (67.8% vs 76.9%) and higher proportions of Black (12.7% vs 9.2%) and Hispanic patients (11.6% vs 8.6%) ($p <$ 0.001). TLS occurred more frequently in hospitals in the West and Northeast (p = 0.036). TLS admissions had significantly longer stays (10.48 vs 5.91 days) and higher charges ($174,972 vs $76,884; $p <$ 0.001). Survey-weighted regression identified several strong predictors of TLS. Bone marrow involvement was one of the strongest independent predictors (OR 13.78 [95% CI 5.45–34.84]). Electrolyte derangements were also powerful predictors: hyperkalemia (OR 8.20 [95% CI 6.82–9.86]), hyperphosphatemia (OR 8.28 [95% CI 6.62–10.36]), and hypocalcemia (OR 7.02 [95% CI 5.67–8.69]). Additional predictors included sepsis (OR 2.29 [95% CI 1.89–2.77]), neutropenia (OR 1.71 [95% CI 1.27–2.31]), HIV infection (OR 1.73 [95% CI 1.05–2.84]), and receipt of inpatient chemotherapy (OR 1.38 [95% CI 1.01–1.87]). Prior chemotherapy (OR 0.44 [95% CI 0.30–0.63]) and radiation therapy (OR 0.61 [95% CI 0.38–0.99]) were protective, suggesting TLS risk is greatest in chemo-naïve or high–tumor burden presentations. **Conclusions:** TLS in hospitalized NHL patients is associated with distinct demographic patterns and substantial increases in healthcare utilization. Early risk stratification incorporating clinical, laboratory, and treatment factors may improve prevention strategies and outcomes. Research Sponsor: None.

Predictors of TLS among hospitalized patients with NHL.

Predictor	Adjusted OR	95% CI	p-value
Bone marrow involvement	13.78	5.45–34.84	<0.001
Hyperkalemia	8.20	6.82–9.86	<0.001
Hyperphosphatemia	8.28	6.62–10.36	<0.001
Hypocalcemia	7.02	5.67–8.69	<0.001
Sepsis	2.29	1.89–2.77	<0.001
Neutropenia	1.71	1.27–2.31	<0.001
HIV infection	1.73	1.05–2.84	0.031
Inpatient chemotherapy	1.38	1.01–1.87	0.041
Prior chemotherapy	0.44	0.30–0.63	<0.001
Radiation therapy	0.61	0.38–0.99	0.046

11179 **Poster Session**

Direct oral anticoagulants versus low-molecular-weight heparin in patients with liver metastases and cancer-associated thrombosis: A multi-center real-world analysis. First Author: Jowan Al-Nusair, Joan C. Edwards School of Medicine, Marshall University, Huntington, WV

Background: Patients with liver metastases are at high risk for cancer-associated thrombosis (CAT) and require therapeutic anticoagulation. Although direct oral anticoagulants (DOACs) are increasingly used, their safety relative to low-molecular-weight heparin (LMWH) in this high-risk population, particularly regarding gastrointestinal (GI) bleeding, remains uncertain. **Methods:** We conducted a retrospective, federated cohort study using the TriNetX Global Collaborative Network, including adult patients with liver metastases and CAT who initiated a DOAC or LMWH within 10 days of CAT diagnosis. The index date was defined as the first qualifying anticoagulant exposure. Propensity score matching was performed to balance measured demographics, comorbidities, and concomitant medications, yielding 19,380 patients per cohort. Outcomes were assessed from 1 to 365 days after the index date and included GI bleeding, thrombotic recurrence by DVT/PE or stroke, intensive care unit (ICU) admission, and all-cause mortality. GI bleeding was identified using diagnosis-based coding algorithms, with exclusion of patients who had GI bleeding prior to anticoagulation initiation. Risk estimates were calculated and time-to-event analyses. **Results:** GI bleeding occurred more frequently among patients treated with DOACs compared with LMWH (9.7% vs 8.3%; hazard ratio [HR] 1.11, 95% CI 1.02–1.19). Thrombotic recurrence was common in both groups (61.4% with DOACs vs 60.0% with LMWH); however, time-to-event analysis demonstrated a modestly lower hazard of recurrence among DOAC-treated patients (HR 0.94, 95% CI 0.92-0.97). ICU admission was infrequent but occurred more often in the DOAC cohort (0.6% vs 0.3%; HR 1.80, 95% CI 1.33–2.46). DOAC use was associated with significantly lower all-cause mortality compared with LMWH (50.8% vs 55.7%; HR 0.84, 95% CI 0.82–0.86). **Conclusions:** In patients with liver metastases and CAT, DOAC therapy was associated with a modestly increased risk of GI bleeding but improved overall survival compared with LMWH. Given the small absolute differences in bleeding risk and the potential for residual confounding from unmeasured factors such as cancer burden, performance status, life expectancy, and hospice referral, these findings may support clinical equipoise between anticoagulation strategies. Individualized treatment decisions remain essential in this vulnerable population. Research Sponsor: None.

Clinical outcomes in propensity-score matched patients with liver metastasis and cancer associated thrombosis.

Outcome	DOAC (n=19,380)	LMWH (n=19,380)	HR	CI
GI bleeding	9.7%	8.3%	1.11	1.02-1.19
Thromboembolic recurrence	61.4%	60.0%	0.94	0.92-0.97
ICU admission	0.6%	0.3%	1.80	1.33-2.46
All-cause mortality	50.8%	55.7%	0.84	0.82-0.86

11180 Poster Session

Arrhythmia phenotype and 30-day readmission in selected cancers: Propensity-matched NRD study. First Author: Mariana Marrero Castillo, Louisiana State University, Shreveport, LA

Background: Cardiac arrhythmias are common in oncology and may increase rehospitalization and resource use, but arrhythmia-type and cancer-specific readmission risk is incompletely characterized. **Methods:** Retrospective cohort of adult index hospitalizations for colorectal, breast, lung, prostate, kidney, or melanoma in the HCUP Nationwide Readmissions Database. Arrhythmias coded during the index stay (atrial fibrillation [AF], atrial flutter [AFL], ventricular tachycardia [VT], supraventricular tachycardia [SVT]) were identified using ICD-10-CM codes. Primary outcome was all-cause 30-day readmission. For each phenotype, propensity-score matching (caliper 0.05) created arrhythmia and no-arrhythmia cohorts balanced on demographics, payer, income quartile, and comorbidity. Multilevel logistic regression with hospital clustering estimated adjusted odds ratios (aOR) with 95% CI and tested arrhythmia-by-cancer interactions. Secondary outcomes were index length of stay (LOS) and total charges, analyzed with mixed-effects models; results are reported as adjusted mean differences (days) and incremental charges (USD). Two-sided $p < 0.05$ was significant. **Results:** Among 1,562,919 index hospitalizations, AF was present in 214,475 (13.7%), AFL 27,545 (1.8%), VT 5,184 (0.3%), and SVT 25,714 (1.6%). After matching/adjustment, AFL was associated with higher 30-day readmission (aOR 1.095, 95% CI 1.03-1.17; p = 0.005). AF (aOR 1.001, 0.98-1.03; p = 0.940), VT (aOR 1.128, 0.99-1.29; p = 0.078), and SVT (aOR 1.018, 0.95-1.09; p = 0.598) were not significant overall. AF demonstrated cancer-specific heterogeneity: lung aOR 1.092 (1.043-1.144; $p < 0.001$) and melanoma aOR 1.143 (1.019-1.283; p = 0.023), while breast was not increased (aOR 0.964, 0.908-1.025; p = 0.242). In the AF model, older age was inversely associated with readmission (aOR 0.974 per year, 95% CI 0.972-0.976; $p < 0.001$). In the AF model, highest income quartile was associated with higher readmission (aOR 1.409, 95% CI 1.275-1.557; $p < 0.001$). AF/VT/SVT increased LOS: AF +0.658 days, VT +1.419 days, SVT +1.146 days ($p <= 0.001$); charges increased: AF +$12,399 (95% CI 8,231-16,569), VT +$48,114 (36,846-59,382), SVT +$26,656 (19,822-33,489) (all $p < 0.001$). **Conclusions:** In selected cancers, AFL was independently associated with higher 30-day readmission, while AF readmission risk varied by cancer type. AF/VT/SVT were linked to increased LOS and charges, with the largest resource impact in VT. Prospective studies incorporating cancer stage and therapy exposures should test phenotype-guided cardio-oncology transitional care to reduce readmissions and costs. Limitations include ICD-coded phenotyping, inability to distinguish incident vs prevalent arrhythmias, and unavailable outpatient therapy/anticoagulation; residual confounding is possible. Misclassification may bias estimates toward null, particularly for VT. Research Sponsor: None.

11181 Poster Session

Trends and factors associated with glucagon-like peptide 1 receptor agonists prescription for cancer populations with type 2 diabetes. First Author: Ilana Graetz, Emory University School of Public Health, Atlanta, GA

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly used in cancer survivors with Type 2 Diabetes (T2D) given its efficacy, yet concerns regarding treatment tolerance, weight loss, and limited oncology-specific guidance during active treatment and survivorship may influence prescribing patterns. To date, little evidence exists regarding the trends and factors associated with GLP-1RA use in cancer populations with T2D. **Methods:** We conducted a retrospective cohort study using SEER–Medicare data to identify patients newly diagnosed with seven most common cancers in 2010-2021 with pre-existing T2D. Pre-existing T2D was defined by relevant diagnosis codes within 12 months prior to cancer diagnosis. Patients with continuous Medicare Parts A & B and Part D enrollment were followed annually from diagnosis until death or end of follow-up (12/31/2022) to assess GLP-1RA use. A non-cancer cohort with T2D was identified using a 5% random sample of Medicare beneficiaries without cancer. We calculated annual proportions of beneficiaries with any GLP-1RA use, stratified by Traditional Medicare (TM) and Medicare Advantage (MA, data available in 2016-2021). Multivariable logistic regression models evaluated patient sociodemographic and clinical characteristics associated with GLP-1RA use in 2021. **Results:** We included 482,878 and 542,285 Medicare beneficiaries with T2D in the cancer and non-cancer cohort respectively (1,927,771 and 3,265,774 person-years in 2010-2022). Among TM beneficiaries, GLP-1RA use in the cancer cohort increased from 0.5% to 8.2% in 2010-2022, compared to an increase from 0.4% to 6.4% among non-cancer cohort; similarly higher GLP-1RA use was observed in cancer than non-cancer cohort among MA beneficiaries in 2016-2021 (1.8% to 6.8% vs. 1.3% to 5.7%; unadjusted p-values < 0.001). Rapid uptake was observed for dulaglutide and semaglutide from 2015, while liraglutide use declined modestly after peaking in 2018. In adjusted analyses within the cancer cohort, patients with breast (0.87 percentage points [ppts], $p < 0.001$), female genital (1.08 ppts, $p < 0.001$), and prostate cancers (0.62 ppts, p = 0.001) were more likely to receive GLP-1RAs than those with colorectal cancer. More advanced cancer stage was associated with lower likelihoods of GLP-1RA use; Non-Hispanic White, higher socioeconomic neighborhoods, and dual eligibility were associated with higher likelihoods of GLP-1RAs use. **Conclusions:** GLP-1RA use increased substantially among Medicare beneficiaries with cancer and T2D, and was consistently higher than those without cancer, which may reflect greater clinical engagement and cardiometabolic risk burden following a cancer diagnosis. Variation by cancer site, stage, and socioeconomic factors suggest that both clinical complexity and structural determinants shape GLP-1RA use in cancer survivors. Research Sponsor: National Cancer Institute; 3P30CA138292.

11182 Poster Session

Organ-specific metastatic progression in non-small cell lung cancer treated with pembrolizumab versus atezolizumab: A TrinetX network analysis. First Author: Athar Nawab, WVU Camden Clark Medical Center, Parkersburg, WV

Background: Immune checkpoint inhibitors (ICIs) targeting the PD-1 (Pembrolizumab) and PD-L1 (Atezolizumab) have revolutionized the first-line management of metastatic non-small cell lung cancer (mNSCLC). While these agents are often considered clinically interchangeable, the differences in molecular binding mechanism and tissue-specific penetration may lead to distinct therapeutic patterns. Since the real-world evidence on the propensity for organ-specific metastatic spread remains limited, we aim to compare organ-specific metastatic progression patterns between the two therapies. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX US Collaborative Network. After identifying adults with stage IV mNSCLC on initial Pembrolizumab or Atezolizumab monotherapy, patients with pre-existing metastases at the specific organ site of interest were excluded. Propensity score matching (1:1) was performed to balance cohorts across demographic and clinical variables. Our endpoints were metastases to the CNS, mediastinum, bone, liver, adrenal glands, and skin over 365 days. Hazard ratios (HR) were estimated using Cox proportional hazards models. **Results:** Atezolizumab was associated with a significantly higher risk of CNS metastases compared with Pembrolizumab (1-year incidence: 16.9% vs 6.1%; HR 3.08, 95%CI: 2.73-3.46; $p < 0.001$). A similar pattern was seen in the mediastinum (HR 1.62, 95% CI: 1.32–1.99), bone (HR 1.53, 95% CI: 1.38–1.70), liver (11.5% vs 7.8%; HR 1.55, 95% CI: 1.37–1.75), and adrenal glands (HR 1.43, 95% CI: 1.20–1.75). In contrast, an inverse relationship was observed in the skin where Atezolizumab showed a significantly lower risk of metastases (1.0% vs 1.7%; HR 0.59, 95% CI: 0.44 - 0.79; p = 0.01). **Conclusions:** Markedly distinct patterns of organ-specific metastasis were seen, where Atezolizumab consistently demonstrated an elevated risk of progression in the CNS and visceral organs, whereas Pembrolizumab showed a greater propensity for cutaneous progression. These observations indicate that the selection between PD-1 and PD-L1 inhibition may influence the location of the subsequent site of disease progression. Research Sponsor: None.

Metastatic Site	Atezolizumab Cohort (Events / N)	Pembrolizumab Cohort (Events / N)	Hazard Ratio* (95% CI)	P-Value
CNS	994 / 5,890	376 / 6,138	3.08 (2.73 – 3.46)	<0.001
Mediastinum	228 / 7,043	150 / 7,153	1.62 (1.32 – 1.99)	0.02
Bone	824 / 4,997	624 / 5,374	1.53 (1.38 – 1.70)	0.43
Liver	602 / 5,250	490 / 6,262	1.55 (1.37 – 1.75)	0.35
Adrenal Gland	287 / 6,821	213 / 6,912	1.43 (1.20 – 1.75)	0.068
Skin	71 / 7,306	123 / 7,177	0.59 (0.44 – 0.79)	0.01

Note: N varies by organ site due to the exclusion of patients with pre-existing metastases at that specific site. *Hazard Ratio > 1.0 indicates increased risk with Atezolizumab; HR < 1.0 indicates increased risk with Pembrolizumab.

11183 Poster Session

Frailty among hospitalized patients with pancreatic cancer: A National Inpatient analysis. First Author: Srijani Thannir, The Brooklyn Hospital Center, Brooklyn, NY

Background: Frailty is increasingly recognized as a key determinant of outcomes in older adults with cancer; however, its prevalence and inpatient correlates among hospitalizations for pancreatic cancer remain incompletely characterized. We examined the national inpatient burden of frailty among adults hospitalized with pancreatic cancer and compared demographics, comorbidities, and healthcare utilization between frail and non-frail patients. **Methods:** We analyzed National Inpatient Sample data (2016–2020) to identify adult pancreatic cancer hospitalizations using ICD-10 codes. Frailty was defined by ICD-10 R54. Survey-weighted analyses accounted for complex sampling, with statistical significance set at $p < 0.05$. **Results:** Among an estimated 775,510 weighted adult hospitalizations with pancreatic cancer, frailty was identified in 0.39%. Frail patients were significantly older (74.96 vs 68.32 years, $p < 0.001$) and more often female (56.4% vs 47.7%, $p < 0.001$). Frailty was more prevalent among patients from lower-income neighborhoods and varied by hospital region (both $p < 0.01$). Frail patients experienced longer hospital stays (7.16 vs 6.16 days, $p < 0.001$), with similar total hospitalization charges ($77,978 vs $75,477). Frailty was associated with higher burdens of congestive heart failure (15.9% vs 10.3%) and sepsis (22.8% vs 17.0%) (both $p < 0.001$). Frail patients demonstrated marked nutritional and functional vulnerability, including underweight status (24.6% vs 9.1%), anemia (52.5% vs 44.0%), malnutrition (46.2% vs 28.8%), chronic pain (24.4% vs 19.5%), and falls or mobility impairment (8.5% vs 3.6%) (all $p < 0.01$). In multivariable analysis, advanced age, female sex, underweight status, malnutrition, anemia, chronic pain, sepsis, congestive heart failure, functional impairment, and lower socioeconomic status remained independently associated with frailty. **Conclusions:** Frailty was uncommon but clinically meaningful among adults hospitalized with pancreatic cancer and was associated with advanced age, nutritional and functional vulnerability, acute illness severity, and socioeconomic disadvantage. These findings underscore the need for improved inpatient frailty recognition and targeted supportive care strategies. Research Sponsor: None.

Predictor of frailty in pancreatic cancer.

Predictors	Frail (%)	Non-frail (%)	p-value
Congestive heart failure	15.9	10.3	<0.001
Sepsis	22.8	17.0	<0.001
Underweight	24.6	9.1	<0.001
Anemia	52.5	44.0	<0.001
Malnutrition	46.2	28.8	<0.001
Chronic pain	24.4	19.5	<0.001
Falls/mobility impairment	8.5	3.6	<0.001
Obesity	4.4	8.6	0.0002
Smoking	9.3	12.2	0.034
Chronic kidney disease	16.2	12.8	0.012

11184 **Poster Session**

Baseline corticosteroid use and outcomes in non–small cell lung cancer patients receiving immune checkpoint inhibitors, stratified by indication. First Author: Angelina Lim, USC Keck School of Medicine, Department of Surgery, Los Angeles, CA

Background: Baseline systemic corticosteroids are often prescribed to patients with non-small cell lung cancer (NSCLC) initiating immune checkpoint inhibitors (ICIs). Prior studies associating steroids with reduced ICI efficacy have largely treated steroid exposure as binary without accounting for indication. We evaluated outcomes following baseline steroid use by indication. **Methods:** We conducted a retrospective cohort study using TriNetX, a federated research network of de-identified electronic medical records. Using approximately 7,000-12,000 patients per stratum, NSCLC patients initiating ICIs were stratified by presence of systemic steroid prescriptions within 30 days prior to ICI initiation by indication: brain metastases (BM), pulmonary disease (PD), autoimmune disease (AI), and palliative indications (PI). In each stratum, steroid-exposed patients were compared with propensity-matched steroid-naive controls adjusting for demographics, non-brain metastases, comorbidities, substance use, and prior cancer treatments. Outcomes included mortality, ICU admission, and infection at 1 month. **Results:** Baseline steroid use was associated with worse 1 month outcomes in an indication dependent manner. Among patients receiving steroids for BM, mortality was higher compared with controls (8.75% vs 5.46%; HR 1.62, 95% CI 1.44-1.82; $p < 0.001$), as were ICU admission (5.06% vs 2.80%; RR 1.81, 95% CI 1.53-2.14; $p < 0.001$) and infection (6.81% vs 4.20%; RR 1.62, 95% CI 1.40-1.88; $p < 0.001$). Similarly, among patients receiving steroids for PI, steroid use was associated with increased mortality (9.68% vs 5.29%; HR 1.87, 95% CI 1.69-2.06; $p < 0.001$), ICU admission (4.83% vs 2.65%; RR 1.82, 95% CI 1.57-2.12; $p < 0.001$), and infection (7.50% vs 4.21%; RR 1.78, 95% CI 1.56-2.03; $p < 0.001$). In contrast, steroid use for PD or AI was not associated with increased mortality. PD was associated with higher ICU admission (3.35% vs 2.61%; RR 1.29, 95% CI 1.10-1.51; p = 0.0027) and infection (6.31% vs 4.23%; RR 1.49, 95% CI 1.31-1.70; $p < 0.001$), while AI was associated with increased ICU admission (3.63% vs 2.68%; RR 1.36, 95% CI 1.11-1.65; p = 0.0039) but not increased infection risk. These survival patterns persisted at longer follow-up, with higher mortality among patients with BM and PI at 6 months (BM HR 1.40, 95% CI 1.32-1.48; $p < 0.001$; PI HR 1.40, 95% CI 1.33-1.47; $p < 0.001$), 1 year (BM HR 1.40, 95% CI 1.33-1.47; $p < 0.001$; PI HR 1.36, 95% CI 1.31-1.42; $p < 0.001$), and 5 years (BM HR 1.30, 95% CI 1.24-1.35; $p < 0.001$; PI HR 1.32, 95% CI 1.27-1.37; $p < 0.001$), while no long-term survival decrement was observed for PD or AI. **Conclusions:** Baseline steroid use prior to ICI initiation is associated with increased early and long-term mortality in NSCLC in BM and PI but not PD and AI. Accounting for clinical indication is important to understand real-world ICI outcomes of patients using steroids. Research Sponsor: None.

11185 **Poster Session**

Cardiovascular-related adverse events (CVD-AEs) and echocardiographic (Echo) changes with immunotherapy (IT): A real-world experience. First Author: Ahmed Nabil Mohamed, Cleveland Clinic Foundation, Cleveland, OH

Background: Immune-checkpoint inhibitors (ICI) are standard of care for many solid tumors but are linked to cardiovascular adverse events (CVD-AEs). Real-world comparative data on CVD-AE incidence between IT & non-IT therapies are limited & no prior studies have evaluated longitudinal Echo changes in IT vs. non-IT patients. **Methods:** We conducted a retrospective cohort of 5,556 adults with solid malignancies at Cleveland Clinic Ohio (2010–2022). IT patients were compared to non-IT systemic therapy. Cancers included bladder (II-IIIA:476; IV:158), endometrial IV (157), gastric (II-III:797; IV:590), H&N IV (36), renal (III:88; IV:223), melanoma (45) & lung: NSCLC non-squamous (IIIB:206; IV:1609), NSCLC squamous (IIIB:182; IV:366) & SCLC IIIB-IV (623). Follow-up began at therapy start & continued until CVD-AE, last follow-up or death. Data were collected on demographics, CTCAE grade, management & outcomes. Incidence rates per 100 person-years (/100 Py) were estimated using Poisson regression, cumulative incidence (CIR) using Kaplan–Meier methods & adjusted hazard ratios (HRs) using time-dependent Cox models. Echo analyses (n = 418) compared baseline to follow-up studies using multinomial regression. **Results:** Of the cohort, 1,291 (23%) & 948 (17%) received 1st- & 2nd-line IT. Median age was 66; 38% were female, & 87% were White. ICI accounted for 99.9% of IT. During follow-up, 163 CVD-AEs occurred, including arrhythmias (n = 59), cardiac arrest (n = 35), myocarditis/heart failure (n = 21), pericarditis (n = 10) & acute coronary syndromes (NSTEMI n = 17, STEMI n = 15, unstable angina n = 5). Median follow-up was 14 months (CI 6-35). The CVD-AE CIRs were slightly higher in IT vs. non-IT groups (0.12 vs 0.11 /100 PY). The 4-year CIR was 5% in IT & 3.5% in non-IT (P = 0.4). In time-dependent Cox models, IT was not associated with a significant increase in composite CVD-AEs, though a borderline association with the composite of cardiac dysrhythmia & conduction disorders was observed (HR 1.43, P = 0.06). Echo analyses showed no association between IT & adverse changes in LV/RV systolic function (EF, GLS, TAPSE), pulmonary pressures or diastolic function (E/e'). In contrast, 1st-line IT was associated with increased odds of aortic root dilation (OR 2.95, p = 0.028), mitral valve sclerosis (OR 4.17, P = 0.02) & a trend toward mitral stenosis (OR 3.7, P = 0.05). Abnormal baseline Echo parameters remained the strongest predictors of future worsening. **Conclusions:** We found that IT was not associated with a significant rise in overall CVD-AEs or myocardial dysfunction, possibly reflecting less use of traditional cardiotoxic agents like anthracyclines. Novel associations with aortic root dilation & mitral valve sclerosis suggest vascular & structural remodeling effects. Findings highlight the need for long-term surveillance of structural heart changes beyond ejection fraction monitoring. Research Sponsor: None.

11186 **Poster Session**

Socioeconomic and treatment-related determinants of long-term cancer survival: A population-based SEER outcomes analysis. First Author: Akhilesh Sharma, New York Medical College: St. Mary's/St Clare's, Denville, NJ

Background: Cancer survival is shaped by tumor biology, treatment access, and socioeconomic context, yet population-level quantification of long-term survival disparities related to chemotherapy use and income is limited. We assessed five-year cancer-specific survival across demographic, treatment, and socioeconomic strata in a national registry. **Methods:** We performed a retrospective, population-based survival analysis using the Surveillance, Epidemiology, and End Results (SEER) database. Cancer-specific survival was evaluated at 12, 24, 36, 48, and 60 months after diagnosis. Outcomes were stratified by sex, race, chemotherapy receipt, and area-level median household income categories. Survival estimates were summarized descriptively and visualized using time-to-event curves. **Results:** Overall cancer-specific survival declined progressively over five years, from ~84% at 12 months to ~58% at 60 months. Sex differences were minimal, with similar five-year survival among males and females (~57–58%). Racial disparities were substantial: Asian/Pacific Islander patients demonstrated the highest survival across follow-up, while Black and American Indian/Alaska Native patients had lower early survival and persistent gaps at five years. Patients with recorded chemotherapy use had improved survival compared with those without or with unknown chemotherapy status; 12-month survival was ~88% versus ~80%, and five-year survival was ~65% versus ~57%, respectively. A pronounced socioeconomic gradient was observed: individuals in areas with median household income $\geq$\$120,000 had higher five-year survival (~67%), whereas those in areas with income $<$ \$40,000 had markedly lower survival (~52%). **Conclusions:** In this national registry analysis, both chemotherapy utilization and higher socioeconomic status were strongly associated with improved long-term cancer survival, whereas persistent racial and income-related disparities remained evident. These findings highlight ongoing inequities in access to oncologic care and support the need for targeted policy interventions and equity-focused treatment delivery models. Interpretation should account for limitations inherent to observational registry data and potential residual confounding. Research Sponsor: None.

11187 **Poster Session**

Impact of diabetes on respiratory infection risk and hospitalization following immune checkpoint inhibitor initiation in non–small cell lung cancer: A propensity-matched retrospective cohort analysis. First Author: Gurasis Singh Sodhi, Jefferson Einstein Philadelphia Hospital, Philadelphia, PA

Background: Immune checkpoint inhibitors (ICIs) are a cornerstone of treatment for non-small cell lung cancer (NSCLC); however, patients with diabetes mellitus may have altered immune responses and higher susceptibility to infections. Data comparing infectious respiratory outcomes, healthcare utilization, and mortality between diabetic and non-diabetic NSCLC patients treated with ICIs is limited. We aimed to evaluate these outcomes in NSCLC patients receiving ICIs, stratified by diabetes status. **Methods:** We conducted a retrospective cohort study using the TriNetX Global Collaborative Network. Adults ($\geq$18 years) diagnosed with NSCLC who initiated immune checkpoint inhibitor therapy (PD-1/PD-L1 or CTLA-4 inhibitors) within one year of diagnosis were included. Two cohorts were defined: patients with type 2 diabetes mellitus (DM) and patients without diabetes (non-DM). Propensity score matching (1:1) was performed based on demographics, comorbidities, cancer stage surrogates, smoking history, chemotherapy exposure, radiation therapy, and concurrent medications. Outcomes were assessed from 30 days to 3 years after ICI initiation and included bacterial pneumonia, viral pneumonia, severe sepsis with or without shock, ER visit/hospitalization, critical care needs, and overall survival. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. **Results:** After propensity score matching, 905 patients were included in each cohort. Baseline characteristics were well balanced between groups. Compared with the non-DM cohort, patients with diabetes had a significantly higher risk of severe infectious complications, including bacterial pneumonia (HR 1.44, 95% CI 1.01–2.08), severe sepsis (HR 1.79, 95% CI 1.29–2.49). Rates of viral pneumonia did not significantly differ between groups (HR 0.79, 95% CI 0.45-1.38). Diabetic patients also demonstrated higher incidence of hospitalization (HR 1.17, 95% CI 1.05–1.30) and critical care utilization (HR 1.27, 95% CI 1.02–1.57). However, no statistically significant difference in overall survival between cohorts was detected (HR 1.12, 95% CI 0.98–1.29). **Conclusions:** Among NSCLC patients treated with immune checkpoint inhibitors, diabetes mellitus is associated with higher risk of respiratory infections and severe sepsis. Hospital visits and critical care utilization were more frequent in the diabetic cohort, without a corresponding difference in overall survival. These findings highlight the importance of heightened infection surveillance and proactive supportive care in diabetic patients undergoing immunotherapy. Prospective studies are warranted to better define underlying mechanisms and to optimize risk mitigation strategies in this vulnerable population. Research Sponsor: None.

11188 **Poster Session**

Association between selective serotonin reuptake inhibitor use and outcomes in metastatic melanoma treated with immune checkpoint inhibitors: A real-world cohort study. First Author: Sandeep Kumar Jain, Atropos Health, New York, NY

Background: Immune checkpoint inhibitors (ICIs) have transformed outcomes for metastatic melanoma, yet substantial variability in response remains. Evidence suggests that concomitant medications may modulate antitumor immunity and influence ICI effectiveness. For example, recent mechanistic and translational studies indicate that selective serotonin reuptake inhibitors (SSRIs) enhance T-cell–mediated antitumor immunity and may synergize with PD-1 blockade, with preliminary clinical signals of improved survival. However, real-world evidence in melanoma is limited. We conducted a real-world cohort study to assess the association between baseline SSRI use and outcomes among metastatic melanoma patients treated with ICIs. **Methods:** We performed a retrospective cohort study using a nationally representative real-world dataset from the Atropos Evidence Network integrating open claims and EHR data mapped to OMOP CDM v5.3. Adults with metastatic melanoma treated with first-line pembrolizumab, nivolumab, or ipilimumab were identified using ICD and RxNorm codes. The index date was ICI initiation. The SSRI cohort required ≥30 days of use prior to index; comparators had no prior SSRI exposure. Patients were matched 1:1 using high-dimensional propensity scores (hdPS) derived from ICD, CPT, and RxNorm features and fitted with LASSO-regularized logistic regression. Outcomes included 1-year overall survival (OS), time to ICI discontinuation, ICI duration, and post-index steroid use. **Results:** Among 3,597 metastatic melanoma patients initiating ICIs, 307 had baseline SSRI exposure and 3,290 had no prior SSRI use. After 1:1 hdPS matching, 304 well-balanced pairs were identified. Baseline SSRI use was associated with a numerically lower but not statistically significant risk of death at 1 year (HR 0.70; 95% CI 0.46–1.06; p = 0.092). No significant difference in ICI discontinuation was observed between cohorts (HR 1.07; 95% CI 0.87–1.31; p = 0.53). Mean duration of ICI was similar in the propensity-matched analysis (158.7 days in no-SSRI vs 142.4 days in SSRI; mean difference −16 days; 95% CI −40 to 7.3; p = 0.175). Post-index steroid use also did not differ between groups (IRR 1.02; 95% CI 0.60–1.73; p = 0.94). Across all endpoints, effect estimates were consistent with no clinically meaningful association between baseline SSRI exposure and immunotherapy outcomes. **Conclusions:** In this large real-world analysis, baseline SSRI use was not associated with improved OS, reduced discontinuation, or increased steroid use among metastatic melanoma patients treated with ICIs. Despite strong mechanistic rationale suggesting potential synergy, these findings highlight a disconnect between preclinical observations and real-world outcomes. Prospective studies are needed to identify subpopulations that may benefit. Research Sponsor: None.

11189 **Poster Session**

Novel myeloma therapy utilization in digital health advocacy users: A large US cohort analysis of >1,500 patients. First Author: Jay R. Hydren, HealthTree Foundation, Lehi, UT

Background: Real-world data consistently demonstrates that access to novel myeloma therapies (CAR-T and Bispecific Antibodies [BsAb]) is restricted by "classic" disparities, including lower income, rural geography, and distance from academic medical centers. However, evidence suggests that strong institutional support and patient navigation can mitigate these factors. While direct-to-patient platforms remain underexplored, high digital engagement—driven by education and medical data ownership—are hypothesized to mitigate traditional barriers. To evaluate this, the HealthTree Registry was queried to determine if its engaged cohort exhibits the disparities observed in the general population. **Methods:** A total of 1,519 Multiple Myeloma patients, diagnosed after 2014, and who connected their Electronic Health Records (EHR) and provided survey data within the HealthTree, were originally extracted. Line of treatment data was extracted from clinical plan and progress notes. Eligibility for novel therapies was retrospectively determined based on FDA approval criteria (lines of therapy and dates). Utilization rates comparisons against demographic variables using Chi-square and ANOVA tests. **Results:** Among the cohort, 277 patients were eligible for CAR-T and 91 for BsAbs. Contrary to general population trends, digital engagement appeared to neutralize classic socioeconomic barriers. We found no significant difference in novel therapy utilization based on median zipcode income (Users: $103k vs. Non-Users: $95k, p = 0.88), distance to clinic (p = 0.64), or rural/urban status (p = 0.808). Utilization rates: 30% (84/277) of eligible patients received CAR-T compared to 54% (49/91) for BsAbs. Patients receiving novel therapies had a mean age of 65.9 years and initiated treatment 3.7 years after diagnosis. BsAbs were utilized later in the disease course (Mean Line of Therapy [LOTs]: 6.0) compared to CAR-T (Mean Line of Therapy: 4.8), due to FDA eligibility criteria restrictions. CAR-T utilization was high during early LOTs (2-4) at 48%. While economic and geographic barriers were mitigated, a significant gender disparity emerged in continuous therapy usage. For BsAbs, 66% (33/50) of eligible men received therapy, compared to only 39% (16/41) of eligible women (p = 0.018). No gender difference was observed for CAR-T (p = 1.0). **Conclusions:** In this cohort, although a greater proportion of patients met eligibility criteria for CAR-T than for BsAb, eligible patients were more likely to initiate BsAb treatment. However, digital engagement of patients facilitated early use of CAR-T therapy and reduced traditional barriers like distance and income, which may be less limiting than previously thought. In contrast, a pronounced gender disparity in BsAb therapy utilization suggests that continuous therapies may impose a disproportionate logistical burden on eligible female patients. Research Sponsor: HealthTree Foundation.

11190 **Poster Session**

Trends and disparities in diabetes-associated cancer mortality in the United States, 1999–2020. First Author: Kashish Magnani, Westchester Medical Center, Valhalla, NY

Background: Diabetes mellitus (DM) is increasingly recognized as an important contributor to cancer mortality, yet long-term population-level trends and sociodemographic disparities in diabetes-associated cancer deaths in the United States remain insufficiently characterized. **Methods:** We analyzed U.S. Multiple Cause of Death data from the CDC WONDER database for 1999–2020. Deaths with neoplasia as the underlying cause of death and diabetes mellitus listed as a contributing cause were included. Annual deaths and crude mortality rates were examined across year, Census region, state, 2013 urbanization level, 10-year age groups, sex, race, and Hispanic origin. Temporal trends were quantified using average annual percent change (AAPC) derived from log-linear regression models over the 1999–2020 period. **Results:** From 1999–2020, diabetes-related neoplasia deaths totaled 588,693 (mean 26,759/year), with annual deaths rising 77.9% (20,427 in 1999 to 36,343 in 2020) and crude mortality increasing 50.7% (7.3 to 11.0 per 100,000), corresponding to an overall AAPC +1.24%/year. By sex, trends increased faster in males (AAPC +1.75%) than females (AAPC +0.55%). By Census region, AAPC was highest in the West (+2.00%) and South (+1.98%), followed by the Midwest (+0.65%), while the Northeast declined (−0.30%). By 2013 urbanization, the steepest rises occurred in Noncore nonmetro (+2.43%) and Micropolitan nonmetro (+1.61%), exceeding Medium metro (+1.54%), Small metro (+1.22%), Large central metro (+0.97%), and Large fringe metro (+0.80%). By race, AAPC was highest for American Indian/Alaska Native (+2.38%) and Asian/Pacific Islander (+2.30%), followed by White (+1.45%) and Black (+0.30%). By Hispanic origin, AAPC was higher in Hispanic/Latino (+2.42%) than Not Hispanic/Latino (+1.33%) (Not stated: insufficient rate series for AAPC). By age, increases were greatest at 35–44 years (+1.45%) and 25–34 years (+1.18%), with smaller increases at 45–54 (+0.62%) and ≥85 (+0.62%), while older mid-life groups declined (65–74: −0.61%, 55–64: −0.27%, 75–84: −0.04%). State-level AAPC ranged from Kentucky (+6.55%), Arizona (+5.07%), Oklahoma (+4.81%), Colorado (+4.66%), and Arkansas (+4.61%) to District of Columbia (−3.44%), Connecticut (−2.91%), Massachusetts (−1.88%), Illinois (−1.38%), and Delaware (−1.24%). **Conclusions:** Diabetes-associated cancer mortality increased substantially in the United States from 1999–2020, with widening disparities by geography, urbanization, race/ethnicity, sex, and age. The disproportionate rise in rural areas, younger adults, and select racial and ethnic groups underscores the need for integrated cancer–diabetes prevention strategies and targeted public health interventions to mitigate future mortality burden. Research Sponsor: None.

11191 **Poster Session**

Time-dependent patterns of immune-related adverse events by obesity status following immune checkpoint inhibitor therapy: A real-world cohort analysis. First Author: Bibek Shrestha, The University of Toledo, Toledo, OH

Background: Immune checkpoint inhibitors (ICIs) substantially improve cancer outcomes but are frequently complicated by immune-related adverse events (irAEs). Obesity alters immune regulation and has been paradoxically associated with enhanced ICI efficacy; however, its influence on the timing and persistence of irAEs remains poorly defined. Prior studies have largely evaluated irAEs as binary outcomes, potentially obscuring time-dependent risk patterns. **Methods:** We conducted a retrospective cohort study using the TriNetX U.S. Collaborative Network. Adults with solid tumors initiating nivolumab, pembrolizumab, ipilimumab, or durvalumab were identified. Patients with pre-existing autoimmune disease, hematologic malignancy, organ transplantation, or prior irAEs were excluded. Patients were stratified by baseline body mass index (BMI ≥30 kg/m² vs 20–24.9 kg/m²). irAEs were identified using diagnosis-based groupings mapped to organ-specific toxicity categories. Survival analyses were performed using landmarked Cox proportional hazards models evaluating early (1–90 days), delayed (91–365 days), and late (366–1825 days) irAE risk. Adjusted hazard ratios (AHR) were calculated after adjustment for age, sex, cancer type, immunotherapy agent, smoking status, diabetes, chronic kidney disease, chronic pulmonary disease, liver disease, and cardiovascular comorbidity. **Results:** Among 29,564 eligible patients (obese: 13,958; normal BMI: 15,606), obesity was not associated with overall irAE risk across 5 years of follow-up (AHR 0.98, p=0.19). In landmark analyses, obesity was associated with lower early irAE risk (AHR 0.94, p=0.003), no significant difference during the delayed period, and a persistent increase in late irAE risk (AHR 1.11, p=0.003).Time-stratified associations were most pronounced for gastrointestinal, renal, endocrine, and dermatologic irAEs, while pulmonary and neurologic irAEs were not significantly increased after multivariable adjustment. **Conclusions:** Obesity demonstrated a time-dependent association with immune-related toxicity following ICI therapy, characterized by attenuated early risk and persistent late risk emerging beyond one year. These findings highlight the importance of time-stratified analytic approaches and suggest that absence of early irAEs may not confer long-term safety in obese patients receiving ICIs. Research Sponsor: None.

Outcome	Time Window	Adjusted HR (95% CI)	p value
Any incident irAE	1–90 d	0.94 (0.90–0.98)	0.003†
Any incident irAE	366–1825 d	1.11 (1.04–1.19)	0.003†
GI irAE	1–1825 d	0.82 (0.77–0.87)	<0.001†
GI irAE	1–90 d	0.76 (0.68–0.86)	<0.001†
GI irAE	91–365 d	0.82 (0.74–0.90)	<0.001†
GI irAE	366–1825 d	0.84 (0.75–0.93)	0.001†
Renal irAE	366–1825 d	1.14 (1.01–1.29)	0.031†
Endocrine irAE	91–365 d	1.04 (0.99–1.09)	0.089
Endocrine irAE	366–1825 d	1.05 (1.00–1.11)	0.069

†p<0.05.

11192 **Poster Session**

Patterns of upper endoscopy use prior to gastric cancer diagnosis among high-risk populations. First Author: Rohit Khullar, Tufts Medical Center, Boston, MA

Background: Gastric cancer is frequently diagnosed at advanced stages in the United States, contributing to poor survival. Although several populations carry elevated risk, real-world patterns of upper endoscopic evaluation before gastric cancer diagnosis remain poorly characterized. Understanding pre-diagnostic endoscopy utilization may identify gaps in care and inform future evaluation strategies. **Methods:** A retrospective cohort study using Epic SlicerDicer identified adults ≥18 years diagnosed with gastric adenocarcinoma at Tufts Medical Center between January 2021 and January 2026. Gastric cancer was identified by ICD-10 codes, excluding patients with prior disease. Upper endoscopy (EGD) performed 6–36 months before diagnosis was assessed overall and across high-risk subgroups. EGDs within 6 months were excluded to distinguish pre-diagnostic from index diagnostic procedures. High-risk features were defined by the 2025 AGA Clinical Practice Update and included Asian race, Hispanic ethnicity, interpreter requirement, and prior *Helicobacter pylori* infection, gastric intestinal metaplasia (GIM), or chronic atrophic gastritis (CAG). Rates of pre-diagnostic EGD utilization were described overall and by subgroup. **Results:** Among 258 patients diagnosed with gastric adenocarcinoma, 77 (29.8%) presented with metastatic disease. Overall, 118 patients (45.7%) underwent EGD 6–36 months before diagnosis, while approximately half had their first documented EGD at the time of cancer diagnosis. Rates were similar across racial groups: White (45.3%), Asian (46.3%), Black (43.8%), and Other (45.7%). Utilization was higher among Hispanic versus non-Hispanic patients (57.7% vs 46.2%) and among those requiring interpreter services (51.8% vs 47.0%). Patients with gastric precursor conditions (34.1%) had similar rates of pre-diagnostic EGD (52.3%), including prior *H. pylori* infection (40.0%), GIM (63.3%), and CAG (55.0%). Of 140 patients without pre-diagnostic EGD, 39 (27.9%) underwent colonoscopy alone, indicating access to endoscopic care without concurrent EGD. **Conclusions:** Most upper endoscopies occurred near the time of cancer diagnosis, suggesting predominantly diagnostic rather than preventive evaluation. Even among patients with recognized risk factors and gastric precursor conditions, only about half underwent prior upper endoscopic assessment. Colonoscopy without concurrent EGD highlights gaps in integrated, risk-based gastrointestinal cancer prevention and an opportunity to improve earlier recognition of gastric cancer in high-risk populations. Research Sponsor: None.

Upper endoscopy use before gastric cancer diagnosis.

High-Risk Feature	Total (N)	Total (%)	% w/ EGD (6–36 mo)
Overall population	258	–	45.7
Asian race	67	26.0	46.3
Hispanic ethnicity	26	10.1	57.7
Requires interpreter	56	21.7	51.8
***H. pylori* infection**	35	13.6	40.0
GIM	60	23.3	63.3
CAG	20	7.8	55.0
Any *H. pylori*, GIM, or CAG	88	34.1	52.3

11193 **Poster Session**

Distinct patient and product-specific phenotypes associated with toxicity and resource utilization after CAR T-cell therapy: A Nationwide Inpatient analysis. First Author: Ayodeji David Johnson, Boston Medical Center - Brighton, Boston, MA

Background: Chimeric antigen receptor (CAR) T-cell therapy improves outcomes in relapsed or refractory hematologic malignancies but is associated with significant toxicity and inpatient resource utilization. Nationally representative real-world data remain limited. We evaluated the incidence, phenotype-specific predictors, and inpatient consequences of CAR T-cell–related toxicities in U.S. practice. **Methods:** We conducted a retrospective cohort study using the 2023 Nationwide Inpatient Sample, identifying adult elective hospitalizations involving CAR T-cell infusion using ICD-10-PCS New Technology Group 7 codes for FDA-approved CAR-T therapies. Interhospital transfers were excluded. Cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), and cytopenias were identified using ICD-10-CM codes during the index hospitalization; toxicity grade was unavailable. Functional status was assessed using APR-DRG loss of function severity. Primary outcomes were coded in-hospital CRS, ICANS, and cytopenias. Secondary outcomes included transfusion requirement, length of stay (LOS), and total inpatient cost, adjusted to 2023 U.S. dollars. Survey-weighted multivariable regression models evaluated predictors of toxicity and resource utilization. **Results:** The weighted cohort represented 3,405 CAR-T hospitalizations nationwide. Indications included multiple myeloma (42.6%), diffuse large B-cell lymphoma (32.0%), follicular lymphoma (9.0%), mantle cell lymphoma (8.6%), B-cell acute lymphoblastic leukemia (7.4%), and chronic lymphocytic leukemia (0.4%). Cytopenias were coded in 45.2% of hospitalizations, CRS in 62.6%, and ICANS in 30.1%. In adjusted analyses, cytopenias were associated with older age, B-cell acute lymphoblastic leukemia, moderate-to-severe functional impairment, and CAR-T product type. CRS risk varied by CAR-T product type and was higher among transplant recipients and patients with severe functional impairment. ICANS was associated with transplant history, selected comorbidities (including metastatic solid tumors), follicular lymphoma, older age, and CAR-T product type. Median LOS was 12 days (IQR, 9–16) and was longer among patients with neutropenia. Transfusion support was required in 6.6% of hospitalizations. Median total inpatient hospitalization cost exceeded $1.3 million and was independently associated with diffuse large B-cell lymphoma, B-cell acute lymphoblastic leukemia, neutropenia, and autologous leukapheresis. **Conclusions:** CAR T-cell therapy is associated with substantial inpatient toxicities, prolonged hospitalization, and high cost, with risk varying by patient and product specific phenotypes. These findings support pre-infusion risk stratification and resource-aligned inpatient care models for CAR-T delivery. Research Sponsor: None.

11194 **Poster Session**

Bridging the gap between clinical utility and coverage: Real-world impact of unreimbursed NGS testing. First Author: Madhuri Paul, NeoGenomics Laboratories Inc., Fort Myers, FL

Background: Genomic testing is the cornerstone of precision oncology, revealing rare yet clinically actionable alterations that define diagnosis, risk stratification, and treatment choice. Despite its proven clinical utility, inconsistent coverage and inadequate reimbursement constrain routine use, reflecting a persistent misalignment between clinical value and payer policy. Evaluating real-world utilization and clinical impact of unreimbursed testing can highlight critical gaps in standard oncology care. **Methods:** Molecular profiles of 7,271 patients were analyzed by integrating Neogenomics sequencing data (09/2025 – 12/2025) with standardized clinical data (cancer diagnoses, ICD-10 codes, medication records, molecular testing results) extracted from comprehensive electronic medical records using the xCures platform. **Results:** Cohort of 7,271 patients insured by commercial (58%), managed (22%), or government (20%) plans had unreimbursed tests with orders originating primarily from hospitals (49%) and physician groups (42%). Testing predominantly targeted hematologic malignancies (> 90%), with solid tumors representing 8%. Among patients with available medical records (n = 3,409), hematologic panels remained most common (67%), led by the Neo Comprehensive Myeloid (n = 1,064), NeoTYPE MDS/CMML Profile (n = 485), Neo Comprehensive Heme (n = 385), NeoTYPE CLL Profile (n = 299) and NeoTYPE Lymphoid Disorders Profile (n = 211). Abnormal molecular findings were identified in 1,056 patients (%), including 470 patients with pathogenic or likely pathogenic variants (SNVs, deletions, insertions, fusions and substitutions), with 23% (104/470) of alterations (i.e. ABL1, ERBB3, KDR, MAP2K1, TOP1, TSC1, TSC2) not identified by previous methods. Of 66 patients receiving targeted therapy after testing, 4 (6%) were treated within 60 days for pathogenic alterations (, JAK2, KIT, BCR-ABL1) identified by Neogenomics. Eleven (17%), initially with unspecified diagnoses, received therapies (venetoclax, obinutuzumab, lenalidomide) for newly defined indications, and 2 (3%) were treated (venetoclax, lenalidomide) based on relevant biomarkers (NPM1, SF3B1) of sensitivity, all guided by test results within 60 days. Among 386 patients with initially unspecified conditions, EMR for 137 patients (36%) confirmed diagnoses within 60 days. **Conclusions:** Genomic testing delivers substantial clinical value by enabling rapid, definitive diagnoses and informing timely, targeted treatment decisions. Despite inconsistent payer coverage, these data show that NGS testing frequently identifies actionable alterations and biomarkers not previously identified by standard testing that directly impact patient management. Aligning reimbursement policies with anticipated clinical utility is critical to closing gaps in standard care and expanding equitable access to precision oncology. Research Sponsor: None.

11195 **Poster Session**

Early mortality and hospitalization following cholangiocarcinoma diagnosis by statin exposure: A TriNetX real-world analysis. First Author: Reshma John, St Joseph's University Medical Center, Paterson, NJ

Background: Statins are widely prescribed among patients with cardiometabolic comorbidities and are frequently continued at the time of cancer diagnosis. While statins have been hypothesized to exert antitumor and immunomodulatory effects, real-world data evaluating early clinical outcomes associated with statin exposure in patients with cholangiocarcinoma are limited. We assessed short-term mortality and hospitalization outcomes following cholangiocarcinoma diagnosis using a large federated electronic health record network. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, comprising 68 healthcare organizations. Adult patients (≥18 years) diagnosed with intrahepatic bile duct carcinoma (ICD-10 C22.1), extrahepatic bile duct carcinoma (C24.0), or ampullary carcinoma (C24.1) between January 1, 2010, and December 11, 2024 were included. Patients were classified based on exposure to statins (rosuvastatin, simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, or pitavastatin) within a prespecified temporal window relative to cancer diagnosis, with the index event defined accordingly. Propensity score matching (1:1) was performed to balance demographics, comorbidities, and laboratory characteristics, mitigating confounding by indication and immortal time bias. Outcomes included all-cause mortality, hospitalization, and sepsis at 30 and 90 days following the index event. Risk estimates and Kaplan–Meier survival analyses were performed. **Results:** After propensity score matching, baseline characteristics were well balanced between statin-exposed and non–statin-exposed cohorts. At 30 days following diagnosis, statin exposure was not associated with a significant difference in all-cause mortality. In contrast, at 90 days, statin exposure was associated with higher all-cause mortality (risk ratio 1.23; hazard ratio 1.30; log-rank P = .012) and increased hospitalization (risk ratio 1.29; hazard ratio 1.37). No significant differences in sepsis risk or hazard were observed between cohorts at either time point. **Conclusions:** In this real-world, propensity score–matched analysis of patients with cholangiocarcinoma, statin exposure was not associated with improved 30-day survival and was associated with higher 90-day mortality and hospitalization. Although causality cannot be inferred, these findings highlight clinically meaningful early outcome differences during the peri-diagnostic period and suggest that commonly prescribed cardiovascular medications may identify patients with increased baseline vulnerability at the time of cancer diagnosis. Future work integrating medication exposure with comorbidity burden, treatment patterns, and early care trajectories may help refine risk stratification during initial cholangiocarcinoma management. Research Sponsor: None.

11196 **Poster Session**

Osteoporosis and osteoporosis-related fractures among older male cancer patients: A nationwide study. First Author: Tasneem Anagreh, Saint Francis Hospital, Evanston, IL

Background: Osteoporosis is commonly viewed as a disease of postmenopausal women, leading to significant underdiagnosis in men. Older male patients with cancer experience accelerated bone loss due to androgen deprivation therapy, corticosteroid exposure, and malignancy-related skeletal remodeling. We examined the prevalence, tumor-specific risk factors, and outcomes of osteoporosis and related fractures in a national cohort of older male cancer patients. **Methods:** We analyzed Nationwide Readmissions Database hospitalizations from 2019–2022, identifying male patients aged ≥60 years with malignancy. Primary outcomes were osteoporosis (ICD-10-CM M80/M81) and major osteoporotic fractures (hip, spine, humerus, wrist); isolated hip fracture was a secondary outcome. Survey-weighted multivariable logistic regression models identified independent predictors, adjusting for age, cancer type, metastatic status, and clinical risk factors. **Results:** Among an estimated 5.17 million weighted cancer admissions, 2.79 million occurred in males. Osteoporosis was diagnosed in 1.29% of males versus 7.16% of females ($P< 0.001$); mean age at diagnosis was 76.5 vs 78.0 years. Men with osteoporosis had markedly higher fracture rates than those without, including hip fracture (5.11% vs 0.85%) and any major fracture (8.36% vs 1.60%) (all $P< 0.001$). In multivariable analysis, odds of osteoporosis diagnosis increased with age (OR 1.06 per year, $P< 0.001$). Diagnoses were most strongly associated with multiple myeloma (OR 1.63), prostate cancer (OR 1.33) (both $P< 0.001$), and leukemia (OR 1.16, $P= 0.008$). Hypogonadism (OR 4.77), hyperparathyroidism (OR 3.53), vitamin D deficiency (OR 2.51), and tobacco use (OR 1.08; $P= 0.009$) were independent clinical predictors. In fracture models, prior osteoporosis diagnosis was the strongest predictor of any major fracture (OR 4.11) and hip fracture (OR 2.41) (both $P< 0.001$). Modifiable risks, including tobacco use (OR 1.55–1.61) and vitamin D deficiency (OR 1.68–1.88) (both $P< 0.001$), consistently increased fracture risk. Prostate cancer increased odds of both major (OR 1.11) and hip fractures (OR 1.21) ($P< 0.001$), whereas multiple myeloma increased odds of major fracture (OR 1.19, $P= 0.004$) but was associated with lower odds of hip fracture (OR 0.80, $P= 0.03$). **Conclusions:** Older men with cancer face substantial, under-recognized risk for osteoporosis and fracture-related morbidity. Tumor-specific patterns and modifiable clinical factors identify clear opportunities for earlier risk assessment and integration of bone health strategies into routine oncologic care. Research Sponsor: None.

11197 **Poster Session**

Sepsis severity and inpatient outcomes in metastatic cancer: A National Inpatient Sample study. First Author: Davin Turku, The Brooklyn Hospital Center, Brooklyn, NY

Background: Sepsis is a major driver of acute decompensation and inpatient death in patients with cancer, with particularly poor outcomes reported among severe sepsis and septic shock. We evaluated national associations between sepsis severity and inpatient outcomes among metastatic cancer hospitalizations. **Methods:** We conducted a retrospective cross-sectional analysis of the National Inpatient Sample (2016–2020). Adult hospitalizations with metastatic cancer were identified using ICD-10-CM codes C77–C79. Sepsis severity was categorized as no sepsis, severe sepsis without shock, or septic shock using ICD-10 diagnosis codes. Survey-weighted multivariable logistic regression estimated adjusted odds ratios (aOR) for in-hospital mortality, mechanical ventilation, and ICU utilization. Survey-weighted linear regression estimated adjusted differences in length of stay (LOS) and total charges. Models adjusted for age group, sex, race/ethnicity, primary payer, hospital bed size, hospital region, and comorbidity burden using vwcheck (van Walraven score derived from Elixhauser comorbidities). **Results:** In the complete-case regression cohort (weighted N=1,011,365), severe sepsis was associated with higher in-hospital mortality versus no sepsis (aOR 1.49, 95% CI 1.44–1.54), and septic shock with markedly higher mortality (aOR 4.75, 95% CI 4.63–4.87). Sepsis severity strongly predicted escalation of care: mechanical ventilation (severe sepsis aOR 1.37, 95% CI 1.24–1.50; septic shock aOR 6.31, 95% CI 5.93–6.71) and ICU utilization (severe sepsis aOR 1.07, 95% CI 1.03–1.11; septic shock aOR 6.44, 95% CI 6.26–6.62). Relative to the Northeast, adjusted mortality odds were lower in the Midwest (aOR 0.72), South (aOR 0.77), and West (aOR 0.81). Septic shock was associated with higher resource use (+1.38 LOS days; +$56,975 charges). **Conclusions:** In hospitalized patients with metastatic cancer, increasing sepsis severity was independently associated with stepwise increases in mortality, need for ICU-level care, and healthcare utilization. Patients with septic shock represented a particularly high-risk subgroup, with markedly elevated mortality and resource use even after adjustment for comorbidity burden. These findings emphasize that sepsis, rather than malignancy alone, is a major driver of inpatient outcomes in advanced cancer and highlight the importance of early recognition and timely escalation of supportive care for this vulnerable population. Research Sponsor: None.

Association of sepsis severity with inpatient outcomes among metastatic cancer hospitalizations (NIS 2016–2020).

Outcome	Severe sepsis (aOR or Δ, 95% CI)	Septic shock (aOR or Δ, 95% CI)
In-hospital mortality	1.49 (1.44–1.54)	4.75 (4.63–4.87)
Mechanical ventilation	1.37 (1.24–1.50)	6.31 (5.93–6.71)
ICU utilization	1.07 (1.03–1.11)	6.44 (6.26–6.62)
Length of stay, days	−0.42	+1.38
Total hospital charges, $	−3,325	+56,975

11198 **Poster Session**

Real-world utilization and outcomes of lenalidomide in MDS with low blasts and isolated deletion 5q (MDS w 5q). First Author: Krishna Sajeev, Rochester General Hospital, Rochester, NY

Background: Lenalidomide is the preferred first-line agent for lower risk MDS w 5q. It is associated with higher rates of transfusion independence and cytogenetic remission and has demonstrated survival benefit in selected clinical trial populations. Large nationwide studies are lacking in this subgroup. **Methods:** We identified adults aged > 18 years with MDS w 5q diagnosed between 2006 and 2021 using the National Cancer Database (NCDB), corresponding to Lenalidomide approval. Demographic, socioeconomic characteristics, insurance status, Charlson-Deyo comorbidity index (CCI), and treatment variables were extracted. The primary outcome was receipt of lenalidomide therapy. Secondary outcomes included overall survival (OS). Patients were categorized into pre-Affordable Care Act (ACA) and post ACA periods. Multivariable logistic regression and relative risk models were used. OS was estimated using Kaplan-Meier methods and differences between groups were compared with log-rank tests. Multivariable Cox proportional hazards model was used to assess factors associated with survival. $P < 0.05$ was considered significant. **Results:** We identified 3,328 individuals with MDS w 5q, median age of 77 years; 56.1% were women. The majority were non-Hispanic white 87%, followed by 6% non-Hispanic blacks and 4% Hispanic patients. Predominant insurance type was Medicare (78.3%). CCI score of 2 and higher was present in 15%. Overall, 21% of patients received Lenalidomide. Utilization increased significantly in the post-ACA, compared with pre-ACA (32% vs 12%, $p < 0.001$). On multivariable analysis, post -ACA period was independently associated with higher odds of Lenalidomide receipt (OR 3.01-4.34, $P < 0.001$), while Medicaid was associated with lower likelihood of treatment compared with Medicare (OR 0.26-0.96, p = 0.04). Other demographic and socioeconomic variables were not independently associated with treatment receipt. Median OS for the overall cohort was 15.7 months. In multivariable Cox analysis, worse OS was associated with age > 80 (HR 1.0; ref = 61-70), receipt of chemotherapy (HR 1.35) and increasing commodity burden [CDS: HR 1.27; CDS: 2 HR 1.45, CDS 3: HR 1.95; all $p < 0.001$). Female sex was associated with improved survival(HR 0.76; $p < 0.001$). Lenalidomide receipt was not independently associated with OS after adjustment (HR 1.05; p = 0.27). **Conclusions:** This is the largest study evaluating receipt of lenalidomide in MDS with 5q deletion. Lenalidomide utilization increased substantially following ACA implementation, leading to improved access to disease modifying therapy. However, Medicaid insurance was associated with lower treatment receipts. Survival outcomes were primarily driven by age, commodity burden and treatment intensity rather than Lenalidomide receipt, highlighting persistent disparities and limitations of registry-based analysis. Research Sponsor: None.

TPS11199 **Poster Session**

A phase II, single-arm, exploratory study of GEMOX combined with tislelizumab and donafenib in the perioperative treatment of potentially resectable intrahepatic cholangiocarcinoma with high recurrence risk. First Author: Sulai Liu, People's Hospital of Hunan Province, Changsha, China

Background: Biliary tract cancer (BTC) is characterized by strong invasiveness and poor prognosis, with a metastasis and recurrence rate of up to 67% within 1 year after surgery and a 5-year overall survival rate of only 5%~15%. Among BTC subtypes, intrahepatic cholangiocarcinoma (ICC) accounts for a relatively high proportion, and its unique biological behaviors result in persistently high postoperative recurrence risk, which seriously endangers patients' life and health. Currently, major guidelines recommend that patients with potentially resectable ICC at high recurrence risk participate in clinical trials to explore optimal treatment strategies. For patients evaluated as "technically resectable but with high-risk recurrence" before surgery, clinical practice has shown that neoadjuvant therapy can effectively eliminate micrometastases and reduce the difficulty of R0 resection; postoperative adjuvant therapy can further prevent recurrence. Therefore, we innovatively propose a perioperative treatment model aimed at breaking through the existing therapeutic predicament. **Methods:** This study is a phase II, single-arm, exploratory study with a fixed sample size of 20 patients. The inclusion criteria are intrahepatic cholangiocarcinoma (ICC) (TNM stage T1-4, N0-1, M0)based on preoperative assessment, initial technical resectability per imaging, and at least one high - risk recurrence factor. High-risk recurrence factors include: tumor diameter >5 cm, regional lymph-node positivity, satellite/multifocal lesions, radiological suspicion of diaphragmatic adhesion, CA19-9 >200 U/ml, and an anticipated surgical margin <1 cm on pre-operative imaging. Treatment involves two 21 - day cycles of GEMOX (gemcitabine 1000mg/m² on day 1 and 8, oxaliplatin 100mg/m² on day 1) with tislelizumab (200mg on day 1) and donafenib (0.2g orally twice daily). If investigators confirm patients meet surgical criteria (R0 resection expected), surgery follows 1 - 2 weeks post - treatment. Post - surgery, adjuvant therapy starts within 5 weeks. The regimen is capecitabine (1250mg/m² orally twice daily on days 1 -14) or S - 1 (40 -60mg orally twice daily on days 1 -14, weight - adjusted) plus tislelizumab (200mg on day 1) and donafenib (0.2g orally twice daily), repeated every 21 days for six cycles. Primary endpoint is event - free survival (EFS). Secondary endpoints are objective response rate (ORR) and disease control rate (DCR) per RECIST1.1, R0 resection rate, major pathological response rate(MPR, the proportion of patients who underwent radical surgery and had ≤10% residual viable tumor in the postoperative specimen), treatment completion rate, overall survival (OS), disease - free survival (DFS), and safety (treatment - related adverse events' incidence and severity). Clinical trial information: ChiCTR2500112067. Research Sponsor: Suzhou Zelgen Biopharmaceuticals Co., Ltd.; BeOne Medicines.

TPS11200 **Poster Session**

Design of an innovative clinical development program using randomized controlled phase 2 trial data and real-world evidence from an expanded access protocol to assess mifomelatide (TCMCB07) in GI cancer cachexia. First Author: Allison Gardner, Endevica Bio, Northbrook, IL

Background: Cachexia is common in GI cancers, occurring in ~50% of patients with colorectal cancer (CRC) and up to 80% of patients with pancreatic ductal adenocarcinoma (PDAC). Resulting muscle mass and energy store depletion reduces chemotherapy tolerance, often leading to dose reductions, treatment delays/discontinuation, and poorer survival outcomes (Franko J, *Eur J Cancer*; 2022:174; Dunne RF, *J Cachexia Sarcopenia Muscle*. 2024;15:1628). Therefore, body weight preservation during chemotherapy may improve treatment effectiveness and outcomes for patients with GI cancer. The central melanocortin (MC) system, including MC3 and MC4 receptors, plays essential roles in regulating appetite, body mass, and energy homeostasis and is a logical therapeutic target to prevent and treat cachexia. Mifomelatide is a novel peptide MC3R/MC4R dual antagonist that is being studied for cancer and chemotherapy-associated weight loss. Our previously published work showed that mifomelatide was safe and effectively ameliorated cancer- and chemotherapy-associated cachexia in preclinical studies of mice, rats, and pet dogs. In a Phase 1 trial, healthy volunteers tolerated mifomelatide and did not experience vital sign or CV abnormalities or drug-related SAEs; they also experienced a modest increase in body weight and hunger compared with placebo. These findings warranted further clinical development of mifomelatide. **Methods:** The mifomelatide clinical development program is designed to generate a multidimensional body of evidence from clinical trial and real-world datasets that span GI cancer types and cachexia stages. First, a randomized, double-blind, placebo-controlled Phase 2 trial is evaluating mifomelatide's effects in 120 patients with newly diagnosed mCRC and pre-cachexia or early weight loss (NCT06937177). Additionally, an intermediate-size Expanded Access Protocol (EAP) was cleared by the US Food and Drug Administration in January, 2026 to make mifomelatide available to 100 eligible cachectic PDAC patients (NCT number pending). In addition to providing mifomelatide for compassionate use to patients with PDAC who have high unmet need and no approved treatment options for their cancer cachexia, the EAP will also facilitate the collection of real-world data that, when combined with findings from the Phase 2 trial, will deepen our understanding of mifomelatide's safety, tolerability, and potential to optimize body weight in patients with GI cancer. Collectively, our innovative hybrid approach to the mifomelatide clinical development program will generate robust insights into the benefit–risk profile of MC3R/MC4R dual antagonism with mifomelatide to treat cachexia across GI cancers and guide key design considerations for a subsequent pivotal trial. Clinical trial information: NCT06937177. Research Sponsor: Endevica Bio, Inc.

TPS11201 **Poster Session**

Economic burden of non-approved alternative therapies among patients with stage IV cancer: A prospective observational study. First Author: Arpana Ashok, Mercy Hospital, Fort Smith, AR

Background: Complementary and alternative therapies, including herbal supplements and over-the-counter medications, are used by 9 to 81% of cancer patients post-diagnosis to alleviate symptoms, side effects, anxiety, depression, or to gain a sense of control. Prior studies suggest higher use among younger, female patients with higher socioeconomic status. However, in our institutional practice, we did not observe any specific pattern on alternative medicine use. Additionally, the financial burden (financial toxicity) of these often-out-of-pocket expenses remains understudied in advanced cancer populations. This prospective observational study aims to assess the financial toxicity and describe patterns of use of non-approved alternative therapies among patients with stage IV cancer. **Methods:** This is a prospective, single-center, observational study conducted at Mercy Clinic Oncology, Fort Smith, AR. Eligible patients are aged $\geq$18 years, diagnosed with any stage IV cancer, and currently receiving systemic therapy. Key exclusions include the inability to read/understand English, incarcerated patients, and patients only on supportive care. A convenience sample of 150 patients will be enrolled for initial analysis with plans to expand the study to a multi-institutional format. Patients meeting eligibility criteria are identified via clinic schedule review and approached in person by a research nurse. Interested patients receive a study information sheet and complete a one-time, anonymous, paper-based survey (approximately 5 minutes) either in-clinic or at home (returned at next visit). The survey includes 6 demographic/cancer/treatment questions and 6 questions on use of specific non-approved alternative therapies and estimated average monthly costs (categorized as $<$ \$25, \$26–\$50, \$51–\$100, $>$ \$100). A specific question on marijuana addresses use for cancer cure (recreational/symptom control categorized as "no"); responses are anonymous with no PHI collected to minimize risk. Analysis will use descriptive statistics (frequencies/percentages) for cost patterns (primary outcome) and therapy types (secondary outcome), with chi-squared tests for subgroup comparisons by demographics. Enrollment started beginning of January 2026, and in two weeks, nine patients were identified and approached, with seven patients completing the survey. No preliminary data are available. Clinical trial information: Not applicable (IRB-approved observational protocol 24-062). Research Sponsor: None.

TPS11202 **Poster Session**

A pragmatic, hybrid observational study evaluating the effectiveness of trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 3+ solid tumors: DESTINY-PanTumor04. First Author: Bradley J. Monk, Late-Phase Clinical Research, Florida Cancer Specialists and Research Institute, West Palm Beach, FL

Background: Patients with advanced or metastatic HER2 IHC 3+ solid tumors have limited treatment options beyond first-line settings, with generally poor outcomes. T-DXd is a HER2-directed antibody-drug conjugate approved in multiple countries, including in the US for patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment and have no satisfactory alternative therapies. Building on existing clinical trial data, DESTINY-PanTumor04 evaluates the real-world effectiveness of T-DXd in HER2-positive (IHC 3+) solid tumors, using a hybrid data collection approach that enhances efficiency for sites and physicians and facilitates study implementation. **Methods:** DESTINY-PanTumor04 (NCT07124000) is a multicenter, pragmatic observational, real-world study evaluating the effectiveness of T-DXd (5.4 mg/kg IV Q3W) in adult patients in the US with previously treated, locally advanced, unresectable, or metastatic HER2-positive (IHC 3+ by local testing) solid tumors. Data collection will use a hybrid approach, combining primary data collection of baseline tumor burden, comorbidities, ECOG status, treatment response, and survival, with secondary data collection from electronic health record (EHR) abstraction for all other data. Approximately 100 patients will be enrolled across US sites, including community oncology practices and academic medical centers within an existing US oncology network from Paradigm Health. Participating sites will use technological resources that support the identification of eligible patients and enable efficient EHR-to-electronic data capture and transfer, minimizing physician time while improving compliance in data completeness and accuracy. Eligible patients must have disease progression following $\geq$1 prior systemic treatment for metastatic or advanced disease, have no alternative treatment options, and have a clinical decision for T-DXd treatment in accordance with the FDA label. Patients with breast cancer, colorectal cancer, non-small cell lung cancer, gastric or gastroesophageal junction cancers, or hematologic malignancies will be excluded. Primary endpoints are real-world objective response rate, defined as the proportion of patients with a complete response (CR) or partial response (PR) as determined by clinician assessment per criteria used in routine clinical practice; and real-world duration of response, defined as the time from first objective response (CR or PR) to disease progression as determined by clinician assessment per criteria used in routine clinical practice, or death. Secondary endpoints include real-world time to treatment discontinuation and real-world time to next treatment. Enrollment began in September 2025 and is ongoing. Clinical trial information: NCT07124000. Research Sponsor: AstraZeneca.

11500 Oral Abstract Session

Primary results of the phase 3 peak study of bezuclastinib + sunitinib vs sunitinib monotherapy in advanced gastrointestinal stromal tumors (GIST). First Author: Andrew J. Wagner, Dana-Farber Cancer Institute, Boston, MA

Background: GIST, the most common mesenchymal malignancy of the gastrointestinal tract, is commonly driven by activating *KIT* mutations. Despite therapeutic advances, treating advanced GIST with KIT tyrosine kinase inhibitors (TKIs) remains challenging due to emergence of heterogeneous resistance mutations inadequately addressed by current approved therapies. Bezuclastinib, an oral, selective type 1 TKI, in combination with sunitinib, a type 2 TKI, inhibits common primary and secondary resistance mutations in advanced *KIT*-mutant GIST. The Peak study evaluated efficacy and safety of bezuclastinib + sunitinib vs standard second-line sunitinib monotherapy in patients with advanced GIST who received prior imatinib therapy. **Methods:** Peak was a multipart study: dose confirmation (Part 1a), 2 drug-drug interaction (DDI) assessments (Part 1b; DDI substudy), and a randomized phase 3 (Part 2; abstract focus). Patients were randomized 1:1 to bezuclastinib 600 mg once daily (QD) + sunitinib 37.5 mg QD (n=204) or sunitinib 37.5 mg QD (n=209). Primary endpoint was blinded independent central review (BICR)-assessed median progression-free survival (mPFS). Key secondary endpoints were objective response rate (ORR) per BICR and overall survival (OS). Crossover to combination was permitted at BICR-confirmed progression. **Results:** Patients (N=413) were randomized to either bezuclastinib + sunitinib or sunitinib monotherapy; median (range) age, 63 (30-88) years; 59.6% and 14.0% had activating *KIT* mutations in exons 11 only and 9 only, respectively. The combination significantly improved mPFS (HR, 0.50; 95% CI, 0.39-0.65; P$<$0.0001). mPFS was 16.5 months (95% CI, 13.8-19.2) for the combination vs 9.2 months (95% CI, 7.2-11.0) for monotherapy. ORR significantly improved with the combination vs monotherapy (46% vs 26%; risk difference, 20%; 95% CI, 10.6-28.6; P$<$0.0001). As of Sep 30, 2025, OS data remain immature. Incidence of adverse events (AEs) was similar between arms. Grade (Gr)$\geq$3 AEs were comparable, with no significant increase in common sunitinib-associated AEs. Higher rates of Gr$\geq$3 ALT/AST elevations and anemia were observed with the combination and were manageable with dose modification. ALT/AST elevations led to bezuclastinib dose reductions in 13.2% and discontinuations in 1.5% of patients in the combination arm; all Gr3 hepatic AEs resolved; no Gr4 events occurred. Additional treatment-emergent AEs leading to discontinuation of either drug in $>$1 patient in the combination arm were neutropenia (2.9%) and diarrhea (1%). No treatment-related AEs led to death in the combination arm. **Conclusions:** Combined KIT inhibition with bezuclastinib + sunitinib significantly improved mPFS vs sunitinib monotherapy, reducing the risk of progression or death by 50% and increasing ORR from 26% to 46%. The combination was well tolerated with no new safety findings. Clinical trial information: NCT05208047. Research Sponsor: Cogent Biosciences, Inc.

11501 Oral Abstract Session

Velzatinib (IDRX-42) as 1L or 2L therapy for advanced gastrointestinal stromal tumors (GISTs) by *KIT* mutation status: A subset analysis of the phase 1/1b StrateGIST 1 study. First Author: Robin Lewis Jones, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom

Background: Most GISTs present with activating *KIT* mutations (exons 9/11) initially responsive to imatinib, but many progress due to diverse *KIT* resistance mutations (largely in exons 13/14/17/18). Velzatinib (subject to USAN approval), a novel selective KIT inhibitor, has broad mutation coverage and robust in vitro/vivo preclinical activity in models with mutations relevant to 1st- (1L) and 2nd-line (2L) GIST. We present results from StrateGIST 1 evaluating the safety and efficacy of velzatinib in patients (pts) with advanced GIST as 1L or 2L therapy by *KIT* mutation status. **Methods:** The study design of StrateGIST 1 has been previously described (Schöffski et al. *J Clin Oncol* 2024). We present updated safety and efficacy data for 1L and 2L pts by *KIT* mutation status treated with velzatinib at the recommended phase 1b dose (RP1bD) of 300-mg tablet or exposure-equivalent 400-mg capsule. **Results:** As of December 15, 2025, 18 pts in 1L and 46 pts in 2L received velzatinib at the RP1bD and were evaluable for the efficacy analysis. In 2L pts, median follow-up (mFU) was 14.7 (95% CI: 12.9, 18.4) mo and median progression-free survival (mPFS) was 13.7 (95% CI: 7.4, 18.4) mo. In 1L, the mFU was 6.4 (95% CI: 1.8, 11) mo, and all pts (18/18) had a reduction in tumor volume, of whom 11 (61%) experienced unconfirmed responses, including 1 complete and 10 partial responses (Table 1). As of the cutoff date, 17 1L pts remained on study treatment. Treatment was well tolerated, with low rates of dose reductions (1L: 0%; 2L: 6%) and withdrawals (1L: 0%; 2L: 4%) due to AEs. **Conclusions:** Velzatinib exhibited promising activity and tolerable safety as 1L and 2L therapy across clinically relevant *KIT* mutations for pts with advanced GIST. These data support further study of velzatinib, including in 1L pts, to address the need for therapeutic options with broad coverage of clinically relevant GIST mutations. This study (NCT05489237) is funded by GSK. Clinical trial information: NCT05489237. Research Sponsor: GSK.

Clinical activity and response by mutation status per mRECIST v1.1.[a]

	1L total (n=18)	2L total (n=46)	2L Ex 9 mutation only (n=8)	2L Ex 11 mutation only (n=14)	2L Ex 11+ATP-binding pocket resistance mutation (13/14) (n=14)	2L Ex 11+activation loop resistance mutation (17/18) (n=3)	2L Other (including ≥2 resistance mutations) (n=7)
Best overall response, n (%)							
Complete response	1 (6)	2 (4)	0	1 (7)	0	0	1 (14)
Partial response	10 (56)	14 (30)	5 (62)	2 (14)	5 (36)	1 (33)	1 (14)
Stable disease	7 (39)	25 (54)	3 (38)	8 (57)	8 (57)	2 (67)	4 (57)
Progressive disease	0	5 (11)	0	3 (21)	1 (7)	0	1 (14)
Not evaluable	0	0	0	0	0	0	0
Objective response rate, n (%) (95% CI)	11 (61) (35.7, 82.7)	16 (35) (21.4, 50.2)	5 (62) (24.5, 91.5)	3 (21) (4.7, 50.8)	5 (36) (12.8, 64.9)	1 (33) (0.8, 90.6)	2 (29) (3.7, 71)

[a]In an efficacy-evaluable population defined as all pts with ≥1 postbaseline disease assessment or prior clinical progression or death.

11502 Oral Abstract Session

Phase 3 study (APROMISS) of catequentinib hydrochloride (AL3818) monotherapy in patients with advanced alveolar soft part sarcoma (ASPS). First Author: Silvia Stacchiotti, Adult Mesenchymal and Rare Tumor Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: To report results from the open-label alveolar soft part sarcoma (ASPS) cohort of the phase III APROMISS trial (NCT03016819) evaluating Catequentinib hydrochloride (AL3818), an oral multitargeted receptor tyrosine kinase inhibitor, in adults with advanced or metastatic ASPS. **Methods:** Adult patients with pathologic and molecularly confirmed advanced ASPS, either treatment-naive or previously treated (excluding cediranib), were enrolled in the open-label, non-randomized ASPS cohort of the phase III APROMISS trial conducted across the United States, Asia, and Europe. Catequentinib hydrochloride was administered orally at 12 mg once daily in 21-day cycles (14 days on/7 days off) until disease progression, toxicity, or death. The primary endpoint was objective response rate (ORR) assessed per RECIST by Blinded Independent Central Review (BICR) (predefined threshold: 31%). Secondary endpoints included duration of response (DOR) with a predefined target of =/$>$6 months, progression free survival (PFS) and overall survival (OS). **Results:** From July 2017 to August 2022, a total of 56 patients entered the trial; 56 patients were evaluable for the primary endpoint. Median (m-) age was 29.5 years (range: 18 – 66), with 24 female and 32 male. Best overall response included 1/56 complete response (1.8%), 14/56 partial responses (25.0%), 36/56 stable disease (64.3%), and 3/56 (5.4%) progressive disease. RECIST ORR by BICR was 26.8% (95% CI, 15.8–40.3); m-DOR was 22.57 months (95%CI: 10.38-NE). The study data was collected close to 8 years for all patients. mPFS was 18.33 months (95% CI, 14.19–23.13), with 6- and 12-month progression-free rates of 88.77% (95% CI, 76.68–94.79) and 65.54% (95% CI, 50.42–77.06), respectively. mOS was 59.27 months (95% CI, 44.09–NE), with 6- and 12-month overall survival rates of 94.64% (95% CI, 84.30–98.24) and 90.81% (95% CI, 79.30–96.08), respectively. Overall, 27/56 (48.2%) patients experienced grade $\geq$3 treatment-related adverse events, most commonly diarrhea (50.0%), hypertension (44.6%), fatigue (37.5%), nausea (35.7%), and palmar-plantar erythrodysesthesia syndrome (30.4%); one patient (1.8%) had a grade 5 event (respiratory failure). **Conclusions:** Catequentinib hydrochloride demonstrated meaningful antitumor activity and durable responses in adults with advanced ASPS. Despite the ORR of 26.8% slightly below the predefined 31% threshold, disease control was prolonged, with a m-DOR exceeding 22 months. Favorable PFS and OS outcomes, together with a manageable safety profile, support its clinical benefit in this ultra-rare sarcoma. Clinical trial information: NCT03016819. Research Sponsor: None.

11503 Oral Abstract Session

Efficacy and safety of vebreltinib in advanced clear cell sarcoma (VEBrant): A multicenter, phase II study. First Author: Binghao Li, Department of Orthopaedics, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Background: Clear cell sarcoma (CCS) is an ultra rare cancer with no established standard systemic therapy of proven efficacy. The c-MET pathway plays an important role in CCS, with MET overexpression frequently observed. Targeted therapy by type Ia MET inhibitor crizotinib revealed a disease control rate (DCR) at 69.2% and objective response rate (ORR) at 3.8%. Vebreltinib is a highly selective type Ib MET inhibitor with verified efficacy in solid tumor harboring MET alterations, such as NSCLC with MET amplification or overexpression. This phase II study aimed to assess the efficacy and safety of Vebreltinib for advanced CCS. **Methods:** Patients (pts) with histopathologically confirmed, unresectable or metastatic CCS were enrolled (NCT07153887), regardless of prior therapy except for any MET inhibitors. Eligible pts received Vebreltinib (200 mg BID) until disease progression, intolerable toxicity, or death occurs. Prior PD1/PDL1 treatment for at least 4 months without tumor reduction are allowed to continue using the same PD1/PDL1 medicine after thorough evaluation by the investigator. Evaluation of tumor response was performed every 2 months. Primary endpoints was ORR per RECIST v1.1. Secondary endpoints included DCR, PFS, OS, 12m-OSR, DoR and treatment safety. MET expression by immunohistochemistry was collected when possible. A Simon's two-stage design was applied: if no responses were seen in the first 13 pts, the study would stop; otherwise, 14 additional pts would be enrolled (total N=27). **Results:** At data cutoff on January 23, 2026, 23 pts were enrolled. Median age was 29 years (range: 16–59), 47.8% were male, 91.3% had prior surgery, and 95.7% received prior systemic therapy. All had metastatic disease, primarily to lung (78.3%), lymph nodes (56.5%), and bone (30.4%). With median follow-up of 134 days and median treatment duration of 103 days, 17 pts were evaluable for response. ORR was 41.2% (7 partial responses) and DCR was 70.6% (7 PR, 5 stable disease), meeting the pre-specified threshold for stage I continuation. Median PFS was 4.14 months (95% CI: 2.3–NA); 6-month PFS rate was 42.8%. Median OS was not reached. Treatment-related adverse events (TRAEs) occurred in 87.0% of pts, mostly grade 1-2. Grade 3-4 TRAEs occurred in 21.7% (n=5; rash n=4, fever n=1). Notably, 4 pts discontinued due to grade 4 rash within 2 weeks of starting vebreltinib combined with immunotherapy. **Conclusions:** Vebreltinib demonstrated notable antitumor activity for advanced CCS, representing a marked improvement over existing therapeutic options. Attention should be paid to the risk of severe rash, particularly when combined with immunotherapy. Longer follow-up is required to further confirm the efficacy and safety. Clinical trial information: NCT07153887. Research Sponsor: Beijing Pearl Biotechnology Co., Ltd.

11504 Oral Abstract Session

The tetravalent death receptor 5 (DR5) agonist ozekibart (INBRX-109) in conventional chondrosarcoma (CS): Secondary efficacy endpoints from the randomized, registrational, phase 2 ChonDRAgon study. First Author: Hans Gelderblom, Department of Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands

Background: Clinical outcomes for unresectable/metastatic CS are poor. There are no approved therapies, and systemic treatment options are limited. Ozekibart (INBRX-109), a novel tetravalent DR5 agonist, was evaluated in ChonDRAgon (phase 2; NCT04950075), the largest randomized, placebo (PBO)-controlled trial in advanced conventional CS. ChonDRAgon met its primary endpoint: ozekibart significantly prolonged median progression free survival (PFS) vs PBO (5.52 vs 2.66 mo; stratified HR, 0.479; 95% CI, 0.335-0.684; $P<.0001$) (Jones et al. CTOS 2025). We present additional efficacy data. **Methods:** Eligible patients (pts) were ≥18 y with unresectable/metastatic conventional CS; those ≥65 y required a BMI <30 kg/m^2. Pts with liver conditions associated with increased risk of hepatotoxicity were excluded. Pts were randomized 2:1 to ozekibart 3 mg/kg IV Q3W or PBO and stratified by grade (2 vs 3), *IDH* mutation status, and prior systemic therapy (No vs Yes). Pts could cross over from PBO to open-label ozekibart upon progression. The primary endpoint was PFS per RECIST 1.1 assessed by real time central independent radiology review (CIRR) in the intention-to-treat population; inter-arm comparison used a stratified log-rank test. The study was powered to detect a HR of 0.571 (90% power; 1-sided family-wise α, 0.025). Secondary efficacy endpoints included overall survival (OS), overall response rate (ORR) per CIRR, quality of life (QOL; EORTC QLQ-C30 pain symptoms and physical functioning scales), duration of response (DOR), and disease control rate (DCR; response, stable disease ≥84 days, non–complete response/non–progressive disease). **Results:** Overall, 137 pts were randomized to ozekibart and 69 to PBO; median duration of follow-up was 10.2 and 9.0 mo at the primary analysis (data cutoff: Sep 30, 2025). Median age for ozekibart and PBO was 54.0 y (range, 20-82 y) and 50.0 y (19-91 y), respectively; 70.1% and 60.9% of pts were male. Most pts had grade 2 CS (ozekibart, 70.1%; PBO, 69.6%) and ≈40% received prior systemic therapy (42.3%; 40.6%). 18.2% of pts in the ozekibart arm and 4.3% in the PBO arm remain on treatment. Ozekibart demonstrated a manageable safety profile (Jones et al. CTOS 2025) and led to a significantly greater DCR than PBO (54.0% vs 27.5%; $P=.0005$). ORR was 5.8% (8/137; all partial responses) with ozekibart and 0 with PBO ($P=.0433$); median DOR was 11.1 mo. OS data were immature. Ozekibart significantly delayed QOL deterioration vs PBO, in both pain (median time to deterioration, 2.76 vs 1.41 mo; HR, 0.605; $P=.0033$) and physical functioning (2.56 vs 1.41 mo; HR, 0.561; $P=.0007$). **Conclusions:** In addition to a PFS benefit, ozekibart significantly improved DCR and delayed QOL deterioration vs PBO in advanced CS. Ozekibart has the potential to become the first standard of care for a population with high unmet need. Clinical trial information: NCT04950075. Research Sponsor: Inhibrx Biosciences, Inc.

11505 Oral Abstract Session

Pooled analyses of clinical outcomes with afamitresgene autoleucel (afami-cel) in metastatic synovial sarcoma. First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Afamitresgene autoleucel (afami-cel) is a melanoma-associated antigen A4 (MAGEA4)-directed genetically modified autologous T cell immunotherapy consisting of CD4 and CD8 positive T cells transduced with a self-inactivating lentiviral vector (LV) expressing an affinity-enhanced T cell receptor (TCR) specific for the human MAGE-A4. Here we report the pooled results of afami-cel in phase 1 and phase 2 trials in patients (pts) with advanced (unresectable/metastatic) synovial sarcoma (SyS). **Methods:** Pts who were HLA-A*02 positive with previously treated, advanced SyS positive for MAGE-A4 received afami-cel after lymphodepleting chemotherapy containing fludarabine and cyclophosphamide. The pooled analyses evaluated overall response rate (ORR) per RECIST v1.1 by investigator review, duration of response (DoR), ORR in sub-populations, overall survival (OS), safety and pharmacokinetics. **Results:** As of May 2025, 153 pts with advanced SyS received afami-cel (1.00 –9.99$\times10^9$ MAGE-A4 TCR positive T cells). The median age was 40 years (range: 13–76 years), 54% of pts were male, and 86% of pts were white. The median MAGE-A4 expression by H-score was 256.0 (range: 60–300). All pts received prior anthracycline and/or ifosfamide therapy and received a median of 2 prior lines of therapy (range: 1–12). ORR by investigator review was 43.8% (95% CI 35.8, 52.0). Responses were observed across all subgroups, including pediatric SyS pts. The median DoR was 7.1 months (95% CI 4.7, 10.6) and ranged from 1 to 58+ months. Median OS was 18.7 months (95% CI: 14.1, 22.5) with 44% of pts censored at the data cut-off. The 12-month or longer and 24-month or longer OS probabilities were 64.4% and 40.5%, respectively. Among the 67 pts who had a RECIST response, the median OS was 37.5 months (95% CI 26.3, 50.5). The most common any-grade non-laboratory TEAEs (≥20% of pts) were cytokine release syndrome (CRS) (73.2%), nausea (64.1%), fatigue (45.8%), pyrexia (33.3%), vomiting (29.4%), constipation (28.1%), diarrhea (27.1%), headache (26.8%), and cough (20.9%). The most common Grade ≥3 laboratory TEAEs (≥20% of pts) were lymphopenia, neutropenia, leukopenia, and anemia. Afami-cel persisted long-term, including >3 years. **Conclusions:** To the best of our knowledge, this is the largest dataset of T-cell therapy treated pts with advanced SyS. The magnitude of ORR supported by DOR demonstrated with afami-cel treatment is considered clinically meaningful in this rare pt population with a poor prognosis and limited effective therapies. CRS and cytopenias were common and manageable. Pts with advanced SyS treated with afami-cel had encouraging survival, especially those pts with a RECIST response. Clinical trial information: NCT04044768, NCT03132922 Research Sponsor: Adaptimmune LLC; USWM CT, LLC.

11506 Oral Abstract Session

RINGSIDE: A phase 3 randomized, placebo-controlled trial of varegacestat for treatment of progressing desmoid tumors. First Author: Mrinal M. Gounder, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Desmoid tumors (DT) are rare, locally aggressive tumors with few effective treatments. Varegacestat (VAR) is an investigational, once daily, oral gamma secretase inhibitor that previously showed antitumor activity in pts with DT in the RINGSIDE Phase 2 study. **Methods:** RINGSIDE Phase 3 was a double-blind, placebo (PBO)-controlled study in adults with progressing DT per RECIST v1.1 (NCT04871282). 156 pts were randomized 1:1 to once daily oral VAR 1.2 mg (n=79) or PBO (n=77). Imaging-based tumor response was assessed per RECIST v1.1 by blinded independent central review. The primary endpoint was progression-free survival (PFS). Alpha-controlled secondary endpoints were confirmed objective response rate (ORR), change in tumor volume (TV) at Week 24, and change in patient-reported worst pain intensity (WPI) at Week 12. **Results:** Demographics and disease characteristics were balanced between treatment arms. As of Oct 7, 2025, median duration of exposure was 20.3 months (range 0.8 – 34.6) for VAR and 11.1 months (range 0.2 – 34.6) for PBO. VAR demonstrated significantly better PFS compared with PBO (hazard ratio [HR]: 0.16 [95% CI: 0.07, 0.38; $P<0.0001$]). PFS consistently favored VAR in all subgroups analyzed. ORR was significantly better with VAR vs PBO (55.7% vs 9.1%; $P<0.0001$), with 3 CRs in the VAR arm and 1 CR in the PBO arm. Median duration of response was not reached in either arm. All alpha-controlled secondary endpoints demonstrated statistically and clinically significant superiority for VAR compared with PBO (Table). Overall, 95% of adverse events (AEs) were Grade 1-2 and there were no Grade 5 AEs. Grade 3/4 AEs were reported in 57% of VAR pts and 17% of PBO pts. AEs led to dose reduction in 63 (80%) VAR pts and 7 (9%) PBO pts; 16 (20%) VAR pts and 5 (7%) PBO pts discontinued due to AEs. In the VAR arm, the most frequently reported AEs were diarrhea (82%), fatigue (44%), and rash (43%). Ovarian toxicity occurred in 20/36 (56%) premenopausal women on VAR, resolved in 11/20 (55%), and did not lead to dose interruption or drug withdrawal. **Conclusions:** VAR demonstrated statistically significant and clinically meaningful antitumor activity and pain relief, achieving the highest ORR reported in a Phase 3 trial of systemic DT therapy, with no new safety signals. Clinical trial information: NCT04871282. Research Sponsor: Immunome Inc.

RINGSIDE phase 3 trial outcomes.

	VAR (n=79)	PBO (n=77)	HR (95% CI) or Difference; P value
Median PFS (95% CI) - radiographic, months	NE (NE, NE)	24.9 (13.8, NE)	0.16 (0.07, 0.38); P<0.0001
Confirmed ORR, n (%)	44 (55.7)	7 (9.1)	P<0.0001
TV change (cm^3) at Week 24, LS mean (SE)	-109.6 (40.64)	122.8 (42.72)	-232.4 (57.39); P<0.0001
WPI (pain) change at Week 12, LS mean (SE)	-2.24 (0.27)	0.18 (0.27)	-2.42 (0.37); P<0.0001
Median best % change in TV*	-83.4	11.3	*
1-year PFS, % (95% CI)*	94.2 (85.3, 97.8)	65.6 (52.3, 76.0)	*
2-year PFS, % (95% CI)*	88.9 (77.9, 94.6)	56.7 (42.6, 68.6)	*

LS, least square; SE, standard error.
*Not alpha-controlled endpoint.

11507 Oral Abstract Session

Trabectedin with concomitant radiotherapy in resectable retroperitoneal L-sarcoma: A multicenter, prospective, phase I/II trial—A collaborative study by the Spanish (GEIS), Italian (ISG), and French (FSG) groups. First Author: Rosa Maria Alvarez Alvarez, Hospital Universitario Gregorio Marañon, Madrid, Spain

Background: Liposarcoma (LPS) and leiomyosarcoma (LMS) account for most retroperitoneal sarcomas. Despite complete resection, local recurrence remains high, particularly in dedifferentiated LPS (DDLPS). While preoperative radiotherapy (RT) may improve local control, optimal multimodal strategies are undefined. Trabectedin (T) is active in L-sarcomas, with emerging clinical evidence supporting its radiosensitizing properties and its efficacy in combination with RT. A preoperative short course of T with concurrent low-dose RT was investigated in a multicenter, phase I/II trial in patients (pts) with centrally confirmed resectable retroperitoneal L-sarcoma (grade 2-3 DDLPS with >30% dedifferentiated component or grade 2-3 LMS). **Methods:** Pts received 3 cycles of T in combination with RT (45 Gy in 25 x 1.8 Gy). Phase I followed a 3+3 dose-escalation design with T dose levels 1.5 (0), 1.3 (-1), and 1.1mg/m^2 (-2). Dose-limiting toxicity was any grade ≥3 adverse events (excluding neutropenia <5 days, elevated transaminases without treatment delay, and nausea/vomiting due to inadequate prophylaxis). Phase I primary endpoint was safety and the determination of the recommended Phase II dose (RP2D). Phase II primary endpoint was centrally assessed Choi response. Secondary endpoints included relapse-free survival (RFS; from surgery), progression-free survival (PFS; from first T cycle), overall survival (OS), RECIST and pathological response, and treatment-related toxicity according to CTCAE v5.0. **Results:** From February 2019 to January 2025, 56 pts, 6 in phase I and 50 in phase II, (M/F: 31/25) with a median age of 61 years (range: 19-75) and a median tumor size of 17 cm (range: 12-30) were enrolled. 51 pts had grade 2-3 DDLPS, and 5 pts had grade 2-3 LMS. A T dose of 1.5 mg/m^2 was the RP2D. Per-protocol therapy was completed in 47 pts (84%); discontinuations were due to local progression (N=1), toxicity (N=6), or refusal (N=2). The most common grade 3/4 toxicities were neutropenia (21.4%), leukopenia (8.9%), fatigue (8.9%), and increased ALT, febrile neutropenia, and thrombocytopenia (7.1% each). 51 pts (91%) underwent surgery, with 96% achieving complete resection. According to the central review, Choi (N=45) showed 12 PR (26.7%) and 33 SD (73.3%). RECIST 1.1 (N=53): PR 1 (2%), SD 51 (96%), PD 1 (2%). At a median follow-up of 40 months (95% CI, 36-43), from the start of T (N=53), 3-year PFS was 70% (95 CI, 56-83) and 3-year OS was 85% (95 CI, 75-95). **Conclusions:** Preoperative concurrent T and RT was feasible and safe for resectable retroperitoneal L-sarcomas, yielding density responses in over 25% of pts and promising survival outcomes. A phase III trial is warranted to compare this regimen against RT alone. Clinical trial information: NCT02275286. Research Sponsor: Pharmamar.

11508 Oral Abstract Session

Final results of a randomized phase II trial of second-line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin, and pazopanib: 2ND-STEP study, JCOG1802. First Author: Makoto Endo, Department of Orthopaedic Surgery, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Background: The optimal second-line treatment for advanced soft tissue sarcomas (STS) after doxorubicin therapy remains unclear. This trial aimed to identify the most promising agent among trabectedin, eribulin, and pazopanib for subsequent phase III comparison against gemcitabine plus docetaxel (GD), which has traditionally been considered a standard treatment. We previously reported the results of the primary analysis at 6 months after accrual completion. Here, we present the final analysis results with an additional year of follow-up. **Methods:** This multicenter, randomized, phase II selection design trial enrolled patients with unresectable or metastatic STS who were refractory to doxorubicin-based chemotherapy. Participants were randomized to receive trabectedin, eribulin, or pazopanib. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), disease control rate (DCR), objective response rate (ORR), and safety. **Results:** From December 2019 to March 2023, 120 patients with advanced STS were enrolled (31 leiomyosarcomas, 26 liposarcomas, 18 translocation-related sarcomas, and 45 other types). The median PFS was 2.9 months (95% CI, 1.3-5.3) for trabectedin, 2.2 months (1.5-3.8) for eribulin, and 3.8 months (2.3-5.2) for pazopanib. The hazard ratios for eribulin and pazopanib compared to trabectedin were 1.22 (0.77-1.94) and 0.99 (0.63-1.56), respectively. When examining the PFS curves for each treatment arm, the three arms appeared to exhibit nearly identical curves; however, the PFS hazard ratio indicated that pazopanib showed the best result. The median OS was 14.7 months (10.8-18.5) for trabectedin, 13.3 months (7.6-20.1) for eribulin, and 15.7 months (9.7-18.0) for pazopanib. The DCR was 50.0% (32.4-67.6) for trabectedin, 37.1% (21.5-55.1) for eribulin, and 64.9% (47.5-79.8) for pazopanib. The ORR was 17.6% (6.8-34.5) for trabectedin, 5.7% (0.7-19.1) for eribulin, and 8.1% (1.7-21.9) for pazopanib. A histological subtype–specific subgroup analysis, demonstrated that the PFS/OS for each arm in liposarcoma were as follows: trabectedin, 3.1 months (95% CI, 1.1–7.2) / 12.9 months (3.7–36.5); eribulin, 3.8 months (1.1–6.8) / 13.3 months (4.3–20.1); and pazopanib, 5.2 months (2.0–10.2) / 18.0 months (4.1–NE). No previously unrecognized adverse events related to the investigational drugs were observed, and no treatment-related deaths occurred. **Conclusions:** Consistent with the primary analysis, pazopanib generally showed favorable PFS, OS, and DCR among the three agents. Based on these results, pazopanib was identified as the most appropriate candidate to be compared with GD in a phase III trial, which is currently being planned. Clinical trial information: jRCTs031190152. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

11509 Clinical Science Symposium

Spatial RNA–protein profiling of antibody–drug conjugate (ADC) targets in leiomyosarcoma (LMS). First Author: Carlos Torrado, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: LMS remains a therapeutically challenging sarcoma with limited targeted options. Although ADCs are a promising strategy, none are FDA approved for sarcoma. Prior studies relying on bulk RNA or single-marker immunohistochemistry fail to capture spatial localization, co-expression, and intratumoral heterogeneity. **Methods:** LMS tissue microarrays were profiled using GeoMx DSP to generate spatial RNA and protein expression of ADC targets across multiple regions of interest (ROIs) per tumor. Cases were classified as soft-tissue (ST-LMS; n=23 patients; 94 ROIs) or uterine LMS (U-LMS; n=32 patients; 92 ROIs). A prespecified panel of 35 clinically relevant ADC targets was interrogated. Expression values were normalized to housekeeping genes with group-level scaling. Unsupervised clustering grouped ROIs by spatial expression. Intratumoral and inter-tumoral heterogeneity was quantified using coefficients of variance (CV) across ROIs. RNA–protein concordance and dual target co-expression were quantified using Spearman correlation (ρ). Survival differences between high- and low-expression groups, dichotomized by the median, were evaluated using Kaplan–Meier analysis. **Results:** Of the 35 ADC targets interrogated, 33 were evaluable at the RNA level and 10 at the protein level. Spatial profiling identified four distinct expression clusters. At the RNA level, F3, AXL, and PTK7 showed the highest expression, whereas CDH11, CD99, and ITGA11 exhibited lower expression. At the protein level, Tissue Factor, AXL, and CD70 showed the highest expression, while HER2, and CD99 were lower. Most ADC targets exhibited positive $\log_{10}$ (CV) values, indicating substantial spatial variability. Across most targets, U-LMS showed greater intratumoral and intertumoral heterogeneity than ST-LMS. RNA–protein concordance was greatest for CD99, CD47, and Fibronectin/EDB ($\rho \approx 0.44–0.69$) and minimal for PDGFRA, AXL, ERBB2, EGFR, and MET ($\rho \approx$-0.15-0.19). RNA co-expression identified seven significant pairs in ST-LMS (e.g., ROR2–FAP, ρ=0.54) and eighteen in U-LMS, including MRC2–CD248 (ρ=0.73). Dual protein co-expression revealed a strong ERBB2–EGFR correlation in both ST and U-LMS ($\rho \approx 0.79–0.81$), with moderate correlations of these two ADC targets to PDGFRA, AXL, and Tissue Factor ($\rho \approx 0.53–0.70$). High expression levels CD47 and AXL were associated with improved survival in ST-LMS (CD47 HR = 0.76, 95% CI 0.08–0.88, p = 0.021; AXL HR = 0.67, 95% CI 0.07–0.72, p = 0.0067). **Conclusions:** This study provides the first spatially resolved RNA–protein map of ADC targets in LMS, revealing differential expression, spatial heterogeneity, variable RNA–protein concordance, dual co-expression patterns, and survival associations. These findings establish a foundation for rational ADC development, biomarker-driven patient stratification, and dual ADC combination strategies in LMS. Research Sponsor: None.

11510 Clinical Science Symposium

Phase 1/2 study of YL201, an anti-B7H3 antibody–drug conjugate (ADC), in patients with relapsed or refractory (R/R) Ewing sarcoma and chondrosarcoma. First Author: Lu Xie, Musculoskeletal Tumor Center, Peking University People's Hospital, Beijing, China

Background: The prognosis for R/R sarcoma remains dismal with limited effective treatment options. YL201 is a B7H3-targeting ADC with promising activity in multiple advanced solid tumors. Here, we report the safety and preliminary efficacy of YL201 monotherapy in patients with Ewing sarcoma (EWS) and chondrosarcoma (CHS) from a phase 1/2 study. **Methods:** Patients with histologically confirmed sarcoma who had an ECOG PS of 0 or 1 and progressed on $\geq$1 prior line of systemic therapies were enrolled and treated with YL201 intravenously Q3W at 2.0 mg/kg or 2.4 mg/kg until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Thirty-two patients with sarcoma were enrolled, including EWS (n=20), CHS (n=10), osteosarcoma (n=1), and soft tissue sarcoma (n=1). The overall population had a median age of 34.0 years (range: 19–69), with 81.3% male and 46.9% having an ECOG PS of 1. Patients had a median of 1 prior line of therapy (range: 1–6), with 96.9% having received prior chemotherapy and 37.5% having received targeted therapy. As of December 12, 2025, the median follow-up was 11.4 months (95% CI: 9.1–13.2). In EWS sub-cohort, the confirmed ORR was 50.0% (95% CI: 27.2–72.8) with a median DoR of 6.5 months (95% CI: 2.8–NR), and DCR was 95.0% (95% CI: 75.1–99.9). Median PFS was 5.5 months (95% CI: 2.8–7.9), while OS data remained immature. In CHS sub-cohort, antitumor activity was observed with a confirmed ORR of 10.0% (95% CI: 0.3–44.5) and a DCR of 90.0% (95% CI: 55.5–99.7). The median PFS was 11.7 months (95% CI: 3.9–NR), and median OS was not reached. Membrane B7H3 expression was detected by immunohistochemistry in 42.1% of EWS and 44.4% of CHS patients, whereas the remainder exhibited no membrane B7H3 expression. However, no association was observed between tumor response and B7H3 expression level in either sub-cohort. Among all 32 patients enrolled, the treatment-related adverse events (TRAEs) of any grade and grade $\geq$3 occurred in 100.0% and 34.4% of patients, respectively. The most common grade $\geq$3 TRAEs included lymphopenia (15.6%), neutropenia (9.4%), thrombocytopenia (9.4%), leukopenia (6.3%), and anemia (6.3%). No interstitial lung disease or pneumonitis was observed. The rate of treatment discontinuation due to TRAEs was low at 3.1%, and no treatment-related deaths were reported. **Conclusions:** YL201 showed promising antitumor activity and manageable safety profile in patients with R/R EWS and CHS, with a particularly encouraging ORR in EWS. Given the high incidence of Ewing sarcoma in adolescents, these findings support further evaluation of YL201 in pediatric populations. Clinical trial information: NCT06057922. Research Sponsor: MediLink Therapeutics.

11511 Clinical Science Symposium

Overall survival analysis of a heavily pretreated population of patients with bone sarcomas treated with mecbotamab vedotin, a conditionally binding ADC targeting AXL. First Author: Anthony Paul Conley, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with metastatic bone sarcomas continue to lack effective therapies. AXL, a cell-surface receptor tyrosine kinase, is highly expressed in bone sarcoma subtypes and has been shown to drive increased metastasis, resistance to chemotherapy, and poor outcomes. Mecbotamab vedotin (Mec-V, BA3011, Conditionally Active Biologic CAB-AXL-ADC) is designed to reduce off-tumor toxicity and improve pharmacokinetics by conditionally binding to AXL under low-pH conditions (pH$<$6.7) of the tumor microenvironment. **Methods:** A phase 1/2 open-label study evaluated Mec-V among adult and adolescent patients with AXL-expressing locally advanced, unresectable, or metastatic osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma with measurable disease by RECIST v1.1. Patients received Mec-V monotherapy intravenously 1.8 mg/kg every 2 weeks (Q2W). **Results:** This report focuses upon the long term follow up among 33 patients treated with Mec-V with osteosarcoma (n=13), Ewing (n=9), chondrosarcoma (n=8) or chordoma (n=3). Patients received a median of 2 prior lines of treatment. Most related treatment-related adverse events (TEAE) in patients with bone sarcomas were low grade (64%) and reversible; the most common related grade 3/4 TEAE of special interest was neutropenia (18%). No grade 5 TEAE were observed. As of March 25, 2025, disease control rate (DCR) was 100% among patients with chondrosarcoma and chordoma. In patients with osteosarcoma and Ewing sarcoma, DCR was 50% with 3 confirmed responses (14%; osteosarcoma n=2, Ewing n=1). The median OS with Mec-V for all bone sarcoma patients was 17.6 months. Observed median OS by tumor type in months: osteosarcoma (11.9 [95% CI: 3.2-Not Estimable (NE)]), Ewing sarcoma (19.4 [95% CI: 5.2–NE]), chondrosarcoma (NE [95% CI: 16.3-NE]), and chordoma (15.1 [95% CI: 7.2-NE]). **Conclusions:** Patients with treatment refractory bone sarcomas treated with Mec-V monotherapy achieved a median OS of 17.6 months which compares favorably to reported outcomes with other therapies including combination therapies. Mec-V monotherapy holds considerable promise for these high unmet need indications with potential increased benefit when used in combination. Clinical trial information: NCT03425279. Research Sponsor: BioAtla, Inc.

11512 Rapid Oral Abstract Session

Maintenance treatment with toripalimab and anlotinib after anthracycline-based chemotherapy in patients with advanced soft tissue sarcoma (TORANS): A single-arm, phase 2 trial. First Author: Yaotiao Deng, Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: To date, there is no established maintenance strategy for patients with advanced soft tissue sarcoma (STS) who achieve disease control following first-line anthracycline-based chemotherapy. Maintenance therapy is therefore under active investigation in this setting. This study assessed the efficacy and safety of toripalimab (a humanized anti-PD-1 monoclonal antibody) combined with anlotinib (a multitargeted tyrosine kinase inhibitor) as a maintenance treatment. **Methods:** Patients with advanced STS who achieved stable disease or a partial response after at least four cycles of first-line anthracycline-based chemotherapy were enrolled in this single-arm, phase 2 trial and received maintenance therapy with toripalimab (240 mg intravenously on day 1) and anlotinib (12 mg orally once daily on days 1–14) in 21-day cycles. The primary endpoint was the 24-week progression-free survival rate ($PFSR_{24w}$), defined as the proportion of patients who remained free from disease progression through 24 weeks after initiation of maintenance therapy. Secondary endpoints included median progression-free survival (PFS), median overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety. **Results:** Between April 2022 and May 2025, a total of 52 patients were enrolled; one patient diagnosed with pathologically confirmed metaplastic carcinoma was excluded. As of December 26, 2025, the median follow-up duration was 20 months. The $PFSR_{24w}$ was 74.5%. The median PFS was 12 months, and the median OS was not reached at the time of data cutoff. Durable partial responses were observed in patients with dedifferentiated liposarcoma (5/14), leiomyosarcoma (2/11), epithelioid sarcoma (2/4), myxofibrosarcoma (1/3), synovial sarcoma (1/3), and pleomorphic rhabdomyosarcoma (1/1), resulting in an ORR of 23.5%. The most common grade 3–4 adverse events were hypertension (n = 10), increased gamma-glutamyltransferase (n = 5), hand-foot skin reaction (n = 3), and hypertriglyceridemia (n = 3). No new safety signals emerged during the course of the trial. **Conclusions:** Toripalimab in combination with anlotinib as maintenance therapy demonstrated promising efficacy and a manageable safety profile in patients with advanced STS following first-line anthracycline-based chemotherapy. Clinical trial information: ChiCTR2100054901. Research Sponsor: The 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University (2021HXFH019); 2021HXFH019.

11513 Rapid Oral Abstract Session

Camrelizumab combined with liposomal doxorubicin and dacarbazine as first-line therapy for advanced, recurrent, and metastatic undifferentiated pleomorphic sarcoma: A phase II study. First Author: Tian Gao, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Bone and Soft Tissue Tumor, Peking University Cancer Hospital, Beijing, China

Background: This phase II study aims to evaluate the efficacy and safety of camrelizumab combined with liposomal doxorubicin and dacarbazine in patients with advanced, recurrent and metastatic undifferentiated pleomorphic sarcoma (UPS). **Methods:** Patients with histologically confirmed advanced, recurrent and metastatic UPS, treatment-naïve for advanced disease, and at least one measurable lesion per RECIST v1.1 were eligible. Camrelizumab was administered in combination with liposomal doxorubicin and dacarbazine for up to six cycles, followed by camrelizumab maintenance therapy. The primary endpoint was investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), overall survival (OS), duration of response (DoR), and safety. **Results:** Between October 2022 and August 2025, 28 pts were enrolled and received study treatment, of whom 24 were evaluable for efficacy analyses. Partial response occurred in 7 patients, with no complete responses observed, resulting an ORR of 29.2% (7/24). Stable disease was achieved in 14 patients, yielding a disease control rate of 87.5% (21/24). Two patients had progressive disease and four patients were not evaluable due to the absence of post-baseline tumor assessments. With a median follow-up of 11.9 months (data cutoff: December 29, 2025), 16 PFS events and 7 death events had occurred. The median PFS was 8.4 months (95% CI, 6.2-NA), while median OS had not been reached. Responses appeared durable, with a median DoR of 4.5 months among responders (n=7), though early progression was observed in some patients. An exploratory analysis revealed PD-L1-positive patients (CPS $\geq$1) showed a trend toward a higher ORR than PD-L1-negative patients (42.9% [3/7] vs 21.4% [3/14]). The most common treatment-related adverse events of any grade were neutropenia (35.7%), leukopenia (28.6%), rash (28.6%), and ALT elevation (25.0%). Grade $\geq$3 adverse events were infrequent, mainly ALT and AST elevations (both 7.1%). Immune-related adverse events included rash (28.6%), pneumonitis (7.1%), and hepatitis (7.1%), leading to treatment discontinuation in two patients. **Conclusions:** Camrelizumab combined with liposomal doxorubicin and dacarbazine demonstrated promising antitumor activity with durable responses and manageable safety as first-line therapy for advanced, recurrent and metastatic UPS. Exploratory analyses suggested that patients with higher PD-L1 expression may derive greater benefit from this regimen, warranting further investigation in larger, controlled studies. Clinical trial information: ChiCTR2100049974. Research Sponsor: None.

11514 Rapid Oral Abstract Session

PEMBROCABOSARC: A phase II trial combining pembrolizumab and cabozantinib in patients with advanced undifferentiated pleomorphic sarcoma. First Author: Maud Toulmonde, Institut Bergonié, Bordeaux, France

Background: There is a growing rationale for combining immunotherapy and VEGF inhibitors in sarcoma. We report results of an open-label multicentre phase 2 study assessing the anti-PD-1 antibody pembrolizumab (pembro) in combination with cabozantinib (cabo) in patients (pts) with advanced undifferenciated pleomorphic sarcoma (UPS). **Methods:** Pts aged $>$ 18 years old, with advanced or metastatic UPS who received no more than three previous lines and no previous history of exposure to anti PD1/L1 or cabozantinib were included to receive cabo 40 mg daily and pembro 200 mg IV q21 days. The primary endpoint was 6-month non-progression (NP) per RECIST v1.1. This trial used a 2-stage optimal Simon's design needing 8 NP at 6 months observed among 29 evaluable pts to be considered positive. **Results:** 33 pts were enrolled from December 27th, 2022 to September 25th, 2024, 32 were assessable for safety and 31 for efficacy. Overall, 13 (40.6%) pts had at least one dose reduction of cabo and 5 (15.6%) stopped treatment for a drug-related adverse event (3 related to cabo, 1 to pembro and 1 to both drugs). The most frequent adverse events related to treatment were asthenia, diarrhea, palmo-plantar syndrom and aminotransferase increase. There was no new emerging toxicity with the combination. One grade 5 pneumothorax was considered possibly related to cabozantinib by the investigator. At a median follow up of 13.8 months [95% CI: 12 – 17.2], 8 pts out of the first 29 evaluable pts were NP at 6 months (27.6% [95% CI: 12.7%-47.2%]). Among the efficacy population, 14 pts experienced tumor shrinkage resulting in a partial response (PR) in 8 (25.8%). Responses were long-lasting. The median overall survival was not reached. **Conclusions:** Combining VEGF and PD-1 inhibition showed favorable activity in unselected UPS compared to available evidence for each treatment in monotherapy. Correlative studies of immune biomarkers on paired tumor biopsies and plasma samples done at baseline and on-treatment are on-going to decipher biomarkers of response and resistance to treatment. Clinical trial information: NCT05182164. Research Sponsor: IPSEN; MSD.

Number of patients with at least one Grade 3 to 5 adverse event related to treatment.

Adverse Event	Grade 3	Grade 5
Diarrhea	2 (6.2%)	0
Palmo-plantar syndrom	2 (6.2%)	0
Aminotransferase increase	2 (6.2%)	0
Hypertension	1 (3.1%)	0
Headache	1 (3.1%)	0
Dysgeusia	1 (3.1%)	0
Skin rash	1 (3.1%)	0
Pyoderma	1 (3.1%)	0
Left ventricular dysfunction	1 (3.1%)	0
Pneumothorax	1 (3.1%)	1 (3.1%)

11515 Rapid Oral Abstract Session

Toxicity and efficacy characterization of doxorubicin and trabectedin association versus doxorubicin alone in patients over 70 years with leiomyosarcoma: Analysis from LMS02 and LMS04 studies. First Author: Imen Ben-Ammar, Institut Gustave Roussy, Villejuif, France

Background: LMS02 (phase II) and LMS04 (randomized phase III) trials demonstrated the superiority of a combination regimen with Doxorubicin (Doxo, 60 mg/m²) and Trabectedin (Trab, 1.1 mg/m²) D1-D21 (Doxo+Trab) versus Doxorubicin (Doxo, 75 mg/m²) alone in the first line setting for metastatic or unresectable leiomyosarcomas with median Overall Survival (mOS) of 33 months (95% CI 26-48 months) *versus* 24 months (95% CI 19-31 months) (HR for death 0.65; 95% CI 0.44-0.95), respectively. The incidence of adverse events (AE), notably Grade 3-4 AE, was higher with the combination regimen compared to Doxo alone (97% versus 56%, p$<$0.001, respectively), although these were manageable. As more than one-third of soft-tissue sarcomas occur in patients (pts) over 65-year-old (yo), a better understanding of the risks and benefits of Doxo+Trab association in elderly patients is needed. **Methods:** Data from case report forms of pts aged $\geq$70 years enrolled in LMS02 and LMS04 were retrospectively analyzed to assess efficacy and toxicity of Doxo+Trab versus Doxo monotherapy. **Results:** 44 pts of 70 yo and older were included: 13 pts in LMS02 (Doxo+Trab 6 cycles, without maintenance), 15 pts in LMS04 arm B (Doxo+Trab : 6 cycles, followed by Trab maintenance for up to 17 cycles), and 16 pts in LMS04 arm A (Doxo monotherapy). The mean age was 74 yo (range 70-86), all pts had ECOG PS 0-1, and lung was the most frequent metastatic site. Median OS was 24 months with Doxo, 39 months with Doxo + Trab, and 48.9 months with Doxo + Trab-Trab (LMS04 cohort). Median PFS was 6.7 months with Doxo, 13.2 months in the Doxo + Trab arm, and 20.5 months with Doxo + Trab - Trab Toxicity analysis included patients from LMS02 and LMS04 as follows: 28 pts treated with Doxo+Trab (from both LMS02 and LMS04) and 16 pts treated with Doxo monotherapy in LMS04. The median number of received cycles was 6 in both groups. Twenty-two pts (80%) treated with the combination experienced Grade $\geq$3 AE, including 13 pts with Grade 4 events. These toxicities were predominantly hematologic; with 12% febrile neutropenia and 9% asthenia. In the monotherapy arm, ten pts (63%) had Grade $\geq$3 AE, including 5 pts with Grade 4 events, with asthenia (17%) and febrile neutropenia (17%) being the most frequent. The lack of statistical significance (p=0.2) should be interpreted cautiously due to limited sample size. **Conclusions:** For pts over 70 yo, the efficacy of the combination Doxo+Trab followed by trabectedin maintenance in advanced LMS in the first line setting, as measured by PFS and OS, did not differ from that in younger patients. Toxicity analysis suggests that age alone is not a limiting factor for this combination. Therefore, age-related frailty should not prevent patients from receiving a potentially life-prolonging treatment. A global geriatric evaluation and active supportive care may make treatment safer. Research Sponsor: None.

11516 Rapid Oral Abstract Session

Phase 1 study results with PRAME-directed T-cell receptor (TCR) T-cell therapies in synovial sarcoma. First Author: Dejka M. Araujo, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Patients with advanced or recurrent synovial sarcoma (SS) have limited treatment options that can provide sustained disease control beyond 6 mos. SS expresses multiple cancer testis antigens, including PRAME, which is expressed in >50 cancers. Anzutresgene autoleucel (anzu-cel, IMA203) is a PRAME-directed TCR T-cell therapy engineered to recognize an intracellular PRAME-derived peptide presented by HLA and initiate a potent and specific antitumor response. IMA203CD8 is a TCR T-cell therapy that additionally engineers a CD8 co-receptor to allow both CD4+ and CD8+ T cells to detect and destroy PRAME-expressing tumor cells that evade conventional therapeutic approaches. Here we present phase 1 results for the subset of pts with SS from IMA203-101 treated with anzu-cel or IMA203CD8 (hereafter TCR T). **Methods:** Pts were ≥18 y, HLA-A*02:01+, PRAME+, with R/R solid tumors, measurable disease (RECIST 1.1), ECOG PS 0-1, and no remaining SOC treatment options. Following leukapheresis and TCR T manufacture, pts underwent lymphodepletion (LD) with Cy (500 mg/m^2 × 4 d) and Flu (30 mg/m^2 × 4 d), followed by TCR T infusion +/- low-dose SUBQ IL-2. **Results:** As of Oct 27, 2025, 21 pts with SS were treated with anzu-cel (n=9) or IMA203CD8 (n=12). The most common TEAEs were LD-related cytopenias (100%). Cytokine release syndrome occurred in 18 pts (86%; G1: 38%, G2: 38%, G3: 10%). One event of G1 immune effector cell–associated neurotoxicity occurred (5%). Twenty pts were evaluable for efficacy and received a low median dose of 1.51 x 10^9 total TCR T cells (range: 0.35-9.36 x 10^9). These pts had a median sum of target lesions at baseline of 10.22 cm (range: 1.24-41.1 cm) and received a median of 2.5 prior lines of therapy (range: 1-5). At baseline, 65% had ≥2 previous lines of systemic therapy and 75% received prior radiotherapy. The confirmed objective response rate (cORR), including all pts evaluable for efficacy across escalating doses, was 50% (10/20), including 1 confirmed CR (8%) with IMA203CD8 at a dose of 2.05 x 10^9 total TCR T cells. Median tumor reduction for pts with confirmed objective response was -63.4%. Median duration of response at these escalating dose levels was 12.7 mo (mFU: 23 mo) with 5 responses lasting for ≥12 mo including 2 ongoing PRs at 27 and 23 mo. Median overall survival was 18 mo. Results include 1 pt who received 3 sequential TCR T-cell therapies: the MAGE-A4-targeted afamitresgene-autoleucel (BOR: SD; PFS: 21.4 mos), PRAME-targeted anzu-cel (BOR: cPR; PFS: 24.4 mo), and IMA203CD8 (BOR: cPR; PFS ongoing at 24.4 mo). **Conclusions:** PRAME-directed TCR T-cell therapies exhibited a safety profile consistent with previous observations, and despite low doses, promising antitumor activity with durable responses that deepened over time in pts with SS. These results warrant further investigation. Clinical trial information: NCT03686124. Research Sponsor: None.

11517 Rapid Oral Abstract Session

Longitudinal plasma and CSF ctDNA profiling as used to define therapeutic landmarks and compartmentalized clonal evolution in rhabdomyosarcoma. First Author: Yizhuo Zhang, Department of Pediatric Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

Background: Current risk stratification in rhabdomyosarcoma (RMS) relies on static pretreatment variables, which fail to capture dynamic tumor evolution and molecular residual disease under therapeutic pressure. Although liquid biopsy offers a non-invasive solution, clinical implementation has been constrained by a reliance on retrospective datasets and the lack of prospectively validated therapeutic landmarks or compartmentalized monitoring strategies. **Methods:** We conducted the largest multi-center, prospective liquid biopsy study to date, enrolling 143 treatment-naïve RMS patients (Aug 2020–Feb 2025; 91.6% intermediate/high-risk). We utilized ultra-deep (>5,000×) sequencing (506-gene panel) on matched tumor, longitudinal plasma (n=292), and cerebrospinal fluid (CSF) from patients with parameningeal or central nervous system (CNS) metastatic disease. Critically, paired tissue and plasma were collected at disease progression (PD) to map evolutionary trajectories. Genomic alterations were correlated with progression-free survival (PFS) and overall survival (OS) using univariate and multivariate Cox regression. **Results:** Baseline profiling identified MYOD1 mutation as the strongest independent predictor of inferior PFS (HR 6.52, P=0.003), while MYCN amplification defined a novel "ultra-high-risk" fusion-positive subset (OS, P<0.001). Baseline ctDNA positivity (66.7%) correlated with advanced disease (P<0.001). Longitudinally, persistent ctDNA at Cycle 5 Day 1 (C5D1) conferred a 12-fold increased progression risk (HR=12.2, P=0.004), establishing C5D1 as the definitive prognostic landmark. Patients with positive longitudinal ctDNA harbored a nearly 6-fold increased risk of progression (HR = 5.97, 95% CI 2.25–15.85, P < 0.001) and a 12-fold increased risk of death (HR = 12.4, 95% CI 1.42–108.37, P = 0.023) compared to those with sustained negativity. Analysis of paired samples at relapse revealed subclonal replacement driven by therapeutic pressure, enriching for acquired resistance alterations in TP53 and DNA damage response (DDR) pathways undetectable by static assays. Additionally, paired CSF-plasma profiling in parameningeal/CNS disease identified the CNS as an evolutionary "sanctuary site" harboring distinct, compartment-specific drivers (e.g., TP53, HRAS) divergent from plasma. **Conclusions:** This prospective study establishes ctDNA as a critical biomarker for RMS, defining MYOD1, MYCN, and TP53 as key genomic risk factors and validating C5D1 as the optimal therapeutic landmark. Deep longitudinal profiling uncovers subclonal replacement and compartmentalized CNS evolution as drivers of treatment failure, advocating for comprehensive, compartment-specific monitoring in next-generation risk-adapted trials. Clinical trial information: NCT05778955. Research Sponsor: None.

11518 Rapid Oral Abstract Session

Safety and pharmacokinetics (PK) of lurbinectedin (lurbi) in pediatric patients (pts) with relapsed/refractory (R/R) solid tumors and preliminary antitumor activity in pediatric and young adult pts with R/R Ewing sarcoma (EwS): Results from a phase 1 study. First Author: Julia Lynne Glade Bender, Memorial Sloan Kettering Cancer Center, New York, NY

Background: About 30% of pediatric cancers are solid tumors. EwS is the second most common bone tumor among children and young adults; 5-year survival rates for R/R EwS are <15%. Lurbi is a trabectedin analogue that alkylates DNA and blocks transcription of EWS-FLI1, a primary driver of EwS. In a phase 2 basket trial, lurbi demonstrated an objective response rate (ORR; complete response [CR] or partial response [PR]) of 14% and disease control rate (DCR; CR, PR, or stable disease) of 57% in 28 adults (median age, 33 years [y]) with R/R EwS. Here, we report phase 1 results from a multicenter, open-label study (NCT05734066) of lurbi in pediatric and young adult pts with R/R solid tumors including EwS. **Methods:** Part 1 evaluated the safety, tolerability, PK, and recommended phase 2 dose (RP2D) of lurbi monotherapy in pediatric pts (aged 2–18 y) with R/R solid tumors. RP2D selection used a Bayesian optimal interval design starting with the approved adult dosage, 3.2 mg/m^2 lurbi IV over 1 hour every 3 weeks. Two additional cohorts were treated at the RP2D: a safety cohort for pts aged <18 y and a histology-specific safety and efficacy cohort for pts aged 2–30 y with R/R EwS. Tumor responses were assessed every 6 weeks per RECIST v1.1. **Results:** As of Oct 22, 2025, 21 pts received ≥1 dose of lurbi (3.2 mg/m^2, n = 17; 4.0 mg/m^2, n = 4). Median (range) age was 16 (10–25) y; 13 (62%) pts had received ≥3 prior lines of treatment (Tx). Median (range) lurbi cycles administered was 3 (1–18); 3 (14%) pts were still receiving lurbi; 18 (86%) discontinued Tx. At 4 mg/m^2, dose-limiting pulmonary edema and rhabdomyolysis/acute kidney injury were observed. Among pts receiving lurbi 3.2 mg/m², 8 (47%) had grade ≥3 Tx-related adverse events (TRAEs); anemia (5 [29%]) and platelet count decrease (5 [29%]) were most common (Table). For pts aged ≥6 y, the RP2D was 3.2 mg/m^2; accrual of pts aged <6 y is ongoing to determine RP2D. Although geometric mean (Geo CV%) C_{max} (163 μg/L [105%]) and AUC_{inf} (1893 μg•h/L [126%]) were higher in children/young adults vs adults in the phase 2 basket trial (increased 53% and 244%, respectively), there was substantial overlap in drug exposures. Among 11 evaluable pts with R/R EwS receiving lurbi 3.2 mg/m², the confirmed ORR was 18%, and the DCR was 55%; 2 responders were progression free at their last assessments (5.7 and 6.9 months). **Conclusions:** Based on these data, lurbi had a manageable safety profile, predictable PK properties, and encouraging preliminary clinical activity in pts with R/R EwS. Phase 2 expansion in pts ≤30 y with R/R EwS is ongoing. Clinical trial information: NCT05734066. Research Sponsor: Jazz Pharmaceuticals.

TRAEs in all pts and by dose.

n (%)	All N = 21	3.2 mg/m^2 n = 17	4.0 mg/m^2 n = 4
Any TRAE	21 (100)	17 (100)	4 (100)
Grade ≥3	12 (57)	8 (47)	4 (100)
Serious	4 (19)	2 (12)	2 (50)
Led to Tx discontinuation	1 (5)	0	1 (25)
Led to death	1 (5)	0	1 (25)[a]

[a]Due to acute kidney injury.

11519 Rapid Oral Abstract Session

Association of NAB2–STAT6 distal fusion with risk level of metastatic disease and thoracic primary site. First Author: Keerthana Sureshkumar, University of Miami Miller School of Medicine, Miami, FL

Background: Solitary fibrous tumors (SFTs) are defined by the NAB2–STAT6 gene fusion, but the clinical significance of these breakpoints remains incompletely understood. Although fusion breakpoint heterogeneity has been implicated in influencing biologic behavior, there are few studies linking variant location to outcomes. Recent genome analyses suggest that proximity based breakpoint clustering approaches can reveal driver loci, suggesting investigation of NAB2–STAT6 fusion breakpoints may be potential prognostic markers. Because individual variants are rare, we used a proximal vs distal breakpoint analysis to evaluate high-risk clinical features. In this study, we evaluated trends between the NAB2–STAT6 breakpoint and metastases, primary tumor location, and recurrence in a single-institution, retrospective cohort study. **Methods:** We performed an analysis of patients with SFTs treated at the Sylvester Comprehensive Cancer Center (n=48). Samples without pathology-confirmed NAB2–STAT6 fusions were excluded. Clinical variables included primary tumor site, size, stage, and recurrence. Molecular data was extracted from next-generation whole transcriptome and exome sequencing reports. Breakpoints were categorized by exon numbers. NAB2 breakpoints were considered proximal if they occurred before exon 6 and distal if they occurred at exon 6 or more distally. STAT6 breakpoints were considered proximal if they occurred at exon 6 or earlier and distal if they occurred at exon 16 or more distally. Associations were analyzed using Fisher exact tests. **Results:** Breakpoint patterns were significantly associated with metastatic presentation at diagnosis. Metastatic disease at the time of diagnosis was not observed in any patients with proximal STAT6 breakpoints (n= 29) but was present in 24% (n = 17) of those with distal STAT6 breakpoints (p=0.02). Additionally, metastatic disease occurred exclusively in tumors with distal NAB2 breakpoints (n=14, p=0.01). Breakpoint patterns were also associated with primary tumor sites. The majority of proximal STAT6 fusions were present mostly in thoracic cavity tumors (55%), while distal STAT6 fusions occurred mainly in tumors at non-thoracic sites (p=0.02). Among fusion subtypes, metastatic presentation was absent in ex4: ex2 tumors but observed in 31% of tumors with ex6: ex16/17 tumors (p=0.02). Distal STAT6 breakpoints also showed trends toward higher recurrence rates and grades as well as larger tumor sizes. **Conclusions:** Our study shows that NAB2–STAT6 distal fusion breakpoint patterns are associated with metastatic disease at diagnosis, non-thoracic primary tumor locations and more aggressive clinical features. These findings support the consideration of breakpoint patterns as part of molecular risk stratification and identifies a potential biomarker for SFT patients with a primary tumor who may benefit from chemotherapy. Research Sponsor: None.

11520 Rapid Oral Abstract Session

Efficacy of velzatinib (IDRX-42) in patients with advanced/metastatic GIST by line of therapy and circulating tumor DNA response in the phase 1/1b StrateGIST 1 trial. First Author: Michael C. Heinrich, Oregon Health & Science University, Portland, OR

Background: Most gastrointestinal stromal tumors (GIST) are driven by mutations in *KIT* or *PDGFRA*. Resistance to standard tyrosine kinase inhibitor (TKI) therapy is largely driven by acquisition of secondary mutations in *KIT* exons 13/14/17/18. Velzatinib (subject to USAN approval) is a broad-spectrum TKI designed to inhibit most common primary *KIT* mutations (exons 9 and 11) as well as secondary mutations. We present updated circulating tumor DNA (ctDNA) results from StrateGIST 1, a phase 1/1b study evaluating the efficacy and safety of velzatinib across primary and secondary mutations in patients (pts) with advanced/metastatic GIST. **Methods:** The study design of StrateGIST 1 has been previously described (Schöffski et al. *J Clin Oncol* 2024). Clinical activity was assessed by mRECIST v1.1. Blood samples for ctDNA analyses (Guardant360 assay) were collected for all pts before and serially during treatment. Data analysis was performed in R and hazard ratios were calculated using Cox proportional hazards regression. **Results:** As of September 2025, 256 pts received velzatinib across all lines of therapy. Velzatinib showed clinical activity against both primary (Exon 9 ORR: 44% [95% CI: 29.1, 60.1]; Exon 11 ORR: 19% [95% CI: 12.7, 27.6]) and secondary (Exon 13 ORR: 17% [95% CI: 8.6, 27.9]; Exon 14 ORR: 20% [95% CI: 2.5, 55.6]; Exon 17 ORR: 23% [95% CI: 14.6, 33.2]) mutations. Clinical activity is supported by ctDNA analysis (n=180 pts); >99% reduction in ctDNA variant allele frequency (VAF) was observed across a broad spectrum of individual mutations (Exon 9: 80%; Exon 11: 67%; Exon 13: 80%; Exon 14: 80%; Exon 17: 83%). We also evaluated the predictive value of different exon mutations in *KIT* detected at baseline via ctDNA. Focusing on pts with primary mutations only, *KIT* exon 9 mutations had 3-fold lower risk of disease progression compared to exon 11 mutations (HR=3.06). No significant difference was observed between major secondary mutations (exon 13 vs exon 17). Additionally, 46 pts without detectable *KIT/PDGFRA* mutations at baseline showed a lower progression risk (HR=0.41) compared to 180 pts with detectable *KIT/PDGFRA* mutations, underscoring the prognostic and/or predictive value of ctDNA analysis, even in low-shedding indications such as GIST. **Conclusions:** Velzatinib has broad activity against clinically relevant *KIT* mutations in pts with advanced and/or metastatic GIST and can substantially reduce ctDNA levels across a broad spectrum of clinically meaningful *KIT* mutation profiles. Baseline exon-level *KIT* mutation status and ctDNA detectability provide potentially useful prognostic and predictive data, justifying further study to discern the relationship between clinical benefit and molecular response. This study (NCT05489237) is funded by GSK. Clinical trial information: NCT05489237. Research Sponsor: GSK.

11521 Poster Session

Feasibility of constructing an external control arm for early efficacy assessment in phase 1a: Methodological framework from the INVOKE trial. First Author: Nicolas Loiseau, Owkin, New York, NY

Background: Phase 1a dose-escalation trials are primarily designed for safety but often lack sufficient visibility into efficacy signals due to small sample sizes and the absence of a comparator arm. This uncertainty can delay decision-making and increase late-stage failure rates. We hypothesized that a synthetic External Control Arm (ECA) aggregating real-world data (RWD) and historical clinical trials could be established to contextualize efficacy readouts from the ongoing OKN4395 Phase 1a study (INVOKE; NCT06789172; Trial in Progress abstract submitted to this meeting). **Methods:** We curated a retrospective dataset of 298 solid tumor patients derived from two complementary sources, RWD and recent clinical trials (inclusion date $\geq$ 2016). To ensure comparability with the INVOKE population, patient selection adhered strictly to the study's inclusion and exclusion criteria, with only individuals who had exhausted all standard-of-care (SoC) options being retained. We further refined the cohort to ensure exact overlap, retaining only external patients who shared an identical baseline covariate profile with at least one patient in the INVOKE cohort. Finally, we applied statistical adjustment methods, including Inverse Probability of Treatment Weighting (IPTW) and G-Computation, to align the remaining cohort on major prognostic variables (e.g. ECOG status, prior lines of therapy, inter alia). **Results:** A total of 13 INVOKE patients with available endpoint data were eligible for ECA matching. The selection process yielded a final robust ECA cohort of 40 patients. In this refined population, we achieved robust covariate alignment between the ECA and the INVOKE cohort, with absolute Standardized Mean Difference (SMD) $<$ 0.13 for all major prognostic variables. Despite the methodological differences between IPTW and G-computation, both statistical approaches yielded highly consistent estimates. Data from INVOKE, a study in early stages, is yet to publish data (TIP presented at this meeting), comparative efficacy data will be disclosed at a later date. **Conclusions:** We demonstrated that constructing a synthetic ECA generating outcomes directly comparable to those of the population of an active Phase 1a dose-escalation study is methodologically feasible. The establishment of this matched external cohort and first application to the INVOKE Phase 1a study provides a proof of concept framework for early efficacy assessment. This "de-risking" tool is now positioned to provide rapid, concurrent contextualization of emerging data from the INVOKE trial upon data maturity. Research Sponsor: None.

11522 Poster Session

AI-assisted systematic review and pooled analysis of anthracycline- versus taxane-based chemotherapy in advanced or metastatic angiosarcoma. First Author: Annarita Peddio, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

Background: Comparative evidence for first-line anthracycline- (Ant) vs taxane-based (Tax) chemotherapy in advanced angiosarcoma (AS) is limited by small, heterogeneous retrospective studies. We performed an AI-assisted systematic review and pooled analysis to overcome fragmented reporting and evaluate efficacy and safety across clinically relevant subgroups, including cutaneous and radiation-induced AS (RIAS). **Methods:** A PubMed search (2000–2025) identified 11 eligible studies, 6 providing quantitative class-specific outcomes. An AI-assisted workflow (GPT-5) harmonized heterogeneous datasets, resolved denominator inconsistencies, and enabled supervised reconstruction of missing subgroup numerators. Endpoints included objective response rate (ORR), disease control rate (DCR), survival outcomes, and toxicity. ORR and DCR were compared using two-proportion z-tests. PFS, OS, and safety outcomes were summarized descriptively based on reported medians, due to incomplete and heterogeneous reporting that precluded pooling. **Results:** Among 426 evaluable patients (Ant n = 245; Tax n = 181), Tax demonstrated higher pooled ORR (44.8% vs 29.0%, p= 0.001) and DCR (63.7% vs 52.6%, p= 0.018). Benefits were marked in cutaneous AS (ORR 50.8% vs 31.5%, p= 0.017) and RIAS (41.8% vs 30.2%, p= 0.036), while non-cutaneous AS showed comparable ORR (25.3% vs 27.8%, p= 0.68). Reported median PFS (6.2 vs 5.0 months) and OS (14.3 vs 12.2 months) numerically favored Tax. Safety analysis, enabled by AI integration of fragmented datasets, showed that Tax was mainly associated with low-grade neuropathy and mild myelosuppression. Ant toxicity reporting was sparse but included fatal neutropenic events, indicating greater hematologic risk. **Conclusions:** Tax shows superior antitumor activity in cutaneous AS and RIAS with favorable tolerability. Anthracyclines remain an option for selected patients, although higher hematologic toxicity is expected. These findings, derived through AI-assisted reconstruction of incomplete datasets, highlight both the therapeutic relevance of Tax in AS and the potential of AI to enhance evidence synthesis in rare cancers. Research Sponsor: None.

11523 Poster Session

Efficacy and safety of continuous intra-arterial cisplatin and recombinant human endostatin combined with systemic chemotherapy in osteosarcoma: A phase II study. First Author: Hongtao Li, Department of Oncology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Previous studies have demonstrated that preoperative intra-arterial cisplatin infusion elicits a favorable histologic response—a key prognostic factor for survival in osteosarcoma. Recombinant human endostatin (rh-endostatin; Endostar), an anti-angiogenic agent, has been shown to significantly improve survival when administered intravenously in combination with chemotherapy for osteosarcoma. Herein, we report preliminary results on the efficacy and safety of continuous intra-arterial cisplatin and rh-endostatin combined with systemic chemotherapy in osteosarcoma (NCT06562673). **Methods:** This open-label, single-arm, single-center, phase II clinical trial enrolled patients with histologically confirmed primary localized extremity conventional osteosarcoma. Patients received 2 cycles of high-dose methotrexate and anthracyclines intravenously. Intra-arterial infusion was performed concurrently with anthracyclines. Rh-endostatin was administered intra-arterially (150 mg over 6 hours); then, cisplatin was administered intra-arterially (100-120 mg/m² over 6 hours). Efficacy and safety were evaluated after surgery. **Results:** Ten patients were enrolled from December 2024, to April 2025, including 7 males and 3 females with a mean age of 17.8 years (range, 12-42 years). Tumor locations included the femur (n=6), tibia (n=3), and humerus (n=1). Preoperative arterial infusions were administered 3 times (n=1), 2 times (n=8), and 1 time (n=1). All patients underwent limb-sparing surgery. The tumor necrosis rate was >90% in 5 cases (50%) and ≤90% in 5 cases (50%). Adverse events included grade 3 vomiting and nausea (n=1), grade 1 renal impairment (n=2), fever (n=1), and skin induration (n=1). Due to grade 3 gastrointestinal toxicity observed in the first enrolled female patient, the cisplatin dose was uniformly reduced to 100 mg/m² for all subsequent patients in the trial. **Conclusions:** Intra-arterial administration of high-dose rh-endostatin and cisplatin combined with systemic chemotherapy in osteosarcoma appears safe and achieves a good histologic response rate of 50%, compared with a historical rate of 30% with intravenous chemotherapy alone. Clinical trial information: NCT06562673. Research Sponsor: None.

11524 **Poster Session**

ICONIC (Improving Outcomes Through Collaboration in Osteosarcoma): Insights from a national prospective cohort trial for newly diagnosed osteosarcoma patients. First Author: Sandra J. Strauss, University College London, London, United Kingdom

Background: There has been little change in osteosarcoma (OS) treatment over the last two decades. Understanding management patterns, better understanding of biology and identifying new biomarkers are key to improving outcomes. **Methods:** ICONIC is a UK-wide prospective observational trial of newly diagnosed OS pts with longitudinal clinical, imaging, tissue and pt experience data collection to address key objectives. These include describing variation in management and outcomes for specific pt groups, establishing an imaging repository to develop imaging biomarkers, analysis of plasma cfDNA, and use of tumor tissue to develop pt-derived models and decode tumor-immune cross talk. Pts were recruited from Oct 2019 to Jan 2025. Progression-free (PFS) and overall survival were analysed using Kaplan-Meier survival statistics and Cox regression. **Results:** A total of 337 pts were recruited from 27 sites. Median age was 19 (range 3-83); 17% had metastases. In total, 229/253 (91%) pts receiving neoadjuvant treatment had methotrexate, doxorubicin, cisplatin (MAP); 259 underwent surgery, of which 52 (20%) had amputations; 101/161 (63%) of eligible pts received mifamurtide. With median follow-up of 2.5 years, 2-year PFS and overall survival were 57% (95% CI 51-63) and 78% (95% CI 72-83) (Table 1). Age, raised ALP, pelvis or trunk primary sites, metastases and inoperability were associated with worse PFS. Pts with a good pathological response to treatment and ≥2mm resection margin had the lowest risk of local recurrence (p=0.02). A pilot radiomics analysis of 32 pts undergoing resection after MAP, demonstrated baseline tumour volume (p=0.044) pre-treatment T2 Gray Level Non-Uniformity (GLNU) (p=0.002), and post-treatment GLNU difference (p=0.008) to be associated with overall survival. Longitudinal blood samples for cfDNA analysis were collected from 226 pts. Patient-derived primary cultures were successfully developed from 12 pts. Spatially-resolved genomic and transcriptomic analysis of tumor tissue to study genomic evolution and immune evasion is ongoing. **Conclusions:** ICONIC trial has identified variation in management and outcomes of OS, which will guide future practice and provided a successful platform for imaging and biomarker analysis, which is ongoing. Clinical trial information: NCT04132895. Research Sponsor: Bone Cancer Research Trust.

Pt characteristics and outcomes according to age and primary site.

	All patients N=337	<16 years N=115	16-24 years N=101	25-39 years N=60	>40 years N=61
Lower limb	228 (68%)	90 (78%)	74 (73%)	34 (57%)	30 (49%)
Upper limb	40 (12%)	18 (16%)	9 (9%)	6 (10%)	7 (11%)
Craniofacial	23 (7%)	3 (3%)	6 (6%)	7 (12%)	7 (11%)
Pelvis/sacrum	22 (7%)	1 (1%)	8 (8%)	4 (7%)	9 (15%)
Trunk	12 (4%)	1 (1%)	4 (4%)	5 (8%)	2 (3%)
Unknown	12 (4%)	2 (2%)	0 (0%)	4 (7%)	6 (10%)
Survival outcome analysis					
2-year PFS (95% CI)	57% (51-63)	65% (55-74)	55% (44-66)	60% (45-73)	44% (30-57)
2-year OS (95% CI)	78% (72-83)	77% (66-84)	87% (77-93)	78% (62-88)	64% (49-75)

11525 **Poster Session**

Efficacy and safety analysis of anlotinib combined with etoposide plus ifosfamide in the treatment of children and adolescents with pulmonary metastatic osteosarcoma. First Author: Hui Li, Northwest Women's and Children's Hospital, Xi'an, China

Background: Osteosarcoma is a highly malignant and aggressive tumor, predominantly occurring in children and adolescents under 20 years of age. It exhibits early metastatic potential, with 15%–20% of patients presenting with distant metastasis at diagnosis. Among these, pulmonary metastases account for 85% of cases. The 5-year survival rate after pulmonary metastasis is <20%. This study retrospectively analyzes the efficacy and safety of anlotinib combined with etoposide and ifosfamide in treating pediatric and adolescent patients with pulmonary metastatic osteosarcoma. **Methods:** This study retrospectively screened children and adolescent patients with pulmonary metastatic osteosarcoma who received etoposide + ifosfamide ± anlotinib at Northwest Women's and Children's Hospital from May 2018 to December 2024. The study was divided into a combination group (anlotinib + etoposide + ifosfamide) and a control group (etoposide + ifosfamide). The dosage of anlotinib: 8 mg for patients < 12 years old, qd, d1-d14, q3w, 12mg for patients ≥12 years old, qd, d1-d14, q3w. Treatment continued until disease progression or intolerable toxicity, with a maximum of 4 chemotherapy cycles. The primary endpoint of the study was objective response rate (ORR), and secondary endpoints included disease control rate (DCR), progression-free survival rate (PFSR), and safety. **Results:** The data cut-off date was December 2024, The study enrolled 38 patients (combination group: n=18, control group: n=20). Efficacy analysis showed the combination group achieved higher ORR (22.2% vs 15%, p=0.057) and significantly better DCR (66.7% vs 45%, p=0.015), and 3-month progression-free survival rates (PFSR) of 44.0% versus 30%. Subgroup analysis indicated superior outcomes with 12 mg versus 8mg anlotinib (p<0.05). Biomarker evaluation revealed patients with high BRCA1/VEGFR2 expression had lower 3-year survival than those with intermediate/low expression, while low PDGFR expression was associated with poorer survival compared to intermediate/high levels. The combination group exhibited higher incidence rates of treatment-related adverse events (TRAEs) compared to the control group, including epistaxis (44.4%), hand-foot syndrome (27.8%), abnormal thyroid function (22.2%), and proteinuria (16.7%). All reported adverse events were grade 1-2 in severity, with no grade 3-4 severe adverse reactions observed. **Conclusions:** The combination therapy of anlotinib with ifosfamide and etoposide demonstrated superior efficacy compared to chemotherapy alone in pediatric patients with pulmonary metastatic osteosarcoma, showing higher ORR, DCR, and 3-month PFSR. These results indicate that anlotinib combined with neoadjuvant chemotherapy can more effectively delay tumor progression and prolong progression-free survival in these patients. Research Sponsor: None.

11526 **Poster Session**

Efficacy and safety of perioperative anlotinib combined with cisplatin and doxorubicin in treatment-naive stage IIB classic osteosarcoma of the extremity: Updated results from the ALTER-S002 trial. First Author: Minxun Lu, Department of Orthopedics, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Background: Clinical studies show overexpression of multiple tyrosine kinase receptors in osteosarcoma, supporting targeted therapy as a promising direction. Anlotinib, a multi-targeted tyrosine kinase inhibitor, exerts anti-tumor angiogenesis effects. Combining anti-angiogenic agents with chemotherapy may yield synergistic tumor control, particularly as perioperative therapy. We present updated long-term efficacy and safety data, including key secondary endpoints, to validate this regimen's clinical value. **Methods:** This was an open-label, single-arm, multicenter phase II trial. Eligible patients (12-40 years) had histologically confirmed primary localized stage IIB classic extremity osteosarcoma and were operable. Patients received anlotinib (10mg, po, d1-14, q3w), doxorubicin (A, 20-25 mg/m², iv, d1-3, q3w) and cisplatin (P, 70-90 mg/m², iv, d1, q3w) for 9 weeks. Radical surgery was performed at week 10 (no contraindications). Postoperatively, A+P was given at weeks 12-14, followed by anlotinib+A+P (same doses) at weeks 15-20. From week 21, anlotinib monotherapy (12mg, po, d1-14, q3w) continued until week 104 or an event-free survival (EFS) event. Primary endpoint: 24-month EFS rate. Secondary endpoints: 36-month EFS rate, local recurrence rate, lung metastasis rate, 3-year overall survival (OS) rate, and safety. **Results:** From May 2020 to April 2022, 52 patients were enrolled, treated, and included in full analysis set (FAS) and safety set (SS). Of these, 84.6% (44/52) were Han and 55.8% (29/52) male. Median follow-up was 42.7 months (IQR 30.4-52.7). The 24-month and 36-month EFS rates were 73.7% (95% CI 59.0-83.9) and 46.6% (95% CI 27.4-63.7), respectively. Median OS was not reached; 36-month and post-hoc 60-month OS rates were 74.6% (95% CI 59.6-84.7) and 71.4% (95% CI 55.5-82.4). Twenty-five percent (13/52) of patients died, mostly due to lung metastasis (13%). Among 51 surgical patients, local recurrence, lung metastasis, and other-site metastasis occurred in 23.5%, 17.6%, and 9.8%, respectively. Median recurrence-free survival (RFS) was 32.4 months (95% CI 25.7-not estimable). Grade 3-4 treatment-related adverse events (TRAEs) occurred in 84.6% (44/52) of patients, with neutropenia most common (28/52 [53.8%]). No grade 5 TRAEs were observed. Serious TRAEs occurred in 40.4% (21/52), mainly myelosuppression (14/52 [26.9%]). None of the 13 on-study deaths were TRAE-related. **Conclusions:** Perioperative anlotinib plus cisplatin and doxorubicin shows promising efficacy in treatment-naïve stage IIB classic extremity osteosarcoma, with manageable safety. It achieves favorable long-term OS, and clinically acceptable local recurrence and lung metastasis rates, serving as a potential new perioperative option for this population. Clinical trial information: ChiCTR 2000033298. Research Sponsor: None.

11527 **Poster Session**

A phase 2 trial of cetuximab for patients with locally advanced/metastatic chordoma. First Author: Anthony Paul Conley, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Unresectable/metastatic chordoma is a rare notochordal malignancy with no approved systemic treatments. EGFR is widely expressed on chordomas. Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that inhibits EGFR signaling. In vivo testing of cetuximab has demonstrated growth inhibition and regression of chordoma. An investigator-initiated, single center, phase II study (NCT05041127) was developed to evaluate the efficacy of cetuximab for patients (pts) with advanced/metastatic chordoma. **Methods:** Eligible pts were ≥18 years of age, had adequate organ function, and had an ECOG performance status (PS) of ≤2. Any prior line of therapy was allowed except EGFR inhibitors. A minimum of 10 pts and maximum of 29 pts were to be enrolled onto the trial based on Simon's two-stage optimal design (H_0 RR 5% vs H_1 RR 20%; one-sided α=0.05; power=80%). Pts received cetuximab 500 mg/m^2 IV Q2 weeks until disease progression or unacceptable toxicity. The primary end point was response rate (RR) according to RECIST 1.1. Secondary objectives included safety/tolerability and survival metrics. Efficacy was assessed in the modified intention-to-treat (mITT) population (≥1 dose; ≥1 post-baseline scan). Exploratory objectives included analysis of the EGFR pathway at 2 time points from research-related biopsies. Pt reported outcomes (PROs) were assessed with MDASI (general and spine) questionnaires at several time points on study. **Results:** From May 2022 to Dec 2025, 29 pts enrolled. 4 were excluded from the efficacy analysis (2 withdrawal, 1 cetuximab allergy, 1 has not completed the 1st imaging assessment). Median age was 58 years (range 21-76), 15 (58%) were men, and 24 (92%) had ECOG PS of 0 or 1. The most common primary site was skull base (46%). Tumor was classified as locally recurrent in 8 pts (31%) and metastatic in 18 pts (69%). One median line of prior systemic therapy was noted (range, 0-6). At a median follow up of 28.7 months, 12 pts (48%) had radiographic cytoreduction (any tumor reduction [ATR]), but only 2 pts (8%) had a partial response (PR). Neither PR was associated with an EGFR gene alteration. Stable disease (SD) was noted in 23 pts (92%). Preliminary median PFS and median OS was 9.9 months (95% CI, 6.3 to 13.4) and 38.8 months (95% CI, 18.6 to NR), respectively. Significantly longer PFS was observed in SD-ATR (log-rank p=0.038), with median of 14.2 months in SD-ATR versus 9.6 months in SD without tumor reduction. 7/26 pts (27%) experienced a grade 3 cetuximab-related adverse event (AE), the most common being rash in 4 pts (15%). No grade 5 AE related to cetuximab was reported. Dose reduction occurred in 2 pts (8%). 4 pts (15%) discontinued the study due to toxicity. 4 pts remain on study. **Conclusions:** Although the primary end point has not been reached, 2 PRs are noted, and pts with SD-ATR have a longer PFS. Translational and PRO analysis are ongoing to better define biological predictors of cetuximab activity in chordoma. Clinical trial information: NCT05041127. Research Sponsor: Chordoma Foundation; Eli Lily.

11528 **Poster Session**

Genomic characterization of conventional, dedifferentiated, and mesenchymal chondrosarcoma: A 550-patient multicenter analysis. First Author: Luyuan Li, North Alabama Medical Center, Florence, AL

Background: The rarity of chondrosarcoma has historically impeded efforts and systematic genomic characterization. However, large, standardized, multi-center databases, such as the AACR Project GENIE, along with other, independent studies, have enabled genetic profiling of hundreds of patients with these cancers. **Methods:** The following datasets were accessed through cBioPortal: the GENIE Cohort v18.0; msk_impact_2017; metastatic_solid_tumors_mich_2017; pog570_bcgsc_2020; msk_ch_2020; msk_ch_ped_2021; sarcoma_msk_2022; sarcoma_mskcc_2022; mixed_kunga_msk_2022; msk_ctdna_vte_2024; and sarcoma_ucla_2024. These datasets included 550 unique patients: 453 conventional chondrosarcoma (CHS), 42 dedifferentiated chondrosarcoma (DDCHS), and 55 mesenchymal chondrosarcoma (MCHS). Mutational and structural variant data were also extracted from each data set and ranked by frequency. This ranked list of genes was then analyzed using g:Profiler enrichment analysis software. Dunn's test with Benjamini-Hochberg correction following Kruskal-Wallis test was performed for statistical analysis. **Results:** The average age at biopsy was 52 for CHS, 63 for DDCHS, and 32 for MCHS. DDCHS displayed the greatest genomic instability, with significantly elevated mutation count and tumor mutation burden (TMB) compared to CHS and MCHS ($p < 0.001$). Despite the higher TMB in DDCHS, the most frequently mutated genes were highly conserved between CHS and DDCHS, with six of the 20 most frequently mutated genes being shared between them. In contrast, MCHS shared only two of the 20 most frequently mutated genes with CHS and DDCHS. *TP53*, *IDH1* and *-2*, and *TERT* were frequently mutated in both CHS and DDCHS. Enrichment analysis indicated that DNA repair pathways were among the most frequently altered in both diseases. These pathways, while still perturbed in MCHS, appeared less prominently, with genes involved in chromatin organization being frequently mutated. Moreover, Enrichment analysis of structurally variant genes in CHS also showed frequent alterations in chromatin organizing genes, along with genes involved in NOTCH signaling. While structural variant genes were not reported with enough frequency in DDCHS and MCHS to permit the analysis, the HEY1-NCOA2 fusion product was frequently detected in MCHS. **Conclusions:** The results of this multi-institutional bioinformatics survey confirms established observations that *IDH1* and *-2* mutations are the most common genetic alterations in CHS following *TP53*. DDCHS bears a similar but more advanced mutational signature with greater genomic instability. MCHS harbors a distinct mutational profile defined by the characteristic HEY1-NCOA2 fusion. Despite these differences, all three subtypes share enrichment in mutations affecting genomic integrity pathways, suggesting this as a common feature of chondrosarcoma biology. Research Sponsor: None.

11529 **Poster Session**

Low-dose apatinib combination with first-line chemotherapy rechallenge in advanced osteosarcoma: A single-center ambispective cohort study. First Author: Jing Chen, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: First-line treatment for osteosarcoma includes various combinations of four agents: high-dose methotrexate (HD-MTX), doxorubicin (DOX), cisplatin (DDP), and ifosfamide (IFO), achieving overall efficacy rate of 41-77% and remaining the most effective systemic therapy to date. However, patients (pts) with progression after first-line therapy lack a defined second-line standard, available treatments yield objective response rate (ORR) $<$20% with 5-year survival $<$10%. Though anti-angiogenic tyrosine kinase inhibitors have limited monotherapy efficacy, preclinical studies show they enhance intratumoral drug delivery and reverse multidrug resistance, thereby synergizing with chemotherapy. Thus, apatinib, a highly selective VEGFR-2 inhibitor, was added to the previously failed first-line chemotherapy-the most effective systemic therapy-to investigate whether it could reverse chemoresistance and restore response to the original regimen. **Methods:** This ambispective cohort study enrolled pts with advanced osteosarcoma who had tumor progression after first-line chemotherapy with HD-MTX, DOX, DDP and IFO at our center. Subsequently, low-dose apatinib (250 mg/d) was administered in combination with the same four-drug chemotherapy regimen. The primary endpoint was the ORR. Secondary endpoints included disease control rate (DCR), median progression-free survival (PFS), median overall survival (OS) and adverse events (AEs). **Results:** From Jan 2018 to Jul 2025, 37 pts were enrolled, with 9 in the retrospective cohort and 28 in the prospective cohort. Of these, 27 (73%) were male and 10 (27%) were female, with a median age of 21 years (range: 10–67). 36 pts were diagnosed as conventional osteosarcoma (96.9%). Primary tumors were located in the femur (21, 56.8%), tibia and humerus (8, 21.6%), pelvis (6, 16.2%), clavicle and rib (2, 5.4%). Metastatic disease was present in 29 pts (78.4%). The most common sites of metastasis were the lung (28, 78.1%) and bone (6, 18.8%). Partial remission was seen in 8 pts, and stable disease in 23 (ORR: 21.6%, DCR: 83.8%). After a median follow-up of 17 months (mos), PFS was 5.8 mos (2.5–9.1), OS was 14.5 mos (10.3–18.7). Pts with lactate dehydrogenase $<$245 U/L had superior PFS (7.2 vs 3.3 mos; HR=0.28, 0.1–0.8, P=0.01), with a trend of OS benefit (14.5 vs 11.6 mos, P=0.74). Pts with alkaline phosphatase $<$150 U/L had a trend of PFS benefit (6.3 vs 5.8 mos, P=0.7) and significant better OS (20.3 vs 11.7 mos; HR=0.41, 0.17–1.01, P=0.046). Prognosis was not associated with gender, age, primary site, stage or first-line therapy response. AEs were consistent with known safety profiles and manageable. **Conclusions:** Low-dose apatinib combined with previously resistant first-line chemotherapy showed promising efficacy, providing a feasible therapeutic strategy for osteosarcoma pts lacking effective second-line choices. Research Sponsor: Chen Xiao-Ping Foundation for the Development of Science and Technology of Hubei Province.

11530 **Poster Session**

First-in-human dose escalation trial of an engineered salmonella delivering L-methioninase in advanced bone and soft tissue sarcomas. First Author: Hongtao Li, Department of Oncology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Advanced bone and soft-tissue sarcomas have limited treatment options. Tumor-selective methionine dependency is a known metabolic vulnerability. SGN1 is designed to deplete methionine locally within tumors via intratumoral colonization of an attenuated *Salmonella* vector expressing L-methioninase. Preclinical studies have demonstrated safety and targeted antitumor activity. Here, we report the results from the escalation and expansion phases of the Phase I study in patients (pts) with advanced bone and soft-tissue sarcomas. **Methods:** The Phase I study includes a dose-escalation phase where pts received intravenous (IV) (2.0×10^8 to 4.0×10^8 CFU) or intra-arterial (IA) infusion (2.0×10^8 to 6.0×10^8 CFU) once a week (QW) in 28-day cycles, followed by an expansion phase with the putative recommended Phase 2 dose (RP2D) (2.0×10^8 CFU for IV or 6.0×10^8 CFU for IA QW) in 6 cohorts, including pts with recurrent either bone or soft tissue sarcoma after at least 2 lines of chemo therapies. SGN1 was administered in combination with physician's choice systemic therapy. Administration of SGN1 was via one of three routes: IV, IA, or a combined IV/IA regimen. Efficacy was assessed by RECIST version 1.1. **Results:** At the cut-off of Aug 19, 2024, 25 pts with advanced bone and soft-tissue sarcomas were enrolled in the escalation and expansion phases (median follow-up of 5.6 months; range, 0.5-18.2), including pts with bone sarcoma (n=10) and soft tissue sarcoma (n=15). Treatment was administered via IV (n=13), IA (n=8), or a combined IV/IA (n=4) route. The disease control rate (DCR) was 76.0% (95% CI: 56.5, 93.0) in all, 70.0% (95% CI: 34.8, 93.3) in bone sarcoma, 80.0% (95% CI: 52.0, 95.6) in soft tissue sarcoma pts, and 69.2% (95% CI: 38.5, 90.9) in IV, 75.0% (95% CI: 34.8, 93.3) in IA, 100% in combined IV/IA route. Quantitative PCR analysis confirmed significant intra-tumoral colonization by SGN1 post-treatment. The median progression-free survival (mPFS) was 11.5 months (95% CI: 11.1, NE) in all, 11.1 months (95% CI: 1.1, NE) in bone sarcoma, not reached (NR) (95% CI: 3.2, NE) in soft tissue sarcoma pts, and NR (95% CI: 2.7, NE) in IV, 11.5 months (95% CI: 1.3, NE) in IA, NR (95% CI: 11.1, NE) in combined IV/IA route. Complete tumor necrosis was observed in at least two soft tissue sarcoma patients. In all pts, the most frequent treatment-related adverse events (TRAEs) were pyrexia (32.0%) and elevation of blood LDH increased (20.0%). No TRAEs leading to temporary drug discontinuation, no serious TRAEs resulting in withdrawal from the study, and no treatment-related deaths occurred. **Conclusions:** SGN1 exhibits a manageable safety profile, and showed encouraging clinical benefit in advanced bone and soft-tissue sarcoma, as evidenced by mPFS and DCR. The promising data from this phase I study supports further testing of SGN1 in Phase II studies. Clinical trial information: ChiCTR2400085361. Research Sponsor: None.

11532 **Poster Session**

Efficacy and safety of DR4/DR5 agonist aponermin monotherapy in advanced chondrosarcoma: Preliminary report from a prospective, multicenter study. First Author: Mengxiong Sun, The Orthopaedic Oncology Department, Shanghai General Hospital, Shanghai, China

Background: Reported median progression-free survival (mPFS) of Chondrosarcoma is less than 4 months for patients receiving first-line systemic therapy. Aponermin, a recombinant circularly permuted human Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL), induces tumor cell apoptosis by activating the extrinsic apoptotic pathway. This study aimed to evaluate the efficacy of Aponermin in patients with advanced chondrosarcoma. **Methods:** This prospective, multicenter, single-arm study (Registration No: ChiCTR2500104488) was approved by an independent ethics committee. The planned enrollment was 32 patients aged 18-75 years with histologically confirmed advanced chondrosarcoma, documented evidence of disease progression within 6 months prior to enrollment, ECOG performance status $\leq$2, and measurable disease per RECIST 1.1. Patients received intravenous Aponermin 10 mg/kg (days 1-5, every 14 days as one cycle) until disease progression, unacceptable toxicity, or investigator's decision to discontinue. The primary endpoint was objective response rate (ORR). Secondary endpoints included 4-month PFS rate, disease control rate (DCR), overall survival (OS), and safety. **Results:** As of January 23, 2026, 21 patients were enrolled and treated. Median age was 51 years (range: 26-70), with a median of 2 prior surgeries (range: 1-6). Eight patients had received prior drug therapy. Histopathological subtypes included: conventional grade 1, 19% (4/21); conventional grade 2, 47.6% (10/21); conventional grade 3, 4.8% (1/21); mesenchymal, 9.5% (2/21); and one case each (4.8%) of myxoid, dedifferentiated, clear cell, and unknown subtype. Twenty patients were evaluable for efficacy. Median treatment duration was 3.6 months (range: 0.5-14.0), with 4 patients still on treatment. Although no objective responses were observed , 80.0% (16/20) of DCR was achieved. Median PFS was 4.2 months (95% CI: 2.9-5.5), and the 4-month PFS rate was 57.9%. Median OS was not reached. Notably, Among patients achieving DCR, 50% maintained clinical benefit for over 4 months, including one patient with conventional grade 3 chondrosarcoma with SD lasting 7.4 months, two patients with conventional grade 2 with SD exceeding 10.0 months, and one patient with clear cell subtype with SD lasting 14 months. Aponermin demonstrated a favorable safety profile. Treatment-related adverse events occurred in approximately 9.5% (2/21) of patients, including one case (4.8%) of grade 1 allergic reaction and one case (4.8%) of hand-foot syndrome, both alleviated with symptomatic treatment. **Conclusions:** Aponermin monotherapy demonstrated promising disease control and a favorable safety and tolerability profile in advanced chondrosarcoma. Given the limited sample size and ongoing enrollment, final efficacy and safety assessments await study completion. Clinical trial information: ChiCTR2500104488. Research Sponsor: None.

11533 Poster Session

Benefit of adjuvant therapy in high-risk GIST: A large-scale real-world analysis of 2,166 patients (DEEPSARC study). First Author: Nicolas Penel, Institute Bergonie Cancer Center, Bordeaux, France

Background: Real-life data on the impact of adjuvant treatment in GIST pts are limited. **Methods:** We conducted a retrospective study (Deepsarc) merging data from the NETSARC+ dataset of the French Sarcoma Group with the exhaustive health data from the national social security system (SNDS). Eligible pts were treated between January 1, 2012, and December 31, 2017 with localized GIST. The relation between overall survival (OS) and adjuvant therapy was studied univariate and multivariate, using different methods to address confounding factors. **Results:** A total of 2166 GIST pts were included, with a median age of 68.0 years (interquartile range (IQR): 58.0, 76.0), a sex ratio of 1.01. The two most common primary sites were gastric (1301, 60%) and small intestine (527, 24%). Median tumor size at diagnosis was 5.3 cm (IQR 3.6-8.1). Median mitotic count was 3.0 (IQR 1.0-5.0). According to Miettinen/AFIP classification, 331/1026 (32%) were high-risk, 192/1026 (19%) intermediate risk, and 503/1026 (49%) very low or low risk vs 490/912 (53%) high-risk, 193/912 (21%) intermediate risk, and 229/912 (25%) very low or low risk with Joensuu classification. From 2012 to 2017, the proportion of pts receiving adjuvant therapy remained remarkably stable at around one third of all GIST, with higher use in high-risk (70%; 231/331) than intermediate-risk (43%; 83/192) and low-risk pts (6%; 32/503). Pts receiving adjuvant therapy were younger ($p<.001$), with less comorbidities ($p<.001$), larger tumor ($p<.001$), higher mitotic count ($p<.001$), higher risk according to Miettinen/AFIP ($p<0.001$), or Joensuu ($p<.001$), higher rate of R1 resection ($p=.019$) and higher rate of tumor rupture ($p=.001$). Median follow-up was 5.0 years (4.8-5.2). Overall, the 5y OS rate was 81% [79-83%]. Regardless of risk, for the entire population, 5y OS rate of those receiving adjuvant therapy was 82% [79%-85%] and for those not receiving adjuvant therapy was 81% [78%-83%]. For both prognostic classifications, in univariate analysis, adjuvant therapy was associated with improved survival only for high-risk pts. Multivariate analysis propensity-score adjusted analyses for age, sex, social deprivation index, morbidity index, and tumor size (3 categories: ≤5/ 5-10/ >10 cm) highlights a benefit of adjuvant therapy for high-risk pts, according to both AFIP/Miettinen or Joensuu classifications (Table). No clear benefit was observed in intermediate-risk pts. **Conclusion:** This study confirms the benefit of adjuvant therapy for high-risk pts (according to AFIP/Miettinen or Joensuu), but not for other risk groups. Research Sponsor: French National Cancer Institute (Institut National du Cancer, INCa); French Ministry of Health (Direction Générale de l'Offre de Soins, DGOS); French National Research Agency (Agence Nationale de la Recherche); [ANR-10-LABX-0061]; INCa-DGOS-INSERM; INCa-DGOS-INSERM ITMO Cancer_18003; Ligue Nationale contre le Cancer; Ligue contre le Cancer (Comité de l'Ain); the Fondation ARC; European Reference Network for Rare Adult Solid Cancers (EURACAN); [EU project 739521]; Health Data Hub (HDH).

Overall survival (risk of death) in high-risk GIST patients according to adjuvant therapy (reference = No adjuvant treatment), Deepsarc study (2012-2017), France.

Risk classification	N	1y HR*	95% CI**	*P*-value
Miettinen/AFIP	214	0.23	0.06 ; 0.92	0.017
Joensuu	312	0.49	0.24 ; 0.98	0.029

*HR = Hazard Ratio, **CI = Confidence Interval.

11534 Poster Session

Standard-dose ripretinib plus sunitinib versus ripretinib dose escalation in advanced GIST after progression on four prior therapies: Preliminary results of a multicenter cohort study. First Author: Hao Xu, Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

Background: Patients with advanced GIST who progress after four lines of therapy, including imatinib, sunitinib, regorafenib, and ripretinib, face limited treatment options. Ripretinib dose escalation is a potential option recommended by NCCN and CSCO guidelines, while combination therapy with TKIs targeting complementary pathways may offer an alternative for patients harboring multiple resistance mutations. This study aims to evaluate the efficacy of ripretinib dose escalation versus combination therapy following progression on standard-dose ripretinib to identify more effective treatment strategies. **Methods:** This study is a multicenter cohort study designed to evaluate the efficacy and safety of ripretinib dose escalation versus combination therapy with sunitinib in patients with advanced GIST who have progressed after four prior lines of therapy. Eligible patients receive ripretinib dose escalation group (150 mg twice daily) or the combination therapy group (ripretinib 150 mg once daily plus sunitinib 25 mg once daily). The primary endpoint was progression-free survival (PFS). **Results:** Between September 2023 and December 2025, 30 patients were enrolled (16 in the ripretinib dose escalation group and 14 in the combination group). Primary KIT11 mutation were identified in 17 patients, 62.5%(10/16) in the dose escalation group and 50% (7/14) in the combination group, while KIT 9 mutations were 2 patients both in the combination group . As of December 30, 2025, 5 patients in the ripretinib dose escalation group remained on treatment with stable disease, whereas all patients in the combination group had experienced disease progression; 3 of these showed slow progression and continued therapy. mPFS1 with standard-dose ripretinib was comparable between groups (6.0 months [95% CI: 4.7–7.3] vs. 7.0 months [95% CI: 5.2–8.8]). Following progression, ripretinib dose escalation achieved a mPFS2 of 8.3 months (95% CI: 4.7–12.0), significantly longer than combination therapy (3.1 months [95% CI: 2.0–4.3]) . OS data remain immature. Ripretinib dose escalation demonstrated better tolerability, with no grade ≥3 adverse events reported. In contrast, the combination group experienced higher toxicity, 35.7% discontinued treatment due to severe adverse reactions. **Conclusions:** Preliminary results indicate that ripretinib dose escalation demonstrated superior efficacy and a more favorable safety profile compared with combination therapy involving sunitinib. These findings support ripretinib dose escalation as the preferred treatment option for patients with advanced GIST who have progressed after four lines of standard therapy. However, the sample size in this study is still small, and further research with a larger sample is needed to validate this conclusion. Research Sponsor: None.

11535 Poster Session

Oncologic equivalence of brand-name vs generic imatinib in neoadjuvant *KIT* exon 11 GIST: A real-world international cohort study. First Author: Tannaz Ranjbarian, UC San Diego Moores Cancer Center, San Diego, CA

Background: Neoadjuvant imatinib is routinely used to facilitate resection of localized gastrointestinal stromal tumors (GIST) with *KIT* exon 11 mutations. However, whether generic formulations achieve oncologic outcomes equivalent to the brand-name drug in curative-intent neoadjuvant therapy remains unknown. **Methods:** We performed a retrospective, international dual-institution cohort study of 131 patients with localized *KIT* exon 11–mutant GIST treated with neoadjuvant imatinib followed by surgical resection (2010–2025) at UC San Diego and Fondazione IRCCS Istituto Nazionale dei Tumori (Milan). Patients received either brand-name or generic imatinib based on institutional practice. The primary endpoint was tumor size reduction. Secondary endpoints included histopathologic response and overall survival. Multivariable regression and Kaplan–Meier analyses were performed. **Results:** Of 131 patients, 71 (54%) received brand-name and 60 (46%) received generic imatinib. Objective response (≥30% tumor reduction) occurred in 54% vs 37%, respectively (P=0.078). Median tumor size reduction was −33.3% with brand-name and −25.5% with generic imatinib (P=0.105). In multivariable analysis, longer neoadjuvant duration was independently associated with greater tumor reduction (β=−0.02 per day; 95% CI, −0.04 to −0.00; P=0.04), whereas imatinib formulation, dose, and treatment center were not. Pathologic outcomes, including viable tumor percentage (P=0.053), necrosis (P=0.777), and mitotic index (P=0.889), were similar between groups. Five-year overall survival was 87.2% with no difference by formulation (log-rank P=0.24). **Conclusions:** In this first international analysis of neoadjuvant therapy for *KIT* exon 11–mutant GIST, generic imatinib demonstrated oncologic equivalence to the brand-name formulation across tumor response, pathologic, and survival outcomes. As generic imatinib use has expanded globally following patent expiration, these findings reinforce its role as a clinically effective, cost-efficient, and accessible therapy. Demonstrating therapeutic equivalence in the neoadjuvant setting has direct implications for practice guidelines, formulary decisions, and equitable delivery of precision oncology worldwide. Research Sponsor: U.S. National Institutes of Health; T32 CA121398; U01 CA278470; R01 CA292590; P30 CA023100; GIST Research Fund #3661; Jon Strong; 3661.

Tumor size reduction and objective response by imatinib formulation.

Outcome	Brand-name (n=71)	Generic (n=60)	P Value
≥30% tumor size reduction	38 (53.5%)	22 (36.7%)	0.078
Any tumor size reduction	59 (83.1%)	49 (81.7%)	1.0
≥20% tumor size increase	5 (7.0%)	2 (3.3%)	0.452
Tumor size reduction, (median [IQR])	−33.3% (−45 to −18.4)	−25.5% (−38.8 to −10.5)	0.11

Note: P values calculated using Fisher's exact test for categorical outcomes and Mann–Whitney U test for continuous variables. Tumor size reduction reported as median (interquartile range, IQR).

11536 Poster Session

Artificial intelligence–based predictive models for recurrence and recurrence-free survival in gastrointestinal stromal tumors: A contemporary systematic review. First Author: Elizaveta Bodrova, Mercy Catholic Medical Center, Darby, PA

Background: Recurrence after complete resection of GISTs is still a major contributing factor to long-term survival. Traditional stratification models for risk depend on clinicopathologic variables and have limited precision. Recent improvements in artificial intelligence (AI), such as machine learning (ML), deep learning (DL), and multimodal methodologies, might enhance personalized prediction of recurrence and recurrence-free survival (RFS). We performed a contemporary systematic review to evaluate the performance and clinical utility of AI-based prognostic models in resected GIST. **Methods:** PRISMA 2020 guidelines were followed for conducting a systematic review. PubMed, Scopus, and Web of Science were analyzed to search published studies published during 2019–2025 that evaluated AI-, ML-, or DL-based models predicting recurrence or RFS following complete surgical resection of localized primary GISTs. Eligible studies included retrospective or multicenter cohorts with radiologic, histopathologic, genomic, or multimodal data. Data extracted included model type, input modalities, validation strategy, and performance metrics (area under the curve [AUC] and concordance index [C−index]). **Results:** Eight studies encompassing approximately 4,000 patients met inclusion criteria. Both deep learning and multimodal fusion models showed the highest prognostic accuracy (C-index values 0.86–0.96, AUC up to 0.995). Radiomics based ML models using CT, MRI, or ultrasound yielded AUCs between 0.85 and 0.92 which were consistently superior to traditional clinicopathologic methodologies. Genomic ML models fine-tuned recurrence risk stratification beyond conventional benchmarks into molecularly distinct prognostic subgroups. DL-based histopathology estimators both predicted for RFS and for key driver mutations (KIT, PDGFRA) by bridging morphologic and molecular features. External validation cohorts showed stable performance (AUC 0.87–0.96), with calibration and decision curve analyses supporting clinical utility. **Conclusions:** AI-based predictive models demonstrate strong and reproducible performance for recurrence and RFS prediction following GIST resection, consistently outperforming traditional risk stratification systems. Multimodal and deep learning approaches integrating radiologic, pathologic, and genomic data appear most promising for precision prognostication and personalized adjuvant therapy selection. Prospective validation and explainable AI integration are needed prior to routine clinical adoption. Research Sponsor: None.

11537 **Poster Session**

Ripretinib as preoperative therapy in patients with potentially resectable advanced gastrointestinal stromal tumors after imatinib failure: Final analysis of a prospective, multicenter study. First Author: Linxi Yang, Department of Gastrointestinal Surgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Background: Cytoreductive surgery may improve outcomes in patients with locally advanced or metastatic gastrointestinal stromal tumors (GIST) after progression on imatinib. Ripretinib has shown a high objective response rate (ORR) and a favorable safety profile in advanced GIST, suggesting its potential for tumor downstaging and enabling surgical intervention. This study evaluated the efficacy and safety of ripretinib as preoperative therapy in patients with imatinib-resistant, potentially resectable advanced GIST. **Methods:** This single-arm, multicenter, exploratory study (NCT05132738) enrolled patients with imatinib-resistant, locally advanced or recurrent metastatic GIST who met the following criteria: 1) ≤5 evaluable lesions on CT/MRI; 2) resection deemed high-risk by multidisciplinary team (MDT) assessment (meeting one of the following): a) The maximum diameter of a single lesion is ≥10 cm; b) Organ function damage surgery is required; c) Multiple organ resection surgery is required. Patients received ripretinib 150 mg once daily (QD) up to 6 months before surgery. The primary endpoint was the no evidence of disease rate (NED Rate). Secondary endpoints included the R0/R1 resection rate, surgery rate, and ORR. **Results:** As of January 2026, 20 patients were enrolled, with a median age of 58 years (range: 31-74). The most common primary tumor site was the small intestine (70%). The median sum of target lesion diameters was 10.8 cm (range: 3.2-33.7). The median duration of preoperative ripretinib was 5 months (range: 2-6). The median best percentage change in the sum of target lesion diameters was -20.5% (range: -47.2% to +56.0%). 8 patients (40.0%) achieved a partial response (PR) and 10 patients (50.0%) had stable disease (SD). Median time to response was 2.0 months (range: 2.0-6.0). 70% (14/20) of patients underwent surgery and the NED rate was 92.9% (13/14). Of the 13 patients who achieved R0 resection, 8 (61.5%) have maintained NED to date. Only 1 patient experienced intestinal fistula as a surgical complication, which was unrelated to ripretinib treatment. After surgery, 6 patients continued ripretinib therapy, while 3 switched to imatinib therapy and 5 switched to sunitinib therapy. With a median follow-up of 20.4 months (range: 8.1–47.6), the median overall survival (OS) was immature. **Conclusions:** These findings demonstrate that preoperative ripretinib effectively reduced tumor burden in patients with imatinib-resistant, potentially resectable advanced GIST, and facilitated successful surgery intervention. Notably, the approach achieved a high NED rate and a low surgical complication rate, supporting ripretinib as a safe and effective preoperative treatment option. Clinical trial information: NCT05132738. Research Sponsor: None.

11538 **Poster Session**

Clinical characteristics and outcomes of germline and sporadic NF1-associated gastrointestinal stromal tumors: Insights from a real-world patient registry. First Author: Denisse Evans, The Life Raft Group, Wayne, NJ

Background: Neurofibromatosis type 1 (NF1)-associated gastrointestinal stromal tumor (GIST) is a rare, distinct molecular subtype, typically lacking KIT or PDGFRA mutations. Standard KIT-targeted therapies show limited efficacy, highlighting the need for alternative systemic approaches. Real-world data on the clinical features, treatment patterns, and outcomes of NF1-associated GIST are limited. **Methods:** The Life Raft Group (est. 2000) Registry is an international, observational registry. Patients with GIST and documented NF1 mutations without another primary oncogenic alteration were included. Demographic, tumor, and treatment characteristics were summarized; group differences were assessed using Fisher's exact test, and disease-free survival (DFS) and overall survival (OS) were estimated by Kaplan–Meier methods. **Results:** A total of 38 patients were identified (1.3% of the total registry, n = 2990) and stratified as germline NF1 (n = 18) and sporadic NF1 (n = 20). Median age at diagnosis was 57 years; 53% (n = 20) of patients were female, with a higher proportion of germline NF1 than sporadic NF1 (60%, n = 12 vs 40%, n = 8). Conversely, among males, sporadic NF1 was more common than germline NF1 (67%, n = 12 vs 33%, n = 6). Tumors predominantly arose in the small bowel (79%). Germline NF1 patients exhibited significantly higher rates of multifocal disease compared with sporadic NF1 patients (85% vs 15%, p = 0.0006). Most patients presented with localized disease (84%, n = 32), with similar proportions between germline and sporadic NF1 (78%, n = 14 vs 90%, n = 18). All localized patients underwent surgical resection, achieving R0 margins in 72% of cases. Among patients who developed advanced disease (de novo metastatic or recurrent disease; n = 18), 67% received systemic therapy including MEK inhibitors in 22% (n = 4). One patient achieved durable disease control on selumetinib for nearly six years and remains on treatment. Median follow-up was 37.6 months (2.5–185). In localized patients, 5-year DFS was 65% (95% CI: 39–100) for germline and 46% (95% CI: 25–84) for sporadic NF1; median DFS was 55.4 months in sporadic NF1 and not reached in germline NF1. 10-year OS was 78% (95% CI: 62–98) overall, 88% (95% CI: 67–100) for germline, and 83% (95% CI: 64–100) for sporadic localized patients. Survival estimates in metastatic patients were highly variable due to small numbers. **Conclusions:** In this real-world registry analysis, NF1-associated GIST shows small bowel predominance and frequent multifocality, particularly in germline NF1. Most patients achieve disease control with surgery. MEK inhibitors may demonstrate potential activity in advanced NF1 GIST. These findings highlight phenotypic differences between germline and sporadic NF1-associated GIST and support further evaluation of MEK-targeted therapy in patients with metastatic disease. Research Sponsor: None.

11539 **Poster Session**

Updated clinical and translational results of olverembatinib (HQP1351) in patients with succinate dehydrogenase (SDH)–deficient tumors. First Author: Haibo Qiu, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China

Background: SDH deficiency causes succinate accumulation and metabolic defects in gastrointestinal stromal tumor (GIST) and paraganglioma. Olverembatinib downregulates lipid uptake protein CD36, restricting fatty acid supply required for SDH-deficient GIST cell growth. We report updated clinical and translational results from study HQP1351SJ0003 (NCT03594422) of olverembatinib in SDH-deficient GIST and paraganglioma. **Methods:** Patients (pts) (≥ 12 years) with GIST and other solid tumors received olverembatinib 30 to 50 mg PO QOD. Primary cells from tumor tissues of 9 pts with SDH-deficient GISTs were used for *ex vivo* analyses. All samples were collected at Sun Yat-sen University Cancer Center, with informed consent from pts. Cell migration/invasion was evaluated by wound healing, Transwell migration, and Matrigel invasion assays. Lipid levels were quantitated by LC-MS. Knockdown of CD36 and p38 was done by siRNA. Protein levels were assessed by western blot. **Results:** As of November 13, 2025, a total of 32 pts, including 26 pts with IHC-confirmed SDH-deficient GIST, had received olverembatinib. The median age of pts with SDH-deficient GIST was 30 (range 13-56) years; 19 (73.1%) were female. Twenty-five pts (96.2%) had received ≥ 1 TKI and 13 (50.0%) ≥ 3. Six (23.1%) pts experienced PR as best response, and the median PFS was 25.7 (range 12.9-NR) months. An additional six pts with paraganglioma had received olverembatinib (all were SDH-deficient as determined by either negative SDHB IHC or *SDHB* gene mutation). The median age was 47.5 (range 31-61) years; all were male. Best responses were observed in four pts, with SD lasting ≥ 4 cycles (CBR, 66.7%); SD represents meaningful clinical benefit in this slow-growing tumor type. The median PFS was 8.25 (range 1.87-NR) months. SDH-deficiency was associated with a higher risk of tumor metastasis. In SDH-deficient (vs. SDH-competent) GIST cells, significantly higher linoleic acid levels were observed. Supplementation of free fatty acids promoted SDH-deficient cell migration, which could be inhibited by olverembatinib at 30 nM. In addition, siRNA knockdown of p38, a kinase target of olverembatinib, and treatment with two p38 inhibitors significantly downregulated CD36 protein levels, suggesting that p38 regulates cellular CD36. Further, western blot analysis showed that olverembatinib dose-dependently inhibited CD36 protein and phosphorylated p38 protein levels in primary cells from SDH-deficient pts. These findings suggest olverembatinib suppresses fatty acid-promoted migration via the p38-CD36 pathway. **Conclusions:** Olverembatinib showed sustained clinical efficacy in SDH-deficient GIST and paraganglioma. Mechanistically, olverembatinib inhibits fatty acid–promoted invasion and migration of SDH-deficient GIST by targeting the p38-CD36 signaling pathway. Clinical trial information: NCT03594422. Research Sponsor: Ascentage Pharma Group Corp Ltd. (Hong Kong).

11540 **Poster Session**

Circulating tumor DNA monitoring for early detection of disease recurrence in bone/soft tissue sarcoma. First Author: Maggie Yuxi Zhou, Stanford University School of Medicine, Department of Medicine, Stanford, CA

Background: Circulating tumor DNA (ctDNA) is a powerful, minimally invasive biomarker of treatment response and patient prognosis in many tumors. Here, we assessed the clinical performance of the Signatera assay in patients with bone and soft tissue sarcomas in assessing molecular residual disease (MRD). **Methods:** We performed a retrospective analysis of patients at our institution who underwent commercial ctDNA testing using the Signatera mPCR-NGS assays after curative intent resection of their primary tumor. Patients with oligometastatic disease were included if they also underwent resection of oligometastatic sites and did not have any evidence of residual disease. Additional inclusion criteria included three or more ctDNA draws in the MRD setting with at least one ctDNA blood collection within one of year of completing curative intent procedures and at least 6 months of clinical follow up after surgery. ctDNA positivity was defined as any detectable level of ctDNA at any time point in the patient's treatment course after surgery. **Results:** We reviewed 305 patients who underwent Signatera ctDNA collection; 107 patients met the inclusion criteria for this study. The most common reason for not meeting inclusion criteria was advanced/unresectable disease (n = 168). The included 107 patients underwent over 1300 plasma ctDNA assessments in the MRD setting (average 12 ctDNA assessments per patient) between September 2019 and November 2025. For the overall cohort, sensitivity was 75% (36/48); specificity was 100% (36/36). One patient with angiosarcoma had ctDNA detected one month prior to data cut-off and was awaiting re-staging imaging. The largest represented histologies were leiomyosarcoma (n = 42) and undifferentiated pleomorphic sarcoma and related tumors (n = 22); sensitivity were 85% (22/26) and 57% (4/7), respectively. The median duration of follow-up after surgery was 41 months (range 1.6 to 79 months). Of the 48 patients with disease recurrence, 27 (60%) developed local disease recurrence only, 17 (38%) developed distant recurrence only, and 4 (9%) developed local and distant disease recurrence. The most common site of distant disease recurrence was in the lungs (n = 16). Sensitivity was lowest in the patients who developed disease recurrence isolated to the lungs (42%, 5 out of 12) compared to patients who developed disease recurrence not confined to the lungs (89%, 32 out of 36). Of the patients who had ctDNA detected at time of recurrence, 47% (17/36) demonstrated ctDNA positivity before detection of recurrence on imaging with an average lead time of 20 days. **Conclusions:** In a cohort of over 100 sarcoma patients with over 1300 plasma samples collected in the MRD setting, Signatera ctDNA assay demonstrated a clinical sensitivity of 75% and specificity of 100% for relapse detection with the highest sensitivity in leiomyosarcoma (85%) and when disease recurrence was not confined to the lungs (89%). Research Sponsor: None.

11541 **Poster Session**

Cell proliferation, immune cell infiltration, and survival outcomes in sarcomas with high cancer-associated fibroblast expression. First Author: Olivia Martin, Roswell Park Cancer Center, Buffalo, NY

Background: Cancer-associated fibroblasts (CAFs) play an integral role in the tumor microenvironment and have been linked to tumor aggravation and promotion of metastatic potential. CAFs are often abundant in sarcomas, but their role is understudied partly because both share a similar mesenchymal origin. We aimed to investigate the relationship between CAFs and clinical characteristics in sarcomas using transcriptomics. **Methods:** Genomic and clinicopathologic data was acquired from The Cancer Genome Atlas Sarcoma cohort. Cases were divided into high and low CAF groups using the median CAF level. Immune cell compositions including CAFs were determined using the xCell algorithm. Institutional Review Board waiver was deemed applicable as the data is de-identified from publicly available databases. **Results:** A total of 258 patients including leiomyosarcoma (LMS, n=83), myxofibrosarcoma/undifferentiated pleomorphic sarcoma (MFS/UPS, n=80), dedifferentiated liposarcoma (DDLPS, n=46), and other pathologies (n=20), were analyzed. DDLPS had significantly greater CAFs than the other subtypes (p=0.0025). CAF expression varied significantly by tumor grade, with grade 3 tumors having the lowest CAF expression and grade 1 & 2 tumors having significantly higher CAF expression ($p<0.001$). Ki67 was significantly lower in the high CAF tumors ($p<0.001$). On GSEA, high CAF sarcomas showed significantly less enrichment in myc targets v1 (NES= -2.67, FDR<0.001), myc targets v2 (NES=-2.25, FDR<0.001), G2M checkpoint (NES=2.39, NES<0.001), E2F targets (NES=-2.66, FDR<0.001), mitotic spindle (NES= -1.33, FDR= 0.015), and mTORC1 signaling (NES=-2.33, FDR <0.001); all consistently showing that high CAF sarcomas are less proliferative. In terms of genomic instability, high CAF sarcomas were significantly associated with less homologous recombination deficiency ($p<0.001$), intratumor heterogeneity ($p<0.001$), aneuploidy (p=0.003), and silent mutation rates (p=0.036). Analysis of immune cell composition revealed significantly less infiltration of B-cells (p=0.004), CD8 T-cells (p=0.013), Th1 cells ($p<0.001$), Th2 cells (p=0.008), and macrophages (p=0.027) in the high CAF group. Differential gene expression analysis demonstrated that C7, SESN1, FAM198A, were the most, and WNT7B, ENO1, TM4SF19 were the least expressed among 20511 genes analyzed in high CAF sarcomas. High CAF sarcoma were associated with significantly better disease-free survival (HR= 0.48 (95% CI 0.34-0.68), $p<0.001$) as well as overall survival compared with low CAF sarcomas (HR= 0.5 (95% CI 0.34-0.76), $p< 0.001$). **Conclusions:** CAFs are associated with less cell proliferation, less immune cell infiltration, and better survival. Further studies are warranted to develop CAFs as a prognostic biomarker for sarcoma patients. Research Sponsor: None.

11542 **Poster Session**

Myxoid/round cell liposarcoma misdiagnosis incidence, etiology, and importance of NY-ESO-1 testing: Retrospective analysis of the Tempus database. First Author: Michael Jason Nathenson, US World Meds, Needham, MA

Background: Liposarcoma is composed of multiple unique sarcoma subtypes, specifically myxoid/round cell liposarcoma (MRCLS), well differentiated and dedifferentiated liposarcoma (WD LPS and DD LPS), and pleomorphic liposarcoma. These are genetically distinct entities with different treatment paradigms. MRCLS is driven by a translocation between DDIT3 and FUS or EWSR1, detectable in 100% of MRCLS. WD and DD LPS are characterized by amplification of MDM2 and CKD4, and pleomorphic LPS is genetically complex. Recently, new treatments for liposarcoma are specific to the LPS type (CDK4/6 inhibitors; CTA directed engineered T Cells) which highlights the importance of an accurate liposarcoma subtype diagnosis. **Methods:** A retrospective analysis of the tempus RNA database for DDIT3 translocations and NY-ESO-1 (CTAG1B) expression in MRCLS was conducted. 101 patients (pts) with MRCLS were identified; 27 pts lacked Next Generation Sequence data for tumor samples leaving 74 pts that were selected for analysis. RNA was sequenced with either the Tempus RS or the RS.v2 assays. Patients' tumor samples with tumor purity $<30\%$ were excluded from assessment of CTAG1B expression. Gene expression values in this analysis were normalized by transcripts-per-million (TPM) transformed to log2(TPM+1) units. The threshold of 2 (log2(TPM+1)) was set as the cut off of true positive for CTAG1B expression. **Results:** The DDIT3 fusion was identified in 65/74 (88%) patients. In 9/74 (12%) patients, there was no DDIT3 fusion detected. Out of the 65 patients that were positive for the MRCLS translocation 60/65 (92%) were DDIT3-FUS, and 5/65 (8%) were DDIT3-EWSR1. The MRCLS DDIT3 fusion-negative samples were 5/9 (56%) positive (pos) for MDM2 amplification and CDK4 amplification. The Tempus tumor of origin algorithm predicted all DDIT3 fusion-pos MRCLS samples to be soft tissue sarcoma (where predictions were made; 53 of 65 pts) and the DDIT3 fusion-neg samples to be fibrosarcoma in one case and liposarcoma in 7 cases. The last fusion-neg case did not have a tumor of origin prediction. The median expression of CTAG1B was 7.14 TPM in all patients, 7.2 TPM (range 3.1 to 8.7) in DDIT3-FUS samples, 7.5 TPM (range 5.7 to 7.7) in DDIT3-EWSR1 samples, and 0.04 (range 0.0 to 3.7) in DDIT3 fusion-neg samples. There was no difference in CTAG1B expression by biopsy site, metastatic status, stage, tumor purity, or center of diagnosis. **Conclusions:** It is of critical importance to accurately determine the liposarcoma subtype which influences the selection of new targeted treatments. This analysis highlights a 12% rate of misdiagnosis of MRCLS and suggests that WD/DD LPS can be misdiagnosed as MRCLS. Additionally, this study predicts that 100% of MRCLS with confirmed DDIT3 translocation will be NY-ESO-1 (CTAG1B) pos which highlights the utility of NY-ESO-1 as a diagnostic marker for NY-ESO-1 directed therapies. Research Sponsor: Adaptimmune; US World Meds CT, LLC.

11543 **Poster Session**

Synovial sarcoma misdiagnosis and potential utility of NGS testing patient identification for autologous T cell therapy: Retrospective analysis of Tempus database. First Author: Michael Jason Nathenson, US World Meds, Needham, MA

Background: Metastatic synovial sarcoma (SS) is commonly treated with anthracycline and other chemotherapy with poor survival outcomes. Afamitresgene autoleucel (Tecelra) is a genetically modified autologous T cell therapy that was FDA approved in August 2024, based on ORR of 43.2% and median DoR of 6 months. It is indicated for previously treated HLA-A*02:01-03 and 06 allele positive patients (pts) with unresectable or metastatic SS whose tumors express MAGE-A4. SS is characterized by SS18-SSX gene fusion in $>$ 95% of cases and this gene fusion is not found in other neoplasms. Commercial NGS testing may contribute to identification of eligible pts. **Methods:** Pts with diagnosis of SS and/or SS18 gene fusion were identified by retrospective analysis of the Tempus database. Demographic and disease characteristics were described for each pt and assessed for correlation with diagnosis and presence of the SS18 gene fusion. RNA was sequenced with the Tempus RS and RS.v2 assays. Gene expression values in this analysis were normalized by transcripts-per-million (TPM) and transformed to log2(TPM+1) units. The threshold of 1.62 (log2(TPM+1)) was set as the cut off for determining true positive of MAGEA4 expression. HLA type and RNA expression of MAGE-A4 was used to identify pts potentially eligible for associated T cell therapies. **Results:** 110 pts were analyzed, including 86 pts (78%) with SS diagnosis with SS18 fusion, 12 pts (11%) with SS diagnosis but no detected SS18 fusion (SS/SS18-), and 12 pts (11%) with SS18 fusion but a non-SS diagnosis. Age at diagnosis, sex, race, state of diagnosis, and institution type (academic vs non-academic) were not associated with misalignment between the reported diagnosis and presence or absence of the SS18 fusion. For SS/SS18- pts the location of the tumor did not differ from expected SS primary locations, and the Tempus tumor of origin predicted SS diagnosis in 2/12 pts, non-SS diagnosis in 7/12 pts, and not reported 3/12 pts. The most common predicted non-SS diagnosis was malignant peripheral nerve sheath tumor (MPNST, 5 pts). Non-SS/SS18+ pts did occur in unusual locations (Pancreas, small intestine, bone, peripheral nervous system), and 10/12 were predicted by the tempus tumor of origin algorithm to be SS. The recorded diagnosis in these 12 pts was more commonly another sarcoma subtype (10/12), rather than a non-sarcoma diagnosis (2/12). MAGE-A4 expression $>$ 1.62 TPM was detected in 71% of all pts, 74% SS/SS18+ pt, 58% of SS/SS18- and 58% of non-SS/SS18 pts. When considering the required HLA type and MAGEA4 expression then 35% of all pts would be potentially eligible for afami-cel. **Conclusions:** Commercial NGS testing may increase identification of pts with SS, which is important for novel T cell therapy eligibility. A low threshold should be considered for diagnosing SS in unusual locations when the SS18 fusion is detected. Research Sponsor: adaptimmune; US World Meds CT, LLC.

11544 **Poster Session**

Ultra-sensitive whole-genome sequencing–based molecular residual disease detection in resectable sarcoma in MONSTAR-SCREEN-3. First Author: Toru Wakamatsu, Osaka International Cancer Institute, Osaka, Osaka, Japan

Background: Circulating tumor DNA (ctDNA)–based molecular residual disease (MRD) detection has shown strong prognostic value in multiple epithelial cancers, but its utility in sarcoma remains poorly defined. Sarcomas are highly heterogeneous and often represent low-shedding tumors, limiting the sensitivity of conventional assays. The MONSTAR-SCREEN-3 evaluates the clinical performance of a whole-genome sequencing (WGS)–based MRD assay in a pan-cancer cohort, including patients with sarcoma. **Methods:** Personalized ctDNA panels were generated using a WGS-based tumor-informed platform (Myriad Genetics), incorporating up to 1,000 tumor-specific variants identified through WGS of matched tumor tissue. Serial plasma samples were collected at baseline, 1 month post-surgery, quarterly during the first year, and biannually thereafter for up to two years. **Results:** As of November 2025, 35 patients with resectable soft tissue sarcoma (n=33) and osteosarcoma (n=2) were enrolled; MRD results were available for 72 samples from 24 patients. Of whom, histology was myxofibrosarcoma (n=7), undifferentiated pleomorphic sarcoma (n=7), myxoid liposarcoma (n=5), dedifferentiated liposarcoma (n=3), epithelioid sarcoma (n=3) and others (n=10). Clinical staging distribution included Stage I/II/III/IV: 15%/19%/50%/15%. Most of patients underwent upfront radical surgery (2 cases received neoadjuvant chemotherapy). Personalized panel creation succeeded in 100% of patients (24/24), identifying a median of 3,510 highly confident tumor-specific alterations per patient (range: 730-7,931) and yielding bespoke panels containing 386-1,000 alterations. Customized panels were created with 96.4% SNVs and 3.6% indels. The assay demonstrated 87.5% baseline ctDNA detection (21/24), with 16.7% detected at ultra-sensitive levels (tumor fraction $<$100 parts per million [ppm]). In the ctDNA-negative cases, ctDNA tumor fractions were 0.0, 0.8 and 6.2 ppm, classified as ctDNA-negative based on a statistical threshold set at 99.615% specificity. Post-surgical MRD positivity rates were 20.0% (4/20) at 1 month, 7.1% (1/14) at 3 months, and 28.6% (2/7) at 6 months. Among these patients, four patients developed radiographic recurrence, with MRD detection preceding imaging by median 1.1 months (0.1-3.0). Extended follow-up and comprehensive longitudinal ctDNA dynamics will be presented. **Conclusions:** The WGS-based ctDNA assay demonstrated high technical feasibility in sarcoma, enabling detection of patient-specific tumor variants across a highly heterogeneous and low-shedding tumor population. In our cohort, MRD positivity was observed exclusively in patients who subsequently developed recurrence, highlighting the potential utility of WGS-based tumor-informed MRD analysis for surveillance and risk stratification in sarcoma. Clinical trial information: UMIN000053975. Research Sponsor: SCRUM-Japan Funds (https://scrum-japan.ncc.go.jp/); Myriad Genetics.

11545 **Poster Session**

Identification of checkpoint inhibitor resistance mechanisms in leiomyosarcoma through enrichment of active chromatin-associated cell-free DNA. First Author: Carlos Diego Holanda Lopes, Princess Margaret Cancer Centre – University Health Network, University of Toronto, Toronto, ON, Canada

Background: Leiomyosarcoma (LMS) is a sarcoma subtype with poor metastatic outcomes and limited treatment options. Checkpoint inhibitors (CPI) combination therapy may benefit LMS patients (pts). We previously showed (Lopes, ASCO 2025) that a liquid biopsy assay enriching for active chromatin–associated cell-free DNA (cfDNAac) identified biomarkers predicting clinical benefit in LMS pts treated with durvalumab plus olaparib or cediranib (NCT03851614). Here, we report longitudinal cfDNAac findings at baseline and progression. **Methods:** Plasma samples at baseline (n=30) and disease progression (n=22) were analyzed using a cfDNAac capture platform. Univariate analysis and recursive feature elimination identified genomic features associated with clinical benefit rate (CBR; complete response/partial response or stable disease >6 months). Molecular transcriptomic profiles, pathway enrichment, and copy number variation (CNV) were analyzed and correlated with CBR and progression-free survival (PFS). Linear mixed-effects models assessed temporal differences in cfDNAac-derived biomarkers between CBR and non-CBR groups. **Results:** A total of 1,570 baseline cfDNAac features distinguished pts who achieved CBR from those who did not (n=8 vs 22, $p < 0.01$). Pts with CBR exhibited enrichment of immune-related signatures (i.e., B and T-cell activation, lymphocyte differentiation, and a decrement of extracellular matrix organization [ECM]), all of which were individually significantly associated with longer PFS ($p < 0.05$). Upon progression, B-cell and T-cell activation significantly decreased, whereas ECM-related signatures increased in CBR compared to non-CBR group, the latter of which remained stable. A higher baseline tumor fraction (>5%) was also associated with reduced CBR ($p < 0.05$) and shorter PFS (HR = 3.33; CI: 1.32-8.40 $p < 0.01$). Recurrent CNV losses on chromosome 15 correlated with improved PFS (HR = 2.48; 95% CI: 0.99-6.22; p = 0.052) and CBR (p = 0.0073). At progression, these CNV reverted in CBR pts but remained stable in non-CBR patients. **Conclusions:** This active chromatin-associated cell-free DNA profiling enables a non-invasive monitoring of dynamic tumor microenvironment remodeling over time and provides insights into emerging mechanisms of resistance to CPI in LMS pts. Research Sponsor: Hold'em for Life.

11546 **Poster Session**

Prognostic biomarkers in retroperitoneal dedifferentiated liposarcoma and their clinical impact on patient management. First Author: Ilaria Tortorelli, Oncology 1 Unit, Department of Oncology, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy

Background: The prognosis of patients (pts) with retroperitoneal dedifferentiated liposarcoma (DDLPS) is mainly driven by tumor size, grade, patient age, and completeness of resection. Furthermore, the expression of myogenic markers has been associated with poorer outcomes. Prognostic nomograms, such as Sarculator, and transcriptomic signatures—most notably the Complexity INdex in SARComas (CINSARC)—have improved risk stratification. However, given the rarity of DDLPS and the limited evidence guiding treatment, identifying robust prognostic biomarkers remains a major challenge. This study evaluated the prognostic impact of clinical, morphological, and molecular features and assessed the performance of Sarculator and CINSARC in retroperitoneal DDLPS. **Methods:** A retrospective observational study was conducted on pts with retroperitoneal DDLPS treated at the Veneto Institute of Oncology (IOV)-IRCCS between 2004 and 2024. Tumor samples with adequate material underwent morphological, immunohistochemical, and molecular analyses, including CINSARC assessment. Disease-free survival (DFS) and overall survival (OS) were evaluated in surgically treated pts (Cohort 1), while progression-free survival (PFS) and OS were assessed in pts receiving first-line chemotherapy (Cohort 2). Sarculator was applied to Cohort 1, and its discriminative ability was evaluated using ROC curves. Concordance between CINSARC and Sarculator was also examined. **Results:** A total of 119 pts were included. In the overall population, tumor grade (3 vs 2: HR, 2.23; 95% CI 1.06 - 4.70; p = 0.03) and age (<65 vs ≥65: HR, 0.43; 95% CI 0.22 - 0.85; p = 0.02) were the most significant predictors of OS. In Cohort 1, these variables remained determinants of survival. In Cohort 2, sex, tumor size and differentiation significantly affected survival, with rhabdomyoblastic differentiation conferring the worst prognosis (p = 0.04). When Sarculator was applied to Cohort 1, a moderate discriminative ability was observed for OS (AUC = 0.75), with a lower performance for DFS (AUC = 0.64). Molecular analyses were performed on 32 samples; MYOG transcripts, indicative of rhabdomyoblastic differentiation, were detected in 8 cases. Based on CINSARC, 11 pts (34.4%) were low risk and 21 (65.6%) high risk. Agreement between Sarculator and CINSARC was moderate for both OS (Cohen's Kappa, $\kappa = 0.40$) and DFS ($\kappa = 0.55$). **Conclusions:** To our knowledge, our study is among the largest conducted in retroperitoneal DDLPS specifically evaluating clinico-pathological features and the performance of Sarculator and CINSARC. Our findings support the negative prognostic impact of rhabdomyoblastic differentiation. Further investigation of differentiation patterns, combined with prognostic nomograms and transcriptomic signatures, may improve the identification of high-risk pts and support more personalized therapeutic strategies. Research Sponsor: None.

11547 **Poster Session**

Unsupervised clustering of RNA-Seq data to identify molecular subtypes of sarcomas. First Author: Michael J. Robinson, Vanderbilt University Medical Center, Nashville, TN

Background: Sarcomas are a rare and heterogeneous group of malignancies, which include over 100 histological subtypes. Their histologic diversity present significant diagnostic and therapeutic challenges. This study aimed to define clinically relevant transcriptional subtypes using RNA-Sequencing (RNA-seq) data, and to further characterize the immune and metabolic microenvironment. **Methods:** This study uses data from the "Cohort to Augment the Understanding of Sarcoma Survivorship Across the Lifespan" (CAUSAL) study, which has enrolled sarcoma patients, treated at VUMC, from 2002-2026 for investigation of health outcomes. We analyzed RNA-seq data from tumor samples of 430 participants representing 42 unique histological sarcoma subtypes. We utilized sparse K-means clustering to identify stable subtypes and developed a classifier using a 310-gene panel. The immune microenvironment was characterized by applying CIBERSORTx deconvolution. Sarcoma subtype reproducibility and prognostic validity were evaluated using the Cancer Genomic Atlas data. **Results:** Among 430 samples, consensus matrices and diminishing gains in Cumulative Distribution Function (CDF) behavior yielded six distinct sarcoma molecular subtypes (SMS), each demonstrating strong correlation with known sarcoma histologies. SMS1 (labeled as "Cytotoxic-Adaptive", n=30) and SMS6 ("Interferon-Activated", n=97) were characterized by robust immune infiltration and interferon signaling, suggesting a potential sensitivity to immune checkpoint blockade. SMS2 ("Myeloid-Dominant", n=93) primarily grouped undifferentiated pleomorphic sarcoma, giant cell sarcoma, and myxofibrosarcoma, and exhibited an immune-suppressive, macrophage-rich phenotype. SMS3 ("Early-Onset", n=58) mostly grouped Ewing and synovial sarcoma and comprised mostly fusion-driven tumors with an immune-desert landscape. SMS4 ("EMT-Stromal", n=107) mostly comprised desmoid and leiomyosarcoma and was defined by epithelial-mesenchymal transition and fibrosis, correlating with the poorest 10-year overall survival (*p=0.022*). SMS5 ("Metabolic", n=45) consisted exclusively of Gastrointestinal Stromal Tumors, with distinct metabolic programming and favorable prognosis. **Conclusions:** Each SMS transcends histological boundaries, grouping tumors based on shared immune, stromal, and metabolic features. This classification highlights distinct vulnerabilities in the tumor microenvironment, offering a functional framework to guide future precision treatment interventions, such as immunotherapy for SMS1/SMS6 and stromal-targeting agents for SMS4. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 4UH3CA260318-03.

11548 **Poster Session**

A subset analysis of clinical activity and pharmacodynamic biomarkers in patients with sarcomas in the phase 1 dose-escalation study of STC-15, a METTL3 inhibitor. First Author: Justin C. Moser, HonorHealth Research Institute, Scottsdale, AZ

Background: The RNA methyltransferase METTL3 is responsible for the generation of N6-methyladenosine (m6A), the most abundant modification on mRNA and long non-coding RNA. Accumulating evidence suggests numerous roles of METTL3 in cancer initiation and progression highlighting the rationale for targeting this enzyme in oncology. STC-15, a first in class small molecule inhibitor of METTL3 developed by Storm Therapeutics, demonstrated efficacy in pre-clinical models of cancer characterized by their dependence on m6A-mediated mRNA metabolism, including sarcomas that derive from a common mesenchymal progenitor. We report the clinical activity and pharmacodynamic (PD) biomarkers observed in a subset analysis of sarcomas from a first-in-human trial in patients with advanced malignancies. Full results of the study have been previously presented. **Methods:** This multi-center, open-label, dose escalation study of STC-15 administered oral capsules daily (QD) or three times a week (TIW) in 21-d treatment cycles. Dose escalation followed a 3+3 modified Fibonacci regimen. Primary objectives (safety and pharmacokinetics (PK)) and secondary objectives (efficacy) were previously presented. A subset analysis of sarcoma and selected patients evaluates anticancer activity and PD biomarkers, including target engagement, gene expression analysis, and targeted m6A RNA sequencing using the EpiPlex platform. **Results:** Of 42 patients enrolled, 35 were evaluable and 13 were sarcoma patients with a mean of 3 prior lines of therapy. Of 13 sarcoma patients with at least 1 on-treatment scan, DCR was 54% at 12 weeks with 1 confirmed PR (8% ORR) in angiosarcoma (DOR 22 months), and mPFS of 5.5 months as of 27 January 2026. Seven sarcoma patients presenting with four subtypes experienced a best response of SD, including tumor regressions. Treatment duration ranged from 15-828 days, with two sarcoma patients remaining on treatment for 590 and 828 days, respectively. An average of >50% reduction in m6A on mRNA in peripheral blood within the first 24h post dosing was observed in dose-escalating cohorts from 60 mg QD to 200 mg TIW, confirming target engagement. Moreover, we present an expanded analysis using the m6A-directed NGS EpiScout platform, where we evaluate both the effects of STC-15 on global m6A mRNA abundance and transcriptional changes that may contribute to an anti-tumor response specific to soft tissue and bone sarcomas. **Conclusions:** Treatment with STC-15 offers a new paradigm for the treatment of a broad range of sarcomas by halting the cell differentiation process from mesenchymal progenitors. Early biomarker data provide proof of mechanism in target engagement and changes in gene expression, consistent with pharmacological activity and clinical response. Further investigation of efficacy and biomarkers of STC-15 in a Phase 2 sarcoma study is ongoing. Clinical trial information: NCT05584111. Research Sponsor: None.

11549 **Poster Session**

Use of subtype-specific patterns of clinically relevant antibody–drug conjugate targets in sarcoma to guide precision oncology strategies. First Author: Sohil Reddy, The Ohio State University, Columbus, OH

Background: Sarcomas are rare, biologically heterogeneous malignancies with limited targeted treatment options. Antibody–drug conjugates (ADCs) have demonstrated clinical efficacy across multiple solid tumors by exploiting tumor-associated surface antigens; however, their development in sarcoma has been limited by incomplete characterization of ADC target expression across subtypes. We evaluated expression of clinically relevant ADC targets across sarcoma histologies using bulk RNA sequencing and compared these patterns to cancer types with established ADC activity to generate a sarcoma-wide map of ADC target expression. **Methods:** We analyzed expression of 18 genes encoding cell-surface ADC targets that are FDA-approved or in active clinical development across more than 1,000 sarcoma samples spanning multiple histologic subtypes. Transcriptomic data were derived from The Cancer Genome Atlas (TCGA), an institutional sarcoma registry, and the Oncology Research Information Exchange Network (ORIEN). Per-sample z-scores were generated using pan-cancer distributions to enable standardized comparison. Z-score distributions were summarized using ordinal bins to define target enrichment across sarcoma subtypes. Parallel pan-cancer analyses were performed for contextual comparison. **Results:** Sarcomas demonstrated heterogeneous but subtype-specific expression of multiple ADC targets across datasets. Several subtypes exhibited elevated expression of select ADC targets, with z-scores comparable to or exceeding those observed in tumor types where ADCs have established clinical activity. ADC targets of particular interest included LRRC15 and CD276 (B7-H3). LRRC15, currently in investigation as an ADC in breast cancer, demonstrated enrichment in sarcoma, with 28% of undifferentiated pleomorphic sarcoma and 38% of dedifferentiated liposarcoma samples exhibiting z-scores $>$ 2, compared to 12% in breast cancer. CD276 similarly showed subtype-specific overexpression across these sarcoma subtypes. No single target was uniformly overexpressed across all sarcomas, underscoring biologic heterogeneity. Pan-cancer comparison revealed that certain sarcoma subtypes ranked among the highest expressors for specific ADC targets. **Conclusions:** Across a cohort exceeding 1,000 sarcoma patients with diverse histological subtypes, we identify subtype-specific overexpression of multiple clinically relevant ADC targets. This subtype expression map provides a biologic rationale for expanding ADC development into molecularly selected sarcoma subpopulations and supports biomarker-enriched approaches to ADC trial design. Ongoing studies will validate these findings at the protein level using a sarcoma surfaceome approach, including immunohistochemistry and mass spectrometry based profiling. Research Sponsor: None.

11550 **Poster Session**

Distinct prognostic roles of *IDH* mutation and high-risk genomic alterations in patients with primary chondrosarcoma. First Author: Akshee Batra, University of Miami Sylvester Comprehensive Cancer Center/Jackson Health System, Miami, FL

Background: Prior studies report mixed associations between IDH mutation and survival in chondrosarcoma. We evaluated the prognostic impact of IDH mutation and high-risk genomic alterations in one of the largest multi-institutional cohorts while accounting for established prognostic factors. **Methods:** We retrospectively analyzed patients with histologically confirmed chondrosarcoma treated at the University of Miami and University of Florida. Patients with available molecular data were included. High-risk genomic alterations were defined as TP53, TERT, or cell-cycle pathway alterations. Endpoints included median overall survival (mOS), progression-free survival (mPFS) after treatment and distant metastasis–free survival (mMFS). Patients with metastatic disease at diagnosis were excluded from mMFS analyses. Multivariable Cox regression models were adjusted for age, sex, tumor grade and tumor type. **Results:** A total of 144 patients were included; 85 (59%) had NGS data. Median age was 60 years, and 46% had grade 3 disease. The majority of patients had conventional chondrosarcoma; 52 patients (36.1%) had dedifferentiated pathology. Among 64 IDH-mutant and 62 IDH-wildtype tumors, high-risk genomic alterations were identified in 48 patients, with comparable positive margin rates between IDH-mutant (14.1%) and IDH-wildtype (14.5%) cases. After multivariable adjustment for age, sex, tumor grade, and tumor type, IDH mutation was not independently associated with mOS (HR 1.26; p=0.48). However, IDH mutation demonstrated a trend toward inferior mPFS that did not reach statistical significance (HR 1.52; p=0.07) and was independently associated with inferior mMFS (HR 2.60; p=0.004). In contrast, high-risk genomic alterations were independently associated with inferior mOS (HR 2.45; p=0.025), mPFS (HR 2.94; p=0.003) and mMFS (HR 2.71; p=0.009) as compared to those patients without high-risk genomic alterations. **Conclusions:** After multivariable adjustment, IDH mutation conferred increased metastatic risk without an overall survival disadvantage, whereas high-risk genomic alterations consistently predicted poor outcomes across all survival endpoints. Research Sponsor: None.

Multivariable Cox regression analyses by survival endpoint in chondrosarcoma.

Endpoint	Comparison	Adjusted HR (95% CI)	p-value
Overall Survival	IDH mutant vs IDH wildtype	1.26 (0.66–2.40)	0.48
	High-risk NGS vs Low-risk NGS	2.45 (1.12–5.38)	0.025
Progression-Free Survival	IDH mutant vs IDH wildtype	1.52 (0.95–2.43)	0.077
	High-risk NGS vs Low-risk NGS	2.94 (1.45–5.96)	0.003
Metastasis-Free Survival	IDH mutant vs IDH wildtype	2.60 (1.35–5.01)	0.0043
	High-risk NGS vs Low-risk NGS	2.71 (1.28–5.74)	0.009

11551 **Poster Session**

Survival outcomes of cabozantinib treatment with and without immune checkpoint inhibition in patients with heavily pretreated advanced sarcoma. First Author: Lauren Li, Stanford Health Care, Palo Alto, CA

Background: Cabozantinib is an oral tyrosine kinase inhibitor (TKI), with key targets including MET, VEGFR2, AXL, RET, and others. It is commonly used to treat specific carcinomas, but its efficacy in treating sarcomas is still emerging, especially in combination with immune checkpoint inhibition. The benefit of cabozantinib with or without immune checkpoint inhibition (ICI) in previously heavily treated patients with advanced sarcoma is unclear, underscoring the need for further investigation. **Methods:** We report results from a retrospective study of heavily pretreated advanced sarcoma patients who received cabozantinib with or without ICI. Eligible patients included those who had locally advanced or metastatic sarcoma and were exposed to cabozantinib for a minimum of one day. Patients who participated in the clinical trial "Randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition versus cabozantinib in metastatic soft tissue sarcoma" were excluded from this study. **Results:** There were 105 eligible patients with thirty-one different histology types, a median age of 55 years old, of which 55% were female patients. The median lines of prior treatment were four. Approximately 40.9% of patients were treated with cabozantinib alone and 59.1% were treated with cabozantinib plus either nivolumab, or nivolumab plus ipilimumab, or pembrolizumab. The progression-free survival (PFS) of the full cohort was 3.3 months. Eight patients (7.6%) obtained a partial response (PR) and forty-two patients (40.0%) had stable disease (SD) longer than 3 months, with a clinical benefit rate (CBR) of 47.6%. Partial responses occurred across a variety of histologic subtypes, including small round cell tumor, UPS, osteosarcoma, leiomyosarcoma, GIST, liposarcoma, and angiosarcoma. Stable disease was observed in a variety as well, including but not limited to LMS, synovial sarcoma, ASPS, chondrosarcoma, and osteosarcoma. The median PFS and OS for the 47.6% of patients who obtained a clinical benefit (PR + SD) were 6.9 and 22.9 months, compared to the median PFS of 2.1 months ($p < 0.001$) and median OS of 7.4 months (p = 0.001) for the patients with progressive disease. Several patients with aggressive histology including osteosarcoma, desmoplastic small round cell tumor, synovial sarcoma and others had PFS more than 12 months. Combination therapy with cabozantinib and an ICI accounted for the majority of PR's observed, including the longest ongoing PR (>15.3 months) in a patient with desmoplastic small round cell tumor. **Conclusions:** In a cohort of heavily treated patients with advanced soft tissue and bone sarcoma, cabozantinib alone or with ICI showed durable CBR in nearly 50% of patients, suggesting cabozantinib alone or with ICI could be of substantial benefits to certain sarcoma patients who have very limited treatment options remaining. Research Sponsor: None.

11552 **Poster Session**

Phase 2 study integrating early palliative care in advanced sarcoma patients for enhanced quality of life (SARQUALITY Trial: NCT06805669): An interim analysis. First Author: Catherine S. Weadick, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Patients (pts) with advanced cancer may experience substantial symptom burden that adversely affects quality of life (QoL). Although early palliative care (EPC) integrated with standard oncologic care (SOC) has demonstrated clinical benefit, patients with sarcoma have been underrepresented in prior studies. This phase II trial evaluates whether EPC combined with SOC improves outcomes in pts with advanced sarcoma compared with SOC alone. Results from the first interim analysis are presented. **Methods:** Adult pts with advanced sarcoma who are systemic treatment naïve were randomized (1:1) to either SOC alone or with EPC. EPC intervention included palliative care (PC) review within 4 weeks of randomization, routine PC contact and access to 24-hour support. Pts receiving SOC alone are referred to PC at time of clinical need. Pts complete Edmonton Symptom Assessment System (ESAS) and EORTC QLQ-C30 questionnaires at baseline, weeks 6, 12 and 24. The primary endpoint is the change in ESAS score at week 12 compared to baseline. Secondary endpoints include EORTC QLQ-C30 score change, emergency department (ED) attendance and overall survival (OS). The aim is to accrue 136 pts, providing 80% power at one-sided 5% level of significance to detect standardised difference of 0.45 between-group in ESAS score from baseline to 12 weeks. **Results:** Enrollment commenced in July 2024. At data lock (November 2025), 44 pts were enrolled (SOC, n=21; EPC, n=23). The cohort was predominantly female (n=29, 66%), with a median age of 60 years (range 29–85). Soft tissue sarcoma accounted for 43 cases (one had osteosarcoma); 39 (89%) pts had metastatic disease and 5 (11%) had locally advanced disease. Age, gender, race, histologic subtype, and number and sites of metastases were balanced between arms. ESAS and EORTC scores for pts in EPC arm (Table 1) but ED attendances were similar (EPC-24, SOC-23). In SOC arm, symptom management interventions (radiation, surgery) occurred more frequently than the EPC arm (12 vs. 2 pts). Seven pts were referred to PC from the SOC arm (median of 3.2 months from randomization). OS data is immature. **Conclusions:** The interim results of SARQUALITY trial demonstrate EPC has an impact on ESAS and EORTC scores, however, further data required to demonstrate if there is a benefit on QoL. There was a reduction in number of symptom management interventions in EPC arm, suggesting EPC may reduce need for additional interventions. Trial accrual is ongoing. Clinical trial information: NCT06805669. Research Sponsor: None.

Mean score change at 6, 12 and 24 weeks compared with baseline.

Week	6			12			24		
Arm	EPC N=20	SOC N=20	p-value	EPC N=18	SOC N=18	p-value	EPC N=14	SOC N=15	p-value
ESAS (95% CI)	-1.8 (-9.0 – 5.5)	3.8 (-0.2 – 7.7)	0.172	-3.4 (-13.9 – 7.1)	3.2 (-2.8 – 9.1)	0.261	-1.8 (-11.4 – 7.9)	4.5 (0.0 – 8.9)	0.220
EORTC QLQ (95% CI)	-0.6 (-6.7 – 5.6)	4.5 (1.2 – 7.7)	0.143	0.2 (-5.6 – 6.0)	3.8 (-2.5 – 10.1)	0.379	0.0 (-6.4 – 6.4)	4.4 (-1.2 – 10.0)	0.274

11553 **Poster Session**

Impact of concomitant medications on immune checkpoint inhibitor outcomes in sarcoma. First Author: Adel Shahnam, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Immune checkpoint inhibitors (ICIs) are an established treatment for many malignancies, with an emerging role in sarcoma. While the impact of concomitant medications (CM) on ICIs has been described in other cancers, it has not been evaluated in sarcoma. We assessed the association between CM use and ICIs outcomes in sarcoma patients. **Methods:** This pooled post hoc analysis included 7 investigator-initiated phase II ICI-based trials enrolling patients with metastatic sarcoma between April 1, 2017, and May 30, 2024. Patients receiving ≥1 dose of ICIs were included. CM taken within 30 days prior to treatment initiation were defined as baseline; PRN medications were excluded. CM were recorded at each cycle through end of treatment and categorized by medication class; supplements/herbal agents included vitamins, minerals, probiotics, botanicals, amino acids, and other dietary substances. For progression-free survival (PFS), baseline and on-treatment CM were analyzed as time-dependent covariates using Cox proportional hazards models. Overall survival (OS) analyses were limited to baseline CM. Logistic regression evaluated associations between baseline CM and objective response (ORR) and immune-related adverse events (irAEs). Toxicity was graded per CTCAE v5.0. **Results:** A total of 321 patients (median age, 58 years) were included. The most common histologies were liposarcoma (all subtypes, 22%), undifferentiated pleomorphic sarcoma (22%), and leiomyosarcoma (19%); 46% had received ≥3 prior lines of therapy. ICI was combined with cytokine/oncolytic therapies (43%), targeted agents (38%), or chemotherapy (19%). After a median follow-up of 47.4 months, ORR was 18%, median PFS was 3.9 months (95% CI, 3.09–5.32), and median OS was 19.9 months (95% CI, 17.5–22.9). Grade ≥3 irAEs occurred in 25% of patients, most commonly hematologic (6%) and hepatic (5%). On-treatment use of supplements/herbal agents was associated with longer PFS (HR 0.64, 95% CI 0.50–0.82; p<0.01), while on-treatment anti-infective use was associated with shorter PFS (HR 1.55, 95% CI 1.06–2.25; p=0.02); baseline anti-infective use was not associated with PFS. Baseline supplement/herbal use was associated with longer OS (HR 0.69, 95% CI 0.53–0.90; p<0.01), whereas baseline non-opioid (HR 1.54, 95% CI 1.10–2.16; p=0.01) and opioid analgesic use (HR 2.14, 95% CI 1.45–3.14; p<0.01) were associated with shorter OS. Baseline antihistamine use showed a trend toward increased gastrointestinal irAEs (OR 2.37, 95% CI 0.97–5.98; p=0.06). No CM class was associated with ORR. **Conclusions:** Concomitant medication use is associated with differential ICI outcomes in metastatic sarcoma and warrants prospective evaluation. Research Sponsor: None.

CM	Timing	Outcome	HR
SH	OT	PFS	0.64
AI	OT	PFS	1.55
AI	BL	PFS	1.37*
SH	BL	OS	0.69
Non-OA	BL	OS	1.54
OA	BL	OS	2.14

*Not statistically significant; SH = Supplements/herbal agents, AI = Anti-infectives, OA = Opioid analgesia, OT = on-treatment, BL = Baseline.

11554 **Poster Session**

Patient-reported global health to predict negative health outcomes in patients with advanced sarcoma. First Author: Marium Husain, The Ohio State University Medical Center James Comprehensive Cancer Center, Columbus, OH

Background: Many patients with sarcoma deal with adverse impacts on their (QoL) related to their underlying disease as well as treatment-related effects. Unplanned hospital admissions and emergency department (ED) visits occur from uncontrolled symptoms that delay treatment and lead to poor hospital system metrics. The PROMIS Global Health v1.2 (PROMIS-10) survey is a validated tool to assess patients' physical and mental well-being at the time of the survey, with a higher number indicating a better state of health. There are limited studies evaluating longitudinal QoL assessments during sarcoma treatment. Our objective was to analyze PROMIS-10 scores for patients with advanced sarcoma and their temporal relationship with negative outcomes of interest. **Methods:** We performed a retrospective registry-based longitudinal analysis of routinely collected PROMIS-10 surveys at The Ohio State University. Patients were consented to the sarcoma registry (NCT02677961) from 6/1/2018 to 12/31/2024. We collected baseline, serial and overall change in physical and mental PROMIS-10 raw and normalized t-scores for each patient during their treatment as well as clinical characteristics, mortality, disease progression (RECIST), and ED visits/unplanned hospital admissions. Survival analyses with time-varying covariates were performed using the marginal Cox model approach for statistical analysis. **Results:** A total of 241 patients were included in the study. Patients with higher PROMIS-10 physical scores had a 13% decrease in risk of death (HR 0.87; $P < 0.001$), 3% decrease in risk of progression (HR 0.97; $P = 0.027$), and 6% decrease in risk of ED visit/unplanned hospital admission (HR 0.94; $P < 0.001$). Patients with a higher PROMIS-10 mental health score had a 7% decrease in risk of death (HR 0.93; $P < 0.001$), but no association with disease progression or risk of hospital utilization. The larger positive change in physical PROMIS-10 score from baseline to final assessment was associated with an 11% decreased risk of mortality (HR 0.89; $P < 0.001$) and 9% decreased risk of ED visit/hospital admission (HR 0.91; $P = 0.032$), but no association with progression. The larger positive change in mental PROMIS-10 score was associated with a 7% decrease in risk of progression (HR 0.93; $P = 0.010$) but there was no association with mortality or hospital utilization. **Conclusions:** We demonstrated that obtaining longitudinal patient-reported outcomes to evaluate patients' physical and mental health during sarcoma treatment can predict mortality, disease progression and ED visits/unplanned hospital admissions. Higher physical PROMIS-10 scores are strongly associated with decreased mortality and hospital utilization risk, whereas a larger positive change in mental PROMIS-10 scores is associated with decreased risk of progression. To our knowledge, this is the largest cohort (241 patients) of advanced sarcoma analyzing QoL impacts. Research Sponsor: None.

11555 **Poster Session**

Neoadjuvant versus adjuvant chemotherapy in cardiac tumor resection: A propensity-matched analysis of perioperative and long-term outcomes. First Author: Fadi Abualhommos, Faculty of Medicine and Health Sciences, An-Najah National University, Nablus, Palestinian Territories (West Bank and Gaza)

Background: Optimal timing of systemic therapy for primary cardiac malignancies is undefined. We compared outcomes after surgical resection when chemotherapy was administered Neoadjuvant (≤4 months before surgery) compared to Adjuvant (≤4 months after). **Methods:** We conducted a retrospective cohort study using the TriNetX database of patients undergoing cardiac tumor resection who received chemotherapy either Neoadjuvant (≤4 months before surgery) or Adjuvant (≤4 months after). Patients were matched 1:1 using propensity scores based on demographics, comorbidities, and treatment variables, yielding 220 patients per group. Primary outcomes were all-cause mortality, infection, and transfusion within 30 days of surgery. Secondary outcomes included tumor recurrence at 1 year (90–365 days), all-cause mortality, and new-onset heart failure during 1–3 years of follow-up. Time-to-event analyses were performed using Kaplan–Meier methods with log-rank testing and hazard ratios (HRs); absolute and relative risks are reported as risk differences (RD) and risk ratios (RR). **Results:** After 1:1 propensity-score matching, 220 patients were included in each group. In the perioperative period (1–30 days), all-cause mortality occurred in 18/217 patients (8.3%) in the Neoadjuvant chemotherapy group compared with 30/213 (14.1%) in the Adjuvant group (RD −0.058, 95% CI −0.117 to 0.002; p=0.057), with a corresponding HR of 0.57 (95% CI 0.32–1.02; p=0.056). Infectious complications were lower with Neoadjuvant chemotherapy (12/220, 5.5%) than with Adjuvant chemotherapy (21/220, 9.5%) (RD −0.041, 95% CI −0.090 to 0.008; p=0.103; HR 0.54, 95% CI 0.27–1.10; p=0.090), while transfusion requirements were similar between groups (14.1% vs 12.3%; p=0.57). At 1 year (90–365 days), malignant cardiac tumor recurrence occurred in 27.7% of Neoadjuvant patients versus 21.4% of Adjuvant patients (RD +0.064, 95% CI −0.017 to 0.144; p=0.12; HR 1.16, 95% CI 0.80–1.70). During longer-term follow-up (1–3 years), all-cause mortality was comparable between groups (44.7% vs 47.4%), with longer median survival observed in the Neoadjuvant group (791 vs 516 days; HR 0.81, 95% CI 0.62–1.07; p=0.14). New-onset heart failure occurred at similar rates in both groups (p=0.98). **Conclusions:** In this cohort study of cardiac tumor resections, Neoadjuvant chemotherapy showed lower 30-day mortality and infection than Adjuvant chemotherapy, without significant differences in transfusion, 1-year recurrence, long-term mortality, or new-onset HF. These hypothesis generating findings suggest neoadjuvant chemotherapy is not associated with worse early or late outcomes and warrant confirmation in prospective, multi-center studies with histology-specific stratification and standardized systemic regimens. Research Sponsor: None.

11556 **Poster Session**

Impact of regorafenib treatment on overall survival (OS) in advanced sarcoma patients. First Author: Clemence Leguillette, Centre Oscar Lambret, Lille, France

Background: Regorafenib has been evaluated in several sarcoma clinical trials and the common primary endpoint of these studies was Progression-Free Survival (PFS) according to RECIST, with OS as secondary endpoint. We aimed to assess the impact of regorafenib on OS using pooled analysis of REGOSARC (NCT01900743, five cohorts: liposarcoma, leiomyosarcoma, synovial sarcoma, other soft tissue sarcoma and non-adipocytic sarcoma post-pazopanib) and (NCT02389244, four cohorts: osteosarcoma, Ewing sarcoma, chondrosarcoma and chordoma). Both trials were placebo-controlled trials with potential switch to regorafenib in placebo-arm at progression. **Methods:** The primary endpoint was OS in months (mo.) from randomisation estimated by Kaplan-Meier method. The Hazard Ratio (HR) of death in a Cox model was stratified by histological . We used 2 methods for controlling regorafenib switch on OS: Rank-Preserving Structural Failure Time Model (RPSFTM; White et al. 1997) and Modified Iterative Parametric Estimation (MIPE: Zhang et al. 2016), with bootstrap-based 95%CI for both methods. Two populations were considered: in the primary analysis included all patients in both trials (n=355), and in secondary analysis excluded chordoma and liposarcoma patients (n=289), since regorafenib failed to demonstrate activity in these subtypes. **Results:** In primary analysis, the median age was 56.0 years (range, 16.0; 85.0); 325 patients (91.5%) had metastatic disease. 218 (61.4%) patients had soft tissue sarcoma and 137 (38.6%) patients had bone sarcoma. Median follow-up was 70.9 mo (IQR: 54.0-87.5). The median OS was 9.5 mo. (95%CI, 7.7-12.4) in Placebo arm versus 12.8 mo. (95%CI, 11.0-15.8) in regorafenib arm (HR: 0.85 (95%CI, 0.67-1.06); p=0.148). When correcting regorafenib switch effect, the estimated HR was 0.59 (0.31-1.25) and 0.62 (0.27-1.46) using RPSFTM and MIPE methods, respectively. **Conclusions:** In this pooled analysis, we observe a marked difference in OS, but which does not reach the , even after exclusion of chordomas and liposarcomas patients (20%-risk reduction, with p=0.083). After controlling for the switch effect, the corrected effect of regorafenib increased dramatically from 20% risk-reduction of death to a 45%-50% reduction in the population excluding chordomas and liposarcomas. Research Sponsor: None.

11557 **Poster Session**

Prevalence of post-traumatic stress disorder and associated factors among adult sarcoma patients. First Author: Sang Minh Nguyen, Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Nashville, TN

Background: A cancer diagnosis and treatment can be extremely stressful and even traumatic for sarcoma patients. However, research on prevalence and risk factors for developing post-traumatic stress disorder (PTSD) symptoms among sarcoma patients has not been well studied. **Methods:** This study used survey data from participants recruited between 4/2022 and 12/2025 for the "Cohort to Augment the Understanding of Sarcoma Survivorship Across the Lifespan" (CAUSAL) study. PTSD symptoms were assessed via the 22-item Impact of Event Scale-Revised (IES-R) at cohort enrollment, and a total IES-R score of ³33 indicates PTSD symptomatology. Associations of demographics and clinical characteristics with PTSD symptoms were evaluated using logistic regression models. The association between PTSD symptoms and health-related quality of life (HRQOL), measured via T-scores for the seven core domains of the PROMIS-57 scale, was then assessed using multivariable linear regression models adjusted for potential confounders. **Results:** Among 1,112 adult sarcoma patients (509 on active treatment and 603 survivors), there are 605 females and 507 males, aged between 18 and 84 (mean age: 54.8). 18.1% of sarcoma patients/survivors reported experiencing PTSD symptoms. Female (20.5%) and younger (15.9-24.3%) sarcoma patients were significantly more likely to experience PTSD symptoms, whereas those with higher household incomes were significantly less likely to experience PTSD symptoms (11.6%-17.6%). Patients who were 5+ years post-diagnosis were less likely to experience PTSD symptoms with adjusted odds ratios (aOR) and 95% confidence intervals (CIs) of 0.56 (0.34, 0.89), compared to those who were $<$ 18 months post-diagnosis. Regular exercise (aOR [95 CI] = 0.59 [0.42, 0.83]) and having emotional support (aOR [95 CI] = 0.63 [0.41, 0.97] for medium and 0.26 [0.15, 0.42] for high support) were inversely associated with PTSD prevalence. PTSD symptoms were significantly associated with a decreased T-score of physical function and social roles and activities with ß(95% CI) of -4.2 (-5.7, -2.7) and -6.8 (-8.3, -5.2), respectively and increased scores for anxiety (ß = 8.9; 95% CI: 7.6, 10.0), depression (ß = 9.4; 95% CI: 8.2, 11.0), fatigue (ß = 7.0; 95% CI: 5.5, 8.5), sleep disturbance (ß = 7.9; 95% CI: 6.6, 9.3), and pain interference (ß = 6.7; 95% CI: 5.2, 8.2). **Conclusions:** PTSD symptoms were reported by an average 18% sarcoma patients and survivors, particularly among female, younger patients, non-exercisers, and those with lower income and low emotional support. PTSD was associated with poor HRQOL. Long-term survival, regular exercise, and increased emotional support were inversely associated with the prevalence of PTSD symptoms. Psychological support and exercise programs should be offered during active cancer treatment and follow-up surveillance to reduce PTSD symptoms in sarcoma patients and survivors. Research Sponsor: None.

11558 **Poster Session**

Enhanced local and systemic efficacy in refractory solid tumors via integrated intra-tumoral injection and radiotherapy: A study of the 'R-ISV-RO' modality. First Author: Wang Xiaolu, The Comprehensive Cancer Centre of Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Background: As for most refractory solid tumors, especially sarcoma, immunotherapy still lacks meaningful improvement in their outcomes. The novel 'R-ISV-RO' in situ vaccine, in which we merged radiotherapy, intratumoral delivery of R837 and OX-40 ligand, together with systemic use of immune-checkpoint blockades, may be clinically beneficial. **Methods:** This was an exploratory, single-center, single-arm clinical trial aimed at evaluating the efficacy and safety of the 'R-ISV-RO' in situ vaccine therapy for advanced solid tumors. Thirty patients aged 18 years or older with advanced solid tumors and at least one measurable lesion were enrolled. The primary endpoint was objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), time to progression (TTP), and clinical benefit rate (CBR). The safety of the treatment and the injection procedures were also evaluated. **Results:** The ORR and DCR for injected lesions were 44.4% and 96.3%. Sarcoma patients exhibited superior outcomes, with a 100% DCR in injected lesions. The median PFS was 15.9 months for injected lesions and median OS was 23.6 months. The abscopal effect occurred in 12 patients. 'R-ISV-RO' treatment was well tolerated, with only 6.7% of patients experiencing grade 3 or higher adverse events. Improved clinical responses were associated with enhanced $CD4^+/CD8^+$ T-cell infiltration and peripheral expansion. Metabolomics analysis revealed therapy-induced metabolic remodeling. **Conclusions:** In this exploratory trial, 'R-ISV-RO' with concurrent immunotherapy demonstrated promising efficacy for both primary and distant tumors, especially for sarcomas. Systemic immune response and metabolic remodeling were also observed after the therapy. Clinical trial information: ChiCTR2100053870. Research Sponsor: National Natural Science Foundation of China; 82272852; Foundation for studies of Clinical Trials, Drum Tower Hospital; 2022-LCYJ-MS-09; Science Fund for Distinguished Young Scholars of Jiangsu Province; BK20240017; Fundings for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University; 2022-LCYJ-PY-21; Nanjing Medical Science and Technology Development Foundation; YKK22086.

11559 **Poster Session**

A phase II, multi-cohort study with pemetrexed plus cisplatin combination in patients with relapsed or refractory advanced soft tissue sarcoma: Leiomyosarcoma cohort (ALBATROSS-SARC-LMS01). First Author: Hyo Song Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Songdang Institute for Cancer Research, Seoul, South Korea

Background: Given the promising results in previous single arm trial (NCT03809637), this histology-specific, multi-cohort, phase II trial was conducted to evaluate the efficacy and safety of pemetrexed plus cisplatin in patients with advanced and refractory soft tissue sarcoma (STS). **Methods:** In this trial (NCT04605770), we enrolled patients with metastatic and/or recurrent STS who had failed 1-2 prior cytotoxic regimens and maintained adequate performance status and organ function. The treatment regimen consisted of pemetrexed 500 mg/m² and cisplatin 75 mg/m² on day 1 of each 3-week cycle up to 6 cycles, followed by pemetrexed monotherapy. A total of 164 patients were planned for assignment into 4 histology- based cohorts (n=41 each) to account for a 10% drop-out rate: Cohort 1 (leiomyosarcoma, [LMS]), Cohort 2 (liposarcoma), Cohort 3 (vascular sarcoma), and Cohort 4 (other sarcomas). The primary endpoint was progression-free rate at 12 weeks (PFR12 weeks) utilizing a Simon's two-stage design (P1=40%, P0=20%, α=β=0.1). In the first stage, 17 patients were accrued; if at least 4 successes were observed, the cohort was to be expanded to 37 evaluable patients. To account for a 10% drop-out rate, the final enrollment target was set at 41 patients per cohort. **Results:** As of October 2025, 74 (45.1%) patients were enrolled. Among those, cohort 1 (LMS) reached full enrolment with 40 patients (median age; 53 years, female; 87.5%, 75% had received 2 prior lines of chemotherapy). Among Of 39 evaluable patients, 7 (17.9%) achieved a confirmed partial response, and 22 (53.8%) had stable disease, resulting in a disease control rate (DCR) of 74.3%. The median progression free survival was 6.3 months (95% CI, 4.9-7.6) with 74.0% of PFR12 weeks. Notably, the observed DCR and PFR12 weeks compare favorably with historical data for other second/third-line regimens in LMS, such as gemcitabine plus docetaxel (typical DCR 50–60%; PFR12 weeks 40–50%). The median OS was 20.5 months (95% CI 14.3-26.7), with a median of 7 treatment cycles administered (range 1-31). Although treatment-related adverse events (TRAEs) occurred in the majority of patients, grade $\geq$3 TRAEs were observed in only 10 (25%) patients, mainly anemia (n=10, 25%), neutropenia (n=7, 17.5%), and nausea (n=3, 7.5%). One TREA (drug hypersensitivity) led to treatment discontinuation due to drug hypersensitivity. **Conclusions:** The combination of pemetrexed and cisplatin was well tolerated and demonstrated promising activity in patients with relapsed, advanced STS, particularly in LMS cohort. The efficacy observed exceeded historical outcomes for standard-of-care second-line therapies, warranting further investigation in future histology-specific studies. Clinical trial information: NCT03809637. Research Sponsor: Ministry of Health & Welfare, Republic of Korea; RS-2025-02233161.

11560 **Poster Session**

Efficacy and safety results of tazemetostat in Japanese patients with advanced epithelioid sarcoma: The phase 2 TAZETTA trial (NCCH2107). First Author: Kenji Tsuchihashi, Department of Hematology, Oncology, and Cardiovascular Medicine, Kyushu University Hospital, Fukuoka, Japan

Background: Epithelioid sarcoma is an ultra-rare soft tissue sarcoma with limited treatment options. Tazemetostat, a selective EZH2 inhibitor, demonstrated antitumor activity in a global phase 2 study (NCT02601950) and has been approved for the treatment of epithelioid sarcoma in the US. We conducted a Japanese phase 2 study (TAZETTA; NCCH2107) as a sub-study within the framework of the nationwide rare cancer registry project in Japan (MASTER KEY Project) to evaluate the efficacy and safety of tazemetostat in patients with advanced epithelioid sarcoma. **Methods:** The TAZETTA study is a non-randomized, single-arm, phase 2 trial. Eligible patients had locally advanced or metastatic epithelioid sarcoma with loss of INI1, had received at least one prior chemotherapy including doxorubicin, had an ECOG performance status of 0–2, and at least one measurable lesion according to RECIST v1.1. Tazemetostat was administered orally at 800 mg twice daily in 28-day cycles. The primary endpoint was the progression-free survival (PFS) rate at 18 weeks by blinded independent central review. The threshold 18-week PFS rate was set at 5% and the expected rate at 30%. With a one-sided alpha of 0.05 and 80% power, the required sample size was 12 patients. To allow for ineligibility or non-treatment patients, 15 patients were planned. Secondary endpoints included PFS, overall survival (OS), objective response rate (ORR), disease control rate, duration of response, and safety. In the ancillary study, biomarker samples were collected and subjected to exploratory analysis. **Results:** Given the smooth patient accrual, 17 patients were enrolled between July 2023 and July 2024. The median age was 43 years; 13 patients were men and 4 were women. Proximal-type disease was observed in 11 patients (64.7%). The centrally assessed 18-week PFS rate was 31.3% (90% CI, 14.0–50.2), and the lower limit of the 90% CI met the predefined efficacy threshold. The median PFS was 2.9 months (95% CI, 1.6–5.6), and the median OS was 12.3 months (95% CI, 4.9–not estimable). Treatment-related adverse event with Grade $\geq$3 included lymphopenia (1pt, 5.9%). No treatment-related deaths were observed. **Conclusions:** Tazemetostat demonstrated clinically meaningful activity and a manageable safety profile in Japanese patients with advanced epithelioid sarcoma, consistent with the previous reports, supporting its role as a therapeutic option in this population. Clinical trial information: jRCT2031220523. Research Sponsor: None.

11561 Poster Session

Neoadjuvant pegylated liposomal doxorubicin plus anlotinib in locally advanced soft tissue sarcoma: Clinical outcomes and multi-omics analysis from a phase II study. First Author: Wei Sun, Department of Musculoskeletal Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China

Background: Neoadjuvant therapy may improve the R0 resection and limb salvage rates in locally advanced soft tissue sarcomas (STS). This phase II trial was designed to evaluate the efficacy and safety of neoadjuvant pegylated liposomal doxorubicin (PLD) combined with anlotinib in the treatment of locally advanced STS. **Methods:** This single-center, single-arm phase II trial (NCT04765228) enrolled treatment-naïve patients with stage II/III. Patients received PLD (50 mg/m² intravenously on day 1) combined with anlotinib (12 mg orally daily on days 8-21) every 3 weeks for 2-4 cycles. Based on a one-proportion test, with α=0.05 (two-sided) and 80% power, to detect an increase in the objective response rate (ORR) from 10% to 26%, 45 patients were planned, accounting for a 20% dropout rate. The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. The exploratory endpoint was biomarker analyses. The corresponding two-sided 95% CIs were estimated using the Clopper-Pearson method. The PFS and OS were estimated using the Kaplan-Meier method. **Results:** A total of 40 eligible patients were treated between November 2020 and November 2022, of whom 34 (85.0%) underwent surgery. The median age was 46.5 years (range: 15-74 years), and 23 (57.5%) of the patients were male. Histologically, the 40 patients included 9 cases of liposarcoma (LPS), 6 cases of malignant peripheral nerve sheath tumor (MPNST), 6 cases of synovial sarcoma (SS), 3 cases of low-grade fibromyxoid sarcoma (LGFMS), 3 cases of myxofibrosarcoma (MFS), 3 cases of spindle cell sarcoma (SCS), 3 cases of undifferentiated pleomorphic sarcoma (UPS), 2 cases of leiomyosarcoma (LMS), and 5 cases of other STS. The most common sites of primary tumor were lower extremities (42.5%), waist/hip region (17.5%) and other regions. The ORR based on RECIST 1.1 was 15.0% (95% CI: 3.4%-26.6%), and the ORR of 36 patients based on Choi's criteria was 58.3%. The median PFS was 14 months (95% CI: 4.22 - 23.79 months), and the median OS was not reached. Pathological response was evaluable in 24 patients, with pathological complete response (pCR) and pathological partial response (pPR) observed in 4.2% (1/24) and 50.0% (12/24) of cases, respectively. Among 34 patients who underwent surgical resection, 30 (88.2%) achieved R0 resection, while 3 (8.8%) had R1 resection. Common treatment-related adverse events (TRAEs) of any grade included mucositis oral (52.5%), neutrophil count decreased (25.0%). Fifteen (37.5%) patients experienced at least one grade 3-4 AE. **Conclusions:** Neoadjuvant PLD combined with anlotinib exhibits promising efficacy and acceptable toxicity in patients with locally advanced STS. Results from multi-omics analyses will facilitate the screening of suitable patients in future clinical practice. Clinical trial information: NCT04765228. Research Sponsor: National Key R&D Program of China; 2023YFC2506400; National Natural Science Foundation of China; 82373385, 82272857, 82441039, 82303608; East Clinical Center of Oncology; ECCO-KY-23003.

11562 Poster Session

Triplet combination of anlotinib plus nab-paclitaxel and gemcitabine (AG) as a first-line strategy for advanced primary cardiac angiosarcoma: A high-volume center experience. First Author: Xi Guo, Department of Medical Oncology, Cancer Center, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Primary cardiac angiosarcoma (PCAS) is an exceedingly rare and lethal mesenchymal malignancy characterized by aggressive growth and high metastatic potential. Despite the use of taxane-based regimens, the prognosis remains dismal, with a historical median overall survival (mOS) of approximately 11 months. Given the highly vascular nature of PCAS, we hypothesized that integrating a multi-target anti-angiogenic TKI (anlotinib) with cytotoxic chemotherapy could synergistically improve outcomes. This study evaluated the efficacy and safety of anlotinib plus nab-paclitaxel and gemcitabine (AG) in advanced PCAS. **Methods:** We retrospectively analyzed patients with metastatic or unresectable PCAS treated at Zhongshan Hospital, Fudan University. The triplet regimen consisted of anlotinib (8-12 mg QD, days 1-14, q3w), nab-paclitaxel (200 mg), and gemcitabine (1000 mg/m²) on days 1 and 8 every 3 weeks. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), and safety (CTCAE v5.0). Survival outcomes were estimated using the Kaplan-Meier method and compared via log-rank tests. **Results:** A total of 24 patients were included, with a median age of 44 years. Most tumors (91.7%) originated in the right atrium, and 70.8% of patients received this regimen as first-line therapy. Efficacy: At a median follow-up of 31.4 months, the ORR was 62.5% and the DCR was 95.8%. Survival: The median PFS was 9.5 months (95% CI, 8.4-20.7). Notably, the median OS reached 24.9 months (95% CI, 15.2-NR), significantly exceeding historical benchmarks. Prognostic Indicators: Subgroup analysis identified liver metastasis (45.8%) as a significant negative prognostic factor for PFS (p = 0.018). Additionally, a numerical trend toward shorter survival was observed in patients with baseline D-dimer $>$ 5 mg/dL (Median OS: 5.5 vs. 10.5 months; p = 0.428). Safety: Treatment-related adverse events (TRAEs) of any grade occurred in 95.8% of patients. Grade$\geq$3 TRAEs (41.7%) were primarily hematological (neutropenia, thrombocytopenia) and were manageable via dose modification. No severe treatment-related cardiotoxicity was observed. **Conclusions:** The triplet combination of anlotinib and AG demonstrates unprecedented survival benefits and a manageable safety profile in advanced PCAS. With a mOS exceeding twice the historical data, this regimen represents a potent new treatment strategy. Liver involvement serves as a critical prognostic indicator for risk stratification, while the clinical significance of baseline D-dimer levels as a surrogate marker for tumor burden warrants further investigation in larger cohorts. Research Sponsor: None.

11563 Poster Session

Outpatient rehabilitation for adults with soft tissue sarcoma: Examining real-world service utilization and outcomes. First Author: Kelley C. Wood, Select Medical, Mechanicsburg, PA

Background: Soft tissue sarcoma (STS) and its treatments frequently result in substantial physical morbidity, leading to impaired function and reduced quality of life. Rehabilitation can improve outcomes, yet real-world utilization and effectiveness in this population remain poorly understood. This study describes outpatient rehabilitation service use among adults with STS and examines changes in physical function and quality-of-life outcomes. **Methods:** Electronic medical record data from outpatient rehabilitation encounters were retrospectively analyzed for adults with a STS diagnosis (identified by ICD code) who completed $\geq$2 visits and had pre- and post-treatment outcome measures available. Rehabilitation characteristics were examined descriptively, including visits, care duration, service type, and treatment indications (identified by ICD code). PROMIS-Physical function (PF) was the primary outcome. Secondary outcomes were PROMIS-Global physical health (GPH), -Ability to participate in social roles and activities (SRA), and -Global mental health (GMH). Mixed-effect models assessed change in T-scores, adjusting for covariates (age, visits per week, care duration) and accounting for within-subject correlation. Estimated marginal (EM) means are reported. Change scores were compared to the established minimal important change (MIC, 2 points) to determine clinical relevance. **Results:** A total of 151 patients met inclusion criteria (mean age 56.0$\pm$16.7 years; 57% female). Most received physical therapy (86.1%), with fewer receiving occupational therapy (13.2%). The median episode of care was 8.3 weeks (IQR 4.3–16.0), with a mean of 1.6$\pm$ 0.7 visits per week. Common treatment indications included pain (37.9%), weakness/deconditioning (35.8%), gait/balance (27.5%), followed by lymphedema (8.5%), fatigue (5.9%), wound/post-surgery care (5.5%), and neuropathy (3.1%). Significant improvements were observed in PF (+2.48, SE: 0.57), GPH (+2.64, SE: 0.50), and SRA (+2.64, SE: 0.57) ($p<.001$), each surpassing the MIC. No significant change was observed in GMH (-0.39, SE:0.48, p=.419). **Conclusions:** In this real-world cohort of adults with STS, outpatient rehabilitation averaged 8 weeks of care and 1-2 visits per week, most commonly addressing pain, weakness, and gait/balance deficits. Significant and clinically meaningful improvements were observed in physical function and the physical and social aspects of quality of life; mental health was not significantly affected. These findings support the role of rehabilitation as an important component of multidisciplinary sarcoma care and underscore the need for complementary strategies to address psychosocial outcomes. Research Sponsor: None.

PROMIS T-scores, EM mean (SE).

Outcome	Pre	Post
PF	36.26 (0.50)	38.74 (0.57)
GPH	39.44 (0.52)	42.08 (0.56)
SRA	43.17 (0.56)	45.82 (0.65)
GMH	47.40 (0.60)	47.02 (0.63)

11564 Poster Session

The investigator-initiated trial (IIT) of GO306 injection, a recombinant oncolytic vaccinia virus, in patients with advanced soft tissue sarcomas. First Author: Qiujun Zhang, Department of Oncology, Anhui Provincial Cancer Hospital, The West District of First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

Background: Oncolytic vaccinia viruses exert anti-tumor effects via direct lysis and systemic immunity induction. Advanced soft tissue sarcomas (STS) are heterogeneous malignancies with limited post-standard therapy options. GO306 is a oncolytic virus expressing PD-1/TGFβ inhibitors for tumor-selective replication and enhanced immunity. We report GO306's preliminary safety and tolerance in pretreated advanced STS. **Methods:** This open-label, single-arm IIT enrolled histologically confirmed advanced STS refractory to standard therapy. A 3+3 dose-escalation design was used, with intratumoral GO306 at 3×10^7 PFU, 3×10^8 PFU and 1×10^9 PFU. A 21-day DLT assessment period was set. Tumor assessment was done on day 28 per RECIST v1.1. Primary endpoints: MTD, DLTs, safety; secondary endpoints: OS, ORR, PFS, immunogenicity, viral shedding. **Results:** As of Dec 5th, 2025, 10 participants were enrolled across 3 dose cohorts, 9 completed the 21-day DLT assessment (1 non-DLT withdrawal). Demographics: median age 52.4 years, 80% male, ECOG 1-2. No DLTs were observed; MTD not reached. A total of 110 AEs were reported, including 52 treatment-related adverse events (TRAEs), 98.8% (51/52) were grade 1-2, with 1 grade 3 pulmonary infection (SAE due to prolonged hospitalization). No grade 4-5 TRAEs occurred. Most common AEs: pyrexia (60%, grade 1-2), followed by hypokalemia, hypocalcemia and hypoalbuminemia (40% each, grade 1-2). Efficacy was evaluable in 8 participants: 87.5% (7/8) SD and 12.5% (1/8) PD. Survival data: 2 participants with OS > 5 months, 1 alive at 260 days (all received subsequent anti-tumor therapies), 2 with 90-day survival documented. Viral shedding: GO306 was below the limit of quantification (BLQ) in feces, urine, throat swabs, and plasma on day 3/7, undetectable on day 30 (some samples pending). PD-1 inhibitor was detectable in 6/10 participants (29.91~19073.64 ng/mL); TGFβ inhibitor in 7/10 participants (80.39 to 460.31 ng/ml). **Conclusions:** Intratumoral GO306 showed favorable safety profile and manageable TRAEs in pretreated advanced STS. Preliminary efficacy support phase I/II expansion and combination studies with other immunotherapies or targeted therapies. Clinical Trial Registration Number: ChiCTR2400088508. Xianhai Zhu and Hu Liu contributed equally as corresponding author. Clinical trial information: ChiCTR2400088508. Research Sponsor: None.

Demographic and overall response of participants.

Screen No.	Age	Gender	ECOG	Malignancy Diagnosis	Overall Response*
S002	60	M	1	Retroperitoneal Liposarcoma	SD
S003	59	F	2	Liposarcoma	SD
S006	70	M	1	Leiomyosarcoma	SD
S007	60	M	2	Retroperitoneal Liposarcoma	PD
S010	48	M	1	Retroperitoneal Leiomyosarcoma	SD
S011	48	M	1	Retroperitoneal Leiomyosarcoma	SD
S012	56	M	1	Chondrosarcoma	SD
S013	30	M	1	Synovial Sarcoma	SD

Abbreviations: *Per RECIST V1.1; 8/10 enrolled participants had evaluable day-28 tumor assessments and are included.

11565 **Poster Session**

Cardiac safety of aldoxorubicin compared to doxorubicin: Integrated results from two randomized studies in advanced soft tissue sarcoma. First Author: Philip Sager, Stanford University School of Medicine, Stanford, CA

Background: Doxorubicin clinical benefit is limited by cumulative, irreversible cardiotoxicity that restricts dosing. Aldoxorubicin is an albumin-binding prodrug of doxorubicin designed to enhance tumor delivery while reducing systemic exposure to cardiotoxic metabolites such as doxorubicinol. Prior reports suggest improved cardiac tolerability of aldoxorubicin, but no integrated analysis across randomized studies has been presented. **Methods:** Cardiac safety data were analyzed from two randomized studies, INNO-206-STS-P2-01 (NCT01514188) and ALDOXORUBICIN-P3-STS-01 (NCT02049905), comparing aldoxorubicin with doxorubicin in advanced soft tissue sarcoma. Left ventricular ejection fraction (LVEF) was assessed at baseline and prespecified intervals during and after treatment. Outcomes included mean and change-from-baseline LVEF, proportion of patients with LVEF $<$45%, treatment-emergent heart-failure and cardiovascular adverse events (AEs), and composite endpoints integrating LVEF decline and cardiac AEs. Cumulative doxorubicin-equivalent dose was calculated using a 0.74 conversion factor. **Results:** Across both studies (N≈383), baseline demographics and cardiac risk factors were balanced. Aldoxorubicin was administered at approximately 3.5-fold higher doxorubicin-equivalent cumulative doses than doxorubicin. Despite higher exposure, aldoxorubicin was associated with smaller mean LVEF declines (pooled lowest on-treatment change -3.17% vs -5.77%; nominal $p<0.05$). Approximately three-fold more doxorubicin-treated patients reached LVEF $<$45% (1.1% vs 3.8%). Composite endpoints favored aldoxorubicin, including HF-AE plus LVEF $<$45% (0.7% vs 3.4%), HF-AE plus $\geq$10-point decline (2.0% vs 4.6%), prespecified cardiovascular AE plus LVEF $<$45% (0.3% vs 1.1%), and prespecified cardiovascular AE plus $\geq$10-point decline (1.4% vs 4.6%). Treatment-emergent prespecified heart-failure events occurred less frequently with aldoxorubicin (3.0% vs 6.9%). LVEF–exposure plots showed higher LVEF with aldoxorubicin despite substantially higher cumulative exposure. In Phase 1 aldoxorubicin pharmacokinetic data, the doxorubicinol-to-doxorubicin exposure ratio was ~5–6%, compared with ~40–60% reported for conventional doxorubicin, consistent with lower systemic doxorubicinol burden and supporting the observed cardiac safety findings. **Conclusions:** Across two randomized studies, aldoxorubicin demonstrated a consistently more favorable cardiac safety profile than doxorubicin despite higher cumulative exposure, with smaller LVEF declines and fewer heart-failure–related events. These findings support aldoxorubicin as a potentially safer anthracycline option for patients requiring sustained exposure. Research Sponsor: Gemini Therapeutics, Inc.

11566 **Poster Session**

Neo-adjuvant radiation and intratumoral immunotherapy followed by surgery: The NARIS trial for extremity soft tissue sarcoma. First Author: Rutian Li, The Comprehensive Cancer Centre of Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China

Background: Patients with STS who failed to respond to standard treatment have limited subsequent treatment options. Radiotherapy combined with immunotherapy has demonstrated efficacy in certain STS subtypes, such as undifferentiated pleomorphic sarcoma (UPS); however, perioperative strategies still require optimization to further improve local control and reduce adverse events, particularly for patients with multiple recurrences yet seeking limb preservation. **Methods:** Patients with pathologically confirmed extremity STS without metastases were enrolled. Eligible participants received two neoadjuvant cycles administered every three weeks. Each cycle consisted of hypofractionated radiotherapy (a total of 5 Gy $\times$ 4 fractions across two cycles) combined with intratumoral injection of a PD-L1 (TQB2450) monoclonal antibody. **Results:** A total of 15 patients were screened, of whom 11 met the eligibility criteria and provided written informed consent. Except for one patient with disease progression after standard chemoradiotherapy, other patients had recurrent disease following one to three prior curative resections at baseline. The ORR and DCR were 36.4% (95% CI, 10.9–69.2%) and 90.9% (95% CI, 58.7–99.8%), respectively. One patient has not yet undergone surgery. Among the 10 patients who received surgery, one achieved a pCR, and two achieved MPR. All three cases occurred in UPS patients. In the 10 evaluable patients with STS, the median percentage of tumor necrosis and fibrosis was 63.5% (IQR 17.5–88.75%), and the median residual viable tumor percentage was 36.5% (IQR 11.25–82.5%). Subgroup analysis showed that the median percentage of tumor necrosis and fibrosis in UPS patients was 97% (IQR 88–99.25%), compared with 25% (IQR 10–55%) in other histological subtypes. The pCR rate and MPR rate in UPS patients were 25% (1/4) and 75% (3/4), respectively. During the neoadjuvant phase, the main TEAEs were local swelling and decreased lymphocyte counts, which were reversible during treatment intervals. No grade 3 TEAEs or immune-related adverse events were observed. Postoperative complications in the 10 surgical patients were as expected and mainly included local soft tissue edema, pain, local stiffness, and limb numbness. No delayed wound healing or surgical site infections were observed. **Conclusions:** Compared with current clinical studies in STS that employ conventionally fractionated radical radiotherapy and intravenous immune checkpoint inhibitors, this study utilized a lower total radiation dose delivered in larger fractions combined with intratumoral administration of immunotherapy, achieving comparable disease control with manageable toxicity. It may be clinically valuable for patients with recurrent disease after multiple surgeries or those with prior exposure to local radiotherapy. Clinical trial information: ChiCTR2200060659. Research Sponsor: National Natural Science Foundation of China; 82272852; Science Fund for Distinguished Young Scholars of Jiangsu Province; BK20240017; Foundation for studies of Clinical Trials, Drum Tower Hospital; 2023-LCYJ-MS-24.

11567 **Poster Session**

Effect of pimicotinib on tumor response and physical function (PF) by tumor location in patients with tenosynovial giant cell tumor (TGCT): Results from the phase 3 MANEUVER trial. First Author: Gabriel Tinoco, The Ohio State University Comprehensive Cancer Center (OSUCCC), Columbus, OH

Background: TGCT is a rare, locally-aggressive, soft-tissue tumor driven by colony-stimulating factor-1 (CSF-1) overproduction, often leading to impaired PF. Pimicotinib (pimi), an oral, highly-selective CSF-1 receptor inhibitor, demonstrated robust tumor responses, clinically meaningful symptomatic and functional improvements, and a tolerable safety profile in patients (pts) with TGCT in the global Phase 3 MANEUVER trial (NCT05804045). Here, we report the effects of pimi on tumor response and PF in joints most commonly affected by TGCT. **Methods:** In MANEUVER, symptomatic adult pts with unresectable TGCT were randomized 2:1 to once-daily pimi 50 mg or placebo for 24 weeks (Part 1). After Part 1, eligible pts received open-label pimi for 24 weeks (Part 2), followed by an ongoing long-term extension period (Part 3). Longer-term objective response rate (ORR) by blinded independent review committee (BIRC) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, Range of Motion (ROM) responses, and Patient-Reported Outcomes Measurement Information System-PF (PROMIS-PF) scores from Part 1 to Part 3, up to data cut-off, are reported by tumor location for pts randomized to pimi in Part 1. **Results:** At baseline, 63 pts were randomized to pimi; 71.4% were female and median age was 41.0 years (range 18–69). Median follow-up was 14.3 months and median treatment duration was 14.2 months. Most pts had diffuse TGCT (84.1%), with an affected lower extremity (85.7%), particularly the knee (52.4%). Tumor responses to pimi were comparable for localized (n=8) and diffuse (n=53) TGCT based on ORR by BIRC per RECIST v1.1 (95% CI): 87.5% (47.3, 99.7) vs 75.5% (61.7, 86.2), respectively. ORRs (95% CI) were comparable for pts with lower extremity (n=54) tumors and upper extremity (n=9) tumors: 75.9% (62.4, 86.5) vs 77.8% (40.0, 97.2), respectively, and for knee tumors (n=33) vs other (n=30) locations: 75.8% (57.7, 88.9) vs 76.7% (57.7, 90.1), respectively. Knee ROM improved from baseline to Week 49 (mean change: 8.9 [SD 8.4]). PROMIS-PF scores for lower extremity measures such as walking, climbing stairs, standing, and bending/kneeling improved from baseline (n=54) to Week 49 (n=43) (Table). **Conclusions:** Pimi provided sustained, clinically meaningful benefits in pts with TGCT, including durable tumor shrinkage and improved ROM and PF, regardless of tumor location. These results support pimi as an effective treatment option for patients with unresectable TGCT. Clinical trial information: NCT05804045. Research Sponsor: Abbisko Therapeutics; Merck KGaA, Darmstadt, Germany.

Longer-term PROMIS-PF scores per item from baseline to week 49.

PROMIS-PF score[a] Mean (SD)	Baseline (N=54)	Week 49 (N=43)
Walk for ≥15 minutes	3.9 (1.0)	4.6 (0.6)
Climb stairs	3.3 (1.1)	4.2 (0.8)
Stand for 1 hour	2.9 (1.2)	3.7 (1.3)
Bend, kneel, or stoop	2.7 (1.3)	3.6 (1.2)

[a]1-Unable to do; 2-With much difficulty; 3-With some difficulty; 4-With a little difficulty; 5-Without any difficulty.

11568 **Poster Session**

Longer-term safety of pimicotinib in tenosynovial giant cell tumor (TGCT): Integrated analysis of phase 1 and phase 3 MANEUVER trial data. First Author: Hans Gelderblom, Department of Medical Oncology, Leiden University Medical Center (LUMC), Leiden, Netherlands

Background: TGCT is a rare, locally-aggressive neoplasm associated with significant morbidity and functional impairment. Colony-stimulating factor-1 receptor (CSF-1R) inhibitors are effective for unresectable TGCT, but current options may be limited by their long-term safety and tolerability. In the Phase 3 MANEUVER trial, pimicotinib (pimi), a highly-selective CSF-1R inhibitor, demonstrated robust tumor responses, clinically meaningful symptomatic and functional improvements, and a tolerable safety profile. This integrated analysis evaluated the longer-term safety of pimi from Phase 1 and 3 trials. **Methods:** Data for adult patients (pts) with TGCT treated with pimi 50 mg once daily from Phase 1 (NCT04192344, cut-off Dec 31, 2024) and Phase 3 (NCT05804045; MANEUVER, cut-off Mar 12, 2025) trials were pooled for an integrated safety analysis. The open-label Phase 1 study assessed safety, tolerability, and pharmacokinetics of pimi in advanced solid tumors. MANEUVER evaluated efficacy and safety of pimi in unresectable TGCT across a 24-week, double-blind, placebo-controlled phase; a 24-week open-label pimi treatment phase; and an ongoing long-term extension. All treatment-emergent adverse events (TEAEs) and adverse events of clinical interest (AECI) were analyzed and reported as frequencies. **Results:** In total, 158 pts were included; 65.8% were female and median age was 40.0 (range 18–76) years. Median pimi exposure was 385.5 days; 12.7% of pts had prior exposure to systemic therapy. TEAEs of any grade were reported by 99.4% of pts (Table); most pts reported a maximum grade of 1 (8.9%; n=14/158) or 2 (53.2%; n=84/158). The most reported AECI of any grade by pts were blood creatine phosphokinase (CPK) elevation (72.2%), aminotransferase elevation (59.5%), edema (excluding periorbital edema [POE]) (54.4%), rash (46.2%) and pruritus (43.0%); 20.9% reported fatigue. There was no evidence of cholestatic hepatotoxicity or drug-induced liver injury. The most common AECI leading to dose reduction were rash (5.1%) and edema (excluding POE) (3.2%); for dose interruption, blood CPK elevation (13.9%) and rash (13.3%) were most common. Most AECI resolved/improved following dose reduction or interruption. Treatment discontinuation due to AECI was rare (face edema, 0.6%; rash, 0.6%). Concomitant medication was most commonly used for rash (n=38/73), pruritus (n=31/68), and edema (n=22/86). **Conclusions:** Pimi showed sustained tolerability with no new safety signals, confirming a favorable safety profile in Phase 1 and 3 trials during extended treatment of $>$1 year in a larger TGCT population. Clinical trial information: NCT04192344; NCT05804045. Research Sponsor: Abbisko Therapeutics; The healthcare business of Merck KGaA, Darmstadt, Germany.

Summary of TEAEs.

TEAE	Pts (N=158) n (%)
Any	157 (99.4)
Grade ≥3	59 (37.3)
Serious	17 (10.8)
DR serious	1 (0.6)
Leading to dose reduction	33 (20.9)
Leading to dose interruption	95 (60.1)
Leading to discontinuation	8 (5.1)
Resulting in death	1 (0.6)
DR resulting in death	0

DR, drug related.

11569 Poster Session

Efficacy and safety of engineered TCR-T cell therapy (afami-cel, lete-cel) in pediatric synovial sarcoma. First Author: Amy E. Armstrong, Washington University in St. Louis, St. Louis, MO

Background: Synovial sarcoma (SyS) represents ~ 5% of adult soft tissue sarcomas, however, SyS is the most common non-rhabdomyosarcoma soft tissue sarcoma in the pediatric population. Both lete-cel, an engineered TCR-T cell therapy targeting NY-ESO-1, and afami-cel, an engineered TCR-T cell therapy targeting MAGE-A4, have shown efficacy and an acceptable safety profile in adult patients with SyS. We report here the largest cohort of pediatric SyS patients treated with either afami-cel or lete-cel. **Methods:** Pediatric SyS patients (pts) were treated on four phase II trials: lete-cel SyS Pilot study (NCT01343043), lete-cel IGNYTE-ESO trial (NCT03967223), afami-cel SPEARHEAD-1 (NCT04044768) and SPEARHEAD-3 (NCT05642455). Initial data from SPEARHEAD-3 will be available and added at the time of presentation. Eligibility for this analysis: advanced (unresectable/metastatic) SyS, human leukocyte antigen (HLA)-A*02, NY-ESO-1 or MAGE-A4 expression, baseline ECOG 0–1 and received any dose of lete-cel or afami-cel as a single infusion. Key efficacy endpoints: independent review-assessed overall response rate (ORR) per RECIST v1.1, best overall response, duration of response (DoR). Key safety endpoints: adverse events (AEs), serious AEs, AEs of special interest (ex. Cytokine release syndrome (CRS)). Data is presented separately for lete-cel and afami-cel. **Results:** Seven pediatric pts (age 10 to 17) were treated with lete-cel for advanced disease. The median lete-cel dose was 4.9 x 10^9 transduced cells. The ORR was 43% (3/7 pts, 2 PR, 1 CR). The duration of response was 2.83, 7.39, and 7.39 months respectively; one response was ongoing at the time of this analysis. Pediatric pharmacokinetics and exposure-response data were in agreement with data from adult pts. Seven pediatric pts (age 13 to 16) were treated with afami-cel for advanced disease. The median afami-cel dose was 8.2 x 10^9 transduced cells. The ORR was 28.6% (2/7 pts, 2 PR). The duration of response was 4.7 and 17.4 months respectively; one response was ongoing at the time of this analysis. Similar pharmacokinetics were observed in pediatric pts compared to adult pts. CRS was common occurring in >50% of pts for both lete-cel and afami-cel; events were grade 1 or 2, except one patient with lete-cel experiencing grade 3 CRS. Cytopenias after lymphodepletion and T cell infusion were the most common grade 3 or 4 adverse events (>30% of pts) for both therapies. **Conclusions:** Engineered TCR-T cell therapy targeting NY-ESO-1 (lete-cel) or MAGE-A4 (afami-cel) has shown responses and durable responses in the pediatric SyS population. The safety profile in this age group is consistent with that observed in the adult population. TCR-T represents a potential new treatment paradigm for pediatric SyS patients. Further studies should help to determine the optimal timing for this cellular therapy. Additional Information: Coauthor Brian Van Tine, MD, died Nov 2025. Clinical trial information: NCT01343043, NCT03967223, NCT04044768, NCT05642455. Research Sponsor: Adaptimmune LLC; USWM CT, LLC.

11570 Poster Session

Outcomes of malignant peripheral nerve sheath tumors in neurofibromatosis type 1 and sporadic patients: A 25-year experience from a sarcoma referral center. First Author: Clio Coste, Centre Leon Bérard, Lyon, France

Background: Malignant peripheral nerve sheath tumors (MPNST) are rare, aggressive soft-tissue sarcomas frequently associated with neurofibromatosis type 1 (NF1). Prospective trials are scarce, and prognostic factors and treatment effects remain incompletely defined. **Methods:** We conducted a retrospective observational cohort study of 200 patients (215 tumor episodes) with histologically confirmed MPNST treated at a national sarcoma referral center between 2000 and 2025. Overall survival (OS) and progression-free survival (PFS) were estimated via Kaplan–Meier methods. Multivariable Cox models with multiple imputation (MICE, m=40) were adjusted for clinical factors. Restricted mean survival time (RMST) at 5 years quantified absolute survival differences. Interaction analyses assessed heterogeneity of radiotherapy (RT) effects. **Results:** Median age was 40 years; 51.5% of patients had NF1. Median OS and PFS were 74.6 and 9.1 months, respectively. NF1-associated MPNST had significantly shorter OS (28.5 vs 141.0m; p=0.012), with a 5-year RMST reduction of 8.5 months (95% CI -15.0 to -2.3; p=0.01). In the multivariable Cox model with multiple imputation, advanced stage (HR 2.28; 95% CI 1.68–3.09; p<0.001), higher FNCLCC grade (HR 1.95; 95% CI 1.39–2.75; p<0.001), NF1 status (HR 1.67; 95% CI 1.11–2.51; p=0.014), central tumor location (HR 1.63; 95% CI 1.02–2.60; p=0.041), and increasing age (HR 1.04 per year; 95% CI 1.02–1.05; p<0.001) were independently associated with inferior OS, whereas female sex was strongly protective (HR 0.43; 95% CI 0.29–0.66; p<0.001). Major biopsy-surgery histologic discordance occurred in 21.6% of cases, and diagnostic delays > 60 days in 28.4%. A significant interaction was observed between RT and surgical margins (p_int=0.028): RT markedly improved OS in R1/R2 resections (HR 0.31, 95% CI 0.16–0.61) and in locally advanced disease, but not after R0 resection. In NF1 patients, imaging-detected tumors had better surgical margins and lower risk of synchronous metastasis despite similar tumor size. **Conclusions:** MPNST outcomes remain poor, particularly in NF1. Radiotherapy confers a clear survival benefit in high-risk surgical contexts. Optimizing diagnostic pathways, especially in NF1 patients, may improve outcomes. Research Sponsor: None.

Survival Predictors (Multivariable OS)	Hazard Ratio (95% CI)	p-value
Stage	2.28 (1.68–3.09)	<0.001
FNCLCC Grade	1.95 (1.39–2.75)	<0.001
NF1-associated	1.67 (1.11–2.51)	0.014
Central Location	1.63 (1.02–2.60)	0.041
Female Sex	0.43 (0.29–0.66)	<0.001
RT Benefit in R1/R2 Resection	0.31 (0.16–0.61)	0.001

11571 Poster Session

Adverse events and their management in patients with tenosynovial giant cell tumor (TGCT) treated with pimicotinib, after longer-term follow-up from the global phase 3 MANEUVER trial. First Author: Vinod Ravi, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: TGCT is a rare, locally aggressive, soft-tissue tumor associated with significant morbidity. Pimicotinib (pimi) is an oral, highly selective, small molecule colony-stimulating factor-1 receptor (CSF-1R) inhibitor. In the Phase 3 MANEUVER trial (NCT05804045), the primary and key secondary endpoints were met; pimi demonstrated robust tumor responses and symptomatic and functional improvements, with a tolerable safety profile. Here, we report the longer-term safety profile and adverse event management strategies with at least one year of pimi treatment. **Methods:** Adults patients (pts) with symptomatic unresectable TGCT were randomized (2:1) to pimi 50 mg once daily or placebo for 24 weeks (Part 1), followed by open-label pimi for an additional 24 weeks (Part 2) and an extension phase. Treatment-emergent adverse events (TEAEs) were monitored for 30 days after the last dose and graded using the Common Terminology Criteria for Adverse Events, version 5.0. **Results:** In total, 63 pts received pimi (median follow-up: 14.3 months). The most frequent laboratory abnormality TEAE was increased creatinine phosphokinase (CPK; 71.4%) and the most common clinical TEAE was pruritus (60.3%). Fatigue occurred in 28.6% of pts. Most TEAEs were Grade 1–2 (Table). Grade ≥3 TEAEs occurred in 46.0% of pts, primarily elevated CPK (15.9%) and rash (6.3%), with no Grade ≥3 periorbital or facial edema observed. TEAEs were managed with dose interruptions (66.7%; median 11 days) and reductions (25.4%), maintaining a high median percentage intended dose (88.2%). Discontinuations were infrequent (6.3%). Concomitant medications were commonly used for AE management; local corticosteroids and antihistamines for rash and pruritus, and diuretics for edema. **Conclusions:** This analysis confirmed the distinct and manageable safety profile of pimi. Most TEAEs were low grade and managed through dose modifications and standard concomitant medications, enabling sustained dosing and minimal discontinuations. These findings support the longer-term tolerability of pimi in TGCT. Clinical trial information: NCT05804045. Research Sponsor: Abbisko Therapeutics; Merck KGaA, Darmstadt, Germany.

Grades of most common TEAEs (≥30%) in patients treated with pimi in the MANEUVER phase 3 trial.

TEAEs, n (%)[a]	Any grade	Grade 1	Grade 2	Grade ≥3
Blood CPK increased[b]	45 (71.4)	20 (31.7)	15 (23.8)	10 (15.9)[c]
Blood LDH increased[b]	36 (57.1)	35 (55.6)	1 (1.6)	0
AST increased[b]	35 (55.6)	33 (52.4)	2 (3.2)	0
Amylase increased[b]	24 (38.1)	16 (25.4)	8 (12.7)	0
Pruritus[d]	38 (60.3)	26 (41.3)	10 (15.9)	2 (3.2)
Face edema[d]	31 (49.2)	22 (34.9)	9 (14.3)	0
Rash[d]	24 (38.1)	18 (28.6)	2 (3.2)	4 (6.3)
Periorbital edema[d]	23 (36.5)	18 (28.6)	5 (7.9)	0

[a]TEAEs were not mutually exclusive; patients may have had more than one TEAE.
[b]Asymptomatic laboratory abnormalities.
[c]Included one patient with Grade 4 event.
[d]Clinical adverse events.
LDH, lactate dehydrogenase; AST, aspartate aminotransferase.

11572 Poster Session

Phase I trial of LB-100 plus doxorubicin as first-line of advanced soft tissue sarcomas: A Spanish Sarcoma Group (GEIS) study. First Author: Javier Martin Broto, Fundación Jimenez Diaz University Hospital, Madrid, Spain; University Hospital General de Villalba, Madrid, Spain; Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz (IIS/FJD; UAM), Madrid, Spain

Background: In sarcomas, blocking the phosphatase PP2A with LB-100 enhanced doxorubicin effectiveness, reducing tumor growth and metastases in *in vivo* experiments. Mechanistically, LB-100 inhibited ATM/ATR-activated DNA damage response. The combination of doxorubicin and LB-100 significantly shrank tumor xenographs compared with either compound alone. The recommended phase 2 dose (RP2D) for LB-100 in monotherapy was 2.33 mg/m^2/d x3 days in a phase I in progressive solid tumors, reporting 1 partial response and 16 SD (including the 2 enrolled patients with sarcoma) out of 20 patients. Based on prior data, we designed a phase I trial (NCT05809830) combining doxorubicin (D) and LB-100 (L) for first-line advanced sarcomas. **Methods:** Adult patients with advanced soft tissue sarcomas and no prior anthracycline treatment were enrolled. The main endpoint was to determine the RP2D. Secondary endpoints were to evaluate the safety profile, efficacy (PFS, ORR,OS), QoL, and translational research. Dose levels were defined as follows, I: D 60 L 1.75; II: D 75 L 1.75; III: D 75 L 2.33; A -I dose-level was defined as D 60, L 1.25. L was administered on days 1 to 3 in a 2-hour IV infusion, followed by D in a 20-minute IV infusion on day 1 of each cycle. After 6 cycles of combination, L was administered as a maintenance phase until disease progression or unacceptable toxicity. **Results:** Between June 2023 and September 2024, 14 out of 17 screened patients were recruited, with 12 eligible for DLT evaluation. The non-DLT-evaluable patients were explained by the use of G-CSF and the altered sequence of drug administration during the first cycle. No DLTs were reported. Grade 3-4 treatment-related adverse events were neutropenia 42.9%, febrile neutropenia 21.4%, LVEF reduction 14.3%, and one patient each for nausea, anemia, and lymphopenia (7.1%). There were 2 partial responses (14%), 6 stabilizations (43%), and 6 progressions (43%) following RECIST criteria of 14 evaluable patients. Responses were seen in patients with UPS and myxofibrosarcoma. The mPFS was 5.7 months (95% CI 0-13.3), and the mOS was 16.7 months (95% CI NA). The only QoL items of EORTC-QLQ-C30 that significantly changed (impaired) between baseline and before the 3rd cycle were nausea and diarrhea. There were 1SD and 2 PD of 3 patients in the first dose-level, 1 PR and 3SD of 4 patients in the second dose-level, and 1 PR, 2 SD, and 4 PD of 7 patients in the third dose-level. In our preclinical investigations, the highest concentrations of L induced an antagonistic effect with D. **Conclusions:** The RP2D is L1.75 and D 75 based on tolerance and activity, and it deserves to be tested in phase II trials. Clinical trial information: NCT05809830. Research Sponsor: None.

11573 **Poster Session**

Who really benefits from chemotherapy in high-risk localized soft tissue sarcoma? A virtual twin analysis of ISG-STS 1001. First Author: Fahima Dossa, Cedars-Sinai Medical Center, Los Angeles, CA

Background: Randomized trials of perioperative chemotherapy in high-risk localized extremity/truncal soft tissue sarcoma (etSTS) show modest average survival benefits, leaving uncertainty about which patients derive clinically meaningful benefit. Conventional hazard ratio-based reporting reflects population-level effects but offers limited guidance for individual decisions. Counterfactual approaches, such as the virtual twin framework, enable estimation of patient-specific outcomes under alternative treatment strategies, translating randomized evidence into clinically interpretable absolute benefit measures. **Methods:** Individual patient data from the ISG-STS 1001 randomized trial in high-risk localized etSTS with updated follow-up were analyzed using a virtual-twin framework with counterfactual predictions to estimate each patient's outcomes under alternative treatment scenarios: standard epirubicin-ifosfamide (EI) vs histotype-tailored (HT) chemotherapy (proxy for no effective chemotherapy). Patients with myxoid liposarcoma were excluded. Cox proportional hazards models for overall survival (OS) and disease-free survival (DFS) were adjusted for pretreatment covariates. For each patient, counterfactual 5-year OS and DFS probabilities under EI and HT were estimated and individualized absolute treatment effects were defined as the difference between counterfactual predictions. Bootstrap resampling was used to quantify uncertainty and treatment benefit explored across levels of baseline risk and tumor characteristics. **Results:** The cohort included 218 pts (median follow-up 116 months). In covariate-adjusted models, mean absolute improvement in 5-year OS with EI was 7.5% (95%CI: 4.5%-10.2%). Absolute OS benefit was inversely correlated with Sarculator-predicted 10-year survival, indicating greater benefit among patients with poorer baseline prognoses. Pts in the highest Sarculator-predicted survival quartile (pOS $>$69%) had a mean 5-year OS benefit of 5.9% (95%CI: 3.5%-9.0%), with 63% achieving $\geq$5% benefit. In contrast, pts in the lowest predicted survival quartile (pOS $<$46%) had a mean benefit of 8.7% (95%CI: 5.3%-10.4%), with 98% achieving $\geq$5% benefit. Benefits varied by histology (undifferentiated pleomorphic sarcoma = 6.6%, leiomyosarcoma = 7.2%, synovial sarcoma = 8.3%, malignant peripheral nerve sheath tumor = 8.9%) and, within each subtype, was inversely correlated with Sarculator-predicted survival. **Conclusions:** Individualized counterfactual prediction reveals substantial heterogeneity in the absolute benefit of chemotherapy in high-risk localized etSTS, driven by baseline prognostic risk and histology. This framework provides clinically relevant, patient-centered estimates that support risk-adaptive decision-making and clarify chemotherapy benefits across risk groups beyond average trial effects. Research Sponsor: None.

11574 **Poster Session**

Sintilimab (PD-1 antibody) plus gemcitabine and docetaxel (GT) as first-line or later-line therapy in patients with advanced epithelioid sarcoma: A prospective, multicenter, single-arm, phase II clinical study. First Author: Xiaowei Zhang, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Shanghai Medical College, Fudan University, Shanghai, China

Background: Advanced epithelioid sarcoma (ES) responds poorly to conventional chemotherapy, with an objective response rate (ORR) of 15-27% and a median progression-free survival (mPFS) of only 4-6 months, highlighting the urgent need for new therapeutic strategies. This study aims to evaluate the efficacy and safety of Sintilimab (An approved PD-1 antibody) plus the gemcitabine and docetaxel (GT) in patients with advanced ES that has not been treated by chemotherapy. **Methods:** This is a single-arm, prospective phase II study conducted in China (ChiCTR2500095527). Patients received Sintilimab (200mg, d1, q3w) combined with gemcitabine (1000mg/m^2, d1,8, q3w) and docetaxel (70mg/m^2, d8, q3w) for up to 6 cycles, followed by Sintilimab maintenance for up to 2 years or until disease progression, intolerable adverse reactions or death. The primary endpoint was ORR, and secondary endpoints included PFS, overall survival (OS), and safety. Additionally, tumor tissue and/or blood samples were collected from patients before treatment and at the time of progression for exploratory biomarker analysis. **Results:** Between October 2024 and January 2026, Of the 19 planned patients, 16 eligible patients were enrolled. The median age was 36 years (range: 22-61), with 5 males and 11 females. All patients had metastatic or unresectable locally advanced disease (ECOG performance status 0: 12.5%; stage IV: 75.0%). With the cutoff date of January 15, 2026, 14 patients were evaluated, the median follow-up time was 8.6 months (range, 2.9 to 14.6 months), the objective response rate (ORR) was 35.71% (5/14), all of them were partial responses (PR), and the disease control rate (DCR) was 100% (14/14). The median PFS and OS were not reached. Treatment-related adverse events (TRAEs) occurred in all patients, with grade $\geq$3 TRAEs observed in 4 (28.57%) patients, included two case of neutropenia, and one case each of thrombocytopenia and transaminase elevation. **Conclusions:** The combination of Sintilimab and GT demonstrated promising efficacy in chemotherapy-naïve patients with advanced ES, achieving an ORR of 35.71% and a remarkably high DCR. Despite limited follow-up, the preliminary PFS data suggest a potential benefit from PD-1 immunotherapy. The combination showed a manageable safety profile with no new safety signals identified. Clinical trial information: ChiCTR2500095527. Research Sponsor: None.

11575 **Poster Session**

Preliminary results of pegylated liposomal doxorubicin, dacarbazine, and toripalimab in patients with advanced primary cardiac sarcoma: An interim analysis. First Author: Zhichao Tan, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Orthopedic Oncology, Peking University Cancer Hospital & Institute, Beijing, China

Background: Primary cardiac sarcoma (PCS) is an ultra-rare malignancy with a dismal prognosis, with previously reported median overall survival (OS) of 8–17.2 months. The roles of chemotherapy and immunotherapy remain controversial, and prospective evidence is scarce. We conducted a prospective, single-arm study to evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD), dacarbazine (DTIC), and toripalimab in patients with advanced PCS (DART-PCS). **Methods:** Patients with locally advanced or metastatic PCS were enrolled from January 2024. Treatment consisted of PLD (35–40 mg/m^2) and DTIC (1.0–1.2 g/m^2), each administered either on day 1 or divided over days 1–2, plus toripalimab (240 mg, day 1), every 3 weeks for six cycles. Tumor responses were assessed every two cycles by CT or MRI. Patients without progression after six cycles underwent multidisciplinary evaluation to determine further combination therapy or immunotherapy maintenance. The primary endpoint was investigator-assessed overall response rate (ORR) per RECIST v1.1. Secondary endpoints included progression-free survival (PFS), OS, and safety. Adverse events (AEs) were graded using CTCAE v5.0. Survival outcomes were estimated using the Kaplan–Meier method. The planned sample size was 30 patients. **Results:** To data cutoff, a total of 20 patients were enrolled (65% male; median age: 36 years). ECOG performance status was 0 in 30%, 1 in 45%, and 2 in 25% of patients. Eighteen patients (90%) had undergone prior surgical resection, although R0 resection was achieved in only 25%. Histologies included angiosarcoma (85%), pleomorphic undifferentiated sarcoma (10%), and epithelioid hemangioendothelioma (5%). All tumors originated in the atrium, with right atrial involvement in 85% and left atrial involvement in 15%. At enrollment, 12 patients (60%) presented with metastatic disease, and 8 (40%) had local recurrence. Responses were evaluable in 18 patients. The ORR was 44.4%, including 3 complete and 5 partial responses. The median duration of response was 21.8 weeks (95%CI: 11.7-32.0). As of January 15, 2026, the median PFS was 23.1 weeks (95%CI: 18.21-29.22), and the median OS 55.0 weeks (95%CI: 37.21-72.78). The 1-year OS rate was 54%. Treatment-related adverse events (TRAEs) occurred in all patients, with grade $\geq$3 TRAEs observed in 18 (90%) patients, most commonly neutropenia (90%), leucopenia (40%) and anemia (30%). One fatal serious AE (hemoptysis) was reported. The median cumulative PLD dose was 221.6 mg/m^2 (range: 69.0-465.1). No clinically significant cardiac dysfunction were observed. **Conclusions:** Preliminary results from the DART-PCS trial demonstrate promising antitumor activity and an acceptable safety profile for PLD, DTIC, and toripalimab in patients with advanced PCS. Further validation is warranted upon completion of the study. Clinical trial information: ChiCTR2400084334. Research Sponsor: None.

11576 **Poster Session**

Impact of modern systemic and multimodality treatments on post-relapse survival in retroperitoneal soft-tissue sarcoma: A digital-twin target trial emulation study. First Author: Roberta Sanfilippo, European Institute of Oncology, Milan, Italy

Background: We previously observed a significant improvement in post-relapse overall survival (OS) in patients with recurrent retroperitoneal soft-tissue sarcoma (RPS) treated in 2012–2021 compared with 2002–2011. This study aimed to determine whether this survival benefit reflects advances in post-relapse treatment strategies, using digital twins to isolate the impact of systemic therapy and multimodality care. **Methods:** Adults with resected RPS and first documented recurrence were grouped by era (pre-2012 vs post-2012). Post-recurrence management was modeled as time-dependent multimodal treatment to account for treatment timing and avoid time-related bias, including repeat surgery, radiotherapy, and systemic therapy (up to five sequential lines). Detailed treatment data (surgery, radiotherapy, number of systemic therapy lines, and use of novel agents available since 2012, within or outside clinical trials) were captured. A Cox model for post-relapse survival was fitted in the post-2012 cohort using baseline covariates and time-dependent treatments. This model was used to predict the counterfactual post-relapse survival on the Monte-Carlo simulated digital-twin trajectories for pre-2012 patients under post-2012 management. The effect of post-2012 systemic therapies was isolated and applied to the pre-2012 cohort to estimate their counterfactual impact. Restricted mean survival time (RMST) at 2 and 5 years was standardized to the pre-2012 baseline distribution. **Results:** Among 872 operated patients, 417 developed recurrence; complete data were available for 86 pre-2012 and 263 post-2012 patients. Post-relapse OS significantly improved over time, with median post-relapse OS of 14.9 months pre-2012 versus 43.8 months post-2012. Observed RMST differences favored the post-2012 cohort by +5.6 months at 2 years, and +18.0 at 5 years ($p < 0.001$). Counterfactual simulation predicted that applying post-2012 management to pre-2012 patients would increase median OS to 33.8 months and RMST by +4.8 and +12.2 months at 2 and 5 years, respectively. Isolating systemic therapy alone reduced the gain by -2.2, and -5.7 months, indicating a partial but not exclusive contribution of systemic treatment advances ($p<0.001$). **Conclusions:** Digital-twin target trial emulation suggests that post-2012 management strategies explain most of the early and a substantial portion of the long-term survival improvement after RPS recurrence. Advances in systemic therapy contribute meaningfully but do not fully explain the observed OS gains, supporting the importance of integrated multimodality post-relapse care. Research Sponsor: None.

11577 **Poster Session**

Real-world outcomes of doxorubicin and paclitaxel in advanced Kaposi sarcoma: A TriNetX retrospective cohort study. First Author: Keun Lee, In-Independent Researcher, Richmond, VA

Background: For decades, pegylated liposomal doxorubicin (PLD) and paclitaxel have been standard antineoplastic therapies for advanced Kaposi sarcoma (KS). However, contemporary estimates of their efficacies remain limited. This limit is particularly profound in HIV-associated KS, where advances in antiretroviral therapy and supportive care reduce the relevance of historical outcomes. **Methods:** In January 2026, the TriNetX database (171 global healthcare organizations) was queried to identify patients with KS (ICD-10-CM code C46 and ICD-O-3 code 9140/3) who received doxorubicin or paclitaxel since 2010. Patients with a history of lymphoma, cervical cancer, anal cancer, or solid organ transplantation were excluded. We extracted demographics, overall survival (OS), and time to next-line treatment or death (TTNT-D) to obtain estimated progression-free survival (ePFS). Outcomes were measured from index treatment initiation (first recorded receipt of doxorubicin or paclitaxel after KS diagnosis). Lastly, HIV-based subgroup analyses were conducted with 1:1 propensity matching by age, sex, race, and prior antineoplastic treatments. Kaplan-Meier analysis was done with significance set at $p<0.05$. **Results:** We analyzed 935 KS patients treated with doxorubicin (including PLD) and 379 treated with paclitaxel. The patients treated with doxorubicin (median age: 45 years, 81.0% male, 48.3% HIV+) had 2- and 5-year OS of 77.5% and 70.0% and ePFS of 63.0% and 56.36% respectively. The patients treated with paclitaxel (median age: 50 years, 78.5% male, 42.7% HIV+) had 2- and 5-year OS of 71.3% and 62.4% and ePFS of 53.8% and 45.1% respectively. Within the doxorubicin cohort, HIV+ patients were younger (median age 40 vs 56 years), more often male (95.0% vs 64.7%), and had higher proportions of African American and Hispanic patients (36.4% and 14.7% vs 12.3% and 7.1%). A matched analysis of HIV+ vs. HIV- patients showed 2-year OS of 86.2% vs 71.7% (p=0.003) and 2-year ePFS of 74.85% vs 52.19% ($p<0.0001$). Within the paclitaxel cohort, HIV+ patients were also younger (median age 40 vs 64 years), more often male (96.5% vs 63.8%), and had higher proportions of African American and Hispanic patients (39.3% and 15.0% vs 9.0% and 5.0%). A matched analysis of HIV+ vs. HIV- patients showed 2-year OS of 60.3% vs 74.1% (p=0.151) and 2-year ePFS of 38.0% vs 57.7% (p=0.023). A matched analysis of doxorubicin vs. paclitaxel in HIV+ patients showed 2-year OS of 86.9% vs 73.0% (p=0.007) and ePFS of 77.7% vs 67.9% (p=0.069). **Conclusions:** This large real-world analysis provides a contemporary assessment of doxorubicin and paclitaxel in advanced KS. HIV+ status was associated with higher OS and ePFS in the doxorubicin cohort, whereas HIV- status was associated with higher ePFS in the paclitaxel cohort. Limitations include the retrospective design and imperfect reliability of TTNT-D as a surrogate for PFS. Research Sponsor: None.

11578 **Poster Session**

Phase I trial of combination gemcitabine (gem) and nab-sirolimus (nab-S) in advanced leiomyosarcomas (LMS) or advanced soft-tissue sarcomas (STS) with *TSC1/2* alterations: Preliminary results. First Author: Elise F. Nassif Haddad, Department of Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Advanced LMS has limited effective therapies, with gem-based regimens being the most prescribed. Preclinical data suggest gemcitabine induces activation of the PI3K–mTOR pathway, supporting combination strategies with mTOR inhibition. Nab-S is a nanoparticle albumin-bound, IV formulation of sirolimus and has demonstrated greater intratumoral accumulation and antitumor activity in preclinical models compared to conventional mTOR inhibitors. **Methods:** This investigator-initiated, single-center phase I study evaluates gem (900mg/m2) plus nab-s (dose levels [DL]: DL1=75mg/m2 or DL2=100mg/m2) in patients (pts) using a Bayesian optimal interval (BOIN) design. Primary objective was to estimate the maximum tolerated dose (MTD) of the combination based on cycle 1 dose-limiting toxicities (DLT). Secondary objectives were to estimate objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). Responses were assessed by RECIST1.1 and adverse events (AE) graded per CTCAEv5. **Results:** As of 01/22/26, all 12 pts initially planned for accrual have completed the DLT period. The original dosing schedule consisted of drug administration on Days 1 and 8 of a 21-day cycle. After the first 6 pts were enrolled, the protocol was amended to administer drugs on Days 1 and 15 of a 28-day cycle. This modification was implemented for all pts due to hematologic toxicities. While expected based on the known safety profile of nab-s and of gem, this frequently prevented Day 8 administration under the original schedule. All pts had advanced LMS, 10 pts were female and 7 had uterine LMS, the median age at time of consent was 55 yo. Three pts were included at DL1, and there was no DLT. DL2 included 9 pts: only one pt experienced a DLT of mucositis and diarrhea grade (Gr) 3 lasting for 3 days. The most frequent treatment-related Gr3-4 AE was thrombocytopenia. One pt had Gr3 pneumonitis attributed to gem and discontinued trial after 2 cycles. There was no other concern for safety. Ten pts were evaluable for response (1 pt died of disease and 1 pt chose to discontinue the trial before their first evaluation). ORR is 30% (n=3/10) at time of data cutoff and 90% pt had clinical benefit: 6 pts had stable disease with 5 pts experiencing shrinkage of disease (range: -8% to -21%) and 1 pt with 0% change. Only 1 pt had progressive disease as best response. With a median follow-up of 4 months (mo) for PFS, the median PFS (95% confidence interval [CI]) is 8.38 (1.68, not reached) mo, the 3-mo PFS (95% CI) is 78% (36%,94%), and the 6-mo PFS (95% CI) is 58% (16%,85%). With a median follow-up of 5.8 mo for OS, the 6-mo OS (95% CI) is 80% (39%,95%). **Conclusions:** The MTD was determined to be gem 900mg/m2 with nab-s 100mg/m2 on Days 1 and 15 of a 28-day cycle. Based on this preliminary safety and efficacy, an expansion with an additional 6 pts at this DL is ongoing. Clinical trial information: NCT06308419. Research Sponsor: Aadi Bioscience.

11579 **Poster Session**

Efficacy and safety analysis of intraoperative radiotherapy for soft tissue sarcoma: The largest-sample, single-center, real-world data review. First Author: Zhichao Liao Sr., Tianjin Cancer Hospital, Tianjin, China

Background: This study aimed to evaluate the efficacy and safety of surgery combined with intraoperative radiotherapy (IORT) versus surgery combined with postoperative adjuvant radiotherapy in the treatment of soft tissue sarcoma (STS). It sought to identify patient subgroups that derive the most benefit from IORT and to provide evidence for treatment selection. **Methods:** This retrospective single-center study was conducted at Tianjin Medical University Cancer Institute & Hospital between May 2021 and December 2024. A total of 420 patients with pathologically confirmed STS were initially screened. After applying strict inclusion and exclusion criteria, 252 eligible patients were enrolled and divided into two groups: 147 patients who underwent surgery combined with IORT using the INTRABEAM 600 System, and 105 patients who received surgery combined with conventional postoperative adjuvant radiotherapy. **Results:** After a median follow-up period of 17.2 months (range: 4.8-47.18 months), the IORT group demonstrated significantly superior outcomes. Multivariate analysis identified three independent risk factors for RFS: radiotherapy modality (IORT vs. postoperative radiotherapy, p = 0.001), primary versus recurrent tumor status ($p < 0.001$), and T stage (p = 0.003). The RFS in the IORT group was significantly better than in the postoperative radiotherapy group (P = 0.001). Subgroup analysis revealed that IORT was particularly advantageous for specific patient populations. Tumor size was a critical determinant: for lesions larger than 5 cm in diameter, IORT significantly improved RFS across all subgroups ($>$ 15 cm: p = 0.008; 10-15 cm: p = 0.008; 5-10 cm: p = 0.004). However, for tumors smaller than 5 cm, no significant difference was observed between the two treatment modalities (p = 0.874). For OS, multivariate analysis identified radiotherapy type (p = 0.01) and AJCC stage (p = 0.007) as independent risk factors. The IORT group showed a trend toward improved OS, though longer follow-up is needed for definitive conclusions. The safety analysis strongly favored IORT. The incidence of treatment-related adverse events was significantly lower in the IORT group across all categories. **Conclusions:** This large-sample, single-center real-world study demonstrates that surgery combined with intraoperative radiotherapy significantly prolongs recurrence-free survival and improves local control in soft tissue sarcoma patients compared to surgery combined with postoperative radiotherapy. The benefits are most pronounced in patients with primary or recurrent tumors larger than 5 cm in diameter. Additionally, IORT offers a substantially more favorable safety profile with significantly reduced rates of radiation-related adverse events. Research Sponsor: None.

11580 **Poster Session**

Secondary genomic alterations and clinical outcomes in myxoid liposarcoma: A multi-institutional analysis. First Author: Daniel Reinhorn, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Myxoid liposarcoma (MLS) is defined by *DDIT3* rearrangements. The clinical and prognostic significance of secondary genomic alterations remains incompletely characterized. We retrospectively evaluated the clinical, pathological, and prognostic implications of commonly co-occurring mutations in patients with MLS. **Methods:** Patients with pathologically confirmed MLS treated at Memorial Sloan-Kettering Cancer Center (MSKCC) and MD Anderson Cancer Center (MDACC) who underwent next-generation sequencing (NGS) on the primary tumor (9/2010-5/2024) were included. To ensure the analysis represented *de novo* mutations rather than acquired alterations, patients with NGS performed only at the time of recurrent disease were excluded. The primary endpoint was disease-free survival (DFS) among surgically treated patients. Associations between genomic alterations and clinico-pathologic characteristics were assessed using univariable and multivariable analyses. **Results:** The cohort included 76 patients (67 MSKCC, 9 MDACC) with a median age of 39 years. At diagnosis, 83% of patients (n = 63) had localized disease and underwent definitive surgery, while 17% presented with de novo metastasis; 45% had high-grade disease ($\geq$5% round cell component). Genomic analysis identified *TERT* promoter mutations in 68%, *PIK3CA* in 30%, and *PTEN* in 18%. Notably, *PIK3CA* and *PTEN* mutations were not mutually exclusive, with 10.5% of the total cohort harboring concurrent alterations in both genes. *TERT* promoter mutations were significantly associated with male sex (75% vs 33%, $p < 0.001$), older age (40 vs 33 years, p = 0.02), high-grade pathology (54% vs 25%, p = 0.026), and larger median tumor size (12.9 vs 7.5 cm, p = 0.002). *PIK3CA* mutations were associated with male sex (83% vs 53%, p = 0.02) and a trend toward larger median tumor size (13.6 vs 9.3 cm, p = 0.061) and *de novo* metastasis (30% vs 11%, p = 0.053). For the 63 patients with localized disease, the median DFS was not reached (95% CI: 55.7–NR) with a 24-month DFS rate of 75% (95% CI 61-84). In univariable analysis for DFS, significant predictors of recurrence included *PIK3CA* mutation (HR 4.61; p = 0.001), *PTEN* mutation (HR 5.15; $p < 0.001$), tumor size (HR 1.06 per cm; p = 0.012), high-grade pathology (HR 2.81; p = 0.024) and male sex (HR 2.79; p = 0.049). The presence of both *PIK3CA* and *PTEN* mutations conferred particularly poor prognosis (HR 16.34 compared to neither mutation; $p < 0.001$). In separate multivariable analyses adjusted for grade, both *PIK3CA* (HR 5.75, $p < 0.001$) and *PTEN* (HR 4.27, p = 0.002) remained independent predictors of DFS. **Conclusions:** Secondary genomic alterations in MLS are highly prevalent and connote distinct clinical phenotypes. While *TERT* promoter mutations correlate with aggressive pathologic features, *PIK3CA* and *PTEN* mutations are independent prognostic factors for DFS and may help risk-stratify patients for potential adjuvant therapies. Research Sponsor: Cancer Center Support Grant; P30 CA008748.

11581 **Poster Session**

Integrating personalized ctDNA into clinical surveillance of soft tissue sarcoma: Performance, timing, and histologic insights. First Author: Amrit Paudel, University of Miami Sylvester Comprehensive Cancer Center/Jackson Health System, Miami, FL

Background: Soft tissue sarcoma (STS), particularly larger and biologically aggressive subtypes, carries a high risk of relapse making effective post-operative surveillance essential. CtDNA utility in STS remains elusive. **Methods:** We conducted a retrospective review of STS who underwent surgical resection and post-operative surveillance with serial personalized ctDNA testing (Signatera) and cross-sectional imaging between April 2023- January 2026. Diagnostic performance was assessed by sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using imaging-confirmed progression as the reference standard. Subgroup analyses by major histologic subtype conducted. Detection times were referenced to surgery, and lead time was summarized using medians and interquartile ranges (IQR). Paired detection times were compared using the Wilcoxon signed-rank test, with Mann–Whitney U test as a sensitivity analysis. **Results:** Total 114 patients with ctDNA samples were screened. 101 patients with paired ctDNA (total 1,005 plasma samples) and imaging surveillance were included. The median age at diagnosis was 53 years, and the cohort was evenly distributed by sex (50.5% male, 49.5% female). Most patients were White (86.1%), 13.9% African American; 58.4% identified as non-Hispanic and 40.6% as Hispanic. Using imaging as the reference standard, 33 patients developed radiographic progression. ctDNA was positive in 27, yielding a sensitivity of 81.8% (95% CI, 65.6%–91.4%). Among 68 patients without progression, 66 remained ctDNA negative, corresponding to a specificity of 97.1% (95% CI, 89.9%–99.2%). The PPV and NPV were 93.1% and 91.7%, respectively. Six patients (18.2%) had radiographic progression despite persistently negative ctDNA, forming a clinically relevant discordant subgroup. Among patients with paired molecular and radiographic progression (n = 27), ctDNA detected progression earlier in 44%, while imaging led in 56%. Overall detection timing did not differ significantly between modalities (median lead time, –0.21 months; IQR, –1.42 to 1.67; p = 0.91). Tumors associated with ctDNA positivity were numerically larger than ctDNA-negative (median, 8.75 cm vs 7.0 cm, p = 0.051). CtDNA detection dynamics varied by histologic subtype, with a nonsignificant numerical trend toward earlier detection in synovial sarcoma. The most common site of metastatic involvement was lung (40%), followed by liver (20%). **Conclusions:** Personalized ctDNA surveillance showed high specificity and strong diagnostic performance in STS and detected progression earlier than imaging in a subset of patients, though no overall lead-time advantage was observed. Histology-specific differences suggest biologic variability in ctDNA detectability and support prospective, subtype-focused studies to define optimal integration with imaging. Research Sponsor: None.

11582 **Poster Session**

Percutaneous cryoablation for the treatment of extra-abdominal desmoid tumors. First Author: Ajay Katwala, Medical College of Wisconsin, Milwaukee, WI

Background: Management of extra-abdominal desmoid tumors (DT) has evolved over the last decade, with emphasis on conservative management based on guidelines from the Desmoid Tumor Working Group. There is growing evidence for ablative therapies, including percutaneous cryoablation (PCA), but there is little data on long-term outcomes with PCA. This large cohort study reports efficacy and long-term outcomes for patients with extra-abdominal DTs with PCA. **Methods:** Patients with pathologically-confirmed extra-abdominal DT were recruited consecutively at a high-volume referral center from 2014-2025. Data points including patient demographics, tumor characteristics, and procedural details for cryoablation were collected. The primary outcome was ablation success using the modified response criteria in solid tumors (mRECIST), measuring change in viable tumor along the longest tumor diameter. Secondary outcomes were change in lesion volume (TLV), complications per Clavien-Dindo classification, patient-reported symptom resolution, and progression-free survival (PFS). **Results:** A total of 53 patients undergoing 83 PCA procedures were identified. 67.9% of patients were female. The median follow up time was 40.1 months. Thirty-two patients were treated with PCA as first-line therapy, while 21 were treated as salvage therapy. The median change in viable tumor volume using mRECIST was -100%; 26 patients had a complete response (CR), 13 had partial response (PR), 7 had stable disease (SD), and 13 had progressive disease (PD). The median change in TLV was -71.7%. One-year and five-year PFS rates were 88.2% and 66.6% respectively. Fifty patients had symptoms including pain, an enlarging mass, or decreased range of motion prior to PCA; 94.0% had symptomatic improvement or resolution after PCA. Two patients had major complications: one inferior epigastric hemorrhage and one small bowel injury treated with a small bowel resection. **Conclusions:** This study provides the largest cohort of extra-abdominal desmoid tumors undergoing PCA. PCA can lead to patient-reported symptom resolution, a substantial decrease in mRECIST and TLV, and has a low complication rate. This study adds further evidence that PCA is safe and effective for treating extra-abdominal desmoid tumors. Research Sponsor: None.

11583 **Poster Session**

Investigating the molecular characteristics underlying desmoid tumor clinical trajectory. First Author: Robert Lawrence Dilley, Dana-Farber Cancer Institute, Boston, MA

Background: Desmoid tumors are locally aggressive mesenchymal neoplasms that primarily affect adolescents and young adults. They demonstrate a range of clinical behavior from spontaneous regression to refractory growth leading to morbidity and sometimes mortality. However, there are no prognostic biomarkers for patients with desmoid tumors and we have a limited understanding of the biology behind the range of clinical behavior. Thus, we aimed to characterize the clinical course of patients with banked desmoid tumors at our institution from across the age spectrum, and correlate clinical behavior with genetic alterations and gene expression signatures. **Methods:** We identified 64 adult patients through our adult sarcoma biobank and 5 patients through our pediatric biobank with desmoid fibromatosis and banked samples. Retrospective chart review was conducted including patient characteristics, disease features, treatment course, and outcomes. Genetic analysis was completed on 61 patients (43 targeted exome sequencing, OncoPanel). To characterize gene expression, we performed single nucleus RNA sequencing (snRNAseq) on 15 samples from 12 patients, with concurrent *CTNNB1* genotyping to accurately identify tumor cells. Primary analyses included cell annotation of clusters and differential gene expression between progressing and stable/regressing tumors. **Results:** A total of 69 patients were included in this study. Median age at diagnosis was 35 years (range 2–83), with 68% female. Median tumor size at diagnosis was 5.2cm (range 0.7–25.0). Tumor location included abdominal wall (41%), mesenteric (25%), trunk/breast (14%), extremity (16%), and head/neck (5%). At time of tissue collection 39% of tumors were progressing, 23% were stable, and 10% were regressing (28% unknown). Among 61 sequenced tumors, 72% and 21% harbored *CTNNB1* and *APC* mutations, respectively, and 7% showed no mutations in either gene. snRNAseq resulted in a dataset of over 180,000 high-quality nuclei. Cell composition differences were identified across the spectrum of disease states. Concurrent single-nucleus *CTNNB1* genotyping revealed expression differences in the tumor cell compartment between progressing and non-progressing tumors, including collagen/extracellular matrix proteins and mesenchymal transcription factors. **Conclusions:** In this cohort of adult and pediatric desmoid tumors, integration of clinical annotation and molecular characteristics identified gene expression programs associated with tumor progression. These findings provide new insights into the biology underlying variable clinical trajectory in desmoid tumors, implicating altered collagen/extracellular matrix and mesenchymal transcription factor programs. Ongoing bulk RNA sequencing and immunohistochemical analyses are being performed to assess the potential of these signatures as predictive biomarkers and therapeutic targets. Research Sponsor: Desmoid Tumor Research Foundation.

11584 **Poster Session**

Phase II pilot study of pembrolizumab (PEM) and neoadjuvant radiation therapy (nRT) in high-risk soft tissue sarcomas (STS). First Author: Lee D. Cranmer, City of Hope National Medical Center Department of Medical Oncology and Therapeutics Research, Duarte, CA

Background: Pathologic necrosis (PN) after neoadjuvant therapy in STS has been associated with improved outcomes. We investigated clinicopathologic outcomes of concurrent PEM/nRT in STS. **Methods:** Adults with localized STS [FNCLCC grade 3 ($>$ 1.5 cm) or grade 2 ($>$ 3 cm)] received 3 doses of PEM (200 mg IV q21 d) concurrently with nRT, followed by surgery. Primary endpoint was the rate of post-treatment complete pathologic necrosis (CPN; $\geq$90% PN). 26 subjects provided 94% power to detect an increase in CPN rate from 15% to 40%; $\geq$7 cases with CPN would exclude a 15% CPN rate. Secondary endpoints included toxicity (CTCAE 5.0), response (RECIST 1.1), and event-free survival (EFS). **Results:** 27 STS patients were enrolled including UPS (10; 37%), DD liposarcoma (8; 30%), myxofibrosarcoma (2; 7%), solitary fibrous tumor (2; 7%), and other STS (5; 19%). 26 patients were evaluable for CPN and 25 for EFS. All except 2 (7%) received 3 planned PEM doses. All completed planned RT (50-50.4 Gy). 2 (7%) with UPS had partial responses prior to surgery. Median tumor size was 10 cm (range 2.1-26 cm). R0 resection was achieved in 92%. 14 (54%) patients had grade 3 tumors; 12 (46%) had grade $\geq$2. Median post-treatment PN was 55% (range 0-99%) with 5/26 (19%) having CPN. Median follow-up time was 33.4 months (m) from PEM initiation (range 1.6-60 m). 12/25 patients had an EFS event. Among all patients (n = 27), 12 developed only distant metastatic disease, and 1 developed local and distant recurrence. AEs were consistent with anticipated effects of PEM and RT. Two grade 5 events occurred (ischemic colitis, prostate cancer), both judged unrelated to study therapy. 3 patients experienced wound dehiscence, and one had wound infection. EFS at 12 m was 68%; at 57.5 m, it was 52%. Post-treatment PN as a continuous variable was inversely associated with EFS (HR = 22.47, p = 0.004). Increased tumor size was also associated with inferior EFS (HR = 1.09/cm, p = 0.04). In multivariable analyses, both necrosis and tumor size remained independently associated with EFS (HR = 26.52 and 1.09, p = 0.004 and 0.041, respectively). Sex, age, histology, tumor grade/location, and radiation modality were not associated with EFS. **Conclusions:** PEM did not increase the proportion of patients with post-treatment CPN after RT. Unexpectedly, increased tumoral necrosis after treatment was associated with inferior EFS. It is possible that increased post-treatment tumoral necrosis may identify a subset of STS patients less likely to benefit from PEM/nRT or who have inherently more aggressive tumor biology. These findings warrant additional studies for validation and exploration of the mechanisms and clinical applications of these findings. PN after PEM/nRT might provide a readily available biomarker that could be used to adjust therapy in those unlikely to benefit from PEM/nRT. Correlative analysis using pre- and post-treatment tumor are on-going and will be presented. Clinical trial information: NCT03338959. Research Sponsor: Merck.

11585 **Poster Session**

Neoadjuvant versus adjuvant chemotherapy for resectable high-grade soft tissue sarcoma: A real-world propensity-matched survival analysis. First Author: Mohammed Aloqaily, University of Maryland Midtown Campus, Baltimore, MD

Background: High-grade soft tissue sarcomas are aggressive malignancies for which complete surgical resection remains the cornerstone of curative-intent therapy. Current clinical guidelines recommend consideration of perioperative chemotherapy for selected high-risk patients; however, the optimal timing of systemic therapy remains uncertain. We performed a real-world analysis to compare survival outcomes between neoadjuvant and adjuvant chemotherapy in patients with resected high-grade soft tissue sarcoma. **Methods:** We conducted a retrospective cohort study using the TriNetX Database, identifying adults (≥18 years) with high-grade soft tissue sarcoma who underwent surgical resection and received combination chemotherapy with doxorubicin and ifosfamide either within 6 months before surgery or after surgery . The index date was defined as time of diagnosis. Propensity score matching (1:1) was performed to balance baseline demographics and various comorbidities. Overall survival (OS) was assessed using Kaplan–Meier methods and Cox proportional hazards models at fixed time points (1, 3, 5, and 10 years) and over the entire follow-up period. **Results:** A total of 714 patients were identified (479 adjuvant; 235 neoadjuvant). After propensity score matching, 229 patients were included in each cohort. At 1 year, overall survival was similar between adjuvant and neoadjuvant chemotherapy (53.1% vs 53.1%; risk ratio [RR] 1.06, 95% CI 0.81–1.37; log-rank p = 0.77). Additionally, analyses at 3, 5, and 10 years demonstrated no statistically significant differences in OS between cohorts, with overlapping Kaplan–Meier survival curves at all evaluated time points. Over the entire follow-up period, survival probabilities at the end of follow-up were 51.5% in the adjuvant cohort and 53.4% in the neoadjuvant cohort. There was no significant difference in overall survival (hazard ratio [HR] 1.04, 95% CI 0.75–1.44; p = 0.73). **Conclusions:** In this large, real-world, propensity-matched analysis of patients with resectable high-grade soft tissue sarcoma, survival outcomes were comparable across short-, intermediate-, and long-term follow-up intervals in both neo-adjuvant and adjuvant chemotherapy cohorts. Current guidelines recommend neo-adjuvant radiation treatment as category 1, and chemotherapy (neo-adjuvant or adjuvant) is a consideration. Neo-adjuvant chemotherapy has the potential to delay definitive treatment, however, this analysis suggests that the timing of chemotherapy does not adversely impact the outcomes in short or long term follow up. There are several limitations to our analysis (size of the tumors and grading was not available and timing of XRT could not be assessed, however, given that AIM chemo cohort was selected, it can be assumed that patients had higher grade, larger tumors and received XRT as standard of care. Research Sponsor: None.

TPS11586 **Poster Session**

A phase 1b study of tegavivint, a TBL1 inhibitor, with gemcitabine in patients with relapsed or refractory osteosarcoma (TIGER). First Author: Thomas Cash, Aflac Cancer & Blood Disorders Center, Children's Healthcare of Atlanta, Emory University School of Medicine, Atlanta, GA

Background: The Wnt-signaling pathway and its downstream transcriptional effector, β-catenin, are dysregulated in osteosarcoma (OS), promoting tumor growth and metastatic spread. When the Wnt pathway is activated, transduction beta-like protein 1 (TBL1) binds nuclear β-catenin, forming a complex that is necessary to dock on the promoters of Wnt-driven genes. Tegavivint is a first-in-class small molecule inhibitor that selectively binds TBL1, inhibiting TBL1-β-catenin complex formation, and resulting in the nuclear degradation of β-catenin and inhibition of oncogenic transcriptional activation. Preclinical testing of *in vivo* OS models demonstrates that tegavivint reduces tumor volume and suppresses lung metastases, and has additive effects when combined with gemcitabine. In a phase 1 trial conducted by the Children's Oncology Group, the recommended phase 2 dose (RP2D) of tegavivint was determined to be 6.5 mg/kg administered intravenously (IV) on a 3 weeks on/1 week off schedule, with no maximum tolerated dose (MTD) determined. The primary objective of this phase 1b study is to define the MTD and/or RP2D of tegavivint combined with gemcitabine, including assessment of toxicities and preliminary efficacy, in patients with relapsed or refractory (r/r) OS. **Methods:** TIGER is a phase 1b, multi-center, dose escalation trial assessing tegavivint combined with gemcitabine in patients with r/r OS. Eligible patients will be 1-30 years of age with either measurable or evaluable disease per RECIST v1.1 who have fully recovered from the clinically significant acute effects of prior therapy and have adequate organ function. Prior treatment with gemcitabine is allowed. Patients with active CNS disease, recent bisphosphonate treatment, metabolic bone disease or disorder, uncorrected hypocalcemia or low vitamin D, and prior receipt of tegavivint are excluded. Patients will receive tegavivint IV at the dose level assigned at study entry on days 1, 8, and 15 and gemcitabine at a fixed dose of 1000 mg/m^2 IV on days 1 and 8 of a 21-day cycle. Patients may receive up to 17 cycles provided they do not experience disease progression or unacceptable toxicity. Tegavivint will be dose escalated using a rolling six design to test two planned dose levels, 5 mg/kg [dose level (DL) 1] and 6.5 mg/kg (DL 2), with dose de-escalation to 3 mg/kg (DL 0) if needed. An additional 6 patients will be enrolled to a dose expansion cohort at the MTD/RP2D to obtain additional pharmacokinetic (PK), safety, and preliminary efficacy data. Peripheral blood for correlative studies will be obtained at serial timepoints to conduct PK studies, pharmacodynamic testing of serum protein biomarkers associated with β-catenin inhibition, and analysis of ctDNA and circulating tumor cells. Tumor tissue will be analyzed for TBL1 and Wnt/β-catenin signaling (sequencing and protein expression). Clinical trial information: NCT07144254. Research Sponsor: Peach Bowl LegACy Fund; Iterion Therapeutics.

TPS11587 **Poster Session**

A phase 1/2, multi-center, open-label study to evaluate the safety, tolerability, pharmacokinetics, radiation dosimetry, and preliminary anti-neoplastic activity of LNTH-2403, a LRRC15-targeted ^{177}lutetium-labeled monoclonal antibody, in patients with relapsed/refractory osteosarcoma. First Author: Noah Federman, UCLA Jonsson Comprehensive Cancer Center, UCLA David Geffen School of Medicine, Los Angeles, CA

Background: Treatment for relapsed and refractory (R/R) osteosarcoma (OST) has not changed for decades. R/R OST has a poor prognosis with a 12% 4-month event-free survival (EFS). Leucine-Rich Repeat Containing 15 (LRRC15) is a type I transmembrane protein on OST cells and cancer associated fibroblasts. Approximately 90% of OST express LRRC15; high expression predicts aggressive disease and shorter survival. LNTH-2403 is a high-affinity LRRC15-targeting fully humanized antibody with a ^{177}lutetium payload. Preclinical data show anti-tumor activity in several OST models, demonstrating LNTH-2403's potential to treat R/R OST. **Methods:** This first-in-human, multicenter, open-label phase 1/2 study will evaluate the safety, tolerability, pharmacokinetics (PK), biodistribution (BD), radiation dosimetry (RD), and preliminary anti-neoplastic activity in patients ≥12 years of age with LRRC15-expressing R/R OST. The primary endpoints are to identify the maximum tolerated dose (MTD; phase 1) and 4-month EFS (phase 2). LRRC15 expression by immunohistochemistry will be confirmed by a central lab; pre-screening is allowed. Initiated in Q1 2026, phase 1 will test LNTH-2403 at 30, 50, and 70 mCi/m^2 every 8 weeks in up to ~30 patients. A 3+3 design will be used to define the MTD and estimate the recommended phase 2 dose (RP2D). Phase 2 will evaluate LNTH-2403 at the RP2D in ~25 patients with R/R OST. Retreatment after Cycle 1 is permitted for patients who continue to meet initial eligibility requirements, have cumulative doses to target organs predicted to be below radiation tolerance limits, and whose bone marrow has recovered. Safety testing includes adverse events (AEs), serious AEs (SAEs), laboratory parameters (chemistry, hematology, coagulation, urinalysis), electrocardiograms, vital signs, and physical examinations. BD and RD are based on serial single photon emission computed tomography (SPECT)/computed tomography (CT) and planar imaging. PK data will be generated from serial blood sampling for radioactivity. Overall response rate (ORR) and EFS are defined by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 per investigator reads. As ORR by RECIST is challenging in OST due to tumor calcification, efficacy testing also includes physiologic response by fluorine-18 (^{18}F)-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT whole body scans and magnetic resonance imaging of the primary site, sites of known and presumed metastases, and the chest, abdomen, and pelvis. For this open-label study, all statistical methods will be descriptive in nature with no formal statistical hypotheses. NCT07357519; Research Sponsor: Lantheus. Clinical trial information: NCT07357519. Research Sponsor: Lantheus.

TPS11588 **Poster Session**

StrateGIST 3: A randomized, phase 3 study of velzatinib (IDRX-42) versus sunitinib in patients with advanced gastrointestinal stromal tumors after imatinib therapy. First Author: Suzanne George, Dana-Farber Cancer Institute, Boston, MA

Background: Most gastrointestinal stromal tumors (GISTs) are driven by mutations in *KIT*. Tyrosine kinase inhibitors (TKIs) such as imatinib and sunitinib (first- and second-line therapies for GIST, respectively) are available, but resistance can develop and is primarily mediated by additional *KIT* mutations in the ATP binding pocket (exon [ex] 13/14) and activation loop (ex 17/18). While sunitinib targets mutations in exon 13/14 in the second-line setting, it has low response rates and short progression-free survival (PFS). Therefore, there is a need for novel therapies with broad mutation coverage, and for patients (pts) with disease progression on, or intolerance to, approved therapies. Velzatinib (subject to USAN approval) is a novel, highly selective, oral KIT TKI that potently and selectively inhibits primary and secondary resistance *KIT* mutations. In StrateGIST 1, an ongoing, phase 1/1b study in adult pts with advanced GIST, velzatinib exhibited promising clinical activity and favorable safety in 2nd- and later-line pts at the recommended phase 3 dose of 300-mg QD tablet (or exposure-equivalent 400-mg QD capsule). As of December 15, 2025, median PFS (95% CI) was 13.7 (7.4–18.4) months and confirmed ORR (95% CI) was 33% (19.5–48.0) in 2nd-line pts (N=46) at the recommended phase 3 dose, supporting the further evaluation of velzatinib in pts with advanced GIST after progression on, or intolerance to, imatinib. **Methods:** StrateGIST 3 is a phase 3, randomized, multicenter, open-label study (NCT07218926) to evaluate velzatinib vs sunitinib in adult pts with advanced GIST after progression on or intolerance to imatinib. Recruitment for this study opened on December 3, 2025, and the total duration of the study is estimated to be approximately 5 years. Pts must have documented mutation status of *KIT* and/or *PDGFRA*, and will be excluded if they have GIST that is wild type for both *KIT* and *PDGFRA* or if they have an activating *PDGFRA* exon 18 mutation. Approximately 450 pts will be randomized (1:1) to receive either velzatinib (300-mg QD tablet, continuous dosing) or sunitinib (50 mg QD, 4 weeks on/2 weeks off). The randomization will be stratified by activating mutation (ex 11 vs ex 9 vs other) and intolerance to first-line imatinib (yes vs no). The primary endpoint is PFS according to modified RECIST for GIST (mRECIST-GIST), by blinded independent central review (BICR). The key secondary endpoint is overall survival, and additional secondary endpoints include PFS per investigator assessment, PFS-2, confirmed objective response rate per BICR and per investigator, time to response per BICR and per investigator, health-related quality of life and functioning, plasma drug concentrations, and safety and tolerability. This trial is now recruiting. This study (NCT07218926) is funded by GSK. Clinical trial information: NCT07218926. Research Sponsor: GSK.

TPS11589 **Poster Session**

Phase 1a/1b study of the safety, pharmacokinetics, and antitumor activity of ziftomenib in combination with imatinib in patients with advanced gastrointestinal stromal tumors (GIST) after imatinib failure. First Author: Mark Agulnik, Keck School of Medicine of University of Southern California, Los Angeles, CA

Background: GIST is the most common mesenchymal neoplasm of the digestive tract and is mainly driven by gain-of-function oncogenic mutations in the receptor tyrosine kinase KIT. Patients with GIST are typically treated with anti-KIT tyrosine kinase inhibitors (TKIs) such as imatinib. However, few patients achieve a complete response, and most eventually progress due to secondary *KIT* alterations that cause resistance to therapy. Other TKIs are approved in later lines but have shown only moderate clinical outcomes, highlighting the need for additional therapeutic approaches. Preclinical studies have shown that the menin-KMT2A complex epigenetically upregulates *KIT* expression in GIST cells. Ziftomenib is a potent and highly selective menin inhibitor that disrupts formation of the menin-KMT2A complex. Ziftomenib plus imatinib has demonstrated synergistic antitumor activity in imatinib-sensitive and -resistant GIST models, with reduced KIT protein levels and downstream oncogenic signaling observed in imatinib-resistant GIST patient-derived xenografts treated with the combination. Together, ziftomenib plus imatinib may enhance KIT recycling while reducing *KIT* transcription. This combination is currently being investigated clinically in patients with imatinib-sensitive and -resistant advanced GIST. **Methods:** KOMET-015 (NCT06655246) is an ongoing phase 1a/1b, open-label study to determine the safety, tolerability, recommended phase 2 dose (RP2D), and preliminary antitumor activity of ziftomenib plus imatinib (400 mg or $<$400 mg if previously reduced due to intolerance) for advanced/metastatic GIST. KOMET-015 includes dose-escalation, RP2D determination, and dose-expansion parts. Eligible patients ($\geq$18 yrs) must have a biopsy-proven diagnosis of advanced/metastatic *KIT*-mutant GIST (T670X excluded) that progressed on imatinib (for dose-escalation and RP2D determination parts), with an ECOG PS of $\leq$2 and measurable disease per RECIST v1.1 modified for GIST (mRECIST). Dose escalation will be based on an i3+3 design to evaluate the safety and tolerability of up to 4 dose levels (with potential for additional doses) of ziftomenib combined with imatinib. Based on escalation, up to 2 dose levels will be selected for comparison to determine the RP2D. The dose-expansion part will examine the preliminary clinical activity of the RP2D in patients assigned to 1 of 3 cohorts: Cohort A: patients who progressed on imatinib as immediate prior therapy, Cohort B: patients who failed imatinib and had received $\geq$2 lines of therapy, and Cohort C: imatinib-naive patients. Tumor response will be assessed per mRECIST. All adverse events will be recorded, monitored, and graded based on CTCAE v5.0. The trial is open and actively recruiting in the United States. Clinical trial information: NCT06655246. Research Sponsor: Kura Oncology, Inc.

TPS11590 **Poster Session**

Clinical feasibility of 68Ga-DOTATATE PET/CT to identify SSTR-positive soft tissue sarcoma for PRRT selection. First Author: Gabriel Tinoco, Division of Medical Oncology, The Ohio State University, Arthur G. James Comprehensive Cancer Center, Columbus, OH

Background: Soft tissue sarcomas (STS) are biologically heterogeneous with limited effective systemic options in advanced disease. While 18F-FDG PET/CT provides metabolic assessment, it does not identify actionable receptor targets. Somatostatin receptor 2 (SSTR2) is expressed in subsets of mesenchymal tumors, and SSTR-targeted imaging with 68Ga-DOTATATE PET/CT is routinely used to select patients with neuroendocrine tumors for peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE. Whether receptor-targeted PET screening can feasibly characterize SSTR expression across STS subtypes and support future PRRT trial design is unknown. This study evaluates the feasibility and yield of 68Ga-DOTATATE PET/CT as a screening strategy in STS. **Methods:** This is a prospective, open-label, single-center pilot study enrolling 30 adults with any-stage STS who are candidates for systemic therapy and who have undergone standard-of-care PET/CT within 30 days. Participants undergo a single 68Ga-DOTATATE digital PET/CT within 14 days of consent, acquired approximately 60 minutes post-injection with non-contrast CT for attenuation correction and anatomic localization. Quantitative metrics including SUVmax and total tumor volume are centrally derived. Optional biobanking permits pre-imaging blood collection for exploratory circulating biomarkers. Key exclusions include recent long-acting somatostatin analog use, pregnancy or lactation, acute infection, hypersensitivity to somatostatin analogs, or inability to complete imaging. The primary endpoint is screening feasibility, defined by successful scan acquisition and interpretable image quality. Secondary endpoints include lesion-level detectability, safety, and characterization of uptake patterns using modified Krenning-style criteria and quantitative PET parameters across histologic subtypes. Imaging findings may be reviewed at multidisciplinary sarcoma tumor board as part of routine clinical care, including discussion of potential PRRT eligibility, but tumor board recommendations are not study endpoints. Exploratory analyses will assess concordance between imaging findings and available tumor immunohistochemistry or circulating biomarkers. Analyses are descriptive. The planned accrual is 30 patients over approximately 24 months at a high-volume sarcoma center. Enrollment and imaging are ongoing. This study will establish the feasibility of receptor-targeted PET screening in STS and characterize the frequency and distribution of SSTR-positive disease, providing data necessary to inform the feasibility and design of subsequent 177Lu-DOTATATE interventional trials. Clinical trial information: NCT06500065. Research Sponsor: None.

TPS11591 **Poster Session**

SARC045: A phase 2 trial of tebentafusp in HLA-A*02:01−positive patients with advanced clear cell sarcoma. First Author: Andrea Napolitano, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom

Background: Tebentafusp (Kimmtrak) is a first-in-class bispecific T-cell engager, specifically a T-cell receptor (TCR)-anti-CD3 fusion protein, approved for HLA-A*02:01+ metastatic or unresectable uveal melanoma. Tebentafusp binds to the HLA-A02:01/gp100 peptide complexes on the tumour cell surface, recruiting polyclonal T cells, via CD3, to release cytokines and cytolytic mediators against the tumour. Clear cell sarcoma (CCS) is an ultra-rare soft-tissue sarcoma subtype with poor prognosis and limited therapeutic options. On histopathology, CCS is characterised by the expression of melanocytic antigens, including gp100. **Methods:** This Phase 2 trial evaluates the efficacy of Tebentafusp in HLA-A*02:01 positive patients with advanced CCS. Twenty-three patients will be treated with weekly I.V. infusion of Tebentafusp at the recommended dose until evidence of clinical benefit or patient withdrawal from study. Baseline and on-treatment biopsies, as well as longitudinal peripheral blood samples will be collected for translational analyses. Prospective data will also be collected from an observational non-comparative cohort of up to 24 patients with advanced CCS not eligible for the study due to incompatible HLA. Enrolment to the study has commenced in October 2025 in the US, with two currently active sites (Memorial Sloan Kettering Cancer Center and University of Southern California). One additional US site (Northwestern University) and one UK site (The Royal Marsden Hospital) are due to open. At the time of submission, 1 HLA-A*02:01 advanced CCS patient had started treatment with Tebentafusp. Clinical trial information: NCT06942442. Research Sponsor: Immunocore.

TPS11592 **Poster Session**

SARC046: A phase II trial of nab-sirolimus in patients with progressing or symptomatic epithelioid hemangioendothelioma. First Author: Michael J. Wagner, Dana-Farber Cancer Institute, Boston, MA

Background: Epithelioid hemangioendothelioma (EHE) is an ultra-rare vascular sarcoma with about 120 cases diagnosed in the US per year. Although it is commonly considered an indolent disease, in its aggressive form clinical outcomes are poor. Molecularly, EHE is characterized by the presence of oncogenic fusions with HIPPO pathway effectors TAZ or YAP; TAZ-CAMTA1 or YAP-TFE3. YAP/TAZ are modulators of mTORC1 in preclinical models, suggesting that mTOR inhibition may be an effective treatment mechanism for EHE. Nab-sirolimus is albumin bound sirolimus, which achieves higher intratumoral accumulation compared to oral sirolimus and has demonstrated increased antitumor activity in preclinical cancer models compared to the oral mTOR inhibitors sirolimus and everolimus. This is an open label, multi-center, single arm, phase II clinical trial with a two-stage design, testing nab-sirolimus for progressing or symptomatic EHE. The primary objective is to determine ORR of nab-sirolimus in patients with EHE who require systemic treatment. We hypothesize that nab-sirolimus will have significant clinical efficacy for EHE as measured by the primary endpoint of objective response rate, as well as by secondary outcomes including progression free survival benefit over historical controls and by improvement in patient reported outcomes (PROs). If positive, this trial could lead to a new standard of care for treating EHE. **Methods:** This is a single arm, multi-center, phase 2 study with a two-stage design. Key inclusion criteria include histologically or cytologically confirmed EHE that is either progressing or clinically symptomatic, not a candidate for curative intent surgery, and requires systemic therapy in the opinion of the investigator, radiographically evaluable disease by RECIST v1.1, age $\geq$18 years, ECOG performance status $\leq$ 2, and adequate end organ function. With a Simon two-stage optimal design with one sided alpha 0.10, power 90%, assuming a historical control ORR 5% to detect an ORR of 20% (alternative hypothesis), 12 patients will be included in the first stage. If there is $\geq$ 1 response, an additional 25 patients will be enrolled to a total of 37 patients. $\geq$ 4 responses are needed for a significant result. The total planned accrual is 41 patients to account for unevaluable patients who may be enrolled, 10% above the required evaluable patients. Planned post hoc subgroup analyses will include outcomes by fusion type and presence of serosal effusions at the time of study enrollment. The trial is registered at clinicaltrials.gov NCT07104331. Clinical trial information: NCT07104331. Research Sponsor: U.S. Department of Defense; HT9425-25-1-0418; Aadi Bioscience.

TPS11593 **Poster Session**

Investigator-initiated phase II trial of ABSK043, an oral PD-L1 inhibitor, in patients with angiogenic sarcoma. First Author: Changsu Lawrence Park, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Angiogenic sarcomas (AS) represent a group of rare mesenchymal malignancies arising from the vascular endothelium. Patients with locally advanced or metastatic disease have poor outcomes due to limited availability of effective systemic treatment options. Emerging data suggest that immune checkpoint blockade (ICB) has activity in select patients, but prospective data is lacking for ultra-rare subtypes of AS including intimal sarcoma and epithelioid hemangioendothelioma (EHE). **Methods:** This is a single institution phase II investigator-initiated open label trial of ABSK043, an oral PD-L1 inhibitor in patients with AS. The primary endpoint is objective response rate. Secondary endpoints include progression free survival, overall survival and incidence of treatment emergent adverse events. Exploratory objectives include tissue- and blood-based correlative analyses to identify molecular biomarkers associated with ICB response/resistance in AS. Key inclusion criteria include histologically proven EHE, intimal sarcoma or scalp angiosarcoma with evidence of disease progression, age $\geq$18 years, ECOG performance status 0-2, adequate organ function, and measurable disease by RECIST v1.1. Exclusion criteria include ongoing systemic immunosuppressive therapy, active autoimmune disease, prior treatment with PD-(L)1 directed therapy, untreated brain metastases, or gastrointestinal conditions that may impair oral drug absorption. Participants will receive ABSK043 800mg orally twice daily until disease progression or unacceptable toxicity. Radiologic assessments by CT or MRI will be performed every 12 weeks. Research bloods will be collected prior to treatment initiation and with radiologic assessments, and biobanked for future correlative analyses (including longitudinal ctDNA assessment). Archival tissue or a fresh biopsy will be collected during screening for all patients. Patients who achieve partial response will undergo on-treatment and post-progression biopsies for correlative analyses (including whole genome and transcriptome sequencing and multiplex immunohistochemistry). This study opened in August 2025 and is actively recruiting. Planned enrollment is 20 patients, with accrual expected to complete by June 2027. Clinical trial information: NCT07014137. Research Sponsor: Abbisko Therapeutics.

TPS11594 **Poster Session**

A phase Ib/II study of mirdametinib in combination with palbociclib in patients with advanced dedifferentiated liposarcoma. First Author: Olayode Babatunde, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Dedifferentiated liposarcoma (DDLPS) is a rare adipocytic malignancy characterized by frequent amplification of *MDM2* and *CDK4* and associated with poor outcomes, with a median overall survival of approximately 15 months. A phase II trial at Memorial Sloan Kettering Cancer Center demonstrated activity of the CDK4/6 inhibitor palbociclib in advanced WD/DDLPS, with a 12-week progression-free survival (PFS) rate of 57%, exceeding historical chemotherapy benchmarks ($<$35%) and leading to its inclusion in the NCCN Guidelines. Despite this, durability of benefit remains limited, and outcomes following progression are poor. Preclinical work from our group demonstrated that CDK4/6 inhibition in DDLPS induces cellular geroconversion from quiescence to irreversible senescence, accompanied by *MDM2* downregulation. This process requires suppression of HRAS signaling and inhibition of the MAPK pathway and is associated with activation of the senescence-associated secretory phenotype (SASP). Preclinical models further suggest that dual CDK4/6 and MEK inhibition enhances SASP activation, providing a mechanistic rationale for combination therapy. Based on these findings, we initiated a phase Ib/II clinical trial of mirdametinib, a MEK1/2 inhibitor, in combination with palbociclib in patients with DDLPS (NCT06843967). **Methods:** This is an ongoing phase Ib/II, single-arm, open-label, single-center study evaluating the safety, tolerability, and efficacy of mirdametinib plus palbociclib in patients with unresectable, recurrent, or metastatic DDLPS (NCT06843967). Patients may enroll at any line of therapy, including first line, consistent with contemporary palbociclib use; patients with prior CDK4/6 inhibitor exposure are eligible for the phase Ib portion. Key eligibility criteria include ECOG performance status 0–2 and RECIST v1.1–measurable disease. Phase Ib uses a Bayesian optimal interval (BOIN) design with three dose levels to determine dose-limiting toxicities, maximum tolerated dose, and recommended phase II dose (RP2D), enrolling up to 24 patients. Phase II will assess efficacy at the RP2D, with the primary endpoint of PFS at 18 weeks by RECIST v1.1 in 30 patients. Enrollment began February 19, 2025. As of January 2026, accrual is ongoing at dose level 2. Enrollment to dose level 3 is anticipated in February 2026. Clinical trial information: NCT06843967. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; 1R01CA296835-01.

TPS11595 **Poster Session**

SATURN-STS: Phase II study of neoadjuvant atezolizumab with doxorubicin, concurrent atezolizumab with pre-operative radiation therapy and adjuvant atezolizumab in patients with high-risk surgically resectable extremity and truncal soft tissue sarcoma. First Author: Ahsan Saleem Farooqi, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: High-risk, localized soft tissue sarcoma (STS) remains associated with high rates of distant relapse despite modern multimodality therapy. Immune checkpoint inhibition (ICI) has demonstrated activity in certain metastatic STS subtypes with signals of enhanced response when combined with doxorubicin in the advanced/metastatic setting, as well as improved disease-free survival when combined with radiotherapy (RT) in the neoadjuvant setting; however, the optimal integration of neoadjuvant chemotherapy, immunotherapy, and RT in resectable disease is unknown. This single-arm phase II trial evaluates whether neoadjuvant atezolizumab combined with doxorubicin, followed by concurrent atezolizumab with preoperative RT and adjuvant atezolizumab, can improve relapse outcomes in patients with resectable, high-risk STS of the extremity and trunk. **Methods:** SATURN-STS is an investigator-initiated phase II study enrolling 50 adults with treatment-naïve, localized, intermediate- to high-grade STS $>$5 cm, including undifferentiated pleomorphic sarcoma, myxofibrosarcoma, de-differentiated/pleomorphic liposarcoma, leiomyosarcoma, and unclassified sarcoma. Neoadjuvant treatment includes 4–6 cycles of doxorubicin (60–75 mg/m^2) plus atezolizumab (1200 mg IV q3w), followed by atezolizumab with preoperative RT (50 Gy in 25 fractions or 42.75 Gy in 15 fractions), surgical resection, and up to 16 cycles of adjuvant atezolizumab. Radiographic imaging is performed at baseline, during neoadjuvant therapy, post-RT prior to surgery, and throughout follow-up. Longitudinal tissue is acquired for translational analyses with biopsy prior to initiation of chemoimmunotherapy and prior to RT/immunotherapy combination, followed by collection at the time of surgery. The primary endpoint is time-to-relapse (TTR), defined from time of surgical resection to the date of documented disease recurrence, compared to a historical control using a single-arm, time-to-event Bayesian monitoring approach. Secondary endpoints include objective response (RECIST 1.1), pathologic response, local recurrence-free survival, distant metastasis-free survival, progression-free survival, overall survival, and safety (CTCAE v5.0). Exploratory objectives include profiling immune microenvironment changes, genomic correlatives, circulating tumor DNA, and spatial analyses. As of January 2026, 6 patients have initiated treatment at an accrual rate of 1-2 patients per month. Clinical trial registration: NCT07049848. Support: The University of Texas MD Anderson Cancer Center and Genentech Strategic Alliance Grant. Clinical trial information: NCT07049848. Research Sponsor: University of Texas MD Anderson Cancer Center and Genentech (Inc) Strategic Alliance.

TPS11596 **Poster Session**

Maintenance pegylated liposomal doxorubicin (PLD) versus active surveillance for advanced soft tissue sarcoma patients who had controlled disease after standard anthracycline-based treatment (MELODY). First Author: Tom Wei-Wu Chen, Center of Excellence for Sarcoma, National Taiwan University Hospital, Taipei, Taiwan

Background: The progression-free survival (PFS) associated with first-line chemotherapy for advanced soft tissue sarcoma (STS) remains unsatisfactory. Extending treatment with an active agent that has demonstrated clinical benefit in a patient (pt)—the maintenance therapy—may offer an opportunity to further delay disease progression. While anthracyclines are the current standard first-line treatment, their cumulative cardiotoxicity limits prolonged use. Pegylated liposomal doxorubicin (PLD) offers a more favorable cardiac safety profile, representing a viable option for extended treatment. **Methods:** MELODY is a randomized, multinational clinical trial designed to evaluate the clinical benefit of maintenance PLD in pts with advanced STS who have achieved disease control following anthracycline-based therapy. The study incorporates patient-reported outcomes (PROs) to explore the balance between extended treatment and active surveillance from the patient's perspective—providing a more holistic understanding of the value of maintenance therapy in this population. Built-in translational studies aim to identify biomarkers that better select pts most likely benefit from maintenance therapy, thereby further personalizing treatment strategies in advanced STS. Eligible criteria include advanced STS patients aged $\geq$ 18 who had either CR, PR, or SD after first-line anthracycline-based therapy (at least five cycles). Pts will be randomized 2:1 to the experimental arm: PLD (40 mg/m^2 every 28 days, up to 12 cycles) or the control arm: active surveillance. The primary endpoint is progression-free survival (PFS) post randomization. Patients in the active surveillance arm will not crossover to PLD upon progression. Secondary endpoints include QoL by EORTC C30 questionnaire, OS, 12-month PFS rate, ORR by RECIST 1.1, and time to next treatment. Left ventricular ejection fraction (LVEF) change will be an interest of safety. Exploratory objectives include efficacy endpoints (PFS, OS, 12-month PFS rate) based on circulating tumor DNA (mandatory) and FDG PET/CT SUVmax (Optional). Based on our systematic review (Lee MJ et al. Ther Adv Med Oncol 2025), the mPFS for the control arm is estimated to be 4 months. A clinically meaningful improvement is anticipated in the experimental arm, with a mPFS of 8 months. Assuming 80% power and an alpha level of 0.1, a total of 63 evaluable subjects are required. Accounting for an anticipated 20% drop-out rate, MELODY plans to enroll a total of 81 subjects. Clinical trial information: NCT06981637. Research Sponsor: Taiwan Oncology Cooperative Group (TCOG) of National Health Research Institute; TTY Biopharm Company Limited; Gene Solutions.

TPS11597 **Poster Session**

STARS (NCT 07265661): Surgical timing after preoperative hypofractionated radiotherapy for patients with primary localized soft tissue sarcoma of the extremity and trunk—A randomized phase 2 clinical trial. First Author: Marco Baia, Sarcoma Service - Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Background: Local management paradigm for localised soft tissue sarcoma of the extremities and trunk (ESTS) has remained relatively stable, due to the excellent outcomes associated with preoperative radiotherapy combined with limb-sparing surgery. Conventional regimens (50 Gy in 25 fractions) are effective but time-intensive and resource-demanding. Ultra-hypofractionated radiotherapy (HFRT) has emerged as a promising strategy, with comparable oncological outcomes, in preliminary retrospective analyses, prospective cohorts, and Phase II non-randomised trials. However, the optimal interval between HFRT and surgery remains undefined. **Methods:** STARS is a national, multicenter, phase II, randomized, non-inferiority trial promoted by a co-sponsorship between the Italian Sarcoma Group and the Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (NCT07265661). Patients with localised, resectable ESTS scheduled for combined radiotherapy and surgery are randomized 1:1 to receive preoperative HFRT (30 Gy in 5 fractions) followed by surgery at either 1–2 weeks (Arm A) or 4–6 weeks (Arm B). Randomization is stratified by tumor size, depth, site, and comorbidities. The primary endpoint is the incidence of postoperative complications (Clavien–Dindo, any grade) within 90 days. Secondary endpoints include quality of life and patient satisfaction, oncologic outcomes (local recurrence, distant metastasis, disease-free and overall survival), pathological and radiological response, treatment-related toxicity, nutritional status, and economic impact. A concurrent observational cohort will capture outcomes of patients treated with standard approaches (surgery with/without standard radiotherapy). Statistical Design: A total of 142 patients (71 per arm) will be enrolled to test non-inferiority, assuming a 35% postoperative complication rate and a non-inferiority margin of 15% (one-sided α=0.05; power 80%). Approximately 30 additional patients are expected in the observational cohort. Significance: STARS is the first randomized trial specifically designed to address surgical timing following HFRT in ESTS. The study is conducted within a novel co-sponsorship framework involving a national academic tertiary cancer center (Fondazione IRCCS Istituto Nazionale dei Tumori) and the leading non-profit cooperative group for rare cancers in Italy (Italian Sarcoma Group), establishing a sustainable platform for high-quality clinical research in rare diseases. By defining the safest and most effective interval between HFRT and surgery, this trial aims to optimize perioperative outcomes while enabling a shorter, patient-centered, and resource-efficient treatment pathway, informing future standards of care and guideline recommendations for localised ESTS. Clinical trial information: NCT 07265661. Research Sponsor: None.

TPS11598 **Poster Session**

The ATLAS study: A first-in-human phase 1/2 trial of [Ac-225]RTX-2358 in patients with relapsed or refractory soft tissue sarcoma. First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Fibroblast Activation Protein (FAP) is expressed on the surface of cancer-associated fibroblasts and is involved in the formation, maintenance, and spread of tumors. Sarcoma frequently demonstrates high expression of FAP on the tumor cells themselves in contrast to other solid tumors, where it is mainly expressed on CAFs within the tumor stroma. Radioligand therapies utilizing alpha emitting isotopes such as Ac-225 have emerged as promising treatment strategies across multiple targets and indications in oncology. Ac-225 and its daughter radionuclides emit high-energy alpha particles capable of inducing double-stranded DNA breaks, leading to significant cytotoxic effects within cells. Early clinical data for other Ac-225-labeled compounds have shown promising outcomes, particularly in settings where traditional therapies have failed. [Ac-225] RTX-2358 (Ratio Therapeutics Inc, Boston, MA) is a novel FAP-targeted radioligand designed for specific high-affinity binding, resulting in prolonged tumor residence and limited normal tissue uptake. This sustained tumor retention leads to extended delivery of cytotoxic radiation to FAP-expressing tumors. A beta-emitting analog, [Lu-177]RTX-2358, has been administered to more than 25 patients under the German §13.2b compassionate use framework across multiple tumor types. Longitudinal SPECT imaging performed as late as 14 days after administration demonstrated persistent tumor retention with minimal washout. Based on time–activity curve analysis from these data, tumor biological half-time is estimated to be well in excess of 1,000 hours. Renal clearance was observed to be consistent with that reported for established lutetium-177–labeled radioligand therapies. **Methods:** This study is a seamless Phase 1 / 2 dose escalation study. The Phase 1 portion consists of a 3 x 3 dose escalation design, with patients treated in 3 planned dose escalation cohorts (7.5, 11.25 and 15 MBq) with up to 6, 8-week cycles of [Ac-225]RTX-2358. Backfill of phase 1 cohorts is permitted to facilitate selection of the recommended administered activity level for the subsequent Phase 2 expansion cohort. Dose escalation / de-escalation decisions will be made by a Safety Review Committee. Patients over 18yrs with a history of histologically confirmed relapsed or refractory soft tissue sarcoma (measurable disease per RECIST v1.1) are eligible if they have a positive [Cu-64]LNTH-1363S FAP PET, an ECOG PS 0 to 1, and adequate organ reserve and renal function. Recruitment of the first cohort was completed in December 2025. The ATLAS Study: NCT07156565 Clinical trial information: NCT07156565. Research Sponsor: None.

TPS11599 **Poster Session**

A phase I/II study of safety/efficacy using lurbinectedin, combined with ipilimumab, and nivolumab, for advanced soft tissue sarcomas (NCT05876715). First Author: Samantha Jeffrey, Sarcoma Oncology Center, Santa Monica, CA

Background: Soft tissue sarcoma (STS) cells exhibit heightened immunogenicity during the early stages of the disease. Therefore, immunotherapies such as ipilimumab (ipi) and nivolumab (nivo), which enhance sustained T-cell activation by suppressing regulatory T cells, are potentially more effective when administered as first-line therapy in combination with lurbinectedin—a synthetic analog of the marine alkaloid trabectedin—that not only induces apoptosis in cancer cells and exposes tumor neoantigens for immune recognition but also depletes tumor-associated macrophages, thereby restoring immune surveillance and potentially enhancing the efficacy of immunotherapy. **Methods:** This Phase I/II open-label single-site study will evaluate the safety and efficacy of lurbinectedin in combination with ipi and nivo in patients with advanced STS. Phase I patients will be previously treated, whereas phase II patients will be untreated. Objectives: Primary: Evaluate MTD of lurbinectedin in combination with fixed doses of ipi and nivo. Secondary: Evaluate objective response rate by RECIST v1.1 via CT/MRI/PET q 6w until end of treatment (EOT); determine progression-free survival (PFS); determine overall survival (OS). Exploratory: correlate response with amount of ctDNA via Signatera testing q 6w until EOT. Schedule: IV lurbinectedin q 3w (Phase I: escalating doses as per standard "cohort of three" design, 2.6 - 3.2mg/m2, Phase 2: determined MTD), IV ipi 1 mg/kg q 12w, and IV nivo 3 mg/kg q 2w. Participants may continue treatment until significant disease progression or unacceptable toxicity occurs. Key Criteria: Inclusion: pathologic diagnosis of locally advanced unresectable or metastatic STS; measurable disease by RECIST v1.1; ECOG $\leq$ 1; life expectancy of $\geq$ 3 months; acceptable hematological status and liver/renal function. Exclusion: untreated CNS metastases; radiation therapy, targeted therapy, other antitumor treatment, or investigational drug or device study, within 2 weeks prior to study entry; chemotherapy within 21 days prior to study entry; prior exposure to anti-CTLA4 or anti-PD-1 inhibitors; pregnancy or breastfeeding; autoimmune disease, carcinomatous meningitis, systemic immunosuppression, skin rash affecting $>$ 25% of body surface area, or inflammatory bowel disease. Analysis: The Intention-To-Treat population (all patients who received at least one dose of study drug) will be used for OS analysis and adverse event analysis. The Modified Intention-To-Treat population (patients who completed the first two 3-week cycles and follow-up imaging) will be used for analysis of PFS. PFS and OS will be estimated by Kaplan Meir method with two-sided 95% confidence interval. Status: This study has enrolled 40 patients. Clinical trial information: NCT05876715. Research Sponsor: Jazz Pharmaceuticals.

12000 **Oral Abstract Session**

Dexamethasone reduction or omission with NEPA and olanzapine for HEC: A phase III trial. First Author: Jian Zhang, Fudan University Shanghai Cancer Center, Shanghai, China

Background: Prolonged dexamethasone (DEX) in antiemetic regimens for highly emetogenic chemotherapy (HEC) may impair immunotherapy efficacy. We evaluated if DEX can be reduced or omitted when combined with NEPA (netupitant/palonosetron) and olanzapine without compromising control. **Methods:** In this open-label, multicenter, phase III non-inferiority trial, adults receiving HEC were randomized 1:1:1 to: Standard Regimen (NEPA day1, olanzapine days1-4, DEX 12mg day1/8mg days2-4); DEX-sparing Regimen (same, DEX 6mg day1 only); or DEX-free Regimen (same, no DEX). The primary endpoint was overall complete response (CR: no emesis/no rescue) 0-120h. A hierarchical testing sequence (DEX-sparing vs Standard, then DEX-free vs Standard) with a -12% non-inferiority margin controlled type I error (one-sided α=0.025). **Results:** Among 644 randomized patients (median age 54.9 years; 66.9% female), the overall CR rates were 72.4% for Standard, 72.2% for DEX-sparing (rate difference [RD] -0.19%, 95% CI -8.77 to 8.38; P for non-inferiority = 0.004), and 70.1% for DEX-free (RD -2.24%, 95% CI -10.81 to 6.38; P for non-inferiority = 0.013). Both experimental regimens met the non-inferiority criterion. Acute-phase (0-24 h) CR rates were 81.5%, 82.6%, and 80.8% (intergroup comparison, P > 0.05), and delayed-phase (24-120 h) CR rates were 77.1%, 77.6%, and 73.9% ((P > 0.05), respectively, with no significant differences. For complete nausea control, the DEX-free regimen was inferior beyond 24 hours, whereas the DEX-sparing regimen remained comparable to Standard throughout. Steroid-related adverse events, such as insomnia, were primarily reported in the Standard regimen group. **Conclusions:** NEPA plus olanzapine with single-day low-dose or no DEX is non-inferior to standard 4-day DEX for CINV prevention in HEC, supporting steroid-sparing strategies relevant for chemo-immunotherapy. Clinical trial information: NCT06331520. Research Sponsor: None.

Baseline patient characteristics and chemotherapy regimen.

	Total (N=644)	Standard Regimen (N=217)	DEX-sparing Regimen (N=213)	DEX-free Regimen (N=214)
Age, years	54.9 ±12.0	54.2 ±11.7	55.2±12.0	55.3 ±12.2
Male	219 (34.0)	73 (33.6)	74 (34.7)	72 (33.6)
Female	425 (66.0)	144 (66.4)	139 (65.2)	142 (66.4)
Breast cancer	280 (43.5)	101 (46.5)	92 (43.2)	87 (40.6)
Lung cancer	141 (21.9)	45 (20.7)	50 (23.5)	46 (21.5)
AC regimen	148 (23.0)	57 (26.3)	52 (24.4)	39 (18.2)
Platinum-based regimen	472 (73.3)	153 (70.5)	152 (71.4)	167 (78.0)

LBA12001 **Oral Abstract Session**

Gabapentin plus tramadol versus tramadol alone for chemoradiotherapy-induced oral mucositis pain in head and neck cancer: Results of a randomized phase III trial. First Author: Minit Jalan Shah, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA12002 **Oral Abstract Session**

Ramelteon for prevention of postoperative delirium in elderly cancer patients: A randomized, double-blind, placebo-controlled multicenter trial, JORTC-PON02/J-SUPPORT2103/NCCH2103. First Author: Ryoichi Sadahiro, National Cancer Center Japan, Tokyo, Japan

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

LBA12003 **Oral Abstract Session**

Nationwide randomized, phase III, placebo-controlled trial of bupropion for cancer-related fatigue: Primary outcome results. First Author: Luke Joseph Peppone, University of Rochester Medical Center, Rochester, NY

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

12004 **Oral Abstract Session**

YOCAS yoga, mood disturbance, and insomnia: A URCC NCORP RB nationwide, phase III, randomized, controlled trial with cancer survivors. First Author: Yuri Choi, Department of Surgery, University of Rochester Medical Center, Rochester, NY

Background: Mood disturbance (MoD) and insomnia are two of the most pervasive and troubling side effects experienced by cancer survivors for years after completing adjuvant treatments. MoD and insomnia significantly interfere with survivors' ability to perform essential daily activities such as cleaning, grocery shopping, cooking, taking medications, driving, and communicating with others. We previously reported that Yoga for Cancer Survivors (YOCAS) is effective for treating insomnia. YOCAS may also alleviate MoD, and changes in MoD may mediate the influence of YOCAS on insomnia. **Methods:** We conducted a nationwide, multisite, phase III randomized, controlled trial to examine: 1) the effects of YOCAS on MoD (i.e., overall MoD, anxiety, and fatigue), and 2) whether changes in MoD mediate the association between YOCAS and changes in insomnia. Survivors were recruited via the University of Rochester Cancer Center NCI Community Oncology Research Program Research Base (URCC NCORP RB). Non-metastatic cancer survivors, between 2-24 months post adjuvant therapy, aged 21 or older, with moderate or greater sleep disruption, and with no participation in yoga during the prior 3 months, were randomized to two arms: 1) standard care and 2) standard care plus the 4-week YOCAS intervention (2x/week; 75 min/session). The YOCAS consists of breathing exercises, 18 gentle Hatha and Restorative yoga postures, and meditation. MoD and insomnia were assessed using the Profile of Mood States and Insomnia Severity Index, respectively, at pre- and post-intervention. **Results:** A total of 410 survivors, recruited from 12 community-based oncology practices across the USA, were randomized (mean age = 54 10.4 years; 96% female; 75% breast cancer survivors). ANCOVAs revealed YOCAS participants, compared to standard care participants, experienced significantly less overall MoD (Mean Difference [Standard Error] = -5.08 [1.36]), anxiety (MD [SE] = -0.72 [0.29]), and fatigue (MD [SE] = -1.49 [0.41]; all $p < 0.05$) at post-intervention. Additionally, YOCAS participants reported significant improvements from pre- to post-intervention on overall MoD, anxiety, and fatigue (all $p < 0.05$), whereas standard care participants did not. Causal mediation analyses revealed changes in overall MoD partially mediated (24.9%; 95% CI: 10.9%, 42.6%) the association between YOCAS and changes in insomnia. Changes in fatigue also partially mediated (24.6%; 95% CI: 11.3%, 43.9%) the association between YOCAS and changes in insomnia (all $p < 0.05$). **Conclusions:** YOCAS yoga is effective for treating overall MoD, anxiety, and fatigue among survivors. Additionally, improvements in insomnia stemming from YOCAS yoga may be mediated by changes in overall MoD and fatigue. Clinicians should consider recommending yoga for survivors who experience overall MoD, anxiety, fatigue, and insomnia. Clinical trial information: NCT00397930. Research Sponsor: National Cancer Institute; UG1CA189961; National Cancer Institute; UG1CA189860; National Cancer Institute; UG1CA189953; National Cancer Institute; UG1CA189972; National Cancer Institute; T32CA102618.

12005 **Oral Abstract Session**

A phase III placebo controlled randomized controlled trial using combination therapy for treatment-related fatigue in patients with prostate cancer. First Author: Sriram Yennu, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: To determine if the combination of exercise (EX) plus methylphenidate (MP) is superior to EX plus placebo (PL) for 12 weeks in the treatment of cancer-related-fatigue (CRF) in patients with prostate cancer receiving androgen deprivation therapy (ADT) and/or radiation therapy (RT). **Methods:** Using a phase III randomized double-blind placebo-controlled design, we assessed treatments combining either EX or its stretching (ST) control with either MP (5mg twice a day, with dose titrated up to 20mg a day) or placebo. Patients were eligible if they had prostate cancer patients who are receiving androgen deprivation therapy and/or radiation therapy and had CRF; Eligible patients were randomized into one of four arms, EX + MP, EX + PL, ST + MP, ST + PL (2:1: 1:1). Primary outcome was assessed using linear mixed-effects model comparing the differences in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores at Weeks 1, 2, 4, 8 and 12. **Results:** 161 eligible patients were randomly assigned to 4 arms EX+MP (n = 65), EX+PL(n = 34), ST+MP (n = 30), and ST+PL (n = 32). Demographics, including mean age (65-67 years) were similarly distributed between arms (all $p > 0.05$). Bone metastases (~25%), and treatment modality distributions (ADT alone, ADT + RT, or RT alone) were comparable among the arms. The baseline FACIT-F scores [mean (SD) were 28.5(11.0), 28.7(8.9), 28.5(9.3), and 30.3(11.0)] respectively in arms EX+MP, EX+PL, ST+MP, and ST+PL arms. All 4 arms showed CRF improvement over time. There was a nonsignificant improvement in CRF in the EX+MP intervention arm, compared with EX+PL arm [FACIT-F coefficient, 2.73(95% CI, −0.49 to 5.96); P = 0.097]. Methylphenidate-containing arms (EX+MP and ST+MP) significantly improved CRF compared with their placebo counterparts (EX+PL and ST+PL), [FACIT-F coefficient, 3.23 (95% CI 0.84 to 5.63), P = 0.008]. There were no significant differences in CTCAE v.5 grade $\geq$3 adverse events by arms ($P > 0.99$). **Conclusions:** EX+MP arm was not superior to EX+PL arm in improvement of CRF. Methylphenidate-containing arms significantly improved CRF compared with their placebo arms. All four treatment arms showed improvement of CRF overtime suggesting strong placebo response. Further methylphenidate-containing multimodal CRF studies are needed. Clinical trial information: NCT03772834. Research Sponsor: National Institute of Health (NCI).

12006 **Oral Abstract Session**

A digital health intervention to enhance well-being among adolescent and young adult survivors of cancer: Results from the EMPOWER full factorial trial. First Author: John M. Salsman, Atrium Health Wake Forest Baptist, Winston Salem, NC

Background: Adolescent and young adult (AYA) survivors of cancer are at significant risk of adverse psychological outcomes, yet scalable, efficacious interventions to address their needs are limited. We evaluated a self-guided digital health intervention with affective, behavioral, and cognitive skills, "Enhancing Management of Psychological Outcomes With Emotion Regulation" (EMPOWER), for improving psychological outcomes. **Methods:** We recruited AYAs (n = 352; 74% female, median age 33 years) from three comprehensive cancer centers between Dec 2021 and Sept 2024. AYAs were diagnosed at and currently aged 15 to 39 years, within 5 years post-curative treatment, and had internet access. In a full factorial design, AYAs were randomly assigned to 5 weekly components, either EMPOWER intervention or attention control (2^5 = 32 arms): 1. positive events, capitalizing & gratitude (vs. cognitive skills); 2. mindfulness (vs. financial literacy); 3. positive reappraisal (vs. nutrition); 4. personal strengths & goal-setting (vs. weight management); 5. acts of kindness (vs. sun protection). Didactic lessons and skills practices were delivered via a website designed specifically for the study. AYAs completed PROMIS measures for positive affect (primary outcome), and depression and anxiety (secondary outcomes) at pre-intervention, post-intervention, and two and four months post-intervention. Using the intent-to-treat principle and a mixed model with linear contrasts, we estimated average within-person changes over time by component (intervention/control) for AYAs and compared changes by component. **Results:** From pre to post-intervention, positive affect increased ($p<0.05$) among those in 3 of the 5 EMPOWER and 4 of the 5 control components (mean change = 1.4 to 1.9) and anxiety decreased ($p<0.05$) for those in 4 of 5 EMPOWER and 4 of 5 control components (mean change = -1.2 to -2.0). Further, anxiety was significantly lower ($p<0.05$) for all EMPOWER and control components at two and four-months post intervention (mean change = -1.3 to -2.4). There was little change in depression for any group. We found no treatment effects for any outcome whereby AYAs who received intervention content had significantly greater improvements than those receiving attention control content. Instead, some EMPOWER (positive events, capitalizing, & gratitude; acts of kindness) *and* control components (nutrition) were associated with clinically meaningful changes in outcomes, based on PROMIS metrics. **Conclusions:** Our findings suggest a range of affective, behavioral, and cognitive strategies drawn from both positive psychology and health education domains are similarly effective in enhancing positive affect and mitigating post-treatment anxiety and highlight the potential benefit of low-touch, self-guided digital health strategies for AYA survivors of cancer. Clinical trial information: NCT04317417. Research Sponsor: National Institutes of Health, National Cancer Institute; CA242849.

12007 **Oral Abstract Session**

Impact of electronic patient-reported outcome measure (ePROM)–triggered, collaborative care (CC)–based symptom intervention on depression and anxiety in young adults (YAs) with cancer. First Author: Michael H. Storandt, Mayo Clinic Rochester, Rochester, MN

Background: YAs with cancer, defined as those diagnosed prior to the age of 40, may experience greater symptom burden compared to those diagnosed at older ages. We evaluated the impact of an ePROM-triggered, CC-based, supportive care intervention on symptom burden in YAs with cancer. **Methods:** The Enhanced, Electronic Health Record-facilitated Cancer Symptom Control (E2C2) trial was a cluster-randomized, pragmatic trial (NCT03892967) that enrolled oncology patients seen at Mayo Clinic Rochester and within the Mayo Clinic Health System (sites in Minnesota and Wisconsin) between March 2019 and January 2023. Patients routinely reported the severity of six SPPADE symptoms (Sleep deficit, Pain, Physical function impairment, Anxiety, Depression, and Energy deficit/fatigue) on 11-point numerical rating scales. Symptom severity was classified as none to mild (0-3), moderate (4-6), or severe (7-10). Those with moderate or severe symptoms were offered symptom management education, while those with severe symptoms were also offered the option to work virtually with a symptom care manager. In this post hoc analysis, we examined the effects of the intervention on change in symptom scores among YAs and time to improvement to a mild/moderate level in those with at least one severe symptom. **Results:** Among 40,659 patients who responded to at least one survey, 2,598 were YAs and 38,061 were adults $\geq$ 40 years. Among YAs, 10.7%, 24.3%, and 65.1% were 18-24 years, 25-31 years, and 32-39 years, respectively. A greater proportion of YA patients were female (61.5% vs 57.0%), of a non-white race (12.4% vs 5.3%), living in an urban setting (65.7% vs 55.1%), single (36.4% vs 9.6%), on non-government insurance (78.1% vs 36.6%), employed (72.6% vs 37.4%), and had a Bachelor's degree or greater (37.8% vs 28.3%, $p< 0.001$ for all). Fewer YA patients had metastatic disease compared to older patients (24.2% vs 35.2%, $p< 0.001$). Compared to a pre-intervention baseline, the mean change in symptom score for YA patients following the intervention demonstrated improvements in anxiety (-0.195) and depression (-0.168, $p< 0.0001$ for both), while physical function impairment worsened over the intervention period (0.101, p= 0.014). Compared to adults $\geq$ 40 years, YAs experienced greater intervention effects for management of depression ($p <0.001$), fatigue (p= 0.01), pain ($p< 0.0001$), and physical function impairment ($p< 0.0001$). Among YAs with a severe symptom during the intervention period, median time to improvement to a mild/moderate level was longer for anxiety compared to those $\geq$ 40 years (3.5 vs 2.7 months, p= 0.009). **Conclusions:** Routine ePROM surveillance, coupled with CC-based symptom management, led to improvements in anxiety and depression among YAs with cancer, although, time to improvement was longer for anxiety compared to adults $\geq$ 40 years. Research Sponsor: NCI of the National Institutes of Health.

LBA12008 **Oral Abstract Session**

SUPPORT+ digital self-management and clinical support for advanced cancer: A randomized controlled trial. First Author: Wing-Lok Chan, Department of Clinical Oncology, The University of Hong Kong, Hong Kong, Hong Kong

The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

12009 **Rapid Oral Abstract Session**

Efficacy of YES, an mHealth intervention for adolescent and young adults (AYA) with breast cancer (BC), to address AYA survivorship concerns. First Author: Shoshana M. Rosenberg, Weill Cornell Medicine, New York, NY

Background: AYA BC survivors often have unmet concerns that are understudied and suboptimally addressed. Primary results from the YES trial (NCT04906200) demonstrated that YES, an AYA-focused mHealth intervention, improved quality of life and reduced specific symptoms in AYA BC survivors at 6 months (mo) post-enrollment. Here we report a prespecified secondary analysis of YES on reducing AYA survivorship concerns. **Methods:** We conducted a multicenter (Dana-Farber Cancer Institute, The Ohio State University, Columbia University Medical Center) RCT of YES, an mHealth intervention which provides tailored information, resources and support in response to monthly electronic patient-reported outcome monitoring, a journal platform, and a chat room. Participants age $\leq$39 at diagnosis (dx) of stage 0-3 BC, $<$ 3 years post-dx were randomized 1:1 to YES or Usual Care (UC). Survivorship concerns were measured at baseline, 3, and 6 mo with AYA HOPE survey items; participants rated their level of concern across a range of domains. Generalized linear mixed effects models analyzed the binary endpoint of somewhat/very vs no/low concern for each issue. Odds of being somewhat/very concerned about a domain at 6 mo were compared between arms, adjusting for baseline concern. **Results:** From 6/2021-12/2024, 360 participants were randomized (YES:179; UC: 181) following baseline survey completion. Participant characteristics were balanced between arms. Median time from dx was 19 (IQR: 12-27) mo. Median age at dx was 34 (IQR: 31-37) yrs; 61% had stage 2 or 3 BC. Overall, a majority of participants endorsed high levels of concern at baseline related to: long-term side effects of treatment (67%), long-term health effects of cancer (70%), recurrence (79%), checking for signs of recurrence (57%), possibility of a new cancer (67%), exercise (60%), nutrition (58%), familial cancer risk (51%), and body image (56%). Other endorsed concerns included: fertility (43%), financial support for medical care (37%), financial concerns (38%), talking about cancer experience with family/friends (27%), having enough information about treatment (25%), meeting other AYAs (22%), alcohol and cancer (15%), and smoking cessation (3%). At 6 mo, adjusting for baseline concern, the YES group (vs UC) had lower odds of being somewhat/very concerned about finances (OR: 0.36, 95% CI: 0.13 – 0.98, p = 0.05), financial support for medical care (OR 0.35, 95% CI 0.13-0.96, p = 0.04), family cancer risk (OR 0.36, 95% CI 0.17-0.77, p = 0.009), and alcohol and cancer (OR 0.15, 95% CI 0.03-0.75, p = 0.02). **Conclusions:** Concerns across a range of survivorship domains are prevalent in AYA BC survivors. The YES mHealth intervention reduced concerns about several survivorship issues, supporting the potential for this highly scalable intervention to help manage these concerns as an adjunct to routine clinical care for AYA BC survivors. Clinical trial information: NCT04906200. Research Sponsor: National Cancer Institute; U01CA246648; Breast Cancer Research Foundation; Susan G. Komen; American Cancer Society.

12010 **Rapid Oral Abstract Session**

Effect of a weight loss intervention (WLI) on quality of life (QOL) and symptoms in women with breast cancer: Results from the Breast Cancer Weight Loss (BWEL) trial. First Author: Jennifer A. Ligibel, Dana-Farber Cancer Institute, Boston, MA

Background: BWEL (Alliance A011401; NCT02750826) is a Phase III trial that randomizes patients (pts) with stage II-III breast cancer and body mass index (BMI) $\geq$27 kg/m^2 1:1 to a 24-month (mo) lifestyle-based WLI + health education (HE) or HE alone. Here we report prespecified secondary outcomes of the impact of the WLI on patient-reported QOL and symptoms. **Methods:** The first 540 BWEL pts (randomized between 9/2016 and 7/2017) were included in this substudy that collected PROMIS 29 Profile 2.0 and Global Health scores at enrollment, 6 and 24 mos. Adjusting for baseline scores, mean physical function (predefined substudy primary outcome), global physical and mental health, fatigue and other scores were compared at 6 and 24 mos using analysis of covariance (ANCOVA). P-values $<$0.05 were considered significant. Positive differences in positive attributes (e.g., physical function) and negative differences in negative attributes (e.g., anxiety) represented better outcomes in the WLI arm. **Results:** At baseline, median BMI was 32.9 kg/m^2 (26.5 – 69.1), median age was 53 (25 - 78) years; 83.9% of pts were non-Hispanic White, 10.7% were Black and 5.9% were Hispanic. At 6 mos, the WLI (vs HE) arm had significantly better physical function (ANCOVA-based mean difference between arms 1.9 [95% CI 0.8, 3.0]; p$<$0.001), global physical health (2.0 [95% CI 0.9, 3.0]; p$<$0.001), global mental health (1.30 [95% CI 0.2, 2.4], p=0.03), social roles and activities (2.3 [95% CI 1.1, 3.6]; p$<$0.001), and fatigue (-1.7 [95% CI -3.1, -0.4], p=0.01) (Table). Improvements were generally maintained at 24 mos. Similar findings were seen in analyses using longitudinal mixed modeling. **Conclusions:** The BWEL WLI demonstrated QOL benefits for patients with breast cancer, resulting in significantly better physical function, global physical and mental health, and symptoms. Future analyses will evaluate which populations experienced the most benefit, as well as the relationships among QOL, symptoms, and weight loss. Support: U10CA180821, U10CA180882, UG1CA189823; U10CA180820; U10CA180868; U10CA180863, CCS 707213; U10CA180888; UG1CA189858; https://acknowledgments.alliancefound.org. Clinical trial information: NCT02750826. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; UG1CA189858; U10CA180821, U10CA180882, UG1CA189823; U10CA180820; U10CA180868; U10CA180863, CCS 707213; U10CA180888; U10CA180820; U10CA180868; U10CA180888; Susan G Komen Foundation; Breast Cancer Research Foundation; American Cancer Society.

Analysis of covariance-adjusted least squares means values at 6-mos adjusted for baseline scores.

QOL/Symptom Attributes	HE	WLI	Between arm difference (95% CI)*	P value
Physical Function	47.1	49.0	1.9 (0.8, 3.0)	<0.001
Global Physical Health	46.2	48.1	2.0 (0.9, 3.0)	<0.001
Global Mental Health	48.6	49.9	1.3 (0.2, 2.4)	0.03
Social Roles and Activities	52.7	55.0	2.3 (1.1, 3.6)	<0.001
Anxiety	50.2	50.0	-0.2 (-1.6, 1.2)	0.77
Depression	47.5	47.5	-0.0 (11.2, 1.2)	0.96
Fatigue	50.6	48.9	-1.7 (-3.1, -0.4)	0.01
Sleep Disturbance	51.0	51.1	0.1 (-0.6, 0.8)	0.80
Pain Interference	51.3	50.3	-1.0 (-2.4, 0.4)	0.15

*Positive differences in positive attributes and negative differences in negative attributes favor WLI arm.

12011 **Rapid Oral Abstract Session**

Association of social isolation with overall survival in cancer patients. First Author: Danlin Zeng, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada

Background: Social isolation has been associated with increased all-cause mortality, particularly in cardiovascular and mental health conditions. Prior studies show that larger social networks, greater perceived social support, and marital status are associated with improved survival. However, the impact of social isolation on cancer patients remains incompletely characterized. This study examines the association between social isolation and overall survival (OS) in a large cancer cohort. **Methods:** 47,562 adult cancer patients treated at British Columbia Cancer between April 1, 2011, and December 31, 2016, who completed the Psychosocial Screen for Cancer (PSSCAN-Revised) questionnaire at their initial visit were included. Patients with prior malignancies were excluded. OS was estimated using Kaplan-Meier methods and compared using log-rank tests. Multivariable Cox proportional hazards regression was used to identify independent associations with OS. **Results:** The mean age was 64.5 years (SD 13.9). 55.2% were female. At their initial visit, 67% had non-metastatic disease, 17% had metastatic disease, and metastatic status was unknown in 16%. Social isolation was prevalent: 24.7% lived alone, 14.1% had lost a partner, 11.6% lacked assistance with instrumental activities of daily living (IADLs), 4.7% lacked regular social contact, 6.9% lacked emotional support, and 29.3% had at least one domain of social isolation. Median OS was shorter across all five domains of social isolation: patients living alone (37 vs 58 months), those who lost a partner (34 vs 56 months), those without regular social contact (32 vs 52 months), those without IADL support (49 vs 53 months), and those lacking emotional support (45 vs 53 months; all p$<$0.05). Anxiety (36.8%) and depression (25.6%) were also associated with worse survival (p$<$0.001). In multivariable Cox regression, independent predictors of increased mortality included metastatic disease (HR 4.41), depression (HR 1.44), anxiety (HR 1.29), lack of regular social contact (HR 1.26), male sex (HR 1.22), living alone (HR 1.18), and older age at presentation (HR 1.04 per year; all p$<$0.001). **Conclusions:** Multiple domains of social isolation were independently associated with shorter OS in cancer patients. These findings highlight social isolation as a clinically relevant prognostic factor and support the incorporation of psychosocial risk assessments into oncology care to inform risk stratification and supportive interventions. Research Sponsor: None.

12012 **Rapid Oral Abstract Session**

Vitamin D insufficiency and risk of taxane-induced peripheral neuropathy: Results from SWOG S1714. First Author: Nam Nguyen-Hoang, University of Michigan, College of Pharmacy, Ann Arbor, MI

Background: Taxane-induced peripheral neuropathy (TIPN) affects up to 70% of patients treated with taxanes and can lead to functional impairment, reduced quality of life, and treatment disruption. There are no proven TIPN preventive strategies. Vitamin D insufficiency is a modifiable factor that has been linked to increased TIPN risk in paclitaxel-treated patients with breast cancer. We analyzed the association between baseline vitamin D levels and TIPN among patients receiving taxane-based treatments in a large, multicenter, prospective cohort study (SWOG S1714). **Methods:** In a prespecified analysis, baseline vitamin D levels were quantified from plasma samples using liquid chromatography-tandem mass spectrometry. Vitamin D insufficiency was defined as total 25-hydroxyvitamin D $\leq$20 ng/mL. The primary endpoint was development of TIPN, defined as an increase of ^{3}8 points from baseline in the sensory subscale of the EORTC QLQ-CIPN20 (0-100 scale, with higher score indicating worse symptoms) by week 24. The secondary endpoint was the greatest worsening from baseline in the sensory subscale CIPN20 score. Multivariable Cox proportional hazards model was used to evaluate time to initial development of TIPN and linear regression was used for the secondary endpoint, both adjusting for age, cancer stage, race/ethnicity, comorbidities, taxane type, and planned treatment duration. Statistical significance was set at α = 0.05. **Results:** Among 1278 evaluable patients, 610 had available serum samples for vitamin D analysis (mean age 54.8 years [standard deviation 11.9]; 98% female; 85% White; 90% breast cancer; 59% paclitaxel-treated). Of these, 134 (22%) were vitamin D insufficient at baseline, and 383 (63%) developed TIPN during 24 weeks of follow-up. At baseline, CIPN20 sensory score did not differ by vitamin D status (p = 0.70). Baseline vitamin D insufficiency was significantly associated with higher risk of TIPN (adjusted hazard ratio 1.35; 95% confidence interval [CI] 1.06-1.72; p = 0.013). Patients with vitamin D insufficiency had more severe worsening of neuropathy (greatest worsening in CIPN20 sensory score: mean 23.4 vs. 18.5 points; adjusted mean difference 4.7 points; 95% CI 1.0-8.4; p = 0.013). **Conclusions:** Baseline vitamin D insufficiency was associated with significantly increased risk and severity of TIPN in this prospective cohort of patients receiving taxane-based therapy across multiple cancer types. These findings highlight vitamin D status as a potentially modifiable biomarker for TIPN risk and support clinical trials of vitamin D supplementation as a TIPN prevention strategy. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; R37CA277043, UG1CA189974.

12013 **Rapid Oral Abstract Session**

An international phase III randomized, double-blind, double-dummy trial comparing duloxetine and pregabalin for opioid-refractory neuropathic cancer pain. First Author: Hiromichi Matsuoka, National Cancer Center Japan, Tokyo, Japan

Background: Management of neuropathic cancer pain (NCP) refractory to standard-dose opioids remains a major clinical challenge, and direct comparative evidence between adjuvant analgesics is limited. This study aimed to compare the efficacy and safety of duloxetine and pregabalin in patients with opioid-refractory NCP. **Methods:** We conducted an international, multicenter, double-blind, randomized controlled trial. Adult cancer patients who continued to experience pain despite opioid analgesia were eligible to participate if they met the International Association for the Study of Pain criteria for neuropathic pain and had a Brief Pain Inventory (BPI) Item 3 (worst pain in the past 24 hours) score of $\geq$4. Inpatients and outpatients from Japan and Australia were randomized at a ratio of 1:1 to the duloxetine group (D group) or the pregabalin group (P group). The study drugs were titrated up to duloxetine 60mg daily or pregabalin 150mg twice daily until day 14 (D14). The primary endpoint was BPI item 3 at D14. Secondary endpoints included the change in BPI item 3 from baseline at D14, and the proportion of patients achieving $\geq$1 points, $\geq$2 points, $\geq$30% and $\geq$50% pain reduction. The primary endpoint was analyzed using a two-sided Student's T-test (α=0.05) under the intention-to-treat principle. A sample size of 64 patients per group was estimated to detect a mean difference of 1.0 (SD 2.0) with 80% power. **Results:** Between February 2020 and June 2025, 147 patients were enrolled across 18 institutions. Baseline BPI item 3 scores were similar between the D and P groups (7.23 vs 7.04). At D14, mean scores were 5.62 and 5.45, with no significant difference (P=0.70), corresponding to mean reductions of 1.57 and 1.55, respectively. Rates of pain reduction ($\geq$1 point, $\geq$2 points, $\geq$30%, $\geq$50%) were similar between groups (D: 53/45/36/25% vs P: 50/36/26/19%). Grade $\geq$2 adverse events included decreased appetite (29%), nausea (21%), fatigue (20%), in the D group, and constipation (23%), decreased appetite (16%), dizziness/fatigue (12%), in the P group. **Conclusions:** No significant difference in analgesic efficacy was observed between duloxetine and pregabalin in patients with opioid-refractory NCP. The magnitude of pain reduction exceeded the mean NRS change typically associated with placebo (approximately 0.5–1.0 points), and the response rates for $\geq$50% pain reduction were substantially higher than the $\approx$3% reported for placebo in a prior NCP study. The estimated numbers needed to treat were low (4.6 for duloxetine and 6.3 for pregabalin) and were smaller than those reported in non-cancer neuropathic pain, suggesting comparable or potentially greater efficacy. However, given the relatively high incidence of adverse events and the distinct adverse event profiles of each drug, careful and individualized treatment selection balancing efficacy and tolerability is warranted. Clinical trial information: jRCTs051190097. Research Sponsor: Japan Agency for Medical Research and Development (AMED).

12014 **Rapid Oral Abstract Session**

A URCC NCORP Research Base nationwide phase II randomized controlled trial (RCT) investigating the effect of exercise on chemotherapy-induced peripheral neurotoxicity (CIPN). First Author: Ian Kleckner, University of Maryland Baltimore, Baltimore, MD

Background: Over 60% of patients with cancer receiving taxane, platinum, or other neurotoxic agents experience CIPN, which presents as numbness, tingling, and sometimes pain in the hands and feet. CIPN reduces quality of life and can increase mortality by limiting chemotherapy dose. With extremely limited treatments for CIPN, exercise has emerged as one of the most promising yet unproven treatments with no Phase III RCTs to date. **Methods:** This phase II RCT examines the effect of exercise on CIPN in the University of Rochester Cancer Center (URCC) NCI Community Oncology Research Program (NCORP) Research Base network, recruiting 111 patients across 37 community oncology practices spanning 11 states in the US. Key eligibility include receiving neurotoxic chemotherapy (taxane, platinum, vinca alkaloid, etc.) in the past 9 months and reporting symptoms of CIPN ($\geq$ 4 of 10 at its worst in the past 2 weeks). Participants were randomized 1:1 to 6 weeks of usual care (UC) or virtually delivered Exercise for Cancer Patients (vEXCAP). vEXCAP is a virtually delivered, standardized, individualized, moderate-intensity, home-based, progressive walking and resistance exercise program. We assessed CIPN both pre- and post-intervention using patient-reported CIPN-20 (0-100 scale) and tactile sensitivity in the finger and toe using monofilaments. Each night, participants rated numbness/tingling in the hands/feet on a 0-10 scale. The primary outcome was CIPN-20 total score with CIPN-20 sensory and motor subscales as exploratory. **Results:** The 111 patients were 59.5 $\pm$10.5 yrs, 76% female, 83% White, 37% breast cancer, 36% gastrointestinal cancer. Exercise yielded statistically and clinically meaningful improvements in CIPN sensory symptoms compared to UC (ΔCIPN-20 = -4.7 [MCID = 4], effect size [ES] = -0.27, p = 0.049). Exercise had a weak effect on CIPN motor symptoms (ΔCIPN-20 = 1.5, ES = 0.08, p = 0.936) and the CIPN-20 total score (ΔCIPN-20 = -1.2, ES = -0.07, p = 0.393). Tactile sensitivity was negatively correlated with CIPN sensory symptoms, as expected (finger: rho = -0.21, p = 0.043, toe: rho = -0.18, p = 0.092). Effects of exercise on tactile sensitivity were beneficial yet small and not statistically significant (ES = 0.04 and 0.07, both p $>$ 0.682). Daily symptom ratings suggest that possible benefits of exercise emerge after 24 days (0.75$\pm$0.46 unit reduction, p = 0.104), with clear benefits after 30 days (0.93$\pm$0.46 unit reduction, p = 0.045) that grow further through study completion. **Conclusions:** Six weeks of walking and resistance exercise may reduce CIPN sensory symptoms for patients with CIPN. A future phase III RCT is needed to definitively test for replication and inform clinical practice. Funded by NCI: UG1CA189961, UG1CA189804, UG1CA189822, UG1CA189819, UG1CA189830, R21CA256154, and K07CA221931. Clinical trial: NCT04888988. Clinical trial information: NCT04888988. Research Sponsor: National Cancer Institute (USA).

12015 **Rapid Oral Abstract Session**

A multicenter randomized phase II trial of topical betamethasone ointment for preventing severe chemoradiotherapy-induced oral mucositis in head and neck cancer. First Author: Sakiko Soutome, Center for Clinical and Translational Research, Toyama University Hospital, Toyama, Japan

Background: Severe oral mucositis (OM) is a major unmet clinical problem during cisplatin-based chemoradiotherapy (CRT) for head and neck cancer, with no established preventive strategy. Although topical dexamethasone has shown benefit during radiotherapy alone, its efficacy during CRT is limited. This study represents the first randomized trial evaluating a potent topical corticosteroid, betamethasone ointment, for preventing severe OM during cisplatin-based CRT. **Methods:** Patients with head and neck cancer receiving CRT with the oral cavity included in the radiation field were enrolled at six institutions in Japan. Upon development of grade 1 OM (CTCAE v5.0), patients were randomized to standard oral care alone (control) or standard oral care plus topical betamethasone ointment applied three times daily (intervention). Treatment continued until completion of radiotherapy or onset of grade 3 OM. The primary endpoint was time to grade 3 OM, analyzed using multivariable Cox proportional hazards models. Secondary endpoints included time to grade 2/3 OM and incidence of oral candidiasis. **Results:** A total of 68 patients were analyzed (intervention n=35; control n=33). The cumulative incidence of grade 3 OM was significantly lower in the intervention group (14.3%) than in the control group (48.5%). Topical betamethasone significantly reduced the risk of grade 3 OM (HR 0.246, 95% CI 0.081–0.749). Betamethasone also delayed the onset of grade 2/3 OM. Non-use of a spacer was independently associated with grade 2 OM. Betamethasone did not increase oral candidiasis, whereas denture use was a significant risk factor. **Conclusions:** Topical betamethasone ointment substantially reduced the incidence of severe OM during cisplatin-based CRT without increasing oral candidiasis. This simple, low-cost, and widely accessible intervention could be rapidly implemented in routine clinical practice to mitigate CRT-induced toxicity. To our knowledge, this is the first randomized trial demonstrating the efficacy of a potent topical corticosteroid for preventing severe OM during cisplatin-based CRT. Clinical trial information: jRCTs071200013. Research Sponsor: None.

12016 **Rapid Oral Abstract Session**

The efficacy and safety of add-on ruxolitinib for patients with severe checkpoint inhibitor pneumonitis management with corticosteroids: A multicenter, open-label, randomised phase 2 trial. First Author: Yan Xu, Peking Union Medical College Hospital, Beijing, China

Background: Checkpoint inhibitor pneumonitis (CIP) stands out as a remarkable complication during ICIs therapy. Severe CIP represents a potentially life-threaten immune-related adverse event (irAE) with limited evidence from clinical trials that guides therapeutic interventions. Ruxolitinib, a selective JAK1/2 inhibitor, effectively attenuates cytokine-release syndrome and show significant anti-fibrotic in mouse lung with BLM model. We conducted a multicenter, investigator-initiated, open-label, phase 2 randomized controlled trial to evaluate the efficacy and safety of add-on ruxolitinib for patients with severe CIP management with corticosteroids. **Methods:** Patients with malignant who were suffered from CTCAE grade (G) 3 or G4 CIP after ICIs therapy were screened. Enrolled CIP patients were randomly assigned 1:1 to control group (only glucocorticoids) or ruxolitinib group (glucocorticoids plus ruxolitinib). Initiated dosage of glucocorticoids was no less than prednisone 1 mg/kg/day (or same steroid equivalent dose) with subsequent tapering off. In ruxolitinib group, enrolled patients were add-on ruxolitinib (5 mg twice daily for 2 weeks, followed with 5 mg daily for 2 weeks). The primary end point was the proportion of patients with a prednisone daily dosage of no more than 10mg and improvement to G1 CIP at week 8. Continuous variables were analyzed using a mixed-effects model for repeated measures with treatment group, study visit and treatment-by-visit interaction. **Results:** From April 2023 to November 2025, a total of 60 eligible patients were recruited and randomly assigned to control group and ruxolitinib group. There were 52 cases of G3 CIP and 8 cases of G4 CIP. There were more patients in the ruxolitinib group improved to G1 CIP and received ≤prednisone 10mg daily at 8th week than in the controlled group (20cases/66.7% vs 11cases/36.7%, p = 0.0379). This effect was more significant in the 2nd and 4th week. Two patients in ruxolitinib group and 4 patients in the control group died within eight weeks. The repeated measures analysis using a generalized linear mixed model demonstrated a significant overall treatment effect, ie. add-on ruxolitinib was associated with significantly higher odds of clinical improvement (adjusted OR = 5.12, 95% CI 1.06 - 24.64; p = 0.04). A total of 13 G3 or higher treatment-related AEs (TRAEs) occurred (7 cases in control group and 6 cases in ruxolitinib group), including 9 cases of infectious diseases. **Conclusions:** Add-on ruxolitinib for malignant patients with severe CIP management with glucocorticoids show with higher resolution rates and earlier response trends than only glucocorticoids treatment. And there were no different adverse events between them. Add-on ruxolitinib with glucocorticoids might be a promising proposed treatment for patients with severe CIP. Clinical trial information: NCT05899725. Research Sponsor: National High Level Hospital Clinical Research Funding; 2022-PUMCH-C-054.

12017 **Rapid Oral Abstract Session**

A randomized phase III trial of dexamethasone mouthwash to prevent chemotherapy-induced oral mucositis in patients with breast cancer. First Author: Sayaka Kuba, Nagasaki University Hospital, Nagasaki, Japan

Background: Oral mucositis is a common adverse event in patients undergoing chemotherapy for breast cancer. A previous randomized phase II trial showed that a dexamethasone-based mouthwash significantly reduced the incidence and severity of chemotherapy-induced oral mucositis. The SMASH-BC trial was designed to confirm the efficacy and safety of dexamethasone-based mouthwash for preventing chemotherapy-induced oral mucositis in patients with breast cancer. **Methods:** This multicenter, open-label, randomized phase III trial was conducted in Japan. Patients with early breast cancer scheduled to receive standard adjuvant or neoadjuvant chemotherapy (AC, EC, dose-dense AC/EC, TC, or pembrolizumab-containing regimens) were randomized 1:1 to receive either a dexamethasone-based mouthwash (10 mL of dexamethasone elixir 0.01%) or tap-water mouthwash as a control. The mouthwash was swished for 2 min and spit, four times daily for 8 weeks, starting on day 1 of chemotherapy. Randomization was stratified by chemotherapy regimen, smoking status, and institution. The primary endpoint was the incidence of all-grade oral mucositis at 8 weeks, assessed using electronic patient-reported outcomes (ePRO). Assuming an all-grade oral mucositis incidence of 55% in the control group and 35% in the intervention group, 212 patients were required to provide 80% power with a two-sided α of 0.05. The planned sample size was 230, allowing for 10% attrition. **Results:** Overall, 230 patients were randomized (intervention, n = 117; control, n = 113), and 220 patients (intervention, n = 114; control, n = 106) were included in the analysis. The incidence of ePRO-assessed all-grade oral mucositis at 8 weeks was 58.8% and 63.2% in the intervention and control groups, respectively (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.75–1.15; P = 0.59). The incidence of ePRO-assessed moderate-to-very severe oral mucositis was 13.2% and 18.9% in the intervention and control groups, respectively (RR, 0.70; 95% CI, 0.38–1.29). During the 56-day study period, mucositis reported by ePRO on a median of 2 and 6 days in the intervention and control groups, respectively (median difference −4 days; 95% CI, −5.3 to 8.3 days). The incidence of physician-assessed oral mucositis was 31.9% vs. 41.5% in the intervention and control groups, respectively (RR, 0.77; 95% CI, 0.54–1.09). The incidence of grade ≥ 3 adverse events was 6.2% and 6.6% in the intervention and control groups, respectively (RR, 0.94; 95% CI, 0.34–2.58). However, the incidence of oral candidiasis was higher in the intervention group (5.4% vs 0%). **Conclusions:** Prophylactic dexamethasone mouthwash did not significantly reduce all-grade oral mucositis at 8 weeks. Overall safety was comparable between groups; however, the incidence of oral candidiasis was higher in the intervention group. Clinical trial information: jRCTs071240036. Research Sponsor: Japan Agency for Medical Research and Development.

12018 **Poster Session**

Cardiovascular disease incidence in women with early-onset breast cancer. First Author: Vidhya Nair, University of Washington, Seattle, WA

Background: Early-onset breast cancer (BC) before age 40 is generally associated with advanced stage at diagnosis and worse outcomes. Improvements in detection and treatment have led to reduction in BC mortality. Cardiovascular disease (CVD) is the leading cause of non-BC death in women with BC, but younger women are traditionally considered to be at lower risk for CVD. Given the limited data on CVD in early-onset BC, this study evaluates incident CVD in women younger than age 40 in the Pathways Heart Study. **Methods:** The Pathways Heart Study (R01/U01CA214057) is an ongoing, prospective cohort study including 14,402 women diagnosed with BC at KPNC from 2005-2013 and followed through 2021. In this study, eligible BC cases were women age 18-39 years at time of stage I-III BC diagnosis without pre-existing CVD. Cases were matched 1:5 to controls without BC on age at diagnosis and race/ethnicity. Cancer treatment, CVD (ischemic heart disease, heart failure, cardiomyopathy, stroke) and cardiometabolic risk factors (hypertension, diabetes, hyperlipidemia) were extracted from electronic health records. Cumulative incidence rates (CIR) were calculated as number of incident CVD events divided by total person-time at risk and expressed per 1,000 person-years. **Results:** A total of 535 women with early-onset BC were matched to 2,651 controls. Mean age was 35.1 years with mean follow up of 7.8 years. Overall, cases had a higher CIR of CVD (3.40 per 1,000 person-years (PY)) than controls (1.37/1000 PY). CIRs of hypertension, dyslipidemia, and diabetes were higher in cases compared to controls (14.89, 12.14, and 9.74/1000 PY, respectively). Among BC types and stage, women with hormone receptor-positive HER2-positive and stage III BC had the highest CVD CIRs (7.14 and 5.65/1000 PY, respectively). Women who received chemotherapy with anthracyclines and those who received endocrine therapy had higher CVD CIRs compared with those who did not, while there were no differences by receipt of radiation therapy (Table 1). **Conclusions:** Although the absolute incidence of CVD was low in BC patients younger than 40 years, these patients experienced a >2 fold higher CVD rate compared with matched controls. Patients treated with anthracyclines and endocrine therapy had higher CIR of CVD compared with those not treated. Future analyses will include formal comparison through survival and regression models of incident CVD and cardiometabolic disease in women with early-onset BC, accounting for confounders, including treatments received, education, income, and comorbidities. Research Sponsor: National Cancer Institute.

Cumulative incidence rates (CIR) of cardiovascular disease (CVD) in women age <40 years in the Pathways Heart Study.

	CIR of CVD per 1,000 person-years (95% CI)
Chemotherapy	
With Anthracycline	4.15 (2.07, 7.43)
Without Anthracycline	3.39 (0.70, 9.89)
None	0.00 (0.00, 6.31)
Endocrine Therapy	
Yes	3.77 (1.88, 6.74)
No	2.50 (0.51, 7.29)
Radiation Therapy	
Yes	3.40 (1.55, 6.45)
No	3.40 (1.10, 7.93)

12019 **Poster Session**

Machine learning (ML)-based prediction of fatal immune checkpoint inhibitor (ICI)–associated myocarditis (MC) with multi-cohort validation. First Author: Hassan M. Abushukair, Stephenson Cancer Center, Oklahoma City, OK

Background: ICI-associated MC is a rare but highly fatal immune-related adverse event (irAE). Identifying clinical predictors of MC-specific fatality remains an unmet need. Herein, we develop and externally validate an ML model to predict ICI-MC fatality using clinical and laboratory features. **Methods:** The WHO Vigibase database was queried through December 22, 2024, to identify cases of ICI-MC with complete clinical data, including age, sex, cancer and ICI type, co-occurring irAEs, overlap status with myositis (MS) and/or myasthenia gravis (MG), MC timing from ICI start, and MC-specific fatality. Multivariable logistic regression was used to assess correlates of MC-specific fatality. An XGBoost ML model using all collected clinical data was trained to predict MC-specific fatality using an 80/20 split of data for training and testing. We augmented our clinical ML model with troponin (T or I) values at the time of ICI-MC diagnosis from two institutions (n = 37: OU n = 13, MGH n = 24), normalized to institutional upper limits of normal. Two additional external cohorts (n = 68: VUMC n = 18, MDACC n = 50) were used to validate our final clinical and augmented models. **Results:** We identified 822 cases from VigiBase with ICI-MC, with a median age of 69 years (IQR: 60-76), 59.1% (n = 486) were males. Pts with lung cancer had the highest proportion of cases (23.7%, n = 195). Most patients received ICI monotherapy (59%, n = 485). Median time to MC onset was 30.4 days (IQR: 21-91.3). MC occurred alone in 588 cases (71.5%) and with MS and/or MG in the remainder. MC-specific fatality occurred in 147 cases (17.9%). After multivariable adjustments, MC onset within the first month of ICI start was associated with higher MC-fatality odds vs. later onset (vs 1-3 months: ROR = 0.38 [0.21-0.67], vs 3-12 months: ROR = 0.5 [0.25-0.95]). Co-occurring non-MC major cardiac adverse events (ROR: 0.27 [0.17 - 0.44]) and pneumobronchitis (ROR: 0.29 [0.11 - 0.78]) were also associated with increased MC-specific fatality. The optimized MC-fatality clinical ML model achieved AUCs of 0.76 (training) and 0.73 (testing), with early MC onset as the most contributing feature. External validation (n = 37) of our clinical model yielded an AUC of 0.74. Augmenting our clinical ML model with baseline troponin (n = 37) significantly improved performance (AUC: 0.79, likelihood-ratio p = 0.046), with a further external validation (n = 68) AUC of our augmented ML model of 0.67. Our ML model is available online for use through: https://ohbiolab.shinyapps.io/ici-mc_fatality_predictor/. **Conclusions:** ICI-MC timing and co-occurring cardio-pulmonary reactions are key determinants of MC-specific fatality. Our findings highlight the potential promise for early risk stratification to identify high-risk pts with ICI-MC who could benefit from closer monitoring or more tailored immuno-suppressive interventions at ICI-MC diagnosis. Research Sponsor: None.

12020 **Poster Session**

Artificial intelligence surrogate models to predict long-term cardiovascular effects of immune checkpoint inhibitor therapies using electrocardiograms. First Author: Frances Dean, University of California, San Francisco, San Francisco, CA

Background: Immune checkpoint inhibitors (ICI) revolutionized the treatment landscape for many cancers, with close to 50% of cancer patients now ICI eligible. Acutely, ICI are associated with myocarditis. Long term cardiovascular effects of ICI are less clear. We built artificial intelligence (AI) models as surrogates for predicting long-term cardiovascular disease (CVD) after ICI using electrocardiograms (ECG). **Methods:** Using data from over 80,000 cancer patients treated from 1986 to 2021 at the University of California, San Francisco, we develop two ECG AI models as surrogates for risk over time of CVD. First, we built a model of observed CVD using true outcomes in a time to event framework. This model is a surrogate for prevalence under the current standard of care. Second, we build a model for causal outcomes using before-and-after data and estimate risk from ECGs for causal analyses. We hold out patients (N=15,277), including all those treated with anthracyclines (N= 3,681), trastuzumab (N=751), or ICI (N= 3,572), for evaluation. Causal effects are estimated with paired pre and post treatment ECGs within three years. **Results:** Models have average AUC across CVDs and years of 0.78 and 0.77. The observed model estimates ICI treated patients compared to those with any other cancer treatment have higher average 10-year risk of ischemic heart disease (IHD) by 10% (95% CI: 2-18%), venous thromboembolism (VTE) by 10% (1-20%), and critical ventricular arrhythmias (CVA) by 10% (3-19%), largely due to high baseline risk. Anthracycline and trastuzumab treated patients did not have higher 10-year heart failure (HF) risk relative to other treatments in aggregate. The causal framework estimates anthracyclines increased average 10-year risk of HF by 45% and trastuzumab by 46%. Anthracyclines and trastuzumab significantly increased risk of atrial fibrillation, IHD, ischemic stroke, CVA, VTE, and conduction disorders as well. ICI increased risk of each of these significantly by smaller amounts. Notably, after ICI, average 10-year risk of HF increased by 32% and IHD by 17%. **Conclusions:** Our study demonstrates potential long-term CVD effects of ICI as estimated from ECGs. This framework can be used to evaluate effects of new therapies in the future. Research Sponsor: U.S. National Science Foundation; DGE 2146752.

10-year pre/post treatment relative risks.

CVD	Anthracycline	Trastuzumab	ICI
Atrial fibrillation	1.34 [1.29, 1.39]	1.30 [1.24, 1.36]	1.25 [1.21, 1.28]
Ischemic heart disease	1.25 [1.21, 1.28]	1.28 [1.23, 1.32]	1.17 [1.14, 1.19]
Heart failure	1.45 [1.39, 1.52]	1.46 [1.38, 1.55]	1.32 [1.27, 1.36]
Ischemic stroke	1.41 [1.32, 1.50]	1.31 [1.22, 1.41]	1.28 [1.21, 1.35]
Critical ventricular arrhythmia	1.18 [1.15, 1.22]	1.14 [1.09, 1.19]	1.10 [1.07, 1.13]
Venous thromboembolism	1.29 [1.24, 1.33]	1.26 [1.21, 1.31]	1.26 [1.21, 1.30]
Conduction disorder	1.19 [1.17, 1.21]	1.19 [1.16, 1.21]	1.15 [1.13, 1.17]

12021 **Poster Session**

The impact of body composition on cardiac function in women with early breast cancer taking cardiotoxic chemotherapy. First Author: Gabriel Aleixo, University of Pennsylvania, Philadelphia, PA

Background: Anthracyclines and HER2-directed therapies have improved survival in early breast cancer (EBC), but cardiotoxicity remains a concern for long-term survivors. Cardiovascular disease may ultimately exceed breast cancer as a cause of death, highlighting the need for better understanding of therapy-related cardiac dysfunction. Body composition abnormalities are linked to adverse cardiovascular outcomes but are not well captured by body mass index are understudied. We evaluated longitudinal associations between baseline CT-derived body composition and echocardiography measures of cardiac structure and function. **Methods:** This is a retrospective analysis of women with stage I–III EBC treated with anthracyclines and/or trastuzumab at the University of Pennsylvania. Eligible patients had a pre-treatment and ≥1 follow-up echocardiogram and pre-treatment abdominal CT or PET-CT imaging for body composition assessment. L3-based segmentation quantified skeletal muscle mass, muscle density (SMD), subcutaneous and visceral adiposity (SAT, VAT), and adipose tissue density (SATD, VATD). Core-lab echocardiographic outcomes included systolic function (LVEF, GLS) and diastolic function (E/e′). Using multivariable-adjusted generalized estimating equations (GEE) models, we evaluated longitudinal associations between baseline body composition (per 1-SD increase) and two complementary outcomes for each metric: (1) absolute values over time (overall burden) and (2) change from baseline (within-participant worsening). **Results:** Across 182 participants, the median age was 49.5 years (Q1-Q3 41–60), HER2-positive disease was present in 64 (35.4%), estrogen receptor–positive disease in 114 (62.6%), and triple-negative disease in 37 (20.4%). Anthracycline-based therapy was administered to 150 (82.4%), radiation therapy to 140 (76.9%), and mastectomy was performed in 106 (58.6%). Baseline hypertension, hyperlipidemia, and diabetes were present in 56 (30.8%), 43 (23.6%), and 12 (6.6%), respectively. In multivariable-adjusted GEE models, higher baseline VAT was associated with a greater decline in LVEF over time (−2.1 LVEF points per 1-SD increase; 95% CI −4.1 to −0.1; p=0.04). We next evaluated diastolic function, where higher baseline VAT was associated with a greater increase in E/e′ over time (β 0.38 per 1-SD increase; 95% CI, 0.01 to 0.74; p=0.04). In models evaluating absolute E/e′ over time, higher VAT (β 0.51; 95% CI, 0.11 to 0.91) and SAT (β 0.37; 95% CI, 0.06 to 0.59), and lower SMD (β −0.34; 95% CI, −0.66 to −0.02) and VAT density (β −0.36; 95% CI, −0.67 to −0.05) were associated with higher E/e′. No adjusted associations were observed for longitudinal change in GLS (all p>0.05). **Conclusions:** Baseline visceral adiposity was associated with worsening in longitudinal changes in systolic and diastolic function during cardiotoxic breast cancer therapy. Research Sponsor: None.

12022 **Poster Session**

Exercise and cardiovascular risk among breast cancer patients. First Author: Erika Libiar Estrada, Kaiser Permanente Southern California, Research and Evaluation Department, Pasadena, CA

Background: Breast cancer is the most common cancer among U.S. females, accounting for 15% of new diagnoses. As survivorship increases, cardiovascular disease (CVD) has become a major cause of long-term morbidity and mortality. Survivors remain at elevated risk for CVD due to treatment-related cardiotoxicity and underlying risk factors. Despite this growing burden, evidence on whether exercise mitigates cardiac dysfunction remains limited and inconsistent. This study examines the association between physical activity and subsequent CVD and mortality outcomes among breast cancer patients with documented Exercise Vital Sign (EVS) data. **Methods:** A retrospective cohort study was conducted within the Kaiser Permanente Southern California (KPSC) health system. Adult members (≥18 years) with primary breast cancer diagnosed from 2011–2019 were identified through the KPSC cancer registry. Eligible patients had ≥12 months of continuous enrollment and at least two encounters (separated by ≥1 month) with EVS data in the year prior to diagnosis. Physical activity was defined using median exercise volume: completely inactive (0 min/week; reference), insufficiently active (IA; > 0– < 149 min/week), and sufficiently active (SA; ≥150 min/week). Outcomes included all-cause, cancer-specific, and CVD mortality; congestive heart failure (CHF); cardiomyopathy; and major adverse cardiovascular events (MACE). Cox proportional hazards models adjusted for demographic factors, lifestyle characteristics, tumor features, insurance type, and pre-existing cardiovascular comorbidities. **Results:** Among the cohort (N = 12,481), compared with the completely inactive group, SA was associated with lower risk of CHF (HR 0.74; 95% CI 0.59–0.89). For MACE, both IA (HR 0.78; 95% CI 0.71–0.86) and SA (HR 0.66; 95% CI 0.59–0.74) demonstrated decreased risk. Similar reductions were observed for all-cause mortality (IA HR 0.75; 95% CI 0.68–0.83; SA HR 0.62; 95% CI 0.54–0.70), cancer-specific mortality (IA HR 0.82; 95% CI 0.71–0.96; SA HR 0.69; 95% CI 0.57–0.83), and CVD mortality (IA HR 0.68; 95% CI 0.58–0.79; SA HR 0.53; 95% CI 0.43–0.65). Physical activity was not associated with reduced cardiomyopathy risk. **Conclusions:** Physical activity appears to reduce cardiovascular and mortality risk among breast cancer survivors in a dose-responsive manner, with SA patients experiencing the greatest benefit. Even insufficient activity was associated with improved prognosis compared with complete inactivity, supporting the incorporation of exercise promotion into survivorship care. Regular physical activity may reduce CVD and mortality risk among breast cancer survivors, supporting routine EVS screening and referral to exercise or cardio-oncology programs in survivorship care. These findings also reinforce the need for institutional and payer policies that prioritize exercise assessment and counseling as standard components of cancer survivorship care. Research Sponsor: The National Heart, Lung, and Blood Institute; 5R01HL151665.

12023 **Poster Session**

Time-resolved cardiovascular risk after immune checkpoint inhibitors: A large real-world cancer cohort study. First Author: Yibin Jia, Qilu Hospital of Shandong University, Jinan, China

Background: With expanding use of immune checkpoint inhibitors (ICIs), immune-related toxicities increasingly influence outcomes beyond tumor control. Cardiovascular events are among the most consequential yet potentially preventable complications. Given the low incidence of major adverse cardiovascular events (MACE) and their relatively narrow post-initiation window, reliable time-resolved risk estimation requires very large cohorts, which remain scarce, limiting evidence to guide surveillance and prevention. **Methods:** We conducted a pan-cancer retrospective cohort study (N = 269,257; mean follow-up 4.5 years) using a large real-world cancer registry from Shandong Provincial Center for Disease Control and Prevention. Patients receiving ICIs after their broad clinical implementation were compared with patients treated in the pre-ICI era without immunotherapy, a design chosen to mitigate indication-related differences observed in the contemporary setting. Propensity scores derived from elastic net regularization were used to construct overlap weights for balancing covariates across cohorts. We evaluated MACE, AMI (acute myocardial infarction), and stroke across four prespecified intervals (0–90, 91–180, 181–270, and 271–365 days) using interval-stratified weighted Cox models. Absolute risk differences were further characterized using weighted incidence density differences and restricted mean survival time. **Results:** All covariates achieved excellent balance (maximum |SMD| = 0.004) after weighting. ICI exposure was associated with higher 1-year MACE risk (HR, 1.17; 95% CI, 1.12–1.23; P < 0.001), corresponding to a weighted incidence density difference of 10.90 per 1,000 person-years (95% CI 8.73–13.06). The largest absolute risk increase was observed during 0–90 days after ICI initiation(weighted incidence density difference, 17.83 per 1000 person-years; 95% CI, 12.43 to 23.24).The risk of AMI peaked early, with a statistically significant association observed only during 0–90 days (HR, 1.86; 95% CI, 1.54–2.24; P < 0.001). In contrast, stroke risk peaked during days 91–180 (HR, 1.27; 95% CI, 1.11–1.44; P < 0.001) and remained significantly elevated through 181–270 days (HR, 1.25; 95% CI, 1.08–1.44; P = 0.003). Stroke accounted for 51% (95% CI: 19% to 83%), 63% (95% CI: 37% to 89%), 66% (95% CI: 43% to 90%), and 67% (95% CI: 45% to 88%) of the total weighted incidence density difference for MACE during days 0–90, 0–180, 0–270, and 0–365, respectively. **Conclusions:** ICI exposure was associated with temporally heterogeneous cardiovascular risk, with AMI concentrated in the first 90 days and stroke risk remaining elevated thereafter. These results suggest a time-tailored approach to cardio-oncology care, characterized by intensified early monitoring for AMI and sustained attention to stroke prevention in subsequent months. Research Sponsor: National Natural Science Foundation of China; the Fund of Taishan Young Scholar Project for Jianbo Wang; the Natural Science Foundation of Shandong Province.

12024 **Poster Session**

The genetic polymorphism underlying immune checkpoint inhibitor–induced endocrine toxicity. First Author: Ming-Hua Cong, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Immune checkpoint inhibitors (ICIs) have transformed cancer therapy by enhancing T cell–mediated anti-tumor immunity; however, immune-related adverse events (irAEs)—particularly endocrine toxicities (e.g., thyroiditis, hypophysitis, adrenal insufficiency; incidence 5–15%)—pose significant clinical risks, including lifelong hormonal dependency. Although germline genetic factors, especially human leukocyte antigen (HLA) variants, are implicated in irAE susceptibility, prior studies lack granularity in toxicity subtyping and comprehensive genetic characterization across diverse clinical contexts. **Methods:** We integrated high-resolution HLA genotyping with precise phenotypic annotation of endocrine irAEs (subclassified by organ specificity, onset, severity per CTCAE v5.0) in multi-center retrospective and prospective cohorts. A hypothesis-free genome-wide approach identified novel HLA loci, followed by functional validation of candidate variants. Machine learning models were trained to predict toxicity risk by integrating HLA markers with clinical covariates (ICI type, cancer diagnosis, baseline characteristics). **Results:** Subtype-specific HLA associations were identified (e.g., distinct *HLA-DRB1* alleles linked to thyroiditis versus hypophysitis). Collinearity analysis revealed significant positive correlations between non-endocrine irAE pairs (e.g., capillary hyperpermeability and gastrointestinal ulcers; $P < 0.01$), suggesting shared immunopathogenic pathways. The integrated risk model demonstrated robust stratification performance for endocrine toxicity susceptibility. Cohort demographics reflected real-world ICI utilization patterns (predominantly lung cancer), while clinical response data underscored challenges in achieving durable remission (notable progression rates). **Conclusions:** This study delineates the HLA-driven genetic architecture underlying endocrine irAEs and elucidates interdependencies among irAE subtypes. Integration of genetic risk profiling with clinical parameters enables personalized toxicity risk assessment, advocating for proactive, multidisciplinary monitoring protocols. These findings advance precision immunotherapy by informing biomarker-guided patient selection, optimizing safety, and refining clinical decision-making frameworks for ICI administration. Clinical trial information: MR-11-25-020518. Research Sponsor: None.

12025 **Poster Session**

Cardiac safety of L-annamycin at high cumulative anthracycline exposure: Pooled analysis. First Author: Robert C. Shepard, Moleculin Biotech, Houston, TX

Background: Anthracyclines are widely used chemotherapeutic agents but limited by dose-dependent cardiotoxicity and lifetime cumulative dose restrictions. L-Annamycin is a next-generation anthracycline designed to eliminate cardiotoxicity and overcome multidrug resistance. In a Phase 1b/2 study in patients with acute myeloid leukemia (AML), L-Annamycin administered in combination with cytarabine as second-line therapy achieved a 50% complete remission (CR) rate and a 60% composite CR (CRc) rate with a median overall survival of 12.39 months (95% CI, 2.07–13.96) in the intent-to-treat population. We evaluated the cardiac safety of L-Annamycin in multiple clinical trials to assess its ability to support sustained anthracycline exposure in patients with AML and soft tissue sarcoma. **Methods:** Cardiac safety was evaluated across sponsor- and investigator-initiated clinical trials of L-Annamycin. Assessments included serial 12-lead electrocardiograms (ECGs), cardiac biomarkers (troponin I and T), and transthoracic echocardiography with centralized evaluation of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), where available. Cardiac data were reviewed independently by a reviewer in the Division of Cardiovascular Medicine at the Cleveland Clinic. Changes in LVEF from baseline to final assessment were analyzed in relation to cumulative L-Annamycin dose and patient age. **Results:** An independent cardiac safety review was conducted for 90 patients who were treated with L-Annamycin across five completed clinical trials; 78 of these patients now have source-verified pre- and post-treatment left ventricular ejection fraction (LVEF) assessments. The median cumulative L-Annamycin dose among these patients was 660 mg/m² (95% CI, 645–690; range, 210–2,970 mg/m²), with most of the cumulative doses exceeding conventional lifetime anthracycline limits. Analysis of the change in LVEF from baseline to final assessment demonstrated no statistically significant difference (mean difference, −0.12%; 95% CI, −1.34 to 1.09; p = 0.84). Linear regression analysis documented no correlation between cumulative L-Annamycin dose and change in LVEF (p = 0.12), nor between patient age and change in LVEF (p = 0.73). Independent review of serial ECGs, cardiac biomarkers, cardiac adverse events, and available global longitudinal strain measurements also demonstrated no evidence of drug-induced cardiotoxicity. **Conclusions:** L-Annamycin was not associated with any detectable cardiotoxicity despite high cumulative anthracycline exposure. These findings suggest that L-Annamycin represents a next-generation anthracycline capable of delivering effective anthracycline therapy without traditional cumulative dose limitations, thus further supporting its ongoing pivotal Phase 2b/3 trial in AML patients. Research Sponsor: Moleculin Biotech.

12026 **Poster Session**

The association between cardiovascular disease risk and breast arterial calcifications identified on screening mammography: A retrospective study. First Author: Tae Hoon Kim, Valley Health System, Paramus, NJ

Background: Screening mammography enables early breast cancer detection and improves outcomes. Breast cancer and cardiovascular disease (CVD) share several overlapping risk factors in women. Breast arterial calcifications (BACs) are non-occlusive calcifications of the medial layer of small to medium-sized arteries in the breast that can be identified on mammography. Prior studies have demonstrated an association between BACs and increased cardiovascular risk with growing evidence suggesting that BACs may serve as a non-invasive, low-cost screening tool for CVD. Currently, routine screening for BACs is not uniformly performed. This study aimed to evaluate the prevalence of BACs in screening mammograms, and to characterize associated atherosclerotic cardiovascular disease (ASCVD) risk scores and cardiovascular risk factors among individuals with BACs. **Methods:** We performed a retrospective analysis of 650 individuals undergoing screening mammography at our institution from 2023 to 2025. Data collected included patient demographics, medical and social history, and cardiovascular risk factors, including blood pressure, diabetes mellitus, and lipid profiles. ASCVD risk scores were calculated for each individual. Statistical analyses, including chi-square test and T-test, were performed to evaluate associations between the presence of BACs, cardiovascular risk factors, and ASCVD scores. **Results:** Among the 650 women who underwent screening mammography, n = 641 had BI-RADS 1 (negative) or 2 (benign) results, while n = 9 had an abnormal mammogram that subsequently led to a breast cancer diagnosis. BACs were identified in 15.1% of the participants (n = 98). BAC prevalence increased significantly with age: 2.3% among women aged 40-49 years, 8% in those aged 50-59 years, 18.4% in those aged 60-69 years, and 42.2% among women aged 70 years and older ($p < 0.001$). Among participants with available ASCVD risk data (n = 429), BAC-positive patients had a significantly higher mean 10-year ASCVD risk when compared with BAC-negative patients (14.0% vs 5.23%, $p < 0.001$). Among the BAC-positive patients, 61.2% were categorized as ASCVD intermediate or high risk versus 20.8% of BAC-negative patients ($p < 0.001$). BAC-positive patients also exhibited higher mean systolic blood pressure (123.76 vs 120.66 mm Hg, p = 0.042). Hemoglobin A1c, total cholesterol, diastolic blood pressure, and smoking status did not differ significantly between the two groups. **Conclusions:** Breast arterial calcifications identified on screening mammograms were significantly associated with less favorable cardiovascular risk profiles. Implementation of routine BAC reporting may enable opportunistic CV risk detection during breast cancer screening, potentially leading to earlier preventive interventions. Research Sponsor: None.

12027 **Poster Session**

Differences in the receipt of recommended cardiovascular assessment among cancer survivors in the United States by atherosclerotic cardiovascular disease status. First Author: Reed Mszar, Yale School of Public Health, New Haven, CT

Background: Cardio-oncology guidelines recommend annual cardiovascular (CV) assessment among cancer survivors, particularly those with pre-existing atherosclerotic cardiovascular disease (ASCVD). Despite this, little is known regarding the proportion of cancer survivors receiving comprehensive CV assessment and whether certain subgroups experience suboptimal uptake. We investigated the prevalence and predictors of receiving recommended comprehensive CV assessment (i.e., cholesterol, blood pressure, blood glucose) among cancer survivors in the United States. **Methods:** We used self-reported, cross-sectional data from the National Health Interview Survey (2012-2018), an annual, weighted survey that uses multistage sampling and interviews to produce nationally representative estimates of the noninstitutionalized U.S. population. Adults with cancer and complete information on ASCVD status (defined as a history of myocardial infarction, stroke, coronary heart disease, or angina) were included. To examine the association between sociodemographic characteristics and lack of recommended CV assessment within the past year, adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated using multivariable logistic regression stratified by ASCVD status. **Results:** Among 16,420 cancer survivors (median age: 65.4 years; 20.1% with ASCVD), representing approximately 15.4 million survivors annually, 38.2% did not receive recommended CV assessment in the past year. Approximately 3.7% of cancer survivors (representing 566,043 individuals annually) received none of the CV assessments. Among cancer survivors with ASCVD, factors associated with increased odds of not receiving recommended CV assessment included lower (vs higher) level of education (aOR, 1.30 [95% CI, 1.01-1.65]). In cancer survivors without ASCVD, these factors included age 18-44 years (vs ≥75 years) (aOR, 1.82 [95% CI, 1.39-2.39]), low/lowest (vs high/middle) income (aOR, 1.23 [95% CI, 1.06-1.44]), uninsured (vs insured) status (aOR, 1.94 [95% CI, 1.37-2.74]), South (vs Northeast) region (aOR, 1.31 [95% CI, 1.05-1.62]), and no (vs yes) usual source of care (aOR, 2.42 [95% CI, 1.66-3.53]). Among all cancer survivors, there was a stepwise increase in receipt of CV assessment with increasing age at initial cancer diagnosis ranging from 52.7% among those aged 18-44 years at diagnosis to 68.5% among those aged 65-74 years at diagnosis ($p < 0.001$). **Conclusions:** More than 1 in 3 cancer survivors did not receive recommended annual CV assessment with several subgroups having even lower screening rates, including by age, socioeconomic status, and access to care. Improving awareness of contemporary cardio-oncology guidelines and targeting interventions during cancer survivorship are needed to increase uptake of optimal CV assessment. Research Sponsor: None.

12028 **Poster Session**

Efficacy of primary cardioprotection with perindopril, bisoprolol, and trimetazidine in high-risk patients with breast and gastric cancer receiving anthracycline- and trastuzumab-containing therapy. First Author: Evgenia Khatkova, Moscow Clinical Scientific Center Named After A.S. Loginov, Moscow, Russian Federation

Background: Anthracyclines and trastuzumab are the most common antitumor agents associated with a substantial risk of cardiotoxicity (CTX). Patients with high or very high cardiovascular risk represent a vulnerable population where even subclinical myocardial injury can translate into clinically significant cardiac dysfunction. The present study is aimed to evaluate the efficacy of primary cardioprotective therapy (CPT) in preventing both subclinical and overt CTX in high-risk patients undergoing anthracycline (A)- and/or trastuzumab (T)-containing treatment. **Methods:** This single-center prospective observational study included 92 cancer patients (pts) with high or very high risk of CTX according to the Mayo Clinic risk score. The study population consisted of 7 men (8%) and 85 women (92%), with a mean age of 60.6 $\pm$ 11.8 years. Breast cancer (BC) was the most common diagnosis (n = 84; 91%), while gastric cancer (GC) accounted for 8 cases (9%). 17 (33.3%) pts in the intervention group and 16 (39%) pts in the control group had a history of congestive heart failure. AC (doxorubicin/cyclophosphamide) regimen was administered in 54 BC patients, AC followed by T in 30 BC pts, T – in 8 GC pts. The intervention group (n = 51) received primary CPT with perindopril and bisoprolol; trimetazidine was added in patients at very high cardiovascular risk or with established coronary artery disease. The control group (n = 41) did not receive CPT due to intolerance or refusal. Echocardiography with left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS), 24-hour blood pressure monitoring, and multibiomarker assessment (troponin I, NT-proBNP, MPO, sST2) were performed at baseline and at 1, 3, 6, 9, and 12 months. **Results:** The control group showed a significant increase in indexed left atrial volume and indexed left ventricular end-diastolic volume at 6 and 9 months, respectively, indicating cardiac remodeling, which represents one of the earliest manifestations of subclinical cardiotoxicity. GLS reduction $\geq$18% occurred in 21.2% of control pts vs. 7.1% in the intervention group ($p < 0.05$). Clinically significant cardiotoxicity with LVEF decline developed in 6 control pts vs. 1 in the intervention group. Cardiovascular complications were 2.5 times more frequent in the control group (70.1% vs. 24.8%). All-cause mortality at 12 months was significantly higher in the control group (11.7% vs. 5.1%, p = 0.04). **Conclusions:** In high-risk pts with BC and GC receiving anthracycline- and trastuzumab-containing therapy, primary CPT with perindopril, bisoprolol, and trimetazidine effectively prevents adverse cardiac remodeling, preserves myocardial systolic function, reduces the incidence of cardiovascular complications, and is associated with a significant reduction in one-year all-cause mortality. Research Sponsor: None.

12029 **Poster Session**

Lipid-lowering therapy use among cancer survivors undergoing lung cancer screening: A cross-sectional analysis. First Author: Sri Gopalsamy Ramaswamy, School of Public Health at Washington University in St. Louis, Saint Louis, MO

Background: Cardiovascular disease (CVD) causes 56% of non-cancer deaths among cancer survivors, yet lipid-lowering therapy (LLT) remains underutilized. Moreover, lung cancer screening (LCS) populations exhibit a dual high-risk profile, characterized by heavy smoking exposure and a history of cancer. We sought to examine the utilization of LLT among cancer survivors undergoing LCS and to identify disparities based on demographics, clinical factors, and social determinants of health. **Methods:** We conducted a cross-sectional study of 7,778 cancer survivors aged 50–80 years who underwent LCS through Barnes-Jewish Healthcare's LCS program between 2015 and 2023. The primary outcome measured was LLT use, specifically statins or statin substitutes, as documented in electronic health records. We assessed for associations with demographics (age, sex, race), clinical factors (prior ASCVD, cancer type), healthcare access (insurance status, rurality via Rural-Urban Commuting Area codes), and the Area Deprivation Index (ADI). The data were analyzed using multivariable logistic regression, adjusted for demographics, insurance status, smoking, indication, and provider, with results stratified by race and sex. **Results:** Overall, 65.8% of cancer survivors undergoing LCS used LLT. Compared with lung cancer, prostate (AOR = 1.35; 95% CI 1.08–1.71), hematologic (AOR = 1.35; 95% CI 1.03–1.76), and other solid cancers (AOR = 1.23; 95% CI 1.07–1.42) were associated with higher LLT use. When stratified by race, among White patients, male sex was associated with higher LLT use (AOR = 1.13; p = 0.036) and rural residence was associated with lower LLT use (AOR = 0.81; p = 0.005); these were not significant factors in Black patients. Prior ASCVD was the strongest associated factor (AOR = 2.54, $p < 0.001$), followed by age $\geq$65 years (AOR = 1.41, $p < 0.001$). Rural residence was associated with 29% lower odds of LLT use (AOR = 0.71, $p < 0.001$) even after adjusting for all other factors. Insurance status, and neighborhood deprivation were not associated with LLT use. **Conclusions:** LLT remains underused among cancer survivors at high cardiovascular risk, even during routine LCS. Rural patients were less likely to receive therapy, underscoring persistent geographic gaps in preventive care. The strong association of prior ASCVD with LLT use suggests that therapy is still primarily utilized reactively rather than preventively. Improving follow-up and care coordination during screening could help close prevention gaps and reduce heart disease deaths in cancer survivors. Research Sponsor: National Cancer Institute; Alvin J. Siteman Cancer Center at Washington University School of Medicine.

12030 **Poster Session**

Predicting fluoropyrimidine cardiotoxicity using a focus beyond routine cardiovascular risk assessment. First Author: Aminat Maaz Yusupova, Moscow Cardio-Oncology Center of S.S.Yudin City Clinical Hospital, Moscow, Russian Federation

Background: Fluoropyrimidines remain backbone of systemic therapy for colorectal cancer (CRC) but are associated with diverse cardiovascular (CV) toxicities ranging from hypertension to heart failure. Current CV risk stratification tools have uncertain predictive value in cancer populations. We aimed to identify clinically actionable predictors of CV complications during fluoropyrimidine-based therapy. **Methods:** Prospective single-center observational registry included 171 consecutive stage I-IV CRC patients initiating fluoropyrimidine-based chemotherapy between (median follow-up 6.5 months, IQR 3.0-8.0). All patients underwent structured baseline cardio-oncology assessment including CV risk stratification per ESC guidelines, 12-lead ECG, transthoracic echocardiography with global longitudinal strain measurement, and serum biomarkers (NT-proBNP, high-sensitivity troponin I). Primary endpoint was incidence of $\geq$1 prespecified CV complication. Missing data ($<$ 5% for laboratory parameters) were addressed via complete-case analysis. Statistical analysis included χ^2 tests, Mann-Whitney U tests, and multivariable logistic regression with backward elimination (SPSS v28.0, significance $p < 0.05$). **Results:** Overall CV complication incidence was 33%. Event spectrum: Blood pressure destabilization (9%), thromboembolism (pulmonary embolism 5%, deep vein thrombosis 3%), arrhythmias 4,3%, coronary ischemia (angina 2.3%), ischemic stroke 0.6%, left ventricular systolic dysfunction (asymptomatic EF decline 1.8%, symptomatic heart failure 0.6%), moderate hydropericardium (2.3%), and isolated biomarker elevation (2.3%). Univariate analysis identified significant associations with CV complications for: diabetes mellitus (DM) (26.8% vs 10.4%, p = 0.006, OR 3.2), obesity (41.1% vs 26.1%, p = 0.047, OR 2.0), age (median 66.3 vs 63.1 years, p = 0.041), and high/very-high baseline CV risk (37.5% vs 14.3%, p = 0.009, OR 3.6). In multivariable analysis adjusting for age, sex, obesity, hypertension, and baseline CV risk category, only DM retained independent predictive value (adjusted OR 3.14, 95% CI 1.35-7.28, p = 0.008). Baseline NT-proBNP elevation correlated with increased all-cause mortality (58.3% vs 22.0%, p = 0.010) despite absence of CV deaths (all 12 deaths from cancer progression). **Conclusions:** Diabetes mellitus is the strongest independent predictor of CV toxicity in CRC patients receiving fluoropyrimidine chemotherapy, associated with 3-fold increased risk. While baseline CV risk stratification showed univariate association, it lost significance in adjusted analysis, highlighting DM's primacy. Systematic cardio-oncology monitoring appears effective given zero CV mortality. These data support prioritizing diabetic patients for intensified CV surveillance during fluoropyrimidine therapy. Research Sponsor: None.

12031 **Poster Session**

Cost-effectiveness of post-discharge home care for reducing potentially avoidable readmissions in stage IV cancer. First Author: Amal AlJuhani, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

Background: Approximately 39% of hospital readmissions among stage IV cancer patients are potentially avoidable. These readmissions increase healthcare costs, reduce quality of life, and increase mortality. Home-based care may reduce avoidable readmissions through symptom management and care coordination, but cost-effectiveness in this population remains unknown. Objective: To evaluate the cost-effectiveness of home with care versus home without care for stage IV solid tumors patients post-discharge, from an Ontario public payer perspective. **Methods:** A four-state Markov model (Care, Readmission, Discharged, Death) was developed with week-long cycles with a 180 day horizon. Weekly potentially avoidable readmission rates were 1.8% (home with care) versus 5.4% (home without care). Utilities (0.65 vs 0.55) and costs (home care $100/day; readmission $994/day) were from Canadian sources. Primary outcome was incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY). One-way, two-way, and probabilistic sensitivity analyses (1,000 simulations) were conducted. Value of information analysis quantified decision uncertainty. Costs and QALYs were discounted at 1.5% annually. **Results:** Home with care produced 0.166 QALYs at $12,251 versus 0.105 QALYs at $7,386, yielding 0.061 incremental QALYs (22 quality-adjusted days) at $4,865 incremental cost (ICER: $79,955/QALY). Home care cost was the most influential cost parameter with a threshold of $115/day. Probabilistic analysis showed 60% probability of cost-effectiveness at willingness-to-pay (WTP) $100,000/QALY, with acceptability curves crossing at $80,000/QALY. Expected value of perfect information peaked at $1,500/patient. **Conclusions:** Home with care may represent a cost-effective option for stage IV cancer patients at or below the commonly accepted Canadian WTP threshold of $100,000/QALY, with robust findings across sensitivity analyses. Program costs are the primary value determinant, supporting policy consideration for post-discharge support services. Research Sponsor: None.

Cost-effectiveness results: Home with care versus home without care.

Outcome	Home with Care	Home without Care	Difference
Total cost	$12,251	$7,386	+$4,865
Total QALYs	0.166	0.105	+0.061
Quality-adjusted days	60.6	38.3	+22.3
ICER	–	–	$79,955/QALY
Probability cost-effective at WTP $100,000/QALY	60%	40%	–

QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; WTP = willingness-to-pay. Costs in 2024 Canadian dollars.

12032 Poster Session

County-level palliative care physician density and socioeconomic determinants of place of cancer death in the United States, 2021-2023. First Author: Ruoxi Teng, Department of Biostatistics, Yale University, New Haven, CT

Background: Palliative care, a specialized approach focused on care for individuals with serious illness including cancer, has been shown to improve end-of-life outcomes, including higher rates of death in preferred settings. However, access to palliative care remains inequitable due to significant geographic disparities in workforce distribution. This study examines the association between county-level palliative care physician density and place of death among US decedents died from cancer. **Methods:** We conducted a retrospective cohort study using CDC WONDER multiple cause of death data (2021-2023) linked with palliative care physician supply data from the American Medical Association (AMA) Physician Masterfile. The primary exposure was county-level palliative care physician density, categorized as zero, below-median, or above-median (among non-zero counties). The primary outcome was the county-level percentage of cancer deaths (ICD: C00-C97) occurring in non-hospital settings (home, hospice, long-term care, or nursing home). Covariates include county sociodemographic characteristics (race/ethnicity, median income, region, metropolitan status) and hospice facility availability. Multivariable regression models estimated associations between physician density and place of death, adjusting for other covariates. All models incorporated county population weighting and state-level clustering. **Results:** Most U.S. counties (n = 2056, 66.27%) had no palliative care physicians in 2020. Counties with palliative care physicians showed higher median household incomes, more hospice facilities and metropolitan status, and were concentrated in the Northeast and West (all $p < 0.001$). The average percentage of non-hospital facility deaths across all counties was 56.6% (SD = 7.1) for all causes, 60.5% (SD = 8.1) for heart disease, and 70.7% (SD = 8.0) for malignant neoplasms. Multivariable regression models revealed a dose-response relationship: counties with non-zero below median and above-median palliative care physician density showed 0.9 percentage points (ppts, $p < 0.05$) and 1.1 ppts ($p < 0.05$) higher proportions of cancer death at non-hospital facility-based facilities than counties without palliative care physicians. In addition, Metropolitan and Micropolitan counties had 2.5 ppts ($p < 0.001$) and 2.1 ppts ($p < 0.001$) higher proportions of cancer death at non-hospital facility-based facilities than non-metropolitan counties respectively. **Conclusions:** Higher county-level palliative care physician density is associated with increased non-hospital facility-based deaths for cancer, demonstrating a clear dose-response relationship. These findings suggest that ensuring access to palliative care, through workforce expansion or care delivery model innovation may facilitate end-of-life care planning aligned with patient preferences. Research Sponsor: None.

12033 Poster Session

Palliative care involvement at the end of life in advanced cancer. First Author: Rhea Sehgal, School of Medicine, Wayne State University, Detroit

Background: High-intensity end-of-life (EoL) care in advanced cancer is common, costly, and often misaligned with patient goals, despite limited survival benefits. Value-based oncology emphasizes high-quality, goal-concordant care while reducing non-beneficial interventions. Palliative care is central to this model, yet its impact on overall spending versus patterns of care intensity near death remains unclear. We evaluated whether palliative care involvement in the final 30 days of life was associated with differences in total expenditures and healthcare resource allocation in patients with advanced cancer. **Methods:** We conducted a retrospective cohort study of adults with advanced cancer who died within an integrated health system between 2022 and 2025. Palliative care exposure was defined as $\geq$1 palliative encounter within 30 days of death. Financial data were obtained from enterprise cost-accounting systems; clinical and utilization data were derived from the electronic health record and institutional cancer registry. Outcomes included total 30-day healthcare charges and proportional spending across major service categories reflecting care intensity. Median charges were compared using Wilcoxon rank-sum tests, and spending distributions were analyzed via chi-square tests. **Results:** Among 1,635 decedents, 195 received palliative care within 30 days of death, a period associated with the highest concentration of EoL healthcare use. Median total 30-day charges did not differ significantly between patients who received palliative care and those who did not ($14,610 vs $17,100; p = 0.054). However, palliative care involvement was associated with a significant shift in spending patterns. Compared with patients without palliative care, those receiving palliative care had a lower proportion of spending on inpatient, procedural, diagnostic, and therapeutic services and a higher proportion on pharmacy, invasive therapeutic, home health, and hospice services. Overall spending distribution differed significantly between groups (p = 0.046). Across the cohort, inpatient and observation services accounted for the largest share of expenditures, followed by pharmacy, procedural, and invasive therapeutic services, with hospice representing a minority of total spending. **Conclusions:** EoL palliative care involvement was not associated with significant reductions in total healthcare spending but was linked to differences in care intensity, reflected by a redistribution of expenditures from inpatient and procedural services to pharmacy, invasive therapeutic, and home health care. The value of palliative care in oncology lies not in cost savings but in promoting high-quality EoL care that aligns with patient goals and oncology care priorities. Future analyses will include patient-reported outcomes to examine how shifts in care intensity and spending relate to EoL symptom burden, quality of life, and goal-concordant care. Research Sponsor: None.

12034 Poster Session

End-of-life anti-cancer treatment (Rx) patterns in patients (pts) with the six most common cancers in the USA. First Author: Umang Swami, Department of Medicine, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: Pts with $\leq$ 6 months of life expectancy qualify for hospice. However, most pts with advanced/metastatic (a/m) cancer continue to receive Rx up to weeks prior to death. Data describing end-of-life Rx patterns in these pts remain limited but are essential to improve clinical care delivery. Herein, we evaluated real-world Rx patterns in relation to the time of death across 6 most common a/m solid tumors: advanced non-small cell lung cancer (aNSCLC), metastatic breast cancer (mBC), metastatic prostate cancer (mPC), advanced colorectal cancer (aCRC), metastatic pancreatic cancer (mPanC), and advanced urothelial carcinoma (aUC). **Methods:** This study used the US-based, electronic health record-derived deidentified Flatiron Health Research Database. Eligibility: diagnosis of aNSCLC, mBC, mPC, aCRC, mPanC and aUC, had a recorded date of death, and information on initiation of first-line (1L) Rx. The data cutoff date was 6/30/2025. Pts were categorized as treatment-free if no systemic Rx was administered within the final 1 or 3 months of life, or on-treatment if systemic Rx was received within 1 or 3 months before death. Demographic and clinical variables at the last line of Rx initiation, including age, race, socioeconomic status, practice type, and insurance, were summarized using medians (IQR) or proportions. **Results:** Of 111,337 pts with aNSCLC, 82,339 had a recorded date of death, of whom 59,777 initiated 1L Rx. Of 43,218 pts with mBC, 26,572 had a recorded date of death, of whom 23,055 initiated 1L Rx. Of 27,979 pts with mPC, 14,793 had a recorded date of death, of whom 9,667 initiated 1L Rx. Of 45,013 pts with aCRC, 29,749 had a recorded date of death, of whom 24,219 initiated 1L Rx. Of 18,942 pts with mPanC, 15,690 had a recorded date of death, of whom 11,528 initiated 1L Rx. Of 15,236 pts with aUC, 10,872 had a recorded date of death, of whom 7,815 initiated 1L Rx. The proportion of pts receiving systemic Rx within 1 month or 3 months before death for each cancer type is summarized in Table. Baseline characteristics, Rx patterns and trends by cancer type will be presented at the meeting. **Conclusions:** Across six most common cancers in the US, systemic Rx use remained common near the end of life, with up to one-third of pts treated in the final month. These findings suggest the need for greater emphasis on early involvement of palliative care teams and timely transition of pts with terminal cancers to comfort care. Research Sponsor: None.

Proportion of pts with a/m cancer receiving systemic Rx within 1 month or 3 months before death.

Cancer type	Eligible pts	Rx within 1 month of death, n (%)	Rx within 3 months of death, n (%)
aNSCLC	59,777	19,268 (32.2)	38,227 (63.9)
mBC	23,055	8,416 (36.5)	15,972 (69.3)
mPC	9,667	2,438 (25.2)	5,762 (59.6)
aCRC	24,219	7,172 (29.6)	15,386 (63.5)
mPanC	11,528	4,191 (36.3)	9,184 (79.7)
aUC	7,815	2,358 (30.2)	5,170 (66.1)

12035 Poster Session

Temporal trends and sociodemographic disparities in place of death among adults with pancreatic cancer in the United States (1999–2023). First Author: Ali Mushtaq, Cleveland Clinic Foundation, Cleveland, OH

Background: Location of death is a critical quality metric for pancreatic cancer due to its rapid trajectory and high symptom burden. While home-based hospice is promoted, it is unclear if shifts from hospital death have been equitable. We analyzed 25-year national trends and independent predictors of place of death. **Methods:** We analyzed CDC WONDER death certificate data (1999–2023) for pancreatic cancer decedents aged $\geq$20 years (ICD-10 C25.x). Place of death categories: Home, Hospice/Nursing Facility, Inpatient, or Outpatient/ER. We calculated annual trends and used multinomial logistic regression to estimate adjusted odds ratios (aOR) with 95% confidence intervals (CI), adjusting for age, sex, race/ethnicity, urbanization, and year. Inpatient death served as the reference category. **Results:** Of 899,332 deaths, acute care hospital deaths declined (34.0% to 21.0%) while home (48.6% to 56.1%) and hospice/nursing facility deaths (15.7% to 21.3%) increased. However, significant disparities persisted. Compared to Non-Hispanic Whites, Black patients were less likely to die at home (aOR 0.55; 95% CI, 0.54–0.56) or in hospice/nursing facilities (aOR 0.63; 95% CI, 0.62–0.65) and significantly more likely to die in Outpatient/ER settings (aOR 1.57; 95% CI, 1.51–1.64). Hispanics were less likely to die in hospice/nursing facilities (aOR 0.57; 95% CI, 0.55–0.58). Rural residents had lower odds of hospice/nursing facility death (aOR 0.89; 95% CI, 0.87–0.91) vs. large metro. Younger age (20–64) was associated with hospital death. **Conclusions:** Despite substantial shifts from hospital to home settings, Black and Hispanic patients remain significantly less likely to access hospice and more likely to die in emergency settings. These findings highlight structural inequities requiring targeted interventions to ensure high-quality end-of-life care for minority populations. Research Sponsor: None.

Multivariable adjusted odds ratios (aOR) for place of death in pancreatic cancer.

Predictor Comparison	Decedent's Home (aOR)	Hospice/Nursing Facility (aOR)	Outpatient or ER (aOR)
Black vs. White	0.55 (0.54–0.56)	0.63 (0.62–0.65)	1.57 (1.51–1.64)
Asian vs. White	0.74 (0.72–0.76)	0.51 (0.49–0.53)	0.85 (0.77–0.95)
Hispanic vs. Non-Hispanic	0.92 (0.90–0.94)	0.57 (0.55–0.58)	1.01 (0.94–1.08)
Rural vs. Large Metro	1.08 (1.06–1.10)	0.89 (0.87–0.91)	0.92 (0.88–0.97)
Male vs. Female	0.90 (0.89–0.91)	0.78 (0.77–0.79)	1.09 (1.05–1.13)
Age 85+ vs. 20–64	1.79 (1.75–1.82)	3.69 (3.61–3.76)	0.66 (0.62–0.71)
Age 75–84 vs. 20–64	1.39 (1.37–1.41)	1.91 (1.88–1.94)	0.81 (0.78–0.85)
Age 65–74 vs. 20–64	1.18 (1.17–1.20)	1.33 (1.31–1.36)	0.89 (0.85–0.92)

Abbreviations: aOR, adjusted Odds Ratio; CI, Confidence Interval; ER, Emergency Room; Ref, Reference Group.

12036 **Poster Session**

Impact of social vulnerability on end-of-life care in hematologic malignancies. First Author: Jude O. Ossai, Rutgers/Newark Beth Israel Medical Center, Newark, NJ

Background: Patients with hematologic malignancies frequently receive intensive inpatient care near theend of life. While disparities in end-of-life (EOL) care are well described in oncology, how cumulative social vulnerability shapes treatment intensity and palliative care involvementamong hospitalized patients with hematologic cancers remains unclear. We examined the association between social vulnerability burden and inpatient EOL care patterns using a nationally representative database. **Methods:** We performed a retrospective cohort study using the 2021–2022 National Inpatient Sample of adult hospitalizations with hematologic malignancies. A composite hematologic social vulnerability index (cSVI-Heme) was constructed using validated proxies available in NIS: minoritized race/ethnicity, Medicaid or uninsured status, and lowest ZIP-code income quartile. Hospitalizations were classified as low (0), moderate (1), or high ($\geq$2) vulnerability.The primary outcome was high-intensity EOL care (invasive mechanical ventilation, cardiopulmonary resuscitation, or acute dialysis). Secondary outcomes included palliative care utilization and in-hospital mortality. Associations were assessed using multivariable logistic regression and inverse probability of treatment weighting, adjusting for demographics, comorbidity burden, acute organ failure, sepsis, malignancy subtype, and hospital characteristics. **Results:** The cohort included 202,802 hospitalizations, of which 54.2% were low, 31.0% moderate, and 14.8% high vulnerability. Overall, 5.9% involved high-intensity EOL care, increasing stepwise across vulnerability tiers (5.1% vs 6.5% vs 7.9%; $p < 0.001$). After adjustment, compared with low vulnerability hospitalizations, moderate vulnerability was associated with higher odds of high-intensity EOL care (aOR 1.25, 95% CI 1.19–1.30), and high vulnerability with substantially higher odds (aOR 1.50, 95% CI 1.42–1.58), demonstrating a clear dose–response relationship. Findings were confirmed in propensity-weighted analyses.This gradient was driven primarily by acute dialysis (3.1% vs 4.6% vs 6.2%; $p < 0.001$), while rates of mechanical ventilation and CPR were similar. High vulnerability was independently associated with higher in-hospital mortality (aOR 1.20, 95% CI 1.12–1.28), whereaspalliative care utilization did not increase after adjustment. **Conclusions:** Among hospitalized patients with hematologic malignancies, greater social vulnerability is associated with higher-intensity end-of-life care and increased mortality, with a clear dose–response relationship. These differences are not accompanied by greater palliative care involvement, highlighting a mismatch between treatment intensity and supportive care. Integrating social vulnerability into inpatient hematologic oncology care may support earlier goals-of-care discussions and more equitable EOL care. Research Sponsor: None.

12038 **Poster Session**

Effects of tai chi qigong on gene expression profiles in older male cancer survivors with fatigue. First Author: Anita Kinney, Department of Biostatistics and Epidemiology, Rutgers School of Public Health, Piscataway, NJ

Background: The HERO trial showed that Tai Chi Qigong (TCQ) reduced fatigue (primary endpoint) in male cancer survivors. Fatigue-related biological pathways influenced by mind-body therapies, such as TCQ, remain poorly defined. This trial hypothesized that TCQ, compared to an exercise-intensity matched (EIM) intervention and usual care (UC), would have a more favorable effect on the regulation of two major fatigue-associated functional gene clusters: a) inflammation-vasodilation-metabolite sensing and b) energy and adrenergic activation among older male cancer survivors with fatigue. **Methods:** In this three-arm randomized trial (NCT 03345563), 113 male cancer survivors aged $\geq$ 55 years with fatigue were randomized to 12 weeks of TCQ (n = 45), EIM (n = 43), or UC (n = 25), delivered twice weekly with recommended home practice. Gene expression profiles were assessed at baseline and at 1 week and 3 months post-intervention using genome-wide transcriptional profiling of blood samples. A key secondary endpoint was changes in gene expression at the 3-month follow-up. A minimum of 8 subjects per study arm is required to achieve 80% power (two-sided alpha = 0.05) to detect a 2.0-fold change in gene expression. Intervention effects were evaluated using an intention-to-treat approach and general mixed linear models, with baseline adjustment and time of sample collection included as time-varying covariates. Multiple comparisons were controlled for using the false discovery rate (FDR). Upregulation of DBI, IL-10, ADRB2, VIPR2, OXTR, ASIC3, P2RX4, P2RX7, ATP5E, NDUFS5 genes and downregulation of TNF, NR3C1, P2RY1, HSPA2 genes were deemed as favorable effects. Mean difference (MD), 95% CI, and FDR corrected p-values were reported. **Results:** TCQ favorably regulated the expression of genes associated with inflammation (TNF: MD = -1.25; CI: -1.97 – -0.53; p = 0.001 and IL-10: MD = 0.51; CI: 0.02 – 1.00; p = 0.043), metabolite-sensing (P2RX4: MD = 0.45; CI: 0.04 – 0.85; p = 0.032), and energy activation (P2RY1: MD = -0.43; CI: -0.95 – -0.08; p = 0.037, ATP5E: MD = 0.15; CI: 0.05 – 0.30; p = 0.035, and NDUFS5: MD = 0.14; CI: 0.02 – 0.28; p = 0.042) at 3 months post-intervention. EIM favorably regulated genes associated with vasodilation (OXTR: MD = 0.89; CI: 0.36 – 1.42; p = 0.001) and inflammation (NR3C1: MD = -0.24; CI: -0.47 – -0.01; p = 0.043). Compared with EIM, TCQ produced greater increases in ADRB2, an adrenergic activator (MD:0.81; CI: 0.26 – 1.35; p = 0.003) and P2RX4 (MD:0.56; CI: 0.12 – 1.01; p = 0.013) and favorably decreased the expression of P2RY1 (MD:-0.93; CI: -1.51 – -0.35; p = 0.002). **Conclusions:** TCQ produced meaningful changes in inflammatory, adrenergic, energy, and metabolic pathways, supporting potential biological mechanisms through which TCQ may reduce fatigue in older male cancer survivors. Larger trials with a broader representation of participants are needed to confirm these pathway-level effects. Clinical trial information: NCT03345563. Research Sponsor: National Cancer Institute; R01CA203939.

12039 **Poster Session**

Digital prehabilitation and functional performance signals in older adults undergoing hepatobiliary cancer surgery: A pilot study. First Author: Mohammed Al-Jumayli, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Older adults undergoing hepatobiliary cancer surgery often have limited functional reserve and face barriers to accessing structured preoperative conditioning. Technology-enabled, home-based prehabilitation may offer a scalable approach to support surgical readiness while generating early signals of functional change. **Methods:** Adults aged $\geq$65 years scheduled for hepatobiliary tumor resection with $\geq$4 weeks before surgery were enrolled in a multimodal, digitally supported prehabilitation program. The intervention combined wearable-monitored aerobic activity ($\geq$90 minutes/week) with twice-weekly, live video–supervised progressive resistance training delivered by certified exercise trainers. Functional performance was assessed using the 30-second chair stand and arm curl tests, and health status was measured with the SF-12 survey at baseline and preoperative follow-up. Implementation and engagement metrics were captured to contextualize delivery in a geographically dispersed population. Analyses of functional outcomes were exploratory and intended to estimate effect sizes and inform future, adequately powered studies. **Results:** Twenty-one participants (median age 78 years; range 66–88) completed baseline and preoperative assessments over a median intervention duration of 4.5 weeks. Participants resided a median of 127 km from the cancer center, supporting remote delivery of the intervention. Improvements were observed in lower extremity function (30-second chair stand: 12.0 $\pm$ 3.2 to 13.8 $\pm$ 4.6 repetitions; p = 0.04) and upper extremity strength (30-second arm curl: 17.7 $\pm$ 5.4 to 22.2 $\pm$ 7.1 repetitions; $p < 0.001$). Patient-reported physical and mental health scores demonstrated favorable, though not statistically significant, trends. Engagement with wearable-monitored aerobic activity exceeded recommended weekly targets, and completion of tele-supervised resistance sessions remained high across the intervention period. **Conclusions:** In this pilot cohort of older adults preparing for hepatobiliary cancer surgery, a digitally supported, home-based prehabilitation model was associated with favorable short-term functional performance signals and high levels of engagement across a geographically dispersed population. These findings are hypothesis-generating and support further evaluation of tele-prehabilitation in trials powered to assess perioperative and clinical outcomes. Research Sponsor: None.

12040 **Poster Session**

Real-world feasibility and efficacy of a tailored exercise program in patients with cancer. First Author: Alice Avancini, University of Verona, Verona, Italy

Background: Exercise (EX) is associated with improved survival, symptom control, and management of treatment-related side effects in patients (pts) with cancer. However, evidence from large, real-world cohorts including unselected pts across different phases of the disease trajectory remains limited. This study aimed to evaluate the feasibility and effectiveness of a tailored EX program implemented in routine clinical practice. **Methods:** A three-month, bi-weekly supervised EX program was offered to consecutive cancer pts referred at the University Hospital of Verona, regardless of treatment status. The program included moderate-intensity aerobic exercise (10–30 minutes/session) and resistance training (2–3 sets of 8–12 repetitions; six exercises). The primary endpoint was feasibility, assessed by recruitment rate, adherence, and dropout. Secondary endpoints included cardiorespiratory fitness (six-minute walking test, 6MWT), muscular strength (handgrip strength test, HST), waist-hip ratio (WHR), and quality of life (QoL), measured using the EORTC QLQ-C30. Pre- and post-intervention outcomes were analyzed using descriptive statistics and paired Student's t-tests. **Results:** A total of 2276pts were recruited (92% recruitment rate) with a median age of 57$\pm$12 years. The most frequent tumor types were upper gastrointestinal cancers (34%) and breast cancer (31,8%). 84% of patients were receiving systemic treatments, and 47% had metastatic disease. Overall, 156 pts completed the intervention (dropout rate 31%, mainly due to disease progression), with an adherence rate of 84%. Significant improvements were observed in WHR ($-$1.2%, p = 0.03), 6MWT (+25 m, $p < 0.001$), and HST (+1.9 kg, $p < 0.01$). QoL significantly improved in physical, role, emotional, and social functioning (all $p < 0.01$), along with reductions in fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, and diarrhea. Global QoL and financial difficulties also significantly improved. **Conclusions:** In a real-world, unselected cohort of cancer pts across different treatment phases, a tailored EX program is feasible and associated with meaningful improvements in physical function and QoL. These findings support the integration of structured exercise programs into routine oncology care beyond controlled clinical trial settings. Clinical trial information: NCT04226508. Research Sponsor: None.

12041 **Poster Session**

Dyadic exercise intervention for LGBTQ+ cancer survivors: Associations with health-related quality of life, fatigue, and inflammation biomarkers. First Author: Hala Awad, University of Rochester Medical Center, Rochester, NY

Background: Mixed training (aerobic/resistance) exercise is a key adjuvant therapy in exercise oncology; it decreases cancer mortality and improves patients' quality of life, in part by modulating the tumor microenvironment, regulating the HPA axis, and inflammatory pathways. LGBTQ cancer survivors and their partners frequently experience excessive fatigue, insomnia, impaired health-related quality of life (HRQOL), and relationship stress, yet remain underrepresented in exercise oncology research. **Methods:** We conducted an RCT with 70 LGBTQ+ cancer survivor-partner dyads (N = 140) to compare a 6-week home-based dyadic exercise program (EXCAP-PA) against a survivor-only intervention. Analyses focused on changes from baseline to post-intervention. Primary outcomes included the Survivor Profile of Mood States (POMS) Fatigue and PROMIS global health change to assess HRQOL. ANCOVA-style linear models regressed change scores on treatment arm and baseline values. Mediation analyses assessed whether changes in dyadic support, cortisol, and C-reactive protein (CRP) mediated the effect of treatment on fatigue and HRQOL. **Results:** Among 56 survivor–partner dyads with analyzable data, delivery of EXCAP-PA was feasible in this LGBTQ+ population. Both survivors and partners in each arm demonstrated improved HRQOL; however, the treatment arm did not significantly predict changes in PROMIS global health for survivors (survivors: B = 0.10, SE = 0.39, p = 0.80; partners: B = 0.03, SE = 0.41, p = 0.94). Baseline symptom burden strongly influenced outcomes: higher baseline fatigue was associated with greater reductions in POMS Fatigue–Inertia (B = −0.55, SE = 0.15, $p < 0.001$), indicating that participants with the highest fatigue experienced the largest improvements. In the CRP model ($n \approx 44$), higher baseline CRP was significantly associated with greater subsequent decreases in log-transformed CRP (B = −0.37, SE = 0.17, p = 0.04). The model relating fatigue change to baseline fatigue, baseline CRP, and CRP change explained a substantial proportion of variance ($R^2 = 0.29$; $F(3,40) = 5.42$, p = 0.003), whereas baseline cortisol was not significantly related to fatigue change. Although mediation analyses using changes in dyadic support, log-transformed CRP, or log-transformed cortisol as mediators of treatment arm effects on fatigue or HRQOL yielded small, non-significant indirect effects, the outcomes are consistent with a beneficial effect in which dyadic processes and reduced inflammation improve symptoms and HRQOL. **Conclusions:** Dyadic EXCAP-PA proved feasible for LGBTQ+ survivor–partner dyads. Although this pilot is underpowered to detect significant effects on global health, fatigue, or inflammation, the findings highlight high-symptom/high-CRP survivors as a priority subgroup for future, larger dyadic exercise trials. Research Sponsor: National Cancer Institute; NCI K07 CA190529.

12042 **Poster Session**

Circulating heat shock protein 90 alpha (Hsp90α) as a biomarker for cancer cachexia. First Author: Syed Hasan Raza Jafri, University of Texas, Houston, TX

Background: Cancer cachexia is defined clinically by a consensus definition of ≥5% unintentional weight loss in cancer patients over previous 6 months. There is a need to develop blood-based biomarkers for more accurately identifying patients with cancer cachexia. Tumor-cell derived Hsp90α has been shown to be a key driver for muscle wasting and systemic inflammation in pre-clinical models of cancer cachexia. **Methods:** We conducted a prospective case control study between April 2020 and February 2025 to identify biomarkers of cancer cachexia. Cases were newly diagnosed patients with stage III/IV cancers with ≥5% unintentional weight loss and serum albumin of < 3.5g/dl (Cachexia group). Controls were newly diagnosed patients with stage I-III cancers without weight loss and serum albumin of ≥3.5g/dl (non- cachexia group). We collected 5ml of blood at first visit and analyzed plasma Hsp90α levels using Enzyme linked immunosorbent assay (ELISA). We performed univariable comparisons of geometric means of Hsp90α between the groups using two sample t-test . To evaluate the classification performance of Hsp90α for identifying cancer cachexia, we used receiver operating characteristic (ROC) analysis with area under the curve (AUC). **Results:** A total of 200 patients were consented and 171 were included in final analysis. There were 110 cases and 61 controls. Mean age of cases was 68 years and of controls 62 years (p=0.003). 64% of cases were males as opposed to 30% in controls ($p < 0.001$). There was no significant difference in race between the groups. Cancer types included lung, gastro-intestinal, breast and other cancers in both cases and controls. Mean plasma Hsp90α at diagnosis was significantly higher in cases 40.60 ng/mL than in controls 32.47 ng/mL ($p < 0.001$). On up to one year follow up (6 visits total) the mean Hsp90α remained significantly elevated in cases as compared to controls ($p < 0.001$). Mean Hsp90α levels among cases was highest in patients with GI cancers (49.98 ng/mL) followed by Lung cancer (40.67 ng/mL) and other cancer types (27.92 ng/mL), $p < 0.001$. Based on ROC analysis, Hsp90α level of ≥35 ng/mL has AUC of 94% for differentiating cancer patient with cachexia from those without cachexia. When stratified by sex, Hsp90α ≥35 ng/mL remained significantly higher in cases than in controls for both men and women ($p < 0.001$). **Conclusions:** Hsp90α is a blood-based biomarker that is significantly elevated in cancer patients with cachexia as opposed to those without cachexia. Plasma Hsp90α ≥35 ng/mL accurately identifies cancer patients with cachexia and represents a promising biomarker for cancer cachexia both in clinical care and research. Research Sponsor: U.S. National Institutes of Health; National Center for Advancing Translational Sciences (NCATS); Biostatistics/ Epidemiology/ Research Design (BERD) component of the Center for Clinical and Translational Sciences (CCTSawarded to the University of Texas Health Science Center at Houston, Texas.

Distribution of Hsp90α amongst case-control based on optimal cutoff (≥35 ng/mL).

Variable	Study group	Cutoff category	Number of patients
Hsp90	Case	< 35	20
Hsp90	Case	≥ 35	90
Hsp90	Control	< 35	61
Hsp90	Control	≥ 35	0

12043 **Poster Session**

Tele-nutritional collaborative care in patients with stage IV gastrointestinal cancer receiving chemotherapy: A randomized clinical trial. First Author: Shihong Xu, Department of Biotherapy, Cancer Center, West China Hospital, Chengdu, China

Background: Cancer cachexia is characterized by systemic inflammation and progressive muscle loss, fundamentally compromising quality of life (QOL) and overall survival. While early nutritional intervention is imperative, patients in resource-constrained regions like Western China often lack timely access. We conducted the tele-nutrition collaborative care (T-NICE) trail to evaluate the efficacy of a hybrid remote care delivery model for patients with stage IV gastrointestinal cancer undergoing chemotherapy. **Methods:** This randomized clinical trial was conducted at West China Hospital. Patients with histologically confirmed stage IV gastrointestinal cancer (esophageal, gastric, or colorectal) were randomly assigned (1:1) to the T-NICE intervention versus Standard Nutrition Care (SNC). The T-NICE group received a collaborative hybrid telecare model involving a lean team (dietitian and social worker), comprising an initial in person education followed by app-based monitoring and adaptive telephone counseling. Primary Endpoint: The incidence of cancer cachexia (defined as involuntary weight loss >5%, or >2% if BMI <20 kg/m²) over 6 months. Secondary Endpoints: Longitudinal changes in nutritional status (PG-SGA, NRS 2002) and body weight. Exploratory end points included the QOL (using the EORTC QLQ-C30), psychology characteristics (using DT, PHQ-9 and HADS) and caregiver burden (using ZBI). Assessments were conducted at monthly intervals through the six months endpoint. **Results:** A total of 160 patients were enrolled (80 to T-NICE, 80 to SNC). Cachexia incidence was significantly lower in T-NICE vs. SNC (22.4% VS. 60.8%; adjusted odds ratio [aOR], 0.18; 95%CI, 0.09-0.37; $P < .001$). After six months, weight stabilized in T-NICE group compared to loss in SNC (mean change, +0.86kg [95% CI, -0.20-1.93] VS −3.61 kg [95% CI, -4.70 to -2.52]), resulting in a mean difference of -4.56 kg (95% CI, -5.73 to -3.39; $P < .001$). The T-NICE group also had lower PG-SGA scores (5.10 [95%CI, 4.14-6.06] VS 6.50 [95%CI, 5.54-7.46]; $P = .015$). T-NICE participants had higher EORTC QLQ-C30 Global Health scores (74.42 vs. 66.67; $P = .004$) and improved various functional status. Psychological benefits and reduced caregiver burden were also observed. **Conclusions:** The T-NICE trial demonstrated that an integrated tele-nutrition model significantly reduced cachexia incidence, improved QOL, nutritional status, psychology status and alleviated caregiver burden. Key strengths included the model's scalability and low staffing requirements, maximizing resource efficiency while delivering substantial clinical benefits. Clinical trial information: NCT06332664. Research Sponsor: None.

12044 **Poster Session**

A mediation analysis of neurocognitive deficits and patient-reported mood among patients with lung cancer with brain metastases. First Author: Mary Catherine Boulanger, Massachusetts General Hospital, Boston, MA

Background: Advances in lung cancer therapeutics have led to a growing population of patients with lung cancer who are facing the challenges of living with the sequela of brain metastases and the therapies used to treat them. Patients experience neurocognitive deficits, difficulties with functioning, and mood symptoms. However, the mechanisms by which neurocognitive deficits contribute to mood symptoms in this patient population remain to be fully elucidated. In this study, we aimed to evaluate patient-reported functioning as a mediator between neurocognitive deficits and mood symptoms. **Methods:** Using a prospectively collected single-site registry, we conducted an exploratory cross-sectional study among patients with lung cancer with brain metastases at the time of evaluation for stereotactic radiosurgery. The registry included data on patient demographic and clinical characteristics, neurocognitive deficits per clinician exam (visual impairment, cranial nerve deficit, sensory deficit, motor deficit, gait impairment/incoordination, decline in ability to concentrate, decline in memory), and patient-reported functioning (self-care, usual activities, mobility) and mood symptoms (anxiety/depression) from the European Quality of Life 5-Dimensions 3-Level Version. First, we selected functional domains significantly associated with mood symptoms in a logistic regression analysis to test as potential mediators. Then, we used a regression-based path analysis to test the selected functional domain as a mediator between neurocognitive deficits and mood symptoms. The mediation model adjusted for age, performance status, tobacco use, extracranial disease status, prior brain surgery, and prior brain radiation. **Results:** Of 463 patients, 33.9% demonstrated any neurocognitive deficit, 38.7% self-reported any functional difficulty (self-care, usual activities, or mobility), and 15.3% reported mood symptoms. Difficulty with usual activities was associated with increased mood symptoms (OR=1.65, 95% CI=1.36, 1.97), which we then tested as a mediator. Motor deficits (OR=1.66, 95% CI=1.30, 2.38) and gait impairment/incoordination (OR=1.50, 95% CI=1.19, 2.09) had positive indirect effects on mood symptoms (i.e. increased mood symptoms) through difficulties with usual activities. No other neurocognitive deficits showed significant effects on mood symptoms. **Conclusions:** Among patients with lung cancer with brain metastases, the associations of motor deficits and gait impairment/incoordination with worsened mood are mediated by difficulties with engaging in usual activities. These findings underscore the potential for tailored supportive care, utilizing strategies from cognitive rehabilitation, palliative care and psychology, to improve patients' mood by helping them adapt to and cope with difficulties in engaging in their usual activities. Research Sponsor: None.

12045 **Poster Session**

ASTRON (OGSG 2401): A multicenter prospective trial of ferric carboxymaltose without erythropoiesis-stimulating agents for iron deficiency anemia in patients with gastric/colorectal cancer receiving chemotherapy. First Author: Ryohei Kawabata, Sakai City Medical Center/Osaka Cancer Institute Center, Osaka, Japan

Background: Iron deficiency anemia (IDA) during chemotherapy for patients with gastrointestinal cancer worsens quality of life (QoL) and may compromise treatment continuity. Ferric carboxymaltose (FCM) enables high-dose intravenous iron supplementation; however, prospective data without concomitant erythropoiesis-stimulating agents (ESAs) remain limited. We conducted a multicenter prospective trial to evaluate intravenous FCM without concomitant ESAs or red blood cell (RBC) transfusion support. **Methods:** This was a multicenter prospective single-arm study. Key eligibility criteria included unresectable or recurrent gastric or colorectal cancer, ongoing chemotherapy, hemoglobin (Hb) $<$10.0 g/dL, and transferrin saturation (TSAT) $<$20%. FCM was administered as three 500 mg doses at $\geq$7-day intervals (total 1500 mg), with all doses completed within 29 days of the first infusion (Day 1). The primary endpoint was Hb improvement rate at week 8, defined as an Hb increase $\geq$1.0 g/dL from baseline without RBC transfusion. The improvement rate was tested against a threshold of 18% using a one-sided exact binomial test (α=0.05). QoL (FACT-An and EQ-5D-5L) was analyzed using linear mixed-effects models. **Results:** Fifty-two patients were enrolled; 51 received FCM. Median age was 72 years (range 45–90). Primary tumors were gastric (71.2%) and colorectal (28.8%); ECOG PS 0/1/2 was 50.0%/46.2%/3.8%. Disease status was unresectable in 55.8% and postoperative recurrence in 44.2%. The primary tumor was present in 40.4%. Most patients (90.4%) were receiving cytotoxic chemotherapy. Baseline median Hb was 9.15 g/dL (IQR 8.50–9.50), TSAT 8.55% (IQR 5.77–12.80), and ferritin 37.6 ng/mL (IQR 17.1–179.0). The week-8 Hb improvement rate was 72.5% (37/51; 95% CI 58.3–84.1; p$<$0.001). Hb improvement rates at weeks 4 and 12 were 58.8% (30/51) and 76.5% (39/51), respectively. FACT-An total score improved at week 8 (mixed-model estimate +4.93; 95% CI 0.23–9.62; p=0.040). EQ-5D also improved at week 8 (estimate +6.72; 95% CI 0.98–12.46; p=0.022). Planned protocol treatment was completed in 49/52 patients (94.2%). No treatment-related serious adverse events or deaths were observed. **Conclusions:** FCM achieved an Hb improvement rate of 72.5% and improved QoL in patients with gastric or colorectal cancer and IDA receiving chemotherapy, with high protocol completing and no treatment-related serious adverse events. These findings support FCM as an effective and feasible option for managing IDA during chemotherapy without ESAs. Clinical trial information: jRCTs051240288. Research Sponsor: Zeria Pharmaceutical Co., Ltd.

12046 **Poster Session**

Correlation of University of Texas Cancer Cachexia Staging (UTCCS) with clinical variables of systemic inflammation, nutritional status, and physical function in patients with cancer cachexia. First Author: Harshit Khosla, University of Texas Health Science Center at Houston, Houston, TX

Background: Cancer cachexia is a heterogenous syndrome characterized by ongoing loss of skeletal mass with or without adipose tissue, that is not entirely reversible. University of Texas Cancer Cachexia Staging (UTCCS) is a recently described novel model for staging cachexia using simple clinical parameters such as body mass index (BMI), serum albumin (alb), neutrophil to lymphocyte ratio (NLR) and resting heart rate (RHR). The validity of this model to correlate with functional status, nutrition and overall survival in patients with advanced or metastatic cancer has been assessed in current study. **Methods:** In a prospective study of newly diagnosed cancer patients with stage III/IV cancers, $>$5% body weight loss and serum albumin $<$ 3.5g/dL biomarkers of cachexia were identified. UTCCS was developed using 4 clinical variables namely (BMI), (Alb), (NLR) and (RHR) using quartile as cut off. Based on these variable patients were categorized into stage I, stage II or stage III cancer cachexia. Blood biomarkers, dietary assessment and functional status were estimated. Kaplan-Meier survival curves were generated for patients in each stage. **Results:** Cancer distribution amongst 110 patients included lung cancer (n=50), GI cancers (n=42) and other cancers (n= 18). Cachexia stage distribution in patients was assessed (stage I= 45%, stage II =36% and stage III=18%). Patients with stage III cachexia had statistically significantly lower ECOG performance status (p=0.006), higher inflammatory state as measured by advanced lung cancer inflammation index (p$<$0.001), lower simplified nutritional appetite questionnaire (SNAQ score) (p=0.01), lower skeletal muscle index (p=0.03) and 30 seconds chair rise time (p$<$0.001). Median overall survival (OS) for stage I was 12.7 months, stage II 7.1 months and stage III 3.5 months (p=0.047). **Conclusions:** UTCCS system is a novel way of estimating the severity of cancer cachexia and correlates with inflammatory, dietary and functional parameters expected in patients with increasing severity of cancer cachexia. Research Sponsor: None.

12047 **Poster Session**

A retrospective cohort studying integrative palliative care in a community oncology practice: Impact and outcomes. First Author: Summiya Nasim, Parkview Hospital Randallia, Fort Wayne, IN

Background: Embedding palliative care within oncology practice supports symptom management and shared decision-making; however, its impact on real-world healthcare utilization and end-of-life planning is less well characterized. In 2018, a dedicated palliative oncology service was implemented at a Midwestern community cancer institute. We evaluated whether this integrated model was associated with differences in healthcare utilization, hospice referral, and advance care planning (ACP) compared with standard oncology care prior to implementation. **Methods:** We conducted an IRB-approved retrospective cohort study of adults with cancer treated at a single institution. Two age-, stage-, and histology-matched cohorts were identified: patients treated after implementation of the embedded palliative oncology service (2018–2021; Cohort A, n=300) and patients treated prior to implementation (2012–2017; Cohort B, n=300). Clinical data were extracted from the electronic medical record. Outcomes included emergency department (ED) visits, inpatient and ICU admissions, inpatient and ICU length of stay, hospice referral, and documented ACP. Continuous variables were compared using two-sample t-tests and categorical variables using χ^2 tests (α=0.05). Post-hoc power analyses were performed for outcomes demonstrating between-group differences. **Results:** Both cohorts were predominantly White (88% in Cohort A vs 93% in Cohort B) with a slight difference in mean age (70.8 vs 75.0 years). Cohort A included a higher proportion of patients with stage III–IV disease (74% vs 53%, p$\leq$0.05). Compared with standard oncology care, the integrated palliative oncology model was associated with a higher mean number of ED visits (4.1 vs 3.0, p$<$0.05). There were no significant differences in inpatient admissions, ICU admissions, or inpatient length of stay between groups. Hospice referral and ACP documentation occurred significantly more frequently in Cohort A (both p$<$0.05). Post-hoc analyses demonstrated adequate power ($>$80%) to detect observed differences in ED utilization, hospice referral, and ACP documentation. **Conclusions:** Implementation of an integrated palliative oncology service was associated with increased ED utilization alongside substantially higher rates of hospice referral and ACP documentation, without an accompanying increase in hospital or ICU admissions or length of stay. These findings suggest that embedded palliative oncology may promote earlier end-of-life planning while maintaining stable inpatient utilization. Prospective studies are needed to better understand drivers of ED use and to further refine integrated palliative oncology care models. Research Sponsor: None.

12048 **Poster Session**

Behavioral predictors of pain control among adult cancer survivors: Examining the impact of smoking, physical activity, and alcohol consumption. First Author: Clifford A. Atuiri, St. Luke's Hospital, Chesterfield, MO

Background: Cancer-related pain remains a prevalent and debilitating symptom among adult cancer survivors, substantially impairing quality of life. While pharmacologic therapies are central to pain management, growing evidence suggests that modifiable lifestyle behaviors may influence pain outcomes. This study examined the association between smoking status, alcohol consumption, physical activity, and pain control among adult cancer survivors in the United States. **Methods:** We conducted a cross-sectional analysis using data from the 2022 Behavioral Risk Factor Surveillance System (BRFSS), a nationally representative survey of U.S. adults. The study population included adults aged $\geq$18 years with a history of cancer who reported physical pain attributable to cancer or its treatment. The primary outcome was self-reported pain control (controlled vs uncontrolled). Primary predictors included smoking status (current, former, never), heavy alcohol consumption (men $>$14 drinks/week; women $>$7 drinks/week), and physical activity in the past 30 days outside of regular employment. Multivariable logistic regression models were used to estimate odds ratios (ORs) with adjustment for age, sex, race/ethnicity, educational attainment, and household income. Sampling weights were applied to account for the complex survey design. **Results:** A total of 1,380 cancer survivors with cancer-associated pain were included. Most participants were aged $\geq$60 years (62.4%), female (63%), and non-Hispanic White (78.9%). Overall, 76% reported controlled pain, while 24% reported uncontrolled pain. Compared to current smokers, participants who had never smoked had significantly lower odds of having uncontrolled pain (OR=0.45; 95% CI 0.25 – 0.81, p=0.001). Former smokers had a 41% lower odds of having uncontrolled pain than current smokers (OR=0.59; 95% CI 0.33 – 0.94, p=0.04). Heavy alcohol consumption was not significantly associated with pain control (OR=1.03, 95% CI 0.48 – 2.21, p=0.94). Physical inactivity was significantly associated with poorer pain outcomes; participants who were inactive in the past 30 days had 72% higher odds of uncontrolled pain compared with those who engaged in physical activity (OR=1.72, 95% CI 1.11 – 2.67, p=0.01). **Conclusions:** Smoking and physical inactivity are significantly associated with poor pain control among adult cancer survivors. Incorporating smoking cessation and exercise promotion into survivorship care plans may enhance pain management and overall quality of life among cancer survivors. Research Sponsor: None.

12049 **Poster Session**

Utilisation of the Henry score in malignant bowel obstruction and characterisation of management approaches and outcomes: Experience from a New Zealand regional centre. First Author: Nicole Lundon, Velindre Cancer Centre, Cardiff, United Kingdom

Background: Malignant Bowel Obstruction (MBO) is a common, life-threatening complication of advanced malignancy associated with a high symptom burden and poor prognosis. Henry et al developed the Henry Score to predict 30-day mortality in MBO patients. It has not been routinely used to guide clinical decision-making regarding the management of MBO or validated in populations outside the United States of America. This study was designed to assess the utility of the Henry Score in predicting 30-day mortality in palliative patients presenting to hospital with malignant bowel obstruction in a New Zealand regional centre and to characterise the management approaches and outcomes of surgical versus non-surgical interventions. **Methods:** Retrospective cohort study of 235 patients admitted with MBO to Palmerston North Hospital (2010-2024). The Henry Score (0-5) incorporating five clinical and laboratory factors was calculated for each patient. Management approaches and survival outcomes were analysed. **Results:** Complete Henry Score data was available for 82.1% of patients. Sixty-four underwent surgical management, 171 non-surgical interventions. Median overall survival was 82.5 days (surgical: 130.5 days; non-surgical: 52 days; p=0.005). The 30-day mortality rate was 33.2%. The Henry Score demonstrated prognostic discrimination, with 30-day mortality of 28.0% for low scores (0-2) vs 43.0% for high scores (3-5) (p=0.034), and corresponding median survivals of 83 vs 39 days. Cox analysis identified hypoalbuminemia as the only factor significantly associated with mortality risk (HR 1.67, p=0.001). Māori patients had higher Henry Scores (68.2% vs 41.9% with scores ≥3, p=0.025) and shorter median survival (37 vs 97.5 days) than New Zealand European patients. **Conclusions:** The Henry Score effectively predicts 30-day mortality in MBO patients in New Zealand. Higher scores were associated with increased 30-day mortality, supporting the potential use of this measure for prognostication and advanced care planning. Hypoalbuminemia was the strongest predictor of mortality. Future prospective studies are needed to determine if clinical implementation of the Henry Score improves patient outcomes. Research Sponsor: None.

12050 **Poster Session**

Genetic associations with chemotherapy-induced nausea and vomiting: A genome-wide association study. First Author: Aasha I. Hoogland, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Nausea and vomiting affect up to 80% of patients treated with chemotherapy, and the costs of healthcare utilization due to chemotherapy-induced nausea are estimated to cost over $6 billion each year in the United States. Existing antiemetic regimens targeting 5-HT3 and NK1 antagonists are suboptimal, as up to 40% of continue to report nausea despite antiemetic treatment. Further, existing risk prediction algorithms have poor discrimination. **Methods:** In this original research study, we conducted a genome-wide association study of genetic factors associated with patient- and clinician-reported nausea and vomiting at 24 hours after infusion (acute) and 5 days after infusion (delayed) in patients treated with moderately- or highly-emetogenic chemotherapy. Participants were recruited from five ORIEN centers: City of Hope, Moffitt Cancer Center, Ohio State University, Rutgers University, and University of Colorado-Denver. Patient-reported CINV was assessed using the MASCC Antiemesis Tool and clinician-reported CINV was assessed using Common Terminology Criteria for Adverse Events (CTCAE) ratings. The study cohort was divided into a training set (70% of the sample) and a test set (30% of the sample). Machine learning was used to evaluate the predictive performance of a polygenic score along with clinical variables, over and above models with clinical variables only. Areas under the curve (AUC) were used to compare the accuracy of each predictive model. **Results:** Participants (n=1,271) were 58 years of age on average (SD=13), and most were female (74%), White (97%), with breast cancer (41%). Half of participants (50%) had early stage cancer and most were treated with a guideline-concordant prophylactic regimen (70%). Any acute and delayed self-reported nausea was reported by 42% and 70% of participants, respectively. For acute nausea, one gene, *C12orf50*, met the threshold for suggestive significance ($P = 4.58 \times 10^{-6}$). For vomiting, the presence of the G allele at rs9712639 (nearest gene: *OR7E23P*) was linked to an increased likelihood of clinician-reported acute vomiting ($P = 1.83 \times 10^{-8}$). A further 11 SNPS reached the threshold for suggestive significance and were associated with both acute and delayed vomiting reported by clinicians; these were mapped to the *FTLP18* gene. Polygenic scores did not improve predictive risk models based on clinical factors only. **Conclusions:** Results of our GWAS indicate that there are different genetic associations for acute and delayed nausea and vomiting, suggesting potentially distinct genetic factors underlying each outcome. However, regardless of outcome, genetic information did not significantly improve models predicting the development and intensity of CINV. Research Sponsor: National Cancer Institute; R01CA219389.

12051 **Poster Session**

Early outpatient palliative care for patients with multiple myeloma: A randomized pilot study. First Author: Breffni Hannon, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Early palliative care is recommended for patients with advanced or incurable cancer. Despite these recommendations, patients with multiple myeloma are often referred late to palliative care, or not at all. We assessed the feasibility of an early outpatient palliative care intervention for patients with multiple myeloma. **Methods:** English-speaking adults (≥18 years) with newly-diagnosed or relapsed multiple myeloma and at least one symptom scored ≥3/10 on the revised version of the Edmonton Symptom Assessment System (with constipation and sleep added, ESAS-rCS) were recruited from multiple myeloma outpatient clinics at the Princess Margaret Cancer Centre, Toronto, Canada. Participants were randomized to routine outpatient care from their multiple myeloma team (usual care arm), or to monthly in-person or virtual interdisciplinary outpatient palliative care clinic visits for 3 months alongside usual multiple myeloma care (intervention arm). The primary outcome was feasibility (recruitment of 40 patients/12 months; ≥60% completion of patient-reported outcome measures monthly for 3 months; ≥60% of those randomized to the intervention arm attending ≥1 palliative care clinic visit). Exploratory efficacy outcomes were measured at 1-, 2- and 3-months (primary endpoint), including quality of life (FACIT-Pal, primary efficacy outcome), symptom burden (ESAS-rCS), mood (PHQ-9) and satisfaction with care (FAMCARE-P16). **Results:** Of 40 patients recruited within 12 months (median age 66.5 years [range 33-92]; 17 [42.5%] female), 21 were randomized to the intervention arm and 19 to usual care. The 1-, 2- and 3-month completion rates among all participants for all measures were 37/39 (94.9%), 36/39 (92.3%), and 33/38 (86.8%), respectively; one intervention arm participant withdrew and one died during the study period. In the intervention arm, 17/21 (80.9%) attended at least one palliative care clinic visit; in the usual care arm, 3/19 (15.8%) were referred to the palliative care clinic during the study period. The mean difference (B) in change in the FACIT-Pal total score at 3-months from baseline between the intervention and usual care arm was 15.5 (standard error [SE] 8.8, p=0.09) after adjusting for baseline scores. The change in ESAS-rCS total distress scores at 3-months was improved in the intervention arm compared with usual care (adj. B=-13.7 [SE 5.4], p=0.02]), as were individual symptom scores for drowsiness (adj. B=-2.1 [SE 0.9], p=0.02), constipation (adj. B=-2.1 [SE 1.0], p=0.03) and sleep (adj. B=-3.6 [SE 0.8], p=0.0002). Changes in PHQ-9 and FAMCARE-P16 total scores at 3-months did not differ between study arms. **Conclusions:** This pilot trial demonstrated that a larger randomized controlled trial of early palliative care versus usual care for patients with multiple myeloma is feasible. Preliminary results are encouraging for improvements in symptom burden and quality of life. Clinical trial information: NCT06485076. Research Sponsor: Helga and Antonio De Gasperis Grand Challenges Clinical Trials in Myeloma.

12052 **Poster Session**

Using IPOS to trigger advance care planning in outpatient palliative oncology: A multicenter real-world study. First Author: Sarah Ananda Gomes, Oncoclinicas & Co - Medica Scientia Innovation Research (MEDSIR), Sao Paulo, Brazil

Background: Advance care planning (ACP) is central to high-quality palliative oncology care; however, in Brazil, ACP is not routinely integrated into clinical practice, making timely patient identification challenging. Patient-reported outcomes, such as the Integrated Palliative Outcome Scale (IPOS), may support earlier and more structured ACP discussions. This study evaluated whether IPOS, alone or combined with functional status and follow-up time, can identify patients undergoing ACP in outpatient palliative oncology. **Methods:** This multicenter, observational study used real-world data from a national Brazilian program across eight states. Adult patients with cancer who completed the IPOS at program entry were included. Functional status was assessed using the Palliative Performance Scale (PPS). ACP was defined as documented initiation during follow-up. Logistic regression models evaluated associations between IPOS domains, PPS, and ACP, adjusting for follow-up time. Discrimination was assessed using receiver operating characteristic (ROC) curves based on predicted probabilities from the final model. **Results:** A total of 1,301 patients were included (median age 68 years; SD 15.4), of whom 61.4% were female. The most common cancer types were gastrointestinal (30.3%), breast (16.6%), genitourinary (12.3%), and lung (11.9%). ACP was initiated in 32.1% of patients during follow-up. Median baseline IPOS total score was 22 (SD 10.1) and median PPS at entry was 70 (SD 15.7). Median follow-up time was 11.3 weeks (SD 20.2). Baseline IPOS total score did not discriminate ACP initiation (AUC 0.48), while functional status showed modest inverse discrimination (AUC 0.59). Time in palliative care demonstrated higher standalone discrimination (AUC 0.64). A multivariable model combining functional status, selected IPOS symptom and psychosocial domains, and follow-up time significantly improved discrimination for ACP (AUC 0.66; 95% CI 0.63-0.69). **Conclusions:** IPOS total score alone does not function as a screening tool for ACP initiation. However, when combined with functional status and longitudinal exposure to palliative care, IPOS symptom and psychosocial domains meaningfully improve identification of patients undergoing ACP. These findings support the use of IPOS as a structured clinical trigger to guide timely ACP discussions in outpatient palliative oncology. Research Sponsor: None.

12053 **Poster Session**

Early symptom signals preceding end-of-life decline in outpatient palliative oncology. First Author: Flavia Santos Dumont Sorice, Oncoclinicas & Co - Medica Scientia Innovation Research (MEDSIR), Sao Paulo, Brazil

Background: Timely recognition of clinical decline is challenging in palliative oncology. Symptom trajectories that precede global deterioration are unclear. We aimed to characterize longitudinal changes in total and domain-specific Integrated Palliative Outcome Scale (IPOS) scores and identify early indicators of decline in outpatient palliative oncology care (OPOC). **Methods:** We conducted a longitudinal study within an OPOC embedded in Brazil. Adults with advanced cancer enrolled for ≥6 months were included. IPOS was assessed at baseline, 3 months, 6 months, and the month of death. Paired comparisons evaluated changes in total IPOS scores and individual domains between baseline-3 months and 6 months-month of death. Clinically relevant decline was defined as worsening between 6 months and death. Logistic regression examined associations between IPOS decline, chemotherapy use near death, and place of death. **Results:** Among 126 patients (mean age 64.1 [SD 14.4]; 62.7% women), gastrointestinal (33.3%), breast (19.8%), and lung cancers (11.1%) were most common. At program entry, mean PPS was 65 (SD 13.5). Total IPOS scores improved from baseline to 3 months (mean difference 2.69, p=0.007). However, a marked deterioration occurred between 6 months and the month of death (mean difference -3.98, p<0.001). Domain-level analyses demonstrated early improvement in appetite loss (mean 1.56 to 1.28, p=0.020) and weakness (1.91 to 1.64, p=0.034) from baseline to 3 months, followed by significant worsening as death approached (appetite: 1.42 to 1.75, p=0.006; weakness: 1.94 to 2.25, p=0.003). Anxiety increased significantly between 6 months and the month of death (1.99 to 2.23, p=0.008), whereas pain and depressive symptoms remained relatively stable over time. Neither chemotherapy use in the last 30 days of life (OR 0.78, p=0.58) nor place of death (OR 0.56, p=0.21) was associated with clinically relevant IPOS decline. **Conclusions:** OPOC is associated with early symptom stabilization, followed by a predictable phase of accelerated deterioration near death. Appetite loss and weakness emerge as early and clinically meaningful indicators of decline within the terminal trajectory, independent of treatment or place of death. Routine longitudinal IPOS monitoring may facilitate earlier recognition of impending decline and support more proactive, patient-centered palliative care. Research Sponsor: None.

12054 **Poster Session**

Prognostic stratification using baseline objective clinical information in patients with stage IV lung cancer receiving best supportive care alone as initial treatment: A multicenter retrospective study (WJOG20824L). First Author: Shunichi Kataoka, Department of Respiratory Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan

Background: Despite expanded systemic therapy for lung cancer, best supportive care (BSC) alone remains the initial treatment for some patients, often due to advanced age, poor performance status (PS), or comorbidities. However, large-scale data on prognostic heterogeneity and risk stratification in this population are limited. We aimed to stratify overall survival (OS) in stage IV lung cancer patients initially managed with BSC alone using baseline clinical information. **Methods:** We analyzed a multicenter database from WJOG15121L including 6,751 patients with stage IV lung cancer diagnosed between January 2016 and December 2019, identifying those who received BSC alone as initial treatment. Sixty-two baseline variables (demographics, comorbidities, genomic alterations, and laboratory data) were assessed. The primary analysis was conducted in complete cases (BSC complete cohort), with multiple imputation (MI) in the entire cohort as sensitivity analysis. A boosting-based model was used to derive a prognostic risk score for OS and to stratify patients into low-, medium-, and high-risk groups based on the risk score distribution. Survival outcomes were summarized using Kaplan–Meier methods with log-rank tests. Cox regression with Lasso regularization (Cox-Lasso) was also performed as an alternative approach to assess robustness. **Results:** A total of 923 patients received BSC alone as initial treatment; 266 comprised the BSC complete cohort. The BSC population was elderly (mean age: 75.8 years) with a high proportion of poor PS (ECOG PS ≥2: 74.8%). Kaplan–Meier–based risk stratification separated OS (median OS: 277 vs 74 vs 25 days for low-, medium-, and high-risk groups, respectively). The Kaplan–Meier–estimated 90-day OS rates were clearly separated across the three groups (75.4% vs 29.8% vs 0%; log-rank p < 0.001). Baseline characteristics differed by risk group, including PS and metastatic burden (e.g., liver metastasis). Risk stratification was largely driven by routinely available laboratory markers (e.g., LDH, neutrophil count, CRP, ALP, platelet count). Findings were consistent in the MI-based sensitivity analysis and were broadly supported by the Cox-Lasso approach. **Conclusions:** Among patients with stage IV lung cancer initially managed with BSC alone, outcomes are heterogeneous and can be stratified into clinically meaningful risk groups using baseline clinical information. Kaplan–Meier summaries (median OS and 90-day OS) demonstrate marked differences across risk strata, and the dominant contribution of routine laboratory variables highlights the potential practicality of this approach in real-world settings. Further validation and comparative analyses with patients receiving systemic therapy who share similar risk profiles are ongoing. Research Sponsor: None.

12055 **Poster Session**

A first-in-human (FiH) phase I study of GFS202A, a GDF15/IL-6 bispecific antibody, in advanced cancer patients (pts) with pre-cachexia or cachexia. First Author: Hongyun Zhao, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Cachexia is a common syndrome in cancer pts, associated with weight loss, impaired quality of life, and poor treatment outcomes. GDF15, a pleiotropic factor of TGF-β super family, has been verified to be correlated with cancer cachexia and anorexia. IL-6 contributes to cancer cachexia progression via both central and peripheral pathways. GFS202A, a first-in-class bispecific antibody dual-targeting GDF15 and IL-6, improves symptoms in preclinical cachexia models with lean body mass and adipose tissue weight increased. Here, we report the preliminary data from the ongoing FiH study of GFS202A. **Methods:** This is the FiH phase I study (NCT06898255) of GFS202A in advanced cancer pts with pre-cachexia or cachexia. Eligible pts are required to have weight loss in the six months prior to the first dose and decreased appetite, with or without anticancer therapy. Enrolled pts will receive GFS202A Q3W at a starting dose of 5 mg for a 12-week treatment period, followed by a 12-week follow-up period. An accelerated titration design, combined with the Bayesian Optimal Interval (BOIN) and backfilling design, is employed. The primary objectives are to assess safety and determine the recommended dose ranges for future clinical studies. The secondary and exploratory objectives include characterization of PK profiles, PD biomarkers, preliminary efficacy and exploratory biomarkers. **Results:** Data cutoff at Dec 26, 2025, 14 pts had received at least one dose of GFS202A ranging from 5 to 400 mg Q3W (5mg: N=1; 25mg: N=4; 100mg: N=4; 200mg: N=4; 400mg: N=1). The overall safety profile was favorable. No DLT was observed. Adverse events (AEs) of any cause were reported in all pts. Six pts experienced at least one treatment-related AEs (TRAEs). Only one pt had G3 hypertension assessed related to GFS202A, which alleviated during the treatment. The pt did not experience any other cardiovascular events and had no clinically meaningful changes in lipid profiles. All other TRAEs were G1. No ≥ 2pt experienced an identical TRAE. GFS202A exposure was approximately dose-proportional from 5-200 mg, and the mean half-life was 82–138 hours. GDF15 was not detectable immediately at the end of infusion from the 5mg cohort, and durable inhibition of GDF15 was observed from the 100mg dosing cohorts during 21-day dosing interval. CRP decreased significantly post-infusion, with suppressions sustained through Week 6 in 12 out of 13 pts in 5-200 mg Q3W groups. Weight gain was observed across different dose groups, with least-squares mean increases of 1.8, 1.5 and 2.5 kg at Week 6 in the 25, 100, and 200 mg Q3W groups, respectively. **Conclusions:** GFS202A demonstrated favorable safety and encouraging efficacy with systemic inflammation alleviated and weight gain. The data support that dual-targeting GDF15 and IL-6 is a feasible way to mitigate cancer cachexia clinically. Future studies are warranted. Clinical trial information: NCT06898255. Research Sponsor: GenFleet Therapeutics (Shanghai) Inc.

12056 **Poster Session**

In-person versus telehealth outpatient palliative care visits in oncology: A multicenter study. First Author: Sarah Ananda Gomes, Oncoclinicas & Co - Medica Scientia Innovation Research (MEDSIR), Sao Paulo, Brazil

Background: As telehealth becomes integral to outpatient palliative care delivery in oncology, evidence comparing consultation duration and time allocation between in-person and remote visits remains limited, especially in low- and middle-income countries. We compared consultation duration and time composition between in-person and telehealth visits after adjustment for visit type and clinical complexity. **Methods:** This observational study evaluated outpatient oncological palliative care consultations conducted between February and May 2025 across seven practices in Brazil. Total consultation time and predefined time components were recorded. Multivariable linear regression models estimated adjusted differences in consultation duration according to care modality, controlling for visit type (first appointment, follow-up, family meeting), performance status (ECOG), quality-of-life (IPOS), and number of participants. **Results:** A total of 269 consultations were analyzed, including 171 in-person and 98 telehealth visits. Care modality was associated with consultation type (p < 0.001): telehealth was less frequently used for first consultations (15% vs. 35%) and more frequently used for follow-up visits (76% vs. 63%) and family meetings (9% vs. 3%). Telehealth visits involved patients with worse performance status (ECOG 3-4: 36% vs. 17%; p=0.007) and poorer quality of life (higher IPOS distribution; p=0.037). In unadjusted analyses, telehealth consultations were shorter than in-person visits, particularly for follow-up visits. After multivariable adjustment, telehealth visits remained independently and significantly shorter by a mean of 10.5 minutes (95% confidence interval [CI] -15.6 to -5.4; p<0.001). Follow-up consultations were consistently shorter than first consultations by 19.4 minutes (95% CI -24.9 to -14.0; p<0.001), regardless of care modality, while family meetings showed no difference in duration compared with first consultations (95% CI -13.8 to 8.9; p=0.70). Each additional healthcare provider was associated with a 2.9 minute increase in consultation time (95% CI 0.1 to 5.6; p=0.04). ECOG was not independently associated with total consultation duration. **Conclusions:** After accounting for visit type and clinical context, differences in consultation duration between telehealth and in-person are modest. Telehealth was preferentially used for follow-up care and among patients with poorer functional status and quality of life, while preserving consultation complexity when clinically indicated. These findings support telehealth as a viable modality for outpatient palliative care delivery in resource-limited settings. Research Sponsor: None.

12057 **Poster Session**

Phase II study of mirogabalin for oxaliplatin-associated chemotherapy-induced peripheral neuropathy in gastrointestinal cancer: The SmiliNg trial. First Author: Reiko Ando Makihara, Department of Pharmacy, National Cancer Center Hospital, Japan, Tokyo, Japan

Background: Oxaliplatin is a key drug in the treatment of unresectable advanced or recurrent gastrointestinal (GI) cancers, however, chemotherapy-induced peripheral neuropathy (CIPN) often limits its use. Mirogabalin is an oral gabapentinoid that alleviates neuropathic pain by binding to the $\alpha 2\delta$ subunit of voltage-gated calcium channels, but evidence regarding the efficacy of mirogabalin for CIPN induced by oxaliplatin remains insufficient. SmiliNg trial evaluated the efficacy and safety of mirogabalin in patients with unresectable advanced or recurrent GI cancers who have oxaliplatin-associated CIPN. **Methods:** This single-center, single-arm exploratory phase II trial enrolled patients with unresectable or recurrent GI cancer who were receiving ongoing first-line oxaliplatin-based chemotherapy or continuing fluoropyrimidine-based therapy after discontinuation of oxaliplatin, and who had painful CIPN (including numbness/tingling) with a numerical rating scale (NRS) score of $\geq$ 4. Mirogabalin was administered orally twice daily and titrated weekly according to Cockcroft–Gault creatinine clearance. The primary endpoint was the change in 24-hour average pain NRS from baseline to week 6. Secondary endpoints included PRO-CTCAE-assessed improvement in numbness/tingling, adverse events (CTCAE v5.0), and attainment of maintenance dose. The planned sample size was 30 patients. Clinical trial information: UMIN000049555. **Results:** Between February 2023 and April 2025, 30 patients were enrolled. The median age was 64 years (range, 36–83), with female patients accounting for 33%. The primary cancer types included colorectal (n=17), small bowel (n=7), gastric (n=6), and esophageal (n=1) cancers. The Mean baseline 24-hour pain NRS was 5.80 (SD 1.97). The mean change from baseline at week 6 was -1.46 (SD 2.66) (p = 0.010; 90% CI -2.35 to -0.57) , thereby the prespecified primary endpoint was achieved. The proportions of $\geq$1 -point responders were 58%. On the PRO-CTCAE, the proportions of patients achieving a $\geq$1-category improvement in worst severity were 38% and 38% at weeks 3 and 6, respectively; the corresponding proportions for interference with daily activities were 34% and 27%. Maintenance-dose attainment rates at weeks 3 and 6 were 59% and 68%, respectively. The most common adverse events were somnolence (83%) and dizziness (38%). Grade $\geq$3 adverse events comprised AST/ALT increased, and pulmonary infection, each occurring in one patient; none were related to mirogabalin treatment. **Conclusions:** This study suggests that mirogabalin is effective and well-tolerated for the management of moderate-to-severe painful CIPN during oxaliplatin-based chemotherapy. These findings warrant further evaluation in a confirmatory trial. Clinical trial information: 000049555. Research Sponsor: None.

12058 **Poster Session**

An automated, EHR-integrated intervention system for patient-reported insomnia symptoms. First Author: Eric S. Zhou, Dana-Farber Cancer Institute, Boston, MA

Background: Insomnia affects >20% of patients on cancer therapy. It is consistently reported to be one of the most burdensome sequelae. Systematic screening for insomnia in cancer patients is uncommon. Without identification, patients cannot access care. Unfortunately, even if insomnia is identified, most cancer centers lack on-site sleep specialists. To address both the screening and treatment gaps, we leveraged our institution's EHR-based patient-reported outcomes (PRO) data collection system to develop a fully automated solution to identify patients with insomnia, and share an evidence-based psychoeducational video intervention with them. **Methods:** Prior to established outpatient appointments at our hospital, all patients are asked to complete eSyM, an electronic PRO-CTCAE symptom assessment. Two insomnia items (symptom severity and interference) are combined to generate an insomnia score (0-3; higher is worse, with present analyses for those reporting a score $\geq$2). Patients with an elevated insomnia score were sent a patient portal message explaining they were identified as having insomnia, and offered an educational video with strategies to improve their sleep. We tracked patient engagement, as well as report of insomnia symptoms via eSyM response at the patient's subsequent appointment closest to 60 days post-Baseline ($\pm$30 days). Data was analyzed from patients who reported completed eSyM insomnia questions at both timepoints between 02/25 to 09/25. **Results:** Patients with insomnia (N=307) were an average of 63 years old, predominantly female (63%), White (84%), married (63%), and possessed a college degree or higher (57%). They were diagnosed with a broad range of cancers (breast = 20%, GI = 15%, thoracic = 10%). The vast majority (92%) opened the patient portal message with the video link, with the video watched in entirety 498 times. Overall, insomnia scores significantly decreased from baseline ($\bar{x}$ = 2.3) to follow-up ($\bar{x}$ = 1.9; $p<.001$), with 42% reporting symptomatic improvement at follow-up (48% no change and 9% worse). Specifically, 41% reported either Severe or Very Severe insomnia symptoms at baseline, improving to 30% at follow-up; 37% reported insomnia interfered with their life Quite a Bit or Very Much at baseline, improving to 23% at follow-up. Multivariate analyses revealed sociodemographic characteristics (Black, Medicare, and disabled) associated with less insomnia improvement. **Conclusions:** We developed a fully automated system that leverages electronic PRO data and our EHR to identify symptomatic cancer patients with insomnia and intervene. Our findings demonstrate that we can successfully connect with patients reporting insomnia and potentially improve outcomes with a low-intensity intervention. This framework can readily be deployed to identify and address other common side effects of cancer treatment (e.g., fatigue, pain) that impair recovery and quality-of-life. Research Sponsor: American Cancer Society.

12059 **Poster Session**

Negative effect of malignant pleural effusion on the efficacy of immunotherapy via IL-6–mediated abscopal immunosuppression in advanced non-small cell lung cancer. First Author: Yaping Guan, Department of Oncology, The First Affiliated Hospital of Shandong First Medical University, Jinan, China

Background: The present study is designed to determine the effect and mechanism of malignant pleural effusion (MPE) on the efficacy of immunotherapy in advanced non-small cell lung cancer (NSCLC). **Methods:** We identified patients with advanced NSCLC who underwent immunotherapy as a first-line or second-line regimen in multiple cohorts. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were analyzed. Using a mouse model with MPE, we determined whether MPE could affect the efficacy of immunotherapy and investigated the mechanism of MPE-related immunosuppression. **Results:** In a cohort with 269 advanced NSCLC patients who received PD-1 inhibitor alone or combined chemotherapy, MPE occurred in 82 (30.5%) patients. Patients with MPE had a shorter median PFS (4.0 vs. 9.8 months) and OS (21.0 vs. 29.9 months) than those without MPE. MPE was an independent factor affecting PFS (HR:1.87) and OS (HR: 2.73). The ORR for patients with and without MPE was 20% and 34%, respectively. In another cohort with 69 advanced NSCLC patients with MPE who receive PD-1 inhibitor plus chemotherapy plus bevacizumab or PD-1 inhibitor plus chemotherapy, there was no significant difference in median PFS (19.1 vs. 13.2 months) and OS (21.8 vs. 21.6 months), ORR (42.1% vs. 36.8%,), and extrapleural ORR (23.9% vs. 26.3%) between the two groups. In addition, IL-6 levels in serum and pleural effusions were significantly higher in NSCLC patients with MPE. Furthermore, in a mouse tumor MPE model by subcutaneous and pleural injection of lung cancer cells, PD-1 inhibitor did not decrease tumor growth and prolong survival in MPE-bearing mice. Immunohistochemistry and flow cytometry demonstrated the proportion of $CD3^+$T cells, $CD4^+$T cells and $CD8^+$T cells were decreased in the subcutaneous tumors with MPE. Dural blockade with PD-1 inhibitor and IL-6 receptor antibody inhibited tumor growth and prolonged survival of MPE-bearing mice. **Conclusions:** The occurrence of MPE is negatively correlated with patient outcomes when receiving PD-1 inhibitor or PD-1 inhibitor plus bevacizumab. Elevated IL-6 levels may be responsible for abscopal inhibitory tumor immune microenvironment and reduced efficacy of immunotherapy. Dural blockade of PD-1 and IL-6 could be a promising therapeutic strategy for advanced NSCLC with MPE. Research Sponsor: None.

12060 **Poster Session**

Guard-01: A randomized, open-label trial of efbemalenograstim alfa as primary prophylaxis for neutropenia during definitive concurrent chemoradiotherapy. First Author: Yuanyuan Chen, State Key Laboratory of Oncology in South China, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: Concurrent chemoradiotherapy (CCRT), a curative cornerstone for locally advanced malignancies, exerts synergistic antitumor efficacy but is frequently hampered by severe hematologic toxicity (mainly neutropenia), leading to treatment delays, dose reductions and compromised outcomes. GM-CSF, previously evaluated for CCRT-induced hematologic AE prophylaxis, is no longer recommended due to increased immune-related toxicities and limited efficacy. While G-CSF is safe in chemotherapy, high-quality data for long-acting G-CSF as primary CCRT prophylaxis is sparse, creating a critical clinical gap that the Guard-01 study aims to resolve. **Methods:** This multicenter, randomized, open-label, controlled trial plans to enroll 120 patients undergoing definitive CCRT for locally advanced malignancies. Eligible participants are randomized 1:1 to either the study arm or control arm, stratified by chemotherapy regimen. Study arm patients receive efbemalenograstim alfa ~48 ($\pm$4) h post each chemotherapy cycle; control arm patients receive no primary G-CSF prophylaxis, with secondary efbemalenograstim alfa permitted for febrile neutropenia (FN) or dose-limiting neutropenia. The primary endpoint is the incidence of grade 3/4 neutropenia across the entire CCRT course. **Results:** As of December 2, 2025, 122 patients were enrolled (60 study arm, 62 control arm). The incidence of grade 3/4 neutropenia during the entire treatment course was 16.67% in the study arm versus 53.23% in the control arm, with a significant between-group difference of -36.56% (90% CI: -48.98%, -22.84%; $p < 0.0001$). Rates were significantly lower in the study arm across the first (5.00% vs. 45.16%; $p < 0.0001$) and second (12.28% vs. 27.27%; p = 0.0393) chemotherapy cycles. Consistent benefit was observed in subgroup analysis, with a significant difference in paclitaxel- or pemetrexed-based regimens (20.00% vs. 64.52%; p = 0.0004). The study arm had shorter grade 3/4 neutropenia duration (0.62 ± 1.57 vs. 3.27 ± 4.84 days; $p < 0.0001$) and higher ANC nadir (2.82 vs. 0.94×10^9/L; $p < 0.0001$). No neutropenia-related chemotherapy dose reductions or discontinuations occurred in the study arm, compared with 6.45% dose reductions and 1.61% discontinuations in the control arm. The most common TEAEs in the study arm were anemia (71.67%), thrombocytopenia (60.00%), and leukopenia (35.00%). Grade $\geq$3 TEAEs were less frequent in the study arm (41.67% vs. 64.52%), with no grade $\geq$3 TRAEs reported in either group. Exploratory endpoints include 2-year PFS and OS, with immature data pending longer-term follow-up. **Conclusions:** Efbemalenograstim alfa significantly reduces the incidence and duration of grade 3/4 neutropenia in patients undergoing definitive CCRT, with consistent efficacy across different chemotherapy regimens and a favorable safety profile. Clinical trial information: ChiCTR2300077504. Research Sponsor: None.

12061 Poster Session

An anti-EpCAM x anti-CD3 bispecific antibody, M701, for the treatment of malignant pleural effusion due to NSCLC: A prospective randomized controlled phase II trial. First Author: Zhengbo Song, Phase I Clinical Trial Unit, Zhejiang Cancer Hospital, Hangzhou, China

Background: Malignant Pleural Effusion (MPE) is a common complication in patients with advanced NSCLC, associated with poor prognosis, severe symptoms, and reduced quality of life. Indwelling pleural catheter (IPC) is the first-line recommended therapy to alleviate MPE-related symptoms; however, no effective pharmacotherapy has been established in current clinical guidelines for MPE management. **Methods:** Patients with advanced NSCLC and symptomatic MPE who had progressed following at least 1 line of systemic treatment were eligible. Patients were randomized 1:1 to experimental arm (Arm E: IPC + M701 IP at 25 μg on day 1, 400 μg on days 4, 7, 10) or control arm (Arm C: IPC + cisplatin IP 40 mg on days 1, 7 or IPC alone), stratified by prior intrapleural chemotherapy (yes/no). Catheters were removed after day 10. Primary endpoint was puncture-free survival (PuFS), defined as time from catheter removal to next puncture or death. Secondary endpoints included time to next puncture (TTNP), overall survival (OS), MPE objective response rate (ORR), investigator-assessed MPE symptoms (Likert scale), and patient-reported symptoms (LC-13 scale). **Results:** As of December 22, 2025, 92 patients were randomized to Arm E (n=45) or Arm C (cisplatin, n=41; thoracentesis, n=6). Baseline characteristics were generally balanced between the two arms. The proportions of patients positive for actionable genomic alterations (AGA) were 77.77% (n=35) in Arm E and 72.34% (n=34) in Arm C, respectively. M701 demonstrated a significant improvement trend in PuFS and TTNP compared with cisplatin (see Table 1). The MPE ORR was 46.7% for Arm E and 34.0% for Arm C (p=0.217). Patients with prior intrapleural (IP) chemotherapy or without AGA had a more favorable treatment response in Arm E relative to Arm C, whereas the remaining patients did not. Dyspnea symptoms also demonstrated a trend toward greater improvement in Arm E, as assessed by both investigators and patients. OS data were immature, and no significant between-group difference was observed (HR=0.94, p=0.855). Grade 3 or higher treatment-related adverse events (AEs) occurred in 2.2% of patients in Arm E and 6.4% in Arm C. Only one serious adverse event (SAE), grade 2 fever, was deemed related to M701. **Conclusions:** M701 IP infusion showed a promising efficacy on re-accumulation of MPE compared with Cisplatin infusion, and was well tolerated, supporting further clinical development, especially in patients with no AGA or patients who received IP chemotherapy priorly. Clinical trial information: NCT05543330. Research Sponsor: Wuhan YZY Biopharma Co. Ltd.

Efficacy of the FAS set and subgroup.

Population	mPuFS (days)	HR	P value	mTTNP (days)	HR	P value
Full analysis (45 vs 47)	170 vs 72	0.72	0.212	NR vs 86	0.05	0.035
Prior IP chemotherapy or no AGA (28 vs 32)	253 vs 55	0.58	0.099	NR vs 65	0.26	0.004
With AGA and no prior IP chemotherapy (17 vs 15)	124 vs 114	1.09	0.832	170 vs NR	1.34	0.582

12062 Poster Session

Performance of the NutriPal nutritional screening algorithm in advanced cancer palliative care: A multicenter study. First Author: Jesse Lopes da Silva, Division of Clinical Research and Technological Development, Brazilian National Cancer Institute (INCA), Rio De Janeiro, Brazil

Background: Malnutrition is highly prevalent in advanced cancer and is closely associated with functional decline, systemic inflammation, symptom burden, and impaired quality of life (QoL). Although several nutritional screening tools exist, none were specifically developed for patients with advanced cancer receiving palliative care. The NutriPal nutritional screening algorithm, which integrates the Patient-Generated Subjective Global Assessment short form and the Glasgow Prognostic Score, was recently developed for this population; however, evidence of its performance outside the development cohort remains limited. The objective was to evaluate the performance of the NutriPal nutritional screening algorithm in identifying nutritional risk among patients with advanced cancer receiving palliative care in a multicenter clinical setting and its association with functional status, inflammation, muscle strength, and QoL. **Methods:** This multicenter, cross-sectional study included adults with locally advanced or metastatic cancer receiving palliative care in four private oncology centers in Brazil from June 2024 to November 2025. Nutritional risk was classified using NutriPal in degrees 1 (lower) to 4 (greater nutritional risk). Karnofsky Performance Status (KPS), handgrip strength (HGS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and QoL (EORTC QLQ-C15-PAL) were evaluated as independent variables. Associations with worsening nutritional risk were examined using ordinal logistic regression. **Results:** A total of 165 patients were included (60% women; 70% ≥60 years). NutriPal classified 54% as degree 1, 25% degree 2, 10% degree 3, and 11% degree 4 nutritional risk. Worse nutritional risk was independently associated with KPS < 60% (OR 2.67; 95% CI 1.17 - 6.07), low HGS in women (< 22 kg; OR 2.69; 95% CI 1.19 - 6.12) and men (< 32 kg; OR 2.06; 95% CI 1.02 - 5.44), NLR ≥2.78 (OR 2.02; 95% CI 1.18–3.15), and PLR ≥171.95 (OR 2.09; 95% CI 1.12 - 3.89). Poorer scores across all QoL domains (except insomnia) were significantly associated with higher nutritional risk (OR range 1.14 - 7.68), including global QoL (OR 4.08; 95% CI 2.14 - 7.61). **Conclusions:** NutriPal effectively discriminated nutritional risk severity and identified clinically relevant profiles characterized by functional impairment, systemic inflammation, and poorer QoL among patients with advanced cancer receiving palliative care in private oncology centers. These findings support its clinical utility as a targeted and pragmatic nutritional screening tool in real-world palliative oncology practice settings. Research Sponsor: None.

12063 Poster Session

Role of palliative care nurse coordination in symptom control and care planning. First Author: Suwanna Rinchai, Bumrungrad International Hospital, Bangkok, Thailand

Background: Effective coordination by palliative care nurses plays a central role in improving communication, symptom assessment, and timely care planning for patients with advanced cancer. However, evidence on the measurable impact of nurse-led palliative coordination—particularly in Asian oncology settings-remains limited. This study evaluates the outcomes of a nurse-coordinated palliative care model on symptom control and care planning among patients with advanced cancer. **Methods:** This retrospective observational study included patients with advanced cancer who received palliative care nurse coordination from January 1, 2025 to December 31, 2025. The intervention consisted of systematic ESAS-based symptom assessment, coordination with oncology teams, family meetings, and facilitation of advance care planning. Outcomes included changes in symptom scores from baseline to follow-up, completion of advance care planning (ACP) and DNR documentation, and health-care utilization indicators.Distress score was derived from the ESAS psychological subscale, calculated as the sum of anxiety and depression scores. Descriptive statistics and paired comparisons were used for analysis. **Results:** A total of 195 patients were included (mean age 60.5 years; range 21–100). Following nurse-led palliative coordination, median pain scores decreased from 8 to 3 ($p < 0.01$). Median dyspnea scores improved from 6 to 1, representing an 83.3% reduction ($p < 0.01$). Median distress scores decreased from 6 to 2, corresponding to a 66.7% improvement ($p < 0.01$).Completion of advance care planning increased from 10% to 97%. DNR documentation improved from 20% to 80%, with the exception of one Arabic patient for whom DNR documentation was not completed. Under the nurse-led palliative care coordination model, 98.5% of patients with advanced cancer did not require unplanned emergency room utilization and avoided unnecessary ICU admissions. These outcomes highlight the effectiveness of proactive symptom management and comprehensive care planning. **Conclusions:** Nurse-led palliative care coordination was associated with significant improvements in symptom control and substantially higher completion rates of care planning among patients with advanced cancer. These results support integrating palliative nurses as key coordinators in oncology settings to enhance patient-centered and goal-concordant care. Research Sponsor: None.

12064 Poster Session

Patterns and timing of palliative care consultation in patients with newly diagnosed metastatic cancer. First Author: Thomas Wayne Butler, University of South Alabama Mitchell Cancer Institute, Mobile, AL

Background: Early integration of palliative care (PC) improves symptom burden, quality of life, and healthcare utilization in advanced cancer, yet referrals frequently occur late in the disease course. We evaluated institutional patterns of PC utilization to quantify consultation rates, timing, and demographic predictors of referral among patients with newly documented metastatic disease. **Methods:** We conducted a retrospective cohort study of adults with newly documented metastatic disease identified using ICD-10 secondary lymph node metastasis codes (C77.x) who received oncology care at the Mitchell Cancer Institute between November 2024 and November 2025. The first metastatic code defined time of diagnosis. Outcomes included PC consultation rate, time from diagnosis to consultation, consultation setting, and timing relative to death. Multivariable logistic regression evaluated associations between age, sex, insurance status, and race with receipt of consultation. **Results:** Among 375 patients (median age 66 years, IQR 56–74), 64 (17.1%) received a PC consultation. Consultation rates varied more than fourfold across primary diagnoses (6%–29%). Among patients with post-diagnosis consultations, the median time to consultation was 66 days (IQR 25–130), with more than half occurring >60 days after diagnosis. Most consultations occurred in the outpatient cancer center (78%). Among decedents who received consultation, 64% were first seen within 90 days of death, consistent with late referral. In multivariable analysis, increasing age was associated with a lower likelihood of consultation (OR 0.97 per year, 95% CI 0.95–0.99, p=0.016), while Black patients had higher odds of consultation compared with White patients (OR 1.82, 95% CI 1.02–3.25, p=0.044). Sex and insurance status were not independently associated with referral. **Conclusions:** PC utilization was low, highly variable, and frequently delayed among patients with metastatic cancer. Although most referrals originated in the outpatient setting, many occurred near the end of life. Diagnosis-triggered referral pathways may promote earlier and more equitable integration of supportive oncology services. Research Sponsor: None.

Palliative care utilization and predictors of consultation.

Characteristic	Value
Total patients	375
Median age, years (IQR)	66 (56–74)
Received PC consultation	64 (17.1%)
Median time diagnosis → consultation, days (IQR)	66 (25–130)
Initial outpatient consultation	78%
Consultation ≤90 days before death (decedents)	64%
Black vs White race, adjusted OR	1.82 (p=0.044)
Age (per year), adjusted OR	0.97 (p=0.016)
Most referrals occurred late in the disease course	>50% after 60 days

PC = palliative care; IQR = interquartile range; OR = odds ratio. Timing calculated among post-diagnosis consultations. Odds ratios from multivariable logistic regression.

12065 Poster Session

Olanzapine for chemotherapy-related anorexia: Impact on body composition. First Author: Sandhya Singuluri, Srivenkateshwara Institute of Cancer Care and Advanced Research, Tirupati, India

Background: Chemotherapy-related anorexia and weight loss are associated with adverse outcomes in patients with advanced gastrointestinal and lung cancers. While olanzapine has demonstrated efficacy in improving appetite and weight gain, the impact of weight gain on body composition remains unclear. We evaluated changes in morphomic parameters among patients receiving olanzapine during chemotherapy. **Methods:** In this phase III, randomized, double-blind, placebo-controlled trial, adults (≥18 years) with untreated locally advanced or metastatic gastric, hepatopancreaticobiliary, or lung cancer were randomized to receive olanzapine 2.5 mg once daily or placebo for 12 weeks, along with standard chemotherapy and nutritional counseling. The primary endpoint was the proportion of patients achieving > 5% weight gain. Secondary endpoints included changes in skeletal muscle index (SMI), subcutaneous fat index (SFI), and visceral fat index (VFI) assessed at the third lumbar vertebra on CT scans. Morphomic analysis was performed in patients with paired baseline and interim CT scans. **Results:** A total of 103 patients (olanzapine, n = 53; placebo, n = 50) were included in the morphomic analysis. Baseline characteristics were comparable between groups. Weight gain > 5% was significantly more frequent in the olanzapine group compared with placebo (60% vs 9%, $p < 0.0001$). Both groups experienced a decline in mean SMI; however, among olanzapine-treated patients with > 5% weight gain, 63% demonstrated improvement or stabilization of SMI. Improvement in SFI was more frequent with olanzapine than placebo (62% vs 40%, p = 0.047). Among patients with > 5% weight gain, a higher proportion in the olanzapine group showed an increase in VFI compared with placebo (72% vs 60%, p = 0.006). **Conclusions:** Olanzapine improves weight gain with favorable changes in skeletal muscle and fat indices, indicating true nutritional gain rather than fluid retention in patients with chemotherapy-related anorexia. These findings suggest that olanzapine may favorably modulate cancer-related anorexia and treatment outcomes, warranting further validation in larger focused studies. Clinical trial information: CTRI/2020/08/027133. Research Sponsor: Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER) - Intramural funding.

12066 Poster Session

Clinical outcomes of gabapentinoids for oncologic pruritus: A retrospective cohort study. First Author: Alim Osman, Department of Medicine, Dermatology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Pruritus is a debilitating symptom in oncologic patients, sometimes leading to interruption of cancer therapy. Gabapentinoids such as gabapentin and pregabalin are effective for the treatment of uremic and neuropathic pruritus. We report on the safety and efficacy of gabapentinoids for oncologic pruritus defined as any pruritus originating from malignancy, oncologic therapies, or other cancer-associated toxicities, such as cutaneous graft-versus-host disease (GVHD). **Methods:** In this single-center retrospective cohort study conducted at the Memorial Sloan Kettering Cancer Center between 4/1/2019 and 8/1/2024, 224 patients who were prescribed gabapentinoids for oncologic pruritus were included. Patients taking gabapentinoids for indications other than pruritus were excluded. The primary efficacy endpoint was ≥ 1-grade improvement for pruritus severity on the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 scale. **Results:** The cohort was predominantly male (54%) and White (67%), with Black (14.3%) and Asian (12.5%) patients also represented; the mean age was 63.2 ± 15 years. Gabapentinoids were most prescribed for drug-induced causes (58.9%) and malignancy-related pruritus (14.3%). Of the drug-induced causes, immune checkpoint inhibitors (40.2%), monoclonal antibodies (12.9%; including mogamulizumab, brentuximab vedotin, and enfortumab vedotin), and tyrosine kinase inhibitors (11.4%) were the most common triggers. Pregabalin was more commonly prescribed compared to gabapentin (80.8% vs. 19.2%). Ninety percent of patients (n=202) experienced a ≥1-CTCAE grade improvement at a median total daily dosage of 50 mg (IQR, 25 mg) for pregabalin and 300 mg (IQR, 50 mg) for gabapentin. Median time for patient-reported improvement was 18.5 days and there was no significant difference in gabapentin response between pruritus etiologies. The most common adverse event was sedation (8.5%), with 3 patients discontinuing gabapentinoids due to fatigue. **Conclusions:** This study is the first to report that gabapentinoids are a safe and effective way to treat oncologic pruritus stemming from malignancy, cancer therapies, or cutaneous GVHD. Prospective trials would further establish gabapentinoids' safety and efficacy profile in the oncologic population. Research Sponsor: None.

Outcomes & adverse events of patients on gabapentinoids.

Variable	Category/Statistic	N (%)
CTCAE Grade Change	Did Not Improve (0 Grade)	22 (9.8%)
	Improved 1 Grade	132 (58.9%)
	Improved ≥ 2 Grade	70 (31.3%)
Antineoplastic Therapy Interrupted Due to Oncologic Pruritus	Yes	26 (11.7%)
	No	157 (70.4%)
	Not Applicable	40 (17.9%)
Adverse Events*	Sedation	19 (8.5%)
	Leg Swelling	2 (0.9%)
	Other	9 (4.0%)

*The remaining 194 (86.6%) patients did not report any adverse events related to the gabapentinoids.

12067 Poster Session

Cancer cachexia and symptomatic toxicity among 706 older adults with advanced cancer receiving treatment: A URCC NCORP nationwide study. First Author: Lindsey Jean Mattick, Department of Surgery, Division of Supportive Care in Cancer, University of Rochester Medical Center, Rochester, NY

Background: Cancer cachexia is a severe wasting condition characterized by rapid weight loss. Its impact on symptomatic toxicity is poorly defined in geriatric oncology populations, who are at high risk for cachexia. Symptomatic toxicity is central to treatment tolerability and is linked to poor quality of life, functional decline, and reduced survival. We evaluated whether cachexia is associated with symptomatic toxicity before and during high-risk cancer treatment in older adults with advanced cancer. **Methods:** In a randomized controlled trial (GAP70+; NCT02054741), adults aged ≥70 with stage III or IV solid tumors or lymphoma were recruited prior to starting a new cancer treatment from 40 community oncology practices affiliated with the University of Rochester NCI Community Oncology Research Program (NCORP) Research Base. Cachexia (≥5% weight loss in the past six months) was assessed at baseline via Mini Nutritional Assessment. Symptoms (fatigue, insomnia, pain, anorexia, dyspnea, concentration problems, nausea, sensory neuropathy, constipation, diarrhea) were assessed at baseline and 3 months using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Symptoms were measured as mild, moderate, severe, or very severe. Log-binomial regression models examined associations of cachexia with baseline and three-month incident symptoms (baseline-adjusted method). **Results:** Among 706 participants (mean age: 77.2 years; 57% male; 59% gastrointestinal or lung cancer; 26% received prior chemotherapy), 42% had cachexia at baseline. Participants with cachexia were more likely than those without to report severe/very severe baseline symptoms (56% vs. 35%, chi-square $p < 0.01$). Analyses show that those with cachexia were 2-3 times more likely to report baseline severe/very severe anorexia (Risk Ratio (RR): 3.64, 95%CI: 2.44 - 5.42), fatigue (RR: 2.28, 95%CI: 1.65 - 3.16), pain (RR: 2.03, 95%CI: 1.36 - 3.04), and constipation (RR: 2.02, 95%CI: 1.27 - 3.22), as well as moderate or worse nausea (RR: 1.72, 95%CI: 1.16 - 2.55) and concentration problems (RR: 1.56, 95%CI: 1.03 - 2.39; all $p < 0.05$). Baseline cachexia was also associated with the development of severe/very severe anorexia (RR: 1.88, 95%CI: 1.20 - 2.94; $p < 0.01$) from baseline to 3-months. **Conclusions:** Nearly half of older adults with advanced cancer initiating a treatment regimen have cachexia. We demonstrate via PRO-CTCAE that cachexia is associated with a significantly worse pre-treatment symptom burden. Cachexia was linked to severe anorexia before and after treatment initiation, highlighting a critical gap in supportive care. As novel agents targeting appetite and cachexia enter phase III trials, further research is needed to establish the temporal course of cachexia-related symptoms to identify ideal timing and candidates for therapeutic strategies. Clinical trial information: NCT02054741. Research Sponsor: National Cancer Institute; UG1CA189961; National Cancer Institute; R01CA177592; National Cancer Institute; T32CA102618; National Cancer Institute; UG1CA189971; National Cancer Institute; UG1CA189847; National Cancer Institute; UG1CA189804.

12068 Poster Session

Enhancing supportive care in malignant bowel obstruction: A QI project using virtual dietitian-led low-fiber diet education. First Author: Bojan Macanovic, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

Background: Malignant bowel obstruction (MBO) is a frequent, debilitating complication in patients with gynecologic malignancies associated with poor prognosis. Low-fibre diet (LFD) is a core component of conservative management; however, adherence is challenging and may be improved with coaching. To address this gap, we implemented a virtual dietitian-led educational intervention and evaluated patient knowledge, attitudes, and practices regarding LFD. **Methods:** This prospective quality improvement project was conducted at Princess Margaret Cancer Centre between October 2024 and April 2025. Adult patients with gynecologic malignancies who had developed or were at risk of MBO participated in interactive virtual LFD classes delivered by a registered dietitian. Electronic surveys assessed patient knowledge, attitudes, and dietary practices at baseline, post-class, and at two-week follow-up. Outcomes were summarized using descriptive statistics. **Results:** Of 71 patients approached, 48 (68%) attended the class. Surveys were completed by 43 patients pre-class (61%), 26 post-class (37%), and 18 at follow-up (25%). Median age was 64 years (range 31–79); 32/43 (74%) had ovarian cancer, and 12/43 (28%) had prior bowel obstruction. At baseline, 40/43 (93%) understood the rationale for LFD, but only 26/43 (60%) reported knowing which foods were permitted and 26/43 (60%) which were restricted. Baseline concerns included inadequate healthy food options (32/43, 74%) and limited cultural food compatibility (12/43, 28%). Following the intervention, understanding of permitted foods increased to 24/26 (92%; +32%) and restricted foods to 22/26 (85%; +24%). Confidence that LFD could reduce the risk of MBO improved from 16/43 (37%) to 16/26 (62%; +25%). The virtual format was well received, with 25/26 (96%) feeling comfortable and 22/26 (85%) identifying the class as an important part of their care. At two-week follow up, 15/18 (83%) felt confident in selecting appropriate foods. Adherence was high with 6/18 (33%) following LFD always and 9/18 (50%) most of the time. Despite improved knowledge and adherence, overall satisfaction with LFD remained low (baseline 7/43, 16%; follow-up 3/18, 17%). Challenges including limited food variety, difficulty identifying appealing options, and managing concurrent dietary restrictions, were reported by 9/18 (50%). Quality of life outcomes were mixed, with equal proportions reporting improved, unchanged or worsened: each 6/18, 33%. **Conclusions:** This quality improvement project demonstrates that a virtual, dietitian-led LFD education is feasible, acceptable, and effective in addressing key knowledge and confidence gaps for patients with or at risk of MBO. Persistent dissatisfaction with LFD highlights the need for future QI efforts focused on developing culturally inclusive resources and integration of multiple dietary needs. Research Sponsor: None.

12069 **Poster Session**

Fatigue and psychostimulant use in patients with advanced cancer in an oncology palliative care clinic: A retrospective cohort study. First Author: Nicolas Chin-Yee, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Cancer-related fatigue (CRF) is the most common symptom experienced by patients with cancer but is underreported and undertreated. Psychostimulants are prescribed for CRF despite limited evidence; data on real-world use of these medications for CRF is scant. We aimed to describe the prevalence and predictors of CRF and psychostimulant use, and the association of psychostimulant use with CRF improvement in an oncology palliative care clinic (OPC). **Methods:** We conducted a retrospective review of new consultations in the Princess Margaret Cancer Centre OPC from Jan 1, 2018 - Jul 30, 2025. Demographic and clinical characteristics, including Palliative Performance Scale (PPS) and Edmonton Symptom Assessment System (revised, with constipation and sleep, ESAS-rCS) scores were recorded. Psychostimulant prescriptions were extracted from Epic, the electronic medical record system as of Jun 4, 2022. We calculated prevalence of fatigue in the total cohort and psychostimulant prescription following initial OPC visit in the subcohort seen on/after Jun 4, 2022. For the latter group, we reviewed charts to assess adherence, CRF severity, patient perception of efficacy and adverse effects. Multivariable logistic regression evaluated baseline factors associated with moderate-severe fatigue ($\geq$4/10 on ESAS-rCS) and psychostimulant prescription. We compared pre- and post-psychostimulant fatigue scores by Wilcoxon signed rank test. **Results:** 8,439 patients (5,812 with complete ESAS-rCS) were seen in the OPC from Jan 1, 2018 - Jul 30, 2025; 74.4% and 40.6% reported fatigue $\geq$4/10 and $\geq$7/10, respectively. Moderate-severe fatigue was independently associated with lower PPS ($<$ 60 vs $\geq$60, OR 1.66, 95% CI 1.15-2.38, $p < 0.01$) and worse ESAS-rCS scores for pain, drowsiness, appetite, dyspnea, depression, and wellbeing ($p < 0.0001$). Among 3,623 patients seen on/after Jun 4, 2022, 140 (3.9%) were prescribed a psychostimulant by the OPC; no baseline patient factors were associated with psychostimulant prescription. Of these 140 patients, 139 were prescribed methylphenidate at a maximum total daily dose $\leq$10 mg; 77 adhered to treatment and had follow up notes reporting effects. Of evaluable patients, 53 (68.8%) reported improved fatigue, 12 (15.6%) no benefit, and 12 (15.6%) had conflicting notes regarding effectiveness; 3 (3.9%) reported non-serious adverse events related to methylphenidate. Median (interquartile range) fatigue scores pre- and post-psychostimulant treatment were 7 (5-8) and 6 (3-7), respectively ($p <$ 0.01). **Conclusions:** Nearly 3/4 of patients with advanced cancer receiving outpatient palliative care experienced fatigue, yet few were treated with psychostimulants. Most patients reported improvement in fatigue with low-dose methylphenidate. Future studies should address knowledge gaps in assessment and management of CRF and the role of psychostimulants. Research Sponsor: None.

12070 **Poster Session**

Association of iterative cannabis care plans with rates of symptom relief and side effect burden in oncology patients. First Author: Brooke Worster, Sidney Kimmel Comprehensive Cancer Center, Jefferson Health, Philadelphia, PA

Background: Cannabis is increasingly used to manage cancer-related symptoms including pain, sleep disturbance, anxiety, and appetite or gastrointestinal complaints. However, patient responses are highly variable, clinicians report limited confidence in guiding use, and optimal dosing is difficult to predict from baseline characteristics. We evaluated whether an iterative, guided cannabis care model incorporating ongoing patient feedback and care-plan adjustments is associated with improved symptom relief and lower side-effect burden in a real-world oncology population. **Methods:** We conducted a retrospective observational analysis of cancer patients receiving cannabis-based symptom management through a structured care-planning program. Baseline demographics, cannabis experience, THC dosing, and number of care-plan adjustments were collected. Patients provided longitudinal feedback on symptom outcomes and tolerability at serial check-ins. Significant symptom relief was defined as a $\geq$3-point reduction in PROMIS T-scores across pain, sleep, anxiety, and appetite/nausea domains. Side-effect burden was assessed as the percentage of follow-up check-ins with reported side effects. Logistic regression examined associations between care-plan adjustments and symptom relief, adjusting for age, cannabis experience, and final THC dose. **Results:** A total of 136 patients receiving active cancer treatment were included (mean age 61 years; range 26–91). Overall, 56% reported significant relief across all symptom domains. Rates of global symptom relief increased with care-plan iteration: 34.6% among patients with no adjustments, 72.4% among those with 1–2 adjustments, and 96.6% among those with $\geq$3 adjustments, demonstrating a strong relationship. Care-plan iteration was also associated with lower longitudinal side-effect burden, with side effects reported at 25.6% of check-ins among patients with no adjustments, 17.5% with 1–2 adjustments, and 11.7% with $\geq$3 adjustments. In adjusted analyses, each additional adjustment was independently associated with higher odds of global symptom relief, while baseline demographic and clinical characteristics were not strong predictors of response. **Conclusions:** Symptom response to cannabis therapy among oncology patients is heterogeneous and not reliably predicted by baseline characteristics. In this real-world cohort, iterative cannabis care plans incorporating ongoing monitoring and adjustment were associated with substantially higher rates of meaningful symptom relief and a lower burden of side effects over time. These findings support adaptive, feedback-driven cannabis care models over fixed dosing strategies in supportive oncology. Research Sponsor: None.

12071 **Poster Session**

Meaning, distress, and desire for hastened death in homebound adults with advanced cancer: A cluster analysis. First Author: Addison Dean Monroe, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Patients with advanced cancer experience significant anxiety and depression exacerbating existential distress, which is often defined as a loss of meaning and dignity, desire for death, hopelessness, and/or demoralization. Such distress is even more pronounced for homebound adults with cancer who are isolated and engage less in enjoyable activities. While meaning in life, affective distress, and existential distress are related, discrepancies exist in the literature which may reflect the presence of distinct psychosocial profiles as opposed to inconsistencies in the literature. **Methods:** Patients with advanced cancer (N = 64) who had recently completed an episode of home care and completed baseline assessments in a pilot randomized controlled trial (RCT) of Meaning-Centered Psychotherapy for Hospitals, Hospice, and Home (MCP-H) served as the study sample. Baseline assessments included measures of meaning in life, anxiety, depression, and desire for hastened death. A hierarchical agglomerative cluster analysis was conducted to identify naturally occurring subgroups of participants. Subgroup differences in predictor variables, physical symptom burden, and demographic variables were explored. **Results:** A 2-cluster solution emerged from the data: *Low Meaning, High Distress and DHD* (n = 29; 45.3%) and *High Meaning, Low Distress and DHD* (n = 35; 54.7%). Subgroups were statistically discrepant on measures of meaning in life (d = 0.57), anxiety (d = 3.07), depression (d = 2.57), and DHD (d = 2.76), with medium to large effect sizes. Subgroups were also significantly different in physical quality of life (d = 16.50). No significant differences were noted demographically between subgroups. **Conclusions:** To our knowledge, this is the first cluster analysis investigating affective and existential distress in a population of homebound adults with advanced cancer. Results suggest the possibility of 2 distinct subgroups of homebound cancer patients, the first of which is prone to clinically significant anxiety, depression, and moderate DHD, possibly due to a subtle difference in meaning in life. Results also point to physical symptom burden and quality of life being exponentially impacted by affective and existential distress. This study provides valuable information which can aid assessment and treatment for vulnerable homebound adults with advanced cancer. Research Sponsor: National Cancer Institute; National Institute of Nursing Research.

12072 **Poster Session**

Race/ethnicity-stratified survival differences associated with psychotropic medication use in pancreatic cancer. First Author: Hussein Khalil, Purdue University, West Lafayette, IN

Background: Pancreatic cancer is linked to poor survival and a high burden of neuropsychiatric symptoms. Psychotropic medications are used to manage these symptoms, yet racial/ethnic disparities in use have been reported. The association between psychotropic use and survival in pancreatic cancer across racial and ethnic groups remains unclear. We evaluated race/ethnicity–stratified differences in 2-year survival associated with psychotropic use among older adults with pancreatic cancer. **Methods:** Retrospective cohort study using SEER–Medicare data (2007–2019) including patients aged $\geq$65 years with incident pancreatic cancer and continuous Medicare Parts A, B, and D coverage. Psychotropic use was defined as $\geq$1 Part D claim for antipsychotics, antidepressants, or anxiolytics. Overall survival was assessed using restricted mean survival time (RMST) up to 730 days post-diagnosis. RMST differences between users and non-users were compared within race/ethnicity strata (non-Hispanic White = NHW, non-Hispanic Black = NHB, Hispanic, Other) Sidak-adjusted chi-square tests. **Results:** Among 81,535 patients, 33.8% received at least one psychotropic medication. Overall psychotropic use was associated with a modest increase in RMST (+8.3 days), driven by antidepressants (+10.7 days) and anxiolytics (+26.8 days), while antipsychotic use was associated with shorter RMST (−13.7 days). RMST gains varied by race/ethnicity, with larger increases among NHB (+17.1 days) and Hispanic patients (+16.4 days), smaller gains among NHW (+4.1 days), and no benefit among Other races (−3.6 days). Antipsychotic-associated RMST deficits were greatest among NHB patients (−34.4 days). Antidepressants were associated with longer RMST across all groups whereas anxiolytic benefits were not observed among Other races. **Conclusions:** In this cohort of older adults with pancreatic cancer, psychotropic medication use was associated with modestly longer survival overall, largely attributable to antidepressants and anxiolytics, while antipsychotic use was associated with shorter survival. Survival associations varied by race and ethnicity, with larger gains among NHB and Hispanic patients. These findings underscore the importance of equitable recognition and management of neuropsychiatric symptoms and support further research incorporating symptom severity and medication use. Research Sponsor: None.

RMST difference (days) comparing psychotropic users vs non-users stratified by race/ethnicity.

	Overall Cohort (N=81,535)	NHW (N=59,059)	NHB (N=8,015)	Hispanic (N=8,993)	Other (N=5,468)
Any psychotropic	**8.3 (1.8)**	4.1 (2.2)	**17.1 (6.0)**	**16.4 (5.7)**	−3.6 (7.4)
Antipsychotics	**-13.7 (3.7)**	**−14.4 (4.4)**	**−34.4 (11.3)**	6.2 (11.9)	−17.0 (14.47)
Antidepressants	**10.7 (2.0)**	**6.6 (2.4)**	**16.3 (6.8)**	**16.2 (6.3)**	**21.1 (8.70)**
Anxiolytics	**26.8 (2.36)**	**23.5 (2.7)**	**44.1 (9.1)**	**34.2 (7.8)**	**−2.4 (10.02)**

Bolded values are statistically significant.

12073 Poster Session

National trends in palliative care use among hospitalized cancer patients: A seven-year analysis of demographic and socioeconomic disparities. First Author: Aishwarya Ramesh, The New York Medical College Graduate Medical Education Program at St. Mary's General Hospital and St. Clare's Health, Denville, NJ

Background: The 2016 ASCO guidelines recommend that patients with advanced cancer receive dedicated palliative care (PalC) services early in the disease course, concurrent with active treatment, within 8 weeks of diagnosis. Despite these efforts, disparities persist in the use of PalC across various demographic groups. Our study evaluated the pattern and temporal trends in PalC use among adult cancer patients to identify inequities across various clinical factors. **Methods:** We analyzed adult cancer hospitalizations from the 2016-2022 National Inpatient Sample. PalC was identified using ICD-10 code Z51.5. Utilization trends were examined by hospital type, demographics (age, sex, race/ethnicity), income quartile, and insurance type. Trends in mean age and in-hospital mortality among PalC recipients were calculated. Survey-weighted regression models assessed temporal trends, accounting for complex sampling design ($p < 0.05$ significant). **Results:** We analyzed 18,574,934 hospitalizations from 2016 to 2022. PalC utilization increased significantly from 10.61% in 2016 to 14.01% in 2022 ($p < 0.001$), representing a 32% relative increase. The mean age of PalC recipients rose from 68.61 years to 69.63 years ($p < 0.001$), while in-hospital mortality remained stable at approximately 28-29% (p = 0.144). Utilization increased across all subgroups (all $p < 0.001$). By hospital type, urban teaching hospitals had the highest overall utilization (12.40%, range 10.72-14.01%), followed by urban nonteaching hospitals (12.07%, range 10.81-14.63%), and rural hospitals had the lowest (10.77%, range 8.81-12.71%). Black patients had the highest overall utilization (13.44%, range 11.75-15.20%), followed by White (12.15%, range 10.52-14.02%) and Hispanic patients (11.57%, range 10.04-12.48%). Females had higher utilization than males (12.72% vs 11.83%). By insurance, Medicaid had 12.79% utilization (range 11.18-14.60%), Medicare 12.72% (range 11.00-14.52%), and private insurance 10.13% (range 8.86-11.56%). The lowest income quartile had 12.47% utilization (range 10.73-14.31%) compared to 12.04% (range 10.45-13.50%) in the highest quartile. All demographic and socioeconomic subgroups demonstrated significant increasing trends over the study period. **Conclusions:** PalC utilization increased significantly across all groups, with stable mortality rates. However, disparities remain, with lower utilization in rural hospitals, among privately insured patients, and among Hispanic populations. Despite progress in overall adoption, these findings highlight ongoing inequities in PalC access that require targeted interventions to achieve equitable guideline implementation. Research Sponsor: None.

12074 Poster Session

Pilot trial of virtual and in-person symptom screening with targeted early palliative care (STEP2). First Author: Camilla Zimmermann, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada

Background: Routine early palliative care (EPC) for patients with advanced cancer improves quality of life. To increase scalability, models of triggered EPC have been encouraged. We assessed feasibility of hybrid virtual/in person Symptom screening and Targeted Early Palliative care (STEP2) to provide EPC triggered by symptoms. **Methods:** Patients with advanced cancer, ECOG 0-2, prognosis 6-36 months, were recruited from lung, gastrointestinal, genitourinary, breast and gynecology outpatient oncology clinics. Symptoms were screened virtually/in person ≤48 hours before oncology visits using Edmonton Symptom Assessment System-revised (ESAS-r+). Moderate to severe symptom scores ("screen positive") triggered an alert to a nurse, who called the patient, offering an EPC visit (in-person/virtual, as per patient preference). Participants completed measures at baseline, 2, 4, and 6 months. The primary endpoint was feasibility, with the following criteria: ≥40 patients accrued in 4 months; ≥60% complete screening for ≥70% of visits; ≥50% triggering a call have ≥1 EPC visit; ≥60% complete all measures. **Results:** From 30/03/2025-26/06/2025 40 patients were enrolled (median age [range], 62 [39-88]; 21/40 [53%] female). Disease site distribution was: 12/40 (30%) lung, 9/40 (23%) gynecology, 8/40 (20%) genitourinary, 6/40 (15%) gastrointestinal, 5/40 (13%) breast. Of the 40 patients enrolled, 36 (90%) completed screening for ≥70% of visits and 29 (73%) screened positive: 18 at baseline and 11 later during the trial. The most common triggering symptoms were anxiety (18/29, 62%), sleep (17/29, 59%), depression (10/29, 35%), pain (8/29, 28%), and dyspnea (8/29, 28%); 21/29 (72%) screen-positive and 0 screen-negative patients received EPC before trial end. Measure completion at 2, 4, and 6 months was 90% (36/40), 85% (34/40), and 83% (33/40). Initial EPC visits were in person for 14/21 (67%) and virtual for 7/21 (33%); 20/21 (95%) of patients received ≥2 follow-up visits. Results for measures at baseline and at trial end are shown in the Table. **Conclusions:** Virtual/in person STEP2 is feasible and directs EPC to those who most need it, with most screen-positive patients accepting EPC. A phase III trial is underway. Clinical trial information: NCT06326554. Research Sponsor: AMS Healthcare.

Variable	Measure (score range)	Time point	N	Mean	Standard Deviation	Difference, 6 mo. vs. baseline (95% CI)
Quality of life	FACIT_PAL14	Baseline	40	42.2	7.2	0.3
	(0-56; higher is better)	6 mo.	34	42.7	7.7	(-0.9, 1.6)
Symptom	ESAS_EDS	Baseline	40	17.5	12.9	0.3
Control	(0-90; higher is worse)	6 mo.	33	18.9	13.2	(-3.1, 3.7)
Depression	PHQ-9	Baseline	40	5.4	3.4	-1.0
	(0-27; higher is worse)	6 mo.	34	4.6	3.1	(-1.9, 0.0)
Anxiety	GAD-7	Baseline	40	4.9	3.8	-1.4
	(0-21; higher is worse)	6 mo.	34	3.7	3.5	(-2.3, -0.5)
Satisfaction	FAMCARE-P16	Baseline	40	72.8	7.2	-5.8
With care	(16-80; higher is better)	6 mo.	34	67.1	12.0	(-10.1, -1.4)

12075 Poster Session

Integrated assessment of cachexia, body composition, and patient-reported outcomes in unplanned hospitalizations of patients with metastatic cancer (PRO-HAND study). First Author: Enes Yeşilbaş, Etlik City Hospital, Department of Medical Oncology, Ankara, Turkey

Background: Patients with metastatic cancer hospitalized for unplanned admissions represent a highly vulnerable population with substantial short-term mortality and readmission risk. Cachexia, altered body composition, and patient-reported outcomes (PROs) frequently coexist in this setting, yet their integrated relevance during hospitalization remains insufficiently characterized. **Methods:** PRO-HAND is a cross-sectional observational study including metastatic cancer patients hospitalized for unplanned admissions between September 2024 and September 2025 who had received systemic anticancer therapy within the preceding 6 months. Cachexia-related indices, bioelectrical impedance analysis (BIA)-derived body composition parameters, and PROs were assessed during hospitalization. Primary outcomes were 30-day mortality, 90-day mortality, and unplanned 30-day hospital readmission. Associations were evaluated using hierarchical multivariable logistic regression models with sequential adjustment for clinical variables, cachexia indices, body composition parameters, and PROs. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). **Results:** A total of 233 patients were included (median age 62 years; 71.2% ECOG ≥2). Median follow-up was 3.35 months. Thirty-day mortality occurred in 21.9%, 90-day mortality in 23.2%, and unplanned 30-day readmission in 57.9%. Lower handgrip strength–based cachexia index (H-CXI) was associated with higher odds of 30-day mortality (OR per 10-unit decrease 1.43; 95% CI 1.19–1.74; $p<0.001$). ECOG ≥2 and lower phase angle were also associated with early mortality, whereas the composite triglyceride–glucose and inflammation index was not. For 90-day mortality, lower global quality-of-life scores and higher pain burden showed stronger associations than cachexia indices. For unplanned 30-day readmission, a higher total body water/fat-free mass (TBW/FFM) ratio was associated with increased risk. **Conclusions:** Cachexia severity, body composition abnormalities, and PROs show distinct, outcome-specific associations in metastatic cancer patients hospitalized for unplanned admissions. Integrated assessment during hospitalization may provide complementary clinical information across these domains. Clinical trial identification NCT07167082. Research Sponsor: None.

Selected baseline characteristics and outcomes.

Characteristic	n (%) or median (IQR)
Age ≥65 years	98 (42.1)
ECOG performance status ≥2	167 (71.7)
Weight loss ≥10% (6 months)	126 (54.1)
H-CXI	34.23 (14.95–71.02)
Phase angle, degrees	4.03 (2.95–5.52)
FFMI, kg/m²	17.14 (15.48–19.31)
FACT-G total score	62 (56–68)
Pain score (VAS 0–10)	4 (2–6)
Unplanned 30-day readmission	135 (57.9)
30-day mortality	51 (21.9)

12076 Poster Session

Dermatologic adverse events (dAEs) and emotional quality of life (QoL) in patients (pts) with breast cancer: A mixed-methods study. First Author: Elyssa Kim, Case Western Reserve University School of Medicine, Cleveland, OH

Background: dAEs are a common and impactful aspect of QoL and have an emotional impact. However, its measurement relating to cancer care is limited. Validated tools focus on dermatology or chemotherapy but can be disconnected. Our pilot study utilized several validated tools to assess overall dAEs and their impact. **Methods:** Mixed methods consisting of a cross-sectional survey with qualitative interviews was conducted on pts with breast cancer who recently completed (<1 year) chemotherapy (acute) or completed chemotherapy ≥1 year ago (longitudinal). A panel of dermatologic and oncologic patient-reported outcome measures (PROMs) was: PRO Version of the Common Terminology Criteria for AEs (PRO-CTCAE), Skindex-16 (S-16), Fear of Cancer Recurrence–Short Form (FCR-SF), and Impact of Events–Intrusive Thoughts subscale (IES). Semi-structured interviews were done to elicit responsiveness to this panel. **Results:** 64 pts were screened & 60 enrolled (mean age: 63.0±19.1). Pts were Female and insured (100%), White (78.3%) & Black (20%). Pts were treated with radiation (70%), surgery (66.7%), hormone therapies (23%), targeted or immunotherapies (15%). Common symptoms were xerosis (73.3%), alopecia (66.7%), pruritus (58.3%). Mean total S-16 score was 19.4 (range: 0 (no impact) to 75.5 (most impact)); PRO-CTCAE 22.2 (0, 48.5); FCR-SF 43.2 (0, 97.2); IES 20.8 (0, 65.6). S-16 scores demonstrated moderate correlations with PRO-CTCAE (r=0.60, CI=0.41-0.74, $p<0.001$), indicating related but nonredundant constructs. The S-16 didn't correlate with the FCR-SF or IES, suggesting distinct emotional burdens on pts with cancer. There was no significant difference in survey scores between acute and longitudinal groups. Qualitative analyses revealed this combination of surveys encapsulated QoL and emotional experiences related to dAEs. Several pts were unaware of the dAEs they could experience as well as how to treat them. **Conclusions:** This is a novel assessment of dAEs in QoL, implementing and comparing cancer-specific PROMs to common dermatologic PROMs. Results indicate that dAEs significantly impact QoL and oncological psychometric outcomes are not fully captured with current dermatologic PROMs. Research Sponsor: None.

Correlations between PROM scores.

Instrument Pair	Correlation (r)	95% CI	P-value
PRO-CTCAE total			
S-16 total	0.60	0.41 to 0.74	<.001
S-16 symptoms	0.65	0.48 to 0.78	<.001
S-16 emotional	0.48	0.26 to 0.66	<.001
S-16 functioning	0.40	0.17 to 0.60`	0.001
FCR-SF total			
S-16 total	-0.15	-0.39 to 0.11	0.252
S-16 symptoms	-0.08	-0.32 to 0.18	0.562
S-16 emotional	-0.17	-0.40 to 0.09	0.207
S-16 functioning	-0.14	-0.38 to 0.12	0.295
PRO-CTCAE total	-0.06	-0.31 to 0.20	0.646
IES total	0.06	-0.20 to 0.31	0.657
IES total			
S-16 total	0.14	-0.12 to 0.38	0.287
S-16 symptoms	-0.03	-0.28 to 0.23	0.845
S-16 emotional	0.19	-0.07 to 0.42	0.148
S-16 functioning	0.19	-0.07 to 0.42	0.142
PRO-CTCAE total	0.24	-0.01 to 0.47	0.062

12077 **Poster Session**

Sociodemographic determinants of end-of-life care settings and place of death among patients with lung cancer in the United States. First Author: Ali Mushtaq, Cleveland Clinic Foundation, Cleveland, OH

Background: Optimizing the place of death is a key component of quality end-of-life (EOL) cancer care, with home and hospice settings generally preferred over acute care hospitals. While lung cancer mortality has declined, disparities in EOL care utilization remain a concern. This study utilized the CDC WONDER database to analyze longitudinal trends and sociodemographic predictors of place of death for lung cancer decedents over a 25-year period. **Methods:** We performed a retrospective analysis of death certificate data for all lung cancer-related deaths in the U.S. from 1999 to 2023. Place of death was categorized as Decedent's Home, Hospice/Nursing Facility, Medical Facility-Inpatient (referent), or Outpatient/ER. Multinomial logistic regression estimated adjusted odds ratios (aOR) with 95% confidence intervals (CI) for predictors, adjusting for age, sex, race, ethnicity, urbanization, and year. **Results:** A total of 3,563,902 lung cancer deaths were identified. The most common place of death was the decedent's home (44.9%), followed by inpatient medical facilities (30.7%) and hospice/nursing facilities (22.1%). There was a significant longitudinal shift away from inpatient death. For every advancing calendar year, the odds of dying at home increased by 3% (OR 1.03; 95% CI 1.03-1.03) and the odds of dying in a hospice/nursing facility increased by 4% (OR 1.04; 95% CI 1.04-1.04). Compared to White patients, Black patients had significantly lower odds of dying at home (OR 0.57; 95% CI 0.57-0.58) or in a hospice facility (OR 0.68; 95% CI 0.68-0.68). Notably, Black patients had 53% higher odds of dying in an Outpatient/ER setting (OR 1.53; 95% CI 1.53-1.53) compared to White patients. Patients in rural areas had higher odds of dying at home (OR 1.17; 95% CI 1.16-1.17) but lower odds of dying in a hospice/nursing facility (OR 0.93; 95% CI 0.92-0.93) compared to those in large metropolitan areas. **Conclusions:** From 1999 to 2023, lung cancer mortality shifted significantly from inpatient settings to home and hospice care. Yet, Black patients remain significantly less likely to utilize home/hospice care and more likely to die in acute ER settings. Additionally, rural patients show high home death rates but lower facility-based hospice use, suggesting infrastructure gaps. Targeted interventions are required to ensure equitable EOL care access. Research Sponsor: None.

12078 **Poster Session**

More than pain relief: Associations between provider compassion, anxiety, and burnout in ED oncology care. First Author: Christopher John Coyne, University of California, San Diego, San Diego, CA

Background: Compassionate care is a cornerstone of high-quality oncology practice, especially in high-stress environments like the emergency department (ED). However, the relationship between perceived provider compassion and patient outcomes such as pain, psychological distress, and provider wellbeing is not well understood. **Methods:** We conducted a cross-sectional survey of oncology patients presenting to the ED. Participants completed validated assessments including the Brief Pain Inventory, the Schwartz Center Compassionate Care Scale (SCCCS), the Pain Catastrophizing Scale, the Pain Anxiety Symptom Scale, and the Self-Compassion Scale. Separately, ED providers were surveyed to assess their own burnout, rated on a 0–8 scale. Patients were grouped into High Compassion (SCCCS $>$100) and Low Compassion ($\leq$100) categories based on their ratings of provider compassion. Group comparisons were performed using t-tests, and linear regressions explored associations between compassion scores and patient-reported and provider-reported outcomes. **Results:** Of 57 patients, 22 (39%) reported high provider compassion. Median final pain was lower in the High Compassion group (2.0 vs 4.0), though not statistically significant (p=0.18). Patients in the High Compassion group had significantly lower pain anxiety scores (29.2 vs 52.5, p=0.014) and were seen by providers with significantly lower burnout scores (3.1 vs 5.6, p=0.022). A trend toward lower pain catastrophizing was also observed (15.6 vs 25.7, p=0.069). No significant differences were found in pain reduction or self-compassion. **Conclusions:** In a cohort of ED oncology patients, higher perceived provider compassion was significantly associated with lower pain anxiety and with lower provider-reported burnout, but not with pain scores. These findings suggest that compassion may be more strongly linked to patients' emotional experiences and the wellbeing of the providers delivering care. Integrating compassionate care practices into acute oncology settings may support both patient psychological health and provider sustainability. Research Sponsor: None.

Key outcomes by compassion group (>100 vs. ≤100).

Outcome	High Compassion (Mean)	Low Compassion (Mean)	p-value
Final Pain (0–10)	2.33	3.67	0.183
Pain Anxiety Total	29.2	52.5	0.014
Catastrophizing Total	15.6	25.7	0.069
Self-Compassion Total	23.7	23.7	0.996
Provider Burnout (0–8)	3.1	5.6	0.022

12079 **Poster Session**

Denosumab versus zoledronic acid in patients with breast cancer: A propensity-matched real-world time-to-event analysis. First Author: Mohammad Salameh, Hamilton Medical Center, Dalton, GA

Background: Bone-modifying agents are routinely used in patients with breast cancer to reduce skeletal-related complications and metabolic disturbances. Denosumab and zoledronic acid are commonly prescribed; however, comparative real-world data evaluating their relative safety and effectiveness remain limited. We compared time-to-event outcomes associated with denosumab versus zoledronic acid in a large real-world cohort of patients with breast cancer. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network, comprising electronic health records from 70 healthcare organizations. Adult patients with breast cancer who received either denosumab or zoledronic acid were identified, excluding those with underlying osteoporosis. Patients were propensity score–matched 1:1 based on demographics, comorbidities, concomitant oncologic therapies, and baseline laboratory parameters, yielding 15,147 patients per cohort. Outcomes assessed over a 5-year follow-up period included time to hypercalcemia, severe hypercalcemia (serum calcium $\geq$14.0 mg/dL), hypocalcemia, pathological fracture in neoplastic disease, and bone pain. Time-to-event analyses were performed using Kaplan–Meier methods and compared with log-rank testing; hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. **Results:** After propensity score matching, 15,147 patients were included in each cohort with well-balanced baseline characteristics. Over 5 years of follow-up, hypercalcemia did not differ between patients treated with zoledronic acid and denosumab (hazard ratio [HR] 0.99, 95% CI 0.88–1.10; log-rank p= 0.831). Severe hypercalcemia (serum calcium $\geq$14.0 mg/dL) was uncommon, with no significant difference between groups (HR 1.25, 95% CI 0.94–1.68; log-rank p= 0.129). Pathological fracture in neoplastic disease occurred less frequently in the zoledronic acid cohort, although this difference did not reach statistical significance (HR 0.88, 95% CI 0.76–1.01; log-rank p= 0.060). Hypocalcemia was significantly less frequent among patients receiving zoledronic acid compared with denosumab (HR 0.44, 95% CI 0.40–0.49; log-rank $p<$ 0.001). Bone pain did not differ significantly between treatment groups (HR 0.95, 95% CI 0.89–1.02; log-rank p= 0.186). **Conclusions:** In this real-world analysis of patients with breast cancer, denosumab and zoledronic acid demonstrated similar time-to-event outcomes for hypercalcemia, severe hypercalcemia, pathological fracture, and bone pain, while zoledronic acid was associated with a significantly lower risk of hypocalcemia. These findings highlight important distinctions in toxicity profiles between agents and may inform individualized selection of bone-modifying therapy. Prospective studies are warranted to further define optimal agent selection in specific clinical subgroups. Research Sponsor: None.

12080 **Poster Session**

BXQ-350 in combination with FOLFOX7 and bevacizumab: Evaluation of effect on oxaliplatin-induced CIPN and neutropenia—A phase 1b/2a trial to assess the efficacy and safety of BXQ-350, a first-in-class sphingolipid metabolism modulator, in newly diagnosed metastatic colorectal carcinoma. First Author: Tariq Arshad, Bexion Pharmaceuticals, Covington, KY

Background: Chemotherapy-induced peripheral neuropathy (CIPN) and Neutropenia are significant side effects associated with many cancer drugs and are highly prevalent in mCRC patients receiving oxaliplatin-based regimens. CIPN can severely impact quality of life (QoL) and may require dose vacation, reduction or interruption. CIPN pathology is complex and not completely understood; preclinical and clinical data have shown inflammatory (IL-6, Il-8, IL-10) and immune involvement as well as elevated levels of sphingolipids, a class of bioactive signaling molecules. Neutropenia can also be a potentially severe side effect and may occur in up to 40% of mCRC patients receiving FOLFOX. BXQ-350 is a nanovesicle formulation of Saposin C, an allosteric activator of sphingolipid metabolism that normalizes dysregulated sphingolipid metabolism by lowering S1P, GM3 and GluCer levels while it increases ceramide level, promoting a return to homeostasis. **Methods:** BXQ-350 is being investigated in a Phase 1b/2 study in combination with mFOLFOX7 and Bevacizumab (SoC) in newly diagnosed mCRC patients (NCT05322590). Primary objectives are to assess safety and preliminary efficacy of this combination, and to determine cumulative oxaliplatin dose. Secondary objectives include intensity, frequency and time to onset of CIPN. **Results:** The Phase Ib trial enrolled 33 oxaliplatin dosing evaluable patients; all patients completed the primary treatment period (6 months of SoC treatment plus BXQ-350). Amongst the 33 patients, 19 completed the full 12 Cycles of oxaliplatin dosing, 28 completed at least 8 Cycles with only 2 patients having dosing halted before Cycle 8 due to CIPN. There were no reported Grade 4 and only 3 reported Grade 3 CIPN AEs, all occurred after Cycle 12. Analysis of Neurofibrillary Light Chain (NfL) biomarkers suggests concordance with physician and patient reported outcomes. Grade 3 or higher Neutropenia was meaningfully reduced to 5% in mCRC patients receiving FOLFOX plus Bevacizumab. **Conclusions:** Results show that BXQ-350 was safe and well tolerated in the combination. Data suggest that BXQ-350 may provide additional clinical benefits and may reduce intensity or delay onset of CIPN while meaningfully reducing Grade 3 or higher Neutropenia, allowing for increased cumulative dosing of oxaliplatin and relative dose intensity in 1L mCRC. Clinical trial information: NCT05322590. Research Sponsor: Bexion Pharmaceuticals.

12081 Poster Session

Results from a pilot feasibility study of a novel community health worker–led intervention delivering stepped palliative care and care navigation for patients with pancreatic ductal adenocarcinoma. First Author: Nikhil Ravi Thiruvengadam, Loma Linda University, Loma Linda, CA

Background: Pancreatic Ductal Adenocarcinoma (PDAC) is associated with substantial morbidity, poor quality of life, and poor overall survival. Early palliative care (PC) has been shown to improve quality of life and reduce symptom burden in PDAC, but specialty PC services are often unavailable for this fast-progressing illness, and even then are only utilized by a minority of PDAC patients. To address this challenge, we developed a digitally enhanced CHW-led intervention to deliver stepped PC to patients with PDAC and to report its feasibility and preliminary efficacy. **Methods:** Adults (aged ≥18 years) with newly diagnosed PDAC (within 2 weeks of diagnosis) were enrolled in a single-arm pilot feasibility study from January to August 2025 (N = 48). The intervention involved early palliative care engagement with targeted escalation (stepping) for patients with untreated symptoms, leading to expedited PC visits, patient education, care navigation, and providing targeted financial resources for patients. The digital component involves using short educational videos and the Twilio SMS to administer the Edmonton Symptom Assessment Scale weekly, with patients with high symptom scores being stepped up to PC visits. The CHW-led intervention was delivered over 12 weeks. Feasibility outcomes were patient engagement with the CHW and completion of the intervention. The acceptability outcome was defined using the AIM-IAM-FIM instrument. Secondary outcomes include symptom burden (NCCN/FACT Hepatobiliary Cancer Symptom Index-18), Advanced Care Planning (ACP) compliance rates, and financial toxicity (measured by the COST instrument). **Results:** The median age of pts (N = 48) was 69 (IQR 62-76), and 29 (60%) were Hispanic. 25 (52%) had metastatic PDAC, 14 (29.1%) had borderline resectable PDAC, and 9 (18.8%) had resectable PDAC at diagnosis. Four patients died before the intervention was completed, while the remaining patients completed it. Regarding acceptability, 94% strongly agreed that the intervention was acceptable. Themes identified from exit-interviews included the critically important role of the CHW in the process, including appointment scheduling, especially as symptoms worsened. Patient's symptom burden (median 68 vs. 55, P = 0.02) and rates of financial toxicity (39% vs. 25%, p = 0.01) decreased from baseline to 12 weeks, while 83% of patients completed ACP by 12 weeks. **Conclusions:** Our digitally-enhanced CHW-led intervention delivering stepped PC was feasible and acceptable to patients with PDAC. The intervention was associated with improvement in symptom burden, reduction in financial toxicity, and higher ACP planning rates. Future prospective comparative studies are needed to understand the intervention's ability to help manage the morbidity associated with PDAC. Research Sponsor: DOD/CDMRP PCARP; PA230343.

12082 Poster Session

Expressive writing for body image distress and anxiety in adolescent and young adult cancer survivors: A pilot, randomized controlled trial. First Author: Victoria A. Wytiaz, Department of Internal Medicine, University of Michigan Rogel Cancer Center, Ann Arbor, MI

Background: Up to 60% of adolescent and young adult cancer survivors (ages 15-39) experience body image distress but this is not well-managed due to multiple factors, including lack of provider expertise and patient hesitancy. Expressive writing invites participants to write openly about their thoughts and feelings related to a traumatic event, such as the cancer experience, to facilitate cognitive and emotional processing of the event. Expressive writing has not been explored in the AYA survivorship population with body image distress. The purpose of this pilot study is to determine the feasibility of implementing a four-week, in-home body image-focused expressive writing intervention for AYA cancer survivors with clinically significant body image distress. **Methods:** AYA cancer survivors with body image distress were recruited from oncology clinics at the University of Michigan and through institutional social media campaigns. Participants were randomized (1:1) to either a 4-week body image-focused expressive writing intervention or a control writing condition. Feasibility was based on recruitment and adherence, defined as completing 75% of writing sessions. Pre- and post-intervention, participants self-reported body image distress and anxiety utilizing the ten-item Body Image Scale (BIS) and the Generalized Anxiety Disorder 7 Scale (GAD-7). Changes in patient-reported outcomes were analyzed using linear mixed-effects models. **Results:** 27 participants were randomized (n=14 expressive writing, n=13 control) and were mainly female (96%) with locally advanced or metastatic cancer (60%). 26/27 (96.3%) completed all writing prompts outcome measures. Both groups demonstrated improvement in body image distress over the 4-week period. Expressive writing participants showed a numerically greater reduction (estimated change −5.57, 95% CI [−8.34, −2.8]). The difference-in-change between groups was −2.77 (time × treatment interaction, not significant). Results in Table 1. **Conclusions:** A four-week, in-home body image-focused expressive writing intervention demonstrated feasibility among AYA cancer survivors with body image distress. AYA cancer survivors face persistent body image distress that can affect quality of life. This intervention can offer a feasible, accessible, and low-cost approach to help mitigate these concerns. Further research is needed to determine the efficacy of the intervention to reduce body image distress among AYA cancer survivors. Clinical trial information: NCT06046014. Research Sponsor: Conquer Cancer Anna Braglia Endowed Young Investigator Award in Cancer Supportive Care.

Estimated change in BIS and GAD-7 from baseline to week 4 by group.

Outcome	Group	Estimated Change	95% CI	p-value
BIS score	Expressive Writing	-5.57	[-8.34, 2.8]	<0.001
BIS score	Control Writing	-2.77	[-5.75, 0.22]	0.0676
GAD-7 score	Expressive Writing	-0.93	[-3.34, 1.48]	0.435
GAD-7 score	Control Writing	-4.67	[-7.26, 2.08]	0.001

12083 Poster Session

The psychosocial status of children who have a parent with cancer. First Author: Erdinc Nayir, Toros University, Mersin, Turkey

Background: While numerous studies have investigated the psychosocial status of children affected by childhood cancer, the number of studies investigating this situation in children whose parents have cancer is extremely limited. The purpose of this study is to determine the prevalence and causes of emotional and behavioral problems in children whose parents have cancer. **Methods:** We conducted the study in the medical oncology outpatient clinics between February and April in 2025. We included 73 children who have a parent diagnosed with cancer (case group) and an age- and gender-matched control group from healthy 59 children between the ages of 8-16. We subjected all the participants to the Revised Child Anxiety and Depression Scale (RCADS), recording their age, gender, parent gender and age, educational status, duration and severity of disease, number of siblings. **Results:** No statistically significant difference was found between the groups in terms of age, gender, education level, parent's age, gender, education level, and number of siblings ($p>0.001$). The case group exhibited significantly elevated anxiety ($p<0.001$) and depression scores (p=0.002), along with higher total scale scores ($p<0.001$), in comparison to the control group . Correlation analyses revealed weak but statistically significant positive correlations between age and total anxiety, depression, and total score in the case group (p= 0.010). Further examination of anxiety subdimensions showed similarly weak yet significant correlations with PaD, SAD, and OCD ($p<0.001$). The females within the case group exhibited significantly higher anxiety (p=0.030) and depression (p=0.035) scores, and higher total scale score (p=0.025) compared to males. Significant differences were observed in anxiety scores (p=0.018) and total scale scores (p=0.047) according to parental education level, with the highest scores consistently found among children whose parents held a master's degree. No significant differences were observed in anxiety, depression, or total scale scores according to the child's educational level, parent age, whether the patient was the father or the mother, disease duration and severity, and sibling status. **Conclusions:** Children of cancer patients are affected by their parents' health problems. These children should be considered in light of the "comprehensive approach to cancer". It should be noted that these children may need psychological rehabilitation at least as much as their parents with cancer. Research Sponsor: None.

12084 Poster Session

Hearing/vestibular dysfunction and longitudinal changes in psychosocial well-being among breast cancer survivors. First Author: Jincong Q. Freeman, Cancer Prevention and Control Research Program, UChicago Medicine Comprehensive Cancer Center, Chicago, IL

Background: Breast cancer treatment, in some cases, can cause hearing/vestibular dysfunction and negatively affect patients' quality of life. The breast cancer survivor population is both growing and aging. Despite evidence that other cancer survivors have higher rates of hearing/vestibular problems than the general population, little is unknown about the impact of hearing/vestibular dysfunction on long-term changes in psychosocial well-being (PSWB) among breast cancer survivors. **Methods:** We surveyed the Chicago Multiethnic Epidemiologic Breast Cancer Cohort regarding whether patients had ever been told by a doctor that they had tinnitus, hearing loss, and/or vertigo between July and September 2023. PSWB was assessed repeatedly using the 10-item PROMIS on psychological distress/social isolation in 2020, 2021, 2022, and 2025. Total scores range from 0 to 40, with higher scores reflecting better PSWB. We fit separate linear mixed-effects models for hearing/vestibular dysfunction, controlling for age, race/ethnicity, marital status, income, insurance, comorbidity, AJCC stage, and treatment modality. Adjusted coefficients (β) and 95% CIs were calculated. **Results:** 1,466 breast cancer survivors were included: the mean age at survey was 63.5 years (SD 11.7); 69.6% identified as White, 22.6% as Black, 3.7% as Asian or Pacific Islander, and 3.6% as Hispanic. Overall, 16.5%, 17.4%, and 8.6% had tinnitus, hearing loss, and vertigo, respectively. The distribution of PSWB scores and trend over time are presented in the table. Survivors with hearing/vestibular dysfunction had lower mean scores than those without. After covariate adjustment, tinnitus (β −1.12; 95% CI −1.93, −0.30), hearing loss (β −1.12; 95% CI −1.93, −0.30), and vertigo (β −1.34; 95% CI −2.44, −0.24) were associated with significantly lower PSWB scores. In all subgroups, the PSWB score increased significantly over the years. Furthermore, Hispanic ethnicity, Medicaid, and being single were correlated with lower scores; whereas higher income levels were associated with higher scores. **Conclusions:** In this diverse cohort, breast cancer survivors with hearing/vestibular dysfunction experienced suboptimal PSWB over the study period. PSWB also varied by socioeconomic status. Oncology programs should consider screening for hearing/vestibular dysfunction and unmet sensory healthcare needs to improve PSWB and quality of life among breast cancer survivors. Research Sponsor: National Institute on Aging; T32AG000243; National Cancer Institute; P20CA233307; Breast Cancer Research Foundation; BCRF-23-071; Susan G. Komen; TREND21675016.

	PSWB score, mean (SD)					
	Tinnitus		Hearing loss		Vertigo	
Survey year	No	Yes	No	Yes	No	Yes
2020	28.7 (6.0)	28.4 (6.0)	28.8 (6.0)	28.2 (5.9)	28.7 (6.0)	28.3 (6.1)
2021	29.4 (5.6)	28.9 (5.9)	29.4 (5.6)	29.0 (5.5)	29.5 (5.6)	27.8 (6.0)
2022	30.1 (5.6)	29.2 (6.1)	30.0 (5.7)	29.7 (6.0)	30.1 (5.6)	28.5 (6.5)
2025	33.3 (5.6)	32.1 (6.4)	33.3 (5.6)	32.4 (6.2)	33.2 (5.6)	31.8 (6.3)
Trend per year (*p*-value)	0.89 (<0.001)	0.75 (<0.001)	0.87 (<0.001)	0.86 (<0.001)	0.89 (<0.001)	0.66 (<0.001)

12085 Poster Session

Cognitive impairment during anti-EGFR targeted therapy in metastatic colorectal cancer patients. First Author: Liubov Yu Vladimirova, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation

Background: Cognitive function is a critical determinant of psychosocial adaptation and quality of life in patients with cancer. Even mild cognitive impairment may negatively affect daily functioning, communication, compliance, and social participation. The psychosocial consequences of cognitive changes during medical treatment are insufficiently studied in metastatic colorectal cancer (mCRC) patients. Anti-EGFR-targeted therapy affects downstream MAPK signaling, a pathway involved in synaptic plasticity and cognitive processes. This provides a biological rationale for investigating cognitive outcomes and their psychosocial relevance. **Methods:** This study included patients with mCRC who received FOLFOX6-based first-line treatment. The main group (n = 50) received FOLFOX6 combined with an anti-EGFR monoclonal antibody (cetuximab or panitumumab), while the control group (n = 50) received FOLFOX6 +/-bevacizumab. Cognitive function was assessed at baseline and after eight cycles of therapy using the Addenbrooke's Cognitive Examination–Revised (ACE-R) and the Frontal Assessment Battery (FAB). Changes in cognitive performance were analyzed in relation to patients' functional vulnerability during ongoing treatment. Cognitive side effects were also evaluated according to CTCAE V.5.0. **Results:** Baseline cognitive performance was comparable between groups. After eight cycles of therapy, patients receiving anti-EGFR-targeted treatment demonstrated a significant decline in cognitive performance, including ACE-R total scores (from 93 [90; 94.5] to 87 [85; 90.5], $p < 0.001$), memory domain scores (from 22 [22; 23.5] to 20 [19; 20], $p < 0.001$), and attention/orientation scores (from 18 [16; 18] to 17 [15; 18], p = 0.005). In contrast, cognitive measures in the control group showed only minimal changes or remained stable over the same observation period. Evaluation according to CTCAE V.5.0. showed cognitive disturbance, memory and concentration impairments of mild and moderate grades, which were significantly more frequent in the anti-EGFR targeted group than in the control group (p<0,005). **Conclusions:** Anti-EGFR-targeted therapy in metastatic colorectal cancer patients may cause significant cognitive impairment, which undoubtedly contributes to psychosocial maladaptation and reduced quality of life. This pattern of selective cognitive decline may compromise functional independence, communication, and psychosocial adaptation during active anticancer treatment. Routine cognitive assessment during treatment may facilitate early identification of patients at risk and support multidisciplinary management strategies. In addition, the role of the MAPK signaling pathway in memory formation should be studied. Research Sponsor: None.

12086 Poster Session

Burnout among caregivers of hospitalized medical oncology patients: A cross-sectional survey study. First Author: Suleyman Sami Guzel, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Medical Oncology, Istanbul, Turkey

Background: Caregivers of patients hospitalized in medical oncology wards play a crucial role in daily care and clinical decision-making, yet they are rarely screened for burnout. While caregiver burden has been widely studied in outpatient and palliative care settings, data focusing on inpatient oncology caregivers remain limited. This study aimed to evaluate burnout levels among caregivers of hospitalized medical oncology patients and to identify associated demographic and caregiving-related factors. **Methods:** This cross-sectional study included 91 caregivers of patients hospitalized in a medical oncology ward. Burnout and psychosocial distress were assessed using a structured 10-item survey developed based on established conceptual domains of burnout and caregiver burden. Items were rated on a 5-point Likert scale, with higher scores indicating greater burnout. Burnout levels were categorized as low (≤2), moderate (2–4), or high (≥4). Internal consistency was assessed using Cronbach's alpha. Group comparisons were performed using Mann–Whitney U and Kruskal–Wallis tests. Correlations were analyzed using Spearman's rho. Multiple linear regression analysis was conducted to identify independent predictors of burnout. **Results:** The median caregiver age was 49 years and 73.6% were female. The median burnout score was 3.0. Overall, 23.1% of caregivers reported low burnout, 57.1% moderate burnout, and 19.8% high burnout. Female caregivers had significantly higher burnout scores compared with males (p = 0.008). Caregivers with additional caregiving responsibilities also reported higher burnout levels (p = 0.026). Burnout scores correlated positively with duration of in-hospital caregiving ($\rho = 0.228$; p = 0.030). In multivariable regression analysis, female gender remained an independent predictor of higher burnout ($\beta = -0.298$; p = 0.003). Table 1 shows demographic and clinical characteristics of caregivers and patients. **Conclusions:** Caregivers of hospitalized medical oncology patients experience substantial levels of burnout, with nearly one in five reporting high burnout. Female caregivers appear to be at particularly high risk. These findings highlight the need for routine psychosocial screening and targeted supportive interventions for caregivers in inpatient oncology settings. Research Sponsor: None.

Variable	N=91 (%)
Caregiver gender (F/M)	67 (73.6)/24 (26.4)
CG age (years) (median)	49 (23-75)
CG Education level (L/Medium/H)	39 (42.9)/27 (29.7)/25 (27.5)
Relationship to patient (Spouse/Child/ First degree relatives/Other)	32 (35.2)/29 (31.1)/19 (20.9)/11 (12.9)
Additional caregiving responsibility (Y/N)	29 (31.9)/62 (68.2)
Burnout level [L/Moderate/H]	21 (23.1)/52 (57.1)/18 (19.1)
Patient gender (F/M/Other)	41 (45.1)/46 (50.5)/4 (4.4)
Patient age (years) (median)	61 (20-81)
Cancer diagnosis groups	
Lung and H&N	27 (29.7)
GI	23 (23.3)
GU+breast	22 (24.2)
Other	8 (8.8)

12087 Poster Session

Longitudinal associations between patient and caregiver quality of life following hematopoietic stem cell transplantation. First Author: Daniel Yang, Duke University School of Medicine, Durham, NC

Background: Caregivers of patients undergoing hematopoietic stem cell transplantation (HSCT) experience high rates of psychological distress, yet patient-level factors most strongly associated with caregiver outcomes over time remain poorly understood. We evaluated longitudinal associations between patient and caregiver quality of life (QoL) following HSCT. **Methods:** We conducted a secondary analysis of the PROTECT randomized trial of integrated palliative care during HSCT. Among enrolled patient-caregiver dyads, we measured patient (FACT-BMT) and caregiver (CarGOQoL) QoL at baseline, week 2, and months 3, 6, and 12. Only patient-caregiver dyads that completed both measures were included in analyses at each timepoint. Linear mixed-effects models were used to assess the relationship between changes in patient QoL and changes in caregiver QoL, adjusting for time and treatment arm. **Results:** Among 186 enrolled patient-caregiver dyads, patients had a mean age of 55.2 ± 12.4 years and 65% were male. Mean CarGOQoL remained stable from baseline through month 12 (range: 74.1–75.9). FACT-BMT declined at week 2 (91.9 ± 20.4) compared to baseline (105.0 ± 18.8), then recovered and improved by month 3 through month 12 (Table 1). In multivariable mixed-effects modeling, within dyads, visits where the patient's QoL exceeded their usual level were associated with higher caregiver QoL ($\beta = 0.11$ per 1-point above the patient's mean; $p < 0.001$), adjusted for time and arm. **Conclusions:** While average caregiver QoL remained stable throughout the follow-up period despite changes in average patient QoL, individual caregiver QoL closely tracked their patient's QoL over the post-HSCT follow-up period. Patient-reported QoL represents a clinically meaningful marker to identify at-risk caregivers. Interventions targeting patient QoL may yield dual benefits for patient-caregiver dyads. Clinical trial information: NCT03641378. Research Sponsor: None.

Patient and caregiver quality of life by timepoint.

Outcome	Baseline (n = 183)	Week 2 (n = 157)	Month 3 (n = 126)	Month 6 (n = 112)	Month 12 (n = 109)
Patient FACT-BMT (mean +/- SD)	105.0 +/- 18.8	91.9 +/- 20.4	107.0 +/- 18.4	111.0 +/- 19.6	112.0 +/- 19.9
Caregiver CarGOQoL (mean +/- SD)	74.1 +/- 12.0	74.1 +/- 12.7	75.9 +/- 12.8	75.8 +/- 13.8	75.7 +/- 14.8
Spearman	0.37 ($p < 0.001$)	0.27 ($p < 0.001$)	0.25 (p = 0.004)	0.40 ($p < 0.001$)	0.38 ($p < 0.001$)

12088 Poster Session

Closing the depression gap in community oncology: Real-world outcomes from collaborative care. First Author: Tyler Jones, Colla Health, Portland, OR

Background: Depression is prevalent among patients with cancer, yet access to evidence-based care remains uneven. Community oncology clinics, where the majority of cancer care occurs, are less likely to offer integrated mental health services compared to comprehensive cancer centers, resulting in higher underdiagnosis, undertreatment, and persistent depressive symptoms. The Collaborative Care Model (CoCM) offers a potential strategy to address this disparity in community oncology. **Methods:** Community oncology patients with clinically significant symptoms of depression, as measured by a baseline PHQ-9 score ≥ 5, and receiving collaborative care, delivered primarily remotely, for at least 80 days were analyzed as part of this observational study. Patients had their PHQ-9 assessed after 90 (≥ 80 & ≤ 100) days, including evidence of remission (PHQ-9 < 5) and signs of response (decrease of PHQ-9 score by ≥ 50% or ≥ 5 points). Mean within-patient changes among all patients, stratified by baseline depression severity, were measured using paired t-tests. **Results:** Among 307 patients, mean PHQ-9 scores were observed to decline from 12.9 (SD 4.7) at baseline to 8.2 (SD 5.1) after 90 days of collaborative care (mean change -4.72, 95% CI -5.30 to -4.14, P< 0.001); 26.7% were observed to have depressive symptoms in remission and 51.5% had a clinical response. Patients with severe depression (PHQ-9 >=20) at baseline had the largest improvement (mean change -9.60, 95% CI -11.78 to -7.42, P < 0.001). **Conclusions:** Community oncology patients with depressive symptoms receiving collaborative care experienced reductions in PHQ-9 scores after 90 days of care, with a substantial proportion experiencing clinical response and/or remission in this brief timeframe. Symptom changes were observed across the full spectrum of symptom severity. These real-world outcomes highlight meaningful decreases in depressive symptoms, underscoring the promise of CoCM as a scalable care model for community oncology clinics. Research Sponsor: None.

Observed depression outcomes among community oncology patients engaged in Collaborative Care Model (CoCM) psychosocial care for 90 days, stratified by baseline PHQ-9 severity.

PHQ-9 Score Category at Baseline	N	Mean PHQ-9 Score at Baseline (SD)	Mean PHQ-9 Score at 90 Days (SD)	N Observed in Remission at 90 Days (%)	N Experiencing Response at 90 Days (%)	Mean Total PHQ-9 Score Change (95% CI)
All (5–27)	307	12.9 (4.7)	8.2 (5.1)	82 (26.7)	158 (51.5)	-4.72*** (-5.30, -4.14)
Mild (5-9)	81	7.2 (1.4)	5.4 (3.6)	36 (44.4)	26 (32.1)	-1.86*** (-2.64, -1.08)
Moderate (10-14)	113	11.9 (1.4)	7.8 (4.2)	28 (24.8)	55 (48.7)	-4.08*** (-4.85, -3.31)
Moderately Severe (15-19)	83	16.5 (1.4)	9.9 (5.5)	15 (18.1)	55 (66.3)	-6.61*** (-7.85, -5.38)
Severe (20-27)	30	21.9 (1.6)	12.3 (6.0)	<11	22 (73.3)	-9.60*** (-11.78, -7.42)

***P<0.001.

12089 **Poster Session**

Impact of structured oncologist-led home visits on psychological distress and resilience in patients with solid tumors undergoing chemotherapy: A comparative study. First Author: Sonya Kircheva Draganova, Nadezhda Hospital, Sofia, Bulgaria

Background: Psychological distress is prevalent among patients receiving chemotherapy. Home-based supportive interventions have the potential to address early psychosocial needs; however, data regarding their impact on both distress and resilience remain limited. **Methods:** Between March 1 and December 1, 2025, chemotherapy-naïve patients with solid tumors were invited to participate in a home-based supportive care study. Patients who opted for the intervention received a structured home visit by a medical oncologist following each of the first two chemotherapy cycles. These visits included patient-led discussions where the oncologist addressed questions regarding disease staging, prognosis, treatment protocols, and anticipated side effects. Before each chemotherapy cycle, patients completed self-reported assessments of psychological distress and resilience. Distress was measured using the Distress Thermometer (scale 0–10), with scores $\geq$4 categorized as high distress. Resilience was evaluated using the 10-item Connor-Davidson Resilience Scale, a unidimensional instrument where items are rated on a 5-point Likert scale. Higher scores indicate greater resilience. The control group consisted of patients who did not receive home visits; they completed the same assessments during routine clinic visits. In both cohorts, breast, lung, and colorectal cancers were the most frequent diagnoses. Distress and resilience outcomes were analyzed within each group across three time points using Cochran's Q and Friedman test. **Results:** The intervention group included 66 patients (12 male, 54 female) with a mean age of 58 years (SD $\pm$13.58). The proportion of patients reporting high distress decreased progressively: 72.7% at baseline, 53.0% after the first visit, and 45.5% after the second visit ($p < 0.001$). Mean distress scores also declined significantly from 4.91 $\pm$ 2.79) at baseline to 3.55 $\pm$ 2.71) and 3.53 $\pm$ 2.59) following the first and second visits, respectively ($p < 0.001$). In contrast, mean resilience scores remained stable (30.26 $\pm$7.06, 29.95 $\pm$ 8.82, and 28.24 $\pm$ 12.12; p = 0.72).The control group included 145 patients (39 male, 106 female) with a mean age of 58 years (SD $\pm$ 12.58). In this group, the prevalence of distress remained relatively stable across the three assessments: 66.2% at baseline, 57.9% at the second assessment, and 56.6% at the third (p = 0.074). Mean distress scores showed minimal variation: 4.45 $\pm$, 4.08 $\pm$, and 4.09 $\pm$, respectively (p = 0.163). Mean resilience scores exhibited a downward trend from 30.19 $\pm$ 7.74) to 27.03 $\pm$ 12.20) and 25.52 $\pm$ 13.21), though this did not reach statistical significance (p = 0.076). **Conclusions:** This study demonstrates that oncologist-led home visits during the early stages of chemotherapy can significantly reduce psychological distress in cancer patients while preserving resilience. Research Sponsor: None.

12090 **Poster Session**

Impact of volunteer-integrated palliative home visits on psychological well-being among metastatic breast cancer patients in northern Malaysia. First Author: Siti Khairizan Binti Rahim, Universiti Sains Malaysia (USM) Medical Center Bertam, Kepala Batas, Malaysia

Background: Metastatic breast cancer patients face overlooked psychosocial challenges, mitigated through home visits. Universiti Sains Malaysia's volunteer-integrated palliative home visits bridge access gaps, support mental health (SDG 3), and foster partnerships (SDG 17). As Malaysia's most common female cancer (2017–2021: 16,430 cases, 22.2% stage IV), breast cancer highlights early palliative integration, yet local home-based outcomes remain unstudied. **Methods:** This prospective cross-sectional study (October 2024 to January 2026) in Northern Malaysia (Penang, Kedah) evaluated the impact of volunteer-integrated palliative home visits on Psychological Well-Being (Ryff 42-item scale, baseline and after 12 weeks). Healthcare professionals provided symptom and psychosocial care, while trained volunteers focused on emotional and practical support. Mixed teams (professionals and volunteers) conducted visits 1 and 6, with flexible staffing for intervening visits. Of 94 recruited patients, 81 completed the study and domain changes analyzed via descriptives, paired t-tests, and Cohen's d. **Results:** Participants were predominantly female (99%), aged 40 to 49 years (34.6%), low-income B40 group (64%) and multi-racial (78% Malay, 15% Chinese, 7% Indian). All had ECOG 0-3 at baseline, but 38% in ECOG 4 post-intervention. High-score groups (>30 on Ryff's subscale sums) increased for positive relations (70% to 95%), environmental mastery (47% to 69%), self-acceptance (45.5% to 68%), and personal growth (70% to 85%), but declined for autonomy (55.6% to 54.3%) and purpose in life (74% to 35%). Paired t-tests (Table 1) revealed significant small-to-moderate improvements in environmental mastery ($p<0.001$, d=0.46), positive relations ($p<0.001$, d=0.41), self-acceptance (p=0.042, d=0.23), and purpose in life (p=0.016, d=0.27). Changes in autonomy and personal growth were not statistically significant. Purpose-in-life declines reflect disease progression. **Conclusions:** The volunteer-integrated palliative care significantly improved environmental mastery, positive relations, self-acceptance, and purpose in life among breast cancer patients, despite ECOG deterioration. Findings support that the home visit enhanced psychological well-being amid disease progression, though refinement is needed for domains with non-significant changes. Research Sponsor: Pfizer Inc; 90835877.

Paired t-test results for Ryff Psychological Well-Being (PWB) domains (pre- vs. post-intervention).

PWB domains	Mean Difference (SD)	t(80)	p value	*Cohen's d*	Effect Size
Autonomy	1.10 (6.51)	1.52	0.133	0.17	Small
Self-Acceptance	1.99 (8.66)	2.07	***0.042**	0.23	Small
Positive Relations with Others	3.00 (7.31)	3.7	***0.000**	0.41	Small to Medium
Personal Growth	1.07 (8.75)	1.11	0.272	0.12	Small
Environmental Mastery	3.27 (7.10)	4.15	***0.000**	0.46	Medium
Purpose in Life	1.59 (5.84)	2.46	***0.016**	0.27	Small

12091 **Poster Session**

Influence of socioeconomic factors on patient-reported provider communication among patients with cancer. First Author: Nishwant Swami, Hospital of the University of Pennsylvania, Philadelphia, PA

Background: Patient-provider communication is central to patient's understanding and overall experience, particularly in multi-disciplinary cancer care. Socioeconomic disadvantages may amplify downstream consequences of poor communication by eroding trust and exacerbating structural and access-related barriers. Using nationally representative survey data, we examined the association between socioeconomic factors and patient-reported communication experiences among adult cancer survivors. **Methods:** We analyzed pooled 2011-2023 data from the US Medical Expenditure Panel Survey (MEPS) to identify adults ($\geq$18 years) with a history of cancer. Patient-provider communication was assessed by how often providers (1) treated patients with respect, (2) listened carefully, (3) explained things in a way they understood, and (4) spent enough time. Survey-weighted estimates compared communication scores across income and insurance groups. Multivariable ordinal logistic regression (MVA) models including survey year, race/ethnicity, education, region, sex, marital status and age estimated adjusted odds ratios (aORs) for the association of income level and insurance with patient-provider communication. **Results:** Among 9,535 cancer survivors, those in the lowest income quintile (family income $<$ federal poverty line (FPL)) reported the lowest rates of effective provider communication across all domains (57% listened, 53% time, 61% respect, and 57% explained). Survivors who reported being uninsured similarly reported the lowest rates of provider communication (50% listened, 43% time, 49% respect, and 51% explained). In adjusted analyses, lowest-income survivors were less likely than the highest income quintile survivors ($> 4\times$FPL) to report being listened to (aOR 0.76, 95% CI 0.63–0.91), respected (aOR 0.76, 95% CI 0.63–0.93), or receiving clear explanations (aOR 0.75, 95% CI 0.63–0.91). Compared with privately insured patients, uninsured survivors were less likely to report clear explanations (aOR 0.57, 95% CI 0.39–0.85), or feeling listened to (aOR 0.56, 95% CI 0.38–0.82). Both uninsured and Medicaid-insured survivors were less likely to report adequate time (uninsured: aOR 0.54, 95% CI 0.36–0.82; Medicaid: aOR 0.89, 95% CI 0.79–0.99), or feeling respected (uninsured: aOR 0.51, 95% CI 0.35–0.73; Medicaid: aOR 0.86, 95% CI 0.76–0.98). **Conclusions:** Lower income and lack of insurance were associated with worse communication among US cancer survivors. Given substantial financial, logistical, and personal burdens of cancer care, these communication gaps may weaken trust and undermine patients' ability to understand and engage with recommended treatments. Targeted provider interventions aimed at improving clinician communication and care coordination will be essential to advancing equitable cancer care and rebuilding trust in an increasingly fractured healthcare system. Research Sponsor: None.

12092 **Poster Session**

Pilot RCT of a patient-centered communication intervention to promote values-based treatment decision-making in older adults with AML. First Author: Rachel Rodenbach, James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY

Background: Older adults with acute myeloid leukemia (AML) often have limited involvement in high-stakes treatment decisions that involve tradeoffs between survival and quality of life. We developed a patient-centered communication intervention (UR-GOAL) to support values-based decision-making. We assessed how patients and oncologists discuss values during treatment decision-making and explored whether UR-GOAL improves these discussions. **Methods:** This pilot RCT randomized patients $\geq$60 years old with newly diagnosed AML to UR-GOAL vs. usual care. UR-GOAL uses best-worst scaling to help patients prior to deciding on treatment to prioritize their values, which are shared with the oncologist. Two team members blinded to arm independently coded transcribed treatment conversations for values talk, defined as discussion of what matters to patients in treatment decisions. Values included patient, disease/treatment, and sociocultural priorities; examples include quality of life, treatment effectiveness, and physician recommendation, respectively. Coders assessed the depth of values discussion (the extent to which the oncologist explored patient values beyond acknowledgment), patient engagement (e.g. patient elaborating on values and asking questions), and values alignment (whether the oncologist incorporated patients' most important values into the treatment plan). Differences in coding were resolved by consensus. Continuous outcomes were compared using t-tests or ANOVA and categorical outcomes using chi-square or Fisher's exact tests. **Results:** We included 92 patients (mean age 74 and SD 7; 63% male; 93% white). A mean of 6.0 values was discussed per encounter (SD 3.0), with fewer explored in depth (mean 1.5; SD 1.5). The number of values discussed in total and in depth did not differ between arms (total values: UR-GOAL 6.4 vs. usual care 5.7, p = 0.28; and in depth: UR-GOAL 1.4 vs. usual care 1.6, p = 0.14). However, patients showed a trend toward greater engagement in values discussions in the UR-GOAL arm compared with usual care (78% vs. 59%, p = 0.07). The values most commonly expressed by patients as most important in driving treatment decisions were treatment effectiveness (44%) and care logistics (e.g. treatment in hospital vs. clinic, 19%), followed by physician recommendation (7%), treatment toxicity (4%), and quality of life (3%). Values aligned with the treatment plan in 70% of cases (UR-GOAL 76% vs. usual care 63%, p = 0.26). Patients whose values aligned discussed more values compared with those whose values were not aligned, not discussed, or indeterminate (6.9 vs. 4.0, $p < 0.01$). **Conclusions:** Older adults with AML discuss several values with their oncologists during treatment decision-making, though fewer in depth. The UR-GOAL communication intervention may promote patient engagement in shared decision-making and value alignment. Clinical trial information: NCT05335369. Research Sponsor: Conquer Cancer Career Development Award; American Cancer Society.

12093 Poster Session

Using the NCCN distress thermometer to evaluate clinically elevated levels of distress among caregivers of HSCT patients. First Author: Christine Vinci, Department of Health Outcomes and Behavior, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Caregivers of patients receiving an allogeneic hematopoietic stem cell transplant (HSCT) play a vital role in the care and recovery of patients. They must be present with the patient 24/7 for up to 100 days post-transplant, and they often report levels of distress higher than patients. Importantly, caregiver and patient distress are interdependent. Thus, knowing when to deploy appropriate resources and support to a distressed caregiver is essential. To date, the NCCN Distress Thermometer (DT) is a validated, single-item clinical measure consistently used in the oncology setting to assess and intervene upon patient distress. If such a tool was available for HSCT caregivers, oncology providers could assess and provide support for those in heightened distress. To date, limited research has been conducted in this area. This study examines the relationship of DT with self-reported depression and anxiety in a large sample of HSCT caregivers with the goal of proposing a potential clinical cut-point of elevated distress on the DT. **Methods:** Caregivers completed the DT, Center for Depression Studies Depression Scale (CESD), and Generalized Anxiety Disorder 7 (GAD7) 1-2 weeks pre-transplant as part of a larger study. Spearman correlation coefficients evaluated the association of the DT with CESD and GAD7. Logistic regression evaluated DT as a predictor of clinically elevated levels of depression (CESD $>$16) and anxiety (GAD7 $>$10). DT cut points (e.g., $\geq$4) as predictors of clinically elevated depression and anxiety were evaluated using sensitivity, specificity, and area under the curve (AUC). **Results:** Caregivers (N = 287) were 73% female, 75% spouse/partner of the patient, and ranged in age from 22-87 years (M = 58.2, SD = 13.4). The DT ranged from 0-10 with M = 4.5 (SD = 2.6). The CESD ranged from 0-51 with M = 13.3 (SD = 10.3) and 36% scored $>$16. The GAD7 ranged from 0-21 with M = 6.4 (SD = 5.5) and 24% scored $>$10. The DT was very strongly correlated (p's $<$ .0001) with the CESD (r_s= .69) and GAD7 (r_s= .76). DT score significantly predicted elevated depression (OR = 1.92, 95% CI[1.64-2.24]) and elevated anxiety (OR = 2.30, 95% CI[1.84-2.86]). Table 1 presents sensitivity, specificity, and AUC for DT cut points of 4-7. **Conclusions:** Findings suggest that although a cut-point of 4 on the DT has high specificity and a cut-point of 7 has high sensitivity, a cut-point of 6 indicates more balanced specificity and sensitivity when considering both depression and anxiety. In the clinical setting, providing the single-item DT as a measure of caregiver distress should allow for a brief and useful assessment indicating a greater need to provide support resources. Research Sponsor: National Cancer Institute.

DT cut point: N (%)		CESD			GAD7		
		Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
4: 173 (60%)	.60	.95	.77	.52	.99	.75	
5: 148 (52%)	.69	.88	.78	.61	.93	.77	
6: 114 (40%)	.80	.75	.78	.74	.85	.80	
7: 80 (28%)	.89	.58	.73	.86	.73	.80	

12094 Poster Session

A digital educational and decision-support intervention for patients with advanced lung cancer receiving immunotherapy: Results of a multi-phase, mixed-methods study. First Author: Matthias Villalobos, Department of Thoracic Oncology, Thoraxklinik, Heidelberg University Hospital and National Center for Tumor Diseases (NCT), NCT Heidelberg, Translational Lung Research Center Heidelberg (TLRC-H), Member of the German Center for Lung Research (DZL), Heidelberg, Germany

Background: Immunotherapy has transformed the treatment of advanced lung cancer, but it has also increased the complexity of information that patients must navigate. Knowledge deficits may compromise disease-management, shared decision-making, and goal-concordant care including timely integration of palliative care. This study aimed to develop and evaluate a digital application to support patients throughout this process. **Methods:** We employed a multiphase, mixed-methods design comprising: (1) a questionnaire-based online-survey with descriptive analysis (n = 186; SPSS); (2) semi-structured interviews with patients with advanced lung cancer analyzed using qualitative content analysis (n = 20; MAXQDA); (3) user-centered app development involving patients and health-care professionals; and (4) a pre-post pilot study (n = 69) analyzed using Wilcoxon signed-rank test. Primary outcomes for the pilot study were decisional conflict and knowledge; secondary outcomes included preparedness for decision-making, self-efficacy, usability, and acceptability. **Results:** Pre-development data integration revealed limited and frequently inaccurate patient knowledge regarding immunotherapy and treatment goals, as well as a discrepancy between patients' desired and actual involvement in treatment decisions, with minimal participation in physician-patient decision-making. The developed app demonstrated high usability and acceptability. In the pilot study, use of the app was associated with a statistically significant reduction in decisional conflict (median [IQR]: 20.3 [6.6–34.0] pre vs. 10.9 [3.1–29.7] post; p = 0.001), significant improvements in knowledge (p $<$ 0.001), and increased preparedness for decision-making. **Conclusions:** Insufficient patient participation in decision-making, combined with knowledge deficits about immunotherapy, underscores the need for enhanced communication strategies. The digital application developed in this study appears to be a feasible, acceptable, and effective tool to support informed decision-making among patients with advanced lung cancer. Future research should evaluate integration into routine clinical workflows, long-term impact, and adaptations to address diverse patient needs and evolving treatment options. Clinical trial information: 00032683. Research Sponsor: AstraZeneca.

12095 Poster Session

Protective factors supporting caregiver well-being in glioblastoma. First Author: Desiree Reinken, CEUFast, Villa Ridge, MO

Background: Caregiving in glioblastoma (GBM) means dealing with cancer symptoms, plus the neurological decline that comes with this disease. Becoming a caregiver is rarely straightforward. Caregivers often become essential to the patient's daily life and well-being, though this may result in neglecting their own health. Most caregivers develop coping strategies (protective factors such as caregiver mastery or spiritual beliefs) to manage the responsibility of caring for a terminally ill loved one. This study looked at how caregiver protective factors shifted across the disease trajectory and whether these factors were connected. **Methods:** This was a secondary analysis of data from a three-group randomized clinical trial testing a needs-based intervention for neuro-oncology caregivers (NINR # R01 NR013170). Caregivers were included if they were 21 or older, identified by the patient as their unpaid primary caregiver, spoke English, had phone access, were not caring for anyone else (except children under 21), and scored above 6 on the CES-D. Recruitment occurred from March 2014 to July 2016 at the University of Pittsburgh Medical Center, the University of Pittsburgh Cancer Institute, and the MD Anderson Cancer Center. Patients and caregivers gave informed consent prior to participation in the primary study. We conducted an a priori power analysis to determine the sample size required for detecting minimal differences in quality of life (QOL). The final sample included 60 caregivers. We measured outcomes at baseline, two, four, six, and ten months. Analysis used paired samples t-test, bivariate correlations, and linear mixed models. **Results:** Caregiver QOL changed significantly over time, particularly from baseline to four months (p = 0.02) and four to six months (p = 0.01). Protective factors correlated with one another at varying strengths (weak, moderate, and strong). At each time point, religion and spirituality were related to other protective factors. Spirituality had significant positive correlations with caregiver mastery (r = 0.32-0.65, p = $<$ .001-0.01) and QOL (r = 0.44-0.70, p = $<$ .001-0.01) throughout the study. After factoring in optimism, we found significant associations for caregiver mastery, positive aspects of caregiving, social support, and religion. **Conclusions:** Spirituality emerged as a key protective factor, yet most caregiver interventions ignore it. Providers should recognize and support spiritual coping mechanisms throughout GBM care, offering resources that match caregiver values and beliefs. Monitoring caregiver QOL is equally critical as tracking patient outcomes. When QOL declines, early interventions can prevent caregiver burnout and improve care quality for both members of the dyad. Research Sponsor: None.

12096 Poster Session

"When I'm translating, I'm a daughter as well": Perspectives of caregivers supporting patients with limited language proficiency. First Author: Rinat Nissim, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: Family caregivers of people with advanced cancer provide essential support but often experience significant emotional distress. Caring for patients with limited language proficiency (LLP) introduces additional, distinct challenges. Patients with advanced cancer and LLP experience barriers to access and quality of care and advance care planning, resulting in increased reliance on family caregivers even when professional language services are available. This study explored the experiences and challenges of caregivers supporting advanced cancer patients with LLP to inform future interventions aimed at improving patient and caregiver outcomes. **Methods:** Caregivers supporting patients with advanced cancer and limited English proficiency treated at the Princess Margaret Cancer Centre (Toronto, Canada) were recruited via clinician referral and study flyers. Participants completed semi-structured interviews or focus groups exploring healthcare navigation, interpreter use, support needs, and recommendations for service improvement for patients with LLP. Transcripts were analyzed iteratively using practical thematic analysis. **Results:** Ten caregivers (ages 34–63; 6 female, 4 male; 2 spouses, 8 adult children; 5 supporting Chinese-speaking patients) participated. Participants acted as informal interpreters and mediators between patients and providers, a form of 'language brokering' that added substantial emotional and cognitive burden. Their experiences are subsumed under 4 interrelated themes: 1) Protective buffering and information gatekeeping: caregivers often filtered or withheld prognosis and end-of-life information to protect patients' emotional well-being or align with cultural values; 2) Interpreter use representing both relief and loss of control: professional interpretation reduced linguistic burden but created new concerns regarding privacy, cultural sensitivity, and control over sensitive discussions; 3) Constant vigilance: caregivers felt constant pressure to monitor and understand patients' symptoms and preferences, communicate them to providers, and support patient understanding and reassurance; and 4) Invisibility of caregiver needs: caregivers rarely recognized or prioritized their own needs, framing language brokering and caregiving as an expected familial or cultural duty. **Conclusions:** Family caregivers supporting patients with advanced cancer and LLP perform substantial emotional and cognitive labor that remains largely unrecognized in clinical practice. Interventions such as consistent and proactive access to professional interpreters and multilingual educational resources delivered across multiple modalities may support both patients and caregivers. These findings highlight an under-recognized but critical dimension of equitable, patient-centered oncology care. Research Sponsor: Princess Margaret Cancer Centre.

12097 **Poster Session**

Assessing loneliness in glioblastoma patients and caregivers using a nationwide survey. First Author: Jacob Ellen, Harvard Medical School, Boston, MA

Background: Loneliness is associated with poorer health outcomes and quality of life in cancer patients, yet its prevalence in the glioblastoma (GBM) population remains understudied. GBM's rapid progression and intensive treatment demands affect both patients and caregivers, but the burden of loneliness in these groups is unknown. We conducted a nationwide survey that assessed loneliness prevalence within the GBM community. **Methods:** OurBrainBank, a patient-led GBM nonprofit, distributed a HIPAA-compliant survey from February to September 2024 to GBM patients, current caregivers, and caregivers bereaved within 12 months. Loneliness was measured using the validated 3-item UCLA Loneliness Scale (range 3–9), with scores $\geq$6 indicating loneliness. Multivariable linear and logistic regression examined associations between caregiver status, race (white vs non-white), and financial difficulties in the past year and loneliness, adjusting for age, gender, and urban vs rural residence. **Results:** Among 525 respondents (404 caregivers, 121 patients), median age at diagnosis was 59 years. Overall, 52.0% (273/525) met criteria for loneliness, and the median UCLA score of the sample was 6.0. Caregivers reported higher loneliness than patients: 57.4% (232/404) vs 33.9% (41/121) were lonely, with mean UCLA scores of 5.88 (SD 1.90) versus 4.78 (SD 1.81). In adjusted models, caregivers had nearly threefold higher odds of loneliness (OR 2.97, 95% CI 1.91–4.67) and UCLA scores 1.22 points higher on average compared to GBM patients (95% CI 0.83–1.61; both $p < 0.001$). Financial difficulty in the last year (29% of sample) was similarly associated with greater loneliness (OR = 1.85 for loneliness, p = 0.002; 0.68-point higher average UCLA scores, 95% CI 0.32-1.05, $p < 0.001$). Finally, non-white respondents (12% of the sample) had higher odds of high loneliness compared to white respondents (OR = 4.00, p = 0.01) and had a 0.59 point higher UCLA score on average (p = 0.03). **Conclusions:** In this nationwide survey, GBM caregivers experienced substantially greater loneliness than patients themselves, and loneliness was also concentrated among those facing financial hardship and among non-white respondents. These findings highlight an underrecognized psychosocial burden and support integrating caregiver-focused and equity-oriented interventions into GBM care. Research Sponsor: None.

12098 **Poster Session**

Parent willingness to enroll children with acute lymphoblastic leukemia in escalation and de-escalation clinical trials. First Author: Kellee Nicole Parker, The University of Utah, Salt Lake City, UT

Background: Patient and parent willingness to participate in clinical trials has and will continue to be essential to improve care for children with acute lymphoblastic leukemia (ALL). Clinical trials for ALL can involve escalation of therapy (i.e., addition or intensification of chemotherapy or immunotherapy) or in subgroups with excellent prognosis, de-escalation of therapy (i.e., removal of agents or blocks of therapy with aim of minimizing toxicity). Understanding parents' decision making for trial participation is particularly important in de-escalation trials. We aimed to characterize parent willingness to enroll children with ALL in escalation and de-escalation clinical trials, identify sociodemographic and clinical determinants of willingness, and delineate decision making information needs. **Methods:** Parents of children currently or previously treated for ALL who are members of the Momcology support and advocacy organization completed an investigator-developed, parent-piloted online survey. Parents were presented with theoretical escalation and de-escalation trial scenarios and completed items about willingness to enroll their child and associated informational needs. Quantitative data were summarized descriptively and Spearman correlations examined associations with sociodemographic and clinical determinants. Qualitative data were analyzed using content analysis. **Results:** A total of 456 parents responded. Mean child age at diagnosis was 5.5 years [SD = 0.2, range 0-19]; 79% (369) had B-ALL and 17% (78) had T-ALL; and 65% (297) had completed therapy and were alive at the time of survey. Results showed that 22% (99) of parents would consider enrolling their child in a de-escalation clinical trial, 47% (216) would not, and 31% (141) were unsure. Responses for escalation trials (N = 423) were similar, with 21% (90) yes, 42% (179) no, and 36% (154) unsure. There was a significant negative correlation between both parent education level (rho = -0.12, p = 0.013) and annual household income (rho = -0.10, p = 0.047) with willingness to consider de-escalation, but not escalation, trial enrollment. Child age at diagnosis, current treatment status and distance from treatment center were not correlated with willingness. Parent decision making information needs clustered into three overarching domains:1) impact on likelihood of relapse, survival outcome, and late effects, 2) evidence credibility, and 3) applicability to their child's individual risk profile. **Conclusions:** Across a large parent sample, substantial hesitation to enroll children with ALL in both escalation and de-escalation trials exists. Sociodemographic factors were associated with de-escalation decision making. Further research is needed to incorporate evidence-based parent decision making support in future ALL trials and to evaluate decision making and correlates in real world scenarios. Research Sponsor: University of Utah, Department of Pediatrics; Children's Oncology Group.

12099 **Poster Session**

New paradigms of cancer and new language: A qualitative study exploring language around goals of cancer surgery. First Author: Bonnie Odelia Wong, Brigham and Women's Hospital, Boston, MA

Background: Cancer interventions are often discussed amongst providers and presented to patients within the dichotomy of "curative" vs. "palliative" interventions. However, as understanding of cancer biology has shifted and as cancer treatments have evolved, some cancers have become chronic diseases for which surgery may have a non-curative but disease-targeted role. Despite new paradigms of cancer care, language has not evolved to reflect new goals of cancer surgery. **Methods:** Semi-structured interviews were conducted with cancer surgeons from throughout the U.S. via purposive and snowball sampling. Interviews included discussions of two hypothetical scenarios describing non-curative surgical operations and discussion of the term "disease-controlling" surgery as a category of neither palliative nor curative surgical intent. Transcribed and de-identified interviews were analyzed inductively using grounded theory. **Results:** 18 surgeons from 16 institutions were interviewed. Surgeons collectively outlined how changes in the paradigm of cancer treatment have resulted in challenges describing intent of cancer surgery. Specifically, responses to the term "disease controlling" surgery elicited examples of cancer pathologies and treatment courses which fail to fit existing treatment-intent language and which captured new roles for surgery in cancer treatment paradigms. These roles of surgery include "surgery as curative treatment" (including both curative intent with probability of cure and curative intent with possibility of cure), "surgery as adjuvant treatment" (targeted surgery to assist systemic therapies with possible change in disease course), and "surgery as palliative treatment" (symptom relief surgery without possible change in disease course). Within the 'targeted surgery' category, participants described expanded surgical roles for numerous metastatic diseases including debulking for improved systemic therapy efficacy, resection of treatment-resistant disease sites, and "resetting the clock" for indolent tumors. These operations require multidisciplinary coordination and understanding of available systemic treatments, as surgical goals are increasingly defined by each patient's broader treatment trajectory. **Conclusions:** Traditional "curative" vs. "palliative" surgical intent categories inadequately describe contemporary cancer surgery. The emergence of life-extending but non-curative treatments necessitates new language frameworks that better align with current understandings of cancer biology and new treatment modalities. New language is necessary to facilitate clearer communication between providers and patients about surgical goals and expected outcomes and to allow for better research evaluating whether surgical treatments achieve those goals and outcomes. Research Sponsor: National Institute of Health National Cancer Institute; T32CA092203.

12100 **Poster Session**

Assessing the efficacy of cognitive behavioral therapy on anxiety, depression, and distress in people with cancer. First Author: Daniela Tregnago, Section of Innovation Biomedicine - Oncology Area, Department of Engineering for Innovation Medicine (DIMI), University of Verona, Verona, Italy

Background: Patients with cancer frequently experience psychological impairments, including anxiety, depression, and emotional distress, which may significantly affect quality of life and overall well-being. Third-generation cognitive-behavioral interventions such as Mindfulness-Based Cognitive Therapy-Cancer (MBCT-Ca), Acceptance and Commitment Therapy (ACT) and Compassion Focused Therapy (CFT) have shown potential benefits in reducing psychological burden, although evidence of their efficacy remains limited. This study aimed to evaluate the efficacy of a structured third-generation cognitive behavioral therapy (CBT) intervention in reducing psychological symptoms in patients (pts) with cancer undergoing active cancer treatment. **Methods:** A third-generation CBT intervention was delivered twice a month. The eight individual 45-minute sessions included psychoeducation, behavioral activation, relaxation and breathing techniques, present-moment awareness, self-compassion, problem-solving, and assertiveness training. Psychological outcomes were assessed using the Hospital Anxiety and Depression Scale (HADS) and Distress Thermometer (DT) at baseline (T0) and post- psychological intervention (T1). Descriptive statistics, Student t-test and Chi-square test were performed. **Results:** Overall 341 pts were recruited. The mean age was 65.8 years (*SD* = 11.80); 60% (n = 204) were women. Most patients were married or partnered 82% (n = 279). Regarding education level, 65% (n = 221) had higher education, 29% (n = 100) secondary education, and 6% (n = 20) primary education.. At baseline psychological assessment, 4.4% of patients (n = 15) had early-stage disease (stage I–II), 50.7% (n = 173) had locally advanced disease (stage III), and 44.9% (n = 153) had advanced-stage disease (stage IV). The most represented cancer sites were gastrointestinal cancer 55.7% (n = 190), followed by lung 11.7% (n = 41) and breast cancer 10.6% (n = 36). Chemotherapy was the most frequently administrated treatment 74% (n = 254), followed by targeted therapy 10% (n = 35) and immunotherapy 10% (n = 34). At T0, clinically significant levels of anxiety, depression, and distress were reported in 33.2%, 31.3%, and 86,9% of patients, respectively. A total of 313 patients completed the intervention (dropout rate 8.2%, mainly due to disease progression), resulting in an adherence rate of 91.8%. At three-months follow up (T1), significant reductions in clinically relevant symptoms were observed for anxiety (-24.6%, $p < 0.001$), depression (-24.0%, $p < 0.001$), and distress (-30.0%, $p < 0.001$). **Conclusions:** These findings support the routine use of validated psychological screening tools in oncology and highlight the clinical value of structured CBT-based psycho-oncological interventions delivered by trained professionals to improve psychological well-being in patients with cancer. Research Sponsor: None.

12101 Poster Session

Baseline predictors of treatment response in the bounce back mind-body resiliency trial for AYA cancer survivors. First Author: Lucy Finkelstein-Fox, Health Promotion and Resilience Intervention Research Center, Massachusetts General Hospital/Harvard Medical School, Boston, MA

Background: Mind-body interventions hold promise for improving coping and reducing psychological distress among adolescent and young adult (AYA) cancer survivors, yet benefits vary across participants. Little research has identified which survivors stand to benefit most from these programs. This secondary analysis of a randomized controlled trial of a mind-body group intervention tested whether baseline emotion regulation-related factors (worry and intolerance of uncertainty) moderated intervention effects on coping and distress (anxiety and depression). **Methods:** AYA cancer survivors (N = 72; ages 18–39) were randomized 1:1 to an 8-week virtual mind-body resiliency program (Bounce Back) or waitlist control. Primary outcomes were PROMIS anxiety and depression scores and total Measure of Current Status (MOCS) coping score at post-intervention (approximately 3-month follow-up), along with coping self-efficacy. Linear regression models, adjusted for baseline levels of each outcome, tested Randomization Group $\times$ Moderator interaction terms for two baseline moderators examined separately: Penn State Worry Questionnaire (PSWQ) and Intolerance of Uncertainty Scale (IUS). Interactions with $p < 0.05$ were considered evidence of moderation. **Results:** Compared to waitlist, participants assigned to Bounce Back showed greater improvements in anxiety and coping outcomes but similar depression outcomes overall. Randomization group differences in post-intervention anxiety were significantly moderated by both worry and intolerance of uncertainty. The intervention–control difference in anxiety (adjusted for baseline) was larger among participants reporting higher baseline worry (interaction $\beta = -0.39$, $p = 0.033$) and higher baseline intolerance of uncertainty ($\beta = -0.48$, $p = 0.033$). Neither moderator significantly altered randomization group differences in depression. For coping-related outcomes, higher baseline intolerance of uncertainty strengthened the intervention effect on coping self-efficacy (interaction $\beta = 1.92$, $p = 0.047$), and there was a trend for greater total MOCS improvement among participants with higher baseline worry (interaction $\beta = 0.33$, $p = 0.086$). **Conclusions:** In this secondary analysis of a randomized trial, the Bounce Back mind-body resiliency program produced the largest anxiety and coping benefits for AYA cancer survivors with relatively higher baseline worry and intolerance of uncertainty, whereas depression outcomes did not vary by these baseline characteristics. These findings suggest that emotion regulation vulnerabilities such as worry and uncertainty intolerance may help identify higher-risk AYAs who are most likely to benefit from group-based mind-body stress-management interventions. Future trials should confirm these moderators and test whether triaging higher-risk AYAs to mind-body programs improves psychological outcomes. Research Sponsor: None.

12102 Poster Session

COMFORT Survey: A comparison of the comfort level of hematologic and solid tumor oncology specialists with serious illness conversations. First Author: Michael J. Tang, Department of Palliative, Rehabilitation and Integrative Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Serious illness conversations (SICs) are essential in aligning medical care with the values and goals of patients with advanced cancer. It is unclear if hematologic and solid tumors specialists (i.e., physicians [MDs] and advanced practice providers [APPs]) differ in their comfort level with SICs, which may drive end-of-life care outcomes. We compared the comfort level with SICs between hematologic and solid tumor specialists and examined contributing factors. **Methods:** We surveyed 186 hematology and 186 solid tumor specialists at MD Anderson Cancer Center. The 64-question survey examined their comfort with SICs under 5 domains (Transitions of Care [TOC, primary outcome], Dying Process [EOL], Prognosis, Goals, Advance Care Planning [ACP]). Responses were rated from 0 (extremely uncomfortable) to 10 (extremely comfortable). The TOC domain included 4 questions (i.e., stopping cancer therapy / transfusions / artificial nutrition and recommending hospice). We compared groups using simple linear and multivariable models accounting for specialist demographics. **Results:** 245 specialists completed this survey, with a response rate of 66%. Hematologic and solid tumor specialists both reported high comfort with TOC (7.0 [2.4] vs 7.1 [2.2]), with no significant difference between groups (mean difference [95% CI]: 0.1 [-0.5, 0.7]; P=0.78). In univariate analysis, APPs were significantly less comfortable with TOC than MDs among both hematologic (2 [1.2, 2.8]; P<0.0001) and solid tumor specialists (1.4 [0.7, 2.2]; P=0.001). In multivariate analysis, APPs remained the only significant variable associated with less comfort with TOC in hematologic (1.5 [0.4, 2.7]) and solid tumor groups (1.2 [0.2, 2.1]). Similarly, we found no significant difference between hematologic and solid tumor specialists in comfort level with the other 4 SIC domains and observed significant differences between APPs and MDs (Table). **Conclusions:** Both hematologic and solid tumor specialists reported high levels of comfort with SIC; however, APPs were significantly less comfortable. Given that APPs are increasingly involved in SIC, our study underscores the need to provide more training and support for APPs. Research Sponsor: None.

Self-reported comfort levels for 5 SIC domains.

	Mean [SD]				MD vs. APP Mean differences [95% CI]; p-value	
Domains	**Solid MD**	**Solid APP**	**Heme MD**	**Heme APP**	**Heme**	**Solid**
TOC	7.8 [1.7]	6.4 [2.5]	8.1 [1.9]	6.1 [2.4]	2 [1.2,2.8]; **<.0001**	1.4 [0.7,2.2]; **0.001**
Prognosis	8.5 [1.4]	7.1 [2.1]	8.6 [1.8]	6.8 [1.8]	1.9 [1.2,2.5]; **<.0001**	1.4 [0.8,2]; **<.0001**
Goals	8.5 [1.2]	7.8 [1.7]	8.9 [1.4]	7.5 [1.9]	1.4 [0.8,2]; **<.0001**	0.7 [0.1,1.2]; **0.09**
EOL	7.9 [1.9]	6.3 [2.6]	8 [2.3]	6.2 [2.8]	1.8 [0.9,2.7]; **0.0005**	1.6 [0.8,2.4]; **0.0009**
ACP	8.6 [1.2]	7.2 [2.5]	9.1 [1.1]	7.3 [2.4]	1.7 [1,2.5]; **<.0001**	1.4 [0.7,2.1]; **0.0006**

12103 Poster Session

Defining when and how to support palliative care communication: International consensus on timing and clinician training priorities for adolescents and young adults with cancer. First Author: Ursula Sansom-Daly, University of New South Wales and Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia

Background: Early, developmentally appropriate palliative care communication is an international standard for adolescents and young adults (AYAs) with cancer, yet remains inconsistently implemented. Clinicians report uncertainty regarding the optimal timing of palliative care discussions and around what training they need. This study aimed to establish international consensus on when key palliative care topics should be introduced with AYAs across the cancer trajectory and to identify clinician training priorities. **Methods:** A three-round international Delphi study was conducted with multidisciplinary health professionals who had worked with at least five AYAs who had died from cancer or its complications. Participants rated the appropriateness of introducing four palliative care communication topics (prognosis/goals of care, emotional/existential issues, quality of life, and end-of-life–related medical care) across prognosis levels and treatment phases. Participants also rated the importance of clinician training topics and likelihood of attending different training modalities. Consensus was defined a priori as $\geq$80% agreement. **Results:** Seventy-seven experts from 14 countries completed the final round. Consensus indicated that emotional and existential issues were appropriate to discuss early, including during active cancer treatment. In contrast, end-of-life–related medical decisions were considered appropriate later, most commonly following relapse, disease progression or poor prognosis. Discussions about prognosis, goals of care and quality of life were generally considered appropriate once cure was uncertain. Conversation timing was the only training topic to reach consensus as a priority (85.8%). Although no training modality reached formal consensus, learning from bereaved family members was the most highly endorsed approach (72.8%), followed by experiential and interdisciplinary learning formats. The presence of complex family or culturally and linguistically diverse dynamics did not fundamentally alter clinicians' views on timing, but was associated with a need for greater team support and time. **Conclusions:** This international consensus provides clear guidance on when different palliative care topics should be discussed with AYAs with cancer and identifies timing as the primary area in which clinicians require additional support. Strong clinician endorsement of experiential and family-informed training approaches highlights opportunities to strengthen workforce capacity for earlier, developmentally appropriate palliative care communication. Research Sponsor: Adolescent and Young Adult Cancer Global Accord; Cancer Institute New South Wales; 2020/ECF1163; National Health and Medical Research Council; APP1111800; APP2008300; Intramural Research Program of the National Institutes of Health (NIH); American Cancer Society; Seattle Children's Research Institute; Cambia Health Solutions; Arthur Vining Davis Foundations; National Palliative Care Research Center; CureSearch for Children's Cancer; Conquer Cancer, the ASCO Foundation.

12104 Poster Session

Reproductive and pregnancy-related outcomes among adolescent and young adult female cancer survivors (15–39 years): A nationwide population-based study in South Korea. First Author: Ja Yoon Heo, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

Background: As survival rates among adolescent and young adult (AYA) female cancer patients improve, increasing numbers of survivors pursue pregnancy and childbirth. However, population-level data on reproductive outcomes and pregnancy-related complications among female cancer survivors remain limited. **Methods:** This study collected de-identified data from the South Korean National Health Insurance Service Database. Among 95,264 women aged 15–39 years newly diagnosed with cancer between 2007 and 2010, we identified 58,107 eligible survivors. This cohort was age-matched 1:10 with 719,213 women without cancer. Reproductive outcomes were assessed in the full cohort, and pregnancy-related complications were evaluated among women with documented pregnancies. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression. **Results:** Compared with matched controls, female cancer survivors had a higher risk of infertility (OR 1.25; 95% CI 1.21–1.28) and lower odds of pregnancy (OR 0.94; 95% CI 0.93–0.96) and childbirth (OR 0.81; 95% CI 0.78–0.84). Among women who became pregnant, cancer survivors experienced higher risks of ectopic pregnancy (OR 1.20; 95% CI 1.11–1.29), miscarriage or abortion (OR 1.23; 95% CI 1.14–1.32), intrauterine infection (OR 1.26; 95% CI 1.01–1.57), and preterm labor (OR 1.21; 95% CI 1.14–1.29). **Conclusions:** AYA female cancer survivors face increased risks of infertility and adverse pregnancy-related outcomes. These findings highlight the need for specialized reproductive counselling and high-risk obstetric care for female cancer survivors. Research Sponsor: National Health Insurance Ilsan Hospital grant (NHIMC 2020-20-009).

Reproductive outcomes in the full matched cohort and pregnancy-related outcomes among the pregnancy cohort.

Outcomes, No. (%)	Survivor (N=58,107)	Control (N=719,213)	OR	95% CI
Reproductive Outcomes				
Infertility	5,439 (9.4)	55,111 (7.7)	1.245	1.209 1.282
Pregnancy	16,974 (29.2)	218,901 (30.4)	0.944	0.926 -0.961
Childbirth	10,912 (18.8)	98,229 (20.8)	0.810	0.780 -0.842
Pregnancy-related Outcomes				
Ectopic pregnancy	783 (4.6%)	8,495 (3.9%)	1.198	1.111 -1.291
Miscarriage / abortion	866 (5.1%)	9,182 (4.2%)	1.228	1.143 -1.319
Preeclampsia / eclampsia	507 (3.0%)	6,488 (3.0%)	1.008	0.920 -1.105
Gestational diabetes	3,139 (18.5%)	40,317 (18.4%)	1.055	0.965 -1.046
Intrauterine infection	85 (0.5%)	872 (0.4%)	1.259	1.007 -1.574
Premature Rupture of Membranes / amniotic fluid disorders	2,131 (12.6%)	28,002 (12.8%)	0.978	0.933 -1.025
Placental disorders	238 (1.4%)	2,776 (1.3%)	1.107	0.969 -1.265
Preterm labor	1,168(6.9%)	12,601 (5.8%)	1.210	1.137 -1.287

CI, confidence interval; No., number; OR, odds ratio.

12105 **Poster Session**

Standardized birth rates and access to assisted reproductive technology among female cancer patients in the United States. First Author: Isabel Beshar, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Fertility after cancer is critically under-defined on a national scale, reflecting a substantial gap in survivorship care. We constructed a novel longitudinal dataset to describe 1) live births and 2) use of assisted reproductive technology (ART) among female cancer patients from 2004-2022. **Methods:** We linked population-based cancer registry data (2004–2018 in 12 states; 2004–2011 in California) with live birth certificates and the Society for Assisted Reproductive Technology database (2004-2022), which captures ~90% of ART cycles nationally, to create a dataset integrating oncologic characteristics, obstetric outcomes, and ART utilization. Female patients aged 15-45 at diagnosis of cancer were included. The primary outcome was the standardized birth ratio (SBR) >9 months after cancer diagnosis stratified by age, race/ethnicity, cancer site, stage, and receipt of systemic therapy calculated using Centers for Disease Control (CDC) general population birth rates from the 13 states. Secondary outcome was ART use after cancer diagnosis (≥1 autologous oocyte/embryo cryopreservation or embryo transfer cycles). Patients were categorized by expected fertility detriment, defined as pelvic malignancy and/or receipt of chemotherapy, hormone therapy, or abdominal/pelvic radiation. Associations with ART were evaluated with Cox proportional hazards models adjusted for age, cancer stage, insurance, and race/ethnicity. Person-years accrued from diagnosis date to first post-diagnosis birth/use of ART, death, age 51 (oldest age a post-cancer birth was observed), or December 31, 2022. The study was approved by the institutional review board. **Results:** 286,198 female cancer patients were included, with 25,586 babies born to 19,713 women over a mean follow up of 8.3 years. The overall SBR compared to the general population was 0.38 [0.36, 0.40], with lowest rates in gynecologic and breast cancers (0.22[0.18, 0.27], 0.26[0.23, 0.30]). 46.2% (n=9,110) of patients with births had thyroid cancer or lymphoma. Median time from diagnosis to birth was 3.27 years (2.00-5.27). Only 1.56% (n=5343) of the cohort used ART, with highest use among patients with breast cancer (n=2506, 46.9%). Expected fertility detriment was associated with higher hazard of ART use (aHR 2.37, 95% CI 2.20, 2.54), specifically cryopreservation (5.53[4.89, 6.26]). The 2022 live birth rate from our cohort (44.0%, 70/159) paralleled national trends (42.5%) reported from 457 fertility clinics by the CDC (p=0.69). **Conclusions:** The burden of infertility among reproductive-aged cancer patients is profound, with observed birth rates less than half that of the general population. Among patients who access ART, however, birth rates mirror those published by fertility clinics nationally. Despite this, ART services among cancer patients are underused, highlighting unmet needs in survivorship care delivery. Research Sponsor: U.S. National Institutes of Health; MD017999.

12106 **Poster Session**

National trends and disparities in early-onset non-colorectal cancer mortality in the United States, 1999–2023: A population-based analysis of 240,190 deaths. First Author: Kumail Mustafa Ali, Jinnah Sindh Medical University, Karachi, Pakistan

Background: Early-onset non-colorectal malignancies account for a substantial share of premature cancer mortality in the United States, yet comprehensive national evaluations of long-term trends and disparities remain limited. **Methods:** We analyzed CDC WONDER Multiple Cause-of-Death data from 1999–2023, identifying deaths among individuals aged 15–54 years with non-colorectal malignancies. Age-adjusted mortality rates (AAMRs) per 1 million population were standardized to the 2000 U.S. standard population. Temporal trends were assessed using Joinpoint regression to estimate annual percent change (APC) and average annual percent change (AAPC). **Results:** A total of 240,190 deaths from early-onset non-colorectal malignancies occurred during the study period. Overall AAMRs declined from 61.45 (95% CI 60.22–62.68) in 1999 to 52.76 (95% CI 51.67–53.87) in 2023. Largest proportion of deaths occurred at home (43.4%), followed by inpatient or medical facilities (39.6%). Among women, AAMRs increased steadily from 36.01 (95% CI 35.02–37.04) in 1999 to 39.03 (95% CI 38.03–40.05) in 2023 (AAPC +0.33%, 95% CI 0.20–0.47). In contrast, men exhibited substantially higher but declining mortality, with an accelerated decline after 2012 (APC −2.25%, 95% CI −2.67 to −2.02). Racial and ethnic disparities persisted. Non-Hispanic Black populations showed significant reductions (AAPC −2.25%), Non-Hispanic Asian/Pacific Islander populations experienced the steepest declines (AAPC −2.22%), while Non-Hispanic American Indian/Alaska Native populations exhibited an early surge (APC +9.57%) followed by prolonged plateauing with persistently high rates. Metropolitan areas experienced faster declines (AAPC −0.72%) than non-metropolitan areas. **Conclusions:** The post-2012 acceleration in mortality reduction suggests progress in cancer management; however, these gains were uneven and masked substantial disparities. Men experienced marked declines but continued to have significantly higher mortality than women, while the steady increase in female mortality raises concern for unaddressed sex-specific risk and disease dynamics. Stagnant trends among individuals aged 15–34 years indicate limited benefit of advances in oncology for the youngest patients. Racial, ethnic, and geographic inequities remained pronounced, with persistently elevated mortality among Non-Hispanic Black and American Indian/Alaska Native populations, slower improvements in non-metropolitan areas, and consistently high rates in several Southern and Appalachian states. Together, these findings indicate that national progress has not translated into equitable outcomes and highlight the urgent need for targeted prevention, earlier diagnosis, and region- and population-specific cancer control strategies to reduce avoidable early-life cancer mortality. Research Sponsor: None.

12107 **Poster Session**

Bone mineral density changes in patients treated with anti-PD-1 immune checkpoint inhibitors. First Author: Roma A. Kankaria, Vanderbilt University School of Medicine, Nashville, TN

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment (tx), with almost half of all cancer patients (pts) today eligible for ICI tx. However, these agents frequently cause immune-related adverse events (irAEs). While many irAEs are well-documented, emerging reports suggest that skeletal toxicity may represent an underrecognized complication of ICI tx, particularly with agents that target PD-1. Preclinical models show that global deletion of the PD-1 gene (*Pdcd1*) or anti-PD-1 tx increases bone resorption, decreases bone formation, and weakens bones. However, skeletal effects remain poorly characterized in humans. We performed a retrospective analysis to assess bone mineral density (BMD) changes via dual-energy X-ray absorptiometry (DXA) results in pts treated with anti-PD-1 ICIs. **Methods:** We retrospectively analyzed adult pts from a single institution who received at least one dose of an anti-PD-1 agent with or without chemotherapy from 2014 to 2025 and who had pre- and post-tx DXA scans available. We collected demographics, cancer and treatment history, DXA data (including BMD, T-scores, and Z-scores), and scan timing relative to ICI tx. Descriptive statistics and paired t-tests ($p<0.05$) were used for data analysis. **Results:** Of 382 pts who received anti-PD-1 tx, 103 had only post-tx DXA scans, and 28 had both pre- and post-tx DXA scans. Of these 28 pts, 93% were female with a median age of 70 at the time of tx (range 58-88). Pts had statistically significant decreases in femur BMD and T-scores pre- vs. post-tx: mean BMD 0.85 vs. 0.81 g/cm^2 (p=0.04) and mean T-score -0.95 vs. -1.66 (p=0.02). Mean Z-scores decreased but were not statistically significant: 0.05 vs. -0.24 (p=0.09). In contrast, there was a trend toward increases in lumbar spine BMD, T-scores, and Z-scores, but none of these changes were statistically significant: mean BMD 1.16 vs. 1.15 g/cm^2 (p=0.93), mean T-score -0.19 vs. -0.06 (p=0.73), and mean Z-score 0.96 vs. 0.99 (p=0.72). **Conclusions:** This is the largest reported study to date examining BMD changes after anti-PD-1 ICI tx. Although this sample size is small and consists of mostly female pts, these results show significant decreases in femur BMD and femur T-scores after anti-PD-1 ICI tx, resulting in potentially increased fracture risk. T-scores in particular are more accurate in this older pt population than Z-scores. The site-specific changes seen in this dataset align with preclinical studies showing that in female PD-1 knockout mice of all ages, spinal bone mass does not change, but femoral bone mass is reduced. This could reflect differences in cortical vs. trabecular bone or mechanical loading. These findings underscore the importance of skeletal monitoring and indicate that prospective studies are needed to validate the observed bone changes and better characterize fracture risk in patients receiving anti-PD-1 therapy. Research Sponsor: Scholarship.

12108 **Poster Session**

Conditional survival in advanced melanoma treated with immune checkpoint inhibitors. First Author: Chloe Lim, BC Cancer - Vancouver, Vancouver, BC, Canada

Background: Immune checkpoint inhibitors (ICI) have improved survival in advanced melanoma, with some patients achieving durable remissions. Traditional survival estimates at diagnosis do not reflect how prognosis changes over time. Conditional survival (CS) provides a framework for time-dependent prognostication in long-term responders. **Methods:** We conducted a population-based retrospective cohort study of patients with unresectable/metastatic cutaneous melanoma treated with ≥1 dose of PD1-inhibitor based therapy in British Columbia (2012 -2022). Progression-free survival (PFS), overall survival (OS), and melanoma-specific survival (MSS) were estimated using Kaplan–Meier methods. Median follow-up was estimated using reverse Kaplan-Meier methods. Conditional PFS was calculated from ICI initiation and stratified by baseline characteristics and treatment response. **Results:** Among 897 patients, median age was 65 years (range 19-99); 48% (n=436) were M1c-d and 32% (n=290) received dual ICI. Median follow-up was 6.0 years (95% CI 5.7-6.3) and median OS was 3.2 years (95% CI 2.8-3.8); 5- and 10-year OS rates were 41% and 27%, respectively, while MSS rates were 49% and 38%, respectively. 5- and 10-year PFS rates were 31% and 22%, respectively. Conditional PFS analyses showed a decreasing risk of progression over time, most pronounced in patients achieving a complete response (Table 1). At 3-years post ICI initiation, patients in a complete response had a 5-year conditional PFS rate of 91% (95% CI 85-95%). Further analysis will assess whether their mortality normalizes relative to age- and sex-matched population controls to contextualize long-term survivorship. **Conclusions:** CS demonstrates dynamic improvement in prognosis among advanced melanoma patients who remain progression-free after ICI and provides clinically meaningful, time-updated prognostic information to guide patient counseling and follow-up strategies. Research Sponsor: None.

Five-year conditional PFS rate at ICI initiation (year 0) and subsequent PFS timepoints.

Strata (%; 95% CI)	Year 0	Year 1	Year 2	Year 3	Year 4
All patients	31% (28-34%)	53% (48-57%)	67% (62-72%)	80% (75-84%)	90% (85-93%)
ECOG 0 or 1	34% (31-38%)	55% (50-59%)	68% (63-73%)	81% (76-85%)	90% (85-94%)
ECOG >=2	17% (11-24%)	42% (28-55%)	60% (40-75%)	72% (48-86%)	86% (55-96%)
M0/M1a/M1b	33% (29-38%)	52% (46-58%)	67% (60-73%)	81% (73-86%)	90% (83-94%)
M1c/M1d	29% (25-33%)	54% (47-60%)	67% (59-74%)	79% (71-85%)	90% (82-94%)
Complete response	77% (71-82%)	82% (76-87%)	88% (82-92%)	91% (85-95%)	95% (90-98%)
Partial response	27% (21-33%)	36% (28-43%)	50% (41-59%)	68% (57-78%)	88% (76-94%)
PD1-inhibitor only	28% (24-32%)	47% (42-52%)	62% (56-68%)	77% (70-82%)	89% (83-93%)
PD1 with CTLA4	38% (32-44%)	66% (57-73%)	78% (69-85%)	87% (77-93%)	92% (82-96%)

12109 **Poster Session**

Impact of prior malignancy on cardiac complications and mortality in patients with COVID-19. First Author: Samuel Condon, UT San Antonio, South Texas Veterans Health Care Center, San Antonio, TX

Background: Cancer accounts for approximately 600,000 deaths annually in the United States, and patients with cancer are estimated to have nearly twice the risk of death following COVID-19 infection. While active malignancy and cancer-directed therapies are known to increase the risk of cardiac complications, it remains unclear whether patients with a prior history of cancer remain at elevated risk for cardiac events or mortality after COVID-19. This study aimed to evaluate whether a prior history of malignancy is associated with increased cardiac complications or all-cause mortality among Veterans diagnosed with COVID-19. We hypothesized that Veterans with a history of malignancy would have higher rates of cardiac complications and mortality following COVID-19 infection. **Methods:** We conducted a prospective observational cohort study of Veterans diagnosed with COVID-19 at the South Texas Veterans Health Care Center in San Antonio, Texas, using REDCap electronic data capture. Index dates ranged from March 13, 2020, through December 31, 2021, with a 10-month follow-up period. Both inpatient and outpatient Veterans were included. Patients with active malignancy or missing post-COVID cardiac outcome data were excluded. Patients were stratified into two groups: those with a prior history of malignancy and those without. The primary outcome was a composite of acute cardiac complications (arrhythmia, myocarditis, viral pericarditis, or viral cardiomyopathy) and all-cause mortality at 30 and 365 days. **Results:** Among 2,042 patients identified, 90 with active malignancy were excluded, leaving 1,952 patients for analysis. Of these, 5.3% (n=103) had a prior history of malignancy and 94.7% (n=1,849) had no malignancy history. Significant differences were observed in age, race, and BMI between groups. The composite primary outcome occurred more frequently in patients with prior malignancy at both 30 days (50% vs. 26%; OR 2.87, 95% CI 1.92–4.28, $p<0.0001$) and 365 days (53% vs. 29%; OR 3.06, 95% CI 2.05–4.58, $p<0.0001$). All-cause mortality was higher among patients with prior malignancy at 30 days (16% vs. 7%; OR 2.51, 95% CI 1.43–4.42, p=0.0013) and 365 days (16% vs. 14%; OR 3.03, 95% CI 1.97–4.66, $p<0.0001$). Cardiac complications alone were also more common in patients with prior malignancy (41% vs. 23%; OR 2.41, 95% CI 1.60–3.62, $p<0.0001$). **Conclusions:** In this large Veteran cohort, patients with a prior history of malignancy were approximately three times more likely to experience cardiac complications or death following COVID-19 infection compared with patients without a cancer history. These findings suggest that increased risk extends beyond active malignancy and highlight the need for targeted strategies to reduce adverse cardiac outcomes in patients with any history of cancer who develop COVID-19. Research Sponsor: None.

12110 **Poster Session**

Microbiome associations with chemotherapy-induced nausea and vomiting: A metagenomic shotgun sequencing study. First Author: Aasha I. Hoogland, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

Background: Chemotherapy-induced nausea and vomiting (CINV) is common, with four out of every ten patients reporting moderate to severe nausea even after treatment with antiemetics. Existing risk prediction models have focused on demographic, clinical, and patient-reported factors, but predictive accuracy remains low. A missing predictor may be the gut microbiome, or gut microorganisms that engage in reciprocal signaling with the brain via many of the same pathways known to cause nausea. **Methods:** In this original research study, we conducted whole-metagenomic shotgun sequencing of the gut microbiome to evaluate its association with patient-reported CINV and improve existing risk prediction algorithms by employing a random forest approach. Nausea and vomiting were reported 24 hours after infusion (acute) and 5 days after infusion (delayed) in patients treated with moderately- or highly-emetogenic chemotherapy using the MASCC Antiemesis Tool. Participants were recruited from five ORIEN centers: City of Hope, Moffitt Cancer Center, Ohio State University, Rutgers University, and University of Colorado-Denver. Fecal samples were collected prior to chemotherapy using at-home fecal occult blood test (FOBT) cards. **Results:** Participants (n=233) were 57 years of age on average (SD=12), and most were female (80%), White (89%), with breast cancer (55%). More than half of participants (65%) had early stage cancer. Any acute and delayed self-reported nausea was reported by 40% and 67% of participants, respectively. Any acute and delayed vomiting was reported by 3% and 12% of participants, respectively; the low rate of acute vomiting precluded additional analyses. No significant difference was observed in microbial diversity and the abundance of dominant bacteria at the phylum level between patients who reported nausea or vomiting and those who did not. Bacillota and Pseudomonadota were two phyla identified as the most significantly enriched in patients who reported nausea or vomiting, at either timepoint (FDR-adjusted $p < 0.05$). The predictive performance of risk models based on established factors were improved by incorporating the top 15 differentially abundant bacterial species for acute nausea (AUC=69% vs. 58%), delayed nausea (AUC=68% vs. 53%), and delayed vomiting (AUC=77% vs. 54%). **Conclusions:** Gut microbial diversity did not differ between patients who self-reported acute or delayed nausea and those who did not, but risk prediction models for acute nausea, delayed nausea, and delayed vomiting were all improved by incorporating differentially abundant bacterial species. Results suggest that the gut microbiome is an important factor associated with the development of CINV. Research Sponsor: National Cancer Institute; R01CA219389.

12111 **Poster Session**

Longitudinal physical activity patterns and patient-reported cognitive function among patients with lymphoma receiving chemotherapy in a nationwide prospective cohort. First Author: Tianming Zhao, Department of Public Health Sciences, University of Rochester Medical Center, Rochester, NY

Background: Up to 70% of patients with cancer experience cancer-related cognitive impairment and physical activity (PA) may prevent or mitigate this concerning symptom. However, longitudinal data on PA before and during therapy for lymphoma and their associations with cognitive function across the treatment continuum are limited. This study examined PA patterns before, during, and after chemotherapy in patients with lymphoma compared with controls, and associations between pre-chemotherapy PA and cognitive changes over time in patients only. **Methods:** Cognitive function was assessed via the patient-reported Functional Assessment of Cancer Therapy-Cognitive Function perceived cognitive impairment subscale, and PA via the Aerobics Center Longitudinal Study questionnaire at pre-chemotherapy (T1), 1 month post-chemotherapy (T2), and 6 months following T2 (T3) in patients with lymphoma and age- and sex-matched non-cancer controls recruited from 19 NCORP sites across the US. MET-hours per week (MET-hrs/wk) were calculated, and meeting PA guidelines was defined as $\geq$150 minutes/week of moderate intensity or $\geq$75 minutes/week of vigorous intensity PA, or an equivalent combination. Linear mixed-effects models (LMMs) examined longitudinal PA changes between patients and controls and pre-chemotherapy PA's association with cognitive changes in patients only, adjusting for age, sex, race, education, cognitive reserve, BMI, anxiety, and depression at T1. **Results:** Participants included 242 patients with lymphoma (74.4% non-Hodgkin) and 209 controls (mean age [SD], 55.3 [14.8] vs 53.7 [14.9] years; male, 62.8% vs 58.9%). In patients, 36.8% met PA guidelines at T1, decreasing to 23.3% at T2 and rising to 40.8% at T3, whereas about half of controls met guidelines across T1-T3 ($p<$ 0.05 at T1 and T2). Compared to controls, patients had lower PA (MET-hrs/wk) at T1 (β*[95% CI]* -4.81[-9.64, 0.02]; p=0.051), which declined to T2, resulting in significantly lower PA at T2 (β*[95% CI]* -7.48[-11.93, -3.03]; p=0.001); from T2 to T3, PA increased more in patients vs controls (β*[95% CI]* 6.38[2.31, 10.45]; p=0.002), reaching comparable levels at T3. Cognition declined from T1 to T2 in patients meeting (β*[95% CI]* -11.42[-15.19, -7.66]; $p<0.001$) and not meeting (β*[95% CI]* -9.29[-12.09, -6.49]; $p<0.001$) PA guidelines at T1; however, only those meeting guidelines showed cognitive recovery from T2 to T3 (β*[95% CI]* 3.64[0.28, 7.00]; p=0.034). **Conclusions:** In patients with lymphoma, PA significantly declined during chemotherapy; despite recovery to pre-treatment levels by 6 months post-chemotherapy, most remained insufficiently active. Further, active patients before treatment showed cognitive recovery after chemotherapy, suggesting that pre-chemotherapy PA may support post-treatment cognitive resilience, warranting further investigation. Research Sponsor: National Cancer Institute; R01CA231014; National Cancer Institute; UG1CA189961; National Cancer Institute; 3UG1CA189830-11S1; National Cancer Institute; 3UG1CA189972-11S1; National Cancer Institute; 3UG1CA189819-11S1.

12112 **Poster Session**

Organ-specific proteomic aging clocks (PACs) and mortality in cancer survivors. First Author: Shuo Wang, University of Minnesota, Minneapolis, MN

Background: Our study suggested that plasma conventional PACs can reflect, on average, accelerated aging in cancer survivors (Wang et al., JNCI 2026), but may overlook organ-specific variations. Organ-specific PACs may better predict CVD and cancer mortality in this group. **Methods:** We compared the associations of one conventional and 11 organ-specific PACs (Oh et al., Nature 2023) with mortality in 806 cancer survivors (aged 66-90) in the Atherosclerosis Risk in Communities (ARIC) study, 2+ yrs post-diagnosis (up to 12-yr follow-up). ARIC measured 4,712 plasma proteins by SomaScan. We computed PACs (conventional, adipose, artery, brain, heart, immune, intestine, kidney, liver, lung, muscle, pancreas) and their deviations from chronological age (age gap) after regressing PAC on age via LOWESS model. Multivariable Cox proportional hazards regression estimated hazard ratios (HRs) for mortality associated with age gap in survivors of any cancer (455 deaths: 127 CVD, 137 cancer deaths) and the most common cancers (165 breast (BrCa), 255 prostate (PrCa), and 78 colorectal cancer (CRC)). **Results:** In BrCa survivors, all age gaps (except intestine) were higher for those diagnosed 2-10 vs. >10 yrs before the start of follow-up. The pattern was opposite for all age gaps in CRC survivors (except heart and lung gaps). There was no specific pattern across age gaps in PrCa survivors. Further, in all cancer survivors, all age gaps, but artery and kidney, were associated with all-cause mortality (all $p<0.05$), with highest HRs for conventional, heart, and liver gaps (Table 1). Only heart age gap was associated with CVD mortality (HR per 1 SD=1.29, $p<0.05$), with no associations of any age gaps with cancer mortality. In BrCa survivors, conventional (HR=1.81) and 4 organ age gaps (brain, heart, immune, intestine; HRs = 1.45–1.68) were associated with all-cause mortality (all $p<0.05$). In PrCa survivors, conventional, heart, and liver age gaps were associated with all-cause mortality [all HRs=1.35, $p<0.05$]. In CRC survivors, conventional, heart, and immune age gaps were positively, but non-significantly, associated with all-cause mortality [HRs = 1.48–1.56], likely limited by sample size. **Conclusions:** Conventional and heart PACs demonstrated consistent associations with all-cause mortality beyond chronological age and lifestyle factors in total and individual cancer survivors. Heart PAC was most strongly associated with CVD mortality. Further work is needed to replicate this analysis and to test these age gaps as a predictor for mortality. Funding: NHLBI, NCI, NPCR. Research Sponsor: National Cancer Institute; National Center for Advancing Translational Sciences (NCATS); National Heart, Lung, and Blood Institute (NHLBI); National Program of Cancer Registries (NPCR).

Age gaps and all-cause mortality in cancer survivors; ARIC (2011-23).

Age gap	HR (95% CI) per 1 SD	Age gap	HR (95% CI) per 1 SD
Conventional	1.48 (1.32, 1.66)	Intestine	1.13 (1.01, 1.26)
Adipose	1.13 (1.00, 1.27)	Liver	1.42 (1.26, 1.60)
Brain	1.19 (1.05, 1.34)	Lung	1.14 (1.02, 1.26)
Heart	1.41 (1.26, 1.59)	Muscle	1.19 (1.06, 1.33)
Immune	1.24 (1.10, 1.40)	Pancreas	1.33 (1.18, 1.49)

12113 **Poster Session**

Common symptoms, quality of life, and lifestyle factors reported by cancer survivors attending the Sydney Cancer Survivorship Multidisciplinary Clinic. First Author: Janette L. Vardy, Faculty of Medicine and Health, University of Sydney & Sydney Cancer Survivorship Centre, New South Wales, Australia

Background: Sydney Cancer Survivorship Clinic (SCSC) provides multidisciplinary care for cancer survivors. During an initial visit, survivors consult with a medical oncologist or hematologist, cancer nurse specialist, dietitian, clinical psychologist, and exercise physiologist. Over 12 years, we assessed the health status of cancer survivors after curative-intent treatment. **Methods:** Survivors completed patient-reported outcomes assessing symptoms (PT-DATA), quality of life (QOL) (FACT-G), distress (Distress thermometer), fear of cancer recurrence (FCR-7, and psychologist assessment), diet, and physical activity (LTEQ) before initial clinic visit. Clinical data were obtained from the medical record. Simple descriptive statistical methods were used. FACT-G scores were standardized and compared to Australian general population and population with cancer (T-score 50, SD 10). **Results:** Between September 2013 and December 2025, 1181 survivors attended initial SCSC; 1081 (95%) consented to the use of their data. Of these, 68% were female; median age 58 years (range 18-91). Median time from diagnosis 10.7 months (IQR 8.4-16.6). Tumor types: 38% breast, 33% colorectal, 16% hematological, 14% other. Primary treatment: surgery 84%, chemotherapy 90%, radiotherapy 40%. Overall, 47% had 5+ symptoms of at least moderate severity (4+/10). Most frequently reported moderate-severe symptoms were: fatigue (50%), insomnia (40%), anxiety (36%), pain (35%), numbness (33%), sore hands/feet (32%), trouble concentrating (32%). Moderate-severe distress was reported in 44%. On the FCR-7, 32% had moderate-severe FCR. The psychologist rated 46% as having moderate-severe FCR. Mean QOL (FACT-G): total 79.9: domains physical 22.1; social 21.2, emotional 18, functional 18.6. Comparison to Australian populations: Total T-score 46.0: physical and emotional domains both 0.8 SD below. 59% were overweight or obese (mean BMI 27.2kg/m^2 (range 16.2-59.1)). Only 7% met national exercise guidelines for both resistance and aerobic exercise (18% resistance exercise alone, 24% aerobic exercise alone). **Conclusions:** Symptom burden remains high almost a year after diagnosis, with 47% reporting at least five moderate-severe symptoms; most commonly distress, fatigue, insomnia, anxiety and FCR. Overweight/obesity (59%) and physical inactivity remain lifestyle risk factors. Research Sponsor: National Health and Medical Research Council Australia.

12114 **Poster Session**

Prevalence and financial burden of WHO-defined disability among childhood cancer survivors: A report from the St. Jude Lifetime Cohort study (SJLIFE). First Author: Joshua Burns, St. Jude Children's Research Hospital, Memphis, TN

Background: Survivors of childhood cancer are at high risk for chronic health conditions that may result in disability. However, the prevalence and financial burden of disability, defined using the World Health Organization International Classification of Functioning, Disability and Health (WHO ICF), have not been described in this population. **Methods:** Disability-related items ascertained using clinical and patient-report data from SJLIFE were classified using standardized WHO ICF childhood cancer components, including impairments in body function or structure (strength, neurocognition, vision, hearing, speech, balance, neuropathy, ataxia, hemiparesis, tone, bowel and bladder, flexibility, gait, posture, pain, fatigue), activity limitations (motor function, communication, personal care), and participation restrictions (physical activity, education, independent living, employment, quality of life). Aggregate disability severity scores (ADSS) were calculated by summing item-level indicators (0 = none/mild; 1 = moderate, severe, or life-threatening disability) across 55 items spanning 3 components (38 body impairments, 5 activity limitations, and 12 participation restrictions). Disability was classified using either age- and sex-specific z-scores derived from 815 community controls (0 = ≥ -1.5; 1 = < -1.5) or NCI Common Terminology Criteria for Adverse Events (CTCAE) grades (0 = < 2; 1 = ≥ 2). Logistic regression evaluated associations between disability and financial burden (cancer-related financial impact), adjusting for sex, race, age at evaluation, and cancer treatment exposures (chemotherapy, cranial radiation, amputation). **Results:** Among 3,549 survivors (mean age at evaluation 33.6 years; range 18.0–68.9; 52.1% male; 80.7% White non-Hispanic), the most common diagnoses were acute lymphoblastic leukemia (31.9%), central nervous system tumors (14.5%), and Hodgkin lymphoma (10.5%). The point (most recent visit) prevalence (95% CI) of $\geq$1 item rated as moderate or greater disability was 87.4% (86.3–88.5). Component-specific prevalence was 74.6% (73.2–76.0) for body impairments, 32.9% (31.3–34.4) for activity limitations, and 63.3% (61.7–64.9) for participation restrictions; all were higher than controls ($p < 0.001$). Higher overall ADSS was associated with greater financial hardship (OR = 2.97; 95% CI 2.05–4.30) with similar associations across all components, including body impairments (OR = 2.67; 95% CI 2.09–3.41), activity limitations (OR = 2.28; 95% CI 1.91–2.72), and participation restrictions (OR = 2.61; 95% CI 2.13–3.21). **Conclusions:** WHO-defined disability is highly prevalent among adult survivors of childhood cancer and is strongly associated with financial burden. These findings highlight the need for integrated survivorship care that addresses both medical and socioeconomic risk factors. Research Sponsor: NIH, NCI; U01 CA195547.

12115 **Poster Session**

The neurotoxicity rating scale: A novel patient-reported outcome (PRO) measure for neuro-psycho-behavioral late effects in head and neck cancer (HNC) survivors. First Author: Matthew Stewart, Vanderbilt University Medical Center, Nashville, TN

Background: Chronic fatigue, mood disorders and cognitive dysfunction are well recognized but understudied late toxicities experienced by HNC survivors. In addition to these well recognized central symptoms, patients also experience an array of less well recognized psycho-behavioral complaints (see table below). These symptoms may profoundly affect a patient's ability to function within society. The neurotoxicity rating scale (NRS) was developed to assess the breadth of neuro-psycho-behavioral symptoms in cancer patients treated with interferon. We conducted a prospective cohort study in HNC survivors to assess the psychometric properties of this tool. **Methods:** Eligible patients included HNC survivors without evidence of disease $\geq$6 months after completion of therapy. The NRS was administered as part of a battery of patient reported outcome measures to assess pain and central symptoms. The NRS is a patient reported outcome measure which includes 36 items ranked from 0-4 (0 = no symptoms, 4 = severe). Hierarchical clustering was applied. **Results:** 243 patients were included with an average age of 72 years. Patients experienced clinically significant levels of neuro-psycho-behavioral symptoms; prevalence for selected items are shown in the table below. Preliminary analysis results in a group of six of clusters. The six-cluster solution was chosen as the most appropriate fit based on expert opinion. Clusters included: pain (α=0.89), sleep (α=0.83), general systemic symptoms (α=0.67), neuromotor-autonomic (α=0.73), cognitive (α=0.82), and psycho-behavioral (α=0.94). **Conclusions:** The NRS is a unique tool that comprehensively captures neuro-psycho-behavioral symptoms not assessed by existing instruments. The preliminary analysis amongst HNC survivors confirms the high prevalence of neuro-psycho-behavioral symptoms in this population. We identified six distinct symptom clusters: all demonstrated good internal constancy. This instrument allows for systematic study of neurotoxicity patterns, identification of high-risk patients, and evaluation of targeted interventions. Future directions include longitudinal validation and correlation with objective neuropsychiatric testing. Research Sponsor: None.

Selected items from the NRS with prevalence.

Item	Prevalence (%)
Tiredness/Fatigue	68%
Difficulty staying asleep	58%
Loss of interest in sex	41%
Restlessness	44%
Distractibility	41%
Word-finding difficulty	41%
No interest in activities	35%
Memory problems	50%
Decreased motivation	43%

12116 **Poster Session**

Effect of "watch and wait" on fear of recurrence in rectal cancer: A multicenter cross-sectional study. First Author: Ahmet Oruc, Necmettin Erbakan University Meram Medical Faculty Medical Oncology Department, Konya, Turkey

Background: Total neoadjuvant therapy (TNT) is now the standard of care for locally advanced rectal cancer. Watch-and-wait (WW) is the most commonly used approach for patients with a complete clinical response. This study aimed to investigate fear of recurrence, presence of depression, clinical symptoms, and functional capacities in WW patients and to identify differences between them and patients who underwent surgery after TNT. **Methods:** In this multicenter, cross-sectional study, patients were interviewed individually and completed the Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF), Patient Health Questionnaire-9 (PHQ-9), and EORTC QLQ-ANL27. The EORTC QLQ-ANL27 results in two parameters: the symptom scale (SS) and the functional scale (FS). **Results:** The study included 121 patients who received TNT. The median age was 60 (54-65), and male patients were in the majority at 71 (58.7%). The most common disease location was the distal rectum at 56 (46.3%). In clinical staging, the most common findings were T3 disease at 86 (71.1%) and N1 lymph node status at 63 (52.1%). The number of patients followed up with WW after TNT was 17 (14%). 27 (22.3%) patients achieved a pathological complete response (pCR) after surgery. The median disease-free survival was 21 (11-37.5) months. In surgical patients (n = 104), FCR was 16 (7.25-21), while in WW patients (n = 17), FCR was 18 (9-25), p = 0.464. The PHQ-9 score was 3 (1–10) in surgical patients and 5 (1–9) in WW patients, p = 0.669. SS was 31.7 (21.5-38.8) in surgical patients and 15.9 (12.1-38.6) in WW patients, p = 0.045. FS was 84 (61.3-87.8) in WW patients and 68.2 (61.1-78.4) in surgical patients, p = 0.045. When WW patients and pCR patients were also evaluated, no statistically significant difference was observed in terms of FCR and PHQ-9. SS was 15.9 (12.1-38.6) in WW patients and 31.8 (21.7-49.2) in pCR patients, p = 0.027. FS was 84 (61.3-87.8) in WW patients and 68.1 (50.7-78.2) in pCR patients, p = 0.027. pCR patients were evaluated according to the presence of a permanent stoma. In patients with a stoma (n:9), FCR was 19 (17.5-24.5), while in patients without a permanent stoma (n:18), FCR was 11.5 (3.75-20), p = 0.022. PHQ-9 was 12 (1.5-17) in those with a permanent stoma and 1.5 (1-8) in those without a permanent stoma, p = 0.020.There was no difference between these two groups in terms of SS and FS, p = 0.253. **Conclusions:** In WW patients, the fear of recurrence does not increase compared to those who underwent surgery after TNT; the level of depression is similar, but their symptoms are fewer, and their functional capacities are better. Considering both the fear of recurrence and the severe depression levels in patients who are particularly pCR and followed up with a permanent stoma, the decision to undergo WW should always be taken into account. Research Sponsor: None.

12117 **Poster Session**

Post-treatment recovery patterns among patients with early-stage cancer who develop taxane-induced peripheral neuropathy (TIPN): SWOG S1714 (NCT03939481). First Author: Meghna S. Trivedi, Columbia University Irving Medical Center, New York, NY

Background: The primary analysis of S1714 developed and validated a TIPN risk prediction model including 5 clinical risk factors. Recovery patterns of TIPN are not well described. Although some symptoms may improve with time, other symptoms may persist or worsen as a result of permanent nerve damage. We describe the incidence of TIPN over 3 years and report on the post-treatment patterns of TIPN in those individuals who report TIPN at the end of taxane treatment (EOT) as a secondary analysis of S1714. **Methods:** S1714 enrolled participants $>$ 18 years with Stage I-III primary lung, breast, or ovarian cancer starting treatment with a taxane-based regimen for a planned duration of 8 to 18 weeks. Participants were followed over the course of 3 years and assessed for TIPN using the patient-reported EORTC QLQ-CIPN20, which is composed of 3 subscale scores reported from 0-100, with increasing scores representing worse TIPN. EOT TIPN was defined as an increase in the CIPN20 sensory subscale score of $\geq$8 points from pre-treatment to EOT. **Results:** Among 1336 enrolled patients, N = 1321 were evaluable: Median age 55.7 years (range 23-85), 98.9% female, 11.3% Black/4.5% Asian/10.5% Hispanic/Latino, 90.7% with breast cancer. Paclitaxel was administered to 60.3% and docetaxel to 39.7%; 98.4% planned to start treatment with full dose of taxane. EOT TIPN was reported in 553 participants (41.9%). We identified 3 patterns of TIPN in these 553 participants over the 3 year period using the EOT CIPN20 sensory score as the reference. Improvement in TIPN from EOT was seen in 268 participants (48.5%), defined as a decrease of $\geq$8 points from the EOT CIPN20 sensory score. Stable TIPN was seen in 187 participants (33.8%), defined as $<$ 8 point increase or decrease from the EOT CIPN20 sensory score. Worsening of TIPN from EOT was seen in 98 participants (17.7%), defined as an increase of $\geq$8 points from the EOT CIPN20 sensory score. Of the 553 individuals with TIPN at EOT, 283 (51.2%) still had clinically meaningful TIPN at 3 years compared to the baseline pre-treatment CIPN20 sensory score (defined as increase in CIPN20 sensory score $>$ 8 points from pre-treatment timepoint to final assessment). **Conclusions:** Among individuals experiencing TIPN at EOT, nearly half experienced clinically meaningful TIPN improvement but almost one fifth had worsening of TIPN by the final 3-year assessment. The identification of clinical and correlative risk factors for persistent or worsening TIPN after completion of taxane treatment will allow for more informed decision-making regarding the long-term risks of taxane treatment and prioritize selection of patients in the investigation of interventions for prevention and treatment of TIPN. Funding: NIH/NCI/NCORP grant UG1CA189974, The Hope Foundation for Cancer Research. Clinical trial information: NCT03939481. Research Sponsor: NIH/NCI/NCORP; UG1CA189974; The Hope Foundation for Cancer Research.

12118 **Poster Session**

Untargeted baseline metabolomic profiling to identify candidate markers of long-term severe cancer-related fatigue (CRF) in breast cancer (BC) survivors. First Author: Antonio Di Meglio, Cancer Survivorship Program, Université Paris-Saclay, UVSQ, Gustave Roussy, Inserm, CESP, Villejuif, France

Background: CRF is common and debilitating among BC survivors; however its predictors and underlying biology remain partially defined. We sought to identify baseline plasma metabolomic markers of subsequent CRF to inform risk prediction and symptom mechanisms. **Methods:** Baseline (pre-treatment [tx]) plasma samples from women with stage I-III ER+/HER2− BC in the CANTO cohort (NCT01993498) underwent untargeted metabolomic profiling (liquid chromatography and high-resolution mass spectrometry with electrospray ionization), yielding metabolic features for analysis. CRF was measured using EORTC QLQ-C30 (severe CRF: score$\geq$40/100). Three penalized regression approaches (lasso, adaptive lasso, elastic net) were used to select baseline metabolites associated with severe CRF, adjusting for clinical covariates, including pre-tx CRF, age, body mass index, comorbidities, socioeconomic status, psychological distress, health behaviors, and tx. The cohort was split 2/3:1/3 (train:test); penalization factor λ was tuned in the train set by cross-validation. Clinical-only and clinical+metabolite features models were compared using test-set AUC, with bootstrap confidence intervals from resampled predictions (B = 1000). Covariate missingness was addressed by multiple imputation on 15 datasets. Metabolite annotation was conducted computationally using W4M, with manual curation and interpretation of spectra to identify key metabolites relevant to CRF. **Results:** In the train set (N = 645), mean age was 58 years (SD 10), 44% received chemo- and 90% endocrine-tx, 20% reported severe pre-tx CRF (similar characteristics in the test set; N = 325). 1935 metabolic features were analyzed. For severe global CRF at year-4 (prevalence 31%) the adaptive lasso clinical+metabolite features model included a 51-feature signature and had AUC = 0.70, specificity = 0.89, and sensitivity = 0.39 (sensitivity difference vs. clinical-only +0.17 [95% CI +0.06 to +0.29; $p < .001$]). Features with the largest penalized coefficients were concordant with univariate associations (all in the same direction) and showed clear differences in standardized levels between severe vs non-severe CRF. Nineteen features belonged to the annotated reference dataset, enabling putative identification of metabolites spanning endogenous pathways (including glycine [inverse association] and chenodeoxycholic acid [positive association]) and a likely exogenous/xenobiotic-related feature (mandelonitrile [positive association]). **Conclusions:** Baseline untargeted metabolomics identified a 51-feature signature associated with severe global CRF at year-4 after ER+/HER2− BC. Adding features selected via adaptive lasso to clinical covariates increased model sensitivity, and putative pathway mapping highlighted candidates for targeted validation and mechanistic studies. Research Sponsor: None.

12119 **Poster Session**

Social determinants of health and long-term outcomes in prostate cancer: Mortality, survival, and comorbidity risks in a propensity score–matched federated database analysis. First Author: Ashu Singh, Division of Hematology Oncology, Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY

Background: Social determinants of health (SDOH) such as housing instability, food insecurity, and low income are known to influence health outcomes, but their long-term effects on prostate cancer (PCa) patients remain underexplored. To compare long-term outcomes, including mortality, sepsis, sexual dysfunction, and comorbidities across major organ systems, between prostate cancer patients with and without adverse SDOH. **Methods:** Retrospective cohort study using the TriNetX federated database (deprecated COVID-19 Research Network, 88 healthcare organizations). Cohort 1 included adults ($\geq$18 years) with PCa (ICD-10-CM C61) and at least one adverse SDOH code (n = 14,595). Cohort 2 included PCa patients without SDOH codes (n = 875,545). Propensity score matching (1:1) balanced cohorts on demographics, external morbidity causes, ECOG status, and BMI (final n = 12,626 per cohort). The index event was the first prostate cancer diagnosis (with SDOH for Cohort 1). Outcomes assessed from 1-day post-index onward (up to 20 years prior exclusion). Risk ratios (RR), hazard ratios (HR) from Kaplan-Meier survival, and mean instances via t-tests for mortality, severe sepsis, sexual dysfunction, and diseases of genitourinary, circulatory, endocrine/metabolic, respiratory, digestive, and infectious systems. **Results:** After matching, cohorts were balanced (mean age ~72 years, ~56% White, ~25% Black). PCa with adverse SDOH had higher mortality risk (22.0% vs 17.3%; RR 1.272 [95% CI, 1.209-1.338]; $p < 0.001$) and worse survival (median 2821 vs 5246 days; HR 2.018 [95% CI, 1.906-2.137]; $p < 0.001$). Severe sepsis risk was elevated (5.6% vs 4.7%; RR 1.199 [95% CI, 1.074-1.339]; $p < 0.001$; HR 1.824 [95% CI, 1.626-2.047]; $p < 0.001$). Sexual dysfunction risk was lower (0.2% vs 0.4%; RR 0.493 [95% CI, 0.305-0.794]; p = 0.003). For comorbidities, PCa with adverse SDOH showed mixed risks—genitourinary diseases had a lower risk but poorer survival (HR 1.113, 95% CI 1.017-1.218, p = 0.020); circulatory diseases showed equivalent risk but worse survival (HR 1.223, 95% CI 1.089-1.374, p = 0.001); endocrine/nutritional/metabolic conditions had similar risk but reduced survival (HR 1.277, 95% CI 1.151-1.418, $p < 0.001$); respiratory diseases had equivalent risk but poorer survival (HR 1.531, 95% CI 1.416-1.656, $p < 0.001$); digestive diseases demonstrated lower risk with worse survival (HR 1.308, 95% CI 1.200-1.425, $p < 0.001$). **Conclusions:** Adverse SDOH are associated with increased mortality and poorer survival in prostate cancer, alongside heightened sepsis risk and differential comorbidity patterns. Interventions targeting SDOH may improve long-term outcomes. Research Sponsor: Dr Roberto Pili, Hematology Oncology, Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA, 14203.

12120 **Poster Session**

Correlative analysis between external and internal lymphedema in head and neck cancer survivors. First Author: Jessica Abene, University of Pennsylvania, Philadelphia, PA

Background: More than 75% of head and neck cancer (HNC) survivors develop lymphedema following cancer treatment. Lymphedema can affect both external (e.g., soft tissue of the face and neck) and internal (e.g., pharynx and larynx) structures. Early identification and timely referral are essential for maintaining functionality and minimizing symptom burden. Understanding the relationship between external and internal lymphedema may inform assessment and treatment strategies. However, data describing the association between external and internal lymphedema remains limited. The purpose of this report is to fill this gap. **Methods:** A prospective, longitudinal descriptive study included 117 patients with oral cavity and oropharyngeal cancer. External lymphedema was evaluated through physical examination using the validated Head and Neck External Lymphedema and Fibrosis Assessment Criteria. Internal lymphedema was evaluated using an endoscopic examination scored with the Modified Patterson Scale. Examinations were performed at baseline and every three months for 12 months post-treatment. Somers'd correlation coefficients were calculated to test associations between external and internal lymphedema measures. **Results:** Both the total number of sites with external lymphedema and the total external lymphedema severity score correlated with the presence of at least one site of internal lymphedema (both d = 0.31). The total number of external sites of lymphedema moderately correlated with internal lymphedema involving the following structures: epiglottis (d = 0.31), pharyngoepiglottic folds (d = 0.35), aryepiglottic folds (d = 0.34), and anterior commissure (d = 0.32). The total external lymphedema severity score correlated with internal lymphedema involving the following structures: the epiglottis (d = 0.32), pharyngoepiglottic folds (d = 0.35), and aryepiglottic folds (d = 0.34). External submental lymphedema correlated with internal lymphedema involving the buccal mucosa (d = 0.27), epiglottis (d = 0.28), pharyngoepiglottic folds (d = 0.28), and pyriform sinus (d = 0.28). External lymphedema of the neck correlated with internal lymphedema in the pharyngoepiglottic folds (d = 0.28), arytenoids (d = 0.27), and anterior commissure (d = 0.29). External cheek lymphedema failed to correlate significantly with internal lymphedema. **Conclusions:** HNC survivors with external lymphedema are likely to have concurrent internal lymphedema. The presence of external lymphedema should initiate evaluation for internal lymphedema, particularly in patients with dysphagia or shortness of breath. The site of external lymphedema correlates with the sites of internal lymphedema: this may help inform assessment and management. Research Sponsor: National Institute of Dental and Craniofacial Research of the National Institutes of Health; R01DE024982.

12121 Poster Session

Estimation of the impact of chemotherapy-induced biological age acceleration on breast cancer survivorship using multi-scale simulation modeling. First Author: Swarnavo Sarkar, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

Background: Treatment of breast cancer with chemotherapy improves breast cancer survival. But chemotherapy also increases the accumulation of senescent cells in breast cancer survivors, which induces more senescent cells through paracrine signaling. The increased accumulation of senescent cells increases inflammation and tissue damage, which leads to earlier onset of aging-related diseases in survivors. We developed a simulation model connecting the biology of aging with breast cancer epidemiology to estimate the impact of chemotherapy-induced biological age acceleration on breast cancer survivorship. **Methods:** We integrated a systems biology model of accumulation of senescent cells with chronological age and an established Cancer Intervention and Surveillance Modeling Network (CISNET) breast cancer simulation model to estimate the impact of biological age-acceleration on breast cancer survivorship outcomes. We used published clinical data on senescence biomarker expression level ($p16^{INK4a}$ mRNA expression) in chemotherapy recipient breast cancer survivors to simulate the elevated senescence expression level in the remaining lifetime of breast cancer survivors. The difference in the senescence expression level in the chemotherapy group was evaluated against the senescence expression level in the general female population to quantify the excess biological age, or the biological age acceleration, after chemotherapy. The modified biological age induced by chemotherapy was used to determine the hazard of non-breast cancer mortality in breast cancer survivors. We used the CISNET breast cancer simulation model to simulate multi-birth cohorts of US females diagnosed with breast cancer to estimate survivorship outcomes after chemotherapy. Outcomes included remaining life years after breast cancer diagnosis, absolute number of non-breast cancer deaths, and the time-point at which the risk non-breast cancer mortality starts to dominate breast cancer mortality. **Results:** Biological age acceleration after anthracycline-based regimes caused a greater loss of life years than anthracycline-free regimens for women diagnosed at ages 30-39 years (median of 11.7 years vs. 2.1 years lost). This loss in life years diminished with increasing age at diagnosis (median of 6.0 years vs. 1.4 years lost for 70-79 year old women). The risk of non-breast cancer mortality exceeded breast cancer mortality up to 10-15 years earlier than expected based on chronological age after anthracycline-based regimens. **Conclusions:** Integration of computational systems biology modeling with breast cancer population-level modeling helps to identify subgroups of breast cancer survivors who are likely to experience survivorship loss due to biological age acceleration and may need survivorship care targeting non-breast cancer mortality. Research Sponsor: National Cancer Institute at the National Institutes for Health Grant; U01CA253911.

12122 Poster Session

The effectiveness of a multidisciplinary pain program in improving adherence to the use of aromatase inhibitors in breast cancer survivors. First Author: Panuch Eiamprapaporn, Department of Medical Oncology, Mayo Clinic Florida, Jacksonville, FL

Background: Aromatase Inhibitors (AI) have become the standard of care to reduce breast cancer recurrence in hormone receptor-positive (HR+) breast cancer patients. AIs have been shown to be effective in reducing the risk of breast cancer recurrence by 47%. However, up to 52% of patients prematurely discontinue their use due to AI-associated musculoskeletal pain symptoms called Aromatase Inhibitor-associated musculoskeletal pain syndrome (AIMSS). No effective treatment exists to treat AIMSS. The present study examined the effectiveness of a multicomponent pain treatment program in reducing symptoms of AIMSS with the goal of improving adherence to AI medication. **Methods:** This trial enrolled breast cancer survivors with AIMSS in an intensive multicomponent pain treatment program. Pain, impact on functioning, fatigue, and mood were assessed with the Brief Pain Inventory, Center for Epidemiologic Studies of Depression- Revised Questionnaire, Pain Catastrophizing Scale, Symptom Impact Questionnaire Revised, and Fatigue Questionnaire at baseline, 3-month, 6-month, 9-month, and 12-month intervals. Adherence to AI medication was obtained from patients' self-reports. The treatment program consisted of a two-day structured intervention focused on Cognitive-Behavioral skills to address strategies to improve pain control, fatigue, sleep disturbance, and stress while educating patients on the efficacy of Aromatase Inhibitors in prolonging cancer-free survival. **Results:** A total of 73 patients were enrolled, with a median age of 63 years (range 31-79). Participants were primarily white, married, and highly educated. The measures showed elevated levels of pain, fatigue, and psychological distress at baseline with decrements in self-reported levels of functioning. Significant improvements across all measures were observed at the 3-month follow-up after participation in the multicomponent pain treatment program. Significant improvements in painrelated outcomes were observed at 3 months (WPI $\Delta -1.6$; SS $\Delta -4.0$; both $p < 0.001$), with sustained reductions in symptom severity through 6-month, 9-month, and 12-month follow-up. Self-report of AI medication adherence at one year showed that 77.9% of patients were still taking their prescribed medication. **Conclusions:** Patients with AIMSS experienced substantial emotional distress, pain, fatigue, and functional impairment at baseline. Following the intervention, significant improvements were observed across pain, physical functioning, fatigue, and psychological distress, with benefits sustained at one year. Importantly, the intervention was associated with high long-term adherence at one-year follow-up, highlighting its potential to improve both quality of life and treatment persistence. Research Sponsor: Linse Block Foundation Grant and the Mayo Women's Health Center Grant.

12123 Poster Session

Cardiac substructure dose signatures as predictors of late cardiovascular events in childhood cancer survivors. First Author: Hrushikesh Reddy Pamreddy, Saint Vincent Hospital, Worcester, MA

Background: Radiation-associated cardiovascular disease (CVD) remains a major late toxicity in childhood cancer survivors. Whole-heart dose may mask heterogeneous substructure exposure, limiting precision in survivorship surveillance and modern radiotherapy planning. **Methods:** Using the Childhood Cancer Survivor Study (CCSS) open-access cardiac substructure dosimetry dataset (12 mean-dose structures; Gy), we modeled time from cancer diagnosis to CAD, CHF, valvular disease, and arrhythmia with elastic-net Cox (α=0.5; 10-fold CV). Bootstrap stability selection (200 resamples) quantified reproducible substructure predictors; "core" structures were defined by selection frequency $\geq$0.80. Parsimonious Cox models were fit using core structures (dose scaled per 5 Gy) and adjusted for sex, race, age at diagnosis, anthropometric category, and smoking. Model discrimination was assessed using the concordance index (C-index). Model-based predicted 20-year absolute risks were used to estimate dose thresholds for clinically interpretable risk targets (reference profile: median covariates; modal factor levels). **Results:** Among 25,481 survivors, events occurred for CAD (n=475), CHF (n=544), valvular disease (n=131), and arrhythmia (n=181). LAD and aorta emerged as reproducible, endpoint-specific predictors: LAD was core across CAD/CHF/valvular outcomes; aorta and LMCA were core for CAD/valvular; pericardium was core for CAD/CHF. In adjusted core models, aortic dose was associated with CAD (HR 1.59 per 5 Gy; 95% CI 1.14–2.21; C-index 0.796) and valvular disease (HR 1.96; 95% CI 1.15–3.32; C-index 0.773). LAD dose was associated with CAD (HR 1.26; 95% CI 1.05–1.53; C-index 0.796) and CHF (HR 1.23; 95% CI 1.02–1.47; C-index 0.818). Absolute risk translation identified interpretable thresholds: predicted 20-year CAD risk crossed ~1% at 13 Gy mean aortic dose and ~2% at 20 Gy; CAD risk crossed ~1% at 24 Gy mean LAD dose. Predicted 20-year CHF risk crossed ~0.5% at 21 Gy mean LAD dose. Predicted 20-year valvular risk crossed ~1% at 23 Gy mean aortic dose. **Conclusions:** Substructure-specific dosimetry yields reproducible radiation "signatures," with LAD and aorta dose consistently linked to late CVD. These dose–risk thresholds provide actionable benchmarks for risk-stratified survivorship surveillance and may inform substructure-sparing dose constraints in contemporary radiotherapy planning moving beyond whole-heart dose to endpoint-specific substructure constraints. Research Sponsor: None.

Substructure-specific dose thresholds for 20-year cardiovascular risk.

Outcome	Core Substructure	HR per 5 Gy (95% CI)	20-Year Risk Target	Dose Threshold (Gy)
CAD	Aorta	1.59 (1.14–2.21)	1%	13
CAD	Aorta	1.59 (1.14–2.21)	2%	20
CAD	LAD	1.26 (1.05–1.53)	1%	24
CHF	LAD	1.23 (1.02–1.47)	0.5%	21
Valvular	Aorta	1.96 (1.15–3.32)	1%	23

12124 Poster Session

Toxicity assessment clinic as an efficacious tool to provide fast care to oncology patients on systemic therapy by minimizing emergency department visits and streamlining admissions directly from the cancer clinics. First Author: Andrew R. Maher, Queen's University, Kingston, ON, Canada

Background: The Toxicity Assessment Clinic (TAC) at the Hudson Regional Cancer Centre was established to improve access to care for cancer patients experiencing treatment-related toxicities, ensuring timely access to oncology-specific symptom management. The TAC is nurse led and utilizes an evidence-based oncology assessment tool to determine the appropriate care pathway, ensuring symptom assessment and treatment in a timely and safe manner. **Methods:** We reviewed the volume and characteristics of patients seen in the TAC for one year (2024), including visit modality, primary causes for TAC consultation, and appropriateness of TAC referrals by identifying related vs. unrelated complaints and determining the proportion of patients without a family physician who utilized TAC services for unrelated concerns. **Results:** There were 15,387 total chemotherapy clinic visits. Among them, there were 692 visits to TAC (4.5%). In total, 94.8% of patients had a family physician. Majority (93.9%) called TAC directly, 4.6% were sent by chemo suite nurses and 1.4% were referred from outside the cancer center. In addition, there were 997 registered nurse phone calls to follow up on health issues occurring within the clinic hours. Median age was 69 years [range 19-93]; 61% of patients were over 65. 61.9% of TAC patients had a solid tumor diagnosis, 24.5% had a hematological malignancy, and 6.8% had gynecological cancers. Gastrointestinal malignancies (26.9%), breast (17.5%) and lung (12.3%) were most prevalent. 47.9% had stage IV cancer, 27.2% had stage III. 93.5% of patients were on active systemic therapy, with 80.8% on first line. In-person TAC visits composed 89.1% of consults, and 10.9% had assessments over the phone. Skin lesions (7.8%), diarrhea (6.9%), disease progression (6.5%), urinary tract infection (5.8%) and respiratory infections (5.6%) were the most common issues. In 92.3% of cases, the presenting complaint was considered directly related to the cancer or therapy. Consult assessment durations were the following: 30 minutes or less (23.2%), 30-60 minutes (71.8%), and $\geq$60 minutes (4.9%). Of note, 76% of phone calls required $\leq$30 minutes compared to 39% patients who attended TAC in person. 52.6% of admitted patients from TAC required $\geq$ 60 min of assessment time. In 85.7% of cases, medical problems were resolved during the TAC visit; 1.4% were sent to ED and 12.9% were directly admitted to hospital. **Conclusions:** The TAC model is feasible and provides rapid assessment of patients on systemic therapy, particularly in the front-line setting. It is a cost-effective alternative to ED visits and streamlines admissions directly from cancer clinics. TAC improves patient flow for vulnerable populations such as elderly and immunocompromised patients. Research Sponsor: None.

12125 Poster Session

A prospective study of the early treatment of recombinant human thrombopoietin for chemoradiation-induced thrombocytopenia in cervical squamous cell carcinoma patients. First Author: Lu Li, Department of Radiation Oncology, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China

Background: To explore the early intervention timing of recombinant human thrombopoietin (rhTPO) for cancer treatment-induced thrombocytopenia (CTIT) in cervical squamous cell carcinoma (CSCC) patients during concurrent chemoradiotherapy. **Methods:** Patients with stage I-IVa CSCC who developed CTIT during radical concurrent chemoradiotherapy were prospectively enrolled in our study. rhTPO intervention was used at the first presentation of G1 or G2 CTIT during concurrent chemotherapy respectively. The key indexes, including nadir platelet count, platelet recovery time, platelet transfusion and incidence of G3-5 CTIT were recorded in two groups. χ^2 test was used for the effective analysis, and univariate and multivariate analyses logistic regression analysis was used to predict the potential factors for the G3-5 CTIT. **Results:** From February 2021 to June 2024, 204 CSCC patients who developed CTIT during radical chemoradiotherapy at Sichuan Cancer Hospital were prospectively enrolled. 75 patients who occurred G1 and G2 CTIT at the first presentation during concurrent chemoradiotherapy received rhTPO intervention. They were included in the intent-to-treat (ITT) population analysis. According to the timing of the rhTPO intervention, the patients were divided into G1 group (100×10^9/L>PLT>75×10^9/L) and G2 group (75×10^9/L>PLT>50×10^9/L). For effective analysis, the nadir platelet count in G1 group was greater than that in G2 group (67×10^9/L vs. 54×10^9/L, p = 0.000), and the platelet recovery time in G1 group was shorter than that in G2 group (8 days vs. 14 days, p = 0.003). Moreover, patients in G1 group had a significantly lower incidence of G3-5 CTIT than that in G2 group (14.3% vs. 35%, p = 0.04). In two groups, only 1 patient in G2 group received 4 apheresis platelet units transfusion. Univariate and multivariate analysis showed the early intervention of the rhTPO was a substantial factor for decreasing the incidence of G3-5 CTIT. The sensitivity was 0.67 and the specificity was 0.74. **Conclusions:** For CSCC patients received with radical concurrent chemoradiotherapy, the early intervention of rhTPO was a substantial factor for decreasing the incidence of G3-5 CTIT. It could significantly improve the nadir platelet count, shorten the platelet recovery time, and reduce the incidence of G3-5 CTIT, thereby ensuring the uninterrupted continuation of treatment. Research Sponsor: None.

Platelet recovery time and the degree of CTIT.

Data	Baseline platelet count($\times10^9$/L)	Days with platelet count recover ≥100×10^9(Days)	Minimal mean platelet count ($\times10^9$/L)	Incidence of G3-5 CTIT(%)
G1 14.3	group	172±64.92	8±5.86	67±15.81
G2 35	group	166±78.43	14±9.59	54±14.37
P 0.04*	value	0.76	0.003*	0.000*

*Statistically significant.

12126 Poster Session

Comparison of prophylactic effects for chemotherapy-induced neutropenia between same-day versus next-day administration of pegteograstim in chemotherapy regimen composed of day 1 intensive myelosuppressive agent: A randomized clinical trial (CONCISE, KCSG PC22-11). First Author: Kwonoh Park, Division of Hematology & Medical Oncology, Department of Internal Medicine, Dongguk University Ilsan Hospital, Goyang, South Korea

Background: Same-day administration of pegylated G-CSF is frequently used in clinical practice despite guideline recommendations favoring next-day administration. This study evaluated whether same-day administration of pegteograstim is noninferior to next-day administration with respect to the duration of grade (Gr) 4 chemotherapy induced neutropenia (CIN) in multi-day regimens containing day 1-intensive myelosuppressive agents. **Methods:** This multicenter, open-label, randomized, noninferiority trial (originally designed as a phase III study) enrolled patients receiving adjuvant/neoadjuvant or first-line palliative chemotherapy, including mFOLFIRINOX, ECb, EP, FOLFIRI, and FOLFOX. Patients were assigned in a 1:1 ratio to receive pegteograstim 6mg either within 4 hours after completion of chemotherapy (same-day group) or 24-36 hours (next-day group). The primary endpoint was Gr 4 CIN duration during cycle 1 (C1). A total sample size of 160 patients was calculated to verify noninferiority with a margin of 0.6 days; however, the trial closed prematurely after enrolling 90 patients. **Results:** Of the 90 enrolled patients, 81 were included in the analyses (37 same-day, 44 next-day). Mean Gr4 CIN duration was 0.43 days (95% CI, 0.13–0.74) in the same-day group and 0.09 days (95% CI, 0.00–0.29) in the Next-day group. The mean difference (Same-day minus Next-day) was 0.342 days (90% CI, 0.037 - 0.646). Because the upper bound exceeded the prespecified noninferiority margin of 0.6 days, noninferiority was not demonstrated (p-value = 0.080 for noninferiority). The incidence of Gr4 CIN was 21.1% (8 patients) of same-day group and 2.3% (1 patient) in the next-day group. During cycles 1-4, febrile neutropenia occurred in 1 patient (2.6%) in the same-day group and 3 patients (6.8%) in the next-day group. Two deaths occurred in each group: one FN-related death occurred in the same-day group. **Conclusions:** Same-day administration of pegteograstim did not meet the prespecified criterion for noninferiority compared with next-day administration. The incidence of grade 4 CIN, a key secondary outcome, favored next-day administration. These randomized data support maintaining next-day pegteograstim as standard practice in multi-day regimens with day 1–intensive myelosuppression. Clinical trial information: KCT0007694. Research Sponsor: GC Pharma.

12127 Poster Session

Evaluating the impact of treatment timing with recombinant human thrombopoietin for cancer treatment–induced thrombocytopenia: A retrospective cohort study. First Author: Xin Wang, Department of Oncology, Nanchong Hospital, Beijing Anzhen Hospital Affiliated to Capital Medical University / Nanchong Central Hospital, Nanchong, China

Background: Recombinant human thrombopoietin (rhTPO) is utilized for cancer treatment-induced thrombocytopenia (CTIT) to ensure timely and full-dose chemotherapy delivery. This study investigated the differential clinical benefits of platelet-guided intervention timing strategies to provide evidence-based support for early initiation protocols. **Methods:** This single-center retrospective cohort study enrolled CTIT patients receiving rhTPO therapy. Participants were stratified into three groups based on platelet count at rhTPO initiation: early intervention group 1 (platelets 75-<100×10^9/L), early intervention group 2 (50-<75×10^9/L), and salvage therapy group (<50×10^9/L). Comparative analyses among the three groups encompassed time to platelet recovery and recovery rates, severe CTIT incidence, platelet transfusion requirements, bleeding event rates, chemotherapy continuity parameters (dose reduction, delay, or discontinuation), and safety profiles. **Results:** Among 456 solid tumor patients with CTIT, 159 (34.9%) were in early intervention group 1, 172 (37.7%) in early intervention group 2, and 125 (27.4%) in the salvage therapy group. Median time to platelet threshold achievement was significantly shorter in group 1 (7.0 d) versus group 2 and salvage therapy (both 11.0 d; P<0.001), with concomitantly shorter rhTPO treatment duration (5.0 d vs. 7.0 d vs. 7.0 d; P<0.001). Severe CTIT incidence was significantly reduced in early intervention groups (12.6% in group 1 and 19.2% in group 2 vs. 56.0% in salvage therapy; both P<0.001). Platelet recovery rates were superior in early intervention groups (81.1% in group 1 and 75.0% in group 2 vs. 59.2% in salvage therapy; P<0.001 and P=0.004, respectively). Platelet transfusion requirements were significantly lower (0.6% in group 1 and 1.2% in group 2 vs. 12.0% in salvage therapy; both P<0.001). Chemotherapy continuity was significantly improved, with lower rates of delay/discontinuation (18.9% in group 1 and 33.1% in group 2 vs. 46.4% in salvage therapy; all P<0.05). No significant inter-group differences in bleeding incidence were observed, and no rhTPO-related serious adverse events or thromboembolic events occurred. **Conclusions:** rhTPO therapy for CTIT exhibits a pronounced threshold effect, with early intervention (platelet count ≥50×10^9/L) conferring substantially greater clinical benefit than salvage therapy. Initiation at 50-<75×10^9/L effectively preserves chemotherapy continuity and reduces transfusion burden, while initiation at 75-<100×10^9/L optimizes platelet recovery kinetics and cost-effectiveness. Research Sponsor: None.

12128 Poster Session

AQP4 and MOG as definers of distinct autoantibody signatures in immune checkpoint inhibitor–induced optic neuritis. First Author: Jingyao Zhang, Department of Medicine, Nuvance Health/Northwell Health Danbury Hospital, Danbury, CT

Background: Checkpoint blockade–induced optic neuritis (CBON) is a rare but vision-threatening immune-related adverse event with limited response to standard immunosuppression and no established diagnostic biomarkers. The humoral immune mechanisms underlying CBON remain poorly characterized, limiting early recognition and mechanistic understanding. **Methods:** We conducted a multicenter study integrating three independent CBON cohorts (n=25, 29, and 34) and 49 ICI-treated controls without neuro-ophthalmic complications, enrolled between January 2020 and June 2025. CBON cases were identified from a prospective biospecimen bank of >2,300 ICI-treated patients. Leveraging pre-ICI baseline, prodromal-phase, onset, and follow-up serum samples (>2,300 total samples), IgG autoantibodies against 25 neural surface antigens were assessed using cell-based assays. Longitudinal antibody dynamics and associations with clinical and oncologic features were evaluated. **Results:** Across 88 CBON patients, the autoantibody response was highly antigen-specific and dominated by aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG). AQP4-IgG or MOG-IgG was detected in 32–48% of CBON cases across cohorts, while paraneoplastic, synaptic, and other neural autoantibodies were rare (<12%). AQP4-IgG and MOG-IgG were largely mutually exclusive, suggesting distinct immunologic subtypes of CBON. These antibodies were virtually absent in ICI-treated controls (0–2%). Longitudinal analyses demonstrated consistent seronegativity prior to ICI exposure, followed by seroconversion at symptom onset with persistent antibody titers during follow-up despite corticosteroid therapy, consistent with a sustained humoral immune response. Autoantibody status showed limited and inconsistent associations with demographic, oncologic, or clinical characteristics. **Conclusions:** CBON is characterized by a distinct, antigen-specific humoral immune response targeting AQP4 or MOG that emerges following ICI exposure. These findings support an ICI-triggered breakdown of immune tolerance and establish a serologic framework for CBON diagnosis and classification. Incorporation of AQP4-IgG and MOG-IgG testing may aid early recognition and risk stratification of visual immune-related adverse events during immunotherapy. Research Sponsor: None.

12129 **Poster Session**

Prevention of paclitaxel-induced neurotoxicity with lithium: Results from a multicenter, randomized, double-blind, placebo-controlled phase 2 trial (PREPARE). First Author: Wolfgang Boehmerle, Charité Universitätsmedizin Berlin, Department of Neurology, Berlin, Germany

Background: Chemotherapy-induced neurotoxicity is a frequent adverse effect of paclitaxel (PTX). It reduces quality of life and often necessitates treatment modifications. The objective of this clinical trial was to determine the safety and efficacy of lithium (Li^+) co-treatment on chemotherapy-induced neurotoxicity in breast cancer patients treated with PTX. **Methods:** Multicenter, randomized, double-blind, placebo-controlled phase-2 trial (parallel-group design) conducted in eight primary care centers in Germany between August 2022 and July 2024. Eligible breast cancer patients aged 18-70 years, with no pre-existing polyneuropathy and to be treated with PTX were randomized 1:1 to either oral Li^+ or placebo with sham dose adjustments. The intervention started 10-14 days prior to the first and lasted until three days after the last PTX infusion. **Results:** A total of 94 patients were enrolled, 86 patients were randomized and 78 were analyzed according to the intention-to-treat principle. Targeted Li^+ trough serum concentrations of 0.5 to 0.8mmol/l were reliably reached prior to PTX therapy. The total neuropathy score reduced (TNSr) was 0.5 points higher in the placebo group than in the Li^+ group (95% CI 1.6 to -0.6, not significant), while serum neurofilament light chain levels showed no difference. Structural MRI showed slightly higher total intracranial volume in the Li^+ group, but no difference in hippocampal volume. Cognitive testing using the CANTAB indicated a strong trend towards better performance in hippocampus-dependent tasks, including delayed matching to sample and spatial working memory for the Li^+ group. The patient reported outcome measures (PROM) completion rates were high (baseline 99%, endpoint 95%). Patients receiving Li^+ consistently reported higher quality of life and less pain scores on the EORTC QLQ-C30 during and after therapy, with between-group differences of 11 AU (95% CI 18 to 4) for global health status and -14 AU (95% CI −27 to -0.2) for pain, exceeding established minimal clinically important differences. The latter finding was supported by a lower reported intake of pain medication in the Li^+ group of 54% vs 70% in the placebo group. Eleven serious adverse events were reported in the trial, six in the placebo group and five in the Li^+ group. Patients in the Li^+ group experienced fewer adverse events compared to patients in the placebo group with a relative risk reduction of 26% for any CTCAE grade and 45% for grade ≥ 3. **Conclusions:** Among breast cancer patients receiving PTX chemotherapy co-treatment with Li^+ was not superior to placebo for the development of polyneuropathy as measured by TNSr. However, there were better patient-reported outcomes including quality of life and pain, as well as lower rates of adverse events. These observations warrant confirmation in a larger phase-3 interventional trial. Clinical trial information: DRKS00027165. Research Sponsor: Federal Ministry of Research, Technology and Space; 01KG2123.

12130 **Poster Session**

Hetrombopag plus caffeic acid tablets for the treatment of chemotherapy-induced thrombocytopenia in solid tumors: A single-center, open-label, phase II trial. First Author: Xiao Li Xiao, Department of Oncology, Zhongshan Hospital of Xiamen University, School of Medicine, Xiamen, Fujian, China

Background: Chemotherapy-induced thrombocytopenia (CIT) frequently complicates cancer therapy, resulting in treatment delays, dose reductions, and premature discontinuation. However, no widely approved therapies are currently available to address this clinical gap. This phase II trial was designed to evaluate the efficacy and safety of the thrombopoietin receptor agonist hetrombopag combined with caffeic acid tablets in this patient population. **Methods:** This is a single-arm, single-center, prospective phase II trial (ChiCTR2400086043) designed to enroll patients with malignancies experiencing thrombocytopenia (platelet count ≤ 75 ×10⁹/L) during anti-cancer therapy. Eligible participants received hetrombopag 5 mg once daily (QD) plus caffeic acid tablets 0.3 g three times daily (TID) for 14 consecutive days. The primary endpoint is the proportion of patients achieving a platelet count ≥100×10⁹/L after treatment; secondary endpoints included time to first response (platelet count ≥100×10⁹/L), proportion of patients with platelet recovery to ≥ 75×10⁹/L, and safety profile of the regimen. **Results:** A total of 65 patients were enrolled between 24 June 2024 and 25 December 2025.The median age of enrolled patients was 60.0 years, and 70.8% of patients had a baseline platelet count of ≥50×10⁹/L. The most common tumor types were colorectal cancer (23.1%) and gastric cancer (13.8%). The majority (41.5%) received oxaliplatin-based chemotherapy, 26.2% received immunotherapy plus chemotherapy, and 18.5% received targeted therapy plus chemotherapy. After treatment with hetrombopag plus caffeic acid tablets, 84.6% (55/65) of patients achieved platelet counts ≥100×10⁹/L and 87.7% (57/65) achieved ≥75×10⁹/L. The median durations from the first dose of hetrombopag plus caffeic acid tablets platelet response ≥100×10⁹/L was 7 days (range:5–9). Adverse drug reactions were reported in 17 patients; no drug-related adverse events of grade ≥3 occurred. **Conclusions:** Hetrombopag plus caffeic acid tablets confer outstanding therapeutic efficacy in CIT while maintaining a well-tolerated safety profile. This oral regimen fulfills an unmet clinical need and provides a practical, non-invasive therapeutic option for CIT management. Clinical trial information: ChiCTR2400086043. Research Sponsor: None.

12131 **Poster Session**

Efficacy of surgical glove-compression therapy as a prevention of paclitaxel-induced peripheral neuropathy: Randomized controlled trial. First Author: Saowani Thantaviraya, Oncology Unit, Department of Medicine, Rajavithi Hospital, Thailand, Bangkok, Thailand

Background: Paclitaxel is a common cause of chemotherapy-induced peripheral neuropathy (CIPN), a dose-limiting toxicity for which no preventive intervention is currently recommended. This randomized controlled trial evaluated the efficacy of surgical glove-compression therapy (SGCT) in preventing paclitaxel-induced peripheral neuropathy. **Methods:** Patients with solid malignancies scheduled to receive paclitaxel every three weeks were randomized 1:1 to SGCT or placebo. SGCT consisted of bilateral double-layer surgical gloves one size smaller than patient's hand size, covered with outer cotton gloves, worn from 30 minutes before paclitaxel infusion until 30 minutes after completion. The placebo group wore non-compression gloves with identical cotton gloves for the same duration. Patients were followed for four cycles of paclitaxel. The primary endpoint was the incidence of paclitaxel-induced sensory neuropathy of Common Terminology Criteria for Adverse Events (CTCAE) version 6.0 grade ≥2. Secondary endpoints included Patient Neurotoxicity Questionnaire (PNQ) grade ≥D, Functional Assessment of Cancer Therapy–Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-NTX) scores, and loss of protective sensation assessed by monofilament testing. Analyses were conducted using the intention-to-treat approach. Sensitivity analyses included per-protocol analysis and treatment effect adjustment for important prognostic factors for CIPN. **Results:** Between November 2024 and November 2025, 39 patients were randomized to SGCT (n=19) or placebo (n=20). Most patients were female, had breast cancer, and received single-agent paclitaxel. In the intention-to-treat analysis, sensory CIPN grade ≥2 occurred significantly less frequently in the SGCT group than in the placebo group (26.3% vs. 60.0%; p=0.034). This finding was consistent in the per-protocol analysis (27.8% vs. 66.7%; p=0.019). The protective effect of SGCT remained statistically significant after adjustment for sex, cancer type, and chemotherapy regimen (adjusted OR 0.10; 95% CI, 0.02 to 0.58; p=0.010). No significant differences were observed in secondary outcomes, including motor CIPN, PNQ grade ≥D, monofilament test abnormalities, or FACT/GOG-NTX scores. Any-grade sensory CIPN was common and did not differ between groups. SGCT was well tolerated, with no serious adverse events and high adherence. **Conclusions:** SGCT significantly reduced the incidence of clinically meaningful paclitaxel-induced sensory neuropathy and was safe and well-tolerated. These findings support SGCT as a simple, low-cost preventive strategy for CIPN. Clinical trial information: NCT06763575. Research Sponsor: Rajavithi Hospital.

12132 **Poster Session**

Natural language processing chatbot and continuous activity monitoring in a phase II randomized trial: Impact on hospitalizations and quality of life. First Author: Casey Hollawell, Hospital of the University of Pennsylvania Radiation Oncology, Philadelphia, PA

Background: Toxicities associated with concurrent chemoradiotherapy (CRT) can lead to hospitalizations and impaired quality of life (QoL). This study reports on secondary endpoints investigating whether combining continuous activity monitoring (CAM) with an AI-driven chatbot can support symptom identification, triage, reduce hospitalizations, and improve QoL. **Methods:** Patients receiving CRT for head and neck (H&N), gastrointestinal (GI) or thoracic cancers were recruited from radiation oncology clinics at a single, urban institution. Subjects were randomized to: (1) CAM with nursing triage or (2) CAM with chatbot triage with as needed symptom assessments. A Fitbit device monitored the step count and heart rate (HR) relative to baseline. Triage was triggered when the daily average HR was >100 or 20% above their resting average or if there was a decrease of >1000 steps from baseline. In the control arm, triage prompted a nursing assessment within 1 business day. In the intervention arm, triage visits were triggered based on a low-, intermediate-, or high-risk symptom algorithm determined by the chatbot (next OTV, next business day, within 24 hrs, respectively). Hospitalizations during CRT and one month post treatment were counted. Logistic regression controlled for ECOG and sex. EORTC C30 QoL instruments were administered at baseline, during OTVs, and during follow-up. A mixed method for repeated measures model assessed global health status/QoL, fatigue, and physical, role, emotional, cognitive, and social functioning scales adjusting for ECOG, race, and stage. All statistical tests were completed on SAS 9.4. **Results:** From June 2023 to January 2025, 77 patients undergoing CRT for their H&N (n=30, 39%), GI (n=29, 38%), or thoracic cancers (n=18, 23%) were enrolled. The median age at consent was 59 years (range 28-81 years). Subjects were randomized to either nursing (N = 36, 50%) or chatbot triage (N = 36, 50%). There were no statistically significant demographic or clinical differences between arms. Subjects in the chatbot arm had significantly fewer hospitalizations (11%, n=4 chatbot; 39%, n=14 nursing triage, p=0.01). On logistic regression, subjects on the chatbot arm (p=0.0125) and those who had ECOG 0 (p=0.0131) were less likely to be hospitalized. In both arms, global QoL/health, fatigue, and physical, social, cognitive, and emotional functioning declined during CRT. Chatbot subjects had significantly inferior global QoL/Health status (p=0.049), cognitive functioning (p=0.005), and physical functioning (p=0.02) vs nursing triage. **Conclusions:** Patients undergoing CRT experience functional decline. While AI-driven chatbots may reduce hospitalizations, they are not a perfect substitute for a compassionate healthcare team. An analysis of alerts and triage visits will be reported with our primary endpoint. Research Sponsor: GI Cancer Service Line.

12133 Poster Session

Applying a large language model to detect immune-related adverse events in electronic health records: Effect of integrating prescription and laboratory data on accuracy. First Author: Yukiko Shimoda Igawa, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Accurate identification of immune-related adverse events (irAEs) is essential; however, manual review of electronic health records poses a significant burden on clinicians. Furthermore, conventional text-only approaches may fail to capture clinically important events. In this study, we evaluated whether a Large Language Model (LLM) with a multimodal approach could improve patient-level identification of irAEs. **Methods:** Among patients who received immune checkpoint inhibitors (ICIs) monotherapy at National Cancer Center Hospital, Tokyo, Japan between October 2014 and July 2023, a subset of patients was randomly sampled for analysis. A zero-shot prompt was designed to identify irAEs. Using a standalone local LLM (gpt-oss-20b), single-modal analysis utilized clinical notes alone, whereas multimodal analysis additionally incorporated systemic steroid prescriptions and laboratory data. Patient-level predictions were aggregated, using the threshold that maximizes the micro-averaged F1-score. The irAEs were clinically adjudicated by board-certified oncologists. Analyses were limited to major irAEs, and performance was evaluated using precision, recall, and the F1-score (α = 0.05). **Results:** The median number of cases reviewed per day by physicians was 18, whereas the LLM processed 25. During the study period, 296 patients (207 with irAEs and 89 without irAEs) were randomly sampled. Among patients with irAEs, irAE types included rash, pneumonitis, endocrine disorders, colitis, and hepatitis. For the identification of irAE occurrence, the precision of the multimodal approach was significantly higher than that of the single-modal approach (88.7% to 83.7%, p = 0.01). In organ-specific analyses, precision for colitis and rash and recall for endocrine were significantly improved. In addition, the multimodal approach reduced false-positive classifications from 33% to 22% and false-negative classifications from 37% to 35%. IrAE onset timing also differed significantly between the two approaches, with earlier identification by the multimodal LLM ($-$21.9 vs $-$17.7 days, p = 0.04); both approaches detected onset earlier than clinical adjudication. **Conclusions:** A multimodal LLM framework improves irAE detection accuracy and may reduce clinician workload. Research Sponsor: National Cancer Center Hospital "Mirai Project".

IrAEs with significant differences between single-modal and multimodal analyses.

		Precision			Recall			F1-score
		%	95%CI	P	%	95%CI	P	%
Any irAE	Multi	88.7	84.2-93.1	0.01	83.1	78.0-88.2	0.62	85.8
	Single	83.7	78.7-88.8		82.1	76.9-87.3		82.9
Rash	Multi	64.5	53.7-75.2	0.03	60.5	49.8-71.1	0.10	62.4
	Single	58.9	48.7-69.1		65.4	55.1-75.8		62.0
Colitis	Multi	80.4	69.5-91.3	<0.01	77.4	66.1-88.6	0.32	78.8
	Single	61.8	50.2-73.3		79.2	68.3-90.2		69.4
Endocrine	Multi	71.2	59.6-82.7	0.37	75.0	63.7-86.3	0.03	73.0
	Single	76.6	64.5-88.7		64.3	51.7-76.8		69.9

12134 Poster Session

Prophylactic vedolizumab to facilitate use of immune-checkpoint inhibitors in cancer patients at high risk of immune-mediated colitis. First Author: Hemant Khandelia, Department of Medicine/Division of Hematology and Oncology, University of Washington, and Clinical Research Division, Fred Hutchinson Cancer Cancer, Seattle, WA

Background: Inflammatory diarrhea/colitis is a frequent immune-related adverse event (IRAE) associated with immune checkpoint inhibitors (ICIs). Treatment with ICI is relatively contraindicated in patients with history of severe ICI-colitis or those with pre-existing severe inflammatory bowel diseases (IBD). Vedolizumab (VDZ), an anti-$\alpha4\beta7$ integrin antibody associated with selective immune suppression in the gastrointestinal (GI) tract, is approved for IBD treatment and is also effective in treating steroid-refractory ICI-colitis. However, limited data exist for its utility as a prophylactic treatment for primary or secondary prevention of ICI-colitis in high-risk patients. **Methods:** We conducted a single-center, retrospective study of patients with advanced skin cancers, who were deemed "high-risk" due to prior severe ICI colitis or IBD, and received VDZ prophylaxis prior to ICI (re) treatment. VDZ efficacy was assessed by analyzing the frequency, severity, duration and treatment details of GI symptoms. In patients with prior ICI-colitis, outcomes with and without VDZ prophylaxis were compared using descriptive statistics. ICI efficacy in the presence of VDZ was evaluated by objective response rate (ORR) per RECIST v1.1. **Results:** We identified 16 high-risk patients (11- prior ICI colitis, 5 – IBD) who received VDZ prophylaxis (typically 300 mg at weeks 0, 2, and 6 initially, then q8 weeks) prior to ICI (re)treatment, between 2015-2025. Median number of VDZ doses before (re) introducing ICI was 2 (range, 1-3). In the ICI-colitis cohort, VDZ prophylaxis prior to ICI re-treatment resulted in less frequent and milder GI symptoms not needing corticosteroids, than previously observed with initial ICI treatment without VDZ prophylaxis (see Table). Among 14 patients with evaluable disease (measurable and progressing at the time of VDZ treatment), ORR was 33% (3/9) in the ICI-colitis cohort and 80% (4/5) in the IBD cohort. **Conclusions:** Use of prophylactic VDZ can facilitate successful, long-term ICI treatment in high-risk patients with prior ICI-colitis or IBD, while mitigating GI symptoms, reducing corticosteroid usage and preserving anti-tumor responses. Research Sponsor: None.

	ICI-colitis cohort, without VDZ prophylaxis (N = 11)	ICI-colitis cohort, with VDZ prophylaxis (N = 11)	IBD cohort, with VDZ prophylaxis (N = 5)
Diarrhea (any grade), n (%)	11 (100)	3 (27)	4
Diarrhea (≥ grade 3), n (%)	8 (73)	0	2 (40)
Symptom duration in days, Median (range)	75 (13, 251)	46 (8, 54)	39 (17, 129)
Corticosteroid use, n (%)	11 (100)	0	2 (40)
Corticosteroid use in days, Median (range)	54 (7, 102)	N/A	59 (59, 59)
Additional biologic therapy, n (%)	10 (91)	0	3 (60)
ICI discontinuation due to diarrhea, n (%)	11 (100)	2 (18)	3 (60)
ICI treatment duration in months, Median (range)	2.1 (1.4, 17.5)	7.7 (1.1, 49.0)*	7.4 (6.7, 20.8)

*4 patients had ongoing ICI treatment.

12135 Poster Session

Gabapentin plus intranasal ketamine for the prevention and treatment of pain in patients undergoing radiotherapy for head and neck cancer: Phase II trial results. First Author: Natalie A. Lockney, Vanderbilt University Medical Center, Nashville, TN

Background: Prophylactic gabapentin decreases pain, opioid use, and weight loss in head and neck (HNC) patients treated with chemoradiotherapy. Nonetheless, significant symptom burden remains. Ketamine is an NMDA receptor antagonist which has neuromodulator and anti-inflammatory properties. We undertook a phase I/II study to explore safety, feasibility, and obtain preliminary efficacy data pertaining to the combination of ketamine and gabapentin in HNC patients undergoing radiation +/- chemotherapy. Results of the phase I study were previously reported. Herein we report preliminary results of the phase II portion of the study. Primary outcomes were toxicity and feasibility; secondary outcomes were symptom burden. **Methods:** Eligibility: locally advanced HNC patients planned for primary or adjuvant radiotherapy +/- chemotherapy. Treatment: Day 1: gabapentin 100 mg PO TID; Day 8: increase gabapentin to 300 mg PO TID; Day 15: continue gabapentin and start intranasal ketamine 30 mg TID. Dose modifications were allowed for both agents. Toxicity: assessed using CTCAE 5.0. Feasibility: data capture by pill counts and patient medication logs. Efficacy: patient reported outcomes measures completed at baseline, weekly during radiation and 1-, 2-, and 3-months post-radiation. **Results:** Patient characteristics: median age 60 yrs, 85% males, 67% p16-positive, 21 post-operative. Toxicity: Of 45 patients who completed treatment, 7 patients (16%) experienced a grade 2+ toxicity (5 were probably related to ketamine). Four patients required ketamine dose de-escalation due to dizziness. Six patients (13%) eventually discontinued ketamine due to toxicity. Feasibility: 41 (91%) patients missed <5% of gabapentin doses; 35 (78%) patients missed <5% of ketamine doses. Preliminary Efficacy: Eight patients (18%) required PEG placement. median score on the pain subscale of the Vanderbilt Head and Neck Symptom Survey 2.0 was highest at the end of treatment (4.3/10) and decreased rapidly (2.4/10 at 1 month and 1.7/10 at 2 months post-treatment). During treatment, 8 patients (18%) required no opioids, and 24 patients (55%) required immediate-release (IR) opioids only. The median of the maximum morphine milligram equivalent (MME) per day for IR opioids alone was 90 MME/day(range 10 – 180 MME/day). The median duration of IR prescription alone was 30 days (range 10 – 347 days). Twelve patients (27%) required addition of extended-release (ER) opioids with a median duration 35 days (range 28 - 220 days). Only 3 patients (7%) required ER opioids for >90 days. **Conclusions:** The combination of gabapentin and ketamine was safe and feasible. Preliminary data indicates the majority of patients experienced low to moderate levels of pain with minimal use of opioids. Larger, randomized studies are warranted to confirm the benefit of the combination of gabapentin and ketamine. Clinical trial information: NCT05156060. Research Sponsor: NCATS/NIH Grant Support for REDCAP use (UL1 TR000445); Ingram Industries Pain & Symptom Management Program Endowment.

12136 Poster Session

The role of pretreatment vitamin D insufficiency in racial disparity in taxane-induced peripheral neuropathy: Results from the SWOG S0221 trial. First Author: Nam Nguyen-Hoang, University of Michigan, Ann Arbor, MI

Background: Taxane-induced peripheral neuropathy (TIPN) affects up to 70% of patients receiving taxanes and can lead to severe, irreversible symptoms that impair daily functioning and quality of life. Approximately 25% of patients require taxane dose modification or discontinuation to prevent TIPN, compromising treatment effectiveness and survival. Self-reported Black patients experience nearly two times greater incidence of TIPN compared to White patients, contributing to treatment alterations and worse cancer outcomes. Vitamin D insufficiency, which is more common among Black patients, has been implicated as a modifiable risk factor for TIPN. This study assessed the extent to which vitamin D insufficiency mediates the racial disparity in TIPN. **Methods:** This secondary analysis included self-reported Black or White female patients with early-stage breast cancer treated with paclitaxel-based chemotherapy on the SWOG S0221 phase III trial. The primary endpoint was clinician-assessed grade ≥3 sensory neuropathy per NCI CTCAE attributed to paclitaxel. The mediator was pretreatment vitamin D insufficiency, defined as total 25-hydroxyvitamin D ≤20 ng/mL. Causal mediation analysis decomposed the total effect of race on TIPN into its direct effect and an indirect effect mediated through vitamin D insufficiency, adjusted for age and paclitaxel regimen (weekly or every other week). Log-linear model with modified Poisson regression and weighted logistic regression were used for the outcome model and the mediator model, respectively. Confidence intervals were computed via bootstrapping, and significance was set at α=0.05. **Results:** A total of 1,106 participants (mean age 51.2 [SD 10] years) were included, of whom 109 were Black and 997 were White. Black patients had a higher prevalence of vitamin D insufficiency (77% vs. 28%, p <0.001) and a higher incidence of grade ≥3 sensory TIPN (29% vs. 14%, p <0.001). The adjusted risk ratio (RR) for TIPN comparing Black to White patients was 2.24 (95% CI, 1.54-3.19; p <0.001). Vitamin D insufficiency statistically mediated this association, with an indirect effect RR of 1.18 (95% CI, 1.01-1.38; p = 0.048), accounting for 27% of the racial disparity in TIPN. The direct effect of race on TIPN, independent of vitamin D status, remained significant (RR 1.90; 95% CI, 1.30-2.85; p <0.001). **Conclusions:** Vitamin D insufficiency contributes to, but does not entirely explain, the racial disparity in TIPN. While other unaccounted factors may interact with or modify this association, vitamin D supplementation in insufficient patients could partially reduce racial disparities in TIPN and improve pharmacoequity. Research Sponsor: American Cancer Society; N030566-497333; National Cancer Institute of the National Institutes of Health, Amgen; U10CA180888, U10CA180819, R01CA116395, R01CA139426; Amgen.

12137 **Poster Session**

Value of risk-directed thromboprophylaxis in ambulatory lung and gastrointestinal cancer care: Economic evaluation of the TARGET-TP randomized trial. First Author: Marliese Alexander, Pharmacy Department, Peter MacCallum Cancer Centre & Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia

Background: Thromboembolism (TE) is a major and preventable hematological complication in patients with cancer, contributing to substantial adverse health impacts for patients and the health system. Targeted Thromboprophylaxis in Ambulatory Patients Receiving Anticancer Therapies (TARGET-TP; ACTRN12618000811202) was an Australian phase III randomized trial of biomarker risk-directed enoxaparin thromboprophylaxis. The TARGET-TP intervention reduced TE (HR 0.31, p = 0.005) and six-month mortality (HR 0.48, p = 0.03) versus usual care (no prophylaxis). This study evaluated the value for money of the TARGET-TP intervention versus usual care. **Methods:** A within-trial and modelled economic evaluation was conducted from the Australian health system perspective. Resource use collected within the trial reflected risk stratification, thromboprophylaxis, side-effect management, and treatment of TE events. Health benefits were quantified as quality-adjusted life years (QALYs), utilities derived from SF-12v2 data. Bootstrapping was used to evaluate sampling uncertainty. A Markov model estimated long-term costs and outcomes over a 5-year horizon. Scenarios assessed the use of oral anticoagulants and stewardship, while probabilistic sensitivity analysis (PSA) tested parameter uncertainty. **Results:** Within-trial analysis showed the TARGET-TP intervention was associated with lower costs, while being more effective (i.e., dominant), reducing costs by $1,095 per patient and generating an additional 0.0097 QALYs, driven mainly by fewer hospitalizations. The TARGET-TP intervention was dominant in $>$ 83% of bootstrap iterations. Modelled analyses supported these findings, with cost savings of $3,551 per patient and a gain of 0.4 QALYs. PSA demonstrated dominance in $>$ 95% of iterations (Figure 1). The oral anticoagulant and stewardship scenarios remained dominant for rivaroxaban, while apixaban was highly cost-effective, driven by bleeding events and drug costs. **Conclusions:** Biomarker-driven primary thromboprophylaxis in patients with lung and gastrointestinal cancer was less costly and more effective from the healthcare system perspective, supporting its implementation in routine care. Clinical trial information: ACTRN12618000811202. Research Sponsor: Victorian Cancer Agency; ECHSRF18006; Australian National Health and Medical Research Council; 1196211.

12138 **Poster Session**

Pharmacokinetic variability with pembrolizumab dosage switching and its impact on immune-related adverse events in patients with non-small cell lung cancer. First Author: Yoshihiro Masui, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan

Background: Pembrolizumab 400 mg every 6 weeks (Q6W) was approved based on population pharmacokinetic (pop-PK) modeling rather than direct pharmacokinetic measurements, leaving its real-world concentrations insufficiently characterized. The impact of concentration changes when switching from 200 mg every 3 weeks (Q3W) to Q6W on immune-related adverse events (irAEs) remains unclear. **Methods:** We retrospectively identified patients with advanced non-small cell lung cancer who switched pembrolizumab from Q3W to Q6W between March 2017 and September 2023. Serum concentrations were quantified by liquid chromatography–tandem mass spectrometry; pop-PK analysis estimated maximum concentration (eCmax) and trough concentration (eCtrough). Inter-cycle variability was expressed as percentage coefficient of variation (% CV) using all available Q3W cycles. Early irAEs were defined as events within 126 days. In exploratory analysis, associations between pop-PK metrics and after switching irAEs (including pneumonitis) were evaluated using Wilcoxon rank-sum tests and multivariable logistic regression. Clinical correlates of %CV-eCmax were examined using multivariable stepwise linear regression. **Results:** Seventy-nine patients switched, and pop-PK analysis was feasible in 66. Median age was 70 years, 50 were male and 62 had a smoking history. Median Q3W cycles were 6 (range, 1–37) and median follow-up after switching was 463 days. After switching, 42 patients developed new or worsened irAEs, with 16 pneumonitis, and 22 had early irAEs, with 12 early pneumonitis. First-dose 400 mg eCmax and cross-regimen exposure ratios were not associated with the occurrence of irAEs. Among 64 patients who received $\geq$2 cycles of Q3W, those who developed irAEs after switching showed higher %CV-eCmax during Q3W (p = 0.036). Similar associations were observed for early irAEs (p = 0.024), pneumonitis (p = 0.023), and early pneumonitis (p = 0.007). %CV-eCtrough during Q3W was not associated with irAEs after switching (irAEs, p = 0.24; early irAEs, p = 0.13; pneumonitis, p = 0.16), with an association observed only for early pneumonitis (p = 0.044). High %CV-eCmax during Q3W was associated with increased odds of irAEs (odds ratio [OR] 8.4, p = 0.02), pneumonitis (OR 14.3, p = 0.03), early irAEs (OR 15.2, p = 0.017), and early pneumonitis (OR 30.0, p = 0.03). No significant associations were observed between %CV-eCtrough and irAEs or early irAEs. Higher platelet count and renal dysfunction were independently associated with increased %CV-eCmax. **Conclusions:** Higher inter-cycle variability in eCmax during 200 mg Q3W was associated with an increased risk of new or worsened irAEs, particularly pneumonitis, after switching to 400 mg Q6W. These findings suggest that inter-cycle variation in Cmax may be an important safety consideration when transitioning to a 400 mg Q6W regimen. Research Sponsor: None.

12139 **Poster Session**

Impact of synbindin deficiency on immune checkpoint blocker–induced systemic inflammation and multi-organ damage. First Author: Zhenghang Xu, Zhongshan Hospital, Fudan University, Shanghai, China

Background: Immune-related adverse events (irAEs) are a major safety limitation for the broad application of immune checkpoint blockade (ICB) in oncology, yet their precise molecular mechanisms remain unclear. Synbindin, a tethering-associated protein involved in vesicular trafficking and related processes, plays a key role in immune-cell activation and activation of inflammatory signaling pathways and therefore may represent an important initiator and predictive factor for irAEs. **Methods:** We generated constitutive whole-body Trappc4 knockout (Trappc4-KO) C57BL/6 mice and administered either anti-PD-1 monotherapy or combined anti-PD-1 plus anti-CTLA-4 immune checkpoint blockade via intraperitoneal injection. Plasma biochemical indices and the extent of organ injury were assessed following treatment. **Results:** Trappc4-KO mice receiving combined anti-PD-1/anti-CTLA-4 treatment exhibited markedly more severe immune-related toxicity and multi-organ injury than wild-type controls. Biochemically, markers of hepatic injury (AST, ALT) were substantially elevated, indicating liver dysfunction; renal function markers (serum creatinine and blood urea nitrogen) were significantly increased, consistent with kidney injury; and cardiac markers (CK-MB, cTnT, cTnI) were also markedly raised. A similar trend, although less pronounced, was observed following anti-PD-1 monotherapy. Histopathological examination corroborated these findings: H&E sections of affected organs showed prominent focal immune cell infiltration, cellular swelling, and areas of necrosis. **Conclusions:** These data demonstrate that Trappc4 deficiency significantly exacerbates ICB-induced systemic inflammation and multi-organ damage, suggesting that Synbindin plays a critical protective role in the development of irAEs. Research Sponsor: None.

12140 **Poster Session**

A randomized controlled pilot study of aromatherapy to reduce anxiety and pain during bone marrow aspiration and biopsy. First Author: Krisstina Gowin, City of Hope, Irvine, CA

Background: Bone marrow aspiration and biopsy (BMAB) is associated with substantial anxiety and pain among patients with hematologic malignancies. Nonpharmacologic strategies to improve procedural tolerance are needed. Aromatherapy with lavender essential oil and its primary active constituent, linalool, has demonstrated anxiolytic effects in preclinical and peri-procedural settings but has not been rigorously evaluated during BMAB. **Methods:** We conducted a single-center, randomized pilot study of adult patients with cancer receiving a BMAB. Subjects were randomized (1:1:1) to lavender essential oil ($\geq$25% linalool), pure linalool oil ($\geq$97%), or placebo (jojoba oil). Aromatherapy was administered via inhalation prior to and throughout the procedure. Primary outcomes included feasibility ($>$70% completion) and patient satisfaction. Secondary outcomes included anxiety and pain assessed by visual analog scales (VAS) before, during, and after BMAB. Exploratory physiologic outcomes included bispectral index (BIS), an electroencephalogram-based measure of cortical arousal. **Results:** Forty-five patients were enrolled, with 43 (96%) completing the study, meeting feasibility criteria. Most participants (88%) agreed or strongly agreed that aromatherapy was relaxing and enjoyable. All groups demonstrated significant within-group reductions in VAS-anxiety from pre- to post-procedure, with the largest reduction observed in the linalool arm (-3.1 ± 0.70 (mean$\pm$SE); $p<0.01$), compared with lavender (-1.8 ± 0.67; p=0.02) and placebo (-2.4 ± 0.61; $p<0.01$). During BMAB, anxiety reduction favored the lavender and linalool arms, with a trend toward between-group significance (p=0.053). Pain increased during BMAB across all groups; however, the linalool arm demonstrated the smallest increase (2.6 ± 0.69; $p<0.01$)) compared with lavender (3.8 ± 0.93; $p<0.01$)) and placebo (4.0 ± 1.3; $p<0.01$). Post-BMAB, between group analysis trended toward significantly less pain with lavender and linalool compared to placebo (p=0.057). Exploratory within-group BIS scores analyses demonstrated significant reductions in average BIS after aromatherapy treatment prior to BMAB with lavender showing the greatest reductions (-6.0$\pm$2.0; p=0.01), as compared to linalool (-3.6$\pm$1.6; p=0.047) and placebo (-1.6$\pm$1.3, p=0.27). No serious adverse events occurred. **Conclusions:** Aromatherapy using lavender and linalool during BMAB is feasible, safe, and potentially associated with meaningful reductions in procedural anxiety and pain. These preliminary findings support a larger randomized control trial to confirm efficacy and explore integration into routine supportive oncology care. Clinical trial information: NCT06581211. Research Sponsor: None.

12141 Poster Session

Cumulative toxicity assessed by area-under-the-curve (AUC) in targeted therapy versus chemotherapy for advanced *EGFR*-mutant NSCLC. First Author: William J. Phillips, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO

Background: Current adverse event (AE) reporting standards emphasize peak toxicity, which may inadequately capture the cumulative burden of persistent low-grade AEs characteristic of targeted therapies. We conducted a post-hoc analysis of the LUX-Lung 3 trial to compare longitudinal toxicity patterns of targeted therapy and chemotherapy over time. **Methods:** This post-hoc analysis used individual, de-identified patient-level data from the phase III LUX-Lung3 clinical trial comparing afatinib with platinum-based chemotherapy as first-line treatment for advanced EGFR-mutant NSCLC, accessed through Vivli. Select treatment-related AEs were evaluated longitudinally by grade. Cumulative toxicity burden was quantified using the area-under-the-curve (AUC) of AE grade prevalence over time. Pearson correlation was used to assess temporal trends in AUC. **Results:** A total of 340 patients had evaluable AE data, including 229 (67%) treated with afatinib and 111 (33%) treated with chemotherapy. The median onset of grade 1-2 AEs generally occurred earlier with chemotherapy than afatinib. The median onset of chemotherapy-related fatigue was 4 days and nausea 2 days, whereas median onset of afatinib-related diarrhea was 4 days, rash 8 days, and paronychia 37 days. Longitudinal AUC analysis (Table 1) demonstrated a significant improvement in grade 1-2 chemotherapy-related nausea (p=0.003) and stomatitis (p=0.05), and a trend towards improvement in fatigue (p=0.2) by 12-months. In contrast, grade 1-2 afatinib-related rash (p=0.4) and diarrhea (p=0.99), remained stable, while paronychia increased over time (p=0.004). For grade 3+ AEs, the AUC improved over time for both the chemotherapy (p=0.04) and afatinib (p=0.02) groups. **Conclusions:** Assessment of time to onset and longitudinal AUC reveal distinct temporal AE patterns for targeted therapy and chemotherapy. Longitudinal toxicity reporting is feasible and highlights the sustained burden of chronic AEs associated with targeted therapies that are clinically meaningful yet underrepresented by conventional peak toxicity reporting. Research Sponsor: Thoracic Oncology Research Initiative (TORI), University of Colorado.

Cumulative toxicity of afatinib and chemotherapy was quantified using the area under the curve of grade 1-2 adverse events prevalence at landmark time points.*

Adverse event	Month 1	Month 3	Month 6	Month 12	Pearson's coefficient	p-value
Afatinib (%)						
Rash	0.24	0.39	0.44	0.45	0.24	0.4
Diarrhea	0.30	0.44	0.47	0.45	-0.002	0.99
Paronychia	0.02	0.20	0.32	0.39	0.74	0.004
Chemotherapy (%)						
Fatigue	0.05	0.09	0.09	0.07	-0.36	0.2
Nausea	0.07	0.17	0.17	0.10	-0.60	0.03
Stomatitis	0.02	0.02	0.02	0.01	-0.56	0.05

*Trends were assessed using Pearson's correlation coefficient and corresponding p-value.

12142 Poster Session

The price of a breath: The economic and mortality burden of checkpoint inhibitor pneumonitis (2016–2020). First Author: Milan Regmi, Southeast Health Medical Center, Dothan, AL

Background: The landscape of oncologic toxicity has drastically changed because of the rapid introduction of Immune Checkpoint Inhibitor (ICI) indications, ranging from the treatment of melanoma to thoracic cancers. Immune-related adverse events (irAEs) are a novel range of toxicities brought about by the rapid growth of ICI. The overall national burden of severe inpatient toxicities is still unknown, despite the well-described outpatient care of irAEs. We measured the prevalence, mortality, and financial impact of severe irAEs necessitating hospitalization using the Nationwide Inpatient Sample (NIS). **Methods:** We evaluated adult hospitalizations secondary to major irAEs (pneumonitis, colitis, hepatitis, and endocrinopathies) using ICD-10-CM codes for a retrospective cohort analysis of the National Inpatient Sample database from 2016 to 2020. Only patient with cancer diagnosis associated complications were included to reduce confounders. Statistical evaluations and outcomes were generated using STATA version 19. The use of mechanical ventilation, total hospital charges, and in-hospital mortality were the major outcomes. Temporal trends and mortality factors were examined using survey-weighted regression models. **Results:** We identified a weighted national cohort of 109,225 irAE-related hospitalizations from 2016 to 2020. Epidemiology: Immune-mediated Colitis was the dominant driver of volume (54.6%) for inpatient admission, followed by Pneumonitis (22.2%) and Hepatitis (18.2%). The proportion of admissions attributable to Pneumonitis was increased from 21.1% in 2016 to 24.0% in 2020 ($p < 0.001$), coincident with expanded ICI use in lung cancer. Outcomes & Acuity: Pneumonitis was associated with the longest mean length of stay (LOS) of 6.9 days and the highest raw mortality (7.8%) compared to Colitis (1.6%). In multivariable analysis, Pneumonitis was the strongest independent predictor of in-hospital mortality (aOR 4.98; 95% CI 4.12–6.02; $p < 0.001$)relative to Colitis. Conversely, female sex was associated with a significant survival advantage (aOR 0.76; p = 0.001). Economic Burden: Pneumonitis was the most resource-intensive toxicity (Mean Charge: $74,298 vs. $43,831 for Colitis). The aggregate national hospital bill for irAEs rose from $1.14 Billion in 2016 to a peak of $1.75 Billion in 2020. **Conclusions:** Pneumonitis is the primary cause of death and economic expense, whereas colitis is the primary cause of irAE hospitalizations. Between 2016 and 2020, the total cost of hospitalization in the United States almost doubled, reaching approximately $1.75 billion per year. Health systems need to prepare for an increase in high-acuity, resource-intensive pulmonary toxicity as ICI indications spread into the adjuvant environment. Research Sponsor: None.

12143 Poster Session

A risk prediction model for severe, life-threatening, and fatal treatment-related toxicity. First Author: Joseph M. Unger, SWOG Statistics and Data Management Center, Fred Hutchinson Cancer Center, Seattle, WA

Background: Adverse events are major contributors to morbidity and mortality in patients receiving systemic cancer therapy. Accurate prediction of high-grade toxicity could inform risk-adapted treatment strategies. **Methods:** This cohort study included data from 18 SWOG adult phase 2 and 3 treatment trials conducted from 1990 to 2022. Baseline patient-reported symptoms (fatigue, pain, and anxiety, classified as clinically meaningful yes vs. no), baseline sociodemographic (age, sex, race, ethnicity), and performance status (PS) variables were used. The aim was to develop a unified risk score applicable across multiple toxicity severity thresholds; adverse events were classified using the Common Terminology Criteria for Adverse Events. The primary outcomes were severe (Grade >3), life-threatening (Grade >4), and fatal toxic events. A training set was derived using a random 60% sample, balanced by study and arm; validation will occur in the remaining 40%. Best-subsets logistic regression was used for variable selection; final models were stratified by cancer type (hematologic, hormone-driven solid tumor, or other solid tumor) and treatment status (untreated vs refractory). Model discrimination was assessed using the concordance (c) statistic. Patients were divided into tertiles according to their total risk score. Toxicity rates and odds ratios were evaluated across tertiles (Ts). **Results:** Of 7,936 patients, 4,776 (60.2%; median age 64.9 (range, 18-95.3); female 28.0%; Black 10.8%) formed the training cohort. Increased toxicity was associated with age ≥60 years, fatigue, female sex, and PS ≥1. The multivariable risk models demonstrated good discrimination for grade ≥3 (c=0.76), grade ≥4 (c=0.77), and grade 5 toxicity (c=0.77). Severe toxicity increased from 15.8% in the lowest risk tertile (T1) to 64.6% in T3; life-threatening toxicity increased from 2.7% in T1 to 26.2% in T3 (Table). Compared with the lowest tertile, the highest risk tertile had markedly higher odds of grade ≥3 (OR 9.76), grade ≥4 (OR 12.96), and grade 5 toxicity (OR 7.15; all p<.001). Model validation results will be presented. **Conclusions:** This risk model accurately identified patients with substantially elevated risk for severe, life-threatening, and fatal toxicities. Risk stratification may support individualized treatment counseling, risk-guided monitoring, and proactive toxicity management. Research Sponsor: The Hope Foundation; National Cancer Institute/U.S. National Institutes of Health; U10CA180888; National Cancer Institute/U.S. National Institutes of Health; U10CA180819; National Cancer Institute/U.S. National Institutes of Health; UG1CA189974.

Observed toxicity rates and odds ratios by predicted-risk tertile.

	Observed Toxicity			Odds Ratios by Model (95% CI, p-value)		
	T1 (n=1536)	T2 (n=1646)	T3 (n=1594)	Increase per risk level	T2 vs. T1	T3 vs. T1
Grade >3	15.8	37.7	64.6	3.11 (2.86-3.39, p<.0001)	3.23 (2.73-3.83, p<.0001)	9.76 (8.23-11.59, p<.0001)
Grade >4	2.7	9.1	26.2	3.58 (3.12-4.11, p<.0001)	3.66 (2.57-5.20, p<.0001)	12.96 (9.32-18.02, p<.0001)
Grade >5	0.2	0.6	1.4	2.54 (1.54-4.18, p<.0001)	3.12 (0.86-11.37, p=.08)	7.15 (2.14-23.94, p=.001)

12144 Poster Session

Dentist-led systematic oral education programs in the prevention of radiation-induced oral toxicities in patients with head and neck cancer (BRIGHT): A randomized clinical trial. First Author: Yu Min, Department of Biotherapy, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

Background: Radiotherapy-induced oral toxicity (RIOT) is a common complication in patients with head and neck cancer (HNC). International guidelines have recognized the role of oral-health education in preventing RIOT. However, most recommendations remained at the level of general principles and lacked a detailed, systematic and operationalized process, which hinders effective clinical delivery of oral-health education. Given that dentists are uniquely positioned to manage oral health, this study aims to evaluate the effectiveness of a dentist-led systematic oral-health education program (OHEP) on RIOT and provide a standard operating procedure (SOP) for its implementation. **Methods:** In this single-centre, assessor-blinded, randomised controlled trial, 150 patients with non-metastatic HNC scheduled for definitive radiotherapy (60–72 Gy) were enrolled at West China Hospital in China. Participants were randomly assigned (1:1) to receive either a dentist-led oral health education program (OHEP) or routine oral health care. The primary endpoint was the incidence of oral mucositis (OM), assessed by the WHO Oral Mucositis Grading Scale. Secondary endpoints included the incidence of severe oral mucositis (SOM, defined as WHO grade 3–4) as well as the time to onset and duration of OM (SOM). Outcome assessments were conducted by trained research assistants blinded to group allocation. Analyses were performed in both intention-to-treat and per-protocol populations, with two-sided $P < 0.05$ considered statistically significant. This study is registered with ClinicalTrials.gov, NCT06690346, and is now complete. **Results:** Of 150 randomised patients, 75 were allocated to each arm, and 142 (94.7%) completed the trial and were included in the intention-to-treat analysis. The incidence of OM was significantly lower in the OHEP arm than in the control arm (70.7% [53/75] vs. 88.0% [66/75] $P = 0.016$), with a significantly delayed onset (median 17 vs. 14 days; $P = 0.006$) and shorter duration (median 39 vs. 60 days; $P < 0.001$). Consistent results were observed in the per-protocol population. However, no significant difference was observed in the incidence, onset, or duration of SOM between arms. **Conclusions:** Dentist-led OHEP significantly reduced the incidence and delayed the onset of radiotherapy-induced OM. These results support dentist-led OHEP as a feasible, non-pharmacological approach to mitigate oral toxicity and improve supportive care in patients receiving radiotherapy for HNC. Clinical trial information: NCT06690346. Research Sponsor: Ministry of Science and Technology of the People's Republic of China; 2023ZD0503000, 2023ZD0503004; National Natural Science Foundation of China; U24A20735; Ministry of Education of the People's Republic of China; 82473434.

12145 **Poster Session**

Efficacy and safety of Meilian Fuxin liquid for radiation-induced oral mucositis in head and neck cancer: A multicenter randomized clinical trial. First Author: Huaju Yang, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China

Background: Radiation-induced oral mucositis (RIOM) is common during head and neck radiotherapy (> 90% incidence), and 40–70% of patients develop severe oral mucositis (SOM; WHO grade 3–4), which markedly impairs quality of life and may lead to radiotherapy interruptions. Given the limited effective therapies and the lack of evidence-based standard of care, we assessed the efficacy and safety of MeiLianFuXin Liquid (*Periplaneta americana* extract) for reducing SOM incidence. **Methods:** This multicenter, randomized, double-blind, placebo-controlled phase II trial was conducted across 7 hospitals in China from June 12, 2024, through October 31, 2025. Eligible patients (18–80 years) had non-metastatic head and neck cancer planned for radiotherapy (planned total dose ≥60 Gy), with cisplatin as the only allowed concurrent agent. Following investigator-confirmed WHO grade 1 oral mucositis, patients were randomized (1:1:1) via a centralized interactive web response system (IWRS) using a dynamic minimization algorithm to receive low-dose MeiLianFuXin Liquid, high-dose MeiLianFuXin Liquid, or a matched placebo. The study drug was administered three times daily until 14 days post-radiotherapy. The primary endpoint was SOM incidence. Adjusted proportion differences were estimated using logistic regression. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. **Results:** In the full analysis set (FAS), 215 patients received treatment (low-dose, n = 72; high-dose, n = 72; placebo, n = 71). The incidence of SOM was 22.2% (95% CI, 13.3 to 33.6) in the low-dose group, 29.2% (95% CI, 19.0 to 41.1) in the high-dose group, and 43.7% (95% CI, 31.9 to 56.0) in the placebo group. Compared with placebo, adjusted proportion differences were −22.5% (95% CI, −37.3 to −7.8; *P* = .0042) for the low-dose group and −16.4% (95% CI, −32.2 to −0.5; *P* = .0463) for the high-dose group. Adverse events and serious adverse events were generally similar across groups. **Conclusions:** To our knowledge, this is the first randomized, double-blind, placebo-controlled trial of a traditional Chinese medicine for RIOM showing that MeiLianFuXin Liquid reduces SOM incidence versus placebo with a favorable safety profile. These findings support MeiLianFuXin Liquid as a promising treatment strategy to mitigate RIOM. Clinical trial information: ChiCTR2400084288. Research Sponsor: the Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0503000, 2023ZD0503004); the Regional Innovation and Development Joint Fund Key Project of the National Natural Science Foundation of China (U24A20735); the National Natural Sciences Foundation of China (82473434); the Fundamental and Interdisciplinary Disciplines Breakthrough Plan of the Ministry of Education of China, the Institutional Joint Innovation Fund from Sichuan University and Nuclear Power Institute of China (1-KJ-FWHT-WU-20240150).

12146 **Poster Session**

Oral mannitol for chemotherapy-induced constipation (CIC): A randomized, multicenter, controlled study. First Author: Chaomin Liu, The First Affiliated Hospital of Chengdu Medical College, Chengdu, China

Background: Chemotherapy-induced constipation (CIC) is a common yet frequently overlooked supportive care issue, currently, there is still a lack of efficient and affordable methods. This trial was designed to compare the efficacy and safety of orally administered mannitol injection versus lactulose in cancer patients with CIC. **Methods:** An open-label, multicenter, prospective RCT (ChiCTR2200056847) planned to enroll 114 adults. Participants were randomized 1:1 to oral mannitol 50 mL post-meal 3–5×/day or lactulose 30 mL once daily for 3 days. Primary endpoint: time to first spontaneous defecation (TFSD). Secondary endpoints included weekly complete spontaneous bowel movements (CSBMs), Bristol Stool Form Scale, PAC-QOL, and CTCAE v5.0 adverse events (AEs). Interim analysis was performed when 112 participants had completed the 7-day assessment; database was locked on 30 January 2026. **Results:** A nationwide survey (14 provinces, n=1,174) revealed significantly higher constipation rates in stage IV cancer patients ($p<0.05$), and found that the managements vary in effectiveness. In an RCT interim analysis (112 patients), baseline demographics were balanced between mannitol (n=56) and lactulose (n=56) groups. Median time to first defecation was significantly shorter in mannitol group with 5.5 hours (IQR 3.0-15.8) than in lactulose with 16.0 hours (IQR 5.3-27.5) (p=0.003)(Fig. 1). Secondary outcomes were comparable: weekly mCSBMs (3.0 vs. 3.0, p=0.083); Bristol Scale improvement ≥1 category (60.7% vs. 58.9%, p=0.847); and PAC-QOL score (-26 vs. -18 points, p=0.105). Both treatments were safe, with only mild, transient adverse events at similar rates (3.6% vs. 5.4%, p=0.647)(Table 1). **Conclusions:** Survey data confirm under-recognition of CIC and therapeutic gaps for advanced-stage patients. In this interim analysis, oral mannitol significantly shorten TFSD than lactulose, with mild adverse events, which is a rapid-onset, low-cost option for CIC management. Clinical trial information: ChiCTR2200056847. Research Sponsor: None.

TFSD, weekly CSBMs, adverse events, PAC-QOL.

Outcome	Mannitol (n=56)	Lactulose (n=56)	p-value
TFSD (median, IQR)	5.5 (3.0–15.8) hrs	16.0 (5.3–27.5) hrs	0.003
Weekly CSBMs (median, IQR)	3.0 (3.0–4.0)	3.0 (2.0–3.0)	0.083
Stool form improvement (≥1 Bristol)	34 (60.7%)	33 (58.9%)	0.847
PAC-QOL change (Δ, mean)	-26 (18.3–40.5)	-18 (12.5-37.5)	0.105
Any AE (%)	2 (3.6%)	3 (5.4%)	0.647

12147 **Poster Session**

Efficacy and safety of mixed formulation aprepitant and palonosetron (QLM2010) for prevention of cisplatin-based highly emetogenic chemotherapy-induced nausea and vomiting: A multicenter, randomized, double-blind, double-dummy, positive-controlled phase III study. First Author: Jieer Ying, Department of Hepatobiliary, Pancreatic and Gastric Medicine, Zhejiang Cancer Hospital, Chinese Academy of Sciences, Hangzhou, Zhejiang, China

Background: QLM2010, a novel fixed-dose intravenous antiemetic combination of aprepitant and palonosetron (PALO), can simultaneously antagonize 5-hydroxytryptamine-3 and neurokinin-1 receptors. This study aimed to assess the efficacy and safety of QLM2010 plus dexamethasone (DEX) versus fosaprepitant (FAPR) combined with PALO and DEX for preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). **Methods:** This was a multicenter, randomized, double-blind, double-dummy, positive-controlled Phase III trial. Chemotherapy-naïve patients with solid tumors were randomly assigned 1:1 to receive QLM2010 (Day 1) or FAPR + PALO (Day 1) prior to cisplatin-based HEC, together with oral DEX (Days 1–4). The primary efficacy endpoint was complete response (CR: no emesis/no rescue medication) during the overall (0–120 hours) phase. **Results:** Baseline demographic and clinical characteristics were well-balanced between the two groups (QLM2010 group: n = 329; FAPR+PALO group: n = 331). The overall CR rate was 82.67% versus 80.97% (risk difference, 1.65%; 95% CI, −4.21–7.50%), confirming the non-inferiority of QLM2010 + DEX to FAPR + PALO + DEX. CR rates in both the acute (0–24 hours) and delayed (24–120 hours) phases were comparable between groups. Across all phases, the QLM2010 group showed similar rates to the FAPR+PALO group for no emesis, no nausea, no significant nausea, no rescue therapy, and complete protection (all P > 0.05). Notably, QLM2010 + DEX showed greater proportions of patients reporting no impact on daily life on Day 2 after treatment compared with FAPR + PALO + DEX (P = 0.0279). A single injection-site reaction (0.30 %) was confined to the FAPR+PALO group; none was observed in the QLM2010 group. The incidence of hiccups was numerically lower in the QLM2010 group compared with the FAPR+PALO group (8.2% vs. 15.1%). **Conclusions:** QLM2010 + DEX was non-inferior to FAPR + PALO + DEX for preventing CINV in cisplatin-based HEC patients and well tolerated, with the potential to reduce the impact of CINV on daily life. QLM2010 furnishes a novel, more convenient therapeutic alternative for the clinical management of CINV. Clinical trial information: NCT07081256. Research Sponsor: None.

12148 **Poster Session**

SARM1 inhibition to prevent chemotherapy-induced peripheral neuropathy: Translational and early clinical evaluation of SIR2501. First Author: Linping Yu, Sironax, Beijing, China

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is a common, cumulative, and often irreversible toxicity that limits dose intensity, disrupts cancer treatment, and substantially impairs quality of life. Despite its prevalence, no approved disease-modifying therapies exist. Axonal degeneration is a central pathological driver of CIPN. Sterile alpha and TIR motif–containing protein 1 (SARM1) is a key executioner of programmed axon degeneration across neurotoxic insults. Inhibiting SARM1 offers a mechanism-based strategy to prevent axonal injury without compromising anticancer activity. SIR2501 is a potent, selective, orally bioavailable small-molecule SARM1 inhibitor in clinical development for CIPN prevention. **Methods:** SIR2501 was evaluated in rodent models of paclitaxel (PTX)-induced peripheral neuropathy using prophylactic and therapeutic dosing paradigms. Endpoints included sensory neuropathy (mechanical allodynia), axonal injury biomarkers (serum neurofilament light chain [sNfL]), and peripheral nerve integrity (intraepidermal nerve fiber density). The impact of SIR2501 on PTX antitumor efficacy was assessed in rodent tumor models.A randomized, double-blind, placebo-controlled Phase 1 study in healthy volunteers evaluated safety, pharmacokinetics (PK), CNS penetration, and pharmacodynamic evidence of SARM1 target engagement following single and multiple ascending doses. **Results:** SIR2501 robustly attenuated PTX-induced neuropathy in preclinical models, with concordant functional, biomarker, and structural protection, and did not impair PTX-mediated tumor growth inhibition. In Phase 1, 82 volunteers received SIR2501 (up to 600 mg single dose; up to 150 mg once-daily multiple dose). SIR2501 was well tolerated, with no dose-limiting toxicities or clinically meaningful neurologic adverse events. PK supported once-daily dosing with minimal food effect and no CYP3A-mediated drug–drug interaction risk. Dose- and exposure-dependent suppression of circulating cyclic ADP-ribose (cADPR) confirmed SARM1 target engagement at plasma exposures aligned with preclinical efficacy. **Conclusions:** These translational data support SARM1 inhibition as a disease-modifying approach for CIPN. These data have enabled initiation of a global Phase 1b/2 trial of SIR2501 in patients receiving taxane-based chemotherapy in the United States, Australia, and China. Research Sponsor: Sironax Inc.

12149 Poster Session

Baseline telomere length and prediction of cognitive recovery after chemotherapy in patients with breast cancer: An NCORP prospective cohort study. First Author: Jonas M. Ndeke, Department of Surgery, Division of Supportive Care in Cancer, University of Rochester Medical Center, Rochester, NY

Background: Chemotherapy-related cognitive impairment (CRCI) affects up to 70% of breast cancer survivors, yet recovery varies. Telomere length (TL), a marker of biological aging, may reflect biological resilience to CRCI. We evaluated whether baseline TL predicts longitudinal cognitive recovery following chemotherapy. **Methods:** In a nationwide prospective cohort study across 19 NCORP-affiliated community oncology clinics (URCC 10055), 185 women with stage I–IIIC breast cancer were assessed before chemotherapy (T1), post-chemotherapy (T2), and 6 months post-chemotherapy (T3). Baseline TL was measured by qPCR, normalized, and categorized into three groups: Short (S, n = 63, 34.1%), Average (A, n = 75, 40.5%), and Long (L, n = 47, 25.4%). Perceived cognitive function was assessed using the Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog; minimum clinically important difference for total ≈7 pts), including total score and subscales for perceived cognitive impairments (PCI), perceived cognitive abilities (PCA), comments from others (OTH), and impact on quality of life (QoL). Changes from T1→T2 and T2→T3 were evaluated using repeated-measures mixed-effects analysis of covariance models adjusted for baseline values. **Results:** Baseline FACT-Cog total scores were similar across TL groups. At T2, all groups experienced comparable acute PCI (FACT-Cog change: S = −13.2, A = −13.3, L = −18.7). By T3, recovery differed by TL. While all groups remained below baseline, patients with long TL demonstrated substantially greater recovery, with a smaller overall decline from T1 (L = −8.6) compared with persistent impairment in Short (S = −14.0) and Average (A = −11.4) groups. This reflected a clinically meaningful improvement in cognitive function from post-chemotherapy to 6-month of +10.0 pts in the Long group (p = .016), whereas changes in the other two groups was not clinically or statistically significant. This recovery pattern was supported by clinically significant improvement in PCI (+7.2) and statistically significant change in OTH (+1.0; p = .003) in the Long group from T2 to T3, while it was attenuated in the Average and Short groups. In contrast, PCA showed minimal change across groups. Impact on quality of life also improved significantly in the Long group over the same period (FACT-Cog QoL T3−T2 change = +2.0; p = .019), reinforcing a coherent cognitive recovery phenotype. **Conclusions:** Baseline TL does not determine susceptibility to acute chemotherapy-related toxicity but strongly predicts cognitive recovery over time. Patients with longer telomeres demonstrate clinically meaningful recovery of cognition, whereas those with shorter telomeres show more persistent perceived cognitive impairment. TL may identify patients at higher risk for long-term impairment who could benefit from early supportive and rehabilitative interventions. Research Sponsor: NIH NCI T32CA102618; NIH NCI R01CA231014; NIH NCI UG1CA189961; NIH NCI UG1CA189858; NIH NCI UG1CA189956; NIH NCI UG1CA239762.

12150 Poster Session

Prophylactic vs reactive PEG tube placement in early-stage head and neck (H&N) cancer treated with curative-intent radiotherapy: Balancing benefit and burden in real-world practice. First Author: Fayaz Aijaz Ahmed Khan, Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background: Timing of Percutaneous Endoscopic Gastrostomy (PEG) placement during curative-intent radiotherapy for H&N cancer remains controversial. We compared 6-month and 1-year outcomes after prophylactic (pPEG) versus reactive (rPEG) PEG placement in real-world practice. **Methods:** We conducted a retrospective study using the TriNetX Network database. Adults (≥18 years) with H&N cancer treated with curative-intent radiotherapy who received PEG were stratified by PEG timing: pPEG (≤30 days before or at radiotherapy initiation) versus rPEG (30–90 days after radiotherapy initiation). The index date was PEG insertion. After 1:1 propensity-matching with demographics, comorbidities, nutrition/weight variables, BMI, stage, chemotherapy/surgery, 2,752 patients remained in each cohort. Outcomes at 6 months and 1 year were analyzed using Kaplan–Meier methods with log-rank tests and Cox proportional-hazards models (HR, 95% CI). **Results:** At 6 months, compared with rPEG, pPEG was associated with lower all-cause mortality, but higher hospitalization, sepsis, PEG tube dependence, and PEG tube complications. ICU admission, aspiration pneumonitis, pneumonia, and dehydration were similar between cohorts. At 1 year, all-cause mortality and ICU admission remained similar between groups. However, pPEG was associated with higher hospitalization, aspiration pneumonitis, pneumonia, sepsis, and PEG tube complications, while dehydration and PEG tube dependence were similar (see Table). pPEG was associated with higher risk of dysphagia at 6 months (HR 1.3, 95% CI 1.1–1.6; p<0.01) and 1 year (HR 1.2, 95% CI 1.1–1.5; p=0.01), and malnutrition at 6 months (HR 1.3, 95% CI 1.1–1.6; p<0.01) and 1 year (HR 1.3, 95% CI 1.1–1.6; p<0.01). Unintentional weight loss and PEG tube removal did not differ between groups. **Conclusions:** In this real-world cohort study, pPEG was not associated with improved 1-year survival and was associated with higher acute care utilization, infections, and PEG-related complications compared with rPEG. These findings support selective, risk-stratified pPEG use rather than routine prophylactic placement. Research Sponsor: None.

Outcome	6 Month HR (95% CI, p-value)	1 Year HR (95% CI, p-value)
All-cause mortality	0.8 (0.7-0.9, p=0.04)	0.9 (0.8-1.1, p=0.6)
Hospitalization	1.3 (1.01-1.6, p=0.04)	1.2 (1.1-1.5, p=0.04)
ICU admission	1.0 (0.8-1.3, p=0.6)	1.1 (0.9-1.3, p=0.3)
Aspiration pneumonitis	1.2 (0.9-1.5, p=0.07)	1.2 (1.1-1.5, p=0.03)
Pneumonia	1.2 (0.9-1.4, p=0.1)	1.2 (1.1-1.4, p=0.04)
Sepsis	1.3 (1.01-1.5, p=0.03)	1.3 (1.1-1.5, p=0.01)
Dehydration	1.6 (0.9-2.6, p=0.08)	1.5 (0.9-2.3, p=0.1)
PEG tube dependence	1.2 (1.01-1.3, p=0.04)	1.1 (0.9-1.3, p=0.07)
PEG tube complication	1.2 (1.1-1.4, p<0.01)	1.2 (1.1-1.3, p<0.01)

HR > 1 indicates higher hazard in pPEG vs rPEG; HR < 1 indicates lower hazard.

12151 Poster Session

The influence of exercise on the mediational relationship between chemotherapy-induced sensory neuropathy and cancer-related fatigue: A nationwide phase II RCT in 111 patients receiving chemotherapy. First Author: Po-Ju Lin, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY

Background: Cancer-related fatigue (CRF) and chemotherapy-induced sensory neuropathy (e.g., numbness, tingling, and pain) are common, sometimes debilitating toxicities that often co-occur in patients receiving neurotoxic chemotherapy. Both CRF and sensory neuropathy significantly diminish daily function and quality of life. Exercise is recommended for treating CRF and may also alleviate sensory neuropathy. Whether exercise-induced reductions in CRF are mediated by improvements in sensory neuropathy remains unknown. **Methods:** We conducted a nationwide phase II randomized controlled trial (RCT) through the University of Rochester Cancer Center NCI Community Oncology Research Program (URCC NCORP) Research Base. Patients who received neurotoxic chemotherapy in the past 9 months and developed moderate or severe (rated ≥4 on a 0-10 numerical scale) chemotherapy-induced sensory neuropathy (e.g., numbness, tingling, hot/burning or sharp/shooting pain in the hands and feet) in the past 2 weeks were randomized to virtually delivered Exercise for Cancer Patients (vEXCAP) or usual care (UC). vEXCAP is a 6-week, individually tailored, progressive walking and resistance band exercise intervention delivered virtually. CRF severity and sensory neuropathy were assessed via the Brief Fatigue Inventory severity score and the EORTC QLQ-CIPN20 sensory subscale (0-100 scale), respectively, at pre- and post-intervention. Causal mediation analyses were conducted to determine the extent to which exercise-induced improvements in CRF were mediated by changes in sensory neuropathy at post-intervention. **Results:** One hundred eleven patients (mean age 59.5 years; 76% female; 84% white; 37% breast cancer; 36% gastrointestinal cancer) were randomized and completed pre- and post-intervention assessments. vEXCAP participants, compared to UC participants, experienced significantly greater reductions in CRF (-0.95±0.33, p = 0.014) and clinically meaningful improvements in sensory neuropathy at post-intervention (-5.38±2.77 [MCID = 4.2], p = 0.055). Causal mediation analyses indicated that reductions in sensory neuropathy significantly mediate exercise-induced improvements in CRF severity (-0.18±0.13, p = 0.056), accounting for 19% (95% CI: 0% - 64%) of the exercise effect on CRF severity at post-intervention. **Conclusions:** vEXCAP reduces CRF severity and chemotherapy-induced sensory neuropathy among patients receiving neurotoxic chemotherapy. Approximately 19% of the exercise-induced improvements in CRF severity are mediated by reductions in chemotherapy-induced sensory neuropathy. Future Phase III RCTs are needed to confirm these findings and further explore the mediational role of chemotherapy-induced sensory neuropathy on CRF to help optimize the treatment of CRF using exercise. Clinical trial information: NCT04888988. Research Sponsor: National Cancer Institute; R21CA256154, K07CA221931, UG1CA189961, UG1CA189804, UG1CA189822, UG1CA189819, UG1CA189830, T32CA102618.

12152 Poster Session

Trilaciclib for myeloprotection in adjuvant and first-line chemotherapy for advanced gastric/gastroesophageal junction adenocarcinoma: A multicohort study. First Author: Wenhui Yang, Department of Gastroenterology, Shanxi Province Cancer Hospital/Shanxi Hospital Affiliated to Cancer Hospital, Chinese Academy of Medical Sciences/Cancer Hospital Affiliated to Shanxi Medical University, Taiyuan, China

Background: Chemotherapy-induced myelosuppression (CIM) has become one of the important limiting factors in the treatment of gastric cancer, which significantly impairs patients' prognosis.Trilaciclib, a highly selective reversible CDK4/6 inhibitor, reduces chemotherapy-induced hematopoietic stem/progenitor cell (HSPC) damage via transient G1 arrest when administered intravenously pre-chemotherapy, while its transient T-cell suppression may modulate the tumor immune microenvironment.This study evaluates trilaciclib's myeloprotective efficacy in adjuvant and first-line metastatic gastric/gastroesophageal junction adenocarcinoma (GA/GEJA) and explores immunomodulatory effects. **Methods:** This prospective multicohort study (ChiCTR2500097520) enrolled Cohort 1 (resectable GA/GEJA, T1-4bN0-3M0 post-D2/R0 resection; n = 75) and Cohort 2 (first-line metastatic GA/GEJA, including recurrence > 6 months post-adjuvant; n = 40). Regimens included SOX/XELOX/FOLFOX ± immune checkpoint inhibitors (ICIs) ± trastuzumab. Trilaciclib (240 mg/m²) was given on days 1 and 3 every 21 days for 6–8 cycles. Primary endpoints: incidence of grade ≥3 neutropenia and febrile neutropenia (FN); exploratory analyses included immune biomarkers and antitumor efficacy. **Results:** As of January 2026, 204 patients were enrolled (male: 158 ; female: 46; median age: 63 years [range: 31–82]). Cohort 1: 118 patients (primary prophylaxis [PP]: 98 ; secondary prophylaxis [SP]: 20). Cohort 2: 86 patients (PP: 48 ; SP: 38). Grade ≥3 CIM incidence: Cohort 1 vs. Cohort 2: 4.46% vs. 2.96%; grade ≥3 neutropenia: 3.24% vs. 1.73%; thrombocytopenia: 1.54% vs. 0.74%; anemia: 0.77% vs. 1.97%. Prophylaxis-stratified analysis showed superior myeloprotection with PP: overall grade ≥3 CIM (PP:3.35% vs. SP: 4.56%), neutropenia (PP: 2.75% vs. SP:1.83%), thrombocytopenia (PP: 0.6% vs. SP: 2.29%), and anemia (PP: 1.32% vs. SP: 0.91%). Furthermore, the collection and detection of immune cells from 97 patients before and after treatment revealed that: the total number of T cells in patients showed an increasing trend after prophylactic medication. The number of CD4+ T cells showed an increasing trend; the number of CD8+ T cells began to decline after more than 3 cycles of chemotherapy; the number of Treg T cells increased and returned to the pre-chemotherapy level after more than 4 cycles. **Conclusions:** Trilaciclib demonstrated effective myeloprotection and immunoregulation in GA/GEJA, with PP showing a favorable trend. Grade ≥3 CIM rates were ≤5.88% (adjuvant) and ≤3.49% (metastatic), with no new safety signals. The studies will continue to analyze the correlation between immune-related indicators and anti-tumor efficacy. Clinical trial information: ChiCTR2500097520. Research Sponsor: None.

12153 **Poster Session**

Machine learning approach for prediction of immune-related pneumonitis. First Author: Barliz Waissengrin, Medicine, Cedars Sinai Cancer Center, Los Angeles, CA

Background: Immune-related adverse events (irAE) associated with immune checkpoint inhibitors (ICI) substantially contribute to treatment-related morbidity, yet reliable pretreatment predictors remain unavailable. Immune-related pneumonitis (irP) is among the most serious irAE and is associated with a significant risk for mortality. Machine learning (ML) offers an opportunity to analyze complex clinical data to improve risk stratification. We aimed to develop a personalized ML-based model to identify and predict irP from electronic health records (EHR) using patient characteristics prior to ICI initiation. **Methods:** We extracted data from the EHR of patients with solid malignancies, in various disease stages, who were treated with ICI at Cedars-Sinai Medical Center between 2015 and 2024. For each patient, we collected comprehensive treatment data, including demographics and clinical variables from structured fields and clinical notes. Variables not reliably captured in structured fields, such as smoking or family history, were extracted using our pipeline. Using a large language model (LLM)-based pipeline, we identified irAE cases, enabling precise extraction and classification of irAE subtypes, and validated results against physician annotations for irP (excluding pneumonitis due to other causes). Chi-square analyses assessed associations between features and irAE. We used TPOT, an automated machine learning tool, to develop predictive models and explore sampling strategies for class imbalance. The model was trained on a balanced dataset, evaluated on an unbalanced test set (80/20 split), and hyperparameter-optimized using five-fold cross-validation. **Results:** Our study included 4,302 cancer patients treated with ICI, of whom 910 were identified by our pipeline as having an irAE and 276 cases of irP. The model achieved a sensitivity of 0.964 on a physician-annotated irP dataset. The best-performing predictive model was a tree-based classifier with an AUC of 0.68. Chi-square analysis identified significant associations ($p < 0.05$) between irP and multiple clinical features, including prior lung disease, radiotherapy, age at immunotherapy, comorbidity burden, and inflammatory markers. Odds ratio analysis based on model-derived risk score quartiles, showing that patients in the highest-risk quartile exhibited an average 10.3-fold increase in the odds of developing pneumonitis compared to those in the lowest-risk quartile. **Conclusions:** This study establishes a strong baseline for ML algorithms to identify and predict irP specifically in patients treated with ICI, using EHR-derived data. Our results demonstrate that pre-treatment clinical and laboratory variables can be effectively used to stratify irP risk. Future research should aim to refine these predictive models and incorporate a broader range of EHR-based features to further improve predictive performance and clinical applicability. Research Sponsor: None.

12154 **Poster Session**

Efficacy and safety of a temperature-controlled oral cryotherapy device in preventing oral mucositis among patients receiving high-risk anticancer regimens. First Author: Xiaojia Wang, Department of Breast Oncology, Zhejiang Cancer Hospital, Hangzhou, China

Background: Oral mucositis (OM) is a severe dose-limiting toxicity in cancer patients receiving intensive chemotherapy or novel antibody-drug conjugates (ADCs). Recent clinical data indicate that the incidence of OM with Sacituzumab Tirumotecan (sac-TMT) is as high as 54.1%, with approximately 11.1% of patients experiencing severe (Grade≥3) events. For Liposomal Doxorubicin, reported OM incidence is approximately 22%. Established therapies such as Docetaxel, Paclitaxel plus Carboplatin, and Sacituzumab Govitecan exhibit OM rates ranging from 10% to 30%. Severe OM frequently leads to excruciating pain, nutritional compromise, and treatment delays. This study evaluated the efficacy of a specialized oral cryotherapy (OC) device in preventing treatment-induced OM across these high-risk regimens. **Methods:** In this prospective trial, patients scheduled for high-risk regimens including Sacituzumab Tirumotecan, Sacituzumab Govitecan, Liposomal Doxorubicin, Docetaxel, or Taxane plus Carboplatin were enrolled. The intervention group received continuous OC using 8°C purified water, delivered via safe, non-toxic intraoral molds regulated by a temperature-controlled device. The protocol was administered 15 minutes prior to, throughout, and 30 minutes post-infusion. Primary endpoints included time to first OM onset, OM incidence, and WHO severity grading. **Results:** From September, 2025 to January, 2026, 116 patients were enrolled, with the most frequent user completing 13 OC sessions. The overall incidence of OM was only 6.9% (8/116), and all cases were Grade 1, with no interference with oral intake. In the Sacituzumab Tirumotecan (sac-TMT) subgroup (n = 26), the OM incidence was 11.5% (3/26)occurring at C2D1 (n = 2) and C4D8 (n = 1). Other subgroup incidences were as follows: Sacituzumab Govitecan, 50.0% (1/2) occurring at C2D1; Liposomal Doxorubicin, 4.2% (1/24) occurring at C2D1; Taxanes, 7.1% (2/28) both occurring at C2D8; and Epirubicin, 5.6% (1/18) occurring in C3D1. Notably, zero Grade ≥ 2 OM events were observed across all cohorts. No serious adverse events related to the temperature-controlled device were reported, and patient compliance with the OC protocol was high. **Conclusions:** Regulated oral cryotherapy using a temperature-controlled device and intraoral molds is a simple, cost-effective, and well-tolerated intervention that significantly reduces the incidence and severity of treatment-induced oral mucositis. Particularly for patients receiving high-risk ADCs such as Sacituzumab Tirumotecan, this standardized OC protocol should be considered a standard prophylactic measure to improve clinical outcomes and treatment adherence. Research Sponsor: None.

12155 **Poster Session**

Cardiovascular toxicity across epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in *EGFR*-mutated non–small cell lung cancer: A population-based retrospective cohort study. First Author: Yun-Gyoo Lee, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the therapeutic backbone for *EGFR*-mutated non-small cell lung cancer (NSCLC) and often requiring prolonged exposure. Adverse cardiovascular events limit a long-term treatment and remain a major concern for cancer survivors. Osimertinib, the 3rd generation EGFR TKI, was associated with cardiac dysfunction. Although Osimertinib is a preferred first-line option, many countries still use first- or second-generation EGFR TKIs upfront; therefore, robust studies are needed to define cardiotoxicity across these earlier-generation EGFR TKIs. **Methods:** In this retrospective cohort study using a nationwide Health Insurance Claim Database in Korea, patients newly diagnosed with NSCLC between 2010 and 2023 were identified. Patients were classified into three groups: first-generation (1G) EGFR TKIs (gefitinib or erlotinib), second-generation (2G) TKIs (afatinib or dacomitinib), and third-generation (3G) TKI sequence (initial first- or second-generation TKI followed by a switched to osimertinib). The incidence of cardiovascular disease (CVD) during treatment period was compared between groups. CVD included ischemic heart disease, heart failure, atrial tachyarrhythmias, and stroke. For patients with pre-existing CVD, only new-onset CVD were counted as events. Follow-up was completed December 31, 2024. **Results:** Among the 51,218 patients (58,317 [51%] female; mean [SD] age, 65.5 [10.8] years), 36,335 (70.9%), 8173 (16.0%), 6710 (13.1%) were treated with 1G, 2G and 3G EGFR TKI respectively. Among all patients, 16.7% were receiving medication for diabetes, 52.7% for hypertension, and 19.8% for dyslipidemia. Before lung cancer diagnosis, 1.1% had coronary artery disease and 2.7% had heart failure. In patients treated with 1G EGFR TKIs, the cumulative incidence of CVD at 1, 2, 3, and 5 years was 4.8%, 8.1%, 11.2%, and 16.2%, respectively. In those treated with 2G EGFR TKIs, the corresponding cumulative incidence was 4.2%, 7.0%, 9.4%, and 12.3%. In the group of 3G TKI sequence, the cumulative incidence of CVD at 1, 2, 3, and 5 years was 2.9%, 6.1%, 8.9%, and 14.8%, respectively. There was no statistically significant long-term difference in CVD incidence between the 1G TKI and the 3G TKI group (p = .245). **Conclusions:** The long-term risk of CVD associated with sustained treatment with 1G EGFR TKIs appears comparable to the risk observed among patients who started with 1G or 2G and switched to 3G EGFR TKI sequence. As long-term survivors with EGFR mutant NSCLC increases in number, ongoing surveillance for cardiotoxicity and proactive risk mitigation are essential. Research Sponsor: None.

12156 **Poster Session**

Oncologic outcomes following biologic therapy for immune-related cutaneous adverse events. First Author: Tara Maier, Stony Brook University, Stony Brook, NY

Background: Biologic agents are increasingly used to treat immune-related cutaneous adverse events (ircAEs). However, limited data exist regarding immune checkpoint inhibitor (ICI) rechallenge and ICI efficacy following biologic therapy for ircAE management. **Methods:** We conducted a retrospective cohort study of patients enrolled under U01AR077511-01 (PIs Leung, Kern, Lacouture) treated with ICIs who developed dermatologist-confirmed grade ≥2 ircAEs. Demographics, ircAE treatments, and dermatologic and oncologic outcomes were collected via chart review and compared using t-tests and chi-square tests. **Results:** We identified 159 patients who developed grade ≥2 ircAEs, including 80 treated with biologic agents. Mean age was 66.8 years; 40% were female, 79% White, and 78% had stage IV disease. The most common tumor types were kidney (20%), lung (16%), and melanoma (12%). Common ICI regimens included ICI monotherapy (46%), ICI–ICI combination (21%), and ICI+chemotherapy (19%). Pruritus (23%), maculopapular rash (21%), and eczema (19%) were the most common ircAEs. Most patients received topical steroids (88%), while systemic steroids were used sparsely (13%). Biologics were used in ~50% of patients; the most common agents were dupilumab (43%), omalizumab (33%), and ustekinumab (11%). Median biologic duration was 16 weeks, with 25% receiving therapy for >40 weeks. ICI rechallenge occurred in 60% of biologic-treated versus 67% of non-biologic patients (p=0.35). Rechallenge rates were 67% vs 65% for grade 2 (p=0.85) and 44% vs 74% for grade 3 ircAEs (p=0.05) (biologic vs non-biologic, respectively). Antitumor outcomes were similar between biologics and non-biologic groups: 31% vs 28% achieved partial/complete response, 43% had stable disease, and 26% vs 29% had progressive disease, respectively. **Conclusions:** In this oncodermatology-managed cohort, ircAEs were primarily treated with topical corticosteroids and targeted biologics, with infrequent systemic steroid use. Biologic therapy enabled ICI rechallenge in most patients, and oncologic outcomes were comparable to those not receiving biologics. Overall, these findings support biologics as a steroid-sparing option for moderate-to-severe ircAEs that may allow continued immunotherapy without apparent loss of antitumor efficacy, warranting prospective validation. Research Sponsor: None.

Clinical characteristics.

Variable	Overall n=159	No Biologics n=79	Biologics n=80
Age at ICI (mean)	66.8	64.3	69.4
Tumor Types Kidney/Lung/Melanoma (%)	20/16/12	22/17/9	18/15/15
Line of treatment 1L/2L/2+L (%)	52/25/23	49/27/24	54/24/22
ircAEs: Pruritus/MPR/Eczema/Others (%)	23/21/19/37	22/33/17/28	25/9/21/45
ircAE Grade 2/Grade 3 (%)	74/26	76/24	71/29
Dupilumab/Omalizumab/Ustekinumab/Others (%)	33/33/11/23	N/A	33/33/11/23
Systemic Steroids - Yes (%)	13	8	18
ICI Rechallenge - Yes (%)	64	67	60
Response CR-PR/SD/PD (%)	30/43/27	31/43/26	28/43/29

12157 **Poster Session**

Major adverse cardiovascular events among prostate cancer patients in the VA, stratified by HIV status and androgen deprivation therapy. First Author: Debanjan Pain, Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite the rapidly increasing trend in incidence of prostate cancer among persons with HIV (PWH), comprehensive data outlining outcomes and treatment toxicities of prostate cancer in this population remain sparse. Notably, both HIV infection and prostate cancer treatment independently increase the risk of cardiovascular disease. We sought to quantify the risk of major cardiovascular adverse events (MACE) among a large Veterans Affairs (VA) cohort of PWH and people without HIV (PWoH). **Methods:** We used patient data from the VA Corporate Data Warehouse and the VA Central Cancer Registry, including demographics, laboratory data, medications administered in inpatient/outpatient pharmacies, International Classification of Diseases 9th Edition and 10th edition diagnoses and procedure codes. Patients were included if they had diagnosis of prostate adenocarcinoma between 1/1/2008 and 12/31/2020. Patients were excluded if they had a diagnosis with any prior invasive cancer on or prior to prostate cancer diagnosis, diagnosis with prostate cancer prior to HIV positive diagnosis, or MACE within 6 months prior to prostate cancer diagnosis. MACE was defined as having a diagnosis code of myocardial infarction, stroke, or arrhythmia, within five years of start of treatment approach for prostate cancer (defined as androgen deprivation therapy (ADT) or active surveillance). We conducted a time-to-event analysis using the Cox proportional hazards model to examine the time to first occurrence of MACE, accounting for censoring and varying follow-up times. **Results:** A total of 87,144 prostate cancer patients were included (654 PWH and 86,490 PWoH). About 37.5% of PWH were $<$ 60-years-old at time of prostate cancer diagnosis (compared with 19.6% of PWoH). Among 62,259 patients with low-risk or intermediate-risk localized prostate cancer, the risk of MACE was 24% greater among PWH compared with PWoH (HR 1.24, 95% CI 1.02-1.51, p = 0.03) after controlling for age, race, and cardiovascular risk factors at time of cancer diagnosis. Among PWH with prostate cancer, receiving ADT was associated with a 3.5 fold increased risk of developing MACE vs. those not receiving ADT (HR 3.51, 95% CI 2.25-5.49, p $<$ 0.01). Among PWoH with prostate cancer, receiving ADT had a 2.7-fold increased risk of developing MACE vs. those not receiving ADT (HR 2.72, 95% CI 2.61-2.84). **Conclusions:** Both HIV infection and ADT increase the risk of MACE among prostate cancer patients. Future studies are warranted to explore the mechanistic links between HIV infection, ADT, and cardiovascular health. Research Sponsor: None.

12158 **Poster Session**

Identification of nutritional risk in chimeric antigen receptor T-cell (CAR-T) therapy: Protein-energy malnutrition and its impact on patient outcomes. First Author: Anu Priyamvadha Ramakrishnan, Nassau Health Care Corporation, East Meadow, NY

Background: Protein-energy malnutrition (PEM), an imbalance between protein and energy intake and the body's requirements, is highly prevalent in cancer, affecting 20–70% of patients, with an overall prevalence of approximately 41%. PEM and cachexia impair therapeutic efficacy, increase treatment-related toxicities, and worsen survival outcomes. Although CAR T-cell therapy has revolutionized oncology, its associated complications—such as cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) further affects nutritional status, creating a complex bidirectional relationship between PEM and CAR-T complications. This study utilizes the National Inpatient Sample (NIS) to assess nutritional status in CAR T-cell therapy recipients and potential impact on outcomes and treatment-related complications. **Methods:** A retrospective cohort study was conducted using the 2021–2023 National Inpatient Sample (NIS) database. Adult patients (aged ≥18 years) who were hospitalized and received CAR-T therapy were identified using ICD-10 codes and stratified according to the presence of PEM. The primary outcome was the inpatient mortality rate, while secondary outcomes included length of hospital stay, total hospital charges, incidence of CRS, ICANS, and other medical complications. **Results:** Among 10,690 hospitalized adult CAR-T recipients, 2,190 (20%) had PEM. In-hospital mortality in this group was 190 (9%). The PEM cohort was predominantly male (79%) and White (74%), with a mean age of 61.5 years. Compared to patients without PEM, those with PEM experienced higher in-hospital mortality (8% vs 1.2%; OR 7.2; P $<$ 0.001), longer hospital stays (LHS) (24 vs 15 days; Coefficient 9.2; P $<$ 0.001), and higher costs ($1,428,895 vs $1,106,642; Coefficient 322,253; P $<$ 0.001) and more CAR-T-related complications, including CRS (44% vs 39%; OR 1.3; P $<$ 0.05), ICANS (12% vs 7%; OR 1.7; P $<$ 0.05), sepsis (OR 3.13; P $<$ 0.001), stroke (OR 4; P $<$ 0.001), and cardiovascular events (OR 1.6; P $<$ 0.001). **Conclusions:** This analysis identifies PEM as a significant predictor of mortality, prolonged hospitalization, higher costs and increased complications among CAR-T recipients. This highlights baseline nutritional status as a critical outcome determinant. This emphasizes the need for pre-treatment nutritional screening and early, targeted interventions to break the vicious cycle of malnutrition, improve treatment tolerance, reduce adverse events, and optimize outcomes. Further studies should evaluate tailored nutritional strategies and supportive care to enhance CAR-T safety and efficacy. Research Sponsor: None.

12160 **Poster Session**

Impact of corticosteroid exposure on long-term immune checkpoint inhibitor responses in solid tumors. First Author: Theresa Medina, University of Colorado, Aurora, CO

Background: Multiple analyses offer conflicting evidence regarding the implications of immune related adverse events (irAE) on survival of patients with solid tumors treated with immune checkpoint inhibitor(s) (ICIs). Furthermore, the treatments used to manage irAEs also have an unclear impact on progression free survival (PFS) and overall survival (OS) on patients with solid tumors treated with ICIs. We present the PFS, OS and tumor specific survival (TSS) for pts with metastatic solid tumors treated with ICIs at an academic cancer center. **Methods:** 848 pts with metastatic solid tumors diagnosed between 2014 through January 2026 were identified via retrospective chart review. PFS was defined as the time from starting ICIs to progression or death, OS was defined as the time from starting ICIs to death and TSS was defined as the time from starting ICIs to death from malignancy (when available). The corticosteroid (CS) exposure was defined as low if prednisone (or equivalent) $<$ 1mg/kg/day and/or length of exposure $<$ / = 21 days. The CS exposure was defined as high if prednisone (or equivalent) was $>$ / = 1mg/kg/day and/or length of exposure $>$ / = 22 days. The CS exposure was defined as very high if prednisone (or equivalent) $>$ 20mg/day and length of exposure was $>$ 42 days. Steroid sparing agents were considered low impact if given once and within 14 days of starting CS. Steroid sparing agents were considered high impact if given more than once. Steroid sparing agents were considered very high impact if given more than once and/or given after 14 days of starting CS. Acute irAE was defined if symptom and immunosuppression resolved within 42 days. Chronic irAE was defined if symptom and/or immunosuppression continued beyond 42 days. The effects of CS, steroid sparing agent exposure on PFS, OS, TSS were evaluated using multivariable Cox proportional hazards models. The effect of acute irAE versus chronic irAE on PFS, OS, TSS were evaluated using multivariable Cox proportional hazards models. **Results:** 64.8% of patients experienced an irAE and 44.7% of patients developed G3-4 irAE requiring corticosteroids +/- steroid sparing agent. The low impact corticosteroid exposure did not affect PFS, OS or tumor specific survival. The very high impact CS exposure was associated with decrease in PFS (p = 0.02) but not with OS or TSS (p = 0.3). The high impact steroid sparing agent was associated with decrease in PFS (not significant) but the very high impact steroid sparing agent was associated with decrease in PFS. The chronic irAE was associated with slight improvement in PFS (not significant). **Conclusions:** The presence of an irAE was not significantly associated with PFS, OS or tumor specific survival treated with ICIs. There was a negative impact on the length of corticosteroid exposure and steroid sparing agents on PFS, TSS. The delay or interruption in treatment due to irAE did not affect survival. Research Sponsor: None.

TPS12161 **Poster Session**

Supporting treatment resilience with optimized nutrition and guided exercise (STRONGER) in head and neck cancer patients undergoing chemoradiation. First Author: Anton Jose Agana, University of Nevada, Reno School of Medicine, Reno, NV

Background: Patients with head and neck cancer (HNC) undergoing concurrent chemoradiation (chemoRT) frequently experience debilitating toxicities, including mucositis, dysphagia, fatigue, and anorexia. These treatment-related effects are associated with weight loss, sarcopenia, and functional decline, which may adversely impact treatment adherence and quality of life. Although patients commonly seek lifestyle-based supportive interventions, evidence-based, structured multimodal programs integrated during active chemoradiation remain limited. The STRONGER pilot study was designed to evaluate the feasibility and acceptability of an integrated nutrition, guided exercise, and wellness education intervention aimed at supporting treatment resilience and characterizing functional and body composition changes in this population. **Methods:** STRONGER is a single-arm pilot study enrolling up to 30 adult patients with biopsy-confirmed squamous cell carcinoma of the head and neck undergoing definitive or adjuvant chemoRT at Renown Health and the William N. Pennington Institute for Cancer. Eligible participants have an ECOG performance status of 0 to 2 and are able to participate in light-to-moderate physical activity. Patients with severe malnutrition, defined by Global Leadership Initiative on Malnutrition criteria and greater than 90% caloric intake via enteral feeding, or with comorbidities precluding safe exercise participation, are excluded. The 20-week multimodal intervention begins at pre-treatment baseline and continues through three months post-chemoRT, incorporating individualized nutrition counseling with calorie and protein targets informed by indirect calorimetry, twice-weekly virtual home-based resistance and mobility training with prescribed daily walking goals, and structured wellness programming, including facilitated group sessions focused on stress and fatigue management and a speech-language pathology education series. The primary objective is to assess feasibility and acceptability, defined by prespecified thresholds for recruitment, retention, and intervention adherence, as well as participant-reported acceptability measured using Likert-scaled surveys. Secondary exploratory outcomes include measures of body composition, physical function, and patient-reported quality of life and symptom burden assessed using validated instruments. Descriptive statistics and exploratory paired analyses will be used to characterize within-participant changes over time. Enrollment is ongoing. As of January 24, 2026, 2 of 30 planned participants have been enrolled. Clinical trial information: NCT07160296. Research Sponsor: Renown Health Foundation.

TPS12162 **Poster Session**

Hetrombopag in patients with chemotherapy-induced thrombocytopenia: A global phase 3, randomized, double-blind study. First Author: Jodi Victoria Mones, Department of Medicine, Hematology Service, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Chemotherapy-induced thrombocytopenia (CIT) is a common complication of cancer therapy, frequently resulting in chemotherapy modifications including dose reduction, delay, or discontinuation. Thrombopoietin receptor agonists (TPO-RAs) represent a therapeutic approach aimed at stimulating platelet production. Given there are limited society-sanctioned therapies, contemporary management converges on platelet transfusions which are limited in global supply or parenteral TPO-RAs which are inconvenient. Hetrombopag is an oral TPO-RA that supports platelet counts and facilitates chemotherapy delivery, as evidenced by a prior positive randomized, controlled study conducted in China (ASH 2025; NCT05864014). This global phase 3 study is designed to evaluate the efficacy and safety of hetrombopag in patients with CIT (NCT07286032). **Methods:** This study comprises two sequential parts: an open-label, single-arm, pharmacokinetic (PK) lead-in part (A) and a randomized, double-blind, placebo-controlled part (B). In Part A, approximately 8-12 non-Asian patients with CIT are planned to be enrolled to receive oral hetrombopag (15.0 mg once daily, fasted) to evaluate the PK profile. Part B will enroll approximately 138 patients with solid tumors who have experienced a $\geq$ 7-day chemotherapy delay due to CIT during platinum- and/or gemcitabine-based therapy at schedule of 21-day cycles. Eligible patients will be randomized in 2:1 to hetrombopag or placebo, stratified by baseline platelet count (PC; $\geq 50 \times 10^9$/L vs. $< 50 \times 10^9$/L) and enrollment region (Asia vs. rest of world). Hetrombopag will be initiated at 7.5-or 15 mg (dose will be finalized after considering results from Part A) once daily, with dose adjustments based on platelet counts. All enrolled patients are expected, per investigator assessment, to be eligible to complete two consecutive cycles of on-study chemotherapy (C1 and C2) of the same regimen administered prior to enrollment. Initiation of each chemotherapy cycle requires a PC $\geq 100 \times 10^9$/L; if the PC remains $< 100 \times 10^9$/L on day 14 after hetrombopag initiation (for C1) or at the C1D21 visit (for C2), the investigator may exercise discretion to proceed with the respective chemotherapy cycle and/or implement rescue therapy (platelet transfusions and/or approved TPO-RAs). The primary endpoint of Part A is the PK profile of hetrombopag in non-Asian patients with CIT; the primary endpoint of Part B is the proportion of treatment responders, defined as patients who achieve a PC $\geq 100 \times 10^9$/L within 14 days of hetrombopag initiation and who complete two consecutive chemotherapy cycles without either thrombocytopenia-related modifications, or thrombocytopenia rescue therapy through C2D21. Clinical trial information: NCT07286032. Research Sponsor: Jiangsu Hengrui Pharmaceuticals.

TPS12163 **Poster Session**

A randomized, double-blind, placebo-controlled trial of antiviral prophylaxis and oral *Herpesviridae* dynamics during radiotherapy for head and neck cancer. First Author: Renata Ferrari, Hospital Sirio Libanes, Sao Paulo, Brazil

Background: Oral mucositis (OM) is a frequent and debilitating toxicity of radiotherapy (RT) for head and neck cancer (HNC), often leading to pain, nutritional compromise, and treatment interruptions. Reactivation of viruses from the *Herpesviridae* family has been proposed as a potential contributor to the pathogenesis and severity of OM, but prospective, controlled data remain limited. Antiviral prophylaxis is not standard of care in this setting, and its role in preventing viral reactivation and modulating OM severity during RT has not been systematically evaluated. This randomized trial investigates the association between oral *Herpesviridae* detection, antiviral prophylaxis, and OM development in patients undergoing RT for HNC. **Methods:** This is a prospective, randomized, double-blind, placebo-controlled phase II trial conducted across four oncology centers in Brazil. Adult patients ($\geq$18 years) with HNC undergoing intensity-modulated radiotherapy (IMRT), with or without concurrent systemic therapy, are randomized 1:1 to receive antiviral prophylaxis or placebo. Randomization is stratified by age ($<$ 60 vs $\geq$60 years) and anatomic tumor site (oral cavity/salivary glands; oropharynx/pharynx; nasopharynx/paranasal sinuses). The investigational intervention consists of oral antiviral prophylaxis administered once weekly throughout the course of RT; the control arm receives a matching placebo. Comprehensive dental evaluation and oral care optimization are performed prior to RT initiation in all patients. Serial oral mucosal and saliva samples are collected weekly during RT and after treatment completion. Quantitative real-time PCR is used to detect and quantify viruses from the *Herpesviridae* family, including HSV-1, HSV-2, VZV, EBV, CMV, HHV-6A/B, HHV-7, and HHV-8. Clinical assessments include OM incidence, severity graded by CTCAE criteria, pain intensity, and timing of OM onset and resolution. Correlative analyses will explore temporal associations between viral detection, viral load, antiviral prophylaxis, and OM outcomes. The planned sample size is 84 patients (42 per arm), providing adequate power to detect differences in viral manifestation and OM-related outcomes. Clinical trial information: NCT07363031. Research Sponsor: None.

TPS12164 **Poster Session**

Symptom monitoring program linked to electronic referrals (SyMPLER): A single-arm pilot feasibility study of remote symptom monitoring with palliative care self-referral. First Author: Julia L. Agne, The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH

Background: Symptoms often fluctuate during an individual's cancer trajectory, and this can impact patients' health-related quality of life (HRQOL). Two evidence-based approaches—symptom monitoring programs (SMPs) and specialty palliative care (PC)—have independently been shown to improve HRQOL through identification and treatment of cancer-related symptoms, especially among patients with thoracic cancers (i.e. lung cancer). However, PC remains underutilized when patients report uncontrolled symptoms via SMPs. Therefore, we developed SyMPLER, a digital SMP with an integrated option for PC self-referral. The primary aim of this phase 1 clinical trial is to determine the feasibility of SyMPLER among patients newly diagnosed with a thoracic cancer. If feasible for remote symptom reporting, SyMPLER may overcome logistical and attitudinal barriers towards provider-driven PC referral processes for cancer symptom management. **Methods:** SyMPLER is a prospective single-arm feasibility study of a novel digital health intervention for remote symptom reporting with an optional PC self-referral for cancer symptom management (NCT06396598). SyMPLER includes 5 main components: (1) a brief education about PC, (2) weekly text reminders to encourage symptom logging, (3) on-demand symptom reporting using the Edmonton Symptom Assessment System on a mobile health application interface, (4) an active choice option for PC self-referral, and (5) the ability to request a callback from oncology clinicians to discuss symptom concerns. Per the IRB-approved protocol, adults ($>$ 18 years) with any stage thoracic malignancy, without a prior PC referral, are consented within the first 12 weeks of outpatient oncology care. The primary outcome is frequency of symptom reporting with a feasibility benchmark set at 50% of participants logging symptoms at least monthly over a 6-month intervention period. PC referrals (secondary outcome) and exploratory outcomes, including telephone encounters with the oncology team, HRQOL (Function Assessment of Cancer Therapy – Lung; FACT-L), and patient satisfaction with medical care (FAMCARE-P13) are measured every 3 months for up to 12 months post-enrollment. Study enrollment commenced in February 2024. The target enrollment of 94 evaluable participants was achieved in August 2025. Data collection is ongoing for 23 patients still active on study. Clinical trial information: NCT06396598. Research Sponsor: None.

TPS12165 **Poster Session**

Structured interventional strategies to prevent and reduce burnout in medical oncologists: The Resilience–Spanish Society of Medical Oncology (SEOM) multicenter project. First Author: Yago Garitaonaindia, National Center for Cancer Immune Therapy, Department of Oncology, Copenhagen University Hospital, Herlev, Denmark

Background: Burnout is highly prevalent among young medical oncologists, with an estimated incidence exceeding 70% in Europe, and poses a growing threat to physician well-being and quality of care. Early-career oncologists are particularly vulnerable due to high clinical workload, emotional burden, and limited access to structured psychological support. Evidence-based interventions integrated into routine professional activity remain scarce. The Spanish Resilience-SEOM project previously demonstrated that communication skills workshops improved personal achievement and group psychotherapy was feasible to address emotional distress. Building on these findings, this study evaluates a structured, hospital-based structured intervention combining communication skills training and psychotherapy to prevent and mitigate burnout in early-career medical oncologists. **Methods:** This is a prospective, post-authorization, multicenter cohort study including residents and medical oncologists across 7 hospitals in Spain, with a planned follow-up of 6 months. Baseline assessments include demographic data, the Maslach Burnout Inventory (MBI), and the Clance Impostor Phenomenon Scale (CIPS). The intervention consists of eight modules: 1) individual interviews, 2) biopsychosocial model workshop, 3) coregulation workshop, 4) communication skills workshop, 5) individual sessions, 6) vulnerability workshop, and 7–8) emotional regulation workshops. The program combines individualized sessions to activate personal coping resources with six progressive group workshops addressing systemic contributors to burnout, holistic patient perception, professional vulnerability, and practical emotional regulation strategies. Follow-up MBI and CIPS assessments are conducted at program completion and at 6- and 12-month intervals. Current enrollment includes 62 participants across 7 hospitals. Research Sponsor: Fundación SEOM.

TPS12166 **Poster Session**

Enhancing communication about cancer management and cancer care delivery for older adults with dementia and their care partners. First Author: Molly Wilgucki, Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY

Background: Dementia affects 7–10% of older adults with cancer and is associated with worse cancer outcomes. Many patients (pts) have reduced decisional capacity, leading care partners (CPs) to play a major role in cancer management decision-making, which can increase CP burden and negatively affect their well-being. Cancer communication in this population is complex, requiring clinicians to balance pt preferences, CP input, and dementia-related considerations. Despite this, no standard approach exists to support triadic communication in this setting. COACH-Cog is a triadic communication intervention that promotes shared decision-making by integrating CP involvement while centering pt values in cancer care. **Methods:** *Eligibility:* Pts are age ≥65 with a diagnosis of dementia and cancer (any type or stage), have an identified CP, and receive oncology care from a participating clinician. CPs are age ≥18 and identified by the pt. Oncology clinicians (physicians or advanced practice providers) must practice at the Wilmot Cancer Institute. *Study Design:* This is a pilot cluster-randomized trial (clinician-level randomization). The COACH-Cog intervention includes: 1) a brief clinician training video on dementia and its relevance to cancer care; 2) distribution of pt geriatric assessment results with care recommendations to clinicians, pts, and CPs; and (3) CP communication coaching to elicit dementia-related concerns and develop questions for the next oncology visit. Baseline measures include pt geriatric assessment and dementia severity, CP well-being (burden, quality of life, depression, anxiety), and pt/CP communication and decision-making preferences. Pts and CPs receive either COACH-Cog or usual care based on clinician randomization. The subsequent clinical encounter is audio-recorded. *Outcome Measures:* The primary outcome is CP autonomy support, which evaluates how supported CPs feel in the decision-making process. Secondary outcomes include healthcare communication and CP well-being. Tertiary outcomes assess goal-concordant care and decisional regret. Exploratory outcomes evaluate communication impact by integrating qualitative clinical encounter data with quantitative measures. Current enrollment includes 36 clinicians and 36 pt/CP dyads (target 40 clinicians, 130 dyads). Accrual initiated April 2025. Data collection will conclude May 2027 (NCT06313853; NIA R01 AG077053). *Novel/Innovative aspects:* (1) This is the first study to prospectively enroll patients with dementia in an oncology intervention trial; (2) We are evaluation of a novel triadic communication intervention targeting clinicians, pts, and CPs; and (3) We have incorporated standard procedures for assessing consent capacity and engaging Legally Authorized Representatives for pts lacking capacity given enrollment of pts with dementia. Clinical trial information: NCT06313853. Research Sponsor: National Institute of Health/National Institute on Aging; R01 AG077053.

TPS12167 **Poster Session**

RISE trial: A novel virtually delivered supervised exercise intervention targeting cognitive impairment and gut microbiome in adolescent and young adult (AYA) brain tumor survivors. First Author: Elizabeth Pan, Duke University, School of Medicine, Durham, NC

Background: Up to 45% of AYA brain tumor survivors experience cancer-related cognitive impairment (CRCI) affecting processing speed, attention, working memory, and executive function—domains critically impacting quality of life (QOL). Moderate-intensity exercise can improve cognitive function by enhancing gut microbiome composition and function. However, only 50% of AYA cancer survivors receive any exercise information from medical providers, with 42% actually meeting physical activity recommendations. Considering developmental milestones and the unique needs of AYA brain tumor survivors, tailoring virtually delivered exercise interventions paired with behavioral coaching and supportive care navigation to promote the adoption of a physically active lifestyle may be a promising approach to reducing CRCI through modulation of gut microbiome health. Few randomized controlled trials (RCTs) have examined this type of exercise intervention for AYA brain tumor survivors. Additionally, the influence of the gut microbiome on the relationship between exercise and cognitive function in AYA brain tumor survivors has not yet been studied. To address these gaps, we developed the Remote Implementation of Supervised Exercise (RISE) intervention, a 12-week personalized aerobic and strength training exercise intervention with behavior coaching and supportive care navigation. The RISE trial aims to evaluate feasibility (primary), cognitive and physical activity (secondary), and gut microbial composition changes (exploratory). **Methods:** RISE is a two-arm 1:1 pilot RCT (NCT06799481) of 40 AYA brain tumor survivors (aged 18-39) with CRCI enrolled at Emory University and MD Anderson Cancer Center. Controls receive an activity tracker and 18 wellness calls from a trainer inquiring about adverse events and survivorship topics. Intervention participants participate in 18 virtual exercise sessions with an exercise coach, consisting of progressive aerobic and strength training exercises with active lifestyle behavior coaching. Intervention participants also receive an activity tracker and participate in self-led exercise sessions via the Physitrack telehealth app for 12 weeks. Assessments at baseline, 6, 12, and 18 weeks measure cognitive function, physical activity levels, gut microbiome, physical function, diet, and QOL. Descriptive analysis will be used to assess feasibility, defined as enrollment of 50% eligible AYAs, 75% adherence to intervention, and 80% retention at the end of the 12-week intervention. As of January 2026, 17 of 40 patients have been enrolled, and accrual is expected to be complete within 1 year. Clinical trial information: NCT06799481. Research Sponsor: NRG Oncology Foundation.

TPS12168 **Poster Session**

Targeting cellular senescence to enhance skeletal muscle recovery in survivors of breast cancer: An ancillary study of the phase II randomized PROFFi clinical trial. First Author: Jingran Ji, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Postmenopausal survivors of breast cancer frequently experience persistent physical function decline after chemotherapy. A key contributor is skeletal muscle dysfunction, leading to weakness, fatigue, and reduced physical activity. One potentially targetable mechanism of chemotherapy-induced skeletal muscle dysfunction is cellular senescence. Senescence is a state of terminal growth arrest that leads to a senescence-associated secretory phenotype marked by the secretion of pro-inflammatory cytokines. These cytokines worsen muscle dysfunction by impairing calcium handling and muscle fiber contractility. Emerging evidence suggests senolytics and exercise may reduce senescent cell (SnC) burden. Senolytics are agents that selectively eliminate Sncs and can improve physical function in non-cancer populations. Exercise not only enhances physical function but also reduces blood markers of senescence. Preclinical studies demonstrate a synergistic effect of senolytics and exercise on SnC reduction. However, no human studies have examined the independent or combined effects of senolytics and exercise on skeletal muscle function and senescence in cancer survivors. We hypothesize that fisetin plus exercise will produce independent and synergistic effects that enhance skeletal muscle recovery in survivors of breast cancer. **Methods:** This site-specific ancillary mechanistic study at UCLA is embedded within PROFFi (Prevention of Frailty with Fisetin), an ongoing phase II multicenter, randomized, placebo-controlled clinical trial evaluating fisetin and exercise in postmenopausal survivors of breast cancer. Eligible participants are within 12 months of completing neo/adjuvant chemotherapy and have reduced physical function as measured by a 6-minute walk distance of 400-480 meters. PROFFi uses a 2x2 factorial design, randomizing 200 participants 1:1:1:1 to exercise plus fisetin, exercise alone, fisetin alone, or placebo for 16 weeks. Fisetin is administered orally at 20mg/kg/day on days 1-3 every 14 days. Exercise is individually tailored and remotely supervised by an exercise physiologist and includes aerobic and resistance exercises. The ancillary study will enroll 84 of the 200 participants (21 per arm) to undergo additional muscle-specific assessments including Biodex strength testing, thigh magnetic resonance imaging (MRI), and vastus lateralis muscle biopsies. The primary objectives of the ancillary study are to evaluate the effects of fisetin and/or exercise on muscle strength (Biodex peak torque), muscle volume (on MRI), and muscle mitochondrial function (oxidative phosphorylation capacity). Secondary objectives include assessing changes in blood and muscle-specific markers of senescence from baseline to end of study. Enrollment to this study began July 2024 and is ongoing (NCT06113016). Clinical trial information: NCT06113016. Research Sponsor: U.S. National Institutes of Health; R01 CA280088; The Breast Cancer Research Foundation; Rising Tide Foundation for Clinical Cancer Research.

TPS12169 **Poster Session**

Exercise therapy in survivors of gastroesophageal cancer: A phase I, randomized dose-finding study of an individually tailored, remotely supervised exercise intervention. First Author: Jingran Ji, UCLA Health Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: Advances in perioperative systemic therapy and surgery have extended survival for patients with locoregional gastroesophageal cancer (GEC). However, intensive multimodality treatment often causes substantial physical function decline, leading to loss of independence and poor quality of life. No evidence-based interventions are currently approved to prevent or reverse this decline. Although exercise can improve fatigue, quality of life, and functional outcomes in other malignancies, it remains poorly studied in survivors of GEC. In patients with colon cancer, exercise after treatment is feasible, improves quality of life, and alleviates anxiety and depression. More recently, the CHALLENGE randomized trial demonstrated that a structured, in-person, supervised exercise intervention after chemotherapy for early-stage colon cancer can improve physical function, decrease cancer recurrence, and increase survival versus health education alone. However, the in-person exercise intervention was limited by low adherence and lack of exercise dose optimization, with only one target dose tested. These findings may not generalize to survivors of GEC, where treatment is more intensive and surgery more morbid. In this patient population, we hypothesize that aerobic exercise up to 225 minutes per week will be feasible, but higher doses will lead to lower levels of relative exercise dose intensity (REDI), defined as the ratio of completed to prescribed exercise dose over the course of the intervention. **Methods:** This phase I, randomized dose-finding study will enroll 24 adults (age ≥18 years) with stage I-III GEC who completed perioperative systemic therapy within 12 months and are sedentary (< 30 minutes/week of moderate-to-vigorous physical activity). Participants will be randomized 1:1:1 to one of three individually tailored, remotely supervised aerobic programs led by an exercise physiologist. Each 16-week program will target either 75 minutes (25 minutes, 3x/week), 140 minutes (35 minutes, 4x/week), or 225 minutes (45 minutes, 5x/week) of moderate-intensity exercise. Demographic and disease/treatment data will be collected at enrollment. Assessments at baseline and post-intervention include measures of cardiorespiratory fitness (submaximal exercise test), other measures of physical, cognitive, and psychological function, and quality of life. Heart rate, body weight/composition, and step count will be measured throughout using remote monitoring devices. The primary outcome is feasibility, as measured by the REDI. An exercise dose will be considered feasible if > 60% of the participants (≥5/8 per arm) achieve a REDI of > 75%. Secondary outcomes include changes in cardiorespiratory fitness and other functional and quality of life measures. This study has been IRB approved and is ongoing (NCI202600630). Clinical trial information: NCI202600630. Research Sponsor: U.S. National Institutes of Health; R03 AG095803; Jonsson Comprehensive Cancer Center Seed Grant.

TPS12170 **Poster Session**

MPOWER: A pilot trial among men with prostate cancer—Optimizing wellness by enhanced relief from hot flashes with acupuncture. First Author: Jeanny B. Aragon-Ching, Inova Schar Cancer Institute, Fairfax, VA

Background: Prostate cancer is the most commonly diagnosed cancer among men, and advanced disease often requires androgen deprivation therapy (ADT). ADT is associated with distressing side-effects, including hot flashes, sleep disturbance, fatigue, and cognitive symptoms. Acupuncture is a nonpharmacologic intervention shown to reduce hot flashes in other hormone-treated cancers, such as breast cancer; however, standardized acupuncture protocols for men receiving ADT are lacking. The primary objective of the MPOWER trial (NCT07335224) is to evaluate the feasibility and acceptability of study procedures, recruitment strategies, and delivery of a standardized acupuncture protocol to reduce hot flashes in men with prostate cancer. Feasibility will be assessed through enrollment and intervention engagement, and acceptability through satisfaction ratings and post-intervention qualitative feedback. Secondary objectives include patient-reported hot flash frequency and severity, hot flash interference, endocrine symptoms, sleep disturbance, and health-related quality of life. **Methods:** This randomized study compares Immediate Start Acupuncture (IA) with an Active Comparator: Delayed-Start Acupuncture (DA), allowing all participants eventual access to the intervention, among 24 men treated with ADT and/or androgen receptor pathway inhibitors. The intervention consists of a standardized 10-week protocol with weekly 30-minute manual acupuncture sessions delivered by a certified acupuncturist with oncology expertise. All participants receive lifestyle education from a nurse navigator as part of usual care. Participants randomized to the IA arm receive the acupuncture protocol during the initial 10-week intervention period, followed by 12 weeks of follow-up without acupuncture. Participants randomized to the activate comparator DA arm will receive lifestyle education per usual care without acupuncture during the initial 10-week comparison period, with bi-weekly check-ins serving as an attention control, and then initiate the acupuncture protocol after the delay period. Study assessments integrate real-time patient-reported hot flash diaries collected via a secure mobile application for remote symptom monitoring (Locus Health), validated patient-reported outcome measures, and continuous Fitbit monitoring to capture physiologic and sleep metrics, including heart rate variability, sleep duration, and nighttime awakenings. Feasibility outcomes include enrollment rates and intervention engagement. Acceptability is assessed quantitatively at multiple time points and qualitatively through semi-structured interviews. The primary patient outcome is the Hot Flash Severity Score, calculated as weekly mean hot flash frequency multiplied by severity. Enrollment began in January 2026, with accrual expected within 12 months. Clinical trial information: NCT07335224. Research Sponsor: Inova Seed Grant.

TPS12171 **Poster Session**

SWIVEL: A randomized phase II trial of switching medications versus guideline-directed interventions for adjuvant aromatase inhibitor side effects in breast cancer patients. First Author: Elaine Patricia Kuhn, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Background: Approximately half of breast cancer patients do not complete the standard 5-year course of adjuvant hormone therapy due to side effects, a finding associated with increased recurrence rates and breast cancer-specific mortality. In clinical practice, side effects are commonly addressed by switching to an alternative hormone therapy; however, this strategy has not been prospectively evaluated. In prior retrospective work, adherence was significantly lower among patients who switched therapies compared with those who remained on the same therapy and received treatment for side effects (62% vs 91%, p=0.013); however, interpretation is limited by the retrospective design. Therefore, a prospective randomized clinical trial was initiated to address this evidence gap by directly comparing medication switching with guideline-directed symptom management. **Methods:** SWIVEL is an ongoing phase II randomized trial comparing medication switching with guideline-directed interventions for the management of aromatase inhibitor side effects. Eligible patients are postmenopausal women or men with stage I–III ER-positive/HER2-negative breast cancer who are planning to initiate aromatase inhibitor monotherapy in the adjuvant setting. Upon enrollment, participants will be screened every 4 weeks with a validated single-item questionnaire (FACIT/GP5). Those who respond that they are 'quite a bit' or 'very much' bothered by side effects of treatment will be randomized to either (1) switch to a different hormone therapy, which may include an alternative aromatase inhibitor or tamoxifen, or (2) initiate an evidence-based intervention for side effects in accordance with NCCN guidelines and patient-provider preference. Participants may crossover between strategies at any time. The primary outcome is change in patient-reported symptom burden at 3 months following randomization or at crossover, whichever occurs first, measured by the FACT-ES survey. Secondary outcomes include patient-reported symptom burden at 6 months assessed in an intention-to-treat analysis using FACT-ES and PROMIS measures, and medication adherence assessed at 3, 6, 12, and 24 months using a multi-modal approach incorporating validated patient-reported measures (VOILS), pharmacy records, and urine testing for drug metabolites. Additional outcomes include patient-reported quality of life (FACT-G) and sexual function (FSFI), factors associated with adherence including access to care among rural communities, and evaluation of a novel screening tool to identify patients at higher risk for non-adherence. The study is open at Dartmouth Health and has enrolled 7 of 200 planned participants (NCT# 07071038). Clinical trial information: RCT07071038. Research Sponsor: Dartmouth Cancer Center.

TPS12172 **Poster Session**

A late-phase randomized open-label multi-cohort trial to evaluate immune-related adverse events with different standard-of-care dosing strategies of standard-of-care immunotherapies: ImmuRAd trial. First Author: Anup Kasi, University of Kansas Cancer Center, Kansas City, KS

Background: Programmed cell death-1 (PD-1) inhibitors, such as nivolumab and pembrolizumab, are widely used in treating solid tumors. These inhibitors have multiple FDA-approved dosing schedules. Extended-interval, higher-dose regimens offer patient convenience and health-system efficiencies. However, there is limited comparative prospective data evaluating immune-related adverse events (irAEs) across different dosing strategies. Our study aims to evaluate this important safety question in routine clinical practice. **Methods:** ImmuRAd is an investigator-initiated, open-label, randomized late phase trial. Adults ($\geq$18 years) with histologically or cytologically confirmed solid tumor malignancies who are scheduled to receive standard-of-care PD-1 inhibitor-based therapy in any disease setting or line of therapy are eligible for the study. Participants are randomly assigned to one of two pre-defined standard dosing strategies based on their physician-selected PD-1 inhibitor cohort. In the nivolumab cohort, patients are randomized 1:1 to receive nivolumab 240 mg every 2 weeks or nivolumab 480 mg every 4 weeks. In the pembrolizumab cohort, patients are randomized 1:1 to receive pembrolizumab 200 mg every 3 weeks or pembrolizumab 400 mg every 6 weeks. Route of administration is at the discretion of the investigator and can be given intravenous or subcutaneous. After completing 12 weeks of therapy, patients meeting predefined treatment-tolerance criteria may transition to extended-interval dosing at the discretion of the treating investigator. The primary objective is to determine the proportion of patients experiencing grade $\geq$3 immune-related adverse events (CTCAE v5.0) in each dosing arm within each cohort. Secondary endpoints include the incidence of all-grade immune-related adverse events, the time to resolution of these adverse events, treatment discontinuation due to immune-related adverse events, the overall response rate (for patients with measurable disease), progression-free or disease-free survival, and overall survival. Exploratory analyses will investigate the associations between immune-related adverse events and factors such as tumor type, treatment setting, microsatellite instability status, tumor mutational burden, and NGS biomarker profiles. The planned sample size is 192 evaluable patients (96 per cohort and 48 per arm). The study will enroll patients over a period of 24 months and will have a follow-up period of up to 2 years. In this IRB approved clinical trial, safety oversight will be provided by the institutional Data Safety Monitoring Committee. Trial Status: The study is actively enrolling at The University of Kansas Cancer Center and affiliated network sites. Clinical trial information: NCT07174453. Research Sponsor: Kansas University IIT Steering Committee.

TPS12173 **Poster Session**

Interrupting sedentary time to improve cardiometabolic health and toxicity in patients with lymphoma receiving chemotherapy: The iSTAND trial. First Author: Rebekah Wilson, Dana-Farber Cancer Institute, Boston, MA

Background: Among lymphoma patients treated with steroids, hyperglycemia is a common side effect. Episodes of hyperglycemia increase the likelihood of chemotherapy alterations, infection risk, and decreased overall survival. Interrupting sedentary time (IST) helps manage glycemic control in the diabetic population but is understudied among lymphoma patients. Additionally, there is preliminary evidence that IST during a chemotherapy infusion may reduce chemotherapy-related adverse effects. Therefore, we designed the iSTAND study to assess the feasibility of a 12-week IST intervention at home and during chemotherapy infusion appointments, and the preliminary efficacy on said intervention on a) cardiometabolic biomarkers and b) chemotherapy completion and toxicities among lymphoma patients. **Methods:** The iSTAND study is a prospective study aiming to recruit 24 patients diagnosed with lymphoma receiving either R-CHOP or POLA-R-CHP chemotherapy regimens. The first 3 enrolled patients will automatically be assigned to the intervention group to pilot the intervention (pre-pilot group). The remaining 21 patients will be randomly assigned IST intervention (n = 14) or control (n = 7). Five patients have been enrolled thus far (January 2026). The 12-week intervention will include a supervised component completed during chemotherapy infusion appointments and a self-directed home-based component. The in-clinic component will involve 2-minutes of walking every 30-minutes at 65-70% age predicted heart rate maximum, and two lower body resistance exercises every hour (1 set, 5-12 repetitions, 6-7 RPE) repeated for up to 4 hours of the infusion appointment. The home-based component will involve walking 250 steps per hour and alternating two lower and two upper body resistance exercises every hour (6 days/week for 6-12 hours/day). Patients will receive a Fitbit and resistance bands. Additionally, patients will receive daily movement prompts via Fitbit and text messages to encourage and assess adherence. Outcomes will be assessed at baseline prior to the second infusion and post-intervention after the 12-week intervention period. The primary outcome will be feasibility assessed via completion of $\geq$70% of prescribed activities, $\leq$50% rate of refusal, $\geq$70% retention rate, and $\geq$70% acceptance rate via acceptability of intervention questionnaire. Secondary outcomes include glucose levels and insulin assessed via continuous glucose monitor and fasting blood. Exploratory outcomes include quality of life, sleep quality, chemotherapy completion rate, and chemotoxicities assessed via questionnaires and medical records. Clinical trial information: NCT06923397. Research Sponsor: Helen B Gurley Foundation.

TPS12174 **Poster Session**

WINSHIP 4468-18: Phase II evaluation of the effect of 2- versus 6-hour oxaliplatin infusions on neuropathy and pharmacokinetics in patients with gastrointestinal cancers. First Author: Olumide B. Gbolahan, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA

Background: Oxaliplatin, a third-generation platinum agent, improves outcomes in gastrointestinal (GI) cancers when combined with fluoropyrimidines. However, it is also associated with clinically significant acute and chronic neurotoxicity. Approximately 33% of patients develop grade 3–4 sensory neuropathy, and up to 11% discontinue therapy due to neuropathy. Acute neurotoxicity is linked to the maximum plasma concentration (Cmax) of platinum ultrafiltrate, and greater acute sensory neuropathic symptoms predict later chronic neuropathy. Prior data suggest that extending infusion duration from 2 hours to 4–6 hours lowers Cmax by ~32–50% and reduces recurrence of acute neuropathic symptoms. We hypothesize that a 6-hour oxaliplatin infusion will reduce platinum ultrafiltrate Cmax and decrease the incidence and severity of chronic sensory neuropathy. **Methods:** WINSHIP 4468-18 is a randomized, open-label phase II trial enrolling a real-world population of patients with gastrointestinal (GI) cancers for whom oxaliplatin-containing combination therapy is indicated. All participants receive IV infusion of oxaliplatin 85 mg/m² every 2 weeks as part of a standard combination regimen. Sixty patients will be randomized 2:1 to 6-hour (n = 40) versus 2-hour (n = 20) oxaliplatin infusion duration. Eligibility includes confirmed GI malignancy, ECOG 0–2, and adequate organ function. Key exclusion criteria are baseline grade $\geq$2 neuropathy and prior hypersensitivity/intolerance to oxaliplatin. The primary endpoint is the between-arm difference in EORTC Chemotherapy Induced Peipheral Neuropathy (CIPN) 20 sensory scores from baseline to cycle 4. Secondary endpoints include comparison of pharmacokinetic parameters, particularly Cmax of platinum ultrafiltrate. With an assumed 10-point between-group difference in CIPN20 sensory score at cycle 4, 60 patients provide 80% power (two-sided α = 0.05). The study is open and accruing (NCT03800693). Clinical trial information: NCT03800693. Research Sponsor: None.

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